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Synthesis, Structural Features, and Molecular Docking of Zn(II), Cu(II), Co(II), and Ag(I) Coordination Compounds with 3-(Thien-2-ylidene)-1-pyrroline

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Abstract

A series of Zn(II), Cu(II), Co(II), and Ag(I) coordination compounds containing organic (pentafluorobenzoate and trifluoroacetate) or inorganic (chloride and nitrate) anions and molecules of 3-(thien-2-ylidene)-1-pyrroline (L) was synthesized. It was shown that the composition, nuclearity, and geometry of the resulting coordination compounds are determined by the nature of the metal and the type of anion. The synthesized compounds were characterized by X-ray diffraction analysis, IR spectroscopy, and elemental analysis (CHNS). The structures and crystal packings of the obtained complexes were analyzed in detail, and the main structure-directing non-covalent interactions in the crystals were identified. Molecular docking was used to study the interactions of the synthesized coordination compounds with the human epidermal growth factor receptor (HER2).

Pyrroline derivatives are an extensive class of compounds that occupy an important place in the chemistry of bioactive compounds due to their wide spectrum of pharmacological applications. Among these compounds, some show pronounced anti-inflammatory [1, 2], analgesic [3, 4], antimicrobial [5,6], and antitumor [7,8] activities. This heterocyclic fragment is also present in the structure of a number of widely used medicinal agents [9].

Such a wide range of pharmacological applications characteristic of this class of compounds is directly related to the simplicity of modifying molecules based on the pyrroline cycle by varying the nature and position of substituents. The incorporation of different functional groups into the pyrroline cycle enables not only tuning biological activity but also varying the coordination capabilities of the resulting proligands. Thus, the incorporation of different substituents containing donor atoms into molecules leads to the formation of ligands with different coordination modes toward metal ions and also affects the systems of non-covalent interactions, which determine the supramolecular structure of the resulting compounds [10].

The incorporation of a thiophene fragment into the structure may lead to both enhancement of biological activity of the molecule [11, 12] and formation of additional coordination centers, since the sulfur atom of the thiophene fragment is capable of forming bonds with transition metal ions, as well as forming numerous non-covalent interactions of different nature [13-15].

As numerous studies show, complexation of biologically active organic proligands with ions of essential metals decreases toxicity while simultaneously increasing the efficacy and bioavailability of the resulting compounds compared to the initial ligands [16, 17]. The interaction of biologically active ligands with transition metals (such as Cu(II), Ni(II), Co(II/III), Ag(I), Zn(II), Pd(II), etc.) represents a well-established strategy for enhancing the therapeutic effect and overcoming drug resistance [18-20].

Therefore, the aim of this research was to investigate the molecular and crystal structure of 3-(thien-2-ylidene)-1-pyrroline, as well as to synthesize and characterize its compounds containing Zn(II), Cu(II), Co(II), and Ag(I) with organic (pentafluorobenzoate, trifluoroacetate) or inorganic (nitrate and chloride) anions. The influence of the nature of the metal and the type of anion on the composition of the resulting compounds, as well as on their molecular and crystal structures, were analyzed. Molecular docking studies were also conducted using a therapeutically relevant target, the kinase domain of human HER2 (PDB ID: 3PP0).

Experimental Section

The synthesis of all compounds was carried out in air. In the work, commercially available reagents and solvents were used: cobalt(II) acetate tetrahydrate ($\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, 99.9%, «Lanhit»), zinc(II) acetate dihydrate ($\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, 99.9%, «Lanhit»), copper(II) acetate monohydrate ($\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, 99.9%, «Lanhit»), 2,3,4,5,6-pentafluorobenzoic acid (Hpfb, 99%, «P&M Invest»), silver(I) nitrate (r.g.), copper(II) chloride tetrahydrate (r.g.), ethanol (EtOH, «96%»), acetonitrile (MeCN, pure). Cobalt(II) trifluoroacetate tetrahydrate ($\text{Co}(\text{CF}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$) [21], silver(I) pentafluorobenzoate [22], and the organic ligand $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ was synthesized according to previously reported procedures [23, 24]. Crystals of $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ were obtained by slow evaporation of a concentrated ethanol solution in air.

IR spectra of the compounds were recorded on a Jasco FT/IR-4700 by the attenuated total reflectance (ATR) in the range $550\text{--}4000\text{ cm}^{-1}$.

Elemental analysis was carried out on an EA1108 Carlo Erba automatic CHNS-analyzer (EuroVector, Pavia PV, Italy).

Synthesis of the compound $[\text{Zn}(\text{L})_2(\text{pfb})_2]$ (1)

Zinc(II) acetate (0.044 g, 0.202 mmol) and pentafluorobenzoic acid (0.086 g, 0.404 mmol) were dissolved in ethanol (10 mL). $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ (0.112 g, 0.404 mmol) was added to the resulting colorless solution, and the reaction mixture was heated at $70\text{ }^\circ\text{C}$ for 1 h. The reaction mixture was then cooled to room temperature and left to evaporate slowly. After 3 days, crystals of compound **1** suitable for X-ray diffraction analysis were obtained. The yield of **1** was 0.067 g (41%), based on the initial amount of zinc(II) acetate.

Calc. for $\text{C}_{32}\text{H}_{18}\text{ZnF}_{10}\text{N}_2\text{O}_4\text{S}_2$, %: C 47.2; H 2.2; N 3.4; S 8.0. Found, %: C 47.0; H 2.1; N 3.2; S 8.1.

IR spectrum (ATR; ν , cm^{-1}): 3069 w, 2915 w, 2857 w, 1730 m, 1709 m, 1649 m, 1590 s, 1496 s, 1403 s, 1321 m, 1219 m, 1149 m, 1105 m, 996 s, 937 m, 884 m, 829 w, 751 m, 703 m, 565 w.

Synthesis of the compound $[\text{Cu}(\text{L})_2(\text{pfb})_2]$ (2)

Copper(II) acetate (0.040 g, 0.202 mmol) and pentafluorobenzoic acid (0.086 g, 0.404 mmol) were dissolved in ethanol (10 mL). $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ (0.112 g, 0.404 mmol) was added to the resulting solution, and the reaction mixture was heated at $70\text{ }^\circ\text{C}$ for 1 h. The blue solution was then cooled to room temperature and left to evaporate slowly. After 4 days, crystals of compound **2** suitable for X-ray diffraction analysis were obtained. The yield of **2** was 0.064 g (39%), based on the initial amount of copper(II) acetate.

Calc. for $C_{32}H_{18}CuF_{10}N_2O_4S_2$, %: C 47.3; H 2.2; N 3.4; S 7.9. Found, %: C 47.6; H 2.0; N 3.5; S 8.3.

IR spectrum (ATR; ν , cm^{-1}): 3082 w, 2924 w, 2858 w, 1732 w, 1705 m, 1651 m, 1589 m, 1496 s, 1404 s, 1319 m, 1227 m, 1146 m, 1107 m, 995 s, 937 m, 883 m, 822 w, 752 s, 702 s, 575 m.

Synthesis of the compound $[Co(L)_2(EtOH)_2(pfb)_2]$ (**3**)

Cobalt(II) acetate (0.050 g, 0.202 mmol) and pentafluorobenzoic acid (0.086 g, 0.404 mmol) were dissolved in a mixture of ethanol (10 mL) and acetonitrile (10 mL). $H[L]^+[CF_3COO]^-$ (0.112 g, 0.404 mmol) was added to the resulting solution, and the reaction mixture was heated at 70 °C for 2 h. The pink solution was then cooled to room temperature and left to evaporate slowly. After 10 days, crystals of compound **3** suitable for X-ray diffraction analysis were obtained. The yield of **3** was 0.056 g (31%), based on the initial amount of cobalt(II) acetate.

Calc. for $C_{36}H_{30}CoF_{10}N_2O_6S_2$, %: C 48.0; H 3.4; N 3.2; S 7.1. Found, %: C 48.0; H 3.2; N 3.3; S 6.8.

