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The Search for Domestic Pharmaceutical Substances among Metal Complexes Based on (Hetero)arylamides of 4-Aryl-2-hydroxy-4-oxo-2-butenoic Acids

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Abstract—The data obtained on the synthesis and search for biological activity among metal complexes based on 4-aryl-2-hydroxy-4-oxo-2-butenoic acid (hetero)arylamides were integrated. The data on the antimicrobial, anti-inflammatory, analgesic, hypoglycemic, antihypoxic, and immunotropic activities of the synthesized compounds were analyzed. The relationship between the chemical structure and biological activity of chelate complexes was discussed and some regular features were identified. Promising compounds for further research and development of new domestic pharmaceutical substances were found.

Keywords: metal complexes of 4-aryl-2-hydroxy-4-oxo-2-butenoic acid (hetero)arylamides, activity

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INTRODUCTION

It is known that the first data on derivatives of 2,4-dioxobutanoic acids appeared in the scientific literature in the late 19th century and were mainly concerned with the synthesis of their esters [1, 2]. In the second half of the 20th and beginning of the 21st century, studies of the chemistry and pharmacological activity of 4-aryl-2-hydroxy-4-oxobut-2-enoic acid derivatives have been actively developed in Russia [3–5] and abroad [6–10]. In particular, compounds possessing antioxidant activity in vitro towards liver cells were found [6], potential neuroprotective agents were detected [7], and data on the anticancer action of this class of compounds were reported [11, 12]. A promising line of research is aimed at identification of compounds with antimicrobial [13–15] and antiviral activities [7–9, 16–19]. Compounds having a pronounced effect on the hemostasis system have been found [20–23].

According to the modern concept of metal–ligand homeostasis [24, 25], complex formation with active and low-toxic ligands is an important current trend of medicinal chemistry. The presence of the 1,3-dicarbonyl moiety in the molecules of 2,4-dioxobutanoic acid derivatives determines the possibility of active chelation of essential metals. Currently, research and development works carried out in Italia [26–29], USA [30], and Serbia [31–34] have revealed compounds with clear-cut cytotoxic, antimicrobial, and antiviral action. In Russia, studies on the synthesis of complexes based on 4-aryl-2-hydroxy-4-oxobut-2-enoic acid derivatives are carried out in Perm, Yekaterinburg [35–38], Orenburg [39–41], and so on.

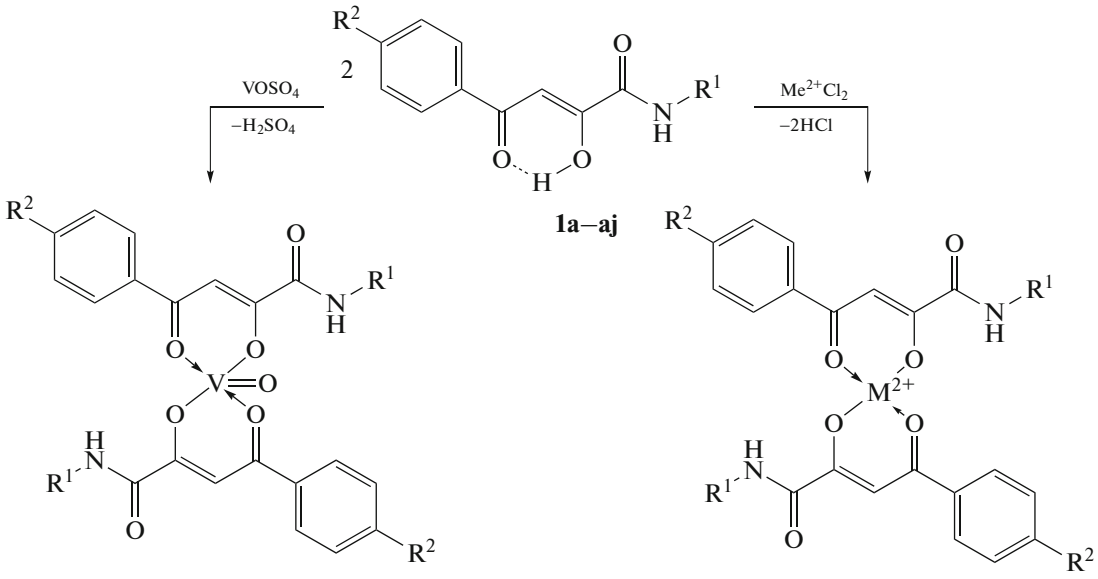
(Hetero)arylamides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids (**1**), which have various types of pharmacological activity, are promising ligands for the synthesis of biologically active chelates [42–48]. The chemical modification of these ligands to give metal complexes can considerably change the intensity of pharmacological action and also lead to the discovery of new types of biological activity. The chosen complexing metals include manganese, cobalt, nickel, copper, and zinc as essential elements; vanadium as a trace element with potential influence on insulin resistance; and cadmium and mercury to enhance the antibacterial action of the ligands.

