Reviews

Metal complexes with *N*-alkenylimidazoles: synthesis, structures, and biological activity

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Data on the synthesis, structures, and biological activities of complexes of *N*-vinyl-, *N*-allyl-, *N*-isopropenyl-, and *N*-allenylimidazoles with transition metal salts were generalized. The high biological activity of the complex bis(*N*-vinylimidazole)zinc diacetate as an antidote against carbon monoxide and that of tetrakis(*N*-vinylimidazole)cobalt dichloride as a hematopoiesis stimulator are discussed.

Key words: metal complexes, transition metal salts, *N*-vinylimidazoles, *N*-allylimidazoles, *N*-isopropenylimidazoles, *N*-allenylimidazoles, bis(*N*-vinylimidazole)zinc diacetate, tetrakis(*N*-vinylimidazole)cobalt dichloride.

Extensive basic and applied investigations of the biological activity of metal complexes are due to their key role in vital processes[1—3] and their high pharmacological activities.[3,4] The discovery of the antitumor properties of cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$,[5] has given birth to metallopharmaceutics and revolutionized cancer therapy.[3—7] Organometallic compounds of radioactive elements such as technetium, rhenium, and gadolinium are widely used in medical diagnostics and therapy.[4,8,9]

Taking into account the unique role of imidazoles in living nature[10—12] and pharmaceutics,[13,14] one can expect that metal complexes with imidazole ligands will be very promising for the design of novel drugs. In this respect, ruthenium complexes with imidazoles have been studied most comprehensively and found to exhibit high antitumor activity.[4,15,16] Being less toxic and specific toward some cancer diseases, they seem to be a promising alternative to platinum complexes. Some metal carbene complexes of the imidazole series show antitumor (Ag (see Ref. 17), Au (see Refs 17, 18), and Pd (see Ref. 17)) and antimicrobial activities (Ag (see Refs 17, 18), Au (see Ref. 17), Rh (see Ref. 17), and Ru (see Ref. 17)); the possibility of their medical use is now under study.

The main achievements in the coordination chemistry of various azoles are extensively discussed in monographs and reviews,[19—22] which, however, lack data on metal complexes with unsaturated derivatives of imidazoles. The only exception is the review[23] concerned with metal complexes of lactams and imidazoles, in which some data

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(available to that time) on complexation between metal salts and *N*-vinylimidazoles are cited.

A wealth of data collected hitherto about the synthesis, structures, and applied (primarily, medical) use of metal complexes with such ligand systems as *N*-vinyl- and *N*-allylimidazoles requires generalization and systematization. The present review gives an idea of the state-of-the-art of coordination chemistry dealing with transition metal complexes of *N*-alkenylimidazoles. Interest in such complexes is due to their high biological activity and possible use as convenient models for the study of competitive coordination of polydentate ligands and for finding general trends in modern coordination chemistry.

1. Metal complexes with *N*-vinylimidazoles

It is known that organic compounds containing heteroatoms with lone electron pairs usually act as electron n-donors in coordination bonding.[24,25] *N*-Vinylimidazoles are distinct from imidazoles mainly by the presence of an additional potential coordination site, *viz.*, the π-system of the exocyclic double bond. Quantum-chemical calculations of some *N*-vinylimidazole molecules show that their electron-donating properties are determined by the lone electron pair of the N(3) atom of the heterocycle, which makes these azoles monodentate ligands.[26—28] The n-donating ability of this "pyridine" N atom decreases when moving from *N*-vinylimidazole to *N*-vinylbenzimidazole, as well as with an increase in the electron-withdrawing effect of the substituent at the N(1) atom and the carbon atom of the heterocycle.[26]

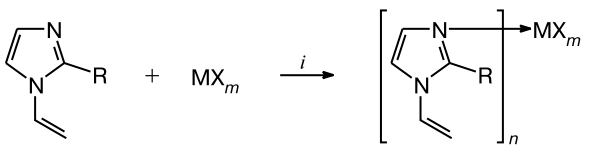
Metal complexes with imidazoles are usually obtained by direct reactions of ligands with metal salts in organic solvents or in melts of appropriate reaction components. The composition and structure of the resulting complex largely depend on the ligand basicity, the metal, and the solvent nature.

Complexes of *N*-vinylimidazole (**1**) with manganese(II),[29] iron(III),[29] cobalt(II),[29,30] copper(II),[29] and nickel(II) chlorides[31] have been obtained by mixing the ligand and the salts at room temperature in organic solvents (ethanol, diethyl ether, or acetone) or water. The reactions of $MnCl_2$, $FeCl_3$, and $NiCl_2$ with vinylimidazole **1** give the complexes $MCl_m \cdot 4L$ (L = **1**), regardless of the initial salt : ligand ratio (1 : 1, 1 : 4, or 1 : 6). Cobalt chloride produces the complexes $CoCl_2 \cdot 4L$ (see Refs 29, 30) and $CoCl_2 \cdot 2L$ (L = **1**)[30] (Scheme 1).

Unlike the aforementioned salts, $CuCl_2$ reacts with *N*-vinylimidazole (**1**) to yield 1 : 1, 1 : 2, and 1 : 4 complexes, depending on the ratio of the reagents (see Scheme 1); however, the complex $CuCl_2 \cdot 6L$ has not been obtained.[29]

Room-temperature syntheses of complexes of *N*-vinylimidazole with zinc salts (see Scheme 1, compounds **3d—f**)[32—37] by mixing the reagents in a solvent[32—36] (ethanol,[32] acetone—diethyl ether,[33—35] and an excess of vinylimidazole[36]) or by a solvent-free procedure involving zinc acetate hydrate[37] have been patented. The resulting complexes of *N*-vinylimidazole with zinc chloride (**3e**),[32] zinc ascorbate (**3f**),[33] and zinc acetate (**3d**)[34—37] act as antidotes against carbon monoxide. A technological line for the production of bis(*N*-vinylimidazole)zinc diacetate (**3d**)[35] (trade name Acyzole) has been developed.

Scheme 1



1, 2a,b **3a—j, 4a—g**

R = H (**1**, **3**): *n* = 1, MX_m = $CuCl_2$ (**3a**); *n* = 2, MX_m = $CoCl_2$ (**3b**), $CuCl_2$ (**3c**), $Zn(OAc)_2$ (**3d**), $ZnCl_2$ (**3e**), $Zn(C_6H_6O_6)$ (**3f**); *n* = 4, MX_m = $MnCl_2$ (**3g**), $FeCl_3$ (**3h**), $NiCl_2$ (**3i**), $CoCl_2$ (**3j**), $CuCl_2$ (**3k**).
R = Me (**2a**, **4a—e**), *n* = 2: MX_m = $CuCl_2$ (**4a**), $CoCl_2$ (**4b**), $MnCl_2$ (**4c**), $FeCl_3$ (**4d**), $NiCl_2$ (**4e**).
R = Et (**2b**, **4f,g**), *n* = 2: MX_m = $CuCl_2$ (**4f**), $CoCl_2$ (**4g**).

