Polyhedron xxx (xxxx) 117295

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Novel conjugated 5-pyridin-2-ylmethylidene 2-thio-4H-imidazol-4-ones and their complexes with copper(II) chloride

Anna V. Berezina [a], Viktor A. Tafeenko [a], Artem V. Semykin [a], Anna A. Moiseeva [a], Xuimei Bai [a], Alexander V. Finko [a], Alisa P. Chernyshova [a,b], Nikolai V. Zyk [a], Elena K. Beloglazkina [a,*]

[a] Lomonosov Moscow State University, Leninskie gory 1-3, Moscow 119991, Russia
[b] Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 117997, Russia

ARTICLE INFO

Keywords:
Imidazol-4-ones
Copper(II) complexes
Electrochemistry
X-Ray crystallography

ABSTRACT

Three novel 2-thio-4H-imidazol-4-ones containing conjugated five, six- or seven-membered S,N-heterocycle and pyridin-2-ylmethylidene moiety (L) were synthesized by two-step reaction sequence starting from 2-thiohydantion. The ligand structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The reactions of the ligands L with copper chloride dihydrate give the complexes of $LCuCl_2$ composition. Copper coordination compounds with 6-(pyridin-2-ylmethylidene)-2,3-dihydroimidazo[2,1-b][1,3]thiazol-5(6H)-one (L1) and 2-(pyridin-2-ylmethylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (L2) were characterized by the X-ray data, demonstrating the distorted tetrahedral copper coordination environment. It was shown that the presence in the ligand L1 of a five-membered thiazolidine ring fused with imidazolone leads to a significant change in the geometric characteristics of the complex: an increase in the Cu-S distance and the flattening of copper coordination polyhedron. Both synthesized complexes were evaluated using cyclic voltammetry and demonstrated the quasi-reversible reduction of Cu(II) at ~ −0.25 V. Testing of the antibacterial activity on the reporter strains E. coli ΔtolC pDualrep2 (AmpR) and E. coli lptDmut pDualrep2 (KanR) showed a lower activity of the synthesized copper-containing complexes compared to the complexes of similar ligand that did not have an additional condensed ring in its structure.

1. Introduction

2-Thiohydantoins (4-oxoimidazolidine-2-thiones) and their S-alkylated derivatives (2-alkylthio-3,5-dihydro-4H-imidazol-4-ones) have a broad spectrum of biological activities. Thiohydantoin-containing organic molecules are known as antimicrobial compounds [1–3]; some thiohydantoin derivatives also possess antibacterial and antifungal properties [4–8]. Substituted 3-aryl and 3-hetaryl-thiohydantoins demonstrated gypoglycemic [9], anti-inflammatory, analgesic [10], antischistosomal [11] and antitumor [12–14] activity. S-Alkylation derivatives of thiohydantoins were also examined for antiviral and antitumor activities [15]. S-Alkylated 5-arylidene-thiohydantoins possess antidepressant and analgetic properties [16].

2-Thiohydantoins and their S-alkylated derivatives containing donor N and S atoms can be coordinated to metals as neutral molecules or (for example, in the case of thiohydantoins containing the NH—C═S fragment) monoanions, which are formed upon deprotonation of the N(1) atom [17–20]. It is known that in some cases the coordination of thiohydantoin molecules with transition metal ions increases their biological activity [21,22].

Previously, we synthesized and structurally characterized copper-containing complexes of 5-pyridylmethylene-2-alkylthio-3,5-dihydro-4H-imidazol-4-ones, which have aryl and alkyl substituents at the nitrogen atom and alkyl (methyl or polymethylene) substituents at the sulfur atom [23–30]. Such copper-containing complexes demonstrated high cytotoxic activity, which strongly depended on the nature of the substituents in the organic ligand and the potential of copper(II) reduction in the complex [23]. However, 5-pyridylmethylene-2-alkylthio-3,5-dihydro-4H-imidazol-4-ones containing additional saturated heterocycles, conjugated with imidazolone, as well as their complexes with any metals, have not been described to date. At the same time, the introduction of an additional ring, which includes sulfur and nitrogen atoms of the original thiohydantoin, into the ligand molecule may change the geometry of the coordination environment of copper in the formed complexes and their redox characteristics. In this article, three novel 2-thio-4H-imidazol-4-ones containing conjugated five, six- or seven-

* Corresponding author.
E-mail address: beloglazki@mail.ru (E.K. Beloglazkina).

https://doi.org/10.1016/j.poly.2024.117295
Received 27 April 2024; Accepted 5 November 2024
0277-5387/

membered S,N-heterocycle and pyridin-2-ylmethylidene moiety as well as two coordination compounds of these ligands with $CuCl_2$ were synthesized (Scheme 1). Their crystal structure and electrochemical properties in the solution were tested. It was found that the introduction of a six-membered condensed S,N-containing ring into the ligand molecule almost does not lead to a change in the geometry of the coordination compound it forms with $CuCl_2$ compared to the previously described 5-pyridylmethylene-2-alkylthioimidazolone complexes. At the same time copper(II) chloride complex with the ligand with five-membered S,N-containing ring in its composition differs significantly from previously known ones due to the geometric limitations of the ligand.

2. Experimental section

2.1. Materials and methods

All starting materials were obtained from commercial sources and used without additional purification. The synthesis of starting compound **1** was described in [31,32]. The progress of the reactions and the purity of the compounds were monitored by thin-layer chromatography (TLC) on Silufol-UV254 plates with a fixed layer of silica gel.

The ^1H and ^{13}C NMR spectra were recorded on a BrukerAvance instrument with an operating frequency of 400 and 101 MHz, respectively. Deuterochloroform and dimethyl sulfoxide-d6 were used as solvents. Chemical shifts are reported in ppm using δ scale relative to hexamethyldisiloxane as internal standard.

IR spectra were recorded using a Fourier transform spectrometer Nicolet iS5 (Thermo Scientific) using an internal reflectance attachment with diamond optical element – attenuated total reflection (ATR, iD7) with 45° angle of incidence. Resolution was 4 cm^{-1}, the number of scans was 20. The OMNIC – Spectra Software (Thermo Scientific) was used to process the IR spectral data.

