

Coordination Complexes of Transition Metals and Schiff Base with Potent Medicinal Activity

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Abstract The ligand *N,N'*-bis(salicylidene)ethylenediamine has been synthesized from the condensation of salicylaldehyde with ethylenediamine and, after isolation in the solid forms, it has been complexed with Ni (II) and Zn (II) ions. During the complexation reaction with transition metal ions, the four dentate ligand is coordinated with the central metal atom by its two active donor atoms N and O and from ¹H NMR, it is also established that C-H is activated with Ni (II) ions. The structures of the complexes have been elucidated by IR, ¹H NMR and a combination of other analytical and physical measurements. UV-Visible spectrophotometer has been used to detect metals and specific absorption has been found for each metal. Some gram-negative bacteria such as *E. Coli*, *Shigella Dysenteriae* and *Shigella Sonnei* have been tested with metal complexes and a significant inhibition of bacterial growth by the metal complexes has been noted. To understand the antibacterial activity of these metal complexes streptomycin and ciprofloxacin have been used as standards during the experiment.

Keywords Metals, Bacteria, NMR, Ciprofloxacin, Ligand

1. Introduction

Nowadays, the use of transition metal complexes as medicine has been established as a powerful tool to fight against human diseases. That's why, all over the world researchers are trying to develop suitable metal complexes that may be used as effective medicine in near future. For human, metal complexes may be used as an anticancer [1-3], antitumor [4-7], antiviral [8], and antimalarial [9] and antioxidant [10-16] agents. Alternately, metal complexes are also trying to apply for capturing images inside the infected organs of human body, instead of using expensive instruments. For example, novel bifunctional chelators (BFCs) containing 1,4,7-triazacyclononane or pyridinophane macrocycles and amyloid-binding 2-phenylbenzothiazole fragments have been synthesized, and their copper coordination properties have been characterized and applied in PET imaging agents for Alzheimer's disease [17]. In addition to that, some coordination complexes have been explored for biological applications and have been found to interact with DNA, and function as drug delivery vectors [18]. This provides an

overview of the 3D structures of coordination complexes that makes the complexes suitable for biomedical applications in future. Alternately, some suitable complexes have been used more precisely, as BODIPY derivatives, for the elaboration of BODIPY-based theranostics [19], multimodal imaging probes, and photodynamic therapy sensitizers. So, by the modification of the ligand with the active coordinating atoms, it is possible to tune the medicinal activity of coordination complexes. For example, recently some coordination complexes of thiosemicarbazones, semicarbazones, hydrazide/hydrazones and dithiocarbamates with strong pharmacological properties have been synthesized and published [20]. Recently, the thiosemicarbazones have achieved considerable attention by medicinal chemists since these are the excellent chelators of transition metals alongside their potential antitumor activity *in vitro* and *in vivo* [21,22].

Along with their medicinal activities, metal coordination complexes have also been studied extensively for applying as antibacterial [23,24] and antifungal [25,26] agents since infectious diseases are spreading worldwide and the microorganisms are showing resistant against most of the traditional drugs [27-29]. For this reason, these compounds are being thought to be used in many commercial products such as soaps, detergents, household cleaners, paints, kitchenware, and school and hospital utensils [30] as inhibitors.

Besides medicinal and antibacterial activities, over the last few decades the coordination chemistry has been

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emerged as a very nice tool for research due to their significant applications in various fields such as luminescent studies [31], solar cells technology [32,33], cytotoxicity studies [34], and as potent catalysts [35-38]. For example, surprisingly a bis-dithiocarbamate nickel complex has been recently tested for the photo catalytic production of hydrogen [39,40]. Moreover, as a potent pesticide, the applications of coordination compounds [41,42] are increasing day by day in plant biological system as rodenticidal, herbicidal, insecticidal, anthelmintical and plant-growth regulator to control unwanted organisms. Nonetheless, the transition metal complexes, derived from Schiff bases have occupied a central role in the development of coordination chemistry. Schiff base named after Hugo Schiff (1864) are the compounds containing azomethine group ($-\text{HC}=\text{N}-$) formed by the condensation reaction of any primary amine with aldehyde or ketone under specific condition [43]. Schiff bases are the nitrogen analogue of aldehyde or ketone in which the active carbonyl group ($>\text{C}=\text{O}$) is replaced by an imine or azomethine group. These bases are the effective chelating due to the presence of potentially coordinating functional groups near the site of condensation. Schiff bases derived from hydrophobic S-alkyl/aryl groups and their complexes reveal promising potential applications [44] in every field. For example, in biological cycle Zn (II) and Cu (II) Schiff base complexes [45-49] are being used for DNA binding and DNA cleavage. Finally, various viruses and bacteria are being reported to introduce a lot of problem to human body along with severe infections which are very difficult to cure and ultimately, the infected person dies due to the poisonous or toxic effect. That's why, the researchers are trying to develop some Schiff base coordination complexes as the potent inhibitors of those microbial growths [50]. Keeping these facts in mind and in view of the significance of metal complexes in medicine (Figure 1), here we report the synthesis and characterization of some Schiff base coordination complexes of Ni (II) and Zn (II) ions.

