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Synthesis, Chemical Characterization and Biological Evaluation of Zn (II), Fe (III) And Sb (III) Metal Complexes of 4-[(3-Bromophenyl)amino]-4-oxobutanoic acid

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Abstract – Present research report elucidates the synthesis, chemistry and biological evaluation of metal complexes of the ligand 4-[(3-Bromophenyl)amino]-4-oxobutanoic acid. The ligand was synthesized by reacting bromo Substituted aniline with succinic anhydride by fusion technique under solvent free condition. The compound was then reacted with Zn (II), Fe (III) and Sb (III) chlorides to form metal complexes. The structures of ligand and complexes were confirmed by physical data, spectral evaluation including FTIR, GCMS, ^{1}H NMR, ^{13}C NMR etc. The ligands and their complexes were screened for Carbonic anhydrase inhibition, alkaline phosphatase inhibition and antioxidant activity. Remarkable results were obtained for Zn and antimony complexes of the ligand.

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Keywords – Metal Complex, Oxobutonic acid, Iron, Zinc

1. Introduction

Search for the new biologically active compounds is the need of the time. Thanks to metals for being the charm of this field since more than half a century. It is well known that metal complexes of many cyclic and heterocyclic compounds have diverse biological activities and most of them proved to be more effective as compared to the parent compounds. And this diversity in pharmacological effects encouraged us to develop some new metal derivatives of our ligands.

Keeping In view the diverse fields of applications of carboxylate complexes, we have synthesized some new metal derivatives with 4-[(3-Bromophenyl)amino]-4-oxobutanoic acid in continuation of our previous work [7-13]. Our aim is to determine the possible use of these compounds as biocides, as well as the structural correlation, i.e., whether the biocidal activity is related to the organic part of the ligand or the organotin moiety. Further, we aim to investigate the spectroscopic behavior and elucidate the structure.

Since the recognition of Cisplatin and its derivatives as anticancer, coordination complexes become a major concern to medicinal scientists. In addition to 'platinum', medicinal chemists and other scientists are now interested in the other metals such as Zinc, Antimony, Copper, cobalt, palladium, ruthenium and gold etc. their complexes are also been synthesized and evaluated for their anticancer, antileshminial antibacterial and antifungal activities.

Since last two decades antimony complexes are of great interest for medicinal chemists because of their potent pharmacological effects as antimicrobial agents, widely used to treat fever, epilepsy, melancholy, syphilis, pneumonia, other inflammatory conditions and all kinds of leishmenia. The antimony complexes also have considerable antitumor activity.

Antimony complexes are synthesized and evaluated for biological effects by a number of chemists. They are also interested in the behavior of the metal with oxygen, nitrogen and sulfur containing ligands. A large number of organoantimony complexes of donor ligands (containing oxygen, nitrogen or sulfur) have been synthesized and biologically screened by Mahajan and co-workers. Interestingly they found the complexes with more potent microbiological effects in comparison to the parent compounds [9-11].

2. Experimental

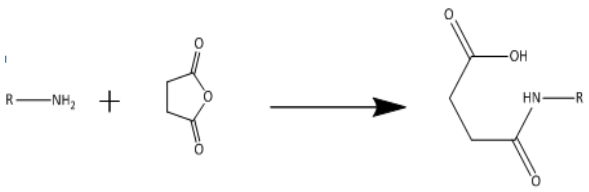
2.1. Chemistry

All the chemicals were of analytical grade and were purchased from sigma Aldrich and Merck. Solvents were used in purest form and of analytical grades. Where necessary, solvents were dried/ distilled using standard procedures (1). Melting points were determined by digital Gallenkamp (SANYO) apparatus and were uncorrected. FTIR spectra were recorded by Bruker Alpha-P FTIR spectrometer (4000-400 cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded by Bruker AV 400RG, AVII 400, and AV 500 Spectrophotometers using Deutrated solvents as an internal reference. Mass spectral data are collected from Agilent 6890N GCMS spectrometer and ESIMS spectrometers.

2.2. General procedure for synthesis of Ligand

Equimolar quantities of succinic anhydride and substituted aniline were weighed accurately and separately. First the reactant (having lower melting point) was heated. As soon as the solid was molten, the other reactant was added with stirring. The reaction mixture may evolve some fumes,

and may change the color and phase. Then heating was continued until a homogenous phase was formed. It was allowed to cool to room temperature. The product was recrystallized by using chloroform.



Where R-NH_2= meta bromo aniline
Scheme I

2.2.1. General procedure for Synthesis of Zinc Complex

1mmol (1 eq) of ligand was dissolved in 10 ml of methanol. 0.6 mmol of (0.5 eq) zinc chloride was dissolved in 10 ml of methanol. Zinc chloride solution was added to ligand solution and then stirred for 1 hour at 60°C. After cooling, the solvent was removed under vacuum. The solid was recrystallized with equivalent portion of hexane: chloroform by slow evaporation at room temperature.

