International Journal of Advance and Applied Research
www.ijaar.co.in
ISSN – 2347-7075 Impact Factor – 7.328
Peer Reviewed Bi-Monthly
Vol.10 No.5 May-June 2023

Synthesis, Physicochemical Characterization And Biological Activities Of Dapsone Derived Schiff Base Ligand And Their Co(II) Complexes

Mrs. Kundalkesha Dharmentra Gaikwad
Department of Chemistry,
Sangameshwar College Solapur, Maharashtra, India
Corresponding Author: Mrs. Kundalkesha Dharmentra Gaikwad
Email: keshagaikwad01@gmail.com
DOI- 10.5281/zenodo.15695249

Abstract:

This work presents the synthesis and characterization of five diphenylsulphone (Dapsone) derived Schiff base ligands (L_1- L_5). Using the aforementioned ligands, Co (II) complexes were synthesized in 1:1 stoichiometric ratio. The synthesized Schiff base and their complexes were characterized by elemental analysis, ^{1}H-NMR, UV-Visible, FT-IR, TGA analysis and magnetic susceptibility measurements. The results from the above analytical techniques showed that the complexes are in an octahedral geometry. The antimicrobial activity of the synthesized ligands and their metal complexes under study was carried out by using the agar well diffusion method. The ligand and complex interactions for biological targets were predicted using molecular docking and high binding affinities.

Keyword: diphenylsulphone; Ligand; Co (II) complex; biological activity

Introduction

Schiff base ligand and coordination compounds play an important role in our daily lives, with applications ranging from biology to industry. Because of their high selectivity and target specificity in treating a variety of life-threatening diseases, coordination complexes are now replacing traditional organic drugs in biology. Metals like copper, calcium, iron, zinc, and cobalt are important elements that have enormous biological activity when combined with certain metal proteins that help transport oxygen and are also useful in electronic transfer reactions and ion storage. The chemistry of Schiff base complexes has progressed quickly, finding solutions in coordination and stereochemistry [1, 2]. Cobalt is a highly essential trace element to all humans and animals [3-5]. Cobalt has several uses in a variety of fields. This metal, in vitamin B12 (cobalamin) form, is important for a variety of biological functions. Cobalamin is essential for red blood cell formation, synthesis of DNA, and child growth and development. Co is also used as a catalyst in several reactions. Cobalt is needed for the formation of amino acids and a few proteins in the myelin sheath in nerve cells. Glutamatase, dialdehydase, methionine synthetase, mutase, and dipeptidase all contain cobalt. It increases ATP turnover, which is essential for red blood cell development and animal growth [6, 7].

Schiff base ligands bound to their metal complexes are widely studied, currently, such complexes are considered successful models of biological compounds. One example is cobalt, which, despite its medicinal potential, is largely overlooked by pharmaceutical chemistry. Although there are some exceptional reviews of cobalt-based therapeutic research [8-10], the biological

activites of cobalt complexes differ significantly based on the chelation strategy. A positively charged metal center on treatment with heteroaromatic moiety produces metal complexes that exhibit various types of geometries, which can easily interrelate with biomolecules [11-12]. Antimicrobials and anticancer agents are only a few of the possible therapeutic activities of cobalt-Schiff base complexes. Cobalt complexes are widely used as catalysts [13-15] asymmetric hetero Diels Alder reactions [16], and asymmetric addition of organometallic reagents to aldehydes [17, 18]. A lot of research has suggested that Co complexes have the potential to target cancer proteins. Schiff base Co(II) complexes, in particular, is to have better anticancer activity than cis-platin against cancer cells [19-23].

The present study deals with the synthesis of Schiff bases and their Co(II) complexes using the known procedures. Further, the antimicrobial activities were performed to know the biological efficacy of the synthesized compounds

Experimental

Materials and methods

4, 4'-diaminodiphenylsulphone, 2-hydroxy-benzaldehyde, 2-hydroxy-1-naphathaldehyde, 2-hydroxy-3-methoxy benzaldehyde, 5-bromo-2-hydroxybenzaldehyde, 5-chloro-2-hydroxybenzaldehyde were of analytical grade. $CoCl_2.6H_2O$ was purchased from Merck Chemical Ltd. All these chemicals were used without further purification. Synthesized complexes were characterized by elemental analysis. The functional groups in the molecules were determined by FT-IR spectroscopy in the range of 400 cm^{-1} to 4000 cm^{-1} in the KBr disc using Perkin-Elmer 1200 FT-IR spectrometer. The thermal response of the investigated complexes can be taken by using thermal analyzer. Electronic absorption of the compounds were investigated using UV-Visible spectrophotometer (Shimadzu, UV-1800). ^{1}H-NMR of the Schiff bases was recorded using Bruker Avance (400 MHz) ^{1}H- NMR spectrometer.

Chemical synthesis

Synthesis of ligands (L_1-L_5)

The preparation of a series of Schiff bases is schematically represented in Scheme 1. 4,4'-diaminodiphenyl Sulfone is made to react with 5-chloro-2-hydroxybenzaldehyde, 2-hydroxy-benzaldehyde, 2-hydroxy-1-naphathaldehyde, 2-hydroxy-3-methoxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde, in 1:2 ratio in ethanol and the reaction mixture is refluxed for 3-4 h to yield Schiff base ligands L_1, L_2, L_3, L_4, and L_5, respectively. The characterization data of the synthesized Schiff base ligands are discussed below:

-(4,4'-sulfonylbis(4,1-phenylene)bis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)-diphenol (L_1):

Yield : 77%; mp: 231°C; FT-IR (KBr, v/cm^{-1}): 3459 (OH), 3376 (Ar-C-H), 1615 (C=N),1566 (C=C), 1274 (asymmetric -SO_2-stretch), 1185 (symmetric -SO_2- stretch); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.56 (1H, s, Ar-OH), 8.80 (1H, s, Azomethine), 6.55-8.05 (8H, m, Ar-H)

(4,4'-sulfonylbis(4,1-phenylene)bis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)-dinapthalen-2-ol (L_2)

Yield : 82%; mp: 239°C; FT-IR (KBr, v/cm^{-1}): 3434 (OH), 3222 (Ar-C-H), 1619 (C=N), 1544 (C=C), 1283 (asymmetric -SO_2-stretch), 1186 (symmetric -SO_2- stretch); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.83 (1H, s, Ar-OH), 8.72 (1H, s, Azomethine), 6.49-8.01 (10H, m, Ar-H)

(4,4'-sulfonylbis(4,1-phenylene)bis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)bis-(4-bromophenol) (L_3)

Yield : 68%; mp: 233°C; FT-IR (KBr, v/cm^{-1}): 3432-3227 (OH), 3230 (Ar-C-H), 1621 (C=N), 1547 (C=C), 1275 (asymmetric -SO_2-stretch), 1182 (symmetric -SO_2- stretch) 547 (C-Br); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.92 (1H, s, Ar-OH), 8.68 (1H, s, Azomethine), 6.67-8.23 (7H, m, Ar-H)

