Research Article

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

Kishwar Sultana[1]*, Najm ul Hassan Khan[1,2], Khadija Shahid[1]
[1]Riphah Institute of Pharmaceutical sciences, Riphah International University, Islamabad, Pakistan.
[2]Islam College of Pharmacy, Pasrur Road, Sialkot, Pakistan.
***Corresponding author's E-mail:** kish_pharm@yahoo.com

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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 ^{1}H NMR, ^{13}C NMR, ^{119}Sn 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)-1*H*-isoindole-1,3(2*H*)-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

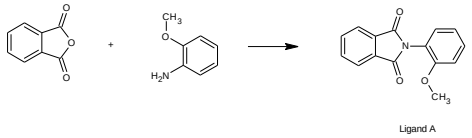
Melting points were determined on Gallenkamp melting point apparatus using open capillary tubes and are uncorrected. FTIR spectra were recorded on Bruker Fourier Transform Infrared spectrophotometer (4000-400 cm^{-1}). ^{1}H NMR, ^{13}C NMR and ^{119}Sn spectra were recorded on Bruker 400MHz and 500MHz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

Synthesis of Ligand and Its Metal Complexes

Synthesis of 2-(2-methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-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.[28] General scheme is given in Figure 1.

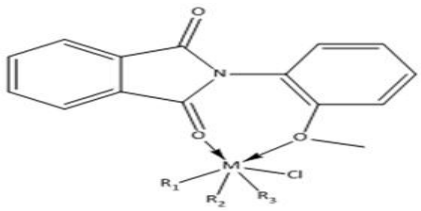


Scheme 1

Figure 1: Synthesis of 2-(2-methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-dione

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

1mmol of the free ligand was suspended in 100ml 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 (1mmol/2mmol) 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 $CH_2Cl_2/CHCl_3$ and ether/n hexane in equal ratio (129).[29] General structure for a tin complex is given in Figure 2.



For complex 1, R1= R2= R3 = Ph
For complex 2, R1= R2= n Bu, R3=Cl
For complex 3, R1= R2= Me, R3 = Cl
For complex 4, R1= R2= R3 = n Bu
For complex 5, R1= R2= Ph, R3 = Cl

Figure 2: General Structure for tin complexes of Ligand A

Synthesis of Zinc (II) complexes of Ligand A

2mmol (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.[30]

Synthesis of Antimony (III) complexes of Ligand A

1mmol of the free 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 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.[31]

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

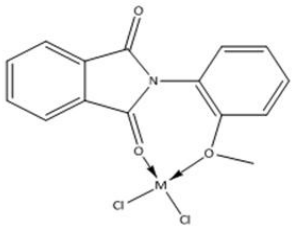


Figure 3: Zn (II) complex of Ligand A

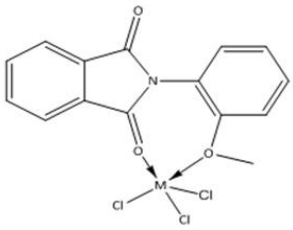


Figure 4: Sb (III) complex of Ligand A

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)-1*H*-isoindole-1,3 (2*H*)-dione (Ligand A) and its complexes