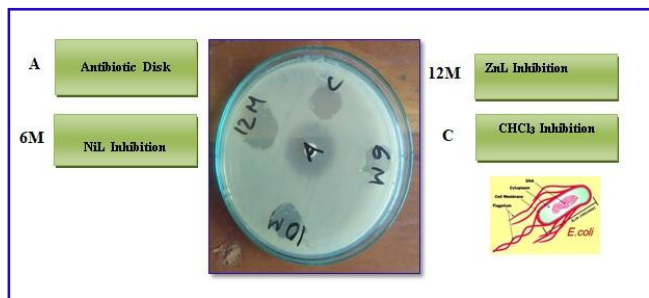


Figure 1. Antibacterial activity (Inhibition of bacterial growth)

2. Experimental

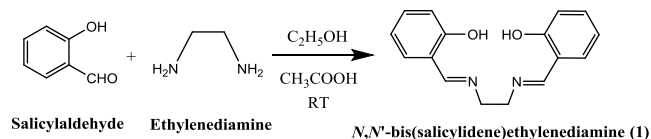
2.1. Materials and Instruments

All the chemicals used were analytical grade. The molar conductance was measured by Elico-Conductometer. The

IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr pellets. The UV-visible spectra were recorded in CDCl_3 and CH_3OH solvent on Beckman DU-64 spectrophotometer with quartz cells of 1 cm path length. ^1H NMR spectra were recorded in CDCl_3 solvent in a Bruker Advance 400 MHz instrument. Elemental analysis was done in Vario EL Cube semi macro and micro elemental analyzer (Germany). Melting point was determined by Fisher melting point apparatus (Dimension $35\times 20\times 45$, up to 350°C).

2.2. Synthesis of Schiff base [$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$] (L)(1)

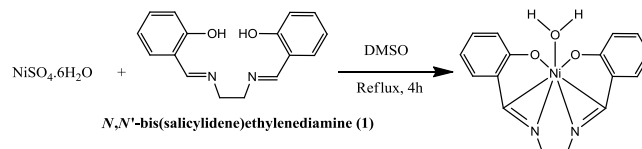
30 mL acidic (1 mL glacial acetic acid) ethanolic solution of salicylaldehyde (8.1412 g, 66.66 mmol) was stirred for 10 min and to this solution ethylenediamine (2 g, 33.28 mmol) was added drop wise and finally, yellow *N,N'*-bis(salicylidene)ethylenediamine was collected by filtering (Scheme 1). The resulting crude product was recrystallized in CHCl_3 at room temperature. Spectral data: Anal. Cal. For $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$: C, 71.56; H, 5.26; N, 10.44. Found: C, 71.69; H, 5.99; N, 10.50. IR (ν CO, KBr): 3455 (OH, b), 3052 (ArC-H, w), 3014 (N=C-H, w), 2937 (CH_2 , w), 2860 (CH_2 , w), 1636 (C=N, vs), 1578 (ArC=C, s), 1198 (C-C, s), 1283 (C-O, m), 1148 (C-N, vs). ^1H NMR (CDCl_3): δ 13.2 (2H, s), δ 7.3-6.9 (8H, m), 8.4 (2H, s), 3.9 (4H, s).