Electronic absorption spectra were measured on the Hitachi U2900 device, with an operating wavelength range of 250–500 nm in DMSO. Ligand concentrations were 0.13 * 10^{-3} M, complex concentrations were 0.08 * 10^{-3} M. The UV Solution 2.2 program (Hitachi High-Technologies Corporation) was used to process the UV–vis spectral data.

Elemental analyses were performed on a Vario MICRO cube CHNS Elementar.

Electrochemical studies were performed at 25°C using a IPC-2000 potentiostat with the refinement program complex (developed in A. N. Frumkin Institute of Physical Chemistry and Electrochemistry, RAS; author V. E. Kasatkin, vadim_kasatkin@ru; see, for example https://www.expo.ras.ru/base/prod_data.asp?prod_id=4687). Glass carbon disks (both 2 mm in diameter) polished with Al_2O_3 (<10 mm) were used as the working electrodes, and a 0.1 M Bu_4NClO_4 solution in DMF served as the supporting electrolyte. Ag/AgCl/KCl(sat.) was used as the reference electrode. The potentials are given with allowance for iR compensation. All measurements were carried out under argon. The samples were dissolved in pre-deoxygenated solvent.

X-ray diffraction data were collected using Cu Kα radiation on STOE diffractometer Pilatus100K detector for **3a** and Mo Kα radiation on a Bruker D8 Quest for **3b**. The intensity data were corrected for absorption and decay by SADABS [33]. All structures were solved by direct methods using SHELXT [34] and refined against F2 using SHELXL-2018 [35]. All C—H hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND [36] software. Crystal data, data collection, and structure refinement details are summarized in Supplementary Information. CCDC **2349016** (compound **3a**) and **2349015** (compound **3b**) contain 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.

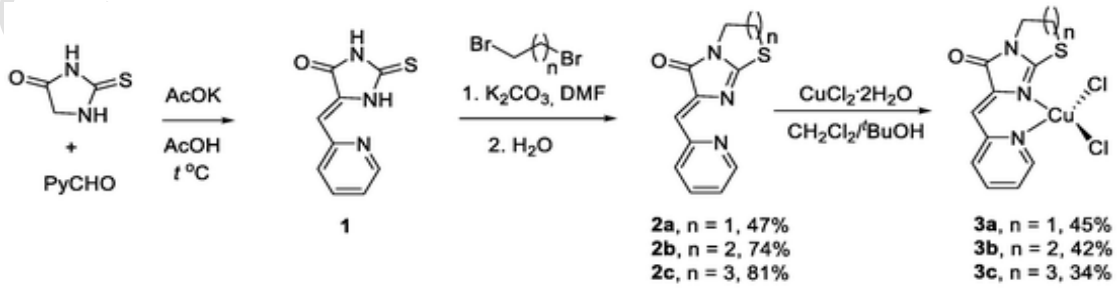
2.2. Synthesis

2.2.1. (Z)-6-(Pyridin-2-ylmethylidene)-2,3-dihydroimidazo[2,1-b][1,3]thiazol-5(6H)-one (**2a**)

Compound **1** (150 mg, 0.73 mmol), K_2CO_3 (300 mg, 2 mmol) and 1,2-dibromoethane (60 μL, 73 mmol) in DMF (3 mL) were mixed and the reaction suspension was stirred for 20 h. TLC showed the reaction was completed. The resulting mixture was poured into the ice and the obtained residue was filtered off and dried in air to obtain 80 mg (yield 47 %) of the target compound as yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 3.80 (t, 2H, N-CH_2-, J = 7.6 Hz), 3.99 (t, 2H, S-CH_2-, J = 7.6 Hz), 7.06 (s, 1H, =CH), 7.20–7.23 (m, 1H, Py), 7.73 (dt, 1H, Py, J_1 = 2.0 Hz, J_2 = 7.1 Hz), 8.21 (d, 1H, Py J_2 = 7.1 Hz), 8.70–8/72 (m, 1H, Py). ^{13}C NMR (101 MHz, $CDCl_3$): 171.75, 165.98, 152.81, 149.57, 146.26, 135.88, 126.56, 123.65, 122.89, 40.40, 33.93. IR (diamond, cm^{-1}): 1708 (C=O), 1665 (C=C), 1635 (C=N), 1580 (C=N), 1514 (C=N). UV–vis (DMF, λ, nm (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1}$)): 326 (4080), 348 (3269). HRMS (ESI) *m/z*: calculated for $C_{11}H_{10}N_3OS$: 232.0545 $[M+H]^+$, found 232.0527.

2.2.2. (2Z)-2-(Pyridin-2-ylmethylidene)-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-3(2H)-one (**2b**)

Compound **1** (170 mg, 0.83 mmol), K_2CO_3 (340 mg, 2.5 mmol) and 1,2-dibromopropane (85 μL, 0.83 mmol) in DMF (3 mL) were mixed and the reaction suspension was stirred for 20 h. TLC showed the reaction was completed. The reaction mixture was poured into the ice, extracted with CH_2Cl_2, and the organic solvent was evaporated at the reducing pressure to obtain 151 mg (yield 74 %) of the target compound as yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 2.30 (m, 2H, –CH_2-), 3.17 (t, 2H, N-CH_2-, J =5.6 Hz), 3.76 (t, 2H, S-CH_2-, J = 6.0 Hz), 7.12 (s, 1H, =CH), 7.16 (dt, 1H, Py, J_1 = 1.2 Hz, J_2 = 7.9 Hz), 7.73 (dt, 1H, Py, J_1 = 2.1 Hz, J_2 = 7.9 Hz), 8.64–8.68 (m, 2H, Py). Спектр ЯМР ^{13}C (101 MHz, $CDCl_3$): 168.18, 164.46, 153.14, 149.89, 139.87, 136.56, 126.31, 123.41, 120.67, 39.62, 25.77, 22.23. IR (diamond, cm^{-1}): 1710 (C=O), 1628 (C=C), 1579 (C=N), 1562 (C=N). UV–vis (DMF, λ,



Scheme 1. Synthesis of ligands 2**a-c** and their copper(II) complexes **3a-c**.

nm (ε, L·mol^{-1}·cm^{-1})): 344 nm (3600), 366 (1230), 370 nm (1000). HRMS (ESI) *m/z*: calculated for $C_{12}H_{12}N_3OS$: 246.0701 $[M+H]^+$, found 246.0731.

