ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 3, pp. 602–620. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © V.N. Demidov, N.A. Kas'yanenko, V.S. Antonov, I.L. Volkov, P.A. Sokolov, T.B. Pakhomova, S.A. Simanova, 2010, published in Rossiiskii Khimicheskii Zhurnal, 2010, Vol. 54, No. 6, pp. 120–135.

Reaction with DNA and Pharmacologic Activity of 1,10-Phenanthroline and Electron-Rich 1,10-Phenanthrocyanine Complexes of *d*-Elements

V. N. Demidov[a], N. A. Kas'yanenko[b], V. S. Antonov[a], I. L. Volkov[b], P. A. Sokolov[b], T. B. Pakhomova[a], and S. A. Simanova[a]

[a] *St. Petersburg State Technological Institute (Technical University), Moskovskii pr. 26, St. Petersburg, 190013 Russia*
e-mail vndemidov@mail.ru

[b] *St. Petersburg State University, St. Petersburg. Russia*

Received November 1, 2010

Abstract—Types of binding with DNA and pharmacologic activity of 1,10-phenanthroline and electron-rich 1,10-phenanthrocyanine complexes of *d*-elements are discussed. The relationship of the electronic and geometric structure of 1,10-phenanthroline complexes of transition metals to their interaction with DNA molecules is analyzed. The concept of redox-mediated antibacterial, antiviral, and antitumor activity of 1,10-phenanthroline complexes of *d*-elements is formulated.

DOI: 10.1134/S1070363212030401

INTRODUCTION

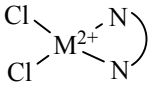
The specific pharmacologic activity of *d*-element complexes with 1,10-phenanthrolines and more complex ligands containing 1,10-phenanthroline fragments, viz. their antibacterial, antiviral, and antitumor effects, is associated with the biochemical activity of these heteroarenes, including their ability to interact with DNA molecules. Such properties of the complexes are due to a high chelating power of 1,10-phenanthrolines, as well as a planar geometry and π-electron deficiency of these ligands.

The growing recent interest in the physicochemical properties of DNA is explained by the fact that DNA solutions are widely used for testing novel drug formulations at the level of model systems, as well as by the possibility of development of DNA-based nanostructures which hold promise for medicine, biology, pharmacology, and nanoelectronics.

DNA molecules are the main target of many antitumor drugs. For example, the antitumor activity of such drugs as cisplatin {*cis*-$[Pt(NH_3)_2Cl_2]$}, oxaplatin, and carboplatin [1–10] is associated with DNA replication inhibition**.** It is commonly accepted that cisplatin mainly interacts with DNA by covalent binding with the N^7 positions of two neighboring guanine bases in the same chain in *d*(GpG) sequences in the major groove of the double helix [11].

The main disadvantages of the known antitumor agents are their toxicity and nonselectivity. Therefore, synthesis and pharmacologic activity testing of potential cytostatic compounds still remains an urgent problem.

Researchers searching for new antitumor agents focus primarily on structural analogs of cisplatin, specifically neutral diamine Pt(II) and Pd(II) complexes *cis*-$[MA_2X_2]$ (M = Pt^{2+}, Pd^{2+}, A = alkyl and heterocyclic amines), including chelate complexes



with N–N chelating amine ligands, such as 2,2'-bipyridyl, polypyridines, and 1,10-phenanthrolines [12, 13]. Thus, for example, both *cis*- and *trans*-$[Pt(py)_2Cl_2]$ with planar pyridine ligands exhibit antitumor activity and inhibit DNA synthesis, but the *cis* isomer stronger binds with thymus DNA than with the *trans* isomer [14].

Over the past time enhanced interest is attached to the pharmacologic activity of binuclear bridged complexes [15–18], including those containing cations like

$$[(N–N)M^{2+}(\mu\text{-}X)_2M^{2+}(N–N)]^{2+},$$

$(M^{2+} = Pt^{2+}, Pd^{2+}, X = OH^-, SR^-)$ [19–21].

Wheate and Collins [21, 22] have formulated a new paradigm of antitumor activity, which brought to the fore binuclear and polynuclear coordination compounds, in particular, study of potential feasibility of binuclear complexes as DNA probles [23]. It was thus found that the destruction of platinum DNA intercalators $[Pt(5,6\text{-}Me_2\text{-phen})L]^{2+}$, $[Pt(5\text{-Me-phen})L]^{2+}$ (phen = 1,10-phenanthroline, L = 1*S*,2*S*- or 1*R*,2*R*-diaminocyclohexane), and $[Pt(5,6\text{-}Me_2\text{-phen})(en)]^{2+}$ under the action of reduced L-glutathione gives rise to binuclear bis-1,10-phenanthroline complexes with a reduced L-glutathione bridge [20]. In terms of the pharmacologic activity of bi- and polynuclear 1,10-phenanthroline complexes, of particular interest are the tetranuclear Pt(II) acetamidate $[(phen)Pt^{2+}(\mu\text{-}NHCOCH_3)\text{-}Pt^{2+}(phen)]_2(NO_3)_4$ and 1,10-phenanthroline platinum blues $Pt(phen)(NHCOCH_3)_2X$ ($X = NO_3^-$, $CF_3SO_3^-$, Cl^-) [24]. Platinum blues like

$$[(Pt^{2+})_3Pt^{3+}(NH_3)_8(\mu\text{-}RCONH)_4](NO_3)_5$$ [25]

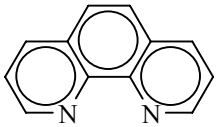
have long attracted interest; in particular, antitumor properties were revealed in stable mixed-valence platinum blues $[(Pt^{2+})_3Pt^{3+}(NH_3)_8(\mu\text{-}L_4)]^{5+}$ (L = deprotonated amidate ligand) [26]. A physicochemical study of the cationic platinum blues formed by the reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with amides (isonicotinamide, malonediamide, and biuret), as potential antitumor agents was performed in [27]. Pt(II), Pt(III), and Pt(II,III) mixed-valence acetates were reduced with molecular hydrogen in the presence of 1,10-phenanthroline to obtain polymeric low-valence Pt(I) complexes $Pt_8^{1+}(phen)_3(OAc)_4(OH)_4(H_2O)_6$ which are considered as precursors of platinum colloids [28]. Clusters and colloids of Pd, Pt, Ag, and Au, having a metal nucleus and a 1,10-phenanthroline-containing shell, were patented as organometallic probes for biochemical applications [29].

The reactions of DNA with a macrocyclic compound **L** comprising two 1,10-phenanthroline cycles tethered by positions 2 and 9 by two –S– bridges, and with the complex $[Cu^{2+}L](OAc)_2$ were studied by spectral methods [30]. The metal-free macrocycle **L** binds with DNA molecules and cleaves in them in the presence of sulfanylpropanoic acid in anaerobic conditions [30]. Porphyrin-like chromophoric cyanine macrocyclic 2,2',9,9'-diaza- and 2,2',9,9'-dimethine-bridged bi-1,10-phenanthrolines and transition metal complexes of these macrocycles, as well an S-bridged Ru(II) complex were studied as DNA probes [31].

Of parcticlar interest in terms of DNA probe applications are electron-rich supramolecular 1,10-phenanthrocyanines of transition metals, coordination compounds of a new cyanine structural class [32–42]. They can be considered as potential pharmacologic agents of a new generation, which form templates with DNA. They tend to take part in biochemical processes responsible for redox-assisted antibacterial, antiviral, and antitumor action. Electron-excessive 1,10-phenanthrocyanine complexes have a more complicated structure than their 1,10-phenanthroline precursors, namely C–C-dimeric or C–C-oligomeric bi- or polynuclear structure and a specific electoron-excessive structure of chromophoric fragments. They exhibit a higher affinity to polymeric substrates and a higher redox activity, are may form basis for enhanced selectivity of binding of such agents with biological targets, such as DNA, and for their activity in redox processes. This expectation is underlain by the fact that much simplier 1,10-phenanthroline complexes bind with DNA in different ways: intercalation, outer-sphere ionic associative or covalent binding, whereas the complexes with redox-active *d*-element ions are capable of cleaving DNA in redox and photoredox processes [43]. The way of coordination with DNA depends on a combination of factors: type and structure of the complex, its thermodynamic stability in solutions, as well as kinetic lability in ligand substitution reactions.

Biochemical and Pharmacologic Activity of 1,10-Phenanthrolines and 1,10-Phenanthroline Complexes of *d*-Elements

1,10-Phenanthroline (1,10-phen) and its derivatives are classed with π-electron-deficient N-heteroarenes.



They are efficient chelating ligands for most *d*-element ions and act as fairly powerful σ-donors and π-acceptors. These ligands can stabilize low oxidation degrees of *d*-elements in complexes and metal clusters and endow complexes with hydrophobic properties [44].

1,10-Phenanthroline is a biochemically active compound, inhibitor of metalloproteases and mitochondrial and chloroplast functions: at a concentration of 10^{-5} M it

decreases by 50% release of O_2 on photosynthesis, at concentrations of 10^{-8} M it inhibits certain Fe-containing enzymes and glutamate hydrogenase, at a concentration of ~0.5×10^{-3} M it inhibits by 28% ubiquinol-cytochrom-*c* reductase [45], and inhibits formation of hydroperoxide-induced single-strand DNA cleavage in HL-90 line cells [46] and growth of lactate bacteria [47]. 1,10-Phenanthroline and its derivaties were tested for mutagenicity on *Salmonella* bacteria [48].

It was founds that 1,10-phenanthroline exhibits tuberculostatic activity with respect to *Mycobacterium phlei* and *Mycobacterium bovis* bacteria [49, 50]. 1,10-Phenanthroline and 2,9-dimethyl- and 2,9-dipropyl-1,10-phenanthroline showed antimycoplasmatic activity [51]. 1,10-Phenanthroline was also found to be a powerful antiamoebic agent against *Entamoeba histolytica*. It reversibly inhibits two human prostate carcinoma cell lines: *PC-3* and *DU* 145 [52], as well as formation of lymphoblastic T- and B-cell colonies [53]. Being a bidentate chelating ligand for metal ions, 1,10-phenanthroline, when combined with the antitumor agent hydroxyurea, enhances the cytotoxicity of the latter with respect to human chronic myeloid leukemia cell line [54].

1,10-Phenanthroline modulates porphyrin biosynthesis, which can be used for developing chemotherapeutic agents on the basis of porphyrin compounds [55]. 1,10-Phenanthroline is also capable of modulating biosynthesis of chlorophyll, and its combination with δ-aminolevulinic acid is recommended as a photodynamic plant defoliant [56]. Agrochemical microbicides for treatment of leaves, containing 1,10-phenanthroline and its alkyl -, alkoxy-, carbonyl-, and mono- and disubstituted halo derivatives (in pyridine rings) were developed [57]. 1,10-Phenanthroline was suggested to use as an immune reagent for radionuclide binding [58]. Synergistic protective systems containing quaternary ammonium bases (like cetylpyridinium chloride) in combination with hydrophobic chelating agents, such as 1,10-phenanthroline, 5-chloro- and 5-nitro-1,10-phenanthroline, were recommended for medical applications as nasal sprays [59]. The fungistatic activity of 1,10-phenanthrolines was studied *in vitro* [60, 61].

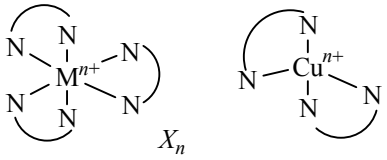
Pyridine and polypyridines, such as 2,2'-bipyridine and 1,10-phenanthroline, as well as their reduced forms have long attracted interest as potential pharmacologic agents [62]. Among 2,2'-bipyridine and 1,10-phenanthroline derivatives, there are natural antibiotics, for example, caerulomycin A (4-methoxy-2,2'-bipyridyl-6-aldoxime) [63]. Antibacterial and antiviral effects of 1,10-phenanthroline, substituted 1,10-phenanthrolines, quaternary halides derived from *N*-alkyl-1,10-phenanthrolines, metal complexes of 1,10-phenanthrolines and its derivatives, as well as an antitumor effect of metal complexes of 1,10-phenanthrolines and their ability to kill dermatophytes have been reported [64–71].

Shulman and White [71] were among the first to correlate the structure and antiviral activity of 1,10-phenanthroline chelate complexes of transition metals. Complexes of Fe(II), Mn(II), Zn(II), Ni(II), and Pt(II) with 1,10-phenanthroline are capable of inhibiting human spermatozoids and inhibit *Neisseria gonorrhoeae* and *Treponema pallidum*; certain of these complexes were patented as efficient contraceptives and antivenereal agents [72]. Therapeutic compositions for dermatological or vaginal use against bacterial infections of animals, plants, and humans, containing as active substances methyl- and phenyl-substituted 1,10-phenanthrolines, *N*-alkyl-1,10-phenanthrolines, as wll as Fe(II), Ni(II), Ru(II), Co(II), Cu(II), Mn(II), and Zn(II) complexes of 1,10-phenanthrolines and its derivatives were patented [73]. Complexes of transition metals with 4,7-diphenyl-1,10-phenanthrolinedisulfonic acid were suggested as medicines for septic shock treatment [74].

