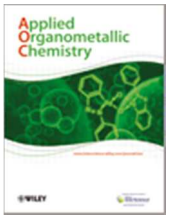
A mixed-ligand quinazoline-based Ni(II) Schiff base complex: Synthesis, characterization, crystal structure, antimicrobial investigation and catalytic activity for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones



A mixed-ligand quinazoline-based Ni(II) Schiff base complex: Synthesis, characterization, crystal structure, antimicrobial investigation and catalytic activity for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones

Journal:	*Applied Organometallic Chemistry*
Manuscript ID	AOC-17-0102
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	10-Feb-2017
Complete List of Authors:	khajoei, Fateme; chemistry khosravan, Mehrji; Shahid Bahonar University of Kerman, chemistry Ebrahimipour, S. Yousef; Shahid Bahonar Univ Kerman, Chemistry bisceglie, franco; university of parma
Keywords:	Catalytic activity, X-ray crystal structure, antibacterial activity, Schiff base, Ni(II) complex

A mixed-ligand quinazoline-based Ni(II) Schiff base complex: Synthesis, characterization, crystal structure, antimicrobial investigation and catalytic activity for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones

Fateme Khajoei[1], Mehrji Khosravan[1], S. Yousef Ebrahimipour[1,2], Franco Bisceglie [3]

[1]Department of Chemistry, Faculty of Science, Shahid Bahonar University of Kerman, Kerman, Iran

[2] Pistachio Safety Research Center, Rafsanjan University of Medical Science, Rafsanjan, Iran

[3]Department of Chemical, Life and Environmental Sustainability Sciences, University of Parma, Italy

Correspond author tel/fax: 0098 34 31312 2143, emails: ebrahimipour@ymail.com, ebrahimipour@uk.ac.ir

Abstract

A tridentate Schiff base ligand, (E)-3-((2-hydroxy-3-methoxybenzylidene)amino)-2-methylquinazolin-4(3H)-one [HL], and its mixed-ligand Ni(II) complex [Ni(L)(imi)], were synthesized and fully characterized using elemental analysis, FT-IR , UV–Vis and ^{1}HNMR spectroscopy techniques. The structure of the synthesized ligand and complex was determined with single crystal X-ray diffraction method. In the complex, a square planner geometry was observed around the Ni(II) central atom coordinated with the donor atoms of the Schiff base ligand and one nitrogen of imidazole group. In addition, the catalytic activity of the complex on the three-component condensation of hydrazine hydrate with phthalic anhydride and dimedone to obtain 2H-indazolo[2,1-b]phthalazine-triones was investigated. Furthermore, in-vitro antimicrobial studies were performed that indicated the great antibacterial activities of the Ni(II) complex against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus cereus* bacteria.

Keywords: Schiff base, Ni(II) complex, Catalytic activity, X-ray crystal structure, antibacterial activity

Introduction

Tridentate Schiff base ligands with ONO donor atoms have attracted much attention due to their rich coordination chemistry [1]. Transition metal complexes with these chelating agents have been widely used in different fields including biochemistry [2] and catalysis [3, 4] . Nickel (II) ion with intrinsic capability to adopt diverse geometries has versatile coordination chemistry [5] which is important for both inorganic chemistry and biochemistry [6, 7]. Moreover, nickel complexes have been reported to show interesting catalytic properties for various reactions such as oxidation, polymerization of olefins [8] and anti-oxidation [9].

Compared with conventional organic reactions, multi-component reactions (MCRs) considered superior synthetic strategies, are green chemical processes with higher efficiency and atom economy requiring minimum time and effort to achieve various compounds with complex structures[10]. For these reasons, hundreds of MCRs have been reported in the literature.

Phthalazine moiety is an important structural motif in numerous biologically active organic compounds [11] such as anti-convulsants [12], cardiotonics [13] and vasorelaxants [14]. Therefore, many efforts have been directed towards the development of new methods for the synthesis of the heterocyclic compounds containing phthala-zine moiety. 2H-indazolo[2,1-b]phthalazine-triones as one of these compounds have been synthesized in the presence of different catalysts. However, these procedures suffer from harsh and strongly acidic conditions [15] and long reaction times [16] required, need to expensive catalysts [17] and toxic organic solvents [18], as well as low yields of the desired products [19]. . Use of a metal complex as the catalyst can obviate some of these issues. Transition metal complexes with variety of structure have potential catalytic activities in addition to biological activity [20]. Our group has reported the use of some metal complexes as catalyst in the synthesis of 2H-indazolo[2,1-b]phthalazine-

triones [21]. In continuing to our previous work, herein we report the use of a novel mixed-ligand Ni(II) complex containing a novel ONO Schiff base ligand for the four-component synthesis of 2H-indazolo[2,1-b]phthalazine-triones.

Moreover, the results of the characterization of the title ligand and its complex using physicochemical and spectroscopic techniques are reported. Finally, the potential antimicrobial activities of the prepared ligand and Ni(II) complex against some Gram-positive and Gram-negative bacteria are evaluated.

Experimental

All chemicals were purchased from Merck and Aldrich and used without further purification. IR spectra were recorded with an 8400-Shimadzu FTIR spectrophotometer. Melting points were measured using an Electrothermal-9100 apparatus. Elemental analyses were obtained using a Thermo Finnigan Flash Elemental Analyzer 1112EA. ^{1}H NMR spectra were recorded at 25 ˚C with Avance BRX 400 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvents. Electronic spectra of the ethanolic solutions of the synthesized compounds were recorded with a Cary 50 UV–Vis spectrophotometer. Conductance measurement was made by means of a Metrohm 712 Conductometer in DMSO.

Synthesis of 3-((2-hydroxy-3-methoxybenzylidene)amino)-2-methylquinazolin-4(3H)-one (HL)

To a solution of 2-methyl-3-amino-quinazoline (1 mmol, 0.175 g) in methanol (10 ml), 3-Methoxy-2-hydroxy benzaldehyde (1 mmol, 0.152 g) was added with continuous stirring. After refluxing the resulting yellow solution for ca. 45 min, crystals were obtained by slow evaporation of the solvent, washed with cold ethanol and dried in a desiccator over silica gel.

