IHJPAS. 37 (1) 2024
Ibn Al-Haitham Journal for Pure and Applied Sciences
Journal homepage: jih.uobaghdad.edu.iq
PISSN: 1609-4042, EISSN: 2521-3407

Synthesis, Biological and Medicinal Evaluation of New Boric Acid Ester Derived from Antibiotic Drug with Some of its Metal Complexes

[1]Simaa Safaa Mahmoud* [2]Asmaa Mohammed Noori
[1,2] Department of Chemistry, College of Sciences, University of Baghdad, Baghdad, Iraq.

*Corresponding Author: saimaa.safaa1205m@sc.uobaghdad.edu.iq

Received 2 February 2023, Received 18 February 2023, Accepted 22 February 2023, Published 20 January 2024

doi.org/10.30526/37.1.3261

Abstract

Synthesis of new ligand, namely [bis(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl) hydrogen borate] (BIB), utilizing the reaction of metronidazole with boric acid in mole ratio (2:1), as well as the metal complexes with [Ni(II) and Cu(II)], were synthesized. All synthesized compounds were characterized by utilizing spectroscopic techniques such as FTIR, 1H-NMR, thermal analysis (T.G., UV-Vis), and atomic absorption (A.A.S.), as well as micro elemental analysis (C.H.N.), melting point (m.p), magnetic susceptibility, molar conductivity, and chloride content measurements. All complexes were paramagnetic, and the electrolyte and the suggested geometries were tetrahedral for nickel and octahedral for copper. In addition, all the transition metal complexes produced were shown to be antibacterial and antifungal against the bacteria *Staphylococcus aureus*, *Escherichia coli*, and the *fungus Candida*. Also, metronidazole and the ligand were evaluated as anticancer agents against human breast cancer (MCF-7). The results showed that ligand was more active as an anticancer than metronidazole.

Keywords: Metronidazole, Boric acid, Spectroscopic techniques, Antibiotic, Anticancer.

1. Introduction

Nitroimidazole compounds have an imidazole ring with two or five active nitro groups. The pharmacokinetic properties of 5-nitroimidazoles are anti-parasitic, while the effects of 2-nitroimidazoles are anti-ischemic and anti-inflammatory [1]. The 5-nitroimidazole compound, namely [metronidazole (MTN)], is the prototype and most commonly utilized drug in this class. It's one of the most versatile antibiotics in clinical use, effective against a wide range of anaerobic microorganisms ranging from protozoa to bacteria. The World Health Organization has classified it as an essential medication [2]. Metronidazole (MTN) is a crystalline powder and is slightly soluble in water [3]; it exhibits a wide range of pharmacological actions, with a particular emphasis on its antiviral, antibacterial, anti-proliferative, and antifungal activities [4]. Metronidazole's initial clinical trials revealed that it could treat amoebic liver abscesses and invasive amoebic dysentery [5].

Boric acid B(OH)3 is a weak inorganic acid that is odorless and soluble in water. It is an efficient acid catalyst in organic synthesis for various selective transformations of simple and complex molecules [6]. It's an antiseptic in mouthwashes, talcum powder, protective ointments, and eye-washes. Also, boric acid is used in industrial applications such as optical and sealing glasses, textile fiberglass, heat-resistant borosilicate glass, porcelain enamels, and ceramic glazes [7].
This study has synthesized a new metronidazole derivative using boric acid as a BIB ligand **Figure 1**. Additionally, we are synthesizing metal complexes of this (BIB) ligand with [Ni (II) and Cu (II)] metal ions. **Figure 2**. All synthesized compounds are characterized using physicochemical and spectral studies to prove the proposed structure. The medicinal uses and biological activities of the synthesized compounds were evaluated.

2. Materials and Methods

The elemental analyzer EuroEA 3000/Italy recorded elemental microanalyses (CHN) for carbon, hydrogen, and nitrogen. The melting points were determined using the Gallen Kamp melting point apparatus. The FT-IR (Fourier transform infrared) spectrophotometry for ligands in the 400–4000 cm^{-1} (KBr) range and complexes in the(200 - 4000 cm^{-1}) range UV-Vis spectrum was measured using a Shimadzu 1800-UV spectrophotometer and distilled water as a solvent. The 1H -NMR spectra in DMSO-d6 were measured using an NMR Bruker 500MHz in Germany. Thermal analyses (TG) were recorded (TG sta. 300, Germany). The Auto Magnetic Susceptibility Balance Model by Sherwood Scientific was utilized to record magnetic susceptibility data at room temperature. Metal content was evaluated using atomic absorption spectroscopy on a Nova 350 spectrophotometer. The Mohr technique was utilized to determine the chloride content of complexes.

2.1 Synthesis of bis(2-(2-methyl-5-nitro-*1H-imidazol*-1-yl)ethyl) hydrogen borate (BIB)

The mixture of metronidazole (0.1 g, 0.5842 mmol) in 8 mL of distilled water and boric acid (0.0180 g, 0.2921 mmol) was heated under reflux for 8 hours with stirring. The TLC technique tested the solution, and the eluent was Toluene, chloroform, and methanol (3:2:0.6, v/v/v). A part of the solution was evaporated, and the white product was obtained by cooling in an ice bath, scratching, washing with cold distilled water, and drying in an oven at 80 0C.

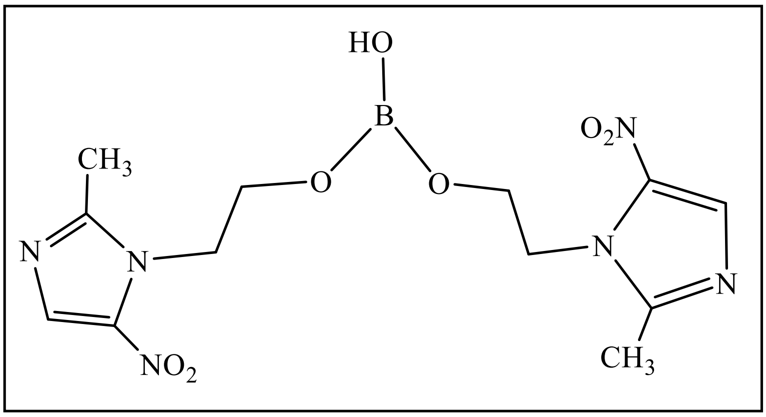

Figure 1. Structure of the ligand (BIB)

2.2 Synthesis of BIB complexes with (Ni (II) and Cu(II)) metal ions (C_1 and C_2)

The warm solution of the BIB (0.1 gm, 0.2718 mmol) in 5 mL distilled water was added to a solution of metal salt (0.0323 gm, 0.0231 gm (0.1355 mmol)) of $NiCl_2.6H_2O$ and $CuCl_2.2H_2O$, respectively, in 2 mL distilled water. The mixtures were heated under reflux for 5 hours with stirring. The solvent was evaporated, and the products were collected in an ice bath and crashing, washed with cold distilled water, and dried in an oven at 80^0C.

2.3 Anti-microbial activity

Using the diffusion technique with 2×10^{-2} M in H_2O solutions, all synthesized compounds were tested for anti-bacterial and anti-fungal activity against (gram-positive Staphylococcus aurous, gram-negative *Escherichia coli* and *Candida*). The diameters of inhibition were examined to assess the anti-bacterial activity [8].

2.4 Anticancer activity

A 96-well plate was used for the MTT cell viability assay to evaluate the cytotoxic effect. The cell lines were seeded at (1×10^4 cells/ well). Cells were treated with the studied compounds after 24 hours. The effectiveness of the anticancer treatment was studied utilizing literature [9], and absorbance at 575 nm was evaluated.

