RESEARCH PAPER

STUDIES OF ANTIMICROBIAL RESISTANCE AND ANTITUMOR EFFICACY OF SOME NEWLY SYNTHESIZED ORGANIC DERIVATIVE OF BISMUTH

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Abstract

The present manuscript covers the synthesis of some novel 2-mercaptobenzimidazole derivative of bismuth through modified method followed by their characterization through sophisticated instrumentation and spectral analysis. The synthesized compounds were also screened for their effectiveness against antimicrobial resistance, antimicrobial activity against pathogenic strains of bacteria and fungi at different concentrations. These compounds were also tested for antitumor activity against human breast adenocarcinoma cell line (MCF-7) and mammary cancer Cell lines (EVSA-7) in-vitro. It was observed that these compounds show remarkable antimicrobial and antitumor activity and shows effectiveness against Antimicrobial Resistance.

Key words: *Antimicrobial Resistance, organobismuth, 2-mercaptobenzimidazole, Antibacterial, antifungal, Antitumor efficacy.*

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Introduction

Metals and their complexes are used in several biomedical and commercial applications since long back but researchers realized their importance in past few decades [1]. Number of organobismuth compound is now used for the treatment of different acute and pathogenic diseases in case of human beings [2]. The salts of organobismuth are highly useful in treatment of gastric disorder along with cancer of early stages [3]. It was found by the observations of the earlier workers on antitumor, antimicrobial and gastroprotective studies of organobismuth compounds that the organic group attached with metal atom or ion act as pro-drugs which make their study more interesting [4]. In recent past, organobismuth compounds have demonstrated increasing utility in organic synthesis [5], catalytic processes [6] and materials science [7]. This heightened interest has catalyzed significant advancements, pushing the boundaries of bismuth-based chemistry toward remarkable new milestones [8]. However, the application of organobismuth species in asymmetric synthesis and C–C bond formation remains a formidable challenge for future investigation [9]. Additionally, the mechanistic pathways of several specialized organobismuth-mediated reactions have yet to be fully elucidated[10].The benzimidazole scaffold represents a versatile structural template for the molecules with profound pharmaceutical and biological relevance [11]. Structurally it is a bicyclic system comprising a benzene ring fused to a five-membered imidazole ring, featuring heteroatoms at 1 and 3 positions. In recent years benzimidazole derivatives have attracted considerable interest because of their therapeutic efficacy against HIV and cancer [12]. The 2-mercaptobenzimidazole,one of the most important derivatives of benzimidazole series exhibited a wide variety of interesting biological activities [13]. These observations have been guiding for the development of new 2-mercaptobenzimidazole derivatives that possess varied biological activities. The present manuscript deals the synthesis of some novel 2-mercaptobenzimidazole derivative of bismuth and their further characterization for antimicrobial resistance and antiproliferative efficacy.

Experimental

Synthesis of 2-mercaptobenzimidazole:

A mixture of o-phenylenediamine (0.01mole), potassium hydroxide (0.01mole) and carbon disulfide (0.01mole), 100 ml of methanol and 15ml of water in a 500ml round bottom flask and heated under reflux for 3hours. The reaction mixture was then filtered. The filtrate was heated to 60-70ºC then100ml water was added followed by acidification with dilute acetic acid

with stirring. The mixture was then placed in the refrigerator for crystallization. The product was collected after filtration and dried. The product was recrystallized with ethanol [14].

Complexation Reaction:

The organobismuth (III) derivatives of 2-mercaptobenzimidazole were synthesized by refluxing thestochiometricamountofthe2-mercaptobenzimidazole with corresponding organobismuth (III) chloride in presence of triethylamine as an HCl acceptor, at ambient temperature in a nitrogen environment using reported method [15].

Antibacterial Activity:

Antibacterial efficacy of the synthesized organobismuth compound was carried out by disc diffusion method [16] 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. The activity was classified as highly active (dia = > 15 mm), moderately active (dia = 10-15 mm) and slight active (dia = 5-10 mm). The diameter less than 5 mm was regarded as inactive.

Antifungal Activity:

The antifungal activity of the organobismuth compound was tested by agar plate diffusion method [17], using ampicillin as standard. The two concentrations of thetest compounds viz., 50 and 100 µg/ml were prepared and tested against two pathogenic fungal strains, *Aspergillus flavus* and *Aspergillus nigar*. The one ml of each compound was poured into a Petri dish containing 20-25 ml of molten potato dextrose-agar medium. Asthe medium solidify, Petri dishes were inoculated at 37°C for 96 hrs in BOD incubator. After 96 hrs the colony diameter was measured and % inhibition was calculated using standard method.

