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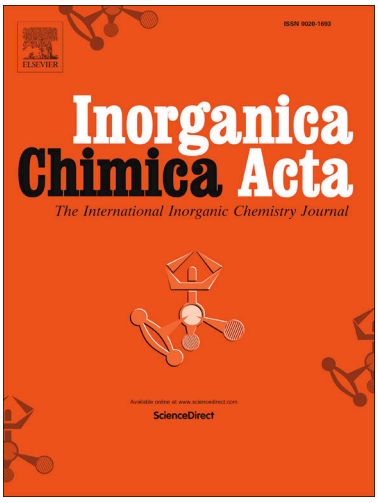

Research paper

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Mn(II), Co(II), Ni(II) and Zn salicylates: synthesis, structure and biological properties studies

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Reaction of acetylsalicylic acid (aspirin) (H_2L) with Mn(II), Co(II), Ni(II) and Zn acetates allow to obtain salicylates of related metals. The solid-state structures of prepared complexes were determined by single crystal X-ray crystallography and spectroscopic techniques. Zinc, nickel and cobalt(II) complexes are mononuclear and their crystal structures composed of neutral discrete molecules $[Zn(sal)_2(H_2O)_2]$, $[Ni(sal)_2(H_2O)_4]$ and $[Co(sal)_2(H_2O)_4]$ while manganese derivative has 2D polymeric structure. The cardiorespiratory and skin microcirculation activity of these metal complexes was evaluated. Particularly, the promising therapeutic activities displayed by 1-4 complexes make them potential candidates for the development of a promising drugs.

Keywords: Metal complexes, aspirin, salicylate, X-ray crystallography microcirculation activity, cardiorespiratory system.

1. Introduction

Since being first synthesized and purified by Felix Hoffmann in 1897, Aspirin is today the most widely used drug all over the world. It belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs) and has a number of therapeutic uses: analgesic, anti-inflammatory, anti-platelet and anti-pyretic [1-2]. Aspirin use in preventing cardiovascular and cerebrovascular diseases has been one of the biggest pharmaceutical achievements of the twentieth century. Low-dose everyday use of aspirin is known to be beneficial in reducing risk of secondary heart-attacks and for the prevention of preterm

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delivery in nulliparous women with a singleton pregnancy [3-6]. Besides possible role of low-dose aspirin in reducing the long-term risk of several cancers has opened a new era of aspirin use [7-10], making a solution to this issue very desirable. In recent years, many clinical epidemiological studies have found that with an increase in aspirin intake, tumor mortality decreases exponentially in the colon, breast, lung, prostate and other organs of cancer patients.

It is well known that in the course of metabolism, aspirin is hydrolyzed to salicylic acid, which is the active biological component [1]. Getting into a complex system of the internal environment, salicylic acid can interact not only with organic components, but also complexation with inorganic cations, which can lead to the formation of new biologically active forms of coordinated salicylic acid [11-15]. Actually, complexing properties of salicylic acid offers one of the routes for its modification. For example, some 3d-metal complexes of salicylic acid and its derivatives are known to be more potent anti-inflammatory agents than the acids themselves, and they have been shown to have low toxicity and less side effects [16, 17]. Moreover, such complexes exhibit antiradical activity and have superoxide dismutase mimetic properties [18–20]. Zinc(II) salicylate complexes possess anticonvulsant action [21]. However, a number of biological activities of metal coordination compounds are still poorly studied, in particular, neuro- and psychotropic properties and the response of the cardiorespiratory system to the introduction of such coordination compounds.

It should be noted, also, that most of the biologically active metal complexes on ssalicylate-anion basis are obtained directly from salicylic acid. This does not correctly reproduce the possible chemistry of the complexation process in the cell when using aspirin as a precursor. Taking into account the fundamental possibility of interaction of acetylsalicylic acid with 3d-metal cations present in the body, it seems interesting to analyze the composition and properties of such complexes. The study of biologically active metal complexes obtained by interaction with aspirin can lead not only to new biologically active compounds of this class, but also explain the mechanism of aspirin action in previously unexplored processes. In this article, we describe structure, physicochemical and some biological properties of Mn(II), Co(II), Ni(II) and Zn coordination compounds with salicylate anions obtained by complexation of corresponding metal acetates with acetylsalicylic acid

2. Experimental

2.1. Materials and physical methods

All reagents and solvents employed were commercially available and used as received without further purification. The purity and composition of the prepared complexes were confirmed by means of elemental analysis, electrospray-ionization mass-spectrometry (ESI–MS), and FT-IR spectroscopy, XRPD and single crystal X-ray structure analysis.

Elemental analyses of C, H, and N were performed with a Perkin–Elmer 240 C analyser. IR spectra were measured with a Spectrum Two PerkinElmer Inc spectrometer in the range 4000-400 cm^{-1}. Electrospray mass spectra of complex were measured with the Finnagan TSQ 700 mass spectrometer in positive ion mode. Samples were prepared at a concentration of ~2 mg/ml MeOH. The mass spectra were acquired over the m/z range of 50-2000; several scans were averaged to provide the final spectrum.

2.2. Synthesis

General procedures for complexes.

Water solution (40 ml) of acetylsalicylic acid (1.8 g, 0.01 mol) was added to an aqueous solution of respected metal(II) acetate (0.005 mol). Vigorous stirring at room temperature followed for two hour and the fltrate left for slow evaporation at room temperature. After a few days crystalline product of tar was deposited and collected by filtration. Target complexes were purified by recrystallization from a minimal volume of water.

White crystals $[Zn(Sal)_2 \cdot 2H_2O]$ - 1. Elemental analysis found: C: 44.80; H: 4.01%; calculated for $C_{14}H_{14}O_8Zn$ C: 44.76; H: 3.76%. IR (cm^{-1}): 3410 (br), 3229 (br), 1625 m, 1600 s, 1563 s, 1445 s, 1386 vs, 1244 s, 755 s, 658 m 428 m; UV-vis (water): λ_{max} = 314 nm (log ε = 3.0). HRMS m/z: 339.3784; calculated for $[Zn(Sal)_2H]^+$ m/z: 339.3275

Pink crystals. $[Co(Sal)_2 \cdot 4H_2O]$ - 2. Elemental analysis found: C: 41.74; H: 4.63%; calculated for $C_{14}H_{18}O_{10}Co$ C: 41.50; H: 4.47%. IR (cm^{-1}): 3390 (br), 1620s, 1608s, 1580 s, 1456 s, 1371 vs, 1241 s, 751 s, 663 m 420 m; UV-vis (water): λ_{max} = 315 nm (log ε = 3.1), λ_{max} = 511 nm (log ε = 0.04),. HRMS m/z: 334.1667; calculated for $[Co(Sal)_2H]^+$ m/z: 334.2418

Nude-colour crystals. $[Mn_3(Sal)_4(OAc)_2 \cdot 4H_2O] \cdot 3H_2O$ - 3. Elemental analysis found: C: 40.32; H: 4.51%; calculated for $C_{32}H_{40}O_{23}Mn_3$ C: 40.14; H: 4.21%. IR (cm^{-1}): 3345 (br), 1681m, 1625m, 1599s, 1555 s, 1456 s, 1386 vs, 1306 m, 1246 s, 754 s, 665 m 466 m;; UV-vis (water): λ_{max} = 315 nm (log ε = 3.0).

