Pharmaceutical Sciences, 2023, 29(2), 236-245
doi:10.34172/PS.2022.43
https://ps.tbzmed.ac.ir/

Research Article

Synthesis, Crystal Structure and Antibacterial Activity of Cu(II) Complex with Nitrogen Donor Pyrazolyl Borate Derivatives

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Article Info

Article History:
Received: 17 June 2022
Accepted: 11 November 2022
ePublished: 18 November 2022

Keywords:
-Antibacterial activity
-Cu (II) complexes
-Molecular docking
-Pyrazolyl borate derivative
-X-ray structure

Abstract

Background: Pyrazolyl borate derivatives are versatile ligands that can be coordinated with transition metals and formated a variety of different coordination modes. Copper complexes are highly active in biological applications and have high bioactivity. Because of the above description and applications, in the present work, synthesis and characterization of pyrazolyl borate derivative ligands and their Cu(II) complex were reported. The structure of the synthesized complex was determined by X-ray crystallography. In addition, the antimicrobial activity of the synthesized compounds along with the molecular docking of them was investigated.

Methods: N-donor pyrazolyl borate derivative ligands abbreviated as $K[HB(Pz^{Me2})_3]$ and $K[H_2B(Pz^{Me2})_2]$ and their Cu(II) complex were synthesized and characterized. The synthesized ligands and complex were evaluated for antibacterial activities against the gram-positive (B. subtilis) and the gram-negative (S. enterica) bacteria. Also, their molecular docking with B. subtilis SMC head domain (PDB ID: 5H67) as the possible targets was investigated.

Results: The *in vitro* and *in silico* results showed, among the investigated compounds, complex $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ indicated the highest antibacterial activity. Also, the Statistical analysis showed that the difference between the obtained data was significant.

Conclusion: We have synthesized N-donor pyrazolyl borate derivatives and their copper (II) complex. Single X-ray results indicated the Cu(II) complex adopted an N_5 environment around the metal center with a distorted square pyramidal geometry. The obtained binding energy of molecular docking studies is in direct correlation with the *in vitro* antibacterial studies. Briefly, the reported Cu (II) complex may be considered as a potential antibacterial candidate.

Introduction

Since the first report of Trofimenko, pyrazolyl borates derivatives have been extensively employed and developed into one of the most versatile tripodal auxiliary nitrogen donor ligands in inorganic chemistry.[1-4] Pyrazolyl borate derivatives are very versatile ligands that can be coordinated to the transition metals and adopt a variety of different coordination modes.[2,5-8] Pyrazole-based metal complexes have been widely applied for this purpose because of their flexible coordination behavior, various electronic and structural properties.[8-14] Also, these compounds have attracted much attention among researchers because of their significant potential in various area of chemistry, especially in pharmaceutical and bioinorganic chemistry.[15-19] On the other hand, the pyrazole-containing compounds attracted considerable interest in bioinorganic chemistry and medicinal chemistry.[7,14,20-23] So, there has been considerable progress in pyrazole chemistry because of the importance of the pyrazole structure in biological processes such as anticancer, antifungal, and antibacterial activities.[24-27] Generally, the heterocyclic compounds containing nitrogen donor atoms in the ring system have been used in the design and synthesis of bioactive compounds, their activity increases with the coordination with the transition metal ions.[28-33] Successful clinical reports of approved pyrazole-based drugs such as pyrazofurin (anticancer), celecoxib and lonazolac (anti-inflammatory), difenamizole (analgesic), sildenafil (vasodilator), and fezolamide (antidepressant) indicated the efficiently and the safety of these compounds in the human cells. Copper complexes are highly active in biological applications and have high bioactivity against viruses, bacteria, yeasts, and fungi.[34-39] In view of the above description and applications, in the present work, the synthesis and characterization of pyrazolyl borate derivative ligands and their Cu(II) complex were reported

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and the single X-ray structure of the synthesized complex was determined. Also, the antimicrobial activity of the synthesized compounds against Gram-positive (*B. subtilis*) and Gram-negative (*S. enterica*) along with the molecular docking of them with *B. subtilis* SMC head domain (PDB ID: 5H67) were investigated.

