New 3- hydrazonoindolin-2-one Cd(II) complexes with amino pyridine ligands, Synthesis, Characterization and biological activity evaluation

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ABSTRACT

This research includes synthesis and characterization of some of Cd(II) complexes with (3-hydrazonoindolin-2-one)(HZI) ligand and amino pyridine ligands. Treatment equimolar of CdCl₂, 2.5H₂O and (HZI) ligand with two moles of n-aminopyridine (n-amp) (n: 2, 3, 4) ligands afford a tetrahedral complexes of the type [Cd(HZI)(n-amp)]Cl₂, where (HZI) ligand behaves as a bidentate chelating fashion through the N atom of azethine group and O atom of carbonyl group. Whereas the (n-amp)(n: 2, 3, 4) was bonded monodentate mode through the N atom of heterocyclic ring. The prepared complexes have been characterized by molar conductivity, elemental analysis, infrared spectra and ¹H-NMR and ¹³C-NMR spectra. Also the evaluation of biological activity of the prepared complexes against two types of gram positive bacteria (Staphylococcus Epidermidis and Staphylococcus aureus) and (Citrobacter Freundii) and gram negative, all prepared complexes showed activity against Staphylococcus aureus more than amikacin, while the [Cd(HZI)(3-amp)]Cl₂ complex showed high activity against Staphylococcus Epidermidis and Citrobacter Freundii more than another prepared complexes.

Introduction

Isatin or Tribulin is a derivative of indole from heterocyclic compounds, and its systemic name (1H-indole-2,3-dione), which was obtained by the scientists Erdman and Laurent in 1840 [1] as a product of the oxidation of Indigo (It is a distinctive blue dye) by nitric acid and chronic acid [2]. The isatin is present inside the human body in the brain and many body tissues and fluids. It also has many biological activities such as causing activities, Antispasmodics, analgesics, anti-convulsions and as a potent against of the receptors atrial peptide in vitro [3,4], antibacterial [5,6], anti-HIV activities [7,8], as well as liver metabolites, are found in nature in plants such as mushrooms [9].

An Isatin use as ligand alone in preparation of many complexes or it was prepared a new isatin derivatives such as shiff base, Hydrazine-derived isatins were found to be active against sarcoma, antibacterial and antifungal [10,11]. Similarly, acetone- and ketone-derived isatins exhibited anticonvulsant activity [12]. Therefore in this study, a new Cd(II) with (3-hydrazonoindolin-2-one) (HZI) with n-aminopyridine as co-ligand was synthesized and characterized and studied the biological properties.

Experimental

Materials and methods

All chemical materials and solvents were supplied and used without purification. C.H.N analysis was recorded on an Elementar vario El III C.H.N elemental analyzer. The Nuclear magnetic resonance was measured on a Bruker 400 MHz spectrometer in DMSO-d⁶ as a solvent. The melting point of the ligands and prepared complexes was recorded on Automatic (SMP30) melting point apparatus. The infrared spectra of compounds were recorded with KBr using a Shimadzu FT-IR 8400S spectrophotometer in the 400-4000 cm⁻¹ range. The molar conductivity of 10⁻³ M Freshly DMSO solution of prepared complexes was measured by using (Starter 3100c) digital conductivity meter.

Preparation of 3-hydrazonoindolin-2-one (HZI)

A solution of 98% hydrazine (0.055g, 1.1mmol) in (10ml) of absolute ethanol was added to a solution of isatin (0.161g, 1mmol) in (10ml) of absolute ethanol
ethanol with a few drops from glacial acetic acid. The mixture was refluxed for an hour, and then cooled to room temperature, where a yellow precipitate was separated. The yellow ppt. produced was filtered and washed with cold ethanol and dried under vacuum and recrystallized from a mixture of EtOH / DMF [13].

**Preparation of the [Cd(2-amp)]Cl₂ complex**
A solution of CdCl₂.2H₂O (0.342g, 0.0015mol) in EtOH (10ml) was added to a suspension of 2-aminopyridine (2-amp) (0.282g, 0.003mol) in (5ml), The mixture was stirred at room temperature for an hour, then a white ppt. was formed. The white product was filtered off, and dried under vacuum in oven (0.700g; 75.5%). The [Cd(3-amp)₂Cl₂] and [Cd(4-amp)₂Cl₂] complexes were prepared and isolated in similar method.

