Structural Diversity of Copper(II) Complexes with N-(2-Pyridyl)Imidazolidin-2-Ones(Thiones) and Their *in Vitro* Antitumor Activity

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**Abstract:** Six series of structurally different mono- and binuclear copper(II) complexes 5–10 were obtained by reacting N-(2-pyridyl)imidazolidin-2-ones (1a–l), N,N’-bis(2-pyridyl)imidazolidin-2-ones (2a,b), N-acyl-N(2-pyridyl)imidazolodin-2-ones (3a–j) and N-(2-pyridyl)imidazolidine-2-thiones (4a–g) with copper(II) chloride at an ambient temperature. The coordination modes of the complexes obtained were established by elemental analysis, IR spectroscopic data and single crystal X-ray diffraction studies. The *in vitro* cytotoxic activities of both the free ligands and copper(II) complexes were evaluated using a crystal violet microtiter plate assay on five human tumor cell lines: LCLC-103H, A-427, SISO, RT-4 and DAN-G. The free ligands 1–4 at concentration attainable in cancer cells of 20 μM showed no meaningful cytotoxic effect with cell viability in the range of 88%–100%. The most potent copper(II) complex of 1-(6-ethoxy-2-pyridyl)imidazolidin-2-one (6b) exhibited selective cytotoxicity against A-427 lung cancer cell line, while the complexes of 1-(5-methyl-2-pyridyl)imidazolidine-2-thione (5h) and
1-(4-tert-butyl-2-pyridyl)imidazolidine-2-thione (5j) showed cytostatic effect against a whole panel of five human tumor cell lines. In conclusion, the only complexes that showed remarkably increased activity in comparison to the free ligands were those obtained from N-(2-pyridyl)imidazolidine-2-thiones 4c and 4e substituted with alkyl group at position 4 or 5 of pyridine ring.

**Keywords:** 1-(2-pyridyl)imidazolin-2-ones; 1-(2-pyridyl)imidazolidine-2-thiones; copper(II) complexes; X-ray crystal structure analysis; *in vitro* antitumor activity

1. Introduction

Among the transition metals copper occupies a unique position with respect to its biological role. Copper, which is found in living organisms, is an essential cofactor in a number of enzymes and is involved in the function of several proteins and physiological processes such as cell metabolism, mitochondrial respiration, antioxidation processes, synthesis of some active compounds [1,2]. Additionally, copper a redox-active metal may form stable complexes with chelate ligands containing donor atoms such as nitrogen, sulfur or oxygen [2].

In the field of medicinal chemistry it has been found that complexes of transient metals such as copper may possess a higher biological activity compared to the free ligands, with lower toxicity and improved physicochemical properties [3]. Moreover, coordination may lead to significant reduction of drug-resistance. Therefore a considerable research has been devoted to the synthesis of copper compounds which exhibit anticancer [3–10], SOD-mimicking [11–13], antimicrobial [14], anti-parasitic [15] and anti-inflammatory properties [16].

Recently, our attention has been focused on the cyclic analogues of N-aryl(heteroaryl)ureas and N-aryl(heteroaryl)thioureas of type I (Figure 1) with proved anticancer activity [17–19]. In this paper, we wish to report the results of our studies on the synthesis and reactions of cyclic ureas and thioureas of Type 2 (Figure 1) with copper(II) chloride, X-ray structure determination of the complexes obtained, as well as the results of evaluation of their *in vitro* cytotoxic activity against several human tumor cell lines.

![Figure 1. N-aryl(heteroaryl)ureas (I) and their cyclic analogues II.](image-url)
2. Results and Discussion

2.1. Synthesis of Ligands

Two series of chelating ligands 1a–l and 2a–b with N, O or S donor atoms are shown in Scheme 1. The bidentate ligand 1a and tridentate ligand 2a were prepared by copper-catalyzed N-heteroarylation of 2-imidazolidinone, i.e., by reacting 2-imidazolidinone with 2-iodopyridine in the presence of CuI, N,N'-dimethylethlenediamine and K₂CO₃ in n-BuOH at 100 °C [20]. The substituted ligands 1b–l and 2b were obtained according to the previously described α-ureidation of corresponding pyridine-N-oxides with 2-chloroimidazole [21,22].

Scheme 1. Synthesis of bidentate ligands 1a–l and tridentate ligands 2a–b.

![Scheme 1](image_url)

Novel N-acyl-imidazolidin-2-one tridentate ligands 3a–j suitable for preparation of the coordination compounds were obtained by the treatment of 1 with acetyl or butyryl anhydride, as shown in Scheme 2. On the other hand, imidazolidin-2-ones 1 were also converted into the corresponding imidazolidine-2-thiones using standard method with Lawesson’s reagent in boiling toluene (Scheme 2).

Scheme 2. Preparation of novel N-acyl-imidazolidin-2-ones 3a–j and imidazolidine-2-thiones 4a–g.

![Scheme 2](image_url)
2.2. Synthesis and Structure of Cu(II) Complexes

The reaction of \(N\)-(2-pyridyl)imidazolidin-2-one(thione) ligands 1, 2, 3 and 4 with \(\text{CuCl}_2\) were carried out at room temperature in either DMF or methanol solution containing 1% of water. Crystals suitable for the X-ray analysis were obtained by slow evaporation of the solvent. According to the X-ray data collected during the study, the following sequence of events is involved in this reaction yielding complexes with different geometries depending on the nature of ligand (Scheme 3):

(i) Initial formation of the LCuCl\(_2\) complex of type 5 from bidentate ligands (2-alkyl-pyridines) with tetrahedral or square planar configuration, or five-coordinate 6 from tridentate ligands (2-alkoxy-pyridines) with square pyramidal or trigonal bipyramidal configuration.

(ii) Four-coordinate complex 5 can then react with a molecule of water to give a five-coordinate complex 7.

(iii) Complexes of type 5 can also form di-\(\mu\)-chloro dinuclear five-coordinate [\(\text{Cu}_2(L)_2\text{Cl}_4\)] complexes of type 8 or react with a second molecule of ligand to give octahedral [\(\text{Cu}(L)_2\text{Cl}_2\)] complexes of type 9.

(iv) A geometrical change occurs upon dissociation of a weakly bonded axially coordinated chloride anion from 9, leading to square pyramidal complexes 10 with the same \(sp^3d^2\) electronic geometry.

It should be pointed out, that the preferential formation of a particular complex type may depend on solubility of 5, i.e., precipitation of 5 prevents subsequent formation of 7, 8, 9 and 10. It is also possible that several species are in equilibrium in solution, and which are obtained in crystalline form depends on solubility, crystallization kinetics and other, medium dependent, properties. List of ligands 1–4 and corresponding complexes 5–10 obtained is presented in Table 1.

| Ligand Complex † | Ligand | Complex |
|------------------|--------|---------|
| 5a               | 1a O   | H       |
| 5b               | 1b O   | 6-CH\(_3\) H |
| 5c               | 1d O   | 4-CH\(_3\) H |
| 6a               | 1e O   | 4-C\(_6\)H\(_5\) H |
| 6b               | 1f O   | 6-OCH\(_3\) H |
| 6c               | 1g O   | 4-OCH\(_3\) H |
| 6d               | 1h O   | 6-OC\(_2\)H\(_5\) H |
| 6e               | 1i O   | 6-\(n\)-OC\(_3\)H\(_7\) H |
| 6f               | 1j O   | 6-\(i\)-OC\(_3\)H\(_7\) H |
| 6g               | 1k O   | 6-CH\(_3\), 4-OC\(_2\)H\(_5\) H |
| 6h               | 1l O   | 6-\(n\)-OC\(_4\)H\(_9\) H |
| 8a               | 2a O   | 2-pyridyl |
| 7                | 2b O   | 4-CH\(_3\) 2-pyridyl |
| 8b               | 3a O   | 5-CH\(_3\) COCH\(_3\) |
Copper(II) complexes exhibit a variety of irregular stereochemistries as a result of the lack of spherical symmetry of this $d^9$ ion. Classification of coordination geometry of the obtained complexes was accomplished based on the equation described by D. Venkataraman and co-workers (Equation (1)), which determines the best fit of the observed structure of complex compound to the ideal coordination polyhedra [23]. The best fit shows minimum of deviation in ligand-copper-ligand bond angles ($\angle$L-Cu-L) between the observed coordination structure and the reference polyhedra with the same coordination number (CN). Such classification is unambiguous since a unique set of angles exists for each of the reference polyhedral. Hence, the coordination geometry is classified as polyhedron that gives the smallest value of the average angular displacement ($\Delta\Theta$) according to the following Equation (1):

$$\Delta\Theta = \sum_{i=1}^{n} \frac{|\Theta_i - \Theta_\circ_i|}{n/2 \times (n-1)}$$  \hspace{1cm} (1)

where: $n$—coordination number, $\Theta_i$—the angle of the observed structure, $\Theta_\circ_i$—corresponding valence angle of the reference polyhedron under consideration, $\Delta\Theta$—evaluation of the average angular displacement.

For example, in the case of a complex 5b with coordination number $n = 4$, the number of valence angles $\angle$L-Cu-L, according to the formula $n = (n/2) \times (n - 1)$, is 6. The geometry of this complex may be: square planar with ideal angles of 90, 90, 90, 90, 180, 180 (°) or tetrahedral with angles 109.5, 109.5, 109.5, 109.5, 109.5 (°). Comparison of the observed angles in the structure of 5b (Figure 2, Table 2) with ideal values of each polyhedron geometry angles determined by the value of ($X$ vs. $Y$ vs. $Z$) indicates that the coordination geometry in CuNOCl$_2$ core is intermediate between square-planar and tetrahedral, however, the copper ion adopts geometry that fit best to the square planar ($\Delta\Theta = 17.79$ for square planar vs $\Delta\Theta = 18.72$ for tetrahedral geometry).
**Scheme 3.** Reaction of \( N \)-(2-pyridyl)imidazolidin-2-one(thione) ligands 1, 2, 3 and 4 with \( \text{CuCl}_2 \).

A similar distorted square planar coordination geometries were found in crystals of imidazolidine-2-thiones 5h, 5i and 5j (Figure 2, Table 2).