IR spectrum (ATR; ν , cm^{-1}): 3217 w, 3109 w, 2954 w, 1674 s, 1631 m, 1570 m, 1550 m, 1415 m, 1342 w, 1296 w, 1192 s, 1138 s, 1045 m, 991 m, 930 m, 833 m, 795 m, 710 s, 671 s, 609 m.

Synthesis of the compound $[Cu_4(L)_4(O)(Cl)_6]$ (**4**)

Copper(II) chloride (0.050 g, 0.237 mmol) and $H[L]^+[CF_3COO]^-$ (0.132 g, 0.474 mmol) were dissolved in ethanol (10 mL). The reaction mixture was heated at 70 °C for 30 min. The green solution was then cooled to room temperature and left to evaporate slowly. After 15 days, crystals of compound **4** suitable for X-ray diffraction analysis were obtained. The yield of **4** was 0.019 g (29%), based on the initial amount of copper(II) chloride.

Calc. for $C_{36}H_{37}Cu_4Cl_6N_4OS_4$, %: C 38.0; H 3.3; N 5.0; S 11.3. Found, C 37.9; H 3.2; N 5.2; S 11.7.

IR spectrum (ATR; ν , cm^{-1}): 3073 w, 2900 w, 1824 w, 1677 w, 1623 w, 1585 m, 1508 w, 1411 m, 1369 w, 1342 m, 1195 m, 1141 m, 1045 w, 995 m, 944 s, 867 m, 710 s, 674 w, 570 w.

Synthesis of the compound $[Co_2(H_2O)(L)_4(CF_3COO)_4]$ (**5**)

Cobalt(II) trifluoroacetate (0.034 g, 0.093 mmol) and $H[L]^+[CF_3COO]^-$ (0.052 g, 0.187 mmol) were dissolved in a mixture of ethanol (10 mL) and acetonitrile (10 mL). The reaction mixture was heated at 70 °C for 30 min. The solution was then cooled to room temperature and

left to evaporate slowly. After 5 days, crystals of compound **5** suitable for X-ray diffraction analysis were obtained. The yield of **5** was 0.022 g (38%), based on the initial amount of cobalt(II) trifluoroacetate.

Calc. for $C_{44}H_{38}Co_2F_{12}N_4O_9S_4$, %: C 42.6; H 3.1; N 4.5; S 10.3. Found, C 42.4; H 3.2; N 4.3; S 10.0.

IR spectrum (ATR; ν , cm^{-1}): 3217 w, 2981 w, 1608 s, 1493 s, 1373 s, 1281 m, 1196 m, 1146 m, 1099 m, 1053 m, 987 s, 926 m, 868 m, 829 m, 737 s, 702 s, 617 m, 582 m.

Synthesis of the compound $[Ag(L)_2](NO_3)$ (**6**)

Silver(I) nitrate (0.009 g, 0.054 mmol) and $H[L]^+[CF_3COO]^-$ (0.030 g, 0.108 mmol) were dissolved in ethanol (5 mL). The reaction mixture was stirred for 30 min. The solution was left to evaporate slowly. After 3 days, crystals of compound **6** suitable for X-ray diffraction analysis were obtained. The yield of **6** was 0.009 g (33%), based on the initial amount of silver(I) nitrate.

Calc. for $C_{18}H_{18}AgN_3O_3S_2$, %: C 43.6; H 3.7; N 8.5; S 13.0. Found, C 43.3; H 3.5; N 8.4; S 13.4.

IR spectrum (ATR; ν , cm^{-1}): 3074 w, 2927 w, 1662 w, 1628 w, 1570 m, 1512 w, 1446 w, 1408 w, 1362 s, 1323 s, 1300 s, 1242 m, 1211 m, 1180 w, 1146 m, 1076 w, 1041 w, 987 w, 930 m, 887 m, 849 m, 825 w, 710 s, 671 m, 579 m.

Single crystal X-ray diffraction analysis of compounds was performed on a Bruker D8 Venture diffractometer equipped with a CCD detector ($MoK\alpha$, $\lambda = 0.71073$ Å, $CuK\alpha$, $\lambda = 1.54178$ Å, graphite monochromator). A semi-empirical absorption correction using the SADABS program was applied to all compounds.

The structures were solved using a dual-space algorithm [25] and refined by full-matrix least-squares methods with anisotropic displacement parameters for all non-hydrogen atoms. The H-atoms were added in the calculated positions and refined using the riding model in isotropic approximation. Calculations were performed using the SHELX [26] programs package within OLEX 2 [27].

Thiophene fragments in ligand L in compounds $H[L]^+[CF_3COO]^-$, **2**, **3**, and **5** are disordered over two positions with occupancies of 0.84/0.16 in $H[L]^+[CF_3COO]^-$, 0.91/0.09 in **2**, 0.87/0.13 in **3**, and 0.66/0.34, 0.87/0.13, and 0.92/0.08 in **5**. The nitrate anion in compound **6** is disordered over two positions with an occupancy ratio of 0.56/0.44. Fluorine atoms in the CF_3COO^- anions in the crystals of $H[L]^+[CF_3COO]^-$ and **5** are disordered over two positions with occupancies of 0.72/0.28 in $H[L]^+[CF_3COO]^-$ and 0.69/0.31, 0.5/0.5, 0.57/0.43, and 0.65/0.35 in **5**.

Crystallographic parameters and refinement details are presented in Tables S1 and S2, with the main bond lengths and angles given in Table 1. Principal intra- and intermolecular interaction distances and angles are listed in Tables S3, 2 and S4. CCDC no 2571195 (1), 2571196 (2), 2571197 (3), 2571198 (4), 2571199 (5), 2571200 (6), 2571201 ($\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.

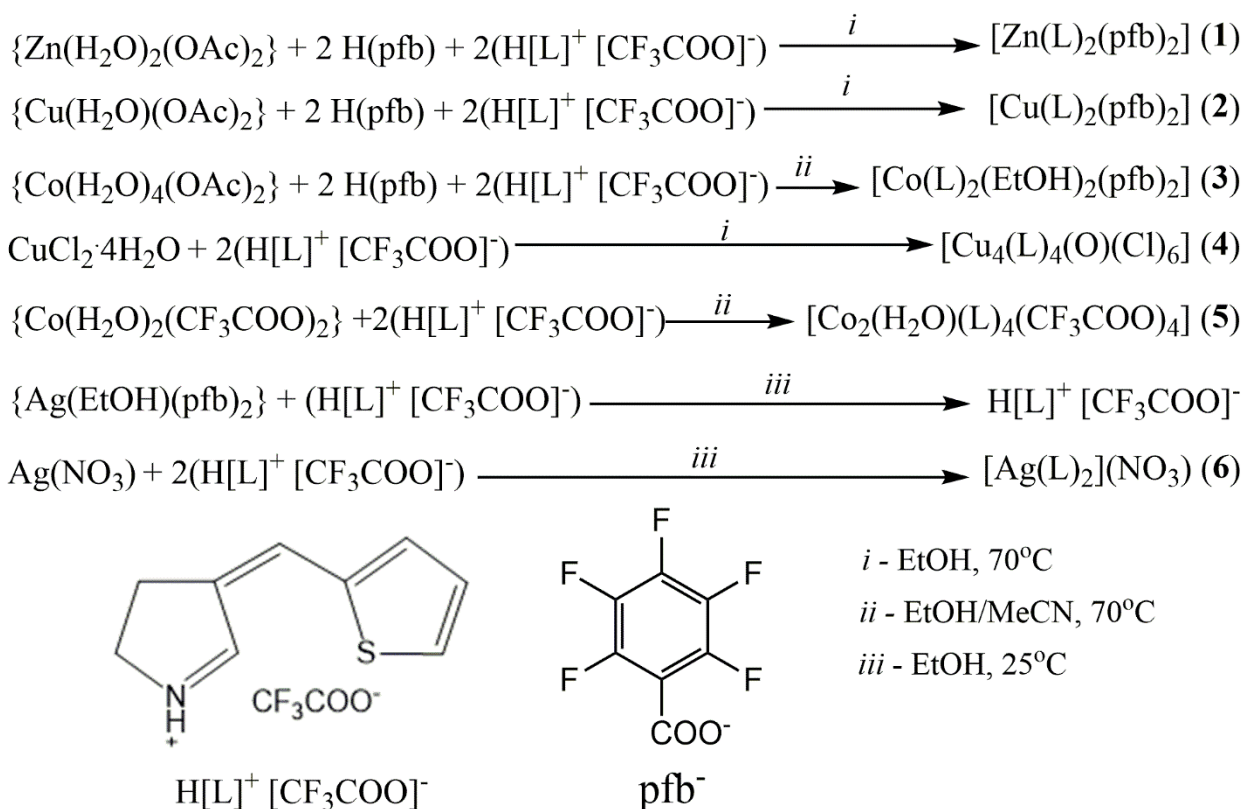
Molecular docking studies were performed using AutoDock 4.2 software [28] to investigate the molecular interactions and binding modes. For this purpose, the 3D crystal structure of Kinase domain of Human HER2 (PDB ID: 3PP0) was obtained from Protein Data Bank (<http://www.rcsb.org>). All water molecules and co-crystal ligands were excluded from the protein structure and the PDB was checked for the missing atom types. The polar hydrogen atoms and Kollman charges were added to the protein structure's amino acid residues using AutoDock Tools (ADT, version 1.5.7) [29], which was also used to convert these corrected PDB files to PDBQT format.