The purpose of the present work is to integrate and systematize the published results of the last decade concerning complexes of 4-aryl-2-hydroxy-4-oxobut-2-enoic acid (hetero)arylamides with the goal to analyze the established chemical structure–biological activity relationships and to search for potential domestic pharmaceutical substances.

EXPERIMENTAL

The metal complexes based on (hetero)arylamides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids were synthesized by reactions of 4-aryl-2-hydroxy-4-oxobut-2-enoic acid (hetero)arylamides (**1a**–**aj**) with vanadyl sulfate or with manganese, cobalt, nickel,

copper, zinc, cadmium, or mercury dichloride at a ligand to metal ratio of 2 : 1. The reactions gave the corresponding bis{3-aryl-1-[(hetero)aryl]carboxamido-1,3-propanedionato}oxovanadium (**2a**–**x**) or -manganese (**3a**–**i**), -cobalt (**4a**–**n**), -nickel (**5a**–**m**), -copper (**6a**–**q**), -zinc (**7a**–**k**), -cadmium (**8a**–**k**), or -mercury (**9a**–**d**). The reactions proceeded in ethanol, a water–ethanol mixture (1 : 1), or a 1,4-dioxane–ethanol mixture (1 : 0.5). The target products were formed in high yields (Scheme 1) [48–54].



Scheme 1.

1: R^1 = 4-$CH_3C_6H_4$, R^2 = H (**a**), CH_3 (**b**), CH_3O (**c**), Cl (**d**); R^1 = 2-C_5H_4N, R^2 = H (**e**), CH_3 (**f**), CH_3O (**g**), Cl (**h**); R^1 = C_5H_3BrN, R^2 = H (**i**), Cl (**j**); R^1 = 3-C_5H_4N, R^2 = H (**k**), CH_3 (**l**), CH_3O (**m**), Cl (**n**); R^1 = C_3H_2NS, R^2 = H (**o**), CH_3 (**p**), Cl (**q**); R^1 = $C_2H_1N_2S$, R^2 = H (**r**), CH_3 (**s**), CH_3O (**t**), Cl (**u**); R^1 = $C_3H_3N_2S$, R^2 = H (**v**), CH_3 (**w**), CH_3O (**x**), Cl (**y**); R^1 = $C_4H_5N_2S$, R^2 = H (**z**), CH_3 (**aa**), CH_3O (**ab**), Cl (**ac**); R^1 = $C_7H_5N_2$, R^2 = H (**ad**), Cl (**ae**); R^1 = C_7H_4NS, R^2 = H (**af**), CH_3O (**ag**), Cl (**ah**); R^1 = C_8H_4ClNO, R^2 = Cl (**ai**); R^1 = $C_{11}H_{11}N_2O$, R^2 = H (**aj**);

2: R^1 = 4-$CH_3C_6H_4$, R^2 = H (**a**) [53], CH_3 (**b**) [53], CH_3O (**c**) [53], Cl (**d**) [53]; R^1 = 2-C_5H_4N, R^2 = H (**e**) [52], CH_3 (**f**) [52], CH_3O (**g**) [52], Cl (**h**) [52]; R^1 = 3-C_5H_4N, R^2 = H (**i**) [52], CH_3 (**j**) [52], CH_3O (**k**) [52], Cl (**l**) [52]; R^1 = $C_2H_1N_2S$, R^2 = H (**m**) [52], CH_3 (**n**) [52], CH_3O (**o**) [52], Cl (**p**) [52]; R^1 = $C_3H_3N_2S$, R^2 = H (**q**) [52], CH_3 (**r**) [52], CH_3O (**s**) [52], Cl (**t**) [52]; R^1 = $C_4H_5N_2S$, R^2 = H (**u**) [52], CH_3 (**v**) [52], CH_3O (**w**) [52], Cl (**x**) [52];