3. Results and Discussion

The physical and analytical data are consistent with the proposed structures of the compounds in the study (**Table 1**).

Table 1. Data from the analysis as well as the physical properties of the (BIB) ligand and its metal complexes

Comp	The molecular formula	Color	Yield %	m.p (°C)	M.wt (g/mol)	(Found) Calc. C%	H%	N%	Metal content %	Chloride content %
BIB	$C_{12}H_{17}BN_6O_7$	White	97%	(148-150)	367.8	39.15 (39.41)	4.65 (5.37)	22.83 (23.22)	___	_____
C_1 Ni(II)	$[C_{24}H_{36}B_2N_{12}O_{15}NiCl]Cl.H_2O$	light green	76%	(158-160)	901.29	31.95 (32.71)	4.21 (4.74)	18.63 (19.39)	6.51 (7.33)	7.87 (8.76)
C_2 Cu(II)	$[C_{24}H_{40}B_2N_{12}O_{17}CuCl].Cl$	green	82%	(156-158)	924.14	31.16 (32.08)	4.32 (5.18)	18.17 (17.21)	6.87 (7.41)	7.68 (6.75)

Table 2. The name of BIB and proposed formula for its metal ion complexes

Comp	Formal	Name
BIB	$C_{12}H_{17}BN_6O_7$	bis(2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl) hydrogen borate.
C_1 Ni(II)	$[(L_1)_2Ni(H_2O)Cl].Cl.H_2O$	[aqua chloro bis{bis(2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl) hydrogen borate} Nickel (II)] hydrate. Chloride.
C_2 Cu(II)	$[(L_1)_2Cu(H_2O)_3Cl].Cl$	[Tri aqua chloro bis{ bis(2-(2-methyl-5-nitro-1*H*- 344midazole-1-yl)ethyl) hydrogen borate} Copper(II)] Chloride.

3.1 The FT-IR spectra

The infrared spectra of (Ni and Cu) complexes showed a shifting in the frequency and a change in the profile of (υ OH) **Table 3** as a result of coordination with metal ions[10].

At (1483–1487)cm^{-1}, a new band appears in the spectra of the ligand and its complexes; this band is attributed to the (υ B-O) group [11]. The stretching of (C=N) the imidazole ring did not show any change in frequency or profile, and this was because of no coordination with metal ions through (C=N) [12]. The spectrum of the Ni (II) complex showed the lattice water at (3437) cm^{-1} and coordinated water at (3365) cm^{-1}, as well as the lower frequency bands [(991) and (678)] cm^{-1}. The coordinate H_2O of Cu (II) complex appeared at (3388) cm^{-1}, and in the lower frequency band [(767) and (680)] cm^{-1}, low-frequency bands appeared in complex spectra due to υ M-O, υ M-Cl [13, 14] as shown in **Figure 3** and **4.**

Table 3. Infrared absorption bands that are specific to the (BIB) ligand and its metal ion complexes

Compound	υ OH	H_2O lattice (coordinate)	υ C=N	υ B-O	υ M-O	υ M-Cl
MTZ	3222	_____	1535	_____	_____	_____
BIB	3415	_____	1535	1487	_____	____
BIB (Ni) C_1	3384	3437 (3365) (991) (678)	1535	1487	457	347
BIB (Cu) C_2	3406	(3388) (767) (680)	1535	1483	424	333

