Biological Activity Of Tris(pentafluorophenyl)bismuth(V) Carboxylates & μ-Oxo Bis [Triphenylbismith(V)] Carboxylates

Isha Rizvi, Prof. Amarika Singh

Abstract- Pentafluorophenylbismuth (V) Carboxylates and μ-oxo bis[triphenylbismuth(V)] Carboxylates have been synthesisssed by the author and screened for its antibacterial (against *Pseudomonas aeruginosa*, *Staphylococous aureus* and *Klebsiella pneumonia*), antifungal (against *Aspergillus flavas* and *Aspergillus niger*), insecticidal [against male and female adult cockroaches (*Periplanata americana*) and housefly (*Musca-domestica*)], and acaricidal (Tetranchus species) activity. These newly synthesised compounds were found to be moderate to significant biologically active

Keywords— Perfluoro organic moieties, anticaterial, antifungal, insecticidal, acaricidal, hydrolytic stability.

1 INTRODUCTION

A variety of organometallic derivatives of group 15 elements, especially those of arsenic, antimony and bismuth have been synthesized in the past two decades. The investigations in the field have centered on the biological activity of organic derivatives of these elements apart from synthetic and structure as features. Much concern has been shown of the synthesis of Organometallic derivatives in which anions are carboxylate; heterocyclic amines or other biologically active groups (1-16). The biological activity is largely affected by the :

(i) Nature of metal ion,
(ii) Oxidation state of metal ion
(iii) nature of organic group bound to metal
(iv) nature of anion/ligand attached to metal.
(v) geometrical arrangement around the metal atom
(vi) physical state & solubility of compounds in water and in lipids.

It is well known that the solubility of organometallic compound in water and in lipids is significantly enhanced on replacing the phenyl group by partially or fully substituted fluoro group the introduction of polar group such as –OH, F, -CF_3 etc. on the ligand itself increases the solubility and as a corollary increases their biological potentiality.

It may be noted that potency of an organometallic compounds enhanced (17) both in vivo and in vitro with the increase of hydrophilic -(to facilifutes acceptance by water wich cells) and lipophilic (essential for crossing the cells membrane) character. Thus the introduction of on group and the partial substitution of H atom by fluorine atom in case of organotin compounds increases in vitro activity and has been investigated (17), probably fascinated by the unusual character of fluroine atom (heavies than H atom 9 times.). Fluorine containing compounds are more soluble in water as well as in non solvents compared to hydro carbon based analogues.

Metal containing compounds may offer advantages over price. The only known effective drug for the treatment of Leishmaniavi; i.e., sodium stibugluconated based on sb-o-sb frame work and still worked and practisied despite of the appearance of many organic drugs son metals.

However sodium stibogluconate and its analogue can not be given for longer period due to associated toxicity to the antiomny compounds and therefore, we have focussed our irrestigations on the synthesis of Bi-o-Bi frame work based carboxylates and evaluted their biological activity as antimicrobial, antifangas and insecticidal.

Carbocylates are very versatic ligand (18-30); it can be unidendcte, bidentate or a bridging group. carboxylates are known to form linear and polymeric metal derivatives with varying solubility in water and organic solvents. They have center of attraction since last several decades due to biological activity and structural aspects.

The greater impact of this work should come out in the synthesis and to evaluate the biological activity of M-O-M (M=Bi) framework having rarying organic groups & carboxylates as ligands (effective biological moieties) should have way for the synthesis of newer antimicrobial, antitu moral and insecticidal derivatives. The therapeutical uses of antimony have been reviewed by Christiansen (15), those of Bismith by Gilman and

• *Author name is Mrs. Isha Rizvi, currently pursuing Ph. D. fromInstitute of Engineering & Technology, Constituent College of G. B. T. U., Sitapur Road Lucknow, India.*

Yale (16) along with some recent work has been include in the review by Burford et. al. (17).

