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Research Article

# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF SOME NOVEL COMPLEXES OF GROUP 15 ELEMENTS (As, Sb, Bi)

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**Abstract-** The present manuscript deals the synthesis of some new di-organocomplexes of group 15 elements especially As, Sb and Bi with 3-amino-6-chloropyridazine. The compounds were synthesized by reported methods and characterized by their melting points, elemental analysis along with IR, NMR spectral analysis to establish the structure of complexes. These compounds were first time screened for their biological efficacy against different pathogenic microbial culture strains. The results are very much promising that few of them compounds are found highly active against biological system.

**Key words-** Group 15 Elements As, Sb and Bi, 3-amino-6-chloropyridazine, antimicrobial, agents.

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## Introduction

Metals have an enormous potential in medicines and their selection may offer the possibility for the discovery of new metal based drugs with novel mechanism of action. The importance of metal based drugs lies in the fact that they are essential components for various physico-chemical processes occurring in living system. The spectrum of the metal based drugs has been expanded as they have found their place among a class of potential biologically active compounds exhibiting antimicrobial, anti-inflammatory, cardiovascular, trypanosomal, anti-herpes and anti-tubercular along with the treatment of cancer and gastric disorders [1-4]. The discovery of synthetic arsenicals, *"Salvarsan"* in 1910 found as an effective medicine against *syphilis*, led to an extensive investigation on the synthesis and biological studies of organo-arsenic compounds [5]. Later on in some reviews and books it was published that organo-metallic compounds of group 15 elements shows higher activity against bacterial, fungal and viral strains of microorganisms [6]. The organo-antimony compounds proved highly effective against infections by *Trypanosomes* and *Leishmanian* organisms [7-10]. Some reports on the microbiological activity of organo-antimony compounds have stated that most of them are toxic [11], but do not have a repetition as potential hazardous to those preparing them. It was found that the organo-antimony (III) derivatives show important bactericidal and fungicidal activity [12]. The organo-bismuth compounds were active against the treatment of gastrointestinal disorders like dyspepsia, diarrhea and in peptic ulcers by inhibiting *E. coli* [13-15]. In recent a series of organo-bismuth compounds show potential antimicrobial activity against fungus and bacterial culture responsible for pathogenic disease [16]. The recent demonstration has shown that the organo-bismuth are useful for *Helicobacter pylori* eradication therapy [17] and has promoted the antibacterial and antifungal studies of various organo-bismuth compounds. The present manuscript deals the synthesis of some new diorgano complexes of group 15 elements especially As, Sb and Bi with 3-amino-6-chloropyridazine. The compounds were synthesized by reported methods and characterized by their melting points, elemental analysis along with IR, NMR spectral analysis to establish the structure of complexes. These compounds were first time screened for their biological efficacy.

## Experimental

The diorgano-bismuth (III) chloride ($R_2BiCl$), diorganoantimony (III) chloride ($R_2SbCl$) and diorgano-arsenic (III) chloride ($R_2AsCl$) were prepared by redistribution reaction reported earlier [18]. The ligand was recrystalised before used while all the reactions were performed under inert/nitrogen atmosphere. Synthesis of some representative organo-bismuth compounds are discussed below.

**Reaction of diphenylbismuth(III)chloride with 3-amino-6-chloropyridazine:**
In the stirring solution of diphenylbismuth(III)chloride (1m mol),3-amino-6-chloropyridazine (1 m mol) was added in the presence of trimethyl amine (1 ml) in benzene and was stirred under anhydrous oxygen free nitrogen atmosphere for 6 hours followed by refluxing for further 2 hours to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives a light off white solid which was recrystalised by petroleum ether (40-60˚C).

**Reaction of diphenylantimony (III) chloride with 3-amino-6-chloropyridazine:**
In the stirring solution of diphenylantimony chloride (1m mol), 3-amino-6-chloropyridazine(1 m mol) was added in the presence of trimethyl amine (1 ml) in benzene and was stirred under anhydrous oxygen free nitrogen atmosphere for 6 hours followed by refluxing for 2 hours to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered off. This filtrate on concentration under vacuum condition gives an off white solid which was recrystalised by petroleum ether (40-60˚C).

**Reaction of diphenylarsenic (III) chloride with 3-amino-6-chloropyridazine:**
In the stirring solution of diphenylarsenic(III) chloride (1m mol), 3-amino-6-chloropyridazine (1 m mol) was added in the presence of trimethyl amine (1 ml) in benzene and was stirred under anhydrous oxygen free nitrogen atmosphere for 6-7 hours followed by refluxing for 3 hours to ensure the completion of the reaction. The flocculent white precipitate of $Et_3N.HCl$ (M.P. 240˚C) was formed and filtered

off. This filtrate on concentration under vacuum condition gives a light off white solid which was recrystalised by petroleum ether (40-60˚C).