Scheme 1. Structure of Schiff base ligand, L= [$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$]

2.3. Synthesis of [NiL] (2)

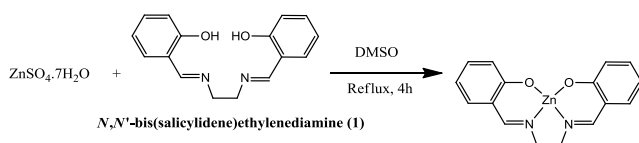
0.4905 g (1.87 mmol) of $\text{NiSO}_4\cdot 6\text{H}_2\text{O}$ was dissolved in 20 mL DMSO and stirred for 30 min with a magnetic spin bar and in another pot, 0.500 g (1.87 mmol) of *N,N'*-bis(salicylidene)ethylenediamine was also dissolved in 10 mL DMSO and it was added to the metal salt solution and the resulting solution was refluxed for 4 h and finally, reddish brown crystal was separated (Scheme 2) and recrystallized in CHCl_3 . Spectral data: Anal. Cal. For $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{Ni}$: C, 56.31; H, 4.14; N, 8.21. Found: C, 57.58; H, 4.41; N, 8.35. IR (ν CO, KBr): 3436 ($\text{H}_2\text{O}-\text{OH}$, b), 3052 (ArC-H, w), 2948 (CH_2 , w), 2852 (CH_2 , w), 1621 (C=N, vs), 1536 (ArC=C, s), 1198 (C-C, s), 1237 (C-O, m), 1145 (C-N, vs), 515 (Ni-N), 461 (Ni-O, m). ^1H NMR (CDCl_3): δ 7.0-7.4 (8H, m), δ 3.4 (4H, s), δ 1.6 (2H- H_2O , s). UV-Visible (λ_{max} , CHCl_3): 253, 329, 412.



Scheme 2. Structure of metal complex

2.4. Synthesis of [ZnL](3)

20 mL solution of 0.5550 g (1.87 mmol) of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ in DMSO was stirred for 30 min and later, 0.500 g (1.87 mmol) of *N, N'*-bis(salicylidene)ethylenediamine solution in DMSO was added to the metal salt solution and the resulting solution was refluxed for 4 h and finally, yellowish crystal was separated (Scheme 3) and recrystallized in MeOH. Spectral data: Anal. Cal. For $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{Zn}$: C, 57.89; H, 4.25; N, 8.44. Found: C, 60.86; H, 4.13; N, 6.73. IR (ν CO, KBr): 3424 (free H_2O -OH, b), 3048 (ArC-H, w), 3018 (N=CH, w), 2922 (CH_2 , w), 2848 (CH_2 , w), 1632 (C=N, vs), 1532 (ArC=C, s), 1187 (C-C, s), 1237 (C-O, m), 1145 (C-N, vs), 531 (Zn-N, m), 465 (Zn-O, m). ^1H NMR (CDCl_3): δ 6.6-7.2 (8H, m), δ 8.5 (2H, s), δ 3.9 (4H, s). UV-Visible (λ_{max} , MeOH): 225, 261, 349.



Scheme 3. Structure of metal complexes

2.5. Analysis of Anti-Bacterial Activity

2.5.1. Preparation of Nutrient Agar media

7.9 g of Nutrient agar was dissolved in 250 mL distilled water and after shaking, it was put in autoclave for $\frac{1}{2}$ h at 121°C . The resulting solution was poured in eight plates (disks) and rested the plates for 10 min. 10 μL *E. coli* gram negative bacteria was applied to all disks uniformly and the standard antibiotic streptomycin and ciprofloxacin were put at the center of the plate. In a test tube, 1 mg metal complexes were dissolved by 1 mL of CHCl_3 and 10 μL of the sample was dropped into the prepared bacterial disk (Figure 1). The solvent CHCl_3 may also inhibit the bacterial growth and, that's why, in a separate disk 10 μL CHCl_3 was dropped to observe the probable inhibition. Same procedure was repeated for *Shigella Dysenteriae* and *Shigella Sonnei* gram negative bacteria.

3. Result and Discussions

3.1. Physical Properties

All the synthesized ligand and metal complexes were air stable (Table 1). Complexes are colorful and crystalline. Molecular conductance values are (3-12 $\mu\text{S}/\text{cm}$) indicating that complexes are poor electrolyte and melting point is above 300°C , except the Schiff base ligand 129°C . From the conductivity measurement it is possible to predict that nonionic complexes were formed, but the conductivity of all complexes is zero in CHCl_3 . Every metal complex gave very good (λ_{max}) UV-Visible absorption.

3.2. Infrared Spectra

The chemical reactions between the Schiff base ligand (L)

and metals are shown in the Scheme 2 and Scheme 3. Spectroscopic data are shown in experimental section (2.2-2.4). In IR, the hydrogen stretching ($=\text{CH}-$) at 3014 cm^{-1} (L) and the C=N stretching at 1636 cm^{-1} (L) confirmed the formation of imine bond ($-\text{CH}=\text{N}-$) (Scheme 1) and no peak was found for aldehyde carbonyl group stretching. Some other IR stretching peaks at 3455 cm^{-1} and 3052 cm^{-1} came up for the phenolic O-H and aromatic hydrogens, respectively. For the aliphatic two CH_2 group the C-H stretching frequencies found at 2937 cm^{-1} (symmetric) and 2850 cm^{-1} (asymmetric).

