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Synthesis , Characterization and Antibacterial Activities of Co (II),Ni(II),Cu(II),Zn(II),Cd(II)and Hg(II) Mixed-Ligand Complexes of L-Proline and Trimethoprim antibiotic

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Abstract
The Co(II), Ni(II) ,Cu(II), Zn(II) ,Cd(II) and Hg(II) complexes of mixed of amino acid (L-Proline) and Trimethoprim antibiotic were synthesized. The complexes were characterized using solubility, melting point, conductivity measurement ,. and determination the percentage of the metal in the complexes by flame(AAS).Magnetic susceptibility, Spectroscopic Method [FT-IR and UV-Vis]. Draw the proposed structure of the complexes using program , Chem. office 3D(2006). The ligands and there metal complexes were screened for their antimicrobial activity against four bacteria (gram + ve) and (gram -ve){Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus}.The proposed structure of the complexes using program , Chem office 3D(2006).The general formula have been given for the prepared mixed ligand complexes $[M(Pro)_2(TMP)(H_2O)]$where L-Proline (abbreviated as (ProH) = $C_5H_9NO_2$ And Pro^- = $C_5H_8NO_2$ deprotonated primary ligand, L-proline . Trimethoprim (abbreviated as (TMP) =$C_{10}H_{11}N_3O_3S$.
Keywords: Trimethoprim antibiotic, L-Proline , Spectral and antibacterial activities.

Introduction

Trimethoprim (Systematic name) 5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine is on the world health organization's list of essential medicines, the most important medications needed in a basic health system [1]. Proline is an atypical amino acid, because it has a cyclic form, where the residue binds to the NH3 group and is an α-amino acid, one of the twenty DNA-encoded amino acids. Systematic name Pyrrolidine-2-carboxylic acid [2].To design effective chemotherapeutic agents and better anticancer drugs, it is essential to explore the interactions of metal complexes with DNA [3]. Mixed metal complexes containing heterocyclic . Drugs and amino acids compounds have been of considerable interest in terms of structural chemistry, and biological functions. [4-6]. If the ligand (Drug) which combine with the metal forms one or more rings with the metal, the resulting structure is said to be a metal chelate and the process is known as chelation[7].The pharmaceutical use of metal complexes, therefore, has excellent potential. A broad array of medicinal applications of metal complexes has been investigated. [8-10].

In this paper we present the synthesis and study of Co (II), Ni (II) ,Cu(II), Zn(II) ,Cd(II) and Hg(II) complexes with L-Proline amino acid as a primary ligand and Trimethoprim antibiotic as a secondary ligand.

2. Experimental

2.1 Materials

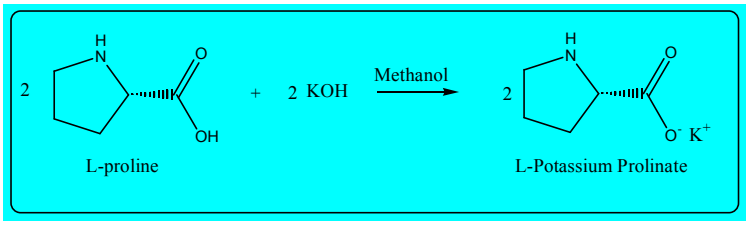
Most of the chemicals used were of Analytical Grade.The drug (Trimethoprim) was obtained from (the state Enterprise for the drugs Industries ,and Medical Appliances) in Samarra- Iraq (SDI)., L-proline was purchased from (Merck), metals chloride and solvents from (B.D.H). The reagents were used without further purification .

2.2 Instruments: FT-I.R spectra were recorded as KBr discs using Fourier transform Infrared Spectrophotometer Shimadzu 24 FT-I.R 8400s. Electronic spectra of the prepared complexes were measured in the region (200- 1100) nm for 10-3M solutions in dimethyl sulfoxide (DMSO) at 25ºC using shimadzu-U.V-160. A Ultra Violet Visible- Spectrophotometer with 1.000 ± 0.001 cm matched quartz cell. While metal contents of the complexes were determined by Atomic Absorption (A.A) Technique using Japan A.A-67G Shimadzu. Electrical conductivity measurements of the complexes were recorded at 25ºC for 10-3 M solutions of the samples in (DMSO) using pw 9527 Digital conductivity meter (Philips). Melting points were recorded by using Stuart melting point apparatus. Magnetic susceptibility measurements were measured using Bruker magnet BM6 instrument at 298°K following the Faraday's method. The proposed molecular structure of the complexes were drawing by using chem. office program, 3DX (2006).