Light green crystals. $[Ni(Sal)_2 \cdot 4H_2O]$ - 4. Elemental analysis found: C: 41.21; H: 4.37%; calculated for $C_{14}H_{18}O_{10}Ni$ C: 41.52; H: 4.48%. IR (cm^{-1}): 3390 (br), 1621s, 1605s, 1582 s, 1453 s, 1373 vs, 1246 s, 751 s, 661 m 421 m; UV-vis (water): λ_{max} = 315 nm (log ε = 3.1), λ_{max} = 511 nm (log ε = 0.04),. HRMS m/z: 334.7164; calculated for $[Ni(Sal)_2H]^+$ m/z: 334.6804

2.3. X-ray Crystallography

The single crystal X–ray diffraction data for 1-3 were collected using the SuperNova diffractometer equipped with a HyPix-3000 detector and a micro-focus CuKα radiation source (λ = 1.54184 Å) at the Centre for X-ray Diffraction Studies of Research park of St. Petersburg State University. The structure of complex was solved by the direct methods and refined in the full-matrix

anisotropic approximation for all non–hydrogen atoms. The hydrogen atoms of water molecule were found in differential Fourier maps and their parameters were refined using the riding model. The hydrogen atoms of the carbon-containing ligand were positioned geometrically and also refined by a riding model. All the calculations were performed by direct methods and using the SHELX–2014 program package [22, 23]. The crystallographic parameters and X-ray diffraction experimental-parameters are given in Table 1.

< Table 1>

2.4. Biological activity studies

All studies on the animals were carried out according to the principles set out in Directive 2010/63/EU of the European Parliament and of the EU Council of 22.09.2010 on the protection of animals used for scientific purposes.

Healthy sexually mature male laboratory Wistar rats, weighing 180-200 gr ("FSUE "Nursery of laboratory animals "Rappolovo") and quarantined for at least 14 days, were selected for the experiment. The experiments were performed on 140 male rats, characterized by an average motor activity and low emotionality in the "open field" test, and which make up the majority of the population; that is why they develop the most typical reaction to the effect of different factors, including the tested chemical compounds. The animals were kept under standard conditions of the vivarium at the temperature of 18–22ºC on the bedding «Rechofix MK 2000» (on the basis of ear shanks) with the natural 12-hour day-and-night cycle, with free access to water (State Standard 33215-2014 «The handbook of keeping and nursing laboratory animals. The regulation rules on housing equipment and procedure organization»), and to full-fledged granulated food of State Standard P-50258-92. The research was carried out at the Center for Collective Use of Scientific Equipment "Experimental physiology and Biophysics" of the Department of Human and Animal Physiology and Biophysics of V.I. Vernadsky Crimean Federal University. Detailed procedures regarding the study of the biological activity of the complexes are given in the Supporting information file.

3. Results and discussion

Synthesis and characterization of the complexes.

Title complexes 1-4 were obtained by direct one-step reaction of corresponding metal acetate and acetylsalicylic acid and isolated by the slow evaporation of aqueous solution at room temperature. Crude sample of 1-4 obtained directly from reaction according of XRD are mixtures of acetylsalicylates and salicylates of related metal in 1:2 molar ratio. Recrystallization from water lead to complete of hydrolysis of acetic group and target complexes are pure salicylates. Composition of 1-4 were determined according elemental and ESI-MS data complexes. Prepared compounds are air-stable and soluble in water, alcohols and dimethylsulfoxide. According to the molar conductivity values (Λ_M), the

complexes are non-electrolytes in water (Λ_M = 7-9 S·cm²·mol⁻¹, in 1 mM solution); thus, we may consider that the compounds remain stable and do not dissociate in water solution

Structural determination of the complexes

Zinc salicylate were previously obtained by reaction of sodium salicylate with zinc chloride and structurally characterized by spectral and XRD techniques [24,25]. P. Lemoine et all demonstrated that the use of sodium acetylsalicylate as a precursor made it possible to isolate zinc acetylsalicylate that was structurally characterized by XRD [21]. Our studies have shown that the reaction of acetylsalicylic acid with zinc acetate is accompanied by crystallization of zinc salicylate. The molecular structure of 1 is the close to the structure of $[Zn(sal)_2(H_2O)_2]$ reported by Klug [24] which was obtained by reaction of sodium salicylate and zinc chloride, so here we didn't describe it in detail.

Figure 1.

Cobalt(II) salicylates also described previously [26,27]. There are several polymorphs were obtained earlier by reaction of sodium salicylate with Co(II) salts meanwhile at this work it was found that the reaction of cobalt(II) acetate with acetylsalicylic acid leads to the crystallization of a new polymorph of cobalt salicylate previously uncharacterized. Complex 2 crystallizes in the monoclinic space group P 2_1/n. The molecular structure of 2 are centrosymmetric with the cobalt(II) ion sitting on a center of symmetry coordinated to two salicylate ligands and four aqua ligands related by the inversion center; therefore, the cobalt atom is six-coordinated having an octahedral geometry (Figure 2).

Figure 2

All the Co-O distances are of the same magnitude with the Co(1)-O carboxylate one being the shortest (Co1-O3= 2.040(2) Å) and the Co1-O2 water (2.141(2) Å) being the longest ones. Taking into account the small differences found in the Co–O distances in combination with the angles around cobalt (O-Co-O) being in the range of 86.94(6)-93.06(6)°, the octahedron displays a slight distortion. The carboxylate group in 2 coordinated in monodentate mode (C7-O6 = 1.245(3) Å and C7-O3 = 1.292(3) Å). This distance compares favorably with the range usually observed for cobalt complexes revealing monodentate coordination of the carboxylato group reported in the literature [30,31]. The two oxygens from the salicylate ligands and two oxygens from two aqua ligands occupy the octahedron's basal plane. Also, two oxygen atoms from two aqua ligands O2, O2' are lying at the axial position. The two salicylate ligands and the four aqua ligands are all lying at *trans* position to one another.

The structure of 2 are further stabilized by *intra* and *inter*-molecular hydrogen bonds. Intra-cluster hydrogen bonds are developed between the phenolic hydrogen atom and the coordinated carboxylato oxygen atoms. Supramolecular structures are further stabilized due to intermolecular interactions involving the aqua and salicylate ligands via O-H···O, C-H···O, and C-H···π interactions between neighboring molecules.

Unfortunately, we were unable to obtain high quality crystals to perform single-crystals XRD, however, powder XRD data indicate that nickel complex is isostructural to 2.

Compound 3 crystallizes in the monoclinic space group P 2_1/c. Complex exhibits 2D coordination networks in which trinuclear units $[Mn_3(Sal)_4(OAc)_2(H_2O)_4]$ are inter-linked by the acetate ligands. As shown in Fig. 3 , there are two crystallographically independent Mn(II) atoms in 3 (Mn1 and Mn2). The central Mn1 atom of the trimers is located on a crystallographic inversion center. The pseudo-octahedral coordination geometry of Mn(1) is defined by four salicylate oxygen from carboxylate group (O(1), O(1), O(4) and O(7)) and two oxygens from acetate-anions in trans positions. Mn(2) is coordinated by two oxygen atoms from water, two oxygen atoms from two different salicylate ligands and two oxygen atoms from two different acetate anions also forming six-coordinated environment (Mn(2)-O distances, 2.263(2)–2.282(2) Å; Mn(2)–O distances, 2.149(4)–2.226(4) Å). The Mn–O bond distances for both Mn1 and Mn2 fall in the range between 2.149(4) and 2.226(4) Å. Trinuclear core is strictly linear with Mn···Mn separation is 3.670 Å.