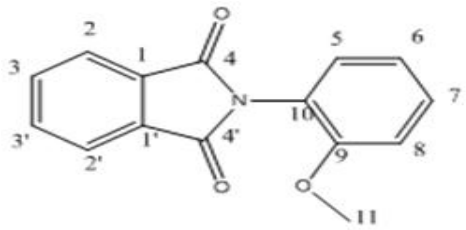


Figure 5 Carbon Numbering of Ligand A

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

Molecular formula: $C_{15}H_{11}NO_3$, 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). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 (d, J=8 Hz, 4H, Ar. CH), 7.80 (d, J=8Hz, 2H, Ar. CH), 7.30 (d, 2H, Ar. CH), 7.07 (t, 1H, Ar. CH), 3.82 (s, 3H, Ar.OCH_3). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 133.7 ($C_{1,1'}$), 129 ($C_{2,2'}$), 133.7 ($C_{3,3'}$), 167($C_{4,4'}$), 111 (C_5), 123 (C_6), 130 (C_7), 119 (C_8), 154 (C_9), 119 (C_{10}), 55.8 (C_{11}). 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, 71.14; 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: $C_{33}H_{26}NO_3SnCl$, Molecular weight: 638, m.p.: 98-100°C, yield: 65 % IR data 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). ^{1}H NMR ((400 MHz, $CDCl_3$) δ (ppm): 7.85- 7.96 (m, J=8 Hz, 4H, Ar. CH), 7.12-7.34 (m, J= 8Hz, 4H, Ar. CH), 3.79 (s, 3H, Ar.OCH_3). ^{13}C NMR ((400 MHz, $CDCl_3$) δ (ppm): 133 ($C_{1,1'}$), 129.4 ($C_{2,2'}$), 133 ($C_{3,3'}$), 167.7 ($C_{4,4'}$), 110 (C_5), 122.9 (C_6), 130 (C_7), 118.6 (C_8), 1543.9 (C_9), 118.6 (C_{10}), 60.5 (C_{11}) 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: $C_{38}H_{40}N_2O_6SnCl_2$, Molecular weight: 810, m.p : 148-150^{o}C , yield: 74 % IR data ν (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, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): 133 ($C_{1,1'}$), 123 ($C_{2,2'}$), 129, 130 ($C_{3,3'}$), 167 ($C_{4,4'}$), 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: $C_{32}H_{28}N_2O_6Sn\ Cl_2$, Molecular weight: 726, m.p: 136-140^{o}C, yield: 69 % IR data ν (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, $CDCl_3$) δ (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}CNMR (400 MHz, $CDCl_3$) δ (ppm):133, 131 ($C_{1,1'}$), 123, 120 ($C_{2,2'}$), 129, 130 ($C_{3,3'}$), 167 ($C_{4,4'}$), 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^+-], 91 (20) [M^+-].

Tin complex (4) of Ligand A (C4)

Molecular formula: $C_{27}H_{38}NO_3SnCl$, Molecular weight: 578, m.p : 124-125^{o}C , yield: 75 % IR data ν (cm^{-1}): 1778, 1734 (C=O) imide, 1384 (C=O), 1597, 1465 (C=C), 1405 (C-N), 2845 (C-H), 1259 (C-O), 472 (M-O). ^{1}H NMR ((400 MHz, $CDCl_3$) δ (ppm): 7.96 (dd), 7.81 (dd), 7.46 (m), 7.28 (m), 7.10 (m), 3.82 (s), 1.32 (s), 0.95 (t). ^{13}CNMR ((400 MHz, $CDCl_3$) δ (ppm): 133 ($C_{1,1'}$), 123 ($C_{2,2'}$), 129, 130 ($C_{3,3'}$), 167 ($C_{4,4'}$), 111 (C_5), 123 (C_6), 129 (C_7), 120 (C_8), 155 (C_9), 120 (C_{10}), 55 (C_{11}), 27 (C_{12}), 17(C_{13}), 26 (C_{14}), 13.25(C_{15}) . ^{119}Sn NMR ($CDCl_3$) with Et4Sn as zero reference = 149.3. ESIMS data (m/z): 580 (29) [M^+], 504 (100) [M^+ -76], 429 (43) [M^+ -151], 391 (51) [M^+ -189], 254 (77) [M^+ -326], 135 (11) [M^+ -445].

Tin complex (5) of Ligand A (C5)

