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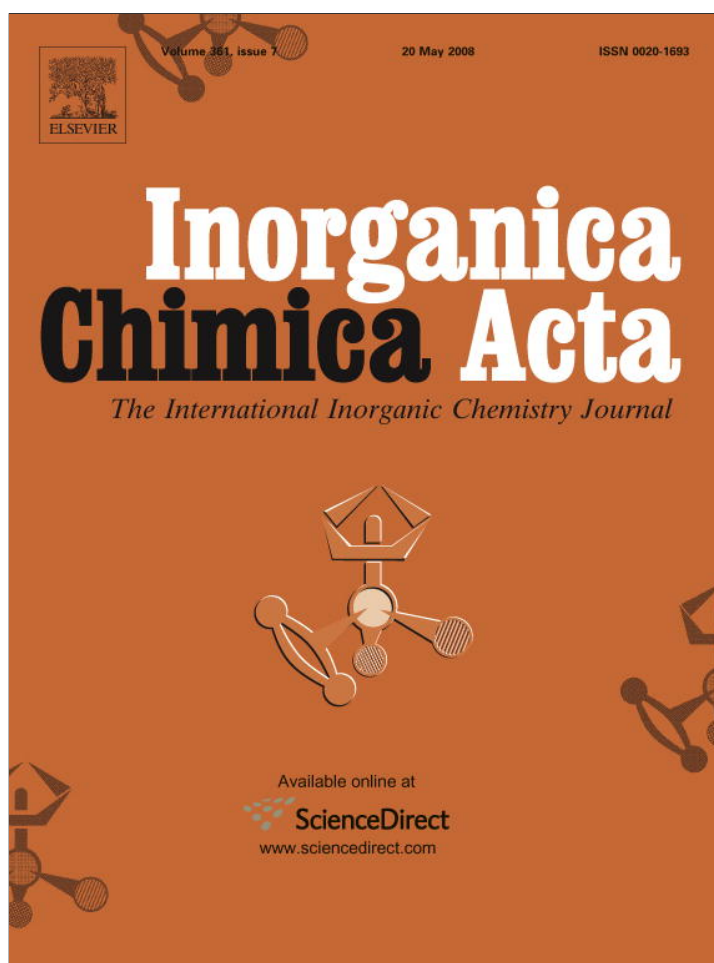


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Synthesis and characterization of disubstituted arylcyanoximes and their several metal complexes

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Dedicated to Prof. Anatoliy Brusilovets (Kiev State University) on occasion of his retirements

Abstract

A series of new disubstituted halogenated arylcyanoximes was synthesized using nitrosation reaction of the respective phenylacetone nitriles by $\text{CH}_3\text{-ONO}$ at room temperature in isopropanol. Six synthesized colorless arylcyanoximes containing two F and/or Cl atoms at 2-, 4-, 5- and 6-positions were characterized by means of NMR, IR, UV–Vis spectroscopy and pK_a studies. Crystal structures were determined for four cyanoximes and revealed the presence of only the *syn*-isomers for fluorinated compounds in a solid state, while the chlorinated arylcyanoxime exists as *anti*-isomer in the crystal. However, five out of the six protonated arylcyanoximes HL exist as a mixture of *syn*- and *anti*-isomers in solutions. Deprotonation of HL with NaOC_2H_5 in ether solutions leads to yellow NaL which were used as precursors for the synthesis of a series of monovalent Ag, Tl and bivalent Pd, Pt complexes. Seven palladium and platinum arylcyanoximates of $[\text{M}(\text{HL})_2\text{Cl}_2]$ composition were synthesized and characterized. Obtained colored compounds are non-electrolytes in solution. However, in EtOH and DMSO solutions Pt(II) cyanoximates undergo two consecutive solvolysis reactions. First order rate constants were measured at 294 K for complexes in both solvents. Binding modes of the cyanoxime ligands and the possible solid state structures of the obtained coordination compounds are suggested on a basis of their IR spectra and MM-2 calculations. Because of their structural resemblance to the cisplatin family of anticancer drugs, synthesized Pd/Pt arylcyanoximates were tested *in vitro* against human colon carcinoma WiDr cell line using *cis*- $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ as positive control. Results showed that two Pd(II) and Pt(II) cyanoximates containing oximino(2,4-dichlorophenyl)acetonitrile exhibit cytotoxicity at 0.25 mM concentrations.

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Keywords: Cyanoximes; Silver(I); Thallium(I); Palladium(II); Platinum(II); IR-, NMR, UV–Vis spectroscopy; X-ray analysis

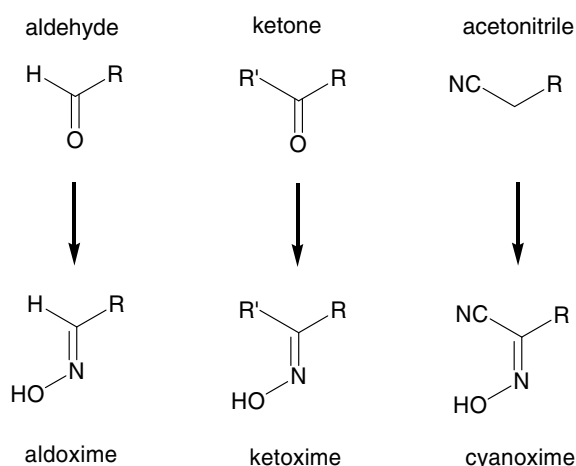
1. Introduction

Oximes represent versatile organic molecules that were extensively used as excellent ligands in analytical [1], inorganic [2,3] and bioinorganic chemistry [4]. The relationship

between different subclasses of oximes and their precursors is shown in Scheme 1. Cyanoximes-compounds with general formula $\text{HO-N}=\text{C}(\text{CN})\text{-R}$ (R = electron withdrawing group)-represent a new class of biologically active molecules [5] that are capable of binding to different metal ions [6]. Presence of the CN-group significantly increases their acidity and makes them better ligands as compared to conventional monoximes. Organic compounds that contain >N-NO or >C=N-O fragments have been known to be

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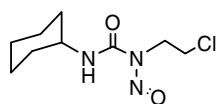
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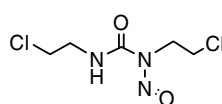
Scheme 1.

biologically active compounds. Thus, *N*-oxides and *N*-nitrosoureas represent established anticancer drugs Tirapazamine[®] [7], Lomustine[®] and Carmustine[®] [8], KF25706 [9] (Scheme 2A), while oximes are known antibiotics *Althiomycin* [10] and *Caerulomycin* [11], insecticides [12], antimicrobial [13,14] and growth-regulating agents [5] (Scheme 2B). The activity of the *Caerulomycin* family of antibiotics is attributed to their irreversible binding as tridentate chelating ligands biologically important metal ions such as Zn, Fe and Co (Scheme 2B). Some of the arylcyanoximes also have shown interesting biological activity [15]. However, their metal complexes have not been examined on that matter since they are largely unknown. Synthesis and investigation of spectroscopic and structural properties of a group of Tl(I) arylcyanoximates was recently published [16]. Continuous search for new ligands

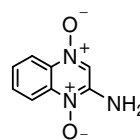
A



lomustine



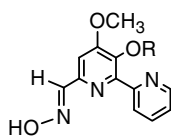
carmustine



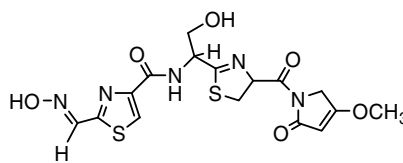
tirapazamine

B

antibiotics:

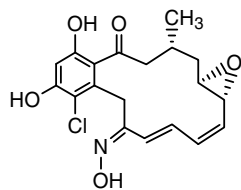


Caerulomycin B (R=H) and Caerulomycin C (R=CH₃)



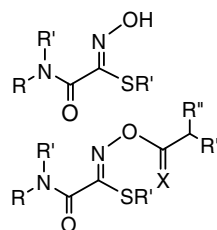
Althiomycin

new anticancer drug:



KF 25706

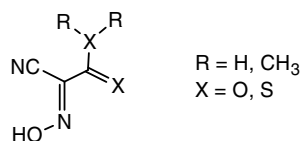
insecticides:



R, R' R'' = alkyl;
X = O, S

thioximes and their esters

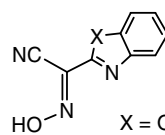
growth regulating and antimicrobial agents:



R = H, CH₃
X = O, S

amide-cyanoximes

herbicide antidots:



X = O, S, NH, N-CH₃

2-hetarylcyanoximes

Scheme 2.

for potential Zn-dependent metallo-proteases inhibitors and cytotoxic metallocomplexes has warranted exploration of new organic ligands and investigation of their metal complexes.

In this paper we report: (1) synthesis and characterization of a series of new disubstituted arylcyanoximes, their Na^+ , Ti^+ salts, Ag^+ and bivalent palladium and platinum complexes, and (2) results of *in vitro* cytotoxicity evaluation of the obtained bivalent Pd and Pt compounds against WiDr human colon carcinoma cell line.

2. Results and discussion

2.1. Characterization of new cyanoxime ligands

2.1.1. Acid–base properties of the arylcyanoximes in solutions

In general, values of acidity for the arylcyanoximes were not known prior to this study. This group of organic ligands only recently has been synthesized [17] and their metal binding properties just started to be examined [18,19]. Since the solubility of protonated disubstituted arylcyanoximes HL was found to be low, CH_3OH was chosen as a co-solvent for pK_a studies. Potentiometric titration of HL was conducted in triplicate using ~ 2 mg samples which were first dissolved in 5 mL of 80% aqueous methanol with the following addition of 9 mL of DI water. The pH of the system was automatically adjusted to 11 by adding of 0.5 M KOH solution. The titration with 0.5 M HCl solution was performed automatically until the pH value of

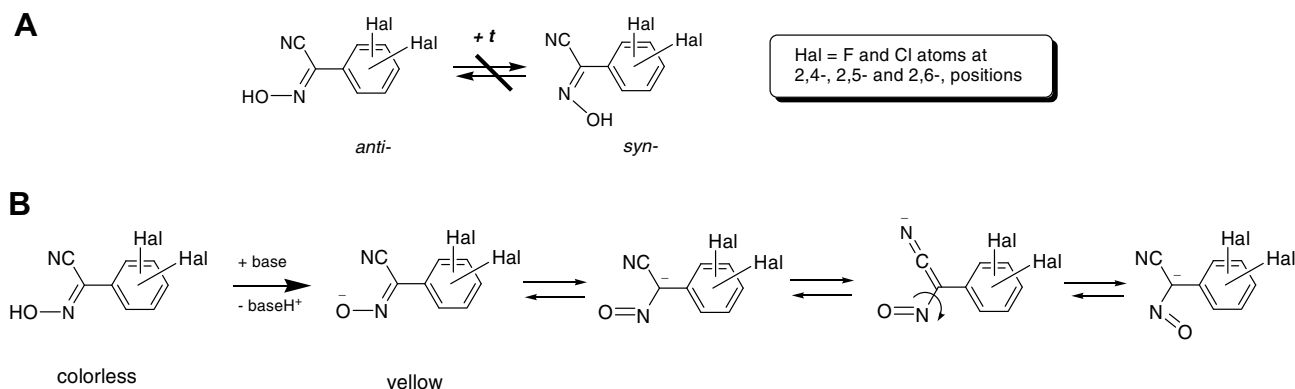
3 was reached. The data from all three titration curves were analyzed using the RefinementPro software (provided with the Sirius Analytical Instruments multifunctional titration station) and presented in Table 1. Results indicate that studied compounds represent weak organic acids as compared to benzoic acid and its derivatives, but similar in strength with substituted phenols. At the same time protonated disubstituted arylcyanoximes, due to the presence of the CN-group, by a factor of ~ 10000 stronger acids than conventional monoximes and dioximes [20]. No direct correlations between the number of halogen atoms attached to the phenyl group, or their positions, or Hammett parameters [21] and pK_a values of the arylcyanoximes were found at present time. Solutions of disubstituted arylcyanoximes in ethanol, acetone and DMSO are non-electrolytes evidencing the absence of ionization.