Figure 3.

Salicylate anion adopts the $(\eta^1\text{-}\eta^1)\text{-}\mu^2$ bidentate bridging coordination mode linking neighboring Mn1 and Mn2 atoms. Additionally, each pair of Mn(1) and Mn(2) ions are bridged by acetate-anion in $(\eta^2\text{-}\eta^1)\text{-}\mu^3$ tridentate coordination mode. Acetate-anion additionally connect individual trinuclear motifs into a polymeric 2D-layer assembly. The shortest distances between manganese ions in trinuclear cores is 4.797 Å. The intramolecular hydrogen bonds of hydroxyl groups of salicylate anions are present in crystal structures of 3. Furthermore O–H···O hydrogen bonds between coordinated and uncoordinated water molecules and carboxylic oxygen atoms of 3 extend the $Mn_3(Sal)_4(OAc)_2(H_2O)_4]n$ layer to 3D-supramolecular assembly (Figure 4).

Figure 4.

IR, UV-vis spectroscopy and TG measurements

Spectral properties of all three complexes are in good agreement with structural data. Infrared spectra of the complexes 1-4 comprise bands confirming the presence of all characteristic functional groups. The presence of water molecules in title complexes is confirmed by one rather broad and asymmetrical O–H absorption band showing one maximum at 3345-3410 cm^{-1} due to similarly strong hydrogen bonds of both water molecule hydrogen atoms.

Typical carboxylate stretching frequencies for asymmetric stretching vibrations $\nu_{as}(COO^-)$ in the range 1555-1608 cm^{-1} and for symmetric stretching vibrations $\nu_{sym}(COO^-)$ in the region 1371-1386 cm^{-1}. The difference between asymmetric and symmetric stretching vibrations (Δ) that usually used to assign the coordination mode of carboxylate anion for 1, 2 and 4 are in 237-214 cm^{-1} range and indicative of

asymmetrically binding mode of binding, while for 3 Δ is 167 cm^{-1} and consistent with bidentate chelating coordination of carboxylate group. Notably that intense band of ester group at 1750 cm^{-1} registered for starting aspirin and crude samples is absent which is a weighty argument in favor of complete hydrolysis of the acetyl group during recrystallization. Stretching vibrations $\nu(C\text{-}O)_{OH}$ are found at 1241-1246 cm^{-1} and practically does not shift upon coordination. Characteristic absorption bands of stretching vibrations ν(M-O) appear, below 460 cm^{-1}.

The electronic spectra of aqueous solution of all studied complexes exhibit intraligand π-π* transition bands at 314-315 nm that bathochromically shift with compare with free salicylate-anion. Broad asymmetric ligand field bands attributed to d→d transitions with a maximum in the position at 511 nm were found for complex 2 assigned to $^4T_{1g}(F)$–$^4T_{1g}(P)$ transition in octahedral high-spin Co(II) containing complexes with CoO_6 chromophore. For nickel complex $^3A_2$-$^3T_1$ transition typical for NiO_6 chromophore was found at 673 nm.

The thermal behavior of 1-4 was studied by TGA techniques. Complexes demonstrate the multi-stage decompositions upon heating and overall weight loss is in agreement with stoichiometry. Complex 1 is stable up to 95 °C. The first weight loss of 9.8 % in the region of 95–175 °C (peak at 154 °C) corresponds to the release of the lattice and coordinated water molecules (calculated 9.6 %). The residual framework starts to decompose beyond 215 °C and does not stop until heating ends at 700 °C. The final product of thermal decomposition was ZnO (the experimental mass 22.8%, the theoretical mass 21.6%).

Thermal behaviors of cobalt and nickel complexes are close to each other. For 2 and 4 the weight loss of the coordinated water occurs in the range of 60–240 °C with hardly to identify each steps. However, the overall weight loss is about which corresponds to the release of four water molecules (calculated 17.33%). The rapid decomposition process occur up to 260-270 °C with the drop of weight loss around 46.0% corresponding the release of 1 mol of phenol together 1 mol of carbon monoxide (calculated 47.9%) and then, a series of complicated weight losses were observed as the temperature increased until heating ends at 700 °C.

For 3, the first weight loss of 5.75 % in the of 95−140 °C range corresponds to release of the lattice water molecules (calculated 5.96%). The second step of weight loss of 49 % in the 190−340 °C range corresponds to the release of the coordinated water, and products of decompositions of acetate and salicylate anions and then, a series of complicated weight losses were observed as the temperature increased until heating ends at 700 °C.

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Indices of the cardiorespiratory system

It was found that in animals of control group at introduction of saline the examined parameters

of cardiorespiratory system (CRS) were within physiological norm (see Table 2, 3).

In the first series of the experimental study, the administration of ASA at a dose of 5 mg/kg resulted in a significant decrease in the HR score per 22.5% ($p \leq 0,05$) relative to that in the control group of animals. A similar trend was recorded when the dose of ASA increased to 10 mg/kg: HR decreased by 21.8% ($p \leq 0,05$) relative to the values of these indicators in the control group of animals (see Table 2). The remaining animal CRS values did not change significantly when the test compounds were administered at a dose of 5 and 10 mg/kg.

The results of the second series of experiments confirmed the data obtained in the 1st series. Thus, in animals with intraperitoneal administration of ASA at doses of 5 and 10 mg/kg, a decrease in the heart rate of bradycardia was observed. Moreover, this effect was almost identical in doses of 5 and 10 mg/kg. i.e. was not dose dependent.

By administering of **2** (see Table 2) at a dose of 5 mg/kg, HR decreased by 14.1% ($p \leq 0.05$) relative to the values of this indicator in the control group of animals. Increasing the dose of **2** to 10 mg/kg also resulted in a significant 6.9% reduction in HR ($p \leq 0.05$) relative to the values in the control group of animals. At the same time, the blood pressure and respiratory rate in animals injected with **2** did not significantly change. However, with an increase in the dose of **2** to 10 mg/kg, a significant increase in HR by 19.2% ($p \leq 0.05$) and a significant decrease in DAP by 14% ($p \leq 0.05$) were recorded relative to the values of these indicators in animals receiving ASA injections of the same dosage. Thus, **2** at doses of 5 mg/kg and especially 10 mg/kg reduces the negative chronotropic effect characteristic of ASA.

The administration of **1** to animals (see Table 2), as with the administration of ASA and **2** was accompanied by a decrease in HR relative to the test indicators values in the control group of animals. Thus, when Zn^{2+} salicylate was administered to animals at a dose of 5 mg/kg, a significant decrease in HR by 17% ($p \leq 0,05$) was recorded in relation to the values of these indicators in the control group of animals. Increasing the dose of this compound to 10 mg/kg also resulted in a 14.3% reduction in HR ($p \leq 0.05$) relative to the values in the control group of animals. However, along with this, there was an increase in RR by 56.3% ($p \leq 0.05$), a decrease in SBP by 5.1% ($p \leq 0.05$), an increase in DBP by 14.7%, which led to a significant decrease in PP by 38.3% ($p \leq 0.05$) compared to similar indicators in the control group of animals.