In IR all metal complexes gave distinctive stretching band for each group. The stretching of water ($-\text{OH}$) found between $3444\text{--}3417\text{ cm}^{-1}$, aromatic hydrogen (Ar-H) $3075\text{--}3044\text{ cm}^{-1}$, imine hydrogen ($\text{N}=\text{CH}-$) $3020\text{--}3002\text{ cm}^{-1}$, aliphatic hydrogens ($-\text{CH}_2-$) $2983\text{--}2913\text{ cm}^{-1}$ (symmetric) and $2863\text{--}2827\text{ cm}^{-1}$ (asymmetric). Since phenolic $-\text{OH}$ coordinated with metal, that's why no band was detected for this group in IR and simultaneously, in Ni (II) complex no band was found for $=\text{CH}-$, since two $=\text{CH}-$ activated with metal.

3.3. Proton magnetic Resonance Spectra

In ^1H NMR, the ligand *N, N'*-bis(salicylidene)ethylenediamine (1) gave distinctive chemical shift for proton. All Ar-H gave the δ between 6.9-7.3 ppm and it was also found δ for CH_2 at 3.9 ppm, δ for imine hydrogens at 8.4 ppm, δ for phenol hydrogens at 13.2 ppm. The two CH_2 group gave singlet due to their similar chemical environment. The two donor atoms N and O of the ligand (1) coordinated with metals Ni (II) (Scheme 2) and Zn (II) (Scheme 3) and exceptionally, the metal complex of the Ni (II), formed C-Ni bond [51,52], since in ^1H -NMR no chemical shift was found for $=\text{CH}-$. Though, it appears exceptional, but it happens at high temperature, since the reaction was refluxed close to 4 h in DMSO (dimethyl sulfoxide) at 189°C . Metal complexes after dissolving in CHCl_3 , unreacted metal salt was separated by filtering off, since both ligand and metal complexes dissolve in CHCl_3 , that's why excess metal salts were used so that unreacted ligand could not present in the reaction mixture. Finally, metal complexes were recrystallized in three times for getting pure crystal. The process was repeated for all complexes.

In ^1H NMR the metal complexes of Ni (II) and Zn (II) gave chemical shift values for aromatic protons between δ 6.9-7.6 ppm (multiplets) and imine hydrogens between δ 8.1-9.9 ppm. None of the complexes gave phenolic hydroxyl peak since phenolic hydroxyls formed complex with metals. Aliphatic protons gave δ between 2.4-2.6 ppm and coordinating water protons δ at 1.6 ppm. The number of protons was calculated according to proton integration. The Zn (II) complex did not give any chemical shift for coordinating water and that's why the complex formed square planer complex with no coordinating water.

Table 1. Physical and analytical data of the Schiff base and Metal Complexes

Compounds/ Mol. Formula	Color	Yields (%)	M.P(°C) /(Decomp.)	Conductivity ($\mu\text{S}/\text{cm}$)	
				DMSO	MeOH
Ligand (L)	Yellow	47	129	0	0
[NiL]	Reddish	90	>300	8.6	12
[ZnL]	Yellowish	52	>300	4.8	4.4

3.4. Antibacterial Activity

The Schiff base ligand (*N, N'*-bis(salicylidene)ethylenediamine) and its metal complexes were screened for their antibacterial activity against the strains the *E. Coli* and *Shigella Dysenteriae*. The susceptibility zones were measured in diameter (mm) and the result are listed in (Table 2). The susceptibility zones were the clear zones around the discs killing the bacteria (Figure 1). The Schiff base and metal complexes individually exhibited varying degrees of inhibitory effects on the growth of tested bacterial species. Most of the metal complexes showed more antibacterial activity than Schiff base ligand. But, none of the complexes showed antibacterial activity against the growth of gram-negative bacteria *Shigella Sonnei*. In this experiment the antibiotic streptomycin was used as standard and the antibiotic also showed good activity against the growth of bacteria.

