Metallatranes and hydrometallatranes: their immunotropic and antitumor properties

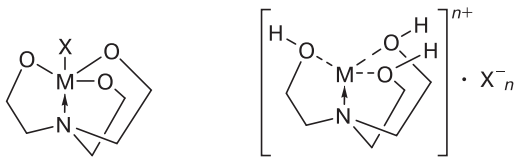
S. N. Adamovich** and *E. N. Oborina

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 ul. Favorskogo, 664033 Irkutsk, Russian Federation.
E-mail: mir@irioch.irk.ru; oborina@irioch.irk.ru

A series of biologically active metallatranes and hydrometallatranes was synthesized *via* the reaction of biogenic triethanolamine with salts or oxides of the essential metals; their toxicity was determined, and the immunotropic and cytotoxic properties were evaluated. Compounds causing immunostimulatory, immunosuppressive, and also competing effects on the immune response were revealed. A pronounced immunosuppressant, 1-oxovanadatran, exhibits a high and selective cytotoxic effect, inhibiting the growth of B16 melanoma cells by 39—80%, but does not affect the tumor cells of L1210 lymphocytic leukemia, P815 mastocytoma, and Lewis lung carcinoma.

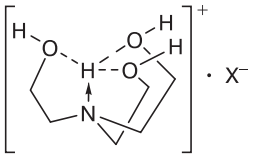
Key words: atranes, metallatranes, hydrometallatranes, immunostimulants, immunosuppressants, cytotoxic activity.

The first silatranes $N(CH_2CH_2O)_3Si—X$ (X = OEt and Ph),[1] which became parents of the class of atranes, have earlier been synthesized *via* a transetherification of triethoxysilanes $X—Si(OEt)_3$ with triethanolamine. Relative metallatranes $N(CH_2CH_2O)_3M—X$ (M = Ge, Sn, *etc.*)[2—5] were obtained later. Their molecules possess a specific tricyclic structure due to the transnannular intramolecular N→M bond. Their hydroxy-containing analogs, hydrometallatranes $[N(CH_2CH_2OH)_3M]^{n+} \cdot nX^-$ (see Ref. 6) and protatranes $[N(CH_2CH_2|OH)_3H]^+ \cdot X^-$ (see Ref. 7), also belong to the class of atranes. In contrast to metallranes, these compounds of triethanolamine with MX_n metal salts or HX protonic acids are ionic ones. They consist of hydrometallatrane (containing N→M and M···OH bonds) or protatrane (bearing N→H and H···OH bonds) cations and X^- anions.



Metallatranes
M = Si, Ge, Sn, *etc.*
X = Hal, Alk, *etc.*

Hydrometallatranes
M = Mg, Co, Zn, Ni, *etc.*
X = Hal, OAc, *etc.*



Protatranes
X = Hal, *etc.*

To date, a large number of atrane compounds possessing specific physical, chemical, and also biological properties has been synthesized. Silatranes are of interest not only as theoretical objects, but also as valuable reagents, materials, as well as physiologically and pharmacologically active compounds due to their unusual architecture, high molecular dipole moment, and strong electron-donating effect of the silatrane moiety.[8] Some silatranes and protatranes have been already employed in agriculture and medicine as protective, growth-promoting, and medicinal drugs. These include 1-chloromethyl- and 1-ethoxysilatranes (Mival and Migugen), protatrane Krezatsin (the complex of triethanolamine and biologically active cresoxyacetic acid) $[N(CH_2CH_2OH)_3H]^+ \cdot {}^-OOCCH_2OC_6H_4Me$-2, and other atranes.[9—16]

At the same time, an urgent problem is the design of new types of metallatrane compounds, search for unknown properties, and also investigation of the structure—activity relationship for them. We believe that promising objects for the design of new atranes are hydrometallatranes, which are potential donors of microbioelements, models of metalloenzymes, and precursors in the case of catalysts and paramagnetic drugs. However, in contrast to silatranes and protatranes, their synthesis, physicochemical properties, and structure have been insufficiently explored, while their physiological activity is represented only by few examples. Thus, hydrometallatranes $[N(CH_2CH_2OH)_3M]^{2+} \cdot 2AcO^-$ were demon-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1723—1728, September, 2019.
1066-5285/19/6809-1723