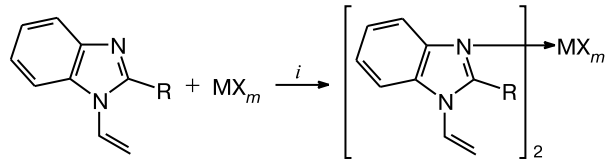
i. Solvent, 20 °C. The solvent is ethanol, diethyl ether, acetone, diethyl ether—acetone, and water.

According to X-ray diffraction data,[38] the centrosymmetric triclinic unit cell of Acyzole contains two crystallographically independent complex molecules A and B linked by short contacts O···H—C. In molecules A and B, the N atoms of the imidazole ligands and the O atoms of the acetate groups make up distorted tetrahedra around the Zn atoms. The Zn—N (2.019—2.050 Å) and Zn—O bond lengths (1.956—1.958 Å) for three acetate groups have typical values. In molecule A, one Zn—O bond is somewhat longer (2.009 Å) and the carbonyl O atom of the corresponding acetate group is also bound to the Zn atom (Zn—O, 2.498 Å).

2-Substituted *N*-vinylimidazoles and benzimidazole analogs yield metal complexes with fewer ligands compared to unsubstituted *N*-vinylimidazole (**1**). For instance, reactions of nickel, manganese, cobalt, iron, and copper chlorides with 2-methyl-1-vinylimidazole (**2**),[39] 2-ethyl-1-vinylimidazole,[30] *N*-vinylbenzimidazole (**5**),[29,30] and 2-alkyl-1-vinylbenzimidazoles (**6**)[40] give the complexes $MCl_m \cdot 2L$ (L = **2**, **5**, and **6**) (see Schemes 1 and 2).

However, with cobalt and copper nitrates, the resulting complexes $Co(H_2O)(NO_3)_2 \cdot 3L$ (L = **2**), $Co(NO_3)_2 \cdot 2L$ (L = **2**), $Cu(H_2O)_2(NO_3)_2 \cdot 4L$ (L = **2**), and $Cu(NO_3)_2 \cdot 2L$ (L = **2**) contain from two to four 2-methyl-1-vinylimidazole ligands (**2**).[41] According to X-ray diffraction data for the complexes $Co(H_2O)(NO_3)_2 \cdot 3L$ and $Cu(NO_3)_2 \cdot 2L$, the coordination polyhedron is a distorted tetragonal bipyramid in which the central ion coordinates the imidazole molecules through the N(3) atom and the NO_3 group

Scheme 2



5, 6a—j **7a—e, 8a—i**

R = H (**5**, **7**): MX_m = $MnCl_2$ (**7a**), $FeCl_3$ (**7b**), $CoCl_2$ (**7c**), $NiCl_2$ (**7d**), $CuCl_2$ (**7e**).
MX_m = $CoCl_2$: R = Me (**6a**, **8a**), Et (**6b**, **8b**), Pr (**6c**, **8c**), Bu (**6d**, **8d**), Am (**6e**, **8e**), Bz (**6f**, **8f**), CH_2CH_2Ph (**6g**, **8g**), *o*- and *p*-C_6H_4Me (**6h**, **8h** and **6i**, **8i**).

i. Solvent, 20 °C. The solvent is ethanol, diethyl ether, acetone, diethyl ether—acetone, and water.

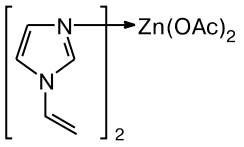
through two O atoms. In the complex with cobalt nitrate, the second NO_3 group is hydrogen-bonded to the water molecule, which is coordinated by the Co ion. The Co—N and Cu—N bond lengths are 2.085—2.147 and 1.960—1.967 Å, respectively.

Based on the small shifts of the absorption bands in the IR spectra of metal complexes with *N*-vinylimidazoles compared to those for free ligands, Kalmykov *et al.*[40] have concluded that the coordination causes small changes in the imidazole ring. The lower intensities of the bands at 1640 and 1600 cm^{-1} are due to a reduced conjugation between the vinyl group and the heterocycle in the complexes.[40]

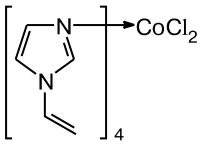
The paramagnetic complexes of *N*-vinylimidazoles with metals (Ni, Co, and Cu) can also be examined by high-resolution NMR spectroscopy proposed by Voronov *et al.*[42] They have studied an electron—nucleus, or hyperfine, coupling between unpaired electrons and resonating nuclei resulting in the characteristic shifts and broadening of the signals, which provides information on the electronic and three-dimensional structures of ligands in paramagnetic complexes.

The coordination sites in complexes of transition metal chlorides with *N*-vinylimidazoles have been located using X-ray photoelectron spectroscopy;[43] the data obtained confirm the donor—acceptor character of the nitrogen—metal bond and its localization at the N(3) atom of the imidazole ring.

Apart from the aforementioned Acyzole, pronounced biological activity is exhibited by a complex of cobalt chloride with four *N*-vinylimidazole molecules (**3j**). The method for its preparation and use as the broad-spectrum hematopoietic stimulant Cobazole has been patented.[44,45]



Acyzole (**3d**)

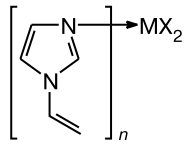


Cobazole (**3j**)

According to X-ray diffraction data[46,47] for tetrakis(*N*-vinylimidazole)cobalt dichloride (Cobazole), the coordination polyhedra of the Co^{2+} ions are slightly distorted octahedra with two apical Cl atoms and four equatorial N atoms of the vinylimidazole ligands. The Co—N bond lengths are 2.04—2.17 Å.

However, Baikalova *et al.*[48] believe that the X-ray diffraction data cited[46] have been obtained for an incorrect space group and that the paper[47] passes over intermolecular contacts and molecular packing. According to more recent data,[48] the Co atoms in the monoclinic unit cell of tetrakis(*N*-vinylimidazole)cobalt dichloride reside on centers of inversion. The coordination environment of the Co atom is a strongly elongated octahedron made up of four equatorial N atoms of the monodentate terminal ligands L(1) and L(1A) and two Cl atoms. The Co—N bond lengths (2.134 and 2.157 Å) are typical of the octahedral coordination of the Co^{2+} cation. The Co—Cl bond (2.518 Å) is lengthened, probably because of short contacts (geometrically similar to hydrogen bonds) between the Cl atoms and one of the independent ligands.

Reactions of *N*-vinylimidazole (**1**) with the salts MX_2 (M = Cd, Mn, Fe, Co, Ni, Zn, and Cu; X = ClO_4^-, BF_4^-, and NO_3^-) in ethanol followed by addition of diethyl ether and cooling to 0 °C give[49] a great number of complexes (**9**) with a coordination number of 6.