Table 2. Antibacterial screening activity of Schiff base metal complexes

Tested Bacteria	Ligand (L)	[NiL]	[ZnL]
<i>E. Coli. (Acetobacter aceti)</i>	10	20	20
<i>Shigella Dsenteria</i>	20	10	10
<i>Shigella Sonnei</i>	-	-	-

4. Conclusions

The present study describes the synthesis and characterization of Ni (II) and Zn (II) complexes of *N, N'*-bis(salicylidene)ethylenediamine. The structures of the complexes were determined successfully by IR, ^1H NMR spectroscopic techniques and elemental analysis. Based on the physico-chemical and spectroscopic data, we propose monodentate coordination of *N, N'*-bis(salicylidene)ethylenediamine to the metal, which is further confirmed by the UV-Visible absorption. In Ni (II) complex, the ligand coordinated to the metal atom through the imine carbon and an octahedral structure for Ni (II) was formed. Furthermore, the results of the antibacterial studies revealed drastic antibacterial effects of these complexes on the growth of gram-negative bacteria. However, further study is going on to get more potent antibacterial agents by synthesizing new metal coordination complexes.

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REFERENCES

- [1] Fandzloch, M., Dobrzańska, L., Jezierska, J., Psurska, B. F., Wiśniewska, J., Salas, J. M., and Łakomska, I. (2018). In search of new anticancer drug-dimethylsulfoxide ruthenium (III) complex with bulky triazolopyrimidine derivative and preliminary studies towards understanding the mode of action. *Polyhedron*, 141, 239.
- [2] Nutting, C. M., Herpen, C. M. C. V., Miah, A. B., Bhide, S. A., Machiels, J. P., Buter, J., Kelly, C., Raucourt, D. D and Harrington, K. J. (2009). Phase II study of 3-AP triapine in patients with recurrent or metastatic head and neck squamous cell carcinoma. *Ann. Oncol.* 20, 1275.
- [3] Ma, B., Goh, B. C., Tan, E. H., Lam, K. C., Soo, R., Leong, S. S., Wang, L. Z., Mo, F., Chan, A. T., Zee B., and Mok, T. (2008). A multicenter phase II trial of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, Triapine®) and gemcitabine in advanced non-small-cell lung cancer with pharmacokinetic evaluation using peripheral blood mononuclear cells. *Invest. New Drugs*. 26, 169.
- [4] Zhang, H., Thomas, R., Oupicky, D. and Peng, F., (2008). Synthesis and characterization of new copper thiosemicarbazone complexes with an ONNS quadridentate system: cell growth inhibition, S-phase cell cycle arrest and proapoptotic activities on cisplatin-resistant neuroblastoma cells. *J. Biol. Inorg. Chem.* 13, 47.
- [5] Kalinowski, D. S., Quach P. and Richardson, D. R. (2009). Thiosemicarbazones: the new wave in cancer treatment. *Fut. Med. Chem.* 1, 1143.
- [6] Yu, Y., Kalinowski, D.S., Kovacevic, Z., Siafakas, A. R., Jansson, P. J., Stefani, C., Lovejoy, D. B., Sharpe, P. C., Bernhardt, P. V., and Richardson, D. R. (2009). Thiosemicarbazones from the old to new: iron chelators that are more than just ribonucleotide reductase inhibitors. *J. Med. Chem.* 52, 5271.
- [7] Arguelles, M. C. R., Vazquez, S. M., Matalobos, J. S., Deibe, A. M. G., Pelizzi, C. and Zani, F. (2010). Evaluation of the antimicrobial activity of some chloro complexes of imidazole-2-carbaldehyde semicarbazone: x-ray crystal structure of cis-NiCl₂(H₂L)(H₂O). *Polyhedron*. 29, 864.
- [8] Shipman, C. J., Smith, S. H., Drach, J. C. and Klayman, D. L. (1986). Thiosemicarbazones of 2-acetylpyridine, 2-acetylquinoline, 1-acetylisoquinoline, and related compounds as inhibitors of herpes simplex virus in vitro and in a cutaneous herpes guinea pig model. *Antiviral Res.* 6, 197.

