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Review Article

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Biological Utility of Palladium, Cobalt, Copper Schiff Base Complexes: New Approach towards Nanomedicines

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Abstract

With the aim to discover molecules which can treat different diseases in the nanomolar scale, various researchers are investigating the properties of transition metal complexes of Schiff base (SB) ligands. These ligands are versatile ones, containing an azomethine group (-CH=N-). They behave as good ancillary ligands since they can be easily synthesized by condensation reaction between primary amines and carbonyl derivative and can form transition metal complexes easily. These complexes have exhibited huge potential in medicinal and pharmaceutical fields as they show a broad range of biological activities. Among these activities, antibacterial as well as antifungal activities were found to be quite prominent. Various research groups have explored the interactions of different transition metal complexes of SB ligands with both gram-positive and gram-negative bacteria as well as with various strains of fungi. Herein, a brief overview of the syntheses and biological activities of different SB ligands along with their palladium (Pd), cobalt (Co), and copper (Cu) complexes was presented.

Keywords

Schiff base ligands, Transition metal complexes, Antibacterial activity, Gram positive bacteria, Gram negative bacteria, Antifungal activity

Introduction

Different techniques involving nanotechnology is developing in leaps and bounds, due to the extensive research work being carried out by different research groups. As part of this development, nanomedicines are also being investigated and designed at a rapid pace [1]. In order to develop nanomedicines, various research groups are trying to discover nanomaterials, which can either be used for detection or for the control of different diseases. Diseases caused by various microbes till afflict our society to a great extent. Hence, researchers have been trying to design medicines, from the molecular level, which can control such microbes. Various classes of molecules have been designed and their bioactivity have been explored to design nanomedicines based on these molecules. One such type of compound is the transition metal complexes of SB ligands.

SB compounds were discovered by Hugo Schiff in 1864 and have a general formula $R_2C=NR'$. These are classified as a subclass of imines and can be synthesized by nucleophilic addition of an aromatic or aliphatic amine and a carbonyl compound [2, 3] These serve as ancillary ligands in the formation of complexes with various metal ions, especially with different transition metal (For example, Pd, Co, Cu, etc.). It has been found that SB metal complexes have various applications in catalysis [4], biological activities [5], and in sensing [6].

These transition metal complexes of SB ligands exhibits different types of biological activities such as antibacterial, antifungal, etc. For the determination of antimicrobial activity, *in vitro* screening are performed on SB ligands and their metal complexes against different microbial strains of bacteria and fungus. In addition, various standard antimicrobial drugs were used as positive controls in these experiments. Streptomycin [7], ciprofloxacin, nalidixic acid, gentamicin, kanamycin, tetracycline [8], etc. are the standard antibacterial drugs whereas fluconazole, nystatin [9, 10], clotrimazole, etc. are the different standard antifungal drugs used.

In order to explore the antimicrobial activity of any metal complex, zone of inhibition and minimum inhibitory concentration (MIC) values are determined [11]. The zone of inhibition is the circular area around the spot of antibiotic in which the microbial colonies do not grow. The zone of inhibition can be used to measure the susceptibility of any microbe towards any antibiotic substance. Similarly, the MIC value of an antibiotic substance is the lowest concentration at which bacterial growth is completely inhibited [12].

Exploring the different transition metal Schiff base complexes

In 2021, H. Kargar and co-workers published the synthesis and antibacterial activity of SBs and their Cu complexes [13]. The SB ligands (L1a-d) were prepared by mixing 4-aminoantipyrene and 3-methoxysalicylaldehyde (L1a), 4-methoxysalicylaldehyde (L1b), 5-methoxysalicylaldehyde (L1c), 6-methoxysalicylaldehyde (L1d) in ethanol (Figure 2). The mixture was stirred at room temperature for 1 h to obtain yellow crystals of SB ligands. From these ligands (L1a-d), Cu complexes were synthesized by adding copper acetate monohydrate to a hot methanolic solution of the ligands. This resulting mixture was stirred at reflux temperature for 3 h upon which precipitate of metal complexes were formed. Four different copper complexes were obtained in 69-81 % yield respectively. *In vitro* antibacterial studies of all the formed compounds were performed against different strains of bacteria as *Escherichia coli* and *Staphylococcus aureus*. Standard antibacterial drug streptomycin was used as positive control for comparison with synthesized compounds. Ligands, (L1a-d) and their Cu complexes showed good abilities to inhibit bacterial growth which were shown in Table 1 as their MIC

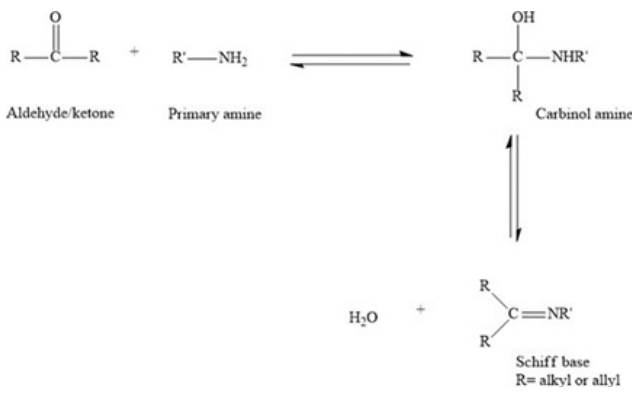

Figure 1: Mechanism of synthesis of Schiff base ligand.