Free 1,10-phenanthrolines can, due to their planar structure, intercalate into DNA double helices. Thus, Liu et al. [75] made use of fluorescence spectroscopy to find that 2,9-dimethyl-1,10-phenanthroline binds with DNA (the binding constant K is 3.3×10^5 M^{-1}), expelling such a typical intercalating agent as Ethidium Br (3,8-diamino-5-ethylphenylethyl-phenanthridinium bromide). This conclusion was drawn from the fluorescence quenching of the Ethidium Br−DNA system. Enhanced cytotoxicity toward cultured L1210 mouse leukemia cells of weed growth inhibitors similar to 1,10-phenanthroline, specifically the herbicides alkyl viologens (*N*-R,*N*'-R-4,4'-bipy)Cl_2 (R = Me, Et, Pr) and their *N,N*'-diamine analogs, carbamoyl methyl viologen (R = CH_2CONH_2), acetylaminoviologen (R = $NHCOCH_3$), and aminoviologen in the presence of polyacrylic acid [76]. The cations of 1,1'-dimethyl-4,4'-bipyridynium chloride (herbicide Paraquat) are electrostatically associated with negatively charged phospholipids of model cellular

membranes [77]. 1,1'-Ethylene-2,2'-bipyridynium bromide (contact herbicide Diquat) inhibits sugarcane flowering. The suggested mechanism of action of this compound consists in destruction of cell membranes, followed by destruction of unsaturated fatty acids under the action of the $O_2^{\bullet-}$ radical anion formed by oxidation of Diquat radical cations [45]. Bisquaternary salts of methyl-substituted 1,10-phenanthrolines, too, were found to act as herbicides [78]. *N*-Alkylquinolinium halides structurally similar to *N*-alkyl-1,10-phenanthroline halides were patented as intercalators showing affinity to DNA [79]. Presumebly, a group of carbocyanine dyes derived from *N*-alkylquinolinium halides are potential antitumor agents [80].

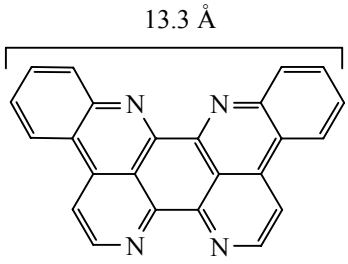
Reactions of pyridine [81] and polypyridine [82–84] complexes of transition metals with DNA have attracted much attention over the last decade. The following thermodynamically stable tris-chelate octahedral 1,10-phenanthroline complexes and coordinately unsaturated bis-chelate compounds



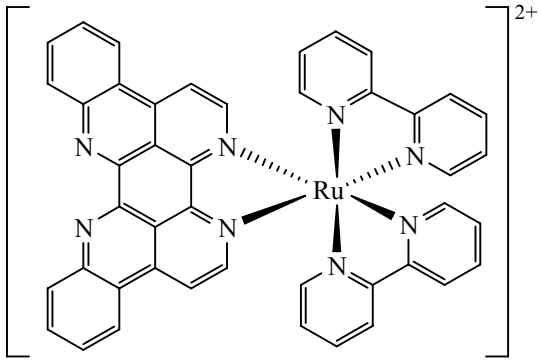
characteristically tend for outer-sphere associative ionic binding and intercalation into DNA. It was shown that polypyridin metal complexes are capable of electrostatic, intercalation, and groove binding with DNA [85, 86]. Cationic metal complexes with planar heteroaromatic ligands like 2,2'-bipyridine and 1,10-phenanthroline bind with DNA by interaction involving stacking of the planar ligands between neighboring base pairs of duplex DNA [87]. It was found that tris-1,10-phenanthroline complexes of Ru(II) show entiomeric selectivity on binding with DNA and can serve as spectroscopic probes for differentiation of right and left DNA helices in solutions [88]. The binding of Ru(II) polypyridine complexes with DNA leads to their luminescence quenching [89]. The intercalation and outer-sphere DNA binding with mixed-ligand Co(III) complexes of 1,10-phenanthrolines and ethylenediamine, as well as their-promoted cleavage of pBR322 DNA plasmids [90]. Polypyridine Co(III) complexes stereospecifically cleave DNA double helices under photoactivation conditions [91]. The high content of DNA conformations with these chiral centers points to the stereospecificity in DNA drug design. Barton [43] reported the use of transitionmetal complexes with 1,10-phenanthroline and its derivatives as photochemical probes for structural stidues on DNA.

Chiral complexes of Rh(III), Ru(II), and Co(III) complexes with 1,10-phenanthrolines and its derivatives [92], as well as 1,10-phenanthroline complexes of Cu(II) [93] and Fe(II) [94] function as DNA-cleaving agents. Complexes of Ru(II) with 1,10-phenanthroline can enatioselectively interacalate into the $d(GTCGAC)_2$ amino acid sequence [95]. Complexes of Ru(II) and Co(III) with 1,10-phenanthroline and its derivatives were suggested as DNA-site-specific anticancer agents and chemical probes for left-rotating DNA [96, 97].

The natural antitumor alkaloid Eilatin comprises condensed 1,10-phenanthroline and 2,2'-bipyridine fragment. This alkaloid and its synthetic analogs 5-nitro-4,7-diphenyl-1,10-phenanthroline and 1,10-phenanthroline-5,6-dione were patented as preparations able to regulate cell growth and suppress growth of cancer cells and induce their differentiation and reversible transformation [98, 99].



Eilatin



Δ-[Ru(eilatin)(bpy)$_2$]$^{2+}$

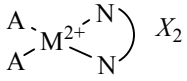
Eilatin can coordinate with *d*-element ions, specifically Ru(II), and fulfill the function of a sterically expansive ligand in mixed-ligand Ru(II) complexes like Δ-[Ru(eilatin)(bipy)$_2$]$^{2+}$. Such compounds are studied as probes for DNA base mismatches [100].

Stereoisomers of the bulky binuclear complex Ru(II)[(phen)$_2$Ru^{2+}(hat)Ru^{2+}(phen)$_2$]$^{4+}$ (hat = 1,4,5,8,9,12-hexazatriphenylene) (ΔΔ and ΛΛ enantiomers with C_2 symmetry axis) containing two chiral "building blocks" Ru(phen)$_2^{2+}$ selectively intercalate into defective domains of denaturated thymus DNA and can serve as their photoprobes [101, 102].

Jackson and Barton [103] described the recognition of DNA base mismatches by means of intercalators, specifically Rh(III) complexes (Δ and Λ enantiomers) [Rh(2,2'-bipy)$_2$L][PF$_6$]$_3$ (L = 5,6-chrisenequinonediimine ligand) obtained by the reaction of [Rh(2,2'-bipy)$_2$(NH$_3$)$_2$][PF$_6$]$_3$ with 5,6-chrisenequinone. Because of the large size of ligand L these complexes cannot intercalate into normal DNA chains but can recognize local per-turbation sites corresponding to mismatched base pairs. Therewith, the strongest photocleavage is observed in the case of the D enantiomer associated with DNA loops containing a cytosine–cytosine (CC) pair. The thermodynamic binding constant of the D enantiomer with the DNA 35-mer including a mismatched CC base pair is 8.4×10^5 M^{-1} [103].

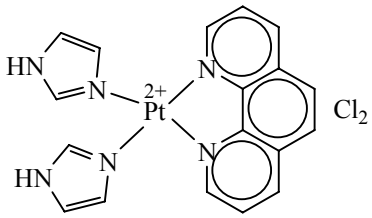
Complexes of Ru(II) with 1,10-phenanthroline and its derivatives are capable of cleaving natural structured RNA to form specific sites, which was suggested to use for structural assessment of RNA [104].

Square-planar mixed-valence complexes [M(N–N)A$_2$]X$_2$



(M = Pd^{2+}, Pt^{2+}, A – amines, X = Cl, Br).

can intercalate into DNA and form outer-sphere associative ionic bonds. A mixed-ligand complex of Pt(II) with 1,10-phenanthroline and imidazole bis-(imidazole)(1,10-phenanthroline)platinum(II)dichloride:



was patented as a chemotherapeutic agent with a cytotoxic antitumor activity [105]. It exhibits enhanced specific reactivity and reduced toxicity. Bis(imidazole)-(1,10-phenanthroline)copper(II) dichloride possesses antibacterial and antiblastic activities [106]. It was found *in vitro* that mixed-ligand complexes of Pt(II) and Pd(II) with 1,10-phenanthroline and diethyldithiocarbamate anions exhibit a cytotoxic effect on the P-388 lymphocytic leukemia cell [107].

In addition to the biochemistry of *d*-element complexes, let us dwell on the physiological activity of tin phenanthroline complexes. Thus, the complexes of di-*tert*-butyltin chloride with 1,10-phenanthroline and 4,7-diphenyl-1,10-phenanthroline showed *in vitro* a higher antitumor activity with respect to *Ehrlich ascites* tumor than the antibiotic *Acalacinomicyn A* [108]. Experiments *in vitro* revealed an antiviral activity of complexes [R$_2$SnX$_2$L] (R = Me, Et, Ph, X = Cl, Br, L = 1,10-phenanthroline) [109].

Sammes and Yahioglu described in their review [44] a wide range of uses 1,10-phenanthroline as ligands in biochemical research. Mixed-ligand complexes Pt(II) with 1,10-phenanthroline and sulfur-containing acido ligands are potential chemotherapeutic agents and probes for structural studies on polynucleotides [110]. Platinum complexes, in particular [Pt(phen)(en)]Cl$_2$, react with DNA like a typical intercalator, specifically ethydium bromide, i.e. from the side of the minor groove [112–114]. The complex [Pt(3,4,7,8-Me$_4$-phen)(en)]Cl$_2$·2H$_2$O induces single-strand breaks and DNA cross-links [115].

Brodie et al. [116] carried out a detailed study of the molecular structure–biological activity relationship for cationic mixed-ligand square-planar complexes [Pt(phen)(en)]Cl$_2$ containing 1,10-phenanthroline and its methyl derivatives (4-methyl-, 5-methyl-, 4,7-dimethyl-, 5,6-dimethyl-, and 3,4,7,8-tetramethyl-1,10-phenanthroline). The biological activity was studied *in vitro* on mouse leukemia L 1210 cell line. The cytotoxicity of the complexes videly varied depending on the position of methyl groups. The complxes with 5-methyl- or 5,6-dimethyl-substituted 1,10-phenanthrolines were found to be the most active, IC$_{50}$ 2.8±0.8 μM and 1.5±0.3 μM, respectively, but less active than cisplatin. The complex with unsubstituted 1,10-phenanthroline had IC$_{50}$ 9.7±0.3 μM, and the other complexes were inactive (IC$_{50}$ > 50 μM). The binding constants of these compounds with DNA were determined by means of circular dichroism. Viscometry and linear dichroroism experiments showed that Pt(II) complexes are intercalators, and for [Pt(4-Me-phen)(en)]Cl$_2$ and [Pt(4,7-Me$_2$-phen)(en)]Cl$_2$ this binding mode with DNA is concentration-dependent. The binding of these compounds with the oligonucleotide *d*(GTCGAC)$_2$ was

studied by ^{1}H NMR. Addition of each of the complexes to *d*(GTCGAC)$_2$ causes upfield shifts of their resonance signals. The ^{1}H NMR data were used to develop a model of binding these complexes with DNA [116] (Fig. 1), involving intercalation from the side of the minor DNA groove.

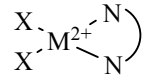
Similar Pt(II) complexes [Pt(phen*)(py)$_2$]Cl$_2$ (phen* = 1,10-phen and its derivatives, "extended" 1,10-phenanthrolines), too, intercalate into DNA double helices [117]. The influence of the chirality of auxiliary ligands and functional groups of the R substituents in 1,10-phenanthroline (R = 5-Cl, 5-CH$_3$, 5-NH$_2$, and 5-NO$_2$) in intercalating complexes [Pt(R-phen)L]Cl$_2$ (L = *S,S*- or *R,R*-1,2-diaminocyclohexane) on cytotoxicity was considered in [118]. Papadia et al. [119] have studied *in vitro* the influence of glutathione on cell growth inhibition with mixed-ligand Pt(II) complexes with 1,10-phenanthrolines and heterocyclic ligands: acyclovir (acy) and pencyclovir (pen)

$$[Pt(N–N)(acy)_2](NO_3)_2,\ [Pt(N–N)(pen)_2](NO_3)_2$$

(N–N = 1,10-phen, 2,9-Me$_2$-phen). Fluorescence spectroscopy was used to study the reaction of complexes [Pt(phen)(AA)]$^+$ (AA = anions of glycine, L-alanine, L-leucine, L-phenylalanine, L-tyrosine, and L-tryptophan) with thymus DNA [120]. It was found that these compounds at low concentrations inhibits intercalation into DNA of ethydium bromide by intercalative binding with DNA, while at higher concentrations a nonintercalative binding takes place. Anticancer activity of complexes [PdLCl$_2$] (L = 1,10-phen, 5-нитро-1,10-phen, 1,10-phen-5,6-dione) was studied [121].

