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Review Article

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An Overview of Chemical Properties and Pharmacological Importance of Organobismuth Compounds

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Abstract

There are several fields of chemistry, biochemistry and pharmaceutical chemistry where bismuth has been acting and potentially used in organic syntheses (phenylation or mild oxidizing agents), catalysts for carbon-carbon bond formation reaction and functional group transformations in many named and processed reaction, has industrial uses as precursors in advanced material science (superconductors, photorefractive systems, sol-gel processes and chemical vapor deposition techniques), bioactivity for the treatment of gastrointestinal disorders and as antitumor, antimicrobial, antibacterial, antispermatogenic and many more areas also. The present review article tends to highlight the chemical properties and potential applications of organobismuth compounds on human body both clinically and industrially.

Keywords: *Organobismuth compounds; Superconductors; Photorefractive systems; Sol-gel processes; Chemical vapour deposition techniques*

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Introduction

Bismuth is a group 15 element of the periodic table, which also includes P, As and Sb. It has an atomic number of 83, an atomic mass of 209, electronic configuration of [Xe] $4f^{14}5d^{10}6s^{2}6p^{3}$ allowing bismuth to accept an electron pair readily as well as availability of unoccupied orbital elevate its affinity to extend coordination. Two main oxidation states (+3 example bismuth (III) halides, bismuth (III) subsalicylate etc. and +5 example bismuth (V) fluoride) and one naturally occurring isotope is (^{209}Bi). Naturally occurring bismuth is found in small quantities throughout Earth's crust both as a pure metal and combined with other elements in various compounds. Bismuth has a relatively low crustal abundance (8ppb), it is 69th element in order of abundance, and is less common than silver, indium, cadmium, and only twice as common as gold [1]. The largest source of bismuth is found in the mineral bismuthinite [2], or bismuth glance (Bi_2S_3), bismite or bismuth ocher (Bi_2O_3) and bismutite [$(BiO)_2CO_3 \cdot H_2O$] [3]. Bismuth occurs naturally as the metal itself and is found as crystals in the sulphides ores of nickel, cobalt, silver and tin. Bismuth is typically obtained as a by-product in refining lead, copper [4], tin, silver, and gold ores found in Bolivia, Peru, Japan, Mexico, and Canada.

Bismuth is a soft, silvery metal with a bright, shiny surface and a yellowish or pinkish tinge. The metal breaks easily at room temperature. Its melting point is 271°C (520°F) and its boiling point is 1,560°C (2,480°F) [5]. Its density is 9.78 grams per cubic centimeter. The compounds of Bi (III) are the most important ones in analytical chemistry. Compounds of bismuth (IV) [6] may also exist. The compounds of bismuth (V) - alkali metal bismuthates - are known only in the solid state. The ions of bismuth (V) do not exist in solution [7].

There is also a single report of Bi (I) complex in solution obtained by dissolving metallic Bi in Conc. HCl however this solution is reported to be unsatable [8].

Reactions of bismuth metal with various reagent [9]

S. No.	Reagents	Reactions with the Reagents
1.	Nitrogen	No Reaction
2.	Bromine	Reacts on heating to form Bi Br3
3.	Water	No Reaction at room temperature, reacts slowly on calcination in a steam atmosphere with oxidation to Bi_2O_3
4.	Hydrogen	No Reaction
5.	Air	No reaction either in dry or in wet air at room temperature; burns on heating to form ‘i_20_3
6.	Iodine	Reacts on heating to form BiI_3.
7.	Nitric Acid	Reacts to form $Bi(NO_3)_3$
8.	Sulfuric Acid	Reacts on heating with liberation of $S0_2$.
9.	Hydrochloric Acid	No Reaction
10.	Lithium	Reacts on heating to form bismuthide
11.	Selenium	Reacts on heating to form $BiSe_3$
12.	Sulphur	React to form Bi_2S_3
13.	Tellurium	Reacts to form Bi_2Te_3
14.	Phosphorus	No Reaction
15.	Chlorine	Reacts with ignition to form $BiCl_3$

Table 1: *Reaction of bismuth to reagents.*

Complexometric titration

Bismuth can be titrated by all of the three methods of complexometric titrations that is back titration, masking and demasking agent and residual titration method [10]. (Raroot S., *et al.*) developed a selective complexometric determination of bismuth with mercaptans as masking agents, and its estimation in alloys, an excess of EDTA is added and the surplus is back-titrated at pH 5–6 with lead nitrate (Xylenol Orange as indicator). Thioglycollic or mercaptopropionic acid is then added to decompose the bismuth-EDTA complex and the liberated EDTA is titrated with lead nitrate [11].