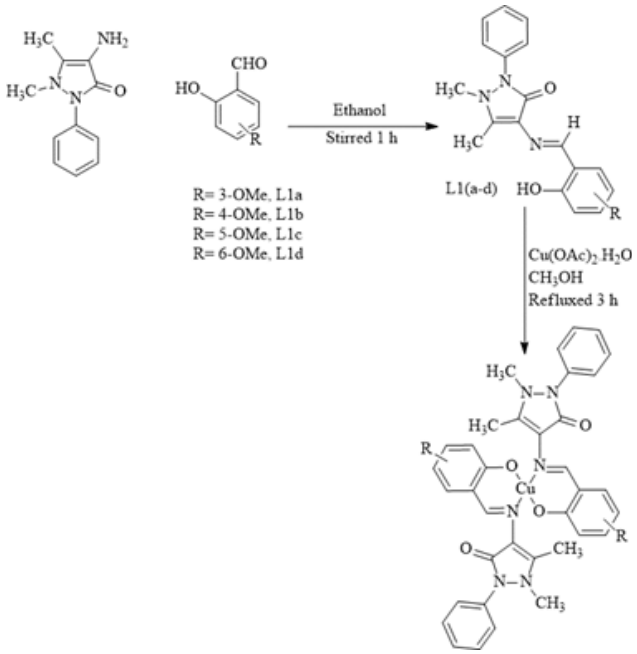

Figure 2: Synthesis of ligands (L1a-d) and their copper complexes.

values. These transition metal complexes can be utilized as effective nanomedicines, since their antimicrobial activity can be observed in the nanoscale range. As an added advantage, the syntheses of these molecules are also quite simple. Maiti and co-workers reported the formation of a different SB ligand and its Cu, Co, and Pd complexes and studied their antimicrobial activity in 2020 [14]. Ligand (L2) was obtained by adding ethanolic solution of 2-benzylthioaniline in solution of 2-hydroxy-4-methoxybenzaldehyde with continuous stirring (Figure 3).

The orange yellow reaction mixture thus formed was refluxed for 30 min and kept undisturbed for 6 h at room temperature. Yellow crystalline product was obtained with 90% yield. For synthesizing Cu and Co complexes, L2 was dissolved in boiling methanol and then methanolic solution of sodium hydroxide was added to it. To the formed solution, boiling methanolic solution of copper acetate monohydrate and cobalt chloride tetrahydrate was added respectively. The mixture was stirred for 30 min upon which color of the solution changed to dark brown. Then this solution was kept undisturbed for a day. Dark yellow crystals of Cu and black colored crystals of Co complex were formed which were obtained in 72% and

Table 1: Antibacterial activity of L1a-d and copper complexes.

	MIC (µg/ml)	
Sample	***E. coli***	***S. aureus***
L1a	512	256
L1b	256	128
L1c	128	64
L1d	256	256
$Cu(L1a)_2$	128	32
$Cu(L1b)_2$	64	32
$Cu(L1c)_2$	64	32
$Cu(L1d)_2$	64	64
Streptomycin	8	4

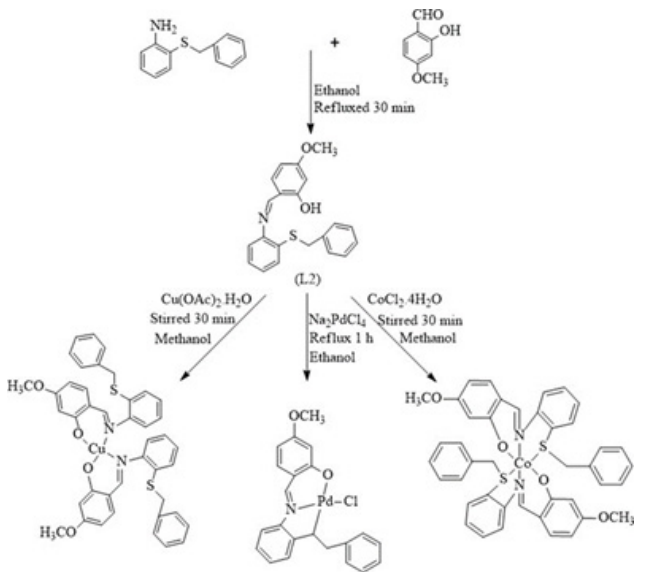

Figure 3: Synthesis of ligand (L2) and its Cu, Pd, and Co complexes.