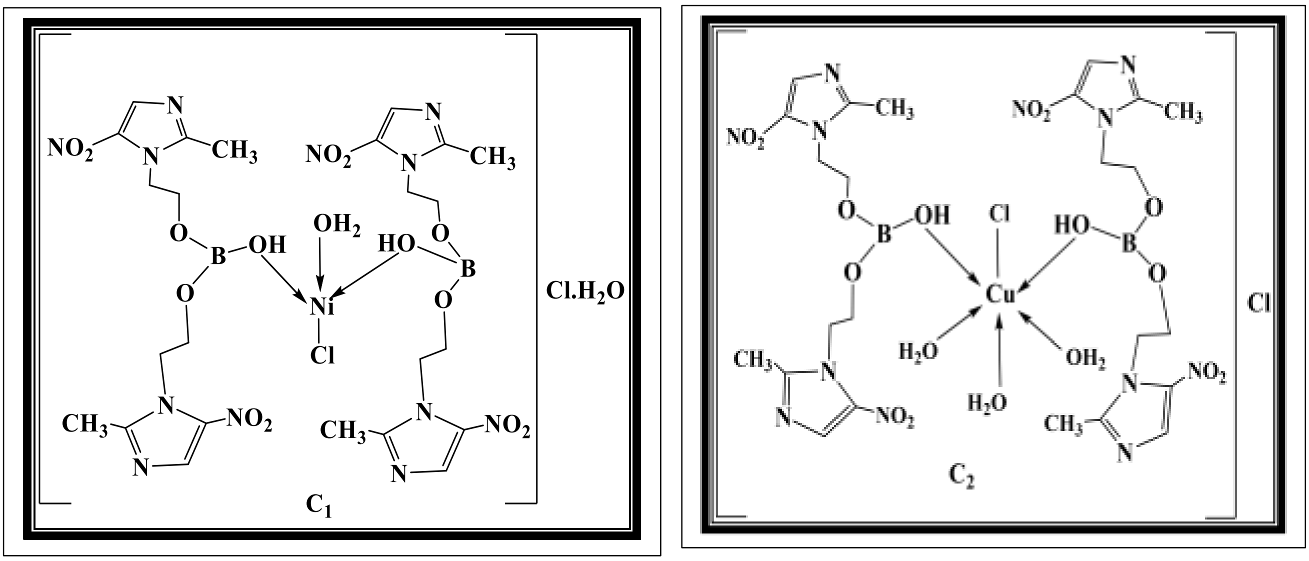

Figure 2. The suggested structures of synthesized complexes

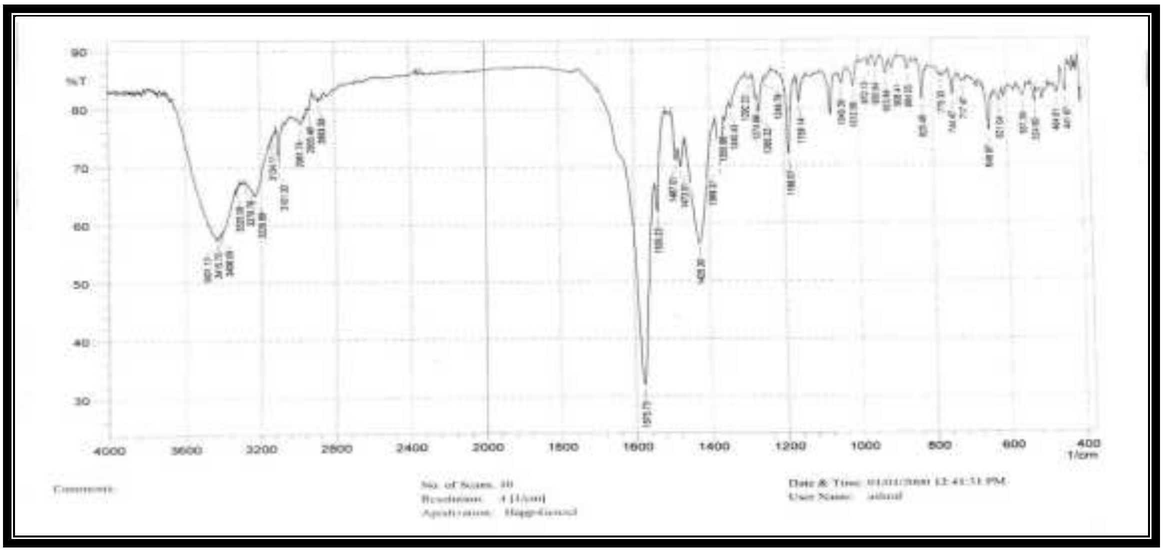

Figure 3. The FT-IR spectrum of the (BIB) ligand

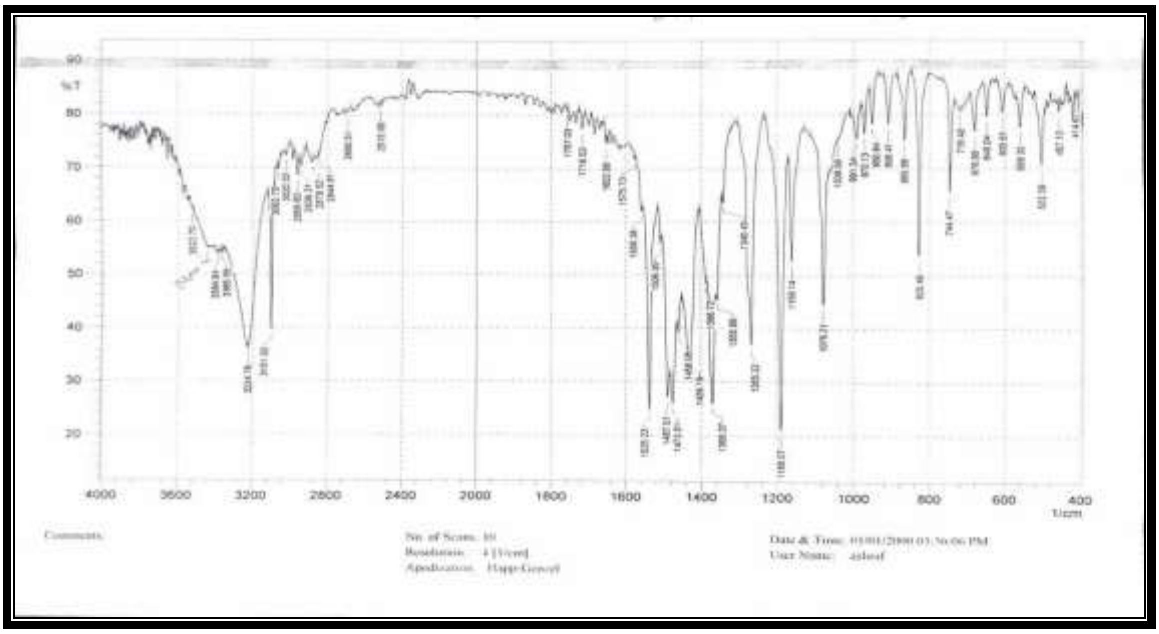

Figure 4. The FT-IR spectrum of the Ni(II) complex C_1

3.2 The ^{1}H-NMR spectroscopy

Table 4 shows the 1HNMR data for the BIB ligand, which is backed up by **Figure 5**, **Figure 6** shows the NMR spectrum in DMSO-d6. The spectrum of the ligand observed a chemical shift at δ(3.99), which is due to the B-OH proton [15, 16]. The multiple peaks observed in the ranges δ (4.35–4.40) and δ (3.66) referred to NCH_2 and $O\text{-}CH_2$, respectively [17, 18]. Chemical shifts of the methyl group CH_3 and residual DMSO-d^6 at δ(2.44) [17] The peak observed at δ(8.04) is attributed to imidazole protons [19].

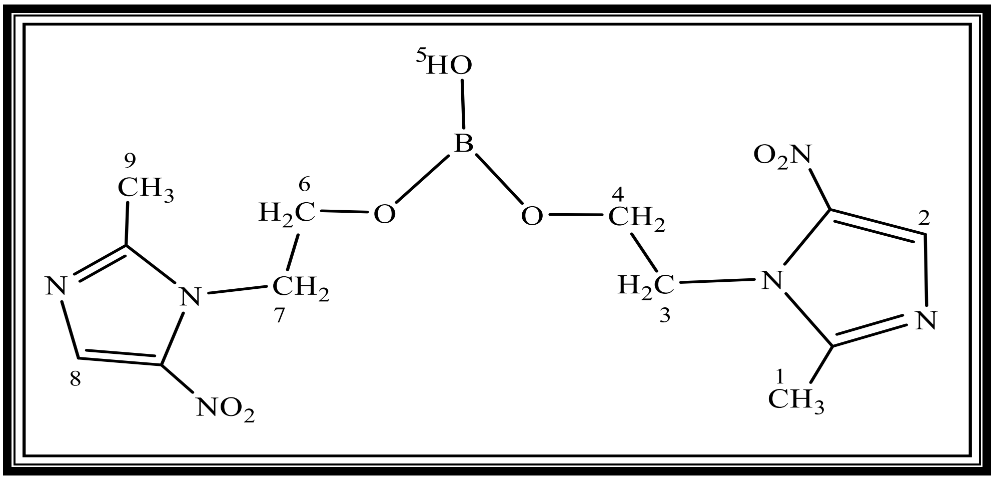

Figure 5. Proton positions in structure of the ligand BIB

Table 4. Chemical shifts for ^{1}HNMR of BIB

Assignments in DMSO-d^6	Mark	Chemical shifts δ (ppm)
CH_3	1, 9	(2.44),6H, s
CH(imidazole)	2, 8	(8.04),2H, s
N-CH_2	3, 7	(4.35-4.40),4H, m
O-CH_2	4, 6	(3.66),4H, m
B-OH proton	5	(3.99)1H, m

