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Synthesis, Characterization, Antimicrobial Activity and Molecular Docking of a Dinuclear Nickel(II) Complex

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ABSTRACT

Bis-(benzidinedioxime) nickel(II) acetate complex was synthesizedby reacting the metal ions with benzidinedioxime in 1:1 mole ratio.The nickel(II) complex was characterized by elemental analysis, NMR, and powder X-ray diffraction. The result obtained from CHN Elemental analysis and ^{1}H nuclear magnetic resonance confirmed that the nickel(II) complex is synthesized by reacting benzidinedioxime with nickel(II) acetate in a 1:1 mole ratio. The powder XRD showed that two Ni(II) coordinated to two benzidinedioxime ligands via the nitrogen atoms of both oxime groups and the two azomethine nitrogen atoms. Powder X-ray diffraction (PXRD) indicated that the nickel(II) complex has little distorted tetrahedral geometry. Nickel(II) complex has a higher antimicrobial activist against *K. pneumonia*, *B. subtilis*, and *Candida* than kanamycin. In addition, the *B. subtilis* shows resistance against kanamycin (inhibition zone 0) while it shows high sensitivity against bis-benzidinedioxime nickel(II) acetate complex (inhibition zone 33.3 ± 0.82 mm, MIC 18.5 µg/mL). The average MICs of bis-benzidinedioxime nickel(II) acetate are found to be for inhibition of each of the five organisms in the range of 6.2–55.65 µg/mL. The molecular docking studies investigations confirmed that the bis-benzidinedioxime nickel(II) acetate is the most potent aminoglycoside enzymes bacterial inhibitors. The bis-benzidinedioxime nickel(II) acetate exhibited high binding energy with the receptor aminoglycoside-3-phosphotransferase enzyme than receptors of other aminoglycoside enzymes families.

KEYWORDS: Dinuclear complexes, aminoglycoside enzymes families, molecular docking, antimicrobial activities, elemental analysis.

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INTRODUCTION

Coordination chemistry is becoming a critical area of research due to the demand for transition metal-based antibacterial compounds [1, 2]. Previous studies have indicated that the metals complex is high activity than the parent organic ligand, and it is a significant deactivation of protein when exposed to protein [3-5]. Schiff base complexes of transitions metal show different behavior with different types of bacteria [6-9]. The complex transition metals ion of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) of a Schiff base derived from m- phenylenediamine and 2-hydroxybenzaldehyde show more activity than the ligand against same microorganisms under identical experimental conditions [9]. New dinuclear cobalt(II), nickel(II), copper(II), and palladium(II) complexes synthesized having N4O4 Schiff-base ligands obtained from the condensation of glycylglycine with *o*-phthalaldehyde [10].

A series of dinuclear nickel(II) complexes are showed a significant structural diversity in the solid-state depending on the type of ligand and salt of nickel(II) [11-13]. The complex nickel(II) with tetradentate N_2O_2 ligand has a slightly distorted square-planar geometric shape, while the complex of nickel(II) with the pyridine ligand, the nickel(II) complex

becomes an octahedral geometry shape [14]. Similarly the complexes $[Ni_2(L)_2(m1,1\text{-}N3)2(N3)2]$ [L = N,N-bis(2-pyridylmethyl) amine and N-(2-pyridylmethyl)-N0,N0-diethylethylenediamine] show ferromagnetic behaviour [15].Many researchers have reported the Schiff base complexes to exhibit high antifungal efficiency than their corresponding ligand and approved drugs [16-19].

The commonly used antibiotics led to a developing rate of bacterial resistance to classical antibiotics [20, 21]. One such class of antibiotics is the aminoglycoside antibiotics family[22, 23]. Aminoglycoside antibiotics are amino sugars linked to an aminocyclitol moiety such as streptomycin and kanamycin [23-25]. Aminoglycosides antibiotics were used for treating aerobic, gram-negative bacteria, and gram-positive bacteria [26, 27].

Resistance to aminoglycosides can occur by three different mechanisms: mutation of the rRNA target, reduced permeability for the drug, and enzymatic modification of the drug leading to inactivation [28, 29]. The most prevalent source of clinically relevant resistance is conferred by aminoglycoside modifying enzymes. There are three families of enzymes responsible for aminoglycoside resistance ATP-dependent O-phosphotransferases (APH), ATP-dependent O-adenyltransferases (ANT), and the acetyl CoAdependent N-acetyltransferases (AAC) [28].