67% yield, respectively. For synthesizing Pd complex, ethanolic solution of sodium tetrachloropalladate was added to a ligand solution. The mixture was heated at 78 °C for 1 h. Orange-red crystals of Pd complex was obtained with 79% yield. Ligand (L2) and its transition metal complexes were tested for antibacterial activities against different strains of bacteria, like *S. aureus*, *E. coli*, *Bacillus subtilis*, *Pseudomonas syringae*, *Mycobacterium smegmatis*, *Proteus vulgaris,* and *Proteus abscessus*. Kanamycin was used as standard reference drug for the bacterial strains. The antibacterial study data of ligand and its complexes with their inhibition zone are shown in Table 2. As shown below, the zone of inhibition for each molecule was tested utilizing 10 nanogram/microlitre of the transition metal complexes, in addition to that of the SB ligand. This data is extremely interesting, due to the fact that such molecules can be effectively used as nanomedicines.

In 2019, N. Turan and co-workers described the synthesis and antimicrobial studies of SB Co complex [15]. The SB ligand L3 was synthesized according to the previously reported procedure by N. Turan and co-workers in 2017, by adding o-vanillin to an ethanolic solution of substituted aromatic amine. The reaction mixture was allowed to reflux at 78 °C for 2 h and a pale yellow crystalline product of SB ligand was obtained with 80% yield [16]. In 2019, N. Turan et al. used this ligand to synthesize Co SB complex. Co complex was synthesized by adding $CoCl_2.6H_2O$ and SB ligand in ethanolic solutions. This mixture was heated at boiling temperature for 3 h upon which brick colored Co complex was obtained with 80% yield (Figure 4). Synthesized ligand and its Co complex were screened for their antimicrobial activities against different bacterial and fungal strains. Different bacterial strains used were *B. subtilis*, *S. aureus*, and *Bacillus megaterium* (gram positive), *Enterobacter aerogenes*, *P. aeruginosa*, *Klebsiella pneumoniae*, *E. coli* (gram negative). *Yarrowia lipolytica*, *Candida albicans,* and *Saccharomyces cerevisiae* are the different fungal strains used. Erythromycin, ampicillin/sulbactam, amikacin, rifampicin, and fluconazole were used as standard reference drugs for antibacterial and antifungal activity, respectively. The antimicrobial screening data were shown in Table 3.

In 2018, H. Pasdar and co-workers reported the synthesis and biological activity of SB Co complexes [17]. SB ligands (L4a-f) were prepared by condensation reaction between terepthalaldehyde and 2-aminophenol, o-nitroaniline and o-anisidine in two different molar ratio 1:2 and 1:1 in an ethanol. N-propyl-benzoguanamine-sulphonate catalyst was added to the above solution. The mixture was heated at reflux temperature for 2-3 h to obtain SB ligands (L4a-f) respectively, of varied color (Figure 5). From these ligands (L4a-f), Co complexes were synthesized by adding $CoCl_2.6H_2O$ to a methanolic solution of SB ligands in molar ratio 2:1 (M_2L) and 1:1 (ML) of metal salt and SB ligands, respectively. The resulting mixture goes through reflux condition for 3-5 h. Six different Co complexes were obtained as Co(L4a-f) in 68 - 87% yield, respectively (Figure 6).

Table 2: Antibacterial activity of L2 and its metal complexes.

	Zone of Inhibition (mm)						
Sample	**Concentration (µg/ml)**	*B. subtilis*	*S. aureus*	*M. abscessus*	*P. vulgaris*	*M. smegmatis*	*E. coli*
L2	10	6	5	6	7	4	4
$Cu(L2)_2$	10	7	12	7	11	8	6
$Co(L2)_2$	10	8	11	9	8	7	7
Pd(L2)Cl	10	8	10	9	12	6	8

Table 3: Antimicrobial activity of ligand and cobalt complex.

	Zone of Inhibition (mm)					
Compounds	***B. subtilis***	***S. aureus***	***E. coli***	***K. pneumoniae***	***C. albicans***	***S. cerevisiae***
L3	15 ± 1.0	15 ± 0.0	14 ± 1.0	23 ± 0.6	15 ± 0.0	18 ± 0.6
Co-complex	30 ± 1.0	32 ± 2.0	28 ± 1.0	28 ± 1.0	30 ± 1.0	33 ± 2.0
Erythromycin	20 ± 0.0	21 ± 1.0	19 ± 1.5	19 ± 1.7	-	-
Fluconazole	-	-	-	-	23 ± 1.5	-

Ligands and Co complexes were tested for their antibacterial activities against both strains of bacteria, i.e., gram positive (*B. subtilis* and *S. aureus*) and gram negative (*E. coli*, *Serratia marcescens,* and *P. aeruginosa*). For comparison, standard antibacterial drug tetracycline was used as reference. The antibacterial study result of L4a-f and Co(L4a-f) were shown in Table 4 as their MIC values. Even though these molecules showed promising antimicrobial activities with respect to the standard antibacterial drugs, their therapeutic effects have to be further investigated to develop them as nanomolecular medicinal drugs.