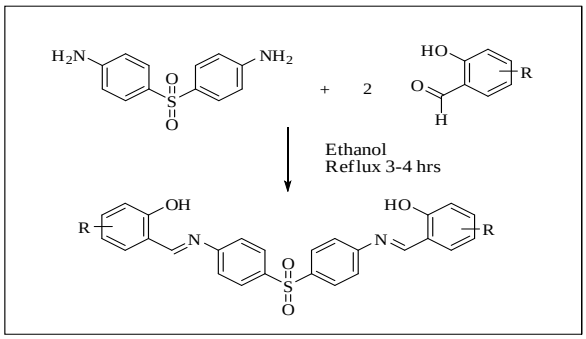
(4,4'-sulfonylbis(4,1-phenylene)bis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)bis-(2-methoxyphenol) (L_4)

Yield : 80%; mp: 249°C; FT-IR (KBr, v/cm^{-1}): 3427 (OH), 3236 (Ar-C-H), 1612 (C=N), 1579

(C=C), 1273 (asymmetric -SO_2-stretch), 1187 (symmetric -SO_2- stretch); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.89 (1H, s, Ar-OH), 8.70 (1H, s, Azomethine), 6.50-7.82 (7H, m, Ar-H), 3.81 (3H, s,-OCH3)

(4,4'-sulfonylbis(4,1-phenylene)bis(azan-1-yl-1-ylidene))bis(methan-1-yl-1-ylidene)bis-(4-chlorophenol) (L_5):

Yield : 86%; mp: 260°C; FT-IR (KBr, v/cm^{-1}): 3457 (OH), 3241 (Ar-C-H), 1627 (C=N), 1563 (C=C), 1268 (asymmetric -SO_2-stretch), 1181 (symmetric -SO_2- stretch), 740(C-Cl); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.70 (1H, s, Ar-OH), 8.51 (1H, s, Azomethine), 6.67-7.97 (7H, m, Ar-H)



Scheme 1: General synthetic route of Schiff base ligands (L_1-L_5)

Synthesis of Co(II) complexes (C_1- C_5).

A solution of 0.1 M (4.56 g) of the Schiff base ligand (L_1) was dissolved in 30 mL of hot ethanol in a round bottom flask. To this, a solution of 0.102 M (2.41 g) of cobalt chloride in 25 mL ethanol was then added dropwise with continuous stirring. The above reaction mixture was refluxed for 3-4 hours. The progress of the reaction was checked by TLC and spots were visualized under UV light. The precipitate obtained was then filtered, washed with ethanol, and dried in a desiccator over anhydrous $CaCl_2$. Co(II) complexes with other Schiff bases were synthesized using the above procedure. The synthesized complexes are characterized using physico-chemical techniques. The structures of the prepared complexes are depicted in Figure 1.

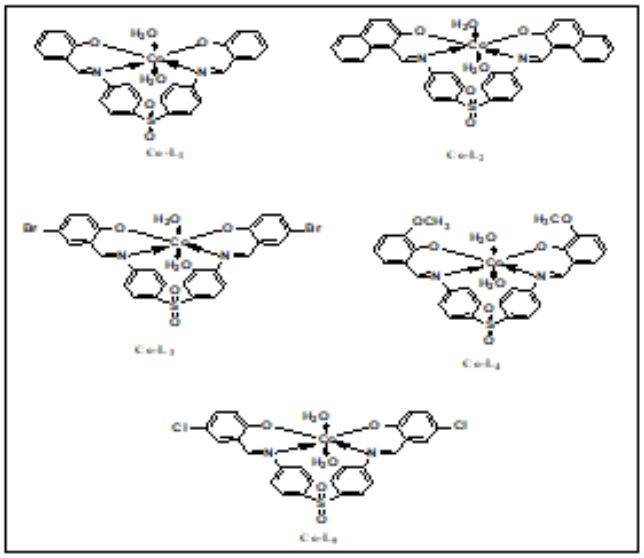


figure 1: Proposed structure of synthesized Co(II) complexes (C_1-C_5).

Biological studies

Antimicrobial studies

The antimicrobial activities of the synthesized Schiff base ligands and their cobalt metal complexes under study were carried out by using the agar well diffusion method. The Gram-positive pathogens *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative pathogens *Klebsiella pneumoni), Pseudomonas aerugino,* and *Escherichia coli* were used in the biological

potency evaluation. The antifungal activity of the compounds was tested against *Aspergillus niger* and *Candida albicans*. Standard drugs used for the study were Ciprofloxacin and Nystatin for bacterial and fungal pathogens respectively [24].

The Muller Hinton agar plate surface was inoculated by the spread plate method with microbial inoculum over the entire agar surface [25]. Then, a hole with a diameter of 6 to 8 mm is punched aseptically with a sterile cork borer, and the volume of the desired antimicrobial compound dissolved in DMSO with desired concentration was introduced into the well. Then, agar plates were incubated under suitable conditions depending on bacterial/fungal species requirements. The antimicrobial agents diffuse in the agar medium and inhibit the growth of the microbial strain tested. The inhibition zones exhibit around the antimicrobial compound and measured as the diameter of the zone of inhibition in millimeters (mm). [26-27]

Molecular Docking Studies

Molecular docking is one of the most essential tools used in drug discovery due to its ability to predict, the conformation of small-molecule ligands within the appropriate target binding site with a substantial degree of accuracy. To find out the possible mode of action of the synthesized Schiff bases (L_1-L_5) and Co(II) complexes (C_1-C_5) molecular docking calculations of cysteine protease human cathepsin ki.-e.CDK7. Auto Grid was used to define the active site and the grid size was set to 46 × 54 × 56 points which covers all the active site residues [28]. The step size of 2.0 Å for translation and 10° for rotation were selected. A total of 10 runs were performed, and for each run, a maximum number of 27000 genetic algorithms (GA) generations were done on a single population of 150 individuals. The best-docked conformation among 10 conformations was obtained with the least binding energy values [29]. Interaction between cysteine protease human cathepsin ki.-e.CDK7 (Cyclin-dependent kinase-7) PDB ID: 1au2 with various ligands under study was visualized using molecular visualization tools. such as Chimera (Pettersen et al. 2004). In addition, by using LigPlot+ tool hydrogen bonding and hydrophobic interactions were predicted for the complex [30]