**Synthesis of [Cd(HZI)](2-amp)₂ complex**
This complex was prepared by two different methods: 
**First:**
A solution of the HZI ligand (0.080g, 0.005mol) in EtOH (10ml) was added to a suspension of [Cd(2-amp)Cl₂] (0.138g, 0.005mol) in EtOH (10ml), The mixture was stirred for 2 hours at a room temperature. The light yellow precipitate was formed, then filtered and dried in the under vacuum (0.5130g, 66.7%).

The following complexes [Cd(HZI)](3-amp)₂Cl₂ and [Cd(HZI)](4-amp)₂Cl₂ were prepared and isolated in the similar method.

**Second 2nd method:**
A solution of CdCl₂.2H₂O (0.342g, 0.0015mol) (10ml) was added to a solution of 2-aminopyridine (2-amp) (0.282g,0.003mol) in EtOH (5ml), the mixture was stirred for an hour at room temperature where the white suspension was formed, then a solution of (HZI) (0.0015mol, 0.241g) in EtOH (10ml) of was added to the white suspension, the mixture was stirred gradually for 2 hours at room temperature where the yellow precipitate was formed, filtered and dried in the oven under vacuum (0.6152 g; 77.8%).

**Results and discussion**

**Molar electrical conductivity**
The results of the molar electrical conductivity of the (10⁻³M) freshly solution of the (25°C) showed that. All the prepared complexes are electrical were in a molar ratio of (1: 2) positive ion: negative ion.

**Table 1: Color, Yield (%), M.P., molar conductivity and Elemental Analysis of the Prepared ligand(HZI) and [Cd(HZI)(n-amp)]Cl₂ n=1,2,3 Compounds**

<table>
<thead>
<tr>
<th>Seq</th>
<th>Compound</th>
<th>Color</th>
<th>M.P. C°</th>
<th>W.t G</th>
<th>Yield %</th>
<th>α (ohm⁻¹ cm² mol⁻¹)</th>
<th>Found(cal)%</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HZI</td>
<td>Yellow</td>
<td>240-242</td>
<td>2</td>
<td>92</td>
<td>-</td>
<td>59.62</td>
<td>39.48</td>
<td>13.14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[Cd(HZI)(2-amp)]Cl₂</td>
<td>Yellow white</td>
<td>236-239</td>
<td>0.19</td>
<td>71</td>
<td>70.01</td>
<td>40.58</td>
<td>40.32</td>
<td>14.31</td>
<td>13.33</td>
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<tr>
<td>3</td>
<td>[Cd(HZI)(3-amp)]Cl₂</td>
<td>Yellow white</td>
<td>233-235</td>
<td>0.20</td>
<td>75</td>
<td>73.76</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>[Cd(HZI)(4-amp)]Cl₂</td>
<td>Yellow white</td>
<td>243-246</td>
<td>0.17</td>
<td>79</td>
<td>80.74</td>
<td>40.58</td>
<td>40.41</td>
<td>13.41</td>
<td>13.35</td>
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</tbody>
</table>

**Infrared spectra**
The infrared spectrum of (HZI) ligand showed a new stretch band of the azomethine group ν(C=N) at (1589cm⁻¹) after the disappearance of the stretch band of ν(C=O) carbonyl group in the free isatin. The ν(C=O) carbonyl amide group showed at (1685cm⁻¹), while the ν(NH) group showed at (3153cm⁻¹) and the symmetrical and asymmetric stretching of the ν(NH₂) group displayed at (3193,3353cm⁻¹) respectively [13].

The spectra of the prepared complexes showed the ν(C=O) carbonyl amide group bands within the (1685-1683cm⁻¹) range, the azomethine ν(C=N) group bands displayed within the (1606-1587cm⁻¹) range, while the ν(NH) group bands showed at (3157cm⁻¹), either symmetric and asymmetric ν(NH₂) bands displayed within the (3207-3197cm⁻¹) and (3362-3353cm⁻¹) range respectively. The ν(C=O) group in aminopyridine ligands were displayed within the (1552-1550cm⁻¹) range [14,15].
Fig. 1: IR spectrum of (HZI) ligand

Fig. 2: IR spectrum of [Cd(HZI)(2-amp)]Cl₂ complex

Table 2: Selected IR stretching vibration bands (cm⁻¹) of the ligand and its complexes