2.3 General Synthesis of (mixing ligands complexes with some metal ions

I -Synthesis of Potassium Prolinate ($C_5H_8NO_2K$) :[11]

A solution [0.23,gm(2mmol)]of L-Prolin with [0.122 gm (2mmol)] solution of Potassium hydroxide in methanol was deprotonated according to the following reaction, see Scheme



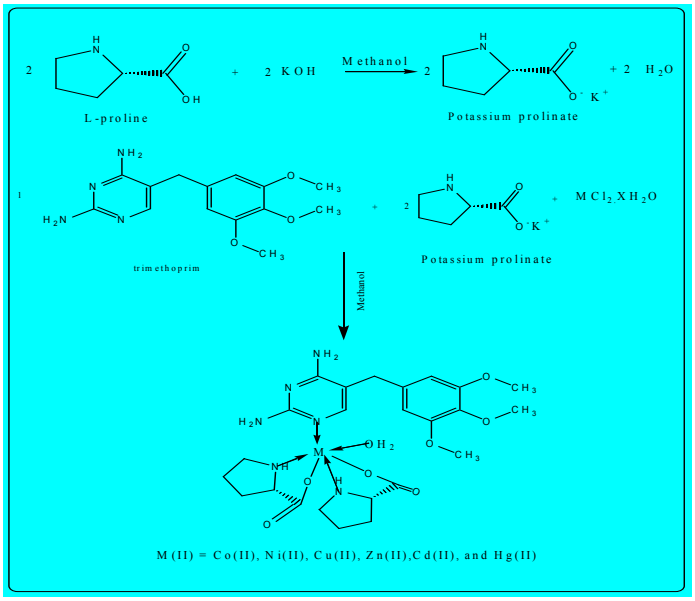
Scheme (1): The synthesis route of L-Potassium Prolinate

II. Synthesis of [Cu(Pro)$_2$(TMP)] complex:

A solution of Trimethoprim (0.290 gm, 1mmole) in methanol (5 mL) and a solution of L-Potassium Prolinate (0.230 gm, 2 mmole) were added to stirred of Cu(II) Chloride dihydrate (0.17 gm, 1 mmole) in methanol (5 ml). The resulting mixture was stirred for (1 hours). Then the mixture was filtered and washed with an excess of ethanol and dried at room temperature during (24 hours). A blue solid was obtained m.p (240-243° C), yield 78%

III. Synthesis of [Co(Pro)$_2$(TMP)(H_2O)]**,[Ni(Pro)$_2$(TMP)**(H_2O)]**, [Zn(Pro)$_2$(TMP)**(H_2O)]**, [Cd(Pro)$_2$(TMP)** (H_2O)] **and [Hg(Pro)$_2$(TMP)** (H_2O)] **,complexes:**[11]

The method used to prepare these complexes was similar method to that mentioned in preparation of [Cu(Pro)$_2$(TMP)] complex in paragraph(II) ,the obtained a solution complexes with Co(II), Ni(II), Zn(II),Cd(II) and Hg(II) were washed with an excess of ethanol and dried at room temperature during (24 hours).See Scheme (2).



Scheme (2): The preparation route of the mixed ligand [M(Pro)$_2$(TMP)(H_2O)]complexes

Results and Discussion

Six metallic complexes of L-Proline and Trimethoprim antibiotic with Co (II), Ni (II) ,Cu(II), Zn(II) ,Cd(II) and Hg(II) ions ,were synthesized from ethanol –aqueous medium; General of reaction as scheme (2) .

Generally, the complexes were prepared by reacting the respective metal salts with the ligands using 1:2:1 mole ratio, i.e. one mole of metal chloride : two moles of potassium prolinate : one mole of Trimethoprim).