The structures of complexes **1-6** and their organic precursor - 3-(thien-2-ylidene)-1-pyrroline were taken from results of single crystal X-ray studies and converted to PDBQT using ADT. The ligands were then docked in the active site of HER2 using AutoDock 4.2, based on the Lamarckian genetic algorithm [30]. A total of 50 runs of docking calculations were carried out. The population size, maximum number of evaluations (medium), and maximum generation were set at 300, 2,500,000 and 27,000, respectively. The grid box was centered on the protein's active site with *x*, *y*, and *z* coordinates of 16.197, 17.394, 26.218 [31]. The number of points in the *x*, *y* and *z* dimensions was 60, 60, 60, the spacing between grid points was set at 0.375 Å.

Parameters of silver and cobalt atoms were added to the *gpf* and *dpf* files to be used in the docking calculation. Visualization of the final docked pose and its analysis has been performed by means of ADT and BIOVIA Discovery Studio 2021 (Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 21.1.0, San Diego: Dassault Systèmes, 2020).

Results and Discussion

Synthesis of Compounds



Scheme 1. Synthesis of compounds 1-6.

The starting 3-(thien-2-ylidene)-1-pyrroline (L) was used in the synthesis of coordination compounds of zinc, copper, cobalt, and silver in the form of the trifluoroacetate salt $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$. Crystals of $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ suitable for X-ray diffraction analysis were obtained by evaporation of a concentrated ethanol solution of the salt in air.

Salts containing anions of fluorinated pentafluorobenzoic and trifluoroacetic acids were used to obtain coordination compounds characterized by the formation of numerous non-covalent interactions of various types [32-34]. Salts with inorganic chloride and nitrate anions were used. These anions are significantly smaller than the organic anions employed and are capable of forming polynuclear structures with transition-metal atoms [35-37].

The reaction of zinc or copper acetate with pentafluorobenzoic acid and $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ in ethanol in a 1:2:2 ratio resulted in the formation of $[\text{Zn}(\text{L})_2(\text{pfb})_2]$ (**1**, **Scheme 1**) and $[\text{Cu}(\text{L})_2(\text{pfb})_2]$ (**2**, **Scheme 1**) crystals. In their structures, two molecules of ligand L are monodentately coordinated to the metal ion via nitrogen atoms. The use of cobalt(II) acetate under the same conditions resulted in the formation of $[\text{Co}(\text{L})_2(\text{EtOH})_2(\text{pfb})_2]$ (**3**, **Scheme 1**) crystals, in which each metal atom is also coordinated by two ligand molecules, while the coordination environment of the cobalt atom is completed to an octahedral geometry by coordination of ethanol

molecules. The use of a 1:2:1 reagent ratio in reactions **1-3** also resulted in the formation of compounds **1**, **2**, and **3**, but with lower yields.

The use of copper(II) chloride as the starting salt resulted in the formation of the tetranuclear compound $[\text{Cu}_4(\text{L})_4(\text{O})(\text{Cl})_6]$ (**4**, **Scheme 1**), in which the metal atoms are connected by chloride anions and an oxo bridge, with each copper atom coordinating one molecule of L.

Whereas the use of cobalt(II) trifluoroacetate under the same conditions as for **1-3** led to the formation of the binuclear compound $[\text{Co}_2(\text{H}_2\text{O})(\text{L})_4(\text{CF}_3\text{COO})_4]$ (**5**, **Scheme 1**), in which the cobalt atoms form a binuclear metal core through two bridging trifluoroacetate anions and a bridging water molecule. The coordination environment of each cobalt atom is completed to an octahedral geometry by coordination of two nitrogen atoms from two molecules of L.

Attempts to obtain silver compounds by the reaction of silver(I) pentafluorobenzoate with $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ did not result in the formation of coordination compound crystals, and only crystals of the starting salt $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ were obtained. In contrast, the use of silver(I) nitrate allowed the isolation of $[\text{Ag}(\text{L})_2](\text{NO}_3)$ (**6**, **Scheme 1**), in which each silver atom is coordinated by two nitrogen atoms from two L molecules.

In all the obtained compounds, L is coordinated through the nitrogen atom, exhibiting a monodentate coordination mode, whereas the sulfur atom is not involved in coordination.

Structure of compounds

The crystal structure of the 3-(thien-2-ylidene)-1-pyrrolinium trifluoroacetate salt ($\text{H[L}^+\text{][CF}_3\text{COO}^-]$) (Fig. 1), as well as a number of the corresponding complexes of the pyrroline with copper (Fig. 2(b, d)), zinc (Fig. 2(a)), silver (Fig. 2(f)), and cobalt (Fig. 2(c, e)) ions, was analyzed as part of the study.

The crystals of $\text{H[L}^+\text{][CF}_3\text{COO}^-]$ are monoclinic, and the pyrrolinium cation is linked to the trifluoroacetate anion by an $\text{N-H}\cdots\text{O}$ hydrogen bond (Table S3). The arylidene-pyrroline fragment is almost planar (the maximum deviation from the plane is 0.039(2) Å for carbon atom C1 and 0.025(2) Å for parts 1 and 2 of the disordered thiophene fragment). The geometry of the pyrroline ring does not differ from that previously described for benzylidene derivatives of pyrroline [38, 39].

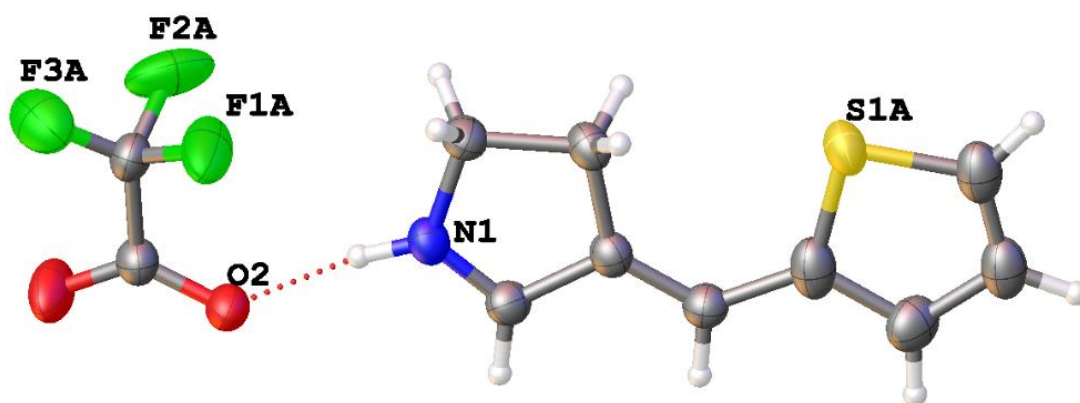


Figure 1. Structure of the 3-(thien-2-ylidene)-1-pyrrolinium trifluoroacetate ion pair ($\text{H[L}^+\text{][CF}_3\text{COO}^-]$) determined by X-ray diffraction analysis. The major components of the disordered fragments are shown. Ellipsoids are drawn at the 50% probability level.