Yield: 0.254g, 82%. m.p.: 194 °C. Anal. Calc. for $C_{17}H_{15}N_3O_3$ (309.32 g mol^{-1}): C, 66.01; H, 4.89; N, 13.58. Found: C, 66.12; H, 4.88; N, 13.62%. FT-IR (KBr, cm^{-1}): *ν*(OH) 3476, *ν*(C-$H_{aromatic}$) 2934-3003, *ν*(C=O) 1683, *ν*(C=N) 1602 , *ν*(C=C ring) 1458, *ν*(C–O) 1255. H-NMR (300 MHz, DMSO-d_6, 25 ºC, ppm): δ = 10.05 (s, 1H; OH), 9.15 (s, 1H; CH=N), 8.16-6.93 (m, 7H; ring), 3.87 (s, 3H; OCH_3), 2.51 (s, 3H; CH_3). UV/Vis (EtOH) λ_{max}, nm (logε, L mol^{-1} cm^{-1}): 235(4.86), 305(4.10).

Synthesis of the Imidazole 2-acetamido-N'-(3-methoxy-2-oxidobenzylidene) benzohydrazonate-Nickel(II) [Ni(L)(imi)]

A mixture of the synthesized HL (0.1 mmol, 0.03 g) and $NiCl_2.6H_2O$ (0.1 mmol, 0.03 g) in methanol (5 ml) was refluxed for 30 min. To the resulting green solution, imidazole (0.3 mmol, 0.02 g) was then added and refluxed was continued for 30 min. After cooling the solution, it was filtered off and left to stand overnight. Reddish crystals suitable for crystallography were appeared in the mother liquor after 3 days.

Yield: 0.030g, 63%. m.p.: 238 °C. Molar conductance (10^{-3} M, DMSO): 9 ohm^{-1} cm^2 mol^{-1}. Anal. Calc. for $C_{20}H_{19}N_5NiO_4$ (452.10g mol^{-1}): C, 53.13; H, 4.24; N, 15.49. Found: C, 53.22; H, 4.28; N, 15.42%. FT-IR (KBr, cm^{-1}): *ν*(NH) 3430, *ν*($NH_{imidazole}$) 3142, *ν* (C-$H_{aromatic}$) 2852-3015, *ν*(C=O) 1673, *ν*(C=N) 1592, *ν*(C=C ring) 1434, *ν*(C–O) 1249, *ν*(Ni–O) 546, *ν*(Ni–N) 467. ^{1}H NMR (300 MHz, DMSO-d_6, 25 ˚C, ppm) δ = 14.19 (s, 1H; $NH_{imidazole}$), 9.91 (s, 1H; CH=N), 9.06 (s, 1H; NH_{amide}), 7.49-6.93 (m, 10H; ring), 3.91 (s, 3H; OCH_3), 2.59 (s, 3H; CH_3). UV/Vis (EtOH) λ_{max}, nm (logε, L mol^{-1} cm^{-1}): 235(4.87), 295 (4.84), 450(4.95), 640(2.03)

Crystal structure determination

The X-ray structures of ligands HL and [Ni(L)(imi)] were collected on a Bruker SMART APEX2 with Mo-Kα radiation (λ = 0.71069 Å). The structures were solved through direct methods with SIR97 [22] and refined with SHELXL97 [23] implemented in WinGX [24]. The drawing were obtained using the ORTEP III program [25].

General procedure for the preparation of the phthalazine derivatives

A mixture containing hydrazinium hydrate (1.2 mmol), phthalic anhydride (1 mmol), dimedone (1 mmol), an aryl aldehyde (1 mmol) and [Ni(L)(imi)] (25 mol%), in acetic acid (5 mL) was reacted at 50 °C to give the corresponding 2H- indazolo[2,1-b]phthalazine-1,6,11(13H)-trione derivative. Thin layer chromatography (TLC) using hexane/ethyl acetate as the eluent was used for monitoring the progress of the reaction.

When the reaction was completed, the solvent was evaporated to give a residue, which was then mixed with 5 mL ethanol. The catalyst was removed by centrifugation and then the crude product was recrystallized from a mixture of ethanol and water.

Under optimized conditions, efficiency of this reaction for the synthesis of a different derivatives of 2H-indazolo[2,1-b]phthalazine-triones in the presence of the title metal complex was evaluated. All of the products obtained were characterized using spectroscopic methods including FTIR, ^{1}H NMR, as well as comparison of their melting points with those of the authentic samples. Spectroscopic data for the selected compounds are given below.

3,4-Dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[2,1-b] phthalazine-1,6,11(13H)-trione (1a): M.P. = 204–206 °C. FT-IR (KBr) (υ_{max}, cm^{-1}): 2895, 1660, 1554. ^{1}H NMR (300 MHz,

$CDCl_3$, 25 °C, ppm): 1.22 (6H, s, 2Me), 2.35 (2H, s, CH_2CO), 3.27 and 3.46 (2H, CH_aH_bCO), 6.47 (1H, s,CHN), 7.34-7.52 (9H,m, Ph).

3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11(13H)-trione (2a): M.P. = 226–228 °C. FT-IR (KBr) (υ_{max}, cm^{-1}): 2939, 1622, 1608. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, ppm): 1.22 (6H, s, 2Me), 2.31 (3H, s, CH_3), 2.35 (2H, s, CH_2CO), 3.26 and 3.46 (2H, CH_aH_bCO), 6.45 (1H, s, CHN), 7.12-8.03 (8H, m, Ph).

3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11(13H)-trione (3a): M.P. = 263–265 °C. FT-IR (KBr) (υ_{max}, cm^{-1}): 2894, 1660, 1600. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, ppm): 1.23 (3H, s, Me), 1.34 (3H, s, Me), 2.35 (2H, s, CH_2CO), 3.25 and 3.53 (2H, CH_aH_bCO), 6.53 (1H, s, CHN), 7.27-8.42 (8H, m, Ph).

3,4-Dihydro-3,3-dimethyl-13-(2,4-dichlorophenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11(13H)-trione (4a): M.P. = 219–221 °C. FT-IR (KBr) (υ_{max}, cm^{-1}): 2957, 1660, 1582. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, ppm): δ = 1.21 (3H, s, Me), 1.24 (3H, s, Me), 2.34 (2H, s, CH_2CO), 3.26 and 3.40 (2H, CH_aH_bCO), 6.64(1H, s, CHN), 7.32-8.37(7H, m, Ph).

