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New Complexes of Organotin(IV) 2-(N-Maleoylamino)-2-methylpropanoate: Synthesis, Spectroscopic Characterization and Biological Activity

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Organotin(IV) complexes of 2-(N-maleoylamino)-2-methylpropanoate were prepared by treating the ligand acid with diorganotin dichloride and triorganotin chloride in 1:2 and 1:1 molar ratios, respectively. These reactions proceeded smoothly to completion and the complexes formed were characterized by elemental analysis, infrared, multinuclear NMR (^{1}H, ^{13}C, ^{119}Sn) and mass spectrometry. The biological activities of the tin complexes were studied by screening the compounds against various animal and plant pathogens. These results show that triorganotin(IV) carboxylates are more active against the animal and plant pathogens tested as compared to diorganotin dicarboxylates.

Key Words: Organotin(IV) carboxylates, spectroscopic studies, biological activity.

Introduction

Organotin(IV) compounds have found an impressive range of applications, e.g., as pesticides, fungicides, algicides, bactericides, antifouling agents and stabilizers[1−5]. In addition, their ability to accommodate all functional groups and their remarkable chemical and thermal stability have made organotin compounds particularly attractive for studies[6−10].

Various reports have shown that the replacement of a ligand in R_2SnL_2 and R_3SnL changes the toxicity of the organotin moiety[11,12].

In this paper, we describe the synthesis, characterization and biological activity of organotin(IV) chloride or dichloride with a ligand (Figure 1) using triethylamine as base.

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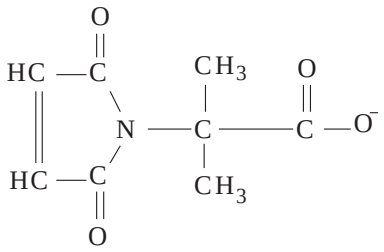


Figure 1. 2-(N-maleoylamino)-2-methylpropanoate (L).

Experimental

Materials and methods

All necessary precautions were observed to exclude oxygen and moisture during the synthesis and handling of the compounds. Analytical grade chemicals were used as received for all experiments and solvents were dried by reported methods[13]. The melting points were determined on an electrothermal melting point apparatus model MPD Mitamura Riken Kogyo (Japan) and are incorrected. The elemental analysis was performed with an organic elemental analyzer, model EA 1110, CE Instruments, Italy.

