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Antimicrobial, antitumor and gastroprotective studies of some new water soluble organic derivatives of bismuth

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Abstract- Some triorganobismuth (V) amide, which are soluble in water, were synthesized by method reported earlier and characterized by their elemental and I.R. spectral analysis along with their antimicrobial, antitumor and gastro protective activity against different pathogenic microbial strains, human breast and mammary cancer cell line and gastric ulcer.
Key words: - Antimicrobial, antitumor, gastro protective, triorganobismuth.

Introduction

There is an enormous potential for the application of metals in medicine [1] and the selection of metal ions offer the possibility for the discovery of metallodrugs with novel mechanism of action [2]. Metal containing compounds may offer certain advantages over pure organic compound in drug therapy i.e., the metal complexes may acts as a pro-drug [3]. The organobismuth compounds have also attracted the attention owing to their microbiological and material utility [4-8] from more than 200 yrs. It was found that organobismuth compounds were active against the treatment of gastrointestinal disorders like dyspepsia, diarrhea and in peptic ulcers by inhibiting *E. coli*. [9-18]. Recently a group of Japanese workers synthesized a series of organobismuth compounds which show potent antimicrobial activity against fungus and bacterial culture responsible for human pathogenic disease[19]. The salts of organobismuth compounds, such as colloidal bismuth sub-salicylate (CBS), bismuth sub-citrate (BSC) and ranitidine bismuth citrate (RBC) are now common for controlling bacterial and fungal infections[20]. The recent demonstrations has shown that these salts are useful for *Helicobacter pylori* eradication therapy, (*Helicobacter pylori* now well known for the formation of gastrointestinal ulcer in Human beings and organobismuth compounds are the only cure against this bacteria) and has promoted the antibacterial and antifungal studies of various organobismuth compounds[21-29]. There are a lot's of thiabismuth heterocyclic compounds were synthesized and characterized as potent antimicrobial agents [30]. Some investigators have to synthesize a lots number of organobismuth compounds which might have highest antimicrobial activity [31-44]. The existence of relationships between, tumor (cancer) and metal is known to all oncologists. However various aspects about these relationships are ignored by many. It is surprising to observe that metals are able to do the best and the worst i.e. metal are able to induce cancer and also to treat the cancer, some are able to perform both. Basically both, transition and non-transition metals plays important role in the treatment of tumors. The synergic administration of cis-platin and bismuth compounds are known to reduce the toxic side effects of cis-platin; an effect that may be traced to the increased production of metallothionein induced by bismuth compounds [45-48]. The organobismuth compounds are extremely potent cytotoxic agent when attached to a monoclonal antibody as these can target leukemia, lymphoma and other tumors [49].

Experimental

The tris(Pentafluorophenyl) bismuth (V) dichloride was synthesized by the method reported earlier [50]. The substituted amides were recrystalised before use. The reactions were performed under nitrogen atmosphere. Preparation of some representative organobismuth compounds are discussed below.

Reaction of tris (Pentafluorophenyl) bismuth (V) dichloride with 5-bromoisatin

In oxygen free nitrogen atmosphere a solution of tris (Pentafluorophenyl) bismuth (V) dichloride (1mmol) in methanol (40ml) and 5-bromoisatin (2mmol) in the same solvent was stirred together in presence of triethylamine at room temperature for 5 hrs. The $Et_3N.HCl$ formed was filtered off under nitrogen atmosphere and the filtrate on concentration in vacuum gives a off-white color crystalline solid which was further recrystalised in pet. ether (40-60^{0}C).

Reaction of tris (Pentafluorophenyl) bismuth (V) dichloride with 6-chloro-5-methoxyisatin

In oxygen free nitrogen atmosphere a solution of tris (Pentafluorophenyl) bismuth (V) dichloride (1mmol) in methanol (40ml) and 6-chloro-5-methoxyisatin (2mmol) in the same solvent was stirred together in presence of triethyl amine at room temperature for 5 hrs. The $Et_3N.HCl$ formed was filtered off under nitrogen atmosphere and the filtrate on concentration in vacuum gives an off-white color crystalline solid which was further recrystalised in pet. ether (40-60^{0}C).