Results and Discussion

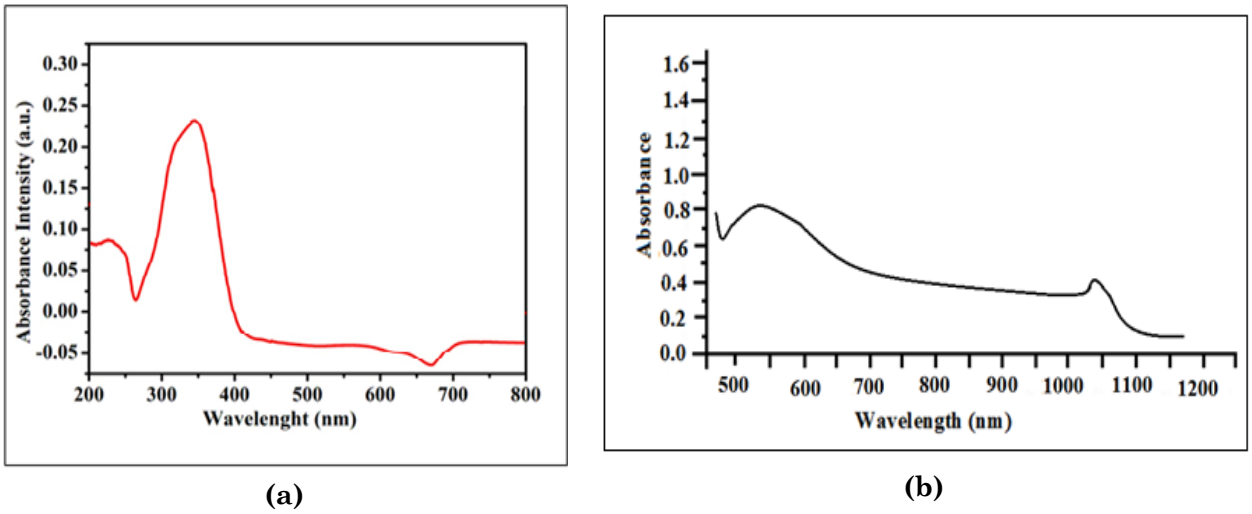
The elemental analysis data of synthesized Schiff bases and their cobalt complexes were found to be consistent with the expected result. The analytical and physical data of all the synthesized Schiff bases (L_1 to L_5) and their Co(II) complexes (C_1 to C_5) are given in Table 1. Theoretical and experimentally observed values of elemental analysis of compounds are in good agreement with the molecular formula.

compound	Mol. Formula	Mol. Wt.	M.P. (°C)	Elemental analysis		
				C% Found (calc.)	H% Found (calc.)	N% Found (calc.)
L_1	$C_{26}H_{20}N_2O_4S$	456	231	68.43(68.41)	4.40 (4.39)	6.21 (6.14)
L_2	$C_{34}H_{24}N_2O_4S$	556	239	73.42 (73.26)	4.65 (4.48)	5.13(5.17)
L_3	$C_{26}H_{18}Br_2N_2O_4S$	614	233	50.18 (50.07)	2.93 (2.86)	4.56 (4.48)
L_4	$C_{28}H_{24}N_2O_6S$	516	249	65.16(65.12)	4.80 (4.74)	5.53 (5.48)
L_5	$C_{26}H_{18}Cl_2N_2O_4S$	524	260	60.46 (60.33)	3.48 (3.41)	5.42 (5.35)
C_1	$C_{26}H_{22}N_2O_6SCo$	549	347	57.19 (56.97)	4.08 (4.00)	5.37 (5.13)
C_2	$C_{34}H_{26}N_2O_6SCo$	649	332	62.98 (62.89)	4.09 (4.03)	4.37 (4.31)
C_3	$C_{26}H_{20}N_2O_6SBr_2Co$	705	319	45.07 (44.56)	2.93 (2.86)	4.12 (3.99)
C_4	$C_{28}H_{26}N_2O_8SCo$	609	352	56.23 (55.34)	4.37 (4.30)	4.77 (4.63)
C_5	$C_{26}H_{20}N_2O_6SCl_2Co$	617	324	51.76 (50.77)	3.32 (3.25)	4.66 (4.55)

Table 1. Elemental analysis data of Schiff base ligands and their Co(II) complexes

Electronic spectral studies and Magnetic moment studies

An electronic absorption spectra of Co(II) Schiff base complexes were recorded at room temperature and the results are shown in Table 2 and Figure 2 respectively. The electronic spectra of C_1, $C_2$and C_3 showed three absorption bands. The first two were in the range 248-290 nm, which are due to π → π*transition of the aromatic ring and the third one was in the range 345-399 nm, which was assigned to n→ π* transition of azomethine group (C=N) The UV-Visible spectrum of $C_4$and C_5 showed two absorption bands. First, one was at 255 and245 nm respectively, which was attributed to π → π* transition of the aromatic ring, and the second one at around 310 and 342 nm, which was assigned to n → π* transition of azomethine group(C=N) of Schiff base. The magnetic moment values of Co(II) complexes were observed in the range of 4.37 to 5.08B.M (Table 2) because of high-spin magnetic moments, corresponding to the unpaired electrons. It appears from the magnetic moment data of Co (II) complexes that they are paramagnetic in nature and hence, are of six-coordinate complexes [31].



(a) **(b)**

Figure 2: The UV- Vis bands of **(a)** L_1 Schiff bases and **(b)** C_1 complexes

Table 2: Electronic spectral and magnetic moment values for Co(II) metal complexes

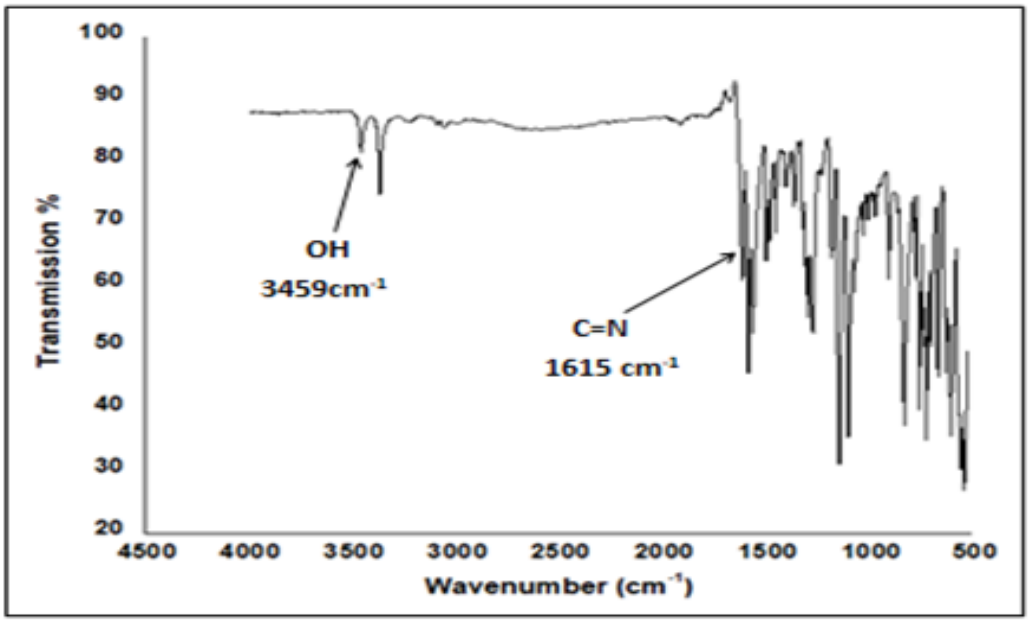
Complex	λ_{max} (nm)	Band assignments	$\mu_{eff.}$ (BM)
C_1	248 289 345	π-π* π-π* n-π*	4.47
C_2	250 283 399	π-π* π-π* n-π*	4.37
C_3	277 290 375	π-π* π-π* n-π*	5.08
C_4	255 310	π-π* n-π*	4.86
C_5	245 342	π-π* n-π*	4.68