The present study deals with less explored biological activity of organobismuth compuands in +5 oxidation state having perfluoro groups directly attached with Bismuth and Organo bismuth compounds having Bi-O-Bi frame work having carboxylate ligands. Their enhance biological activities are attributed to per fluoro groups and CF_3- containing carboxaylates the bismuth having +5 oxidation state (31-40) in all above compounds and surrounded by bulkier. legands enhance hydrolytic stability. The perfluon moietic alters its solubility. In view of the large spectrum of biological activity shown by organobismuth compounds, coupled with our research group's interest on antimicrobials, in secticidal, antifungal (41-51). activity for such derivatives, especially carboxylates which exhibit both hydrophilic and lipophilic character the author considered is worth to investigate afore said activities of such representatives carboxylates since biological activity of perfluorophenyl, drifluoro methyl etc. attached as Bi atom containing compounds has remained untouched area so far, we initiated the present study to address structural function relation ship of fully fluoninates substituted any bismuth and compounds having Bi-O-Bi frame work compounds against some selected fungal and bacterial species as well as some selected insects. All these assayed compounds are found to be moderate to significantly biologically actie especially having F-atom as perfluoro groups directly or indirectly attached with Bi (+5) atom.

2 Results and discussion

2.1 Antibacterial activity

Antibacterial activity of these compounds was studied against three human pathogenic bacteria viz. Pseudomonas aeruginosa, staphylococeus aureus and klebsiella pneumonia, using 10μg/ml cone of the test compounds.

It was found that compounds 2,3,5 show moderated activity against the Pseudomonan aeruginosa. compounds 4,7,8 shows highest activity against these bacteria while the compound 1,6 showed least activity. It has been reported that variation in activity is affected because of change in organic moiety as well as nature of ligand. Against staphylococcus aureus, the compounds 4,3,5 shows moderate activity while compound 7,8 show highest activity. Apart from this, compound 1,2,6 shows least activity. The activity of these compounds against kleb siella pneumonia do not differ much than the former cases. The compounds 2,3,4,5,7 are moderately active while compound 1,6 shows least activity compound 8 shows highest activity for klebsiella phenmonia. It was found that organometallic compounds containing fluoro and pentafluorophenylcring are more effective because of their water and upto solubrility. The fluorine containing compounds may ioneally form complexes with metallo enzyme, particularly those which responsible in basic physiology such as cytochrome oxidase. These compounds may react with peptidogly can layer of bactevial cell was and damage it by penetrating in such a manner which can causes death of bacterial cell. It was also abserved that these compounds in low concentration may cause bacteria static condition by slow down the group th of bacteria.

2.2 Antifungal activity

Antifungal activity of these compounds was tested against two fungal strain viz. Asper gillus flavas and asper gillus higar at different concentration namely 10μg/ml, 20μg/ml, 50μg/ml, & 100μg/ml of the test compounds. At 10μg/ml conc. of compounds 4,7,8 show higher inhibition (%) against aspergillas flavas and the remaining componds show moderate (2,5) to least (1,3,6) activity In case of aspergillas higar, the compounds 4,8 show higher activity while the compounds 2,5,7 show moderate activity. The variation in fungicidal activity of these compounds is due to the presence of Bi-O-Bi frame work and presence of perfluoro groups attached to bismuth. At 20μg/ml concentration of test compounds, the compound 4, 8, 2 shows higher percentage inhibition against Aspergillus flavus and compound 4, 8, 2 shows higher percentage inhibition against aspergillas higar. The compounds containing C_6F_5-Bi direct Bonds are moderately to significant active. At 50μg/ml & 100μg/ml concontration approximately all compounds how higher percentage of in hibition against fungal strains. It may be noted that CF_3- & C_6F_5- moieties attached directly or indirectly with bismuth show higher activity compare to phenyl analogues.

2.3 Insecticidal Activity

Insecticidal activity of these compounds was checked against male and female adult cockroaches (Peri planata americana) and housefly (Musca-domestica) using parathion as standard compounds 2,3,4,5,8 show high activity while remaining compounds show moderate activity. These compounds generally respond though the nervous system of insect due to high lipid solubility and ultimately causes death.