Reaction of tris (Pentafluorophenyl) bismuth (V) dichloride with 6-methoxy-5-bromoisatin

In oxygen free nitrogen atmosphere a solution of tris (Pentafluorophenyl) bismuth (V) dichloride (1mmol) in methanol (40ml) and 6-methoxy-5-bromoisatin (2mmol) in the same solvent was

stirred together in presence of triethyl amine at room temperature for 5 hrs. The $Et_3N.HCl$ formed was filtered off under nitrogen atmosphere and the filtrate on concentration in vacuum afforded yellow color crystalline solid which was further recrystalised in pet. ether (40-60^{0}C).

Reaction of tris (Pentafluorophenyl) bismuth (V) dichloride with 7-chloroisatin

In oxygen free nitrogen atmosphere a solution of tris (Pentafluorophenyl) bismuth (V) dichloride (1mmol) in methanol (40ml) and 7-chloroisatin (2mmol) in the same solvent was stirred together in presence of triethylamine at room temperature for 5 hrs. The $Et_3N.HCl$ formed was filtered off under nitrogen atmosphere and the filtrate on concentration in vacuum afforded off-white color crystalline solid which was further recrystalised in pet. ether (40-60^{0}C).

Antimicrobial Activity

The antimicrobial activity of all these compounds was performed by disc diffusion method [51]. In this techniques the filter paper (whatmann No-1) sterile disc of 5 mm diameter impregnated with the test compounds (10ug/ml ethanol) were placed on the nutrient agar plate at 37^{0}C for 24 hrs. The inhibition zone around the dried impregnated discs were measured and reported after 24 hrs.

Antitumor Activity

The *in-vitro* antitumor activity of these compounds was carried out by MTT-method [52]. 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 tetrazolium MTT [3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyl tetrazoleum 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 fine out the optical density and cell count value.

Anti-Ulcer screening

Aspirin (ASP) Induced Ulcers:-Aspirin in dose of 200mg/ kg (20mg/ml) was administered to the animals on the day of the experiment and ulcers were scored after four hrs. The animals were sacrificed and the stomach was then excised and cut along the greater curvature, washed carefully with 5 ml of 0.9% NaCl and ulcers were scored by a person unaware by the experimental protocol in the glandular portion of the stomach. Ulcer index was calculated by adding the total number of ulcers/ stomach and total severity of ulcers/stomach. The pooled group ulcer score was then calculated by reported method [53].

Ethanol (EtOH) induced Ulcers:-The gastric ulcers were induced in rats by administering ethanol (1ml/200gm/kg for 1 hr) and the animals were sacrificed by cervical dislocation and the stomach was incised along the greater curvature and examined for ulcers. The ulcer index was scored, based upon the product of length and width of the ulcers present in the glandular portion of the stomach (mm^2/rats).

Results and discussion

The tris (pentafluorophenyl) bismuth(V) amides can be easily obtained by using metathetical reaction where a respective isatin reacted with tris(pentafluorophenyl) bismuth(V) dichloride in an appropriate ratio in presence of triethylamine which behaves as a hydrogen chloride acceptor.

$$R_3BiCl_2+2HL \xrightarrow{Et3N} R_3BiL_2+2Et_3N.HCl$$

$R=C_6F_5$, HL = HNR_2 = 6-Chloro-5Methoxy, 6-Methoxy-5 Bromo, 7-Chloro 6-Bromo-5Methoxy, 5-bromo and 5 methoxy isatin

All the reactions were performed in room temperature and under nitrogen atmosphere. The organobismuth compounds which were obtained have sharp melting point and stable towards air and moisture. These compounds were also characterized on the basis of their elemental analysis, I.R. spectra and their antimicrobial and antitumor activity in various pathogenic microbial strains along with human breast and mammary tumor cell line *in-vitro*.

Infrared Spectra

The I.R. spectra of these compounds show almost similar absorption bands due to presence of Pentafluorophenyl group. The position and pattern of these absorption bands do not differ much from the I.R. data of tris (Pentafluorophenyl) bismuth (V) halides. A remarkable features in the I.R. spectra of all these compound is the absence of V_{sym}(Bi-C) absorption corresponding to 't' mode which should be located in the region of 250-300 cm^{-1} . The absorption frequencies having diagnostic values are listed in table.