Thus, the reaction of animal CRS to the administration of **1** at a dose of 5 mg/kg was unidirectional with ASA, which manifested itself in a negative chronotropic action. Increasing the dose to 10 mg/kg led to a decrease in the severity of the negative chronotropic effect on the heart rhythm of the test compound, as well as the appearance of new properties in **1** other than ASA, namely, an increase in DBP and RR and a decrease in SBP and PP.

< Table 2>

When **3** was administered to animals at a dose of 5 mg/kg, the most pronounced changes in rat CRS rates occurred, with both ASA and **1** and **2** which was expressed in a significant increase in HR by 5%, DBP - by 5%, PP - by 15% (see Table 3). Increasing of the dose of **3** to 10 mg/kg, HR increased by 7%, however, PI, on the contrary, decreased by 14% relative to the values in the control group of animals, and the remaining indicators did not significantly change. At the same time, RR in animals with **3** 10 mg/kg was 25% lower compared to that in rats with the same compound at a dose of 5 mg/kg.

Thus, the administration of **3** to animals (see Table 3) resulted in effects other than the precursor molecule (ASA), which manifested itself primarily in a positive chronotropic effect and an increase in DBP. At the same time, the detected effects of **3** showed dose dependence: tachypnea was registered at a dose of 5 mg/kg, and tachypnea was replaced by bradypnea at a dose of 10 mg/kg.

When **4** was administered at a dose of 5 mg/kg, there was a significant 15% reduction in RR compared to control group of animals (see Table 3). With an increase in the dose of the test compound to 10 mg/kg, the orientation of the animal CRS reaction to the administration of **4** remained, however, the severity of the reduction in RR increased and amounted to 74% of that in the control group of animals. Thus, **4**, in contrast of ASA, does not affect HR, but leads to an increase in DBP at both doses tested and a decrease in RR, especially expressed at a dose of 10 mg/kg, i.e., bradypnoea development.

< Table 3>

Indices of skin microcirculation of rats under action of acetylsalicylic acid and 1-4

The results of the study showed that the administration of ASA at doses of 5 mg/kg and 10 mg/kg led to a significant increase in the amplitudes of endothelial oscillations (Ae), neurogenic (An), respiratory (Ap) rhythms, an blood of pressure (BP) relative to those in the control group of animals (see Table 4, 5).

In general, the dynamics of changes in MR values when ASA is administered to animals indicates an increase in endothelium-dependent vasodilation, a decrease in peripheral resistance, an increase in blood flow to the nutritive microvascular bed, an improvement in venular outflow. Changes in these indicators reflects of the development to skin microvessels hyperemia. At the same time, dose dependence in the response of skin microcircuit to the action of ASA in the analyzed concentrations was not detected.

Using of complexes **1-4** instead of ASA lead to significant change in the parameters of skin microhemodynamics of animals (see Table 4, 5). So, with the introduction of complex **2** at a dose of 5 mg/kg, the oscillation amplitudes of all rhythms increased. Thus, the vasotropic effect of **2** is similar to that of ASA and is expressed in the development of vasodilation and hyperemia, however, unlike ASA, compound **2** more increases the metabolic activity of endothelium and reduces the tone of precapillary metarterioles due to the development of Ca^{2+} dependent muscle relaxation (Am increase), however, is

significantly inferior to ASA in the ability to modulate blood flow in all frequency bands (reduced MSD) and activation of vasomotor control of microvascular bed tone (reduced Kv).

When complex **1** was administered to animals, as well as complex **2**, it caused an increase in all oscillatory and non-oscillatory parameters of microcirculation and, accordingly, the development of vasodilation. It can be concluded that complex **1**, like the initial substance of ASA, leads to the development of vasodilation and hyperemia, however, unlike ASA, this effect is due to an increase in the metabolic activity of the endothelium, a decrease in the Ca^{2+}-dependent tone of precapillary sphincters and precapillary metarterioles, an increase in the flow of arterial blood into the microarm and activation.

When administering complex **4** at a dose of 5 mg/kg (see Table 5), there was only an increase in Ae by 75.1% ($p \leq 0,05$) and a decrease in non-oscillatory basal blood flow: MSD - by 62.3% ($p \leq 0,05$) and Kv - by 66.7% ($p \leq 0,05$), respectively, relative to values these indicators in the control group of animals. Thus, the vasotropic effect of complex **4** is to increase the metabolic activity of the endothelium and reduce the modulation of the microcircuit, this effect is manifested only at a dose of 5 mg/kg, and at a dose of 10 mg/kg this compound is not effective.

When complex **3** was administered (see Table 5) to animals at a dose of 5 mg/kg, it increased the metabolic activity of the endothelium. With an increase in the dose of compound **3** to 10 mg / kg, the maximum increase in Ae was observed, which was reflected in an increase in tissue perfusion and an improvement in venous outflow. Thus, complex **3**, as well as complex **4** inhibiting almost all units of microcirculation regulation, prevents the development of hyperemia observed with the action of ASA.

< Table 4>

< Table 5>

Antioxidant activity of the complexes

Nowadays, antioxidants that exhibit free radical scavenging activity are receiving increasing attention. Free radicals are species which have unpaired electron(s) having an important role in the inflammatory process. The transfer of the unpaired electron(s) of free radicals to a neighboring molecule will induce the ignition of chain reactions which are responsible for a variety of undesired side-effects in the organisms including swelling, inflammations, or even cancer. Antioxidants can scavenge free radicals and/or inhibit the production of novel radicals and, subsequently, terminate the radical-initiated side reactions. Consequently, compounds with antioxidant properties may be expected to offer protection for a variety of undesired side-effects in the organisms including swelling, inflammations, or even cancer. ASA and mainly its salicilate metabolite strongly scavenge HO radical [28,29]. The major evidence for this activity is the ability of ASA and SA to undergo aromatic hydroxylation by reacting with $HO\cdot$. At the same time, there is no information in the literature on the antioxidant activity of transition metal complexes based on salicylic acid. Within this context we used DPPH and ABTS-

radical method to evaluate antioxidant activity of 1-4. Results are summarizes in table 6.

< Table 6>

Our results demonstrate that the ability of ASA and complexes 1 and 4 to scavenge DPPH radical (RA% = 21–28 %) is mainly time-independent, while the activity of complexes 2 and 3 against the radical presents a noteworthy increase during time. The DPPH scavenging activity of 2 and 3 was found in the range 54–60 % indicating about noticeable antioxidant activity. Despite of higher activity of 2 an3 obtained value is lower than that of the reference compounds NDGA

The scavenging of the cationic ABTS radicals is applicable for screening the total antioxidant activity. The ABTS scavenging activity of the complexes 1-4 (ABTS % = 68–76%) was significant but lower than that of the reference compound trolox (ABTS % = 92%) with complexes 2 (ABTS% = 84 %) and 3 (ABTS % = 88 %) being the most active ABTS scavengers. Similar scavenging selectivity has been reported in the literature for many transition metal complexes showing selective scavenging activity against either DPPH radicals or ABTS radicals [30-32]. Furthermore, we may conclude that the present complexes 1-4 may exhibit selective scavenging ability towards ABTS radicals in contrast to DPPH radicals

In general, the complexes exhibit higher radical scavenging than the corresponding free ASA; we may, thus, conclude that the coordination of the ASA to metal centers enhances their antioxidant ability. Obtained results is quite high to be considered as potential antioxidants.