Gravimetric Estimation

The sample is dissolved in HNO_3 is precipitated after dilution by the addition of ammonium carbonate in excess and boiling, The precipitate is then filtered off, washed with hot water, dried, ignited and weighed. The ignition should performed carefully above a low red heat, the oxide (Bi_2O_3) formed has a colour of dark yellow or brown and becomes yellow on cooling [12].

Volumetric Methods

Various methods of estimation of bismuth have been described volumetrically. A solution is made in HNO_3 and from this basic bismuth oxalate is precipitated with ammonium oxalate. Then the precipitate is dissolved in HCl, the solution is neutralised with ammonium hydroxide, and any precipitated hydroxide is redissolved if H_2SO_4. This final solution is then heated to 70^0C and titrated with a standard solution of $KMnO_4$ [13].

Colorimetric and spectrophotometric methods

Thiourea, $CS(NH_2)_2$ reacts with bismuth ions in HNO_3 or H_2SO_4 solutions to form an intense yellow coloration which is suitable for calorimetric determination of bismuth, especially when the amount of bismuth is larger than 1mg. The absorption maxima are at 322 nm and 470 nm, and fourfold sensitivity is obtained in the ultra violet region. When potassium iodide solution is added to a dilute H_2SO_4 solution containing a small amount of bismuth, a yellow to orange coloration, due to the formation of an IodobismuthateIon, is produced. The color intensity increases with Iodide concentration up to about 1% KI and then remains practically constant. Small amounts of bismuth in the range 0.05-0.5 mg can be determined by this method at 460 nm [14].

Chromatographic method

A forced flow liquid chromatographic method was reported in which bismuth (III) is retained on a cation exchange column from dilute acid and is then separated from other metal ions by elution with 0.5 M Hydrobromic acid. The separation method is selective and rapid for bismuth [15]. An another method by Reverse phase extraction chromatography using liquid anion exchanger N-n-octylaniline as a stationary phase on silica as solid support was reported. Bismuth (III) was eluted from column with acetate buffer and analyzed spectrophotometrically with potassium iodide metod [16].

Nuclear Magnetic Resonance (NMR) and infrared (IR) spectroscopy

These are common techniques used to determine structure of organometallic compounds. Vibration spectroscopy such as Raman or infrared spectroscopy is used to determine the chemical composition of a material based on detection of vibration modes of constituent molecules. NMR is a research technique that exploits the magnetic properties of certain atomic nuclei. It determines the physical and chemical properties of atoms or the molecules in which they are contained. It relies on the phenomenon of nuclear magnetic resonance and can provide detailed information about the structure, dynamics, reaction state, and chemical environment of molecules [17].

Structure and properties of organobismuth compounds

Bismuth being a radioactive element, it is stable because of it's an extremely long half life ($t_{1/2}$~2×10^{18} years) makes it practically stable, [18,19] it is a semimetal with interesting electronic properties such as high carrier mobility, low effective mass, low carrier density, long mean free path; moreover, it is highly anisotropic in its Fermi level, presenting a high magnetoresistance [20]. These properties are due to the spatial arrangement of its atoms [21]. Organobismuth compounds show great structural diversity which ranges from monomeric to polymeric supramolecular assemblies and due to lewis acid and eco-friendly nature [22] find extensive applications as biocides, catalysts, [23-29] additives for lubricants [30], and even in medicines etc [31-33]. Bi (III) catalysts are generally crystalline solids and are commercially available at low cost [34]. Decreasing availability and increasing diffuseness of the s electrons makes the +5 oxidation state less stable when compared with phosphorus, arsenic and antimony. Due to its more pronounced metallic character than antimony and arsenic, bismuth forms formal stoichiometric [35] compounds with other metals. Typical examples include M_3Bi and MBi (M = Li, Na, K), $M_3\ Bi_2$ (M = Mg, Ca), and MBi (M = La, Ce, Nd, Gd, Sm, Y, etc.).