FT- IR spectral studies

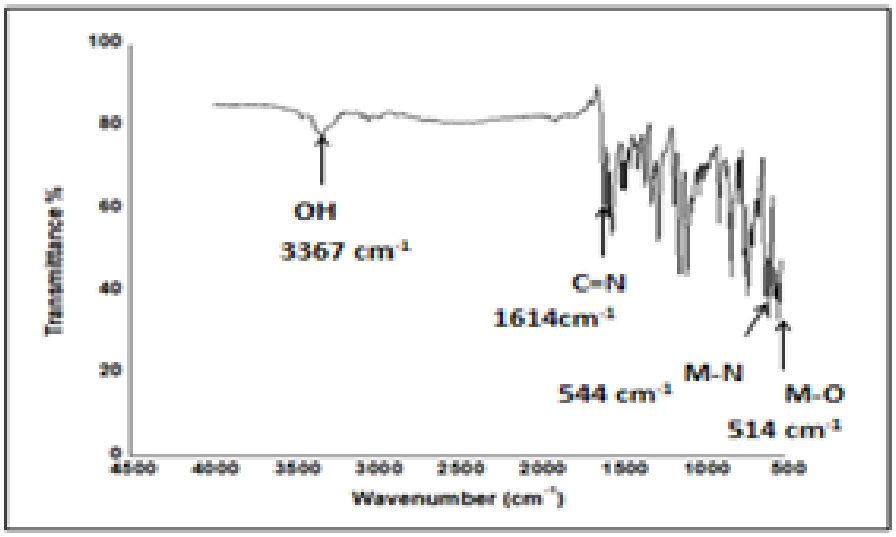
The formation of Co (II) complexes were confirmed as important shifts in azomethine group (C=N) and phenolic -OH bands by comparing the infrared spectroscopic data of metal complexes and their respective ligands. The IR spectral data of metal complexes are presented in Table 3. and Figure 3. The stretching vibrational band observed around 1627-1614 cm^{-1} is a characteristic of the azomethine (C=N) nitrogen atom present in the free Schiff base ligand. Due to metal coordination, the expected typical imine band in the range 1620-1596 $cm^{-1}$was observed in the Co(II) complexes. In addition, the –OH stretching and bending vibrational frequencies of the substituted salicylaldehyde appeared in the region 3459-3427 cm^{-1} The disappearance of these two peaks in the spectra of all the Co(II) complexes indicates that the coordination takes place via the enolic –OH group. Furthermore, the presence of a broad band at around 3435 - 3367 cm^{-1}in the Co(II) complexes suggests the presence of coordinate water molecules to the central metal ion [32-34]. Additional evidence for the coordination of the azomethine nitrogen is the presence of ν (M-N) bands in the frequency range of 562-544cm^{-1} and ν (M-O) bands in the frequency range of 517-505cm^{-1} [35-37]. It is noteworthy to see the unchanged band position of sulphonyl groups suggests that sulphone is not taking part in the coordination. Figure 3b and Figures S6-S9) [38-39].

Table 3: FT-IR absorption bands (in cm^{-1}) of the Schiffbases and their Co(II) complexes.

Compound	υ(OH/H_2O)	υ(C=N)	υ(M-N)	υ(M-O)
L_1	3459	1615	-	-
L_2	3434	1619	-	-
L_3	3427	1621	-	-
L_4	3432	1614	-	-
L_5	3457	1627	-	-
C_1	3367	1614	544	514
C_2	3433	1620	552	511
C_3	3435	1610	562	510
C_4	3402	1596	547	505
C_5	3369	1601	552	517



(a)



(b)

Figure 3: FT-IR spectra of L_1 and C_1 complex.

^{1}H–NMR spectral studies

The ^{1}H-NMR spectra of all the synthesized Schiff base ligands were recorded in DMSO solvent and expressed in ppm. The ^{1}H–NMR spectra of the synthesized compounds exhibit signals due to aromatic protons as a multiplet at 6.49-8.23 ppm. In the ^{1}H–NMR spectrum of the Schiff base ligands, a singlet observed downfield around 12.56-12.92 ppm, integrating for one proton, is assigned to –OH [40]. Similarly, the azomethine proton (attached to the carbon close to the nitrogen atom) appears around 8.68-8.80 ppm as a singlet signal [41]. Representative proton ^{1}H–NMR spectra of L_4 are shown in Figure 4

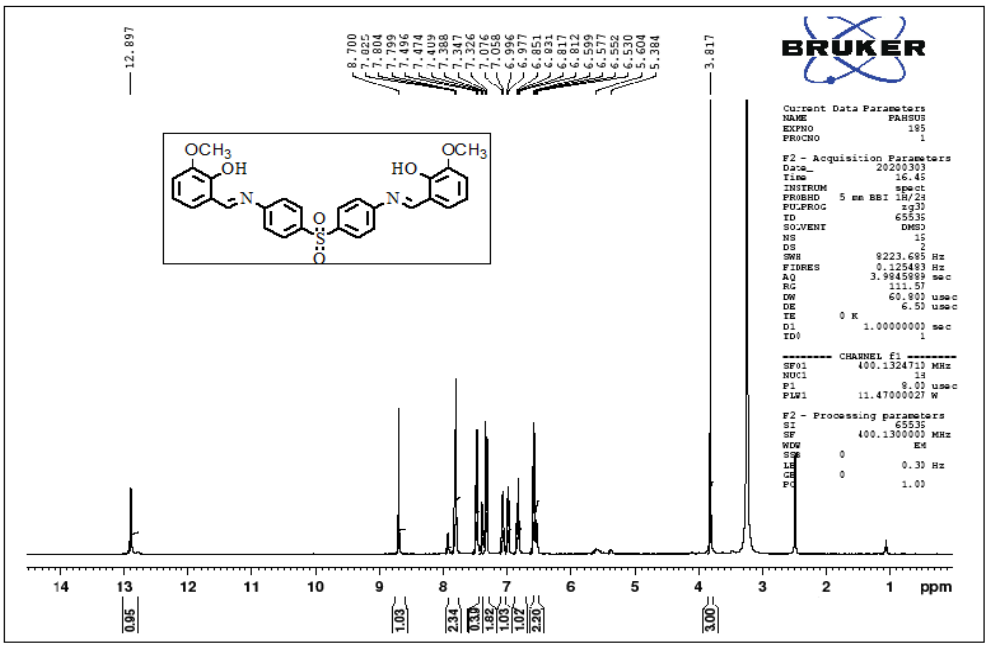
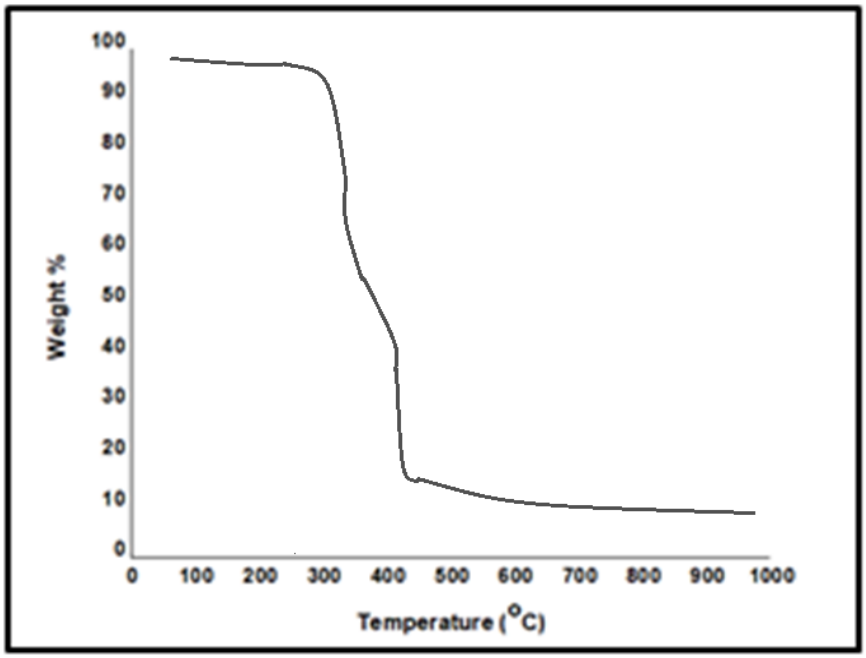