2.2.3. (Z)-2-(Pyridin-2-ylmethylene)-5,6,7,8-tetrahydroimidazo[2,1-b][1,3]thiazepin-3(2H)-one (2c)

Compound **1** (150 mg, 0.73 mmol), K_2CO_3 (300 mg, 2 mmol) and 1,4-dibromobutane (90 μL, 73 mmol) in DMF (3 mL) were mixed and the reaction suspension was stirred for 24 h. TLC showed the reaction was completed. The resulting mixture was poured into the ice, extracted with CH_2Cl_2, and the organic solvent was evaporated at the reducing pressure to obtain 154 mg (yield 81 %) of the target compound as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.86–1.88 (m, 2H, –CH_2-), 2.16–2.19 (m, 2H, –CH_2-), 3.05 (t, 2H, N-CH_2-, J = 5.3 Hz), 3.89 (t, 2H, S-CH_2-, J = 5.2 Hz), 7.21–7.23 (m, 1H, Py), 7.25 (s, 1H, =CH), 7.75 (dt, 1H, Py, J_1 = 2.1 Hz, J_2 = 7.9 Hz), 8.70–8.72 (m, 2H, Py). IR (diamond, cm^{-1}): 1708 (C═O), 1643 (C═C), 1584 (C═N), 1552 (C═N), 1517 (C═N). UV–vis (DMF, λ, nm (ε, L·mol^{-1}·cm^{-1})): 335 (4038), 351 (3669), 375 (1676), 396 (1265). HRMS (ESI) *m/z*: calculated for $C_{13}H_{14}N_3OS$: 260.3204 $[M+H]^+$, found 260.3216.

2.2.4. General synthesis of complexes 3a-c

1 equiv of the compound **2** was dissolved in 2 ml of methylene chloride; 1 equiv of copper(II) chloride dihydrate was dissolved in 2 ml of *tert*-butanol. The resulting solutions were carefully added to each other to form a two-phase system and left in the dark for 3 days. As a result, dark brown needle-shaped crystals or powders were formed.

2.2.5. The reaction of compound 2a with $CuCl_2{\cdot}2H_2O$ (preparation of complex 3a)

From 24 mg (1 mmol) of 6(Z)-6-(pyridin-2-ylmethylidene)-2,3–dihydroimidazo[2,1-*b*][1,3]thiazole–5(*6H*) **2a** and 17 mg (1 mmol) of copper(II) chloride dihydrate, 16 mg of coordination compound **3a** (yield 45%) was obtained. IR (diamond, cm^{-1}): 1738 (C═O), 1651 (C═C), 1593 (C═N), 1468 (C═N), 1428 (C═N). UV–vis (DMF, λ, nm (ε, L·mol^{-1}·cm^{-1}): 326 (5662), 340 (4987), 368 (3062), 374nm (2700), 378 (2225). Calculated for $C_{11}H_9Cl_2CuN_3OS$: C, 36.13; H, 2.48; N, 11.49. Found: C, 36.22; H, 2.85; N, 11.69.

2.2.6. The reaction of compound 2b with $CuCl_2{\cdot}2H_2O$ (preparation of complex 3b)

From 36 mg (1.5 mmol) of (2*Z*)-2-(Pyridin-2-ylmethylidene)-6,7-dihydro-5H-imidazo[2,1-*b*][1,3]thiazin-3(*2H*)-one **2b** and 25 mg (1.5 mmol) of copper(II) chloride dihydrate, 24 mg of coordination compound **3b** (yield 42%) was obtained. IR (diamond, cm^{-1}): 1737 (C═O), 1651 (C═C), 1590 (C═N), 1425 (C═N). UV–vis (DMF, λ, nm (ε, L·mol^{-1}·cm^{-1}): 344 (4825), 367 (4175), 372 (3575), 376 (2975), 378 (2762). Calculated for $C_{12}H_{11}Cl_2CuN_3OS$: C, 37.95; H, 2.92; N, 11.07. Found: C, 37.79; H, 2.85; N, 11.04.

2.2.7. The reaction of compound 2c with $CuCl_2{\cdot}2H_2O$ (preparation of complex 3c)

From 39 mg (1.5 mmol) of (Z)-2-(Pyridin-2-ylmethylene)-5,6,7,8-tetrahydroimidazo[2,1-b][1,3]thiazepin-3(2H)-one **2c** and 25 mg (1.5 mmol) of copper(II) chloride dihydrate, 20 mg of coordination compound **3c** (yield 34%) was obtained. IR (diamond, cm^{-1}): 1706 (C═O), 1643 (C═C), 1585 (C═N), 1465 (C═N). UV–vis (DMF, λ, nm (ε, L·mol^{-1}·cm^{-1}): 264 (5037), 334 (5112), ~375 (4350), ~ 380 (4050). Calculated for $C_{13}H_{13}Cl_2CuN_3OS$: C, 39.65; H, 3.33; N, 10.67. Found: C, 39.19; H, 3.35; N, 10.44.