Antitumor Activity:

The *in-vitro* antitumor activity of these compounds was carried out by MTT-Method [18]. This method was performed to estimate the effect of compounds on the growth of cell. The human breast adenocarcinoma (MCF-7) and mammary cancer (EVSA-7) cell lines were used for this purpose. The principle behind this assay depends upon the reduction of tetrazoleum salt. The yellow colored tetrazoleum MTT[3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazoleum bromide] was reduced partially by metabolically active cells by the action of dehydrogenase enzyme to generate NADH and NADPH as reducing equivalents. The resulting intracellular purple Color zone was solubilized and quantified by spectrophotometer. The MTT was first dissolved in Phosphate buffer saline at a concentration of 5 mg/ml. The MTT solution (50 µl)was added to each well of 96 well culture plate containing 100 µl of culture medium and incubates at 37°C for 4 hrs. The medium was then removed carefully without disturbing the crystals of purple colored zone.50 ml of DMSO was then added to each well and mixed thoroughly to dissolve the crystals of the zone. The plate was then read on a micro ELISA plate reader at a wavelength of 570 nm to find out the optical density and cell count value.

Results and Discussion

All of the recently created organobismuth compounds were soluble in ordinary organic solvents, air stable and crystalline solids. In order to determine their structures and investigate their biological capabilities, the compounds were further characterized by their melting temperatures and analytical methods such elemental analysis, infrared, and NMR spectroscopy. According to results from additional study, the novel compounds feature pyramidal structures and acute melting temperatures.

IR and NMR Spectral Analysis:

New organobismuth compounds infrared spectra were captured in the 4000-200 cm^{-1} region using a Perkin-Elmer spectrophotometer. Phenyl, p-fluorophenyl, and pentafluorophenyl groups exhibit absorption bands in the infrared spectrum. The absorption frequencies have been completely allocated. For phenyl and pentafluorophenyl compounds, the Bi-C vibration that corresponds to the y mode occurs between 448 and 460 cm^{-1}. The multiplet in the range of δ7.82 ppm to δ8.12 ppm in the ^{1}HNMR spectra of the organobismuth compound representative might be attributed to aromatic protons. The ^{19}FNMR spectra revealed peaks that appeared between -108.30 ppm and -112.30 ppm , indicating the p-fluorophenyl groups. Thus, a pyramidal structure was reported to the newly synthesised organobismuth (III) compounds based on the spectral findings.

Antibacterial Efficacy:

All the organobismuth(III) derivatives of 2-mercaptobenzimidazole were tested for antibacterial activity against three pathogenic bacterial strains

Pseudomonas aeruginosa, *Staphylococcus aureus* and *Klebsiela pneumoniae* using 10 µg/ml concentration of test compound. The compounds show higher to moderate activity against the bacterial strains. It was found that compounds having fluoro and pentafluorophenyl ring are more effective because of their polarity and lipid solubility. The fluorinecontaining compounds may generally form complexes with metaloenzymes, particularly those which responsible in basic physiology such as cytochrome oxidase. These compounds may interact 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 Efficacy:

The antifungal activity of all the organobismuth (III) derivatives of 2-mercaptobenzimidazole were tested against *Aspergillus flavus* and *Aspergillus niger* using50 and 100 µg/ml concentration. The potential efficacy of these compounds was found variable at 50µg/ml concentration but at higher concentration all the derivatives show high efficacy against fungal strains. Presence of nitrogen, sulphur, phenyl and pentafluorophenyl ring along with bismuth in +3 oxidation state are considered for antifungal efficacy. The role of ligands was also commendable. These compounds generally damage the fungal strains by puncturing the cell wall similarly as in the case of bacteria. Solubility of these compounds, due to presence of fluorine, also increases the efficacy.

Antitumor Efficacy:

The antitumor activity of these compounds was studied against the human breast adenocarcinoma (MCF-7) and mammary cancer (EVSA-7) cell lines. The compounds show moderate to high activity against tumor cell lines. It was found that these compounds are in +3 oxidation state and the slight variation in their activity is due to presence of ligand along with fluorine on main moietyof the compound. The compounds generally interactwith the receptor site of multienzyme complex responsible for the cytostatic and cytotoxic conditions. The compounds generally binds with nitrogen 7 position of purine bases in DNA molecule and form complexes with DNA strands affecting replication and transcription of DNA molecule and stop the cell division along with protein synthesis.

Conclusion

The above discussion of results clearly indicates that the organobismuth(III)derivatives of 2-mercaptobenzimidazole are structurally stable and show better results against tumor cell lines *in-vitro* along with bacterial and fungal strains. These compounds would be treated as drugs in future for antimicrobial resistance and other chronic diseases.

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Table-1:Physicochemical Properties

S.N.	Compounds	Formula Weight	M.P (°C)	Elemental Anlaysis			
				C%	H %	N%	S%
1	(C6H5)2Bi(SN2H5C7)	512	118	44.53	2.92	5.46	6.25
2	(C6F5)2Bi(SN2H5C7)	692	104	32.94	0.72	4.04	4.62
3	(FC6H4)2Bi(SN2H5C7)	548	116	41.60	2.37	5.10	5.83
4	(C6H5)BiCl(SN2H5C7)	470.5	124	33.15	2.12	5.95	6.80
5	(C6H5)Bi(SN2H5C7)2	584	112	41.09	2.56	9.58	10.95
6	(C6F5)BiCl(SN2H5C7)	560.5	108	27.83	0.89	4.99	5.70
7	(C6F5)Bi(SN2H5C7)2	674	98	35.60	1.48	8.30	9.49
8	(FC6H4)2BiCl(SN2H5C7)	488.5	122	31.93	1.84	5.73	6.55

