Synthesis, Characterization and In Vitro Antibacterial Evaluation of Sn, Sb, and Zn Coordination Complexes of 2-(2-Methoxyphenyl)-1H-Isindole-1, 3(2H)-Dione

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ABSTRACT

Hunting of new biologically active compounds is the need of time. Thanks to metals for being the charm of this field since more than half a century. Present report describes the synthesis, chemistry and biological evaluation of metal complexes of N-aryl phthalimides, a very interesting class of compounds in terms of their wide biological and chemical applications. Ortho anisidine is reacted with phthalic anhydride under solvent free condition to give N-substituted aryl phthalimide (Ligand A). The resultant phthalimide is then reacted with different metals like alkyl Tin (IV) halides, Antimony (III), and Zinc (II) to form novel coordination complexes (C1-C7). All the synthesized compounds have been characterized by 1H NMR, 13C NMR, 119Sn NMR, FTIR, Mass spectrometry for m/z ratio. Fascinatingly, the synthesized complexes have shown improved antibacterial effects in comparison to their parent ligands against standard Ciprofloxacin.

Keywords: Alkyl tin halide, Antimony, Antibacterial, Metal complex, N-aryl phthalimides.

INTRODUCTION

Antimicrobial resistance affords a survival benefit to microbes and makes it harder to abolish infections from the body. Eventually, the increasing difficulty in fighting off microorganisms directs to an increased risk of acquiring infections. To overcome this problem, searching for new antibacterial moieties is the interest of the scientists since last few decades. Compounds having oxygen and nitrogen atoms as donor sites are attributed for their prospective biological effects. Study of coordination potential of these ligands with the biological system is of great importance; consequently to study the structure activity relationships of a variety of new derivatives containing antitumor activity.1-10 Scientists have altered their attention towards metal complexes of different pharmacologically active ligands. The synthesis of organotin carboxylate has drawn our attention to explore new metal carboxylate that may have better biological properties.11-15 Recently the pharmaceutical properties of organotin complexes have been investigated with particular reference to their antitumor activity.16-17 Nitrogen heterocycles is an important part of the chemical structures of many natural and synthetic products with a range of properties and applications in medicinal and pharmaceutical chemistry.18 Among the bicyclic, non-aromatic nitrogen heterocycles, phthalimides is an interesting class of compounds with a large range of applications.19 Phthalimides have served as starting materials and intermediates for the synthesis of numerous types of alkaloids and pharmacophores.20 Recently, phthalimides and some of their derivatives proved to have important biological effects similar or even higher than known pharmacological molecules and so their biological activity is being a matter of biomedical research.21-24

The metal complexes of tin are of great biochemical importance because of their significant bactericidal, fungicidal and cytotoxic activities.25 It is observed that ligands when coordinated with metal ions show considerably enhanced antimicrobial activities.26-27 To synthesize the ligand (precursor) for further derivatives is most of the times a very tedious and multistep reaction resulting less yield and use of toxic solvents. Keeping these problems in view, 2-(2-methoxyphenyl)-1H-isindole-1,3(2H)-dione (Ligand A) has been synthesized by single step under solvent free condition using literature method.28 Various novel coordination complexes have been synthesized by reacting with tin (IV) chlorides, antimony (III) chloride and Zinc (II) chloride.

MATERIALS AND METHODS

Melting points were determined on Gallenkamp melting point apparatus using open capillary tubes and are uncorrected. FTIR spectra were recorded on Bruker Fourier Transform Infrared spectrophotometer (4000-400 cm⁻¹). 1H NMR, 13C NMR and 119Sn spectra were recorded on Bruker 400MHz and 500MHz using Deutrated solvents.