2.3. Antibacterial activity

2.3.1. Reporter Assays on Agar Plates

Two *E. coli* reporter strains – *E. coli lptDmut pDualrep2 (KanR)* and *JW*5503 Δ*tolC pDualRep2 (AmpR)* – were used to analyze antibacterial activity of selected samples as previously described [37]. In short, the overnight cultures of reporter strains were diluted with fresh LB medium to an optical density of 600 nm (OD600) of 0.05–0.1. The culture was transferred to LB agar plates that contained 100 mg/mL ampicillin or 50 mg/ml kanamycin for *JW*5503 Δ*tolC pDualRep2* or *E. coli lptDmut pDualrep2 (KanR)* strains, respectively. Samples dissolved in DMSO at a concentration of 10 mg/mL were applied to the agar plates in an amount of 10 μg along with two control antibiotics: erythromycin (Ery, 5 mg/mL) and levofloxacin (Lev, 25 mg/mL). Plates were incubated at 37 °C overnight and then scanned by ChemiDoc (Bio-Rad) in the modes 'Cy3-blot' for RFP and 'Cy5-blot' for Katushka2S. In case of SOS-response activation the expression of the *rfp* gene occurred, the RFP protein signal was displayed as green on scan, while the expression of *katushka2S* gene took place in the case of a violation of translation, when the ribosome was stalled on the mRNA template, the signal on scan was red.

3. Results and discussion

3.1. Synthesis

Synthetic route to the ligands **2a-c** is shown in Scheme 1. Using *N*-unsubstitutes 5-pyridylmethylene-2-thiohydantoin **1** and 1,ω-dibromoalkanes as starting compounds, the target ligands **2** were obtained in reasonable yields. All the ligands were characterized and identified by ^{1}H NMR, ^{13}C NMR, IR and HRMS. Compounds **2a-c** are yellow powders; these yields are minimal for imidazolone **2a**, and increases with increasing the size of conjugated N,S-containing ring, possibly due to lower solubility of formed compounds **2b** and **2c**.

Complexes **3a-c** were synthesized using slow diffusion of a solution of the ligand in CH_2Cl_2 into a solution of $CuCl_2{\cdot}2H_2O$ in ^{t}BuOH (Scheme 1). The dark brown crystals of the target complexes were formed in the reaction tube after 2–3 days. The reactions of $CuCl_2{\cdot}2H_2O$ with the ligands **2a,b** give the well-formed crystals suitable for X-ray investigations; in contrast, in the reaction with ligand **2c**, the copper-containing complex is formed as a dark brown amorphous powder. The composition and structures of the coordination compounds **3** were confirmed by elemental analysis, IR and UV–vis spectroscopy as well as X-ray (for the compounds **3a** and **3b)** data.

The IR spectra of complexes **3a-c** show a shift of the C═N absorption band compared to that observed in the spectra of the starting ligands, so this confirms the involvement of the nitrogen atoms in the coordination of the metal atom.

In the UV–vis spectra of complexes **3a-c** 2 and 3 (Figs. S10–S12) there are bands in the region 280–350 nm, which are similar to the bands of corresponding free ligands **2a-c**. The additional bands at 360–400 nm appear in the spectra upon complexation, similar to that described previously for other complexes with 5-pyridylmethylene-2-thioimidazolones [38]. Any absorption bands of noticeable intensity are absent in the visible region and the observed dark-brown color of complexes **3** apparently is due to the above absorption bands, the absorption maximum of which is in the UV region, but absorption also occurs in the visible region. For coordination compounds 3, absorption bands in the near IR region with maxima at 860–900 nm of very low intensity are also observed (ε 15–40 L·mol^{-1}·cm^{-1}; see Fig. 13S, Supplementary Information).

The ligands **2** and their complexes show the high energy bands at 320–380 nm in DMF solution, apparently due to π→π* and n→π* transitions correspond C═O and C═S groups as previously were observed for 2-thioimidazolones [39]. For copper complexes **3** the additional

bands appeared at long-wave area may be assigned to ligand to metal charge transfer (LMCT) transitions. As for the absence of observed absorption bands with maximums in the visible region, it is known that the number of absorptions in the visible region is determined by the distortion degree of the copper coordination polyhedron [40]. For tetrahedral copper complexes with small distortion the theory predicts one experimental d-d band for tetrahedral copper complexes [41]; however, the intensity and position of the bands in the experimental electronic spectrum can vary greatly depending on the type of ligand [42].

3.2. X-ray structures of complexes *3a, 3b*

The structures of complexes **3a** and **3b** were established by Xray diffraction (Fig. 1). The Selected bond lengths (Å) and angles (deg) for compounds **3a**, **3b** and structurally similar copper complexes, described previously, are given in Table 1. The details of X-ray diffraction study and characteristics of the structure refinement are given in Supplementary Information. In both complexes, the copper atoms have a distorted tetrahedral ligand environment and are coordinated by two nitrogen atoms of the pyridine and thiohydantoin rings and two chloride anions. Thiohydantoin and pyridine rings in molecules **3a** and **3b** are planar and are nearly coplanar.

Comparing the values of bond lengths and bond angles for complexes **3a**, **3b** given in Table 1, with the values of these parameters for previously described copper complexes of structurally similar organic ligands, in which the sulfur and nitrogen atoms are not interconnected by a polymethylene bridge, one can note a noticeable difference in the geometry of complex **3a**, containing a thiazolidine ring fused with an imidazolone, from the geometry of both complex **3b** and the complexes described in [25,28] (see Table 1). The main differences concern the distance from the coordinated copper atom to the S atom of ligand, as well as the S—C(2)-N(2) angle. While for complexes with non-fused ligands and complex **3b**, which contains a six-membered 1,3-thiazinan ring, the S-Cu distance is approximately 3.6 Å, and the S—C(2)-N(2) angle is 134.4°, in complex **3a** the S- distance Cu increases to 3.84 Å, and the S—C(2)-N(2) angle decreases to 123.5°; in this case, the distance between directly unbound Cu and Cl(1) atoms is the same for all complexes (~ 3.2 Å; see Fig. 10S in Supplementary Information). Apparently, such differences are due to the strained geometry of ligand **2a**

