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EVALUATION OF POTENTIAL ANTIINFLAMMATORY ACTIVITY OF COPPER (II) AND ZINC(II) BENZENE-1,4-DIYLBIS(OXYACETATES), FREE BENZENE-1,4-DIYLBIS(OXYACETIC)ACID AND THEIR MIXTURES IN RATS

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Using rat paw dextran- and/or carageenan-induced edemas, the antiinflammatory activity of copper(II) and zinc(II) benzene-1,4-diylbis(oxyacetates) (compexes **1c** and **1z**) and free benzen-1,4-diylbis(oxyacetic)acid (**1a**) and their equimolar mixtures (**1cz, 1ac** and **12az**) were evaluated plethysmometrically. All the tested compounds were administered intraperitoneally in the single dose 50μmol/kg of body weight (calculated for the carboxylate fragment) 30 minutes before injecting the irritant. The antiphlogistic activity of the compounds (expressed as a mean edema reduction) was found as: **1a** 27.6 % / -23,0 % < **1c** 44.2 % / 34.7 < **1z** 69.2 % / 30.3 % < **1cz** 59.7 % / 67.0 % < **1ac** 53.1 % / 77.6 % < **1az** 83.8 % / 85.5 %. The relationships between the coordination-chemical properties and the biological effects on the corresponding compounds are discussed.

***Key words**: copper(II) and zinc(II) complexes mixtures – rat paw carageenan- and dextran-induced edemas – anti-inflammatory activity*

INTRODUCTION

Carboxylatocopper(II) and -zinc(II) complexes seem to be beneficial in suppressing-the inflammation and other pathological processes [1-3]. These types of coordination compounds with aryloxyacetate acidoligands possess significant anti-inflammatory activity influencing the experimental rat oedemas [4-6]. In effort to define basic relationship between chemical structure and the biological activity of a relative compounds, assumed antiphlogistic activity of a new group of Cu(II) and Zn(II) complexes with double oxyacetate groups on phenylene moiety has been studied.

EXPERIMENTAL

Benzene-1,4-diylbis(oxyacetic) acid (**1a**) was prepared according Ettel et al. [7]. Copper(II) benzene-1,4-diylbis(oxyacetate) trihydrate (**1c**) and dihydrate of zinc(II) salt (**1z**) were synthesized by reaction of the sodium salt of parent acid with the corresponding metal(II) sulphates as the water insoluble compounds.

Elemental analysis. The acid (**1a**) – $C_{10}H_{10}O_6$ (M_r = 226.19) – calc./found: 53.10/53.29 % C and 4.42/4.50 % H. Complex **1c** – $C_{10}H_{14}O_9Cu$ (M_r = 341.76) – calc./found: 35.14/34.97 % C; 4.42/4.50 % H and 18.59/18.64 % Cu. Complex **1z** – $C_{10}H_{12}O_8Zn$ (M_r = 325.57) – calc./found: 36.89/36.97 % C; 3.82/3.80 % H and 20.08/20.27 % Zn.

Coordination compounds prepared belong probably to polymer triaqua[benzene-1,4-diylbis(oxyacetato)]copper(II) and diaqua[benzene-1,4-diylbis (oxyacetato)]zinc(II) complexes with distorted tetragonal or tetrahedral geometry of the central atom (M^{II}) as it was found in Cu(II) complex of the 1,3-derivative [8].

All compounds were dispersed in sterilized saline with the content of 0.05 % Tween® 80 (Merck) by sonication in an ultrasound bath in concentration of 50 μmol/cm^3 (calculated for oxyacetate-fragment). The mixed two-component species (**1cz**, **1ac** and **1az**) were prepared by the same above-mentioned procedure from the acid and corresponding complexes in equimolar ratio, i.e. 12.5 μmol/cm^3 for each of them. Wistar male rats (Dobrá Voda, Slovakia) weighting 260 ± 20 g were used.