<table>
<thead>
<tr>
<th>Compounds</th>
<th>HZI</th>
<th>Amine ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vC=O</td>
<td>vN=N</td>
</tr>
<tr>
<td>HZI</td>
<td>1685s</td>
<td>1589s</td>
</tr>
<tr>
<td>Cl₂Cd(HZI)(2-amp)₂Cl₂</td>
<td>1685s</td>
<td>1587s</td>
</tr>
<tr>
<td>Cl₂Cd(HZI)(3-amp)₂Cl₂</td>
<td>1683s</td>
<td>1606s</td>
</tr>
<tr>
<td>Cl₂Cd(HZI)(4-amp)₂Cl₂</td>
<td>1685s</td>
<td>1587s</td>
</tr>
</tbody>
</table>

s = strong, m= medium, w= weak , Ar.= Aromatic

NMR Spectra

¹H-NMR of (HZI) ligand
The ¹H-NMR spectrum of (HZI) ligand in DMSO-d⁶ showed the protons Hₐ and Hₜ as doublet of doublets at δ=7.36ppm and δ=6.87ppm with coupling constant (³Jₐₜₜₜ=8.03Hz) and (³Jₐₜₜₜ=7.87Hz) respectively. Whereas the proton in position Hₘ and Hₜ appeared as doublet of triplets at δ=6.98ppm and δ=7.16ppm with coupling constant (³Jₐₜₜₜ=7.78 Hz) and the spectrum showed two doublet at δ=9.53ppm and δ=10.54ppm with coupling constant (³Jₐₜₜₜ=13.94 Hz) respectively attributed to each of (NH₂) proton [13], and showed a single signal at δ=10.67ppm attributed to the (NH) proton for isatin.
1H-NMR of [Cd(HZI)(2-amp)$_2$]Cl$_2$ complex

The spectrum of [Cd(HZI)(2-amp)$_2$]Cl$_2$ complex showed a doublet signal at $\delta$H=6.86 ppm with coupling constant ($^3$J$_{Ha-Hb}$=7.74 Hz) due to the H$_d$ proton, and a triplet of doublets at $\delta$H=6.97 ppm with coupling constant ($^3$J$_{Hb-Hc}$=7.50 Hz), ($^4$J$_{Hb-Hd}$=1.02 Hz) attributed to proton H$_b$ proton, another signal showed a triplet of doublets at $\delta$H=7.15 ppm with coupling constant ($^3$J$_{Hc-Hb}$=7.61 Hz), ($^4$J$_{Hc-Ha}$=1.31 Hz) attributed to the H$_c$ proton, the spectrum showed a doublet at $\delta$H=7.36 ppm attributed to the H$_a$ proton, with coupling constant ($^3$J$_{Ha-Hb}$=7.56 Hz), the spectrum also showed two doublets at $\delta$H=9.53 ppm and $\delta$H=10.54 ppm with coupling constant ($^3$J$_{H1-H2}$=14.22 Hz) and ($^3$J$_{H1-H2}$=14.12 Hz) respectively attributed to each of (NH$_2$) protons[13], and showed a single signal at $\delta$H=10.68 ppm attributed to the (NH) proton for isatin.

The spectrum showed the signals of protons of the 2-amp as a broad singlet at $\delta$H=5.99 ppm attributed to the (NH$_2$) where the integration value confirms the presence of 4 protons of the two (NH$_2$) groups, and the protons of H4 and H2 showed a multiple at $\delta$H=6.48 ppm, and the H3 appeared a triplets of doublet at $\delta$H=7.90 ppm due to the H1 proton with coupling constant ($^3$J$_{H1-H2}$=5.1 Hz), ($^3$J$_{H1-H3}$=1.08 Hz).
The $^{13}$C-$^{1}H$ NMR spectrum of complex in DMSO-d$_6$ showed a signal at $\delta$C=139.39 ppm due to the carbon of (N=C) group, and the $\delta$C=149.39 ppm carbon in position 5 in 2-amp and at $\delta$C=159.79 ppm to the carbon position 1 in 2-amp, a signal at $\delta$C=163.51 ppm attributed to the carbon of (C=O) group, while the another signals of the carbon atoms showed within $\delta$C=137.63-109.95 ppm range.