3,4-Dihydro-3,3-dimethyl-13-(3-nitrophenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11(13H)-trione (5a): M.P. = 270–272 °C. FT-IR (KBr) (υ_{max}, cm^{-1}): 2896, 1661, 1600. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, ppm): δ = 1.18 (3H, s, Me), 1.29 (3H, s, Me), 2.28 (2H, s, CH_2CO), 3.22 and 3.37 (2H, CH_aH_bCO), 6.38(1H, s, CHN), 7.59-8.31 (8H, m, Ph).

3,4-Dihydro-3,3-dimethyl-13-(4-methoxyphenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11(13H)-trione (6a): M.P. = 219–221 °C. FT-IR (KBr) (υ_{max}, cm^{-1}): 2923, 1661, 1600. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, ppm): δ = 1.22(3H, s, Me), 1.26(3H, s, Me), 2.39(2H, s, CH_2CO), 3.21 and 3.46 (2H, CH_aH_bCO), 6.40 (1H, s, CHN), 7.83-8.47 (8H, m, Ph).

Biological activity

To evaluate the antimicrobial activity of HL and [Ni(L)(imi)], agar well diffusion method and minimum inhibitory concentration (MIC) were used. *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus cereus* bacteria studied here were grown overnight and then suspended in Muller Hinton broth to match the 0.5 McFarland standards [1].

In well diffusion method, the inoculums suspension of the microbial stains was swabbed on the entire surface of the agar media. Wells were made and then 50 µl of each compound in two different concentrations (500 µg/ml and1000µg/ml) was added to each well. The plates were incubated at 37°C for 24-48 hours. Antimicrobial activity was assayed by measuring the diameter of the inhibition zone (IZ) formed around the wells in millimeter (mm). DMSO (as the solvent) was used as a negative control, whereas azithromycin (a standard antibiotic) were used as positive controls [1].

MIC is defined as the lowest concentration of a typical compound or drug that completely inhibited the growth of a given strain. The values of MIC for the ligand and its Ni(II) complex were calculated. Serial two-fold dilution (1000 to 7.8 µM) for the ligand and the Ni(II) complex in DMSO were made in the agar media. Overnight broth culture of *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Bacillus cereus* were prepared with bacteria suspension (make $\frac{1}{140}$ dilution of the 0.5 McFarland turbidity). The assay was

performed in Nutrient broth for bacteria. Plates were incubated at specific conditions according to the microbe under assay (37 °C).In the final phase, we read immediately the turbidity of the wells using the micro plate reader device. Then the absorbance read at 620 nm wavelength, until the growth of bacteria reached the stationary phase after 24 hours [26].

Result and discussion

Characterization

A square planner Ni(II) complex was prepared from the reaction of $NiCl_2.6H_2O$ with the synthesized ONO tridentate ligand (HL). The resulting complex was stable in air. It was soluble in several organic solvents, including DMSO and DMF and insoluble in water and *n*-hexane. The molar conductivity of the complex was found to be in agreement with its non- electrolytic nature.

Reaction

Figure 1 shows the synthesis of the complexes schematically. The Ni(II) complex is coordinated by ONO atoms of the ligand and N atom of imidazole.

Mechanism of this reaction is depicted in details in Fig. 2. Free HL molecule has one –OH group which can be converted to $–O^-$ anion. However, due to the complexation reaction, hydrolysis of the ligand occurs resulted in the formation of another $–O^-$ group which can be bound to the Ni(II) central ion. On the other words, after hydrolysis, HL acts as a dibasic ONO ligand which can occupy three position of the coordination sphere around the Ni(II) ion. The forth position is occupied by imidazole molecule resulted in a four-coordinated Ni(II) complex with square planner geometry.

Spectral characterization

Assignments of the prominent bands in the FT-IR spectra of the title compounds are listed in the experimental section. In the FT-IR spectrum of the free HL, a broad band in the region of 3476 cm^{-1} was observed assigned to the vibration of phenolic OH [27]. This peak was disappeared in the spectrum of the complex due to the coordination to the Ni(II) ion after deprotonation of the oxygen. Also the 6-cm^{-1} red shift of ν(C-O) observed in the complex spectrum relative to the free ligand confirmed the coordination of the ligand to the nickel center. The strong band at 1602 cm^{-1}corresponding to ν(C=N) in the free ligand spectrum shifted towards lower frequencies (1592 cm^{-1}) after complexation, indicating the coordination of the azomethine nitrogen atom to the Ni(II) ion [28]. In the complex spectrum, the stretching vibrations owning to N-H band of the amide and imidazole moieties were located at 3430 and 3142 cm^{-1}, respectively. The spectrum of the free HL displayed a strong band at 1683 cm^{-1} attributed to the carboxyl group of the quinazoline ring [29]. Due to the ligand hydrolysis occurred during the complexation, the vibration of C=O in the complex structure was observed at 1673 cm^{-1}. In the IR spectrum of the complex, stretching vibrations of Ni-O and Ni-N were appeared at 546 and 467 cm^{-1}, respectively

^{1}H-NMR study

The ^{1}H-NMR spectra of the synthesized compounds recorded in DMSO-d_6 are given in Fig. S1 and S2. The ^{1}H NMR spectrum of the ligand displayed a singlet signal at 10.05 ppm correlated to OH proton. Absence of this signal in the spectrum of the complex indicated the coordination of the ligand through the deprotonated hydroxyl group. In both compounds, protons of the aromatic rings were observed as multiplets in the range of 6.93–8.16 ppm. The azomethine proton of the free ligand was appeared at 9.15 ppm, whereas proton of the azomethine group coordinated to

the Ni(II) ion showed a significant downfield shift. The spectrum of the complex revealed two singlet bands at 9.06 and 14.19 ppm attributed to NH of the amide group and that of the imidazole moiety, respectively. The protons of the methyl and methoxy groups were respectively observed at 2.59 and 3.91 ppm in the complex and 2.5 and 3.87 ppm in the ligand spectra.