2.1.2. NMR spectra

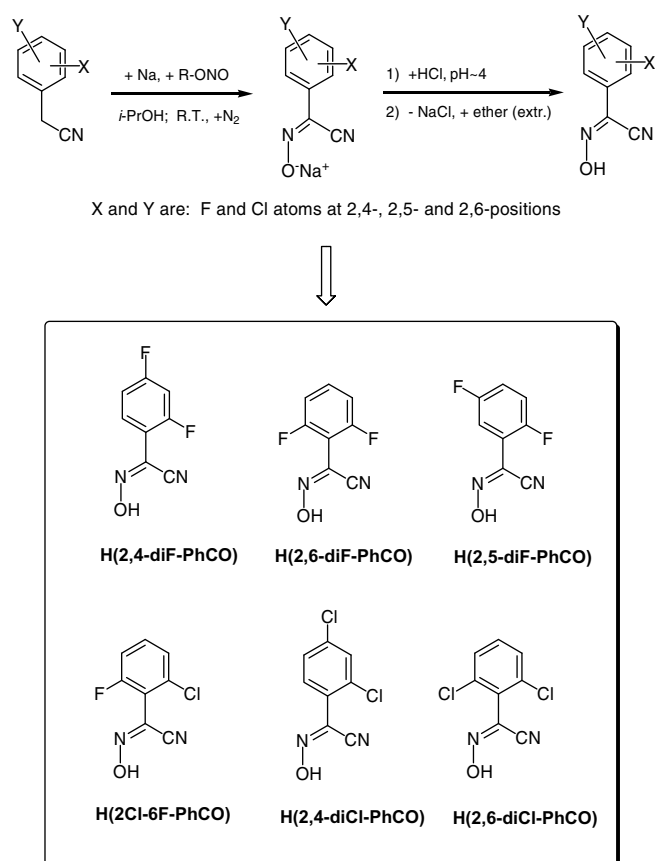
The exact assignment of signals in ^1H and ^{13}C NMR spectra was carried out using 2D COSY and HMQC methods. Five out of six synthesized dihalogen substituted arylcyanoximes demonstrate in solutions the presence of both *syn*- and *anti*-isomers. Thus, $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of protonated arylcyanoximes HL in $\text{DMSO}-d_6$ solutions contain a double set of signals with the exception of $\text{H}(2,5\text{-diF-PhCO})$, representing a monoisomeric compound. The exact assignment of the NMR signals of the individual isomers within the mixture was conducted for $\text{H}(2,4\text{-diCl-PhCO})$ and $\text{H}(2,4\text{-diF-PhCO})$ (since those molecules contain sensitive to the *syn*-configuration hydrogen atoms at *ortho*-position) using 2D NOE and HMQC ($^1\text{H}-^{13}\text{C}$) correlation experiments. Proton NMR spectra of the arylcyanoximes—that represents an isomeric mixture in dry $\text{DMSO}-d_6$ —also show the presence of two broadened signals at ~ 14 ppm at room temperature. Contrary to the several cyanacetamides [22], there is no thermally induced inter-conversion of isomers in the mixture (Scheme 3A). For example, the ratio between isomers does not change upon heating the DMSO solutions of $\text{H}(2,4\text{-diCl-PhCO})$ and $\text{H}(2,6\text{-diCl-PhCO})$ up to 120°C , evidencing the coexistence of both isomers in solutions. The ratio between *syn*- and

Table 1
 pK_a values for synthesized dihalogen-substituted arylcyanoximes measured at $25 \pm 1^\circ\text{C}$

Compound	pK_a
$\text{H}(2,4\text{-diF-PhCO})$	6.49 ± 0.04
$\text{H}(2,6\text{-diF-PhCO})$	6.28 ± 0.01
$\text{H}(2,5\text{-diF-PhCO})$	6.52 ± 0.01
$\text{H}(2\text{Cl-6F-PhCO})$	5.93 ± 0.01
$\text{H}(2,4\text{-diCl-PhCO})$	6.44 ± 0.02
$\text{H}(2,6\text{-diCl-PhCO})$	6.17 ± 0.01



Scheme 3.



Scheme 4.

anti-isomers and an effect of heat on solutions of other cyanoximes in DMSO- d_6 is present in SM 1 (Supplementary material). At the same time, the variable temperature ^1H NMR spectra of fluorinated compounds—such as H(2,4-diF-PhCO), H(2,6-diF-PhCO), and H(2Cl-6F-PhCO) in DMSO solutions—demonstrates the coalescence of signals that correspond to the protons of the oxime groups (Fig. 1), indicating proton exchange between the two isomers. ^{13}C NMR spectra of solutions of these compounds still show two sets of signals at elevated temperatures. By using the values of peaks' separation of individual isomers in the absence of exchange and coalescence temperatures the thermodynamic parameters for the process (Table 2) were calculated using the following equations:

$$k_c = \pi \frac{\sqrt{2}}{2} (v_a - v_b) \quad k_c = \chi \left(\frac{k_B T_c}{h} \right) e^{\left(\frac{-\Delta G^\ddagger}{RT_c} \right)}$$

v_a and v_b frequencies of individual signals
 k_c rate of proton exchange
 k_B Boltzmann constant
 T_c coalescence temperature
 h Plank's constant

Interestingly, heating of the DMSO solutions of the fluorinated compounds such as H(2,4-diF-PhCO), H(2,6-diF-PhCO) and H(2Cl-6F-PhCO) resulted in intramolecular

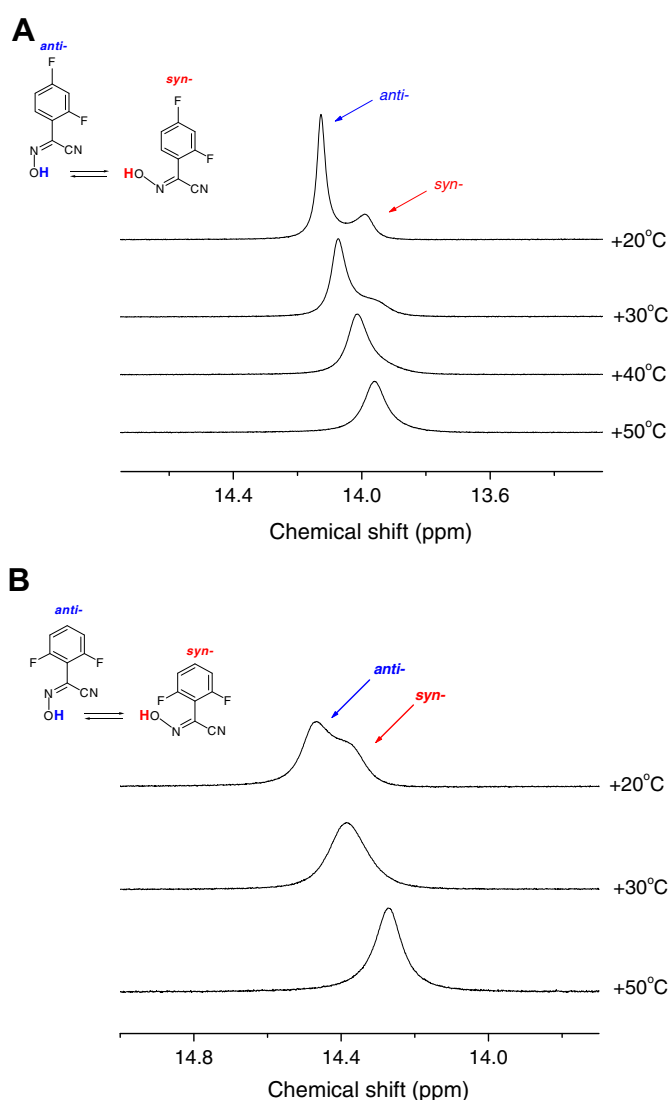


Fig. 1. Fragments of variable temperature ^1H NMR spectra of H(2,4-diF-PhCO) (A) and H(2,6-diF-PhCO) (B) in DMSO- d_6 at room temperature showing proton exchange between the two isomers.

cyclization reaction with the formation of halogen-substituted benz(isoxazoles) [18] (SM 2). A detailed description of these interesting reactions is out of the scope of this paper and publication of these results is forthcoming.

2.1.3. Structures of protonated ligands

The crystal structures of four out of six new dihalogen-substituted arylcyanoximes were determined (Table 3). The top and side views of these molecules are presented in Fig. 2 and the geometrical parameters of the cyanoxime fragment are shown in Table 4. There are two crystallographically independent molecules in the structure of H(2,6-diF-PhCO). Both adopt the same configuration and have similar geometries. All studied compounds are non-planar and show different values of dihedral angles α between planar haloaryl- and cyanoxime-fragments reflecting the steric bulkiness of the haloaryl-group at 2- and 2,6-positions. The smallest value of $\alpha = 43.7^\circ$ was determined

Table 2

Thermodynamic parameters for proton exchange between the two isomers in DMSO- d_6 solutions of fluorinated disubstituted arylcyanoximes obtained from variable temperature ^1H NMR experiments

Compound	$\Delta\nu^a$ (Hz)	T_c^b ($^\circ\text{C}$)	k_c (s^{-1})	ΔE^c (KJ/mol)
H(2,6-diF-PhCO)	42.1	30	94	62 ± 1
H(2,4-diF-PhCO)	63.5	40	141	63 ± 1
H(2Cl-6F-PhCO)	129.5	70	287	68 ± 1

^a Separation of signals in the absence of fast exchange at room temperature.

^b Coalescence temperature.

^c Value of the activation energy ΔE was set here as equal to ΔG^\ddagger value.

for the H(2,5-diF-PhCO) which has free of halogen atom 6-position. The H(2,6-diCl-PhCO) has the largest value of dihedral angle $\alpha = 77.1^\circ$ (Fig. 2) having the two chlorine atoms at both 2- and 6-positions on the phenyl group. It is important to note that all fluorinated arylcyanoximes adopt in the crystal state a rare *syn*-configuration. Only one similar configuration was documented earlier for the 2-oximino-cyanomethyl(4-methylthiazole), HTLCO [23]. Valence angles between the N1–C7–C(phenyl group) in fluorinated cyanoximes with *syn*-geometry are less than expected 120° angles for the sp^2 -hybridized carbon atom (Table 4). H-bon-

Table 3

Crystal data and structure refinement for the obtained new disubstituted arylcyanoximes

Parameter	H(2,5-diF-PhCO)	H(2,6-diF-PhCO)	H(2Cl-6F-PhCO)	H(2,6-diCl-PhCO)
Chemical formula	$\text{C}_8\text{H}_4\text{F}_2\text{N}_2\text{O}$	$\text{C}_8\text{H}_4\text{F}_2\text{N}_2\text{O}$	$\text{C}_8\text{H}_4\text{ClF}_2\text{N}_2\text{O}$	$\text{C}_8\text{H}_4\text{Cl}_2\text{N}_2\text{O}$
Formula weight (g/M)	182.13	182.13	198.58	215.03
Experiment temperature (K)	173(2)	296(2)	173(2)	173(2)
Crystal system	monoclinic	monoclinic	monoclinic	tetragonal
Space group	$P2_1/n$	$P2_1/n$	$C2/c$	$P4_{321}$
a (\AA)	3.7176(4)	7.6997(17)	9.2125(15)	7.8047(9)
b (\AA)	16.8592(19)	17.156(3)	11.5840(19)	7.8047(9)
c (\AA)	12.3818(14)	12.2802(17)	16.204(3)	31.713(7)
α ($^\circ$)	90	90	90	90
β ($^\circ$)	95.904(2)	98.916(14)	103.152(3)	90
γ ($^\circ$)	90	90	90	90
Volume (\AA^3)	771.92(15)	1602.5(5)	1683.9(5)	1931.8(5)
Z	4	8	8	8
D_{calc} (Mg/m^3)	1.567	1.510	1.567	1.479
Absorption coefficient (mm^{-1})	0.139	0.134	0.426	0.630
$F(000)$	368	736	800	864
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0487$	$R_1 = 0.0482$	$R_1 = 0.444$	$R_1 = 0.0619$
R indices (all data)	$R_1 = 0.0907$	$R_1 = 0.1007$	$R_1 = 0.0489$	$R_1 = 0.0769$

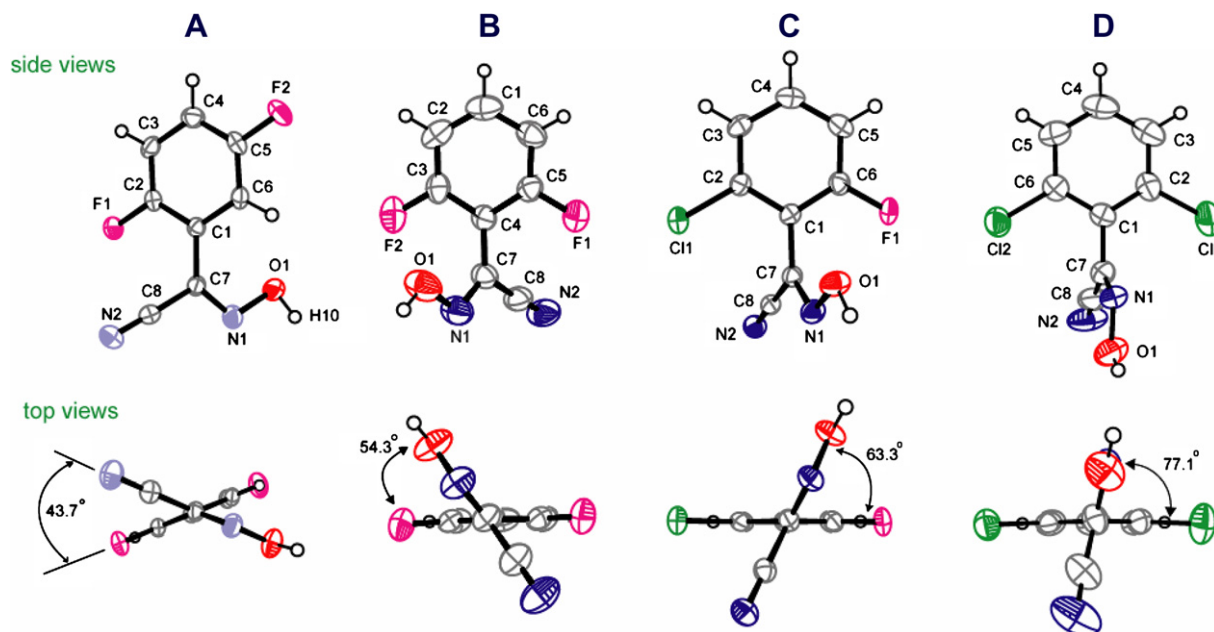


Fig. 2. Molecular structures of dihalogen substituted arylcyanoximes: (A) – H(2,5-diF-PhCO), (B) – H(2,6-diF-PhCO), (C) – H(2Cl-6F-PhCO), (D) – H(2,6-diCl-PhCO); an ORTEP drawing at 50% probability of thermal ellipsoids.