9

X	M	*n*
BF_4^-	Cd, Co, Ni	6
	Zn, Cu	4
ClO_4	Cd, Mn, Fe, Co, Ni	6
	Co, Zn, Cu	4
NO_3^-	Cd, Co, Ni	6
	Ni, Zn, Cu	4
	Cd, Mn	3

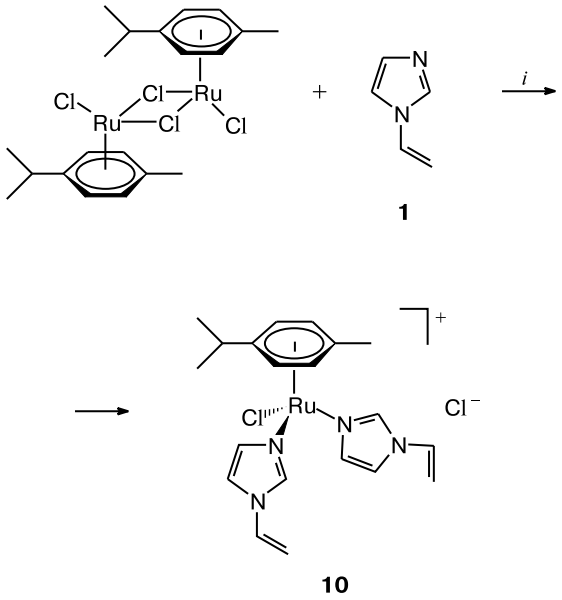
Reflux of a mixture of *N*-vinylimidazole (**1**) with Co^{II}, Mn^{II}, Fe^{II}, Ni^{II}, Zn^{II}, and Cu^{II} hexafluorosilicates affords the complexes $MSiF_6 \cdot 4L$ (L = **1**). The crystal structure of $CoSiF_6 \cdot 4L$ as an example has been examined.[50]

A reaction of *N*-vinylimidazole (**1**) with Fe(TPP) (TPP is tetraphenylporphyrin) in CH_2Cl_2 gives the complex [Fe(TPP)·2L] (L = **1**),[51] in which the ligand is coordinated through the N(3) atom and the planes of the axial imidazole ligands are parallel to each other (X-ray diffraction data).

In a search for novel anticancer drugs, a number of new η^6-arene imidazole complexes of ruthenium have been

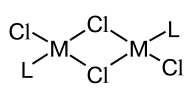
obtained and pretested, including complex **10** with *N*-vinylimidazole (**1**) (Scheme 3).[15]

Scheme 3



i. 118 °C, 4 h, BuOH.

The complexes of nickel and zinc salts with 4,5-diphenyl-1-vinylimidazole (**11**) contain no more than two bulky ligand molecules: $MCl_2 \cdot 2L$ (L = **11**; M = Ni and Zn).[52] Copper can form both the complexes $CuCl_2 \cdot 2L$ and $CuCl_2 \cdot L$ (L = **11**), while Cd, Fe, and Co chlorides form complexes with only one ligand molecule.[52] Chloride-bridged binuclear structures (**12**) have been proposed for the complexes $MCl_n \cdot L$ (L = **11**; M = Co, Cu, and Cd). The octahedral structure (**13**) proposed for the adduct $FeCl_3 \cdot L$ (L = **11**) in the crystalline state results from intermolecular association. The complexes $MCl_m \cdot 2L$ (L = **11**; M = Ni and Zn) have tetrahedral structures.[52]



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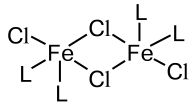

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N-Vinylimidazole derivatives containing substituents with additional coordination sites can act as both monodentate and bridging ligands, exhibit the properties of a bidentate ligand, and form chelate complexes. In this case, the compositions and structures of the resulting complexes depend on the metal, its salt anion, and the ligand : salt ratio in the reaction mixture. For instance, 2-hydroxymethyl-1-vinylimidazole (**14**) and 2-hydroxymethyl-1-vinylbenzimidazole (**15**) react with transition metal chlorides and sulfates to give complexes with one to three ligand molecules, depending on the ratio of the starting reagents (salt : ligand = 1 : 1 (**16**, **17**), 1 : 2 (**18**, **19**), and 1 : 3 (**20**, **21**)). The complexes of compounds **14** and **15** with metal acetates contain no more than two ligand molecules ($M(OAc)_2$: ligand = 1 : 1 (**16**, **17**) and 1 : 2 (**18**, **19**)) and those with copper acetate are always 1 : 1 complexes (**16**, **17**) (Scheme 4).[53,54]

According to IR spectra, 1 : 1 complexes (**16**, **17**) are alkoxide chelates (see Scheme 4): the shifts of the absorption bands of the heterocycle to shorter wavelengths suggest the coordination through the N(3) atom; the band due to the OH group disappears.[53,54]

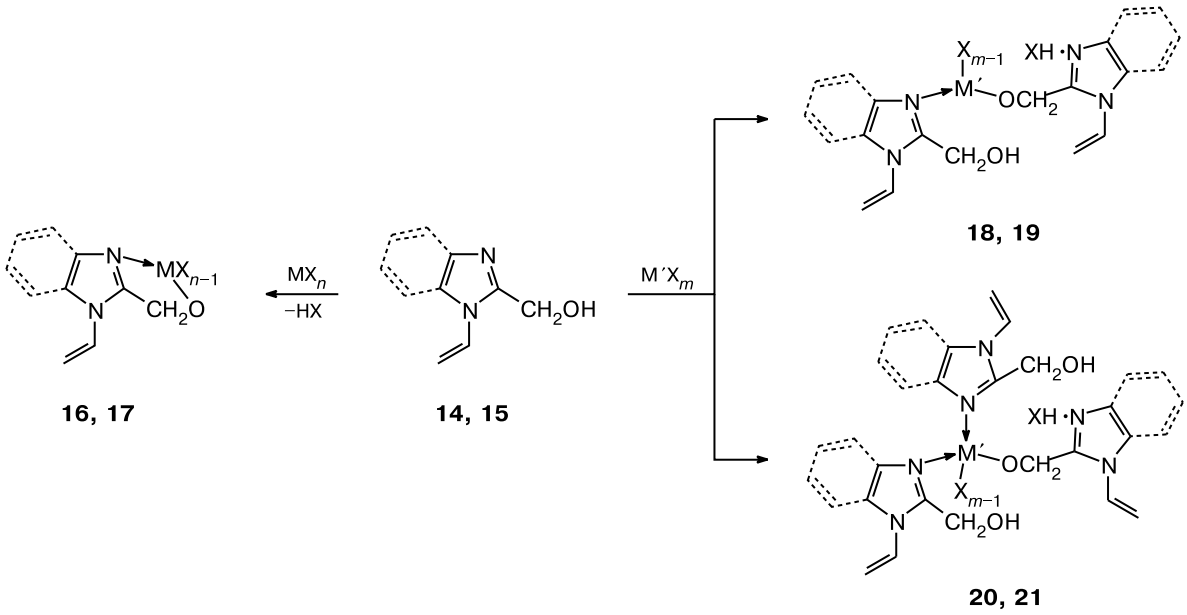
The IR spectra of 2 : 1 (**18**, **19**) and 3 : 1 adducts (**20**, **21**) contain the bands due to the intermolecular hydrogen bond and the NH^+ cation; this confirms the formation of mixed alkoxide chelates in which the metal is coordinated to, and the salt formation occurs at, the "pyridine" N atom (see Scheme 4, adducts **18**—**21**).[53,54]