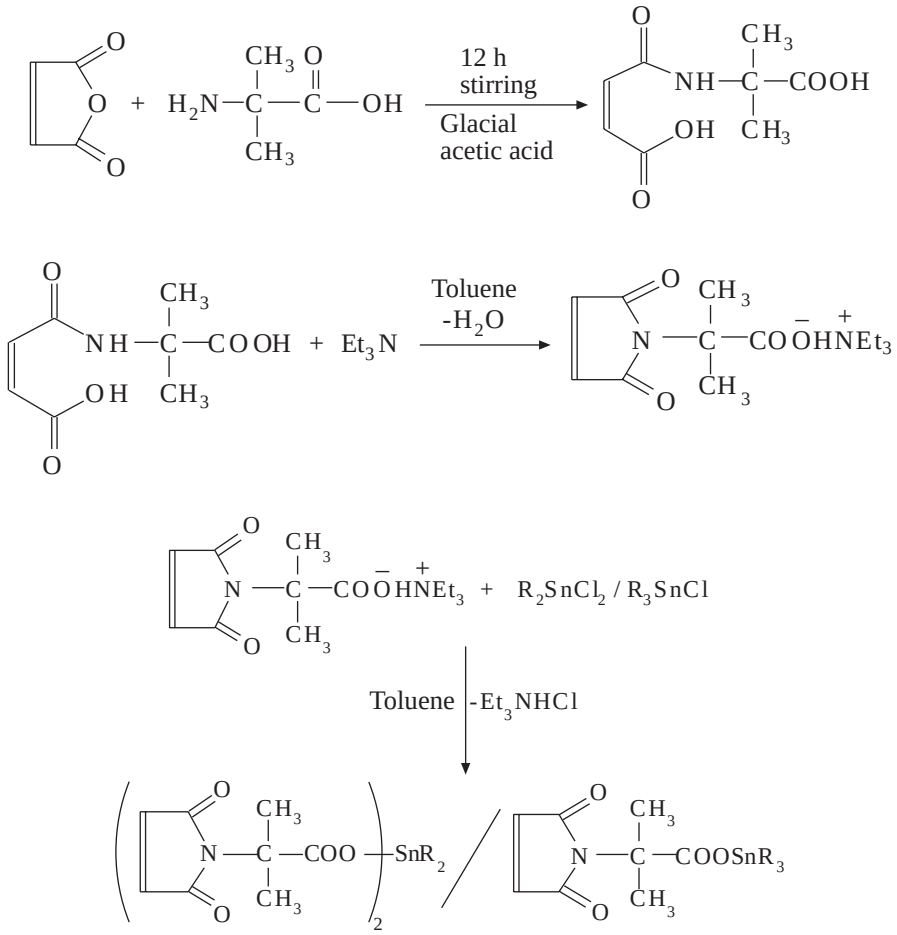
Infrared spectra were recorded in the range 4000-400 cm^{-1} as KBr/CsI pellets on a Perkin Elmer FT-IR spectrometer, model 1000. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 250 spectrometer (Germany), using $CDCl_3$ as an internal reference [δ ^{1}H ($CDCl_3$) = 7.24: δ ^{13}C ($CDCl_3$) = 77.0]. ^{119}Sn NMR spectra were obtained on a Bruker ARX 250 spectrometer (Germany) with Me_4Sn [(Sn) = 37.296665 MHz] as an external reference. Mass spectra were recorded on a MAT 8500 Finnigan (Germany) and m/z values were calculated assuming H = 1, C = 12, Sn = 120, O = 16 and N = 14.

General procedure for synthesis of ligand and complexes

The 2-(N-maleoylamino)-2-methylpropanoate ligand was prepared by stirring equimolar quantities of maleic anhydride and α-aminoisobutyric acid in acetic acid for 12 h (Scheme 1). The precipitates of the intermediate formed were filtered off, washed with cold water and air dried.

Then this intermediate (16.8 mmol) was suspended in dry toluene and treated with triethylamine (35.5 mmol). The mixture was refluxed with vigorous stirring for 4 h. The water formed was continuously removed via a Dean and Stark trap (Scheme 1). After cooling, the toluene was removed from the orange layer, diorganotin(IV) dichloride (8.4 mmol) or triorganotin(IV) chloride (16.8 mmol) was added to the toluene and the mixture was refluxed for a further 4 h. On cooling, the triethylammonium chloride was filtered off, and the toluene was removed by rotary evaporator under reduced pressure. The solid mass obtained was recrystallized from a chloroform/n-hexane (1:1) mixture.

The synthesis of compounds (**1**)−(**4**) was achieved as given in Scheme 1.



Scheme 1

$\mathbf{R}_2$	n-C_4H_9	(**1**)	CH_3-C_6H_5	(**2**)
$\mathbf{R}_3$	CH_3	(**3**)	n-C_4H_9	(**4**)

Results and Discussion

All the synthesized complexes are soluble in common organic solvents. They have sharp melting points. The tin derivatives are stable at ambient temperature and are non-hygroscopic. Physical and analytical data are reported in Table 1.

Infrared spectroscopy

Infrared spectra of di- and triorganotin(IV) of 2-(N-maleoylamino)-2-methylpropanoate were recorded as KBr/CsI pellets in the region 4000-400 cm^{-1}. Important vibrational frequencies for structural elucidation are given in Table 2. The $-COO$ stretching frequencies have 2 absorbance bands. The denticity of the carboxylate group can be determined with a high level of probability on the basis of the values of $\nu_{asym}(COO)$ and $\nu_{sym}(COO)$ and their difference $\Delta\nu$[14−16]. It is clear from the tabulated values that in all compounds the carboxylate group acts as a bidentate, i.e. the $\Delta\nu \leq 200$[16]. The appearance of medium intensity bands in the range 580-450 cm^{-1} due to $\nu(Sn-C)$ and $\nu(Sn-O)$ further confirms the formation of the complexes.