Lastly, research showed that combinatorial transition metals with antibiotics are higher activity and sensitivity to different bacterial resistant strains and low toxicity [30]. All previous studies suggest that the organometallic compounds and complex compounds will play a paramount role in future developments of antimicrobial agents and treatments against infections caused by susceptible and resistant strains [31-33]. Current approaches to the synthesis of drugs face to synthesize new compounds containing dinuclear metal ions and test them as bacterial inhibitors and study molecular docking against aminoglycoside enzymes families.

MATERIALS AND METHODS

Materials

Nickel(II) acetate (Assay = 98.0%, Loba Chemie, Spain). Ethanol (99.9%, Duksan, Germany). Methanol (Assay = 99.8%, Sigma-Aldrich, Germany). Diethyl ether (97.5%, Alpha Chemika, India). Dimethyl sulphoxide (99.9, Alpha Chemika, India). Glacial acetic acid (85%, Alpha Chemika, India), molar hentun media, and yeats were used as received. Benzidinedioxime was synthesied and chractrized in previous study[34].

Synthesis of the metal complexes

The metal complexes were prepared by the addition of a hot solution of the appropriate nickel(II) acetate (2.5 mmol) in ethanol to a hot solution of the benzidinedioxime ligand (2.5 mmol) in ethanol. The resulting mixture was stirred under reflux for 20 hours and was upon the complexes precipitated. The precipitate was filtered off and was washed several times with cold ethanol and diethyl ether.

Elemental analysis measurement

The percentage of carbon-hydrogen and nitrogen containedin bis-benzidinedioxime nickel(II) was analyzed using Flash EA 1112 CHN.

^{1}H-Nuclear magnetic resonance (^{1}HNMR)

The ^{1}H NMR spectrum of the nickel(II) complex solution in DMSO D_6 (0.05 mM) was determined using Bruker DPX 250 and 300 MHz spectrometers. Standard pulse sequences were used for the 1H one-bond and long-range HMBC spectra.

Powder X-ray diffraction (PXRD)

The crystal structure was determined by powder XRD using a Shimadzu 7000 X-ray diffractometer. At room temperature, data was collected for a 2θ range of 20–80^O at a step size of 0.02 and a 5 second count time.

Molecular docking

The molecular docking studies were carried out using Molecular Operating Environment (MOE 2014). The crystal structure of aminoglycoside 2-acetyltransferase enzyme (PDB: 1M3I), aminoglycoside 3-phosphotransferase enzyme (PDB ID: 1ND4), and nucleotidyltransferase enzyme (PDB ID: 1KNY) were obtained from protein data bank server (https://www.rcsb.org/). All enzymes and ligands (bis-benzidinedioxime nickel(II) acetate and kanamycin) were minimized and performed with MOE until an rmsd gradient of 0.01 kcal/mol Å with an MMFF94X force field. The optimized poses were ranked using the London DG free-energy estimates.

Antimicrobial activity

The antimicrobial activity of nickel(II) complex and kanamycin was evaluated by the cup plate method according to Seeley *et al* [35] using many standards and isolated microorganisms gram-positive bacteria: *Staphylococcus aureus*, ATCC25923, and *Bacillus subtilis* MCTC8236. Gram-negative bacteria*K. pneumonia*, *Escherichia coli* ATCC25922, and fungi as *candidaalbicanus* ATCC4430373. All strainswere provided by the National Research Centre (NRC); in Khartoum, Sudan.

Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration (MIC) was determined by adding 1 ml of bacterial and fungi culture containing 10^{-8} M McFarland of organisms to serial dilution of nickel(II) complex in Luria broth. The MIC concentration of the nickel(II) complex was measured as the lowest concentration required to inhibit the visible growth of bacteria after overnight incubation of the cultures at 37 °C.

RESULT AND DISCUSSION

Synthesis

The yield of bis-benzidinedioxime nickel(II) acetate is found to be 88.8%.It is not melting until 400℃, and it is soluble in ethanol and DMSO.