The synthesis of mixed - ligand Metal complexes may be represented as shown in the general equation below:

Pro H +KOH→ Pro$^-$ K^+ + H_2O

2 Pro$^-$ K^+ +TMP+ MCl_2. nH_2O→[M(Pro)$_2$(TMP)(H_2O)]+ 2KCl

proH= amino acid L-proline (as aprimary ligand).

TMP = Trimethoprim (as a secondary ligand).

The physical properties of the complexes are shown in (Table 1), All the complexes are colored, non-hygroscopic The complexes decomposed at high temperature on heating. The complexes are are insoluble in water and most of the organic solvents like (benzene , carbon tetrachloride, Petroleum ether and Chloroform), and partially soluble in (methanol, ethanol and acetone) but soluble in strong donor polar DMF and dimethyl sulfoxide (DMSO).[12] .The observed molar conductance (ΛM) of 10^{-3}solutions of the complexes in DMSO lie

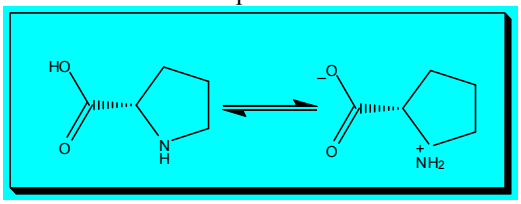
in low range (3.32 to 19.6) Ω^{-1} cm^2 mol^{-1} supporting their non-electrolytic behavior[13]. The electrical conductivity of these complexes found in the order:

Co > Cu > Ni > > Hg > Zn> Cd. Insolubility of these complexes in water and there non-electrolytic nature provide sufficient evidence for covalence of the ligands.[13]

The atomic absorption measurements (Table-1) for all complexes gave approximated values for theoretical values .The analysis data (Table-1) of metal complexes are consistent with their general formulation as 1:2:1, mixed ligand complexes of the type [M $(Pro)_2$(TMP)].The test for chloride ion with $AgNO_3$ solution was negative (Nil%) indicating that there is no chloride ion outside the coordination sphere of the central metal [14],

Fourier-transform infrared spectra and m[of coordination :

The relevant vibration bands of the free ligands and the complexes are in the region 400–4000cm^{-1}[15-16]. Comparative study of IR spectra of the mixed ligand complexes with ligand reveals that several peaks are shifted, vanished or have newly appeared. The FT-IR spectra assignment off free ligand (L-proline), was summarized in (Table 2) , and (Trimethoprim),was summarized in Table (3).The important IR peaks of the complexes are given in (Table 4) . As regards the chelation of amino acid such , L-proline is evidently present in its zwitterionic form and, therefore, the N-H moiety must be protonated, generating a NH_2^+ group whereas the acid group remains in the anionic COO- form , Scheme (3) and the IR spectra of these cannot be compared entirely with those of metal complexes as amino acids in metal complexes do not exist as zwitterions.[17,18] .



Scheme (3): zwitterions of L-proline

The absorption band for stretching vibration C-N single bond appeared at1242 cm-1.The absorption band for stretching vibration .All free amino acids shows a strong carboxyl asymmetric stretching band aυsym(COO-)at (1506-1650)cm-1 and weaker symmetric stretching υsym(COO-) band at ~ (1400-1360)cm-1 [17] in the spectrum of L-proline it appears at (1508 and 1379) cm-1 respectively. υ = [υasym (COO-) - υsym(COO-)] is (159 cm-1). The asymmertic stretching band of υ(COO-) was shifted to a higher frequency in all metal complexes within the range (1593-1604) cm-1, whereas the symmertic stretching band was shifted to a lower frequency in all metal complexes within the range (1330-1377)cm-1,these values are quite agreeable with the values reported earlier [17].

The energy difference between both vibrations [υasym (COO-) - υsym(COO-)] , > 200 cm^{-1}, from FT-IR data) that's supports the collaboration of this group in monodentate binding [17,18,19].