Electronic spectra

The electronic spectra of the synthesized compounds were recorded in ethanol at room temperature. In the ligand spectrum, two bands were observed at 235 nm and 305 nm. The former which was more intense was attributed to $\pi \rightarrow \pi^*$ transitions of the aromatic rings and the latter was originated from $n \rightarrow \pi^*$ transitions of the C=N moiety. the spectrum of the d^8 square planar nickel complex showed an absorption peak at 450 nm correlated to O/N(p)→Ni(d) charge transfer (LMCT) suggesting the coordination of the Ni(II) ion by the donor atoms of the ligand. It was expected that the complex showed three spin-allowed d–d transition bands corresponding to $^1A_1g \rightarrow {}^1A_2g$, $^1A_1g \rightarrow {}^1B_1g$ and $^1A_1g \rightarrow {}^1Eg$, however, tailing of the CT band toward the visible region disappeared these bands [30].

X-ray crystal structure

Main Crystal data and structure refinement for HL and [Ni(L)(imi)] are reported in Table 1, while their ortep views are shown in Figures 3 and 4 respectively. HL molecule can be divided into two planar parts: quinazoline-one and methoxy-phenol moieties. The angle between the two parts is 28.93°. The conformation of the molecule is determined by a strong intramolecular hydrogen bond between O2 and N2 (N2...O2 = 2.6095(3) Å, O2-H15...N2 = 145.98(1) °). It is interesting to note that packing is mainly determined by CH-O interactions between molecules in

an equivalent position. C12...O3 (-x,+y+1/2,-z+1/2+1 position) = 3.50 Å, C12-H9...O3 = 167 °; C13...O2 (-x,+y+1/2,-z+1/2+1 position) = 3.33 Å, C13-H10...O2 = 131°. In the case of aromatic C–H donors, C–H···O interactions are not linear due to influence of aromatic ring substituents near the interacting C-H group. Weak van der Waals interactions between adjacent molecules contribute to the packing and no intermolecular stacking interactions between the aromatic systems are observed.

The introduction of a coordinating metal ion affects dramatically the configuration of HL ligand, since the energy implied in coordination prevails on that of the hydrogen bonds found in the ligand molecules and complexation imposes a rearrangement of the configuration on the ligands by forming three coordinative bonds, i.e. with the phenolic oxygen, the imino nitrogen and the carboxylic oxygen. Ligand HL is also modified during complexation as previously described as can be verified comparing figures 1 and 2. In [Ni(L)(imi)] nickel ion is involved in a square planar geometry, bonding HL *via* ONO and the fourth position is occupied by the imidazolic nitrogen. N2-Ni-N4 = 175.44(3)° and O1-Ni-O2 = 178.03(3)°. HL is deprotonated, and neither chlorides nor solvent are present in the structure. The overall complex entity is planar, and the angle between the quinazoline-one and methoxy-phenol planes decreases up to 7.75°. It is noteworthy that C16-O2 distance is 1.350 Å in the free ligand and 1.316 Å in the metal complex, while O1- C1 is 1.219 Å in the free ligand and 1.301 Å in the metal complex. Table 2 reports the main length of ligand bonds involved in coordination.

The packing of metal complex is mainly determined by a strong intramolecular hydrogen bond between N3 and N1 (2.66 Å, N3-H-N1= 140.31°) and by an hydrogen bond between the imidazolic N5 and O4 in x,-y+1/2,+z-1/2 position (2.77 Å, N5-H-O4 = 162.54°).

Catalytic activity

The experimental conditions for the catalytic synthesis of 2H-indazolo[2,1-b]phthalazine-triones (Fig. 5) were optimized. For this purpose, the reaction of benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), dimedone, and phthalic anhydride in the presence of [Ni(L)(imi)] as catalyst was conducted in different solvents. Table 3 gives the obtained results. It was found that, the highest yield and shortest reaction time was obtained when acetic acid was used as the solvent.

For the optimization of the amount of the catalyst, the condensation of hydrazine hydrate with benzaldehyde, phthalic anhydride, and dimedone in acetic acid was performed in the presence of different quantities of [Ni(L)(imi)] . As revealed in Table 4, use of 0.25 mol% of the catalyst resulted in the highest yield of the product.

Moreover, the generality of the synthesis method was examined under the optimized conditions. In this case, the reaction of hydrazine hydrate, dimedone, and phthalic anhydride in the presence of the complex was carried out using different kinds of aromatic aldehydes. The obtained results reported in Table 5 indicated that [Ni(L)(imi)] was an effective catalyst in the four-component synthesis of 2H-indazolo[2,1-b]phthalazine-triones using a range of aromatic aldehydes.

Furthermore, the results of this study were compared with those of other catalysts reported previously for the synthesis of 3,4-dihydro-3,3-dimethyl-13- phenyl-2H-indazolo[2,1-b] phthalazine-1,6,11(13H)-trione derivatives [Table 6-. It was found that, cleaner reaction profile, shorter reaction time and higher yield as well as an environmentally friendly procedure were the advantages of the catalyst proposed in the present study.

Finally, the reusability of the catalyst in the synthesis of 2,2-dimethyl-13-phenyl-2,3-dihydro-1H-indazolo[2,1-b]phthalazine-4,6,11(13H)-trione was studied. After completion of the reaction, the solvent was evaporated and the obtained residue was suspended in 5 mL EtOH. The

catalyst was then recovered by centrifugation and recrystallization from a mixture of ethanol and water. According to the obtained results depicted in Fig. 6, the recovered catalyst could be reused at least three times while displaying satisfactory yield percentages indicating good reusability of the catalyst.

Antibacterial activity

Antibacterial activity of HL and [Ni(L)(imi)] against some gram-positive and gram-negative bacteria namely *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Bacillus cereus* was evaluated by measuring the inhibition zone (IZ) and MIC values for each compound. Table 7 reveals the values of IZ obtained for the synthesized compounds at two concentrations (500 and 1000 µg/ml) as well as the positive and negative controls. As one can see, [Ni(L)(imi)] shows the highest antibacterial activity against *E. coli* and *P. aeruginosa*. However, the complex has less antibacterial properties than azithromycin against *S. aureus* and *B. cereus*. Surprisingly, [Ni(L)(imi)] has antibacterial activity against *P. aeruginosa* while this species is resistant to azithromycin. Consequently, the synthesized N(II) complex is effective on both Gram negative and Gram positive bacteria.