Reactions of Mn, Co, and Zn salts with imidazoles **14** and **15** yield molecular 2 : 1 complexes. The IR spectra reveal the coordination only through the "pyridine" N atom[53,54] and show no absorption band of NH^+. According to X-ray photoelectron data, the ionization energy of the Co2*p* electrons increases when moving from a complex of cobalt dichloride with *N*-vinylimidazole (**1**) ($CoCl_2 \cdot 4L$) to an analogous complex with 2-hydroxymethyl-1-vinylimidazole (**14**) ($CoCl_2 \cdot 2L$); this suggests additional coordination through the O atom of the CH_2OH group.[43] A single-crystal X-ray diffraction study[55] of bis-(2-hydroxymethyl-1-vinylimidazole)cobalt dichloride (**22**) has revealed that imidazole **14** is ambidentate in this complex. One imidazole molecule functions as a monodentate ligand coordinated through the N(3) atom, while the second molecule forms a five-membered chelate ring involving the coordination of the Co atom to the N(3) and hydroxymethyl O atoms (Scheme 5). The coordination polyhedron of the Co atom is a distorted trigonal bipyramid with the N atoms of both ligands and one Cl atom in the equatorial plane and with the O atom and the other Cl atom in the apical positions.

In complexes of metal chlorides with 1-vinyl-2-vinyloxymethylimidazole (**23**), the salt : ligand ratio is mostly 1 : 1 or 1 : 2; a benzimidazole analog (**24**) forms 1 : 1 complexes only. The exception is the complex $NiCl_2 \cdot 4L$ (L = **23**). According to data from IR, NMR, and X-ray photoelectron spectroscopy, the coordination involves only the N(3) atom of the heterocycle.[56]

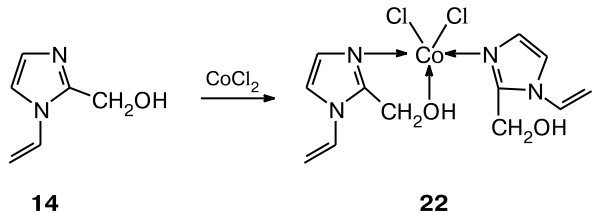
2-Formyl-1-vinylimidazole (**25**) and 2-formyl-1-vinylbenzimidazole (**26**) are of interest as ambidentate electron-donating ligands with several coordination sites. Nevertheless, in complexes with transition metal chlorides, they are coordinated to the metal ion only through the N(3) atom of the heterocycle. The ligand : salt ratio varies from 1 : 1 to 3 : 1. The complexes can be hydrated to

Scheme 4



MX_n = $CoSO_4$, $Co(OAc)_2$, $Ni(OAc)_2$, $Cu(OAc)_2$, $CuCl_2$, $FeCl_2$, $NiCl_2$, $CdCl_2$.
$M'X_m$ = $NiCl_2$, $NiSO_4$, $Ni(OAc)_2$, $CuCl_2$, $CuSO_4$, $FeCl_3$, $FeSO_4$, $CoCl_2$, $ZnCl_2$, $CdCl_2$.

Scheme 5

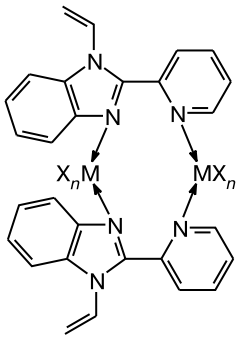


give stable N(3)-coordinated *N*-vinylimidazol(benzimidazol)-2-ylmethanediols.[57]

Even when a ligand contains an exocyclic amino group (as in 2-amino-1-vinylbenzimidazole (**27**)), its coordination to Co^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, and Fe^{3+} chlorides involves the N(3) atom with retention of the intermolecular hydrogen bond between the NH_2 groups of the ligand. The complexes have the molecular formula $MCl_m \cdot nL$ (m = 2—4; n = 1 and 2).[58]

Reactions of 2-(2-pyridyl)-1-vinylbenzimidazole **28** with Co^{2+}, Ni^{2+}, Fe^{3+}, Cu^{2+}, Zn^{2+}, and Cd^{2+} chlorides yield high-melting 1 : 1 complexes, regardless of the ratio of the starting reagents.[59] Potentiometric and spectroscopic (NMR, ^{35}Cl NQR, UV, and IR) data suggest that these complexes in the crystalline state can form dimeric (**29**) or polymeric structures (**30**) with compound **28** as a bridging *N*,*N*-bidentate ligand.

In solution, these complexes dissociate into mononuclear entities (**31**, **32**) with differently coordinated metal



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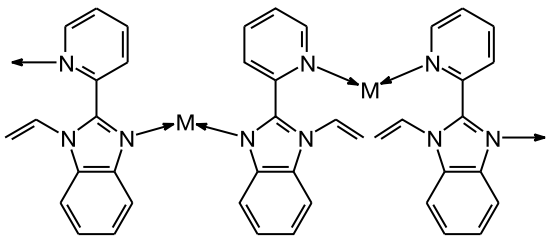
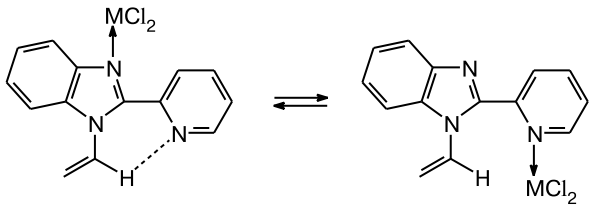


30

ions (to either the benzimidazole or pyridine N atom of the ligand).[59]

Interest in the study of metal complexes with 2,2′-biimidazolyl and its derivatives is due to the potential polyfunctionality of biimidazolyl. It has been found that reac-

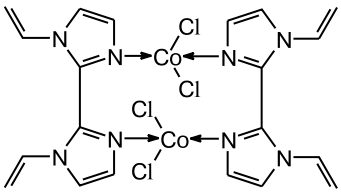


31 **32**

M = Cd, Zn

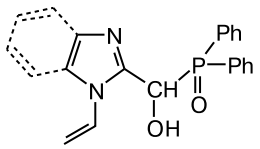
tions of 1,1′-divinyl-2,2′-biimidazolyl (**33**) with manganese, iron, copper, zinc, cadmium,[60,61] and cobalt chlorides[62,63] give 1 : 1 complexes, regardless of the ligand : salt ratio or the metal nature (**34a**—**f**, respectively).

The denticity of biimidazolyl ligand **33** has been determined[62,63] from X-ray diffraction data. It has been demonstrated that the crystals of a complex of cobalt chloride with ligand **33** ($CoCl_2 \cdot L$ (**34f**)) are built from the dimers $Co_2Cl_4L_2$ with bridging divinylbiimidazolyl ligands **33** coordinated to cobalt through the N(3) atoms. The other two vertices of the tetrahedron around the Co atom are occupied by the Cl atoms. Divinylbiimidazolyl ligand **33** is in the cisoid conformation.