Among the pentavalent organobismuth (V) compounds, only R_3BiX_2 compounds are well studied and have pentacoordination around the bismuth with a trigonal bipyramidal or square pyramidal configuration [36-38]. It is well known that group 15 elements characteristically exhibit structural changes on increasing or decreasing the content and the nature of organic group(s) bound to the central element as well as the anionic group [39]. As a matter of fact this fascinating aspect, apart from other consideration, makes their study rather more interesting. Unlike pentacoordinated covalent R_3BiX_2 compounds R_4BiX are ionic in nature and R_4Bi moiety has a charged tetrahedral configuration $(R_4Bi)^+$ [40], which is especially true in case of halide only. Further studies have shown that R_4BiOR' (R= phenyl) to be covalent molecules with pentacoordination around bismuth, parallel to the observation made in case of R_4SbOR compounds which also has a trigonal bipyramidal configuration. In both cases the oxygen atom occupies an apical position [39].

S. No.	Compounds	Application	Ref.
1.	Ph_4BiF	Reagent	41
2.	Organobismuth chloride and Triphenyl germylpropionate	Antiproliferative activity	42
3.	$Bu_4N[PhBiX_2Y]$	Lewis acid	43
4.	$C_6H_{11}N(CH_2C_6H_4)2BiBF_4$	Catalyst	44
5.	Water-soluble non-ionic triarylbismuthanes	X-ray contrast media	45
6.	Cyclopropylbismuth	Reagent	46
7.	$Ar_3Bi(OAc)_2$ and Ar_3BiCl_2	Reagent	47
8.	Dibismuthanes	Reagent	48
9.	$[S(CH_2C_6H_4)2Bi(OH_2)]+[ClO_4]-$	Catalyst	49
10.	$Ar_3Bi=NCOR$	Reagent	50
11.	Tris[ortho-chloromethylphenyl] bismuthane	Reagent	51

Table 2: *Examples of organobismuth compounds with applications.*

Examples of organobismuth compounds with application

Synthetic applicability of organobismuth compounds

The recent advances in Bismuth (III) chemistry have expanded the versatility and flexibility of modern green/eco-friendly catalysts for the reactions having carbon-carbon bond formation and functional group transformations along with in many named reactions like Michael Reaction, Friedel-Crafts Acylation, Hanztsch Reaction, Strecker Reaction, Diels Elder Reaction, Pechmann Reaction, Aldol Condensation, Knoevenagel Reaction, Reformatsky Reaction, Doebner condensation and in processed reaction like aliphatics, alicyclics, aromatics, amino acids, peptides, terpenes and steroids having pharmaceutical interest.

S. No.	Organobismuth compounds used	Uses in Name/ Processed reaction	Ref.
1.	$BiCl_3$	Michael Reaction	52
2.	$Bi(NO_3)_3$	Oxidation of alcohols	53
3.	$Bi\text{-}ZnF_2$	Aldol Condensation	54
4.	$Bi^{(0)}/O_2$	Epoxides to α-diketones	55
5.	$BiBr_3$	Benzylation of alcohols	56
6.	Bismuth Acetate	Protodeboration of Di/Triborylated Indoles	57
7.	$Bi\ (OTf)_3{\cdot}xH_2O$	Doebner condensation	58
8.	BiI_3 and $Bi_2(SO_4)_3$	Synthesis of Thioacetals	59
9.	Bi (TFA)	Biginelli Reaction	60
10.	$Bi(OTf)_3{\cdot}xH_2O$	Friedel-Crafts alkylation of phenol	61
11.	$Ac_2O/Bi(OTf)_3{\cdot}xH_2O$	Acetylation of geraniol	62
12.	$Bi(OAc)_3$	cholesterol and cholesterol formate into the corresponding 3β-acetoxy derivative	63

13.	$Bi(NO_3)_3 \cdot 5H_2O$	oxidation of the allylic alcohol moiety of carveol to Carvone	64
14.	$BiCl_3$	Strecker Reaction, Pechmann Reaction	65,66
15.	bismuth(III) mandelate	Oxidatiojn of epoxides	67,68

Table 3: O*rganobismuthcompounds and their application in organic synthesis.*

Industrial applications of Bismuth as precursors in advanced material science

Bismuth is potentially used as superconductors, photorefractive systems, sol-gel processes, and chemical vapor deposition techniques. Bi High temperature superconductors draw attention owing to extraordinary correlation between superconducting characteristics and special features of crystal lattices [41-45].

