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Short communication

Comparison of the anti-neoplastic effects of dirhodium(II) tetrapropionate and its adducts with nicotinate and isonicotinate anions in mice bearing Ehrlich tumors

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Abstract

Rhodium(II) propionate, $[Rh_2(prop)_4]$, and its adduct with nicotinate (nic^-) and isonicotinate ($isonic^-$) anions, $[Rh_2(prop)_4(nic)_2]^{2-}$ and $[Rh_2(prop)_4(isonic)_2]^{2-}$, respectively, were prepared for study. The compound effects on the survival rate of mice bearing Ehrlich ascites tumors were tested and presented in the form of a survival table, and analyzed by the Mantel–Haenszel chi-square test for N animals in each group. The survival rates of animals were significantly higher than that of control group ($P < 0.001$) without distinguishing among the experimental groups. The estimated probability for an animal in the control group to survive up to the end of the observation period (30 days) was below 33%, whereas the animal groups in the treated group with complex, and its nicotinate and isonicotinate groups showed 85%, 85% and 90%, respectively, of surviving over the same period. The *T*/*C* values (survival average of the animals treated group/survival average of the animals control group) were obtained for each compounds being for the dirhodium propionate $T/C = 250$, and for its adducts with nicotinate and isonicotinate anions, 267 and 264, respectively.

Keywords: Rhodium; Anti-tumor; Ehrlich tumors; Carboxylate

1. Introduction

Cisplatin (*cis*-diaminedichloroplatinum(II)) has been used clinically as one of the most effective anticancer drugs in the treatment of a variety of human solid tumors, such as genitourinary, and testicular [1]. Unfortunately, its usefulness is limited due the to development of resistance in tumor cells and its significant side effects. Thus, a continuing effort has been made to develop analogs to overcome the above shortcomings. In 1972, Bear and co-workers have found that dirhodium(II) tetracarboxylates exhibit carcinostatic activity prompted several investigations dealing with the chemical properties and biological effects of this complexes [2,3], leading to a new class of anticancer compounds. Aspects of the chemistry, the mechanism of action, and the anti-neoplastic potential of these compounds has been objective of several papers and reviews [4–8].

Dirhodium tetracarboxylates have a common tetrabridged acetate structure with a short Rh-Rh bond (Fig. 1), whose axial positions can be readily occupied by Lewis bases [4]. The antitumor activity increases in the series $[Rh_2(OOCR)_4]$ (**R** = alkyl groups) with lipophilicity of the **R** groups and is independent of its reduction potential [9,10], showed a considerable variation in their antitumor activity against Ehrlich ascites tumor cells in mice.

Although a number of rhodium compounds showed no evident nephrotoxic activity some authors have correlated the toxic effects with the lipophilic character of active complexes [9]. Thus, several hydrophilic carboxylates have been synthesized, including citrate [11], ketogluconate, glucuronate [12], sulfosalicylate [13], and as well as, inclusion compounds in β-cyclodextrin [14], where only the rhodium citrate was tested its antitumoral activity.

An alternative to this situation was reported by Souza and co-workers [15] using isonicotinate axial anion ligand to concern a larger solubility in rhodium acetate, propionate, and butirate. The results have shown that isonicotininate anion adduct dissociates into the parent compounds when in the biological system. Concluding that nicotinate and isonicotinate anions when coordinated may be used as carrier of metal complexes to cells. Continuing our work the dirhodium(II) tetrapropionate adducts with nicotinate and isonicotinate anions were

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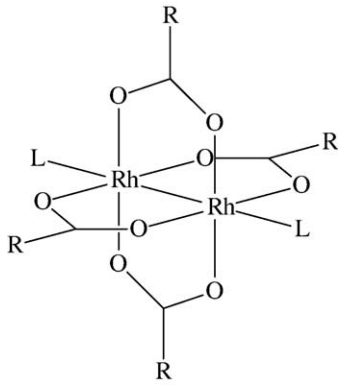

Fig. 1. General molecular structure of the rhodium(II) carboxylates with two labile positions (L).

prepared and its effects on the survival rate of mice bearing Ehrlich ascites tumors.

2. Experimental

2.1. Preparation of the nicotinic and isonicotinic adducts

Rhodium(III) chloride hydrate was purchased from OMG. Rhodium(II) carboxylates, corresponding adducts and the preparation of water soluble complexes were obtained by the method previously described [15].

2.2. Determination of survival rates

Sixty female Balb/C mices, with medium weight of 20.0 g, were inoculated intraperitoneally (*ip*) with 5×10^6 Ehrlich ascites cells. Twenty-four hours after implantation, all mice were randomly divided into three groups (twenty animals each). All adduct compound solutions were freshly prepared each day prior to injection, by the method previously described [14]. The control group received 0.25 ml physiological saline by the *ip* route daily for 4 days, whereas the experimental groups (20 animals) were similarly treated with 43.8 μg of rhodium compounds dissolved in 0.25 ml saline (total dose, 11.8 μmol/kg equivalent to DL10). All three groups were kept under identical conditions for up to 32 days after inoculation. Survival was considered to be statistically significant when $P < 0.001$. The differences among means of groups were analyzed using the Tukey's test.

3. Results and discussion

The metal-metal bonded dirhodium tetrapropionate complex readily form adducts in which the axial sites (Fig. 1) were occupied by nicotinate and isonicotinate anion ligands as described in the literature [15]. The *T*/*C* values (survival average of the animals treated group/survival average of the animals control group) were obtained for each compounds being for the dirhodium propionate $T/C = 250$, and for its adduct with nicotinate and isonicotinate anions, 267 and 264, respectively.