**Antibacterial Activity**

Antibacterial activity of the synthesized compound was carried out by disc diffusion method [19] using ampicilin 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 [20], using ampicilin as standard. Four concentrations of the test compounds *viz.,* 10, 20, 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 [21].

**Results and Discussion**

The synthesis of di-organo complexes of group 15 elements especially As, Sb and Bi with 3-amino-6-chloropyridazine was performed in laboratory with the help of following reactions.

$$R_3M + MCl_3 \xrightarrow{\text{Neat}} R_2MCl$$

$$R_2MCl + HL \xrightarrow{Et_3N} R_2ML + Et_3N.HCl$$

Here:

R = [$C_6H_5$, $C_6F_5$, $C_6H_4F$]

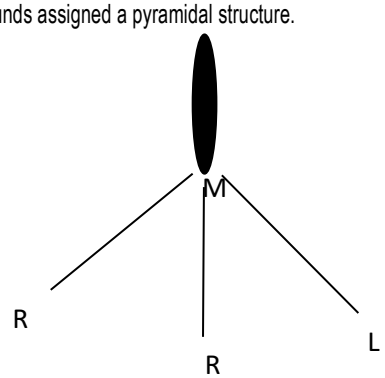
M = As, Sb, Bi

HL = 3-amino-6-chloropyridazine

All the newly synthesized compounds were crystalline solids, air stable and soluble in common organic solvents. The compounds were further characterized by their melting points and analytical techniques such as elemental analysis, infrared and NMR spectroscopy to ascertain their structures and explore their biological properties. The new compounds have sharp melting points and posses pyramidal structure as per results obtained by further analysis.

**IR and NMR Spectral Analysis**

The IR spectra of new compounds were recorded in Perkin–Elmer spectrophotometer in 4000-200 $cm^{-1}$range. The IR spectra of these compounds show absorption bands due to phenyl and pentafluorophenyl groups. The absorption frequencies have been fully assigned. The M-C vibration in case of phenyl and pentafluorophenyl derivatives corresponding to the y mode appears in the range of 448-460 $cm^{-1}$. The IR data suggested a monodentate coordination mode of the ligands. The $^1$HNMR spectra of the representative compounds showed a multiplet in the range δ7.82ppm to δ8.12ppm which could be assigned to aromatic protons. The $^{19}$FNMR spectra of the compound was carried out at room temperature and the compounds showed peaks appearing in the range -108.30ppm to -112.30ppm consistent with the presence of fluorophenyl groups. Thus on the basis of above discussions the newly synthesized diorganobismuth (III) compounds assigned a pyramidal structure.




R = [$C_6H_5$, $C_6F_5$, $C_6H_4F$]

M = As, Sb, Bi

L = 3-amino-6-chloropyridazine

**Suggested structure**

**Antibacterial activity:**

All the compounds show higher to moderate activity against the bacterial strains. It was found that compounds having water and lipid solubility are more effective. The compounds generally form complexes with metaloenzymes, particularly those which responsible in basic physiology such as *cytochrome oxidase*. These compounds 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.

**Fig 1- Antibacterial activity**

**Antifungal Activity:**

The activity of these compounds was found variable at 50µg/ml concentration but at higher concentration all the compounds 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. Water and lipid solubility also increases the activity.

**Fig 2- Antifungal Activity**

**Table-1** *Physicochemical Analysis of compounds*

| S N | Compounds | Formula Weight | Yield % | M.P °C | Solvent | Elemental Analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C% | H% | N% |
| 1 | $C_{16}H_{13}N_3ClAs$ | 357.5 | 70 | 79 | Pet-Ether | 53.70 | 3.63 | 11.74 |
| 2 | $C_{16}H_{11}N_3F_2ClAs$ | 393.5 | 68 | 78 | Pet-Ether | 48.79 | 2.79 | 10.67 |
| 3 | $C_{16}H_3N_3F_{10}ClAs$ | 537.5 | 72 | 81 | Pet-Ether | 35.72 | 0.55 | 07.81 |
| 4 | $C_{16}H_{13}N_3ClSb$ | 404.5 | 70 | 80 | Pet-Ether | 47.46 | 3.21 | 10.38 |
| 5 | $C_{16}H_{11}N_3F_2ClSb$ | 440.5 | 66 | 76 | Pet-Ether | 43.58 | 2.49 | 09.53 |
| 6 | $C_{16}H_3N_3F_{10}ClSb$ | 584.5 | 60 | 89 | Pet-Ether | 32.84 | 0.51 | 07.18 |
| 7 | $C_{16}H_{13}N_3ClBi$ | 491.5 | 60 | 90 | Pet-Ether | 39.06 | 2.64 | 08.54 |
| 8 | $C_{16}H_{11}N_3F_2ClBi$ | 527.5 | 62 | 79 | Pet-Ether | 36.39 | 2.08 | 07.96 |
| 9 | $C_{16}H_3N_3F_{10}ClBi$ | 671.5 | 60 | 75 | Pet-Ether | 28.59 | 0.44 | 06.25 |

