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Antimicrobial Activities of Co (III), Mono and Tri-nuclear Ni Complexes Containing Schiff base Functionalized Imidazolium based Ligands

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

We reported the antimicrobial activities of cobalt and nickel complexes containing imino-NHC ligands. Complex **2** was synthesized by direct reaction of the insitu generated free carbene from 2-[2-(3-benzylimidazol-1-yl)ethyliminomethyl]phenol ligand with $NiCl_2$ diglyme while complexes **3-5** were previously reported as catalysts in the transfer hydrogenation reaction of ketones. The compounds **1-5** were screened for antimicrobial sensitivity test against four gram-negative bacteria *Escherichia Coli (E-coli), Shigella, Klebsiella Pneumoniae (K. Pneumoniae)* and *Salmonella Typhi (S.Typhi)* and a gram positive bacteria *Staphylocossus aureus (S.aureus).* At a varying concentrations of 100, 200, 300, 400 and 500 µg/mL, significant activities were recorded using disc diffusion methods. The cobalt complex **3** was found to have higher activities compared with the corresponding nickel complexes and among the three nickel complexes, nickel complex with pyridine as wingtip was found to be more active than the one with a benzyl group. Similarly, the nickel centre with mononuclear was found to be more active than the tri-nuclear nickel complex. Except for the cobalt complex **3** no activity was recorded against *S. typhi* for all the nickel compounds.

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Keywords: Schiff base; N-heterocyclic carbene; antimicrobial activities; imino-NHC; nickel complex; cobalt complex.

1. INTRODUCTION

Imino *N*-heterocyclic carbenes (imino-NHC) comprised multifunctional ligand derived from the combination of Schiff base moiety and NHC in one ligand framework [1]. The idea is to enrich the chemistry of the NHC family of ligands by providing additional binding sites that can lead to the subsequent harnessing of the combined properties of both the Schiff base and the carbene. In addition to the catalysis, the enhanced application of NHC compounds in the development of new drugs to combat drug-resistant ailments has also attracted the attention of researchers [2].

To this effect, there are several reports on the use of Ag, Au, Pt, and other metal NHC complexes in the development of biologically active drugs including some NHC-metal based drugs with potential activities in the treatment of cancers and other infectious diseases [3].

On the other hand, Schiff bases represent an important class of ligands in coordination chemistry, producing very stable complexes with several transition metals in variable oxidation states [4,5]. Thus their electronic and steric properties have been extensively investigated, as electrode modifiers in electroanalysis [6,7] as antitumor [8] antifungal, antiviral, antimalarial, and antibacterial agents [9] as well as mimetic models for the transport of oxygen in metalloenzyme complexes and several other applications. Impressed by the significant progress recorded in the investigation of the biological activities of metallodrugs obtainable from Schiff base and the NHC complexes, we, therefore, aimed to harness the synergetic effects by combining the Schiff base and the NHC moieties in one ligand framework. Similarly, transition metals like (Co and Ni) were selected due to their low cost, low toxicity and availability [10]. There are numerous reports on the biological applications of the Schiff base complexes synthesized from the aforementioned metals however, to the best of our knowledge no report on the biological application of their Imino-NHC complexes.

2. EXPERIMENTAL

2.1 General Information

All reactions were performed using standard Schleck techniques under an inert atmosphere. All solvents were dried and purified using standard procedures prior to use. Glassware was dried in an oven at 120 °C. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-III 400 MHz spectrometer at ambient temperature with tetramethylsilane (TMS at 0.00 ppm) as an internal standard. All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz (Hz). Abbreviations used for the multiplicity of the NMR signals are: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of the doublet. Infrared spectra were recorded on a Perkin Elmer universal ATR Spectrum 100 FT-IR spectrometer. Mass spectrometry were recorded on Waters Micromass LCT Premier TOF MS-ES^{+}. Thin Layer Chromatography (TLC) was carried out on Machery-Nagel polygramSil/G/UV254 pre-coated plates. Melting points analysis were recorded using an Electrothermal 9100 melting point apparatus. All other chemicals were purchased from Sigma-Aldrich and used without further purification. The synthesis and characterization were carried out at the School of Chemistry and Physics, University of KwaZulu-Natal, Westville, Durban, South Africa.