Antimicrobial Activity

The organobismuth compounds were tested for antibacterial activity against three bacterial strains *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiela pneumoniae* using 10 µg/ml concentration of test compound. All the compounds show moderate to higher activity against the bacterial strains. It was

found that organometallic compounds containing fluoro and pentafluorophenyl ring are more effective because of their water and lipid solubility. The fluorine-containing compounds may 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 two phenyl ring gets entered inside the cell by puncturing it followed by death of bacterial cell. Some times these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacteria.

Antitumor Activity

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 higher activity against tumor cell lines. It was found that the slight variation in their activity is due to presence of different amides as ligand along with presence of fluorine on main moiety of the compound. The compound generally interacts with the receptor site of multienzyme complex responsible for the cytostatic and cytotoxic conditions for a cell. It may be noted that the organobismuth compound generally binds with nitrogen 7 position of purine bases in DNA molecule, where they reacted with labile hydrogen and form complex with DNA strands affecting replication and transcription of DNA molecule and stop the cell division along with protein synthesis.

Anti-Ulcer screening

Anti-ulcer activity was performed on Sprague-Dawley rats (140-180g). The compounds exhibit higher activity than the standard Ranitidine when the tests were carried out with Aspirin (ASP) induced and moderate activity was seen when the tests were done with Ethanol (EtOH) induced. It was known that aspirin caused mucosal damage by interrupting the synthesis of prostaglandin and increasing acid secretion and back diffusion of H^+ ions, which results in overproduction of leucotrienes and other products of 5-lipoxygenase pathways. Hence the protective action of these compounds against aspirin-induced gastric ulcer could possibly be due to its inhibitory effect on 5-lipoxygenase enzymes pathway. In case of ethanol induced ulcer which is predominantly occurs at glandular part of stomach was reported to stimulate the formation of leucotrienes C-4, mast cell secretary products and reactive oxygen species, which results in the damage of gastric mucosa of rat. These compounds could possibly play an important role in inhibition of these pathways.

Conclusion

Organobismuth (V) compounds have great potential as antiulcer, anticancer and antimicrobial agents. These compounds may be exploited for the development of new drugs for the treatment of diseases like ulcer, cancer and caused by various microorganisms.

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Table 1- Physicochemical and spectral data of organobismuth compounds

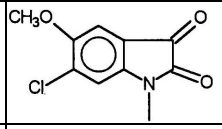
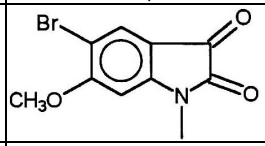
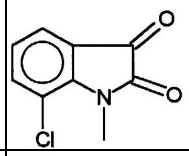
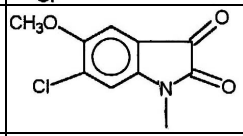
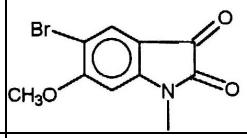
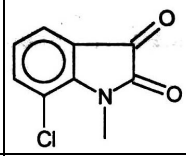
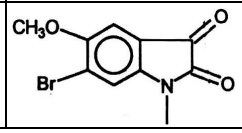
Sr.No.	Compound	M.P. (^{0}C)	Yield (%)	IR (in cm^{-1})		
				asym (CO)	sym (CO)	Bi-C
	$(C_6F_5)_3Bi(NR_2)_2$ $-NR_2=$					
1.		172	75	1738	1312	454
2.		185	70	1728	1322	462
3.		195	70	1740	1316	448
4.		176	65	1730	1316	448
5.		172	70	1726	1310	452
6.		182	75	1712	1314	460
7.		178	70	1740	1324	458

Table 2- Analytical data of organobismuth compounds

Compound No.	Empirical Formula	Elemental Analysis %		
		C	H	N
1.	$C_{36}H_{10}F_{15}N_2O_6Bi$	40.75	0.94	2.64
2.	$C_{36}H_{10}F_{15}Cl_2N_2O_6Bi$	38.19	0.88	2.47
3.	$C_{36}H_{10}Br_1N_2O_6Bi$	50.52	1.16	3.27
4.	$C_{36}H_6F_{15}N_2O_4Bi$	42.18	0.58	2.73
5.	$C_{36}H_{10}Br_2F_{15}N_2O_6Bi$	35.40	0.81	2.29
6.	$C_{33}H_5ClF_{20}NO_3Bi$	36.41	0.45	1.28
7.	$C_{33}H_5BrF_{20}NO_3Bi$	34.98	0.44	1.23