The acute antiphlogistic activity was measured by the reduction of rat paw edema, induced by an injection of 0.1 cm^3 of 6.0% dextran or 0.1 cm^3 of 1% carrageenan (Serva) in sterilized saline. The tested compounds were applied intraperitoneally. in a single dose of 50 μmol/kg of body weight, 30 min before injecting the irritant substance. The control group (**CG**) received only a vehicle. The changes of edema volume were evaluated plethysmometrically during period of 180 and/or 360min. respectively [9]. All values are represented as mean (± SEM). Statistical evaluation was performed using the Student's t-test with statistical significance at $p< 0.05$.

RESULTS AND DISCUSSION

Using rat paw dextran-/carrageenan-induced oedemas the anti-inflammatory activity of copper(II) and zinc(II) benzene-1,4-diylbis(oxyacetates) (complexes **1c** and **1z**), free benzene-1,4-diylbis-(oxyacetic) acid (acid **1a**) and their two-component mixtures (**1cz**, **1ac** and **1az**) was assayed plethysmometrically (Tables 1 and 2). The average activities of the tested species for both edema types, expressed as a measure of oedema volume reduction, were increasing in order: **1a** 27.6 % / -23,0 % < **1c** 44.2 % / 34.7 < **1z** 69.2 % / 30.3 % < **1cz** 59.7 % / 67.0 % < **1ac** 53.1 % / 77.6 % < **1az** 83.8 % / 85.5 %. It was found that the complexation of benzene-1,4-diylbis(oxyacetate)(2-) with cations Cu^{2+} and Zn^{2+} allowed the enhancement of anti-inflammatory effect in comparison to that of the uncomplexed acid (**1a**). Thus, Cu(II) and Zn(II) benzene-1,4-diylbis(oxyacetates) and their mixed species with the acid can be advantageous for the controlled liberation

of the corresponding carboxylate and M^{2+} ions acquired for the formation of pharmaco-active entities under *in vivo* conditions. It seems that the synergistic effect of uncomplexed acid in both examined edema models was exhibited mainly for the mixtures **1az** and **1ac**. The maximal anti-inflammatory effect have been already developed in 60^{th} min. after administration of compounds and persisted till 180min. when the activity gradually declined (Tables 1 and 2).

Our findings are in good correlation with the similar ones which have been performed previously [10]. The equimolar mixture of structurally relative Cu(II) and Zn(II) complexes of 3,6,-dimethylsalicylates was in the carrageenan-induced local inflammation model significantly more antiedematously active in comparison with the free 3,6-dimethyl-salicylic acid.

Table 1. Results of pharmacological screening – dextran-induced edema

Compd.	**Edema volume changes, ΔV (± SEM) [cm^3] / Edema reduction (%)**			
	Time interval (measured in minutes)			
	30^{th}	60^{th}	120^{th}	180^{th}
CG	0.421 (0.02)	0.454 (0.03)	0.349 (0.03)	0.293 (0.03)
1a	0.328 (0.03) 22.1	0.282* (0.04) 37.9	0.257* (0.04) 26.4	0.223* (0.04) 23.9
1c	0.242* (0.02) 42.5	0.260* (0.01) 42.7	0.214* (0.02) 38.7	0.138** (0.03) 52.9
1z	0.176** (0.02) 58.2	0.140** (0.01) 69.2	0.096** (0.02) 72.5	0.068*** (0.02) 76.8
1cz	0.212* (0.02) 49.6	0.180** (0.01) 60.4	0.135** (0.02) 61.3	0.095** (0.04) 67.6
1ac	0.178** (0.01) 57.7	0.214* (0.01) 52.9	0.174** (0.01) 50.1	0.142** (0.01) 51.5
1az	0.125** (0.02) 70.3	0.082*** (0.02) 81.9	0.047*** (0.01) 86.5	0.010*** (0.00) 96.6

CG = control group (n = 12). For the compounds see Experimental.
Statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (n = 8)