2.2 2-[2-(3-benzylimidazol-1-yl) ethyliminomethyl] Phenol Nickel Complex (**2**)

A clean Schleck tube was connected to nitrogen gas and charged with a stir bar, (0.117 g, 0.3 mmol) of **1** in 10 ml of dry methanol was added to it and stirred for few seconds, and upon addition of ($KO^{t}Bu$) (0.13 g, 1.16 mmol) the brown colour of the solution immediately became reddish and after some minutes of refluxed, the colour change to orange. At this point, $NiCl_2$ diglyme (0.06 g, 0.3 mmol) was slowly added to the mixture and the reflux continued for 4 h. After the reaction was completed, the solvent was evaporated under reduced pressure and the residues were extracted in hot toluene to afford a red crystalline solid 0.08 g of **2**. Yield (62%) mp 86 -88 ℃, m/z = 431.2975 (M+ -Br).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, HC=N), 7.37 (1H, dd, Ar), 7.23 (2H, m, Ar), 7.23 (2H, m, Ar), 7.16 (3H, m, Ar), 7.04 (1H, m, Ar), 6.88(2H, m, Ar), 6.14 (1H, d, NCH), 6.03 (1H, d, CHN), 4.73 (2H, s, NCH_2C), 3.85 (2H, t, NCH_2), 3.73 (2H, t, CH_2-N), $^{13}CNMR$ ($CDCl_3$) 161.55, 157.02, 151.92, 135.78, 135.21, 133.26, 127.95, 127.34, 126.82, 121.77, 117.72, 116.84, 115.42, 110.37, 109.41, 46.22, 43.96, 41.70. MS m/z= 431.2975

2.3 Supporting Information

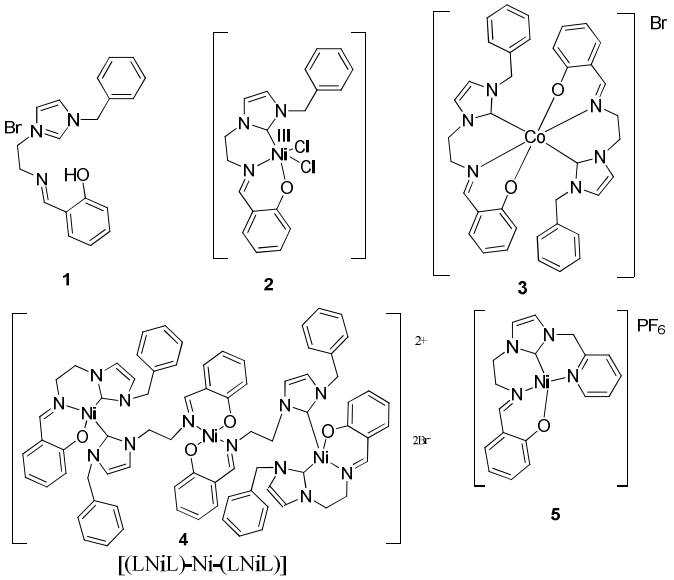
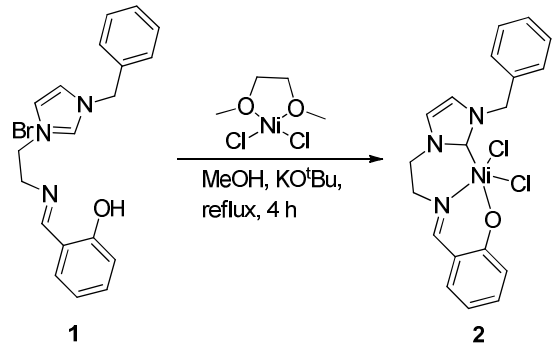