Conclusion

Thus, our approach in creating new coordination compounds in which, in addition to a ligand with bioactive properties, there is a transition metal-microelement, made it possible to obtain new compounds that modulate the available biological properties of ASA and exhibit new ones.

In general, the results of the study showed that reaction of metals ions (Co^{2+}, Zn^{2+}, Mn^{2+}, and Ni^{2+}) with ASA changes the ability of the precursor molecule to affect peripheral microcirculation. It is this property that is essential for compounds used for the prevention and treatment of cardiovascular diseases. At the same time, complexes **1** and **2** lead to the development of vasodilation and hyperemia, which in some parameters exceeds that with the introduction of ASA. Complexes **3** and **4**, on the contrary, cause a decrease in almost all microcirculatory parameters and inhibition of hyperemia caused by ASA. The complexes were more active than the corresponding free ASA in regard to the ability to scavenge in vitro DPPH, and especially ABTS radicals.

Thus, the new coordination compounds obtained are promising for further studies of their biological and pharmacological effects. The results of these experiments allow further deeper

investigation of the therapeutic potential of complexes, creating new compounds for analysis.

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6. Supplementary data

CCDC 2085284-2085286 contains supplementary crystallographic data for compounds **1, 2** and **3**. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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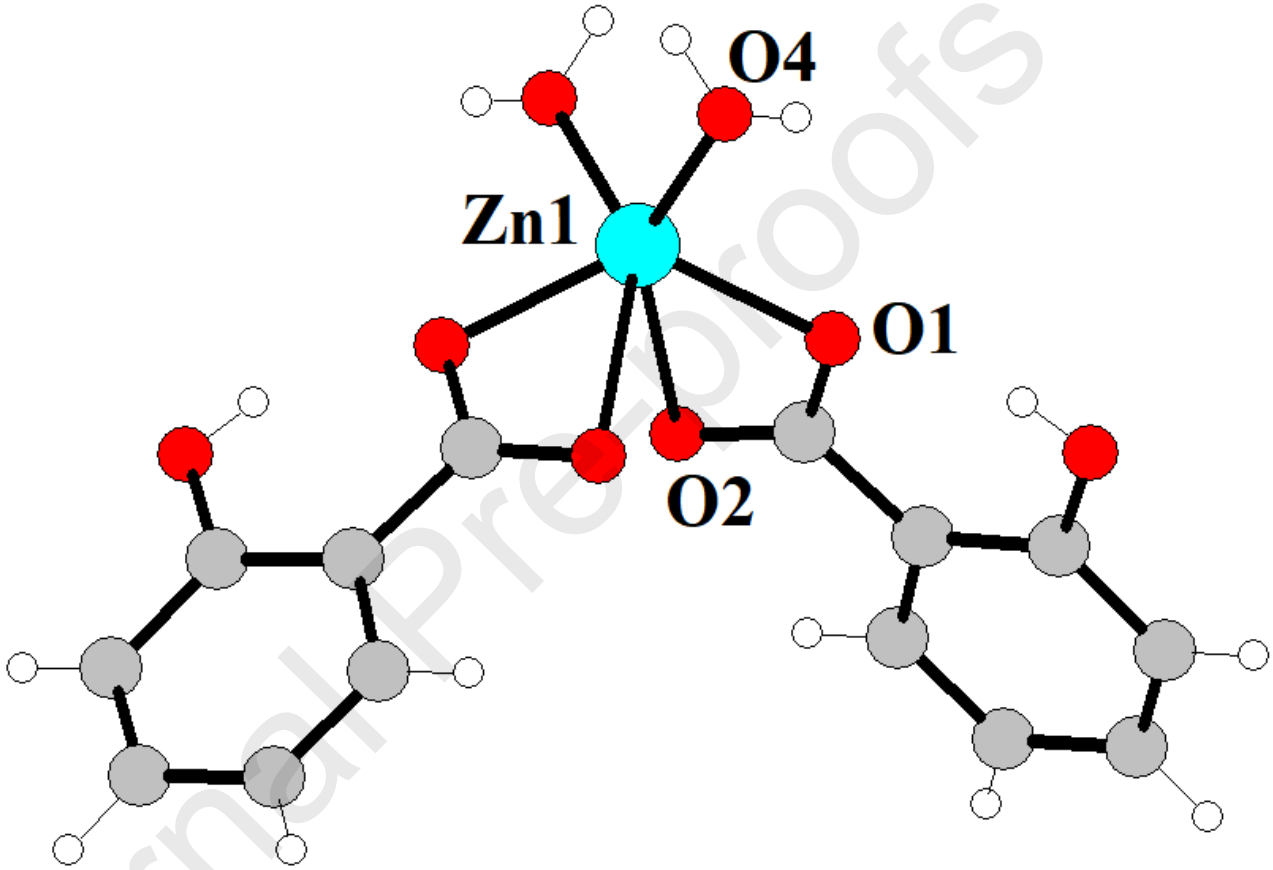

Figure 1.

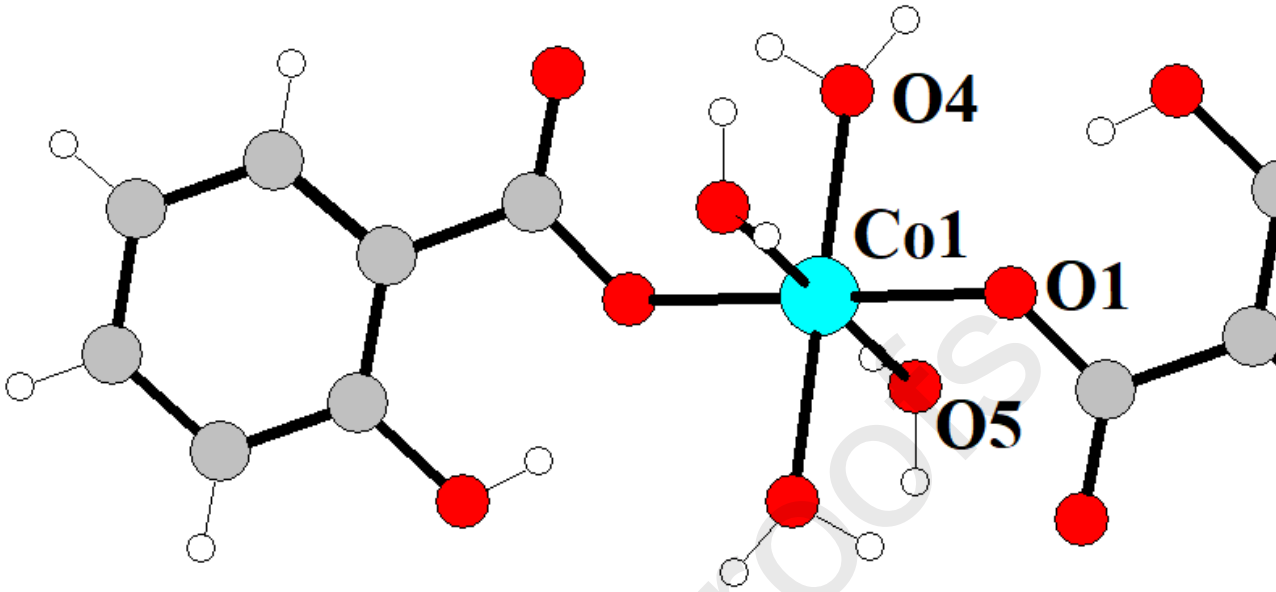

Figure 2.