Table 2: Results of pharmacological screening – carrageenan-induced edema

Compd.	Edema volume changes, ΔV (±SEM) (cm^3) / Edema reduction (%)						
	Time interval (measured in minutes)						
	30^{th}	60^{th}	120^{th}	180^{th}	240^{th}	300^{th}	360^{th}
CG	0.190 (0.05)	0.244 (0.05)	0.322 (0.07)	0.430 (0.06)	0.323 (0.06)	0.237 (0.06)	0.377 (0.06)
1a	0.243 (0.06) -27.9	0.326 (0.06) -33.6	0.389 (0.05) -20.8	0.357 (0.05) 17.0	0.390 (0.06) -20.7	0.391 (0.05) -65.0	0.414 (0.05) -9.8
1c	0.172 (0.03) 9.5	0.235 (0.04) 3.7	0.205 (0.03) 36.3	0.200* (0.06) 53.5	0.205 (0.03) 36.5	0.085 (0.04) 64.1	0.228 (0.04) 39.5
1z	0.190 (0.04) 0	0.290 (0.05) -18.9	0.272 (0.03) 15.5	0.252* (0.03) 41.4	0.115* (0.05) 64.4	0.058* (0.04) 75.5	0.247 (0.05) 34.5
1cz	0.052* (0.02) 72.6	0.063* (0.03) 74.2	0.112* (0.02) 65.2	0.125** (0.02) 70.9	0.182 (0.02) 43.7	0.100 (0.01) 57.8	0.058** (0.03) 84.6
1ac	0.086 (0.02) 54.7	0.033** (0.03) 86.5	0.003** (0.02) 100.9	0.104** (0.02) 75.8	0.109* (0.02) 66.3	0.040* (0.01) 83.1	0.090** (0.03) 76.1
1az	0.030* (0.02) 84.2	0.008** (0.01) 96.7	0.068** (0.01) 78.9	0.083** (0.02) 80.7	0.110* (0.03) 65.9	0.027* (0.03) 88.6	0.012** (0.02) 103.2

CG = control group (n = 11). For the compounds see Experimental.
Statistical significance: * $p < 0.05$, ** $p < 0.01$ (n = 8)

The mode of action of the complexes tested is probably similar to that of Cu-based non-steroidal anti-inflammatory drugs with carboxylate moiety and based on inhibition of prostaglandin synthesis *via* the cyclooxygenase isoenzyme system and/or could be related to the modulation of superoxide dismutation, nitric oxide synthetase, and some immunobiological functions [1,2]. The antioxidant functions both zinc(II) and Zn(II) complexes could be obviously responsible for the protection of protein –SH groups and/or reduction of hydroxyl radical formation from hydrogen peroxide through the antagonism of redox-active transition metals, such as iron and copper [3].

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HODNOTENIE POTENCIÁLNEJ PROTIZÁPALOVEJ AKTIVITY KUPRUM(II) A ZINKUM(II) BENZEN-1,4-DIYLBIS(OXYACETATU), VOĽNEJ BENZEN-1,4DIYLBIS(OXYOCTOVEJ KYSELINY) A ICH ZMESÍ U POTKANOV

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Protizápalová aktivita kuprum(II) a zinkum(II) benzén -1,4-diylbis(oxyacetátu) (komplexy **1c** a **1z**) a voľná benzén-1,4-diylbi-(octová kyselina) (kyselina **1a**) a ich ekvimólové zmesi **(1cz, 1 ac** a **1az**) bola hodnotená pletyzmometricky na dextranovom, resp. karagenínovom edéme na potkanoch. Všetky testované látky boli podané *i.p.* v jednorázovej dávke 50μmol/kg telesnej hmotnosti zvieraťa (počítané na karboxylátový fragment) 30 min. pred injikovaním iritanta. Priemerná antiflogistická aktivita látok (vyjadrená ako miera redukcie edému) bola zistená v tomto poradí: **1a** 27.6 % / -23,0 % < **1c** 44.2 % / 34.7 < **1z** 69.2 % / 30.3 % < **1cz** 59.7 % / 67.0 % < **1ac** 53.1 % / 77.6 % < **1az** 83.8 % / 85.5 %.Diskutujeme vzťahy medzi koordinačno-chemickými vlastnosťami a biologickým účinkom príslušných komplexov

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