3: Me^{2+} = Mn^{2+}, R^1 = 2-C_5H_4N, R^2 = Cl (**a**) [50]; R^1 = C_5H_3BrN, R^2 = H (**b**) [50]; R^1 = 3-C_5H_4N, R^2 = H (**c**) [51]; R^1 = C_3H_2NS, R^2 = Cl (**d**) [50]; R^1 = $C_2H_1N_2S$, R^2 = H (**e**) [50]; R^1 = $C_3H_3N_2S$, R^2 = H (**f**) [51]; R^1= $C_4H_5N_2S$, R^2 = H (**g**) [50]; R^1 = C_7H_4NS, R^2 = H (**h**) [47], CH_3O (**i**) [47];

4: Me^{2+} = Co^{2+}, R^1 = 2-C_5H_4N, R^2 = H (**a**) [50], Cl (**b**) [50]; R^1 = C_5H_3BrN, R^2 = H (**c**) [50]; R^1 = 3-C_5H_4N, R^2 = H (**d**) [51], Cl (**e**) [51]; R^1 = C_3H_2NS, R^2 = H (**f**) [50], Cl (**g**) [50]; R^1 = $C_2H_1N_2S$, R^2 = H (**h**) [50], Cl (**i**) [50]; R^1 = $C_3H_3N_2S$, R^2 = H (**j**) [50]; R^1 = $C_4H_5N_2S$, R^2 = H (**k**) [50]; R^1 = C_7H_4NS, R^2 = H (**l**) [47], CH_3O (**m**) [47], Cl (**n**) [47];

5: Me^{2+} = Ni^{2+}, R^1 = 2-C_5H_4N, R^2 = H (**a**) [50]; R^1= C_5H_3BrN, R^2 = H (**b**) [50]; R^1 = 3-C_5H_4N, R^2 = Cl (**c**) [50]; R^1 = C_3H_2NS, R^2 = H (**d**) [50], Cl (**e**) [50]; R^1 = $C_2H_1N_2S$, R^2 = H (**f**) [50], Cl (**g**) [50]; R^1 = $C_3H_3N_2S$, R^2 = H (**h**) [50]; R^1 = $C_4H_5N_2S$, R^2 = H (**i**) [50]; R^1 = C_7H_4NS, R^2 = H (**j**) [47], CH_3O (**k**) [47], Cl (**l**) [47]; R^1 = C_8H_4ClNO, R^2 = Cl (**m**) [50];

6: Me^{2+} = Cu^{2+}, R^1 = 2-C_5H_4N, R^2 = H (**a**) [48], Br (**b**) [48]; R^1 = C_5H_3BrN, R^2 = H (**c**) [48]; R^1 = 3-C_5H_4N, R^2 = H (**d**) [48]; R^1 = C_3H_2NS, R^2 = H (**e**) [48], CH_3 (**f**) [48], Br (**g**) [48]; R^1 = $C_2H_1N_2S$, R^2 = Cl (**h**) [48]; R^1 = $C_3H_3N_2S$, R^2 = H (**i**) [48], Cl (**j**) [48];

$R^1 = C_4H_5N_2S$, $R^2 = H$ (**k**) [48], CH_3 (**l**) [48], Cl (**m**) [48]; $R^1 = C_7H_4NS$, $R^2 = H$ (**n**) [47], CH_3O (**o**) [47], Cl (**p**) [47]; $R^1 = C_{11}H_{11}N_2O$, $R^2 = H$ (**q**) [49];