Table 1. Physical and analytical data of the investigated compounds.

Comp. No.	Empirical Formula	M.P. (°C)	Yield (%)	Molar Ratio	Elemental Analysis Calcd./(Found)		
					% C	% H	% N
(**1**)	$C_{24}H_{38}N_2O_8Sn$	86-88	70	1:2	48.16 (48.55)	5.68 (5.99)	4.68 (5.02)
(**2**)	$C_{30}H_{30}N_2O_8Sn$	193-195	45	1:2	54.05 (55.2)	4.50 (5.20)	4.20 (4.89)
(**3**)	$C_{11}H_{17}NO_4Sn$	95-97	80	1:1	38.04 (37.98)	4.90 (5.22)	4.03 (4.62)
(**4**)	$C_{20}H_{35}NO_4Sn$	–	72	1:1	50.74 (49.32)	7.40 (7.88)	2.96 (3.23)

Table 2. Characteristic vibrational frequencies[a] (cm^{-1}) of the investigated compounds.

Comp. No.	General Formula	ν (COO)		$\Delta\nu$	ν (Sn−C)	ν (Sn−O)
		Asym.	Sym.			
(**1**)	Bu_2SnL_2	1600 s	1404 w	196	581 w	460 w
(**2**)	Bz_2SnL_2	1596 s	1405 w	191	579 w	457 w
(**3**)	Me_3SnL	1604 s	1400 s	204	584 w	464 w
(**4**)	Bu_3SnL	1604 w	1407 w	197	570 w	455 w

L = 2-(N-Maleoyl)-2-methylpropanoate
[a]s = strong; w = weak

NMR spectroscopy

The ^{1}H NMR spectra of the reported compounds were recorded in $CDCl_3$ and the data are given in Table 3. The following observations are made from the ^{1}H NMR data:

- In all complexes, the signal for all types of protons was identified and the number of protons in various groups observed from the integration found is in agreement with the proposed structure.
- Compound (**3**) gives a sharp singlet at δ 0.53 ppm with tin satellites on either side, with coupling constants of 56 and 58 Hz. The bond angle calculated by Lockhart's equation is 112°, showing the tetrahedral geometry of the central tin atom in the solution.[17−19]
- Butyl groups in compounds (**1**) and (**3**) appeared in the range δ 0.84 to 1.38 ppm.
- In compound (**2**), the aromatic protons of the benzyl group are observed as a multiplet at δ 7.0-7.30 ppm, while the methylene protons of the benzyl group gave a singlet at δ 3.06 ppm.
- Protons of the ligand moiety appear as 2 singlets at 1.70-1.47 ppm for 2 methyl groups and 6.55-6.50 ppm for HC=CH from the ring.

The ^{13}C NMR spectral data of di- and triorganotin(IV) derivatives of 2-(N-maleoyl)-2-methylpropanoate are given in Table 4.

All the carbon atoms present in the ligand and its derivatives were assigned and following observations are made:

- Signal for 2 carbonyl groups of the ring appears in the range 169.5-170.9 ppm.
- Signal for the carboxyl group appears in the range 177.8-182.7 ppm.
- Butyl signals appear at δ 13.5-27.7 ppm while $-CH_3$ appears at –2.4 ppm and the $-CH_2$ group of benzyl appears at 24.3 ppm.
- In compound (**3**), $^1J[^{119}Sn-^{13}C]$ coupling was observed at 407 Hz. Applying Lockhart's equation, the C-Sn-C angle was calculated as 112.4^o, consistent with the value calculated by $^2J[^{119}Sn-^1H]$ coupling, which confirms the tetrahedral geometry in the solution.

The ^{119}Sn NMR spectrum was recorded in $CDCl_3$ for compound (**3**) and the $\delta(^{119}Sn)$ value is 145.8 ppm, which confirms the tetrahedral geometry around the central tin atom[18−20].