**Table 2.** Selected bond lengths and bond angles in copper complexes 5b, 5h, 5i and 5j.

| No. | Bond Lengths (Å) | Bond Angles (°) |
|-----|------------------|----------------|
|      | \( \text{Cu1-Cl1} \) | 2.2239(5) | \( \text{Cl1-Cu1-N1} \) | 98.45(5) |
|      | \( \text{Cu1-Cl2} \) | 2.2096(5) | \( \text{Cl1-Cu1-Cl2} \) | 103.57(2) |
|      | \( \text{Cu1-N1} \) | 1.977(2) | \( \text{Cl1-Cu1-O1} \) | 135.46(4) |
|      | \( \text{Cu1-O2} \) | 1.980(1) | \( \text{O1-Cu1-Cl2} \) | 93.53(4) |
| 5b   | \( \text{Cl2-Cu1-N1} \) | 143.81(6) | \( \text{O1-Cu1-N1} \) | 90.43(7) |
Table 2. Cont.

| No. | Bond Lengths (Å) | Bond Angles (°) |
|-----|------------------|-----------------|
|     | Cu1-Cl1          | 2.261(1)        | Cl1-Cu1-Cl2      | 100.99(3) |
| 5h  | Cu1-Cl2          | 2.2139(6)       | Cl1-Cu1-S1       | 141.86(3) |
|     | Cu1-N7           | 1.977(1)        | Cl1-Cu1-N7       | 97.01(6)  |
|     | Cu1-S1           | 2.2324(8)       | Cl2-Cu1-N7       | 139.51(6) |
|     |                  |                 | Cl2-Cu1-S1       | 93.25(3)  |
|     |                  |                 | S1-Cu1-N7        | 94.50(6)  |
| 5i  | Cu1-Cl1          | 2.239(3)        | Cl1-Cu1-Cl2      | 97.44(2)  |
|     | Cu1-Cl2          | 2.239(4)        | Cl1-Cu1-S1       | 91.17(2)  |
|     | Cu1-N7           | 1.983(3)        | Cl2-Cu1-N7       | 94.33(4)  |
|     | Cu1-S1           | 2.2708(8)       | Cl1-Cu1-N7       | 149.94(4) |
|     |                  |                 | Cl2-Cu1-S1       | 152.71(2) |
|     |                  |                 | N7-Cu1-S1        | 90.88(4)  |
| 5j  | Cu1-Cl1          | 2.239(3)        | Cl1-Cu1-Cl2      | 96.92(1)  |
|     | Cu1-Cl2          | 2.243(3)        | Cl2-Cu1-S1       | 90.85(9)  |
|     | Cu1-N1           | 2.011(6)        | Cl1-Cu1-N1       | 146.47(9) |
|     | Cu1-S1           | 2.245(2)        | Cl2-Cu1-N1       | 143.0(2)  |
|     |                  |                 | Cl1-Cu1-N1       | 96.94(1)  |
|     |                  |                 | Cl2-Cu1-S1       | 90.87(9)  |

Figure 2. ORTEP [24] representation of molecular structure of 5b, 5h, 5i and 5j.

Ligands 1 and 4 containing alkoxy group at position 6 of pyridine ring form mononuclear five-coordinate (4 + 1) copper(II) complexes with the central atom chelated by neutral ligand and bound to two chloride ions and oxygen of alkoxy group. In the complex 6a both pyridine and imidazolidine rings are approximately planar with N1-C2-N7-C8 torsion angle of 14.4°. As exemplified by the crystal structure of 6a (Figure 3, Table 3), the geometry around Cu(II) is best described as distorted trigonal bipyramid. Atoms -Cu1-N1-C2-C8-N7-O12- form six-membered ring
and atoms -Cu1-N1-C6-O13- form four-membered ring of considerable tension. The length of the bond between the atoms Cu1 and O13 of the methoxy group is longer (2.647 Å) than that between Cu1 atom and the oxygen atom O12 of the carbonyl group (1.994 Å).

**Figure 3.** ORTEP representation of molecular structure of 6a.

![Figure 3](image)

**Table 3.** Selected bond lengths and bond angles in copper complex 6a.

| Bond Lengths (Å) | Bond Angles (°) |
|------------------|-----------------|
| Cu1-Cl1          | 2.2325(2)       |
| Cu1-Cl2          | 2.1848(2)       |
| Cu1-O12          | 1.9943(2)       |
| Cu1-O13          | 2.6472(3)       |
| Cu1-N1           | 1.9754(2)       |
| Cl1-Cu1-Cl2      | 104.23          |
| N1-Cu1-Cl2       | 147.16          |
| O12-Cu1-Cl2      | 94.11           |
| O13-Cu1-Cl2      | 104.53          |
| N1-Cu1-O12       | 88.06           |
| O12-Cu1-O13      | 134.79          |
| O12-Cu1-N1       | 130.17          |
| O13-Cu1-N1       | 54.71           |
| O13-Cu1-N1       | 84.85           |
| N1-Cu1-N1        | 99.10           |

Interesting five-coordinated mononuclear complex 7 was prepared by reacting equimolar amount of 1,3-*bis*(4-methyl-2-pyridyl)imidazolidin-2-one (2b) with copper(II) chloride in methanol containing 1% of water. Elemental analysis data suggested the presence of water molecule in the complex compound, which was confirmed by IR spectrum revealing a broad absorption band with a maximum at 3372 cm$^{-1}$. X-ray analysis (Figure 4, Table 4) indicate that the molecule 7 is not isostructural with 6a, but it does have a similar molecular structure. Thus, central atom chelated by neutral ligand 2b and bound to two chloride ions and oxygen of H$_2$O. The coordination geometry around the central atom is best described as distorted trigonal bipyramid due to differences in the five Cu-donor bond lengths.

**Table 4.** Selected bond lengths and bond angles in copper complex 7.

| Bond Lengths (Å) | Bond Angles (°) |
|------------------|-----------------|
| Cu1-Cl1          | 2.362(2)        |
| Cu1-Cl2          | 2.289(8)        |
| Cu1-N14          | 2.007(8)        |
| N14-Cu1-O1       | 87.58(7)        |
| N14-Cu1-Cl1      | 89.40(6)        |
| N14-Cu1-Cl2      | 95.83(6)        |
Table 4. Cont.

| Bond Lengths (Å) | Bond Angles (°) |
|------------------|-----------------|
| Cu1-O1           | 2.042(3)        |
| Cu1-O1W          | 1.974(4)        |
| O1W-Cu1-Cl1      | 92.45(5)        |
| O1W-Cu1-O1       | 84.87(7)        |
| Cl2-Cu1-O1       | 119.07(5)       |
| O1W-Cu1-N14      | 172.37(8)       |
| Cl1-Cu1-O1       | 111.82(4)       |
| Cl1-Cu1-Cl2      | 128.99(3)       |

Figure 4. ORTEP representation of molecular structure of 7.

1,3-Bis(2-pyridyl)imidazolidin-2-one (2b) and 1-acyl-3-(2-pyridyl)imidazolidin-2-ones (3a–j) subjected to the reaction with copper(II) chloride gave rise to the formation of the products 8a–k, which appear to be binuclear five-coordinate di-μ-chloro copper(II) complexes. The determination of the three-dimensional structure of the complexes 8a and 8c by X-ray diffraction (Figure 5, Table 5) indicates that symmetrical coordination polyhedra of these complexes are square-pyramidal with the central atom displaced from the plane of the four basal atoms towards the apical position. It is noteworthy, however, that the arrangement of ligands in both complexes is different. Thus, in 8c the apical position is occupied by non-bridging Cl atom which is basal to the other copper in the dimer, while complex 8a incorporates O atom in that position.

Figure 5. ORTEP representation of molecular structure of 8a and 8c. Displacement ellipsoids are shown at the 50% probability level. Only the symmetry independent part of the molecule is labelled.
Table 5. Selected bond lengths and bond angles in copper complexes 8a and 8c.

| No.  | Bond  | Bond Lengths (Å) | Bond Angles (°) |
|------|-------|------------------|-----------------|
|      |       | Cl1-Cu1          | Cl1-Cu1-Cl1     |
|      | 8a    | 2.3260(5)        | 85.06(2)        |
|      |       | Cl1-Cu1          | Cl1-Cu1-Cl2     |
|      | 2.3064(6) | Cl1-Cu1-Cl2    | 92.25(2)        |
|      | Cl2-Cu1 | 2.2492(5)       | 91.17(5)        |
|      | Cu1-N7 | 2.014(2)         | 91.72(5)        |
|      | Cu1-O1 | 2.143(1)         | 92.84(4)        |
|      |       | O1-Cu1-Cl1       | 102.79(4)       |
|      |       | O1-Cu1-Cl1       | 86.65(6)        |
|      |       | O1-Cu1-N7        | 106.24(4)       |
|      |       | N7-Cu1-Cl1       | 176.55(4)       |
|      |       | Cl1-Cu1-Cl2      | 150.94(2)       |
|      | 8c    | 2.2889(1)        | 85.15           |
|      |       | Cl1-Cu1          | Cl1-Cu1-O1      |
|      |       | 2.6261(5)        | 86.80           |
|      |       | Cl2-Cu1          | Cl2-Cu1-N7      |
|      |       | 2.2349(1)        | 97.38           |
|      |       | Cu1-N7           | Cl1-Cu1-Cl2     |
|      |       | 2.0651(1)        | 92.09           |
|      |       | Cu1-O1           | N7-Cu1-Cl1      |
|      |       | 1.9829(1)        | 170.49          |
|      |       | O1-Cu1-Cl2       | 152.31          |
|      |       | Cl1-Cu1-O1       | 94.23(1)        |
|      |       | Cl1-Cu1-N7       | 85.37(1)        |
|      |       | Cl1-Cu1-Cl2      | 113.35(1)       |
|      |       | Cl1-Cu1-Cl1      | 90.15(1)        |

*N-(5-methyl-2-pyridyl)imidazolidin-2-one (1c) reacted with copper(II) chloride with the formation of mononuclear complex trans-CuCl2L2 (compound 9, Figure 6, Table 6). A similar structure was previously obtained using N,N’bis(2-pyridyl)urea [25]. The six-coordinate copper ion sits upon crystallographic inversion center, with ligand chelated through its oxygen atom and 2-pyridyl nitrogen atom. The axial positions are occupied by two chloride ligands. The bond angles around the copper ion are close to 90°, indicating a slight distortion of the octahedral coordination sphere.