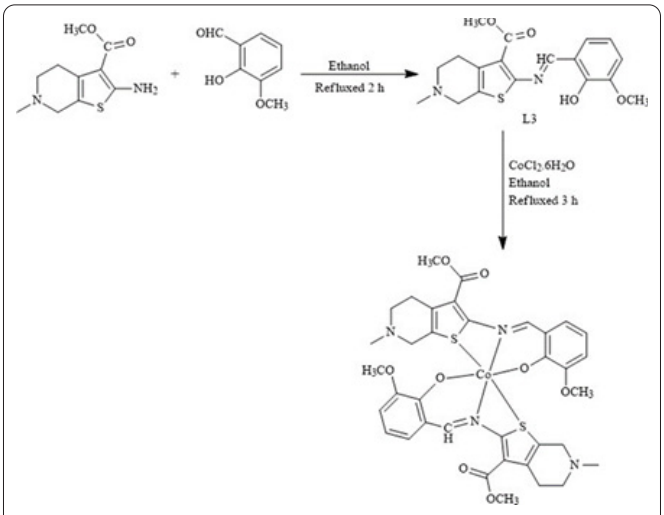

Figure 4: Synthesis of ligand (L3) and its Co complex.

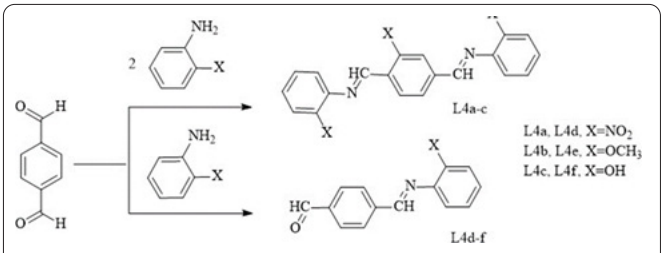

Figure 5: Synthesis of ligands (L4a-f).

In 2018, J. Yadav et al. described the formation of Cu and Co SB complexes of isatin and studied their antimicrobial activity [18]. Ligands (L5a-b) were synthesized by reacting o-aminophenol derivatives with isatin in methanol and to this solution a few drops of acetic acid was added.

The reaction mixture thus formed was heated at 65 °C for 5 h to acquire solid product of ligands. With the help of above formed ligands, Cu and Co complexes were formed by adding methanolic solution of formed ligands to a solution of hydrated metal salt [$Co(NO_3)_2.xH_2O$ and $Cu(NO_3)_2.xH_2O$]. Then methanolic solution of 8-hydroxyquinoline was added to the above mixture and this mixture was refluxed for 4 h to obtain Cu and Co SB complexes (Figure 7). All the synthesized compounds were examined for their anti-microbial activity against bacteria (*P. aeruginosa*, *P. mendocina*, *B. subtilis,* and *Micrococcus luteus*) and fungi (*Cladosporium herbarium*, *Verticillium dahlia* ,and *Trichophyton soudanense*). Streptomycin and fluconazole were the standard drugs used for bacteria and fungi, respectively. The antimicrobial study data were shown in Table 5 as their zone of inhibition.

In 2018, K. Mahmood et al. reported the synthesis of SB and its Pd and Cu complexes and studied their antibacterial activities [19]. Ligand (L6) was synthesized by adding 4-(1H-benzoimidazole-2-yl)aniline and 5-bromosalicylaldehyde in dry ethanol (Figure 8). Mixture was heated for 6 h under refluxing condition. Orange colored precipitate of ligand was obtained with 81% yield. This ligand (L6) was used to synthesize Pd and Cu complexes. For synthesizing Pd complex, ligand was dissolved in hot ethanol and a solution of $Pd(CH_3COO)_2$ was added dropwise to the solution of L6 and the mixture was heated for 3 h. Dark brown precipitate of Pd complex was obtained in 65% complex was synthesized by adding solution of ligand and $Cu(CH_3COO)_2.2H_2O$ in EtOH and the mixture was stirred under reflux condition for 6 h. A greenish yellow precipitate of Cu complex was obtained with 80% yield. Ligand L6, Pd and Cu complexes were investigated for their antibacterial activity against gram negative bacteria (*E. coli* and *E. aerogenes*) and gram-positive bacteria

Table 4: Antibacterial activity of ligands (L4a-f) and cobalt complexes.

	MIC (mg/mL)				
Compound	***B. subtilis***	***S. aureus***	***E. coli***	***S. marcescens***	***P. aeruginosa***
L4a	2.5	10	5	5	2.5
L4b	2.5	10	2.5	5	2.5
L4c	1.25	5	5	2.5	0,31
L4d	-	-	-	-	-
L4e	2.5	1.25	2.5	5	2.5
L4f	2.5	2.5	2.5	2.5	1.25
CoL4a	1.25	2.5	2.5	2.5	2.5
CoL4b	1.25	5	10	2.5	1.25
CoL4c	0.15	2.5	1.25	0.31	0.15
CoL4d	2.5	1.25	1.25	1.25	0.62
CoL4e	1.25	1.25	1.25	0.62	0.62
CoL4f	1.25	1.25	2.5	1.25	0.62
Tetracycline	5	2.5	5	5	5