Materials and Methods

Materials and instrumentation

All of the solvents and materials were purchased from Merck Company and were used without further purification. FT-IR spectra were prepared with an FT-IR Spectrometer Bruker with KBr disks in the 400–4000 cm^{-1}. Melting points were measured with a Stuart Scientific SMP1 apparatus. Elemental analysis (C.H.N) was performed on ElementarVario ELIII. Antibacterial investigations were performed using the disk diffusion method.[40]

Synthesis of the ligands

*Synthesis of the hydrotris(3, 5-dimethylpyrazolyl)borate, $K[HB(Pz^{Me2})_3]$ **(1)***

The mixture of synthesized 3, 5-dimethylpyrazole (0.3 g, 3 mmol) and KBH_4 (0.05 g, 1 mmol) under nitrogen atmosphere was heated to 98 ˚C and H_2 evolution started at this point. Then the temperature was raised to 160 ˚C gradually and was controlled evolution of hydrogen. When (67.2 ml, 3 mmol) of hydrogen had been evolved, the reaction was finished and the resulting white precipitate was washed with the mixture of THF and n-hexane and finally was dried in vacuum over P_2O_5 (Figure 1).

$K[HB(Pz^{Me2})_3]$ (**1**): Yield: 0.21 g (65%). FT-IR:(KBr, cm^{-1}): 2925-2877(w), 2435- 2254(m), 1631(w), 1595(m), 1440(w), 1422(s), 1357(s), 1174(s), 1028(m), 1008(m), 945(m), 888(m), 735(s). Elem Anal. (%) Calcd for $C_{15}H_{22}BKN_6$: C, 53.57; H, 6.59; N, 24.99. Found: C, 53.39; H, 6.42; N, 24.32. m.p: 225 °C.

*Synthesis of the dihydrobis(3, 5-dimethylpyrazolyl)borate, $K[H_2B(Pz^{Me2})_2]$ **(2)***

According to the reported papers,[41-43] and similarly to the synthesis of the ligand $K[HB(Pz^{Me2})_3]$, this ligand was synthesized. The only difference between the synthesis of this ligand and ligand $K[HB(Pz^{Me2})_3]$ was the difference in reaction temperature, which must be controlled at about 120 ˚C. Other steps were similar to the synthesis of the ligand $K[HB(Pz^{Me2})_3]$. In summary, the mixture of KBH_4 (0.005 g, 1 mmol) and the synthesized 3,5-dimethylpyrazole (0.2 g, 2 mmol) under nitrogen atmosphere was heated to 98 ˚C, in this temperature evolution started. Then the temperature was raised to 120 ˚C. When (44.8 ml, 2 mmol) of hydrogen had been evolved, the reaction was finished and finally the resulting white precipitate was washed and dried (Figure 1).

*Synthesis of the Cu(II) complex, $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ **(3)***

The mixture of the synthesized ligands $K[HB(Pz^{Me2})_3]$ (0.336 g, 1 mmol) and $K[H_2B(Pz^{Me2})_2]$ (0.242 g, 1 mmol) was dissolved in a mixture of dichloromethane (15 ml) and methanol (5 ml), a methanolic solution of $Cu(CH_3COO)_2.H_2O$ (0.199 g, 1 mmol) was added to the ligands solution and reaction mixture was stirred at room temperature for 12 h (Figure 1). The resulting precipitate of the complex was collected and the remainder solution was allowed to evaporate slowly at room temperature, after several days afforded blue crystals. The single crystal structure of the Cu (II) complex was determined using X-ray crystallography.

$[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ (**3**): Yield: 0.41 g (74%). FT-IR (KBr, cm^{-1}): 2959-2925(w), 2458-2221(m), 1584(m), 1534(s), 1420(s), 1384(s), 1206(m), 1182(s), 1112(s), 1060(m), 895(m), 825(m), 786(m), 629(m), 463(w). Elem Anal. (%) Calcd for $C_{25}H_{38}B_2CuN_{10}$: C, 53.25; H, 6.79; N, 24.84. Found: C, 53.92; H, 6.45; N, 25.01. m.p: >300 °C (Dec.).

X-ray crystallography

X-ray single crystallography data for **(3)** was collected by Bruker APEX2 using optics Cu/Kα (λ = 1.54178 Å) radiation at 100 K. The structure was solved and refined by direct methods using SHELXS97 (Sheldrick, 2008) Software. Hydrogen atoms were assigned ideal positions and refined isotropically as riding atoms. Crystallographic data for compound **(3)** are listed in Table 1.