The survival rate results are presented in Tables 1–3. The data are presented in the form of a survival table and analyzed by the Mantel–Haenszel chi-square test for *N* animals in each group. The survival rate of animals receiving rhodium compounds were significantly higher than that of control ($P < 0.001$) without distinguishing among experimental groups. The estimated probability for an animal in the control group to survive up to the end of the observation period (30 days) was below 33%, whereas the animal groups in the treated with the complex, and the nicotinate and isonicotinate groups showed 85%, 85% and 90%, respectively, of surviving over the same period. These results are similar to those obtained by Souza et al. [15] in vitro tests with cultured line K562 tumor cells and LD10 values, where practically difference is not observed among the treatments. Thus, the suggestion that in the presence of blood lipids or cellular membrane, the nicotinate and isonicotinate anion adducts dissociate into the parent compound, and the dirhodium(II) tetrapropionate becomes the chemotherapy agent it is still more evident with the results obtained in that work. In fact, a significant difference was not observed in the probability of survival when the experimental groups are compared.

At the end of the observation period, 23 of 52 survivors in both the experimental groups exhibited a characteristic solid tumor instead of the ascitic form usually present after *ip* inoculation of tumor cells. The remaining six animals were apparently healthy, being five of them treated with isonicotinate and only one with nicotinate adducts.

This study shows a similar antitumor activity of complex and its adducts presented in the probability of survival and in the *T*/*C* values. Thus, believed that the pyridinecarboxylate anion, when coordinated by nitrogen, have little influence on the biological activity of the dirhodium tetrapropionate compound.

Table 1
Effect of dirhodium tetrapropionate, $[Rh_2(prop)_4]$, on the survival of mice bearing Ehrlich tumor cells

Period	Day	Control group					Experimental group, $[Rh_2(prop)_4]$				
		N	Death (*d*)	Probability of death (*q*)[a]	Probability of survival (*p*)[b]	Probability of survival to the end of the period (*N*/20)	*N*	Death (*d*)	Probability of death (*q*)[a]	Probability of survival (*p*)[b]	Probability of survival to the end of the period (*N*/20)
0	0–21	20	1	0.050	0.950	1.000	20	1	0.050	0.950	1.000
1	22–24	19	7	0.368	0.632	0.950	19	0	0	1	0.950
2	25–27	12	9	0.750	0.250	0.600	19	2	0.105	0.895	0.950
3	28–30	3	2	0.667	0.333	0.150	17	2	0	1	0.850
4	31–33	1				0.050	17				0.850

prop: propionate; *N*: number of alive mice in the period; $Chi^2_{4df} = 15.6$; $P < 0.001$.

[a] Probability of death (*q*) = death (*d*)/*N*.

[b] Probability of survival (*p*) = 1 − *q*.

Table 2
Effect of dirhodium tetrapropionate with its nicotinate anion adduct, $[Rh_2(prop)_4(nic)_2]^{2-}$, on the survival of mice bearing Ehrlich tumor cells

Period	Day	Control group					Experimental group, $[Rh_2(prop)_4(nic)_2]^{2-}$				
		N	Death (*d*)	Probability of death (*q*)[a]	Probability of survival (*p*)[b]	Probability of survival to the end of the period (*N*/20)	*N*	Death (*d*)	Probability of death (*q*)[a]	Probability of survival (*p*)[b]	Probability of survival to the end of the period (*N*/20)
0	0–21	20	1	0.050	0.950	1.000	20	0	0	1	1.000
1	22–24	19	7	0.368	0.632	0.950	20	0	0	1	1.000
2	25–27	12	9	0.750	0.250	0.600	20	2	0.100	0.900	1.000
3	28–30	3	2	0.667	0.333	0.150	18	1	0.056	0.944	0.900
4	31–33	1				0.050	17				0.850

prop: propionate; isonic: nicotinate anion; *N*: number of alive mice in the period; $Chi^2_{4df} = 13.8$; $P < 0.001$.
[a] Probability of death (q) = death (d)/N.
[b] Probability of survival (p) = 1 − q.

Table 3
Effect of dirhodium tetrapropionate with its isonicotinate anion adduct, $[Rh_2(prop)_4(isonic)_2]^{2-}$, on the survival of mice bearing Ehrlich tumor cells

Period	Day	Control group					Experimental group, $[Rh_2(prop)_4(isonic)_2]^{2-}$				
		N	Death (*d*)	Probability of death (*q*)[a]	Probability of survival (*p*)[b]	Probability of survival to the end of the period (*N*/20)	*N*	Death (*d*)	Probability of death (*q*)[a]	Probability of survival (*p*)[b]	Probability of survival to the end of the period (*N*/20)
0	0–21	20	1	0.050	0.950	1.000	20	0	0	1	1.000
1	22–24	19	5	0.263	0.737	0.950	20	1	0.050	0.950	1.000
2	25–27	14	10	0.714	0.286	0.700	19	0	0	1	0.950
3	28–30	4	3	0.750	0.250	0.200	19	1	0.053	0.947	0.950
4	31–33	1				0.050	18				0.900

prop: propionate; isonic: isonicotinate anion; *N*: number of alive mice in the period; $Chi^2_{4df} = 16.7$; $P < 0.001$.
[a] Probability of death (q) = death (d)/N.
[b] Probability of survival (p) = 1 − q.

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