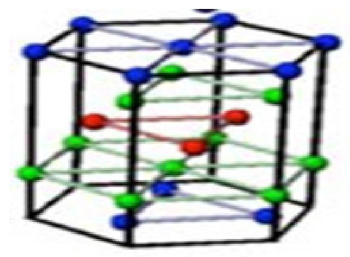


Figure 1: *Crystal structure of bismuth.*

It was found that the crystal structure of Bi HTSCs represent spaces with confined dimensionality, the layered and quasi2D character of these structures determines the sharp anisotropy of their physical properties. Therefore some specific features of high temperature superconductors, namely, prominent dependence of critical current on temperature, broadening of the temperature range of the superconducting transition in a magnetic field, and creep effect of magnetic vortexes at temperatures far lower than the temperature of transition into the superconducting state appear in them most distinctly. The anisotropic character of Bi HTSCs should be taken into account in the technology to form microstructures of superconducting composites [46-69]. The bismuth tellurite, generally photorefractive material for holographic data storage offering unique fixing capabilities due to orthorhombic structure and optically biaxial without centre of symmetry [70].

The synthesis of bismuth nanoparticles has been recently reported by using sol-gel method like bismuth oxide nanoparticles, due to its optical and electrical properties such as refractive index, large energy band gap, dielectric permittivity as well as remarkable photoluminescence and photoconductivity. These properties make bismuth oxide an interesting candidate for applications in the fields such as optoelectronics, optical coatings, and gas sensors [71]. The bismuth Ferrite nano particles, because of their simultaneous coexistence of ferroelectric and anti-ferromagnetic order parameters in perovskite structure, are useful for applications is non linear optics, thin film capacitors, photo electrochemical cells, non volatile memories etc [72]. It was reported that the bismuth vanadate ($BiVO_4$) nano particles, one of the photocatalysts, has been recently recognized as high potential application for the degradation of organic pollutants in wastewater [73-75]. The bismuth titanate electroceramic thin films as reported are strongly anisotropic in terms of ferroelectric properties such as polarization and coercive field [76].

The chemical vapour deposition (CVD) is bottom-up approach to make micro or nanoscale materials. It has applications in processing low dimension thermoelectric materials. There are many types of CVDs including ambient pressure, photo-thermal, metal-organic, plasma enhanced and ion beam CVD etc. The simplest ambient pressure deposition has been used to make Bi_2Se_3 nanowires on graphite papers without using catalysts [77]. Metal-organic chemical vapor deposition (MOCVD) has caught attention and been used for depositing the Bi-Te and Sb-Te thermoelectric films [78-79]. The molded rubber compositions have been widely used in a variety of applications particularly in automotive field as gaskets, seals, hoses, grommets, tubing, rubstrips and bumpers. The bismuth dimethyldithiocarbamate $Bi[(CH_3)_2NC(S)S]_3$ are still potentially applicable as an vulcanization accelerator for natural rubber and SBR, especially in cable covers and mechanical goods [80].

The extensive application of plastics in biomedical science and engineering makes radiopacities a highly desirable property for polymers. It permits the utilization of radiography as a non-destructive diagnostic tool for plastics. The triphenylbismuth (Ph_3Bi) is an effective X-ray contrast additive for plastics [81-82]. It gives homogeneous blends of high radiopacity with polyacrylates, polystyrene, poly(vinylchloride), polyalkenes, and other polymers. The materials are not affected by moisture and Ph_3Bi, unlike the halides, does not interfere with amine accelerators. Moreover the leaching of bismuth can be eliminated by using polymerizable triphenylbismuth derivatives [83].