Table 1. The effect of compounds **1**—**16** on spontaneous proliferation and that stimulated by concanavalin A (Con A) and pokeweed mitogen (PWM) of cell proliferation *in vitro* (antiproliferative properties). The data are presented relative to the corresponding control (100%)

Compound	Dose /μg mL^{-1}	Spontaneous proliferation	Con A	PWM
		%		
$N(CH_2CH_2O)_3B$ (**1**)	1	16	18	32
	5	12	19	25
	10	31	5	2
$N(CH_2CH_2O)_3V{=}O$ (**2**)	0.01	16	13	—
	0.1	20	19	—
	1	−35	−55	−50
	5	−77	−69	−81
	10	−87	−85	−90
$N(CH_2CH_2O)_3Mo(O)(OH)$ (**3**)	1	−1	−3	39
	5	9	29	20
	10	4	17	14
$[N(CH_2CH_2OH)_3Co]^{2+}\cdot 2Cl^-$ (**4**)	1	−4	−15	−43
	5	−28	−55	−81
	10	−68	−85	−91
$[N(CH_2CH_2OH)_3Co]^{2+}\cdot 2AcO^-$ (**5**)	1	−12	−15	−23
	5	−33	−63	−68
	10	−35	−74	−77
$[N(CH_2CH_2OH)_3Zn]^{2+}\cdot 2Cl^-$ (**6**)	1	63	31	−13
	5	58	12	7
	10	58	2	13
$[N(CH_2CH_2OH)_3Zn]^{2+}\cdot 2AcO^-$ (**7**)	1	−25	19	−10
	5	−15	−24	−25
	10	−26	−20	0
$[N(CH_2CH_2OH)_3Mn]^{2+}\cdot 2AcO^-$ (**8**)	1	12	29	−2
	5	3	8	−14
	10	−35	−33	−25
$[N(CH_2CH_2OH)_3Cu]^{2+}\cdot 2Cl^-$ (**9**)	1	−14	−1	1
	5	−35	69	−5
	10	−65	49	−35
$[N(CH_2CH_2OH)_3Cu]^{2+}\cdot 2AcO^-$ (**10**)	1	−68	−29	−33
	5	−76	−77	−28
	10	−75	−58	−26
$[N(CH_2CH_2OH)_3Cd]^{2+}\cdot 2AcO^-$ (**11**)	1	1	23	9
	5	8	9	−23
	10	−13	3	−7
$[N(CH_2CH_2OH)_3Ni]^{2+}\cdot 2AcO^-$ (**12**)	1	−6	23	4
	5	14	13	−25
	10	44	3	−6
$[N(CH_2CH_2OH)_3Mg]^{2+}\cdot 2Cl^-$ (**13**)	1	22	29	35
	5	16	35	55
	10	21	37	38
$[N(CH_2CH_2OH)_3Fe]^{3+}\cdot 3Cl^-$ (**14**)	1	12	29	14
	5	2	38	44
	10	−1	29	19
$[N(CH_2CH_2OH)_3Na]^{+}\cdot Cl^-$ (**15**)	1	6	13	−6
	5	5	12	0
	10	−3	3	−9
$[N(CH_2CH_2OH)_3Rh]^{3+}\cdot 3Cl^-$ (**16**)	1	1	−53	—
	5	−24	−72	2
	10	0	−55	−11

Table 2. Cytotoxic effect of 1-oxovanadatrane (**2**) on the tumor cells of L1210 lymphocytic leukemia, B16 melanoma, LLC, and P815 mastocytoma *in vitro*

Dose/μg mL^{-1}	Inhibition (%)			
	L1210	B16	LLC	P815
1	−34	−39	1	19
5	−28	−77*	7	13
10	−39	−80*	−13	−24

* Reliable towards the corresponding control, $p < 0.05$.

strated as stimulators (M = Zn) or inhibitors (M = Mn and Ni) of the plant cell growth.[17] Investigations of hydrometallatrane $[N(CH_2CH_2OH)_3Zn]^{2+} \cdot 2(^{-}OOCCH_2\text{-}OC_6H_4Me\text{-}2)$, which was named as "Crezoxyzincatran", revealed it as a promising new drug causing antiangiogenic and antisclerotic effects.[18]