Table 4

Selected^a bond lengths and valence angles (°) for the cyanoxime fragment in several structurally characterized disubstituted arylcyanoximes

Distance (Å)	Angle (°)	Distance (Å)	Angle (°)
<i>H(2,5-diF-PhCO)</i>			
O(1)–N(1) 1.369	C(7)–N(1)–O(1) 111.7	O(1)–N(1) 1.362	C(7)–N(1)–O(1) 111.4
N(1)–C(7) 1.293	N(1)–C(7)–C(8) 112.1	N(1)–C(7) 1.287	N(1)–C(7)–C(8) 114.2
N(2)–C(8) 1.141	N(1)–C(7)–C(1) 129.2	N(2)–C(8) 1.136	N(1)–C(7)–C(4) 128.2
C(1)–C(7) 1.486	C(8)–C(7)–C(1) 118.7	C(4)–C(7) 1.477	C(8)–C(7)–C(4) 117.6
C(7)–C(8) 1.448	N(2)–C(8)–C(7) 178.2	C(7)–C(8) 1.441	N(2)–C(8)–C(7) 175.9
<i>H(2Cl-6F-PhCO)</i>			
O(1)–N(1) 1.364	C(7)–N(1)–O(1) 112.6	O(1)–N(1) 1.352	C(7)–N(1)–O(1) 108.1
N(1)–C(7) 1.289	N(1)–C(7)–C(8) 111.9	N(1)–C(7) 1.323	N(1)–C(7)–C(8) 124.0
N(2)–C(8) 1.139	N(1)–C(7)–C(1) 127.9	N(2)–C(8) 1.134	N(1)–C(7)–C(1) 116.2
C(1)–C(7) 1.484	C(8)–C(7)–C(1) 120.1	C(1)–C(7) 1.474	C(8)–C(7)–C(1) 119.8
C(7)–C(8) 1.447	N(2)–C(8)–C(7) 178.9	C(7)–C(8) 1.439	N(2)–C(8)–C(7) 177.2

^a Geometry of the phenyl group with attached halogen atoms is normal and not shown.

ing is essential for packing the arylcyanoximes into crystal. Thus, infinite polymeric chains of molecules are formed due to the H-bonds between the nitrogen atoms of the cyano- and the oxime groups in all structurally characterized arylcyanoximes (Fig. 3). A “slipped” π – π stacking interactions between the haloaryl-fragments provide additional stabilization of the structures in all cases and are responsible for the interesting lattice architecture.

2.1.4. Anionic cyanoximes

The deprotonation of colorless cyanoximes with $\text{N}(\text{C}_4\text{H}_9)_4\text{OH}$ in solutions in different solvents leads to a

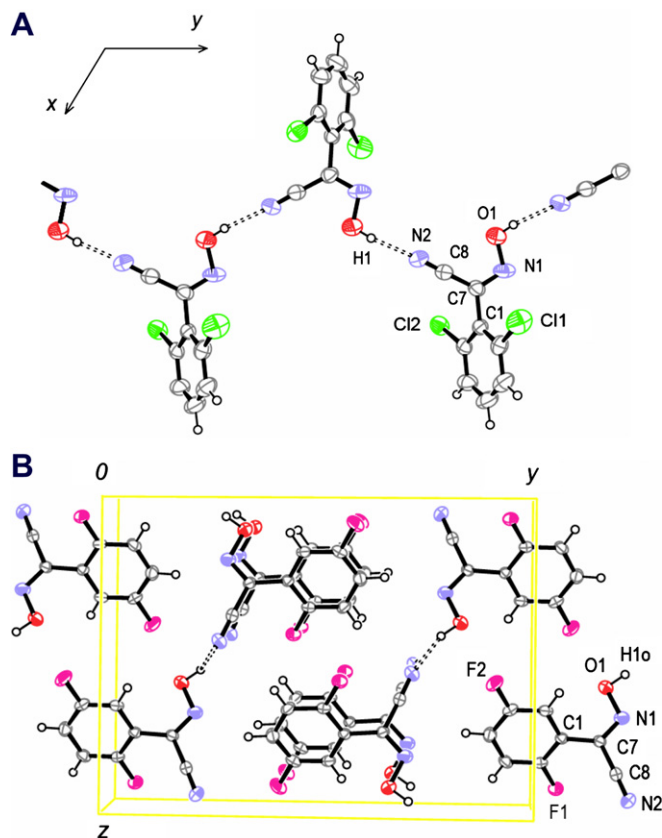


Fig. 3. Hydrogen bonding in the structure of *anti*-H(2,6-diCl-PhCO) (A) and crystal packing diagram for *syn*-H(2,5-diF-PhCO) (B).

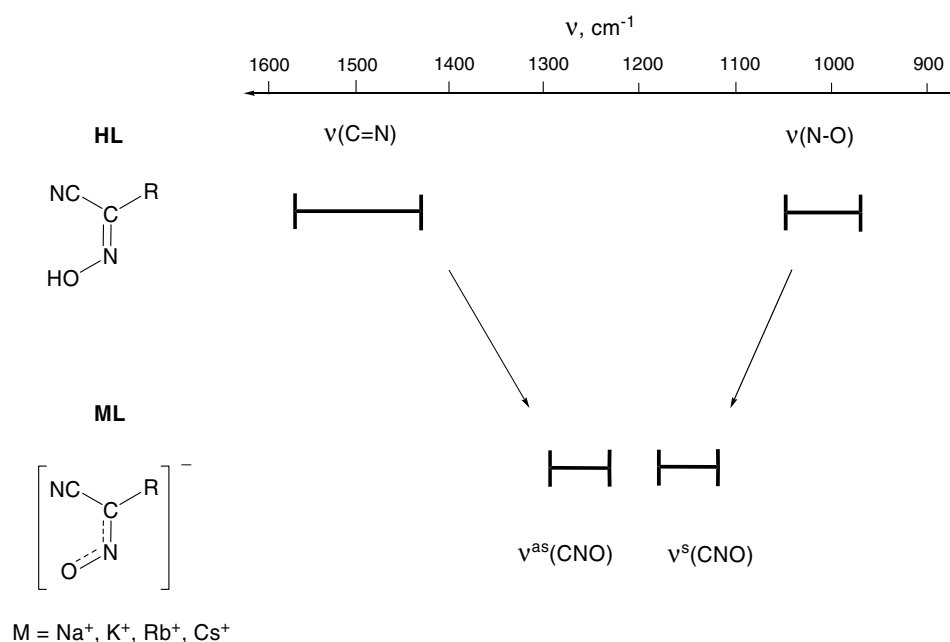
formation of a yellow conjugated anionic species (Scheme 3B). Contrary to sodium salts, tetrabutylammonium cyanoximates were not isolated in a solid state; rather, they were studied in solutions. The color of anions originates from $n \rightarrow p^*$ transition in the nitroso-chromophore [24] with typical values of the molar extinction ϵ ranging from 20 to 200 $\text{dm}^3 \text{cm}^{-1} \text{M}^{-1}$. A position of this transition in UV–Vis spectra is solvent dependent [22,25,26] (SM 3). Thus, all six dihalogen-substituted anionic arylcyanoximes clearly exhibit a negative solvatochromic effect [27] associated with polarity difference in molecules being in ground and excited states. The alkali metal salts ML of other ionic cyanoximates [28] in solid state adopt planar structures in which bond lengths indicate conjugation between functional groups in the anions. The delocalization of a negative charge throughout the anion can be described using several resonance forms (Scheme 3B) where most of them have *nitroso* character [29,30]. New arylcyanoximes discussed in this paper follow the same trend (SM 4). It is important to note in context of the charge delocalization and conjugation discussion that the ^{13}C NMR spectra of ionic NaL (L = synthesized dihalogen-substituted arylcyanoximes) in $\text{DMSO}-d_6$ contain only one set of signals, reflecting the absence of *syn*–*anti*-isomerism in anionic species due to rotation around C–NO bond (Scheme 3B).

2.2. Characterization of metal complexes

2.2.1. Sodium salts and monovalent Tl and Ag complexes

Synthesized dihalogen-substituted arylcyanoximes represent weak organic acids able to bind different metal ions. Thus, arylcyanoximes easily form ionic salts of ML composition ($\text{M} = \text{Na}^+, \text{Tl}^+$) and covalent AgL complexes [16–19].

Sodium and thallium(I) salts form 1:1 electrolytes in water, DMSO, EtOH and DMF evidencing complete dissociation of these ionic salts in solutions. The $\nu(\text{N}=\text{O})$ vibrations of the oxime group in the IR spectra are of high intensity due to a significant change in the dipole moment, while $\nu(\text{C}=\text{N})$ vibrations have medium to low intensity in the IR spectra [31]. Both these vibrations do not have



Scheme 5.

defined place in the IR spectra of the protonated arylcyanoximes HL, and typically move in the range up to ~ 150 cm⁻¹ in both directions from their position observed in acetone-oxime, (CH₃)₂C=N-OH [31,32]. Deprotonation of the >C=N-OH group of cyanoximes leads to significant redistribution of the electron density and change position of bands in the IR spectra of the ionic Na⁺ salts (Scheme 5; SM 5–7). Since the electron density (and bond lengths [28,33]) in the CNO fragment in the anions L⁻ practically leveled, the assignment of vibrations was suggested by Köhler [34] and Lampeka [35] to be as ^{as}ν(CNO) and ^sν(CNO), respectively.

Both sodium and thallium salts possess yellow color due to the n→p* transitions in the >C-NO chromophores of the cyanoxime anions. Unfortunately, in spite of numerous efforts, we did not succeed in growing suitable for the X-ray analysis crystals of the TIL and AgL. Therefore, binding mode of anions in these complexes was deduced after analysis of their IR spectra (Table 5; and SM 5–7) using previously established spectroscopic criteria for the oxime/nitroso-group coordination [32,36–40]. No change in intensity and position of the ν(C≡N) stretching vibrations in spectra of NaL and TIL indicated absence of the anion binding via cyano-group in the latter compounds. Values of frequencies for both vibrations with participation of the oxime group for the obtained in this work TIL are practically identical to those for structurally characterized thallium(I) complexes with monosubstituted arylcyanoximes [16,17]. Therefore, we suggest for the disubstituted arylcyanoximes reported in this work binding mode III (Table 5) in their Tl(I) complexes which have structural motif depicted in Scheme 6A.

Six silver(I) complexes also form conductive solutions in polar aprotic donor solvents, but the value of electrical

conductivity is lower than expected for the 1:1 electrolytes indicating partial dissociation of compounds which reflects stronger binding between Ag⁺ and arylcyanoxime anion. Silver(I) complexes of disubstituted arylcyanoximes also possess yellow-orange color and were found to be very light sensitive. Careful analysis of the IR spectra of AgL concluded that they have positions of the ^{as}ν(CNO) and ^sν(CNO) vibrations similar to those in Ag(ECO) [ECO=NC-C(NO)-C(O)OEt] [41] crystal structure of which recently has been determined [42]. Thus, there is ~ 20 – 40 cm⁻¹ increase in frequency of the ν(C≡N) stretch in the IR spectra of described here silver(I) disubstituted arylcyanoximates in comparison with their ionic Na-salts. This high energy shift unequivocally indicates the participation of the cyano-group in coordination [43]. Both ^sν(CNO) and ^{as}ν(CNO) vibrations underwent $\sim 30 \pm 10$ cm⁻¹ decrease in frequencies consistent with engagement of the nitroso-group into metal binding type V (Table 6). This is a clear manifestation of the bridging function of the cyanoxime anion using both nitrogen and oxygen atoms of the CNO-group parallel to that in Ag(ECO) (SM 20) and other silver(I) cyanoximates [33,44]. Similarities of their IR spectra allowed us to suggest polymeric structure of the AgL (L = disubstituted arylcyanoximates) presented in Scheme 6B leaving the proof of correctness for such assessments to be validated when crystallographic information will become available.