The MIC values calculated for HL and its Ni(II) complex are given in Table 8. It can be seen that, the MIC values of the ligand are in the range of 62.5–1000 µM while those of the complex are in the range of 62.5-250 µM. These data indicate the higher efficacy of the complex relative to the ligand against the tested bacteria.

Chelation theory can be used for the explanation of the improved antimicrobial activity of the complex compared with the ligand. It has been demonstrated that, the following five factors determine the antimicrobial property of a typical metal complex, i: the chelate effect, ii: nature of

the ligands coordinating the metal ion, iii: total charge of the complex, iv: nature of the counter ion neutralizing the charge of the ionic complex and v: nuclearity of the metal center of the complex [35]. According to Tweedy's chelation theory, polarity of the metal ion diminishes after complexation due to the partial sharing of the positive charge of the metal ion with donor groups of the chelating agent [36]. On the other hand, Overtone's concept states that delocalization of π-electrons over the whole complex ring increases the lipophilicity of the complex compared with the free ligand which in turn enhances the penetration of the complex into the lipid membranes of the microorganisms [36]. Additionally, metal complexes have been reported that can influence the respiration process of the microorganism cells, disturb the synthesis of proteins and finally, restrict further growth of the microorganism [37].

Conclusion

In this work, a new mixed-ligand Ni(II) complex containing a new tridentate ONO Schiff base ligand and imidazole were synthesized and fully characterized using different spectroscopic methods. X-ray structural determination showed that the Ni(II) complex had a square planar geometry. The synthesized complex was applied as an efficient catalyst for the synthesis of 2H-indazolo[2,1-b]phthalazine-triones via a multi-component reaction. Compared with the previously reported procedure, the protocol proposed here was found to offer several advantages, including operational simplicity, high yields and clean reaction conditions. Furthermore, the Ni(II) complex showed promising antimicrobial activities against some Gram-negative and Gram-positive bacteria.

Supplementary data

CCDC 1528496 and 152849 contain the supplementary crystallographic data for HL and [Ni(L)(imi)]. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 UnionRoad, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033, or e-mail: deposit@ccdc.cam.ac.uk, web page: http://www.ccdc.cam.ac.uk/cgibin/catreq.cgi

Acknowledgements

Authors gratefully acknowledge the financial support of the Shahid Bahonar University of Kerman.

Refrences

[1] S.Y. Ebrahimipour, I. Sheikhshoaie, J. Simpson, H. Ebrahimnejad, M. Dusek, N. Kharazmi, V. Eigner, *New J. Chem.* **2016**, 40, 2401.

[2] S.Y. Ebrahimipour, I. Sheikhshoaie, M. Mohamadi, S. Suarez, R. Baggio, M. Khaleghi, M. Torkzadeh-Mahani, A. Mostafavi, *Spectrochim. Acta A* **2015**, 142, 410.

[3] S.Y. Ebrahimipour, H. Khabazadeh, J. Castro, I. Sheikhshoaie, A. Crochet, K.M. Fromm, *Inorg. Chim. Acta* **2015**, 427, 52.

[4] M. Cindrić, G. Pavlović, R. Katava, D. Agustin, *New J. Chem.* **2017**, 41, 594.

[5] E. Ferentinos, D. Maganas, C.P. Raptopoulou, A. Terzis, V. Psycharis, N. Robertson, P. Kyritsis, *Dalton Trans.* **2011**, 40, 169.

[6] D. Nakane, S.-i. Kuwasako, M. Tsuge, M. Kubo, Y. Funahashi, T. Ozawa, T. Ogura, H. Masuda, *Chem. Commun.* **2010**, 46, 2142.

[7] D. Nakane, Y. Wasada-Tsutsui, Y. Funahashi, T. Hatanaka, T. Ozawa, H. Masuda, *Inorg. Chem.* **2014**, 53, 6512.

[8] D. Zhang, G.-X. Jin, *Organometallics,* **2003**, 22, 2851.

[9] H. Wu, J. Yuan, Y. Bai, G. Pan, H. Wang, X. Shu, *J. Photochem. Photobiol. B* **2012**, 107, 65.

[10] L.H. Choudhury, T. Parvin, *Tetrahedron,* **2011**, 67, 8213.

[11] A. Khalil, M. Berghot, M. Gouda, *Eur. J. Med. Chem.* **2009**, 44, 4448.

[12] S. Grasso, G. De Sarro, A. De Sarro, N. Micale, M. Zappalà, G. Puja, M. Baraldi, C. De Micheli, *J. Med. Chem.* **2000**, 43, 2851.

[13] Y. Nomoto, H. Obase, H. Takai, M. Teranishi, J. Nakamura, K. Kubo, *Chem. Pharm. Bull.* **1990**, 38, 2179.

[14] N. Watanabe, Y. Kabasawa, Y. Takase, M. Matsukura, K. Miyazaki, H. Ishihara, K. Kodama, H. Adachi, *J. Med. Chem.* **1998**, 41, 3367.

[15] H.R. Shaterian, M. Ghashang, M. Feyzi, *Appl. Catal. A,* **2008**, 345, 128.

[16] K. Mazaahir, C. Ritika, J. Anwar, *Chin. Sci. Bull.* **2012**, 57, 2273.

[17] H.R. Tavakoli, S.M. Moosavi, A. Bazgir, *J. Korean Chem. Soc.* **2013**, 57, 472.

[18] J.M. Khurana, D. Magoo, *Tetrahedron Lett.* **2009**, 50, 7300.

[19] E. Mosaddegh, A. Hassankhani, *Tetrahedron Lett.* **2011**, 52, 488.

[20] D. E. Çıralı, Z. Uyar, İ. Koyuncu, N. Hacıoğlu, *Appl. Organomet. Chem.* **2016**. 10.1002/aoc.3601.

[21] B. Afzalian, J.T. Mague, M. Mohamadi, S.Y. Ebrahimipour, E.T. Kermani, *Chinese J. Catal.* **2015**, 29, 536.