Synthesis of Ligand and Its Metal Complexes

Synthesis of 2-(2-methoxyphenyl)-1H-isindole-1,3(2H)-dione (Ligand A)

Equimolar quantities of phthalic anhydride and 2-methoxy aniline were weighed accurately and separately. The reactant with the low melting point was taken in a china dish and heating was started soon as the solid was molten the other reactant was added with continuous stirring. The reaction evolved some fumes and changed
the color and phase. Then heating was continued for a while until a homogenous phase was formed. It was allowed to cool to room temperature. The product obtained was recrystallized from chloroform. General scheme is given in Figure 1.

![Figure 1: Synthesis of 2-(2-methoxyphenyl)-1H-isindole-1,3(2H)-dione](image1)

**Synthesis of tin complexes of 2-(2-methoxyphenyl)-1H-isindole-1,3(2H)-dione**

1 mmol of the free ligand was suspended in 100 ml of dry toluene and 1 mmol of triethylamine was added to the flask. This mixture was then refluxed for 3-4 hrs. To this reaction mixture the metal salt, i.e dirganotin dichloride/triorganotin chloride (1 mmol/2 mmol) was added as a solid with continuous stirring. The mixture was allowed to reflux for 8-10 hrs. The filtrate contained the metal derivative of the ligand. The solvent was removed by a rotary evaporator and the solid obtained was recrystallized from CH₂Cl₂/CHCl₃ and ether/n hexane in equal ratio (129). General structure for a tin complex is given in Figure 2.

![Figure 2: General Structure for tin complexes of Ligand A](image2)

**Synthesis of Zinc (II) complexes of Ligand A**

2 mmol (1 eq) of the ligand was dissolved in 10 ml of methanol. 1 mmol (0.5 eq) of zinc chloride was dissolved in 10 ml of methanol. The zinc solution was added to the free ligand solution and then the mixture was stirred for 1 hr at 60°C on a heating magnetic stirrer. After cooling, the solvent was removed under vacuum. The solid was recrystallized with a mixture of equivalent portion of hexane and chloroform by slow evaporation.

**Synthesis of Antimony (III) complexes of Ligand A**

1 mmol of the free ligand was dissolved in 15 ml of acetonitrile (solution 1). In a separate beaker 1 mmol of antimony (III) chloride was dissolved in acetonitrile (solution 2). Solution 1 was added to solution 2. On mixing the color of the solution turned brown. After stirring for about 1 hour, the solution became clear. The solvent was allowed to evaporate at room temperature. A colored crystalline solid was obtained after one week.

General structure for Zn and Sb complexes is given in Figure 3 and 4.

![Figure 3: Zn (II) complex of Ligand A](image3)

**RESULTS AND DISCUSSION**

**Physical Data**

All the complexes are off white to colored powders or crystalline solids. The complexes are air stable at room temperature. These are frequently soluble in chloroform, acetone, methanol and DMSO.

IR, NMR and Mass data of 2-(2-methoxyphenyl)-1H-isindole-1,3 (2H)-dione (Ligand A) and its complexes

2-(2-methoxyphenyl)-1H-isindole-1,3 (2H)-dione (Ligand A)

Molecular formula: C₁₃H₁₂NO₃, Molecular weight: 253, m.p.: 152-155°C, yield: 86% IR ν (cm⁻¹): 1778, 1704 (C=O) imide, 1594, 1463 (C=C), 1452 (C-N). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.69 (d, J=8 Hz, 4H, Ar. CH), 7.80 (d, J=8 Hz, 2H, Ar. CH), 7.30 (d, J=2 Hz, Ar. CH), 7.07 (t, 1H, Ar. CH), 3.82 (s, 3H, Ar.OCH₃). ¹³C NMR (400 MHz, CDCl₃) δ (ppm): 133.7 (C₁), 133.7 (C₂), 133.7 (C₃), 157.6 (C₄), 111.1 (C₅), 123.0 (C₆), 130.0 (C₇), 154.0 (C₈), 119.0 (C₉), 55.8 (C₁₀). Mass data (m/z): 253 [M⁺], 235 [M⁺-18], 222 [M⁺-31], 210 [M⁺-43], 195 [M⁺-58], 179 [M⁺-74], 120 [M⁺-133], 51 [M⁺-202]. Elemental Analysis Calc: C, 68.40; H, 4.38; N, 5.53. Found: C, 69.40; H, 4.32; N, 5.16. Tin complex (1) of Ligand A (C₁)