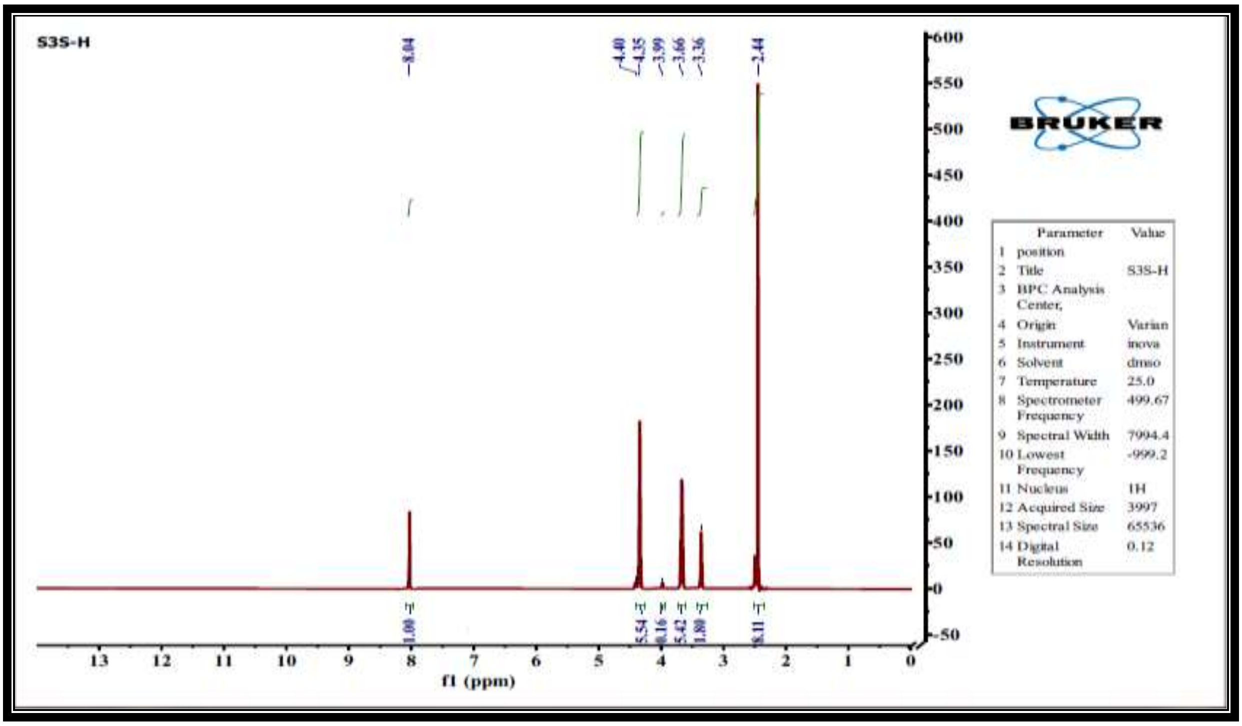

Figure 6. The ^{1}H-NMR Spectrum of BIB

3.3 Thermogravimetric analysis (TGA)

The thermogravimetric analysis was conducted under argon gas at a heating rate of (10 ºC/min) and a temperature range of (25 – 800) ºC. This technique characterized the suggested structures and the studied thermal st and synthesized compounds. In the following order, the BIB ligand and its complex's thermal stability were increased: (C1 > BIB > C2) **Table 5** [3]. The thermal decomposition was utilized to confirm the structures where the degradation results exhibit high agreement of found mass loss and calculation, confirming the proposed construction of the synthesized compounds. The ligand (BIB) and nickel complex C1 thermogram are shown in **Figures 7** and **8**.

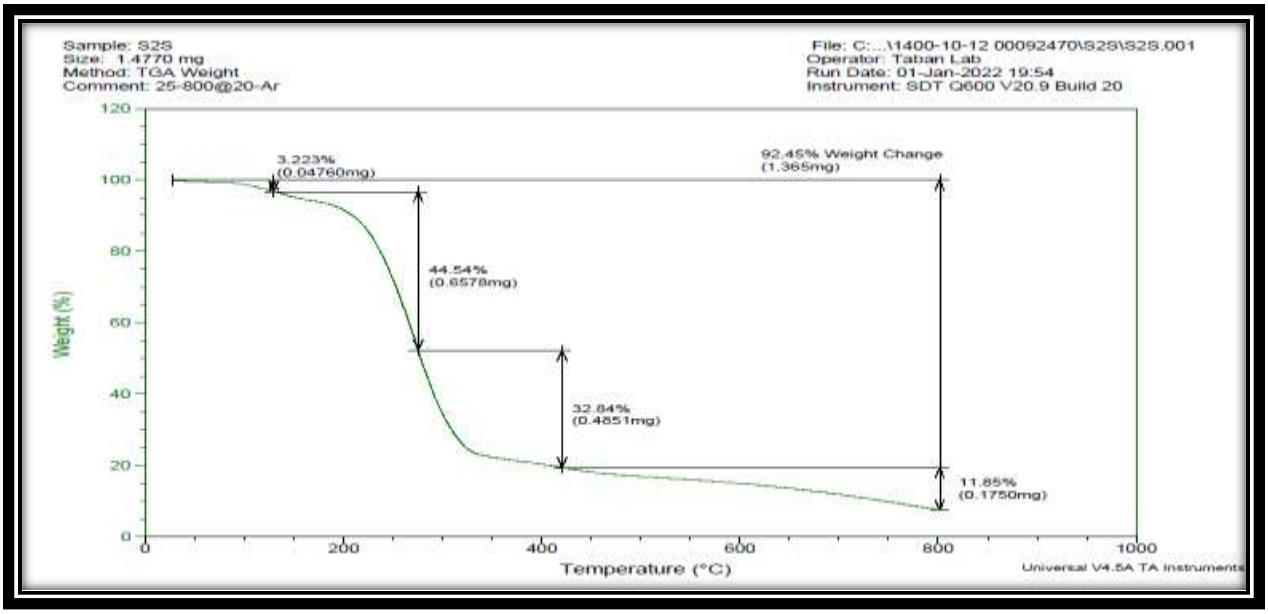

Figure 7. The thermogram of the (BIB) ligand

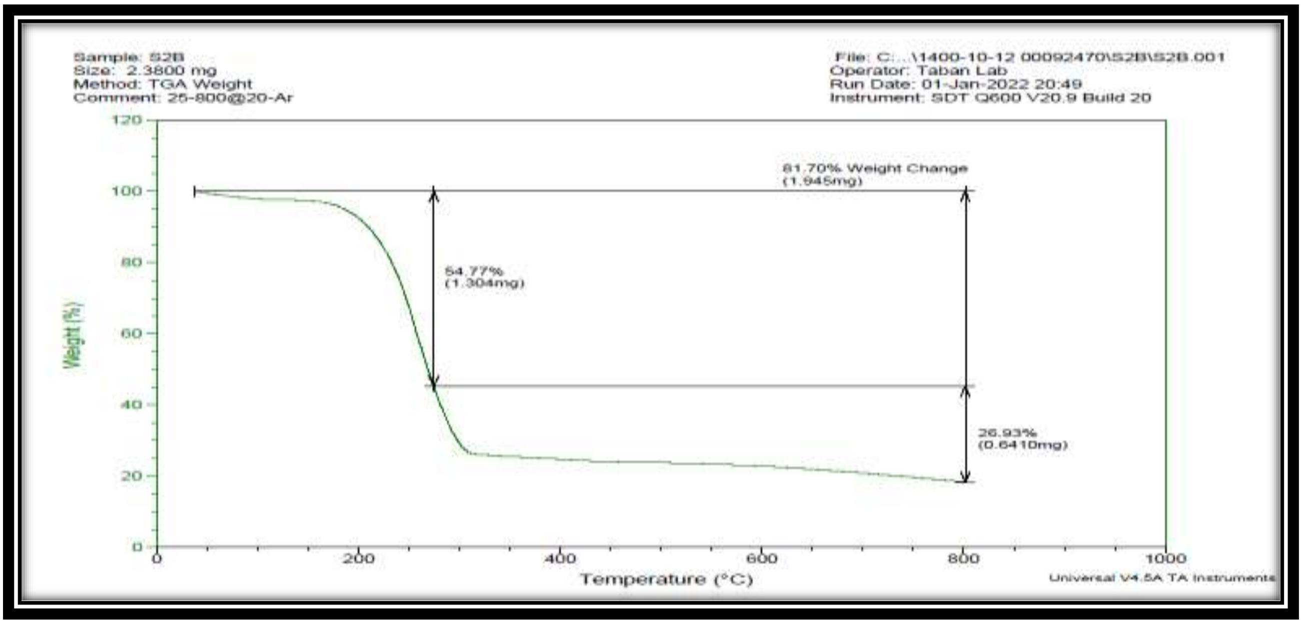

Figure 8. The thermogram of nickel complex C_1

Table 5. The TGA of ligand (MBIB) and their complexes

Comp	Compounds (M.wt) (gm/mol)	Step	Temp. rang of the Decomposition ºC	Suggested Assignment	Mass loss% Cal.	Mass loss% Found
BIB	$C_{12}H_{17}BN_6O_7$ 367.8	1	25-135	CH_3	4.078	3.223
		2	135-275	$N_3C_7O_2H_9$	45.40	44.54
		3	275-420	$N_3C_2O_3H_5$	32.35	32.84
		4	420-800	2C+O	10.87	11.85
		Residue	>800	B+O	7.28	7.55
C_1	$[C_{24}H_{36}B_2N_{12}O_{15}NiCl]Cl.H_2O$ 901.29	1	25-278	$2H_2O+2Cl+N_6O_7C_{13}H_{20}+B$	54.34	54.77
		2	278-800	$N_6O_4C_8H_7$	27.84	26.93
		Residue	> 800	$O_3H_7C_3B$ Ni	17.80	18.30
C_2	$[C_{24}H_{40}B_2N_{12}O_{17}CuCl].Cl$ 924.14	1	25-262	$3H_2O+2Cl+2(N_3O_2C_6H_8)+O$	48.58	48.94
		2	262-800	$N_6O_9C_{12}H_{18}B+Cu$	50.24	50.26
		Residue	>800	B	1.16	0.81