Numerous attempts to synthesize bivalent first row transition metal complexes (Co, Cu, Fe and Ni) did not lead to isolable stoichiometric compounds. We attribute this fact to inability of disubstituted arylcyanoximes to act as chelating ligands, therefore, causing instability of the formed metal complexes containing monodentate oxime ligand in solutions.

Table 5
Results of IR spectroscopic studies of synthesized disubstituted arylcyanoximes and their metal derivatives

Ligand	Compound	Assigned frequencies, cm ⁻¹ in the:		
		Cyano-group		CNO-fragment
		$\nu(\text{C}\equiv\text{N})$	$\nu(\text{C}=\text{N})$	$\nu(\text{N}-\text{O})$
	HL	2240	1478	983
	NaL	2222	1182 ^a	1010 ^a
	TiL	2207	1413	1105
	AgL	2238	1256 ^a	1112 ^a
	Pt(HL) ₂ Cl ₂ ·H ₂ O	2218	1423	986
	HL	2250, 2235 ^b	1411	981
	NaL	2210	1170 ^a	1014 ^a
	TiL	2208	— ^c	1138
	AgL	2246	1252 ^a	1110 ^a
	Pd(HL) ₂ Cl ₂ ·xH ₂ O	2214	1440	1004
	HL	2246	1408	978
	NaL	2206, 2215 ^b	1165 ^a	1005 ^a
	TiL	2212	— ^c	1142
	AgL	2234	1254 ^a	1118 ^a
	Pt(HL) ₂ Cl ₂ ·xH ₂ O	2210	1390	1010
	HL	2246	1475	1009
	NaL	2214	1170 ^a	1030 ^a
	TiL	2210	— ^c	1143
	AgL	2248	1255 ^a	1120 ^a
	Pt(HL) ₂ Cl ₂	2234	1470	1002
	Pd(HL) ₂ Cl ₂	2234	1470	1004
	HL	2194	1405	980
	NaL	2202	1170 ^a	1000 ^a
	TiL	2202	— ^c	1137
	AgL	2238	1263 ^a	1128 ^a
	Pt(HL) ₂ Cl ₂	2220	1420	981
	Pd(HL) ₂ Cl ₂	2218	1430	994
	HL	2248	1350	973
	NaL	2210	1155	1068
	TiL	2208	— ^c	1152
	AgL	2246	1265	1117

^a Assigned as ^{as} $\nu(\text{CNO})$ and ^s $\nu(\text{CNO})$ vibrations according to [34,35].

^b Perhaps due to two crystallographically different positions in the lattice.

^c Overlapped with Nujol.

2.2.2. Bivalent Pd/Pt complexes

Only seven out of twelve palladium and platinum disubstituted arylcyanoximates were obtained from aqueous solutions. It is noteworthy that the protonated HL do not react with the transition metal sources K₂[MCl₄] (M = Pd, Pt) in aqueous solutions. However, the anionic cyanoximates do react with K₂[MCl₄] since L[−] are better nucleophiles in substitution reactions at square-planar metal centers. Synthesized and characterized seven transi-

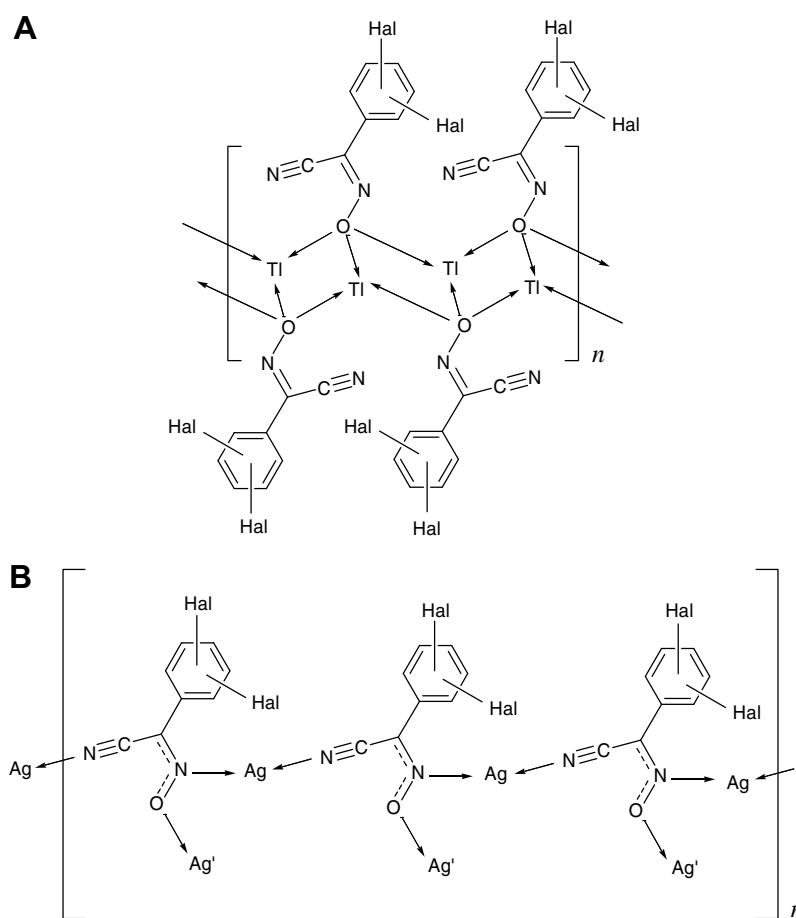
tion metal complexes have [M(HL)₂Cl₂](H₂O)_n composition (M = Pd, Pt; n = 0 or 1). These compounds have received special attention in our work due to their resemblance of famous cisplatin family anticancer drugs.

2.2.3. Solid state IR-spectroscopy

Despite numerous attempts, we were unable to grow single crystals of Pd/Pt arylcyanoximates suitable for X-ray analysis. Therefore, structural considerations (such as the binding mode of the cyanoxime ligand to the metal center) for the obtained transition metal complexes were made upon careful analysis of their solid state IR spectra. The results of the IR spectroscopic investigation of the obtained ligands HL and their Pd/Pt-derivatives are summarized in Table 5, while the rest of the data can be found in SM 5–7. Contrary to the amide-cyanoximes [22,25,45] monosubstituted and disubstituted arylcyanoximes are not capable of forming chelate rings: they belong to a group of ligands that use exclusively the oxime group for coordination to the metal center [17,18]. A schematic representation of established coordination modes for oximes is shown in Table 6. These coordination modes were directly linked to their IR spectroscopic signatures. Summarized in Table 6 observations were made using ¹⁵N labels incorporated into the >CNO-group and also based upon a comparison of crystallographic data with available spectroscopic information and theoretical calculations [32,36–40]. The binding mode II (Table 6) of the cyanoxime ligands in synthesized Pd(II) and Pt(II) complexes presented in this paper was deduced according to the established criteria of the cyanoximes coordination [39], extensive literature data for other transition metal complexes [46], and carried out in this work MM-2 calculations. The solutions' electrical conductivity studies evidenced the non-electrolyte nature of the obtained complexes and suggest the binding mode II for the compounds (Table 6).

2.2.4. Platinum group metal complexes in solutions

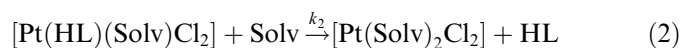
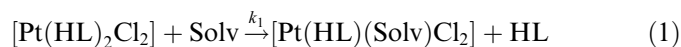
Synthesized bivalent Pt and Pd disubstituted arylcyanoximates are soluble in ethanol, acetone and DMSO. Stability and integrity of metal complexes in solutions is an important issue that has implications on biological studies [47]. Therefore, we investigated the behavior of several coordination compounds in solutions during 24 h using methods of UV–Vis spectroscopy, and electrical conductivity measurements in absolute ethanol and DMSO. Data of the latter method for 1 mM solutions of Pd/Pt arylcyanoximates in ethanol and DMSO evidenced the non-electrolyte nature of the obtained complexes with insignificant (<10%) conductivity rising during that time period (SM 8). Careful analysis of UV–Vis spectra of the same complex compounds in ethanol and DMSO indicated the presence of two close isosbestic points that originated at different times. A full set of recorded in kinetic mode UV–Vis spectra for [Pt{H(2,4-diF-PhCO)}₂Cl₂] and [Pt{H(2,4-diCl-PhCO)}₂Cl₂] is shown in SM 9 and SM 10, while fragments of selected spectra and monitored time traces are displayed



Scheme 6.

in Figs. 4 and 5. All kinetic experiments were conducted at 294 K three times.

Considering the results of an electrical conductivity studies and data of UV–Vis spectroscopic observations, it is evident that in ethanol and DMSO solutions two consecutive solvolysis reactions take place:



HL = disubstituted arylcyanoxime ligands

Solv = EtOH, DMSO

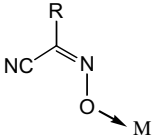
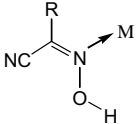
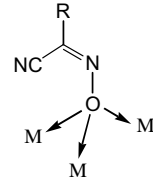
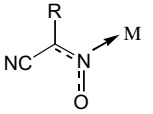
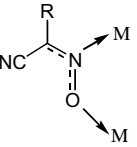
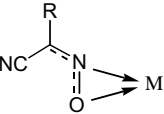


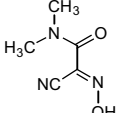
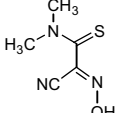
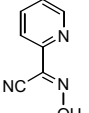
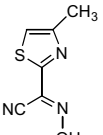
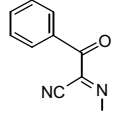
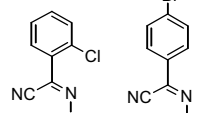
Values of the first order rate constants for the observed reactions 1 and 2 are shown in Table 7. In both studied solvents the first cyanoxime substitution reaction is significantly faster than the second reaction. Thus, in ethanol solutions the second solvolysis reaction is slower ~4.5 times for the $[\text{Pt}\{\text{H}(2,4\text{-diF-PhCO})\}_2\text{Cl}_2]$, and ~10 times for the $[\text{Pt}\{\text{H}(2,4\text{-diCl-PhCO})\}_2\text{Cl}_2]$ (Table 7). The difference in both steps of solvolysis is not great for DMSO solutions: the reaction 1 is approximately 1.7 times faster than the reaction 2. However, overall solvolysis of investigated metal complexes in DMSO is considerably faster than that

in ethanol (Table 7). At 21 °C it takes 12–20 min to complete the first ligand substitution reaction in pure DMSO, which is consistent with the $t_{1/2}$ values and is in agreement with k_1 values observed by Lippard and co-workers [47] for the *trans*-complexes of Pt(II). However, in our case solvent molecules substitute the cyanoximes molecules, which, apparently, are weakly bound to the metal center. It is important to note that there were no changes observed in UV–Vis spectra within 6 h when quickly prepared (~10 s; 0.1 mL) DMSO solutions of the Pt cyanoximates were mixed with water (3.0 mL) in the cuvette. Therefore, DMSO solutions of bivalent Pd and Pt complexes for *in vitro* cytotoxicity studies were quickly prepared fresh each time prior to the testing, and immediately added to the cell culture in order to avoid prolonged exposure of compounds to organic solvent [47] as described in Section 3. Based on results of kinetic studies and literature data (*trans*-effect) [48,49] we suggest the *trans*-geometry for the obtained Pt(II) cyanoximates. Proton NMR spectroscopy turned out to be not informative for studies of bivalent platinum and palladium cyanoximates in solutions.