2.4 Insect Toxicological activity

2.4.1 Contact Toxicity

The contact toxicity of these compounds was tested against the fourth in star larvae of spodoptera litura using different concentration of the test compounds in acetone by adding tween-20 amulsifier. The mortality data was used for calculating LC50/LD50 of respective compounds. It was found that compounds 2,3,4,5,8 show higher activity against the larvae of insect. The activity again depends upon the perfluoro-organic moieties directly or indirectly attached with bismuth and on carboxylate ligands.

2.4.2 Stomach toxicity

The stomach toxicity of these compounds was checked against the same larvae of insect, Spodoptera litura using different concentration of the compounds in acetone and by adding tween 20 as emulsifier. The mortality data were used to calculate LC_{50}/LD_{50} value. It was found that activity of the compounds 4,8,2 show highest mortality.

2.5 Anti-feedant Activity

Anti feedant activity of these compounds was evaluated against fourth instar larve of spodoptera litura using different concentration of the test compound in acetone by adding tween 20 emulsifier. Mortality data was used to calculate the LC_{50}/LD_{50} of the respective compounds**.**

2.6 Acaricidal Activity

The acaricidal activity of these compounds was assayed against mites Tetranchus species. Different concentrations of the compounds were prepared in acetone and by adding tween 20 as emulsifier. Approximately all these compounds show moderate to higher activity against mites.

3 Experimental

The tris (penta fluorophenayl) bismuth (v) chloride and μ–oxo bis [tri pheryl bismuth (v)] chloride were obtained by reported methods via Grignard Reaction followed with oxidative addition reaction and all other compounds were newly synthesized already discussed in chapter 6 & 7 by replacement reaction; all the data associated with these hereby synthesized compounds are described in chapter 6 & 7. All the compounds were recrystalized before subjected to biological activity. The experimental techniques followed for assaying the biological activity are given below!

3.1Anti Bacterial Activity

Anti-bacterial activity of these compounds was determined by disc diffusion method (23). In this technique, the filter paper (Whatman No. 1) sterile discs of 5 mm diameter, impregnated with the test compounds (10 g/ml of ethanol) were placed on the nutrient agar plate at 37°C for 24 hrs. The inhibition zones around the dried impregnated discs were measured after 24 hrs. The activity was classifieds as 'highly active' (diameter > 14 mm); "moderately active" (diameter = 10-14 mm) and 'slightly active' (diameter = 6-10). The diameter less than 6 mm was regarded as inactive. The activity is given in Table-1

3.2 Anti-Fungal Activity

The antifungal activity of these compounds (Table 2 & 3) was tested by agar diffusion method (24) using four concentrations of the tests compounds, *viz*, 10,20,50 and 100 g/ml; against the two Human pathogenic fungus aspergillus flavus *and* Aspergillus nigar. The one ml of each compound was poured into a petridish having about 20-25 ml of molten agar medium of potato dextrose. As the medium gets solidify, petridishes were inoculated separately with the fungal isolates and kept at 26°C for 96 hrs. All the values (% inhibition) were recorded. The % inhibition of these compounds was calculated by using following mathematical equation. The percentage inhibition of these compounds given table 2-5.

$$\text{Percentage}(\%)\text{inhibition} = \frac{C - T}{C} \times 100$$

Here

C = Diameter of fungus in control.

T = Diameter of fungus in test compounds.

3.3 Insecticidal studies

The insecticidal activity (Table 6-9) of these compounds was tested against male and female adult cockroaches (Periplanata americana) and in housefly (Musea domestica) using the method of Nash (25). In this process a 0.1% and 0.5% acetonic solution of the compounds and the acetone solution as a standard (control). The test compounds (dissolved in acetone) were injected between the 4^{th} and 5^{th} abdominal segments on the ventral side of the body of male and female cockroaches; and sprays on the housefly with the help of microsyrings. The treated insects were kept under observation for about 48 hours at room temperature and no food was given in this period. At last the knock/down value was recorded.