7: $Me^{2+} = Zn^{2+}$, $R^1 = 2\text{-}C_5H_4N$, $R^2 = H$ (**a**) [49], Cl (**b**) [48]; $R^1 = C_5H_3BrN$, $R^2 = Cl$ (**c**) [48]; $R^1 = 3\text{-}C_5H_4N$, $R^2 = H$ (**d**) [48], Cl (**e**) [48]; $R^1 = C_3H_2NS$, $R^2 = H$ (**f**) [48], Cl (**g**) [48]; $R^1 = C_2H_1N_2S$, $R^2 = Cl$ (**h**) [49]; $R^1 = C_3H_3N_2S$, $R^2 = H$ (**i**) [49], Cl (**j**) [49]; $R^1 = C_7H_5N_2$, $R^2 = Cl$ (**k**) [49];

8: $Me^{2+} = Cd^{2+}$, $R^1 = 2\text{-}C_5H_4N$, $R^2 = H$ (**a**) [49], Cl (**b**) [48]; $R^1 = 3\text{-}C_5H_4N$, $R^2 = H$ (**c**) [49], Cl (**d**) [48]; $R^1 = C_3H_2NS$, $R^2 = H$ (**e**) [48], Cl (**f**) [48]; $R^1 = C_3H_2NS$, $R^2 = H$ (**g**) [49]; $R^1 = C_4H_5N_2S$, $R^2 = H$ (**h**) [48], CH_3 (**i**) [48], Cl (**j**) [48]; $R^1 = C_7H_5N_2$, $R^2 = H$ (**k**) [49];

9: $Me^{2+} = Hg^{2+}$, $R^1 = 2\text{-}C_5H_4N$, $R^2 = Cl$ (**a**) [48]; $R^1 = 3\text{-}C_5H_4N$, $R^2 = H$ (**b**) [48], Cl (**c**) [48]; $R^1 = C_3H_2NS$, $R^2 = H$ (**d**) [48], where $R^1 = 2\text{-}C_5H_4N$ (2-pyridyl), C_5H_3BrN [2-(5-bromopyridyl)], $3\text{-}C_5H_4N$ (3-pyridyl), C_3H_2NS [2-(1,3-thiazolyl)], $C_2H_1N_2S$ [2-(1,3,4-thiadiazolyl)], $C_3H_3N_2S$ [2-(5-methyl-1,3,4-thiadiazolyl)], $C_4H_5N_2S$ [2-(5-ethyl-1,3,4-thiadiazolyl)], $C_7H_5N_2$ [2-benzimidazolyl], C_7H_4NS [2-benzo[d]thiazolyl], C_8H_4ClNO [2-(5-chloroisoxazolyl)], $C_{11}H_{11}N_2O$ (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-4-pyrazolyl).

Totally 139 compounds (**2**–**9**) were synthesized. They were colorless or colored (depending on the nature of the metal) high-melting crystalline solids soluble in DMSO, DMF, and a DMSO–1,4-dioxane mixture (1 : 1); poorly soluble in benzene, chloroform, and 1,4-dioxane; and insoluble in water.

The structures of metal complexes **2**–**9** were proved by a set of data from IR and ^{1}H NMR spectroscopy, inductively coupled plasma mass spectrometry, atomic adsorption analysis, thermogravimetry, and quantitative determination of the composition and confirmed by quantum chemical calculations. According to the results, (hetero)arylamides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids were coordinated to metals as bidentate O–O ligands [48–54].

