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SYNTHESIS AND ANTIBACTERIAL STUDY OF ORGANOTIN(IV) COMPLEXES CONTAINING HYDRAZINOPYRIDINE LIGAND

(Sintesis dan Kajian Antibakteria Kompleks Organostanum(IV) yang Mengandungi Ligan Hidrazinopiridin)

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Abstract

Nowadays, the studies on organotin(IV) complexes with hydrazone ligand become more interesting due to their potential in various applications including medicinal area. In our recent studies, four new organotin(IV) complexes $MeSnCl_2(C_{12}H_{12}N_4)$ (**2**), $BuSnCl_2(C_{12}H_{12}N_4)$ (**3**), $PhSnCl_2(C_{12}H_{12}N_4)$ (**4**) and $Ph_2SnCl(C_{12}H_{12}N_4)$ (**5**) were synthesized by the direct reaction of methyl-2-pyridylketone-2-hydrazinopyridine ligand (**1**) and organotin(IV) chloride(s) in absolute methanol. These complexes have been characterized by UV-Visible, FT-IR, ^1H and ^{13}C NMR spectroscopies. All of the synthesized compounds were screened for antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. However, the complexes showed weak activity against the bacteria compared to the free ligand.

Keywords: hydrazone ligand, spectral studies, coordination, biological potential

Abstrak

Pada masa ini, kajian tentang kompleks organostanum(IV) dengan ligan hidrazon semakin menarik kerana sangat potensinya dalam banyak aplikasi termasuk bidang perubatan. Dalam kajian ini, empat organostanum(IV) kompleks iaitu $MeSnCl_2(C_{12}H_{12}N_4)$ (**2**), $BuSnCl_2(C_{12}H_{12}N_4)$ (**3**), $PhSnCl_2(C_{12}H_{12}N_4)$ (**4**) dan $Ph_2SnCl(C_{12}H_{12}N_4)$ (**5**) telah disintesis melalui tindak balas terus metil-2-piridilketon-2-hidrazinopiridin ligan dan organostanum(IV) klorida di dalam metanol. Kesemua kompleks telah dicirikan oleh kajian spektrum UV-nampak, FTIR, ^1H dan ^{13}C RMN. Semua sebatian yang disintesis telah diuji untuk aktiviti antibakteria terhadap *Escherichia coli* dan *Staphylococcus aureus*. Walaubagaimanapun, kompleks menunjukkan aktiviti yang agak lemah menentang bakteria berbanding ligan bebas.

Kata kunci: ligan hidrazon, kajian spektra, koordinasi, potensi biologi.

Introduction

Schiff base metal complexes containing hydrazone group have been studied extensively due to the interesting ligand systems containing different donor sites in heterocyclic rings. Hydrazones are the organic molecule that usually bonded to the metal atom through nitrogen and oxygen but also there was through sulphur atom. These hydrazone chelate derivatives also act as good potential oral drugs to cure the genetic disorders for example thalassemia [1]. Besides, hydrazones have many pharmacological properties including anti-tubercular activities and iron scavenging [2, 3]. The biochemical activity of organotin compounds commonly depend on the structure of the molecule and the coordination number of the tin atoms [4]. Organotin(IV) complexes are known to stimulate therapeutic effects on

various tumor cells [5]. Besides, Sharma and Kaushik [6] found that they are suitable as wood preservatives and active either towards Gram-positive or Gram-negative bacteria.

Thus, there are many of previous researchers reported on the potential of hydrazone metal complexes in biological activities. Bendre et al. [7] have been produced copper(II) complexes of 1,3-bis(2'-pyridyl)-1,2-diaza-2-butene and all of the synthesized compounds showed inhibition activities against mushroom tyrosinase. A few years later, organotin(IV) complexes with vitamin-K_3-2-hydrazinopyridine have been successfully synthesized and evaluated for toxicity and anti-termitic potential by Affan et al. [8]. The result indicated that ligand and organotin(IV) moderately active against *Artenia salina* and *Coptotermes* sp. Again, organotin(IV) complexes with *ortho*-vanillin-2-hydrazinopyridine exhibited better toxicity against *A. salina* and moderate to high activity against four types of bacteria which were *Bacillus cereus, Staphylococcus aureus, Escherichia coli* and *Enterobacter aerogenes* [9]. Evidently, the transition metal and organotin(IV) complexes with 2-hydrazinopyridine derivatives showed many potentials especially in biological activities studies.