Molecular formula: $C_{42}H_{32}N_2O_6SnCl_2$, Molecular weight: 850, m.p.: 130-134^{o}C, yield: 73 %. IR data ν (cm^{-1}): 1779, 1735 (C=O) imide, 1382 (C=O), 1600, 1469 (C=C), 1405 (C-N), 2845 (C-H), 1259 (C-O), 453 (M-O). ^{1}H NMR ((400 MHz, $CDCl_3$) δ (ppm): 7.96 (dd, *J*=8.2 Hz, 4H, Ar. CH), 7.80 (dd, *J*=8.2 Hz, 4H, Ar. CH), 7.46 (m, *J*=8 Hz, 4H, Ar. CH), 7.10 (m, *J*=8 Hz, 4H, Ar. CH), 3.82 (s, 3H, CH3), 1.43 (s, 3H, CH3). ^{13}C NMR ((400 MHz, $CDCl_3$) δ (ppm): 132 ($C_{1,1'}$), 124 ($C_{2,2'}$), 129, 130 ($C_{3,3'}$), 167 (4, 4'), 111 (C_5), 124 (C_6), 129 (C_7), 120 (C_8), 155 (C_9), 120 (C_{10}), 45.50 (C_{11}). ^{119}Sn NMR: -54.73. ESIMS data (m/z): 850 (39) [M^+], 759 (30) [M^+ -91], 429 (54) [M^+ -421], 391 (27) [M^+ -459], 254 (100) [M^+ -596]. Elemental analysis: Calc: C, 64.72; H, 4.14; N, 3.59. Found: C, 66.12; H, 4.91; N, 4.02.

Zinc complex (6) of Ligand A (C6)

Molecular formula: $C_{30}H_{22}N_2O_6Zn$ Cl2, Molecular weight: 642, m.p : 136-138^{o}C , yield: 69 % .

IR data ν (cm^{-1}): 1778, 1740 (C=O) imide, 1384 (C=O), 1597, 1467 (C=C), 1405 (C-N), 2843 (C-H), 1258 (C-O), 471 (M-O). ^{1}H NMR (400MHz, DMSO) δ (ppm): 7.94 (d, *J*=8 Hz, 8H, Ar. CH), 7.90 (d, *J*=8Hz, 4H, Ar. CH), 7.53-7.10 (m, Ar. CH), 1.97 (s, 6H, Ar.CH_3). 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: $C_{15}H_{11}NO_3SbCl_3$, Molecular weight: 481, m.p.: 145-147^{o}C, yield: 68 %. IR data ν (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 (400MHz, DMSO) δ (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), 1.92 (s, 3H, Ar.CH_3). 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)-1*H*-isoindole-1,3(2*H*)-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 ν(O-H) and ν(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}HNMR spectrum of Ligand A showed a distinct singlet at 3.82 ppm for the H of ortho 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 and C=O 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

the range of 438-473 cm^{-1}. NMR and Mass spectrum further proved the formation of complexes. In case of complexes (C1-C5) ^{1}H NMR and ^{13}C 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 ^{119}Sn 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

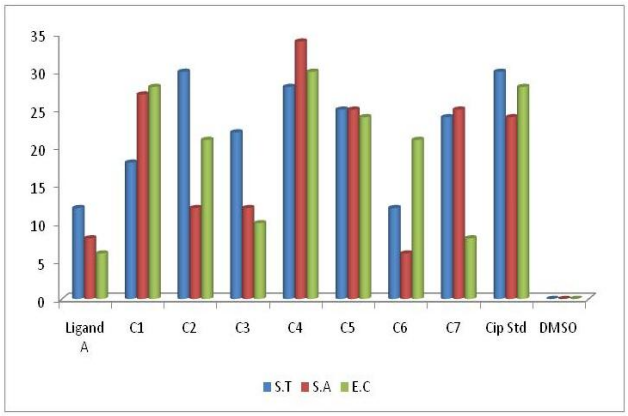
Antibacterial Assay

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.[32] Antibacterial results are illustrated in Table 1.

Table 1: Antibacterial Activity for Ligand A and its Complexes

Sample	S.T	S.A	E.C
Ligand A	12	8	6
C1	18	27	28
C2	30	12	21
C3	22	12	10
C4	28	34	30
C5	25	25	24
C6	12	6	21
C7	24	25	8
Cip. (std)	30	24	28
DMSO(control)	0	0	0

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



X-Axis = codes of compounds; Y-Axis= zone of inhibition; Colors representing particular bacterial specie

Figure 6: Graphical representation of antibacterial activity of compounds

CONCLUSION

In summary, we have synthesized 2-(2-methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-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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REFERENCES