Ligand–Receptor Interactions in Square-Planar Complexes [M(N–N)X$_2$]–DNA Systems

Square-planar mixed-ligand neutral complexes [M(N–N)X$_2$]



M = Pd^{2+}, Pt^{2+}, X = Cl, Br.

can, in principle, enter covalent binding with DNA, but this not always the case. When the N–N ligands include planar heterocyclic fragments, the major type of binding of [M(N–N)X$_2$] complexes with DNA is intercalation.

The reactions of DNA with neutral Pd(II) complexes with 2,2'-bipyridine and 1,10-phenanthroline were studied [122, 123] to find that the 2,2'-bipyridine Pd(II) complex [Pd(2,2'-bipy)Cl$_2$] induces quenching of the intense fluorescence of ethydium bromide (about 605 nm at excitation at 527 nm), induced its intercalative binding with DNA [122]. A conclusion was thus drawn that the Pd(II) complexes intercalate in the DNA double helix, which is consistent with the rate constants of hydration of the complex [Pd(2,2'-bipy)Cl$_2$], which occurs in two steps to form cationic complexes active toward DNA (measured in the same work):

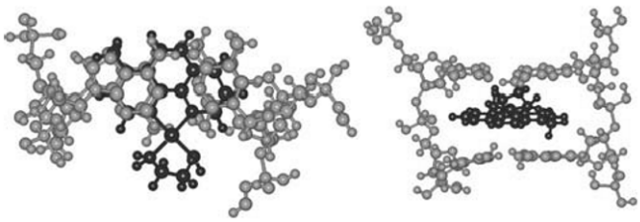


Fig. 1. HyperChem model of the intercalation of the [Pt(4-Me-phen)(en)]Cl$_2$ complex into the minor groove of the *d*(GTCGAC)$_2$ hexamer.

$$[Pd(2,2'\text{-bipy})Cl_2] + H_2O = [Pd(2,2'\text{-bipy})(H_2O)Cl]^+ + Cl^-,$$

$$[Pd(2,2'\text{-bipy})(H_2O)Cl]^+ + H_2O = [Pd(2,2'\text{-bipy})(H_2O)_2]^{2+} + Cl^-.$$

Navarro et al. [123] revealed a hypsochromic effect (12%) of the metal-ligand charge transfer band of an analogous Pd(II) complex with 1,10-phenanthroline [Pd(phen)Cl$_2$] in the presence of DNA. Based on the measured complex–DNA binding constant (3.5±0.7)× 10^4 M^{-1} and viscometry data, the authors concluded the binding of [Pd(phen)Cl$_2$] with DNA is electrostatic in nature. It should also borne in mind that, according to [19], qiaqua complexes [M^{2+}(N–N)(H$_2$O)$_2$]$^{2+}$ (M = Pd^{2+}, Pt^{2+}) are a source of binuclear dihydroxo-bridged cations [(N–N)M^{2+}(μ-OH)$_2$M^{2+}(N–N)]$^{2+}$. The latter are formed by dimerization of the [M^{2+}(N–N)(H$_2$O)(OH)]$^+$ cations resulting from acid dissociation of the strating diaqua forms:

$$[M^{2+}(N–N)(H_2O)_2]^{2+} + H_2O = [M^{2+}(N–N)(H_2O)(OH)]^+ + H_3O^+,$$

$$2[M^{2+}(N–N)(H_2O)(OH)]^+ = [(N–N)M^{2+}\mu\text{-}OH)_2M^{2+}(N–N)]^{2+} + 2H_2O.$$

Binuclear complexes [(N–N)M^{2+}μ-OH)$_2$M^{2+}(N–N)]$^{2+}$, in their turn, too, are capable of reacting with DNA. Hydration of 1,10-phenanthroline and 2,2'-bipyridine complexes can involve covalent addition of H$_2$O to hetereroarene ligands, largely by the 1,2 position {with nucleophilic addition of OH$^-$ to the 2-C(*sp*^{2}) atom}, to form coordination pseudobases [124]. However, with

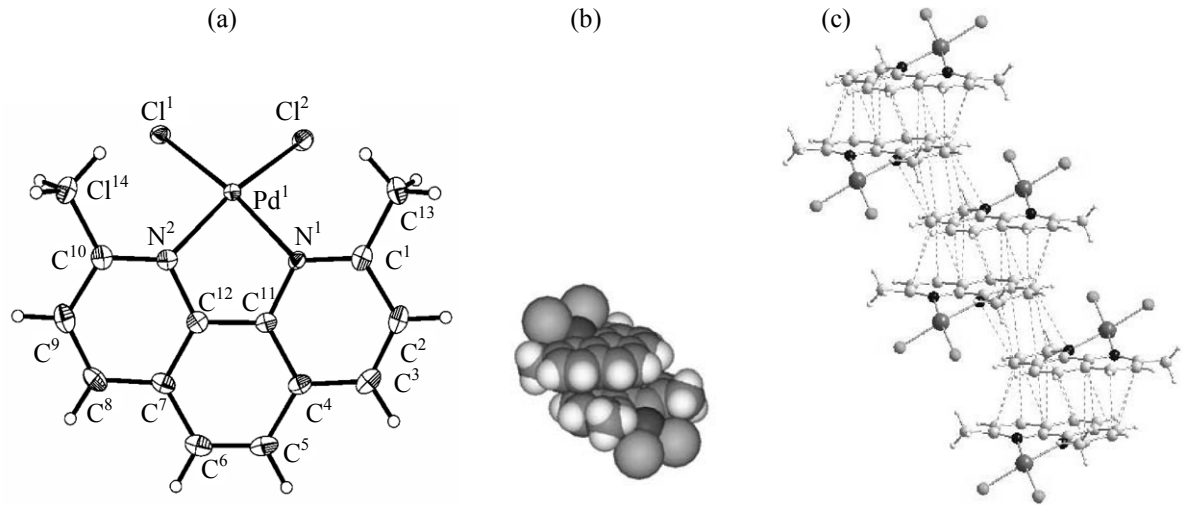
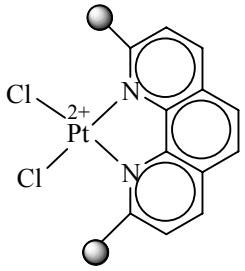


Fig. 2. (a) Molecular structure of a sterically distorted [Pd(2,9-Me_2-phen)Cl_2] complex, (b) π–π-stacking dimers, and (c) columnar structures.

2,9-dimethyl-1,10-phenanthroline Pd(II) complexes [Pd(2,9-Me_2-phen)X_2] (X = Cl, Br, I), no pseudobase formation was observed, which was explained by the blocking steric effect of methyl groups [124]. It was found that bischelate complexes like [Pd(2,9-Me_2-phen)$_2X_2$] exist in solutions as five-coordinate easily dissociating cations [Pd(2,9-Me_2-phen)$_2$X]$^+$ [125].

The major reaction mode of a square-planar complex [Pd(2,2'-bipy)(bmal)]·$2H_2O$ (bmal = benzyl-malonate anion), a potent antitumor agent agaist the AGZY-83a human lung adenocarcinoma (IC_{50} 55.4 mkg ml^{-1}), with DNA is noncovalent intercalation [102]. The adsorption maximum of the complex at 258 nm (π→π*) shifts blue in the presence of DNA, as the concentration of the latter is increased. The crystal structure of [Pd(2,2'-bipy)(bmal)]·$2H_2O$ includes 1D chains formed by π–π stacking between planar 2,2'-bipyridine ligands, whereas hydrogen bonds between the oxygen atom of the benzyl malonate ligand and a molecule of water of crystallization bind the 1D chains into a 3D carcass [126]. Such interparticle (interligand) interactions, characteristic of the [Pd(2,2'-bipy)(bmal)]·$2H_2O$ complex, favor specifically its noncovalent intercalation into DNA [126].

Sokolov at al. [127] employed spectral and hydrodynamic methods to study complex formation with a high-molecular thymus DNA (relative molecular weight 8×10^6) of a sterially distorted Pd(II) 2,9-dimethyl-1,10-phenanthroline complex



[Pd(2,9-Me_2-phen)Cl_2]

A characteristic feature of this compound is that it when crystallized from solutions, forms π–π-stacking columnar structures from π–π-stacking dimers (Fig. 2) [128].

Such dimers should be present in solutions of this compound. According to [129, 130], 1,10-phenanthroline complexes of *d*-elements are prone to dimerization in solutions. Thus, at a high concentration of [Pt^{2+}(4,7-Ph_2-1,10-phen)$(CN)_2$] (6×10^{-4} M) in methylene chloride and polyethylene glycol, the luminescence spectrum shows, along with bands at 520 and 530 nm, respectively, new bands at 615 and 630 nm, belonging to eximers (photoexcited dimers) with a Pt–Pt bond [129]. The rate constant of excimer formation in polyethylene glycol is 5.6×10^9 M^{-1} s^{-1}. A solid cationic square-planar complex [Pt(phen)$_2$]Cl_2 was found to undergo photodimerization with excimer formation [130].

A sterically distorted complex [Pd(2,9-Me_2-phen)Cl_2] reacts with DNA in a fashion different from that

characteristic of square-planar [Pd(phen)Cl_2], which is associated with steric reasons. The complex [Pd(2,9-Me_2-phen)Cl_2] is poorly soluble in water, and, therefore, its reaction with DNA was studied in mixed binary solvents DMSO–H_2O or DMF–H_2O (the compound was initially dissolved in DMSO or DMF, and the resulting solution was diluted with water). When water is added to a DMSO solution of [Pd(2,9-Me_2-phen)Cl_2], the complex can partly precipitate, but on addition of DNA solutions to this mixed-solvent solution, the system stabilizes. Apparently, the complex formation between DNA and [Pd(2,9-Me_2-phen)Cl_2] involves the inner coordination sphere of Pd (II), thus preventing transformation of the Pd(II) complex into a water-insoluble form.

The resulting data allow the conclusion that [Pd (2,9-Me_2-phen)Cl_2] most likely reacts with DNA in two ways: intercalation and covalent binding [127].

The reaction with a sterially distorted complex [Pd(2,9-Me_2-phen)Cl_2] with DNA leads to compaction of DNA molecules, which is never observed in [2,9-Me_2-phen]–DNA systems (Fig. 3).

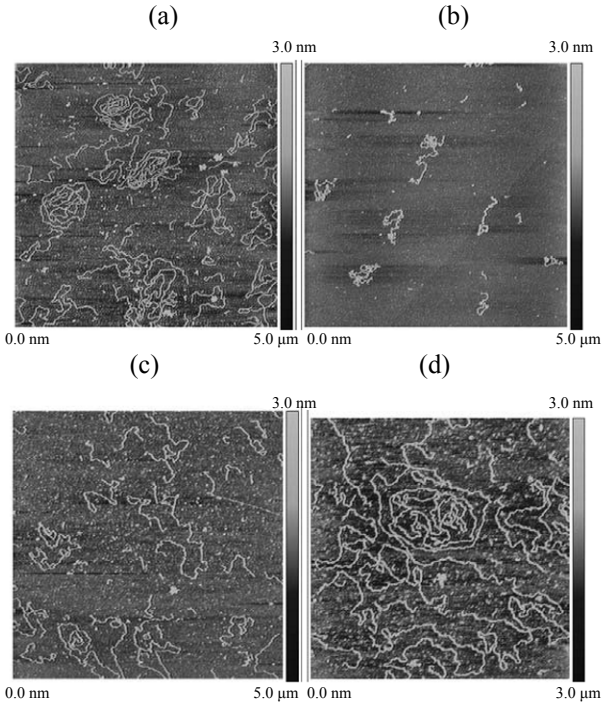


Fig. 3. ASM images of (a) thymus DNA and its complexes with (b) [Pd(2,9-Me_2-phen)Cl_2] and (c, d) 2,9-Me_2-phen. c(DNA) = 5×10^{-4}%, c([Pd(2,9-Me_2-phen)Cl_2]) = 1.25×10^{-5} M, c(2,9-Me_2-phen) = 1.25×10^{-5} M, c($MgCl_2$) = 1×10^{-3} M.

Redox-Assisted Antibacterial, Antiviral, and Antitumor Effects of 1,10-Phenanthroline Complexes

The approaches to research into the mechanisms of inhibition of pathogenic bacteria, primarily *Mycobacterium avium* (cause AIDS-associated diseases and tuberculosis), can be based on the concepts of the role of redox processes in the antimicrobial action of drugs. The expediency of this approach is evidenced by the progress in understanding redox regulation of cell functions [131].