Fig. 1. Compounds tested as antimicrobial agents



Scheme 1. Synthetitic route to complex 2

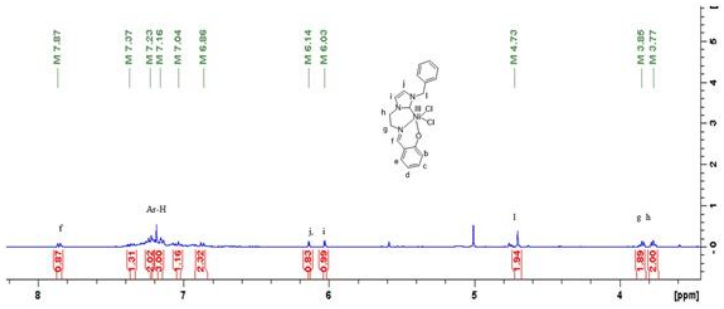


Fig. 2. Proton NMR spectrum of complex 2 in $CDCl_3$

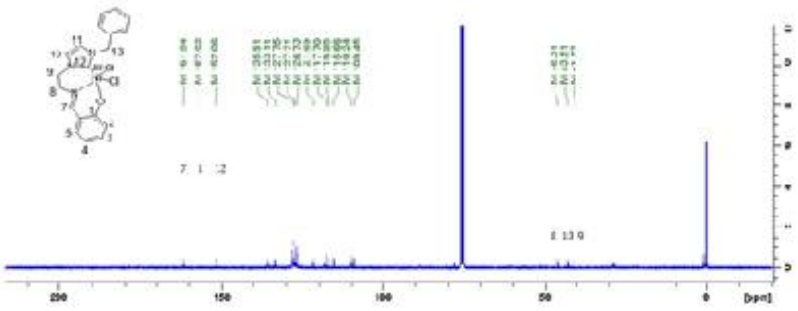


Fig. 3. ^{13}C NMR spectrum of complex 2 in $CDCl_3$

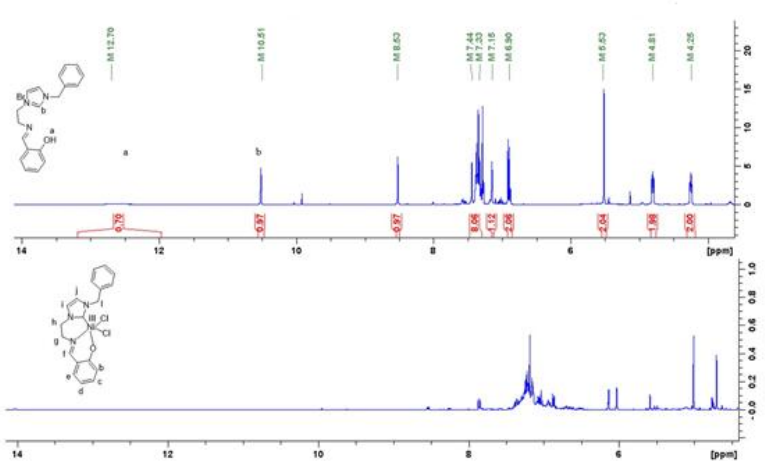


Fig. 4. Comparison between the proton NMR spectrum of ligand 1 and the NMR spectrum of complex 2 in $CDCl_3$

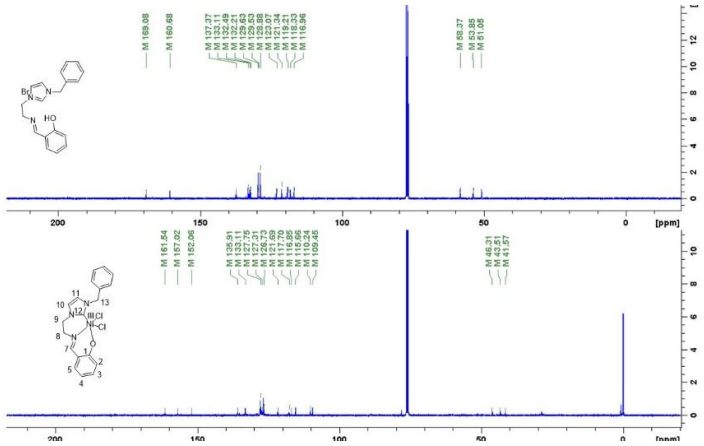


Fig. 5. Comparison between ^{13}C NMR of ligand 1 and the NMR spectrum of complex 2 in $CDCl_3$