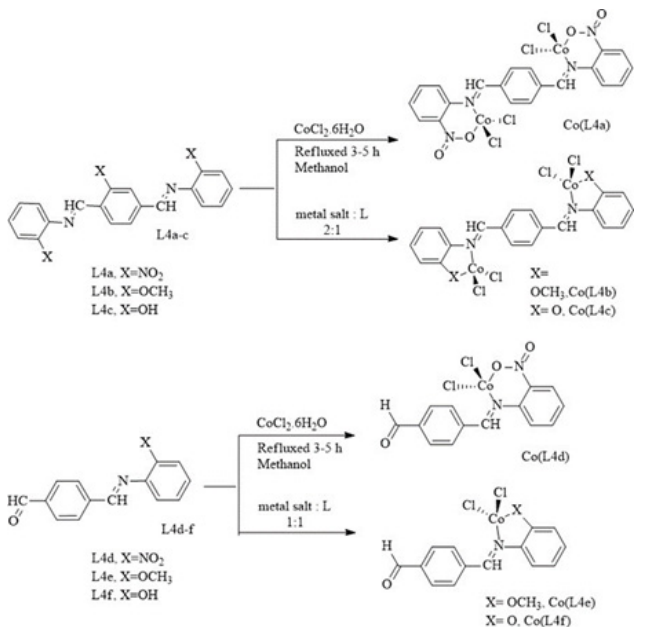

Figure 6: Synthesis of cobalt complexes.

as standard reference drug. The antibacterial study data were shown as their zone of inhibition in Table 6.

In 2017, G. More et al. reported the synthesis of tri-dentate SB ligands and their Co complexes and examined their antimicrobial activity [20]. Four different SB ligands (L7a-d) were obtained by reacting ortho-aminothiophene derivative with o-hydroxyl aldehyde derivative in ethanol. The reaction mixture was refluxed for 2-3 h, yielding SB ligands (L7a-d) in 76 - 87% yield and varied colors, due to different substituents.

All the synthesized ligands were utilized in the formation of different Co complexes Co(L7a-d)$_2$, by adding boiling ethanolic solution of cobalt (II) chloride to an ethanolic solution of SB ligands. Ethanolic ammonia was added to the formed reaction mixture for adjusting the pH to 6.5. The mixture was heated for 6 - 8 h and then kept overnight (Figure 9). Varied colored crystalline Co complexes Co(L7a-d)$_2$ were obtained respectively. All the synthesized compounds, (L7a-d) and Co(L7a-d)$_2$ were examined for their anti-microbial activity against different strains of bacteria. The value of zone of inhibition of all the studied compounds were shown in Table 7.

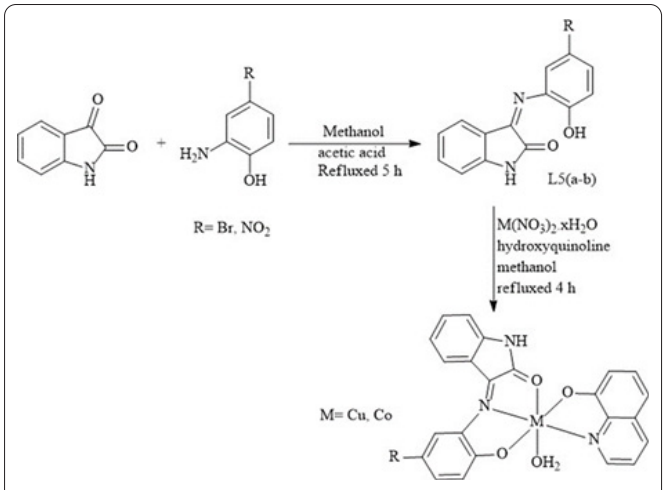

Figure 7: Synthesis of ligands (L5a-b) and their copper and cobalt complexes.

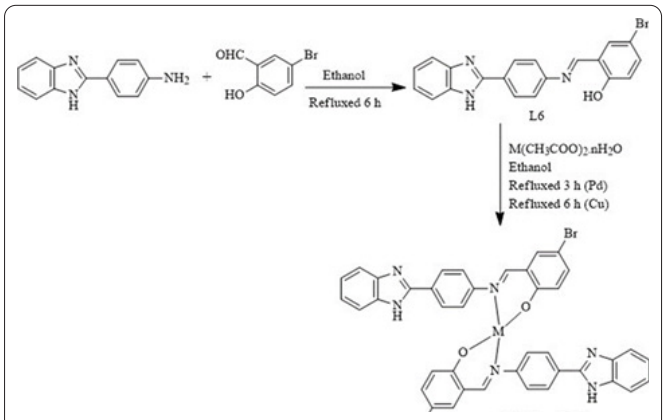

Figure 8: Synthesis of ligand (L6) and its Pd, Cu complexes.

Table 6: Antibacterial study of ligand (L6) and its complexes.