Figure 4: ^{1}H-NMR spectra of Schiff base ligand L_4.

Thermogravimetric analysis

The loss of water molecules was observed below 150°C, which is due to the presence of lattice water molecules [42, 43]. This further tells us that the coordinated water molecules occupy some position in the coordination sphere of the central metal ion, these water molecules are more strongly bonded to the metal ions thus eliminated at the higher temperatures. Further rise in the temperature leads to the loss of mass which may be caused due to decomposition of metal complexes by fragmentation and thermal degradation of organic parts and at the end,

the metal oxide was formed as residue [44]. The thermal data are provided in Table 4 and representative thermal graphs of Co (II) complexes C_1 is shown in Figure 5.



(a)

Figure 5: TGA-DTA graphs of an (a) C_1 complex.

Table 4: Stepwise thermal decomposition of Co (II) metal complexes.

Compound	Thermogravimetry (TG)		Mass loss (%)		Decomposition product loss
	Stage	Temp (°C)	Found	Calculated	
C_1	I	120-250	7.05	6.55	$-2H_2O$
	II	250-440	80.74	82.91	Organic moiety
	III	440-1000	11.02	10.19	-CoO
C_2	I	120-260	6.11	5.47	$-2H_2O$
	II	260-410	81.03	82.98	Organic moiety
	III	410-1000	10.91	11.55	-CoO
C_3	I	120-320	6.14	5.11	$-2H_2O$
	II	320-425	83.69	84.26	Organic moiety
	III	425-1000	11.11	10.63	-CoO
C_4	I	120-305	7.02	5.91	$-2H_2O$
	II	305-410	82.31	81.79	Organic moiety
	III	410-1000	10.96	12.30	-CoO
C_5	I	120-250	4.96	5.83	$-2H_2O$
	II	250-450	83.03	82.03	Organic moiety
	III	450-1000	12.35	12.14	-CoO

Antibacterial and antifungal activities

Antibacterial activity of synthesized Co(II) complexes was carried out using different pathogens which include Gram-positive *Bacillus Subtilis* and *Staphylococcus aureus* and Gram-negative *Klebsiella Species*, *E. coli*, and *Pseudomonas aeruginosa* and fungal pathogens *Aspergillus niger* and *Candida albicans* (Figure 9) Antibacterial activity against DMSO and standard drugs Ciprofloxacin and Nystatin were also carried out. Bacterial and fungal pathogens showed

the different zone of inhibitions against cobalt complexes (Figure 8).

Considering the case of *Bacillus Subtilis*, for synthetic complex compounds (C_1 - C_5) and DMSO, there was no zone of inhibition observed. The zone of inhibition for the standard drug Ciprofloxacin was 32 mm. However, in the case of *Staphylococcus aureus*, for synthetic compounds, C_1, C_3, C_4, and C_5 the zone of inhibition was 16, 16, 27, and 20, respectively. There was no zone of inhibition in the case of C_2 and DMSO. The zone of inhibition for the standard drug Ciprofloxacin is 30 mm. Similarly, for *Klebsiella pneumonia*, for synthetic compounds, C_3, and C_4 the zone of inhibition was 8 and 16 mm, respectively. There was no zone of inhibition in the case of C_1, C_2, C_5, and DMSO. The zone of inhibition for the standard drug Ciprofloxacin is 28 mm. Similarly, with *E. coli*, for synthetic compounds, C_2, C_4, and C_5 the zone of inhibition was 15, 36, and 30 mm, respectively. There was no zone of inhibition in the case of C_1, C_3, and DMSO. The zone of inhibition for the standard drug Ciprofloxacin was 30 mm. In the case of *Pseudomonas aeroginosa,* for synthetic compounds, C_4, and C_5 the zone of inhibition was 16 and 12 mm, respectively. There was no zone of inhibition in the case of C_1, C_2, and DMSO. The zone of inhibition for the standard drug Ciprofloxacin was 28 mm.

It is interesting to note that all the Schiff bases and their Co(II) complexes showed antibacterial activity against Gram-positive and Gram-negative bacteria (Table 5 and Table 6). It indicates the broad spectrum ability of these compounds against the different pathogens. Ciprofloxacin as a standard drug and DMSO as a control were used for all bacterial species.The Schiff base L_4 showed the highest antibacterial activity when compared with the other ligands (Figure 7 and 9). These compounds are not only active against bacteria but also exhibit antifungal activity Further, L_4 exhibited strong antifungal activity against *Aspergillus niger*. It is noteworthy that antifungal activity is more than the standard antifungal drug Nystatin.

On the other hand, It was observed from these results that the Co (II) complexes were less effective against both Gram positive and Gram negative also only a few complexes shows antifungal activities. There was no zone of inhibition shown by any cobalt complex against *Bacillus subtilis*. Out of five cobalt metal complexes only C_4 showed antibacterial activity against both Gram positive, Gram-negative, and fungal pathogens Figure 8 and 9

Table 5: Antibacterial and Antifungal activities of Schiff bases.

Microorganisms	**L_1**	**L_2**	**L_3**	**L_4**	**L_5**	**DMSO**	**Standard**[a]
	Zone of growth inhibition in diameter (mm)						
Gram Positive							
Bacillus subtilis	23	18	-	27	21	-	40
Staphylococcus aureus	15	14	-	17	16	-	30
Gram negative							
Klebsiella pneumonia	-	-	14	16	12	-	36
Escherichia coli	13	15	16	18	15	-	26
Pseudomonas aeruginosa	-	14	12	18	-	-	36
Fungal pathogens							
Aspergillus niger	22	27	14	36	26	-	17
Candida albicans	16	16	12	13	18	-	30

[a]**Standard used for antibacterial and antifungal activity was Ciprofloxacin and Nystatin respectively.**

Table 6: Antibacterial and Antifungal activities of Co (II) complexes.