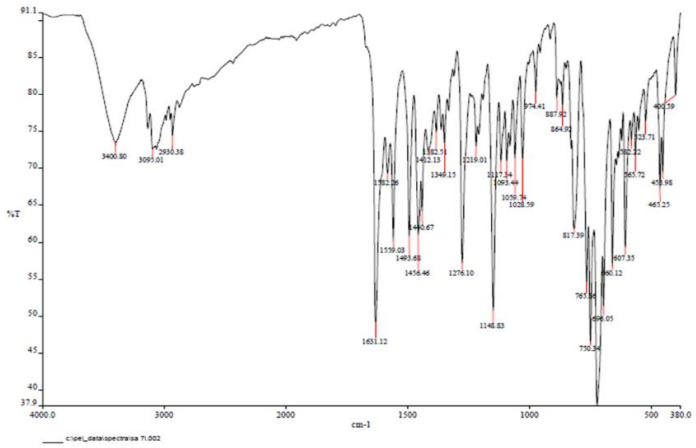


Fig. 6. FTIR Spectrum of the ligand 1

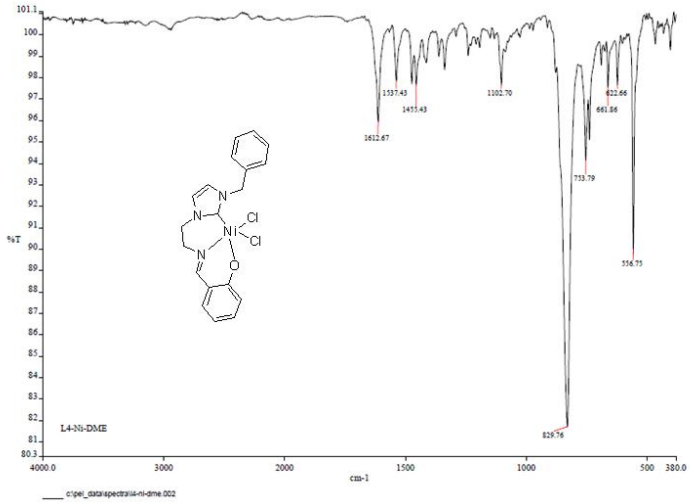


Fig. 7. FTIR Spectrum of the complex 2

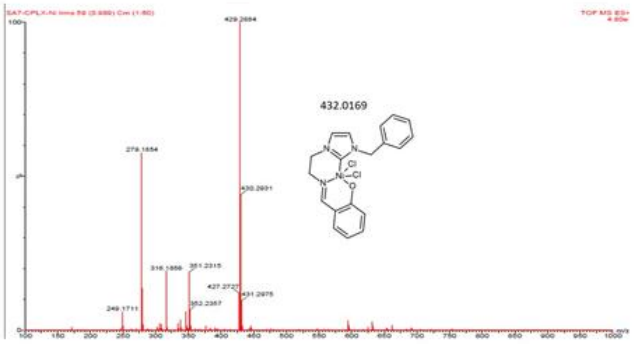


Fig. 8. LCMS Spectrum of complex 2

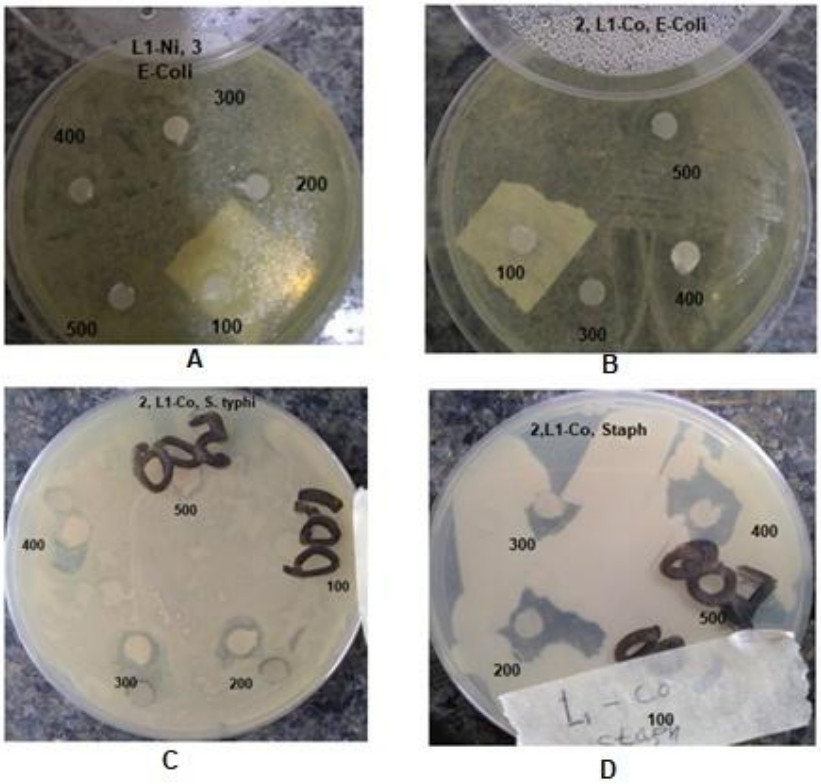


Fig. 9. Zone of inhibitions: A showing compound 2 against *E-coli*, B compounds 3 against *E-Coli*, C showing 3 against *S.typhi* and D showing 3 against *Staph*

3. RESULTS AND DISCURSION

3.1 Synthesis

The ligand precursor **1** and the metal complexes **3-5** (Fig. 1) were initially developed and reported as precatalysts in the transfer hydrogenation of ketones [11,12]. While the metal complex **2** was synthesized according to (Scheme 1) and has not been reported in any previous work. The insitu generated free carbene was reacted with $NiCl_2$ diglyme and refluxed for 4 h. the detailed procedure described in the experimental section. The complex was isolated as red coloured crystalline solid yield 62 % and mp 86-88℃. The compound was stable in air and soluble in methanol, chloroform, DMSO, acetonitrile and other polar solvents.

3.2 Spectroscopy