Therefore, it is our interest to synthesize, characterize and evaluate the antibacterial activities of organotin(IV) complexes with methyl-2-pyridylketone-2-hydrazinopyridine. This is because this ligand contains N,N-donor atoms which are also still limited, plus the Sn-N coordination bond formed with complexes was believed to contribute to the antibacterial activities of the complexes.

Materials and Methods

Preparation of methyl-2-pyridylketone-2-hydrazinopyridine ligand (1)

A solution of methyl-2-pyridylketone (0.242 g, 0.002 mol) in ethanol (10 mL) was added dropwise to a refluxing ethanolic solution of 2-hydrazinopyridine (0.218 g, 0.002 mol). Three drops of concentrated sulphuric acid were added to the reaction mixture, which was later refluxed for 3 hours. Next, the reaction mixture was allowed to cool to room temperature for one hour. The pink precipitate formed were filtered off and the filtrate was evaporated until milky yellow colour precipitate form. The milky yellow precipitate obtained was recrystallized by slow evaporation of hot absolute ethanol solution at room temperature.

Synthesis of [$MeSnCl_2(C_{12}H_{12}N_4)$] (2)

The ligand ($C_{12}H_{12}N_4$) (**1**) (0.212 g, 0.001 mol) was dissolved in hot absolute methanol (10 mL) in a Schlenk round bottom flask. A methanolic solution of methyltin(IV) chloride (0.240 g, 0.001 mol) was added dropwise into the resulting mixture causing the solution to change from orange to red in colour. The solution was refluxed further for another 5 hours and allowed to cool to room temperature. The precipitate formed was filtered and finally dried in vacuum over silica gel overnight. The methyltin(IV) complex was obtained as shiny red precipitate by recrystallization from methanol.

Synthesis of [$BuSnCl_2(C_{12}H_{12}N_4)$] (3)

Complex **3** was synthesized using the same procedure as **2** with organotin(IV) chloride (0.282 g, 0.001 mol).

Synthesis of [$PhSnCl_2(C_{12}H_{12}N_4)$] (4)

Complex **4** was synthesized using the same procedure as **2** with organotin(IV) chloride (0.302 g, 0.001 mol).

Synthesis of [$Ph_2SnCl(C_{12}H_{12}N_4)$] (5)

Complex **5** was synthesized using the same procedure as **2** with organotin(IV) chloride (0.343 g, 0.001 mol).

Antibacterial activity

The antibacterial activity of ligand (**1**) and its complexes (**2-5**) were studied against *Escherichia coli* O157:H7 and *Staphylococcus aureus* using turbidimetric kinetic method [10]. The inoculums could grow on media containing nutrient broth at 37 °C with permanent shaking at 250 rpm for 18 hours. 7 mL of culture medium with increasing concentration of the compounds dissolved in DMSO were inoculated with 0.14 mL of inoculums and the mixture was shaken again at 250 rpm at 37 °C. The solvent was used as negative control and the clinical antibiotic, amoxicillin was used as positive control. Aliquots of each replicate were taken at every 1 hour interval for 6 hours and the transmittance (T) was registered in a Metertech Plus SP-830 UV-Visible spectrophotometer. The

antibacterial activity was determined by graph as ln Nt which related to the number cfu/mL (colony forming units/mL) for the bacteria versus time.

Results and Discussion

Characterization study: Methyl-2-pyridylketone-2-hydrazinopyridine ligand (1)

Yield: 0.321g, 70%. M.p: 82-83 °C. UV-Visible (DMSO) λ_{max}(nm): 331. IR (ν_{max} cm^{-1}) (KBr): 3343 (NH), 1605 (C=N), 994 (N-N), 776 (pyridine in plane). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.98 (s, 1H, NH), 8.55 (d, 1H, py-H_6), 7.68-8.16 (m, 3H, py-H_3-H_5), 6.84-7.32 (m, 3H, pyridine ring), 2.39 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 157.21 (1C, ***C***=N), 107.34-155.80 (10C, pyridine ring), 11.33 (1C, H_3***C***–C=N) ppm.

