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Palladium(II) Pincer Complexes of Functionalized Amides with S-Modified Cysteine and Homocysteine Residues: Cytotoxic Activity and Different Aspects of Their Biological Effect on Living Cells

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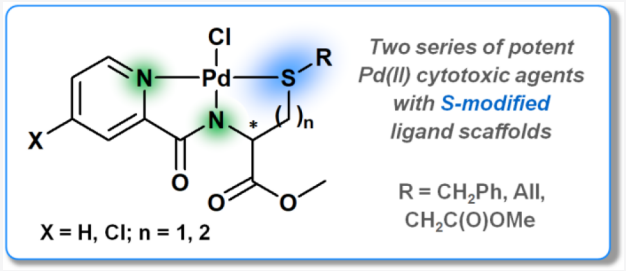
ABSTRACT: In the search for potential new metal-based antitumor agents, two series of nonclassical palladium(II) pincer complexes based on functionalized amides with S-modified cysteine and homocysteine residues have been prepared and fully characterized by 1D and 2D NMR (^{1}H, ^{13}C, COSY, HMQC or HSQC, ^{1}H−^{13}C, and ^{1}H−^{15}N HMBC) and IR spectroscopy and, in some cases, X-ray diffraction. Most of the resulting complexes exhibit a high level of cytotoxic activity against several human cancer cell lines, including colon (HCT116), breast (MCF7), and prostate (PC3) cancers. Some of the compounds under consideration are also efficient in both native and doxorubicin-resistant transformed breast cells HBL100, suggesting the prospects for the creation of therapeutic agents based on the related compounds that would be able to overcome drug resistance. An analysis of different aspects of their biological effects on living cells has revealed a remarkable ability of the S-modified derivatives to induce cell apoptosis and efficient cellular uptake of their fluorescein-conjugated counterpart, confirming the high anticancer potential of Pd(II) pincer complexes derived from functionalized amides with S-donor amino acid pendant arms.



INTRODUCTION

Over a history of about a half-century, pincer complexes have emerged as some of the most prominent organometallic and metal−organic compounds, largely contributing to the development of many sustainable chemical processes.[1] Although catalysis still remains the area of major achievements for this privileged class of metal complexes featuring highly tunable tridentate ligands with a meridional geometry that offer an unprecedented level of control over the complex properties,[2] they have continuously attracted attention in many other fields, including medicinal chemistry.[3] A promising line of research is the creation of new antitumor agents based on pincer-type complexes, which has already afforded a range of highly potent gold, ruthenium, copper, palladium, and platinum derivatives (Figure 1).[4] Some of these complexes have proven their efficiency in *in vivo* experiments.[4e,k,n,o]

Predictably, considerable attention has been paid to Pt(II) compounds since the development of platinum-based chemotherapeutics became a milestone in cancer research. However, the pincer concept seems to be more beneficial for palladium—the closest platinum congener. The point is that palladium(II) complexes exhibit coordination behavior similar to that of their platinum(II) counterparts but are highly susceptible to different deactivation processes in biological media due to much more rapid ligand-exchange processes.[5] A pincer-type ligation can provide firm coordination of Pd(II) ions and thus ensure a high thermodynamic stability of the resulting complexes. At the same time, the tunable nature of a tridentate motif offers ample opportunities to achieve the desired level of kinetic stability.

Recently, our research group has shown the utility of nonclassical pincer ligands based on functionalized carboxamides for the synthesis of highly cytotoxic Pd(II) complexes.[6] It should be noted that pincer ligands with central secondary amide units are of particular interest owing to their readily modifiable molecular architecture and a possibility of rapid expansion of libraries of new compounds by simple modular assembly of building blocks—functionalized carboxylic acids and amines.[7] A rationale behind our project was to provide an N,S-hemilabile coordination of palladium(II) ions by ancillary donor groups, incorporating picolinic or 4-chloropicolinic acid

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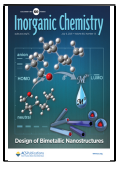