Figure 6. ORTEP representation of molecular structure of 9. Displacement ellipsoids are shown at the 50% probability level. Only symmetry independent part is labelled.
Table 6. Selected bond lengths and bond angles in copper(II) complex 9.

| Bond Lengths (Å) | Bond Angles (°) |
|------------------|-----------------|
| Cu1-Cl1          | 2.8254(8)       |
| Cu1-N7           | 2.019(2)        |
| Cu1-O1           | 1.950(2)        |
| O1-Cu1-N7        | 88.31(8)        |
| N7-Cu1-O1        | 91.69(8)        |
| Cl1-Cu1-O1       | 92.31(6)        |
| O1-Cu1-Cl1       | 87.69(6)        |
| N7-Cu1-Cl1       | 90.71(6)        |
| O1-Cu1-O1        | 180.00(8)       |
| N7-Cu1-N7        | 180.00(9)       |
| Cl1-Cu1-Cl1      | 180.00(2)       |

As shown in Table 6, in octahedral complex Cu(II)L₂Cl₂ (9) the Cu(II)-Cl bonds are elongated (2.8254 Å), and therefore, are susceptible to dissociation. Indeed, in polar solvents ligands 1e (1-(4-phenyl-2-pyridyl)imidazolidin-2-one) and 1g (1-(4-methoxy-2-pyridyl)imidazolidin-2-one) subjected to the reaction with copper(II) chloride gave the monocationic complexes 10a/b and 10c of general structure [CuL₂Cl]⁺ whose charge is neutralized by either the Cl⁻ (10a and 10c) or CuCl₃⁻ (10b) ion. Their crystal structures show (Figure 7, Table 7) that two bidentate ligands arranged in trans fashion are coordinated to the copper(II) ion through N(pyridine) and O(imidazolidin-2-one) atoms. The fifth coordination comes from chloride ion, and the Cu-Cl bond lengths of 2.4910–2.4877 Å are shorter than those in the octahedral complex 9 discussed above. The geometries around the central atom are best described by square-pyramidal with trigonal-bipyramidal distortion. The counterions, i.e., Cl⁻ in complexes 10a and 10c and CuCl₃⁻ in complex 10b, remain uncoordinated, however were found to engage in several weak hydrogen-bonding interactions.

Figure 7. ORTEP representation of molecular structure of 10a (Cl⁻ counterion), 10b (CuCl₃⁻ counterion) and 10c (Cl⁻ counterion). Hydrogen bonds are shown with dashed lines.
Table 7. Selected bond lengths and bond angles in copper(II) complexes 10a, 10b and 10c.

| No. | Bond Lengths (Å) | Bond Angles (°) |
|-----|------------------|-----------------|
| 10a | Cu1-C11          | 2.4274(5)       | Cl1-Cu1-O1A 101.91(4) |
|     | Cu1-N1A          | 2.053(2)        | Cl1-Cu1-O1B 107.23(4) |
|     | Cu1-N1B          | 2.041(2)        | O1A-Cu1-O1B 150.84(6) |
|     | Cu1-O1A          | 1.967(1)        | N1A-Cu1-O1A 87.52(6)  |
|     | Cu1-O1B          | 1.922(1)        | N1A-Cu1-C11  94.08(5)  |
|     |                  |                 | N1A-Cu1-N1B  171.28(6) |
|     |                  |                 | N1A-Cu1-O1B  89.42(6)  |
|     |                  |                 | N1B-Cu1-C11  94.58(5)  |
|     |                  |                 | N1B-Cu1-O1A  89.74(6)  |
|     |                  |                 | N1B-Cu1-O1B  88.95(6)  |
| 10b | Cu1-C11          | 2.4877(6)       | Cl1-Cu1-O1A 111.06(5) |
|     | Cu1-N1A          | 2.019(2)        | Cl1-Cu1-O1B  92.85(5)  |
|     | Cu1-N1B          | 2.015(2)        | O1A-Cu1-O1B  156.09(7) |
|     | Cu1-O1A          | 1.946(2)        | N1A-Cu1-O1A  86.87(7)  |
|     | Cu1-O1B          | 1.964(2)        | N1A-Cu1-C11  97.44(6)  |
|     | Cu2-C12          | 2.195(1)        | N1A-Cu1-N1B  172.10(8) |
|     | Cu2-C13          | 2.3018(8)       | N1A-Cu1-O1B  89.79(7)  |
|     |                  |                 | N1B-Cu1-C11  90.45(6)  |
|     |                  |                 | N1B-Cu1-O1A  89.95(7)  |
|     |                  |                 | N1B-Cu1-O1B  90.19(7)  |
|     |                  |                 | Cl2-Cu2-C13  120.59(4) |
|     |                  |                 | Cl3-Cu2-C13  118.81(3) |
| 10c | Cu1A-C11A        | 2.4910(5)       | N1B-Cu1A-C11A 90.04(5) |
|     | Cu1A-N1A         | 2.031(1)        | O2A-Cu1A-C11A 105.98(5) |
|     | Cu1A-N1B         | 2.044(2)        | N1A-Cu1A-C11A 97.78(5) |
|     | Cu1A-O2A         | 1.928(2)        | O2B-Cu1A-C11A 94.12(5) |
|     | Cu1A-O2B         | 1.948(2)        | O2B-Cu1A-N1A  88.03(7) |
|     |                  |                 | N1A-Cu1A-O2A  89.02(7) |
|     |                  |                 | O2A-Cu1A-N1B  89.78(7) |
|     |                  |                 | O2B-Cu1A-N1B  88.65(7) |
|     |                  |                 | O2-Cu1A-O2B   159.90(6) |
|     |                  |                 | N1B-Cu1A-N1A  166.96(7) |

2.3. In Vitro Antitumor Activity

The in vitro antitumor potential of the free ligands 1–4 and copper(II) complexes 5–10 against human lung cancer (either LCLC-103H or A-427), human bladder cancer (either 5637 or RT-4), human cervical cancer (SISO), and human esophagus cancer (KYSE-520) cell lines was evaluated using a crystal violet microtiter plate assay as described earlier [26]. Primary screening of the new compounds was performed to indicate whether a substance possesses enough activity to inhibit cell growth by 50% at a concentration attainable in cancer cells, i.e., 20 µM.

The free ligands 1–4 were inactive, while the complexes of type 5 and 6 obtained from imidazolidin-2-ones, including those substituted with acyl group at the nitrogen atom, showed a remarkable inhibitory activity against lung cancer A-427 cell line (Table 8). It should be pointed out, however, that some copper(II) complexes, although fairly soluble in aprotic polar solvents such as
DMF or DMSO, showed rather poor solubility in water and precipitated out of culture media. Therefore, Table 8 incorporates the results of primary screening obtained for the complexes that remained in solution at the test concentration of 20 μM.

**Table 8.** Percent of cell growth relative to untreated control at a concentration of 20 μM (values are averages of three independent determinations with standard deviations, otherwise averages of two determinations without SD. Values were calculated according to Equation (2)).

| Cell Line No. | LCLC-103H | 5637 | A-427 | SISO | KYSE-520 | RT-4 |
|---------------|-----------|------|-------|------|----------|------|
| 5a            | 38.74     | nd   | 35.57 | 96.68| nd       | nd   |
| 5b            | nd        | 101.05| nd    | 113.65| 95.75    | nd   |
| 5e            | 88.2 ± 17.4| 135.9 ± 43.6| 34.9 ± 9.8| nd  | nd       | nd   |
| 5f            | 91.78     | nd   | 79.82 | 85.30| nd       | nd   |
| 5g            | 63.17     | 96.67| 44.69 | nd   | nd       | nd   |
| 5h            | 36.52     | nd   | 45.11 | nd   | nd       | 31.67|
| 5i            | 89.38     | 33.48| nd    | nd   | nd       | 71.86|
| 5j            | 38.28     | nd   | 29.18 | nd   | nd       | 41.65|
| 6a            | 101.2 ± 13.1| 106.2 ± 31.1| 48.30 ± 11.13| nd  | nd       | nd   |
| 6b            | 91.5 ± 8.8 | 87.4 ± 20.6| -40.6 ± 31.8| nd  | nd       | nd   |
| 6c            | 75.9 ± 21.7| 104.05 ± 40.54| 30.4 ± 10.1| nd  | nd       | nd   |
| 6d            | 78.4 ± 21.2| 145.6 ± 30.8| 26.6 ± 11.3| nd  | nd       | nd   |
| 7             | 66.93     | 93.78| nd    | nd   | nd       | 94.21|
| 8a            | 27.45     | nd   | 18.30 | 89.69| nd       | nd   |
| 9             | 69.23 ± 23.21| 135.88 ± 10.66| 75.12 ± 13.31| nd  | nd       | nd   |
| 10c           | 216.63 ± 14.43| 105.96 ± 24.06| 79.4 ± 6.26| nd  | nd       | nd   |

**Note:** † nd: = not determined.

For secondary screening aimed at determining cytotoxic potencies (IC₅₀) we selected imidazolidine-2-thione complexes 5h and 5j which exhibited a pronounced activity against at least three cancer cell lines. The results of secondary screenings are presented in Table 9. Thus, for complexes 5h and 5j, both of which exhibited growth inhibitory effects against LCLC-103H, A-427, SISO, RT-4 and DAN-G cell lines, the calculated IC₅₀ values were in the range of 8–25 μM. It is worth noting that most active (IC₅₀ in the range of 8.55–12.80 μM) was compound 5j containing tert-butyl substituent at the position 4 of pyridine ring. This observation is in line with recent findings that an electron-donating tert-butyl group may stabilize a copper(II) complexes by increasing the electron density at the central ion which, in turn, elicits a “self-activating” mechanism of DNA strand scission through the generation of reactive oxygen species (ROS) that are possibly responsible for the DNA cleavage [27–29]. Further work will be needed to confirm this, however.

**Table 9.** IC₅₀ (μM) values in five human cancer cell lines obtained after 96 h exposure †.

| Cell Line No. | LCLC-103H | A-427 | SISO   | RT-4   | DAN-G   |
|---------------|-----------|-------|--------|--------|---------|
| 5h            | 11.16 ± 3.20 | 24.38 ± 14.28 | 24.81 ± 13.78 | 8.25 ± 3.79 | 24.88 ± 3.04 |
| 5j            | 11.71 ± 5.06 | 8.55 ± 3.10 | 10.83 ± 3.05 | 9.64 ± 4.95 | 12.80 ± 0.64 |
| cisplatin *   | 0.90 ± 0.19 | 1.96 ± 0.54 | 0.24 ± 0.06 | 1.61 ± 0.16 | 0.73 ± 0.34 |

**Notes:** † Values are average of three independent determinations with standard deviations; * Ref. [26].
3. Experimental Section

Melting points both the ligands and copper(II) complexes were determined on a Boetius apparatus and are uncorrected. FT-IR spectra were measured by Nicolet-380 spectrophotometer and \(^1\)H-NMR and \(^{13}\)C-NMR spectra were recorded on a Varian Gemini instrument operating at 200 MHz and 50 MHz, respectively, in CDCl\(_3\) or DMSO-\(d_6\) as a solvent. Chemical shifts are shown in parts per million (ppm) on the \(\delta\) scale. Coupling constants are shown in hertz (Hz).