Elemental analysis measurement

The CHN elemental analysis result indicates that the investigation complex could have 1:1 metal to ligand stoichiometry. The CHN-elemental analyses data of the complex as reported the chemical structure is $[Ni_2(C_{20}H_{22}N_4O_2)_2](CH_3COO)_4$ and the experimentalpercentage and calculate percentage of CHN are found to be C55.4%(54.65%), H 5.29 (5.31%) and N 10.8% (10.63%).

^{1}H-Nuclear magnetic resonance

The result obtained from ^{1}H-NMR of the complex showed that the complex has different hydrogen environments for biphenyl groups and methyl groups. The proton of the di benzene rings appeared as a quartet signal around (6.52–6.8 ppm) and (7.14–7.8 ppm) due to one phenyl group being found perpendicular to the other [7, 36, 37]. Protons of the oxime group appeared as a doublet signal at 11.82 ppm. The chemical shift range 1.5 to 2.24 ppm is due to the twelve methyl protons in different environments.

The change of chemical shift value and intensity of protons of aromatic rings of complex seem to indicate the formation of coordinate bonds between para imine groups with metals.

Powder X-ray diffraction

The data of powder XRD was analyzed using a direct method within EXPO 2014 software. The result obtained was found to be that the stereochemistry of the central metal of nickel(II) has a highly symmetrical tetrahedron coordination geometry defined by the two chelating benzidinedioxime ligands. The crystal structure of the complex has no symmetry plane. The crystal properties of bis-benzidinedioxime nickel(II) are reported that the molecular formula $[Ni_2(C_{20}H_{22}N_4O_2)_2](CH_3COO)_4]$, molecular weight 1054 Crystal system: triclinic Space group: P1 with a = 9.937 A˚, b = 10.12 A˚, c = 10.075 A˚, and α = 88.065 A˚, β = 91.748 A˚, ɣ = 89.737 A˚. The crystal structure of benzidinedioxime has not plane symmetry. As well as one of the phenyl rings is perpendicular to the other phenyl ring as well as that the two diacetylmonoxime substituting are not in the same plane Fig 1. Both powder XRD and NMR analyses confirm that the nickel(II) complex has two biphenyl rings and dimethyl groups in different environments.

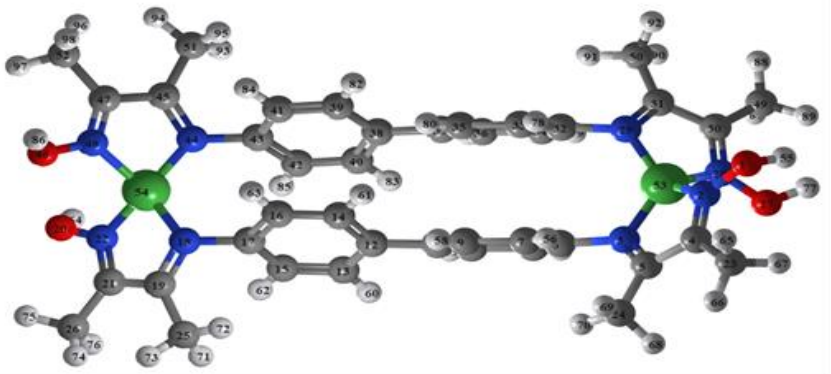


Fig. 1. Chemical structure of bis-(benzidinedioxime) nickel(II) acetate

The atoms central of Nickel(II) have slight distortion tetrahedron coordination geometry result bytetra imine groupshown in Fig 2. The selected metal bond lengths and anngles are shown in table 1 and 2.

Table 1. Selected metal bond lengths

Atoms	Bond length A˚	Atoms	Bond length A˚
N7-Ni1	1.82	N9-Ni2	1.92
N8-Ni1	1.82	N10-Ni2	1.91
N11-Ni1	1.80	N13-Ni2	1.92
N12-Ni1	1.82	N14-Ni2	1.92

Table 2. Selected metal bond angles

Bond	Angles ˚A^3	Bond	Angles ˚A^3
N7-Ni1-O8	91.28	N9-Ni2-N10	90.1
N7-Ni1-N11	102.69	N9-Ni2-N13	117.04
N7-Ni1-N12	126.69	N9-Ni2-N14	130.08

N8-Ni1-N11	127.15	N10-Ni2-N13	128.62
N8-Ni1-N12	117.98	N10-Ni2-N14	128.62
N11-Ni1-N12	93.25	N13-Ni2-N14	89.17