3.4 The UV-Vis spectral studies:

The UV-Vis spectra of (BIB) and its metal complexes in distilled water are listed in **Table 6**. The spectrum of the ligand **Figure 9** showed an intense band at [313 nm (31948 cm^{-1})] due to the ($\pi \rightarrow \pi^*$) transition [20]. The Ni(II) complex **Figure 10** exhibited a shift of the ligand band ($\pi \rightarrow \pi^*$). Two bands showed at [962 nm (10395 cm^{-1}) and 785 nm (12738 cm^{-1})] which were assigned to [$^3T_1(F) \rightarrow ^3A_2$ and $^3T_1(F) \rightarrow ^3T_1(P)$] transitions of Tetrahedral Ni(II) complexes [21].The M_{eff} of Ni(II) was 2.78 B.M. This value is in agreement with Tetrahedral geometry [20, 21]. **Table 6** shows a list of the data. Two absorption bands were observed in the spectrum of copper complex (C_2) **Figure 11** at [960 nm (10416 cm^{-1}) and 739 nm (13531 cm^{-1})] which were attributed to[$^2B_1g \rightarrow ^2A_1g$ and $^2B_1g \rightarrow ^2B_2g$] transitions, respectively [20]. The magnetic moment of the copper complex was 2.23 B.M, and these values of M_{eff} agree with Octahedral geometry [22–24]. In distilled water, the molar conductance for each synthesized complex was measured using (10^{-3} M). The complexes (C1 and C_2) have electrolyte behavior [25–27].

Table 6. Electronic transitions of the BIB and its complexes, proposed geometry, molar conductivity, and magnetic susceptibility

Comp	ƛ nm (cm^{-1})	Assignment	Molar conductivity ($S.cm^2.mol^{-1}$) in H_2O	M_{eff} (B.M)	Geometry
BIB	313(31948)	(π -π^*)	———	———	———
C_1(Ni)	315(31746) 785(12738) 962(10395)	(π -π^*) $^3T_1(F) \rightarrow ^3T_1(P)$ (υ_2) $^3T_1(F) \rightarrow ^3A_2(F)$ (υ_1)	131	2.78	Tetrahedral
C_2(Cu)	357(28011) 739(13531) 960(10416)	(π -π^*) $^2B_1g \rightarrow ^2B_2g$ (υ_2) $^2B_1g \rightarrow ^2A_1g$ (υ_1)	139	2.23	Distorted octahedral