Our analysis of the results of research on the mechanisms of pharmacologic action of antituberculosis drugs like Isoniazid [132, 133–139], as well as hydrazides derived from *N*-(*p*-nirobenzoyl)-DL-asparagine and *N*-(*p*-acylaminobenzoyl)-DL-asparagine [140], suggests that they inhibit *Mycobacterium tuberculosis* due to their reductive properties.

All known antituberculosis drugs relate to compounds with an expressed tendency for redox reactions and play the role of reducers. For example, it is safe to state that Isoniazid (isonocotinic hydrazide inhibits Kat G in the catalytic cycle of NAD(P)H oxidation to NAD(P) under the action of H_2O_2 and its associated inhibition of *Mycobacterium tuberculosis* involving the reduced forms of NADH [132]. Apparently, NAD(P)H and INH in these processes compete for H_2O_2 and/or for a biological target. Oxidation of carbohydrates with a *Saccharomyces cerevisae* culture is sensitive to oncoactive Pt(II), Pd(II), and Mn(II) complexes [141].

The redox-assisted antibacterial, antiviral, and antitumor action of pharmacologically-active substances is quite a common mechanism of their biochemical activity. Tatsuoet al. [142] studied the effect of bipyridynium salts (Paraquat, Diquat) on the generation of photocurrent by *Rhodospirillum rubrum* cells. Delaney et al. [143] found that salicylic acid play a key role in imparting resistance to viral, bacterial, and fungal infections and diseases and induced systemic resistance to plants. Metallointercalators, too, are capable of entering redox reactions. The reductive and oxidative damage of DNA under the action of water-soluble photoactive Pt(II) 1,10-phenanthroline intercalators was studied by Lu et al. [144]. Williams et al. used the example of mixed-ligand 1,10-phenanthroline complexes of Rh(III) and Ru(II) to study the effect of photooxidants on DNA-mediated charge transport [145]. Yang and Thorp [146] reported the results of a kinetic study, by means of catalytic

Electron-rich 1,10-phenanthrocyanines: microbiological and antitumor activity

System	k_r, l mol^{-1} s^{-1}	k_s, cm s^{-1}	E^o, V
$Cu_{aq}^{2+/+}$	10^{-5}		0.159
$[Cu(dipy)_2]_{aq}^{2+/+}$	160		0.120
$[Cu(phen)_2]_{aq}^{2+/+}$	68		0.170
$[Cu(5\text{-}NO_2phen)_2]_{aq}^{2+/+}$	93		0.264
$[Cu(2,9\text{-}Me_2phen)_2]_{aq}^{2+/+}$	2×10^4		0.615
$[Fe(dipy)_3]_{aq}^{3+/2+}$	$>10^8$	0.80	1.120
$[Co(phen)_3]_{aq}^{3+/2+}$		4.8×10^{-2}	0.400

electrochemistry and stopped-flow spectrometry, of one-electron oxidation of guanine in polymer DNA and oligonucleotides under the action of complexes $[M(2,2'\text{-bipy})_3]^{3+}$ (M = Fe^{3+}, Ru^{3+}) and suggested a model of such oxidation. Binary catalytic systems whose effect is based on redox processes were recommended as new antitumor drugs [147, 148].

Khudolei et al. [149] formulated quite an important concept concerning the involvement of chemical reducers in canrcinogenesis inhibition, according to which many antitumor agents are involved in biochemical redox processes in the reduced form. Proliferating, actively dividing cells characteristically show a reduced ratio of protein (and increased ratio of nonprotein, glutathione) SH- and S–S group in the cytoplasm and its increase in the nucleus and nucleolus [150]. The shift of the total cellular redox equilibrium $2\,SH - 2\,e^- \rightleftarrows -S-S- + 2H^+$ to the left favors cell division.

Over the past years the complexes of transition metals, especially Cu(I), with 1,10-phenanthroline and its derivatives (neocuproine, 4-phenylneocuproine, bathocuproine dusolfonic acid) have attracted enhanced interest as agents inhibiting HIV-1 and HIV-2 viruces [151–154]. Heterocyclic agents inhibiting HIV-1 and HIV-2 viruses at 50% inhibitory concentrations (IC_{50}) of 0.006 and 0.01 μg ml^{-1}, respectively, were synthesized on the basis of 2,9-bis(bromomethyl)-1,10-phenanthroline [155]. Even though free 1,10-phenanthrolines are inactive at concentrations below 100 μM, Cu(I) bis-1,10-phenanthroline complexes with neocuproine, 4-phenylneocuproine, as well as 2,3,4,-7,8,9-hexamethyl-1,10-phenanthroline and 2,3,4,7,8-pentamethyl-1,10-phenanthroline inhibit HIV-I viruses (IC_{50} for integrative ranging vary between 1 and 10 μM). Disintegrative inhibition by these complexes occurs at slightly higher concentrations, between 10 and 40 μM) [151, 152].

Cleavge of DNA during superoxide anion formation on the oxidation of 1,10-phenanthroline complexes of Cu(I) $[Cu(phen)_2]^+$ with oxygen was reported in [156]. McMillin and McNett [157] in their review on the photophysics of Cu(I) complexes $Cu(N–N)_2]^+$ (N–N = 1,10-phenanthroline and its derivatives) reacting with DNA have considered a scheme of hydrogen peroxide-induced breakage of DNA associated with $[Cu(phen)_2]^+$ complexes:

$$[Cu(phen)_2]^+ + DNA \rightleftarrows [Cu(phen)_2]^+/DNA,$$

$$[Cu(phen)_2]^+/DNA + H_2O_2 \rightarrow \text{nicked DNA} + [Cu(phen)_2]^{2+}.$$

By intercalating a fragment of a 1,10-phenanthroline Cu(II) complex into a viral RNA-associated protein, such as the TAT protein of the HIV virus, antiviral reagents inhibiting this virus were obtained [158]. Oligonucleotide conjugates with 1,10-phenanthroline in the presence of Cu^{2+} ions *in vitro* cleave LTR sequences of the HIV-1, which was suggested to use for a diagnosis of viral infections and control of viral gene expression [159]. 2,9-Dimethyl-, 2,9-dichloro-, 2,9-dibutyl-, and 2-ethoxy-substituted 1,10-phenanthrolines in the presence of Cu^{2+} ions affect the properties of cell membranes, thereby working as potent antimicrobial agents [160]. Copper(II) and other chelate complexes with 1,10-phenanthroline and its derivatives were patented as catalysts for the inactivation of nucleotide sequences by oxidative cleavage [161].

Byrnes et al. [162] established that cationic complexes of Cu(II) with 1,10-phenanthroline and 2,9-dimethyl-1,10-phenanthroline exhibit much a higher actitumor activity with respect to *Ehrlich ascites* tumor than Cu_{aq}^{2+} ions and 1,10-phenanthrolines. Veal et al. studied the effect of reducers and 1,10-phenanthroline concentrations on DNA cleavage by the 1,10-phenanthroline−Cu(II) system [163]. It was found [164] that the $[Cu(phen)_2]^{2+}$ complex mediates DNA chemiluminescence in the $[Cu(phen)_2]^{2+}$−ascorbic acid−H_2O_2 system and induces DNA damage. Toxicity data for Cu(II) complexes of 2,9-dimethyl-1,10-phenanthroline were reported in [165].

The fact that complex formation strongly affects the biochemical activity of the Cu^{2+}/Cu system suggests that at least one route of HIV virus inhibition is associated with the redox transitions I or II:

I. $Cu^{+}_{aq} - e^{-} = Cu^{2+}_{aq}$, $E^0(Cu^{2+/+}) = 0.15$ V,

II. $CuL^{+}_{2aq} - e^{-} = CuL^{2+}_{2aq}$, $E^0(CuL^{2+/+})$,

where L = 1,10-phen, 2,9-Me_2-1,10-phen, etc.

From our viewpoint that the influence of complex formation of 1,10-phenanthrolines with Cu^{2+} ions on the antitumor activity of the latter, like the antiviral activity of the Cu^{2+}/Cu^{+} system, is associated with stabilization by the ligands of the reduced form CuL^{+}_{2aq} (via the dative interaction between the reduced form of of Cu^{+} with coordinated 1,10-phenanthrolines, due to expressed p-acceptor properties of the 1,10-phenanthroline ligands). As a result, the standard oxidative potential [$E^0(CuL^{2+/+}) > E^0(Cu^{2+/+})$] is increased, and the rate of electron exchange for system II increases compared to system I (see the table).

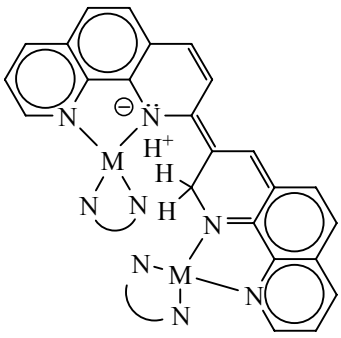
We developed syntheses and studied the coordination compounds of a new structural class of cyanines, specifically electron-excessive supramolecular (glassy in the solid state and colloid in solutions) complexes of 1,10-phenanthrocyanines with the transition methals Ni(II), Pd(II), and Pt(II) (configuration d^8), Co(II) (d^7), Cr(III) (d^3), Rh(III) (d^6), and Zn(II), Cd(II), and Ag(I) (d^{10}), as well as metal free *N*-alkyl-1,10-phenanthrocyanines [32–42]. The developed synthetic approaches are based on metal-promoted direct CH–CH coupling of coordinated and quaternized 1,10-phenanthrolines. The precursors of 1,10-phenanthrocyanines are 1,10-phenanthroline complexes of transition metals and *N*-alkyl-1,10-phenanthroline halides.

1,10-Phenanthrocyanine *d*-metal complexes are chromophoric binuclear complexe with cations like $[A_2M^{n+}(\mu\text{-}1,10\text{-phencyanine})M^{n+}A_2]^{2n+}$

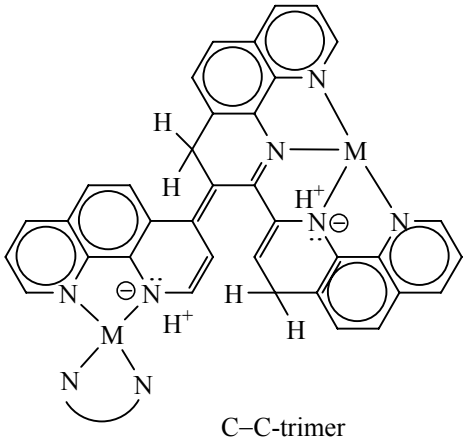
$(N–N)M^{n+}(\mu\text{-}1,10\text{-phencyanine})M^{n+}(N–N)^{2n+}$,

$[(N–N)_2M^{n+}(\mu\text{-}1,10\text{-phencyanine})M^{n+}(N–N)_2]^{2n+}$

as well as oligonuclear compounds with electron-excessive bridging 1,10-phenanthrocyanine ligands (μ-1,10-phencyanine) with valence-isomeric, tautomeric forms of dihydro-bi-1,10-phenanthroline C–C dimers (less frequently tetrahydro-tri-1,10-phenanthroline C–C trimers).



C–C-dimer



C–C-trimer

Structurally, electron-rich 1,10-phenanthro-cyanine and metal 1,10-phenanthrocyanine azachro-mophores characteristically include planar nitrogen-containing heteroaromatic fragments possessing intercalative and reductive properties, which allows us to expect that compounds of this class will exhibit an expressed pharmacologic activity toward certain microbes, viruses, and tumors. New 1,10-phenanthrocyanine and metal 1,10-phenanthrocyanine azachromophores, including bi- and polynuclear complexes of *d*-metals, are related to polypyridine and polyphenanthroline [168], as well as polycyanine nitrogenous heterocycles. Synthesis and helical self-organization, as well as biochemical issues as the possibility to form complexes isostructural to biopolymers, belong to the most promising lines of research in the chemistry of nitrogenous heterocycles [169].

In terms of structure and methodology of synthesis, electron-rich 1,10-phenanthrocyanines are the most close to apocyanine dyes, specifically apoquinocyanine diazachromophores [170–179]. Certain diquinolones relative to apocyanines are analogs of the Norphloxacine antibiotic and exhibit expressed

antibacterial properties [180]. At the same time, metal 1,10-phenanthrocyanines and 1,10-phenanthrocyanine azachromophores which are the reduced forms of derivatives of coordinated or quaternized di- and poly-1,10-phenanthrolines [168, 181, 182] are structurally related to quaternary benzo[*h*]quinoline derivatives, analogs of antitumor benzo[*c*]phenanthridine alkaloids (Fagaronine and Nitidine) [183–185]. Electron-excessive 1,10-phenanthrocyanines and metal 1,10-phenanthrocyanines could be expected to exhibit a high tuberculostatic effect, which proved the case. On the other hand, azachromophores we studied as potential antibacterial agents contain dihydroheterocycles and are related, in this respect, to dihydronaphthalines, a new class of tubulin polymerization inhibitors [186], which suggests their ability to disturb formation of bacterial cell cyto-skelenon.