1. Cardarelli NF, Tin as Vital Nutrient, 1st Ed, CRC Press Inc, BocaRaton, Florida, 1986.
2. Crowe AJ, The chemotherapeutic properties of tin compounds, Drugs Future, 12, 1987, 255– 275.
3. Ukita T, Na ka mura Y, Kubo A, Ya ma moto Y, Ta ka ha shi Y, Koetera J, Ikeo T,1-Arylnaphthalene lignan: a novel scaffold for type 5 phosphodiesterase inhibitor, Journal of Medicinal Chemistry, 42, 1999, 1293.
4. Gielen M, El-Kholoufi A, Biesemans M, Willem R, Meunier-Piert, 2-Methylthio-3-Pyridinecarboxylato)-diethyltin and -di-n-butyltin compounds: synthesis, spectroscopic characterization and *in vitro* antitumour activity. X-ray crystal structure of bis[diethyl(2-methylthio-3-Pyridinecarboxylato)tin] oxide and of diethyltin bis (2-methylthio-3-pyridinecarboxylate, Journal of Polyhedron, 11, 1992, 1861.
5. Gielen M, Lelieveled P, de Vos D, Pan H, Willem R, Biesemans M, Fiebig H, Inorganic Chemistry Acta, 115, 1992, 196.
6. Song X, Yang Z, Xie Q, Li JJ, journal of Organometallic chemistry, 103, 1998, 566.

7. Gielen M, Biesemans M, de Vos D, Willem R, Synthesis, characterization and in vitro antitumor activity of di- and triorganotin derivatives of polyoxa- and biologically relevant carboxylic acids, J. Inorg. Biochem., 79, 2000, 139.

8. Camocho-Comacho C, de Vos D, Mahieu B, Gielen M, Kemmer M, Biesemans M, Willem R, Organotin (IV) derivatives of 3, 4-(methylenedioxy) phenylacetic acid: Synthesis, spectroscopic characterization and in vitro antitumor properties, Main Group Metal Chemistry Journal, 23, 2000, 433.

9. Nath M, Yadav R, Gielen M, Dalil H, de Vos D, Eng G, Synthesis, characteristic spectral studies and in vitro antimicrobial and antitumour activities of organotin(IV) complexes of Schiff bases derived from amino-acids, Applied Organometallic Chemistry, 11, 1997, 727.

10. Kemmer M, Bieseman, M, Gielen M, Martins JC, Gramlich V, Willem R, Complexation *of* triorganotin derivatives *of [*18*]*crown-6-*and ... of [*18*]*crown-6-*and [*15*]*crown-5-*(*benzo-4-carboxylate*) with* alkali thiocyanates*",* European Journal of Chemistry, 7*(*21*),* 2001*,* 4686.

11. Masood MT, Ali S, Danish M, Mazhar M, Synthesis and Characterization of Tri-, Di-, and Chlorodiorganotin (IV) Derivatives of 3-Benzoyl-alpha-methylphenylacetic Acid and 3-(2-Thienyl)acrylic Acid, Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry, 32, 2002, 9-24.

12. Ahmed S, Ali S, Ahmed F, bhatti MH, Badshah A, Mazhar MK , Synthesis, Spectroscopic Characterization and Biological Applications of Organotin(IV) Derivatives of 2-(N-Maleoyl)-3-phenylpropanoic Acid, Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry, 32, 2002, 1725.

13. Parvez M, Shahid K, Shahzadi S, Ali S, 2-[(4-Bromoanilino) carbonyl]prop-2-enoic acid. Acta cryst, E60, 2004, 02079-02081.

14. Ali S, Khokhar MN, Bhatti MH, Mazhar M, Masood MT, shahid K, Badshah A (2002) ^{1}H, ^{13}C and ^{119}Sn NMR, IR, Mass, Thermal and Biological Studies of Organotin(IV) Derivatives of [4-*p*-(Chlorophenyl)-2-phenyl-5-thiazoleacetic acid], Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry, 13, 2002, 1373.

15. Ahmed F, Ali S, Parvez M, Munir A, Mazhar M, Khan KM, Shah TA, Synthesis, Characterization and Biological Studies of Tri- and Diorganotin(IV) Complexes with 2',4'-Difluoro-4-hydroxy-[1,1']-biphenyl-3-carboxylic Acid: Structure of $[(CH_3)_3Sn(C_{13}H_7O_3F_2)]$, Heteroatom Chemistry, 13, 2002, 638.