Table 1. Basic geometric characteristics of compounds 1–6.

Compound	1 M = Zn	2 M = Cu	3 M = Co	4 M = Cu	5 M = Co	6 M = Ag
M–N (L)	1.999(2)	1.989(2)	2.139(2)	1.931(6)- 1.954(6)	2.070(5)- 2.111(5)	2.061(2), 2.064(2)
M–O (RCOO)	1.951(2)	1.949(2)	2.108(1)	-	2.066(4)- 2.117(4)	-
M–O (Solv)	-	-	2.069(2)	-	2.150(3), 2.168(4)	-
M–O (O)	-	-	-	1.892(4)- 1.915(4)	-	-
M–Cl	-	-	-	2.367(2)- 2.446(2)	-	-
M $\cdots$ M	6.219 (1)	5.112(1)	7.229(1)	3.081(2)	3.694(1)	3.772(1)

Table 2. $\pi \cdots \pi$ interactions in crystal packing of complexes $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$, **2-6**.

Interactions	Cg $\cdots$ Cg, Å	Symmetry code	Cg $\cdots$ Perp, Å	α , deg
Compound $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$				
L $\cdots$ L	3.685(10)	-x,2-y,1-z	3.396(7)	4.4(9)
Complex 2				
L $\cdots$ L	3.769(11)	1+x,y,z	3.395(2)	5.1(2)
L $\cdots$ L	3.796(2)	1+x,y,z	3.481(1)	6
Complex 3				
L $\cdots$ pfb	3.616(2)	x,-1+y,z	3.400(1)	4.9(2)
L $\cdots$ pfb	3.643(6)	x,-1+y,z	3.392(6)	3.9(6)
Complex 4				
L $\cdots$ L	3.865(5)	1-x,2-y,1-z	3.668(4)	4.6(5)
Complex 5				
L $\cdots$ L	3.800(4)	1+x,y,z	3.408(2)	7.0(3)
L $\cdots$ L	3.642(4)	-1+x,y,z	3.521(2)	8.9(4)
Complex 6				
L $\cdots$ L	3.685(10)	-x,2-y,1-z	3.396(7)	4.4(9)

Note. Cg is the centroid of aromatic rings, Perp is perpendicular to the plane of the ring, α is the angle between the planes of aromatic fragments.

Zinc, copper, cobalt, and silver complexes $[\text{Zn}(\text{L})_2(\text{pfb})_2]$ (**1**), $[\text{Cu}(\text{L})_2(\text{pfb})_2]$ (**2**), $[\text{Co}(\text{L})_2(\text{EtOH})_2(\text{pfb})_2]$ (**3**), and $[\text{Ag}(\text{L})_2](\text{NO}_3)$ (**6**) have mononuclear structures, in which each metal ion coordinates two pyrroline fragments, while the number of anions in the compositions compensates for the positive charge of the metal ion. Thus, the zinc and copper ions in complexes **1** and **2** coordinate four ligands – two pyrroline fragments and two pentafluorobenzoate anions (Table 1), forming characteristic coordination polyhedra: square planar in the case of copper and tetrahedral in the case of zinc. The tetrahedral zinc complex (**1**, Fig. 2(a)) is centrosymmetric and occupies a special position at an inversion center in the crystal. The structure of the copper complex $[\text{Cu}(\text{L})_2(\text{pfb})_2]$ (**2**, Fig. 2(b)) consists of an almost planar fragment formed by two pyrroline fragments linked by the copper ion (Table 1, the maximum deviation from plane is observed for atom C9 - 0.148(3) Å). The aromatic fragments of the pentafluorobenzoate anions are located above and below the plane at an angle of 28.2(1)°.

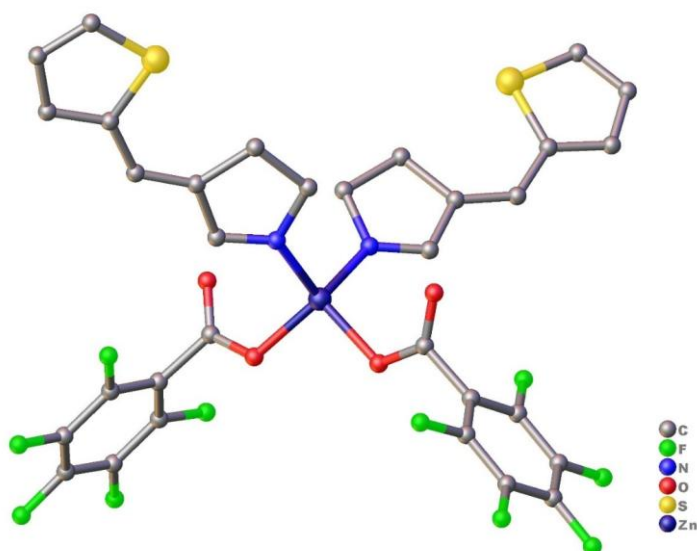
In the complex $[\text{Co}(\text{L})_2(\text{EtOH})_2(\text{pfb})_2]$ (**3**, Fig. 2(c)), the cobalt ion coordinates two pyrroline fragments, two pentafluorobenzoate anions, and two ethanol molecules, forming a centrosymmetric octahedral complex (Table 1). The coordinated pyrroline molecules occupy two opposite vertices of the octahedron, forming the main plane of the molecule. The pentafluorobenzoate anions are coordinated in the same plane. However, their aromatic fragments are located above and below the plane and are almost parallel to it (the interplanar angle is 5.4(2)°). The ethanol molecules are also coordinated above and below the plane but are nearly perpendicular

to it (the angle is $87.53(9)^\circ$). The molecular structure is stabilized by classical O-H $\cdots$ O hydrogen bonds between the hydrogen atoms of the ethanol molecules and the non-coordinated oxygen atoms of the carboxyl groups (Table S3).

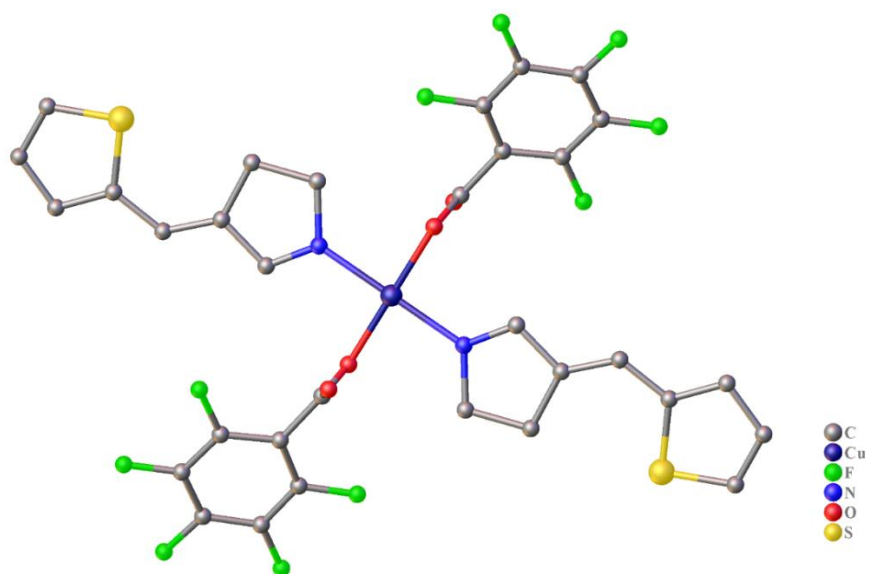
The central fragment of the copper complex $[\text{Cu}_4(\text{L})_4(\text{O})(\text{Cl})_6]$ (**4**, Fig. 2(d)) has a cage structure $\text{Cu}_4\text{Cl}_6\text{O}$, in which the oxygen atom is located inside the Cu_4Cl_6 cage and coordinates all four copper ions while simultaneously compensating for the charge (Table 1). The Cu-Cl and Cu-O distances are in the ranges 2.36-2.45 Å and 1.89-1.91 Å, respectively. Each copper ion coordinates one pyrroline molecule, with the four molecules located at the four vertices of the structure, approximately along the extensions of the Cu-O bonds.