The expectation of intercalative properties in new chromophores is based on their structural similarity to known DNA intercalators, the antibiotics Actinomycin D and acriflavines, as well as ethydium bromide and homodimer, whose molecules contain planar heteroaromatic fragmentscapable of intercalating into the structures of biopolymers or binding to them.

As shown in [187–192], the intercalation of certain complexes of transition redox metals with 1,10-phenanthrolines and 2,2'-bipyridines into DNA may assist electron transfer. This phenomenon was given thename "DNA-mediated charge transfer" [187, 188]. A more general approach to the organization of the reaction center consists in that the intercalating fragment, by binding it to the biological target, mediates the subsequent chemical reaction.

This effect was observed in a number of processes: fast photoinduced electron transfer through DNA intercalation [189]; DNA-mediated electron transfer to intermediate π-stacking [190]; DNA guanine oxidation under the action of $[Ru(phen)_2(dppz)]^{3+}$ (dppz is dipyrido[3,2-*a*:2',3'-*c*]phenazine) [191]; and DNA hydrolysis under the action of a zinc-binding peptide linked to a rhodium intercalator [192]. Thus it is safe to state that we deal here with intercalators of a new generation, which are capable of forming reaction centers near DNA binding sites and acquiring, due to such binding, enhanced reactivity in redox processes. Apparently, the relative spacial separation of the binding and reaction centers makes possible the catalytic influence of the first center to the second one.

The actibacterial, antiviral, and cytostatic activity of Co(II), Ag(I), Zn(II), Pd(II), and Pt(II) 1,10-phenanthrocyanines, as well as metal-free *N*-alkyl-1,10-phenanthrocyanines *N*-R-phencyanine$^+$I$^-$ (R = Me, Et, Pr, Bu, Oct) makes them effective agents against *Mycobacterium tuberculosis* and *Herpes virus* with IC_{50} 0.1–3.0 and 0.1–10.0 μg ml^{-1}, respectively, as determined in experiments on inhibition of Hep's tumor cells *in vitro* and Ehrlich ascites tumor cells *in vivo* and on apoptosis induction. *In vivo* mice tests at the Petrov Research Institute of Oncology (with the participation of Dr. Biol. Sci. V.A. Filov) of the purple violet form of Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine complex $[Pd_2(2,9\text{-}Me_2\text{-}phen)_2\mu\text{-}2,9\text{-}Me_2\text{-}phencyanine)]Cl_4$ revealed its expressed antitumor activity with respect of the Ehrlich ascites tumor.

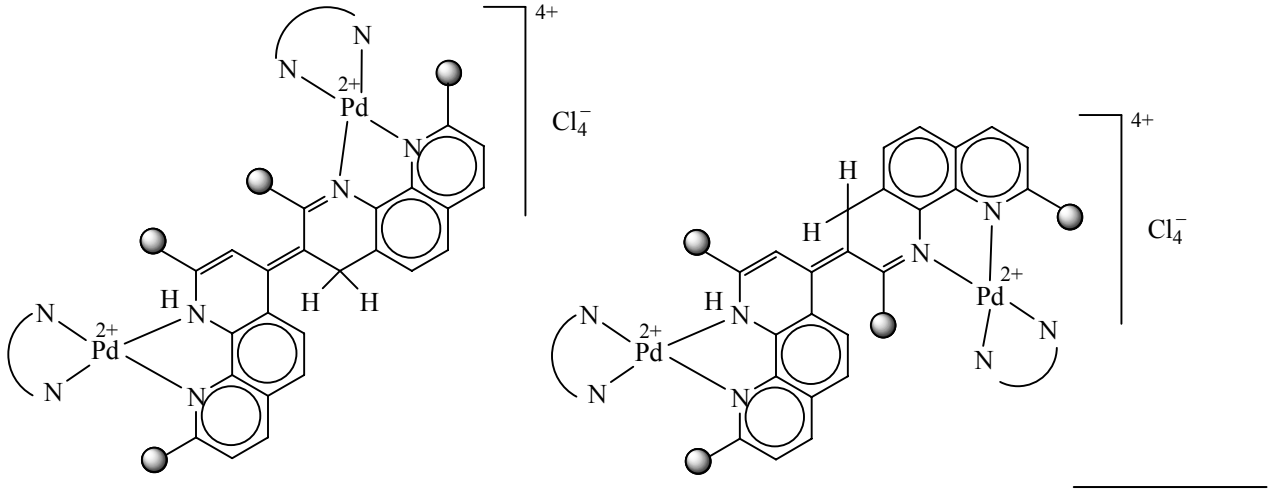
The 50% inhibitory concentrations (IC_{50}) of 1,10-phenanthrocyanine complexes of transition metals proved to be much lower (as a rule, an order of magnitude or more) than those for respective 1,10-phenanthroline complexes. The high pharmacologic activity of electron-rich 1,10-phenanthrocyanines may be explained by the fact that their redox-sensitive dihydropyridine components are potential competitors or antagonists of nicotinamide adenine dinucleotide and its phosphate NAD^+/NADH and $NADP^+$/NADPH, which are the principal participants of the process of energy supply to cells [193–195]. Diquinolones, analogs of the antibiotic Norfloxacin, too, contain dihydro forms [196]. The antibacterial and antiviral activity of *d*-metal 1,10-phenanthrocyanines increases in the following metal series: Pd(II), Pt(II) < Zn(II) < Ag(I), Co(II). It was found that the antibacterial activity of substituted metal 2,9-dimethyl-1,10-phenanthrocyanines is 2-3 times lower compared to their unsubstituted analogs.

Ligand–Receptor Interactions in the System Pd(II) 2,9-Dimethyl-1,10-phenanthrocyanine–DNA

By atomic force microscopy, spectrophotometric titration, circular dichroism, low-gradient viscometry, gel electrophoresis, and other methods we studied complex formation with thymus DNA in solutions of varied ionic strength (NaCl) of the purple-violet form of Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine,

$$[Pd_2(2,9\text{-}Me_2\text{-}phen)_2\mu\text{-}2,9\text{-}Me_2\text{-}phencyanine)]Cl_4,$$

which is present as the following tautomers:



It was found by atomic force microscopy (AFM) that the system purple-violet Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine–DNA system in low ionic strength solutions involves ligand–receptor interactions leading to directed template structuring of the complex to form giant supramolecular fractal clusters with an intricate relief, which "decorate" DNA molecules (Fig. 4) [197, 198].

The AFM data are consistent with the results of spectrophotometric titration and viscometry. Increase of the relative viscosity of DNA solutions in the presence of purple-violet Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine is accompanied by a certain increase of the optical anisotropy of the statistical segment of the DNA macromolecule. This suggests that the template binding orients the 2,9-dimethyl-1,10-phenanthroline fragments of the complex in parallel to the plane of the nitrogenous bases of the DNA macromolecule. The increased relative viscosity of the solutions does not contradict intercalation of these fragments of the complex into the DNA double helix. However, the visible absorption spectrum of the Pd(II) complex in itself show no changes which could be associated with intercalation. Electrophoretic mobility data provide further evidence for the existence of supramolecular cluster structure and for the important role of electrostatic interactions in their formation.

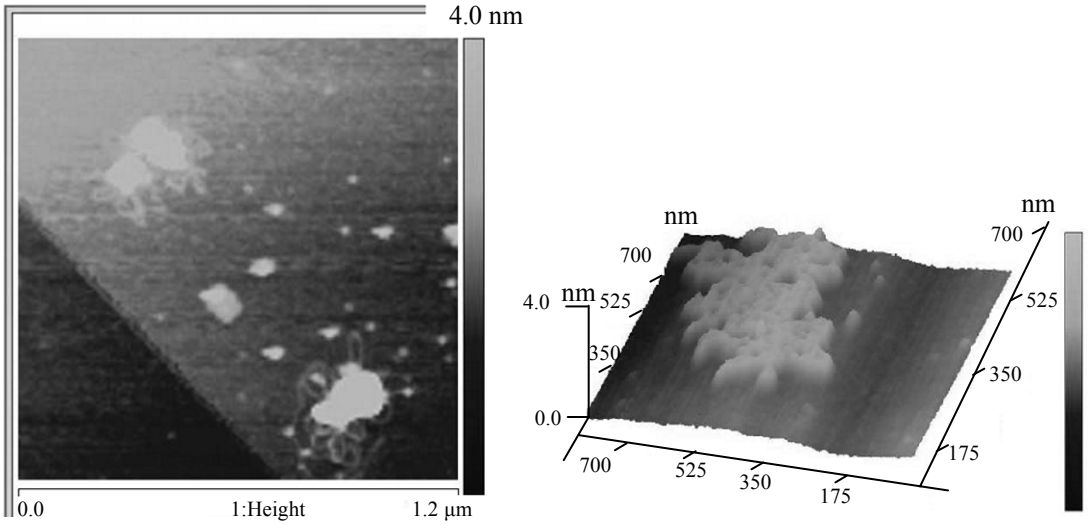


Fig. 4. Topographic ASM images of the supramolecular fractal clusters of purple violet $[Pd_2(2,9\text{-}Me_2\text{-}phen)_2(\mu\text{-}2,9\text{-}Me_2\text{-}phen\text{-}cyanine)]Cl_4$ bound to a DNA template. c(NaCl) = 0.005 M, c(DNA) = 0.0004%.

The resulting data imply an outer-sphere association of purle-violet Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine with DNA phosphate groups. The high charge of the complex ion favors attraction to it of DNA segments belonging both to the same and to different macromolecules, which leads to aggregation and increases the relative viscosity of the solutions. Charge shielding by DNA molecules associated with the Pd(II) cations of the complex is likely to be of lower importance than cluster formation, since DNA compaction due to charge shielding would have appreciably decreased the relative viscosity of the solutions. At the same time, when the complex concentrations are higher than 2×10^{-5} M, DNA tends to precipitate. This fact suggests that purple-violet Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine induces aggregation of DNA molecules to form a separate (solid) phase.

The studied Pd(II) purple-violet 2,9-dimethyl-1,10-phenanthrocyanine shows no intrinsic circular dichroism and lacks induced circular dichroism in the visible spectral range. This fact allows us to assign the changes in the circular dichroism spectrum of DNA in the presence of the Pd(II) complex specifically to the manifestation of spectral properties of the former. It was found that the positive maximum of the circular dichroism spectrum of DNA in shifted to the left and increases in amplitude. Such spectral behavior is characteristic of DNA complexes with the $[Co(NH_3)_6]^{3+}$ cation, which induce DNA structuring up to condensation (reversible compaction of the double-helix molecule) to form discrete toroidal structures [199]. As a rule, the condensing agents are multiply charged cations (charge $\geq$ 3), and DNA condensation is possible only if its charges are neutralized by 88–90%.

The observed effects are consistent with general properties of cynine compounds. Self-association of cyanines in solutions or at the solid–liquid interface is a commonly faced phenomenon associated with strong intermolecular attraction forces (like van der Waals ones). The outer-sphere groove aggregation on a DNA template is, along with intercalation, one of the characteristic types of binding of cyanine chromophores with DNA molecules [200]. Therewith, according to [200], it can be realized both with cyanine H- and J-aggregates.

However, in the case of Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine, in view of the fact that its visible absorption spectum remains almost unchanged on introduction of DNA into its solution, we more likely deal with template structuring on DNA from solution of slightly different aggregates, specifically, spherolithic supramolecular formations. Such dichroic spheroliths formed duting J-aggregate transformation were studied by means of atomic force microscopy on an example of 1,7-bis(dimethylamino)heptamethine-cyanine perchlorate [201, 202].

New electron-rich *d*-element 1,10-phenanthrocyanine complexes are pharmacologically much more active than the corresponding 1,10-phenanthroline precursors. This is associated with the geometric and electronic features of the former. The electron-rich bridged 1,10-phenanthrocyanine ligands of these new binuclear compounds comprise dihydro-1,10-phenanthroline fragments incorporated into an extended π-conjugated chromophoric system, which should entail specific ligand–receptor inter-actions in *d*-element 1,10-phenanthrocyanines−DNA systems. In particular, the ligand–receptor interactions in the purple violet Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine−DNA system in low ionic strength solutions (NaCl) leads to outer-sphere binding of the Pd(II) complex and its subsequent structuring. Therewith, DNA functions as a template, and the process involves oriented molecular lwayering of Pd(II) 2,9-dimethyl-1,10-phenanthrocyanine. According to the model of self-organization processes in the DNA−Pd(II) 1,10-phenanthrocyanine system, initially the "ligand" $[Pd_2(2,9\text{-}Me_2\text{-}phen)_2\mu\text{-}2,9\text{-}Me_2\text{-}phencyanine)]Cl_4$ interacts with the "receptor" DNA by ionic association (outer-sphere complex formation) between DNA phosphate groups and $[Pd_2(2,9\text{-}Me_2\text{-}phen)_2\mu\text{-}2,9\text{-}Me_2\text{-}phencyanine)]^{4+}$ cations. Apparently, as a result of such binding the planar 2,9-dimethyl-1,10-phenanthroline fragments of the Pd(II) complex form stack-like supramolecular structures at the outside the DNA double helix. In low ionic strength solutions this induces formation of fractal clusters. The latter process may be a consequence of the formation of bridging associative bonds between the complex Pd(II) cations with different segments of the DNA chain or segments of different DNA molecules.