The spectrum of complex showed a doublet of doublets at $\delta$H=6.86 ppm with coupling constant ($^{3}$J$_{Hd-Hc}$ = 7.83 Hz), ($^{4}$J$_{Hd-Hb}$ = 2.53 Hz) due to the H$_d$ proton, and a triplet of doublets at $\delta$H=6.97 ppm with coupling constant ($^{3}$J$_{Hb-Hc}$ = 7.54 Hz), ($^{4}$J$_{Hb-Hd}$ = 2.72 Hz) attributed to proton H$_b$ proton, another signal showed as a triplet at $\delta$H=7.16 ppm with coupling constant ($^{3}$J$_{Hc-Hb}$ = 7.63 Hz), attributed to the H$_c$ proton, the spectrum showed a doublet at $\delta$H=7.36 ppm with coupling constant ($^{3}$J$_{Ha-Hc}$ = 8.51 Hz), attributed to the H$_a$ and H$_1$ of 3-amp protons where the integration value confirms the presence of 3 protons, the spectrum also showed two doublets at $\delta$H =9.54 ppm and $\delta$H =10.54 ppm with coupling constant ($^{3}$J$_{H4}$ =14.54 Hz) and ($^{3}$J$_{H1}$ =14.84 Hz) respectively attributed to each of (NH$_2$) protons[13], and showed a single signal at $\delta$H=10.68 ppm attributed to the (NH) proton for isatin.

The spectrum showed signals of 3-amp as a broad singlet at $\delta$H=5.13 ppm attributed to the (NH$_2$) where the integration value confirms the presence of 4 protons of the two (NH$_2$) groups, and showed a doublet at $\delta$H=6.44 ppm attributed to the H$_3$ protons with coupling constant ($^{3}$J$_{H3-H2}$ =9.26 Hz), ($^{4}$J$_{H3-H1}$ =2.33 Hz), and a triplet at $\delta$H =6.57 ppm attributed to proton H2 with coupling constant ($^{3}$J$_{H2-H1}$ =8.13 Hz), and a doublet at $\delta$H =7.90 ppm attributed to the H4 protons with coupling constant ($^{3}$J$_{H4-H1}$ =4.16 Hz)[16].
**13C-NMR of [Cd(HZI)(3-amp)]2Cl2 complex**

The spectrum of complex showed a signal at \( \delta C=139.13 \) ppm attributed to the carbon of benzene ring which was bonded to N pentagonal ring, the spectrum showed a signal at \( \delta C=149.39 \) ppm attributed to the carbon Position 5 in 3-amp, signal at \( \delta C=160.17 \) ppm attributed to the carbon Position 5 in 3-amp, a signal at \( \delta C=163.25 \) ppm attributed to the carbon of (C=O) group, while the another signals of the carbon atoms showed within \( \delta C=108.66-127.51 \) ppm range[16].

**1H-NMR spectrum of [Cd(HZI)(3-amp)]2Cl2 complex**

The spectrum of complex showed a doublet at \( \delta H=6.86 \) ppm with coupling constant \( \left(J_{Hd-Hc}=7.66\text{Hz}\right) \) due to the H\(_d\) proton, and a triplet at \( \delta H=6.97 \) ppm with coupling constant \( \left(J_{Hb-Hc}=7.56\text{Hz}\right) \) attributed to proton H\(_b\) proton, another signal showed a triplet of doublets at \( \delta H=7.14 \) ppm with coupling constant \( \left(J_{Hc-Ha}=7.61\text{Hz}\right) \) \( \left(J_{Hc-Ha}=1.49\text{Hz}\right) \), attributed to the H\(_c\) proton, the spectrum showed a doublet at \( \delta H=7.36 \) ppm attributed to the H\(_3\) with coupling constant \( \left(J_{Hb-Hd}=6.88\text{Hz}\right) \), the spectrum also showed two doublets at \( \delta H=9.53 \) ppm and \( \delta H=10.54 \) ppm with coupling constant \( \left(J_{H2-H1}=13.95\text{Hz}\right) \) and \( \left(J_{H1-H1}=10.00\text{Hz}\right) \) respectively attributed to each of (NH\(_2\)) protons[13], and showed a single signal at \( \delta H=10.68 \) ppm attributed to the (NH) proton for isatin.