Table 3. ^{1}H NMR data[a−c] of the investigated compounds.

Comp. No.	Proton Number					
	3,3′	5,5′	α	β	γ	δ
(**1**)	1.70 s	6.54 s	1.38 m	1.35 m	1.24 m	0.85t (7.1)
(**2**)	1.47 s	6.53 s	3.06 s	7.0-7.30 m	–	–
(**3**)	1.67 s	6.55 s	0.53 s ^2J[56,58]	–	–	–
(**4**)	1.57 s	6.50 s	1.32 m	1.21 m	1.26 m	0.84t (7.1)

[a] Chemical shift (δ) in ppm, $^3J(^1H-^1H)$ and $^2J[^{119/117}Sn-^1H]$ in Hz.

[b] Multiplicity is given as s = singlet, t = triplet, m = multiplet.

[c]

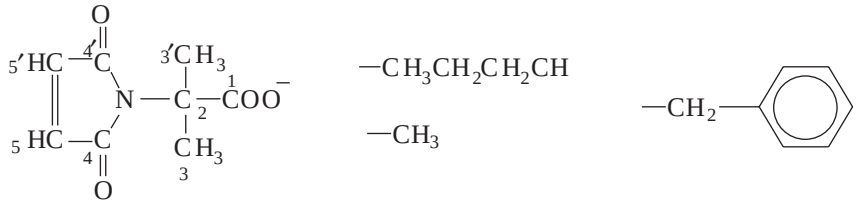


Table 4. ^{13}C NMR data[a] of the investigated compounds.

Comp. No.	Carbon Number									
	1	2	3,3′	4,4′	5,5′	α	β	γ	δ	η
(**1**)	182.7	60.2	24.6	170.7	134.1	20.7	26.6	26.4	13.5	–
(**2**)	182.5	59.9	24.2	170.6	134.1	24.3	135.8	128.5	128.8	125.6
(**3**)	177.8	60.5	24.7	170.9	133.9	-2.4 ^1J[407]	–	–	–	–
(**4**)	181.7	57.5	24.1	169.5	133.9	16.7	27.7	27.6	13.5	–

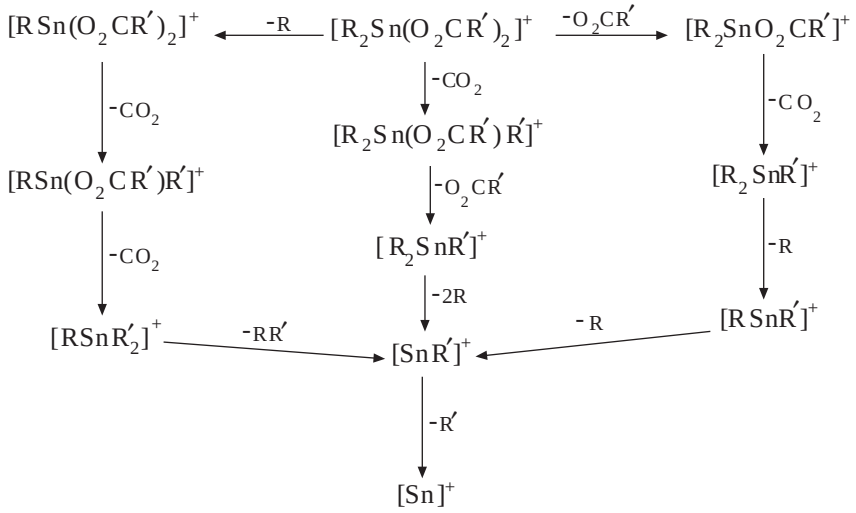
[a] For numbering see footnote to Table 3.