Pronounced immunoactive properties of some atranes and their analogues have earlier been briefly reported.[11,12,19] Recent and latest works (published in 2015—2019) have also indicated an antitumor activity of the atranes and similar ionic complexes of Zn, V, Ti, Ru, and Pt with amines.[20—25]

In order to expand these researches in the present work, we have synthesized boratrane (**1**), 1-oxovanadatrane (**2**), 1-oxo-1-hydroxymolybdatrane (**3**), and a series of hydrometallatranes (**4—16**) *via* the reaction of biogenic triethanolamine with salts or oxides of some metals essential for life (Table 1).[26,27]

The determined toxicity, estimated immunoactive properties, and evaluated antitumor properties of the synthesized compounds have been for the first time revealed (Tables 1—4) in the collaboration with the Research Institute of Fundamental and Clinical Immunology (Novosibirsk, Russian Federation). The toxicity determination was performed using the intragastric route of administration on outbred white mice. Compounds **1—16** were found as low toxic ones (LD_{50} of 675—4000 mg kg^{-1}).

The immunotropic properties of compounds **1—16** were explored on CBF1 and BDF1 hybrid mice according to the standard tests for their ability to influence:

— on spontaneous proliferation of mouse spleen cells *in vitro* and that stimulated by concanavalin-A (Con A) and pokeweed mitogen (PWM) (antiproliferative properties, see Table 1);

— on the amount of IgM antibody-producing cells (APC) *in vivo* (humoral immune response, see Table 3);

Table 3. Effect of compounds of **1**, **3—5**, **7**, **8** on the number of IgM antibody-producing cells (APC) *in vivo*

Compound	Amount of APC			
	BDF1		CBF1	
	Average value of two experiments	Part of the control (%)	Average value of two experiments	Part of the control (%)
Control	7710	—	26416	—
1	4954	−36	11533	−56
3	5017	−35	30211	14
4	4311	−44	19878	−25
5	1895	−76	23199	−12
7	2948	−62	23578	−11
8	2451	−69	16586	−37

Table 4. Effect of compounds **1**, **3—5**, **7**, **8** on the delayed-type hypersensitivity (DTH) *in vivo*

Compound	DTH			
	BDF1		CBF1	
	Average value of two experiments	Part of the control (%)	Average value of two experiments	Part of the control (%)
Control	55.7	—	35.6	—
1	53.6	−4	41.6	17
3	56.5	1	44.0	23
4	56.4	1	29.6	−17
5	75.3	35	31.6	−11
7	66.1	19	30.8	−14
8	81.7	46	49.4	39

— on the delayed-type hypersensitivity (DTH) test (cellular immune response, see Table 4).

The antitumor activity of compounds *in vitro* was evaluated according to the standard protocol (^{3}H-thymidine test, see Table 2).

Table 1 shows the data on the effect of compounds **1**—**16** on the spontaneous and mitogen-stimulated proliferation of spleen cells in the intact mice of CBF1 hybrids.

As one can see from Table 1, the cobalt, vanadium, and copper compounds possess pronounced antiproliferative properties: they inhibit the spontaneous, Con A- and PWM-stimulated proliferation of T and B spleen cells *in vitro* at the administered doses (1—10 μg mL^{-1}). Among the inhibitors of proliferation, 1-oxovanadatrane (**2**) and hydrometallatranes **4** and **5** demonstrate the maximum inhibitory properties. The latter exhibit a dose dependence (LD_{50} of 675 mg kg^{-1} for **5**), while 1-oxovanadatrane (**2**) either stimulates or suppresses the spontaneous and mitogen-induced proliferation of splenocytes depending on the dosage. Boratrane (**1**) and hydrometallatranes **7**, **13**, and **14** demonstrated immunostimulating properties on the *in vitro* culture. In contrast to **1**, **13**, and **14**, complex **7** stimulates the spontaneous proliferation to a greater extent. The immunoactive properties of other compounds were significantly difficult to evaluate: for example, rhodium complex **16** exhibited a higher inhibitory effect on the Con A-stimulated proliferation than that on spontaneous and PWM-stimulated ones. The remaining compounds demonstrated mild antiproliferative properties. 1-Oxovanadatrane (**2**), which exhibited the highest antiproliferative and immunosuppressive activities (see Table 1), was evaluated *in vitro* for the antitumor activity in the cell cultures of B16 melanoma tumor, L1210 lymphocytic leukemia, P815 mastocytoma, and Lewis lung carcinoma (LLC) (see Table 2).