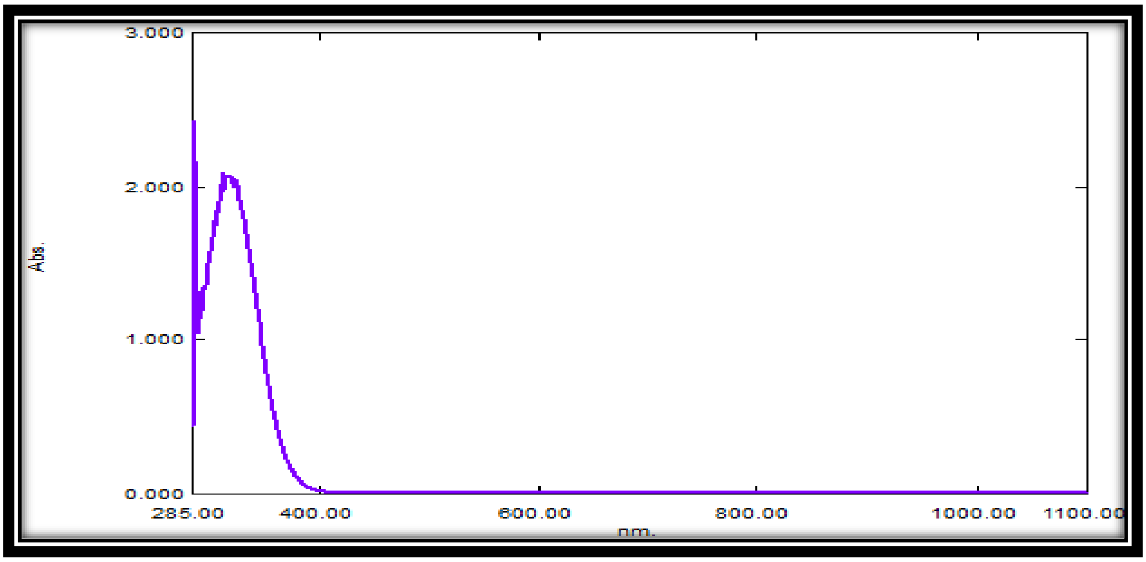

Figure 9. The UV-Vis spectrum of BIB

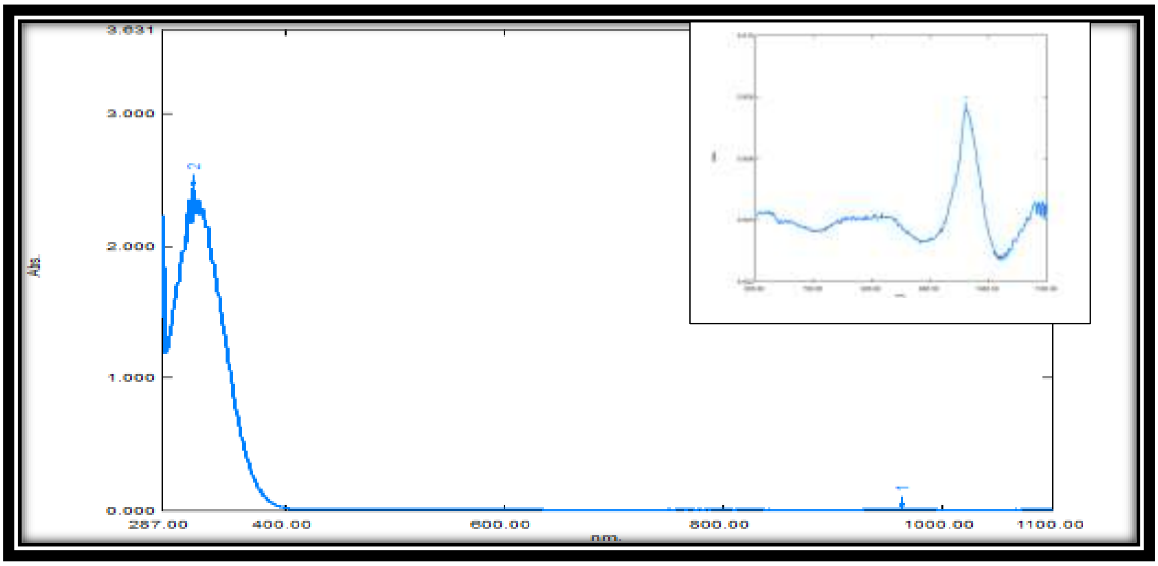

Figure 10. The UV-Vis spectrum of C_1 complex

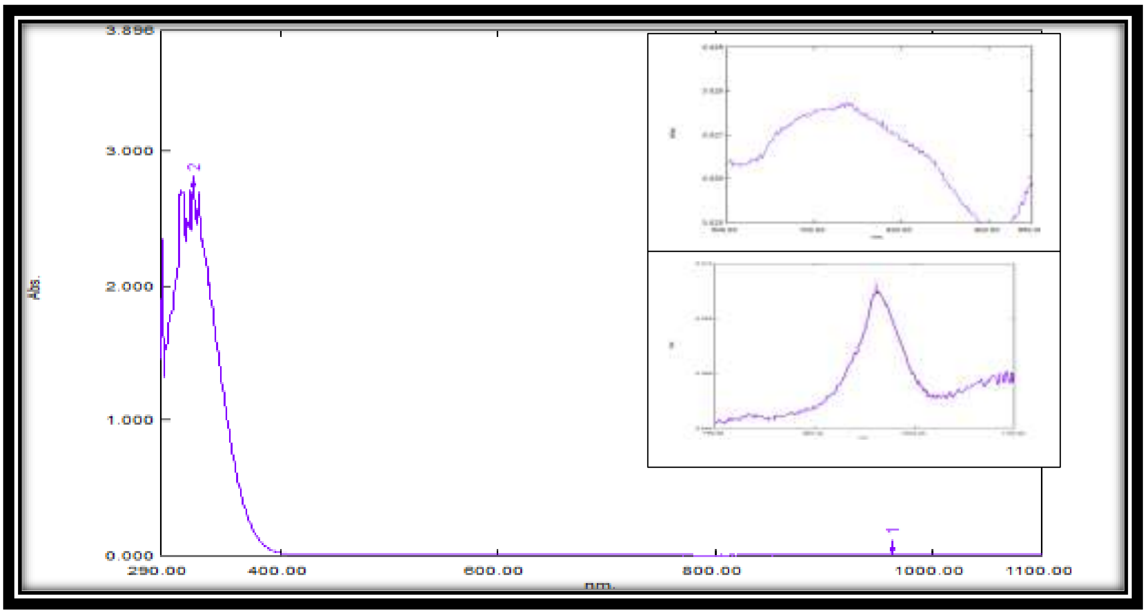

Figure 11: The UV-Vis spectrum of C_2 complex

3.5 Anti-cancer Activity

Metronidazole and (BIB) ligands were evaluated for their ability to inhibit human breast cancer (MCF-7) cells by the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) assay technique **Figures 12** and **13**. The results showed that (BIB) ligand was more active as an anticancer than the original material (metronidazole), and the killing capability of cancer cells for the BIB ligand was higher than that of metronidazole [28]. This is due to the presence of a boron atom in the ligand.

Table 7. Cytotoxicity effects of metronidazole on (MCF-7) and WRI-68 cells after 24 hours incubation at 37 °C

Cell line	Conc. µg/mL						IC_{50} µg/mL	P-value
	200.00	**100.00**	**50.00**	**25.00**	**12.50**	**6.25**		
MCF-7	55.67± 3.64	61.00±1.48	76.08± 1.77	89.82±2.34	92.86±4.65	95.02±1.45	53.29	<0.0001
WRL	77.28±1.62	87.96±1.51	92.13± 1.56	95.41±0.37	95.79±0.71	94.91±2.20	297.4	

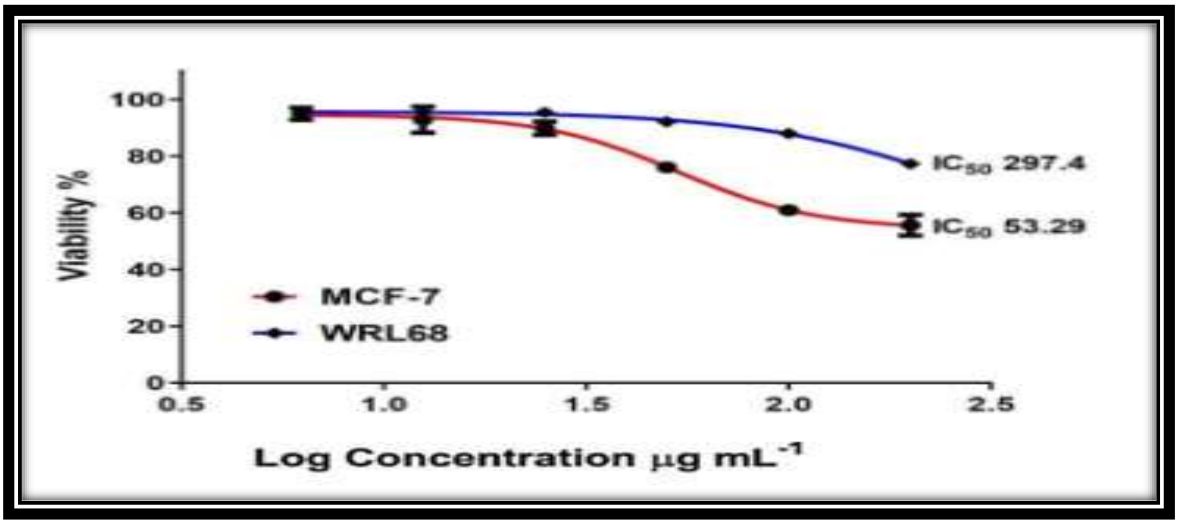

Figure 12: Cytotoxicity effect of Metronidazole on MCF-7 cells after 24 hours incubation period at 37 ºC

Table 8. Cytotoxicity effects of (BIB) ligand on (MCF-7) and WRI-68 cells after 24 hours incubation at 37 °C

Cell line	Conc. µg/mL						IC_{50} µg/mL	P-value
	200.00	**100.00**	**50.00**	**25.00**	**12.50**	**6.25**		
MCF-7	43.21±2.20	49.19±4.36	66.09±2.71	72.57± 2.91	86.19±3.92	94.41±0.55	37.42	<0.0001
WRL	74.38±4.21	85.57±2.34	92.94±0.81	95.72± 0.53	94.91±1.51	95.18±0.41	120.7	

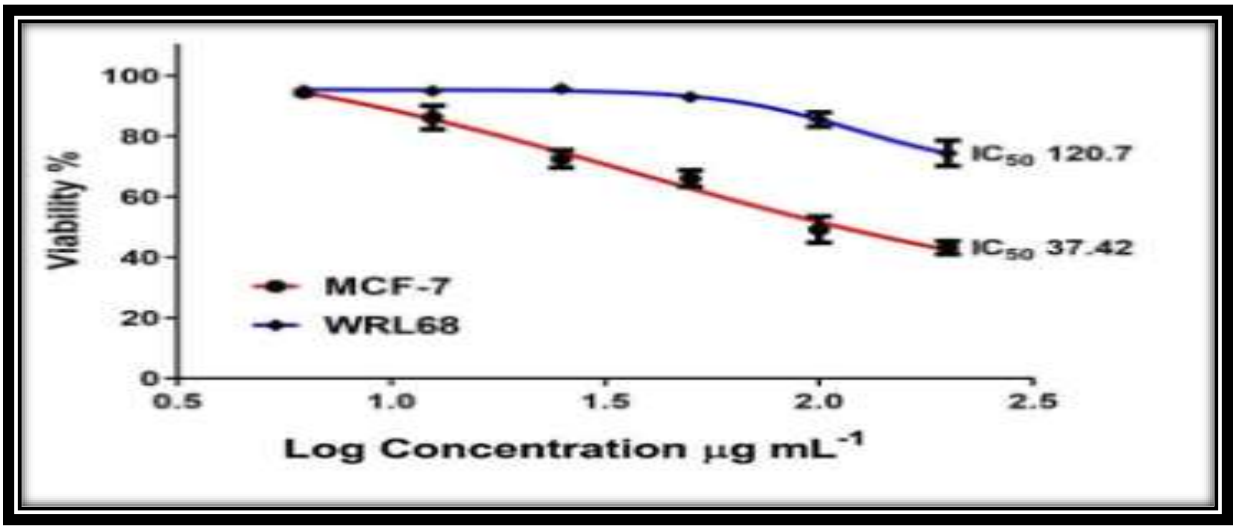

Figure 13. Cytotoxicity effect of (BIB) Ligand on MCF-7 cells after 24 hours incubation period at 37 ºC