	Zone of Inhibition (mm)	
Compound	***M. luteus***	***E. coli***
Kanamycin	24.6 ± 0.6	21.2 ± 0.5
L6	6.0 ± 0.2	17.0 ± 1.2
Pd-complex	9.0 ± 0.5	-
Cu-complex	14.9 ± 1.0	11.8 ± 0.9

Table 5: Antibacterial activity of L5a-b, 8-hydroxyquinoline and complexes.

	Zone of Inhibition (mm)						
Compound	***P. aeruginosa***	***P. mendocina***	***B. subtilis***	***M. luteus***	***C. herbarium***	***V. dahlia***	***T. soudanense***
L5a	15	16	15	16	50.2	52.4	49.3
L5b	13	14	14	15	49.9	52.8	48.8
HQ	10	11	11	11	46.8	48.9	43.7
Co(L5a)QH$_2$O	19	18	18	17	63.4	58.2	58.9
Co(L5b)QH$_2$O	18	18	18	18	59.8	58.9	58.4
Cu(L5a)QH$_2$O	25	21	21	23	62.2	62.4	59.9
Cu(L5b)QH$_2$O	21	23	21	20	60.4	62.2	59.4
Streptomycin	28	30	26	25	-	-	-
Fluconazole	-	-	-	-	81.9	81.2	83.3

Table 7: Antibacterial studies of ligands (L7a-d)2 and their cobalt complexes.

	Zone of Inhibition (mm)					
Compound	***C. diversus -2***	***E. coli- 10***	***P. mirabilis- 7***	***P. aeruginosa***	***C. amalonaticus***	***K. pneumoniae***
L7a	0	11	0	12	16	0
L7b	0	11	0	15	17	0
L7c	0	10	0	15	15	10
L7d	0	10	0	15	15	0
$Co(L7a)_2$	13	12	12	15	22	12
Co(L7b)2	13	12	12	14	17	11
$Co(L7c)_2$	12	12	12	12.5	13	10
$Co(L7d)_2$	12	12	13	12	16	12

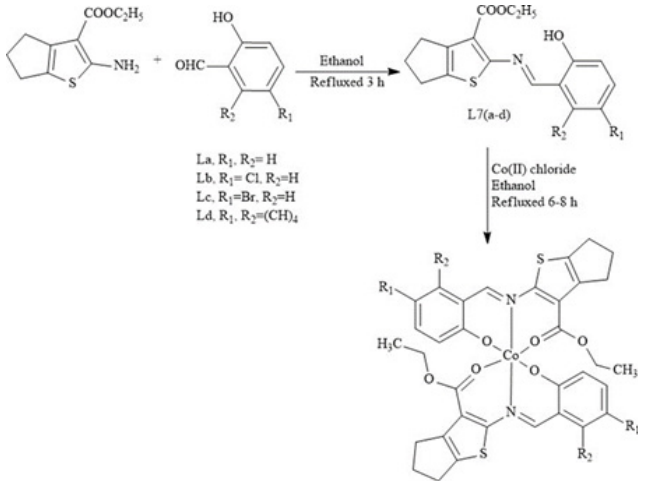

Figure 9: Synthesis of ligands (L7a-d) and $Co(L7a-d)_2$.

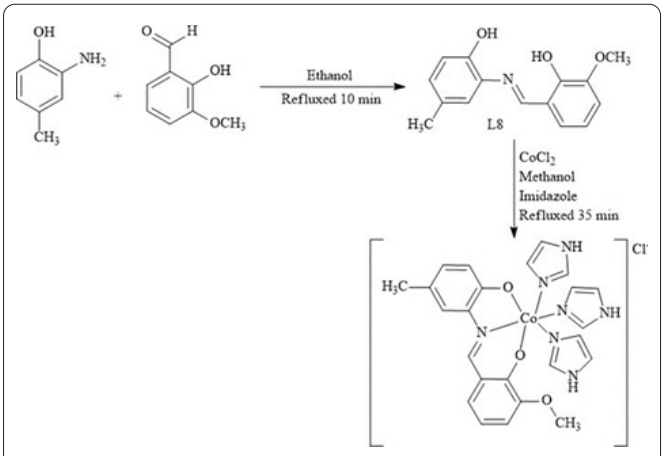

Figure 10: Synthesis of Schiff base ligand (L8) and cobalt complex $CoCl_2$, imidazole, L8 and $[Co(L8)(Im)_3]Cl$ complex were tested for their antimicrobial activity.

Table 8: Antimicrobial activity data of different compounds.