Table-2:Antibacterial activity

S.N.	Compounds	*Pseudomonasaeruginosa*	*Staphylococcus aureus*	*Klebsiela pneumoniae*
1.	(C6H5)2Bi(SN2H5C7)	++	+++	+
2.	(C6F5)2Bi(SN2H5C7)	++	++	++
3.	(FC6H4)2Bi(SN2H5C7)	++	+++	++
4.	(C6H5)BiCl(SN2H5C7)	+++	+++	+++
5.	(C6H5)Bi(SN2H5C7)2	++	++	++
6.	(C6F5)BiCl(SN2H5C7)	+++	+++	++
7.	(C6F5)Bi(SN2H5C7)2	++	++	+++
8.	(FC6H4)2BiCl(SN2H5C7)	+++	++	+++
9	(FC6F5)Bi(SN2H5C7)2	++	+++	+++
10	Control(standard)	-	-	-

+=6-10mm; ++=10-14mm; +++=>14mm; – = Inactive

Table-3: Antifungal Activity at 50µg/ml conc.

S. N.	Compounds	*Aspergillus flavus* Col. Dia. (mm)	% Inhibition	*Aspergillus niger* Col. Dia. (mm)	% Inhibition
1	$(C_6H_5)_2Bi(SN_2H_5C_7)$	0.7	76.6	0.7	65.0
2	$(C_6F_5)_2Bi(SN_2H_5C_7)$	0.8	73.3	0.8	60.0
3	$(FC_6H_4)_2Bi(SN_2H_5C_7)$	0.8	73.3	0.8	60.0
4	$(C_6H_5)BiCl(SN_2H_5C_7)$	0.7	76.6	0.6	70.0
5	$(C_6H_5)Bi(SN_2H_5C_7)_2$	0.7	76.6	0.5	75.0
6	$(C_6F_5)BiCl(SN_2H_5C_7)$	0.5	83.3	0.4	80.0
7	$(C_6F_5)Bi(SN_2H_5C_7)_2$	0.7	76.6	0.6	70.0
8	$(FC_6H_4)_2BiCl(SN_2H_5C_7)$	0.8	73.3	0.8	60.0
9	$(FC_6F_5)Bi(SN_2H_5C_7)_2$	0.7	76.6	0.6	70.0
10	Control	3.0	–	2.0	–

Table-4:Antifungal Activity at 100μg/ml conc.

S. N.	Compounds	*Aspergillus flavus* Col.Dia. (mm)	% Inhibition	*Aspergillus niger* Col. Dia. (mm)	% Inhibition
1	$(C_6H_5)_2Bi(SN_2H_5C_7)$	0.4	86.7	0.2	90.0
2	$(C_6F_5)_2Bi(SN_2H_5C_7)$	0.5	83.3	0.4	80.0
3	$(FC_6H_4)_2Bi(SN_2H_5C_7)$	0.8	73.3	0.5	75.0
4	$(C_6H_5)BiCl(SN_2H_5C_7)$	0.4	86.7	0.2	90.0
5	$(C_6H_5)Bi(SN_2H_5C_7)_2$	0.1	96.7	0.2	90.0
6	$(C_6F_5)BiCl(SN_2H_5C_7)$	0.4	86.7	0.2	90.0
7	$(C_6F_5)Bi(SN_2H_5C_7)_2$	0.6	80.0	0.5	75.0
8	$(FC_6H_4)_2BiCl(SN_2H_5C_7)$	0.7	76.6	1.0	50.0
9	$(FC_6F_5)Bi(SN_2H_5C_7)_2$	0.5	83.3	0.4	80.0
10	Control	3.0	–	2.0	–

Table-5:Antitumor activity

S.N.	Compounds	MCF-7 CellNo.x10^4	EVSA-7 Cell No.x10^4	Activity
1	$(C_6H_5)_2Bi(SN_2H_5C_7)$	9.19±0.92	9.29±0.88	+
2	$(C_6F_5)_2Bi(SN_2H_5C_7)$	9.17±0.90	8.6±0.69	+
3	$(FC_6H_4)_2Bi(SN_2H_5C_7)$	9.59±1.06	9.29±1.02	+
4	$(C_6H_5)BiCl(SN_2H_5C_7)$	9.29±0.88	9.89±0.92	+
5	$(C_6H_5)Bi(SN_2H_5C_7)_2$	8.95±0.67	8.55±0.62	+
6	$(C_6F_5)BiCl(SN_2H_5C_7)$	8.79±0.52	8.42±0.46	+
7	$(C_6F_5)Bi(SN_2H_5C_7)_2$	9.52±1.02	9.82±1.06	+
8	$(FC_6H_4)_2BiCl(SN_2H_5C_7)$	8.31±1.02	8.39±1.03	+
9	$(FC_6F_5)Bi(SN_2H_5C_7)_2$	9.19±0.92	9.29±0.88	+
10	Negative control	10.21±1.01	10.22±1.01	–
11	Positive control	40.26±3.23	41.23±3.28	–

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