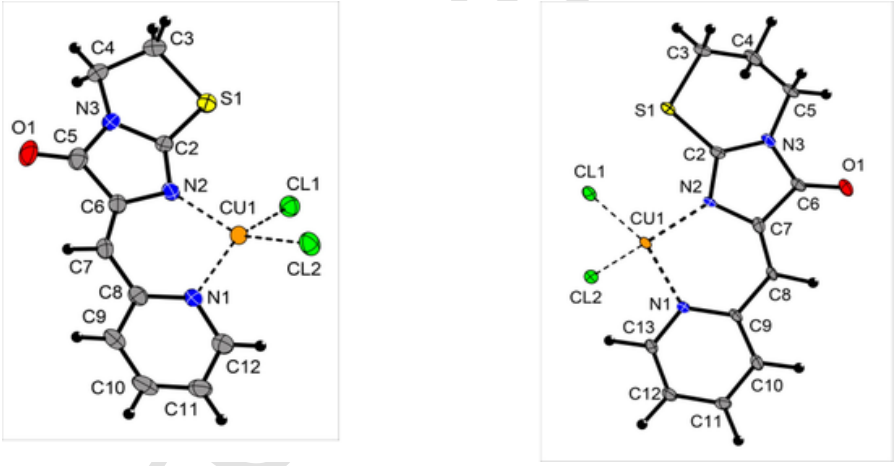
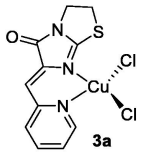
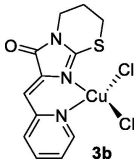
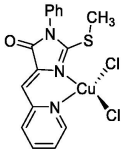
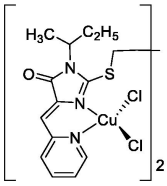


Fig. 1. Molecular structures of the compounds 3a (*left*) and 3b (*right*). The numbering of atoms in the molecules is shown. Oscillation ellipsoids are given with 30% probability.

Table 1
Selected bond lengths (Å) and angles (deg) for compounds **3a**, **3b** and structurally similar copper complexes. The distance Cu—S and S—Cl(1) between atoms not directly bonded to each other is also indicated.

Bond length (A) or angle (deg)	 **3a**	 **3b**	 Ref. [29]	 Ref. [26]
Cu—N(1)	1.965(3)	1.960(6)	1.967(5)	1.972(5)
Cu—N(2)	2.034(3)	1.997(6)	2.032(5)	2.042(5)
Cu—Cl(1)	2.2163(10)	2.208(2)	2.202(2)	2.2030(19)
Cu—Cl(2)	2.2243(9)	2.235(2)	2.228(2)	2.2334(19)
S—Cl(1)	3.2	3.2		
N(1)—Cu—N(3)	93.65(12)	93.9(2)	93.5(3)	93.5(2)
N(1)—Cu—Cl(2)	146.00(9)	139.5(2)	141.39(17)	145.14(17)
N(2)—Cu—Cl(2)	93.68(8)	99.07(8)	99.8(2)	98.30(15)
N(1)—Cu—Cl(1)	96.52(9)	94.84(18)	96.89(16)	94.95(16)
N(2)—Cu—Cl(1)	142.11(9)	136.63(19)	132.02(18)	138.84(15)
S—C(2)—N(2)	134.4	123.5		
Cl(2)—Cu—Cl(1)	97.84(4)	99.07(8)	100.46(9)	97.32(8)
Cu—S	3.840	3.609		

associated with the presence of a short two-carbon bridge between the S and N(3) atoms.

Thus, the coordination copper in structure **3a** is flattened compared to structure **3b** and previously described complexes without a linker between the sulfur and nitrogen atoms in the ligand. This observation is consistent with the quantitative assessment of the geometry of four-coordinate complexes using the parameter τ_4 proposed by Lei Yang, Douglas R. Powell and Robert P. Houser [43–45]. The values of s_4 will range from 1.00 for a perfect tetrahedral geometry to zero for a perfect square planar geometry. Intermediate structures fall within the range of 0 to 1.00. In our case $\tau_4 =$ 0.51 for the compound **3a**, and τ_4 = 0.59 for the compound **3b**.

Why is this happening? Apparently, the sulfur atom in complex **3a** is forced to move away from the copper atom to a greater distance, as a consequence of the smaller internal angle at the *C*2 (sp^2) atom in a 5-membered ring of ligand **2a** compared to a 6-membered ring of ligand **2b**. In this case, the distance from sulfur to Cl1 is the same (3.2 Å) in both structures. Consequently, the coordination of copper tends to be planar, but the distance of 3.2 Å determines the maximum possible distance of mutual repulsion of sulfur and chlorine (Fig. 10S).

3.3. Electrochemistry

Ligands **2a**, **2b** and their complexes **3a**, **3b** were investigated using cyclic voltammetry (CV) and a rotating disk electrode (RDE) on a glassy carbon (GC) electrode in DMF solutions in the presence of Bu_4NClO_4 as supporting electrolyte. The measured redox potentials are given in Table 2, typical CV and RDE curves are shown in Fig. 2.

The reduction of ligands occurred in three (for ligand **2a**) or two (for ligand **2b**) successive stages at ~ −1.40–2.4 V (irreversible peaks), and oxidation in one stage at ~ +1.7 V (Table 2, Fig. 2a). The CV curves of the complexes **3a**,**b** show the additional quasi-reversible peaks (ΔE_p ~ 0.30 V and i_{pa}/ipc ~ 1:1) in the anodic region at ~ +0.25/0.55 V (Table 2, Fig. 2b), corresponding to the reduction of coordinated copper (+2)

Table 2
Electrochemical reduction (E_p^{Red}) and oxidation (E_p^{Ox}) potentials measured on a GC electrode relative to Ag|AgCl KCl (sat.) by CV method in DMF. C = 10^{-4} M.

Compound	E_p^{Red}, V	E_p^{Ox}, V
2a	−1.40; −1.93; −2.38	1.68
3a	+0.25/+0.54; −1.07; −1.39; −2.06	1.26
2b	−1.69; −1.92	1.70
3b	+0.25/+0.56; −1.05; −1.32; −1.69; −1.99	1.25

ions. According to the electrochemical study on RDE, these reductions processes are one-electron. Complexes **3a**,**b** also have oxidation peaks of coordinated chloride anions at −1.25 V in their CVs. In general, the electrochemical characteristics of both ligands **2** and both complexes **3** are almost identical, that is, the presence of a five- or six-membered conjugated saturated ring in the ligand has practically no effect on the electrochemical characteristics of ligands and complexes.