The cobalt complex $[\text{Co}_2(\text{H}_2\text{O})(\text{L})_4(\text{CF}_3\text{COO})_4]$ (**5**, Fig. 2(e)) has a binuclear structure in which the cobalt ions are linked by two bridging trifluoroacetate anions and one bridging water molecule. In addition, the cobalt ions coordinate two pyrroline molecules and one trifluoroacetate anion, which act as monodentate ligands. The molecule has a symmetric structure stabilized by two classical hydrogen bonds between the hydrogen atoms of the water molecule and the non-coordinated oxygen atoms of the monodentate carboxylate anions (Table S3). The disorder of all trifluoromethyl fragments and three of the four thiophene cycle precludes crystallization of this complex in a special position.

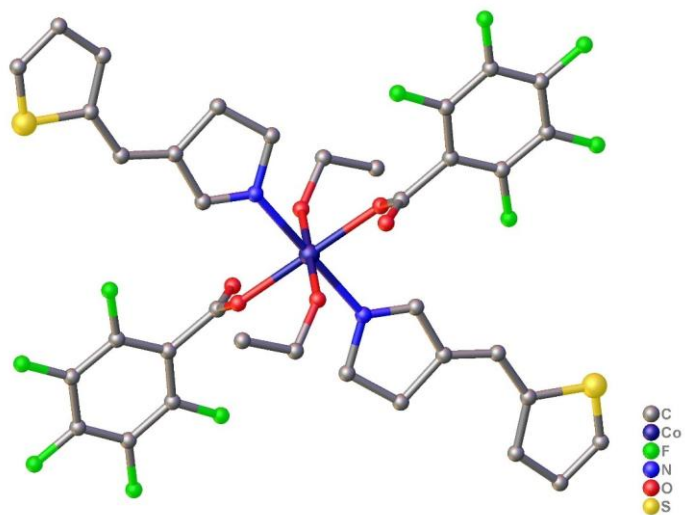
The silver ion in the complex $[\text{Ag}(\text{L})_2](\text{NO}_3)$ (**6**, Fig. 2(f)) forms a linear complex, coordinating two pyrroline fragments oriented at an angle of $94.5(5)^\circ$ to each other. The nitrate anion is not coordinated but is associated with the complex cation through Ag $\cdots$ O non-covalent interactions (the distances are 2.55(4) Å and 2.99(3) Å for the two parts of the disordered anion) and a weak C-H $\cdots$ O hydrogen bond involving a hydrogen atom of the pyrroline cycle (Table S3).



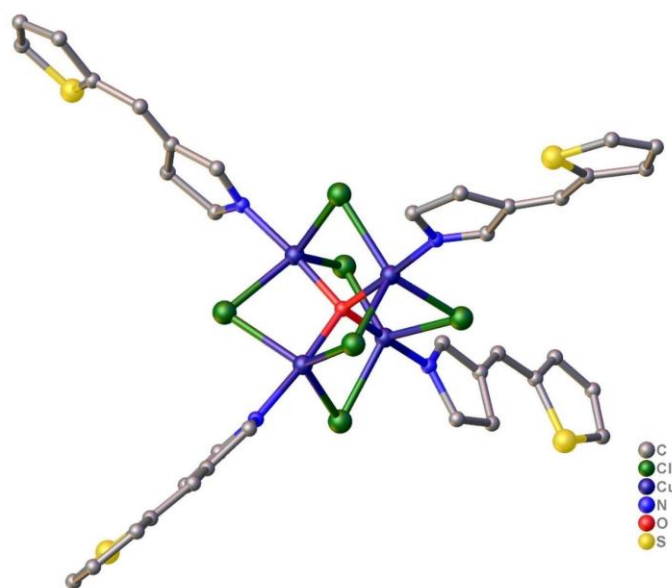
a)



b)



c)



d)

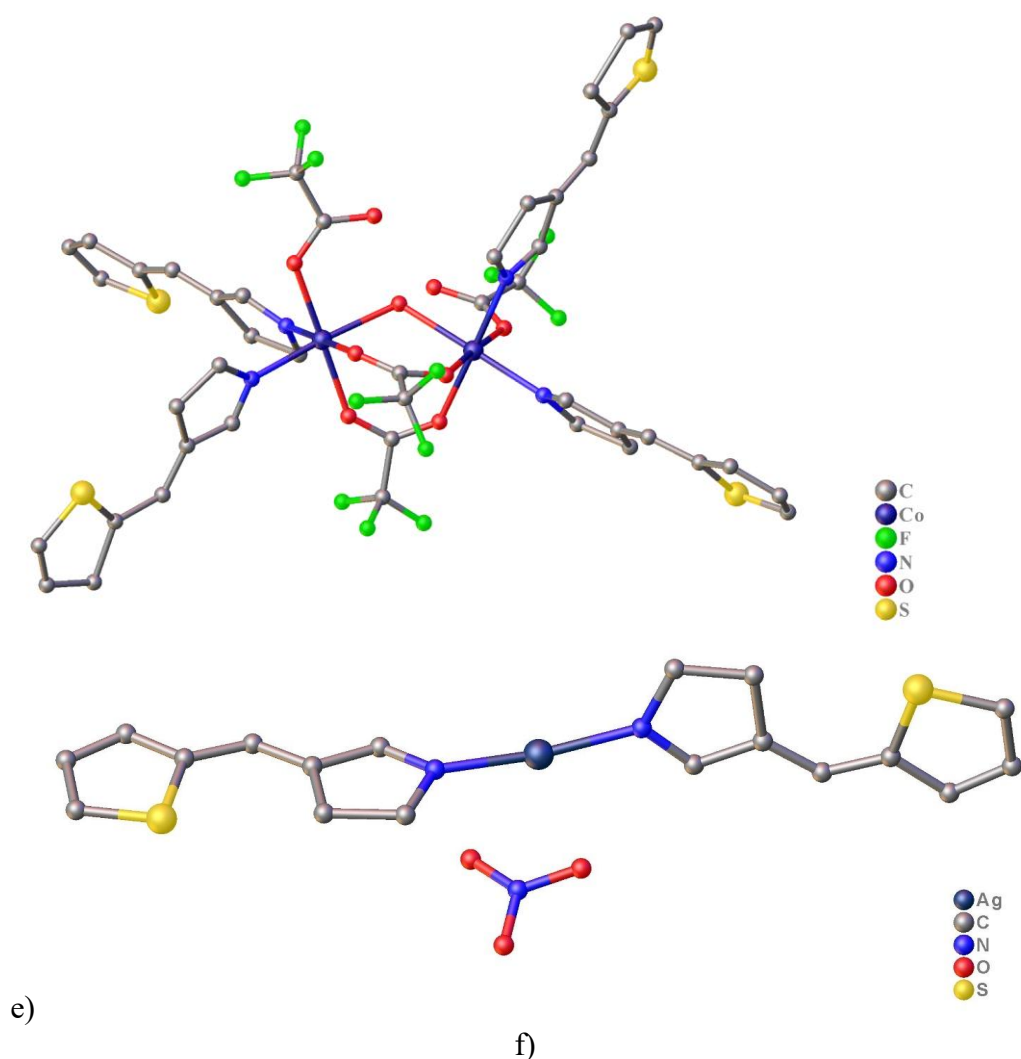
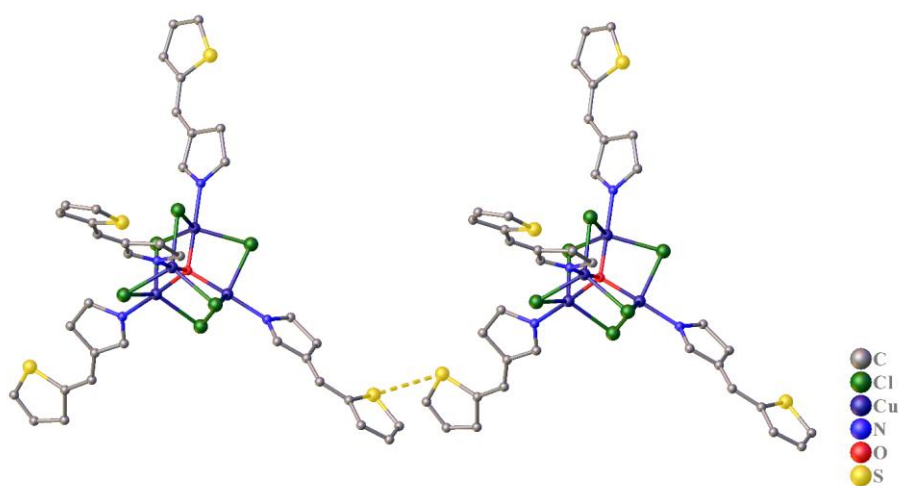