34f

Functionalized *N*-vinylimidazoles with phosphine oxide and hydroxy substituents (**35a,b**)[64] have been employed as ligands for the synthesis of metal complexes because they contain several potential electron-donating sites, which enables competitive coordination of metals. Imidazoles **35a,b** react with zinc, cadmium, and cobalt chlorides to give the complexes $ZnCl_2 \cdot L$ (L = **35a,b**), $CdCl_2 \cdot L$ (L = **35a**), $CdCl_2 \cdot 2L$ (L = **35b**), and $CoCl_2 \cdot L$ (L = **35b**).[65] In the structures proposed for the crystalline 1 : 1 complexes, phosphine oxides **35a,b** act as bridging N(3),O-bidentate ligands, thus forming polymer chains. In the 1 : 2 complexes, these ligands are coordinated in a monodentate fashion through the O atom of the O=P group.

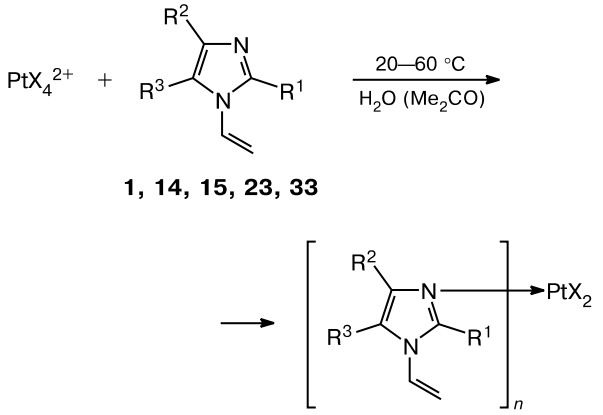


35a,b

Although platinum, palladium, and copper(I) salts are soft Lewis acids, the coordination of their halides with *N*-vinylimidazoles occurs at the "hard" electron-donating site (the N(3) atom of the ring) rather than at the π-system of the double bond, regardless of the ligand basicity and the reaction conditions.[66—73] An analysis of the IR, ^{1}H NMR, and X-ray photoelectron spectra[69] shows that the same coordination site is involved in complexes with functionalized *N*-vinylimidazoles containing substituents with electron-donating N and O atoms and π-donor *N*- and *O*-vinyl and phenyl groups.

Reactions of potassium tetrahaloplatinates with *N*-vinylimidazoles in water, ethanol, or acetone give a number of platinum(II) complexes (**36a—j**).[66,70] The resulting complexes contain one to four ligands, depending on the ratio of the starting reagents and the presence of bulky substituents in the imidazole ligand (Scheme 6).

Scheme 6



1, 14, 15, 23, 33

36a—j

$R^1 = R^2 = R^3 = H$ (**1**, **36a—f**): X = Cl, *n* = 2 (**36a**), 4 (**36b**); X = Br, *n* = 2 (**36c**), 4 (**36d**); X = I, *n* = 2 (**36e**), 4 (**36f**).
$R^1 = CH_2OH$ (**14**, **15**, **36g,h**), X = Cl, *n* = 2: $R^2 = R^3 = H$, (**14**, **36g**), $R^2 + R^3 = (CH)_4$ (**15**, **36h**).
$R^1 = CH_2OCH{=}CH_2$, $R^2 = R^3 = H$, X = Cl, *n* = 1 (**23**, **36i**).
$R^1 = C_5H_6N_2$, $R^2 = R^3 = H$, X = Cl, *n* = 1 (**33**, **36j**).

Imidazole complexes with $PtCl_4$,[67,69] $PdCl_2$,[68—72] and CuCl (see Ref. 73) can be easily obtained by direct reactions of these salts with *N*-vinylimidazoles at 20—95 °C in organic solvents (ethanol or acetone) or water. In most of the resulting complexes, the ligand : salt ratio is two ($PtCl_4 \cdot 2L$, L = **1** and **5**;[67,69] $PdCl_2 \cdot 2L$, L = **1**,[68,69,72] **5**,[68] **11**,[71] **14**,[70] **24**,[70] **25**,[71] **26**,[71] and **27**;[71] $CuCl \cdot 2L$, L = **14** (see Ref. 73)). Using an excess of the ligand, one can obtain complexes with up to four vinylimidazole molecules ($PtCl_4 \cdot 3L$, L = **1** and **5**;[67] $PtCl_4 \cdot 4L$, L = **1**;[67] $PdCl_2 \cdot 3L$, L = **5**;[68] $PdCl_2 \cdot 4L$ (see Ref. 68) and $PdCl_2(3H_2O) \cdot 4L$, L = **1** (see Ref. 72)). When used in an equimolar ratio, the starting reagents (especially in the

case of bulky ligands) produce 1 : 1 complexes ($PdCl_2 \cdot L$, L = **14**,[70] **24**,[70] and **33**;[70,71] $CuCl \cdot L$, L = **1**, **5**, **23**, and **33** (see Ref. 73)).

The crystal and molecular structure of a complex of $PdCl_2$ with *N*-vinylimidazole has been determined.[72] The crystals of $PdCl_2 \cdot 2L$ (L = **1**) are monoclinic. The complex is diamagnetic and shows square planar coordination around the Pd^{2+} ions.

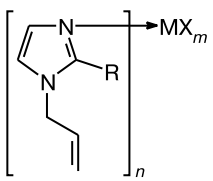
2. Metal complexes with *N*-allyl- and *N*-isopropenylimidazoles

Like *N*-vinylimidazoles, *N*-allylimidazoles form complexes with metal salts by coordinating to the metal atom through the N(3) atom of the heterocycle.[74—79] Such complexes have been obtained by mixing the starting reagents in a solvent (typically, propan-2-ol containing trimethyl *o*-formate[74—77] or acetone acidified with HCl[78,79]).

In the centrosymmetric binuclear complex $Cu_2(NO_3)_4 \cdot 4L$ (L is unsubstituted *N*-allylimidazole), the nitrate anions are linked to the Cu^{2+} cations by the bidentate O atoms. In the complex $Cu(NO_3)_2 \cdot 4L$, the copper cation lies on the center of symmetry of a tetragonal bipyramid. The *N*-allylimidazole ligands are coordinated to the Cu atoms through the "pyridine" N atom.[74]

Reactions of *N*-allylimidazole with Co^{II} and Ni^{II} nitrates in propan-2-ol (ligand : salt = 4 : 1) yield heptacoordinate isomorphic complexes of the general formula $M(NO_3)_2 \cdot 3L$.[75] The coordination sphere of the central metal atom contains three *N*-allylimidazole molecules and two bidentate NO_3 groups. The ligand is coordinated through the "pyridine" N(3) atom, which is confirmed by X-ray diffraction data and IR spectra.[75]

When the ligand : salt ratio in the reaction mixture is higher, the resulting octahedral Co^{II} and Ni^{II} complexes with *N*-allylimidazole have the formula $M(NO_3)_2 \cdot 6L$.[76] The complexes have been characterized by X-ray diffraction and IR and UV spectroscopy. According to potentiometric data, the *N*-allylimidazole complexes are somewhat more stable in water than the *N*-vinylimidazole ones. The complexation follows the Bjerrum model with retention of the six-coordinate geometry of the central ion.