Mass spectrometry

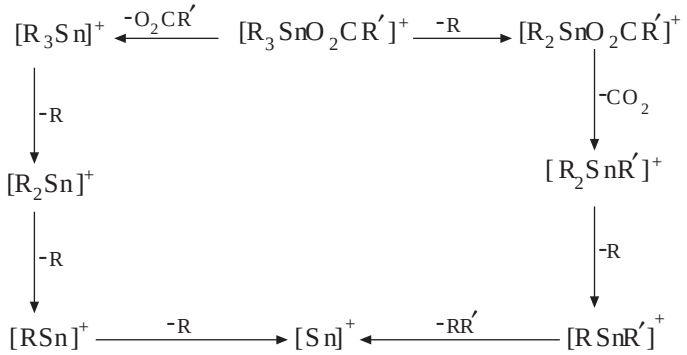
Mass spectral data of di- and triorganotin(IV) derivatives of 2-(N-maleoylamino)-2-methylpropanoate are given in Tables 5 and 6. The fragmentation patterns follow the established routes[21−24]. A molecular ion peak of very low intensity was observed only in compound (**3**), while the base peak of this compound appeared at m/z = 165 due to the loss of the ligand. Fragments due to the loss of R groups from the molecular ion were

observed in all compounds. The base peak of compound (**2**) appeared at m/z = 302, which was also observed in the spectra of other compounds with variable intensities, particularly low intensity in triorganotin(IV) derivatives.

General fragmentation patterns for di- and triorganotin(IV) derivatives are given in Schemes 2 and 3.



Scheme 2. General fragmentation pattern for diorganotin dicarboxylates.



Scheme 3. General fragmentation pattern for triorganotin carboxylates.

Table 5. Mass spectral data for diorganotin(IV) derivatives.

Fragments	(**1**) m/z (%)	(**2**) m/z (%)
$[R_2SnC_{16}H_{16}N_2O_8]^{+\bullet}$	598 (n.o.)	666 (n.o.)
$[RSnC_{16}H_{16}N_2O_8]^+$	541 (30)	575 (95)
$[R_2SnC_{15}H_{16}N_2O_6]^+$	554 (n.o.)	622 (2)
$[R_2SnC_8H_8NO_4]^+$	416 (n.o.)	484 (45)
$[RSnC_8H_8NO_4]^+$	359 (3)	393 (n.o.)
$[SnC_8H_8NO_4]^+$	302 (77)	302 (100)
$[C_8H_9NO_4]^+$	183 (5)	183 (1)
$[C_7H_8NO_2]^+$	138 (23)	138 (25)
$[C_4H_9]^+$	57 (97)	57 (n.o.)
$[HSn(OH)_2]^+$	155 (100)	155 (n.o.)

Table 6. Mass spectral data for triorganotin(IV) derivatives.

Fragments	(**3**) m/z (%)	(**4**) m/z (%)
$[R_3SnC_8H_8NO_4]^+$	347 (1)	473 (n.o.)
$[R_3SnC_7H_8NO_2]^+$	303 (32)	429 (4)
$[R_2SnC_8H_8NO_4]^+$	332 (62)	416 (100)
$[RSnC_8H_8NO_4]^+$	317 (2)	359 (n.o.)
$[SnC_8H_8NO_4]^+$	302 (1)	302 (3)
$[C_8H_9NO_4]^+$	183 (18)	183 (n.o.)
$[C_7H_8NO_2]^+$	138 (97)	138 (58)
$[R_3Sn]^+$	165 (100)	291 (10)
$[R_2Sn]^+$	150 (18)	234 (5)
$[RSn]^+$	135 (40)	177 (7)
$[HSnC_8H_8NO_4]^+$	303 (32)	303 (n.o.)
$[SnH]^+$	121 (n.o.)	121 (6)

Biological activity

Antifungal activity

The newly synthesized di- and triorganotin(IV) derivatives of 2-(N-maleoylamino)-2-methylpropanoate were tested for their antifungal activity by tube diffusion [25,26]. The data are given in Table 7 and Figure 2. Most of the compounds showed moderate fungicidal activity as compared to the reference standard drugs. Compound (**3**) is found to be best for the inhibition of fungal growth except in the case of *Candida albicans*, while compound (**2**) has the least activity.