Chromatographic separations were performed on silica gel 60 PF254 containing gypsum (Merck) by use of chromatotron or flash column chromatography (silica gel 0.040–0.063 mm). Thin-layer chromatography (TLC) was performed with Merck silica gel plates and spots were visualized with UV light at 254 nm.

The diffraction data for single crystals were collected with KM4CCD, Oxford Diffraction Xcalibur or Oxford Diffraction SuperNova diffractometers. The intensity data were processed using the CrysAlis software [30]. The structures were solved by direct methods with the program SHELXS-97 [31] and refined by full-matrix least-squares method on \(F^2\) with SHELXL-97 [31].

Crystallographic data for compounds have been deposited with the Cambridge Crystallographic Data Centre, with the deposition Nos CCDC 986094, 986095, 986193–986202. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Elemental analyses of C, H and N were within ±0.4% of the theoretical values.

All cell culture reagents were purchased from Sigma (Deisenhofen, FRG). Cancer cell lines: human large cell lung carcinoma LCLC-103H, human urinary bladder carcinoma 5637, human lung carcinoma A-427, human uterine cervical adenocarcinoma SISO, esophageal squamous cell carcinoma KYSE-520, human bladder cell carcinoma RT-4 and human pancreas cell adenocarcinoma DAN-G were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, FRG). The culture medium for cell lines was RPMI-1640 medium containing 2 g/L HCO\(_3\), and 10% FCS. Cells were grown in 75 cm\(^2\) plastic culture flasks (Sarstedt, Nümbrecht, FRG) in a humid atmosphere of 5% CO\(_2\) at 37 °C and were passaged shortly before becoming confluent.

For the cytotoxicity studies, 100 \(\mu\)L of a cell suspension were seeded into 96-well microtiter plates (Sarstedt) at a density of 1000 cell per well except for the LCLC-103H cell line, which was plated out at 250 cells per well. One day after plating, the cells were treated with test substance at five concentrations per compound. The 1000-fold concentrated stock solutions in DMF or DMSO were serially diluted by 50% in DMF or DMSO to give the feed solutions, which were diluted 500-fold into culture medium. The controls received just DMF or DMSO. Each concentration was tested in eight wells, with each well receiving 100 \(\mu\)L of the medium containing the substance. The concentration ranges were chosen to bracket the expected IC\(_{50}\) values as best as possible. Cells were then incubated for 96 h, after which time the medium was removed and replaced with 1% glutaraldehyde/PBS. Staining with crystal violet was done as previously described [26]. O.D. was measured at \(\lambda = 570\) nm with an Anthos 2010 plate reader (Salzburg, Austria).

Corrected T/C values were calculated using MS Excel 2007 program by the equation:

\[
(T/C)_{\text{corr}}(\%) = \frac{(\text{O.D.}_T - \text{O.D.}_c,0)}{(\text{O.D.}_C - \text{O.D.}_c,0 )} \times 100
\]

where O.D._T is the mean absorbance of the treated cells; O.D._C the mean absorbance of the controls and O.D._c,0 the mean absorbance at the time drug was added. The IC\(_{50}\) values were estimated by a
linear least-square regression of the $T/C_{corr}$ values *versus* the logarithm of the substance concentration; only concentrations that yielded $T/C_{corr}$ values between 10% and 90% were used in the calculation. The reported IC$_{50}$ values are the averages of 3 independent experiments.

### 3.1. Synthesis of 1-Acyl-3-(2-pyridyl)imidazolidin-2-ones 3a–j (General Procedure)

Imidazolidin-2-one (0.001 mol) was refluxed in 5 mL of acetic anhydride or butyric anhydride for 6 h. The reaction mixture was concentrated under reduced pressure and basified with 20% solution of K$_2$CO$_3$. Precipitated was collected by suction, washed with water and dried. In case when oily residue was formed after addition of K$_2$CO$_3$ the product was extracted with chloroform (3 × 15 mL), dried with anhydrous MgSO$_4$, filtrated and concentrated under reduced pressure. Product was purified by use of chromatotron, flash column chromatography or crystallization. According to described general procedure were obtained following compounds:

#### 1-Acetyl-3-(5-methyl-2-pyridyl)imidazolidin-2-one (3a).

Compound 3a was purified by use of chromatotron (eluents: dichloromethane/ethyl acetate, 7:3, v/v); yield 60%; mp. 179–181 °C; IR (KBr) ν [cm$^{-1}$]: 2999, 2953, 2853, 1731, 1680, 1484, 1403, 1375, 1291, 1246, 1023; $^1$H-NMR (500 MHz, CDCl$_3$): δ 2.30 (s, 3H, CH$_3$), 2.57 (s, 3H, CH$_3$), 3.93 (t, 2H, CH$_2$), 4.10 (t, 2H, CH$_2$), 7.54 (d, $J = 8.3$ Hz, 1H, Ar-H), 8.13 (d, $J = 8.3$ Hz, 1H, Ar-H), 8.16 (s, 1H, Ar-H); Anal. Calcd. for C$_{11}$H$_{13}$N$_3$O$_2$: C, 60.26; H, 5.98; N, 19.17; Found: C, 60.11; H, 5.78; N, 19.08.

#### 1-Acetyl-3-(4-methyl-2-pyridyl)imidazolidin-2-one (3b).

Compound 3b was purified by use of chromatotron (eluents: dichloromethane/acetone, 95:5, v/v); yield 70%; mp. 152–154 °C; IR (KBr) ν [cm$^{-1}$]: 3017, 2920, 1732, 1679, 1605, 1485, 1426, 1373, 1296, 1249, 1195; $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): δ 2.33 (s, 3H, CH$_3$), 2.43 (s, 3H, OCH$_3$), 3.76 (t, 2H, CH$_2$), 3.96 (t, 2H, CH$_2$), 6.97 (d, $J = 4.5$ Hz, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 8.22 (d, $J = 4.5$ Hz, 1H, Ar-H); Anal. Calcd. for C$_{11}$H$_{13}$N$_3$O$_2$: C, 60.26; H, 5.98; N, 19.17; Found: C, 60.08; H, 5.81; N, 18.96.

#### 1-Butyryl-3-(4-methyl-2-pyridyl)imidazolidin-2-one (3c).

Compound 3c was purified by use of chromatotron (eluents: chloroform); yield 54%; mp. 82–83 °C; IR (KBr) ν [cm$^{-1}$]: 3058, 2967, 2878, 1734, 1677, 1603, 1560, 1374, 1323, 1246, 1190; $^1$H-NMR (500 MHz, CDCl$_3$): δ 1.00 (t, 3H, CH$_3$), 1.73 (sextet, 2H, CH$_2$), 2.38 (s, 3H, CH$_3$), 2.97 (t, 2H, CH$_2$), 3.93 (t, 2H, CH$_2$), 4.10 (t, 2H, CH$_2$), 6.87 (d, $J = 5.4$ Hz, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 8.19 (d, $J = 5.4$ Hz, 1H, Ar-H); Anal. Calcd. for C$_{13}$H$_{17}$N$_3$O$_2$: C, 63.14; H, 6.93; N, 16.99; Found: C, 62.99; H, 6.81; N, 16.89.

#### 1-Acetyl-3-(4-tert-butyl-2-pyridyl)imidazolidin-2-one (3d).

Compound 3d was purified by use of chromatotron (eluents: dichloromethane/ethyl acetate, 4:1, v/v); yield 59%; mp. 163–166 °C; IR (KBr) ν [cm$^{-1}$]: 2970, 2919, 2870, 1726, 1685, 1598, 1547, 1484, 1420, 1374, 1293, 1252, 1120; $^1$H-NMR (200 MHz, CDCl$_3$): δ 1.35 (s, 9H, C(CH$_3$)$_3$), 2.60 (s, 3H, CH$_3$), 3.94–3.98 (m, 2H, CH$_2$), 4.10–4.14 (m, 2H, CH$_2$); Anal. Calcd. for C$_{14}$H$_{19}$N$_3$O$_2$: C, 64.35; H, 6.93; N, 16.99; Found: C, 64.17; H, 6.81; N, 15.86.

#### 1-Acetyl-3-(4-phenyl-2-pyridyl)imidazolidin-2-one (3e).

Compound 3e was purified by use of flash column chromatography (eluents: chloroform/ethyl acetate:methanol, 5:2:1, v/v/v); yield 76%; mp.
156–157 °C; IR (KBr) ν [cm\(^{-1}\)]: 3067, 3021, 2960, 2918, 1747, 1685, 1594, 1545, 1474, 1420, 1377, 1368, 1308, 1251; \(^1\)H-NMR (200 MHz, (CD\(_3\))\(_2\)SO): δ 2.45 (s, 3H, CH\(_3\)), 3.77–3.85 (m, 2H, CH\(_2\)), 3.99–4.07 (m, 2H, CH\(_2\)), 7.45–7.58 (m, 4H, Ar-H), 7.72–7.77 (m, 2H, Ar-H), 8.43–8.48 (m, 2H, Ar-H), \(^{13}\)C-NMR (50 MHz, (CD\(_3\))\(_2\)SO): δ 23.98, 38.55, 41.05, 110.29, 117.28, 127.07 (two overlapping signals), 129.58 (two overlapping signals), 129.66, 137.72, 148.68, 149.18, 152.32, 153.02, 170.09; Anal. Calcd. for C\(_{16}\)H\(_{15}\)N\(_3\)O\(_2\): C, 68.31; H, 5.37; N, 14.94; Found: C, 68.22; H, 5.23; N, 14.78.

1-Butyryl-3-(4-phenyl-2-pyridyl)imidazolidin-2-one (3f). Compound 3f was purified by use of chromatotron (eluent: chloroform); yield 70%; mp. 155–156 °C; IR (KBr) ν [cm\(^{-1}\)]: 3110, 3069, 2962, 2918, 2872, 1735, 1682, 1593, 1474, 1374, 1248, 1224; \(^1\)H-NMR (500 MHz, CDCl\(_3\)): δ 1.02 (t, 3H, CH\(_3\)), 1.75 (sextet, 2H, CH\(_2\)), 3.00 (t, 2H, CH\(_2\)), 3.97 (t, 2H, CH\(_2\)), 4.16 (t, 2H, CH\(_2\)), 7.28 (d, \(J = 5.4\) Hz, 1H, Ar-H), 7.43–7.50 (m, 3H, Ar-H), 7.70 (d, \(J = 7.8\) Hz, 2H, Ar-H), 8.39 (d, \(J = 5.4\) Hz, 1H, Ar-H), 8.53 (s, 1H, Ar-H); Anal. Calcd. for C\(_{18}\)H\(_{19}\)N\(_3\)O\(_2\): C, 69.88; H, 6.19; N, 13.58; Found: C, 69.79; H, 6.02; N, 13.50.