The coordinated between the (H_2O) molecules and the (M^{+2}) resulted in the appearance of vibrational bands at range (770-771) cm-1 (M-OH2) in the all complexes complexes [20]. TMP has characteristic very strong band at 3471 cm^{-1} and at 3319 cm^{-1}which account for ν(N-H_2)asym and ν (N-H_2) sym respectively. The N—H stretching frequencies of the pyrimidine NH2 in the free trimethoprim shifted slightly in the metal complexes. It was observed in the same region, 3479-3379 cm-1, as in the free ligands. The slight shift is ascribed to hydrogen bonding and other noncovalent interactions in the metal complexes. the complexes are comparable with the bands in the ligand, so we can conclude that the NH2 groups are not involved in the metal ligand vibration.[19] . three (–OCH_3 aromatic groups) has vibrations bands at 1128 cm^{-1}. [16, 20].

The band for stretching vibration of (C = N) showed at 1633 and1565 cm^{-1} .[18] The absorption bands at 1263 and 1236 cm^{-1} which account for C-O-C str. (asym.) and C-O-C str. (sym.) respectively .Assessment of TMP , pro K showed that TMP bands corresponding to NH_2 and C-H aromatic stretching vibration were difficult to analyses due to overlapping with NH and CH of the proline . A sharp very strong frequency band at 1633 cm^{-1} in trimethoprim assigned to the pyrimidine nitrogen ν(C=N) shifted to [1643,1643,1647,1631,1635 and 1624]cm^{-1} in [Co(Pro)$_2$(TMP)(H_2O)],[Ni(Pro)$_2$(TMP)(H_2O)],Cu(Pro)$_2$(TMP)(H_2O)],[Zn(Pro)2(TMP)(H_2O)],[Cd(Pro)$_2$(TMP)(H_2O)] and [Hg(Pro)$_2$(TMP)(H_2O)]respectively. The significant shifts to a higher frequency band for all complexes except for [Hg(Pro)$_2$(TMP) (H_2O)] suggest the coordination of the metal ion to the ligand through the pyrimidine nitrogen of the ligands. Interestingly, the C-N in the imine aromatic which confirms that the nitrogen has interacted with the carboxylic group of proline acid. The symmetrical and asymmetrical stretching bands of the –NH group in the higher frequency region [17-18] are displaced slightly change frequency after coordination, which may be due to inter and intra molecular hydrogen bonding, an effect caused by the interactions of the metal with the ligand [19,20].The CH_2 stretching vibrations bands show in and the CH2 bending vibrations show important mixing with ring modes in the region below 1000 cm–1 . IR of the

complexes also showed new low intensity bands non-ligand band in the region 430-460cm-1 and 510-520cm-1, which could be assigned to υ (M-O) and υ (M-N) modes respectively [6,21]. The region related to the CH and CH_2 stretching vibrations is very reach in bands , Most of the deformational modes were found in similar ranges as in the "free" ligand. [20,21].OCH_3 aromatic groups did not show any strong changes. New bands of weak intensity observed in the regions around (524-590) $cm^{-1}$and (416-482) cm^{-1} may be ascribed to M-N and M-O vibrations, respectively [11, 21].It may be noted that, these vibrational bands are absent in the spectra of the ligands .All the complexes are in agreement with octahedral geometry as proposed .[17,19]. Trimethoprim complexes of coordination of the metal to the ligands is through the nitrogen of the pyrimidine group

Table (1): Some physical properties of the ligands and their complexes

Compounds Chemical Formula	M. wt Calc	Color	Yield %	M .p°c (de) °c	Λ_m $\Omega^{-1}cm^2mol^{-1}$	Metal% Theory (exp)
TMP	290.32	White	___	238		___
L-Proline	115.13	White	___	222	5.45	___
$[Co(Pro)_2(TMP)(H_2O)]$	595.51	Violet	70	254	18.03	9.90 (10.61)
$[Ni(Pro)_2(TMP)(H_2O)]$	595.27	Green	66	221	8.66	9.86 (10.75)
$[Cu(Pro)_2(TMP)(H_2O)]$	600.12	Blue	78	243	19.6	10.59 (11.03)
$[Zn(Pro)_2(TMP)(H_2O)]$	601.97	White	65	247	5.01	10.86 (10.83)
$[Cd(Pro)_2(TMP)(H_2O)]$	648.99	White	80	205	3.32	17.32 (16.01)
$[Hg(Pro)_2(TMP)(H_2O)]$	737.17	Yellow	59	167	5.90	27.21 (28.21)