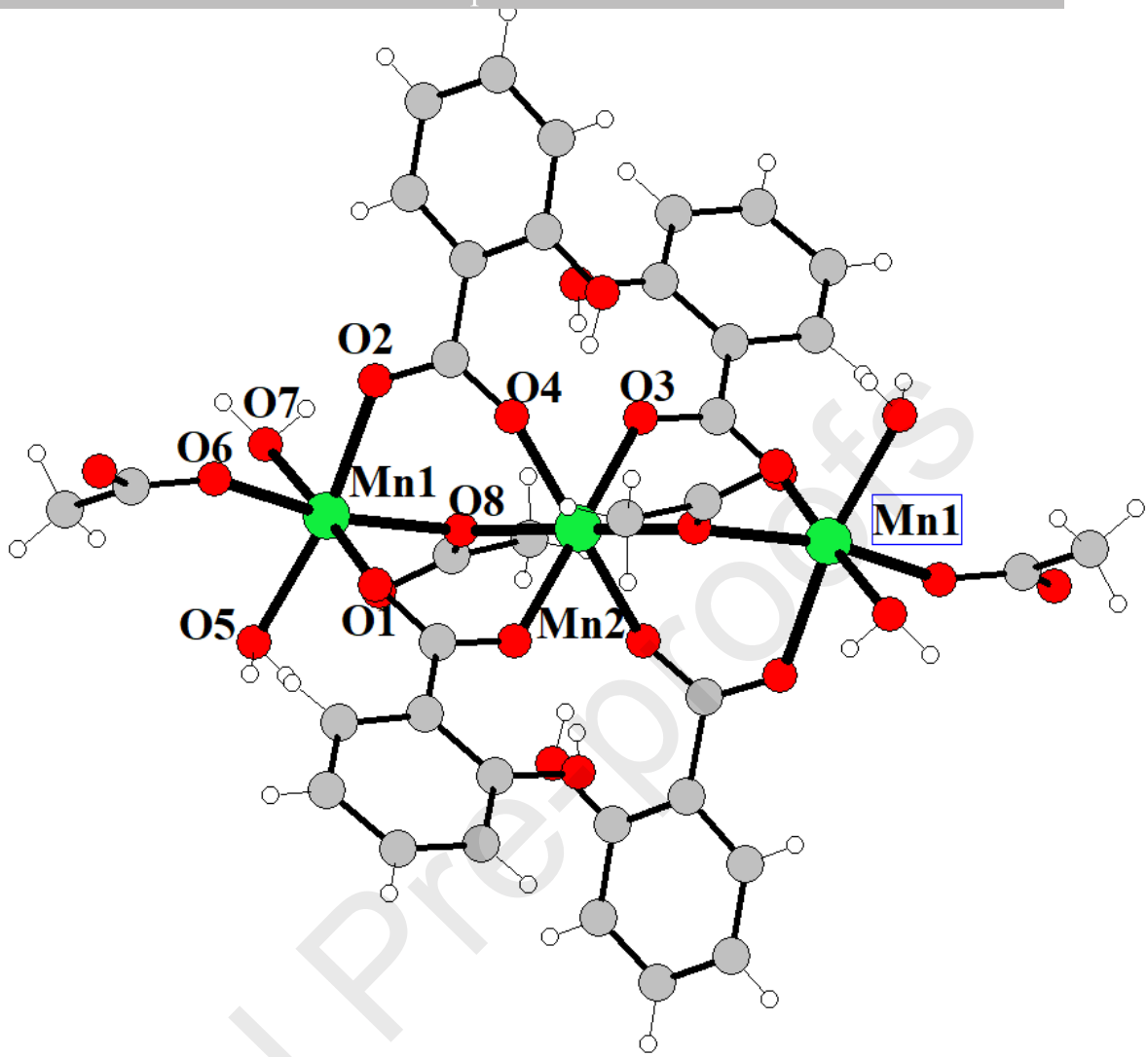

Figure 3.