	MIC (mg/ml)				
Compounds	***S. aureus***	***P. aeruginosa***	***M. luteus***	***E. coli***	***C. albicans***
L8	-	6.25	-	12.5	-
$[Co(L8)(Im)_3]Cl$	3.125	1.562	0.781	3.125	3.125
imidazole	12.5	12.5	12.5	6.25	3.125
$CoCl_2$	6.25	-	1.56	-	12.5

In 2017, S. Y. Ebrahimipour and co-workers described the preparation and antimicrobial activities of Co SB complex [21]. The synthesis of SB ligand (L8) was achieved by adding ethanolic solution of 2-amino-4-methylphenol to an ethanolic solution of o-vanillin. The resulting mixture was refluxed for 10 min and then set to cool so as orange precipitate of SB ligand was formed and obtained with 79% yield. The ligand was used in the formation of Co complex by adding methanolic solution of $CoCl_2$ to a solution of L8 and this mixture was refluxed for 5 min. Then, methanolic solution of imidazole was added to the above mixture and the mixture was again allow to reflux at 65 °C for 30 min. After slow evaporation of solvent red crystals of Co complex $[Co(L8)(Im)_3]Cl$ was obtained with 58 % yield.

$CoCl_2$, imidazole, L8 and $[Co(L8)(Im)_3]Cl$ complex were tested for their antimicrobial activity against different bacterial strains as *S. aureus, P. aeruginosa, M. luteus, E. coli* and one fungus as *C. albicans*. The antimicrobial activity of varied compounds was shown in Table 8 as their MIC values. From the reported data, it was observed that these molecules can be effectively utilized as nanomedicines, due to their efficacy as antimicrobial agents. A wide variety of microbes can be controlled with the specific cobalt complex of Schiff base ligands.

Conclusion and Future Scope

Due to their ability to form stable complexes with transition metal ions and their pharmacological properties, SB are regarded as a very important class of organic compounds. In this review different types of SB ligands were discussed, where a variety of aldehyde and amines were reacted. These SB ligands were used to form different SB transition metal complexes of Pd, Co, and Cu. All reviewed SB metal complexes

were utilized in different types of biological activities including antibacterial and antifungal ones, where their activities were interpreted in terms of zone of inhibition or their respective MIC values. While some of these newly developed molecules showed promising results and can be utilized in nanoscale, there exists a wide area for improvement.

Even though there have been remarkable advances in the understanding of the molecular cause of microbial infection, ideal therapeutic methods are still lacking. It is extremely crucial to develop new antimicrobial agents. The therapeutic potential of diverse ligands and transition metal complexes can be fully utilized in the development of novel and effective antimicrobial agents, as nanomedicines. So, it would be beneficent to explore different SB-transition metal complexes with antimicrobial properties. Beside this, investigations involving targeting specific microbes and activation strategies may aid in the development of future generations of antimicrobial agents capable of overcoming the drawbacks of currently available agents. Modern analyzing techniques, such as nuclear magnetic resonance spectroscopy and mass spectrometry, are extremely useful and can improve our understanding of drug chemical and biochemical reactivity, potentially assisting in the establishment of meaningful structure activity relationships. As a result, chemical studies of antimicrobial agents under physiologically related conditions have become essential in drug development rationale. These, in turn, provide the future opportunities for detailed investigations with SB ligands and their transition metal complexes. In addition, the effects of newly designed nanoparticles have to be investigated in details because of the existence of a variety of biological situations [22]. Different biological systems, both on the cellular level as well as on the macroscopic level can have different implications from nanomedicines. Hence, optimizing those results over a heterogeneous patient population require extensive research work and it would enable the development of efficacious and personalized therapeutic nanoparticles.