Table (2) : Selected FT-IR bands for L-Proline

Com.	ν (N-H)asy ν (N-H) sym or ($N-H_2^+$)	ν (CH_2)	ν (CH)	ν (-COO) asym	ν (- COO) ym	Δν (COO^-) asym - sym	C-N single Bond ν w(CH2) + ν (CH)	ν (C-C)	ν (CCN) + ν (CC)
L-ProH	3423 vs 2989w	771 m	2611m	1622vs	1408s	214	1238	1049 w	839m 777m

Table (3) : Selected FT-IR bands for Trimethoprim

Compound	ν (N-H) asym	ν (N-H) sym	ν(C=N) Pyrimidine nitrogen	C-O-C str. (asym.)	C-O-C str. (sym.)	$-OCH_3$
Trimethoprim	3471vs	3363	1633vs 1597vs	1263s	1236s	1128vs

Table (4) : Selected FT-IR bands for [M(Pro)$_2$(TMP)(H$_2$O)]complexes

Complexes	ν OH-(H$_2$O)	ν(N-H)asy ν (N-H) sym	δ νNH$_2$ + ν(C=N) Pyrimidine nitrogen	ν –OCH$_3$	-COO asym	ν -COO sym	Δν (COO) asym - sym	ν pr(H$_2$O) ν pw(H$_2$O)	ν (M-OH$_2$)	ν M-N	ν M-O
[Co(Pro)$_2$(TMP)(H$_2$O)]	3406vs	3325 3166	1643vs	1130vs	1589s	1342m	247	829m 574w	700	574 532w	459 416 w
[Ni(Pro)$_2$(TMP) (H$_2$O)]	3452v s	3398vs 3332s 3159	1643vs	1128vs	1589s	1334vs	255	825m 582w	763s	582 551 w	470 482
[Cu(Pro)$_2$(TMP)(H$_2$O)]	3406vs	3321s 3336s	1647vs	1134vs	1589s	1342s	247	825s 528m	765s	590 w 536	474w 432 w
[Zn(Pro)$_2$(TMP)(H$_2$O)]	3500v s	3421vs 3336s 3217vs	1631vs	1126s	1604vs	1377	227	848m 524m	765s	551 524 w	482 w 439 w
[Cd(Pro)$_2$(TMP)(H$_2$O)]	3510v s	3471vs 3317s	1635s	1130vs	1593 vs	1330	263	833m 532m	771s	578 532	478 443
[Hg(Pro)$_2$(TMP)(H$_2$O)]	3529v s	3468vs 3379vs	1624vs	1132vs	1593 vs	1330	263	528m	767s	565 528	418 474

3-5- The ultra violet visible spectra and Magnetic measurements for the mixed- ligand :
Magnetic moments μ_{eff} (μ B) of each of the complexes are given in Table (5). These values suggest octahedral geometry which is in good agreement with data of electronic transition [7,20].

UV/Visible spectra of the ligands
The electronic spectral data of the free ligands TMP and L-proline and their complexes are summarized in table-5. The u. v- vis spectrum of TMP in DMSO solvent appeared a high intense absorption band at (257nm) (38910cm^{-1}) (ε max=2431 molar1.cm^{-1}). is attributed to [$\pi \rightarrow \pi^*$/n→π* (overlap of the two peaks)aromatic ring and (C=N) of the pyrimidine group] transitions .The electronic absorption spectrum of the L- Proline showed three band at 240,284 and 349 nm.the first one may be assigned to intraligand π→π* transition, where as the second and third band may be assigned to the n→π* transition of the heterocyclic and COO- groups [nnn]. It is found that these bands were shifted to lower energy on complexation , [22.24]

UV/Visible spectra of the metal complexes [M(Pro)$_2$(TMP)(H$_2$O)] **complexes (1 to 6)** :
[Co(Pro)$_2$(TMP) (H$_2$O)] complex (1)
The spectrum of the complex [Co(Pro)2(TMP)] shows two absorption bands at (275nm)(36363 cm-1)(ε max =1995 molar^{-1} .cm^{-1}), attributed to the charge transfer transition and at (774nm)(12919 cm^{-1})(ε max =9 molar^{-1}.cm^{-1}) attributed to the 4T1g(F) →4T2g(F) suggesting octahedral geometry of this complex [23,24].