1-Acetyl-3-[4-(3-phenylpropyl)-2-pyridyl]imidazolidin-2-one (3g). Compound 3g was purified by use of chromatotron (eluent: dichloromethane/ethyl acetate, 4:1, v/v); yield 64%; mp. 89–90 °C; IR (KBr) ν [cm\(^{-1}\)]: 3060, 3024, 2943, 2925, 2858, 1722, 1683, 1601, 1560, 1483, 1438, 1402, 1379, 1305, 1278, 1254; \(^1\)H-NMR (500 MHz, (CD\(_3\))\(_2\)SO): δ 1.90 (q, 2H, CH\(_2\)), 2.45 (s, 3H, CH\(_3\)), 2.60–2.64 (m, 2×CH\(_2\)), 3.79 (t, 2H, CH\(_2\)), 3.98 (t, 2H, CH\(_2\)), 7.02 (d, \(J = 4.9\) Hz, 1H, Ar-H), 7.16–7.29 (m, 5H, Ar-H), 8.07 (s, 1H, Ar-H), 8.27 (d, \(J = 4.9\) Hz, 1H, Ar-H); Anal. Calcd. for C\(_{19}\)H\(_{21}\)N\(_3\)O\(_2\): C, 70.57; H, 6.55; N, 12.99; Found: C, 70.43; H, 6.51; N, 13.20.

1-Acetyl-3-(4-methoxy-2-pyridyl)imidazolidin-2-one (3h). Compound 3h was purified by use of chromatotron (eluent: dichloromethane/ethyl acetate, 4:1, v/v); yield 87%; mp. 139–140 °C; IR (KBr) ν [cm\(^{-1}\)]: 3023, 2983, 2920, 1731, 1687, 1594, 1566, 1455, 1406, 1382, 1309, 1257, 1223, 1179; \(^1\)H-NMR (500 MHz, (CD\(_3\))\(_2\)SO): δ 2.44 (s, 3H, CH\(_3\)), 3.78 (t, 2H, CH\(_2\)), 3.84 (s, 3H, OCH\(_3\)), 3.97 (t, 2H, CH\(_2\)), 6.77 (dd, \(J_1 = 1.9\) Hz, \(J_2 = 5.9\) Hz, 1H, Ar-H), 7.77 (d, \(J = 1.9\) Hz, 1H, Ar-H), 8.19 (d, \(J = 5.9\) Hz, 1H, Ar-H); Anal. Calcd. for C\(_{11}\)H\(_{13}\)N\(_3\)O\(_3\): C, 56.16; H, 5.57; N, 17.86; Found: C, 55.99; H, 5.51; N, 17.80.

1-Butyryl-3-(4-methoxy-2-pyridyl)imidazolidin-2-one (3i). Compound 3i was purified by use of chromatotron (eluent: chloroform); yield 66%; mp. 112–113 °C; IR (KBr) ν [cm\(^{-1}\)]: 3112, 3016, 2943, 2921, 2875, 1736, 1691, 1595, 1564, 1482, 1398, 1375, 1255, 1216, 1178; \(^1\)H-NMR (200 MHz, CDCl\(_3\)): δ 1.01 (t, 3H, CH\(_3\)), 1.72 (sextet, 2H, CH\(_2\)), 2.98 (t, 2H, CH\(_2\)), 3.89 (s, 3H, OCH\(_3\)), 3.92–4.00 (m, 2H, CH\(_2\)), 4.07–4.16 (m, 2H, CH\(_2\)), 6.61 (dd, \(J_1 = 2.2\) Hz, \(J_2 = 5.9\) Hz, 1H, Ar-H), 7.86 (d, \(J = 2.2\) Hz, 1H, Ar-H), 8.14 (d, \(J = 5.9\) Hz, 1H, Ar-H); Anal. Calcd. for C\(_{13}\)H\(_{17}\)N\(_3\)O\(_3\): C, 59.30; H, 6.51; N, 15.96; Found: C, 59.21; H, 6.46; N, 16.00.

1-Acetyl-3-(4-benzyloxy-2-pyridyl)imidazolidin-2-one (3j). Compound 3j was purified by use of chromatotron (eluent: chloroform/ethyl acetate, 4:1, v/v); yield 70%; mp. 154–155 °C; IR (KBr) ν [cm\(^{-1}\)]: 3101, 3069, 3027, 2916, 1743, 1737, 1673, 1596, 1563, 1481, 1452, 1386, 1318, 1255, 1215, 1011, 868; \(^1\)H-NMR (500 MHz, (CD\(_3\))\(_2\)SO): δ 2.45 (s, 3H, OCH\(_3\)), 3.78 (t, 2H, CH\(_2\)), 3.98 (t, 2H, CH\(_2\)), 5.21 (s, 2H, OCH\(_3\)), 6.86 (dd, \(J_1 = 1.9\) Hz, \(J_2 = 5.9\) Hz, 1H, Ar-H), 7.36–7.49 (m, 5H, Ar-H),
7.87 (d, $J = 1.9$ Hz, 1H, Ar-H), 8.21 (d, $J = 5.9$ Hz, 1H, Ar-H); Anal. Calcd. for C$_{17}$H$_{17}$N$_3$O$_3$: C, 65.58; H, 5.50; N, 13.50; Found: C, 65.42; H, 5.28; N, 13.71.

3.2. Synthesis of $N$-(2-Pyridyl)imidazolidine-2-thiones 4a–c, e–g (General Procedure)

Appropriate $N$-(2-pyridyl)imidazolidin-2-one (0.001 mol) was refluxed with Lawesson’s reagent (0.00075 mol) in anhydrous toluene (8 mL) for 12 h and concentrated under reduced pressure. The residue was extracted with chloroform (2 × 20 mL), dried with anhydrous MgSO$_4$, filtrated and concentrated under reduced pressure. Product was separated from oily residue by use of chromatotron. According above given procedure were obtained following compounds:

**1-(2-Pyridyl)imidazolidine-2-thione (4a).** Compound 4a was purified by use of chromatotron (eluent: chloroform/ethyl acetate/acetone, 8:1:1, v/v/v); yield 50%; mp. 99–102 °C; IR (KBr) $\nu$ [cm$^{-1}$]: 3196, 3036, 2993, 1591, 1567, 1533, 1466, 1438, 1413, 1347, 1228; $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 3.68 (t, 2H, CH$_2$); 4.44 (t, 2H, CH$_2$); 6.96 (bs, 1H, NH); 7.01–7.07 (m, 1H, Ar-H); 7.64–7.73 (m, 1H, Ar-H); 8.33–8.36 (m, 1H, Ar-H); 8.93 (d, $J = 8.0$ Hz, 1H, Ar-H); $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 40.93, 49.43, 116.33, 119.62, 136.69, 147.32, 152.32, 181.27; Anal. Calcd. for C$_8$H$_9$N$_3$S: C, 53.61; H, 5.06; N, 23.44; Found: C, 53.54; H, 4.92; N, 23.37.

**1-(6-Methyl-2-pyridyl)imidazolidine-2-thione (4b).** Compound 4b was purified by use of chromatotron (eluent: dichloromethane/ethyl acetate, 1:1, v/v); yield 31%; mp. 133–135 °C; IR (KBr) $\nu$ [cm$^{-1}$]: 3222, 3101, 3029, 2974, 1588, 1519, 1456, 1397, 1346, 1254, 1231; $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): $\delta$ 2.41 (s, 3H, CH$_3$), 3.53 (t, 2H, CH$_2$), 4.26 (t, 2H, CH$_2$), 6.97 (d, $J = 7.3$ Hz, 1H, Ar-H), 7.64 (t, 1H, Ar-H), 8.60 (d, $J = 8.4$ Hz, 1H, Ar-H), 9.00 (s, 1H, NH); $^{13}$C-NMR (50 MHz, (CD$_3$)$_2$SO): $\delta$ 24.25, 41.05, 49.09, 113.18, 118.54, 137.04, 152.14, 156.09, 180.19; Anal. Calcd. for C$_9$H$_{11}$N$_3$S: C, 55.93; H, 5.74; N, 21.74; Found: C, 55.86; H, 5.64; N, 21.48.

**1-(5-Methyl-2-pyridyl)imidazolidine-2-thione (4c).** Compound 4c was purified by use of chromatotron (eluent: dichloromethane/ethyl acetate, 7:3, v/v); yield 51%; mp. 200–203 °C; IR (KBr) $\nu$ [cm$^{-1}$]: 3271, 2969, 1608, 1570, 1514, 1479, 1388, 1341, 1239, 1217; $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): $\delta$ 2.26 (s, 3H, CH$_3$), 3.53 (t, 2H, CH$_2$), 4.24 (t, 2H, CH$_2$), 7.59 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.5$ Hz, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 8.67 (d, $J = 8.5$ Hz, 1H, Ar-H), 8.96 (s, 1H, NH); $^{13}$C-NMR (50 MHz, (CD$_3$)$_2$SO): $\delta$ 17.52, 40.65, 49.12, 115.84, 128.49, 137.28, 147.28, 150.70, 180.15; Anal. Calcd. for C$_9$H$_{11}$N$_3$S: C, 55.93; H, 5.74; N, 21.74; Found: C, 55.81; H, 5.63; N, 21.68.

