INJ INTERNATIONAL NEUROUROLOGY JOURNAL

Synthesis And Antitumor Studies Of Novel Organic Derivatives Of Antimony

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Abstract

The present manuscript presented herewith describes the synthesis of novel organic derivatives of antimony through modified method followed by their characterization as antitumor/anti cell proliferation agent. The new organic derivative of antimony shows potential antitumor activity against human breast cancer (MCF-7) and mammary cancer (EVSA-7) cell lines.

Key Words: Organoantimony, cytotoxic, antitumor, carcinogens.

Introduction

It is observed that organoantimony compounds play an important role in controlling the tumor growth (1). Early work on organoantimony (III) both *in-vitro* and *in-vivo* showed that these compounds were more active than their organotin congeners against Ehrlich ascites tumor (2). The cross resistance of this compound and cis-platin in a human ovarian carcinoma and other human cell line has been demonstrated and the results suggesting that these complexes share a common mechanisms of resistance due to an accumulation defect (3-5). The recent studies indicated that these compounds are implicated in over expression of the multi-drug resistance associated protein (MRP), which is a drug export pump (6-8). This is a possible mechanism by which human cells can avoid the cytotoxic effect of heavy metals administered as drugs (9).

Experimental

Synthesis: The synthesis of organoantimony compounds was performed by following novel method (10).

Reaction of Diphenylantimony(III)chloride with glycine

In the stirring solution of diphenylantimony(III) chloride (1m mol), glycine (1m mol) was added in the presence of trimethyl amine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6-7 hr followed by refluxing for 3 more hr 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 recrystallized by petroleum ether (40-60˚C).

Reaction of phenylantimony(III)dichloride with glycine

In the stirring solution of phenylantimony(III) dichloride (1m mol), glycine (2m mol) was added in the presence of trimethyl amine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 7 hr followed by refluxing for 3 more hr 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 recrystallized by petroleum ether (40-60˚C).

Reaction of phenylantimony(III)dichloride with glycine

In the stirring solution of phenylantimony(III) dichloride (1m mol), glycine (1m mol) was added in the presence of trimethyl amine (1ml) in toluene and stirred under anhydrous oxygen free nitrogen atmosphere for 6 hr followed by refluxing for 2 more hr 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 white solid mass which was recrystallized by petroleum ether (40-60˚C).

Antitumor activity

This method was carried out to estimate the effect of test compound on the growth of tumor cells. The human breast cancer cells lines (MCF-7) and mammary cancer (EVSA-7) cell lines were employed. The cancer cell lines were co-incubated with the test compounds at 1 µg/ml doses for 96 hrs and the cell growth count was measured by MTT assay (11). The basic principle involved in this assay depends upon the reduction of tetrazolium salt. The yellow colored tetrazolium MTT, [3-(4, 5-dimethylthiazol-2-yl)-2, 5,-diphenyl tetrazolium bromide] is reduced by metabolically active cells in part by the action of dehydrogenase enzymes to generate reducing equivalents such as NADH and NADPH. The resulting intra cellular purple colour zones was solubilized and quantified by spectrophotometer method. The MTT was dissolved in PBS at a concentration of 5

ISSN:2093-4777 | E-ISSN:2093-6931
DOI: 10.5123/inj.2023.4.in96
Vol. 27 Iss. 4 (2023)

mg/ml. Then 50 µl of the MTT solution was added to each well of the 96 well culture plate, containing the 100 µl culture along with test compound and incubated at 37°C for 4 hrs. The medium was then removed carefully without disturbing the purple colored formazon crystals. Then, 50 ml of dimethylsulfoxide (DMSO) was added to each well and mixed thoroughly to dissolve the crystals of the formzon. The plates were then read on ELISA plate reader at a wavelength of 570 mm. The readings were presented as optical density/ cell count.

Results And Discussion

The hitherto unreported glycine derivatives of antimony (III) were readily be obtained by the metathetical

S. N.	Compounds	MCF-7 Cell No. x 10^4	EVSA-7 Cell No. x 10^4	Activity
1	$C_{14}H_{14}NO_2Sb$	9.19±0.92	9.29±0.88	Positive
2	$C_{10}H_{13}N_2O_4Sb$	9.17 ± 0.90	8.6 7 ± 0.69	Positive

reaction of phenyl/diphenyl antimony (III) chlorides with glycine in presence of triethylamine as hydrogen halide acceptor in benzene. The reactions were conducted at room temperature and the products were recrystallized from petroleum ether (40-60°C) or in benzene. The complexes were off-white solids and obtained as a sticky mass which on treatment with sodium in dry benzene, solidified and subsequently crystallized with benzene/pet-ether. The complexes are fairly stable on air and moisture and have sharp melting point. There is no regular trend of the melting point of the complexes and they melt without decomposition. Complexes are also soluble in chloroform and acetonitrile. They can be stored at room temperature without decomposition for several weeks. The consistency in melting points after repeated crystallization as well as TLC run in chloroform hexane mixture (1:1) with the observation of a single spot excluded the presence of mixture of reactants. The molar conductance of 10^{-3} M solution were recorded in methanol and were in the range of 15-25 Ohm^{-1} $mole^{-1}$ cm^2 indicating the absence of ionic species in solution. The complexes were found to be monomeric in nitrobenzene.

Physicochemical Analysis:

S.N.	Formula of Compound	Formula Weight	Molecular Weight	M.P. (^{0}C)	Elemental Analysis		
					C%	H%	N%
1	$C_{14}H_{14}NO_2Sb$	349.76	350.00	124	48.00	4.00	4.00
2	$C_{10}H_{13}N_2O_4Sb$	332.00	332.00	128	36.14	3.92	4.21
3	$C_8H_9ClNO_2Sb$	307.50	308.00	126	31.22	2.93	4.55

Antitumor Screening (In-Vitro):

MTT method was used to estimate the effect of compound on the growth of tumor cell lines. The human breast cancer (MCF-7) and mammary cancer (EVSA-7) cell lines were employed for screening of antitumor activity. Cell lines were co-incubated with the test compounds at 1 µg/ml doses for 96 hrs and the cell growth count was measured. The basic principle involved in this assay depends upon the reduction of tetrazoleum salt by metabolically active cells by the action of dehydrogenase enzymes to generate reducing equivalents such as NADH and NADPH. The plates were read on ELISA plate reader at a wavelength of 570 nm and findings were presented as optical density/ cell count to evaluate the activity. 17β estradiol was used as positive control. It was found that the organoantimony compounds generally interacts with nitrogenous bases of nucleotides of nucleic acid and inhibit the cell division by interfering the replication and transcription of DNA molecules. It is also reported that these compounds may also affect the multienzyme complexes responsible for replication and transcription of DNA therefore stops the proliferation of cells.

Antitumor Activity:

DOI: 10.5123/inj.2023.4.in96
ISSN:2093-4777 | E-ISSN:2093-6931
Vol. 27 Iss. 4 (2023)

3	$C_8H_9ClNO_2Sb$	11.59±1.06	11.29±1.02	Negative
4	Negative control	10.21±1.01	10.22±1.01	–
5	Positive control	40.26±3.23	41.23±3.28	–

Conclusion

The synthesized organoantimony compounds are novel and have pyramidal geometry. They show potential antitumor activity against human breast cancer (MCF-7) and mammary cancer (EVSA-7) cell lines exhibiting their antitumor efficacy.

Acknowledgement

The authors are thankful to the Vice Chancellor, Mangalayatan University, Aligarh for providing necessary laboratory facilities and Managing Director, Helix BioGenesis Pvt. Ltd. Noida for antitumor studies of the compound.

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