2.2.5. Optimization of geometry: MM-2 calculations

The optimization of geometry MM-2 calculations were carried out for two platinum complexes $[\text{Pt}\{\text{H}(2\text{Cl-6F-}$

Table 6
Binding modes of cyanoximes and related compounds in metal complexes

Ligand status	Binding mode	Compound	Ref.
Oxime-form	I 	SbPh ₄ L (L = ACO [−] , BCO [−] , DCO [−]) SnMe ₃ (TLCO) Fe(TPP)(CCO)	[40,57] [58] [37]
	II 	Ni(DMG) ₂ DMG = dimethylglyoxime PtHL(DMSO)Cl HL = phenylaldoxime	[46a,46b,46c] [46d]
	III 	Tl(2Cl-PhCO) Tl(4Br-PhCO)	[17] [16]
Nitroso-form	IV 	NiEn ₂ L ₂ M(CCO){PPh ₃ } ₂ (M = Pd, Pt; L = CCO [−]) ePy ₄ (CCO) ₂ Ni(ACO) ₂ · xH ₂ O Cu(DCO) ₂ · xH ₂ O	[32] [36] [59] [60] [61]
	V 	Ag(BCO), Ag(CCO) Tl(PCO) Tl(TDCO)	[44] [39a] [62]
	VI 	Tl(TLCO) UO ₂ L ₂ L = 1-nitroso-2-naphtol	[63] [64]
<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;">  CCO[−] </div> <div style="text-align: center;">  HACO </div> <div style="text-align: center;">  HDCO </div> <div style="text-align: center;">  HTDCO </div> <div style="text-align: center;">  HPCO </div> <div style="text-align: center;">  HTLCO </div> <div style="text-align: center;">  HBCO </div> <div style="text-align: center;">  H(2Cl- & 4Br-PhCO) </div> </div>			

PhCO)}₂Cl₂] and [Pt{H(2,4-diCl-PhCO)}₂Cl₂] using PC adapted the CACHE 6.0 program (Molecular Structure Group, Fujitsu Inc.) and geometrical parameters for the

ligands available from their crystal structures [25]. This program package has been known for its accurate prediction [50] of geometry for both organic and coordination

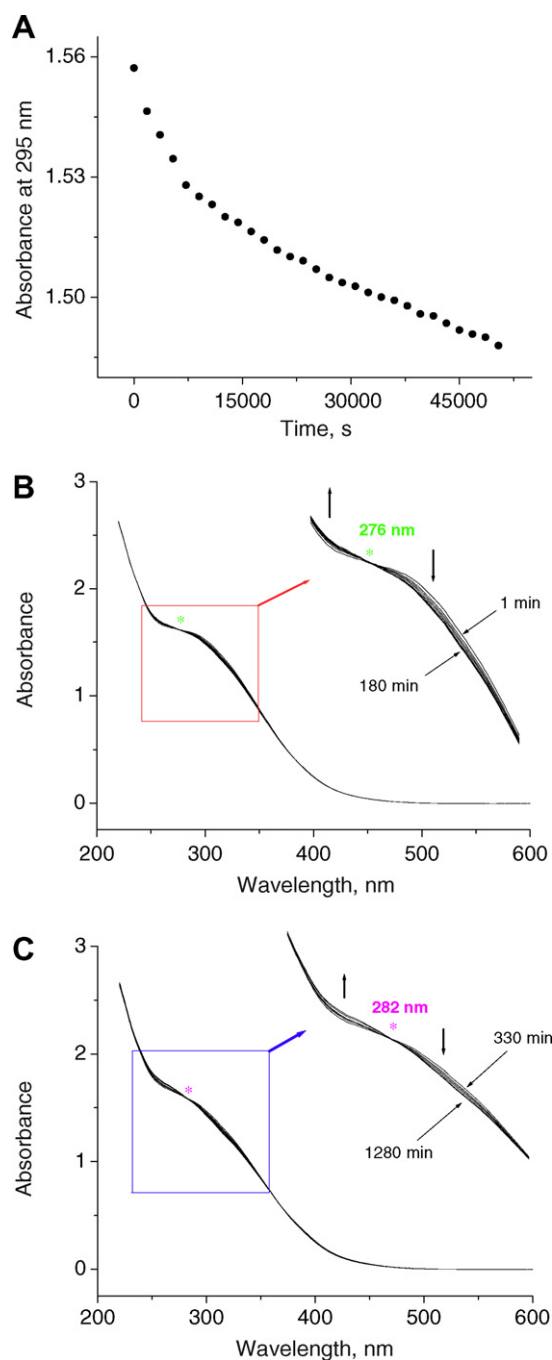


Fig. 4. Solvolysis of 1mM solution of $[\text{Pt}\{\text{H}(2,4\text{-diF-PhCO})\}_2\text{Cl}_2]$ in ethanol at 294 K. (A) – time trace at 295 nm; (B) – fragment of UV–Vis spectra during first 180 min of the reaction with the inset indicating the first isosbestic point; (C) – fragments of spectra recorded at later times with the inset showing the second isosbestic point.

compounds. There were four principal initial settings used: (1) a complex of the *trans*-geometry with the cyanoxime molecule either in *syn*- or *anti*-configuration, and (2) a complex of the *cis*-geometry with the cyanoxime molecule having *syn*- or *anti*-configuration. All geometry optimizations were carried out for the isolated (“gas-phase”) molecules of coordination compounds without taking into consideration any intermolecular interactions. The selection of the

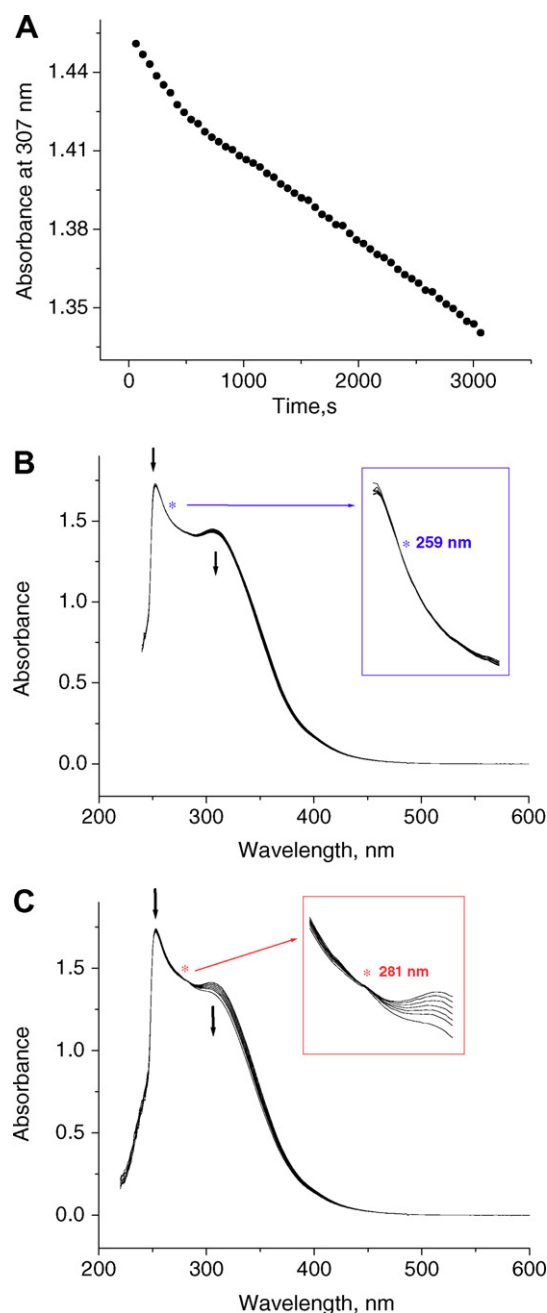


Fig. 5. Solvolysis of 1 mM solution of $[\text{Pt}\{\text{H}(2,4\text{-diCl-PhCO})\}_2\text{Cl}_2]$ in DMSO at 294 K. (A) – the reaction time trace monitored at 307 nm; (B) – fragments of UV–Vis spectra recorded during the first 7 min with shown inset for the first isosbestic point; (C) – fragments of spectra recorded within the last 50 min of the reaction with the inset showing the second isosbestic point.

particular structure was based on the calculated minimal value of the molecule total formation energy after several routes of geometry optimization when the program has normally stopped. The general structural motif for the obtained platinum group metal cyanoximates is shown in Fig. 6. Suggested *trans*-geometry of Pt(II) arylcyanoximates is based on indirect evidence from kinetics of solvolysis studies. It is interesting to note the pronounced

Table 7

Values of the first order rate constants for solvolysis of two moderately *in vitro* cytotoxic Pt(II) cyanoximates in DMSO and ethanol at 294 K

Complex	Solvent	
	EtOH	DMSO
$[\text{Pt}\{\text{H}(2,4\text{-diF-PhCO})\}_2\text{Cl}_2]$	$k_1 = 2.5 \times 10^{-6} \pm 1.8 \times 10^{-7}$ $k_2 = 5.5 \times 10^{-7} \pm 1.2 \times 10^{-8}$	$k_1 = 9.6 \times 10^{-5} \pm 2.7 \times 10^{-7}$ $k_2 = 5.9 \times 10^{-5} \pm 3.5 \times 10^{-7}$
$[\text{Pt}\{\text{H}(2,4\text{-diCl-PhCO})\}_2\text{Cl}_2]$	$k_1 = 5.1 \times 10^{-6} \pm 2.3 \times 10^{-7}$ $k_2 = 5.0 \times 10^{-7} \pm 1.4 \times 10^{-8}$	$k_1 = 1.2 \times 10^{-4} \pm 2.3 \times 10^{-6}$ $k_2 = 7.2 \times 10^{-5} \pm 6.2 \times 10^{-7}$

attractive interactions between the oxime OH group and Cl ions coordinated to Pt(II), or F atom on the aryl group of the cyanoxime regardless of the *syn*-, *anti*-conformation of the ligand or *cis*-, *trans*-geometry of the complex (Fig. 6, SM 11 and SM 12).

2.2.6. *In vitro* antiproliferative activity studies for Pd(II) and Pt(II) cyanoximates

Synthesized bivalent palladium and platinum cyanoximates of $[\text{M}(\text{HL})_2\text{Cl}_2]$ composition contained coordinated chloride anion and resemble known cytotoxic cisplatin family drugs. Therefore, it was interesting to examine antiproliferative activity for seven synthesized Pt(II) and Pd(II) complexes using human cancer cells. We selected for these studies colon carcinoma WiDR cells which are not resistant to cisplatin. These are the first known arylcyanoximates ever tested *in vitro* against human cancer cell line. Details of the cytotoxicity protocol as well as relevant tables and actual cell pictures are presented in SM 13–17 of Supporting material, respectively. The DMSO was found to be the most suitable for making solutions for *in vitro* studies since ethanol even at low concentrations exhibits certain cytotoxicity itself [51,52]. Antiproliferative activity of the syn-

thesized Pd and Pt cyanoximates was tested at concentration 0.01 mM, 0.1 mM, 0.25 mM and 0.50 mM. Protonated cyanoxime ligands HL itself did not show any cytotoxicity.

The least active coordination compounds among studied complexes were found to be Pd (II) and Pt(II) cyanoximates with the fluorinated ligands H(2,4-diF-PhCO) and H(2,5-diF-PhCO). Bivalent palladium and platinum complexes bearing chlorine-containing cyanoxime ligands showed cytotoxicity with the most effective being $[\text{Pt}\{\text{H}(2,4\text{-diClPhCO})\}_2\text{Cl}_2]$ and $[\text{Pd}\{\text{H}(2,4\text{-diCl-PhCO})\}_2\text{Cl}_2]$ at 0.25 mM concentration leading in a massive cell death. These two complexes demonstrated antiproliferative activity against WiDR cells found to be ~20% of that for cisplatin at similar conditions

3. Experimental

3.1. Solvents and reagents

Solvents used for carrying out reactions and crystallizations were HPLC grade and employed without further purification. Acetone, ethanol and DMSO employed in kinetic and conductivity studies were additionally dried according to standard procedures [31]. The inorganic salts of bivalent palladium and platinum were purchased from Sigma–Aldrich: *cis*-diamineplatinum(II) dichloride (Sigma, P 4394), potassium tetrachloropalladate(II) (Aldrich #205796), and potassium tetrachloroplatinate(II) (Aldrich, #20675), while metallic Na and NaNO_2 were obtained from FLUKA. The initial dihalogen-substituted phenylacetonitriles $\text{NC-CH}_2\text{-R}$ can be synthesized using different routes [17]. Commercially available precursors, such as 2,4-dichlorophenylacetonitrile, 2,6-dichlorophenylacetonitrile, 2-chloro-6-fluorophenylacetonitrile, 2,4-difluorophenylacetonitrile, 2,5-difluorophenylacetonitrile, and 2,6-difluorophenylacetonitrile from Sigma–Aldrich were of good quality and were used in this work without additional purification. Neat organic nitrite $\text{CH}_3\text{-ONO}$ was obtained fresh before every nitrosation reaction according to published procedures [53]. The organic base used for deprotonation of ligands during UV–Vis spectroscopic studies was tetrabutylammonium hydroxide as 1.0 M solution in methanol (Sure-Seal, Aldrich). Silicagel-on-glass plates with indicator (Merk) were used for TLC using EtOAc/hexane = 1:4 mobile phase. Elemental analysis for the

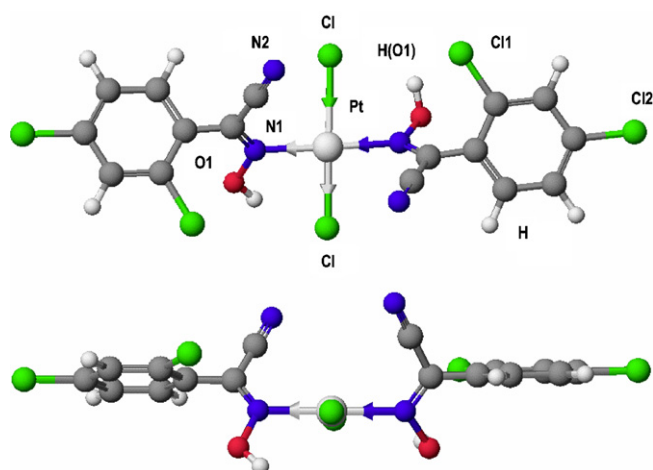


Fig. 6. Suggested structures of platinum arylcyanoximate: MM-2 optimized geometry of the *trans*- $[\text{Pt}\{\text{H}(2\text{Cl-6F-PhCO})\}_2\text{Cl}_2]$; the cyanoxime adopts *syn*-configuration. (A) – top view and (B) – side views; $E_{\text{tot}} = -4.22$ kcal/mol. Coloring scheme: green – Cl, yellow – F, red – O, blue – N, grey – C, large light grey – Pt. (For interpretation of the references in color in this figure legend, the reader is referred to the web version of this article.)