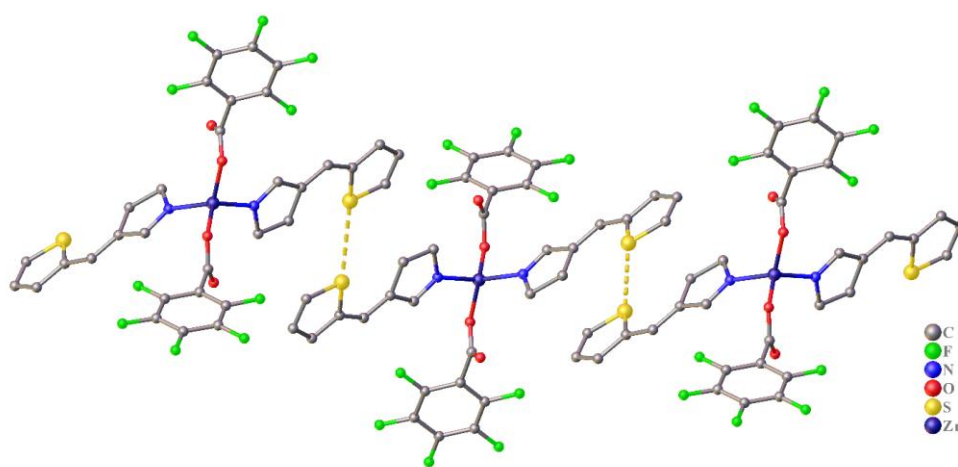
Figure 2. Molecular structures of compounds **1(a)**, **2(b)**, **3(c)**, **4(d)**, **5(e)**, and **6(f)**.

Hydrogen atoms are omitted for clarity.

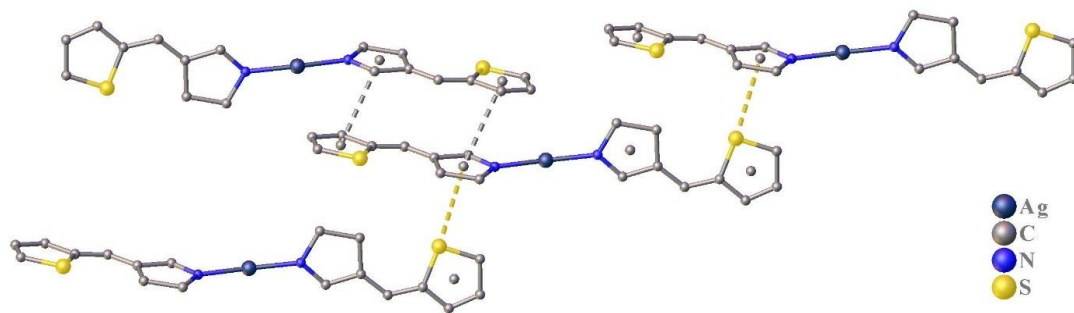
An important structural feature of the studied complexes is the geometry of the arylidene-pyrroline fragment, which is capable of relatively facile rotation about a C-C single bond. Both in the crystal of the 3-(thien-2-ylidene)-1-pyrrolinium salt and in the crystals of the complexes, the corresponding molecule is planar within hundredths of an angstrom. However, in the crystals of $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$ and complexes $[\text{Cu}(\text{L})_2(\text{pfb})_2]$ (**2**), $[\text{Co}(\text{L})_2(\text{EtOH})_2(\text{pfb})_2]$ (**3**), as well as in three of the four arylidene-pyrroline fragments of $[\text{Co}_2(\text{H}_2\text{O})(\text{L})_4(\text{CF}_3\text{COO})_4]$ (**5**), the thiophene fragments are disordered (0.84/0.16 in $\text{H}[\text{L}]^+[\text{CF}_3\text{COO}]^-$, 0.91/0.09 in **2**, 0.87/0.13 in **3**, and 0.66/0.34, 0.87/0.13, and 0.92/0.08 in **5**), which is also a consequence of the lability of the C-C single bond.



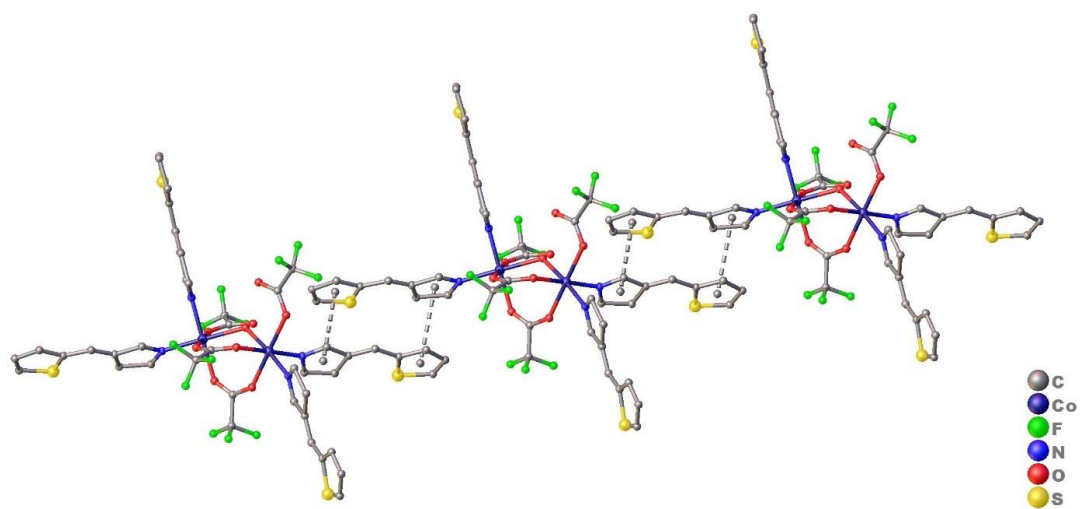
a)



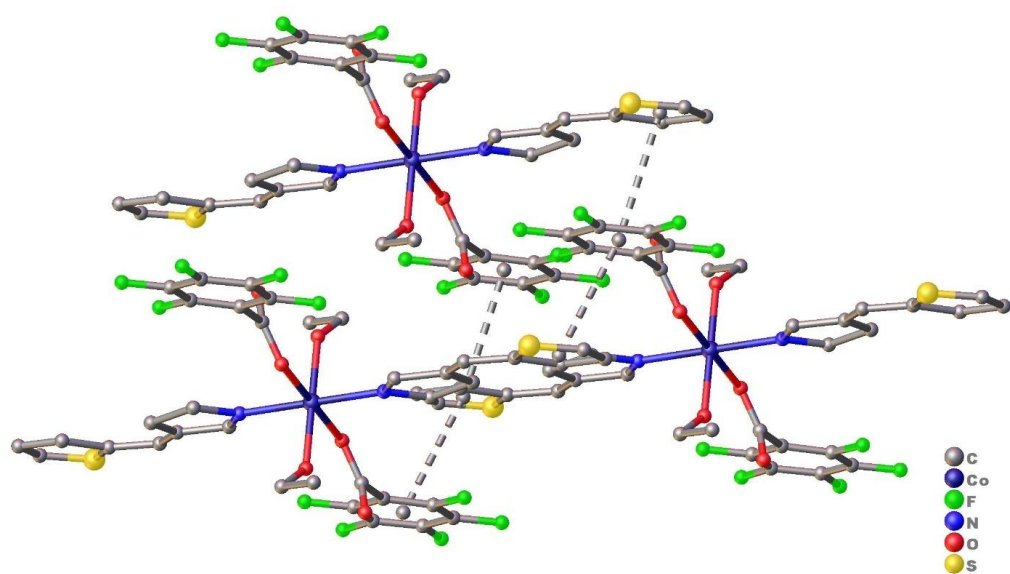
b)