CONCLUSIONS

Analysis of the experimental data on the antibacterial, antiviral, and antitumor effects of *d*-element 1,10-phenanthroline complexes shows that such complexes exhibit a well-prononuced pharmacologic

activity associated with the physicochemical features of their behavior in biosystems: ability to take part in redox reactions and to effectively bind, both covalently and intercalatively, with DNA molecules.

The studies on ligand–receptor interactions gave evidence showing that the electron-rich *d*-element 1,10-phenanthrocyanine complexes–DNA systems involve intricate supramolecular self-organiza-tion processes. Such studies have just been initiated, and we can now expect to obtain new interesting data on the structure and properties of the template cluster structures formed in these systems. The results of microbiological, pharmacological, and antitumor activity testing of new 1,10-phenanthrocyanines revealed their potential as biocide agents. Research into the potential use of 1,10-phenanthrocyanine complexes as carcinostatics for tumor chemotherapy is in progress.

ACKNOWLEDGMENTS

The work was financially supported by the Russian Foundation for Basic Research and the *Functionalized Nanoparticles on the Basis of Metal Complex Compounds for Medical and Medica Biological Applications* Institutional Targeted Program RNP 2009–2011.

REFERENCES

1. Reedijk, J., *Platinum Met. Rev*., 2008, vol. 52, no. 1, pp. 2–11.
2. Rosenberg, B., *Biochimie*, 1978, vol. 60, no. 9, pp. 859–867.
3. Lippard, S.J., *Science*, 1982, vol. 218, no. 4577, pp. 1075–1082.
4. Martin, R.B., *Cisplatin*, Lippert, B., Ed., Weinheim: VHCA and Wiley–VCH, 1999, pp. 183–205.
5. Reedijk, J., *Chem. Rev*., 1999, vol. 99, no. 9, pp. 2499–2510.
6. Farrell, N., *Transition Metal Complexes as Drugs and Chemotherapeutic Agents*, Dordrecht: Kluwer, 1989.
7. Volchenskova, I.I., *Biologicheskie aspekty koordinatsionnoi khimii* (Biological Aspects of Coordination Chemistry), Yacimirskii, K.B., Ed., Kiev: Naukova Dumka, 1979, pp. 149–180.
8. Douple, E.B., *Noble Met. Biol. Syst*., 1992, pp. 349–376.
9. Fenton, R.R., Easdale, W.J., Meng, Er H., O'Mara, S.M., McKeage, M.J., Russell, P.J., and Hambley, T.W., *J. Med. Chem*., 1997, vol. 40, no. 7, pp. 1090–1095.
10. Cepeda, V., Fuertes, M.A., Castilla, J., Alonso, C., Quevedo, C., and Pérez, J.M., *Anticancer Agents Med. Chem*., 2007, vol. 7, no. 1, pp. 3–18.
11. Arutyunyan, S.G., Mamasakhlisov, E.Sh., Morozov, V.F., Dalyan, E.B., Khachikyan, R.E., Vardevanyan, P.O., Karapetyan, A.T., Orioli, P., and Bruni, B., *Biofizika,* 1997, vol. 42, no. 2, pp. 372–377.
12. Perez-Benito Jaaquin, F., Arias, C., and Amat E., *New J. Chem*., 1995, vol. 19, no. 10, pp. 1089–1094.
13. Kostova, I., *Recent Patents Anticancer Drug Discov*., 2006, vol. 1, no. 1, pp. 1–22.
14. Farrell, N., Kelland, L.R., Roberts, J.D., and Van Beusichem, M., *Cancer Res*., 1992, vol. 52, no. 18, pp. 5065–5072.
15. Ongeri, S., Aitken, D.J., Husson, H.-Ph., Kozelka, J., and Viossat, B., *Inorg. Chem*., 2000, vol. 39, no. 26, pp. 6131–6133.
16. Gao, E.J., Wang, K.H., Gu, X.F., et al., *J. Inorg. Biochem*., 2007, vol. 101, pp. 1404–1409.
17. Bogdanov, A.A., Kosmotynskaya, Yu.V., Yakovlev, K.I., and Kas'yanenko, N.A., *Zh. Strukt. Khim*., 2006, vol. 47, no. 1, pp. 178–184.
18. Kas'yanenko, N.A. and Yakovlev, K.I., Abstracts of Papers, *XVIII Mezhdunarodnaya Chernyaevskaya konferentsiya po khimii, analitike i tekhnologii platinovykh metallov* (XVIII Int. Chernyaev Conf. on Chemistry, Analytics, and Technology of Platinum Metals), Moscow, October 9−13, 2006, no. 1.13, pp. 58–60.
19. Goutam K. Ghosh, Sankar Chandra Moi, and Apurba K. Patra, *Rasāyan J. Chem.*, 2009, vol. 2, no. 3, pp. 724–732.
20. Kemp, Sh., Wheate, N.J., Pisani, M.J., and Aldrich-Wright, J.R., *J. Med. Chem*., 2008, vol. 51, no. 9, pp. 2787–2794.
21. Wheate, N.J. and Collins, J.G., *Curr. Med. Chem. Anti-cancer Agents*, 2005, vol. 5, pp. 267–279.
22. Wheate, N.J. and Collins, J.G., *Coord. Rev*., 2003, vol. 241, p. 133.
23. O'Reilly, F.M. and Kelly, J.M., Abstracts of Papers, *16th IUPAC Symp. Photochemistry*, Helsinky, July 21−26, 1996, p. 445.
24. Koroteev, P.S., Fedotova, T.N., Kuznetsova, G.N., Dobrokhotova, Zh.V., and Eremenko, I.L., Abstract of Papers, *XXIV Mezhdunarodnaya Chernyaevskaya konferentsiya po khimii, analitike i tekhnologii platinovykh metallov* (XXIV Int. Chernyaev Conf. on Chemistry, Analytics, and Technology of Platinum Metals), St. Petersburg, June 15−19, 2009, p. 303.
25. Matsumoto, K., *Izv. Akad. Nauk, Ser. Khim*., 2003, no. 12, pp. 2439–2448.
26. Barton, J.K., Rabinowitz, H.N., Szalda, D.J., and Lippard, S.J., *J. Am. Chem. Soc*., 1977, vol. 99, pp. 2827–2830.

27. Stetsenko, A.I., Tikhonova, L.S., Iozep, L.I., Demkin, A.M., and Kostikov, Yu.P., *Koord. Khim*., 1990, vol. 16, no. 11, pp. 1570–1573.
28. Moiseev, I.I., Rudy, R.I., Cherkashina, N.V., Shubochkin, L.K., Kochubey, D.I., Novgorodov, B.N., Kryukova, G.A., Kolomiychyk, V.N., and Vargaftik, M.N., *Inorg. Chim. Acta*, 1998, vol. 280, nos. 1–2, pp. 339–347.
29. US Patent 5,728,590 (Cl. 436-547; G 01 N 33/53), 17 Mar. 1998, US Appl. 282,929. 29 Jul. 1994.
30. Hirai, M., Shinozuka, K., Sawai, H., and Ogawa, S., *Chem. Lett*., 1992, vol. 21, no. 10, pp. 2023–2026.
31. Hirai, M., Shinozuka, K., Ogawa, S., and Sawai, H., *Ibid.*, 1996, vol. 25, no. 12, pp. 1113–1114.
32. Demidov, V.N., Puzenko, V.G., Savinova, A.I., Panina, N.S., Pakhomova, T.B., Vedeneeva, L.N., and Simanova, S.A., *Vestn. Mosk. Inst. Tonkoi Khim. Tekhnol*., 2007, vol. 2, no. 3, pp. 36–43.
33. Panina, N.S., Demidov, V.N., and Simanova, S.A., *Zh. Obshch. Khim*., 2008, *Vestn. Mosk. Inst. Tonkoi Khim. Tekhnol*., vol. 78, no. 5, pp. 771–776.
34. Panina, N.S., Demidov, V.N., and Simanova, S.A., *Ibid.*, 2008, vol. 78, no. 5, pp. 777–782.
35. Demidov, V.N., Simanova, S.A., Savinova, A.I., and Pakhomova, T.B., *Ross. Khim. Zh. (Zh. Ross. Khim. O-va im. D.I. Mendeleeva),* 2009, vol. 53, no. 1, pp. 128−134.
36. Demidov, V.N. and Pakhomova, T.B., *Izv. Sankt-Peterb. Gos. Tekhnol. Inst. (Tekh. Univ.),* 2009, no. 5, issue 31, pp. 11−19.
37. Demidov, V.N., Pakhomova, T.B., Savinova, A.I., Zinchenko, A.V., and Simanova, S.A., *Ibid.*, 2009, no. 6, issue 32, pp. 3−12.
38. Demidov, V.N., Panina, N.S., and Savinova, A.I., Abstracts of Papers, *XVI Int. Conf. on Chemical Thermodynamics in Russia (RCCT 2007),* Suzdal, 2007, vol. II, pp. 5/S−677.
39. Demidov, V.N. and Simanova, S.A., Abstracts of Papers, *XXIV Mezhdunarodnaya Chugaevskaya konferentsiya po koordinatsionnoi khimii* (XXIV Int. Chugaev Conf. on Coordination Chemistry), St. Petersburg: Russkii Zapad, 2009, pp. 60–61.
40. Savinova, A.I., Demidov, V.N., Simanova, S.A., and Pakhomova, T.B., *Ibid.*, pp. 148–149.
41. Demidov, V.N., Savinova, A.I., Potapov, P.Yu., Makhova, A.A., Pakhomova, T.B., Zinchenko, A.V., and Aleksandrova, E.A., Abstracts of Papers, *XVII Int. Conf. on Chemical Thermodynamics in Russia (RCCT 2009),* Kazan: Butlerov Heritage, 2009, vol. 1, p. 261.
42. Demidov, V.N., Savinova, A.I., Potapov, P.Yu., Makhova, A.A., Shuman, V.B., Zinchenko, A.V., Pakhomova, T.B., and Aleksandrova, E.A., *Ibid.*, p. 262.
43. Barton, J.K., *Photochemical Probes in Biochemistry*, *NATO ASI Ser.*, *Ser. C*, 1989, vol. 272, pp. 195−197.
44. Sammes, P.G. and Yahioglu, G., *Chem. Soc. Rev.,* 1994, vol. 23, no. 5, pp. 327–334.
45. Dawson, R., Elliott, D., Elliott, W., and Jones, K.M, *Data for Biochemical Research*, London: Oxford Univ. Press, 1986.
46. Byrnes, R.W., *Arch. Biochem. Biophys*., 1996, vol. 332, no. 1, pp. 70–78.
47. Mac Leod, R.A., *J. Biol. Chem*., 1952, vol. 197, pp. 751–761.
48. Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., and Speck, W., *Environ. Mutagen*., 1987, no. 9 (Suppl. 9), pp. 1–109.
49. Turian, G., *Schweiz. Z. Allgem. Pathol. Bakt*., 1951, vol. 14, pp. 338–344.
50. Polster, M., *Lek. Listy*, 1953, vol. 8, pp. 354–355.
51. Pijper, P.J., Van der Goot, H., Timmerman, H., and Nauta, W.T., Eur. *J. Med. Chem*., 1984, vol. 19, no. 5, pp. 399–404.
52. Ware, J.L., Paulson, D.F., and Webb, K.S., *Biochem. Biophys. Res. Commun*., 1984, vol. 124, no. 2, pp. 538–543.
53. Cohen, P.S. and Smith, S.D., *Hum. Tumor Cloning, Proc. 4th Conf*., Salmon, S.E. and Trent, J.M., Orlando, FL: Grune and Stratton, 1984, pp. 425–434.
54. Kamath, N.S., Satyamoorthy, K., Chitnis, M.P., and Advani, S.H., *Oncology*, 1989, vol. 46, no. 3, pp. 193–197.
55. Rebeiz, N., Kelley, K.W., and Rebeiz, C.A., *ACS Symp. Ser*., 1994, vol. 559, pp. 233–246.
56. US Patent 5321001, MKI5 A 01 N 37/02 no. 915896. Zayavl. 17.07.92. Opubl. 14.06.94. NKI 504/171.
57. Patent Jpn. Kokai Tokkyo Koho JP 63,190,804 [88, 190, 804]. Cl. A 01 N 43/90. 08 Aug. 1988, Appl. 87/23,893; 03 Feb. 1987.
58. PCT Int. Appl. WO 93 21,957 (Cl. A 61 K 47/48), 11 Nov. 1993, Appl. 92/ US 3858, 07 May 1992.
59. PCT Int. Appl. WO 9427,436 (Cl. A 01 N 31/00), 08 Dec. 1994, US Appl. 64,470, 20 May 1993.
60. Blank, F., *Nature,* 1951, vol. 168, pp. 516–517.
61. Zsolnai, T., *Biochem. Pharmacol*., 1961, vol. 7, pp. 195–220.
62. Coutts, R.T. and Casy, A.F., *Pyridine and Its Derivatives*, vol. 14, suppl. part IV, 1973, pp. 445–524.
63. Borovik, V.P. and Shkurko, O.P., *Khim. Geterotsikl. Soedin*., 1997, no.. 8, pp. 1011–1029.
64. White, D.O., Harris, A.W., Dwyer, F.P., and Shulman, A., *Aust. J. Exp. Biol. Med. Sci*., 1963, vol. 41, no. 5, pp. 517–526.
65. White, D.O., Harris, A.W., and Shulman, A., *Ibid.*, 1963, vol. 41, no. 5, pp. 527–538.
66. Dwyer, F.P., Mayhew, E., Roe, E.M.F., and Shulman, A., *Brit. J. Cancer*, 1965, vol. 19, p. 195.