Microorganisms	**C_1**	**C_2**	**C_3**	**C_4**	**C_5**	**DMSO**	**Standard[a]**
	Zone of growth inhibition in diameter (mm)						
Gram Positive							
Bacillus Subtilis	-	-	-	-	-	-	32
Staphylococcus Aureus	16	-	16	27	20	-	30
Gram Negative							
Klebsiella pneumonia	-	-	08	16	-	-	28
Escherichia coli	-	15	-	36	30	-	30
Pseudomonas aeruginosa	-	-	-	16	12	-	28
Fungal Pathogens							
Aspergillus niger	18	16	-	-	-	-	28
Candida albicans	15	-	-	13	-	-	29

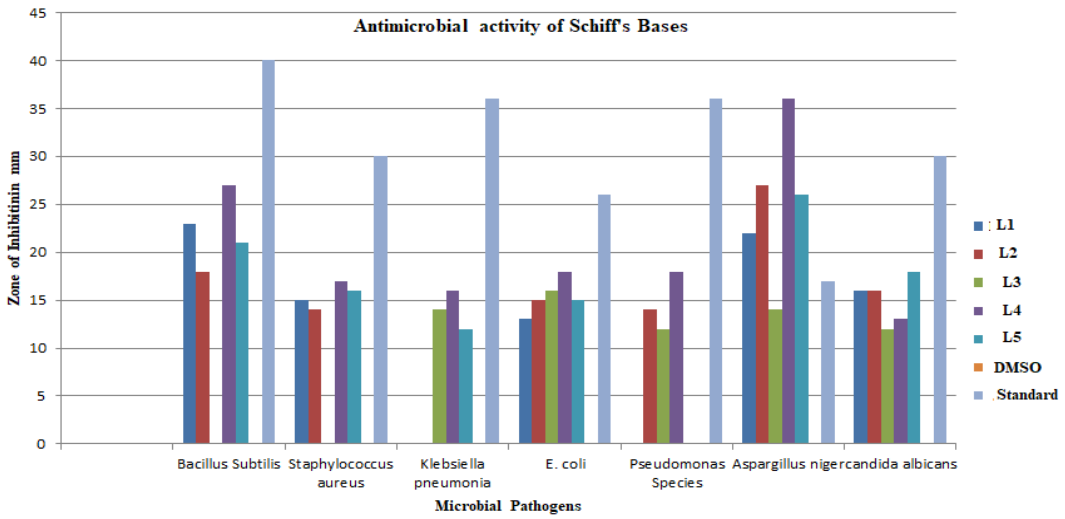


Figure 6: Graphical representation of **a**ntibacterial and antifungal activities of Schiff bases against bacterial and fungal pathogens

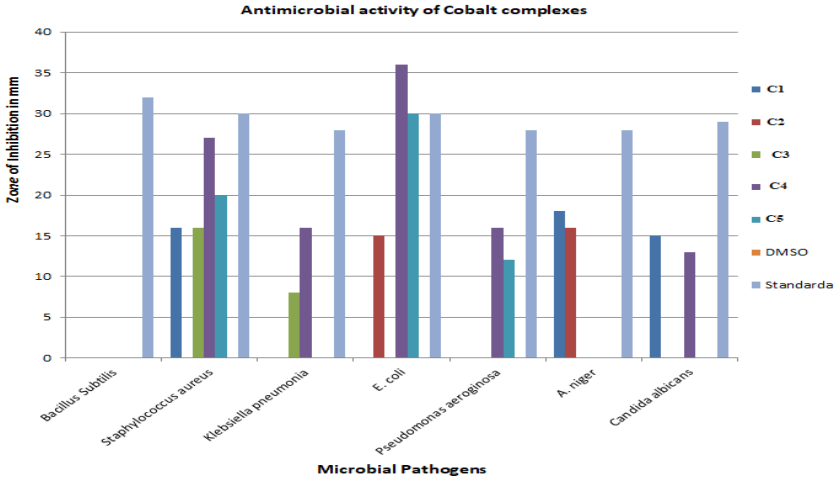
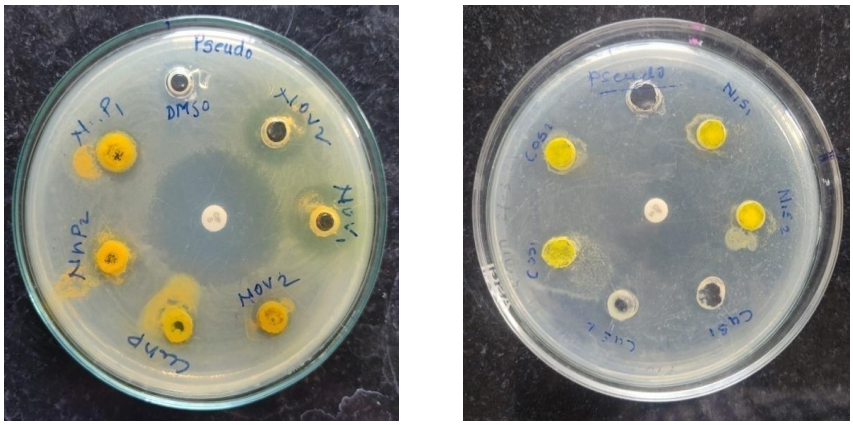


Figure 7: Graphical representation of **a**ntibacterial and antifungal activities of Co(II) complexes against bacterial and fungal pathogens.



Antibacterial activity against *Pseudomonas aeruginosa*

Figure 9: Zone of inhibition of Schiff base ligands (L_1- L_5) and their Co(II) complexes against *Pseudomonas aeruginosa*

Molecular docking studies

To know the most preferred conformation of all Schiff base ligands with protein PDB ID :1au2, we performed the docking study of each ligand for 10 confirmations. The best-docked conformation among 10 conformations was obtained with the least binding energy. The Binding values are -9.25 kcal/mol, -9.40 kcal/mol, -9.12 kcal/mol, -7.11 kcal/mol, +285.63 kcal/mol, for ligands CDK-7-L_1, CDK-7-L_2, CDK-7-L_3, CDK-7-L_4 and CDK-7-L_5, respectively(Table 7a).Further, the best-docked complexes were analyzed for hydrogen bonding interactions and hydrophobic interactions.