Molecular formula: C₁₃H₁₂NO₃SnCl, Molecular weight: 638, m.p.: 98-100°C, yield: 65% IR ν (cm⁻¹): 1779, 1736 (C=O) imide, 1384 (C=O), 1620, 1450 (C=C), 1405 (C-N), 2844 (C-H), 1259 (C-O), 446 (M-O). ¹H NMR ((400 MHz, CDCl₃) δ (ppm): 7.85-7.96 (m, J=8 Hz, 4H, Ar. CH), 7.12-7.34 (m, J=8 Hz, 4H, Ar. CH), 3.79 (s, 3H, Ar.OCH₃). ¹³C NMR ((400 MHz, CDCl₃) δ (ppm): 133 (C₁), 129.4 (C₂), 133 (C₃), 167.7 (C₄), 110 (C₅), 122.9 (C₆), 130 (C₇), 118.6 (C₈), 1543.9 (C₉), 118.6 (C₁₀), 60.5 (C₁₁), 128-130 (all
carbons of phenyl rings of triphenyl tin chloride), \(^{119}\)SnNMR: -46.24 ppm. Mass data (m/z): 351 (79 [M\(^+\)], 274 (44) [M\(^+\)-77], 253 (100) [M\(^+\)-98], 120 (36) [M\(^+\)-231], 77 (14) [M\(^+\)-274]. Elemental analysis: Calc. C, 65.70; H, 4.34; N, 2.32. Found: C, 63.54; H, 4.97; N, 2.09.

**Tin complex (2) of Ligand A (C2)**

Molecular formula: C\(_{36}\)H\(_{32}\)O\(_{12}\)SnCl\(_{2}\). Molecular weight: 810, m.p.: 148-150°C, yield: 74 % IR data v (cm\(^{-1}\)): 1778, 1730 (C=O) imide, 1384 (C=O), 1600, 1462 (C=C), 1405 (C-N), 2845 (C-H), 1258 (C-O), 472 (M-O). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 7.96 (dd, J=8 Hz, 4H, Ar. CH), 7.80 (dd, J=8 Hz, 4H, Ar. CH), 7.46 (m, J=8 Hz, 4H, Ar. CH), 7.10 (m, J=8Hz, 2H, Ar. CH), 3.82 (s, 3H, Ar.CH3), 1.58 (m, 1.44(m), 1.28(t, 1H, CH3 ), 0.98 (t, 1H, CH3). \(^{13}C\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 133 (C\(_{1}\)), 123 (C\(_{2}\)), 129, 130 (C\(_{3,3}\)), 167 (C\(_{4}\)), 111 (C\(_{5}\)), 123 (C\(_{6}\)), 129 (C\(_{7}\)), 120 (C\(_{8}\)), 155 (C\(_{9}\)), 120 (C\(_{10}\)), 55 (C\(_{11}\)), 16 (C\(_{12}\)), 23(C\(_{13}\)), 25(C\(_{14}\)), 8.27(C\(_{15}\)). \(^{119}\)Sn NMR: 146 ppm. Elemental analysis: Calc. C, 61.72; H, 5.45; N, 3.79. Found: C, 60.21; H, 5.17; N, 3.82.