The NMR data of complex **2** indicated the formation of bonds between the ligands and the Ni(III) centre. Evidence is the disappearances of the notable peaks on the ligand precursor. For instance, there is a disappearance of the OH proton and the carbene NCHN peaks at around 12.5 and 10.5 ppm respectively. In addition, there is a general upfield shift of the other protons such as the shift of the imine NH proton from 8.5 ppm observed in the ligand to 7.8 ppm on the metal complex and also the shift of the bridging CH_2 protons α and β to the imine from their initial positions of 4.8, 4.2 ppm to 3.8 and 3.7 ppm respectively (Figs. 2 and 4). The ^{13}C-NMR data of the complex also indicated a ligand to metal bonding. For instance, a downfield shift was noted for the carbene (NCN) signal which was at 137 ppm in **1**, but due to the dπ-pπ interaction [13] between the carbene and the Ni(III) centre in **2** was observed at 152 ppm (Figs. 3 and 5).

The IR spectra of the complex showed the disappearance of the ligand hydroxyl (-OH) absorption peaks (around 3400 cm^{-1}) and slight shifts in wavenumbers toward lower frequencies for the imine (C=N) from 1631 cm^{-1} to 1612 cm^{-1}. (Figs. 6 and 7) In addition, positive electrospray mass spectrometric data of 2 revealed m/z

=231.29 corresponding to the loss of a proton from **2** (Fig. 8).

