
Article

Synthesis of Novel Pentafluorophenyl Derivatives of As, Sb, Bi and Their Efficacy Against Antimicrobial Resistance

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Abstract

The present invention summarizes the synthesis of a novel pentafluorophenyl derivative of As, Sb, Bi through modified method followed by their characterization with sophisticated instrumental analysis to ascertain their structural geometry. They also screened for their antimicrobial activity against pathogenic strains of bacteria and fungi at different concentrations to find out their efficacy against Antimicrobial Resistance (AMR). It was found that these compounds show remarkable antimicrobial activity and highly effective against Antimicrobial Resistance with novel Structure-Activity Relationship.

Keywords: Pentafluorophenyl, pathogenic, antimicrobial resistance, antibacterial, antifungal.

1. Introduction

The organometallic complexes of group-15 elements (As, Sb, Bi) are used for the treatment of various acute and pathogenic diseases in case of human beings [1-5]. Due to higher interest in medicinal application of metal-based drugs, the present investigation was undertaken to explore the antimicrobial resistance efficacy of some new organometallics of group-15 elements (As, Sb, Bi) having water and lipid solubility [6-9]. The interest in organometallic chemistry of fluorine containing compounds gained momentum in recent past due to the unusual character of fluorine and the intrinsic properties shown by fluorocarbon-based organometallics [10-12]. Perfluoroalkyl and perfluoroaryl derivatives of metals and non-metals provide much instructive comparison with compounds based on hydrocarbon residue [13]. The presence of fluorine atom either in organic group bound to metal or fluorine substituted ligand facilitate the solubility in lipid as well as in water and thus enhancing their bioavailability. In past two decades pentafluorophenyl derivatives of group 15 elements have been explored for their biological potential [14] and in fact have shown promising trends related to antimicrobial and antitumor activity [15].

2. Experimental

The synthesis of pentafluorophenyl derivatives of As, Sb, Bi was performed by following methods [16] under oxygen free nitrogen atmosphere.

Reaction of (C₆F₅)AsCl₂ with glycine:

In the stirring solution of pentafluorophenylarsenic(III)dichloride (1mmol), glycine (1mmol) was added in the presence of trimethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 5 hr followed by refluxing for 2 more hr to ensure the completion of the reaction. The flocculent off-white precipitate of Et₃N.HCl (M.P. 240°C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a light brown solid mass which was recrystallized by petroleum ether (40-60°C).

Reaction of (C₆F₅) SbCl₂ with glycine:

In the stirring solution of pentafluorophenylantimony(III)dichloride (1mmol), glycine (1mmol) was added in the presence of trimethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6-7 hr followed by refluxing for 2 hr more to ensure the completion of the reaction. The flocculent white precipitate of Et₃N.HCl (M.P. 240°C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a light off-white solid which was recrystallized by petroleum ether (40-60°C).

Reaction of (C₆F₅) BiCl₂ with glycine:

In the stirring solution of pentafluorophenylbismuth(III)dichloride (1mmol), glycine (1mmol) was added in the presence of trimethylamine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 hr to ensure the completion of the reaction. The flocculent white precipitate of Et₃N.HCl (M.P. 240°C) was formed and filtered off. This filtrate on concentration under vacuum condition gives an off-white solid which was recrystallized by petroleum ether (40-60°C).

Antibacterial Activity

Antibacterial activity of the synthesized pentafluorophenyl derivatives was carried out by disc diffusion method [17] using *ampicillin* as standard. The filter paper (Whatman No.1) sterile disc of 5 mm diameter, impregnated with the test compounds (10 µg/ml of ethanol) along with standard were placed on the nutrient agar plate at 37°C for 24 hrs in BOD incubator. The inhibition zone around the dried impregnated disc was measured after 24 hrs.