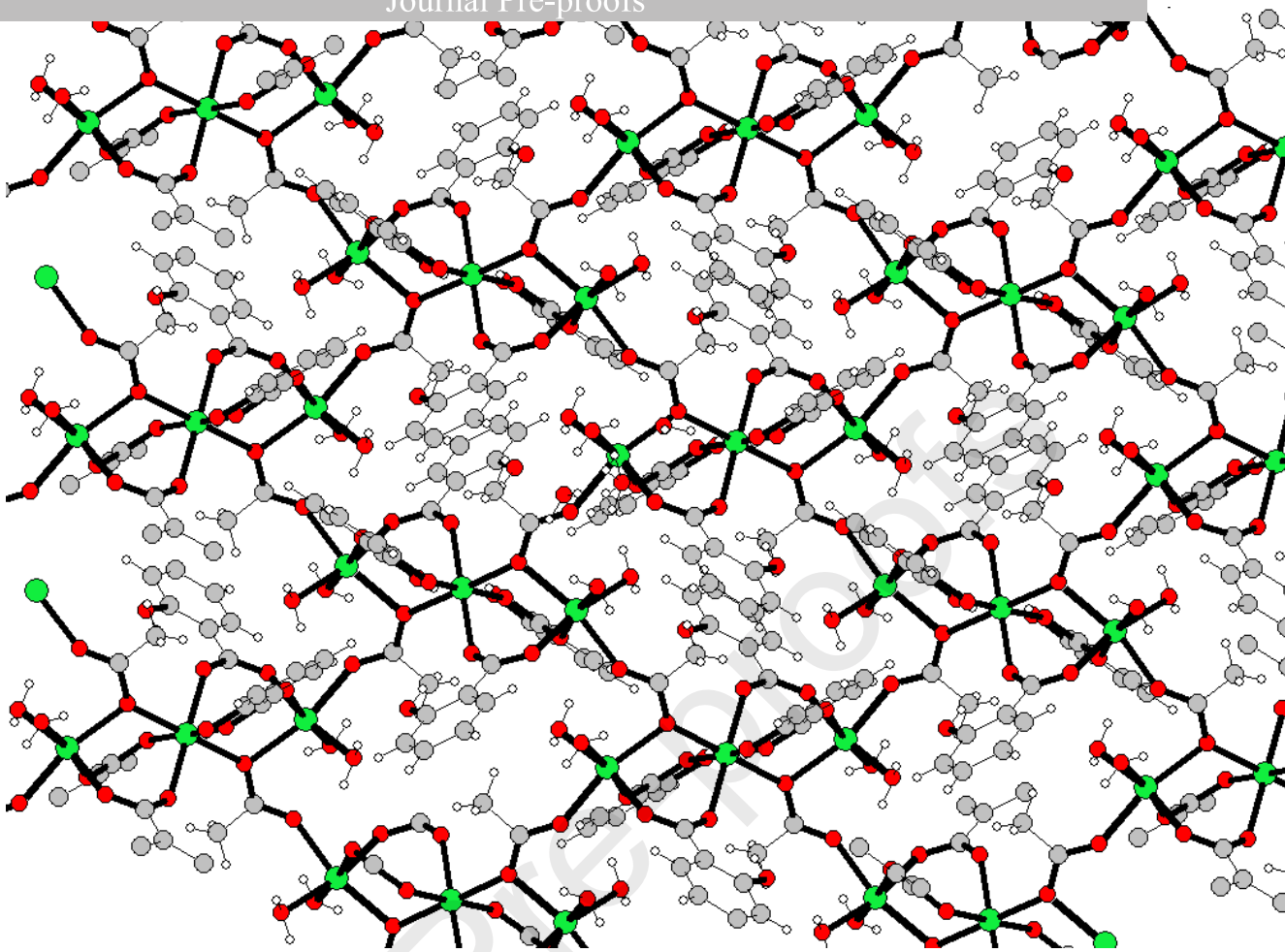

Figure 4.

Captions

Figure 1. Molecular structure of cobalt(II) salicylate – complex 1.

Figure 2. Molecular structure of cobalt(II) salicylate – complex 2.

Figure 3. Molecular structure of manganese(II) salicylate – complex 4.

Figure 3. Crystal structure of 4. View along b-axis

Table 1. Crystal data and structure refinements for the reported compounds.

Parameter/Complex	**1**	**2**	**3**
Formula	$C_{14}H_{12}O_8Zn$	$C_{14}H_{16}CoO_{10}$	$C_{32}H_{42}Mn_3O_2$ 5
Crystal system	monoclinic	monoclinic	monoclinic
Space group	C2	P 2_1/n	I 2/a
a, Å	15.4415(7)	6.82280(10)	9.35230(10)
b, Å	5.3633(3)	5.11540(10)	16.0918(2)
c, Å	8.9178(4)	22.7707(5)	27.9243(4)
β°	93.145(4)	91.080(2)	96.2110(10)
V, Å 3	737.43(6)	794.59(3)	4177.81(9)
Z	2	2	_4
μ_{Mo}. mm^{-1}	2.709	8.988	8.072
Parameters	107	117	287
Number of symmetry-independent reflections/ Number of reflections with I > 2σ(I)	1487/1474	1652/1568	3951/3771
GOOF	1.061	1.069	1.058
R(I > 2σ(I))	0.0283	0.0451	0.0376
wR_2	0.0742	0.1222	0.1027

Table 2. The characteristics of the cardiorespiratory system in rats after injecting the

acetylsalicylic acid (ASA) and complexes **1** and **2** at different doses

Group		SBP, mm m.c.	DBP, mm m.c.	PP mm m.c.	HR, b./min	RR, r.r./min
Control	(1)	118.41±1.66	74.32±1.49	44.11±1.56	468.19±9.22	98.14±4.34
ASA	5 mg/kg (2)	114.20±1.86	76.53±1.05	37.71±2.33	363.25±10.72 $p_1 \leq 0.05$	98.42±3.27
	10 mg/kg (3)	117.71±1.89	79.21±1.03	38.55±1.85	366.15±10.73 $p_1 \leq 0.05$	100.15±3.23
1	5 mg/kg (4)	114.73±0.72	78.40±1.60	36.13±3.53	389.40±6.14 $p_1 \leq 0.05$	99.53±2.43
	10 mg/kg (5)	112.47±0.32 $p_1 \leq 0.05$ $p_3 \leq 0.05$	85.27±0.38 $p_1 \leq 0.05$	27.12±1.05 $p_1 \leq 0.05$ $p_3 \leq 0.05$	402.27±0.34 $p_1 \leq 0.05$	153.87±0.46 $p_1 \leq 0.05$ $p_3 \leq 0.05$
2	5 mg/kg (6)	114.73±4.01	72.07±1.02	42.66±1.14	403.00±7.92 $p_1 \leq 0.05$	97.53±5.15
	10 mg/kg (7)	111.67±0.61	68.13±0.26 $p_3 \leq 0.05$	43.54±1.31	436.87±2.75 $p_1 \leq 0.05$ $p_3 \leq 0$	95.73±1.46

					.05	

Note: M – mean, M±m –error of mean, p1-7 – the confidence level of indices difference according to Mann-Whitney test concerning the corresponding animal groups; SBP – a systolic blood pressure;

DBP – a diastolic blood pressure; HR – heart rate; RR – a respiratory rate.

Table 3. The characteristics of the cardiorespiratory system in rats after injecting the

acetylsalicylic acid (ASA) and complexes **3** and **4** at different doses

Group		SBP. mm m.c.	DBP. mm m.c.	PP mm m.c.	HR. b./min	RR. r.r./min
Control	(1)	113.14 ±1.32	72.20 ±0.91	41.12 ±0.98	378.24± 15.23	109.67 ±4.38
ASA	5 mg/kg (2)	114.06 ±1.18	70.17 ±1.07	43.09 ±0.99	334.08± 16.72 $p_1 \leq 0.05$	109.19 ±3.59
	10 mg/kg (3)	112.11 ±1.18	70.07 ±0.94	41.93 ±0.90	347.63± 6.31 $p_1 \leq 0.05$	106.8± 4.38
3	5 mg/kg (4)	114.60 ±1.94	75.73 ±1.25 $p_1 \leq 0.05$ $p_2 \leq 0.05$	38.87 ±1.41	396.13± 11.85 $p_1 \leq 0.05$ $p_2 \leq 0.05$	126.07 ±8.26 $p_1 \leq 0.05$ $p_2 \leq 0.05$ $p_5 \leq 0.05$ $p_6 \leq 0.05$
	10 mg/kg (5)	112.40 ±2.08	75.07 ±0.79 $p_3 \leq 0.05$	37.33 ±1.23	406.73± 9.86 $p_1 \leq 0.05$ $p_3 \leq 0.05$ $p_7 \leq 0.05$	94.53± 1.79 $p_1 \leq 0.05$ $p_3 \leq 0.05$ $p_4 \leq 0.05$ $p_7 \leq 0.05$
4	5 mg/kg (6)	113.73 ±1.95	73.53 ±1.07 $p_2 \leq 0.05$	40.12 ±0.98	412.87± 16.56 $p_7 \leq 0.05$	93.13± 2.71 $p_1 \leq 0.05$ $p_4 \leq 0.05$ $p_7 \leq 0.05$
	10 mg/kg (7)	111.20 ±2.09	75.67 ±1.08 $p_3 \leq 0.05$	35.53 ±1.11	333.13± 12.89 $p_5 \leq 0.05$ $p_6 \leq 0.05$	81.01± 2.16 $p_1 \leq 0.05$ $p_3 \leq 0.05$ $p_5 \leq 0.05$ $p_6 \leq 0.05$

Notes: the same as in table 2.