3.3 Antimicrobial Testing

The synthesized compounds were screened for in vitro antimicrobial activities against four gram-negative *Escherichia Coli (E-coli), Shigella, Klebsiella Pneumoniae (K. Pneumoniae)* and *Salmonella Typhi (S.Typhi)* and a gram positive *Staphylocossus aureus (S.aureus)* bacteria strains. The test was conducted using disc diffusion methods because of its affordability ease of work, efficiency and convenience Balouiri, et al. [14]. The stock solution was prepared by dissolving 5 mg of the samples in 5 mL of Acetonitrile solvent. A serial dilution of different concentrations of 100 µg/mL, 200 µg/mL, 300 µg/mL, 400 µg/mL and 500 µg/mL was then prepared from the stock. The solvent Acetonitrile was used as negative control and standard antibacterial drug Ciprofloxacin (CPX) 10 µg/disc was used as a positive control for comparison of activities with the synthesised compounds. The bacteria were then subcultured in the Muller Hilton agar medium. What man filter paper discs of size 6 mm diameter were sterilized in an autoclave and then soaked in the chosen concertation of the compounds and placed in the Petri dishes containing the Muller Hilton agar media seeded with the respective bacteria strain. The culture was then incubated in an oven at 37℃. The diameters of the zones of inhibition were measured after 18 hours of incubation. The antimicrobial activities were calculated as an average of three replicates (Table 1). The zones of inhibitions (Fig. 9) were measured using a ruler in millimetres (mm), and the following criteria were adopted. Strong activity (> 14 mm), moderate activity (9–14 mm), weak activity (5–8 mm), NA; no activity (inhibition zone < 5 mm), solvent: Acetonitrile (NA) [15].

Table 1. Antimicrobial activities

Sample	Conc. (µg/mL	Gram-Negative				G. Positive
		E-coli	*Shigella*	*K. pneumoniae*	*S. typhi*	*Staph*
1	100	11	12	13	NA	6
	200	12	-	10	NA	10
	300	12	-	13	NA	8
	400	12	-	11	NA	10
	500	15	11	11	NA	13
2	100	14	11	12	NA	6
	200	9.5	-	12	NA	6
	300	15	-	12	NA	8
	400	11	11	-	NA	10
	500	13	10	12	NA	11
3	100	17	14	9	11	10
	200	-	-	-	12	13
	300	12	20.5	15	13	15
	400	17.5	15	10	12	15
	500	13	24	9	12	18
4	100	10	10	12	NA	6
	200	10	10	9	NA	6
	300	10	10	12	NA	8
	400	12	-	-	NA	12
	500	10	-	11	NA	15
5	100	15	12	11	NA	6
	200	16	15	10	NA	8
	300	-	-	-	NA	11
	400	10	17.5	13	NA	13
	500	12	17.5	10	NA	18
CPX	-	25	26	13.5	17	21
Acetonitrile	-	NA	NA	NA	NA	NA

Strong activity (> 14 mm), moderate activity (9–14 mm), weak activity (5–8 mm), NA; no activity (inhibition zone < 5 mm), solvent: Acetonitrile (4 mm) (Jones et al., 1985).

The antimicrobial screening showed that the ligand precursor 1 was also active against the selected pathogens. The ligand recorded its lowest inhibition zone of 6 mm at 100 µg/mL against Staph and the highest inhibition zone of 15 mm at 500 µg/mL against *E.Coli*. Generally, the ligand precursor has an average zone of inhibition of 12 mm against all the selected pathogens. However, a substantial increase in the activities was noted with the metal complexes when compared with the activities of the free ligand. The activities of the metal complexes range between a zone of inhibition 11 mm and 20.5 mm. Weak to moderate activities were seen at concentrations of 100 µg/mL with a significant increase recorded at 400 and 500 µg/mL for all the compounds. It is worth mentioning that, at 100 µg/mL the maximum antimicrobial activity, was observed with imino-NHC cobalt complex **3**, zone of inhibition (17 mm against *E-Coli*, 14 mm against *Shigella*, 9 mm against *K. Pneumonia*, 11 mm against *S. typhi* and 10 mm against *S. aureus*). These activities compared relatively with the standard and with similar work reported in the literature [16]. It was also observed that the square planner nickel complex **5** with N^C^N^O tetra dentate coordinate has higher activity compared with the tridentate C^N^O nickel complex **2** bearing benzyl as a wingtip. Such increased activity of the metal chelates can be explained based on Overtone's concept and chelation theory [17]. Furthermore, the mononuclear nickel complexes **2** and **5** were observed to have higher activities compared with the tri-nuclear nickel complex **4** with two bridging ligands. The reasons for the lowering of activities in **4** may be connected with the bulkiness of the complex that may potentially weaken the active site.