[22] A. Altomare, M.C. Burla, M. Camalli, G.L. Cascarano, C. Giacovazzo, A. Guagliardi, A.G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, 32, 115.

[23] G. Sheldrick, *University of Göttingen, Germany,* **1997**.

[24] L.J. Farrugia, *J. Appl. Crystallogr.* **1999**, 32, 837.

[25] L.J. Farrugia, *J. Appl. Crystallogr.* **2012**, 45, 849.

[26] F. Heidari, S.J.A. Fatemi, S.Y. Ebrahimipour, H. Ebrahimnejad, J. Castro, M. Dušek, V. Eigner, *Inorg. Chem. Commun.* **2017**, 76, 1.

[27] S.Y. Ebrahimipour, I. Sheikhshoaie, J. Castro, M. Dušek, Z. Tohidiyan, V. Eigner, M. Khaleghi, *RSC Adv.* **2015**, 5, 95104.

[28] S.Y. Ebrahimipour, Z.R. Ranjabr, E.T. Kermani, B.P. Amiri, H.A. Rudbari, A. Saccá, F. Hoseinzade, *Transit.Metal Chem.* **2015**, 40, 39.

[29] I. Sheikhshoaie, S.Y. Ebrahimipour, M. Sheikhshoaie, H.A. Rudbari, M. Khaleghi, G. Bruno, *Spectrochim. Acta A* **2014**, 124, 548.

[30] S.Y. Ebrahimipour, M. Mohamadi, J. Castro, N. Mollania, H.A. Rudbari, A. Saccá, *J. Coord. Chem.* **2015**, 68, 632.

[31] M. Sayyafi, M. Seyyedhamzeh, H.R. Khavasi, A. Bazgir, *Tetrahedron,* **2008**, 64, 2375.

[32] M. Shekouhy, A. Hasaninejad, *Ultrason. Sonochem.* **2012**, 19, 307.

[33] A. Hasaninejed, M.R. Kazerooni, A. Zare, *Catal. Today* **2012**, 196, 148.

[34] S. Rostamnia, E. Doustkhah, *Tetrahedron Lett.* **2014**, 55, 2508.

[35] C. Dendrinou-Samara, G. Psomas, C.P. Raptopoulou, D.P. Kessissoglou, *J. Inorg. Biochem.* **2001**, 83, 7.

[36] R. Takjoo, A. Akbari, S.Y. Ebrahimipour, M. Kubicki, M. Mohamadi, N. Mollania, *Inorg. Chim. Acta* **2017**, 455, 173.

[37] M. Imran, J. Iqbal, S. Iqbal, N. Ijaz, *Turkish J. Biol.* **2007**, 31, 67.

Figure Captions:

Fig. 1. Schematic diagram for complexation processes.

Fig. 2. Schematic diagram for hydrolysis processes.

Fig. 3. Ortep view of HL. Ellipsoids are at 50% probability level.

Fig. 4. Ortep view of [Ni(L)(imi)]. Ellipsoids are at 50% probability level.

Fig. 5. Four-component synthesis of 2H-indazolo[2,1-b]phthalazine-triones.

Fig. 6. The results of reusability of [Ni(L)(imi)] as catalyst for the reaction of hydrazine monohydrate with phthalic anhydride, benzaldehyde, and dimedone.