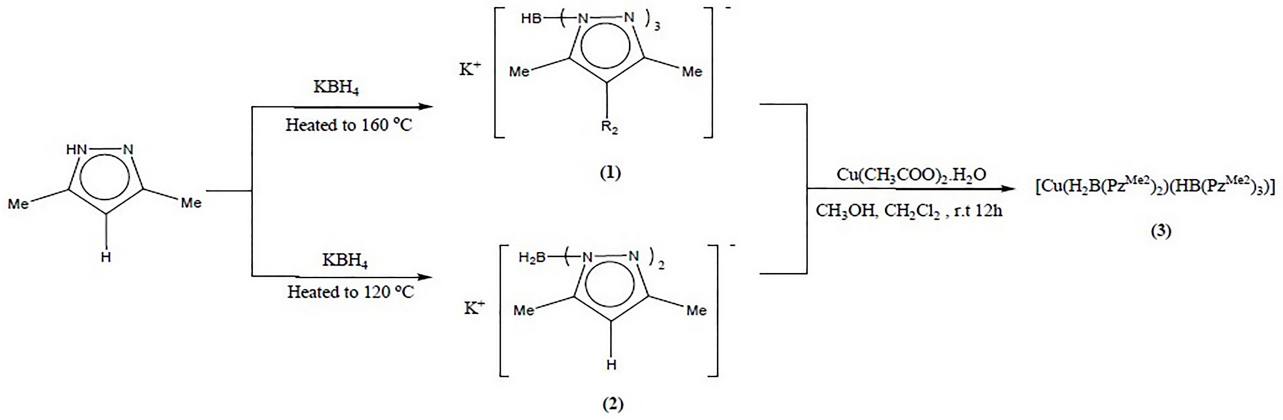

Figure 1. The route of synthesis of ligands **(1, 2)** and Copper (II) complex **(3)**.

Table 1. Crystallographic data and refinement for complex $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ **(3)**.

Empirical formula	$C_{25}H_{38}B_2CuN_{10}$
Formula weight/g mol^{-1}	563.81
Radiation	Cu/Kα(λ = 1.54178Å)
Temperature/K	100
Crystal shape and color	Plate, blue
Crystal size/mm	0.12 × 0.08 × 0.07
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	12.8487 (9)
b/Å	13.5485 (11)
c/Å	16.0273 (10)
β/°	93.484 (4)
Volume/Å^3	2784.9 (3)
Z	4
Dx / Mg m^{-3}	1.345
μ/mm^{-1}	1.37
F(000)	1188
Θ range for data collection/°	5.6–65.3
T_{min}, T_{max}	0.857, 0.916
Index ranges	-14 ≤ h ≤ 12 -15 ≤ k ≤ 14 -19 ≤ l ≤ 18
Measured reflections	15964
Reflections with I > 2σ(I)	3220
R_{int}	0.053
S	0.97
Goodness of fit on F^2	0.970
R[F^2> 2σ(F^2)]	0.049
wR(F^2)	0.156
Data/restraints/parameters	4621/0/353
Max electron density/e·Å^{-3}	0.37
Min electrondensity/e·Å^{-3}	−0.40

Antimicrobial activity

The antimicrobial investigations of synthesized ligands **(1, 2)** and their Cu (II) complex **(3)** were evaluated by two laboratory control strains of bacteria, the Gram-positive: *B. subtilis* (ATCC6633) and the Gram-negative: *S. enterica* (ATCC14028). All tests were performed in the disk diffusion method. Gentamicin was used as the standards for comparing the activity of the compounds and Dimethyl sulfoxide (DMSO) was used as a negative control. Antibacterial tests of investigated compounds were determined at a concentration of 60 mM in DMSO. The filter paper disk of 6 mm diameter was impregnated with 10 μL of investigated synthesized compounds and their efficacy was assessed on Muller Hinton agar disks. The bacterial cultures were grown at 37 ˚C for 24 h in a broth medium and then were diluted to 0.5 McFarland standards.[40] After an overnight incubation of plates at 37 ˚C, the inhibition zone of compounds was determined by measuring the minimum dimensions of the zone of no bacterial growth surrounding the disk. All tests were done independently in triplicate wells, and the average of these determinations was recorded. Statistical analysis was performed with One-way ANOVA and a post-test of Tukey by using GraphPad Prism software.