The results revealed that Arg179, ARG136, TYR190, and ARG188 residues of cysteine protease human cathepsin are involved in hydrogen bonding interactions. Whereas GLU99, ILE133, LEU134, ARG136, ASP137, LEU138, LYS139, PRO140, PHE156, GLY157, LEU158, PHE162, THR175, ARG176, TRP177, ARG179, LEU183, LEU184, ASP218, ARG188, MET189, TYR190 residues involved in hydrophobic interactions. Compound L_2 has the highest binding affinity followed by L_1, L_3, and L_4, whereas compound L_5 has the lowest affinity among all the docked ligands which is 285.63 K. Cal/ Mol. Further, the L_2 molecule and its interaction with amino acids like ARG188, TYR190, and PHE156 and hydrophobic and other interactions with, LUE158, LEU134, ARG136, ASP137, THR175, ARG176, ARG179, and PHE162. The highest binding affinity of L_2 than the other Schiff bases is mainly due to the involvement of ARG188in hydrogen bonding interaction and TYR190, LEU134, ARG136, ASP137, LEU158, THR175, ARG176, ARG179, and PHE162 in hydrophobic and other interaction with amino acid. Data of docking interactions 2D and 3D images are shown in Figure 10. Ligand L_1 has the highest binding affinity followed by L_3 L_4, and L_5 and whereas ligand L_5 has the lowest affinity among all the docked Schiff base ligands, which is 285.63 kcal/mol. On the other hand, the docking results of Co(II) complexes revealed that GLN22, PHE23 SER161, ARG136, ARG179, TYR 190, and ARG188 residues of cysteine protease human cathepsin are involved in hydrogen bonding interactions. Whereas ALA198, LEU183, ALA180, VAL194, TYR178, LYS139, THR175, ASP137, LEU138, LYS41, ASN142, and PHE162. residues involved in hydrophobic interactions, as depicted in Table. 7b The compound has C_2 highest binding affinity followed by C_3, C_5, and C_1, whereas compound C_5 has the lowest affinity among all the docked ligands that is -2.47 K. Cal/ Mol. Further, C_2 complex and its interaction with amino acids like LEU134, PHE156, ILE133, GLU62, LUE158, ILE55, ARG136, ASP137, PHE162, ARG176, and ARG179 are involved in hydrophobic and other interactions.

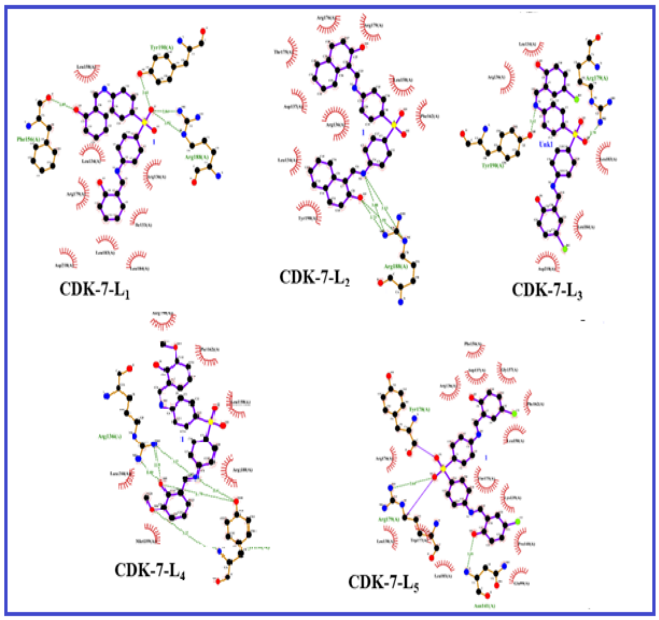


Figure 10: Binding interaction of Schiff base ligands (L_1-L_5) with CDK-7 protein.

Table 7a: The Binding values of Schiff base ligands with CDK-7 protein.

Compounds	Lowest Binding affinity (kcal/mol)	RMSD from reference structure (Å)	Hydrogen bond interaction	Hydrogen Bond length in Å	Hydrophobic and Other interactions
CDK7-L_1	-9.25	42.421	PHE136	2.85	LEU158, LEU134, ARG179, LEU183, ILE133, ARG136, LEU184, ASP218
			ARG188	2.81	
				2.84	
			TYR190	2.61	
CDK7-L_2	-9.40	35.068	ARG 188	2.59	TYR190, LEU134, ARG136, ASP137, LEU158, THR175, ARG176,ARG179, PHE162
				2.73	
				3.08	
				3.13	
CDK7-L_3	-9.12	37.191	ARG179	2.79	LEU134, ARG136,LEU183, LEU184,ASP218
			TYR190	3.02	
CDK7-L_4	-7.11	43.983	ARG136	2.89	ARG179, PHE162, LEU158, ARG188, MET189, LEU134
				2.95	
				3.27	
			TYR190	3.27	
				2.6	
CDK7-L_5	+285.63	35.985	ARG179	2.64	GLU99, LYS139, PRO140, TRP177, THER175, ARG176, ARG136, LEU183, LEU138, LEU158,GLY157, PHE162
			ASN141	3.05	

Table 7b: The Binding values of Co(II) metal complexes with CDK-7 protein

Compounds	Lowest Binding affinity (kcal/mol)	RMSD from reference structure(Å)	Hydrogen bond interaction	Hydrogen Bond length in Å	Hydrophobic and Other interactions
CDK-7-C_1	-2.47	39.661	GLN22	2.46	ALA198, LEU183, ALA180, VAL194, TYR178, LYS139, THR175, ASP137, LEU138, LYS41, ASN142, PHE162
			PHE23	3.22	
			SER161	2.56 2.94	
			ARG136	2.36	
			ARG179	2.64	
CDK-7-C_2	-8.09	42.083	TYR190	2.80	LEU134, PHE156, ILE133, GLU62, LEU158, ILE55 ARG136, ASP137, PHE162, ARG176, ARG179
CDK-7-C_3	-4.18	43.033	ARG188	3.00 2.53	MET189, ILE55, PHE162, LEU134
			TYR190	3.25	
CDK-7-C_4	-3.00	41.939	ARG188	3.08 2.98	MET189, PHE162, ILE55, GLY163, PRO165
			TYR190	2.79 2.81	
CDK-7-C_5	-3.92	42.169	ARG188	2.99	MET189, LEU134, LEU158, PHE162, ILE55
			TYR190	2.90 2.56	

Conclusions

To sum up, the synthesized Schiff bases act as a tetradentate ligand and coordinated with the Co (II) ion through imine nitrogen and phenolic oxygen atoms. The binding of ligand to a metal ion is confirmed by elemental analysis, spectral studies (UV-Visible and FT-IR), and TGA measurements. The Co (II) complexes are found to exhibit octahedral geometry. All the Schiff bases (L_1-L_5) and their Co (II) complexes showed moderate to good antimicrobial activities against the tested microbial species.

The docking studies showed that among all the five Schiff base Ligands (**L_1**-**L_5**) ligand **L_2** has the best and most significant binding free energy (Gibbs free energy) value is -9.40 kcal/mol which is the least energy. Therefore compound **L_2** has the highest binding affinity followed by **L_1**, **L_3**, **L_4** and **L_5**. Schiff base **L_5** has the lowest affinity among all the docked ligands which is 285.63 kcal/ mol. Similarly, complex Co-L_2 has the highest binding affinity followed by Co-L_3, Co-L_5, Co-L_4 and Co-L_1, whereas compound Co-L_1 has the lowest affinity among all the docked complexes. Based on these observations, compounds have good stability within the protein cavity and are anticipated to show enhanced anticancer activity.