[Ni (Pro)$_2$(TMP) (H$_2$O)] complex (2)
T he spectrum of the [Ni (Pro)$_2$(TMP)(H$_2$O)]complex shows two absorption bands at (274nm)(36493cm^{-1})(ε max =1917 molar^{-1} .cm^{-1}) attributed to the charge transfer transition and at (882nm)(11337 cm-1)(ε max =3 molar-1 .cm-1) attributed to 3A2g → 3T2g suggesting octahedral geometry of this complex [23,24].

[Cu (Pro)$_2$(TMP)(H$_2$O)]complex (3)
The electronic absorption spectrum for [Cu (Pro)2(TMP)(H2O)]complex shows three absorption band at about 12224 cm^{-1} – 36363 cm^{-1} but they are overlapped. Because, octahedral complexes of Cu(II) are observable distorted by Jahn-Teller effect and the structure of complex is to name distorted octahedral. It was to taken notice of top of the peak as absorption band and d–d transition at about (798nm)(12533cm^{-1}) (ε max =14 molar^{-1} .cm^{-1}) and (818nm)(12224cm^{-1}) (ε max =10 molar^{-1} .cm^{-1}) may be due to due to 2Eg → 2T2g transition, [19-.20] and the uv-visible peak corresponding to the π→π*transitions in the ligands were observed at(275nm) (36363cm^{-1})(εmax=1995molar^{-1}.cm^{-1}) attributed to the charge transfer transition (CT).[22,23].

[Zn(Pro)$_2$(TMP)(H$_2$O)]complex(4),[Cd(Pro)$_2$(TMP)(H$_2$O)](5)and[Hg(Pro)$_2$(TMP)(H$_2$O)](6)complexes:
The Zn(II), Cd (II) and Hg (II) complexes table (5) showed diamagnetic as expected from their electronic configuration and did not display any peak in the visible region, no ligand field absorptions band was observed, therefore the bands appeared in the spectra of complexes could be attributed to charge transfer transitions [15, 24]. The electronic spectra of d^{10} [Zn(II) ,Cd(II) and Hg(II)] complex shows absorption bands at range (26595-37313) cm^{-1}, attributed to the MLCT (metal to ligand charge transfer) transition, which are compatible with those complexes that have the octahedral structure [23,25].

Table (5): Electronic Spectral data, magnetic moment of the studied Complexes and two ligands

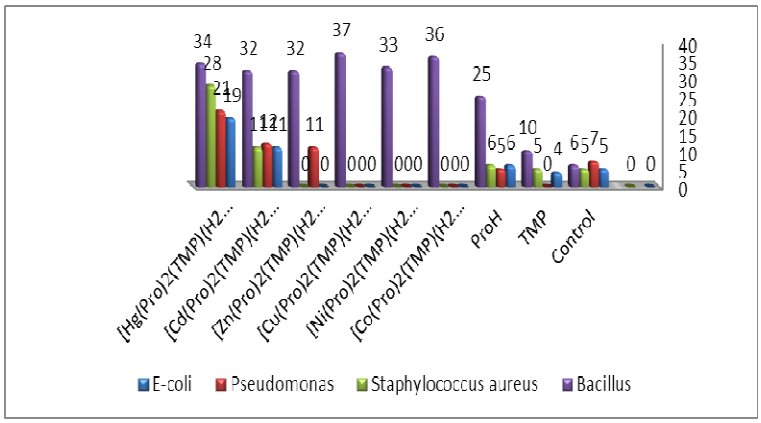
Compounds	λ nm	ύ cm^{-1}	ε_{max} ($molar^{-1}.cm^{-1}$)	Electronic transition assignment	μ_{eff} (μ B)
TMP	257	38910	2431	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$	-
L-Proline	240 284 349	41666 35211 28653	312 131 40	π→π* n→π* n→π*	-
$[Co(Pro)_2(TMP)(H_2O)]$	275 774	36363 12919	1995 9	CT 4T1g(F)→4T2g(F)	4.28
$[Ni(Pro)_2(TMP)(H_2O)]$	274 882	36493 11337	1917 3	CT A2g(F)→T2g(F)	3.78
$[Cu(Pro)_2(TMP)(H_2O)]$	275 798 818	36363 12533 12224	1997 14 10	CT 2Eg → 2T2g	1.46
$[Zn(Pro)_2(TMP)(H_2O)]$	235 282	42553 35460	2036 1732	MLCT MLCT	diamagnetic
$[Cd(Pro)_2(TMP)(H_2O)]$	237 268	45892 43840	2179 2281	MLCT MLCT	diamag,netic
$[Hg(Pro)_2(TMP)(H_2O)]$	288 332	34722 30120	1681 707	MLCT MLCT	diamagnetic