3.6 Antimicrobial activity:

The synthesized compounds' antibacterial and antifungal behavior was evaluated against gram-positive bacteria *Staphylococcus aureus*, gram-negative bacteria *Escherichia coli*, and *Candida* [29-31]. The results indicated that ligand (BIB) has more activity than metronidazole(MTZ) in *Staphylococcus aureus*, according to the following activity order (BIB > Boric acid > MTZ) depending on inhibition zone (23 > 22 > 20) mm. respectively. In *Escherichia coli*, according to the following order, boric acid has higher activity (boric acid > BIB > MTZ) depending on the inhibition zone (12 > 11 > 9) mm, respectively.

Comparison of the biological activities in *Staphylococcuss aureus* of BIB and its metal complexes was in the following order (C1 > BIB > C2 = boric acid > MTZ) at the inhibition zone (24 > 23 > 22 > 20) mm. In *Escherichia coli*, the complexes were more energetic than BIB, and the order was as follows (Cu (C2) > Ni (C1) = boric acid > BIB > MTZ) depending on the inhibition zone (13 > 12 > 11 > 9) mm, respectively [32-34]. **Table 9** shows the antibacterial and antifungal date results, while **Figures 14, 15**, and **16** show the inhibition zones.

Table 9. The biological activity of the substances under tudy in (2×10^{-2} M)

Compound	*Staphylococcus aureus*(G+) inhibition zone diameter (mm)	*Escherichia coli*(G-) Inhibition zone diameter (mm)	*Candida* (nm)
H_2O	--	--	--
MTZ	20	9	10
Boric acid	22	12	16
BIB	23	11	15
Ni(C_1)	24	12	14
Cu(C_2)	22	13	12

Figure 14. The zone of inhibition towards *Staphylococcus aureus* (G+) in the case of the ligand (BIB) and its metal complexes, boric acid, and metronidazole

Figure 15. The zone of inhibition towards *Escherichia coli* (G-) in the case of the ligand (BIB) and its metal complexes, boric acid, and metronidazole

Figure 16. The zone of inhibition towards Candida in the case of the ligand (BIB) and its metal complexes, boric acid, and metronidazole

4. Conclusion

A new ligand (BIB) was synthesized from the reaction of metronidazole with boric acid, and its metal complexes with Ni(II) and Cu(II) were synthesized in a 2:1 (BIB: M) mole ratio—spectral and physicochemical methods characterized all synthesized compounds. The proposed structure of the Ni(II) complex was tetrahedral geometry and the octahedral geometry of the Cu(II) complex, and the results showed that the complexes have electrolytic behavior. All synthesized compounds were tested as anti-biofilm agents against (Pseudomonas autogiros (Gram-negative) bacteria (G-). The results showed that, compared to other compounds, copper complexes were more active. The medicinal application (anticancer) in human breast cancer cells (MCF-7) was studied of the ligand (BIB) and gave a good result in testing.

Acknowledgment
The authors thank the Department of Chemistry/ College of Science/ University of Baghdad staff for their assistance in performing this research.

Conflict of Interest
The authors declare that they do not have any competing interests.

Funding
There is no financial support.

Ethical Clearance
This work has been approved by the Institutional Scientific Committee at the University of Baghdad/ College of Science.

References

1. Çelik, A.; Ateş, A.N. The frequency of sister chromatid exchanges in cultured human peripheral blood lymphocyte treated with metronidazole in vitro. *Drug and Chemical toxicology*, **2006**, *29*(*1*),85-94. https://doi.org/10.1080/01480540500408663.
2. Kapoor, V.K.; Chadha, R.; Venisetty, P.K.; Prasanth, S. Medicinal significance of nitroimidazoles—some recent advances, *Journal of Scientific& Industrial Research*, **2003**, 62,659-665. https://nopr.niscpr.res.in/bitstream/123456789/17609/1/JSIR%2062(7)%20659-665.pdf.
3. Ali, A.E.; Elasala, G.S.; Ibrahim, R.S. Synthesis, characterization, spectral, thermal analysis and biological activity studies of metronidazole complexes. *Journal of Molecular Structure*, **2019**,*1176*,673-684. https://doi.org/10.1016/j.molstruc.2018.08.095.
4. Radko, L.; Stypuła-Trębas, S.; Posyniak, A.; Żyro, D.; Ochocki, J. Silver (I) complexes of the pharmaceutical agents metronidazole and 4-hydroxymethylpyridine: comparison of cytotoxic profile for potential clinical application. *Molecules*, **2019**,*24*(*10*),1949. https://doi.org/10.3390/molecules24101949.

5. Siddappa, K.; Mallikarjun, M.; Reddy, P.T.; Tambe, M. Spectrophotometric determination of metronidazole through Schiff's base system using vanillin and PDAB reagents in pharmaceutical preparations. *Eclética Química*, **2008**, *33*,41-46. https://doi.org/ 10.1590/ S0100-46702008000400005.
6. Pal, R. Boric acid in organic synthesis: Scope and recent developments. *ARKIVOC: Online Journal of Organic Chemistry*. **2018**. https://doi.org/10.24820/ark.5550190.p010.462.
7. Gujral, S.S. UV-Visible spectral analysis of boric acid in different solvents: a case study. *International Journal of Pharmaceutical Sciences and Research*, **2015**, *6*(*2*),830. http://dx.doi.org/10.13040/IJPSR.0975-8232.6(2).830-34
8. Sulaiman, G.M.; Jabir, M.S.; Hameed, A.H. Nanoscale modification of chrysin for improved of therapeutic efficiency and cytotoxicity. *Artificial cells, nanomedicine, and biotechnology*, **2018**, *46*(sup1),708-720. https://doi.org/10.1080/21691401.2018.1434661.
9. Ogwuegbu Martin, O.C.; Kenechukwu, E.C.; Stanley, O.C.; Patricia, E.N.; Ebere, E.C. Stoichiometric determination of Fe (II), Ni (II) and Cu (II) complexes of metronidazole. *International Journal of Chemical* Science, **2019**,*3*(*1*), 25-29. https://www.chemicaljournals.com/archives/2019/vol3/issue1/3-1-18.
10. Ramukutty, S.; Ramachandran, E. Crystal growth by solvent evaporation and characterization of metronidazole. *Journal of crystal growth*, **2012**, *351*(*1*),47-50. https://doi.org/10.1016/j.jcrysgro.2012.04.017.
11. Al-Mathkhury, H.J.F.; Al-Dhamin, A.S.; Al-Taie, K.L. Antibacterial and antibiofilm activity of flaxseed oil. *Iraqi Journal of Science*, **2016**,1086-1095. https://ijs.uobaghdad.edu.iq/index.php/eijs/article/view/7252.
12. Al-Azzawi, A.M.; Huseeni, M.D. Design and synthesis of novel homo and copolymerization based on 4-(N-maleimidylmethylbenzylidene)-4'-(N-citraconamic acid)-1, 1'-biphenyl. *Egyptian Journal of Chemistry*, **2022**, *65*(*1*),159-166. https://doi.org/10.21608/ejchem.2021.78334.3888.
13. Hasan, N.A.; Baqer, S.R. Preparation, characterization, theoretical and biological study of new complexes with mannich base, 2chloro–N-5-(Piperidin-1-ylmethylthio)-1, 3, 4-thiadiazol-2-yl) acetamide. *Ibn AL-Haitham Journal For Pure and Applied Sciences*, **2023**, *36*(*1*),260-271. https://orcid.org/0000-0003-3950-6183.
14. Obaleye, J.A.; Lawal, A. Synthesis, characterization and antifungal studies of some metronidazole complexes, *JASEM* , **2007**,*11*(*4*),15-18. http://www.bioline.org.br/ja.
15. Gao, S.; Liu, Y.; Feng, S.; Lu, Z. Synthesis of borosiloxane/ polybenzoxazine hybrids as highly efficient and environmentally friendly flame retardant materials. *Journal of Polymer Science Part A: Polymer Chemistry*, **2017**,*55*(*14*), 2390-2396. https://doi.org/10.1002/pola.28628.
16. Jiang, N.; Zhou, Z.; Xu, W.; Ma, H.; Ren, F. Preparation of heat resistant boron-containing phenyl silicone oil and its initial degradation mechanism in air. *Materials Research Express*, **2021**, *8*(*6*),065304. http://dx.doi.org/10.1088/2053-1591/ac0178.
17. Waszczykowska, A.; Żyro, D.; Jurowski, P.; Ochocki, J. Effect of treatment with silver (I) complex of metronidazole on ocular rosacea: Design and formulation of new silver drug with potent antimicrobial activity. *Journal of Trace Elements in Medicine and Biology*, **2020**, *61*, 126531. https://doi.org/10.1016/j.jtemb.2020.126531.
18. Kalinowska-Lis, U.; Felczak, A.; Chęcińska, L.; Zawadzka, K.; Patyna, E.; Lisowska, K.; Ochocki, J. Synthesis, characterization and antimicrobial activity of water-soluble silver (I)