In silico molecular docking

In silico molecular docking studies were performed using Autodock Tool (ADT) version 1.5.6 and AutoDock version 4.2.6. Based on the literature,[44-47] *B. subtilis* SMC head domain is a possible target for our type of synthesized compounds with the capability of antimicrobial effects. The 3D crystal structure of *B. subtilis* SMC head domain (PDB ID: 5H67) protein was obtained from the Protein Data Bank website (RCSB) (http://www.rcsb.org/pdb/). The cif format files of the single crystal of Cu (II) complex and the optimized structure of synthesized ligands were applied in the molecular docking studies. Autodock Tool was used to eliminating the macromolecule from water molecules and nonstandard protein residues. The polar hydrogens were added, and Gastegier charges were assigned and saved in PDBQT file format.[48,49] The docking site was defined by fixing the grid box to the dimensions of 126×126×126 Å grid box (grid spacing=0.375Å). Then the macromolecule receptor docking investigation was carried out for 100 independent runs to evaluate the binding free energy of the inhibitors within the macromolecules.[50]

Results and Discussion

Synthesis and characterization

The synthesized ligands and Cu(II) complex were characterized by elemental analysis and FT-IR analyses. As we described in previous papers,[41,42] the absence of the ν(N-H) band of 3,5 dimethylpyrazole in the range of 3200±50 cm^{-1} and the appearance of the ν(B-H) group bands in the 2200- 2500 cm^{-1} confirmed of the syntheses of the ligands. With the coordination of ligands to the Cu(II) center, all of the bands attributed to the various groups of ligands a little shifted.[41,51] Furthermore, the band assigned to ν(Cu-N) stretching vibrations appeared at 463 cm^{-1}.[52] Furthermore, the X-ray crystallography structure of the synthesized copper complex confirm the correct synthesis of ligands and Cu (II) complex.

Crystal structure of complex $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ (3)

The molecular structure of the complex $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ has been determined by single crystal X-ray crystallography. The synthesized copper (II) complex crystallizes in the monoclinic crystal system in space group $P2_1/n$. The molecular structure and labeling of the atoms in the structure of complex **(3)** are displayed in Figure 2. The selected angles and bond lengths are collected in Table 2. In the structure of the synthesized mononuclear complex, the Cu (II) center adopt a five-coordinate geometry via the synthesized ligands, hydrotris(3,5-dimethylpyrazolyl) borate **(1)** and dihydrobis(3,5-dimethylpyrazolyl) borate **(2)** ligands as nitrogen donor chelating ligands. In the structure of the complex **(3)** both of the ligands through the nitrogen atom of pyrazole rings were coordinated to the Cu (II) center. The monoclinic unit cell contains four

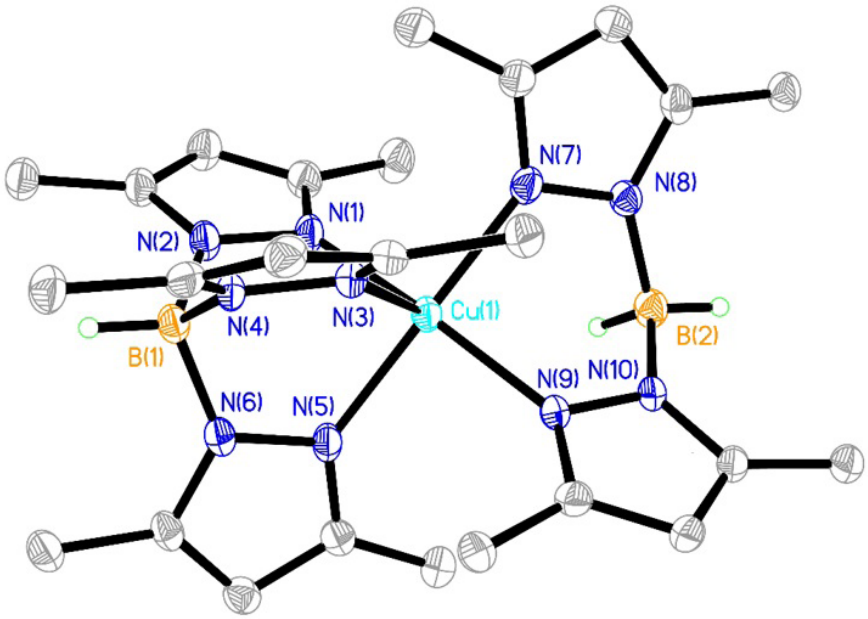

Figure 2. Molecular structure of complex [Cu($H_2B(Pz^{Me2})_2$)($HB(Pz^{Me2})_3$)] **(3)**.

Table 2. Selected bond lengths (Å) and angles (°) of complex [Cu($H_2B(Pz^{Me2})_2$)($HB(Pz^{Me2})_3$)] **(3)**.