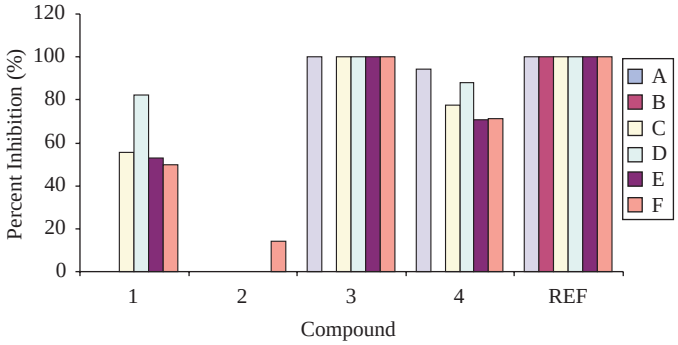


Figure 2. Antifungal activity of organotin(IV) derivatives against various fungi.

Names of Fungi
A: *Trichoehyton longiformis*
B: *Candida albicans*
C: *Aspergillus flavis*
D: *Microsporum canis*
E: *Fusarium solani*
F: *Fusarium moniliformis*

Table 7. Antifungal activity of organotin(IV) derivatives.

Name of Fungus	Percent Inhibition (**1**)	(**2**)	(**3**)	(**4**)	Standard Drug
Trichoehyton longiformis	0.0	0.0	100	94.44	Miconazole Ketoconazole
Candida albicans	0.0	0.0	0.0	0.0	Miconazole Ketoconazole
Aspergillus flavis	55.55	0.0	100	77.77	Amphotericin.B Flucytosine
Microsporum canis	82.35	0.0	100	88.23	Miconazole Ketoconazole
Fusarium solani	52.92	0.0	100	70.58	Benlate Naban
Fusarium moniliformis	50.0	14.28	100	71.42	Benlate Naban

Antibacterial activity

The synthesized complexes were screened for antibacterial activity by agar well diffusion[27]. The data are given in Table 8 and Figure 3. The data reveal that all compounds show moderate antibacterial activity. However, the antibacterial activity is less than that of the standard drug.

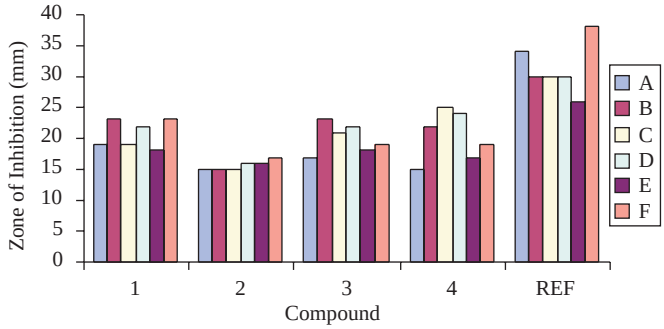


Figure 3. Antibacterial activity of organotin(IV) derivatives against various bacteria.

Names of Bacteria
A: *Corynebacterium diphtheriae*
B: *Bacillus subtilis*
C: *Streptococcus pyogenes*
D: *Staphylococcus aureus*
E: *Pseudomonas aeruginosa*
F: *Salmonella typhi*

Table 8. Antibacterial activity of organotin(IV) derivatives.

Name of Bacterium	Zone of Inhibition (mm)				*Reference
	(**1**)	(**2**)	(**3**)	(**4**)	Drug
Corynebacterium diphtheriae	19	15	17	15	34
Bacillus subtilis	23	15	23	22	30
Streptococcus pyogenes	19	15	21	25	30
Staphylococcus aureus	22	16	22	24	30
Pseudomonas aeruginosa	18	16	18	17	26
Salmonella typhi	23	17	19	19	38