As one can see from Table 2, non-toxic (LD_{50} of 3000 mg kg^{-1}) 1-oxovanadatrane (**2**) does not affect the proliferation of L1210 lymphocytic leukemia, P815 mastocytoma, and LLC tumor cells. However, compound **2** exhibits a cytotoxic effect, inhibiting the growth of B16 melanoma cells (by 39—80%). For comparison, cytostatic cisplatin widely used in the clinic practice suppressed in the present work at the doses of 0.5, 2.5, and 5 μg mL^{-1} the proliferation of B16 melanoma cells by 60, 93, and 94%, respectively. However, it is highly toxic (LD_{50} of 30 mg kg^{-1}) and causes undesirable side effects as compared to compound **2**.

Compounds demonstrated *in vitro* the immunoactive properties were evaluated in the tests of IgM antibody formation (humoral immune response) and DHT (cellular immune response) *in vivo* (see Tables 3 and 4).

The data presented in Table 3 show that the investigated compounds at the dose of 10 mg kg^{-1} administered to BDF1 mice cause the suppression of humoral immune response (by 35—76%, on the average by 54%). In the case of CBF1 mice, the similar dose causes a lower inhibition of the response (by 11—56%, on the average by 28%). Hydrometallatrane **5** causing the greatest immunosuppression in BDF1 mice causes practically no effect at the same dose on the antibody formation in CBF1 mice. Boratrane (**1**) possesses the pronounced immunosuppressive effect, causing the inhibition by 36% in BDF1 mice and by more than 50% in CBF1 mice.

Table 4 provides the data on the effect of compounds on the cellular immune response *in vivo*.

As one can see from Table 4, the studied compounds cause various effects on the degree of HRT in BDF1 and CBF1 mice, *e.g.*, compound **5** stimulates the HRT by 35% in BDF1 mice and slightly suppresses the response in CBF1 mice. The data on the ability of complex **8** to efficiently suppress the humoral response and to stimulate the cellular immune one are the most interesting. Rhodium complex **16** causes the same opposite effect, suppressing the IgM response by 23% and stimulating the HRT by 52%.

Therefore, the series of biologically active metallatranes and hydrometallatranes, including previously unknown ones, has been synthesized *via* the reaction of biogenic (participating in the vital activity) triethanolamine with salts or oxides of the certain essential metals. The screening performed in the both *in vitro* and *in vivo* tests revealed the low-toxic highly efficient substances possessing the both immunostimulating and immunosuppressive properties. Non-toxic 1-oxovanadatrane possessing the most pronounced immunosuppressive properties has exhibited the high and selective cytotoxic effect. Similarly to the well-known but toxic cisplatin, it inhibits the growth of B16 melanoma cells by 39—80%, but does not affect the tumor cells of L1210 lymphocytic leukemia, P815 mastocytoma, and LLC. Assessing the overall data on the immunoactive and antitumor properties of synthesized atranes and hydrometallatranes, it should be noted that the unique substances causing the competing effect on the cellular and humoral immune responses have been found among them. This makes them promising candidates for the design of new drugs capable of tuning the immune balance in the desired direction.

Experimental

Materials, synthesis, and characterization of compounds 1—16. Triethanolamine was purified by the triple distillation. The used metal salts were purchased from Sigma-Aldrich and met the "analytical grade" standard. Compounds **1**—**16** were synthesized according to the known procedures[26,27] and fully characterized by the IR spectroscopy (a Bruker IFS-25 spectrophotometer) and ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy (a Bruker DPX-400 spectrometer).

Biological evaluations of compounds 1—16: materials and methods. *Used cultural media, reagents, and assays:* medium RPMI-1640; medium 199 (NPO Vector, Russia); Hanks solution; physiological saline buffered with phosphate buffer (0.2 mol L^{-1},

pH 7.4); Linbro 96-well round-bottomed plates for the cultivation (Flow Lab, USA).