[$MeSnCl_2(C_{12}H_{12}N_4)$] (2)

Yield: 0.391 g, 87%. M.p: 285-287°C. UV-Visible (DMSO) λ_{max}(nm): 331, 499. IR (ν_{max} cm^{-1}) (KBr): 3069 (NH), 1599 (C=N–N=C), 1001 (N-N), 781 (pyridine in plane), 566 (Sn–C), 414 (Sn–N). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 10.18 (s, 1H, NH), 8.55 (d, 1H, py-H_6), 8.06-8.36 (m, 3H, py-H_3-H_5), 2.58 (s, 3H, CH_3), 1.57 (s, 3H, Sn-CH_3) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 157.11 (1C, ***C***=N), 113.58-144.59 (10C, pyridine ring), 12.14 (1C, H_3***C***–C=N) 12.70 (1C, Sn-***C***H_3) ppm.

[$BuSnCl_2(C_{12}H_{12}N_4)$] (3)

Yield: 0.320 g, 65%. M.p: 253-254°C. UV-Visible (DMSO) λ_{max}(nm): 331, 500. IR (ν_{max} cm^{-1}) (KBr): 3049 (NH), 1597 (C=N–N=C), 997 (N-N), 771 (pyridine in plane), 565 (Sn–C), 417 (Sn–N). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.96 (s, 1H, NH), 8.77 (d, 1H, py-H_6), 7.96-8.33 (m, 3H, py-H_3-H_5), 6.74-7.75 (m, 4H, pyridine ring) 2.58 (s, 3H, CH_3), 0.95-2.25 (m, 9H, Sn-$CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 157.24 (1C, ***C***=N), 113.51-144.82 (10C, pyridine ring), 12.17 (1C, H_3***C***–C=N) ppm 30.09, 28.56, 25.20, 13.74 (4C, Sn-***C***H_2***C***H_2***C***H_2***C***H_3).

[$PhSnCl_2(C_{12}H_{12}N_4)$] (4)

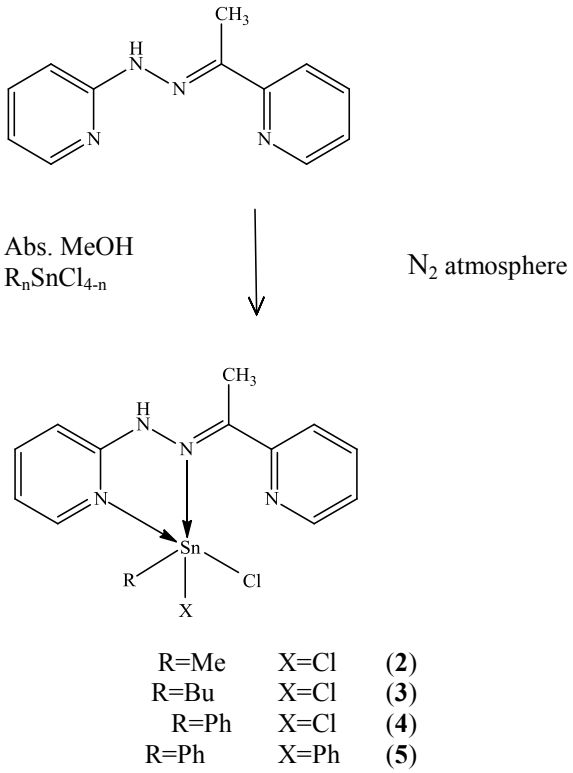
Yield: 0.352 g, 85%. M.p: 268-269°C. UV-Visible (DMSO) λ_{max}(nm): 332, 406. IR (ν_{max} cm^{-1}) (KBr): 3070 (NH), 1598 (C=N–N=C), 1000 (N-N), 778 (pyridine in plane), 566 (Sn–C), 445 (Sn–N). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.96 (s, 1H, NH), 8.55 (d, 1H, py-H_6), 7.65-7.69 (m, 5H, Sn-C_6H_5), 6.66-8.35 (m, overlapping of pyridine-H and phenyl ring protons of phenyl ring attached to the center tin(IV) atom), 2.65 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 157.08 (1C, ***C***=N), 113.74-144.37 (pyridine ring/Sn-***C***$_6H_5$, 15C), 12.12 (1C, H_3***C***–C=N) ppm.