Bond lengths (Å)			
Cu1—N7	2.005 (3)	Cu1—N9	2.012 (3)
Cu1—N1	2.006 (3)	Cu1—N5	2.022 (3)
Cu1—N3	2.187 (3)		
Bond angles (°)			
N7—Cu1—N1	91.70 (12)	N7—Cu1—N5	170.08 (12)
N7—Cu1—N9	90.46 (12)	N1—Cu1—N5	84.00 (12)
N1—Cu1—N9	168.26 (12)	N9—Cu1—N5	92.01 (11)
N7—Cu1—N3	98.09 (12)	N9—Cu1—N3	100.04 (11)
N1—Cu1—N3	91.08 (11)	N5—Cu1—N3	90.94 (12)

mononuclear units (z = 4). Figure 3 indicates a view of the molecular packing diagram of single crystal.

The exact coordination geometry and distortion around the metal center can be expressed with the parameter τ_5,[53,54]

$$\tau_5 = \frac{\beta - \alpha}{60}$$

Where: $\beta > \alpha$ are the two greatest valence angles of the coordination center. When τ_5 is close to 0 the geometry is similar to square pyramidal, while if τ_5 is close to 1 the geometry is similar to trigonal bipyramidal.

In the single crystal structure of the synthesized complex, the N7—Cu1—N5 (170.08˚) and N1—Cu1—N9 (168.26˚) are the two greatest valence angles around the Cu (II) center and the calculated value for this complex is 0.030, that confirming a distorted square pyramidal geometry for the synthesized copper (II) complex **(3)**.

Antimicrobial studies

The synthesized ligands **(1, 2)**, their corresponding Cu (II) complex **(3)**, standard drug and negative controls were screened separately to evaluate their antibacterial activity against the Gram-positive: *B. subtilis* (ATCC6633) and the Gram-negative: *S. enterica* (ATCC14028). The results are summarized in Figures 4 and 5.

According to the obtained results, the inorganic coordinated Cu(II) complex **(3)** indicated higher

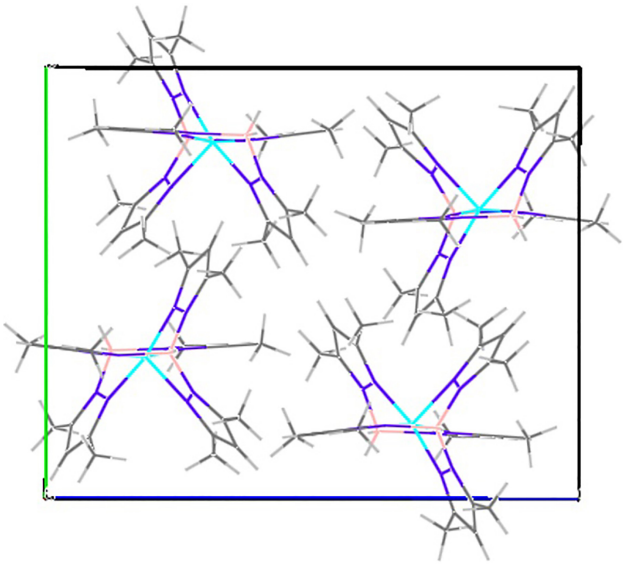

Figure 3. The unit-cell packing diagram of complex [Cu($H_2B(Pz^{Me2})_2$)($HB(Pz^{Me2})_3$)] **(3)**.

antibacterial activity in comparison with the uncoordinated ligands **(1, 2)**. However, in this concentration that we used for antimicrobial investigations, the ligands revealed no inhibitory effect against the *S. enterica* bacteria, but they showed a zone of inhibition ranging from 10.30 mm and 12.22 mm against *B. subtilis* strains. Furthermore, the synthesized compounds indicated considerable antibacterial activity against the Gram-positive in comparison with the Gram-negative strains, the lack of an outer membrane in the Gram-positive strains is the reason of these findings.[55,56] Positive control (Gentamicin) indicated significant inhibition zones in ranging from 29.66 to 30 against the investigated bacterial strains. The negative control (DMSO) revealed no inhibitory effect against any of the test microorganisms. Chelation theory can be explained the increasing of bioactivity of complexes relative to ligands. The polarity of the metal center is reduced with the coordination of ligands to metal ions and this enhances the lipophilicity of the compounds. The lipophilicity of material is the main parameter that controls biological activity.[23,41,57] Our finding indicated, that inorganic coordinated compounds are more bioactive than the free uncoordinated ones that can be further applied in the various area of medicine area such as an antibacterial agents.