It was reported that the replacement of phenyl group of triphenylbismuth with styryl or a-methylstyryl moiety prevents leaching of bismuth and the plasticizing effect of free Ph3Bi is largely eliminated. Transparent materials with radiopacities exceeding that of aluminium can easily be obtained [84]. The bismuth-containing polymers are also used as bactericidal paints and coatings in hospitals as reported by some workers [85]. The Farzin Marandi., *et al*. reported a new 3D coordination polymer of bismuth with nicotinic acid N-oxide $\{[Bi(NNO)_2(NO_3)].1.5H_2O\}n$ characterized by elemental analysis, IR and 1H-NMR spectroscopy along with single-crystal X-ray diffraction analysis [86]. The bismuth catalysts are also used for synthesis of various biodegradable and biocompatible polymers [87]. The organometallic or metal-oxide compounds of various other metals were also considered and being elucidated at the following metal ranking order: Ti > Ge > Zr ~ Sn > Hf > Sb > Bi [88].

Pharmacological activity of organobismuth compounds

Organometallic compounds played an important role in medicine and other areas for years, ever since humans have walked in the planet, although people have only recently realized their significance [89-93]. The use of organometallic medicinals is widespread. Some examples include:

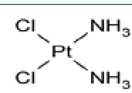
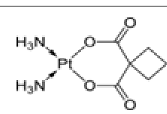
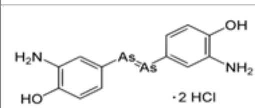
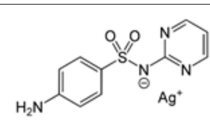
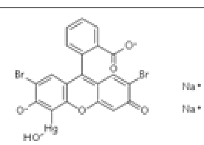
S. No.	Name of Drug	Structure of Drug	Organo-element Present	Ref.
1.	Cisplatin		Platinum	89
2.	Carboplatin		Platinum	90
3.	Salvarsan		Arsenic	91
4.	Silver sulfadizine		Silver	92
5.	Mercurochrome		Mercury	93

Table 4: *Some organometallic drugs with organo-element present.*

Gastroprotective activity of organobismuth compounds

Gastrointestinal Protective

Bismuth drugs such as bismuth subcitrate (BSS) [94], colloidal bismuth subcitrate (CBS) [95] and ranitidine bismuth citrate (RBC) [96] are effective in treating and eradicating *Helicobacter pylori* together with antibiotics. Colloidal bismuth subcitrate may rearrange from colloidal particles to form a 3-D polymer at neutral pH. This polymeric structure may represent the protective bismuth coating found on ulcer craters [97]. Bismuth compounds hydrolyze in the stomach and form bismuth salts or bismuth polymers, and exert bactericidal effects. For example, bismuth subsalicylate hydrolyzes in gastric juice at pH 3 and releases salicylic acid together with the formation of bismuth oxychloride, these salts interact with the gastric mucus and bind to the proteins within the ulcer crater [98-100]. Bismuth exerts its anti-helicobacter activity by four different ways: (a) forms complexes in the bacterial wall and periplasmic space, (b) *H. pylori* produces several enzymes including urease, proteases, alcohol dehydrogenase, and phospholipases that promote bacterial colonization. Inhibition of the enzymatic activity of the bacterial urease is an important mechanism of action of bismuth-based drug, (c) inhibits ATP synthesis of bacteria, and (d) inhibits adherence of *H. Pylori* to the gastric mucosa [101-102].

Gastro-duodenal Protective

The antibacterial effects of bismuth compounds against *H. pylori* facilitates healing of gastroduodenal ulcers also [103]. Bismuth salts have both *in-vitro* and *in-vivo* against *H. pylori* as well as exert other effects on various sites on gastric and duodenal mucosa. Organobismuth drugs like CBC etc. exert cytoprotective action with protection against gastric lesions in rats when exposed to stressful agents, this effect is mediated by protaglandins, epithelial growth factor (EGF) & mucosal bi-carbonate secretion [104]. These agents inhibit action of pepsin & gastric juice [105].