3.4. Antibacterial activity screening

We have studied antibacterial activity of ligands **2a-c** and complexes **3a-c** on the reporter strains *E. coli ΔtolC pDualrep2 (AmpR)* and *E. coli lptDmut pDualrep2 (KanR)*. Two control antibiotics were used in this assay: the macrolide antibiotic erythromycin, which disrupts protein biosynthesis in the bacterial cell (inducing the expression of the Katushka2S protein, which is visualized in red during scanning) and levofloxacin, a DNA gyrase inhibitor that induces the cell's SOS-response (expression of the TurboRFP protein is visualized as green). For comparison, studies were also conducted on the antibacterial activity of the previously described [23] (*Z*)-3-(4-fluorophenyl)-2-(methylthio)-5-(pyridin-2-ylmethylene)-3,5-dihydro-4H-imidazol-4-one, a ligand of a similar structural type that does not contain a bridging fragment between the y-thioimidazolone nitrogen and sulfur atoms, and its copper-containing coordination compound. The results obtained are shown in Fig. 14S in Supplementary Information.

Most of the tested compounds do not show significant antibacterial activity against any of the reporter strains. In all cases, the antibacterial activity of the complexes was higher than the activity of the corresponding ligands. However, the ligands synthesized in this work were more toxic than *Z*)-3-(4-fluorophenyl)-2-(methylthio)-5-(pyridin-2-ylmethylene)-3,5-dihydro-4H-imidazol-4-one. Complex **3a** was the most active of the complexes synthesized in this work, demonstrating weak antibacterial activity against efflux deficient strain *E. coli ΔtolC pDualrep2*. However, its activity was inferior to that of the earlier described complex with a (*Z*)-3-(4-fluorophenyl)-2-(methylthio)-5-(pyridin-2-ylmethylene)-3,5-dihydro-4H-imidazol-4-one ligand that did not have an additional condensed ring in its structure. B, inhibition zones diameter 6 and 8 mm respectively (see Supplementary Information, Fig. 14S). None of the samples demonstrates strong induction of the reporter proteins, indicating that their antibacterial action is not associated with either disruption of protein translation processes or induction of the SOS response in cells. All the studied compounds had significantly lower antibacterial activity than levofloxacin and erythromycin.

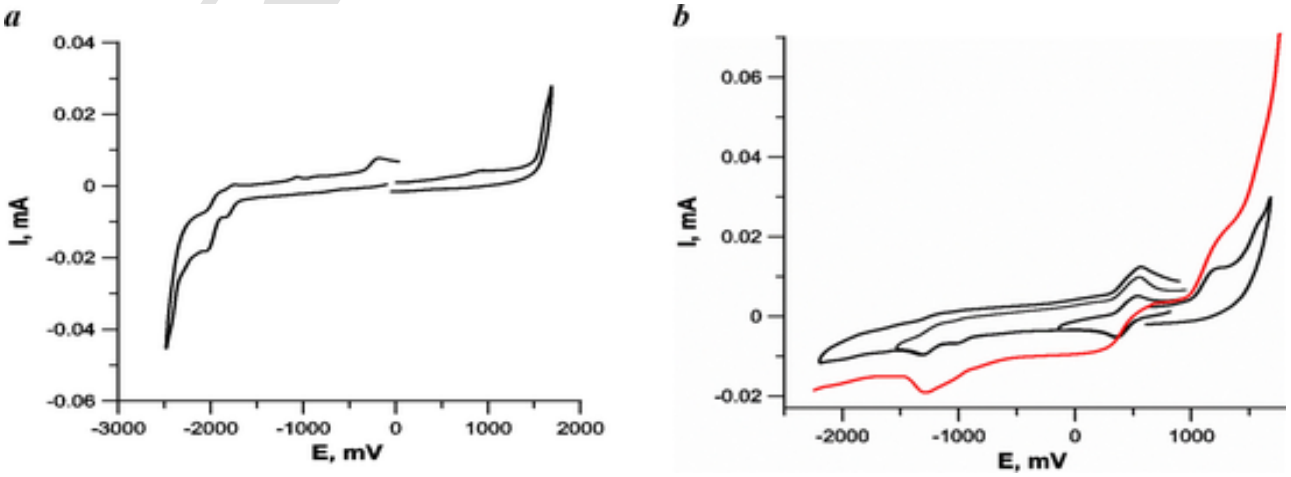


Fig. 2. Voltammograms: (a) CV of ligand 2b and (b) CV (black line) and RDE (red line) of complex **3b** in DMF solution. 10^{-4} M, 0.1 M NBu_4ClO_4.

4. Conclusion

In summary, three novel 2-thio-4H-imidazol-4-ones containing conjugated five, six- or seven-membered S,N-heterocycle and pyridin-2-ylmethylidene moiety (**L**) and their copper complexes with $CuCl_2$ of **$LCuCl_2$** composition were synthesized. The ligand structures were confirmed by ^1H NMR, ^{13}C NMR and HRMS. Two of the obtained coordination compounds were characterized by the X-ray and voltammetry data.

This work indicates that the introduction of additional conjugated 5- or 6-membered heterocycle to 5-(2-pyridylmethylene)-2-thio-4H-imidazol-4-one molecules does not lead to a significant change in the electrochemical characteristics of copper complexes obtained on their basis compared to previously studied compounds of similar structural type. However, the presence in the ligand of a five-membered thiazolidine ring fused with imidazolone leads to a significant change in the geometric characteristics of the complex: an increase in the Cu-S distance and the flattening of copper coordination polyhedron.

Testing of the antibacterial activity of the obtained compounds on the reporter strains *E. coli ΔtolC pDualrep2 (AmpR)* and *E. coli lptDmut pDualrep2 (KanR)* showed a lower activity of copper-containing complexes **3a-c** compared to ligand that did not have an additional condensed ring in its structure.