The obtained metal complexes **2**–**9** were studied for acute toxicity and subjected to pharmacological screening in order to find biologically active compounds with antimicrobial, anti-inflammatory, analgesic, hypoglycemic, antioxidant, or immunotropic activity. The acute toxicity of the compounds was studied using white outbred mice of both sexes weighing 18–22 g, with LD_{50} being determined by the method of G.N. Pershin [55]. The antimicrobial activity of the synthesized compounds against the test bacterial cultures *St. aureus* ATCC 6538-P and *E. coli* ATCC 25922 was determined using serial twofold dilutions in the liquid culture medium. For each of the compounds, the minimal inhibitory concentration (MIC) in μg/mL was determined [55]. Chlorhexidine and dioxidine served as the reference compounds. The analgesic activity was determined using white outbred mice (males) weighing 18–22 g upon thermal pain stimulation of their paws in the 'hot plate' test [56]. Metamizole sodium (50 mg/kg) and diclofenac (50 mg/kg) served as reference drugs. The anti-inflammatory activity was found in experiments on white outbred rats of both sexes weighing 220–260 g. The compounds were administered orally 1 h before the acute inflammation induced by subplantar injection of 0.1 mL of a 1% carrageenin solution into the hind paw of the rat [55]. Diclofenac in a dose of 50 mg/kg served as the reference drug. The hypoglycemic activity was studied for white outbred rats of both sexes weighing 180–200 g. The experimental hyperglycemia was modeled by subcutaneous administration of alloxan trihydrate in a dose of 170 mg/kg. The glucose concentration in the animal blood was determined by the glucose oxidase method using the Glucose FKD kit (Russia) and a photoelectric colorimeter before and 30 and 120 min after the administration of test compounds [57]. The antihypoxic activity was studied on a model of normobaric hypoxia with hypercapnia on white outbred mice weighing 18–22 g. The life spans of animals were recorded, and the efficiency of test compounds was evaluated based on this value. Piracetam in a dose of 50 mg/kg, administered orally as a suspension in a 2% starch solution, was used as the reference drug [57]. The response of the immune system was evaluated by the T- and B-lymphocyte counts and phagocytosis [55]. The test compounds were introduced in a dose of 50 mg/kg as a suspension in a 2% starch solution 1 h before the experiments. All of the compounds were investigated for pharmacological activity.

The results of pharmacological studies were statistically processed using Student *t*-test and analysis of variance. The differences between data were considered to be significant at the level $p < 0.05$ for all values presented in the review. The statistical processing of the results was done using the Sigma Stat 3.5 program and statistical programs of Windows XP (Excel).

RESULTS AND DISCUSSION

The chemical modification of (hetero)arylamides **1** to metal complexes **2**–**9** reduces the acute toxicity in comparison with the initial ligands or inorganic salts. For most of the test compounds, LD_{50} are approximately 1500–4800 mg/kg and, in general, these chelates can be referred to hazard classes 4 and 5 according to the chemical product classification [58]. For metal complexes **2d**, **3f**, **4m**, and **7a**, the LD_{50} values are 2800, 4800, 4300, and 3500 mg/kg, respectively [48, 50, 59, 60]. Note that the manganese and cobalt chelates are less toxic. On going to vanadium- and zinc-containing products, the toxicity slightly

Table 1. Antimicrobial activity of the most active compounds

Compound	MIC, μg/mL	Compound	MIC, μg/mL
	St. aureus ATCC 6538-P/ *E. coli* ATCC 25922		*St. aureus* ATCC 6538-P/ *E. coli* ATCC 25922
3d	62/62	**8d**	62/62
3f	125/125	**8e**	2.0/3.9
4c	7.8/15.6	**8f**	1.0/1.0
7a	31/3.9	**9b**	3.9/7.8
7b	31/62	**9c**	0.25/2.0
8a	2.0/2.0	Chlorhexidine	125/125
8c	15.6/62	Dioxidine	62/62

increases. Cadmium and mercury chelates are more toxic than parent amides **1**, but significantly less hazardous than the parent inorganic salts or reference agents [50, 61, 62].

It was found that chemical modification of (hetero)arylamides **1** to complexes **2**–**9** markedly enhanced the antibacterial activity. The most pronounced effect, which substantially exceeded the activity of reference samples, was found for cadmium complexes **8a**,**c**,**d**–**f** and mercury complexes **9b**,**c** containing 2- and 3-pyridyl and 2-thiazolyl moieties. Manganese chelates **3** showed different activities depending on the structure of the heterocyclic moiety; the most pronounced effect comparable with that of dioxidine was observed for compound **3d** containing a 2-thiazolyl moiety in the molecule. Metal complex **3f** containing a 2-(5-methyl-1,3,4-thiadiazolyl) moiety acted only at a chlorhexidine level. The activity of zinc chelates **7a**,**b**, also containing a 2-pyridyl substituent, was comparable with that of dioxidine. Nickel derivatives **5** showed, most often, a weak antimicrobial action, irrespective of the structure of heterocyclic and aroyl moieties [50, 51]. The other studied metal complexes (including cobalt chelates **4**) had different degrees of specific activity, but their activity was inferior to that of the reference drugs. The results for most active derivatives are summarized in Table 1.