They show healing effect both as duodenal and gastric ulcer as well as protection against NSAIDS, aspirin and alcohol induced damage is also noted [106]. Colloidal bismuth subcitrate, bismuth subsalicylate, bismuth subnitrate, and ranitidine bismuth citrate are different bismuth salts which are currently under use in the treatment of gastroduodenal ulcers [107].

Antimicrobial activity of organobismuth compounds

In addition to *H. pylori,* Bi compounds have been effectively used to treat a host of bacterial associated infections such as syphilis (e.g., potassium bismuth tartrate, bismuth quinine iodide and iodobismitol), colitis (bismuth subnitrate, bismuth citrate), diarrhea (BSS and bismuth nitrate) and wound infections (bismuth oxide) [108-109]. In recent a group of Japanese workers synthesized a series of organobismuth compounds which shows potent antimicrobial activity against fungus and bacterial culture responsible for human pathogenic disease [110].

Antibacterial Activity

It is known that bismuth salts have antibacterial activity against multiple gastrointestinal pathogens such as *Escherichia coli, Vibrio cholera, Campylobacter jejuni, Salmonella, Shigella*, and *Yersinia*. Because of this activity, bismuth salts are used in the treatment of some form of gastroenteritis such as traveler's diarrhea. Synergism between bismuth salts and antibiotics was present like metronidazole and bismuth were administered together [111]. Kotani T., *et al*. synthesize some Cyclic Organobismuth(III) Compounds and reported them as potent antibacterial [112]. Marzano et.al. synthesize some new Complex of Bismuth(III) with Sulfapyridine $[BiCl_3(C_{11}H_{11}N3O_2S)_3]$. The structure of the complex reveals a distorted octahedral geometry around the bismuth atom, which is bound to three sulfonamidic nitrogens from sulfapyridine, acting as a monodentate ligand, and to three chloride ions, and report them 3 times more potent than the ligand against *Salmonella typhimurium*, 4 times against *Staphylococcus aureus, Shigella dysenteriae*, and Shigella sonnei and 8 times more potent against *Pseudomonas aeruginosa* and *Escherichia coli* [113].

Antifungal Activity

A series of hypervalent organobismuth (III) compounds derived from alkyl aryl ketones [XBi(5-R'C_6H_3-2-COR) (Ar)] was synthesized by Murafuji., *et al*. & their antifungal activity against the yeast *Saccharomyces cerevisiae* with their structure activity relationships was repoted, the synthesized compounds were seems to be active towards yeast *Saccharomyces cerevisiae* [114]. Various new organobismuth compounds like tetraorganobismuth(V) aryloxyacetate [115], new organobismuth amides [116], triorganobismuth (V) amide [117], new diphenylbismuth (III) chloride [118], new tris (Pentafluorophenyl) bismuth (V) dichloride [119] were synthesized and reported for their antibacterial and antifungal activity.

Organobismuth compounds in cancer treatment

Ten most active metals towards anticancer activity are arsenic, antimony, bismuth, gold, vanadium, iron, rhodium, titanium, gallium and platinum [120]. Bismuth complexes of 6-mercaptopurine were the first antitumour compounds tested. They yielded promising results, as compared to platinum(II) analogues [121]. Treatment with inorganic bismuth results in regression of gastric lymphoma caused by *H. pyroli* & reduction of toxic side effects of cisplatin by tissue specific induction of metallothionein [122]. A number of recent publications from Henan University, Kaifeng, China contribute to the story in relation to bismuth thisosemicarbazone or thiocarbonohydrazone complexes as anti-cancer agents [123-124].

Bismuth(V) complexes of lapachol have been synthesized by the reaction of Ph_3BiCl_2 with lapachol (Lp) and characterized by several physicochemical techniques such as IR, and NMR spectroscopy and X-ray crystallography by Oliveira., *et al.* Bismuth (V) complex formed is a dinuclear compound bridged by an oxygen atom, $(Lp)_2(Ph_3Bi)_2O$. The compound inhibited the growth of a chronic myelogenous leukemia cell line and the complex of Bi(V) was also about five times more active than free lapachol [125].