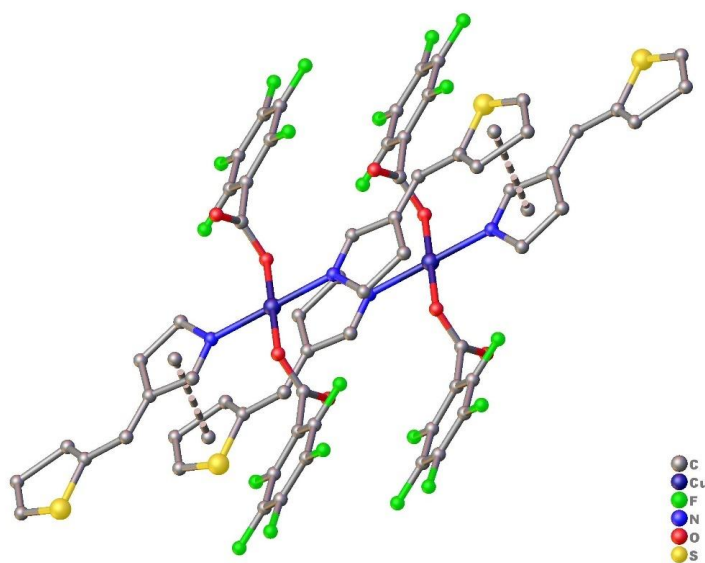
c)



d)



e)



f)

Figure 3. Non-covalent interactions involving sulfur atoms in the crystals of complexes **4** (a), **1** (b), **6** (c), **5** (d), **3** (e), and **2** (f). S $\cdots$ S and S $\cdots$ π interactions are shown by dashed lines. Hydrogen atoms are omitted for clarity. The nitrate anions are also omitted in panel (c).

It should be noted that an S $\cdots$ S interaction is observed in the disordered crystal of compound [Co₂(H₂O)(L)₄(CF₃COO)₄] (**5**). This interaction is similar in geometry to that previously described for the crystal of H[L]⁺[CF₃COO][−]. In the salt crystal, the interaction is formed between atoms of the minor component, with a distance of 3.51(3) Å, whereas in the crystal of complex **5**, it occurs between atoms of the major component, with a distance of 3.44(3) Å.

Analysis of the crystal packing in the studied crystals showed that the main structure-directing motif is $\pi\cdots\pi$ interactions of different topologies (Table 2). The only exception is complex **1**, in which the packing is determined by the S $\cdots$ S interactions, as well as weaker interactions involving π -systems, hydrogen atoms, and fluorine atoms (Table S4). Moreover, an unusual lp $\cdots\pi$ interaction between a non-coordinated oxygen atom of the carboxyl group and the π -system of the pentafluorobenzoate ring is observed in the crystal of this compound (Table S4).

The crystals of H[L]⁺[CF₃COO][−] form a three-dimensional structure consisting of parallel-oriented stacking dimers connected into infinite layers through C-H $\cdots\pi$ and C-H $\cdots$ O interactions (Table S3). The trifluoroacetate anions are located between the layers and are linked to one arylidene-pyrroline molecule by a classical N-H $\cdots$ O hydrogen bond and to the other by weak C-H $\cdots$ O interactions (Table S3). Upon formation of the stacking dimer, the arylidene-pyrroline molecules are oriented strictly parallel to each other in a “head-to-tail” arrangement with a slight shift, as a result of which the thiophene fragment is located above the exocyclic C-H group, which most likely determines the planar geometry of the molecules in the crystal. A very similar geometry of the $\pi\cdots\pi$ interaction is observed in the crystal of silver complex **6** (Table 2). In addition, parallel and perpendicular stacking alternate in this crystal, making its structure very similar to that of the organic salt.

The arylidene-pyrroline fragments are also oriented in a “head-to-tail” manner in the crystals of complexes [Cu₄(L)₄(O)(Cl)₆] (**4**) and [Co₂(H₂O)(L)₄(CF₃COO)₄] (**5**). However, no shift along the arylidene-pyrroline fragment is observed in this case. The cycles are located one above the other with a slight transverse shift to achieve the most effective overlap (Fig. 3(d), Table 2). In addition, an aromatic ring is located almost directly above the central part of the arylidene-pyrroline fragment in the crystal of complex [Co(L)₂(EtOH)₂(pfb)₂] (**3**) (Fig. 3(e), Table 2).

In the crystal of complex [Cu(L)₂(pfb)₂] (**2**), a short Cu $\cdots\pi$ contact (3.803(1) Å) is observed, resulting in the maximum shift along the arylidene-pyrroline molecules arranged in a

“head-to-head” manner. This is due to the geometry of the carboxylate anions, which allows the planar aromatic fragments to be located at a minimum distance and parallel to each other, resulting in a common $\pi \cdots \pi$ overlap of two arylidene-pyrroline fragments linked by the copper ion (Table 2, Fig. 3(f)).

Molecular Docking Analysis

Understanding the molecular basis of ligand-protein interactions is crucial for rational drug design. While experimental studies provide valuable information about biological activity, they often cannot specify the precise binding mode or identify the key residues involved in molecular recognition for a given series of compounds (complexes). Computational approaches, in particular molecular docking, have emerged as powerful complementary tools that can reveal atomic- (or group)-level details of these interactions. In the present work, we employed molecular docking simulations (AutoDock 4.2) to investigate the binding modes of the studied complexes 1-6 and their organic precursor - 3-(thien-2-ylidene)-1-pyrroline with a therapeutically relevant target: Kinase domain of Human HER2 (PDB ID: 3PP0). The results are summarized in Table 3.

Table 3. Results of molecular docking of the studied compounds with Kinase domain of Human HER2.

Compound	3PP0, kcal/mole	Key interactions
Ligand	-5.70	H-bond: SER A783; $\pi\cdots\sigma$: LEU A796, $\pi\cdots$ alkyl: LEU A785, ALA A771
1	-8.87	H-bond: HIS A809; Carbon H-bond: LEU A726; Halogen (F): ASP A808, GLU A812, PRO A802, LEU A726; $\pi\cdots$ anion: ASP A808; $\pi\cdots\sigma$: LEU A852; $Lp\cdots\pi$: TYR A803; $\pi\cdots$ alkyl: ALA A751, VAL A734, attractive charge: LYS A724, ASP A808; unfavorable positive-positive
2	-8.33	H-bonds: CYS A805, ARG A811, THR A862; Carbon H-bond: GLY A729, ARG A849, ASP A808; Halogen (F): ASP A808, SER A728, ASP A863; π -cation: ARG A849; $\pi\cdots\sigma$: GLY A804, LEU A726, VAL A734
3	-7.17	H-bonds: CYS A805, ARG A849, ARG A811, SER A728, THR A862; Halogen(F): ASP A808, ASP A863; $\pi\cdots$ cation: ARG A849; $\pi\cdots\sigma$: VAL A734; Carbon H-bond: GLY A729, ARG A849; unfavorable negative: ASP A808
4	-8.96	Attractive charge: ARG A849; $\pi\cdots$ cation: ARG A811; $\pi\cdots\sigma$: LEU A807; $\pi\cdots\pi$: PHE A731
5	-6.13	H-bonds: SER A728, ARG A849; Halogen (F): GLY A729, ASN A850, GLY A727; $\pi\cdots\pi$: PHE A731; Carbon H-bond: SER A728, ARG A849; attractive charge: ARG A811, $\pi\cdots$ cation: ARG A756
6	-8.30	Carbon H-bond: THR A862; $\pi\cdots$ alkyl: LEU A785, ALA A771, LEU A796, MET A774, LEU A800, ALA A751, LEU A852, LEU A726

The docking results reveal a clear hierarchy of binding affinities, with metal complexes consistently showing higher binding affinities than the free organic ligand. The latter exhibited the weakest binding (-5.70 kcal/mol), relying on one hydrogen bond and a few hydrophobic contacts. Metal complexes in turn demonstrated substantially higher affinities (ranging from -6.13 to -8.96 kcal/mol) and established extensive networks of H-bonds, carbon-hydrogen bonds, halogen contacts, and diverse π -interactions.