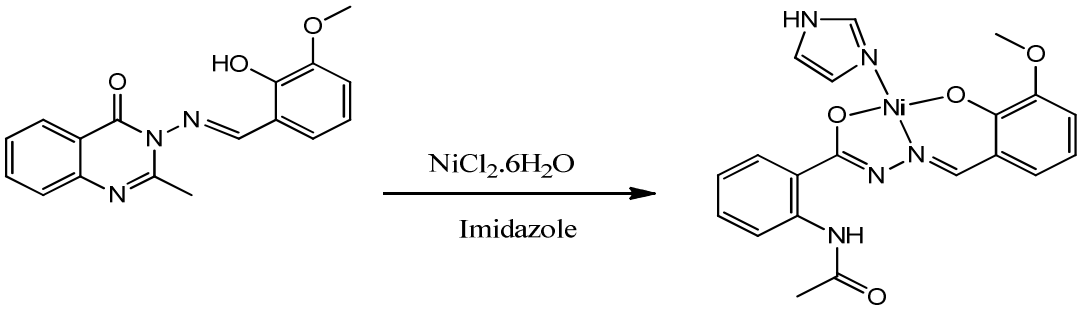


Fig. 1

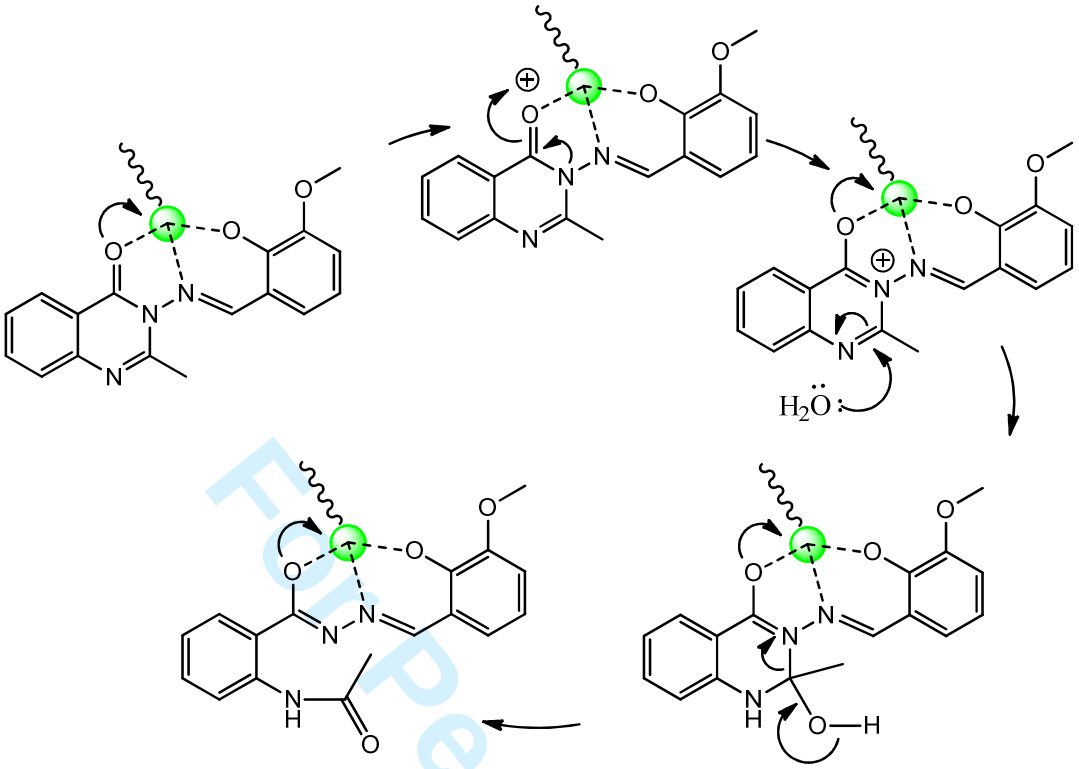


Fig. 2.

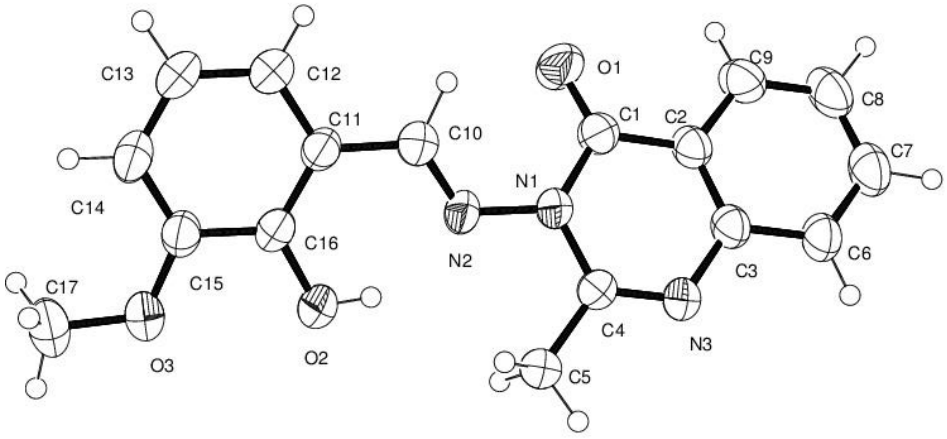


Fig. 3

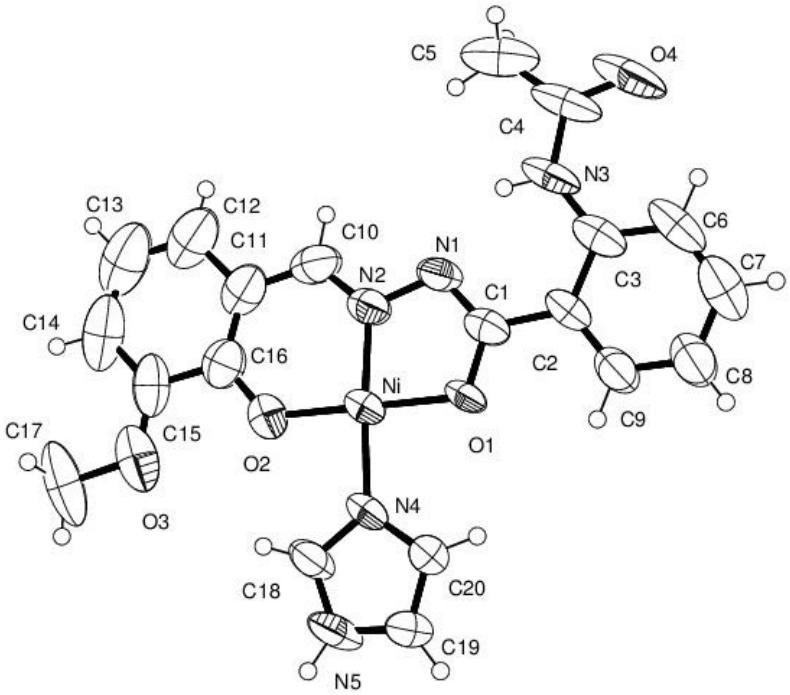


Fig. 4

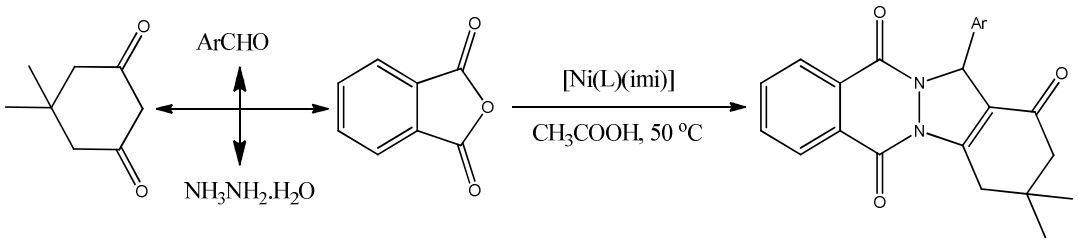


Fig. 5.

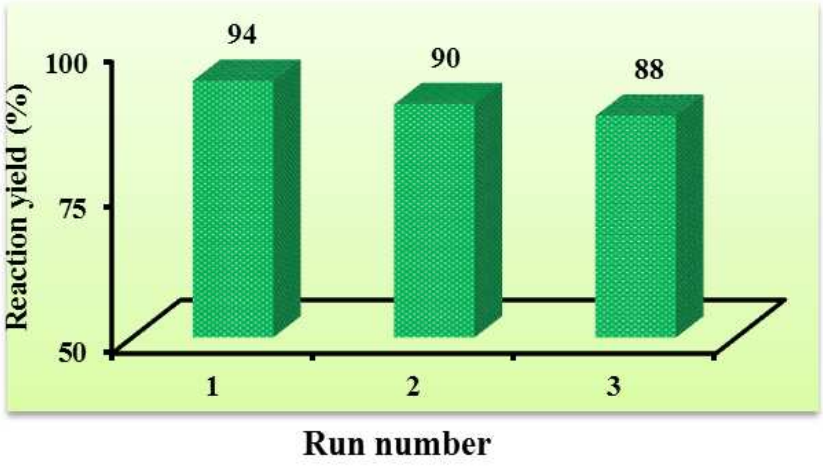


Fig. 6.