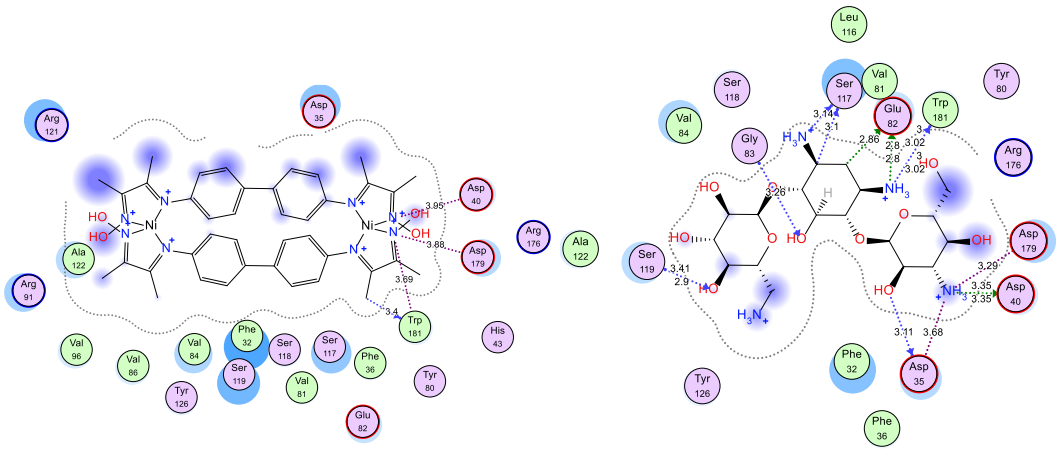
Molecular Docking

Molecular docking studies were examined using aminoglycoside enzymes families (PDB ID: 1M3I), (PDB ID: IND4), and (PDB ID: 1KNY), obtained from the Protein Data Bank server. Molecular docking results revealed that the complex of bis-benzidinedioxime nickel(II) acetate and kanamycin showed the best potent inhibitor against Aminoglycoside-3-Phospho-transferase, shown in table 3. The similarity value of binding energy of the nickel(II) complex and kanamycin with aminoglycoside enzymes families suggests that the nickel(II) complex inhibited aminoglycoside enzymes by the same mechanism as kanamycin.

Table 3. Binding energy and RMSD-refine of dock dioxime benzidine and complexes with 3frb (DHFR enzyme) and (DHBS enzyme)

Compounds	Bis-benzidinedioxime nickel(II) acetate		Kanamycin	
	S	RMSD-refine	S	RMSD-refine
Aminoglycoside 2-acetyltransferase (PDB ID: 1M3I)	-23.03	2.9	-24.75	1.2
Aminoglycoside 3-Phosphotransferase (PDB ID: 1ND4)	-32.89	2.54	-33.8	2.38
Nucleotidyltransferase enzyme (PDB ID: 1KNY)	-20.49	3.33	-19.11	2.45

The aminoglycoside binding site is formed from five acidic amino acid side chains (Asp35, Asp40, Glu82, Asp152, and Asp179) as well as the C-terminal carboxyl group of Trp181. Sequence analysis suggests that the β barrel and C-terminal Try residues are conserved elements of aminoglycoside 2-acetyltransferase. 2D ligand interaction of bis-benzidinedioxime nickel(II) acetate represented that complex interaction with the binding pocket of aminoglycoside 2-acetyltransferase with two acidic side chains (Asp40 and Asp179) in addition to the C-terminal carboxyl group of Trp181 shown in Fig 2.