Among the series of chelates **2**–**9**, we found compounds that exhibited clear-cut phlogolytic action (Fig. 1). It was found that their anti-inflammatory effect is affected, to a greater extent, by the structure of the heterocycle and the nature of the complex-forming metal. In particular, manganese complex **3f** had a pharmacological effect at the peak of inflammation almost 1.8 times higher than the reference drug in the used dose ($p < 0.05$). Furthermore, it was 6.4 times less toxic than diclofenac [59]. Among cobalt, zinc, and cadmium derivatives, most active were compounds containing a pyridyl moiety (compounds **4d**,**e**, **7c**,**d**, **8c**). The replacement of the pyridyl moiety by 2-thiazole or 5-R-1,3,4-thiadiazole moiety did not induce an increase in the anti-inflammatory action [51, 60]. Nickel metal complexes **5** mainly showed low anti-inflammatory effect, and no significant influence of the nature of substituents in the heterocyclic and aromatic part of the molecule on the pharmacological effect was detected. However, derivative **5j** with a benzo[d]thiazole moiety had an effect comparable to that of the reference drug [48]. The other metal complexes showed specific activities that were less pronounced than those of reference agents.

The chelate complexes that have passed biological screening increased the latent period of the defensive reflex in mice to different extents (Fig. 2). For copper (**6**) and mercury (**9**) chelates, no significant analgesic effect was detected. Nickel and cadmium complexes **5a** and **8a** and arylamide-based oxovanadium chelates **2c**,**d** were least active, with their activity being inferior to that of the reference drugs [54, 63]. Cobalt chelate **4d** was comparable in the intensity of action with the reference drugs, while **4f** was more active, 30 min after administration, than metamizole sodium [54]. However, the highest activity was found for manganese complex **3f**, which showed an almost two times stronger effect than metamizole sodium ($p < 0.05$). In addition, it was shown to have a high phlogolytic activity, which makes it promising for further investigation [59].

It was found that introduction of complex-forming metals into molecules of initial amides **1** significantly potentiates the glucose-reducing pharmacological effect of the compounds. The greatest contribution to

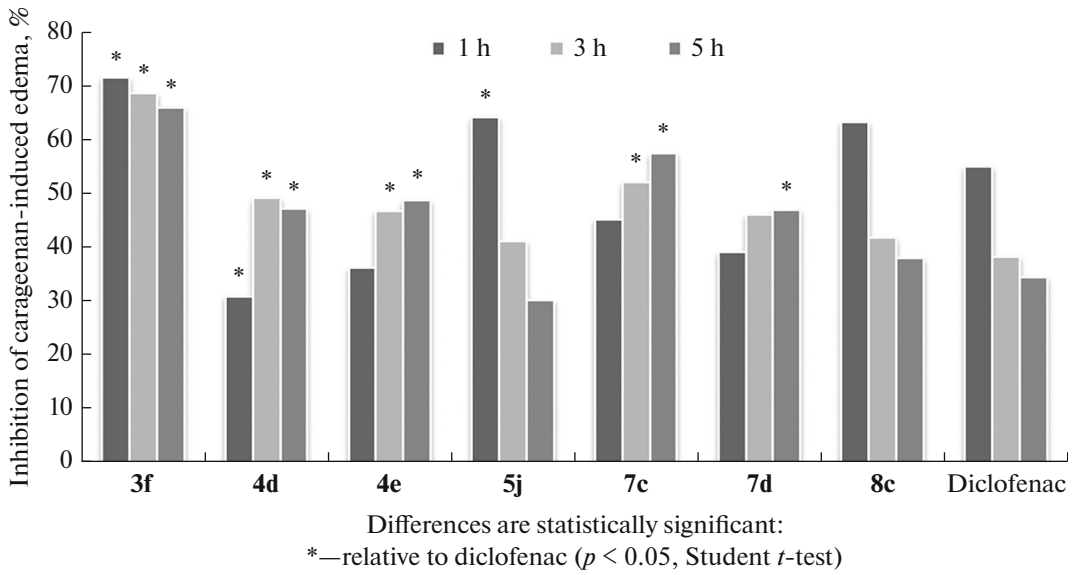


Fig. 1. Comparative characteristics of the anti-inflammatory activity of the most active compounds and diclofenac.