37a—i

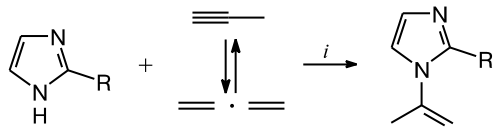
R = H: *n* = 4, MX_m = $Cu_2(NO_3)_4$ (**37a**); $Cu(NO_3)_2$, (**37b**);
n = 3, MX_m = $Co(NO_3)_2$ (**37c**); $Ni(NO_3)_2$ (**37d**);
n = 6, MX_m = $Co(NO_3)_2$ (**37e**); $Ni(NO_3)_2$ (**37f**);
n = 4, MX_m = $Pd(H_2O)_3Cl_2$ (**37g**).
R = Me: *n* = 2, MX_m = $Cu(NO_3)_2$ (**37h**); $Co(NO_3)_2$ (**37i**).

In the complexes of the general formula $M(NO_3)_2 \cdot 2L$ (M = Co and Cu; L is 1-allyl-2-methylimidazole), the metal ion is surrounded by two N atoms of the imidazole ring and four O atoms of the chelating NO_3 group. The structure of either complex is a strongly distorted tetragonal bipyramid.[77] The M—N bond lengths are 1.964(2) Å for M = Cu and 2.036(2) and 2.041(2) Å for M = Co.

Heating of palladium chloride with *N*-allylimidazole in acidified acetone gives the complex $PdCl_2(H_2O)_3 \cdot 4L$, which decomposes into the complex $PdCl_2 \cdot 2L$ under controlled heating from 90 to 140 °C.[78,79]

Unlike *N*-allylimidazole complexes, metal complexes with isomeric *N*-isopropenylimidazoles still remain poorly studied. This is because the ligands themselves have been virtually inaccessible until recently. Development of direct *N*-isopropenylation of azoles (including imidazoles) with propyne and allene in KOH—DMSO (Scheme 7)[80] allows easy preparation of *N*-isopropenylimidazoles, which can further be used in organic synthesis and coordination chemistry (as ligands).

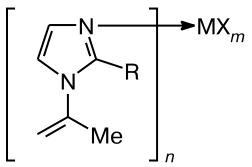
Scheme 7



38a,b

i. KOH/DMSO. 125—145 °C, 5—7 h.
R = H (**38a**, 60—70% yield), Me (**38b**, 34% yield).

Like *N*-vinyl- and *N*-allylimidazoles, *N*-isopropenylimidazole (**38a**) and 1-isopropenyl-2-methylimidazole (**38b**) act as monodentate ligands[81] in complexes with Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Pd^{2+}, and Sn^{4+} salts, being coordinated only through the N(3) atom. More basic 1-isopropenyl-2-methylimidazole (**38b**) provide higher yields of metal complexes. The yields of the complexes with stronger Lewis acids ($ZnCl_2$ and $SnCl_4$) are lower than those attained for $CoCl_2$ or $PdCl_2$ (98%).[81]



39a—t

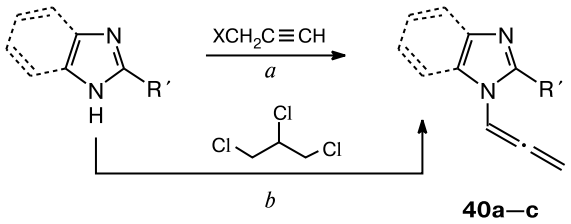
R = H: *n* = 1, MX_m = $CdCl_2$ (**39a**), $CuCl_2$ (**39b**), $Zn(OAc)_2$ (**39c**), $PdCl_2$ (**39d**);
n = 2, MX_m = $CoCl_2$ (**39e**), $CuCl_2$ (**39f**), $ZnCl_2$ (**39g**), $SnCl_4$ (**39h**), $PdCl_2$ (**39i**);
n = 4, MX_m = $CuCl_2$ (**39j**), $NiCl_2$ (**39k**).
R = Me: *n* = 1, MX_m = $CuCl_2$ (**39l**), $CdCl_2$ (**39m**), $Zn(OAc)_2$ (**39n**), $PdCl_2$ (**39o**);
n = 2, MX_m = $CoCl_2$ (**39p**), $NiCl_2$ (**39q**), $ZnCl_2$ (**39r**), $PdCl_2$ (**39s**), $SnCl_4$ (**39t**).

The crystal and molecular structures of complexes of copper[82] and cobalt dichlorides[48] with *N*-isopropenylimidazole have been determined by X-ray diffraction. In the complexes of the general formula $MCl_2 \cdot 2L$ (M = Co and Cu; L is *N*-isopropenylimidazole), the metal ion is surrounded by two N atoms of the imidazole ring and two Cl atoms. In contrast to the tetrahedral complex of cobalt, the coordination polyhedron of the Cu atom is intermediate between a tetrahedron and a square. In these molecular complexes, the monodentate terminal *N*-isopropenylimidazole ligands are coordinated to the metal atom through the "pyridine" N atom.

3. Metal complexes with *N*-allenylimidazoles

While the coordination chemistry of *N*-vinyl-[26—73] and *N*-allylimidazoles[74—79] is widely covered in the literature, data on *N*-allenylimidazole complexes have been lacking until recent development of an efficient one-step preparative method for direct allenation of azoles with propargyl halides[83,84] or 1,2,3-trichloropropane,[83] which provides easy access to this class of ligands (Scheme 8).

Scheme 8



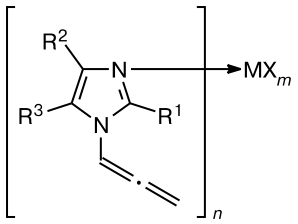
40a—c

X = Cl, Br

R′ = H (imidazole **40a**, 47—75% yield); R′ = Me (imidazole **40b**, 76% yield); R′ = H (benzimidazole **40c**, 75% yield).

Reagents and conditions: KOH/DMSO, 0.5—1.0 h, 25—40 °C (*a*), 40—50 °C (*b*).

Since allenes readily undergo oligomerization, the formation of both mononuclear and polynuclear metal complexes with *N*-allenylimidazoles should be expected. However, the only reaction products are stable mononuclear complexes (**41a—w**) of the formula $MX_m \cdot nL$, where M = Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Pd^{2+}, and Sn^{4+}; X = Cl and OAc; L is *N*-allenylimidazole, 1-allenyl-2-methylimidazole, and *N*-allenylbenzimidazole; $m = 2$ and 4; $n = 1$, 2, and 4.[85,86] The reaction easily occurs at room temperature in an anhydrous solvent (ethanol, acetone, diethyl ether, or their mixtures), the ligand : acceptor ratio being 1 : 1, 2 : 1, 4 : 1, or 1 : 2. In the resulting complexes, *N*-allenylimidazoles act as monodentate ligands coordinated through the N(3) atom of the heterocycle; the group CH_2=C=CH— is stabilized by the coordination of the imidazole ring to the metal atom, which reduces the electron transfer from the heterocycle to the allenyl fragment.