Table 4. Indicators of the skin microcirculation in rats under the action of acetylsalicylic acid

(ASA) and complexes **1** and **2** in different doses

Group		Oscillatory indices					Non-oscillatory indices		
		Aear b. unit	Anarb. unit	Amar b. unit	Apar b. unit	Arar b. unit	BPperf. unit	MSDperf. unit	Kv. %
Control	(1)	3.2±0.3	3.5±0.4	3.1±0.3	2.4±0.2	3.1±0.4	4.0±0.7	3.6±0.2	54.4±0.9
ASA	5 mg/kg (2)	4.8±0.5 p_1≤0.05 p_4≤0.05 p_6≤0.05	5.4±0.6 p_1≤0.05	3.9±0.6	4.1±0.7 p_1≤0.05	4.4±0.9	7.2±0.8 p_1≤0.05 p_6≤0.05	3.1±0.5	56.7±0.5
	10 mg/kg (3)	5.0±0.6 p_1≤0.05 p_5≤0.05	5.5±0.5 p_1≤0.05	4.2±0.6	4.2±0.6 p_1≤0.05	4.6±0.8	7.3±0.5 p_1≤0.05	3.1±0.5	57.1±0.7 p_1≤0.05
1	5 mg/kg (4)	6.5±0.5 p_1≤0.05 p_2≤0.05	6.5±0.6 p_1≤0.05	5.2±0.9 p_1≤0.05	4.9±0.2 p_1≤0.05	6.1±0.8 p_1≤0.05	7.1±0.5 p_1≤0.05	4.5±0.5 p_4≤0.05	61.9±0.9 p_1≤0.05 p_2≤0.05 p_4≤0.05
	10	5.	6.0	4.	4.	5.	7.5	3	64

	mg/kg (5)	3±0.1 p_1 ≤0.05 p_5 ≤0.05 p_6 ≤0.05	±0.6 p_1≤ 0.05	7±0.5 p_1 ≤0.05	3±0.3 p_1 ≤0.05	2±0.8 p_1 ≤0.05	±0.4 p_1≤ 0.05	.8±0.1 p_5≤0.05	.5±0.8 p_1 ≤0.05 p_3 ≤0.05 p_5 ≤0.05
2	5 mg/kg (6)	5. 7±0.9 p_1 ≤0.05 p_2 ≤0.05	5.8 ±0.9 p_1≤0.05	5. 3±0.95 p_1 ≤0.05	5.3 ±0.8 p_1 ≤0.05	5. 7±0.7 p_1 ≤0.05	6.2 ±0.6 p_1≤ 0.05	1 .9±0.3 p_1≤0.05	28 .5±0.6 p_1 ≤0.05 p_2 ≤0.05
	10 mg/kg (7)	6. 9±0.8 p_1 ≤0.05 p_3 ≤0.05	6.5 ±0.5 p_1≤ 0.05	6. 0±0.4 p_1 ≤0.05 p_3 ≤0.05	5. 0 ±0.5 p_1 ≤0.05	5. 2±0.8 p_1 ≤0.05	6.8 ±0.5 p_1≤ 0.05	1 .6±0.1 p_1≤0.05 p_3≤0.05	32 .8±0.9 p_1 ≤0.05 p_3 ≤0.05

Note: M –mean, M ± m –error of the mean, p1-7 – the level of significance of differences according to the Mann-Whitney criterion relative to those in the groups indicated 1 to 7, respectively; Ae – the amplitudes of endothelial genesis, An – the amplitude of neurogenic oscillations, Am – the amplitude of myogenic oscillations, Ar – the amplitude of respiratory oscillations, and Ap – the amplitudes of pulse oscillations. BP – an blood of pressure, MSD – mean square deviation (flux, MSD, perf. Units),

Kv – the coefficient of variation (KV,%).

Table 5. Indicators of the skin microcirculation in rats under the action of acetylsalicylic acid

(ASA) and complexes 3 and 4 in different doses

Group		Oscillator indicators					Non-oscillatory indicators		
		Aear b. unit	Anar b. unit	Amar b. unit	Apar b. unit	Arab. unit	BP. perf. unit	MSD perf. unit	Kv. %
Control	(1)	6.3±0.7	15.3±1.6	16.6±1.2	13.5±0.8	9.4±0.7	8.0±0.5	3.9±0.4	49.7±5.7
ASA	5 mg/kg (2)	9.2±1.8 p1≤0.05	23.7±1.6 p1≤0.05	21.3±1.5	23.2±0.9 p1≤0.05	13.3±4.0	14.4±0.7 p1≤0.05	3.3±0.3 p1≤0.05	51.7±5.8
	10 mg/kg (3)	9.9±1.2 p1≤0.05	24.3±0.4 p1≤0.05	22.7±0.8	23.7±0.9 p1≤0.05	13.8±1.5	14.8±0.3 p1≤0.05	3.4±0.3 p1≤0.05	52.3±9.9
3	5 mg/kg (4)	11.2±2.1 p1≤0.05	13.0±1.3	15.6±1.6	13.5±0.6 p5≤0.05	11.6±0.9	5.7±0.5 p6≤0.05 p5≤0.05	2.3±0.3	40.3±4.8 p6≤0.05
	10 mg/kg (5)	13.4±1.4 p1≤0.05 p3≤0.05	16.1±1.3	11.9±1.5 p7≤0.05	9.5±1.2 p1≤0.05 p3≤0.05 p4≤0.05 p7≤0.05	8.1±1.5	11.1±0.8 p1≤0.05 p3≤0.05 p4≤0.05 p7≤0.05	2.7±0.9	24.5±8.5

4	5 mg/kg (6)	11.1±1.3 p1 ≤0.05	17.8±3.1	16.4±3.5	10.8±1.3	10.0±1.3	9.5±0.4 p2 ≤0.05	1.5±0.2 p1≤0.05	16.5±3.4 p1≤0.05 p2≤0.05 p4≤0.05
	10 mg/kg (7)	9.5±0.8	17.0±1.9 p3 ≤0.05	17.6±1.3 p3 ≤0.05 p5 ≤0.05	13.2±0.8 p5 ≤0.05	9.2±0.7 p3≤0.05	9.0±1.2 p3 ≤0.05	2.0±0.3	24.1±5.0

Notes: the same as in table. 4.

Table 6. DPPH scavenging ability (RA %, for 0.1mM), superoxide radical scavenging activity

(ABTS %, for 0.1mM), for the acetylsalicylic acid and the complexes 1-4.

Compound	RA% (60 min)	ABTS%
ASA	22.1	71.1
1	21.0	68.4
2	54.8	84.1
3	60.3	88.3
4	28.4	76.2
NDGA	82.1	-
Trolox	-	91.4

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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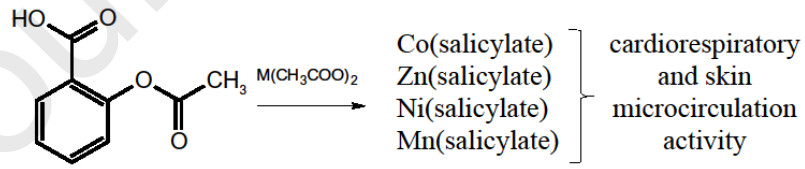

Co(II), Zn, Ni(II) and Mn(II) salicylates were successfully prepared by the reaction of aspirin with respected 3d acetates.

The cardiorespiratory and skin microcirculation activity of these metal complexes was evaluated