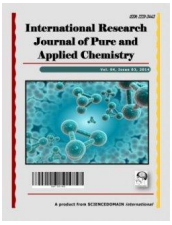

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Mutagenic Effects of Some Metal Complexes I. Cytotoxic Activity of Bis (L-glutaminato) Tetrachloropalladate (II)

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Authors' contributions

This work was carried out in collaboration between all authors. Author AFB designed the study and wrote the protocol. Authors AFB, AHS, MH and ZA preformed the statistical analysis, managed the literature search and wrote the first draft of the manuscript with assistance from authors AFB and ZA. All authors read and approved the final manuscript.

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ABSTRACT

The tetrachloropalladate (II) complex salt which with glutamine of formula [(Pd Cl4) H2. (L-Glutamine)2], was prepared and characterized through IR spectroscopy. The compound was found cytotoxic to TA 98 bacterial cells of Salmonella typhimurium. To our knowledge this is the first anionic Pd complex salt of L-glutamine exhibiting potential cytotoxic activity.

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Keywords: Tetrachloropalladate (II); glutamine; cytotoxic; mutagenic; metal complexes.

1. INTRODUCTION

The previous studies have shown that, the enzyme, L-glutaminase [1], possess antitumor activity [2]. It is believed that, the amino-acid, L-glutamine, must be supplied to, L-glutaminase-sensitive tumor cells, because these cells are deficient in L-glutamine synthetase activity. The synthesized, characterized and performed cytotoxicity studies with several Pd (II) complexes of proflavine were studied by Tatyana et al. [3] Pallidium (II) and platinum (II) chelates of L-glutamine have been shown to have a significant anticancer activity [4].

Antitumor tests have shown that, amino acid derivatives of cis-platin displayed some activity against P 388 and L 1210 leukemias [5]. Moreover, the L-aspartic acid derivative of trans-Pt (DAC) completely controlled Ehrlich as cites tumor growth [6]. Although two platinum drugs, cisplatin and carboplatin have played a major role in the chemotherapeutic treatment of variety of cancers over the past 40 years [7,8]. It was found that, their antitumor activity is limited due to intrinsic and/or acquired resistance to the compounds.

Since, Doadrio [9] initiated the research on the antitumor assay of some complex salts by tetrachloropalladate (II) anion with piperzine and antipyrine, it will be interesting to study the cytotoxic effect of tetrachloropalladate (II) complex salt with L-glutamine.

2. EXPERIMENTALS

Elemental analyses were from the micro analytical laboratory King-Abdul- Aziz University, Geddah. Infrared spectra were reported in SP 3-100 Pye Unicam spectrophotometer (250-4000 cm^{-1}) in KBr pellets.

3. PREPARATION OF COMPLEX

Bis (L-glutaminato) tetrachloropalladate (II) is prepared by reacting a solution of Pd Cl_2 was dissolved in 6 N HCl and the L-glutamine was dissolved in a hot water by stoichiometric ratios of 1:2. The reaction's mixture was heated under vigorous stirring, subsequent slow evaporation gives rise to crystals which were washed with ether dried in a vacuum desiccator over $CaCl_2$ pellets. Anal.: found % C, 18.2; H, 3.8; N, 8.3; $C_{10}\,H_{22}\,N_4\,O_6\,Cl_4\,Pd$ [(Pd Cl_4) H_2. (L-glutamine)$_2$] requires, %: C, 18.4; H, 3.4; N, 8.6.

4. CYTOTOXIC ACTIVITY

Aliquots (0.L ml) of overnight broth cultures of the bacterial cells Ta 98 mutants of Salmonella typhimurium requiring histidine for growth are mixed with different doses of tetrachloropalladate (II) complex in 2 mL volume of soft agar and then plated on synthetic agar medium lacking histidine in Petri dishes. Aroclor- induced rat liver homogenate with co-factor is used for metabolic activation. The plates are incubated for 3 days at 37°C and then observed for histidine revertants. If the test chemical is mutagenic there should be at least a 2- fold increase in the number of histidine non-requiring colonies over the spontaneous ones. A decline in the number of colonies is often an indication of toxicity.

5. RESULTS AND DISCUSSION

5.1 Preparation and Characterization of the Complex

L-Glutamine complexes are known for many metals, but to the best of our knowledge no tetrachloropalladate derivative has been reported. We have prepared tetrachloropalladate (II) derivative of L-glutamine: an anionic water soluble complex by reaction of Pd Cl_2 dissolved in 6 N HCl and L-glutamine. In the recent years there has been renewed interest in the study of the compounds of the series [(M Cl_4) H_2. ($C_n\,H_{2n+1}\,NH_2$)$_2$] (n=1, 2 and M= Ni, Fe Cu, Pd) [10-12]. It consists of nearly quadratic layers of metal ion which are surrounded by halogen sharing octahedral corners within the layer. The layers are separated by alkyl-ammonium groups. The complex [(Pd Cl_4) H (L-glutamine)] is a member of the family of the above general formula.

For our compound, in the IR spectrum, we observed a broad strong absorption in the 2340-3150 cm^{-1} resulting from H_3^+ stretching band. The complex presents a weak asymmetric NH_3^+ bending band near 1640 cm^{-1}; a fairly strong symmetrical NH_3^+ bending band near 1500 cm^{-1}. A strong band at 1220 cm^{-1} arises from stretching and strong carbonyl absorption at 1720 cm^{-1} from glutamine hydrochloride. The PdCl vibration of the $(Pd\,Cl_4)^2$ ions is assigned by a sharp band centered around 325 cm^{-1}. This band, clearly supports the existence of well defined entity $(Pd\,Cl_4)^2$.

Table 1. Mutagenecity testing of the [(Pd Cl_4) H_2. (L-glutamine)$_2$] in the Ames assay using the tester strains TA 98 of *Salmonella typhimurium*

No. of plates / dose	Dose i.e. conc./plate In ug	Average no. of histidine revertants/ plate observed in ames tester strains	
		TA 98	
		W/o Metabolic activation	W/Metabolic activation
3	0(control)	36	50
3	31.9	46	51
3	63.7	51	51
3	95.6	73*	52
3	127.4	70	56
3	159.3	52	68
3	191.1	40	69
3	254.8	21	71

**2-fold increase (mutagenic)*

6. BIOLOGICAL STUDIES

The complex (Pd Cl_4) H_2. (L-glutamine)$_2$ was evaluated for genotoxicity in the Ames assay using the tester strains TA 98 of Salmonella typhimurium, Table 1 above. The data show a 2-fold increase in the number of histidine revertants/plate in TA 98 at a concentration of 95.6 ug/plat followed by a gradual decline in the number of colonies/plate indicating toxicity. This preliminary data suggest that [(Pd Cl_4) H_2. (L-glutamine)$_2$] is active in cytotoxicity and genotoxicity. The cytotoxic properties of the complex in mammalian cells are under study.

7. CONCLUSION

The complex (Pd Cl_4) H_2. (L-glutamine)$_2$. was prepared, characterization and evaluated for genotoxicity in the ames assay using the tester strains TA 98 of salmonella typhimurium. It found that increasing in the number of histadine revertants/plate in TA 98 at concentration 95.6 ug/plat followed by a gradual decline in the number of colonies/plate indicating toxicity. This preliminary data suggest that [(Pd Cl_4) H_2. (L-glutamine)$_2$] is active in cytotoxicity and genotoxicity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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