References

1. Soares S, Sousa J, Pais A, Vitorino C. 2018. Nanomedicine: principles, properties, and regulatory issues. *Front Chem* 6: 360. https://doi.org/10.3389/fchem.2018.00360
2. Abu-Dief AM, Mohamed IMA. 2015. A review on versatile applications of transition metal complexes incorporating Schiff bases. *Beni Suef Univ J Basic Appl Sci* 4(2): 119-133. https://doi.org/10.1016/j.bjbas.2015.05.004
3. Xavier A, Srividhya N. 2014. Synthesis and studies of schiff base ligands. *IOSR Journal of Applied Chemistry* 7(11): 6-15.
4. Layek S, Anuradha, Agrahari B, Pathak DD. 2017. Synthesis and characterization of a new Pd(II)-Schiff base complex [Pd(APD)2]: an efficient and recyclable catalyst for Heck- Mizoroki and Suzuki-Miyaura reactions. *J Organomet Chem* 846: 105-112. https://doi.org/10.1016/j.jorganchem.2017.05.049
5. Rudbari HA, Iravani MR, Moazam V, Askari B, Khorshidifard M, et al. 2016. Synthesis, characterization, X-ray crystal structures and antibacterial activites of Schiff base ligands derived from allylamine and their Vanadium(IV), Cobalt(III), Nickle(II), Copper(II), Zinc(II) and Palladium(II) complexes. *J Mol Str* 1125: 113-120. https://doi.org/10.1016/j.molstruc.2016.06.055
6. Berhanu AL, Gaurav, Mohiuddin I, Malik AK, Aulakh JS, et al. 2019. A review of the applications of the Schiff bases as optical chemical sensors. *Trends in Anal Chem* 116: 74-91. https://doi.org/10.1016/j.trac.2019.04.025
7. Al-Shaalan NH. 2007. Antimicrobial activity and spectral, magnetic and thermal studies of some transition metal complexes of a schiff base hydrazone containing a quinoline moiety. *Molecules* 12(5): 1080-1091. https://doi.org/10.3390/12051080
8. Shebl M. 2014. Synthesis, spectroscopic characterization and antimicrobial activity of binuclear metal complexes of a new asymmetrical Schiff base ligand: DNA binding affinity of copper(II) complexes. *Spectrochim Acta A Mol Biomol Spectrosc* 117: 127-137. https://doi.org/10.1016/j.saa.2013.07.107
9. Joseyphus RS, Nair MS. 2008. Synthesis, characterization and antimicrobial activity of transition metal complexes with the Schiff base derived from imidazole-2-carboxaldehyde and glycylglycine. *J Coord Chem* 62(2): 319-327. https://doi.org/10.1080/00958970802236048
10. Naureen B, Miana GA, Shahid K, Asghar M, Tanveer S, et al. 2021. Iron (III) and zinc (II) monodentate Schiff base metal complexes: Synthesis, characterization and biological activities. *J Mol Str* 1231: 129946. https://doi.org/10.1016/j.molstruc.2021.129946
11. Sinha D, Tiwari AK, Singh S, Shukla G, Mishra P, et al. 2008. Synthesis, characterization and biological activity of Schiff base analogues of indole-3- carboxaldehyde. *Eur J Med Chem* 43(1): 160-165. https://doi.org/10.1016/j.ejmech.2007.03.022
12. McKinnon PS, Davis SL. 2004. Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. *Eur J Clin Microbiol Infect Dis* 23(4): 271-288. https://doi.org/10.1007/s10096-004-1107-7
13. Kargar H, Aghaei-Meybodi F, Behjatmanesh-Ardakani R, Elahifard MR, Torabi V. 2021. Synthesis, crystal structure, theoretical calculation, spectroscopic and antibacterial activity studies of copper(II) complexes bearing bidentate schiff base ligands derived from 4- aminoantipyrine: influence of substitutions on antibacterial activity. *J Mol Str* 1230: 129908. https://doi.org/10.1016/j.molstruc.2021.129908
14. Maiti SK, Kalita M, Singh A, Deka J, Barman P. 2020. Investigation of DNA binding and bioactivities of thioether containing Schiff base Copper(II), Cobalt(II) and Palladium(II) complexes: Synthesis, characterization, spectrochemical study, viscosity measurement. *Polyhedron* 184: 114559. https://doi.org/10.1016/j.poly.2020.114559
15. Turan N, Buldurun K, Alan Y, Savci A, Colak N, et al. 2019. Synthesis, characterization, antioxidant, antimicrobial and DNA binding properties of ruthenium(II), cobalt(II) and nickel(II) complexes of Schiff base containing o-vanillin. *Res Chem Intermed* 45(6): 3525-3540. https://doi.org/10.1007/s11164-019-03806-3
16. Turan N, Buldurun K, Gunduz B, Colak N. 2017. Synthesis and Structures of Fe(II), Zn(II) and Pd(II) complexes with a schiff base derived from Methyl 2-Amino-6-Methyl- 4,5,6,7-Tetrahydrothieno[2,3-c] Pyridine-3-Carboxylate and comparison of their optical constants for different solvents and molarities. *J Nanoelectronics and Optoelectronics* 12: 1028-1040. https://doi.org/10.1166/jno.2017.2151
17. Shaygan S, Pasdar H, Foroughifar N, Davallo M, Motiee F. 2018. Cobalt (II) complexes with schiff base ligands derived from terephthaladehyde and ortho-substituted anilines: synthesis, characterization and antibacterial activity. *Appl Sci* 8(3): 385. https://doi.org/10.3390/app8030385
18. Devi AJ, Batra N, Yadav J. 2018. Antimicrobial activity of transition metal complexes derived from schiff bases of isatin and aminophenols. *J Chem and Pharma Res* 10(5): 121-125.
19. Mahmood K, Hashmi W, Ismail H, Mirza B, Twamley B, et al. 2018. Synthesis, DNA binding and antibacterial activity of metal(II) complexes of a benzimidazole Schiff base. *Polyhedron* 157: 326-334. https://doi.org/10.1016/j.poly.2018.10.020
20. More G, Raut D, Aruna K, Bootwala S. 2017. Synthesis, spectroscopic characterization and antimicrobial activity evaluation of new tridentate

Schiff bases and their Co(II) complexes. *J Saudi Chem Soc* 21: 954-964. https://doi.org/10.1016/j.jscs.2017.05.002

21. Ebrahimipour SY, Machura B, Mohamadi M, Khaleghi M. 2017. A novel cationic cobalt(III) Schiff base complex: Preparation, crystal structure, Hirshfeld surface analyses, antimicrobial activities and molecular docking. *Microb Pathog* 113: 160-167. https://doi.org/10.1016/j.micpath.2017.10.034
22. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, et al. 2021. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov* 20(2): 101-124. https://doi.org/10.1038/s41573-020-0090-8