[$Ph_2SnCl(C_{12}H_{12}N_4)$] (5)

Yield: 0.256 g, 46%. M.p: 269-270 °C. UV-Visible (DMSO) λ_{max}(nm): 331, 496. IR (ν_{max} cm^{-1}) (KBr): 3068 (NH), 1598 (C=N–N=C), 999 (N-N), 778 (pyridine in plane), 566 (Sn–C), 446 (Sn–N). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 9.95 (s, 1H, NH), 8.55 (d, 1H, py-H_6), 7.28-7.93 (m, 10H, Sn-$(C_6H_5)_2$), 6.66-8.35 (m, overlapping of pyridine-H and phenyl ring protons of phenyl ring attached to the center tin(IV) atom), 2.65 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 157.33 (1C, ***C***=N), 113.76-148.40 (22C, pyridine ring/Sn-$(***C***_6H_5)_2$, 12.13 (1C, H_3***C***–C=N) ppm.

Synthesis

The methyl-2-pyridylketone-2-hydrazinopyridine (**1**) was initially synthesized by the acid-catalyzed condensation reaction of methyl-2-pyridylketone with 2-hydrazinopyridine in ethanolic solution in 1:1 mole ratio. Afterwards, four new organotin(IV) complexes (**2-5**) were synthesized by direct reaction of organotin(IV) chloride(s) with ligand (**1**) under nitrogen atmosphere. The organotin(IV) complexes were prepared as shown in Scheme 1. All the newly synthesized organotin(IV) complexes were coloured solids and soluble in DMSO, pyridine and DMF.



R=Me X=Cl (**2**)
R=Bu X=Cl (**3**)
R=Ph X=Cl (**4**)
R=Ph X=Ph (**5**)

Scheme 1. Synthesis route of organotin(IV) complexes (**2-5**)

UV-visible spectra

The absorption spectrum of ligand (**1**) was recorded in methanol with concentration of $1x10^{-4}$ M at room temperature. There is only one absorption band appeared at λ_{max} of 331 which are suggested to be causes by n-π* transition of imine group. The electronic absorption spectra of complex (**2-5**) were also recorded in DMSO at room temperature. The first peak at 331-332 nm region is attributed to n-π* transition which has bathochromic shift suggested the free imine (>C=N) group of ligand (**1**) is coordinated to the tin(IV) atoms. Another new peak in the range 496-502 nm indicated the complexation occurred via ligand-to-metal transfer (LMCT) transition [11].

Infrared spectra

To clarify the mode of the ligand coordination to the tin centre, IR spectra in the range of 4000 – 400 cm^{-1} were recorded. The IR spectrum of ligand (**1**) in showed the peak appeared at 3343 cm^{-1} was assigned to NH strectching bond. Another important stretching bands are at 1605 and 994 cm^{-1} which are assigned to υ(C=N), υ(N–N) and υ(pyridine in plane), respectively.

Upon complexation, the stretching vibration azomethine (C=N) is shifted to the lower frequency in all complexes (**2-5**) indicating that azomethine nitrogen is involved in coordination with tin(IV) ion [1]. The υ(N–N) stretching vibration value also shifted to the higher frequency which is 997-1001 cm^{-1} compared to the free ligand further supporting that the coordination of azomethine nitrogen to the Sn(IV) atom. A very strong band of υ(pyridine in plane) also showed increases in its value after complexation compared to the free ligand which is 776 cm^{-1}. The band of υ(pyridine in plane) went to the higher frequencies at 778 – 781 cm^{-1} in all complexes (**2-5**), indicating that the pyridyl ring nitrogen involved in coordination to the Sn(IV) atom. This is probably because of the occurrence of electron reduction upon complexation [8].