CRediT authorship contribution statement

Anna V. Berezina: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Viktor A. Tafeenko:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis. **Artem V. Semykin:** Investigation, Formal analysis. **Anna A. Moiseeva:** Visualization, Validation, Methodology, Investigation. **Xuimei Bai:** Investigation. **Alexander V. Finko:** Methodology, Formal analysis, Data curation. **Alisa P. Chernyshova:** Investigation. **Nikolai V. Zyk:** Supervision. **Elena K. Beloglazkina:** Writing – review & editing, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work in part of NMR study and X-ray diffraction investigation was supported by the M.V. Lomonosov Moscow State University Program of Development.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

CCDC **2349016** and **2349015** contains the supplementary crystallographic data for complexes **3a**, **3b**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Supplementary data to this article can be found online at https://doi.org/10.1016/j.poly.2024.117295.

References

[1] S.-S. Ferreira Brandao, J.-A. Rocha Filho, J. Chantegrel, J.-F. Cavalcanti Albuquerque, E. Azevedo Ximenes, S. Lins Galdino, I. Rocha Pitta, M. Perrissin, C. Luu-Duc. *Ann. Pharm. Franc.* 55 (1997) 206-211.
[2] A. M. Sh. El-Sharief, A. M. Hussein, M. S. A. El-gaby, A. A. Atalla, A. A. Ahmed. *Phosphorus, Sulfur and Silicon and the Related Elements* 170 (2001) 47-63.
[3] Y. A. Ammar, S. Y. Abbas, M. A. M. Sh. El-Sharief, M. Abd El-Rashid Salem, A. R. Mohamed. *Eur. J. Chem.* 8 (2017) 76-81.
[4] A.M.S. El-Sharief, Z. Moussa, Eur. J. Med. Chem. 44 (2009) 4315–4334.
[5] Z. Moussa, M.A.M.S. El-Sharief, A.M.S. El-Sharief, Eur. J. Med. Chem. 46 (2011) 2280–2289.
[6] Y.A. Ammar, M.A.M.S. El-Sharief, M.M. Ghorab, Y.A. Mohamed, A. Ragab, S.Y. Abbas, Curr. Org. Synth. 13 (2016) 466–475.
[7] S.Y. Abbas, M.A.M.S. El-Sharief, R.A.K. Al-Harbi, E.W. El-Gammal, A.M.S. El-Sharief, Medicinal Chemistry (Sharjah, United Arab Emirates) 17 (2021) 638–645.
[8] Z. Moussa, M.A.M.S. El-Sharief, S.Y. Abbas, Eur. J. Med. Chem. 122 (2016) 419–428.
[9] J.F.C. Albuquerque, L.C. Azevedo, S.L. Galdino, J. Chantegrel, I.R. Pitta, C. Luu-Duc, Ann. Pharm. Franc. 53 (1995) 209–214.
[10] M.A.M.S. El-Sharief, S.Y. Abbas, A.M.S. El-Sharief, N.M. Sabry, Z. Moussa, S.M. El-Messery, A.R. Elsheakh, G.S. Hassan, M.T. El Sayed, Bioorg. Chem. 87 (2019) 679–687.
[11] A. L. da Silva, J. F. de Oliveira, W. L. Silva, A. F. Luis, E. de Farias Santiago, A. de Almeida, A. S. A. de Almeida Jr, T. B. de Oliveira, V. C. A. de Souza, A. F. de Barros, I. da Rocha Pitta, S. A. de Oliveira, M. do Carmo Alves de Lima. *Biomedicine & Pharmacotherapy* 83 (2016) 502-507.
[12] C. Tran, S. Ouk, N.J. Clegg, Y. Chen, P.A. Watson, V. Arora, J. Wongvipat, P.M. Smith-Jones, D. Yoo, A. Kwon, T. Wasielewska, D. Welsbie, C.D. Chen, C.S. Higano, T.M. Beer, D.T. Hung, H.I. Scher, M.E. Jung, C.L. Sawyers, Science 324 (2009) 787–790.
[13] M.E. Voss, P.H. Carter, A.J. Tebben, P.A. Scherle, G.D. Brown, L.A. Thompson, M. Xu, Y.C. Lo, G. Yang, R.-Q. Liu, P. Strzemienski, J.G. Everlof, J.M. Trzaskos, C.P. Decicco, Bioorg. Med. Chem. Lett. 13 (3) (2003) 533–538.
[14] M.A.M.S. El-Sharief, Z. Moussa, A.M.S. El-Sharief, J. Fluorine Chem. 132 (2011) 596–611.
[15] A.I. Khodair, Carbohydr. Res. 331 (2001) 445–453.
[16] K. Kiec-Kononowicz, J. Karolak-Wojciechowska. *Phosphorus, Sulfur, Silicon* 73 (1992) 235-248.
[17] M. Arca, F. Demartin, F.A. Devillanova, A. Garau, F. Ifaia, V. Lippolis, G. Verani, Inorg. Chem. 37 (1998) 4164–4165.
[18] A.M.A. Hassaan, Sulfur Lett. 13 (1991) 1–13.
[19] R.S. Srivastava, R.R. Srivastava, H.N. Bhargava, Bull. Soc. Chim. Fr. 128 (1991) 671–676.
[20] S. Sharma, M. Kumar, T. Sharma, J. Ind. Chem. Soc. 62 (1985) 781–786.
[21] M. Kumar, A. Chaudhary, S. Sharma, Ind. J. Chem., Sect. A 25A (1986) 281–287.
[22] S.Y. Al-Raqa, A.M.S. El-Sharief, S.M.E. Khalil, A.M. Al-Amri, Heteroatom Chem. 17 (2006) 634–647.
[23] O.O. Krasnovskaya, D.A. Guk, A.E. Naumov, V.N. Nikitina, A.S. Semkina, K.Y. Vlasova, V. Pokrovsky, O.O. Ryabaya, S.S. Karshieva, D.A. Skvortsov, I.V. Zhirkina, R.R. Shafikov, P.V. Gorelkin, A.N. Vaneev, A.S. Erofeev, D.M. Mazur, V.A. Tafeenko, V.I. Pergushov, M.Y. Melnikov, M.A. Soldatov, V.V. Shapovalov, A.V. Soldatov, R.A. Akasov, V.M. Gerasimov, D.A. Sakharov, A.A. Moiseeva, N.V. Zyk, E.K. Beloglazkina, A.G. Majouga, J. Med. Chem. 63 (2020) 13031–13063.
[24] A.V. Finko, D.A. Guk, A.S. Saakian, A.A. Moiseeva, V.A. Tafeenko, E.S. Shiryaeva, V.I. Pergushov, M. Ya Melnikov, A.S. Komlev, A.A. Beloglazkin, R.S. Borisov, N.V. Zyk, A.G. Majouga, E.K. Beloglazkina, Polyhedron 225 (2022) 115998.
[25] E.K. Beloglazkina, O.O. Krasnovskaya, D.A. Guk, V.A. Tafeenko, A.A. Moiseeva, N.V. Zyk, A.G. Majouga, Polyhedron 148 (2018) 129–137.
[26] K. Tishchenko, E. Beloglazkina, M. Proskurnin, V. Malinnikov, D. Guk, M. Muratova, O. Krasnovskaya, A. Udina, D. Skvortsov, R.R. Shafikov, Y. Ivanenkov, V. Aladinskiy, I. Sorokin, O. Gromov, A. Majouga, N. Zyk, J. Inorg. Biochem. 175 (2017) 190–197.
[27] D. Guk, A. Naumov, O. Krasnovskaya, V. Tafeenko, A. Moiseeeva, V. Pergushov, M. Melnikov, N. Zyk, A. Majouga, E. Belolglazkina, Dalton Trans. 49 (2020) 14528–14535.
[28] E.K. Beloglazkina, S.Z. Vatsadze, A.G. Majouga, N.A. Frolova, R.B. Romashkina, N.V. Zyk, A.A. Moiseeva, K.P. Butin, Russ. Chem. Bull. 54 (2005) 2771–2782.
[29] A.G. Majouga, M.I. Zvereva, M.P. Rubtsova, D.A. Skvortsov, A.V. Mironov, D.M. Azhibek, O.O. Krasnovskaya, V.M. Gerasimov, A.V. Udina, N.I. Vorozhtsov, E.K. Beloglazkina, L. Agron, L.V. Mikhina, A.V. Tretyakova, N.V. Zyk, N.S. Zefirov, A.V. Kabanov, O.A. Dontsova, J. Med. Chem. 57 (2014) 6252–6258.