67. Mayhew, E., Roe, E.M.F., and Shulman, A.J., *Roy. Microsc. Soc*., 1965, vol. 84, p. 475.
68. White, D.O., Harris, A.W., Cheyne, I.M., Shew, M., Shulman, A., and Bradley, T.R., *Aust. J. Exp. Biol. Med. Sci*., 1969, vol. 47, no. 1, pp. 81–89.
69. Dwyer, F.P., Reid, I.K., Shulman, A., Laycock, G.M., and Dixson, S., *Ibid.*, 1969, vol. 47, no. 2, pp. 203–218.
70. Shulman, A., Cade, G., Dumble, L., and Laycock, G.M., *Arzneimittel-Forsch*., 1972, vol. 22, no. 1, pp. 154–158.
71. Shulman, A. and White, D.O., *Chem. Biol. Interact*., 1973, vol. 6, pp. 407–413.
72. Australian Patent 498,201 (Cl. A 61 K 27/00), 22 Feb. 1979, Appl. 74/75,251, 12 Nov. 1973.
73. Brit. Patent 958,132 (Cl. A 61 k). May 13 1964; Aust. Nat. Univ.; Aust. Appl., Jan. 26 1960.
74. PCT Int. Appl. WO 94 26,263 (Cl. A 61 K 31/295), 24 Nov. 1994, GB Appl. 93/9,387, 06 May 1993.
75. Liu, L., Chi, H.-X., Yin, H.-X., and Gao, E.-J., *J. Chin. Clin. Med*., 2008, vol. 3, no. 2, pp. 1–4.
76. Shimizu, N., Wu, W., Kohara, A., Kohda, K., Suzuki, T., and Kawazoe, Y., *Biol. Pharm. Bull*., 1997, vol. 20, no. 2, pp. 168–170.
77. Bertoluzza, A., Bonora, S., Fini, G., Francioso, O., and Morelli, M.A., *Chem. Phys. Lipids*, 1995, vol. 75, no. 2, pp. 137–143.
78. Summers, L.A., Adv. Heterocycl. Chem., 1978, vol. 22, pp. 1–69.
79. PCT Int. Appl. WO 9501,341 (Cl. C 07 D 221/12), 12 Jan. 1995, US Appl. 86,285, 30 Jun. 1993.
80. *Methoden der organischen Chemie (Houben-Weyl)*, vol. E7a, Hetarene II/part 1, Stuttgart: Thime, 1991, p. 543.
81. Nagababu, P., Kumar, D.A., Reddy, K.L., Kumar, K.A., Mustafa, Md.B., Shilpa, M., and Satyanarayana, S., *Metal-Based Drugs*, 2008, vol. 2008, Article ID 275084.
82. Erkkila, K.E., Odom, D.T., and Barton, J.K., *Chem. Rev*., 1999, vol. 99, no. 9, pp. 2777–2795.
83. *DNA and RNA Binders: From Small Molecules to Drugs*, Demeunynck, M., Bailly, C., and Wilson, W.D., Eds., Weinheim: Wiley–VCH, 2003.
84. *Metallotherapeutic Drugs and Metal-Based Diagnostic Agents: The Use of Metals in Medicine*, Gielen, M. and Tiekink, E.R.T., Eds., New York: Wiley, 2005.
85. Cowan, J.A., *Curr. Opinion Chem. Biol*., 2001, vol. 5, no. 6, pp. 634–642.
86. Ji, L.-N., Zou, X.-H., and Liu, J.-G., *Coord. Chem. Rev*., 2001, vols. 216–217, pp. 513–536.
87. Barton, J.K., *Science*, 1986, vol. 233, no. 4765, pp. 727–734.
88. Barton, J.K., *J. Biomol. Struct. Dynam.*, 1983, vol. 1, no. 3, pp. 621–632.
89. Xiong, Y. and Ji, L.-N., *Coord. Chem. Rev*., 1999, vols. 185–186, pp. 711–733.
90. Nagababu, P. and Satyanarayana, S., *Polyhedron,* 2007, vol. 26, no. 8, pp. 1686–1692.
91. Barton, J.K. and Raphael, A.L., *J. Am. Chem. Soc*., 1984, vol. 106, no. 8, pp. 2466–2468.
92. Barton, J.K., *Pure Appl. Chem*., 1989, vol. 61, no. 3, pp. 563–564.
93. Pendergrast, P.S., Ebright, Y.W., and Ebright, R.H., *Science*, 1994, vol. 265, no. 5174, pp. 959–962.
94. Eur. Patent Appl. EP 552,931 (Cl.C12Q 1//68), 28 Jul 1993, US Appl. 827,021, 22 Jan 1992.
95. Dupureur, C.M. and Barton, J.K., *Inorg. Chem*., 1997, vol. 36, no. 1, pp. 33–43.
96. PCT Int. Appl. WO 86 04,358 (Cl. C 12 Q 1/68), 31 Jul. 1986, US Appl. 693,019, 18 Jan. 1985.
97. PCT Int. Appl. WO 86 04,244 (Cl. A 61 K 49/00), 31 Jul. 1986, US Appl. 693,023, 18 Jan. 1985.
98. PCT Int. Appl. WO 94 03,433 (Cl. C 07 D 219/04), 17 Feb. 1994, US Appl. 924,194, 03 Aug. 1992.
99. US Patent 5,432,172 (Cl. 514-224,5; A 61 K 31/54), 11 Jul 1995, US Appl. 924,194, 03 Aug 1992.
100. Zeglis B.M., Barton J.K. *Inorg. Chem*., 2008, vol. 47, no. 14, pp. 6452–6457.
101. Brodkorb, A., Keene, R., and Kirsch-De Mesmaeker, A., Abstracts of Papers, *XVIII IUPAC Symp. on Photochemistry*, Dresden: Tech. Univ. Dresden, July 22–27, 2000, pp. 184–185.
102. Rutherford, T.J., Van Gijte, O., Kirsch-De Mesmaeker, A., and Keene, R., *Inorg. Chem*., 1997, vol. 36, pp. 4465–4474.
103. Jackson, B.A. and Barton, J.K., *J. Am. Chem. Soc*., 1997, vol. 119, no. 52, pp. 12986–12987.
104. Chow, C.S. and Barton, J.K., *Ibid.,* 1990, vol. 112, no. 7, pp. 2839–2841.
105. RF Patent no. 2089555, MKI6 S 07 F 15/00, *Byul. Izobret.,* 1997, no. 25.
106. Vlasov, V.V., Kazakov, S.A., Plotnikov, V.M., Slyudkin, O.P., and Skorik, N.A., Ross. Patent, 493, no. 2190616.
107. Mital, R., Jain, N., and Srivastava, T.S., *Inorg. Chim. Acta*, 1989, vol. 166, no. 1, pp. 135–140.
108. Hu, C., Wang, S., Zhao, S., Shen, W., and Wang, P., *Zhongguo Yaowu Huaxue Zazhi*, 1994, vol. 4, no. 1, pp. 32–35.
109. Ward, S.G., Taylor, R.C., Crowe, A.J., Balzarini, J., and De Clercq, E., *Appl. Organomet. Chem*., 1989, vol. 3, no. 5, pp. 431–436.
110. Datt, M.S. and Sacht, C., Abstracts of Papers, *31st Int. Conf. on Coordination Chemistry*, Vancouver, August 18–23, 1996, vol. 1, pp. 27, 36.
111. Jennette, K.W., Lippard, S.J., Vassiliades, G.A., and Bauer, W.R., *Proc. Natl. Acad. Sci. USA*, 1974, vol. 71, p. 3839.

112. Lippard, S.J., *Acc. Chem. Res*., 1978, vol. 11, pp. 211–221.
113. Barton, J.K. and Lippard, S.J., *Nucleic Acid–Metal Ion Interactions*, Spiro, T.G., Ed., New York: Wiley Interscience, 1980, p. 31.
114. Collis, J.G., Rixon, R.M., and Aldrich-Wright, J.R., *Inorg. Chem*., 2000, vol. 39, pp. 4377–4385.
115. Mc Fadyen, W.D., Wakelin, L.P., Roos, I.A., and Leopold, V.A., *J. Med. Chem*., 1985, vol. 28, no. 8, pp. 1113–1116.
116. Brodie, C.R., Collins, J.G., and Aldrich-Wright, J.R., *Dalton Trans*., 2004, no. 8, pp. 1145–1152.
117. Cusumano, M., Di Pietro, M.L., and Giannetto, A., *Inorg. Chem*., 2006, vol. 45, no. 1, pp. 230–235.
118. Kemp, S., Wheate, N.J., Buck, D.P., Nikac, M., Collins, J.G., and Aldrich-Wright, J.R., *J. Inorg. Biochem*., 2007, vol. 101, pp. 1049–1058, *www.sciencedirect.com, www.elsevier.com./locate/jinorbio*.
119. Papadia, P., Margiotta, N., Bergamo, A., Sava, G., and Natile, G., *J. Med. Chem*., 2005, vol. 48, no. 9, pp. 3364–3371.
120. Mital, R. and Srivastava, T.S., *J. Inorg. Biochem*., 1990, vol. 40, no. 2, pp. 111–120.
121. Zhang Xiaoxin and Gao Enjun, *Shenyang Huagong Xueyuan Xuebao*, 1997, vol. 11, no. 4, pp. 247–251.
122. Gao, E.J., Yin, H.X., Zhu, M.C., Sun, Y.G., Gu, X.F., Wu, Q., and Ren, L.X., *Zh. Strukt. Khim*., 2008, vol. 49, no. 6, pp. 1086–1091.
123. Navarro, M., Betancourt, A., Hernández, C., and Marchán, E., *J. Braz. Chem. Soc*., 2008, vol. 19, no. 7, pp. 1355–1360.
124. Serpone, N., Ponterini, G., Jamieson, M.A., Bolletta, F., and Maestri, M., *Coord. Chem. Rev*., 1983, vol. 50, no. 3, pp. 209–302.
125. Plowman, R.A. and Power, L.F., *Aust. J. Chem*., 1971, vol. 24, pp. 303–313.
126. Gao, E., Sun, Y., Liu, Q., and Duan, L., *J. Coord. Chem*., 2006, vol. 59, no. 11, pp. 1259–1300.
127. Sokolov, P.A., Kas'yanenko, N.A., Volkov, I.L., Zyryanova, I.M., and Demidov, V.N., Abstracts of Papers, *XXIV Mezhdunarodnaya Chugaevskaya konferentsiya po koordinatsionnoi khimii* (XXIV Int. Chugaev Conf. on Coordination Chemistry), St. Petersburg: Russkii Zapad, 2009, pp. 597–598.
128. Demidov, V.N., Simanova, S.A., Savinova, A.I., Zinchenko, A.V., Pakhomova, T.B., and Aleksandrova, E.A., *Zh. Strukt. Khim*., 2010, vol. 51, no. 2, pp. 334–340.
129. Kunkely, H. and Vogler, A., *J. Am. Chem. Soc*., 1990, vol. 112, no. 14, pp. 5625–5627.
130. Miskowski, V.M. and Houlding, V.H., *Inorg. Chem*., 1989, vol. 28, no. 8, pp. 1529–1533.
131. Oktyabr'skii, O.N. and Smirnova, G.V., *Biokhimiya*, 2007, vol. 72, no. 2, pp. 158–174.
132. Yew, W.W., *Ther. Drug. Monit*., 1998, vol. 20, no. 5, pp. 469–472.
133. Mitscher, L.A. and Baker, W.R., *Pure Appl. Chem*., 1998, vol. 7, no. 2, pp. 365–371.
134. Sepkowitz, K.A., Raffalli, J., Riley, L., Kiehn, T.E., and Armstrong, D., *Clin. Microbiol. Rev*., 1995, vol. 8, no. 2, pp. 180–199.
135. Sacchettini, J.C. and Blanchard, J.S., *Res. Microbiol*., 1996, vol. 147, pp. 36–43.
136. Maddry, J.A., Suling, W.J., and Reynolds, R.C., *Ibid.,* 1996, vol. 147, pp. 106–112.
137. Rastogi, N., Goh, K.S., Van Ginkel, S.Z., Wright, E.L., and Barrow, W.W., *Ibid.,* 1996, vol. 147, pp. 97–105.
138. Wengenack, N.L., Todorovic, S., Yu Lian, and Rusnak, F., *Biochemistry,* 1998, vol. 37, no. 45, pp. 15825–15834.
139. Burgos, M.V., Chambers, H., Daley, C., and Small, P.M., Abstracts of Papers, *34th Tuberculosis−Leprosy Research Conf. US-Japan Cooperative Medical Science Program*, San Francisco, June 27–30, 1999, Post. 42, p. 298.
140. Sunel, V. and Soldea, C., *Indian J. Chem., Sect. B*, 1995, vol. 34, no. 3, pp. 227–229.
141. Petrovchuk, A.S., Polovnyak, V.K., and Busygina, T.E., *Mezhvuz. Sb. Nauchn. Tr., Izhevsk: Udmurt. Univ*., 1996, pp. 161–170.
142. Erabi, T., Matsumoto, K., Okamoto, T., Mariuchi, M., Ikeda, T., Yokoyama, Y., Hayase, S., and Wada, M., *Bull. Chem. Soc. Jpn*., 1995, vol. 68, no. 6, pp. 1545–1550.
143. Delaney, T.P., Ukness, S., Vernooij, B., Friedrich, L., Weymann, K., Negrotto, D., Gaffney, Th., Gut-Rella, M., Kessmann, H., Ward, E., and Ryals, J., *Science*, 1994, vol. 266, no. 5188, pp. 1247–1250.
144. Lu, W., Vicic, D.A., and Barton, J.K., *Inorg. Chem*., 2005, vol. 44, no. 22, pp. 7970–7980.
145. Williams, T.T., Dohno, C., Stemp, E.D., and Barton, J.K., *J. Am. Chem. Soc*., 2004, vol. 126, no. 26, pp. 8148–8158.
146. Yang, I.V. and Thorp, H.H., *Inorg. Chem*., 2000, vol. 39, no. 21, pp. 4969–4976.
147. Chissov, V.I., Yakubovskaya, R.I., Pankratov, A.A., Karmakova, T.A., Trapeznikov, N.N., Gerasimova, G.K., Treshchalina, E.M., Zhukova, O.S., Vorozhtsov, G.N., Kaliya, O.L., Luk'yanets, E.A., and Levitin, I.Ya., *Ross. Onkol. Zh.,* 2000, no. 6, pp. 23–26.
148. Osinskii, S.P., Levitin, I.Ya., Sigan, A.L., Bubnovskaya, L.N., Ganusevich, I.I., Kampanella, L., and Uordmen, P., *Izv. Akad. Nauk, Ser. Khim*., 2003, no. 12, pp. 2495–2504.
149. Khudolei, V.V., Mizgirev, I.V., Maiorova, I.G., and