complexes of metronidazole drug and selected counter-ions. *Dalton Transactions*, **2015**, *44*(*17*),8178-8189. https://doi.org/10.1039/C5DT00403A.

19. Khaleel, A.M.N.; Jaafar, M.I. Synthesis and characterization of boron and 2-aminophenol Schiff base ligands with their Cu (II) and Pt (IV) complexes and evaluation as antimicrobial agents. *Oriental Journal of Chemistry*, **2017**,*33*(5), 2394-2404. http://dx.doi.org/10.13005/ojc/330532
20. Eugene-Osoikhia, T.T. Synthesis, characterisation and antimicrobial studies of metal (II) complexes of ofloxacin and metronidazole. *Chem Search Journal*, **2020**,*11*(*1*),74-82. https://www.ajol.info/index.php/csj/article/view/197387.
21. Al-Jebouri, G.S.; Noorikhaleel, A.M. Synthesis of new boron compounds with amoxicillin and some of its metal complexes with use them in antibacterial, assessment of hepatoprotictive and kidney activity, anticancer and antioxidant applications. *Synthesis*, **2019**,*12*(*3*). http://dx.doi.org/10.22159/ajpcr.2019.v12i3.30912.
22. Abdul-Ghani, A.J.; Khaleel, A. Synthesis and characterization of new schiff bases derived from N (1)-substituted isatin with dithiooxamide and their co (II), Ni (II), Cu (II), Pd (II), and Pt (IV) complexes. *Bioinorganic Chemistry and Applications*, **2009.** https://doi.org/10.1155/2009/413175.
23. Saja, A.J.; Asmma, M.N. Synthesis and characterization of new schiff base compound from levofloxacin and L-cysteine with its Cu(II) and Pt(IV) complexes and estimation antibacterial and antifungal activities, *Biochemical and Cellular Archives*, **2021**, *21*, 2187-2195. https://connectjournals.com/03896.2021.21.2187.
24. Khaleel, A.M.N. Synthesis and characterization of trihydro mono and dihydrobis (indole-3-acetic acid) borate ligands and some of their metal complexes. *Iraqi Journal of Science*, **2015**, *56*(4A),2762-2772. https://ijs.uobaghdad.edu.iq/index.php/eijs/article/view/9453.
25. Ali, I.; Wani, W.A.; Saleem, K. Empirical formulae to molecular structures of metal complexes by molar conductance. *Synthesis and reactivity in inorganic, metal-organic, and nano-metal chemistry*, **2013**, *43*(*9*),1162-1170. http://dx.doi.org/10.1080/15533174.2012.756898.
26. Yoshino, T. Laboratory electrical conductivity measurement of mantle minerals. *Surveys in Geophysics*, **2010**, *31*(*2*),163-206. https://doi.org/10.1007/s10712-009-9084-0.
27. Hussein, N.A.; Abbas, A.K. Synthesis, spectroscopic characterization and thermal study of some transition metal complexes derived from caffeine azo ligand with some of their applications. *Eurasian Chem Commun*, **2022**, *4*(*1*),67-93. https://doi.org/10.22034/ecc.2022.307545.1245.
28. Czarnomysy, R.; Muszyńska, A.; Rzepka, Z.; Bielawski, K. Mechanism of anticancer action of novel imidazole platinum (II) complex conjugated with G2 PAMAM-OH dendrimer in breast cancer cells. *International Journal of Molecular Sciences*, **2021**, *22*(*11*), 5581. https://doi.org/10.3390/ijms22115581.
29. Al-Mathkhury, H.J.F.; Al-Dhamin, A.S.; Al-Taie, K.L. Antibacterial and antibiofilm activity of flaxseed oil. *Iraqi Journal of Science*, **2016**,*57*(2B),1086-1095. https://ijs.uobaghdad.edu.iq/index.php/eijs/article/view/7252.
30. Abid, N.; Hamad, E.; Ibrahim, M.; Abid, H. Antibacterial and antibiofilm activities of taxifolin against vancomycin-resistant S. aureus (VRSA). *Baghdad Journal of Biochemistry and Applied Biological Sciences*, **2022**, *3*(*04*), 262-272. https://doi.org/10.47419/bjbabs.v3i04.126.

31. Ali, R.; Shanan, Z.J.; Saleh, G.M.; Abass, Q. Green synthesis and the study of some physical properties of MgO nanoparticles and their antibacterial activity. *Iraqi Journal of Science*, **(2020)**,266-276. https://doi.org/10.21123/bsj.2023.8385.
32. Tawfeeq, H.K.; Hamid, M.; Al-Mathkhury, F.H.J. The prevalence of pseudomonas aeruginosa among Baghdad hospitalised patients. *Medico-Legal Update*, **2021**, *21*(*2*). https://doi.org/10.37506/mlu.v21i2.2749.
33. Sweedan, E.G. Estimate antimicrobial activity and anti-biofilm formation of bark cinnamomum zeylanicum on klebsiella pneumoniae isolated from urinary tract infections. *Iraqi Journal of Science*, **2018**, *59*(3C),1560-1566. https://ijs.uobaghdad.edu.iq/index.php/eijs/article/view/503.
34. Al-Ammash, M.S.J. Study the effect of alcoholic extract of Nigella sativa seeds on Trichomomas vaginalis in vitro. *Ibn AL-Haitham Journal For Pure and Applied Science*, **2017**, *30*(*3*),10-18. https://doi.org/10.30526/30.3.1596.