Antifungal Activity

The antifungal activity of the compound was tested by agar plate diffusion method [18], using *ampicillin* as standard wherein concentrations of the test compounds viz., 50 and 100 µg/ml were prepared and tested against two pathogenic fungal strains, *Aspergillus flavus* and *Aspergillus niger*. The 1 ml of each compound was poured into a petri dish containing 20-25 ml of molten potato dextrose-agar medium. As the medium solidify, petri dishes were incubated at 37°C for 96 hrs in

BOD incubator. After 96 hrs the colony diameter was measured and % inhibition was calculated using standard method.

3. Results and Discussions

All the reactions were conducted under strict oxygen free atmosphere at room temperature and the final products were recrystallized in petroleum ether (40-60°C) or in benzene. The complexes were light brown, light off-white and off-white color, obtained as a sticky mass which on treatment with dry benzene gets solidified and subsequently crystallized with benzene/pet-ether. The complex has sharp melting point and soluble in chloroform and acetonitrile.

IR Spectra

As expected infrared absorptions inherent to pentafluorophenyl group bound to metal have no difference appreciably. The Infrared absorptions having diagnostic value related to the ligand, has been identified which on preliminary stage indicates the mode of bonding with ligand. The characteristic $\nu(\text{OH})$ absorption band of ligand which appeared around 3400cm^{-1} in the free ligand, was found missing in the newly synthesized complexes.

^1H NMR Spectra

^1H NMR spectra of the compound was recorded in CDCl_3 using TMS as an internal reference at 25°C. The disappearance of OH proton signals ($\delta 9.1$ ppm) present in the ligand clearly indicates the formation of glycine derivative. The appearance of singlet for $-\text{CH}_3$ protons at $\delta 4.85$ ppm showed the ligand is in one plane.

UV Spectra

The electronic spectra obtained for representative compound was recorded in chloroform in the range 200-400nm. The UV absorption due to COO group appears at 274 ± 6 and 294 ± 2 . On the basis of IR, NMR and UV spectral analysis data, it may be concluded that the present study behaves

Antibacterial activity:

The compounds show higher to moderate activity against the bacterial strains. It was found that compound with water and lipid solubility is more effective. It generally form complexes with metalloenzymes, particularly those which responsible in basic physiology such as *cytochrome oxidase*. The compound may react with peptidoglycan layer of bacterial cell wall and damage it by penetrating in such a manner that the phenyl ring gets entered inside the cell by puncturing it followed by death of bacterial cell. Sometimes these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacteria.

Antifungal Activity:

The activity of compound was found variable at 50µg/ml concentration but at higher concentration compound show moderate to high activity against fungal strains. Presence of nitrogen, phenyl ring along with metal in +3 oxidation state are considered for fungal activity. The role of ligand was also commendable. These compounds generally damage the fungal strains by puncturing the cell wall similarly as in the case of bacteria.

Physicochemical Properties of Pentafluorophenyl derivatives of group-15 Elements (As, Sb, Bi)

S.N.	Compounds	Formula weight	Molecular weight	M.P. (°C)	Elemental Analysis		
					C%	H%	N%
1	C ₈ H ₄ ClNO ₂ F ₅ As	335.5	336.0	117	28.61	1.19	4.17
2	C ₈ H ₄ ClNO ₂ F ₅ Sb	382.5	382.0	114	25.09	1.04	3.66
3	C ₈ H ₄ ClNO ₂ F ₅ Bi	469.5	470.0	108	20.44	0.85	2.98

Antibacterial Screening

S.N.	Compounds	Control	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	<i>Klebsella pneumoniae</i>
1	C ₈ H ₄ ClNO ₂ F ₅ As	—	+++	+++	+++
2	C ₈ H ₄ ClNO ₂ F ₅ Sb	—	+++	+++	+++
3	C ₈ H ₄ ClNO ₂ F ₅ Bi	—	+++	+++	+++