The acute toxicity of the synthesized compounds has been determined on outbred white mice upon a single intragastric route of the administration and showed that they are low toxic: LD_{50} of 675—4000 mg kg^{-1}. All the compounds were dissolved in RPM-1640 medium and used at different doses relative to LD_{50}. The RPMI-1640 medium was administered to the control animals in the same volume and mode. The tests were carried out in several series of the experiments, each of them contained its own control. The control and experimental groups consisted of 10 mice.

Healthy and sexually mature hybrid mice (CBA1/2C57BL/6) F1 (CBF1) and (C57BL/61/2DBA/2)F1 (BDF1) of both genders, 8—10 weeks old, and weighing 18—20 g were used. The spread by the initial body weight in the groups did not exceed 10%. The control and experimental animals of the same age were simultaneously obtained from the one farm (Rassvet, Russia). The control and experimental animals were kept in a vivarium under the same conditions: in standard plastic cages with small wood shavings (no more than 10 species) on a standard diet. All the studies were performed at the same time of a day (in the morning). The experiments were carried out according to the rules established by the European Convention for the Protection of Animals (Strasbourg, 1986) and approved by the Committee on Biomedical Ethics at the Research Institute of Fundamental and Clinical Immunology of the Siberian Branch of the Russian Academy of Medical Sciences.

Determination of the amount of IgM antibody-producing cells (APC) *in vivo*. Tested compounds at the dose of 10 mg kg^{-1} in the volume of 0.5 mL were daily administered intraperitoneally once a day for five days. The control animals were treated with RPMI-1640 medium in the same volume and mode. The animals were intravenously immunized with sheep erythrocytes (SE) at the dose of 0.5 mL$\times 10^7$ on the day of the last administration of compounds or simultaneously with the administration of SE. The amount of IgM-APC in the spleen of mice was evaluated on the fourth day after the immunization by the number of local hemolysis zones in a semi-liquid medium according to the modified method.[28] The results were expressed as the absolute amount of IgM-APC in the spleen.

Delayed-type hypersensitivity test *in vivo*. The studied compounds at the dose of 10 mg kg^{-1} in the volume of 0.5 mL were daily administered intraperitoneally once a day for five days. The control animals were treated with RPMI-1640 medium in the same volume and mode. The mice were sensibilized on the day of the last administration of compounds by intraperitoneal administration of 0.25% SE solution in the volume of 0.5 mL; on the fourth day after the sensibilization, a resolving dose of the antigen was administered under the plantar aponeurosis of the right hind leg (50% SE in the volume of 50 μL). The solvent was injected into the contralateral leg in the same volume. The control animals were treated with RPMI-1640 medium in the same volume and mode. The reaction was evaluated by the local DTH procedure 24 h after the administration of the resolving dose of SE, and the degree of edema was determined by a caliper. The results were expressed as a percentage.[29]

Evaluation of the effect of compounds on the spontaneous proliferation and that stimulated by concanavalin-A (Con A) and pokeweed mitogen (PWM) of cells *in vitro*. The spleens of mice were taken under sterile conditions, and a cell suspension was prepared: the spleens were placed in bottles with medium, cut out with scissors, repeatedly passed through a syringe equipped with needles of decreasing diameter, filtered through a metal mesh, and washed three times by the centrifugation at 1000 rpm for 10 min with a change of the medium. The spleen cell pellet was resuspended in complete RPMI-164 medium containing fetal calf serum (10%), Hepes (10 mmol L^{-1}), 2-mercaptoethanol ($4\cdot10^{-5}$ mol L^{-1}), L-glutamine (2 mmol L^{-1}), and gentamicin (50 μg mL^{-1}); and their total number was calculated. The resulting cell suspension was adjusted to the concentration of $0.7\cdot10^6$ cells per 1 mL of the complete medium and placed in 96-well round-bottom culture plates by 10^5 cells per 1 well in the volume of 150 μL per 1 well. The optimal doses of Con A and PWM mitogens determined in preliminary experiments (2 and 1 μg mL^{-1}, respectively) were added in the volume of 10 μL. The RPMI-1640 medium (10 μL) was added to the wells for the evaluation of spontaneous proliferation. All the samplings were performed in triplets. Compounds **1—16** were added at various doses to the wells simultaneously with the mitogens. The cell culture was incubated at 37 °C under an atmosphere containing CO_2 (5%) for 72 h. The proliferative activity of cells was evaluated by the incorporation of H^3-thymidine into the DNA of self-duplicating cells. The label (1 μCi in the each well of the assay) was introduced 16 h before the end of cultivation. On this purpose, the stock solution of ^{3}H-thymidine was initially dissolved in RPMI-1640 medium to the concentration of 100 μCi mL^{-1}, and then the resulting solution (10 μL) was added to the each well of the plate. At the end of incubation, the cells were harvested on glass fiber filters (Flow Lab, USA) using a Harvester apparatus (Titertek, USA). The filters were placed in scintillation counting bottles, and the radioactivity was counted in the scintillator (4 g of diphenyloxazole and 0.1 g of diphenyloxazolylbenzene per 1 L of toluene) by a Delta liquid scintillation counter (USA). The results were evaluated as a percentage. The incorporation of ^{3}H-thymidine in the absence of studied compounds (*i.e.*, the solvent only) was estimated as the negative control, and these results were taken as 100%.