3.3.1 Stomach toxicity

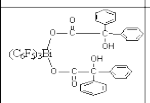
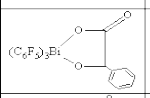
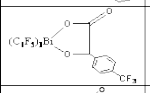
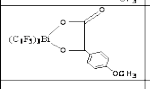
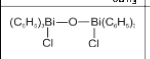
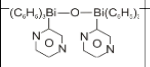
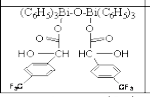
The stomach toxicity (Table-6) of these compounds was tested by the leaf-dip method (26). In this technique, the leaf discs of about 25 cm^2 were prepared out of caster leafs and were dipped for 30 sec in various concentration of the test compounds. (The compounds were dissolved in acetone and various concentrations were prepared). The leaf discs dipped only in acetone alone are served as control. Now air dried the leaf discs to evaporate the excess acetone. The fourth instar larvae of Spodoptera litura were used for this purpose ten larvae were used for each replication and three replications were used (maintained) for each concentration. The dried leaf discs were now offered for feeding. The mortality was recorded after 24 hrs and treatment mortality was corrected with control mortality. The mortality data were used for calculating LC_5o.

3.3.2 Contact toxicity

The contact toxicity (Table-7) of these compounds was tested by the topical application method (27). Fourth instar larvae of *Spodoptera litura* were used for this purpose. About 30 larvae were used for each concentration. The compounds were first dissolved in acetone and different concentrations were prepared. Now each concentrations were applied on the dorsal surface of the larvae (about 10 p! in each larvae separately). Insects treated only with acetone are served as control and left for 24 hrs. After 24 hrs the mortality was recorded and treatment mortality was corrected with the control mortality. These mortality data were used for calculating LC_{50}.

5 TABLES

Table – 1 Anti Bacterial Activity

S. No.	Compounds	Control	Pseudomonas aeru siginosa	Sta phylococus aureus	Klebsiella pneumonia.
1.	$(C_6F_5)_2Bi\ Cl_2$	–	+	+	+
2.		–	+ +	+	+ +
3.		–	+ +	+ +	+ +
4.		–	+ + +	+ +	+ + +
5.		–	+ +	+ +	+
6.		–	+	+	+
7.		–	+ + +	+ + +	+ +
8.		–	+ + +	+ + +	+ + +

$+ = 6 - mm(dia)\ +\ += 10 - 14mm\ +\ ++ > 14mm - Inactive; control$

Table - 2 Anti fungal activity of 10 µg/ml conc. of compound

Compound No.	Aspergillus flavus col. dia. (mm)	% Inhibition	Aspergillus nigar col. dia. (mm.)	% Inhibition.
1.	1.6	40	1.7	39
2.	1.5	65	1.5	65
3.	1.6	40	1.7	39
4.	0.8	73.3	0.7	74
5.	1.5	65	1.5	65
6.	1.6	40	1.7	39
7.	0.8	73.3	1.5	65
8.	0.8	73.3	0.7	74

Table - 5 Anti fungal activity of 50 µg/ml conc. of compound

Compound No.	Aspergillus flavus col. dia. (mm)	% Inhibition	Aspergillus nigar col. dia. (mm.)	% Inhibition
1.	0.8	73.3	0.5	83.3
2.	0.0.1	96.7	0.1	95
3.	0.5	83.3	0.4	84.0
4.	0.01	96.7	0.1	95
5.	0.01	96.7	0.1	95
6.	0.8	73.3	0.5	83.3
7.	0.01	96.7	0.1	95
8.	0.01	96.7	0.1	95

Table - 7 Contact toxicity at 24 hrs.