**Table-2** *Antibacterial Activity of compounds*

| S. N. | Compounds | Control | *Pseudomonas aeruginosa* | *Staphylococcus aureus* | *Klebsiela pneumoniae* |
|---|---|---|---|---|---|
| 1 | $C_{16}H_{13}N_3ClAs$ | – | ++ | ++ | ++ |
| 2 | $C_{16}H_{11}N_3F_2ClAs$ | – | +++ | ++ | +++ |
| 3 | $C_{16}H_3N_3F_{10}ClAs$ | – | +++ | ++ | +++ |
| 4 | $C_{16}H_{13}N_3ClSb$ | – | ++ | ++ | ++ |
| 5 | $C_{16}H_{11}N_3F_2ClSb$ | – | +++ | ++ | +++ |
| 6 | $C_{16}H_3N_3F_{10}ClSb$ | – | +++ | ++ | +++ |
| 7 | $C_{16}H_{13}N_3ClBi$ | – | ++ | ++ | ++ |
| 8 | $C_{16}H_{11}N_3F_2ClBi$ | – | +++ | +++ | +++ |
| 9 | $C_{16}H_3N_3F_{10}ClBi$ | – | +++ | +++ | +++ |

**Table-3** *Antifungal Activity of compounds at 50µg/ml conc*

| S. N. | Compounds | *Aspergillus flavus* Col. Dia. (mm) | % Inhibition | *Aspergillus niger* Col. Dia. (mm) | % Inhibition |
|---|---|---|---|---|---|
| 1 | $C_{16}H_{13}N_3ClAs$ | 0.7 | 76.6 | 0.8 | 60.0 |
| 2 | $C_{16}H_{11}N_3F_2ClAs$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 3 | $C_{16}H_3N_3F_{10}ClAs$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 4 | $C_{16}H_{13}N_3ClSb$ | 0.5 | 83.3 | 0.8 | 60.0 |
| 5 | $C_{16}H_{11}N_3F_2ClSb$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 6 | $C_{16}H_3N_3F_{10}ClSb$ | 0.2 | 93.3 | 0.7 | 65.0 |
| 7 | $C_{16}H_{13}N_3ClBi$ | 0.7 | 76.6 | 0.4 | 80.0 |
| 8 | $C_{16}H_{11}N_3F_2ClBi$ | 0.8 | 73.3 | 0.8 | 60.0 |
| 9 | $C_{16}H_3N_3F_{10}ClBi$ | 0.8 | 73.3 | 0.8 | 60.0 |
| 10 | Control | 3.0 | - | 2.0 | - |

**Table-4** *Antifungal Activity of compounds at 100µg/ml conc*

| S. N. | Compounds | *Aspergillus flavus* Col. Dia. (mm) | % Inhibition | *Aspergillus niger* Col. Dia. (mm) | % Inhibition |
|---|---|---|---|---|---|
| 1 | $C_{16}H_{13}N_3ClAs$ | 0.5 | 83.3 | 0.4 | 80.0 |
| 2 | $C_{16}H_{11}N_3F_2ClAs$ | 0.2 | 93.3 | 0.3 | 75.0 |
| 3 | $C_{16}H_3N_3F_{10}ClAs$ | 0.2 | 93.3 | 0.1 | 95.0 |
| 4 | $C_{16}H_{13}N_3ClSb$ | 0.4 | 86.7 | 0.3 | 75.0 |
| 5 | $C_{16}H_{11}N_3F_2ClSb$ | 0.1 | 96.7 | 0.2 | 90.0 |
| 6 | $C_{16}H_3N_3F_{10}ClSb$ | 0.1 | 96.7 | 0.1 | 95.0 |
| 7 | $C_{16}H_{13}N_3ClBi$ | 0.2 | 93.3 | 0.4 | 80.0 |
| 8 | $C_{16}H_{11}N_3F_2ClBi$ | 0.1 | 96.7 | 0.2 | 90.0 |
| 9 | $C_{16}H_3N_3F_{10}ClBi$ | 0.1 | 96.7 | 0.1 | 95.0 |
| 10 | Control | 3.0 | -- | 2.0 | -- |

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**Author Contributions:** All author equally contributed

**Author statement:** All authors read, agree and approved the final manuscript

**Abbreviations:**
IR-Infrared
NMR- Nuclear Magnetic Resonance
ELISA- Enzyme Linked Immuno Sorbent Assay

**Conflict of Interest:** None declared

**Ethical approval:** This article does not contain any studies with human participants or animals performed by any of the authors.

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