Besides, a new band has been identified at 414 – 446 cm^{-1} in all the organotin complexes (**2-5**) confirming that there were Sn–N bond have been formed and showed that the coordination occurred at azomethine nitrogen and pyridine-N atom. Furthermore, the new band of υ(Sn–C) also indicating that alkyl or aryl group coordinated to the Sn(IV) atom [8].

^{1}H NMR spectra

The ligand (**1**) showed resonance signals at 9.98, 8.55, 7.68 – 8.16, 6.84 – 7.32 and 2.39 ppm due to the NH, py-H_6, py-H_3-H_5, pyridine ring and H_3C–C=N respectively. The ^{1}H NMR spectra of complexes (**2-5**) were also successfully obtained. Upon complexation, the NH resonance signals for the complex (**2**) shifted to the downfield region (10.18 ppm) while complexes (**3-5**) shifted to the upfield region (9.95 – 9.96 ppm). This showed the occurrence of complexation NH–C=N nitrogen atom to the tin(IV) atom. The py-H_6 signal shifted to downfield region at 8.55 – 8.87 ppm compared to the free ligand (**1**) in all complexes (**3-5**), suggesting the involvement of pyridyl ring nitrogen atom in the coordination to tin(IV). Other signals for pyridine ring protons were also shifted to the downfield region but the signals could not be identified properly because of the overlapping of pyridyl ring protons. The H_3C–C=N resonance signal for complexes (**3-5**) shifted to the downfield region (2.58 – 2.65 ppm) compared to the free ligand (**1**) also supported the complexation of H_3C–C=N nitrogen atom to the tin(IV) atom. In complex (**2**), a sharp resonance signal appeared as singlet at 1.57 ppm attributed to methyl group attached to tin(IV) atom. The resonance signals were appeared at 0.95 – 2.25 ppm in spectra of complex (**3**) assigned to the butyl group attached to tin(IV) atom. Complexes (**4**) and (**5**) exhibited multiplet signals in the region of 7.28 – 7.93 ppm due to the Sn-Ph protons.

^{13}C NMR Spectra

The ^{13}C NMR spectrum of free ligand (**1**) showed the resonance signals at 157.21, 107.34 – 155.80 and 11.33 are due to the δ(***C***=N), δ(pyridine ring) and (H_3***C***−C=N), respectively. After complexation, the carbon signals of the ***C***=N group shifted to the 157.08 – 157.33 ppm in the complexes (**2-5**) when comparing to the ligand (**1**), indicating participation of the ***C***=N group in coordination to the tin(IV) atom. Besides, the coordination of ligand (**1**) to the tin(IV) atom can be observed through the chemical shifts shown by H_3***C***−C=N in the free ligand (**1**) was observed at 11.33 ppm which were shifted to down field region at 12.12 – 12.17 ppm. These observations indicated that the azomethine-N is coordinated to the tin(IV) moiety [12]. The δ value of carbon atoms in pyridine ring slightly shifted to upfield in the complexes (**2-5**) as compared to the free ligand showed that the pyridine ring nitrogen coordinated to the Sn(IV) atom.

The methyl group attached to the tin(IV) core appeared at 12.70 ppm in complex (**2**). The butyl group attached to the organotin(IV) moiety in complex (**3**) gave four resonance signals at 30.09, 28.56, 25.20 and 13.74 ppm. Apart from that, the phenyl group in complexes (**4**) and (**5**) probably overlapped with pyridine ring from ligand (**1**) and result to the appearance of the resonance signals at 113.74 – 148.40 ppm.

