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Synthesis Of Novel Organoarsenic And Their Antitumor Efficacy Against Mcf-7 And Evsa-7 Tumor Cell Lines

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Abstract
The present manuscript describes the novel route for the synthesis of new organoarsenic derivatives of glycine through modified method followed by their characterization as antitumor/anti cell proliferation agent against human breast cancer (MCF-7) and mammary cancer (EVSA-7) cell lines. It was found that the new organic derivatives of arsenic show potential efficacy against tumor cell lines.

Key Words: Organoarsenic, cytotoxic, antitumor, carcinogens.

Introduction

Experimental
The importance of metal based drugs lies in the fact that they are essential components for various physico-chemical processes occurring in living system (1). The spectrum of the metal based drugs has been expanded as they have found their place among a class of potential biologically active compounds (2-5). It is surprising to observe that metal are able to induce cancer and also to treat the cancer while some are able to perform both (5). It is known that almost all metals are able to generate reactive oxygen species, which extend for the treatment of cancer (6). Arsenic can induce the cancer and also used to treat the cancer that is it shows paradox behavior (7). Arsenic is well known to its acute toxicity and it can induce the cancer (8). Although it does not seem to be a mutagen *in-vivo*, it interacts with DNA molecules. Arsenic exposure in certain animal modules and in human contributes to skin neoplasia by stimulation of several growth factors (9). Arsenic acts as a tumor promotion by modulating the signaling pathways which are responsible for cell growth (9). Arsenic induces chromosomal abnormalities and disruption of DNA methylation and repair systems (10). Arsenic induced oxidative stress with subsequent DNA damage which could explain its toxicity. By inducing the apoptosis, arsenic can eliminate transformed cells, which could protect organisms from cancer and possibly could be its mechanisms of action against tumors cells (11).

Experimental
Synthesis: The synthesis of novel organic derivatives of arsenic was carried out by following method (12).

Reaction of Diphenylarsenic(III)chloride with glycine

In the stirring solution of diphenylarsenic(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 phenylarsenic(III)dichloride with glycine

In the stirring solution of phenylarsenic(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 phenylarsenic(III)dichloride with glycine

In the stirring solution of phenylarsenic(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).

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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 (13). 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

S. N.	Compounds	MCF-7 Cell No. x 10^4	EVSA-7 Cell No. x 10^4	Activity
1	$C_{14}H_{14}NO_2As$	08.59±0.22	08.29±0.72	+
2	$C_{10}H_{13}N_2O_4As$	08.27±0.90	08.67±0.68	+

solubilized and quantified by spectrophotometer method. The MTT was dissolved in PBS at a concentration of 5 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 organoarsenic derivative can readily be obtained by the metathetical reaction of mono/diphenylarsenic(III)chloride with glycine in presence of triethylamine as hydrogen halide acceptor in benzene. The reaction was conducted at room temperature and the product was recrystallized from petroleum ether (40-60°C) or in benzene. The complex is light brown solid and obtained as a sticky mass which on treatment with sodium in dry benzene, solidified and subsequently crystallized with benzene/pet-ether. The complex is fairly stable on air and moisture and have sharp melting point. They can be stored at room temperature without decomposition and 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	$C_{14}H_{14}NO_2As$	303.00	305.00	112	55.44	4.62	4.62
2	$C_{10}H_{13}N_2O_4As$	300.00	300.00	116	40.00	4.33	9.33
3	$C_8H_9ClNO_2As$	261.50	262.00	122	36.71	3.44	5.35

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 organoarsenic 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.

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3	$C_8H_9ClNO_2As$	09.59±0.26	09.29±0.32	+
4	Negative control	10.21±1.01	10.22±1.01	–
5	Positive control	40.26±3.23	41.23±3.28	–

Antitumor Studies:

Conclusion

The synthesized organoarsenic 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.

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