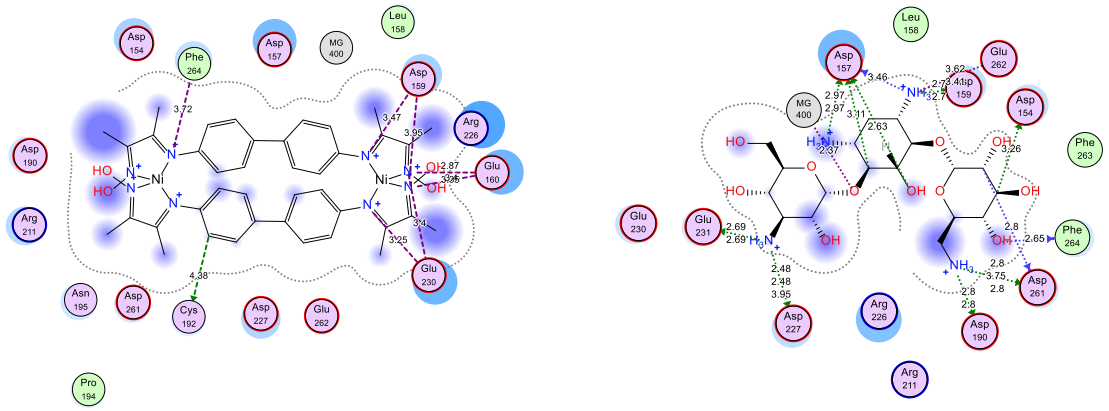


(A) (B)

Fig. 2. 2D interaction of bis-benzidinedioxime nickel(II) acetate and kanamycine with aminoglycoside 2-acetyltransferase (PDB ID: 1M3I), (A) and (B) are bis-benzidinedioxime nickel(II) acetate and kanamycine respectively

The 2D ligand interaction of nickel(II) complex and kanamycin with the Aminoglycoside-3-Phospho-transferase (PDB ID: 1ND4) is shown in Fig 3. The 2D interaction diagram explained that nickel(II) complex and kanamycin interacted with polar amino acid residue in the active site. The bis-benzidinedioxime nickel(II) acetate has a strong ligand interaction with enzymes by forming hydrogen bonds with the sidechain and the backbone residues. The donor hydrogen bonds were created between the methyl group and Cys192, whereas eight ionic bonds formed between Glu160, Glu230,

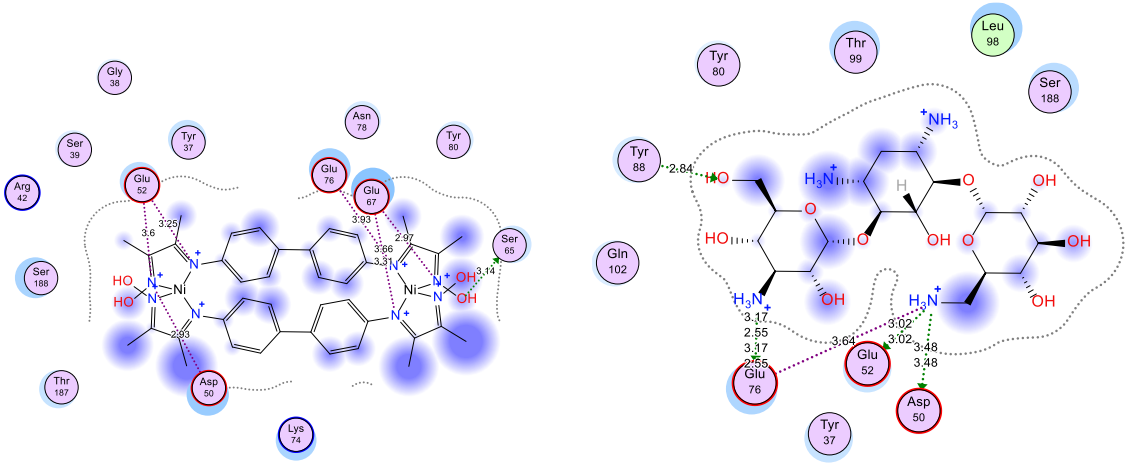
Asp159, and Phe264 with the imine groups and nitrogen atoms at oxime groups.



(C) (D)

Fig. 3. 2D interactionbis-benzidinedioxime nickel(II) acetate and kanamycine with Aminoglycoside-3-Phospho-transferase (PDB ID: 1ND4).(C) and (D) are bis-benzidinedioxime nickel(II) acetate and kanamycine respectively.

The 2D interactions of the co-crystallized bis-benzidinedioxime nickel(II) acetate complex and kanamycin within the active site of nucleotidyltransferase enzyme (PDB ID: 1KNY) are reported in Fig 4. The 2D interaction diagram displays that the positive charge of nitrogen atom on both complexes of nickel and kanamycin played important role in a fit of ligand into an active site of the enzyme, as well as led to created strong ionic bond and hydrogen bond with the main amino acid residue on active site.