[30] A.G. Majouga, E.K. Beloglazkina, O.V. Shilova, A.A. Moiseeva, N.V. Zyk, Russ. Chem. Bull. 58 (2009) 1392–1399.
[31] V. Chazeaul, M. Cussacl, A. Boucherle, Eur. J. Med. Chem. 27 (1992) 615–625.
[32] M. S. Faillace, A. P. Silva, A. L. Alves Borges Leal, L. M. Costa, H. M. Barreto, W. J. Peláez. *ChemMedChem.* 15 (2020) 851–886.
[33] L. Krause, R. Herbst-Irmer, G.M. Sheldrick, D. Stalke, J. Appl. Crystallogr. 48 (2015) 3–10.
[34] G.M. Sheldrick, Acta Crystallogr. A 64 (2008) 112–122.
[35] L. Krause, R. Herbst-Irmer, G.M. Sheldrick, D. Stalke, *Acta Crystallogr. Sect. C Struct. Chem.* 71 (2015) 3–8.
[36] K. Brandenburg, DIAMOND, Release 2.1d; Crystal Impact GbR: Bonn, Germany, 2000.
[37] I.A. Osterman, M. Wieland, T.P. Maviza, K.A. Lashkevich, D.A. Lukianov, Y.V. Komarova, R. Zakalyukina, D.I. Buschauer, S.A. Shiriaev, J.E. Leyn, M.V. Zlamal, D.A. Biryukov, V.N. Skvortsov, V.I. Tashlitsky, J. Polshakov, Y.S. Cheng, A.A. Polikanov, A.L. Bogdanov, S.e. Osterman, E. Dmitriev, R. Beckmann, O.A. Dontsova, D.N. Wilson, P.V. Sergiev, Nat. Chem. Biol. 16 (2020) 1071–1077, https://doi.org/10.1038/s41589-020-0578-x.
[38] A.A. Chorbu, E.S. Barskaya, A.A. Moiseeva, D.A. Guk, O.O. Krasnovskaya, K.A. Lyssenko, A.V. Rzheutski, M.S. Abramovich, M.N. Polyakova, A.V. Berezina, N.V. Zyk, E.K. Beloglazkina, Polyhedron 221 (2022) 115838, https://doi.org/10.1016/j.poly.2022.115838.
[39] E.K. Beloglazkina, A.G. Majouga, A.V. Mironov, A.V. Yudina, A.A. Moiseeva, M.A. Lebedeva, A.N. Khlobystov, N.V. Zyk, Polyhedron 63 (2013) 15–20, https://doi.org/10.1016/j.poly.2013.07.014.
[40] G. Sciortino, J.n-D. Maréchal, I. Fábián, N. Lihi, E. Garribba, *J. Inorg. Biochem.* 204 (2020) 110953. doi: 10.1016/j.jinorgbio.2019.110953.
[41] B.J. Hathaway, D.E. Billing, Coord. Chem. Rev. 5 (1970) 143–207, https://doi.org/10.1016/S0010-8545(00)80135-6.
[42] G. Tabbì, A. Giuffrida, R.P. Bonomo, J. Inorg. Biochem. 128 (2013) 137–145, https://doi.org/10.1016/j.jinorgbio.2013.07.035.
[43] L. Yang, D.R. Powell, R.P. Houser, Dalton Trans. 9 (2007) 955–964, https://doi.org/10.1039/b617136b.
[44] A. Okuniewski, D. Rosiak, J. Chojnacki, B. Becker, Polyhedron 90 (2015) 47–57, https://doi.org/10.1016/j.poly.2015.01.035.
[45] D. Rosiak, A. Okuniewski, J. Chojnacki, Polyhedron 146 (2018) 35–41, https://doi.org/10.1016/j.poly.2018.02.016.