Antibacterial Activities

The ligands and synthesized metal complexes were screened for their antimicrobial activity by well plate method in nutrient agar. The activities were expressed in terms of millimeter (mm) by measuring inhibition zone diameters.(IZ) and compared with the standard DMSO
(as control) . [24-26]. Table (6) and **Scheme (4)** reveal that the synthesized compounds were potent as bacteriostatic agents. The plates were incubated in incubator at 37°C for 24 hours.. In order to ensure that solvent had no effect on bacteria, a control test was performed with DMSO and found inactive in culture medium. [26,27] .Trimethoprim showed activity against **E-coli,** *S. aureus* and **Bacillus** with 4. 5 and 10 mm zones of inhibition respectively, while L-proline exhibit activity, against all bacterial used, which suggests that L-proline is more active than trimethoprim .Cd (II) and Hg (II) complexes exhibited a broad spectrum antimicrobial activity as they are active against all selected bacterial isolates. They have also shown a stronger antibacterial activity than the free ligands as well as the DMSO(as control).The investigation of antibacterial screening data revealed that most of the synthesized complexes were found to possess various antimicrobial activities toward *Bacillus* microorganism. On chelation, the ligand with the N and O donor system might have inhibited enzyme production, since enzyme which requires a free –OH group for their activity appear to be especially susceptible to deactivation by the ions of the complexes. The chelation also reduces the polarity of central metal ion because of partial sharing its + ve charge with the donor group and possible π electron delocalization within the whole chelate ring. [27].The other factors like solubility and bond length between the metal and ligand may also increase the activity [28].

Table(6):Biological activity of the mixed ligands complexes (Zoneof inhibition) (mm)

Compound	*E-coli* (G -ve)	*Pseudomona*	*Staphylococcus aureus* (G +ve)	*Bacillus*
Control	5	7	5	6
TMP	4	0	5	10
ProH	6	5	6	25
$[Co(Pro)_2(TMP)(H_2O)]$	0	0	0	36
$[Ni(Pro)_2(TMP)(H_2O)]$	0	0	0	33
$[Cu(Pro)_2(TMP)(H_2O)$	0	0	0	37
$[Zn(Pro)_2(TMP)(H_2O)]$	0	11	0	32
$[Cd(Pro)_2(TMP)(H_2O)]$	11	12	11	32
$[Hg(Pro)_2(TMP)(H_2O)]$	19	21	28	34



Scheme (4): Chart of biological effects of the studied compounds

CONCLUSION

Six mixed M(II) complexes of L-Proline and trimethoprim have been synthesized and characterized by test solubility, electric conductivity, melting point, and infrared Spectroscopy,.Electronic spectra and magnetic susceptibility measurement reveal octahedral geometry for all complexes.

$[Cd(Pro)_2(TMP)(H_2O)]$ and $[Cd(Pro)_2(TMP)(H_2O)]$ complexes show stronger antibacterial activity than the free drugs ,thus potential metal based bactericidal are identified.

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