*Tetracycline

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References

1. L. Pellerito and L. Nagy, **Coord. Chem. Rev., 224**, 111 (2002).
2. S.J. Blunden, P.A. Cussack and R. Hill, **The Industrial Uses of Tin Compounds.,** Royal Society of Chemistry, London, (1985).
3. Y. Arakawa, **Main Group Met. Chem., 17**, 225 (1994).
4. M. Gielen, M. Boualam, B. Bahieu and E.R.T. Tiekink, **Appl. Organomet. Chem., 8**, 19 (1994).
5. A. Kumari, I. Singh and J.P. Tandon, **Appl. Organomet. Chem., 9**, 127 (1995).
6. H. Masood, S. Ali, M. Mazhar, S. Shahzadi and K. Shahid, **Turk. J. Chem., 28**, 75 (2004).
7. K. Shahid, S. Ali, S. Shahzadi and Z. Akhtar, **Turk. J. Chem., 27**, 209 (2003).
8. S. Ahmad, S. Ali, F. Ahmed, M.H. Bhatti, A. Badshah, M. Mazhar and K.M. Khan, **Synth. React. Inorg. Met.-Org. Chem., 32**, 1521 (2002).
9. S. Ali, M. Danish and M. Mazhar, **Heteroatom. Chem., 8**, 273 (1997).
10. S. Shahzadi, M.H. Bhatti, K. Shahid, S. Ali, S.R. Tariq, M. Mazhar and K.M. Khan, **Monatsh. Chem., 133**, 1089 (2002).
11. A. Badshah, S. Anwer, S. Ali, M. Danish, M. Mazhar and M.I. Chaudhary, **Pak. J. Pharmacol., 13**, 49 (1996).
12. A. Kalsoom, M. Mazhar, S. Ali, M.F. Mahon, K.C. Molloy and M.I. Chaudhary, **Appl. Organomet. Chem., 11**, 47 (1997).

13. W.F.F. Armarego and C.L.L. Cahi, **Purification of Laboratory Chemicals.,** 5^{th} Ed., Butterworth: Oxford, (2003).
14. H.K. Sharma, S. Lata, K.K. Sharma, K.C. Molloy and P.C. Waterfield, **J. Organomet. Chem., 9**, 353 (1988).
15. C. Vasta, V.K. Jain, T. Kesavadas and E.R.T. Tiekink, **J. Organomet. Chem., 135**, 410 (1991).
16. G.K. Sandhu and N.S. Boparoy, **J. Organomet. Chem., 423**,183 (1992).
17. T. P. Lockhart, W.F. Manders and E.M. Holt**, J. Am. Chem. Soc., 108**, 6611 (1986).
18. M. Danish, S. Ali, A. Badshah, M. Mazhar, H. Masood, A. Malik and G. Kehr, **Synth. React. Inorg. Met.-Org. Chem., 27**, 863 (1997).
19. A.K. Gupta, S. Sharma, H.P.S. Chauhan and R.J. Rao, **Synth. React. Inorg. Met.-Org. Chem., 21**, 497 (1991).
20. R. Willem, H. Dialil, P. Brockaert, M. Biesemans, L. Ghys, K. Nooter, D. de Vos, F. Ribot and M. Gielen, **Main Group Met. Chem., 20**, 535 (1997).
21. M. Gielen, A. El-Khloufi, M. Biesemans and R. Willem, **Appl. Organomet. Chem., 7**, 119 (1993).
22. M. Gielen, J.M. Piret, M. Biesemans, R. Willem and A. El-Khloufi, **Appl. Organomet. Chem., 6**, 59 (1992).
23. M. Dansih, S. Ali, M. Mazhar, A. Badshah, M.I. Choudhary, A.G. Helmut and G. Kehr, **Polyhedron., 14**, 3115 (1995).
24. M.H. Bhatti, S. Ali, H. Masood, M. Mazhar and S.I. Qureshi, **Synth. React. Inorg. Met.-Org. Chem., 30**, 1715 (1997).
25. H. Blank and G. Rewbell, **Arch. Derm., 92**, 319 (1965).
26. S.S. Shaukat, N.A. Khan and F. Ahmed, **Pak. J. Bot., 12**, 97 (1980).
27. Atta-ur-Rahman, M.I. Choudhary and W.J. Thomsen, **Bioassay Techniques for Drug Development;** Harward Academic Press: Amsterdam, (2001).