C,H,N content of the obtained Na, Pt and Pd complexes were done by Atlantic Microlab, Inc (Norcross, GA).

3.2. Physical methods

3.2.1. Instrumentation

Melting points (without correction) for ligands and Na⁺ salt derivatives were obtained by using a Mel-Temp II apparatus (Thomas Hoover) in open capillary tubes. Electrical conductivity measurements for several complexes and organic ammonium salts were carried out in 1 mM solutions in an anhydrous acetone, ethanol and DMSO using the YSI Conductance–Resistance meter Model 34. Solutions of tetrabutylammonium bromide, tetraphenylphosphonium bromide (as 1:1 electrolytes) and hydrazonium dichloride (as 1:2 electrolyte) were used for the electrode calibration. Measurements of pK_a values for synthesized benz(2-hetroaryl)cyanoximes were carried out using a Sirius Analytical Instruments automated titration station (Sussex, UK) equipped with a temperature-controlled bath. Since protonated cyanoximes HL are poorly soluble in water, all measurements were conducted in mixed solvent systems using methanol as solubilizing co-solvent. AtenololTM and LidocaineTM (from Aldrich) were used for calibration of the instrument [54]. Measurements consisted of the three-step multi-stage titration in water/CH₃OH mixtures from 18.9 wt% to 23.8 wt% content of organic solvent with ionic strength adjusted to 0.15 with KCl. The pH in titration experiments ranged from 3 to 11. The values were extrapolated to “zero” CH₃OH content to obtain an aqueous pK_a value using the Yasuda–Shedlovsky procedure (Table 1).

3.2.2. Spectroscopic methods

¹H and ¹³C NMR spectra of protonated (HL) and deprotonated (NaL) ligands were recorded using a Varian Gemini 200 MHz NMR spectrometer in DMSO-*d*₆ (with 0.1% TMS). Variable temperature (in DMSO-*d*₆ from 296 to 406 K in 10° ± 0.1° steps) (Table 2), and 2D NMR experiments (HMQC, COSY and HSQC–NOESY) for HL and NaL were conducted using the Avance DRX-500 BRUKER NMR spectrometer. IR spectra for the solid ligands, HL, their Na⁺ salt derivatives and the Pt(II)/Pd(II) complexes were recorded in KBr pellets in the range of 4000–400 cm^{−1} with an FT-IR Nicolet Magna 550 spectrometer (with OMNIC 1.20 software) (Table 5). UV–Vis spectra of solutions of protonated HL and deprotonated L[−] disubstituted arylcyanoximes were recorded in several organic solvents (CH₃OH, EtOH, *n*-PrOH, *t*-BuOH, DMSO, DMF, acetone, CH₃CN) and H₂O. UV–Vis spectra were obtained using an Agilent 8453E UV–Vis Spectroscopy System at 294 K in the range of 190–1100 nm in 1 mm and 1 cm quartz cuvettes (Starna). Kinetic of solvolysis of Pt(II) cyanoximates was recorded as spectroscopic changes of their 1 mM solutions in dried DMSO and EtOH in 1 mm cells (Table 7). Similar solutions (10 mL) were used for the monitoring of an electrical conductivity within 24 h.

3.2.3. X-ray crystallography

Crystal and molecular structures were determined for four disubstituted arylcyanoximes: H(2,5-diF-PhCO), H(2,6-diF-PhCO), H(2Cl-6F-PhCO) and H(2,6-diCl-PhCO). Suitable single crystals were grown from dilute solutions (aqueous, mixture of organic solvents) upon slow solvent evaporation. A single crystal was mounted on a thin glass fiber using viscous oil and then cooled to the data collection temperature (173 K) for the three compounds, while a single crystal of the H(2,6-diF-PhCO) was studied at room temperature (Table 3). A Bruker SMART CCD diffractometer operating in ω -scans mode was used for data collection using Mo K α radiation (λ = 0.71070 Å). The data were corrected for decay and absorption using the SADABS program [55]. Direct methods structure solutions, difference Fourier calculations, and full-matrix least squares refinements against F^2 were performed with SHELXL-97 program package. All non-hydrogen atoms were refined with anisotropic displacement parameters, while hydrogen atoms were placed in geometrically idealized positions and refined using a riding model. The crystal and refinement data for the studied compounds are listed in Table 3. An ORTEP program package [56] was used to draw figures of crystal structures. Respective *.CIF files for studied compounds are available (Supporting material).

3.3. Synthesis of organic ligands

The route for preparation of the disubstituted arylcyanoximes is shown in Scheme 4. Side reactions associated with the initial nitrosating agent, unfortunately, were encountered during this preparation. Isolated, spectroscopically and structurally characterized examples of products of the side reactions are shown in SM 2. The commercial products – alkylnitrites – from Aldrich were of poor quality. Therefore, alkylnitrites *n*-C₃H₇–ONO or CH₃–ONO must be prepared fresh before use, and small quantities (5–20 g) of it were made each time prior to use in oximes syntheses according to published procedures [53]. Previously, we successfully used nitrosation reaction at basic conditions for the synthesis of monosubstituted arylcyanoximes [17–19] and some amide-cyanoximes [22,45]. The typical procedure for the synthesis of dihalogenated arylcyanoximes is presented below.

3.4. Synthesis of oximino(2,6-difluorophenyl)acetonitrile, H(2,6-diF-PhCO)

Metallic sodium (0.754 g; 0.033 mol) was dissolved at room temperature and under N₂ protection in 300 mL of isopropanol. The starting 2,6-difluorophenylacetonitrile, NC–CH₂–C₆H₃F₂ (5.000 g; 0.033 mol), was dissolved in 50.0 mL of isopropanol and then added to the sodium isopropoxide solution. Gaseous methylnitrite, CH₃ONO, generated on site from cold aqueous solutions of NaNO₂, methanol and H₂SO₄ [53], was bubbled through the mixture of NaOC₃H₇ and NC–CH₂–C₆H₃F₂ in *i*-propanol

within 10 min. The reaction mixture's color changed to yellow, and the mixture was kept overnight at $\sim 4^\circ\text{C}$. The solvent was removed and the remaining yellow solid residue of NaL^* ($\text{L} = 2,6\text{-diF-PhCO}$) was dried at room temperature under vacuum. The solid NaL was re-dissolved in 50 mL of water and the solution was slowly acidified with 1.0 M HCl . At $\text{pH} \sim 7$ white precipitate started to appear in the flask. The precipitate of HL was filtered, washed with water and dried in a desiccator resulting in 5.124 g (0.028 mol) of the cyanoxime at 86% yield. $\text{M.p.} = 99\text{--}100^\circ\text{C}$, $R_f = 0.29$ ($\text{EtOAc/hexane} = 1:4$). $\text{C}_8\text{H}_4\text{F}_2\text{N}_2\text{O}$ requires: C, 52.76; H, 2.21; N, 15.38. Found: C, 52.71; H, 2.18; N, 15.43%. NMR spectra evidenced the mixture of *syn* ($\sim 50\%$) and *anti* ($\sim 50\%$) isomers. Data for *syn*-isomer: ^1H NMR, ppm: 14.46 (1H, s, oxime group); 7.68 (1H, ten lines multiplet); 7.30 (2H, seven lines multiplet); ^{13}C NMR, ppm.: 160.00 (carbon at 2-position; $^1J(^{13}\text{C}\text{--}^{19}\text{F}) = 254\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 5.1\text{ Hz}$), 112.74 (carbon at 3-position; $^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 20.5\text{ Hz}$, $^4J(^{13}\text{C}\text{--}^{19}\text{F}) = 4.3\text{ Hz}$), 110.01 (carbon at 4-position), 134.05 (*ipso*-carbon; $^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 10.8\text{ Hz}$), 123.91 (oxime carbon), 105.62 (CN-group). Mass-spectrometry: for $\text{C}_8\text{H}_4\text{F}_2\text{N}_2\text{O}$ found (required) – 182.0299 (182.0292). UV–Vis spectrum, λ_{max} (EtOH)/nm, $\varepsilon/\text{dm}^3\text{ M}^{-1}\text{ cm}^{-1}$: 210 (5900), 244 (5550). X-ray quality needle-like crystals were obtained by slow evaporation of its aqueous solution.

Other cyanoximes follow:

3.4.1. Oximino(2,4-difluorophenyl)acetonitrile, $H(2,4\text{-diF-PhCO})$

Colorless crystalline substance; yield = 89%, $\text{m.p.} = 64\text{--}65^\circ\text{C}$, $R_f = 0.37$ in $\text{EtOAc/hexane} = 1:4$ mobile phase. $\text{C}_8\text{H}_4\text{F}_2\text{N}_2\text{O}$ requires: C, 52.76; H, 2.21; N, 15.38. Found: C, 52.80; H, 2.24; N, 15.47%. NMR spectra evidenced the mixture of *syn* (60%) and *anti* (40%) isomers in $\text{DMSO-}d_6$. Data for *syn*-isomer: ^1H NMR, ppm: 14.12 (1H, s, oxime group); 7.75 (1H, multiplet at 6-position; $^3J(^1\text{H}\text{--}^1\text{H}) = 8.0\text{ Hz}$, $^5J(^1\text{H}\text{--}^1\text{H}) = 2.0\text{ Hz}$, $^4J(^1\text{H}\text{--}^{19}\text{F}) = 8.5\text{ Hz}$); 7.47 (1H, multiplet at 5-position; $^3J(^1\text{H}\text{--}^1\text{H}) = 8.5\text{ Hz}$, $^4J(^1\text{H}\text{--}^1\text{H}) = 2.5\text{ Hz}$, $^3J(^1\text{H}\text{--}^{19}\text{F}) = 11.5\text{ Hz}$, $^5J(^1\text{H}\text{--}^{19}\text{F}) = 3.0\text{ Hz}$); 7.25 (1H, multiplet at 3-position; $^3J(^1\text{H}\text{--}^1\text{H}) = 8.0\text{ Hz}$, $^4J(^1\text{H}\text{--}^{19}\text{F}) = 6.5\text{ Hz}$). ^{13}C NMR, ppm.: 163.87 – carbon at 2-position, ($^1J(^{13}\text{C}\text{--}^{19}\text{F}) = 251\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 12.3\text{ Hz}$), 159.82 – carbon at 4-position ($^1J(^{13}\text{C}\text{--}^{19}\text{F}) = 255\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 12.8\text{ Hz}$), 131.09 – carbon at 6-position ($^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 10.4\text{ Hz}$, $^3'J(^{13}\text{C}\text{--}^{19}\text{F}) = 4.0\text{ Hz}$), 126.31 – oxime carbon, 113.17 – *ipso*-carbon ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 22.0\text{ Hz}$, $^4J(^{13}\text{C}\text{--}^{19}\text{F}) = 3.3\text{ Hz}$), 110.28 – CN-group, 105.82 – carbon at 3-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 25.9\text{ Hz}$), 105.62 – carbon at 5-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 25.1\text{ Hz}$, $^4J(^{13}\text{C}\text{--}^{19}\text{F}) = 2.0\text{ Hz}$). UV–Vis spectrum, λ_{max} (EtOH)/nm, $\varepsilon/\text{dm}^3\text{ M}^{-1}\text{ cm}^{-1}$: 261 (6200).