**1-(4-Tert-butyl-2-pyridyl)imidazolidine-2-thione (4e).** Compound 4e was purified by use of chromatotron (eluent: dichloromethane/ethyl acetate, 7:3, v/v); yield 50%; mp. 160–163 °C; IR (KBr) $\nu$ [cm$^{-1}$]: 3197, 3018, 2962, 2927, 2859, 1602, 1548, 1521, 1482, 1412, 1311, 1236, 1119, 830, 553; $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ 1.34 (s, 9H, 3×CH$_3$), 3.68 (t, 2H, CH$_2$), 4.46 (t, 2H, CH$_2$), 6.76 (br.s, 1H, NH), 7.06 (dd, $J_1 = 1.6$ Hz, $J_2 = 5.5$ Hz, 1H, Ar-H), 8.25 (d, $J = 5.5$ Hz, 1H, Ar-H), 9.01 (d, $J = 1.6$ Hz, 1H, Ar-H); $^{13}$C-NMR (50 MHz, CDCl$_3$): $\delta$ 31.02 (three overlapping signals), 35.73, 41.52, 50.06, 114.33, 117.67, 147.21, 152.85, 161.89, 181.86; Anal. Calcd. for C$_{12}$H$_{17}$N$_3$S: C, 61.24; H, 7.28; N, 17.85; Found C, 61.02; H, 6.18; N, 17.78.
1-(4-Phenyl-2-pyridyl)imidazolidine-2-thione (4f). Compound 4f was purified by use of chromatotron (eluent: dichloromethane/ethyl acetate, 4:1, v/v); yield 51%; mp. 201–202 °C; IR (KBr) [cm\(^{-1}\)]: 3204, 2969, 1597, 1532, 1466, 1412, 1230; \(^1\)H-NMR (200 MHz, (CD\(_3\))\(_2\)SO): δ 3.58 (t, 2H, CH\(_2\)), 4.33 (t, 2H, CH\(_2\)), 7.44–7.60 (m, 4H, Ar-H), 7.73–7.77 (m, 2H, Ar-H), 8.43 (d, J = 5.2 Hz, 1H, Ar-H), 9.16 (s, 1H, NH), 9.25 (s, 1H, Ar-H); \(^{13}\)C-NMR (50 MHz, (CD\(_3\))\(_2\)SO): δ 41.06, 49.12, 113.36, 117.10, 127.01 (two overlapping signals), 129,58 (three overlapping signals), 137.82, 147.69, 148.29, 153.54, 180.19; Anal. Calcd. for C\(_{14}\)H\(_{13}\)N\(_3\)S: C, 65.85; H, 5.13; N, 16.46; Found: C, 65.78; H, 5.04; N, 16.24.

1-(6-Methoxy-2-pyridyl)imidazolidine-2-thione (4g). Compound 4g was purified by use of chromatotron (eluent: chloroform); yield 43%; mp. 186–190 °C; IR (KBr) [cm\(^{-1}\)]: 3365, 3008, 2947, 1594, 1584, 1431, 1397, 1361, 1247; \(^1\)H-NMR (500 MHz, (CD\(_3\))\(_2\)SO): δ 3.56 (t, 2H, CH\(_2\)), 3.84 (s, 3H, OCH\(_3\)), 4.32 (t, 2H, CH\(_2\)), 6.53 (d, J = 7.8 Hz, 1H, Ar-H), 7.68 (t, 1H, Ar-H), 8.47 (d, J = 7.8 Hz, 1H, Ar-H), 9.05 (s, 1H, NH); \(^{13}\)C-NMR [50 MHz, (CD\(_3\))\(_2\)SO]: δ 39.40, 48.88, 53.20, 104.42, 107.59, 139.81, 150.72, 162.09, 179.98; Anal. Calcd. for C\(_9\)H\(_{11}\)N\(_3\)OS: C, 51.65; H, 5.30; N, 20.08; Found: C, 51.52; H, 5.24; N, 19.79.

3.3. Synthesis of Copper(II) Complexes 5a–8k (General Procedure)

To a solution of appropriate ligand in 5 mL of ethanol or methanol was added dropwise at ambient temperature, copper(II) chloride dissolved in 1 mL of ethanol or methanol (in 1:1 molar ratio). The solution was left at room temperature and then the solvent was slowly evaporated. The resulting precipitate (a few minutes to 48 h) was filtered and washed with ethanol or methanol and dried in a desiccator. The following complexes were prepared according to above given procedure:

Dichloro[1-(2-pyridyl)imidazolidin-2-one]copper(II) (5a). Solvent: ethanol, dark green crystals, yield 55%; mp. 241–245 °C; IR (KBr) [cm\(^{-1}\)]: 3251, 3126, 2923, 1675, 1606, 1474, 1451, 1436, 1317, 1284, 1170, 769; Anal. Calcd. for C\(_8\)H\(_9\)Cl\(_2\)CuN\(_3\)O (297.63): C, 32.28; H, 3.05; N, 14.12; Found: C, 32.14; H, 2.91; N, 13.79.

Dichloro[1-(6-methyl-2-pyridyl)imidazolidin-2-one]copper(II) (5b). Solvent: methanol, dark brown crystals; mp. 211–215 °C; IR (KBr) [cm\(^{-1}\)]: 3316, 3069, 2920, 1662, 1604, 1494, 1443, 1351, 1285, 1087; Anal. Calcd. for C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)O (311.66): C, 34.68; H, 3.56; N, 13.48; Found: C, 34.42; H, 3.50; N, 13.28.

Crystal data for 5b CCDC no. 986196: C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)O, M = 311.65, monoclinic, space group P2\(_1\)/n (no. 14), Z = 4, a = 6.7379(2) Å, b = 16.9634(3) Å, c = 9.9351(2) Å, β = 105.290(2), V = 1095.36(4) Å\(^3\), T = 100 K, \(\mu\) (Mo Kα) = 2.460 mm\(^{-1}\), 12880 reflections measured, 2816 unique (\(R_{int} = 0.0200\)) which were used in all calculations. The final wR\(_2\) was 0.0630 (all data) and R\(_1\) was 0.0217 [I > 2σ (I)].

Dichloro[1-(4-methyl-2-pyridyl)imidazolidin-2-one]copper(II) (5c). Solvent: methanol, light green crystals, yield 65%; mp. 237–238 °C; IR (KBr) [cm\(^{-1}\)]: 3202, 1658, 1625, 1508, 1480, 1461, 1317, 1290, 1249, 1024, 828, 818, 742; Anal. Calcd. for C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)O (311.66): C, 34.68; H, 3.56; N, 13.48; Found: C, 34.42; H, 3.46; N, 13.17.
Dichloro[1-(4-methoxy-2-pyridyl)imidazolidin-2-one]copper(II) (5d). Solvent: ethanol, green crystals, yield 47%; mp. 223–227 °C; IR (KBr) v [cm\(^{-1}\)]: 3185, 2975, 1678, 1619, 1561, 1485, 1474, 1455, 1294, 1062, 1029, 833, 751, 737; Anal. Calcd. for C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)O\(_2\) (327.65): C, 32.99; H, 3.38; N, 12.82; Found: C, 32.86; H, 3.32; N, 12.48.

Dichloro[1-(4-ethoxy-6-methyl-2-pyridyl)imidazolidin-2-one]copper(II) (5e). Solvent: ethanol, brown crystals, yield 87%; mp. 189–193 °C; IR (KBr) v [cm\(^{-1}\)]: 3336, 2985, 1673, 1612, 1459, 1430, 1300, 1205, 1154, 1047, 851, 837, 744, 715, 636; Anal. Calcd. for C\(_{11}\)H\(_{15}\)Cl\(_2\)CuN\(_3\)O\(_2\) (355.71): C, 37.14; H, 4.25; N, 11.81; Found: C, 37.02; H, 4.17; N, 11.68.

Dichloro[1-(2-pyridyl)imidazolidine-2-thione]copper(II) (5f). Solvent: ethanol, dark green crystals, yield 74%; mp. 195–198 °C; IR (KBr) v [cm\(^{-1}\)]: 3198, 1601, 1575, 1540, 1466, 1440, 1353, 1323, 1238, 777, 670, 543; Anal. Calcd. for C\(_8\)H\(_9\)Cl\(_2\)CuN\(_3\)S (313.69): C, 30.63; H, 2.89; N, 13.40; Found: C, 30.52; H, 2.86; N, 13.76.

Dichloro[1-(6-methyl-2-pyridyl)imidazolidine-2-thione]copper(II) (5g). Solvent: ethanol, dark green crystals, yield 65%; mp. 230–233 °C; IR (KBr) v [cm\(^{-1}\)]: 3322, 3064, 1662, 1604, 1462, 1444, 1351, 1286, 1087, 801, 747, 734; Anal. Calcd. for C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)S (327.72): C, 32.98; H, 3.38; N, 12.82; Found: C, 32.88; H, 3.30; N, 12.58.

Dichloro[1-(5-methyl-2-pyridyl)imidazolidine-2-thione]copper(II) (5h). Solvent: ethanol, dark green crystals, yield 59%; mp. 186–190 °C; IR (KBr) v [cm\(^{-1}\)]: 3202, 3058, 2962, 2912, 1613, 1539, 1504, 1429, 1385, 1321, 1232, 1053, 821; Anal. Calcd. for C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)S (327.71): C, 32.98; H, 3.38; N, 12.82; Found: C, 32.84; H, 3.27; N, 12.61.

Dichloro[1-(4-methyl-2-pyridyl)imidazolidine-2-thione]copper(II) (5i). Solvent: methanol, dark green crystals; mp. 179–181 °C; IR (KBr) v [cm\(^{-1}\)]: 3174, 3070, 1618, 1566, 1547, 1440, 1347, 1239; Anal. Calcd. for C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)S (327.71): C, 32.98; H, 3.38; N, 12.82; Found: C, 32.84; H, 3.32; N, 12.78.

Crystal data for 5h CCDC no. 986201: C\(_9\)H\(_{11}\)Cl\(_2\)CuN\(_3\)S, \(M = 327.71\), triclinic, space group \(P-1\) (no. 2), \(Z = 2\), \(a = 8.1363(3)\) Å, \(b = 9.0505(4)\) Å, \(c = 9.9441(3)\) Å, \(\alpha = 63.452(4)\), \(\beta = 77.213(3)\), \(\gamma = 69.989(4)\), \(V = 613.46(4)\) Å\(^3\), \(T = 296\) K, \(\mu(\text{CuK\(\alpha\)}) = 7.908\) mm\(^{-1}\), 12399 reflections measured, 2531 unique \((R\text{int} = 0.0378)\) which were used in all calculations. The final \(wR2\) was 0.0942 (all data) and \(R1\) was 0.0318 \([I > 2\sigma(I)]\).