- [9] Usman, A., Razak, I. A., Chantrapromma, S., Fun, H. K., Varughese, P., Sreekanth, A., Sivakumar, S. and Kurup, M. R. P., (2002). Di-2-pyridyl ketone N^d,N^d -(butane-1,4-diyl)thiosemicarbazone. *Acta Cryst.* 58C, 652.
- [10] Pelosi, G. (2010) Thiosemicarbazone metal complexes: from structure to activity. *Open Crystallog.* J. 3, 16.
- [11] Tojal, J. G., Orad, A. G., Diaz, A. A., Serra, J. L., Urtiaga, M. K., Arriortua, M. I., and Rojo, T. (2001). Biological activity of complexes derived from pyridine-2-carbaldehyde thiosemicarbazone: Structure of $[Co(C_7H_7N_4S)_2][NCS]$. *J. Inorg. Biochem.* 84, 271.
- [12] El-Ayaan, U., Youssef, M. M. and Al-Shihry, S. (2009). Mn (II), Co (II), Zn (II), Fe (III) and U (VI) complexes of 2-acetylpyridine 4N-(2-pyridyl) thiosemicarbazone (HAPT); structural, spectroscopic and biological studies. *J. Mol. Struct.* 936, 213.
- [13] Prabhakaran, R., Kalaivani, P., Poornima, P., Dallemer, F., Paramaguru, G., Padma, V. V., Renganathan, R., Huang, R., Natarajan, K. (2012). One pot synthesis of structurally different mono and dimeric Ni (II) thiosemicarbazone complexes and N-arylation on a coordinated ligand: a comparative biological study. *Dalton Trans.* 41, 9323.
- [14] Lukmantara, A. Y., Kalinowski, D. S., Kumar N. and Richardson, D. R. (2013). Synthesis and biological evaluation of substituted 2-benzoylpyridine thiosemicarbazones: Novel structure-activity relationships underpinning their anti-proliferative and chelation efficacy. *Bioorg. Med. Chem. Lett.* 23, 967.
- [15] Serda, M., Kalinowski, D. S., Wilczkiewicz, A. M., Musiol, R., Szurko, A., Ratuszna, A., Pantarat, N., Kovacevic, Z., Merlot, A. M., Richardson, D. R. and Polanski, J. (2012). Synthesis and characterization of quinoline-based thiosemicarbazones and correlation of cellular iron-binding efficacy to anti-tumor efficacy. *Bioorg. Med. Chem. Lett.* 22, 5527.
- [16] Walcourt, A., Loyevsky, M., Lovejoy, D. B., Gordeuk, V. R., and Richardson, D. R. (2004). Novel aroylhydrazones and thiosemicarbazone iron chelators with anti-malarial activity against chloroquine-resistant and-sensitive parasites. *Int. J. Biochem. Cell Biol.* 36, 401.
- [17] Sharma, A. K., Schultz, J. W., Prior, J. T., Rath, N. P. and Mirica, L. M. (2017). Coordination Chemistry of bifunctional chemical agents designed for applications in ^{64}Cu PET imaging for alzheimer's disease. *Inorg. Chem.* 56, 13801.
- [18] Casini, A., Woods, B. and Wenzel, M. (2017). The promise of self-assembled 3D supramolecular coordination complexes for biomedical applications. *Inorg. Chem.* 56, 14715.
- [19] Bertrand, B., Passador, K., Goze, C., Denat, F., Bodio E. and Salmain, M. (2018). Metal-based BODIPY derivatives as multimodal tools for life sciences. *Coord. Chem. Rev.* 358, 108.
- [20] Pavana, F. R., Maia, P. I. D. S., Leite, S. R. A., Deflon, V. M., Batista, A. A., Sato, D. N., Franzblau, S. G. and Leite, C. Q. F. (2010). Thiosemicarbazones, semicarbazones, dithiocarbazates and hydrazide/hydrazones: Anti-mycobacterium tuberculosis activity and cytotoxicity. *Eur. J. Med. Chem.* 45, 1898.
