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Antiinflammatory activity of aqua(cresoxyacetato)-copper(II) complexes

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It is known that low molecular weight (carboxylato)-copper(II) complexes can be beneficial in influencing inflammation reactions [1–4]. The antiphlogistic activities of (phenoxyacetato)-, (chlorophenoxyacetato)- and (naphthoxyacetato)copper(II) aquacomplexes were assayed in rat paw dextran- or carrageenan-indued edemas [5, 6]. This paper is devoted to the study of antiedematous activity of the mononuclear aquabis(cresoxyacetato)copper(II) complexes with $[Cu(H_2O)_n(ROCH_2COO)_2]$ composition, where R = 2-methylphenyl (n = 2, complex **1**); 3-methylphenyl (n = 2, complex **2**) and 4-methylphenyl (n = 3, complex **3**), including the corresponding isomeric cresoxyacetic acids (**1a**–**3a**).

On the basis of the different coordination of $ROCH_2COO^-$ acidoligands the complexes **1**–**3** belong to two groups of mononuclear (aryloxyacetato)copper(II) complexes with tetragonal symmetry [7]. In diaquacomplexes **1** and **2** the acidoligands are coordinated by a chelate mode to Cu(II) atom via both carboxylate and ether oxygen atoms yielding the similar molecular structure as it was found for diaquabis(phenoxyacetato)copper(II) [8]. On the other hand, triaquacomplex **3** is represented by a square-pyramidal structure with the monodentate acidoligand coordination which is typical for phenoxyacetate copper(II) trihydrate [9].

Using a routine plethysmometric method, the evaluation of antiedematous activity of all compounds was carried out in the rat paw carrageenan-induced edema model (Table). The effects of the tested Cu(II) complexes **1**–**3** were compared to those of the free isomeric cresoxyacetic acids **1a**–**3a**. Aqua(cresoxyacetato)copper(II) complexes are clearly more effective than the acids, with the exception of a pair of the ortho derivative. The average antiinflammatory activities of the compounds (ordered by a measure of the effect of complexes) decreased in the following order: **2/2a** (71.0/37.1%) ≈ **3/3a** (70.8/46.5%) > **1/1a** (43.0/46.5%). In the case of complex **1**, the increased stability of $[Cu(H_2O)_n(ROCH_2COO)_2]$ species under *in vivo* conditions could be explained by the ortho-effect of the methyl group protecting the chelate coordination of $ROCH_2COO^-$ acidoligands in ether moiety against the aquation reactions. In contrast, complexes **2** and **3** are bioavailable to the formation of pharmaco-active forms though the controlled liberation of aryloxyacetate and Cu^{2+} ions. These two complexes were more active than a salicylate pair – salicylic acid (mean edema reduction 40.7%) and dihydrate diaquabis(salicylate)copper(II) complex (57.4%) – under the same conditions [6].

Table: Antiinflammatory activity of compounds 1–3 and 1a–3a

Compd.	Edema volume changes ΔV (±SEM) (cm^3)						
	Time interval (min)						
	30	60	120	180	240	300	360
CG	0.14 (0.03)	0.24 (0.03)	0.34 (0.04)	0.32 (0.02)	0.33 (0.03)	0.35 (0.04)	0.38 (0.04)
1	0.07 (0.01)	0.18 (0.02)	0.25 (0.02)	0.21** (0.02)	0.20* (0.04)	0.15** (0.04)	0.12** (0.05)
1a	0.15 (0.03)	0.30 (0.03)	0.15** (0.02)	0.13** (0.01)	0.09** (0.02)	0.05** (0.02)	0.06** (0.02)
2	0.09 (0.01)	0.14 (0.02)	0.12** (0.02)	0.07** (0.01)	0.04** (0.01)	0.02** (0.01)	0.02** (0.01)
2a	0.11 (0.02)	0.20 (0.04)	0.32 (0.03)	0.25 (0.04)	0.17** (0.04)	0.11** (0.03)	0.10** (0.03)
3	0.09 (0.00)	0.15 (0.00)	0.11** (0.01)	0.07** (0.01)	0.04** (0.01)	0.20** (0.01)	0.20** (0.01)
3a	0.07 (0.02)	0.13* (0.01)	0.15** (0.01)	0.18 (0.02)	0.23 (0.03)	0.21* (0.04)	0.20* (0.04)

CG control group of animals (n = 11); statistical significance * $P < 0.05$, ** $P < 0.02$ (n = 8)

Experimental

The complexes **1**–**3** and the corresponding carboxylic acids **1a**–**3a** were used for biological tests. Their preparation and basic physico-chemical characterization were published previously [6]. All compounds were dispersed in sterilized saline with a concentration of 50 μmol/cm^3 (calculated for aryloxyacetate fragment) and stabilized by 0.05% Tween 80 (Merck). Wistar male and female rats (Velaz, Prague), weighing 230 ± 20 g, were used. Acute antiedematous activity (Table) was measured by reduction of rat paw edema, induced by injection of 0.1 ml of 1% carrageenan (Serva) in sterilized saline. The tested compounds were applied i.p. in a single dose of 50 μmol/kg body weight, 30 min before injecting the irritant substance [6]. Control animals received only vehicle. The changes of edema volume were evaluated plethysmometrically [10]. Statistical significance of results was established using the Student's t-test. All differences were considered significant at $P < 0.05$.

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Antifungal activity of 2′-substituted furanocoumarins and related compounds

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With the advent of the AIDS era in the 1980's, a broad range of fungal infections are being reported in the medical practice. *Candida* species are now ranked as the third most common causative agent of nosocomial blood stream