Dichloro[1-(4-tert-butyl-2-pyridyl)imidazolidine-2-thione]copper(II) (5j). Solvent: methanol, dark green crystals, yield 76%; mp. 165–168 °C; IR (KBr) v [cm\(^{-1}\)]: 3163, 3054, 2957, 2923, 1615, 1554, 1536, 1442, 1294, 1247, 1020, 863, 843; Anal. Calcd. for C\(_{12}\)H\(_{17}\)Cl\(_2\)CuN\(_3\)S (369.79): C, 38.97; H, 4.63; N, 11.36; Found: C, 38.92; H, 4.58; N, 11.21.
Crystal data for 5j CCDC no. 986094: C_{12}H_{17}Cl_{2}CuN_{3}S, M = 369.79, orthorhombic, space group Pbca (no. 61), Z = 8, a = 14.6475(9) Å, b = 11.3493(8) Å, c = 18.1891(13) Å, V = 3023.7(4) Å³, T = 130 K, μ(CuKα) = 6.490 mm⁻¹, 16551 reflections measured, 3117 unique (R_{int} = 0.0944) which were used in all calculations. The final wR₂ was 0.1678 (all data) and R₁ was 0.0583 (I > 2σ(I)). In the diffraction pattern reflections with l = 2n + 1 were weak. The structure is strongly disordered with the complex molecule adopting three different overlapping orientations. The main orientation has an occupancy of 0.689(4) and the remaining ones 0.153(4) and 0.158(4). The atoms forming the minor orientation of the molecule were refined with a common isotropic temperature factor, except Cu, Cl and S atoms which were refined anisotropically. The geometry of the molecules in minor orientation was restricted to be the same as for the major orientation. Some restraints were also imposed on the planar fragments of the molecules.

Dichloro[1-(4-phenyl-2-pyridyl)imidazolidine-2-thione]copper(II) (5k). Solvent: ethanol, dark green, yield 59%; mp. 165–170 °C; IR (KBr) ν [cm⁻¹]: 3207, 3052, 3004, 2960, 1613, 1552, 1466, 1437, 1276, 1236, 763, 696, 556; Anal. Calcd. for C_{14}H_{13}Cl_{2}CuN_{3}S (389.79): C, 43.14; H, 3.36; N, 10.78; Found: C, 42.99; H, 3.26; N, 10.43.

Dichloro[1-(6-methoxy-2-pyridyl)imidazolidin-2-one]copper(II) (6a). Solvent: ethanol, brown crystals, yield 91%; mp. 207–209 °C; IR (KBr) ν [cm⁻¹]: 3316, 3293, 3082, 3030, 2905, 1673, 1606, 1474, 1440, 1295, 1267, 1168, 1117, 1030, 796, 746, 736; Anal. Calcd. for C_{9}H_{11}Cl_{2}CuN_{3}O_{2} (327.65): C, 32.99; H, 3.38; N, 12.82; Found: C, 32.83; H, 3.34; N, 13.16.

Crystal data for 6a CCDC no. 986200: C_{9}H_{11}Cl_{2}CuN_{3}O_{2}, M = 327.65, triclinic, space group P-1 (no. 2), Z = 2, a = 7.3569(8) Å, b = 8.7648(8) Å, c = 9.7086(10) Å, α = 86.242(8), β = 86.557(9), γ = 77.925(9), V = 610.17(11) Å³, T = 293 K, μ(CuKα) = 6.521 mm⁻¹, 7294 reflections measured, 2226 unique (R_{int} = 0.0366) which were used in all calculations. The final wR₂ was 0.1024 (all data) and R₁ was 0.0342 (I > 2σ(I)).

Dichloro[1-(6-ethoxy-2-pyridyl)imidazolidin-2-one]copper(II) (6b). Solvent: ethanol, brown crystals, yield 23%; mp. 199–202 °C; IR (KBr) ν [cm⁻¹]: 3329, 3079, 2982, 2925, 1670, 1605, 1480, 1466, 1451, 1429, 1294, 1264, 1164, 1118, 1034, 1017, 786; Anal. Calcd. for C_{10}H_{13}Cl_{2}CuN_{3}O_{2} (341.68): C, 35.15; H, 3.83; N, 12.30; Found: C, 35.02; H, 3.79; N, 12.63.

Dichloro[1-(6-n-propoxy-2-pyridyl)imidazolidin-2-one]copper(II) (6c). Solvent: ethanol, brown crystals, yield 68%; mp. 185–187 °C; IR (KBr) ν [cm⁻¹]: 3249, 3094, 2958, 2925, 2877, 1712, 1676, 1605, 1474, 1445, 1425, 1294, 1266, 1165, 1113, 1091, 993, 962, 792, 735; Anal. Calcd. for C_{11}H_{15}Cl_{2}CuN_{3}O_{2} (355.71): C, 37.14; H, 4.25; N, 11.81; Found: C, 37.10; H, 4.08; N, 12.08.

Dichloro[1-(6-isopropoxy-2-pyridyl)imidazolidin-2-one]copper(II) (6d). Solvent: ethanol, brown crystals, yield 56%; mp. 211–212 °C; IR (KBr) ν [cm⁻¹]: 3303, 3112, 3056, 2983, 2931, 1672, 1603, 1469, 1441, 1425, 1372, 1293, 1266, 1166, 1115, 1092, 987, 952, 798, 734; Anal. Calcd. for C_{11}H_{15}Cl_{2}CuN_{3}O_{2} (355.71): C, 37.14; H, 4.25; N, 11.81; Found: C, 36.98; H, 4.18; N, 11.80.
Dichloro[1-(6-n-butoxy-2-pyridyl)imidazolidin-2-one]copper(II) (6e). Solvent: ethanol, golden crystals, yield 48%; mp. 187–189 °C; IR (KBr) v [cm⁻¹]: 3229, 3104, 2956, 2871, 1678, 1607, 1467, 1444, 1428, 1294, 1294, 1265, 1166, 1094, 790, 735; Anal. Calcd. for C₁₂H₁₇Cl₂CuN₃O₂ (369.73): C, 38.98; H, 4.63; N, 11.36; Found: C, 38.91; H, 4.56; N, 11.62.

Dichloro[1-(6-methoxy-2-pyridyl)imidazolidine-2-thione]copper(II) (6f). Solvent: ethanol, brown crystals, yield 49%; mp. 149–154 °C; IR (KBr) ν [cm⁻¹]: 3159, 3066, 2953, 2923, 1604, 1543, 1468, 1435, 1418, 1286, 1232, 1129, 787; Anal. Calcd. for C₉H₁₁Cl₂CuN₃OS (343.72): C, 31.45; H, 3.23; N, 12.23; Found: C: 31.38; H, 3.19; N, 11.88.

Dichloro[1,3-bis(4-methyl-2-pyridyl)imidazolidin-2-one]copper(II).H₂O (7). Solvent: methanol, green crystals; mp. 170–172 °C; IR (KBr) ν [cm⁻¹]: 3372, 1635, 1506, 1472, 1436, 1335, 1261, 1195.

Crystal data for 7 CCDC no. 986194: C₁₅H₁₈Cl₂CuN₄O₂, M = 420.77, triclinic, space group P-1 (no. 2), Z = 2, a = 8.9310(7) Å, b = 10.6693(7) Å, c = 10.9789(9) Å, α = 112.749(7), β = 95.298(7), γ = 111.370(7), V = 864.67(11) Å³, T = 293 K, μ(MoKα) = 1.587 mm⁻¹, 7039 reflections measured, 3517 unique (Rᵣᵣ = 0.0181) which were used in all calculations. The final wR₂ was 0.0742 (all data) and R₁ was 0.0287 (I > 2σ(I)).

Dichloro[1,3-bis(2-pyridyl)imidazolidin-2-one]copper(II) (8a). Solvent: ethanol, yellow-green crystals, yield 77%; mp. 265–267 °C; IR (KBr) ν [cm⁻¹]: 3074, 2901, 1679, 1604, 1587, 1463, 1438, 1412, 1351, 1312, 1245, 1138, 781, 752, 740; Anal. Calcd. for C₁₃H₁₂Cl₂CuN₄O (374.71): C, 41.67; H, 3.23; N, 14.95; Found: C, 41.64; H, 3.19; N, 14.92.

Crystal data for 8a CCDC no. 986095: C₂₆H₂₄Cl₄Cu₂N₈O₂, M = 749.43, monoclinic, space group P2₁/n (no. 14), Z = 2, a = 7.83450(10) Å, b = 16.3329(2) Å, c = 10.8358(2) Å, β = 90.7160(10), V = 1386.44(4) Å³, T = 130 K, μ(MoKα) = 1.963 mm⁻¹, 22938 reflections measured, 3444 unique (Rᵣᵣ = 0.0379) which were used in all calculations. The final wR₂ was 0.0665 (all data) and R₁ was 0.0293 (I > 2σ(I)).

Dichloro[1-acetyl-3-(5-methyl-2-pyridyl)imidazolidin-2-one]copper(II) (8b). Solvent: ethanol, green crystals, yield 50%; mp. 233–235 °C; IR (KBr) ν [cm⁻¹]: 3091, 2984, 2927, 1698, 1658, 1468, 1434, 1401, 1323, 1291, 1256, 1042, 962, 839, 740, 617; Anal. Calcd. for C₁₁H₁₃Cl₂CuN₃O₂ (353.69): C, 37.35; H, 3.70; N, 11.88; Found: C, 37.28; H, 3.64; N, 12.18.

Dichloro[1-acetyl-3-(4-methyl-2-pyridyl)imidazolidin-2-one]copper(II) (8c). Solvent: ethanol, green crystals, yield 62%; mp. 222–225 °C; IR (KBr) ν [cm⁻¹]: 3091, 3060, 2986, 1708, 1683, 1622, 1455, 1412, 1372, 1321, 1271, 1192, 1150, 1038, 971, 841, 749, 742, 619, 456; Anal. Calcd. for C₁₁H₁₃Cl₂CuN₃O₂ (353.69): C, 37.35; H, 3.70; N, 11.88; Found: C, 37.28; H, 3.64; N, 12.18.
Dichloro[1-butyryl-3-(4-methyl-2-pyridyl)imidazolidin-2-one]copper(II) (8d). Solvent: ethanol, green crystals, yield 93%; mp. 236–240 °C; IR (KBr) ν [cm⁻¹]: 3123, 3089, 3054, 2960, 2936, 2877, 1705, 1681, 1622, 1455, 1413, 1384, 1322, 1272, 1227, 1211, 1180, 847, 743, 709, 663, 458; Anal. Calcd. for C₁₃H₁₇Cl₂CuN₃O₂ (381.74): C, 40.90; H, 4.49; N, 11.01; Found: C, 40.82; H, 4.42; N, 10.98.

Dichloro[1-acetyl-3-(4-tert-butyl-2-pyridyl)imidazolidin-2-one]copper(II) (8e). Solvent: ethanol, green crystals, yield 53%; mp. 150–155 °C; IR (KBr) ν [cm⁻¹]: 2966, 1662, 1619, 1478, 1445, 1377, 1283, 1063, 734, 617; Anal. Calcd. for C₁₄H₁₉Cl₂CuN₃O₂ (395.77): C, 42.49; H, 4.84; N, 10.62; Found: C, 42.38; H, 4.82; N, 10.31.