Molecular docking studies

Molecular docking studies of pyrazolyl borate derivative ligand and corresponding copper (II) complex were done against the *B. subtilis* SMC head domain (PDB ID: 5H67) as the possible target. *In silico* molecular docking results are tabulated in Table 3. As can be seen, among the investigated compounds, the Cu (II) complex has a better binding energy than the uncoordinated ligands. Complex $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ **(3)** bound to *B. subtilis* SMC head domain target with the binding energy of -7.91 kcal/mol and the ligands $K[HB(Pz^{Me2})_3]$ **(1)** and $K[H_2B(Pz^{Me2})_2]$ **(2)** bound to this macromolecule with a binding energy of -7.09 kcal/mol and -6.56 kcal/mol, respectively. The control group is bound to the selected target with a binding energy of -10.97 kcal/mol. The obtained molecular docking results of the synthesized compounds are comparable with the similar reported antibacterial agents and indicate the validity of this applied docking study.[40] Figure 6 showed the docking poses between the selected target and complex $[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ **(3)**. The molecular docking model of macromolecule and ligands **(1)** and **(2)** are represented in Figures 7 and 8.

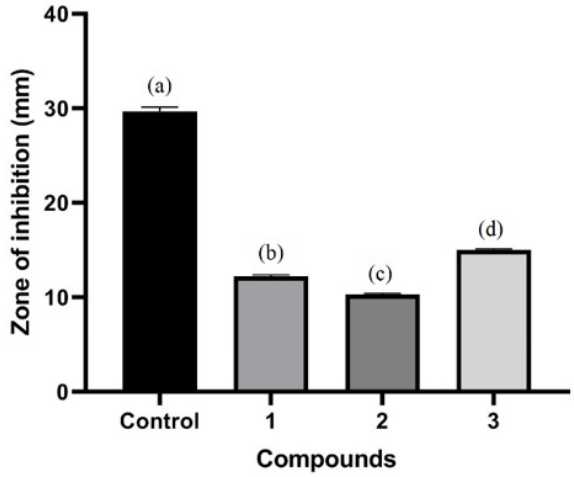

Figure 4. Zone of inhibition of the investigated compounds against the Gram-positive (*B. subtilis*). Statistical analysis with One-way ANOVA and post-test of Tukey showed that the difference between all columns are significant with p<0.001. The columns followed by the same lowercase letter are not significantly different.

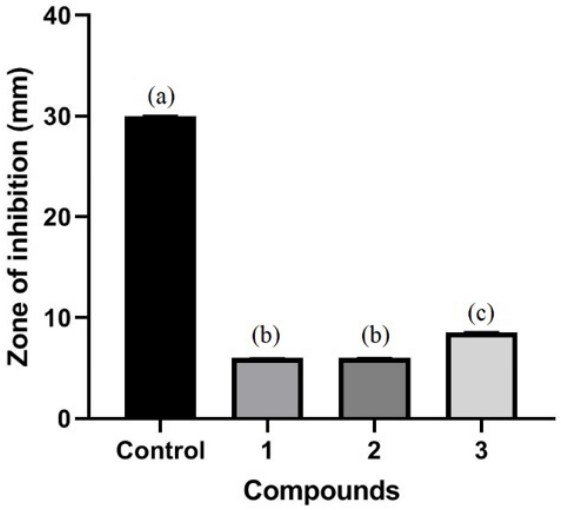

Figure 5. Zone of inhibition of the investigated compounds against the Gram-negative (*S. enterica*). Statistical analysis with One-way ANOVA and post-test of Tukey showed that the difference between all columns are significant with p<0.001 except compound 1 and compound 2. The columns followed by the same lowercase letter are not significantly different (P > 0.05).

The presence of the uncoordinated nitrogen atoms in the structures of ligands causes a formation of the hydrogen bond between the ligand and the investigated macromolecule. Figure 9 shows the formation of the H-bond between the Val1173 group of *B. subtilis* SMC head domain and the nitrogen atom of the pyrazole ring in $K[HB(Pz^{Me2})_3]$ (**1**). The hydrogen bond between the N atom of $K[H_2B(Pz^{Me2})_2]$ (2) and the Arg45 group of possible target indicated in Figure 10. Thus, *in silico* molecular docking investigations together with *in vitro* antibacterial studies is indicated that inorganic coordination compounds have the best bioactivity in comparison with free organic ligands. The obtained binding energy of molecular docking studies is in direct correlation with the *in vitro* antibacterial studies, with the increase of the binding energy between compounds and macromolecule, the calculated zone of inhibition of the compounds against the tested strains increases.

Conclusion

In the present investigation, pyrazolyl borate derivative ligands and their copper complex were synthesized and characterized using various methods. The structure of the synthesized Cu(II) complex was confirmed using

Table 3. The results of the docking of compounds **(1-3)** and selected target (PDB ID: 5H67).