**Tin complex (3) of Ligand A (C3)**

Molecular formula: C\(_{36}\)H\(_{32}\)O\(_{12}\)SnCl\(_{2}\). Molecular weight: 726, m.p.: 136-140°C, yield: 69 % IR data v (cm\(^{-1}\)): 1779, 1738 (C=O) imide, 1384 (C=O), 1597, 1467 (C=C), 1405 (C-N), 2844 (C-H), 1259 (C-O), 448 (M-O). \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 7.96 (dd, J=7.6 Hz, 4H, Ar. CH), 7.80 (dd, J=7.6 Hz, 4H, Ar. CH), 7.46 (m, 4H, Ar. CH), 7.10 (m, 4H, Ar. CH), 3.82 (s, 3H, CH3), 1.28(s, 3H, CH3). \(^{13}C\)NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm): 133, 131 (C\(_{1,1}\)), 123, 120 (C\(_{2,2}\)), 129, 130 (C\(_{3,3}\)), 167 (C\(_{4}\)), 111 (C\(_{5}\)), 123 (C\(_{6}\)), 129 (C\(_{7}\)), 120 (C\(_{8}\)), 155 (C\(_{9}\)), 119 (C\(_{10}\)), 55 (C\(_{11}\)), 8 (C\(_{12}\)). \(^{119}\)SnNMR: -63.7 - 116.18 ppm. Mass data (m/z): 726 (37 [M\(^+\)], 253 (100) [M\(^-\), 179 (76) [M\(^-\)-193], 179 (53) [M\(^-\)-267], 120 (23) [M\(^-\)-326].

**Zinc complex (6) of Ligand A (C6)**

Molecular formula: C\(_{36}\)H\(_{32}\)No\(_{2}\)ZnCl\(_{2}\). Molecular weight: 642, m.p.: 136-138°C, yield: 69 %.

IR data v (cm\(^{-1}\)): 1778, 1740 (C=O) imide, 1384 (C=O), 1597, 1467 (C=C), 1405 (C-N), 2842 (C-H), 1259 (C-O), 483 (M-O). \(^{1}H\) NMR (400 MHz, DMSO) \(\delta\) (ppm): 7.94 (d, J=8 Hz, 4H, Ar. CH), 7.90 (d, J=8Hz, 4H, Ar. CH), 7.53-7.10 (m, Ar. CH), 1.97 (s, 6H, Ar.CH3). ESIMS data (m/z): 643 [M\(^+\)]. 390 [M\(^-\)-253], 319 [M\(^-\)-324], 253 [M\(^-\)-390], 179 [M\(^-\)-464], 120 [M\(^-\)-523], 91 [M\(^-\)-552].

**Antimony complex (7) of Ligand A (C7)**

Molecular formula: C\(_{36}\)H\(_{32}\)N\(_{2}\)O\(_{2}\)SbCl\(_{4}\). Molecular weight: 481, m.p.: 145-147°C, yield: 68 %. IR data v (cm\(^{-1}\)): 1780, 1744 (C=O) imide, 1394 (C=O), 1680, 1467 (C=C), 1405 (C-N), 2842 (C-H), 1259 (C-O), 483 (M-O). \(^{1}H\) NMR (400 MHz, DMSO) \(\delta\) (ppm): 7.94 (d, J=8 Hz, 4H, Ar. CH), 7.90 (d, J=8Hz, 2H, Ar. CH), 7.53-7.10 (m, 2H, Ar. CH). Mass data (m/z): 446 (37 [M\(^+\)], 253 (100) [M\(^-\)-193], 179 (53) [M\(^-\)-267], 120 (23) [M\(^-\)-326].

**RESULTS AND DISCUSSION**

We have succeeded to synthesize N-aryl Phthalimide 2-(2-methoxyphenyl)-1H-isindole-1,3(2H)-dione by using the simple, solvent free method. The reaction was performed by fusion of phthalic anhydride with ortho-methoxy aniline, obtaining a good yield and relatively pure product. It is noteworthy adding here that FTIR spectrum of Ligand A proves the cyclic structure of imide as there are no absorption bands for v(O-H) and v(N-H) confirming success of dehydration and formation of 5 membered ring containing Nitrogen. Presence of two bands near 1780 cm\(^{-1}\) and 1708 cm\(^{-1}\) correspond to the asymmetric and symmetric carbonyl bands of cyclic imides.