3.4.2. Oximino(2,5-difluorophenyl)acetonitrile, $H(2,5\text{-diF-PhCO})$

Colorless needle-type crystals; yield = 91%, $\text{m.p.} = 64\text{--}67^\circ\text{C}$, $R_f = 10.24$ ($\text{EtOAc/hexane} = 1:4$). $\text{C}_8\text{H}_4\text{F}_2\text{N}_2\text{O}$

requires: C, 52.76; H, 2.21; N, 15.38. Found: C, 52.80; H, 2.26; N, 15.47%. Only one isomer (*syn*) in solutions. ^1H NMR, ppm: 14.29 (1H, s, oxime group); 7.49 (1H, multiplet, ddd); 7.45 m (2H, multiplet, ddd). ^{13}C NMR, ppm.: 158.39 – carbon at 2-position ($^1J(^{13}\text{C}\text{--}^{19}\text{F}) = 242\text{ Hz}$, $^4J(^{13}\text{C}\text{--}^{19}\text{F}) = 2.1\text{ Hz}$), 155.69 – carbon at 5-position ($^1J(^{13}\text{C}\text{--}^{19}\text{F}) = 248\text{ Hz}$, $^4J(^{13}\text{C}\text{--}^{19}\text{F}) = 2.3\text{ Hz}$), 126.12 – oxime carbon, 119.82 – carbon at 3-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 24.3\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 8.9\text{ Hz}$), 119.41 – *ipso*-carbon ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 12.9\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 8.2\text{ Hz}$), 118.96 – carbon at 4-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 22.8\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 8.2\text{ Hz}$), 115.34 – carbon at 6-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 26.5\text{ Hz}$, $^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 2.5\text{ Hz}$), 110.06 – CN-group. UV–Vis spectrum, λ_{max} (EtOH)/nm, $\varepsilon/\text{dm}^3\text{ M}^{-1}\text{ cm}^{-1}$: 204 nm ($\varepsilon = 16080\text{ dm}^3\text{ M}^{-1}\text{ cm}^{-1}$), 259 (7320). X-ray quality needle-like crystals were obtained by slow cooling in thermostat hot solution of compound in CCl_4 .

3.4.3. Oximino(2-chloro-6-fluorophenyl)acetonitrile, $H(2\text{Cl-6F-PhCO})$

Colorless needles; yield 45%, $\text{m.p.} = 119\text{--}120^\circ\text{C}$, $R_f = 0.38$ ($\text{EtOAc/hexane} = 1:4$). $\text{C}_8\text{H}_4\text{FCIN}_2\text{O}$ requires: C, 48.39; H, 2.03; N, 14.11. Found: C, 48.33; H, 2.09; N, 14.23%. NMR spectra indicate mixture of *syn* (73%) and *anti* (27%) isomers in $\text{DMSO-}d_6$. The following data for *syn*-isomer. ^1H NMR, ppm: 14.51 (1H, s, oxime group); 7.66 (1H, multiplet at 5-position; $^3J(^1\text{H}\text{--}^1\text{H}) = 8.5\text{ Hz}$, $^3J(^1\text{H}\text{--}^{19}\text{F}) = 8.51\text{ Hz}$); 7.53 (1H, doublet at 3-position; $^3J(^1\text{H}\text{--}^1\text{H}) = 8.5\text{ Hz}$); 7.45 (1H, multiplet at 4-position; $^3J(^1\text{H}\text{--}^1\text{H}) = 7.5\text{ Hz}$, $^4J(^1\text{H}\text{--}^{19}\text{F}) = 1.0\text{ Hz}$). ^{13}C NMR, ppm.: 159.31 – carbon at 6-position ($^1J(^{13}\text{C}\text{--}^{19}\text{F}) = 251\text{ Hz}$), 134.07 – carbon at 4-position ($^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 9.6\text{ Hz}$), 132.79 – carbon at 2-position ($^3J(^{13}\text{C}\text{--}^{19}\text{F}) = 4.6\text{ Hz}$), 126.32 – carbon at 3-position ($^4J(^{13}\text{C}\text{--}^{19}\text{F}) = 3.0\text{ Hz}$), 126.26 – oxime carbon, 116.32 – carbon at 1-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 20.7\text{ Hz}$), 115.85 – carbon at 5-position ($^2J(^{13}\text{C}\text{--}^{19}\text{F}) = 21.3\text{ Hz}$), 114.72 – CN-group. UV–Vis spectrum, λ_{max} (EtOH)/nm, shoulders at 214 and 261 nm.

3.4.4. Oximino(2,4-dichlorophenyl)acetonitrile, $H(2,4\text{-diCl-PhCO})$

Colorless fibrous crystalline substance; yield 95%, $\text{m.p.} = 151^\circ\text{C}$, $R_f = 0.34$ ($\text{EtOAc/hexane} = 1:4$). $\text{C}_8\text{H}_4\text{Cl}_2\text{N}_2\text{O}$ requires: C, 44.68; H, 1.87; N, 13.03. Found: C, 44.71; H, 1.98; N, 13.23%. NMR spectra show mixture of *anti* (70%) and *syn* (30%) isomers in $\text{DMSO-}d_6$. Presented data for *anti*-isomer. ^1H NMR, ppm: 14.24 (1H, s, oxime group), 7.82 (1H, s, at 3-position), 7.66 (1H, multiplet, at 5-position), 7.58 (1H, at 6-position). ^{13}C NMR, ppm.: 136.71 – carbon at 2-position, 132.92 – carbon at 3-position, 132.45 – carbon at 4-position, 130.36 – carbon at 5-position, 128.64 – carbon at 6-position, 127.70 – oxime carbon, 110.13 – CN-group. UV–Vis spectrum, λ_{max} (EtOH)/nm, $\varepsilon/\text{dm}^3\text{ M}^{-1}\text{ cm}^{-1}$: $\sim 225\text{ nm}$ shoulder, 265 nm ($\varepsilon = 11200\text{ dm}^3\text{ M}^{-1}\text{ cm}^{-1}$).

3.4.5. Oximino(2,6-dichlorophenyl)acetonitrile, *H*(2,6-diCl-PhCO)

Colorless microcrystalline substance; yield 60%, m.p. = 94–96 °C, R_f = 0.29 (EtOAc/hexane = 1:4). $C_8H_4Cl_2N_2O$ requires: C, 44.68; H, 1.87; N, 13.03. Found: C, 44.75; H, 1.94; N, 13.12%. NMR spectra evidenced the mixture of *syn* (45%) and *anti* (55%) isomers. Data for *anti*-isomer are shown. 1H NMR, ppm: 14.41 (1H, s, oxime group), 7.68 (2H, multiplet), 7.59 (1H, multiplet). ^{13}C NMR, ppm: 135.26 – carbons at 2,6-positions, 133.26 – carbons at 3,5-positions, 129.07 – carbon at 4-position, 127.27 carbon at 1-position, 129.64 – oxime carbon, 114.29 – CN-group. UV–Vis spectrum, λ_{max} (EtOH)/nm, $\epsilon/dm^3 M^{-1} cm^{-1}$: 216 nm (ϵ = 15080 $M^{-1} cm^{-1}$), 269 nm shoulder. Block-type single crystals, suitable for X-ray analysis, were obtained during slow evaporation within ~2 weeks of the ethyl ether/ CCl_4 solvent mixture.

All synthesized cyanoximes are weak organic acids and represent colorless crystalline substances that are soluble in ether, alcohols, acetone, ethylacetate, DMSO, DMF, acetonitrile, and chlorocarbons, sparingly soluble in water, but not soluble in hydrocarbons. Dissolution protonated cyanoximes HL in amines (pyridine, triethylamine, ethylenediamine) leads to the formation of yellow solutions of deprotonated cyanoximate anions L^- .

3.5. Preparation of sodium, thallium(I) salts and transition metal complexes

The following paragraph describes typical methods of synthesis of ionic sodium salts that are used as precursors for the preparation of Pd(II) and Pt(II) cyanoximates, and also preparation of monovalent Tl and Ag complexes (Scheme 7).

3.5.1. Sodium salt of oximino(2-chloro-6-fluorophenyl)acetonitrile, *Na*(2Cl-6F-PhCO)

One gram (0.005 mol) of the starting oxime *H*(2Cl-6F-PhCO) was dissolved in 100 mL of ethyl ether. Sodium metal (0.116 g; 0.005 mol) was thinly sliced and dissolved

in 3.5 mL of ethanol under N_2 protection. The sodium ethoxide solution was added at once to the HL solution under intensive stirring resulting in an immediate precipitation of yellow NaL in the flask (route 1, Scheme 7). The precipitate was filtered, washed with cold ethyl ether and dried under vacuum giving 0.665 g (0.003 mol) of NaL (yield = 60%).

All sodium salts of dihalogen-substituted arylcyanoximes represent yellow hygroscopic powdery solids that are soluble in water, DMF, DMSO, and pyridine; they are insoluble in propanol, chlorocarbons and hexane. Yields, and data of element content determination for other synthesized NaL, are presented in SM 18.

Typical preparation of thallium(I) salts is presented below

3.5.2. Synthesis of thallium(I) oximino(2,4-difluorophenyl)acetonitrile, *Tl*(2,6-diF-PhCO)

287.7 mg (0.61 mmol) of Tl_2CO_3 were dissolved in 15 mL of water and mixed with 250.4 mg (1.2 mmol) of *Na*(2,6-diF-PhCO) dissolved in 20 mL of water (route 3, Scheme 7). The yellow solution was heated to boil for ~5 min and then filtered into the large mouth test tube immersed into the Dewar flask containing preheated to 95 °C water and left to cool. After several days yellow/orange fibrous thin crystals of the Tl(I) complex appeared in the test tube. The compound was filtered, washed with 5 mL of cold water and dried in desiccator charged with $H_2SO_{4(c)}$. Yield 68%; complex decomposes during heating above 160 °C. *Anal. Calc.* for $C_8H_3F_2N_2OTl$: C, 24.92; H, 0.78; N, 7.27. Found: C, 24.50; H, 0.81; N, 7.35%.

Other Tl(I) disubstituted arylcyanoximates follow:

Tl(2,4-diF-PhCO): yellow fibrous solid, yield 75%. *Anal. Calc.* for $C_8H_3F_2N_2OTl$: C, 24.92; H, 0.78; N, 7.27. Found: C, 24.79; H, 0.83; N, 7.15%.

Tl(2,5-diF-PhCO): dark-yellow needles, yield 82%. *Anal. Calc.* for $C_8H_3F_2N_2OTl$: C, 24.92; H, 0.78; N, 7.27. Found: C, 24.97; H, 0.81; N, 7.36%.

Tl(2Cl-6F-PhCO): yellow microcrystalline solid, yield 70%. *Anal. Calc.* for $C_8H_3FCIN_2OTl$: C, 23.90; H, 0.75; N, 6.97. Found: C, 24.07; H, 0.78; N, 7.14%.

Tl(2,4-diCl-PhCO): dark-yellow fibrous solid, yield 65%. *Anal. Calc.* for $C_8H_3Cl_2N_2OTl$: C, 22.96; H, 0.72; N, 6.70. Found: C, 23.11; H, 0.77; N, 6.85%.

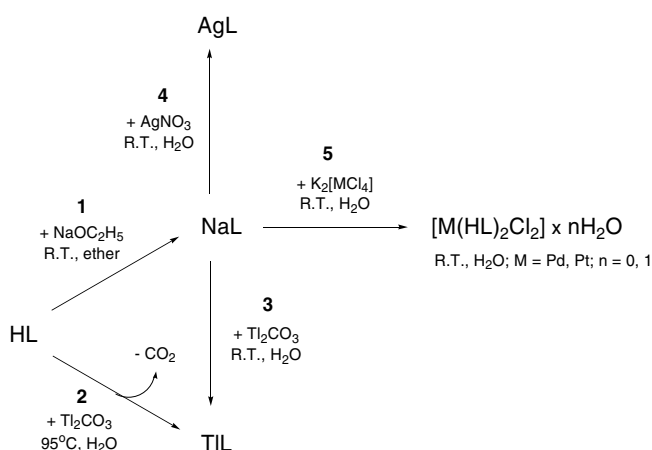
Tl(2,6-diCl-PhCO): yellow solid, yield 88%. *Anal. Calc.* for $C_8H_3Cl_2N_2OTl$: C, 22.96; H, 0.72; N, 6.70. Found: C, 22.81; H, 0.82; N, 6.73%.

Actual photographs of some of the thallium(I) arylcyanoximates are shown in SM 19.

Synthesized Tl(I) complexes are soluble in DMSO, DMF and pyridine and its homologs, sparingly soluble in cold water, and insoluble in ethanol, acetone, chlorohydrocarbons and aromatic hydrocarbons.

3.5.3. Synthesis of silver(I) oximino(2,4-difluorophenyl)acetonitrile, *Ag*(2,4-diF-PhCO)

The sodium salt of the ligand was the precursor for the preparation of the Ag(I) complex (route 4, Scheme 7).



Scheme 7.