Compound	Binding Energy	Intermol energy	(Van der Waals + Hbond + desolv) energy	Electrostatic energy	Total internal	Unbound energy	Torsional energy	Ki
$K[HB(Pz^{Me2})_3]$ (1)	-7.09	-7.99	-7.84	-0.15	-1.55	-1.55	0.89	6.34
$K[H_2B(Pz^{Me2})_2]$ (2)	-6.56	-7.16	-6.91	-0.25	-0.45	-0.45	0.6	15.51
$[Cu(H_2B(Pz^{Me2})_2)(HB(Pz^{Me2})_3)]$ (3)	-7.91	-8.51	-8.55	0.04	-1.23	-1.23	0.6	1.59
Control	-10.97	-13.37	-9.47	-3.9	2.65	2.65	2.39	8.9

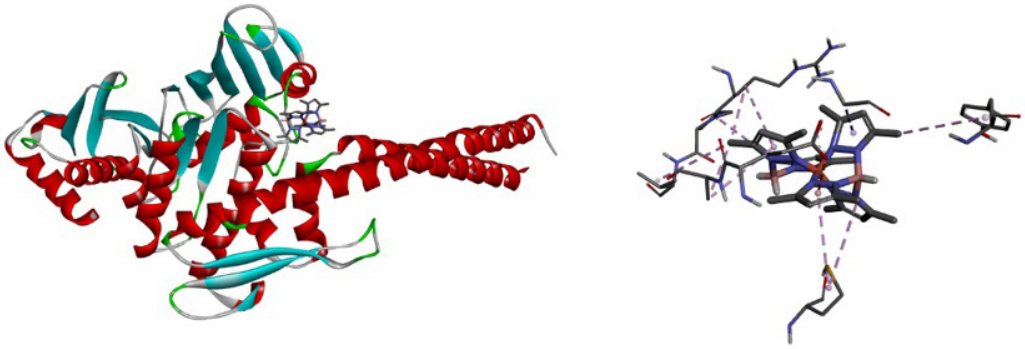

Figure 6. Representing the docking poses between selected target (PDB ID: 5H67) and complex **(3)**.

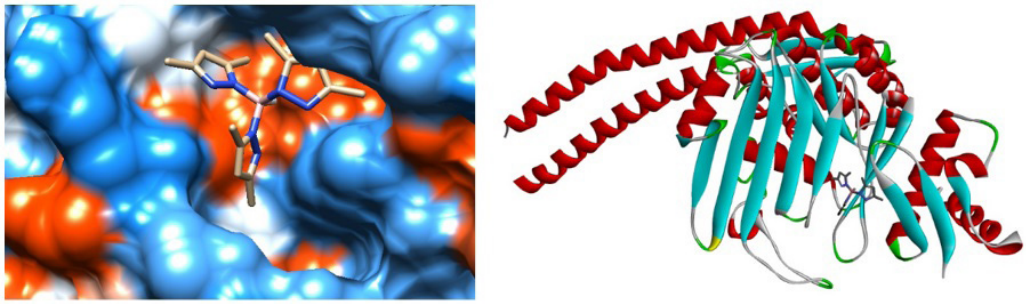

Figure 7. Representing the docking poses between selected target (PDB ID: 5H67) and ligand **(1)**.

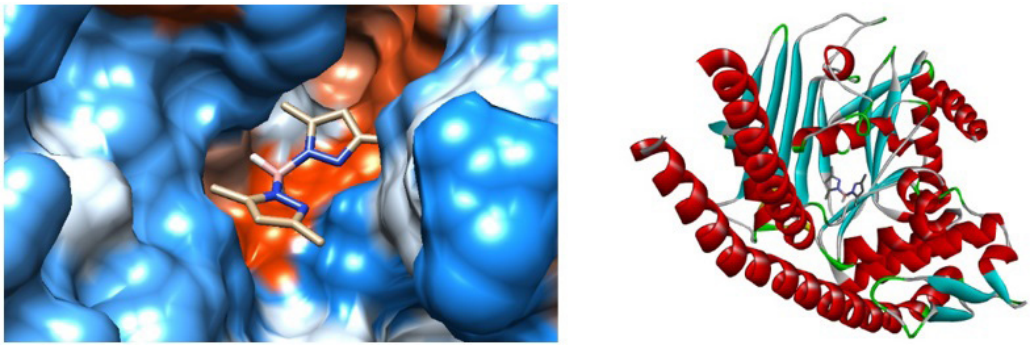

Figure 8. Representing the docking poses between selected target (PDB ID: 5H67) and ligand **(2)**.