The spectrum showed signals of 4-amp as a broad singlet at \( \delta H=5.98 \) ppm attributed to the (NH\(_2\)) where the integration value confirms the presence of 4 protons of the two (NH\(_2\)) groups, and showed a doublet of doublets at \( \delta H=6.45 \) ppm attributed to the H2 protons with coupling constant \( \left(J_{H2-H2}=7.94\text{Hz}\right) \) \( \left(J_{H2-H2}=3.91\text{Hz}\right) \), and showed a doublet of doublets at \( \delta H=6.58 \) ppm attributed to the H1 protons with coupling constant \( \left(J_{H1-H1}=8.80\text{Hz}\right) \) \( \left(J_{H1-H1}=3.99\text{Hz}\right) \).
$^{13}$C-$^1$H-NMR Spectrum of $[\text{Cd(HZI)}(4\text{-amp})_2]\text{Cl}_2$ complex
The spectrum showed a signal at $\delta C = 110.16$ ppm due to the carbon of position 2 in 4-amp and a signal at $\delta C = 136.51$ ppm due to the carbon of (C-N) group, and a signal at $\delta C = 139.39$ ppm attributed to the carbon of benzene ring which was bonded to N pentagonal ring, the spectrum showed a signal at $\delta C = 149.47$ ppm attributed to the carbon of position 1 in 4-amp and a signal at $\delta C = 153.97$ ppm due to the carbon of position 3 in 4-amp, a signal at $\delta C = 163.51$ ppm attributed to the carbon of (C=O) group, while the another signals of the carbon atoms showed within $\delta C = 112.01$-129.64 ppm range.

Biological activity study of the prepared compounds
The evaluation of biological activity of the prepared complexes against two bacterial types Staphylococcus Epidermidis and Staphylococcus aureus (gram positive) and Citrobacter freundii (gram negative) by hole method in ($10^{-3}, 10^{-4}, 10^{-5}$ M) of solution of the prepend complexes in DMSO-$d^6$ [17-19] compared with Amikacin as standard antibiotic. All complexes showed high activity against Staphylococcus aureus more than amikacin, while the $[\text{Cd(HZI)}(3\text{-amp})_2]\text{Cl}_2$ complex showed high activity against Staphylococcus Epidermidis and Citrobacter freundii more than another complexes.
Scheme 2: The biological activity of the prepared complexes against three types of bacteria species.

Conclusions
A new tetrahedral complexes of the type [Cd(HZI)(n-amp)_2]Cl_2 (if n=2,3,4) when prepared by the react equal molar of CdCl_2.2.5H_2O and HZI ligand with two moles of n-aminopyridine (n=2,3,4). The HZI ligand behaves as a bidentate chelating ligand thought the N atom of the azomethine group and O atom of carbonyl group, whereas the n-aminopyridine ligands bonded as a monodentate through the N atom of heterocyclic ring. And the prepared complexes showed a high biological activity against the Staphylococcus aureus mor than amikacin, while the [Cd(HZI)(3-amp)_2]Cl_2 complex showed activity against Staphylococcus Epidermidis and Citrobacter freundii compared with free ligand and Amikacin.

Table 3: Dimeter inhibition zone (in mm) of the prepd complexes in DMSO (DIZ) in (mm)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Concentration (mm)</th>
<th>Staphylococcus aureus (mm)</th>
<th>Staphylococcus epidermidis (mm)</th>
<th>Citrobacter freundii (mm)</th>
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<tr>
<td>Amikacin</td>
<td>1*10^-5</td>
<td>15</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>(HZI)</td>
<td>1*10^-3</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1*10^-4</td>
<td>36</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1*10^-5</td>
<td>36</td>
<td>30</td>
<td>10</td>
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<tr>
<td>[Cd(HZI)(2-amp)_2]Cl_2</td>
<td>1*10^-3</td>
<td>38</td>
<td>8</td>
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<td>1*10^-4</td>
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</tr>
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<tr>
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<td>10</td>
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<td>38</td>
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<td>8</td>
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<td></td>
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<td>38</td>
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References
تحضير وتشخيص وتقليم الفعالية البايولاجية لبعض معقدات Cd(II) مع مزيج من ليكادات

3-هيدروازونوбинولين-2-أون والآمينات

ليلى وليد محمد، أحمد عبد الناصر أرّوفي
قسم الكيمياء، كلية التربية للعلوم الصرفة، جامعة تكريت، تكريت، العراق

المختص

يتضمن هذا البحث تحضير وتشخيص عدد من معقدات الكادميوم (II) مع ليكادات، أمينو بيريدين، (3-hydrazoneindolin-2-one) عدد من (HZI) (n=2,3,4) (n-amp) مع مول من (CdCl2.2.5H2O) مع من مجموعات [Cd(HZI)(n-amp)]Cl2 عند تفاعل مول واحد من ملح الفاز. أرجعت النتائج المتوقعة على نشاطات الدراسة، [Cd(HZI)(3-amp)]Cl2 والكادميوم (II) للعدوى النوعين من البايولوجيا البايولاجية Staphylococcus و Staphylococcus aureus. أظهرت جميع المعقدات المذكورة فعالية عالية اتجاه Amikacin (119-126).