- [21] Yu, Y., Kalinowski, D. S., Kovacevic, Z., Siafakas, A. R., Jansson, P. J., Stefani, C., Lovejoy, D. B., Sharpe, P. C., Bernhardt, P. V. and Richardson, D. R., (2009). Thiosemicarbazones from the old to new: iron chelators that are more than just ribonucleotide reductase inhibitors. *J. Med. Chem.* 52, 5271.
- [22] Richardson, D. R., Sharpe, P. C., Lovejoy, D. B., Senaratne, D., Kalinowski, D. S., Islam M. and Bernhardt, P. V. (2006). Dipyrindyl thiosemicarbazone chelators with potent and selective antitumor activity form iron complexes with redox activity. *J. Med. Chem.* 49, 6510.
- [23] Ramachandran, R., Rani, M. and Kabilan, S. (2009). Design, synthesis and biological evaluation of novel 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones as a new class of antimicrobial agents. *Bioorg. Med. Chem. Lett.* 19, 2819.
- [24] Yildirim, H., Guler, E., Yavuz, M., Ozturk, N., Yaman, P. K., Subasi, E., Sahin, E. and Timur, S. (2014). Ruthenium (II) complexes of thiosemicarbazone: Synthesis, biosensor applications and evaluation as antimicrobial agents. *Mater. Sci. Eng. C.* 44, 1.
- [25] Parrilha, G. L., Silva, J. G. D., Gouveia, L. F., Gasparoto, A. K., Dias, R. P., Rocha, W. R., Santos, D. A., Speziali, N. L. and Beraldo, H. (2011). Pyridine-derived thiosemicarbazones and their tin (IV) complexes with antifungal activity against candida spp. *Eur. J. Med. Chem.* 46, 1473.
- [26] Alomar, K., Gaumet, V., Allain, M., Bouet G. and Landreau, A. (2012). Synthesis, crystal structure, characterisation, and antifungal activity of 3-thiophene aldehyde semicarbazone (3STCH), 2,3-thiophene dicarboxaldehyde bis(semicarbazone) (2,3-BSTCH₂) and their nickel (II) complexes. *J. Inorg. Biochem.* 115, 36.
- [27] Kamalakannan, P. and Venkappayya, D. (2002). Synthesis and characterization of cobalt and nickel chelates of 5-dimethylaminomethyl-2-thiouracil and their evaluation as antimicrobial and anticancer agents. *J. Inorg. Biochem.* 90, 22.
- [28] Islam, M. S., Farooque, M. A., Badruddoza, M. A. K. E., Mosaddeq M. A. and Alam, M. S. (2002). Antimicrobial and toxicological studies of mixed ligand transition metal complexes of schiff bases. *J. Biol. Sci.* 2, 797.
- [29] Agwara, M. O., Yufanyi, D. M., Foba-Tendo, J. N., Atamba, M. A. and Ndinteh, D. T. (2011). Synthesis, characterisation and biological activities of Mn (II), Co (II) and Ni (II) complexes of hexamethylenetetramine. *J. Chem. Pharm. Res.* 3, 196.
- [30] Kabbani, A. T., Hammud H. H. and Ghannoum, A. M. (2007). Preparation and antibacterial activity of copper and cobalt complexes of 4-Chloro-3-nitrobenzoate with a nitrogen donor Ligand. *Chem. Pharm. Bull.* 55, 446.
- [31] Soulis, K., Gourlaouen, C., Daniel, C., Quatela, A., Odobel, F., Blart, E., and Pellegrin, Y. (2018). New luminescent copper (I) complexes with extended π -conjugation. *Polyhedron.* 140, 42.
- [32] Marinakis, N., Wobill, C., Constable, E. C., and Housecroft, C. E. (2018). Refining the anchor: Optimizing the performance of cyclometallated ruthenium (II) dyes in p-type dye sensitized solar cells. *Polyhedron,* 140, 122.