X-ray crystallography analysis. Single crystal experiments results indicated that the Cu(II) complex adopted an N_5 environment around the metal center with a distorted square pyramidal geometry. Antimicrobial studies indicated that inorganic compounds have high inhibition in comparison with the free ligands. Furthermore, the investigated compounds indicated considerable antibacterial activity against the Gram-positive in comparison with the Gram-negative strains, the lack of an outer membrane in the Gram-positive strains is the reason for these findings. Molecular docking studies of the synthesized ligands and corresponding Cu (II) complex indicated similar results. The copper complex showed good binding energy in docking with the possible target in comparison with organic ligands. The obtained binding energy of molecular docking studies is in directly correlated with the in vitro antibacterial studies. Overall, the coordination of metal center to ligands causes the decrease of lipophilicity and

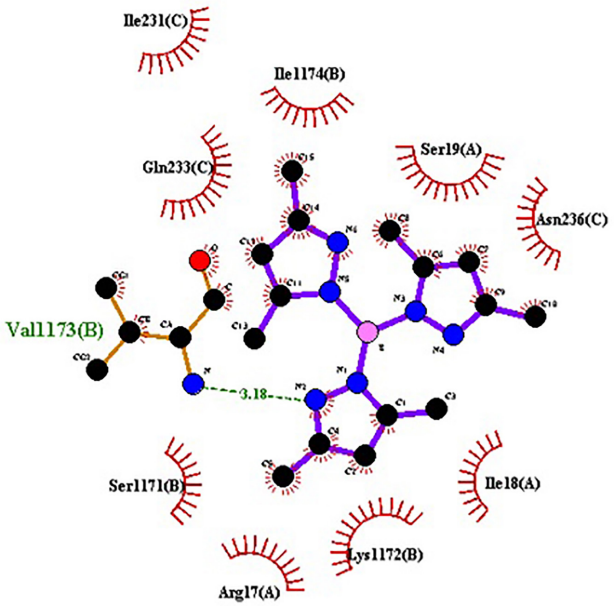

Figure 9. Binding mode of ligand K[HB(Pz^{Me2})$_3$] (**1**) and the macromolecule (PDB ID: 5H67), the H-bond (green line) is displayed as line.

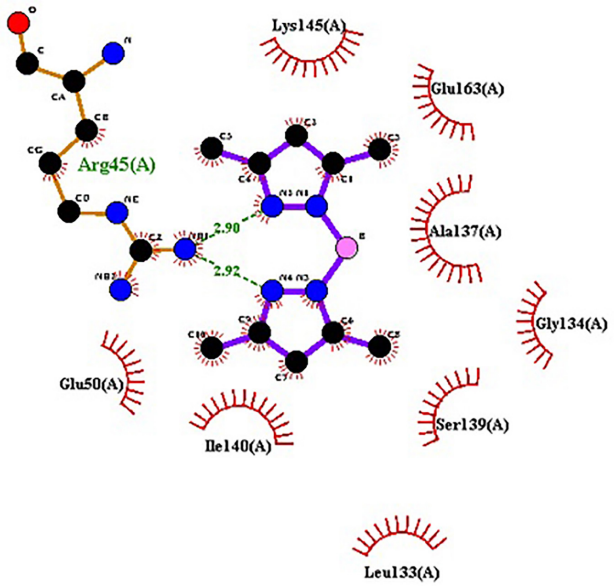

Figure 10. Binding mode of ligand K[H_2B(Pz^{Me2})$_2$] **(2)** and the macromolecule (PDB ID: 5H67), the H-bond (green line) is displayed as line.

along with increasing bioactivity. Briefly, the reported Cu (II) complex may be considered as a potential antibacterial candidate.

Acknowledgments

We are grateful to the University of Azarbaijan Shahid Madani for supporting of this research. Single crystal X-ray diffraction experiments were performed at the University of Akron. We thank them for their helpful collaboration.

Author Contributions

BS: Participated in the design of the study, analysis, revising the manuscript, interpretation of data, drafting the manuscript and final approval of the version to be published. MG: Participated in the design of the study, analysis, revising the manuscript, interpretation of data and drafting the manuscript. SB: Participated in the design of the study, analysis. ME: Participated in the design of the study, revising the manuscript, interpretation of data and final approval of the version to be published. CZ: X-ray crystallography analysis. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors report no conflicts of interest.

Supplementary Data

CCDC 2179519 contain the supplementary crystallographic data for **3.** These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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