Compound No.	Fiducial Limits	Slope	Chi square	LC_{50}/LD_{50} at 24 hrs.
1.	1.87-12.08	1.09 ± 0.19	1.60(3)	3.53
2.	0.40-0.62	1.67 ± 0.15	5.12(3)	0.38
3.	0.29-0.38	1.97 ± 0.16	4.39(3)	0.34
4.	0.40-0.59	1.66 ± 0.15	5.66(3)	0.48
5.	0.48-0.75	1.61 ± 0.16	2.94(3)	0.59
6.	1.61-9.55	1.01 ± 0.17	0.68(3)	2.97
7.	1.33-3.99	1.32 ± 0.20	2.38(3)	2.01
8.	0.76-1.21	1.59 ± 0.16	2.44(3)	1.01

CONCLUSION

The activities of these compounds are due to perfuoro organic moieties, carboxylate ligands. Bi-O-Bi framework in some compounds makes them hydrolytically stable. The perfluoro groups make them more lipid soluble which is the cause of enhanced biological activity. These compounds were found to be moderate to significant biological active against screened bacterial stain, insects etc.

These complexes are monomeric and stable to atmospheric moisture and oxygen.

ACKNOWLEDGMENT

The author is thankful to the Head, Chemistry Department, I. E. T., Constituent college of G. B. T. U. , Lucknow for providing necessary laboratory facilities, and special thanks to my husband Intezaar Ahmad Abidi, Former State Minister, for their precious cooperation.

REFERENCES

[1] Thayer J.S. .1974) J. Organomet. Chem. 76, 265.
[2] Doak G.O. L.D. Freedman L.D(1973) Wiley Interscience, New York.
[3] Christiansen W.G. (1925) Catalog. Co. New York, 101.
[4] Sijpesteijn A.K., Luijten J.G.A. & Van der Kerk, GJM. Fungicides., ed. D.C. Torgeson. (1969), An Advanced Treatise ,Academic Press, New York 331.
[5] Barnes.JM. & Magas.L.,(1968) Organomet. Chem. Rev. 3:137.
[6] Langer H.G. US. 3:442922 (1970). Chem. Abstr. 72,12880 .
[7] Varsanyl D,, Margot A., Sohwinn F,, African S.(1971) 7006908, 94 June, Swiss Appl. 15,234/69, 10 Oct., (1969), 35pp, (1972), Chem.Abst, 76,141028.
[8] Burrell R.E., Corke C.T. & Goel R.G. (1983) J. Agri. Food Chem., 31, 85.
[9] Hu S.Z., Fu Y.M., Tang W.D., Yu W.J. (1997) Main group Met. Chem. 20, 169 .
[10] Hu S.Z., Tu L.D., Huang Y.Q Li X.Z, (1965),Inorg. Chem. Acta 232,161.
[11] Raj P., Singhal K., Ranjan A. & Rastogi, R. (1984). "Synth. Pract. Inorg. Met. Org. Chem. 14(2), 269.
[12] Singhal, K., Rastogi R& Raj.P. (1987) Ind. J. Chem. 26A, 146 (1987).
[13] Singhal K., Kant, R Shukla S.K., Chandrashekhar K,, A. Ranjan A. & Raj. P. (2008). Phosphorus, Sulphur, Silicon 183(8), 2029.
[14] Raj P., Singhal, K., Kant R., Saxena A.K. (2004) Global Patent No. 0388NF.
[15] Christiansen W.G., (1925) Chem, Catalog Co. New York, 101.
[16] Gilman H. & Yale H.L. (1992). Chem. Rev. 30, 281.
[17] Briand G.G. & Burford, N. (1999). Chem. Rev. 99, 2601.
[18] Langer, H.G. (1970). Chem. Abstr. 72, 12880.
[19] Gill, B.S. (1971) Trans, Roy. Soc. Trop. Med. Hyg. 65, 347.
[20] Gill, B.S. (1973). Biol, Abstr. 55, 41813.