16. Gielen M, Cardarelli NF, Tin as a vital nutrient : Implication in cancer prophylaxis and other physiological processes, Antitumour active organotin compounds, CRC Press, 1986.

17. Shaukat S,S, Khan NA, Ahmed F, Herbicide influence on germination and seedling growth of Vigna mungo (L) Hepper and V. radiata (L) Wilczek, Pakistan Journal of Botany, 12, 1980, 97-106.

18. Jayakumar R, Balaji R, Nanjundan S, Studies on copolymers of 2-(N-phthalimido)ethyl methacrylate with methyl methacrylate, European Polymer Journal, 36, 2000, 1659-1666.

19. Ribeiro da, Silva MAV, Santos CPF, Monte MJS, Sousa CAD, Journal of thermal analysis and calorimetry, 83, 2006, 533-539.

20. Luzzio FA, Zacherl PD, Figg WD, A Facile Scheme for Phthalimide/Phthalimidine Conversion, Tetrahedron Letter, 40, 1999, 2087-90.

21. Lima LM, Brito FCF, Souza SD, Miranda ALP, Rodrigues CR, Fraga AM, Barreiro EJ, Bioorganic Medicinal Chemistry Letters, 12, 2002, 1533.

22. Sena VLM, Srivastava M, Silva RO, Luis VLM, Synthesis and hypolipidemic activity of N-substituted phthalimides, Part V, Farmaco II, 58, 2003, 1283-1288.

23. Barman S, Newhouse EI, Neely WC, The oxidative degradation of imide polymers. I: Ozonolysis of a model compound, N-phenylphthalimide, Polymer Engineering Sciences, 34, 2004, 279.

24. Wang T, Zhang YH, Ji H, Chen YP, Peng SX, Synthesis and bioactivity of novel phthalimide derivatives, Chinese Chemical Letters, 19(1), 2008, 26-28.

25. Saxena AK, Organotin compounds, toxicology and biomedicinal applications, Applied Organometallic Chemistry, 1, 1987, 39-56.

26. Singh K, Singh DP, Barwa MS, Tyagi P, Mirza Y, Antibacterial Co(II), Ni(II), Cu(II) and Zn(II) complexes of Schiff bases derived from fluorobenzaldehyde and triazoles, Journal of Enzyme Inhibition Medicinal Chemistry, 21, 2006, 557–562.

27. Singh K, Singh DP, Barwa MS, Tyagi P, Mirza Y, Some bivalent metal complexes of Schiff bases containing N and S donor atoms, Journal of Enzyme Inhibition Medicinal Chemistry, 21(6), 2006, 749–755.

28. Sultana K, Khan NUH, Shahid K, Efficient solvent free synthesis and x ray crystal structure of some cyclic moieties containing imide and amide, Middle east journal of scientific research, 18(4), 2013, 438-443.

29. Shahid K, Shahzadi S, Ali S, Synthesis, coordination and biological aspects of organotin(IV) derivatives of 4-[(2,4-dinitrophenyl)amino)]-4-oxo-2-butenoic acid and 2-[{(2,4-dinitrophenyl)amino} carbonyl]benzoic acid, Journal of Serbian Chemical Society, 74, 2009, 141–154.

30. Kulkarni NV, Revankar VK. Synthesis, antimicrobial screening, and DNA-binding/cleavage of new pyrazole-based binuclear CoII, NiII, CuII, and ZnII complexes, Journal of Coordination Chemistry, 64(4), 2011, 725-741,

31. Lizarazo-Jaimes EH, Monte-Neto RL, Reis PG, Fernandes NG, Speziali NL, Melo MN, et al. Improved Antileishmanial Activity of Dppz through Complexation with Antimony (III) and Bismuth (III): Investigation of the Role of the Metal, Molecules, 17(11), 2012, 12622-35.

32. Rahman A, Choudhary MI, Thomsen WJ, Bioassay Techniques for Drug Development, Hardward Academic Press, Amsterdam, 14, 2001.

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