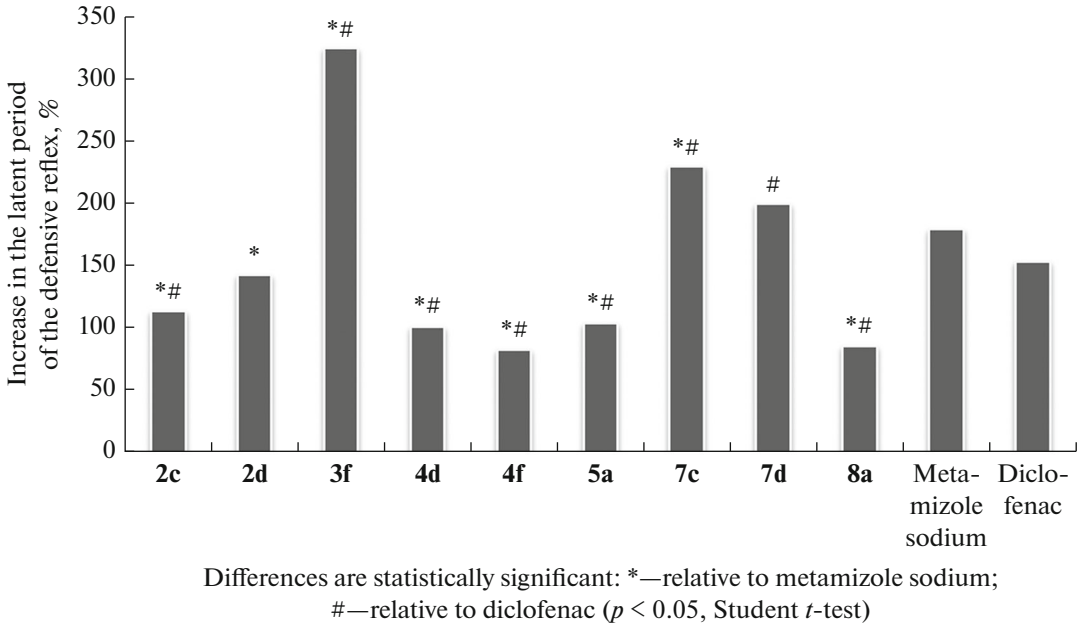


Fig. 2. Comparative characteristics of the analgesic activity of the most active compounds, metamizole sodium, and diclofenac.

this effect is made by oxovanadium, manganese, zinc, and cadmium and also by the chemical structure of the ligand. For example, arylamide derivatives **2c**,**d** containing vanadyl showed a 1.1–1.3 times more pronounced hypoglycemic action than the metformin substance on the 2nd hour of observation and acted at the same level as the reference on the 30th min of the experiment. This effect was 1.4–2.6 times more pronounced than the effect of vanadyl sulfate throughout the experiment ($p < 0.05$) [60, 63, 64]. Zinc and cadmium chelates **7c**,**d** and **8a** based on 2(3)-(5-*R*)-pyridylamides and cadmium complex **8k** based on 2-benzimidazolylamide exhibited clear-cut hypoglycemic properties, which were more pronounced than those of the initial ligands ($p < 0.05$) [53, 62, 63]. Among manganese complexes, the most pronounced contributions were made by the 1,3,4-thiadiazole and benzo[d]thiazole moieties. Most cobalt and nickel chelates have virtually no effect on the glucose level in the blood of animals, irrespective of the nature of the