41a—w

$R^1 = R^2 = R^3 = H$: $n = 1$, $MX_m = CdCl_2$ (**a**), $PdCl_2$ (**b**);
$n = 2$, $MX_m = CoCl_2$ (**c**), $NiCl_2$ (**d**), $ZnCl_2$ (**e**), $CuCl_2$ (**f**), $Zn(OAc)_2$ (**g**), $SnCl_4$ (**h**); $n = 4$, $MX_m = CuCl_2$ (**i**), $NiCl_2$ (**j**);
R^1 = Me, $R^2 = R^3 = H$: $n = 1$, $MX_m = Zn(OAc)_2$ (**k**), $CdCl_2 \cdot 2H_2O$ (**l**), $NiCl_2 \cdot 3H_2O$ (**m**); $n = 2$, $MX_m = ZnCl_2$ (**n**), $CuCl_2$ (**o**), $SnCl_4$ (**p**), $CoCl_2$ (**q**); $n = 4$, $MX_m = CuCl_2$ (**r**), $NiCl_2$ (**s**);
$R^1 = H$, $R^2 + R^3 = (CH)_4$: $n = 2$, $MX_m = CoCl_2$ (**t**), $ZnCl_2$ (**u**), $CdCl_2$ (**v**), $CuCl_2$ (**w**).

4. Biological activity of metal complexes with *N*-alkenylimidazoles

An analysis of the literature data reveals a variety of wide applications of vinylazole derivatives as biologically active compounds. Considerable advances in this area have been promoted by systematic investigations performed since the 1970s by Skvortsova and her disciples at the Irkutsk Institute of Organic Chemistry (now the A. E. Favorsky Institute of Chemistry of the Siberian Branch of the Russian Academy of Sciences) in cooperation with Russian medical institutions. At present, these investigations are being actively continued in the context of the development of a methodology of organic and organoelement synthesis from acetylene and its derivatives. Investigations performed during many years into the synthesis of new classes of unsaturated heteroatomic structures based on acetylene and its derivatives and into the design of various metal complexes with such ligands have been successful in selecting the compounds most promising for practical use.

Bis(*N*-vinylimidazole)zinc diacetate (Acyzole) (**3d**)[34—37] and tetrakis(*N*-vinylimidazole)cobalt dichloride (Cobazole) (**3j**)[44,45] are most familiar among them.

Acyzole proved to be a potent antihypoxic agent[87—108] and has been recommended for medical use as an antidote against acute intoxications with lethal doses of carbon monoxide and other combustion products.[34—37,87—103,107]

The antidote effect of Acyzole in CO-intoxicated patients is due to its ability to decrease the relative affinity of hemoglobin for carbon monoxide, which is manifested by a lower Douglas constant and more rapid removal of CO from an organism. Acyzole lowers the cooperative interaction of hemoglobin subunits, which is evident from the

lower Hill coefficient and is clinically manifested by the disappearance of the Haldane effect. In the presence of this agent, the oxygen affinity of hemoglobin increases and the oxyhemoglobin dissociation curve is shifted to the left.[96,97,102,103] Thus, Acyzole is also an efficient antihypoxic agent in the case of oxygen deficiency.

Acyzole maintains the vital functions of the organism exposed to acute intoxication with carbon monoxide and combustion products. Administration of Acyzole to severely intoxicated victims in mass fire zones increases their chances of survival, accelerates the removal of CO, and makes subsequent treatment more successful. As a preventive measure, Acyzole may be taken under the threat of inhalation of CO and other combustion products, which is most important for members of emergency teams.[87—103,107]

Use of Acyzole as an antihypoxic agent and an antioxidant enhances the working capacity and physical endurance of the organism through zinc reduction in enzyme systems, optimization of tissue respiration, and improvement of the oxygen-binding properties of blood. Even a single preventive application of Acyzole enhances the physical condition, endurance, and resistance of the human organism to prolonged loads, the drug´s positive effect persisting several days after its course administration.[103,109,110]

Acyzole is suitable for the treatment of zinc-deficient conditions since zinc contained therein can make up the organism´s zinc deficiency and normalize the cascades of metabolic processes involved in the functioning of zinc-dependent enzyme systems.[103,111]

Acyzole has been used to develop a method for pathogenetic therapy of psoriasis.[112,113] This drug affects the key mechanisms regulating the psoriasis initiation and progress: it normalizes the oxygen balance of skin by arresting the hypoxic condition of the epidermal basal cells and thus stopping hyperproliferation and the zinc contained in Acyzole prevents the untimely triggering of the apoptosis of keratinocytes.

Pharmacologically, Acyzole can also be regarded as a hepatoprotector. Experimental preclinical trials have revealed the high efficiency of this drug against liver intoxication with such poisons as dichloroethane, phenacetin, and carbon tetrachloride.[103,109,114] Acyzole is superior to the registered drugs of this pharmacological group (Carsil, Legalon, and Essentiale) in hepatoprotective effect.

As a coronary-active antiischemia and antiarrhythmic agent, Acyzole makes it possible to confine the necrosis zone in acute myocardial ischemia, reduce the complication and mortality rates, normalize the atrioventricular and intraventricular conductivities, and prevent cardiac fibrillation.[103,115]

In experimental and laboratory studies, Acyzole has been found to be promising for use in comprehensive therapy of inflammatory periodontal diseases,[103,116—119] including type II diabetes patients.[116,119]

The use of Acyzole as a pathogenetic agent for the treatment of pneumonias aggravating the course of acute intoxications with neurotoxic products substantially lowers the mortality rates. For instance, under conventional therapy of nosocomial pneumonia, the mortality rate was 43.3%, while the application of Acyzole reduced the mortality to 8—10%.[103,120]

In clinical trials, Acyzole has proved to be efficient for prevention and treatment of toxic-hypoxic encephalopathies aggravating the course of acute intoxications with CO and other combustion products: acceleration of consciousness recovery, prevention of severe neurological problems in 70% of patients, reduction of the risk of psychical disorders in a third of patients, reduction of the pneumonia evolution rate by a factor of 2.4, reduction of the mortality rate by a factor of 2.75, and reduction by half of invalidating complications.[103,120]

Acyzole´s membrane-protective properties arising from its antihypoxic and antioxidant effects account for its high preventive efficiency against intoxications with heavy metal salts[103,121—128] and nitrites.[129] These pharmacological properties of Acyzole are useful for substantial reduction of the toxic effect of exhaust gases and smog on the organism.[99,103]

Creams, gels, liniments, pastes, and solutions containing bis(*N*-vinylimidazole)zinc diacetate (1—6%) for external use are also highly efficient for the treatment of such skin diseases as neurodermatitis, allergic dermatoses (diatheses), persistent (trophic) ulcers, a bedsore, and other inflammatory skin pathologies and as a cosmetic that restores the structural processes in skin, removes lentigines, diminishes wrinkles, *etc.*[130] The specific effect of Acyzole is due to (1) stimulation by this zinc-containing complex of systems providing antioxidant protection to epidermal cells from untimely programmed cell death (apoptosis) and (2) stimulation of the oxygenation mode in the damaged skin area *via* the antihypoxic effect, which normalizes the main structural epidermis-forming processes.

