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Research Article

ANTIMICROBIAL STUDIES OF SOME NOVEL ORGANOBISMUTH COMPOUNDS

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Abstract- The present manuscript deals with the synthesis and characterization of some novel organobismuth derivatives of isatin for their antimicrobial activity. These compounds were synthesized by the reported method and characterized with the help of M.P., elemental, I.R spectral analysis along with their efficacy against pathogenic bacterial and fungal strains. It was found that the compounds exhibit higher activity than the standard drug for bactericidal and fungicidal activity.

Keywords- Organobismuth, isatin, antibacterial, antifungal.

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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., they may act as a pro-drug [3]. The bismuth based compounds have attracted considerable interest owing to their biological and medicinal utility in recent past [4-8]. They have been utilized from more than two centuries in the treatment of microbial infections, gastrointestinal disorders such as dyspepsia, diarrhea and peptic ulcer. Bismuth salts such as colloidal bismuth sub-citrate (CBS), bismuth sub-salicylate (BSS), and ranitidine bismuth citrate (RBC) are common agents used for *Helicobacter pylori* eradication therapy and therefore promoted these compounds as antimicrobials[9-11]. The utility of bismuth formulations has motivated many studies into their possible mechanism of action and to the discovery of their biological targets.

The present manuscript deals the synthesis and characterization of some novel organobismuth derivatives of isatin for their antimicrobial activity. These compounds were synthesized by the reported method and characterized with the help of M.P., elemental, I.R spectral analysis along with their efficacy against pathogenic bacterial and fungal strains.

Experimental

The bis(Pentafluorophenyl) bismuth (III) chloride was synthesized by the methods reported earlier[12] . The substituted isatin derivatives were recrystalised before used and all reactions were performed in under nitrogen atmosphere. Preparation of some representative organobismuth compounds are discussed below.

Reaction of bis (Pentafluorophenyl) bismuth (III) chloride with 6-chloro-5-methoxy isatin

In oxygen free nitrogen atmosphere a solution of bis (Pentafluorophenyl) bismuth (III) chloride (1mmol) in methanol (40ml) and 6-chloro-5-methoxy isatin (1mmol) in the same solvent was stirred together in presence of triethylamine at room temperature for 6 hrs. The $Et_3N.HCl$ formed was filtered off under nitrogen atmosphere and the filtrate on concentration in vacuum gives a yellow color crystalline solid which was further recrystalised in pet. ether (40-60^{0}C).

Reaction of bis (Pentafluorophenyl) bismuth (III) chloride with 6-methoxy-5-bromo isatin Under oxygen free nitrogen atmosphere a solution of bis (Pentafluorophenyl) bismuth (III) chloride (1mmol) in methanol (40ml) and 6-methoxy-5-bromo isatin (1mmol) in the same solvent was stirred together in presence of triethylamine at room temperature for 6 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 bis (Pentafluorophenyl) bismuth (III) chloride with 7-chloroisatin

In oxygen free nitrogen atmosphere a solution of bis (Pentafluorophenyl) bismuth (III) chloride (1mmol) in methanol (40ml) and 7-chloroisatin (1mmol) in the same solvent was stirred together in presence of triethylamine at room temperature for 6 hrs. The $Et_3N.HCl$ formed was filtered off under nitrogen atmosphere and the filtrate on concentration in vacuum gives a yellow color crystalline solid which was further recrystalised in pet. ether (40-60^{0}C).

Reaction of bis (Pentafluorophenyl) bismuth (III) chloride with 5-methoxy-6-bromo isatin Under nitrogen atmosphere a solution of bis (Pentafluorophenyl) bismuth (III) chloride (1mmol) in methanol (40ml) and 5-methoxy-6-bromo isatin (1mmol) in the same solvent was stirred together in presence of triethylamine at room temperature for 6 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).

Antimicrobial Activity

The antimicrobial activity of all these compounds was performed by disc diffusion method [13]. 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.

Results and Discussion

The bis(pentafluorophenyl) bismuth(III) isatin derivatives easily obtained by using metathetical reaction where a respective isatin reacted will bis (pentafluorophenyl) bismuth (III) chloride in an appropriate ratio in presence of triethylamine which behaves as a hydrogen chloride acceptor.

$$R_2BiCl + HL \xrightarrow{Et_3N} R_2BiL + Et_3N.HCl$$

R = C_6F_5,

HL = HNR_2 = 6-chloro-5-methoxy isatin, 6-methoxy-5-bromo isatin, 7-chloroisatin,
5-methoxy-6-bromo 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 activity in various pathogenic microbial strains.

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 bis(pentafluorophenyl) bismuth (III) chloride. 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 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. Sometimes these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacteria.

Table-1 Physicochemical and spectral data of organobismuth (III) isatin derivatives

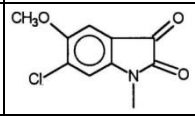
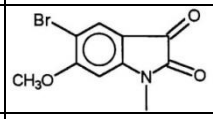
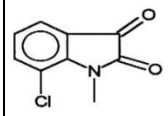
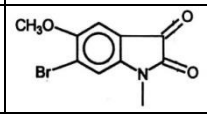
S.N.	Compound	M.P. (°C)	Yield (%)	IR (in cm^{-1})		
				$_{asy}$(CO)	$_{sym}$(CO)	Bi-C
	$(C_6F_5)_2Bi(NR_2)$ -NR_2=					
1		142	75	1738	1312	454
2		146	63	1728	1322	462
3		140	68	1740	1316	448
4		148	72	1740	1324	458

Table-2 *Analytical data of organobismuth (III) isatin derivatives*

S.N.	Empirical Formula	Formula Weight	Elemental Analysis %		
			C	H	N
1	$C_{21}H_5F_{10}NO_3ClBi$	743	64.74	4.58	2.00
2	$C_{21}H_5F_{10}NO_3BrBi$	787	41.32	0.94	2.66
3	$C_{20}H_3F_{10}NO_2ClBi$	713	31.04	0.86	2.44
4	$C_{21}H_5F_{10}NO_3BrBi$	787	37.78	0.47	1.32

Table-3 *Antimicrobial activity of organobismuth (III) isatin derivatives*

S.N.	Compounds	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Klebsiela pneumoniae*
1	$C_{21}H_5F_{10}NO_3ClBi$	11.00±0.57	8.10±0.16	12.00±1.15
2	$C_{21}H_5F_{10}NO_3BrBi$	10.94±0.48	8.04±0.10	11.88±0.70
3	$C_{20}H_3F_{10}NO_2ClBi$	11.33±0.66	11.00±0.57	8.58±0.29
4	$C_{21}H_5F_{10}NO_3BrBi$	11.24±0.60	8.70±0.26	12.06±0.77
5	Ampicilin (standard)	18.0±0.21	12.66±0.50	16.26±0.30

Application of research: Applicable for study of antimicrobial activity of Organobismuth compounds.

Research Category: Antimicrobial activity

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Conflict of Interest: None declared

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