Thus, 250.1 mg (1 mmol) of Na(2,4-diF-PhCO) were dissolved in 20 mL of water, while silver nitrate (AgNO_3), (208.3 mg; 1 mmol) was dissolved in 5 mL of water. The two solutions were then mixed under stirring. The reaction was carried out in the dark to prevent a photodegradation of the $\text{Ag}(2,4\text{-diF-PhCO})$. Thick yellow precipitate appeared immediately after the mixing. Solution was stirred for ~ 10 min then filtered, and precipitate was washed with cold water, methanol, and ether. The Ag-salt appeared to be slightly soluble in methanol; dry product was kept from ambient light in a desiccator using protection of aluminum foil since the complex is very light sensitive. The amount of isolated dry $\text{Ag}(2,4\text{-diF-PhCO})$: 0.278 g (79% yield). *Anal.* Calc. for $\text{C}_8\text{H}_3\text{AgF}_2\text{N}_2\text{O}$: C, 33.25; H, 1.05; N, 9.69. Found: C, 33.49; H, 1.03; N, 9.75%.

Other Ag(I) disubstituted arylcyanoximates follow:

$\text{Ag}(2,6\text{-diF-PhCO})$: yellow-orange solid, yield 92%. *Anal.* Calc. for $\text{C}_8\text{H}_3\text{AgF}_2\text{N}_2\text{O}$: C, 33.25; H, 1.05; N, 9.69. Found: C, 33.31; H, 1.12; N, 9.82%.

$\text{Ag}(2,5\text{-diF-PhCO})$: dark-yellow solid, yield 85%. *Anal.* Calc. for $\text{C}_8\text{H}_3\text{AgF}_2\text{N}_2\text{O}$: C, 33.25; H, 1.05; N, 9.69. Found: C, 33.22; H, 1.17; N, 9.61%.

$\text{Ag}(2\text{Cl-6F-PhCO})$: yellow solid, yield 80%. *Anal.* Calc. for $\text{C}_8\text{H}_3\text{AgClF}_2\text{N}_2\text{O}$: C, 31.46; H, 0.99; N, 9.17. Found: C, 31.29; H, 1.04; N, 9.26%.

$\text{Ag}(2,4\text{-diCl-PhCO})$: yellow solid, yield 80%. *Anal.* Calc. for $\text{C}_8\text{H}_3\text{AgCl}_2\text{N}_2\text{O}$: C, 29.85; H, 0.94; N, 8.70. Found: C, 30.03; H, 1.01; N, 8.76%.

$\text{Ag}(2,6\text{-diCl-PhCO})$: orange solid, yield 88%. *Anal.* Calc. for $\text{C}_8\text{H}_3\text{AgCl}_2\text{N}_2\text{O}$: C, 29.85; H, 0.94; N, 8.70. Found: C, 29.97; H, 0.98; N, 8.82%.

Obtained silver(I) compounds are light sensitive, insoluble in CHCl_3 , CH_2Cl_2 , aromatic hydrocarbons and slightly soluble in organic solvents such as acetone and CH_3OH , but well dissolve aqueous ammonia, dimethylamine solution, pyridine, DMSO and DMF, thiosulfate $\text{S}_2\text{O}_3^{2-}$ solution.

3.5.4. Bivalent Pd and Pt cyanoximates

Fine colored precipitates of complexes were obtained in aqueous solutions at room temperature upon mixing of $\text{K}_2[\text{MCl}_4]$ ($\text{M} = \text{Pd}, \text{Pt}$) with two equivalents of sodium salts of dihalogen substituted arylcyanoximates (route 5, Scheme 7). Seven out of twelve possible complexes were synthesized using this method. The Pd(II)-arylcyanoximates formed much faster and with better yields compared to their Pt(II) analogs, where precipitation was complete within hours. This is contrary to the quick formation of bivalent palladium and platinum complexes with amide-containing cyanoximates that formed five-membered chelate metallocycles observed earlier [22,45]. Typical preparation for the platinum(II) complex is presented below.

3.5.5. Synthesis of $\text{Pt}[H(2,4\text{-diCl-PhCO})_2]\text{Cl}_2$

100.8 mg (4.25×10^{-4} mol) of NaL were dissolved in 4 mL of water and mixed with 87.1 mg (2.10×10^{-4} mol)

of the potassium tetrachloroplatinate(II) in 6 mL of water under an intensive stirring at the ratio of $\text{K}_2\text{PtCl}_4/\text{NaL}$ 1:2. The reaction mixture was left to stir for 24 h. The reaction mixture gained a yellow color and fine yellow precipitate was filtered, washed with cold water and dried in a vacuum desiccator. Yield of yellow $\text{Pt}[H(2,4\text{-diCl-PhCO})_2]\text{Cl}_2$ was 31%. *Anal.* Calc. for $\text{C}_{16}\text{H}_8\text{Cl}_6\text{N}_4\text{O}_2\text{Pt}$: C, 27.61; H, 1.16; N, 8.05. Found: C, 28.14; H, 1.47; N, 8.18%.

Other platinum group metal complexes follow:

$\text{Pt}[H(2,4\text{-diF-PhCO})_2]\text{Cl}_2 \cdot x\text{H}_2\text{O}$: yellow solid, yield 63%. *Anal.* Calc. for $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{F}_4\text{N}_4\text{O}_3\text{Pt}$: C, 29.64; H, 1.55; N, 8.64. Found: C, 29.50; H, 1.41; N, 8.55%.

$\text{Pt}[H(2\text{Cl-6F-PhCO})_2]\text{Cl}_2 \cdot x\text{H}_2\text{O}$: yellow solid, yield 18%. *Anal.* Calc. for $\text{C}_{16}\text{H}_{10}\text{Cl}_4\text{F}_2\text{N}_4\text{O}_3\text{Pt}$: C, 28.21; H, 1.48; N, 8.23. Found: C, 28.09; H, 1.50; N, 8.17%.

$\text{Pt}[H(2,5\text{-diF-PhCO})_2]\text{Cl}_2$: brown solid, yield 32%. *Anal.* Calc. for $\text{C}_{16}\text{H}_8\text{Cl}_2\text{F}_4\text{N}_4\text{O}_2\text{Pt}$: C, 30.49; H, 1.28; N, 8.89. Found: C, 31.83; H, 1.51; N, 9.34%.

$\text{Pd}[H(2,4\text{-diCl-PhCO})_2]\text{Cl}_2$: reddish/orange, yield 95%. *Anal.* Calc. for $\text{C}_{16}\text{H}_8\text{Cl}_6\text{N}_4\text{O}_2\text{Pd}$: C, 31.64; H, 1.33; N, 9.22. Found: C, 31.12; H, 1.33; N, 9.08%.

$\text{Pd}[H(2,5\text{-diF-PhCO})_2]\text{Cl}_2$: orange solid, yield 78%. *Anal.* Calc. for $\text{C}_{16}\text{H}_8\text{Cl}_2\text{F}_4\text{N}_4\text{O}_2\text{Pd}$: C, 35.48; H, 1.49; N, 10.35. Found: C, 36.55; H, 1.16; N, 10.61%.

$\text{Pd}[H(2,6\text{-diF-PhCO})_2]\text{Cl}_2 \cdot x\text{H}_2\text{O}$: reddish/orange, yield 63%. *Anal.* Calc. for $\text{C}_{16}\text{H}_{10}\text{Cl}_2\text{F}_4\text{N}_4\text{O}_3\text{Pd}$: C, 34.34; H, 1.80; N, 10.01. Found: C, 34.04; H, 1.56; N, 9.84%.

The synthesized transition metal complexes are poorly soluble in water, soluble in acetone and ethanol, and well soluble in donor solvents such as DMF, DMSO and pyridine.

According to the results of magnetic susceptibility measurements (Gouy method; Johnson Matthew Mark-III magnetometer; $\text{K}_3[\text{Cr}(\text{oxalate})_3]$ as calibrant), all obtained bivalent platinum and palladium complexes represent diamagnetic at 296 K substances with square-planar geometries of the metal centers.

3.5.6. In vitro cytotoxicity studies

Antiproliferative activity of the obtained disubstituted arylcyanoximes and their Pd(II) and Pt(II) complexes was examined using a WiDR human colon carcinoma cell line (ATTC, catalog #CCL-218) following in general the basic procedures and operations with animal cells [51,52]. We developed and successfully used slightly different protocol and data collection for our *in vitro* experiments details of which are presented in SM 3 and SM 4. Several solutions of different concentration (0.01 mM, 0.1 mM, 0.25 mM, 0.50 mM, 0.75 mM and 1.0 mM) were prepared for the testing. Since rapid solvolysis of cisplatin and related compounds in pure DMSO [47] had been previously established, Pd and Pt cyanoximates were quickly dissolved in DMSO within 20 seconds and then appropriate aliquots were mixed with aqueous buffer during one minute and added to plated cells. No re-precipitation of complexes in the 24-well plates was observed.

During all *in vitro* experiments, WiDr cells were used in the exponential phase of their growth, and were allowed to grow 24 h after being plated before any compounds were added to the medium. All *in vitro* studies of synthesized compounds and control substances (cisplatin, DMSO) were conducted in duplicate. The viable/non-viable stained cells count method was used for the evaluation of cytotoxicity of the synthesized compounds. Digital pictures of cells were taken with an Olympus DP70 digital camera attached to an Olympus BX41 Microscope at 100× magnification. Three random views were photographed with subsequent cell counts and data analysis.

4. Conclusions

1. High-yield preparation of new disubstituted arylcyanoximes was developed using the nitrosation reaction at basic conditions despite several side reactions. Six new synthesized arylcyanoximes were characterized by means of NMR, IR and UV–Vis spectroscopy. Crystal structures were determined for four cyanoximes and it was found that the fluorinated compounds adopt rare *syn*-configuration in solid state. Nevertheless, five out of six protonated arylcyanoximes HL exist as a mixture of *syn*- and *anti*-isomers in solutions. No interconversion between the two isomers was observed upon heating of their solutions in DMSO- d_6 .
2. Six thallium(I) and six silver(I) dihalogenated arylcyanoximates were synthesized from protonated ligands HL and Na-salts respectively. Obtained coordination polymers were characterized using spectroscopic methods. The cyanoxime anions perform bridging function upon coordination utilizing the oxime group (Tl^+), or cyano-group and the oxime groups (Ag^+) as deduced from their IR-spectra analogous to several structurally characterized thallium and silver cyanoximates.
3. First-row transition metals ions do not form isolable coordination compounds with studied disubstituted arylcyanoximes due their inability to form chelate-type complexes common for other cyanoximes.
4. Seven new bivalent Pd and Pt arylcyanoximates of general formula $[M(HL)_2Cl_2]$ were synthesized and studied using IR, UV–Vis spectroscopy and the solutions' electrical conductivity. Monodentate binding mode of the cyanoxime ligands via nitrogen atom of the oxime fragment are suggested based on data of their IR spectra and MM-2 calculations with optimization of geometry. A square-planar geometry for the obtained coordination compounds with Cl anions and monodentate cyanoximes being in *trans*-position to each other was offered as a solid state structure.
5. Both Pd and Pt complexes are non-electrolytes in ethanol and DMSO. Nevertheless, a stepwise solvolysis of the Pt(II) arylcyanoximates leading to the oxime displacement was observed in these solutions. Kinetics of these first order reactions was measured using UV–Vis spectroscopy. In both solvents the first cyanoxime substitution reaction is significantly faster (4.5–10 times) than the second reaction. The overall solvolysis of investigated metal complexes in DMSO by factor of 20–110 faster than that in ethanol.
6. Results of *in vitro* cytotoxicity studies of synthesized arylcyanoximes and their Pd and Pt complexes on human colon carcinoma WiDr cell line showed absence of cytotoxicity of the uncomplexed ligands and all metal complexes at low concentrations (0.01–0.1 mM). Two bivalent palladium and platinum cyanoximates containing H(2,4-diCl-PhCO) showed the greatest antiproliferative activity at 0.25 mM concentrations found to be ~20% of that for cisplatin at the same conditions.

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Appendix A. Supplementary material

Summary of the NMR spectra for HL and NaL and effect of heat on solutions (SM 1); products of encountered during nitrosation side reactions (SM 2); representative data for cyanoximates' solvatochromism (SM 3); charge delocalization in anions (SM 4); tables of IR-spectra of synthesized compounds (SM 5–SM 9); data of solutions electrical conductivity studies of two Pd and Pt complexes (SM 10); UV–Vis spectra of the two Pt complexes in kinetic mode (SM 11, SM 12); results of MM-2 optimization of geometry calculations (SM 13, SM 14); cytotoxicity protocol (SM 15, SM 16); photographs of controls used in *in vitro* experiments (SM 17); actual photos of WiDR cells with added Pt-cyanoximate (SM 18); chart with the cytotoxicity data for several Pd and Pt cyanoximates (SM 19); composition and properties of NaL (SM 20); optical and EM photographs of some of the TIL crystals (SM 21); X-ray structure of related Ag(I) complex (SM 22). An X-ray crystallographic files (CIF) for all reported structures. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ica.2007.10.019](https://doi.org/10.1016/j.ica.2007.10.019).

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