2.2.2. Synthesis of Iron Complex

Equimolar solutions of the free ligand and ferric chloride were prepared separately. Then the ethanol solution of ferric chloride was added to the free ligand solution with continuous stirring and the reaction mixture was then refluxed with stirring for about one hour. The resulting colored solution was cooled to room temperature. The product was removed by filtration and washed with cooled absolute ethanol. The product was recrystallized from methanol /acetonitrile and dried under vacuum.

2.2.3. Synthesis of Antimony Complex

1mmol of ligand was dissolved in 15 ml of acetonitrile (solution 1). In a separate beaker 1mmol of antimony III chloride was dissolved in acetone (solution 2). Solution 1 was added in solution 2. On mixing color of solution turned to brown. Stirred for about 1 hour, solution became clear. Solvent allowed evaporating at room temperature. Colored crystalline solid obtained after a week.

2.3. Analysis Data

2.3.1. 4-[(3-Bromophenyl)amino]-4-oxobutanoic acid

Molecular formula: C10H10NO3Br, Molecular weight: 272, m.p.: 113 oC, % yield:72 %IR data ν (cm-1): 3299 (O-H), 3256 (N-H), 1726, 1651 (C =O), 1585, 1478 (C =C). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.81 (d, Ar. CH), 7.10-7.39 (m, Ar. CH), 7.19 (s, NH), 10.3 (s, OH), 2.78 (t, 2H), 2.51 (t, 2H). 13C NMR δ (ppm): 137.5 (C1), 120.3 (C2), 122.7 (C3), 130.2 (C4), 129.4 (C5), 121.5 (C6), 176.5 (C7), 26.5 (C8), 30.6 (C9), 167 (C10). Elemental Analysis: Calc. (%): C, 44.14; H, 3.70; N, 5.15. Found (%): C, 43.54; H, 3.96; N, 4.91.

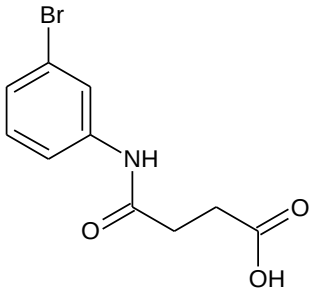


Figure 1. 4-[(3-Bromophenyl)amino]-4-oxobutanoic acid

2.3.2. Zinc Complex of Ligand

Molecular formula: C20H18N2O6Br2Zn, Molecular weight: 607, m.p. 133 -135 oC, % yield : 64IR data ν (cm-1): 3350 (N-H), 1724, 1641 (C=O), 1583, 1474 (aromatic C=C), 437 (M-O). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.83 (d, Ar. CH), 7.10-7.41 (m, Ar. CH), 7.18 (s, NH), 2.81 (t, 2H), 2.54 (t, 2H). 13C NMR δ (ppm): 137 (C1), 120.7 (C2), 122 (C3), 130.8 (C4), 129.6 (C5), 122.1 (C6), 176.7 (C7), 27 (C8), 30.3(C9), 169 (C10). Elemental Analysis: Calc. (%): C, 39.54; H, 2.99; N, 4.61. Found (%): C, 40.10; H, 3.15; N, 4.93.

2.3.3. Iron Complex of Ligand

Molecular formula: C10H9Cl2NO3BrFe, Molecular weight: 397, m.p. 87-94 oC, % yield: 53IR data ν (cm-1): 3341(N-H), 1698, 1641 (C=O), 1584, 1475 (aromatic C=C), 459 (M-O). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.81 (d, Ar. CH), 7.08-7.39 (m, Ar. CH), 7.20 (s, NH), 2.80 (t, 2H), 2.52 (t, 2H). 13C NMR δ (ppm): 136.8 (C1), 120.6 (C2), 122.7 (C3), 130.2 (C4), 129.4 (C5), 122.5 (C6), 177 (C7), 27 (C8), 30.9 (C9), 169.3 (C10). Elemental Analysis: Calc. (%): C, 30.19; H, 2.28; N, 3.52. Found (%): C, 30.06; H, 2.96; N, 3.82.

2.3.4. Antimony Complex of Ligand

Molecular formula: C20H18N2O6Br2Sb, Molecular weight: 463, m.p. 217-225 oC, % yield: 61IR data ν (cm-1): 3346(N-H), 1700, 1642 (C=O), 1571, 1499 (aromatic C=C), 521 (M-O). 1H NMR (400 MHz, CDCl3) δ (ppm): 7.82 (d, Ar. CH), 7.09-7.39 (m, Ar. CH), 7.18 (s, NH), 2.79 (t, 2H), 2.52 (t, 2H). 13C NMR δ (ppm): 136.9 (C1), 121.3 (C2), 123 (C3), 130.2 (C4), 129.4 (C5), 121.7 (C6), 176.8 (C7), 27.5 (C8), 30 (C9), 168.7 (C10). Elemental Analysis: Calc. (%): C, 36.18; H, 2.73; N, 4.22. Found (%): C, 36.42; H, 2.91; N, 4.52.