\(^{1}H\)NMR spectrum of Ligand A showed a distinct singlet at 3.82 ppm for the hydrogen of methoxy (OCH\(_{3}\)) group and two multiplets at 7.4 and 7.80-7.96 ppm are assigned to the protons of the two aromatic rings. Absence of NH or OH signals confirms the presence of 5 membered ring. \(^{13}C\)NMR spectrum of the compound showed peaks at 55.48, 155.08 and 167.02 ppm for methoxy, C of methoxy group attached to C and N respectively. The signals for both aromatic rings lie in between (111-133.7) ppm. Results for elemental analysis further confirm the statement. Then we synthesized the metal complexes of the ligand A.

Moreover, the change in IR frequency of C=O bond in the complexes indicated the involvement of C=O bond of the imide in the metal-ligand bond formation. C=O bond frequency shifted from 1700 to 1740. Also the M-O bond formation is confirmed by the new bands that appear in

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the range of 438-473 cm⁻¹. NMR and Mass spectrum further proved the formation of complexes. In case of complexes (C1-C5) ¹H NMR and ¹³C NMR clearly indicated the presence of alkyl groups associated with tin along with peaks for ligand, may confirming the attachment of ligand with alkyl metal halide. In case of Tin complexes ¹¹⁹Sn NMR gave a clear proof for the tin complexes as confirmed by the literature. Mass spectrum shown to have exact molecular weight in case of tributyltin complex (C4) but gave a fragment ion peak at 351 in case of triphenyltin complex (C1). All these findings lead us to find the proposed structure of metal complexes as illustrated in the Figure 2-4.

From antibacterial evaluation it has been observed that some of newly synthesized compounds (C1, C4 and C7) are found to be more effective antibacterial agents even then the standard drug Ciprofloxacin against particular species. On the whole most of them proved to have enhanced activity than their parent ligand especially tin complexes and antimony complex.

**Biological Assay**

**Antibacterial Assay**

The antibacterial activities of the reported organometallic compounds against *Escherichia coli*, *Staphylococcus aureus*, Salmonella typhi ATCC bacterial strains using agar well diffusion method.²⁹-³⁰ Ciprofloxacin Hydrochloride disc was used as standard drug. The solution of the test sample (conc. 1 mg/ml in DMSO) was poured into the respective wells which are dug by using sterile borer. DMSO and Ciprofloxacin drugs acting as negative and positive control were also poured into wells respectively. The plates were incubated immediately at 37°C for 24 h. The activity was determined by measuring the diameter of zone of inhibition around the wells. Growth inhibition was calculated with reference to positive control.³⁰ Antibacterial results are illustrated in Table 1.

**Table 1: Antibacterial Activity for Ligand A and its Complexes**

<table>
<thead>
<tr>
<th>Sample</th>
<th>S.T</th>
<th>S.A</th>
<th>E.C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand A</td>
<td>12</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>C1</td>
<td>18</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>C2</td>
<td>30</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>C3</td>
<td>22</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>C4</td>
<td>28</td>
<td>34</td>
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<td>C5</td>
<td>25</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>C6</td>
<td>12</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>C7</td>
<td>24</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Cip (std)</td>
<td>30</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>DMSO(control)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

S.T = Salmonella typhi, S.A = Staphylococcus aureus, E.C= Escherichia coli, Cip (std) = Ciprofloxacin (standard)

**CONCLUSION**

In summary, we have synthesized 2-(2-methoxyphenyl)-1H-isooindole-1,3(2H)-dione (Ligand A), under solvent free condition which have many advantages over the already known methods. For instance, this reaction offers advantages of an easy work-up, high yields, fast reaction rates etc. We moved a step forward to describe the coordination complexes and their antibacterial activity. It is proved by the results that introduction of metals in the ligand enhances the antibacterial activity. This is a very good sign for designing and development of new antibacterial candidates.

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