Table-3 Antimicrobial activity

S. No.	Compounds	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Klebsiela pneumoniae*
1.	$C_{36}H_{10}F_{15}N_2O_6Bi$	11.00±0.57	8.10±0.16	12.00±1.15
2	$C_{36}H_{10}F_{15}Cl_2N_2O_6Bi$	10.94±0.48	8.04±0.10	11.88±0.70
3.	$C_{36}H_{10}Br_1N_2O_6Bi$	11.33±0.66	11.00±0.57	8.58±0.29
4.	$C_{36}H_6F_{15}N_2O_4Bi$	11.24±0.60	8.70±0.26	12.06±0.77
5	$C_{36}H_{10}Br_2F_{15}N_2O_6Bi$	11.42±0.68	11.12±0.0.62	8.72±0.32
6	$C_{33}H_5ClF_{20}NO_3Bi$	11.33±0.66	11.00±0.57	8.54±0.22
7	$C_{33}H_5BrF_{20}NO_3Bi$	12.06±0.77	10.94±0.48	11.00±0.57
8	Ampicilin (standard)	18.0±0.21	12.66±0.50	16.26±0.30

Table 4- Antitumor activity

S. No.	Compounds	Cell No. x 10^4 (MCF-7)	Activity	Cell No. x 10^4 (EVSA-7)	Activity
1.	$C_{36}H_{10}F_{15}N_2O_6Bi$	9.69±0.92	+	10.68±1.08	-
2.	$C_{36}H_{10}F_{15}Cl_2N_2O_6Bi$	9.66±0.90	+	10.62±1.06	-
3.	$C_{36}H_{10}Br_1N_2O_6Bi$	8.28±0.46	+	9.69±0.92	+
4.	$C_{36}H_6F_{15}N_2O_4Bi$	8.22±0.42	+	9.68±0.88	+
5.	$C_{36}H_{10}Br_2F_{15}N_2O_6Bi$	9.62±0.52	+	9.62±0.90	+
6.	$C_{33}H_5ClF_{20}NO_3Bi$	9.67 ± 0.54	+	9.69 ± 0.92	+
7.	$C_{33}H_5BrF_{20}NO_3Bi$	9.69±0.92	+	9.66±0.90	+
8.	Negative Control	10.21±1.01	-	10.23±1.03	-
9.	Positive Control	40.26±3.23	-	42.24±4.22	-

***Negative Control- Culture Medium only, **Positive Control – 17 β estradiol**

Table 5- Antiulcer (Gastro protective) activity

S. N0.	Compounds	Aspirin Induced		Ethanol Induced	
		Ulcer Index (mm^2/rat)	Protective Ratio (%)	Ulcer Index (mm^2/rat)	Protective Ratio (%)
1	$C_{36}H_{10}F_{15}N_2O_6Bi$	7.2±0.58	61.68	19.9±5.4	18.21
2	$C_{36}H_{10}F_{15}Cl_2N_2O_6Bi$	7.2±0.58	61.68	19.7±5.2	18.17
3	$C_{36}H_{10}Br_1N_2O_6Bi$	7.1±0.54	61.21	19.8±5.5	18.18
4	$C_{36}H_6F_{15}N_2O_4Bi$	7.3±0.58	61.72	19.8±5.4	31.24
5	$C_{36}H_{10}Br_2F_{15}N_2O_6Bi$	6.2±0.28	62.16	14.4±2.2	34.70
6	$C_{33}H_5ClF_{20}NO_3Bi$	7.2±0.54	61.68	19.6±5.3	33.72
7	$C_{33}H_5BrF_{20}NO_3Bi$	7.2±0.56	61.70	19.6±5.2	31.20
8	Ranitidine	7.6±0.53	58.46	10.3±3.3	57.43
9	Aspirin	18.3±1.6	-	-	-
10	Ethanol	-		24.2±6.5	-