Evaluation of the antitumor activity of compounds *in vitro*. The cultivation of cells and evaluation of their proliferative activity was carried out according to the protocol described above for the cultivation of lymphoid cells; the number of line cells was 10^4 per 1 well, the cultivation time was 24 h, and ^{3}H-thymidine was added 4 h before the end of cultivation. Compound **2** at various doses was introduced into the culture medium at the initial moment of cultivation in the volume of 10 μL. Water was used as the solvent of preparation. The effect caused by the drug was expressed as the following percentage: [(proliferation in the presence of drug — proliferation without the drug)/(proliferation without the drug)]×100%. The acquired data were (partially) processed using the nonparametric Mann—Whitney criterion *U*.

The authors are grateful to O. P. Kolesnikova (Research Institute of Fundamental and Clinical Immunology, Novosibirsk, Russian Federation) for her help in conducting the experiments and in the interpretation of acquired data.

The major results were obtained using the equipment of the Baikal Analytical Center for Collective Use of the Siberian Branch of the Russian Academy of Sciences.

References

1. US Pat. 2953545; *Chem. Abstr.*, 1961, **55**, 4045.
2. M. G. Voronkov, V. M. Dyakov, S. V. Kirpichenko, *J. Organomet. Chem.*, 1982, **233**, 1; DOI.org/10.1016/S0022-328X(00)86939-9.
3. S. S. Karlov, G. S. Zaitseva, *Chem. Heterocycl. Comp.*, 2001, **37**, 1325.
4. R. G. Swisher, R. O. Day, R. R. Holmes, *Inorg. Chem.*, 1983, **22**, 3692; DOI: 10.1021/ic00167a005.
5. T. Zoller, C. Dietz, L. Iovkova-Berends, O. Karsten, G. Bradtmoller, A.-K. Wiegand, Yu Wang, V. Jouikov, K. Jurkschat, *Inorg. Chem.*, 2012, **51**, 1041; DOI: 10.1021/ic202179e.
6. J. G. Verkade, *Coord. Chem. Rev.*, 1994, **137**, 233; DOI. org/10.1016/0010-8545(94)03007-D.
7. M. G. Voronkov, A. I. Albanov, T. N. Aksamentova, S. N. Adamovich, N. N. Chipanina, R. G. Mirskov, T. A. Kochina, D. V. Vrazhnov, M. Yu. Litvinov, *Russ. J. Gen. Chem.*, 2009, **79**, 2339; DOI: 10.1134/S1070363209110097.
8. J. K. Puri, R. Singh, V. K. Chahal, *Chem. Soc. Rev.*, 2011, **40**, 1791; DOI: 10.1039/b925899j.
9. M. G. Voronkov, V. P. Baryshok, *Silatrany v meditsine i sel´skom khozyaistve* [*Silatranes in Medicine and Agriculture*], SO RAN Publ., Novosibirsk, 2005, 255 pp. (in Russian).
10. M. G. Voronkov, V. P. Baryshok, *Pharm. Chem. J.*, 2004, **38**, 3; DOI.org/10.1023/B:PHAC.0000027635.41154.0d.
11. A. N. Mirskova, G. G. Levkovskaya, O. P. Kolesnikova, O. M. Perminova, E. V. Rudyakova, S. N. Adamovich, *Russ. Chem. Bull.*, 2010, **59**, 2236; DOI.org/10.1007/s11172-010-0384-9.