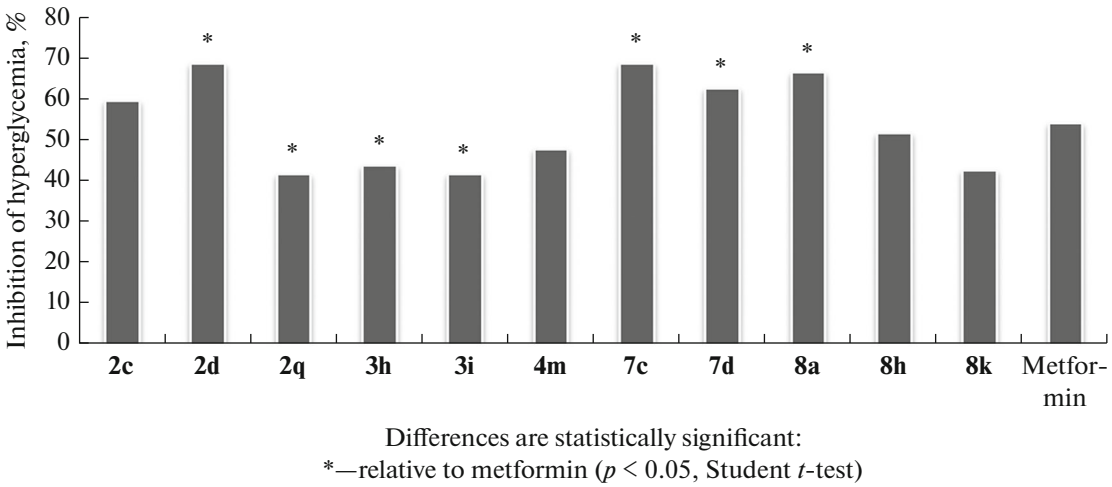


Fig. 3. Comparative characteristics of the hypoglycemic activity of the most active compounds and metformin 120 min after the administration.

heterocycle. The exception is cobalt chelate **4m**, which had a pronounced hypoglycemic action [48, 52, 63]. The results for the most active compounds are presented in Fig. 3.

A study of the structure–antihypoxic activity relationship demonstrated that the greatest effect was inherent in oxovanadium complexes **2c**,**d**, which were less effective than piracetam, but much more active than vanadyl sulfate. The level of antihypoxic effect is not significantly influenced by the nature of substituent at C^1; the activity of metal complexes based on acid 4-methylphenylamide markedly increases when the aryl moiety contains an electron-withdrawing substituent. Zinc chelates **7c**,**d** were inferior in the efficiency to the reference drug and to vanadium complexes. Cadmium chelate **8k** had absolutely no effect on the life span of animals under normobaric hypercapnia [63, 65]. The other chelates showed less pronounced specific activity and did not reach the level of reference drugs.

Oxovanadium chelate **2d**, which was most active as a hypoglycemic agent, was also studied for the immunotropic activity in the alloxan-induced diabetes. It was found that administration of the metal complex eliminated the suppression of the cellular immunity, reduced the severity of autoimmune processes, restored the leukocyte count in rats with experimental diabetes mellitus to the level inherent in intact animals, and stabilized the total count of lymphocytes. In addition, the monocyte level was restored and the number of plasma cells decreased. It should be noted that increase in the monocyte count up to the control level attests not only to elimination of immunosuppression, but also to the restoration of cooperation of the cellular and humoral immunity [63, 66].

Thus, the studies attest to high promise of the search for new pharmaceutical substances among the complex compounds based on 4-aryl-2-hydroxy-4-oxobut-2-enoic acid (hetero)arylamides. Two most active compounds can be distinguished: bis{3-phenyl-1-[2-(5-methyl-1,3,4-thiadiazolyl)]carboxamido-1,3-propanedionato}manganese (**3f**), which has an anti-inflammatory, analgesic, and antimicrobial action; and bis[3-(4-chlorophenyl)-1-(4-methylphenyl)carboxamido-1,3-propanedionato]oxovanadium (**2d**), possessing hypoglycemic activity with additional immunotropic and antihypoxic effects. For lead compounds, the strategy of subsequent pharmacological investigation was developed, methods for identification and purification are being selected, and a set of process parameters for the preparation of their active substances is being formed with the goal of developing possible dosage forms. In particular, for derivative **3f**, it is more rational to develop soft dosage forms (ointments, suppositories), while for chelate **2d**, oral hard dosage forms (tablets, capsules) should be produced. The identified trends can be used for targeted synthesis of new metal complex derivatives based on 4-(hetero)aryl-2-hydroxy-4-oxo-2-butenoic acid.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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