[21] Varsanyi, D., Margot A. & Schwinn F. (1972). Chem. Abstr. 76, 141028 .
[22] Curry, .J.D (1972). British Patent 134, 1331.
[23] Singhal, R., Mishra R. & Raj P. (2008).Heteroatom Chemistry 19(7), 688.
[24] Ulfvarson. V. In: "Fungicides", Jorgeson D. (Ed.), (1969). Academic Press, New York Vol. II, Chapter 6.
[25] B.S. Gill, Trans. *Roy. Soc. Trop. Med. Hyg.* 65 (1971) 347.
[26] C. Ludwig, M. Dolny, H. J. Gotze, *Spectro Chem. Acta A.* 56 (2000) 547-555.
[27] Pankaj Sharma, Diego Perez, Armando Cabrera, Noe Rosas, Jose Luis Arias, *Acta Pharmacologica Sinica,* 29(8), (2008) 881-890.
[28] R.Kant, K.Singhal, S.K.Shukla, K.Chandrashekar, A.K.Saxena, A.Ranjan, P.Raj, *Phosphorus, Sulfur and Silicon*, 183(8), (2008) 2029-2039.
[29] Kiran Singhal, Rahul Misra Prem Raj, Hetetoatom Chem, (2008)
[30] Kiran Singhal, Rajiv Rastogi and Prem Raj. *Ind. J. of Chemistry.* 26A (1987) 146-150.
[31] Prem Raj, I. Husain and K. Singhal. *Arzinimittal Forsch. / Drug Res.* 44(1) 2 (1994) 178- 181.
[32] Prem Raj, Ashok Ranjan, Kiran Singhal, Rajiv Rastogi. *Synth. React. Inorg. Met. Org. Chem.* 14(2) (1984) 269-282.
[33] Kiran Singhal, Prem Raj, V.D. Gupta, Seema Srivastava, S.K. Naman, A.K. Saxena. *Spectrochem. Acta, A.* (Communicated).
[34] B.K. Keppler, C. Silvestru, I. Haiduc, *Metal-Based Drugs.* 1 (1994) 73-77.
[35] C. Socaciu, I. Pasca, C. Silvestru, A. Bar, I. Haidue, *Metal-Based Drugs* 1 (1994) 291- 297.
[36] Yu. Lin, Y.Q. Ma, G.C. Wang, Z.S.Li, G.H. Du, J.J. Hu, *J. Organomet. Chem.* 671 (2003) 122-127.
[37] J.S. Li, Y.Q. Ma, J.R. Cui, R.Q. Wang, *App. Organomet. Chem.* 15(2001) 639-645.
[38] J.S. Li, Y.Q. Ma, Yu. Lin, J.R. Cui, R.Q. Wang, Synth. *React. Inorg. Met. Org. Chem.* 32(3): (2002) 583-593.
[39] E.R.T. Tiekink, Critical Review in Oncology /Haematology. 42 (2002) 217-224.
[40] K. Chandrashekhar, H.M. Behl, V. Kumar, O.P. Sidhu, Ch. V. Rao, S.K. Shukla A.K. Saxena, A. Ranjan, Ravi Kant, K. Singhal, Prem Raj, P.C.T. Filed, No. IN04/00407/2004, Date, 24-12-2004.
[41] P.A Andrews, S.B.Howell, *Cancer Cells*, 2(1990) 35-43.
[42] S.L.Bruhn, J.H.Toney, S.J.Lippard, *Prog. Inorg. Chem*, 38(1990)477-516; G.Chu, *J.Biol Chem.*, 269(1994)787-790.
[43] S.W.Lowe, H.E.Ruley, T.Jacks, D.E.Housman, *Cell*, 74(1993)957-967.
[44] U. M. Ohndorf, J. P. Whitehead, N. L. Raju, S. J. Lippard, *Biochemistry*, 36(1997)14807- 14815.
[45] P. Raj, A.K. Saxena, A.K. Aggarwal, *J. Fluorine Chem.* 42 (1989) 163-172.
[46] A.A. Van-de-Loosdrecht. *J. Immunol. Meth.* 174 (1994) 311 -320.
[47] R.S. Verma, S.A. Imam. *Ind. J. Microbiol.* 13 (1973) 45.
[48] J.G. Horshfall, *Bot. Rev.* 5 (1945) 357.
[49] R. Nash. *Ann. Appl.* 41 (1954)652.
[50] V.G. Dethie, L.B. Browne, C.N. Smith: *J. Econ. Entomol.* 53 (1960) 134-136.
[51] S.D. Deshmukh, M.N. Borle, *Ind. J. Entomol.* 37(1) (1976) 11-18.