(E) (F)

Fig. 4. 2D interaction bis-benzidinedioxime nickel(II) acetatewith nucleotidyltransferase enzyme (PDB ID: 1KNY). (E) and (F) are bis-benzidinedioxime nickel(II) acetate and kanamycine respectively

Biological activity

In addition, the *B. subtilis* shows resistance against kanamycin (inhibition zone 0), while it shows high sensitivity against bis-benzidinedioxime nickel(II) acetate complex (inhibition zone 33.3 ± 0.82 mm, MIC 18.5 µg/mL). High antimicrobial activity of the complexes as compared to the standard drugs might be due to their highest lipophilicity, this causes an increase in their penetration ability through the lipid membrane and which could block inhibit the growth of the microorganism [38, 39]. In addition, the *B. subtilis* shows resistance against kanamycin (inhibition zone 0), while it shows high sensitivity against bis-benzidinedioxime nickel(II) acetate complex (inhibition zone 33.3 ± 0.82 mm, MIC 18.5 µg/mL). High antimicrobial activity of the complexes as compared to the standard drugs might be due to their highest lipophilicity, this causes an increase in their penetration ability through the lipid membrane and which could block inhibit the growth of the microorganism[40, 41].Similar observations were reported by the research [4, 41].The data are summarized in table 4.

Table 4. Antibacterial Inhibition Zone in mm ± Standard Deviation of bis-benzidinedioxime nickel(II) acetate

Bacterial and fungi	Diameter of the inhibition zone (mm)	
	Bis-benzidinedioxime nickel(II) acetate	Kanamycin
E. coli	15.0 ± .82	19
K. pneumonia	29.3 ± 1.63	20
S. aruse	21.3 ± 1.08	21
B. subtilis	33.3 ± 0.82	0
Candida	26.0± 1.41	20

Determination Minimum inhibitory concentration (MIC) of bis-benzidinedioxime nickel(II) acetate

Minimum inhibitory concentration (MIC) represents the lowest concentration of an antimicrobialthat inhibits the visible growth of a microorganism after an appropriate incubation time. The results obtained from MIC as shown in table 5. The data obtained shows that the complex apparent higher sensitivity against particular *K. pneumonia*(inhibition zone 29.3 ± 1.63mm, MIC 6.2 µg/mL),*candida* (inhibition zone 26.0± 1.41 mm, MIC 6.2 µg/mL), and*B. subtilis* (inhibition zone 33.3 ± 0.82 mm, MIC 18.5 µg/mL).While *E. coli* (inhibition zone 15.0 ± .82 mm, MIC 55.6 µg/mL) and *S. aruse*(inhibition zone 21.3 ± 1.08 mm, MIC 55.6 µg/mL) exhibited slight higher sensitivity against bis-benzidine dioxime nickel(II) acetate (inhibition zone 26.0± 1.41 mm, MIC 6.2 µg/mL).

Table 5. Minimum inhibitory concentrationMIC (µg/mL) of bis-benzidinedioxime nickel(II) acetate

Bacterial and fungi	MIC (µg/mL) of bis-benzidinedioxime nickel(II) acetate
E. coli	55.6
K. pneumonia	6.2
S. aruse	55.6
B. subtilis	18.5
Candida	6.2

CONCLUSION

The complex nickel(II) was synthesized from benzidinedioxime and nickel(II) acetate by a molar ratio of 1:1. The elemental analysis and ^{1}HNMR conducted on the complexes provide data that are in agreement with the empirical structures of the complex. The results of powder XRD analyses deduced that the complex of bis-benzidinedioxime nickel(II) acetate highly symmetrical tetrahedron coordination geometry. Molecular docking studies revealed that the bis-benzidinedioxime nickel(II) acetate and kanamycin have higher activity against Aminoglycoside-3-Phosphotransferase than aminoglycoside-2 N-acetyltransferase and aminoglycoside nucleotidyltransferase. In vitro antibacterial and anti-fungal study shows that the bis-benzidinedioxime nickel(II) acetate is biologically high active against the tested organism. The complex of nickel(II) appearances highest activity against*B. subtilis* (inhibition zone 33.3 ± 0.82 mm, MIC 18.5 µg/mL) while it appears higher sensitivity against particular *K. pneumonia* (inhibition zone 29.3 ± 1.63 mm, MIC 6.2 µg/mL), and*candida* (inhibition zone 26.0± 1.41 mm, MIC 6.2 µg/mL).

CONFLICTS OF INTEREST

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