12. A. N. Mirskova, S. N. Adamovich, R. G. Mirskov, M. G. Voronkov, *Russ. Chem. Bull.*, 2014, **63**, 1869; DOI. org/10.1007/s11172-014-0679-3.
13. T. I. Vakul´skaya, S. S. Khutsishvili, D. V. Pavlov, Yu. I. Bolgova, I. V. Sterkhova, O. M. Trofimova, *Russ. Chem. Bull.*, 2017, **66**, 2276; DOI.org/10.1007/s11172-017-2014-2.
14. S. N. Adamovich, V. V. Novokshonov, I. A. Ushakov, V. G. Elshina, E. N. Oborina, *Russ. Chem. Bull.*, 2018, **67**, 1744; DOI.org/10.1007/s11172-018-2286-1.
15. S. N. Adamovich, A. N. Mirskova, É. A. Zelbst, *Russ. Chem. Bull.*, 2017, **66**, 168; DOI.org/10.1007/s11172-017-1716-9.
16. S. N. Adamovich, N. V. Vchislo, E. N. Oborina, I. A. Ushakov, I. B. Rozentsveig, *Mendeleev Commun.*, 2017, **27**, 443; DOI: 10.1016/j.mencom.2017.09.003.
17. V. I. Shmakov, Yu. M. Konstantinov, G. A. Kuznetsova, M. G. Voronkov, *Dokl. Biol. Sci.* (*Engl. Transl.*), 2006, **410**, 414; DOI.org/10.1134/S0012496606050206.
18. M. M. Rasulov, M. G. Voronkov, M. K. Nurbekov, M. V. Zvereva, A. N. Mirskova, S. N. Adamovich, R. G. Mirskov, *Dokl. Biochem. Biophys.* (*Engl. Transl.*), 2012, **444**, 147; DOI. org/10.1134/S1607672912030064.
19. S. N. Adamovich, A. N. Mirskova, R. G. Mirskov, U. Schilde, *Chem. Central J.*, 2011, **5**; DOI:10.1186/1752-153X-5-23.
20. G. N. Kaluđerović, T. Krajnović , M. Momcilovic, S. Stosic-Grujicic, S. Mijatović, D. Maksimović-Ivanić, E. Hey-Hawkins, *J. Inorg. Biochem.*, 2015, **153**, 315; DOI. org/10.1016/j.jinorgbio.2015.09.006.
21. M. Miller, O. Braitbard, J. Hochman, E. Y. Tshuva, *J. Inorg. Biochem.*, 2016, **163**, 250; DOI.org/10.1016/j.jinorgbio. 2016.04.007.
22. D. Gibson, *J. Inorg. Biochem.*, 2019, **191**, 77; DOI. org/10.1016/j.jinorgbio.2018.11.008.
23. K. Dankhoff, A. Ahmad, B. Weber, B. Biersack, R. Schobert, *J. Inorg. Biochem.*, 2019, **194**, 1; DOI.org/10.1016/j.jinorgbio.2019.02.005.
24. Shixian Hua, Feihong Chen, Xinyi Wang, Yuanjiang Wang, Shaohua Gou, *J. Inorg. Biochem.*, 2019, **195**, 130; DOI. org/10.1016/j.jinorgbio.2019.02.004.
25. S. N. Adamovich, *Appl. Organomet. Chem.*, 2019, **33**, e4940; DOI.org/10.1002/aoc.4940.
26. M. G. Voronkov, V. P. Baryshok, *J. Organomet. Chem.*, 1982, **239**, 199; DOI.org/10.1016/S0022-328X(00)94113-5.
27. A. A. Naiini, V. Young, J. G. Verkade, *Polyhedron*, 1995, **14**, 393; DOI.org/10.1016/0277-5387(95)93020-2.
28. A. J. Cunningham, A. Szenberg, *Immunology*, 1968, **14**, 599.
29. A. J. Crowle, *Adv. Immunol.*, 1975, **20**, 197.

Received March 14, 2019;
in revised form June 4, 2019;
accepted July 5, 2019