References

1. A.A. Khandar, K. Nejati, Z. Rezvani, *Molecules* **2005,** 10, 302.
2. A.E. Martell, D.T. Sawyer, Oxygen-Co complexes and Oxygen Activation by Transition Metals.Plenum Press, New York, **1998.**
3. T. Nagata, K. Yorozu, T. Yamada, T. Mukaiyama, *AngewandteChemie International Edition in English* **1995,** 34, 2145.
4. G.L. Estiu, A.H. Jubert, J. Costamagna, J. Vargas, *Inorganic chemistry* **1996,** 35, 263.
5. Y.L. Zhang, W.J. Ruan, X.J. Zhao, H.G. Wang, Z.A. Zhu, *Polyhedron* **2003,** 22, 1535.
6. R. Cini, S.J. Moore, L.G. Marzilli, *Inorganic chemistry* **1998,** 37, 6890.
7. R. Sethi, M. Ahuja, *International Journal of PharmTech Research* **2016,** 9, 35.
8. P. Ghosh, A.R. Chowdhury, S.K. Saha, M. Ghosh, M. Pal, N.C. Murmu, P. Banerjee, *InorganicaChimica Acta* **2015,** 429, 99.
9. M. Ghosh, M. Layek, M. Fleck, R. Saha, D. Bandyopadhyay, *Polyhedron***2015,** 85, 312.
10. U. Singh, A.M. Malla, I.A. Bhat, A. Ahmad, M.N. Bukhari, S. Bhat, A.A. Hashmi, *Microbial pathogenesis* **2016,** 93, 172.
11. E. Canpolat, H. Şahal, M. Kaya, S. Gur, *Journal of the Chemical Society of Pakistan* **2014,** 36, 149.
12. A.E. Mil'grom,A.S. Chegolya, A.V. Filippova, G.V.Vladyko, N.I. Karako, *Pharmeutical Chemistry Journal* **1984,** 18, 179.
13. D. Jayaraju, Y.V. Gopal, A.K. Kondapi, *Archives of biochemistry and biophysics* **1999,** 369, 68.
14. N. Wang, Q.Y. Lin, J. Feng, Y.L. Zhao, Y.J. Wang, S.K. Li, *InorganicaChimica Acta* **2010,** 363, 3399.
15. C.R. Munteanu, K. Suntharalingam, *Dalton Transactions* **2015,** 44, 13796.
16. P. Ghosh, A.R. Chowdhury, S.K. Saha, M. Ghosh, M. Pal, N.C. Murmu, P. Banerjee, *Inorganica Chimica Acta* **2015,** 429, 99.
17. A.P. King, H.A. Gellineau, J.E. Ahn, S.N. MacMillan, J.J. Wilson, *Inorganic Chemistry* **2017,** 56, 6609.
18. S. Banerjee, A.R. Chakravarty, *Accounts of chemical research***2015,**48, 2075.
19. D.J. Wasylenko, C. Ganesamoorthy, J. Borau-Garcia, C.P. Berlinguette, *Chemical Communications* **2011,** 47, 4249.
20. G. Cahiez, A. Moyeux, *Chemical Reviews* **2010,** 110, 1435.
21. C.H. Peng, T.Y. Yang, Y. Zhao, X. Fu, *Organic & biomolecular chemistry* **2014,** 12, 8580.
22. D. Jayaraju, Y.V. Gopal, A.K. Kondapi, *Archives of biochemistry and biophysics,***1999**, 369, 68.
23. P. Ghosh, A.R. Chowdhury, S.K. Saha, M. Ghosh, M. Pal, N.C. Murmu, P. Banerjee, *Inorganica Chimica Acta* **2015,**429, 99
24. A.P. King, H.A. Gellineau, J.E. Ahn, S.N. MacMillan, J.J. Wilson, *Inorganic Chemistry,***2017**, 56, 6609.
25. S. Banerjee, A.R. Chakravarty, *Accounts of Chemical Research,***2015**, 48, 2075.
26. S. Mirdya, M.G. Drew, A.K. Chandra, A. Banerjee, A. Frontera, S. Chattopadhyay, *Polyhedron,***2020**, 179, 114374
27. Z. Albobaledi, M.H. Esfahani, M. Behzad, A. Abbasi, *Inorganica Chimica Acta,***2020**, 499, 119185

28. R. Bikas, P. Mirzakhani, N. Noshiranzadeh, J. Sanchiz, M.S. Krawczyk, D.A. Kalofolias, T. Lis, Inorg Chim Acta, **2020,**505, 119461.
29. A.A. Nejo, G.A. Kolawole, A.O. Nejo, *Journal of coordination chemistry* **2010,** 63, 4398.
30. L.A. Saghatforoush, F. Chalabian, A. Aminkhani, G. Karimnezhad, S. Ershad, *European Journal of Medicinal Chemistry* **2009,** 44, 4490.
31. M. Sebastian, V. Arun, P.P. Robinson, P. Leeju, D. Varghese, G. Varsha, K.K. Mohammed Yusuff, *Journal of Coordination Chemistry* **2010,** 63, 307.
32. A. Barakat, S.M. Soliman, M. Ali, A. Elmarghany, A.M. Al-Majid, S. Yousuf, A. El-Faham, *InorganicaChimica Acta* **2020,** 503, 119405.
33. K. Ghosh, T. Dutta, M.G. Drew, A. Frontera, S. Chattopadhyay, *Polyhedron* **2020,** 198, 114432.
34. X.Q. Luo, Q.R, Liu, Y.J. Han, L.W. Xue, *Acta ChimicaSlovenica* **2020,** 67, 159.
35. Z. Hricovíniová, M. Hricovíni, K. Kozics, *Chemical Papers* **2018,** 72, 1041.
36. B. Tang, T. Yue, J. Wu, Y. Dong, Y. Ding, H. Wang,*Talanta,* **2004**, 64, 955.
37. E. Tas, A. Kilic, M. Durgun, I. Yilmaz, I. Ozdemir, N. Gurbuz. *Journal of OrganometallicChemistry,* **2009**, 694, 446.
38. G. Venkatachalam, R. Ramesh, *Inorganic Chemistry Communications,* **2006**, 9, 703
39. R.G. Kalkhambkar, G.M. Kulkarni, C.M. Kamanavalli, N. Premkumar, S.M. Asdaq, C.M. Sun, *European Journal of Medicinal Chemistry,* **2008**, 43, 2178.
40. R.Ramu, P.S. Shirahatti, F. Zameer, D.B. Lakkapa, M.N. Nagendra Prasad, *International Journal of Pharmacy and Pharmaceutical Sciences* **2014,** 7, 136.
41. H.M. Vinusha, S.P. Kollur, H.D. Revanasiddappa, R. Ramu, P.S. Shirahatti, M.N. Prasad, M. Begum, *Results in Chemistry* **2019,** *1*, 100012.
42. N.Razali, R. Razab, S.M. Junit, A.A. Aziz, *Food chemistry* **2008,** 111, 38.
43. J. Dundas, Z. Ouyang, J. Tseng, A. Binkowski, Y. Turpaz, J. Liang, *Nucleic Acids Research,* **2006**, 34, 116.
44. R.A. Laskowski, M.B. Swindells, *Journal of Chemical Model*, **2011**, 51, 2778
45. Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J.T.; Bokesch, H.; Kenney, S.; Boyd, M.R. New colorimetric cytotoxicity assay for anticancer-drug screening. J Natl Cancer Inst.,**1990,** 82, 1107.