The highest binding affinities were achieved by 4 (-8.96 kcal/mol) and 1 (-8.87 kcal/mol). Remarkably, these top-performing complexes employ fundamentally different binding strategies. Complex 4 forms no classical hydrogen bonds, instead achieving exceptional stability through electrostatic complementarity (attractive charge interactions) and aromatic stacking (fig. 4). This demonstrates that strong metal-mediated electrostatic and π -interactions can completely substitute for traditional H-bonding. Complex 1, conversely, combines minimal classical H-bonding with an extensive network of halogen contacts, π -interactions, and attractive charge interactions,

suggesting that diversification of interaction types yields superior binding. Moreover, it has one unfavorable interaction which does not prevent this complex from having a high affinity.

Interestingly, 2 and 6 achieved nearly identical binding energies (-8.33 and -8.30 kcal/mol, respectively) via fundamentally different mechanisms. Complex 2 maintains a robust network of both classical and carbon-hydrogen bonds, supplemented by halogen and π -cation interactions. In contrast, 6 completely lacks classical hydrogen bonding and instead relies almost exclusively on extensive hydrophobic packing, forming a dense cluster of $\pi \cdots \text{alkyl}$ interactions.

The cobalt complexes (3 and 5) exhibited progressively weaker binding (-7.17 and -6.13 kcal/mol). Notably, 3 displays an unfavorable negative interaction with ASP A808, which likely compromises its stability despite forming multiple favorable contacts. This highlights that the presence of repulsive interactions can significantly diminish affinity even when numerous favorable contacts are present. Complex 5, while avoiding such unfavorable contacts, appears unable to establish the dense electrostatic and π -interaction networks characteristic of higher-affinity binders.

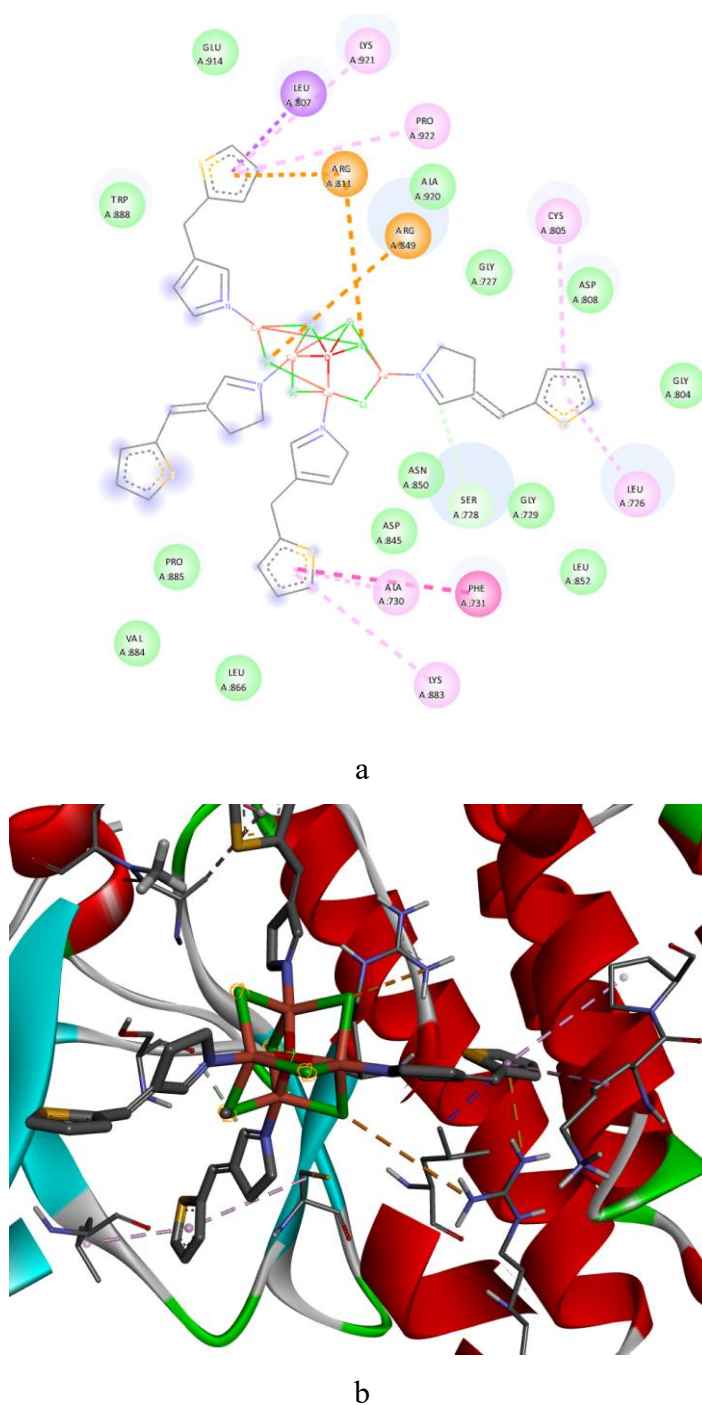


Figure 4. 2D (a) and 3D (b) graphical illustration of the interactions between the active site of HER2 and complex **4**.

Thus, it was established that the interaction of 3-(thien-2-ylidene)-1-pyrroline with salts of Zn(II), Cu(II), Co(II), and Ag(I) leads to the formation of structurally diverse coordination compounds: mononuclear complexes $[\text{Zn}(\text{L})_2(\text{pfb})_2]$ (**1**), $[\text{Cu}(\text{L})_2(\text{pfb})_2]$ (**2**), $[\text{Co}(\text{L})_2(\text{EtOH})_2(\text{pfb})_2]$ (**3**), and $[\text{Ag}(\text{L})_2](\text{NO}_3)$ (**6**), tetranuclear $[\text{Cu}_4(\text{L})_4(\text{O})(\text{Cl})_6]$ (**4**), and binuclear $[\text{Co}_2(\text{H}_2\text{O})(\text{L})_4(\text{CF}_3\text{COO})_4]$ (**5**). The reagent ratio in reactions **1-3** did not affect the

composition of the resulting compounds, whereas the nature of the metal ion and anion determined both the composition and geometry of the complexes. In all compounds, ligand **L** is coordinated in a monodentate mode through the nitrogen atom of the pyrroline cycle, while the sulfur atom of the thiophene fragment plays an important role in the formation of S $\cdots$ S and S $\cdots$ π non-covalent interactions.

The main structure-directing interactions in the crystals of the obtained complexes are $\pi\cdots\pi$ interactions of different topologies, except for complex **1**, where the packing is mainly determined by S $\cdots$ S contacts, while hydrogen bonds and weak interactions of various types play an auxiliary role. The crystal structure of the trifluoroacetate salt of ligand **L**, H[L]⁺[CF₃COO]⁻, was also studied, revealing that the main motifs of non-covalent interactions characteristic of this compound are retained in the crystals of the complexes.

Molecular docking showed that the interaction energies of the synthesized coordination compounds with the HER2 kinase domain are significantly higher than the binding energy of the free ligand. The most favorable binding energies were obtained for the tetranuclear copper complex **4** (-8.96 kcal/mol) and zinc complex **1** (-8.87 kcal/mol), indicating the possibility of controlling the activity of the compounds by varying the nature of the metal and anion. These results support the potential of these compounds as HER2 inhibitors.

Supplementary Information The online version contains supplementary material available at

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Data availability statement

The structure parameters of obtained compounds were deposited with the Cambridge Structural Database (2571195 (**1**), 2571196 (**2**), 2571197 (**3**), 2571198 (**4**), 2571199 (**5**), 2571200 (**6**), 2571201 (H[L]⁺[CF₃COO]⁻); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif.

Conflicts of Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

J.K.V.: Writing – original draft, Investigation, Methodology, Funding acquisition; G. A. R.: Investigation; A. S. C.: Writing – original draft, Investigation; M. A. S.: Writing – review & editing, Investigation; I. L. E.: Supervision.

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