4. CONCLUSIONS

The work discovered both the ligand type and the metal have played a role in the performance of the complexes as antimicrobial agents against the selected pathogens. For instance, it was found that the nickel complex with pyridine as one of the coordinating ligands was more active than the nickel complex with a benzyl as a wingtip. It was also revealed that the mononuclear complexes performed better than the tri-nuclear nickel complex **4** and only the cobalt complex 3 showed some activities against *S. typhi*. And finally, the cobalt complex **3** with octahedral geometry was found to have better performance than the remaining compounds.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Dastgir S, Coleman KS, Cowley AR, Green MLH. A Stable Crystalline Imino-N-Heterocyclic Carbene Ligand and Its Corresponding Palladium(II) and Rhodium(I) Complexes. Organometallics. 2006;25(1):300-306.
2. Porchia M, Pellei M, Marinelli M, Tisato F, Del Bello F, Santini C. New insights in Au-NHCs complexes as anticancer agents. European Journal of Medicinal Chemistry. 2018;146:709-746.
3. Oehninger L, Rubbiani R, Ott I. N-heterocyclic carbenemetal complexes in medicinal chemistry. Dalton Transactions. 2013;42 (10):3269-3284.
4. Arnold PL, Pearson S. Abnormal *N*-heterocyclic carbenes. Coordination Chemistry Reviews. 2007;251(5):596-609.
5. Peris E. Smart *N*-heterocyclic carbene Ligands in Catalysis. Chemical Reviews. 2018;118(19):9988-10031.
6. Power PP. Main-group elements as transition metals. Nature. 2010;463:171.
7. Hansmann MM, Bertrand G. Transition-Metal-like Behavior of Main Group Elements: Ligand Exchange at a Phosphinidene. Journal of the American Chemical Society. 2016;138(49): 15885-15888.
8. Arnold PL, Mungur SA, Blake AJ, Wilson C. Anionic Amido *N*-heterocyclic carbenes: Synthesis of Covalently Tethered Lanthanide–Carbene Complexes. Angewandte Chemie. 2003; 115(48): 6163-6166.
9. Brendel M, Wenz J, Shishkov IV, Rominger F, Hofmann P. Lithium Complexes of Neutral Bis-NHC Ligands. Organometallics. 2015;34(3):669-672.
10. Gupta KC, Sutar AK. Catalytic activities of Schiff base transition metal complexes. Coordination Chemistry Reviews. 2008; 252 (12):1420-1450.
11. Abubakar S, Bala MD. Application of Ni(II) complexes of air-stable Schiff base functionalized N-heterocyclic carbene ligands as catalysts for the transfer hydrogenation of aliphatic ketones. Journal of Coordination Chemistry. 2018;71: 2913-2923.

12. Abubakar S, Ibrahim H, Bala MD. Transfer hydrogenation of ketones catalyzed by a trinuclear Ni(II) complex of a Schiff base functionalized N-heterocyclic carbene ligand. Inorganica Chimica Acta. 2019;484:276-282.
13. Nirmala M, Prakash G, Ramachandran R, Viswanathamurthi P, Malecki JG, Linert W .Nickel(II) complex incorporating methylene bridged tetradentate dicarbene ligand as an efficient catalyst toward CC and CN bond formation reactions. Journal of Molecular Catalysis A: Chemical. 2015; 397:56-67.
14. Balouiri M, Sadiki M, Koraichi SI. Methods for in vitro evaluating antimicrobial activity: A review. Journal of Pharmaceutical Analysis. 2016;6:71–79.
15. Jones RN, Barry AL, Gavan TL, Washington IIJA. In: Lennette, E.H. Ballows, A. Hausler, WJ, Shadomy HJ (Eds.). Manual of Clinical Micro-biology. American Society for Micro-biology, Washington DC. 1985;972 (4th edn).
16. El-Ayaan U, Abdel-Aziz AM. Synthesis, antimicrobial activity and molecular modelling of cobalt and nickel complexes containing the bulky ligand: *bis*[*N*-(2,6 diisopropylphenyl) imino] acenaphthene. European Journal of Medicinal Chemistry. 2005;40:1214–1221.
17. Raman N, Muthuraj V, Ravichandran S, Kulandaisamy A. Proceedings of the Indian Academy of Science. 2003;115: 161.

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