- [33] Colombo, A., Carlo, G. D., Dragonetti, C., Magni, M., Biroli, A. O., Pizzotti, M., Roberto, D., Tessore, F., Benazzi, E., Bignozzi, C. A., Casarin, L., and Caramori, S., (2017). Coupling of zinc porphyrin dyes and copper electrolytes: a springboard for novel sustainable dye-sensitized solar cells. *Inorg. Chem.* 56, 14189.
- [34] Glišić, B. D., Runic, J. N., Ilic-Tomic, T., Wadepohl, H., Veselinović, A., Opsenica, I. M., and Djuran, M. I., (2018). Synthesis, cytotoxic activity and DNA-binding properties of copper (II) complexes with terpyridine. *Polyhedron*, 139, 313.
- [35] Hein, N. M., Pick, F. S. and Fryzuk, M. D. (2017). Synthesis and reactivity of a low-coordinate iron (II) hydride complex: applications in catalytic hydrodefluorination. *Inorg. Chem.* 56, 14513.
- [36] Wang, D. and Bruner, C. O. (2017). Catalytic water oxidation by a bio-inspired nickel complex with a redox-active ligand. *Inorg. Chem.* 56, 13638.
- [37] Liu, X., Manzur, C., Novoa, N., Celedón, S., Carrillo D. and Hamon, J. R., (2018). Multidentate unsymmetrically-substituted schiff bases and their metal complexes: Synthesis, functional materials properties, and applications to catalysis. *Coord. Chem. Rev.* 357, 144.
- [38] Oohora, K., Meichin, H., Kihira, Y., Sugimoto, H., Shiro, Y. and Hayashi, T. (2017). Manganese (V) porphycene complex responsible for inert C–H bond hydroxylation in a myoglobin matrix. *J. Am. Chem. Soc.* 139, 18460.
- [39] Beshir, A. B., Guchhait, S. K., Gascon, J. A. and Fenteany, G. (2008). Synthesis and structure–activity relationships of metal–ligand complexes that potently inhibit cell migration. *Bioorg. Med. Chem. Lett.* 18, 498.
- [40] Zangrando, E., Begum, M. S., Sheikh, M. C., Miyatake, R., Hossain, M. M., Alam, M. M., Hasnat, M. A., Halim, M. A., Ahmed, S., Rahman M. N. and Ghosh, A. (2017). Synthesis, characterization, density functional study and antimicrobial evaluation of a series of bischelated complexes with a dithiocarbamate Schiff base ligand. *Arab. J. Chem.* 10, 172.
- [41] Yuan, Y. F., Wang, J. T., Gimeno, M. C., Laguna A. And Jones, P. G. (2001). Synthesis and characterisation of copper complexes with N-ferrocenoyl-N'-aryl (alkyl) thioureas. *Inorg. Chim. Acta.* 324, 309.
- [42] Zhang, Y. M., Wei, T. B., Xian, L., and Gao, L. M. (2004). Phosphorus, Sulfur Silicon Relat. Elem. 179.
- [43] Zhang, Y. M., Wei, T. B., Wang, X. C. And Yang, S. Y. (1998). Synthesis and Biological Activity of N-Aroyl-N'-carboxyalkyl Thiourea Derivatives. *Ind. J. Chem. Sect. B.* 37, 604.
- [44] Zhou, W. Q., Li, B. L., Zhu, L. M., Ding, J. G., Yong, Z., Lu, L. and Yang, X. J. (2004). Structural and spectral studies on N-(4-chloro) benzoyl-N'-(4-tolyl) thiourea. *J. Mol. Struct.* 690, 145.
- [45] Eweis, M., Elkholy, S. S., and Elsabee, M. Z., (2006). Antifungal efficacy of chitosan and its thiourea derivatives upon the growth of some sugar-beet pathogens. *Int. J. Biol. Macromol.* 38, 1.
- [46] Sabounchei, S. J., Ahmadianpoor, M., Hashemi, A., Mohsenzadeh F. and Gable, R. W. (2016). Synthesis, spectroscopic and structural characterization and antibacterial activity of new dimeric and polymeric mercury (II) complexes of phosphonium ylide. *Inorg. Chim. Acta.* 458, 77.
- [47] Schiff, H. (1864). Mittheilungen aus dem Universitätslaboratorium in Pisa; Eine neue reihe organischer basesb. *Justus Liebig's Ann. Chem.* 131(1), 118.
- [48] Wise, C. F., Liu, D., Mayer, K. J., Crossland, P. M., Hartleya, C. L. and McNamara, W. R. (2015). A nickel complex of a conjugated bis-dithiocarbamate Schiff base for the photocatalytic production of hydrogen. *Dalton Trans.* 44, 14265.
- [49] Ghorai, P., Saha, R., Bhuiya, S., Das, S., Brandão, P., Ghosh, D., Bhaumik, T., Bandyopadhyay, P., Chattopadhyay, D. and Saha, A. (2018). Syntheses of Zn (II) and Cu (II) Schiff base complexes using N, O donor Schiff base ligand: crystal structure, DNA binding, DNA cleavage, docking and DFT study. *Polyhedron.* 141, 153.
- [50] Bhowmick, A., Islam, M., Bhowmick, R., Sarkar, M., Shibly, A. and Hossain, E. (2019). Synthesis and structure determination of some schiff base metal complexes with investigating antibacterial activity. *Am. J. Chem.*, 9(1), 21.
- [51] Owen, G. R., White, A. J. P. and Vilar, R. (2009). Palladium iminoacyl imine complexes: strategies toward imine insertion. *Organometallics*, 28, 5783.
- [52] Das, R., Blumberg, J., Daniliuc, C. G., Schnieders, D., Neugebauer, J., Han, Y. F. and Hahn, F. E. (2019). Regioselective N- and C- metalation of neutral 2-halogenobenzimidazole derivatives. *Organometallics*, DOI:10.1021/acs.organomet.9b00357.