Antibacterial activity

The antibacterial activities of ligand (**1**) and its complexes (**2-5**) were assayed at the concentration 50, 80, 100 ppm against bacteria *E. coli* O157:H7 and *S. aureus* at 37 °C. The antibacterial activities of ligand (**1**) and complexes (**2-5**) were compared with DMSO and amoxicillin as a control. All the synthesized compounds demonstrated a quite similar of bacteriostatic activities upon introduction at different concentrations. The equation of $\ln N_t = 27.1 - 8.56T$ was used to indicate the condition of the microbial specific growth and the amount of drug concentration used. The graph of control showed inactive for antibacterial activity, when tested against *E. coli*. The effect of ligand (**1**) and complexes (**2-5**) was also further shown by their minimum inhibitory concentrations (MIC). The MIC of these compounds were determined by extrapolating the concentration at the zero growth rate of *E. coli* (μ=0) [13]. Compound with the MIC value >200 ppm is not suitable to be used as antibacterial agent for clinical purpose [14]. The MIC of these compounds were determined by extrapolating the concentration at the zero-growth rate of bacteria (μ=0).

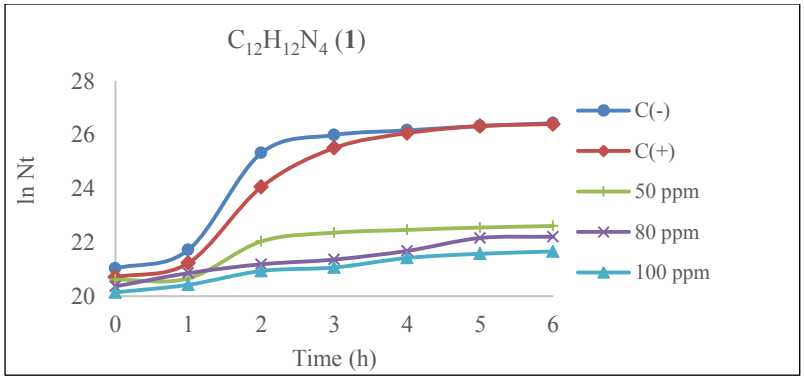
Table 1 shows the MIC values for all synthesized compounds. According to the table, MIC value for ligand (**1**) was lower than 200 ppm, while all complexes (**2-5**) were greater 200 ppm. Based on the results, almost all organotin

complexes (**2-5**) showed weak activities against *E. coli* and *S. aureus*. Meanwhile, the antibacterial activity of the ligand (**1**) showed relatively better antibacterial activity than all of the complexes. Among all of the complexes, complex (**5**) showed the moderate activity against the bacteria strain. Hence, the coordination of tin(IV) atom to the ligand did not raise much of the antibacterial activities. The presence of phenyl group in the complexes (**4**) and (**5**) bonded with the tin atom can improve the antibacterial activity, however in this scenario it is turned out into moderate activity. This is due to the presence of steric hindrance which is preventing the active sites to contact receptor site of the bacteria [9].

Table 1. MIC of ligand (**1**) and complexes (**2-5**)

Compound	**MIC (ppm)**	
	E. coli	***S. aureus***
$C_{12}H_{12}N_4$ (**1**)	127.9	160
$[MeSnCl_2(C_{12}H_{12}N_4)]$ (**2**)	>200	339.4
$[BuSnCl_2(C_{12}H_{12}N_4)]$ (**3**)	>200	371.6
$[PhSnCl_2(C_{12}H_{12}N_4)]$ (**4**)	>200	>200
$[Ph_2SnCl(C_{12}H_{12}N_4)]$ (**5**)	463.3	203.7
Amoxicillin	>200	85.4

In addition, the chloride ion(s) in the structure of the complexes (**2-5**) should be improved the antibacterial activity due to the ability of chloride(s) ion to kill the microbes by inhibiting the multiplication of the bacteria through blockage of the bacteria active sites [9]. However, the presence of the chloride(s) ion in this complexes series did not contribute much to the activity of the complexes. Generally, all the synthesized compounds also more effective against Gram positive bacteria. When comparing the MIC values of the compounds with the clinical antibiotic, amoxicillin, all of the compounds have better activities against *E. coli* but weak activities against *S. aureus*. Figure 1 and 2 shows the inhibition activities of compounds (**1-2**) towards *E. coli* shown as ln N_t for *E. coli* growth *vs.* time and inhibition activities of compounds (**1-2**) towards *S. aureus* shown as ln N_t for *S. aureus* growth *vs.* time, respectively.