Luchi., *et al.* synthesized some novel heterocyclic organobismuth compounds that have potent antibacterial properties, they also examined their anticancer activity and found that these compounds have particularly potent anticancer activities against leukemia cell lines. One of them, bi-chlorodibenzo [c,f] [1,5] thiabismocine, inhibited the growth of the human promyelocytic leukemia cell line HL-60 at a concentration of 0.22 microM [126].

Cui L,. *et al.* synthesized three novel organobismuth(V) complexes $Ph_3Bi(OOCC_6H_3F_2)_2$, $Ph_3Bi(OOCC_6H_4CF_3)_2$ and $Ph_3Bi(OOCC_4H_3S)_2$. The interaction of the first complex with calf-thymus DNA (CT-DNA) was investigated by UV absorption spectroscopy, fluorescence emission spectroscopy and viscosity. All results revealed that this complex binds to DNA via intercalative mode. Furthermore the proliferation inhibitory activities of the all three complexes on MDA-MB-231 breast cancer cells were investigated. The results indicated that all of the three complexes have superior inhibition of cellular proliferation [127]. The organobismuth compounds are extremely potent cytotoxic agent when attached to a monoclonal antibody as these can target leukemia, lymphoma and other tumors [128].

Anti-Leishmaniasis activity of organobismuth compounds

Leishmaniasis constitutes a spectrum of diseases that range in severity from self-healing to fatal. It is caused by protozoan parasites of the *Trypanosomatidae* family and typically contracted by the bite of an infected female sand fly. Potassium antimony tartrate, a Sb(III) compound was developed at the start of the 20th century, was initially used and increased survival rates but was highly toxic to the patient [129].

Rocha., *et al.* by using the classic microscopic *in vitro* model have analyzed the effects of a series of lapachol and chlorides complexes with antimony (V), bismuth (V), and tin (IV) against *L. amazonensis* and found that all seven compounds exhibited antileishmanial activity, but most of the antimony (V) and bismuth (V) complexes were toxic against human HepG2 cells and murine macrophages [130].

Andrews., *et al*. recently reported a series of Bi(III) β-thioxoketonate complexes as anti-leishmanial agents. They hypothesised that Bi complexes with a more thermodynamically stable Bi-S bond would be less labile than for example a carboxylate analogue and in turn possess improved hydrolytic stability which should positively influence purity, reproducibility and activity in biological systems [131].

Although different complexes of bismuth like β-thioxoketones complexes of formula R1C-(=O)CH_2(=S)R_2 and their Bi complexes of formula [Bi{R_1C(=O)CHC(=S)R_2}$_3$], the bismuth derivatives of free acid and $BiPh_3$, naproxen tris-carboxylato Bi(III)complex were reported for the activity by different workers but in general the Bi complexes displayed little or no selectivity, which would suggest that they are not suitable candidates for the treatment of Leishmaniasis and the development of compounds with selective anti-leishmanial activity is the challenge.

Antispermatogenic Activity of organobismuth compounds

Rising human population throughout the world has detrimental effects on the life supporting system on the earth. Fertility regulation comprising contraception and management of infertility forms an important component of reproductive health. Though considerable progress has been made in development of contraception among females, progress and possibilities in males are still slow and limited [132]. The chemical compounds affecting testicular function includes different groups: Serotonin, Melatonin, Levenogestral, Cyproterone Acetate, Depot Medroxy progesterone Acetate etc and various steroidal drugs but they all have various side effects and hazards at reproductive organs.

A series of Bi(III) and As(III) complexes with two N & S donor ligands, 1-(4-chloro-2-oxo-2H-chromen-3-yl)-methylene)-thiosemicarbazide(L1H)andN`-[1-(2-oxo-2H-chrome-3yl-ethylidene]-hydrazinecarbodithionic acid benzyl ester (L^2H) have been synthesized by the reaction of $BiCl_3$ and Ph_3As with ligands in 1:1 and 1:2 molar ratios by Dawara., *et al.* Antimicrobial activity and antifertility activity in male albino rats of the synthesized compounds was tested and the metal complexes have shown to be more antimicrobial against the microbial species as compared to free ligands. Also marked reduction in sperm motility and density resulted in infertility. Significant alterations were found in biochemical parameters of reproductive organs in treated animals as compared to control group. It is concluded that all these effects may finally impair the fertility of male rats [133].

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