Acyzole is manufactured in two medicinal forms: a solution for intramuscular injection (60 mg mL^{-1})[89,131] and 120-mg capsules.[132,133] The compositions of the transdermal medicinal form of Acyzole with polyacryl or "water-in-oil" emulsion formulations as a depot for the active component have been proposed.[134]

The specific activity and safety of Acyzole in the above medicinal forms have been extensively studied at the Institute of Toxicology of the Ministry of Health and Social Development of the Russian Federation.[103] It has been found that Acyzole shows a wide range of therapeutic action and is safe when daily given intramuscularly, intragastrically, or orally to test warm-blooded animals (rodents and dogs) for a prolonged (90 days) period of time. The use of Acyzole causes no pathological shifts of the biochemical characteristics nor has a negative effect on the main physiological systems and internal organs. The

tested medicinal forms of Acyzole are not irritant or provoke no allergic reactions. In the tested doses and routes of administration, Acyzole shows no embryotoxic or teratogenic properties, nor it affects the reproductive function in test animals upon 90-day administration.

Apart from Acyzole, complexes of *N*-vinylimidazole with zinc chloride (bis(*N*-vinylimidazole)zinc dichloride (**3e**))[32,96] and zinc ascorbate (bis(*N*-vinylimidazole)zinc ascorbate (**3f**))[33,96] are also highly efficient against acute intoxication with carbon monoxide; a zinc sulfate complex with *N*-vinylimidazole is a slightly inferior antidote.[135] A complex of zinc methylphenoxyacetate with *N*-vinylimidazole makes the organism more resistant to NO_2 and hypobaric hypoxia.[96,136] Antihypoxic properties under various types of hypoxia are also exhibited by complexes of iron chloride with *N*-vinylimidazole (**3h**)[108] and zinc acetate with *N*-isopropenylimidazole (**39c**),[108] *N*-allenylimidazole (**41g**),[108] and 1-allenyl-2-methylimidazole (**41k**).[108]

It is known that drugs containing such microelements as Fe, Cu, and Co occupy a special place among antianemic agents. Tetrakis(*N*-vinylimidazole)cobalt dichloride (**3j**)[29,30] is the active component of the novel original drug Cobazole[44,45] designed for medical use as a broad-spectrum hematopoiesis stimulator.[44,45,53,93—97,137—145] Cobazole efficiently arrests posthemorrhagic, iron-deficient, and iron-resistant anemias, as well as cytotoxic and postradiation leukopenias. The improvement of the peripheral blood characteristics in patients treated with Cobazole suggests its higher efficiency compared to common hematopoietic stimulants (vitamin B_{12}, iron drugs, and leukogen) used in traditional therapeutic methods.[45,53,141] For instance, Cobazole is considerably more efficient (5—6 times) against leukopenias than leukogen, which makes it possible to really maintain the normal level of leukocytes under the conditions of antitumor chemotherapy and radiation therapy.[96,137—145] Clinical trials have demonstrated that Cobazole stimulates leukopoiesis in cancer patients with progressive leukopenias caused by cytotoxic therapy; the clinically significant effect has been observed in 73% of patients with grade 2 or 3 leukopenia. The immunomodulating and antibacterial effects of Cobazole improve its clinical value for the treatment of anemias and leukopenias.[45,139] Cobazole is also efficient against acute and chronic posthemorrhagic anemias in 88.3% of patients.[141—143,145] Its clinical effect on grades 2 and 3 leukopenias in gynecological cancer patients is 96.6%; the discovered protective effect of Cobazole will allow cyclic chemotherapy with the planned dose intensity.[140—142,144,145] The course use (five to seven injections) of Cobazole against anemias ensures its long aftereffect (30 days) with retention of normal values of the main blood parameters.[96,141—145]

In compliance with the requirements of the Committee of Pharmacology at the Ministry of Health and Social Development (CP MHSD) of the Russian Federation, Cobazole has been subjected to comprehensive preclinical trials in mice, rabbits, and dogs for safe use (acute, chronic, and specific types of toxicity; pharmacokinetics; organ distribution).[45] According to the CP MHSD resolutions (protocols No. 1 adopted January 27, 1994 and January 29, 1998), the clinical trials (phases I and II) of Cobazole have been performed at the Irkutsk Regional Oncological Center, the Gynecological Department of the Angarsk Oncological Center, and the Gynecological Department of the Irkutsk State Institute of Advanced Medical Training, and methodological recommendations for wide medical use of Cobazole as a promising drug for the treatment of various types of anemias have been made.

Areas for promising use of other metal complex with *N*-alkenylimidazole derivatives have been outlined. Tests of Zn-, Ni-, and Co-containing complexes with *N*-vinyl derivatives of 2,2′-biimidazolyl,[53,96,146,147] 2-hydroxymethylimidazole,[53,96,146,148] and 2-hydroxymethylbenzimidazole[53,96,146,148] have revealed their high radioprotective effects (30—50%), which decrease in the order Ni > Co > Zn.[53,96]

Complexes of Cd^{2+}, Pt^{2+}, Pt^{4+}, and Pd^{2+} with *N*-vinylimidazole and 2-hydroxymethyl-1-vinylimidazole exhibit antitumor activity.[53,96,149,150] For instance, a $CdCl_2$ complex with 2-hydroxymethyl-1-vinylimidazole (salt : ligand = 1 : 1) inhibits the growth of the solid form of sarcoma-37 by 41%, Ehrlich ascites carcinoma by 15%, Pliss lymphosarcoma by 23%, carcinoma-755, Lewis lung carcinoma, and Guérin carcinoma by 32—37%. It should be noted that the use of a complex of bis(*N*-vinylimidazole)cadmium dichloride (salt : ligand = 1 : 2) inhibits the growth of sarcoma-45 and Guérin carcinoma by 51 and 43%, respectively. The antiblastic effect of (2-hydroxymethyl-1-vinylimidazole)cadmium dichloride on sarcoma-37 is comparable with those of the Pt^{2+}, Pt^{4+}, and Pd^{2+} complexes with *N*-vinylimidazole (tumor growth suppression by 38—42%). Among Pt complexes, melanoma-16 is best suppressed by bis(*N*-vinylimidazole)platinum tetrachloride (48%), while tetrakis(*N*-vinylimidazole)-platinum tetrachloride and tetrakis(*N*-vinylimidazole)-platinum dibromide provide 38% protection of animals.[53,96,149,150]

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