Table 1. Crystal data and structure refinement for HL and [Ni(L)(imi)]

	[HL]	[Ni(L)(imi)]
Empirical formula	$C_{17}H_{15}N_3O_3$	C20 H19 N5 Ni O4
Formula weight	309.32	452.11
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	P 21/c	P 21/c
Unit cell dimensions	a = 4.9584(8) Å α= 90° b = 12.9113(19) Å β= 95.558(3)°. c = 23.112(3) Å γ = 90°.	a = 10.688(5) Å α= 90°. b = 7.001(4) Å β= 99.594(10)°. c = 27.735(14) Å γ = 90°.
Volume	1472.6(4) $Å^3$	2046.4(18) $Å^3$
Z	4	4
Density (calculated)	1.395 Mg/m^3	1.467 Mg/m^3
Absorption coefficient	0.098 mm^{-1}	0.985 mm^{-1}
F(000)	644	936
Crystal size	0.4 x 0.4 x 0.4 mm^3	0.6 x 0.4 x 0.2 mm^3
Theta range for data collection	1.771 to 26.688°.	1.489 to 26.823°.
Index ranges	-6<=h<=6, -16<=k<=16, -28<=l<=29	-13<=h<=13, -8<=k<=8, -31<=l<=35
Reflections collected	17871	15445
Independent reflections	3108 [R(int) = 0.0475]	4344 [R(int) = 0.1051]
Completeness to theta = 25.242°	100.0 %	100.0 %
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	3108 / 0 / 265	4344 / 0 / 271
Goodness-of-fit on F^2	1.047	0.911
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1096	R1 = 0.0543, wR2 = 0.1055
R indices (all data)	R1 = 0.0729, wR2 = 0.1263	R1 = 0.1697, wR2 = 0.1438
Largest diff. peak and hole	0.178 and -0.152 $e.Å^{-3}$	0.264 and -0.296 $e.Å^{-3}$

Table 2. Main lengths (Å) of bonds involved in coordination.

	[HL]	[Ni(L)(imi)]
C16-O2	1.351	1.316
C10-N2	1.280	1.293
N2-N1	1.408	1.400
N1-C1	1.412	1.309
C1-O1	1.219	1.301
Ni-O(2)		1.809
Ni-N(2)		1.821
Ni-O(1)		1.846
Ni-N(4)		1.891

Table 3. .Optimization of the reaction time and solvent in the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones from the reaction of benzaldehyde with hydrazine hydrate, dimedone, and phthalic anhydride in the presence of [Ni(L)(imi)].

Solvent	Amount of the catalyst (mol%)	Temperature	Time (min)	Isolated yield %
EtOH	0.25	Reflux	70	55
THF	0.25	Rt	90	21
$EtOH/H_2O$	0.25	50	70	40
CH_3COOH	0.25	Rt	80	75
CH_3COOH	0.25	30	45	89
CH_3COOH	0.25	50	25	94
CH_3COOH	0.25	60	25	93

Table 4. Optimization of the amounts of [Ni(L)(imi)] used as catalyst for the four-component synthesis of 3,4-dihydro-3,3-dimethyl-13- phenyl- 2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione from the reaction of benzaldehyde with hydrazine hydrate, dimedone, and phthalic anhydride in acetic acid at 50 °C.

Amount of the catalyst (mol%)	Time (min)	Isolated yield %
---	60	20
0.2	25	82
0.25	20	94
0.27	20	94

Table 5. Four-component synthesis of a series of 2H-indazolo[2,1-b]phthalazine-trione derivatives from the reaction of phthalic anhydride with hydrazine monohydrate, dimedone, and a series of aromatic aldehydes in the presence of [Ni(L)(imi)] as the reaction catalyst.

Entry	Aldehyde	Time (min)	Isolated yield %	Melting point (˚C)	
				Found	Reported
1	Benzaldehyde	20	94	204-206	204-206[31]
2	3-Nitrobenzaldehyde	18	92	270-272	270-272[31]
3	4-Methoxybenzaldehyde	23	84	219-221	218-220[21]
4	4-Methylbenzaldehyde	25	85	226-228	227-229[31]
5	4-chlorobenzaldehyde	18	91	263-265	262-264[31]
6	2,4-Dichlorobenzaldehyde	15	90	219-221	219-221[21]

Table 6. Comparison of the catalyst used here ([Ni(L)(imi)]) with those previously reported for the synthesis of 3,4-dihydro-3,3- dimethyl-13-phenyl-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione.

Catalyst	Reaction conditions	Time (min)	Yield (%)	Ref.
[Bmim]Br (0.5 g)	Stirring, RT[a]	180	31	[32]
PEG-OSO_3H (8 mol%)	Solvent free, 80 °C	13	87	[33]
SBA-15 (0.02 g)	TFE, 65 °C	180	92	[34]
$[Cu(pzca)_2(H_2O)_2]$(0.2%mol)	CH3COOH, 50 °C	30	92	[21]
[Ni(L)(imi)] (0.25%mol)	CH3COOH, 50 °C	20	94	This work

[a] Room temperature

Table 7: The values of inhibition zone obtained for the tested compounds against using agar well diffusion method.

Microorganism	Inhibition zone (mm)					
	HL		[Ni(L)(imi)]		Positive control	Negative control
	500 µg/ml	1000 µg/ml	500 µg/ml	1000 µg/ml	Azithromycin (15 µg/ml)	DMSO
E. coli	....	7	25.2	26	25	…..
S. aureus	7	8	8	9	25.5	…..
B. cereus	5	15.4	14.2	18	20	…..
P. aeruginosa	6	14	8.2	16.2	……	…..

Table 8: MIC values of [HL] and [Ni(L)(imi)] (μM)

Compound	MIC (μM)			
	E. coli	*S. aureus*	*B. cereus*	*P. aeruginosa*
[HL]	62.5	250	1000	500
[Ni(L)(imi)]	62.5	250	125	250