Filov, V.A., *Usp. Sovr. Biol*., 1996, vol. 116, no. 3, pp. 332–345.

150. Akoev, I.G., *Biofizika poznaet rak* (Biophysics Explores Cancer), Moscow: Nauka, 1988.
151. Mazumder, A., Gupta, M., Perrin, D.M., Sigman, D.S., Rabinovitz, M., and Pommier, Y., *AIDS Res. Hum. Retroviruses*, 1995, vol. 11, no. 1, pp. 115–125.
152. Davis, D.A., Branca, A.A., Pallenberg, A.J., Marschner, T.M., Patt, L.M., Chatlynne, L.G., Humphrey, R.W., Yarchoan, R., and Levine, R.L., *Arch. Biochem. Biophys*., 1995, vol. 322, no. 1, pp. 127–134.
153. Inouye, Y., Kanamori, T., Yoshida, T., Bu, X., Shionoya, M., Koike, T., and Kimura, E., *Biol. Pharm. Bull*., 1994, vol. 17, no. 2, pp. 243–250.
154. PCT Int. Appl. WO 9427,594 (Cl. A 61 K 31/30), 08 Dec 1994, US Appl. 71,440, 02 Jun 1993.
155. PCT Int. Appl. WO 93 12,096 (Cl. C 07 D 257/02), 24 Jun 1993, GB Appl. 91/26,677, 16 Dec. 1991.
156. Graham, D.R., Marshall, L.E., Reich, K.A., and Sigman, D.S., *J. Am. Chem. Soc*., 1980, vol. 102, no. 16, pp. 5419–5421.
157. McMillin, D.R. and McNett, K.M., *Chem. Rev*., 1998, vol. 98, no. 3, pp. 1201–1219.
158. PCT Int. Appl. WO 93 12,234 (Cl. C 12 N 15/49), 24 Jun 1993, US Appl. 808,452, 13 Dec 1991.
159. PCT Int. Appl. WO 93 12,230 (Cl. C 12 N 15/11), 24 Jun 1993, US Appl. 808,452, 13 Dec 1991.
160. Seydel, J.K., Van der Goof, H., and Timmerman, H., *Chemotherapy*, 1994, vol. 40, no. 2, pp. 124–135.
161. PCT Int. Appl. WO 9320,241 (Cl. C 12 Q 1//68), 14 Oct 1993, US Appl. 863,622, 03 Apr 1992.
162. Byrnes, R.W., Antholine, W.E., and Petering, D.H., *Free Radical Biol. Med.,* 1992, vol. 12, no. 6, pp. 457–469.
163. Veal, J.M., Merchant, K., and Rill, R.L., *Nucleic Acids Res*., 1991, vol. 19, no. 12, pp. 3383–3388.
164. Ma Wenjian, Cao En-Hua, Zhang Jian, and Qin Jing-Fen., *J. Photochem. Photobiol. B,* 1998, vol. 44, no. 1, pp. 63–68.
165. Florence, T.M. and Stauber, J.L., *Aquat. Toxicol*., 1986, vol. 8, no. 1, pp. 11–26.
166. Maletin, Yu.A., *Ukr. Khim. Zh*., 1993, vol. 59, no. 5, pp. 519–526.
167. Kravtsov, V.I., *Ravnovesiya i kinetika elektrodnykh reaktsii kompleksov metallov* (Equilibrium Kinetics of Electrode Reactions of Metal Complexes), Leningrad: Khimiya, 1985.
168. Saitoh, Y. and Yamamoto, T., *Chem. Lett*., 1995, no. 3, pp. 785–786.
169. Bassani, D.M. and Lehn, J.-M., *Bull. Soc. Chim. Fr.,* 1997, vol. 134, nos. 10–11, pp. 897–906.
170. Hamer, F.M., *The Chemistry of Heterocyclic Compounds*, Weissberger, A., New York: Interscience, 1964, vol. 18.
171. Griffiths, J., *Colour and Constitution of Organic Molecules*, London: Academic, 1976, pp. 240–250.
172. Reichardt, C., Harms, K., Kinzel, M., Schafer, G., Stein, J., and Wocadlo, S., *Justus Liebigs Ann. Chem*., 1995, no.2, pp. 317–327.
173. Afarinkia, K., Ansari, M.-R., Bird, C.W., and Gyambibi, I., *Tetrahedron Lett.,* 1996, vol. 37, no. 27, pp. 4801–4804.
174. Kaufmann, A. and Strübin, P., *Chem. Ber*., 1911, vol. 1, pp. 690–701.
175. Mills, W.H. and Ordish, H.G*., J. Chem. Soc*., 1928, part 1, pp. 81–86.
176. Orlov, N.N., *Uspekhi v oblasti krasitelei i poluproduktov* (Advances in the Field of Dyes and Half-Products), Kiev: Gos. Nauch.-Tekh. Izd., 1936.
177. Acheson, R.M., *An Introduction to the Chemistry of Heterocyclic Compounds*, New York: Interscience, 1960.
178. Aksenov, A.V., Aksenova, I.V., Borovlev, I.V., and Smushkevich, Yu.I., *Khim. Geterotsikl. Soedin*., 1997, no. 8, issue 362, pp. 1094–1099.
179. Sliva, V., *Ibid.,* 1995, no. 7, pp. 882–898.
180. Coppel, R.L., Deady, L.W., Loria, P.M., Olden, D.C., and Turnidge, J.D., *Aust. J. Chem*., 1996, vol. 49, 0 no. 2, pp. 255–259.
181. Case, F.H., *J. Heterocycl. Chem*., 1964, vol. 1, no. 2, p. 112.
182. Chi-Ying Hung, Tie-Lin Wang, Zhiqiang Shi, and Thummel, R.P., *Tetrahedron*, 1994, vol. 50, no. 36, pp. 10685–10692.
183. Kerry, M.A., Mackay, S.P., and Meth-Cohn, O., *J. Pharm. Pharmacol. B*, 1995, vol. 47, no. 12, pp. 1079–1085.
184. Patent Jpn. Kokai Tokkyo Koho JP 10 152,474 [98 152,474] (Cl. C 07 D 221/18), 9 Jun. 1998, Appl. 96/324,857, 21 Nov. 1996.
185. Nakanishi, T. and Suzuki, M., *J. Nat. Prod*., 1998, vol. 61, no. 10, pp. 1263–1267.
186. Pinney, K.G.I., *Drugs*, 1998, vol. 1, no. 1, pp. 26–27.
187. O'Neill, M.A. and Barton, J.K., *Top. Curr. Chem*., 2004, vol. 236, pp. 67–115.
188. Barton, J.K., *Chimia*, 1997, vol. 51, no. 7, p. 366.
189. Murphy, C.J., Arkin, M.R., Ghatlia, N.D., Bossmann, S., Turro, N.J., and Barton, J.K., *Proc. Natl. Acad. Sci. USA*, 1994, vol. 91, no. 12, pp. 5315–5319.
190. Hall, D.B. and Barton, J.K., *J. Am. Chem. Soc*., 1997, vol. 119, no. 21, pp. 5045–5046.
191. Stemp, E.D.A., Arkin, M.R., and Barton, J.K., *Ibid.,* 1997, vol. 119, no. 12, pp. 2921–2925.

192. Fitzsimons, M.P. and Barton, J.K., *Ibid.,* 1997, vol. 119, no. 14, pp. 3379–3380.
193. Matern, A.I., Charushin, V.N., and Chupakhin, O.N., *Usp. Khim*., 2007, vol. 76, no. 1, pp. 27–45.
194. Postovskii, I.Ya., Chupakhin, O.N., and Matern, A.I., *Khim. Geterotsikl. Soedin*., 1984, no. 11, pp. 1299–1314.
195. Matern, A.I., *Doctoral (Chem.) Dissertation*, Yekaterinburg, 2007.
196. Coppel, R.L., Deady, L.W., Loria, P.M., Olden, D.C., and Turnidge, J.D., *Aust. J. Chem*., 1996, vol. 49, no. 2, pp. 255–259.
197. Volkov, I.L., Demidov, V.N., Bazlov, N.V., Bondarenko, A.S., Vyvenko, O.F., and Kas'yanenko, N.A., *Tr. 50-i nauchnoi konf. MFTI* "*Sovremennye problemy fundamental'nyh i prikladnyh nauk". Ch. IV. Molekul. i biologich. Fizika* (Proc. 50th Scientific Conf. Mosk. Phys. Chem. Inst. "Modern Problems of Basic and Applied Sciences", ch. IV. Mol. Biol. Fiz., Moscow: Mosk. Phys. Chem. Inst., 2007, pp. 54–55.
198. Volkov, I.L., Kas'yanenko, N.A., Sokolov, P.A., Zyryanova, I.M., and Demidov, V.N., Abstracts of Papers, *XXIV Mezhdunarodnaya Chernyaevskaya konferentsiya po khimii, analitike i tekhnologii platinovykh metallov* (XXIV Int. Chernyaev Conf. on Chemistry, Analytics, and Technology of Platinum Metals), St. Petersburg, June 15−19, 2009, p. 579.
199. Kas'yanenko, N.A. and Afanas'eva, D.A., *Zh. Strukt. Khim*., 2006, vol. 47, no. 1, pp. 170–177.
200. Armitage, B.A., *Top. Curr. Chem*., 2005, vol. 253, pp. 55–76.
201. Mishra, A., Behera, R.K., Behera, P.K., Mishra, B.K., and Behera, G.B., *Chem. Rev*., 2000, vol. 100, no. 6, pp. 1973–2011.
202. Daehne, L., Tao, J., and Mao, G., *Langmuir*, 1998, vol. 14, pp. 565–569.