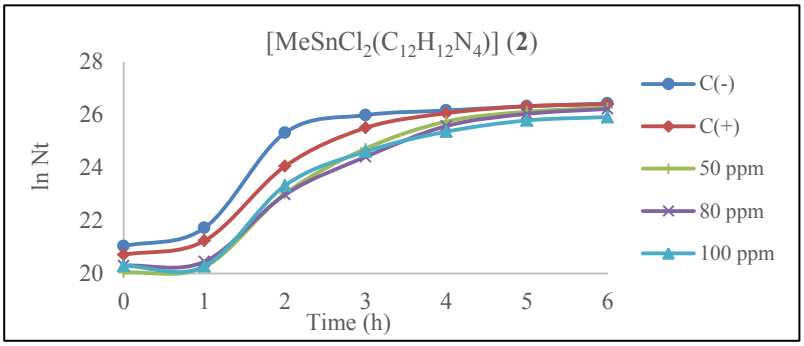


Figure 1. Inhibition activities of compounds (**1**-**2**) towards *E. coli* shown as ln N_t for *E. coli* growth *vs.* time

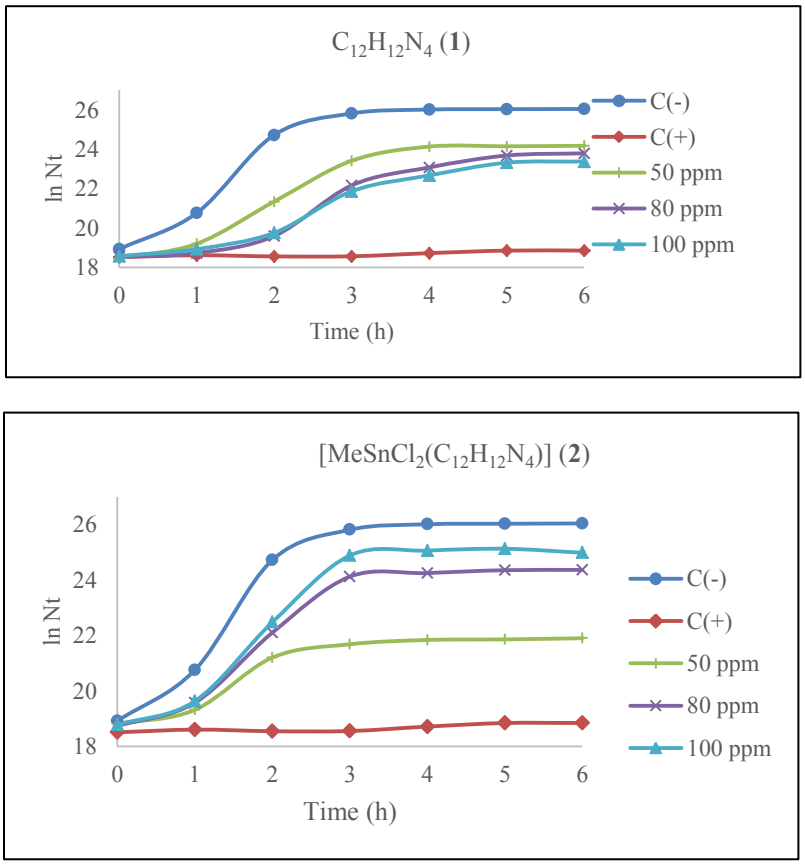


Figure 2. Inhibition activities of compounds (**1**-**2**) towards *S. aureus* shown as ln N_t for *S. aureus* growth *vs.* time

Conclusion

From the spectral analysis, it is suggested the bonding of ligand to the Sn(IV) atom was at the azomethine nitrogen (C=N) and pyridyl nitrogen atoms. The antibacterial activity evaluation showed that the complexation does not raise the antibacterial activities of the complexes in this study since ligand showed better activity than all of the

complexes. Therefore, it is recommended to investigate more on structure-activity relationship in order to improve the activity of the complexes and screened the antibacterial activities against more than one species of bacteria.

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