3. Results and discussion

We have already reported a simple and efficient route for synthesis of substituted Phthalimides and phenyl acetamides [12-13]. We prepared carboxylates by reacting succinic anhydride with substituted anilines by fusion of the reactants through heating without use of any solvent or catalyst. We got good yields of ligands and further purified by recrystallization using chloroform. Now we are reporting the Zn (II), Fe (III) and Sb (III) metal complexes of 4-[(3-Bromophenyl)amino]-4-oxobutanoic acid.

Melting points and Infra Red spectra were corresponding with the formation of metal complexes. Further characterizations through ^{1}H NMR, ^{13}C NMR, GCMS, Elemental analysis further confirmed the structures assigned. ^{1}HNMR spectrum of Ligand showed two distinct singlets at δ = 7.19 and 10.3 ppm for NH and OH respectively. One doublet and a multiplet in the range of 6.80 - 7.90 belong to the protons of aromatic ring. ^{13}CNMR results verified the structure of the Ligand. A distinct signal at 176.5, 26.5, 30.6, 167 for C=O, CH_2, and C=O of COOH respectively. The signals for aromatic ring appeared between (120-140) ppm.

Furthermore, the change in IR frequency of C=O bond in the complexes indicated the involvement of C=O bond of the carboxylic acid in the metal-ligand bond formation. Absence of OH band in the IR spectra and OH signal in proton NMR confirmed the formation of complexes. C=O bond frequency shifted from 1651 to 1641 in case of Zinc complex. Also the M-O bond formation is confirmed by the new bands that appear in the range of 400-600 cm^{-1}. ^{1}H NMR, ^{13}C NMR and Mass spectrum further proved the formation of complexes.

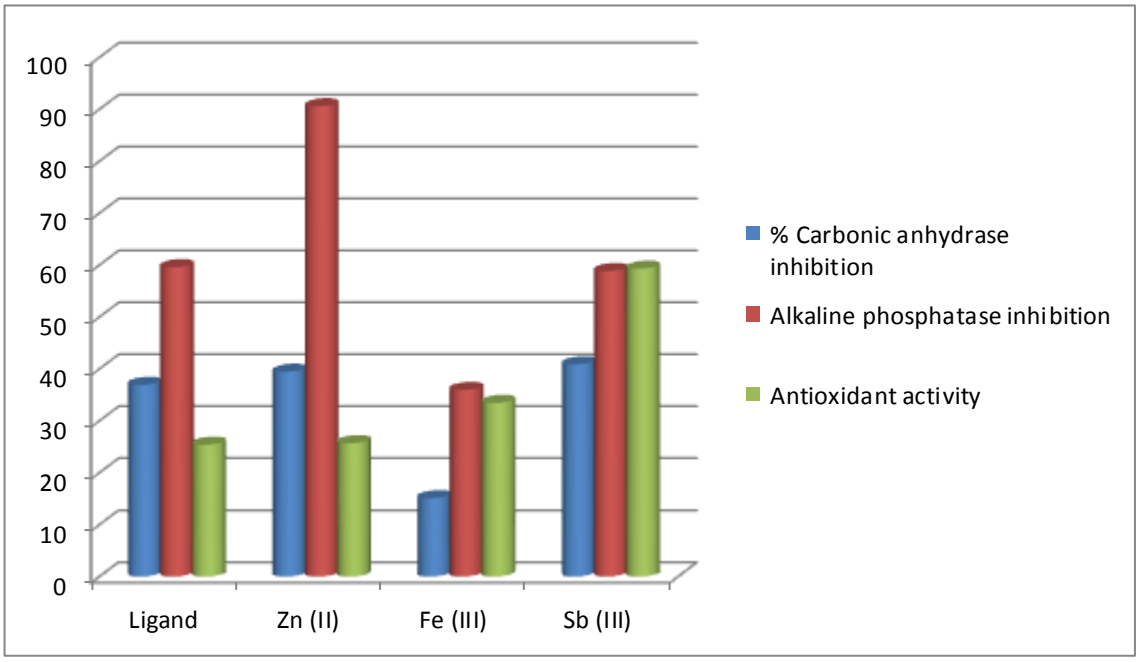


Figure 2. Graphical presentation of biological activities of Ligand and its metal complexes

4. Conclusion

As it is evident from the biological evaluation the introduction of metal into the ligand enhanced the activity. It is particularly significant in case of zinc complex which has shown potent alkaline phosphatase inhibition. Antioxidant activity is increased in case of antimony complex.

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