Dichloro[1-acetyl-3-(4-phenyl-2-pyridyl)imidazolidin-2-one]copper(II) (8f). Solvent: ethanol, green crystals, yield 95%; mp. 227–233 °C; IR (KBr) ν [cm⁻¹]: 3055, 2962, 2926, 1718, 1673, 1615, 1473, 1436, 1410, 1372, 1278, 1237, 965, 771, 740, 630, 615; Anal. Calcd. for C₁₆H₁₅Cl₂CuN₃O₂ (415.76): C, 46.22; H, 3.64; N, 10.11; Found: C, 46.01; H, 3.61; N, 10.02.

Dichloro[1-butyryl-3-(4-phenyl-2-pyridyl)imidazolidin-2-one]copper(II) (8g). Solvent: ethanol, dark green crystals, yield 77%; mp. 178–184 °C; IR (KBr) ν [cm⁻¹]: 3051, 2963, 2873, 1671, 1616, 1474, 1437, 1409, 1372, 1284, 1222, 1178, 768, 629; Anal. Calcd. for C₁₈H₁₉Cl₂CuN₃O₂ (443.81): C, 48.71; H, 4.32; N, 9.47; Found: C, 48.68; H, 4.26; N, 9.45.

Dichloro{1-acetyl-3-[4-(3-phenylpropyl)-2-pyridyl]imidazolidin-2-one}copper(II) (8h). Solvent: ethanol, dark green crystals, yield 56%; mp. 160–164 °C; IR (KBr) ν [cm⁻¹]: 3078, 2920, 2860, 1713, 1671, 1649, 1623, 1476, 1451, 1420, 1375, 1282, 1245, 966, 735, 701, 615; Anal. Calcd. for C₁₉H₂₁Cl₂CuN₃O₂ (457.84): C, 49.84; H, 4.62; N, 9.18; Found: C, 49.79; H, 4.58; N, 9.46.

Dichloro[1-acetyl-3-(4-methoxy-2-pyridyl)imidazolidin-2-one]copper(II) (8i). Solvent: ethanol, light green crystals, yield 69%; mp. 190–194 °C; IR (KBr) ν [cm⁻¹]: 3143, 3117, 3085, 3030, 2993, 2929, 1709, 1667, 1617, 1477, 146, 1377, 1281, 1232, 1037, 968, 845, 741, 616; Anal. Calcd. for C₁₁H₁₃Cl₂CuN₃O₃ (369.69): C, 35.74; H, 3.54; N, 11.37; Found: C, 35.69; H, 3.46; N, 11.38.

Dichloro[1-butyryl-3-(4-methoxy-2-pyridyl)imidazolidin-2-one]copper(II) (8j). Solvent: ethanol, green crystals, yield 66%; mp. 210–213 °C; IR (KBr): 3104, 2967, 2930, 2873, 1671, 1618, 1468, 1419, 1382, 1285, 1220, 1176, 1048, 842, 738, 708; Anal. Calcd. for C₁₃H₁₇Cl₂CuN₃O₃ (397.74): C, 39.26; H, 4.31; N, 10.56; Found: C, 39.11; H, 4.26; N, 10.35.

Dichloro[1-acetyl-3-(4-benzyloxy-2-pyridyl)imidazolidin-2-one]copper(II) (8k). Solvent: ethanol, green crystals, yield 49%; mp. 195–199 °C; IR (KBr) ν [cm⁻¹]: 3086, 2990, 2923, 1683, 1613, 1480, 1448, 1415, 1378, 1278, 1245, 1036, 1022, 834, 738, 622; Anal. Calcd. for C₁₇H₁₇Cl₂CuN₃O₃ (445.79): C, 45.80; H, 3.84; N, 9.43; Found: C, 45.71; H, 3.76; N, 9.76.

Dichloro[bis[1-(5-methyl-2-pyridyl)imidazolidin-2-one]copper(II)]2H₂O (9). 1-(5-Methyl-2-pyridyl)imidazolidin-2-one (0.1 g; 0.00056 mol) was dissolved in 7 mL of N,N-dimethylformamide and copper(II) chloride (0.144 g, 0.00085 mol) was added. After week of slow evaporation at room temperature green crystals suitable for the X-ray analysis were collected, washed with small amount of...
solvent and dried. Obtained 0.06 g of complex compound 9, yield 43%: C_{18}H_{22}Cl_2CuN_6O_2·2H_2O (524.89); mp. 224–229 °C; IR (KBr) ν [cm\(^{-1}\)]: 3169, 3068, 2915, 1657, 1618, 1576, 1483, 1453, 1319, 1287, 1170, 824, 742.

Crystal data for 9 CCDC no. 986199: (C_{18}H_{22}CuN_6O_2)Cl_2·2(H_2O), M = 524.89, monoclinic, space group C2/c (no. 15), Z = 4, a = 12.3708(7) Å, b = 13.6659(5) Å, c = 13.1220(16) Å, β = 109.417(1), V = 2092.2(3) Å\(^3\), T = 130 K, μ(MoKα) = 1.340 mm\(^{-1}\), 7717 reflections measured, 1832 unique (R_int = 0.0450) which were used in all calculations. The final wR\(^2\) was 0.0803 (all data) and R\(_1\) was 0.0321 (I > 2σ(I)).

Dichloro{bis[1-(4-phenyl-2-pyridyl)imidazolidin-2-one]}copper(II) (10a, 10b). 1-(4-Phenyl-2-pyridyl)imidazolidin-2-one (0.1 g, 0.00042 mol) was dissolved in 7 mL of N,N-dimethylformamide and copper(II) chloride (0.107 g, 0.00063 mol) was added. After two weeks of slow evaporation at room temperature green crystals suitable for the X-ray analysis were collected, washed with small amount of solvent and dried. Obtained 0.06 g of a mixture of complex compounds 10a and 10b, mp. 208–211 °C; IR (KBr) ν [cm\(^{-1}\)]: 3447, 3056, 1669, 1616, 1473, 1446, 1319, 1296, 1070, 1014, 855, 763, 740.

Crystal data for 10a CCDC no. 986198: (C_{28}H_{26}ClCuN_6O_2)Cl·2(H_2O), M = 649.02, triclinic, space group P-1 (no. 2), Z = 2, a = 10.5234(4) Å, b = 11.7728(5) Å, c = 12.5141(4) Å, α = 97.231(3), β = 106.598(3), γ = 108.593(4), V = 1367.46(9) Å\(^3\), T = 100 K, μ(MoKα) = 1.042 mm\(^{-1}\), 14433 reflections measured, 5552 unique (R_int = 0.0169) which were used in all calculations. The final wR\(^2\) was 0.0695 (all data) and R\(_1\) was 0.0263 (I > 2σ(I)).

Crystal data for 10b CCDC no. 986197: (C_{28}H_{26}ClCuN_6O_2)\(_2\)[CuCl_3]\(_0.75\)Cl\(_0.5\)·2.15(H_2O)·C_3H_7NO, M = 1413.85, monoclinic, space group I\(_2\)/a (no. 15), Z = 4, a = 13.8269(3) Å, b = 16.8610(3) Å, c = 25.7704(5) Å, β = 93.988(2), V = 5993.4(2) Å\(^3\), T = 100 K, μ(MoKα) = 1.246 mm\(^{-1}\), 34078 reflections measured, 6096 unique (R_int = 0.0240) which were used in all calculations. The final wR\(^2\) was 0.0827 (all data) and R\(_1\) was 0.0297 (I > 2σ(I)). The [CuCl\(_3\)]\(^2-\) anion and one of the water molecules are located on a twofold axis. The Cu\(_1\) and the Cl atom of the anion in special position occupy their positions in 75% whereas the water molecule in 25%. The remaining Cl atoms fully occupy their positions.

Dichloro{bis[1-(4-methoxy-2-pyridyl)imidazolidin-2-one]}copper(II)H_2O (10c). 1-(4-Methoxy-2-pyridyl)imidazolidin-2-one (0.1 g; 0.00052 mol) was dissolved in 7 mL of N,N-dimethylformamide and copper(II) chloride (0.173 g, 0.00078 mol) was added. After two weeks of slow evaporation at room temperature blue crystals suitable for the X-ray analysis were collected, washed with small amount of solvent and dried. Obtained 0.05 g of complex compound 10c, yield 36%: C_{18}H_{22}Cl_2CuN_6O_4·H_2O (538.87); mp. 214–216 °C; IR (KBr) ν [cm\(^{-1}\)]: 3431, 3176, 2985, 1670, 1615, 1473, 1446, 1319, 1296, 1070, 1014, 855, 763, 740.

Crystal data for 10c CCDC no. 986195: (C_{18}H_{22}ClCuN_6O_4)Cl·H_2O, M = 538.87, monoclinic, space group P2\(_1\) (no. 4), Z = 4, a = 10.9160(1) Å, b = 13.4955(2) Å, c = 15.1544(2) Å, β = 107.429(2), V = 2130.00(5) Å\(^3\), T = 120 K, μ(MoKα) = 1.322 mm\(^{-1}\), 36883 reflections measured, 9877 unique (R_int = 0.0225) which were used in all calculations. The final wR\(^2\) was 0.0576 (all data) and R\(_1\) was 0.0227 (I > 2σ(I)).
4. Conclusions

The X-ray crystallography revealed that the 1-(2-pyridyl)imidazolidin-2-ones 1–3 and 1-(2-pyridyl)imidazolidine-2-thiones 4 behaved as neutral bidentate ligands, bonding to the copper(II) ion through the nitrogen atom of pyridine ring and oxygen or sulfur atom of imidazolidin-2-one(thione) moiety. Analysis of the structure–activity relationships of anticancer activities of the diverse complexes 5-10 revealed that the most active against a panel of 5 human tumor cell lines was dichloro[1-(4-tert-butyl-2-pyridyl)imidazolidine-2-thione]copper(II) (5j), which may act as a “self-activating” chemical nuclease, and therefore, may serve as a lead structure for further development of novel anticancer agents.

Author Contributions

Conceived and designed the project: Franciszek Sączewski and Łukasz Balewski. Performed chemical experiments: Łukasz Balewski and Ewa Borys. Performed X-ray crystal structure analysis: Maria Gdaniec. Designed the biological tests: Patrick J. Bednarski. Performed biological tests: Ewa Borys, Anna Makowska. Wrote the paper: Franciszek Sączewski, Łukasz Balewski, Patrick J. Bednarski. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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**Sample Availability:** Samples of the compounds 1–10 are available from the authors.