Antifungal Screening at 50µg/ml

S.N.	Compounds	<i>A. flavus</i> Col. Dia. (mm)	% Inhibition	<i>A. niger</i> Col. Dia. (mm)	% Inhibition
1	C ₈ H ₄ ClNO ₂ F ₅ As	0.2	93.3	0.7	65.0
2	C ₈ H ₄ ClNO ₂ F ₅ Sb	0.2	93.3	0.7	65.0
3	C ₈ H ₄ ClNO ₂ F ₅ Bi	0.4	86.7	0.6	70.0
4	Control	3.0	—	2.0	-

Antifungal Screening at 100µg/ml

S. N.	Compounds	<i>A. flavus</i> Col. Dia.(mm)	% Inhibition	<i>A. niger</i> Col. Dia.(mm)	% Inhibition
1	C ₈ H ₄ ClNO ₂ F ₅ As	0.1	96.7	0.4	80.0
2	C ₈ H ₄ ClNO ₂ F ₅ Sb	0.2	93.3	0.3	75.0
3	C ₈ H ₄ ClNO ₂ F ₅ Bi	0.1	96.7	0.3	75.0
4	Control	3.0	-	2.0	-

4. Conclusion

The newly synthesized pentafluorophenyl derivatives of As, Sb, Bi are novel having pyramidal geometry. They show prominent antimicrobial activity against pathogenic bacterial and fungal strains and shows prominent efficacy against antimicrobial resistance.

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References

1. Ravi Kant, Amresh, G., Chandrashekar. K., Anil. K.K. S, *Phosphorus*, (2008) *Sulfur, Silicon*, 183, 1410-1419.
2. Dominico P., Salo R.J., Novick S.G., Schoch P.E., Horn K.V., Cunha, B.A. , *Antimicrobial agent Chemother*, 41, 1697-1703, 1997.
3. Veldhuyzen V.Z., Sherman P.M., (1994) *Can. Med. Asso. J.*, 150, 189-198,.
4. Lambert, J.R. (1991) *Rev. Infect. Dis.*, 13(8), S691-S695, 1991.
5. Lambert, J.R. , Midolo, P. , (1997) *Aliment. Pharmacol. Ther*, 11(1), 27-33.
6. Dominico P., Salo R.J., Novick S.G., Schoch P.E., Horn K.V., Cunha B.A.,(1997) *Antimicrobial agent Chemother*, 41, 1697-1703.
7. Stratton. C.W. , Warner, P.E. Coudron, N.A. Lilly, (1999), *J. Antimicrobial. Chemother*, 43, 659-666.
8. Ravi Kant, Shukla. S.K., Singhal. K., Chandrashekar. K., Saxena. A.K., A.Ranjan, P.Raj, *Phosphorus, Sulfur, Silicon*, 183, 2029-2039, 2008.
9. Ravi Kant, Amresh. G., Chandrashekar. K., Sanjeev K. Shukla,(2009) *Phosphorus, Sulfur, Silicon*, 184(9), 2453-2464.

10. Tripathi. D.M., Amresh G., Ravi Kant, *Inter. (2012) J. Chem. Res.*, 4(1),110-113,
11. Ravi Kant, Ashish Bhatt, Krishna Srivastava (2019) *Chemical Biology Letters*, 6(2).
12. Dipti Mani Tripathi, Ravi Kant, Krishna Srivastava, (2020) *Asian J. Pharm. Clin. Res.*, 13(5), 62-65.
13. Dipti Mani Tripathi, Ravi Kant, Krishna Srivastava (2020), *Asian J. Pharm. Clin. Res.*, 13(5), 57-61.
14. Singhal. K., Ravi Kant, Goswami, A.K., Prem Raj, (2003), *J. Flourine chemistry*, 122, 229-232.
15. Singhal K., Ravi Kant, Yadav R.N.P., Pandey P.C., Prem Raj, (2004), *Synth. React. Inorg. Met-org. chem.* 34(3), 455-464.
16. Singhal K., Ravi Kant, Yadav R.N.P., Prem Raj, Naman S.K., (2004), *J. Saudi. Chem. Soc.* 8(2), 295-306.
17. Verma R.S., Imam S.A., (1973) *Ind. J. Microbial*, 13, 45.