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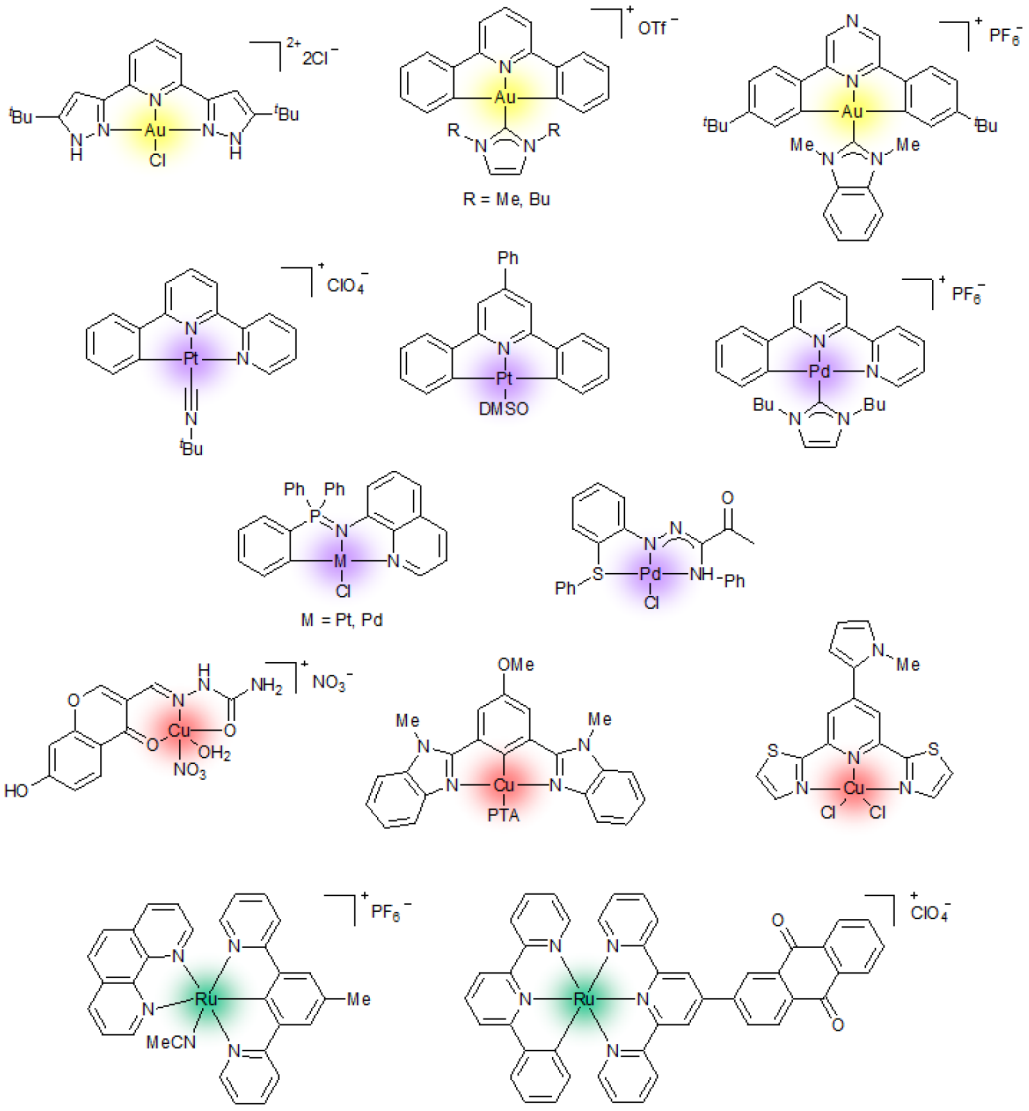

Figure 1. Selected examples of potential antitumor agents based on transition-metal pincer complexes (PTA denotes a quaternized phosphaadamantane derivative).

as an acid component and an S-donor amino acid (*S*-methyl-L-cysteine or L-methionine) derivative as an amino component (compounds **I**, Figure 2).

The importance of amino acids in tumor metabolism has generated great interest in the development of strategies targeting or involving them in other functions for cancer therapy.[8] S-donor amino acids play an important role in the biological activity of the platinum-based antitumor agents and their palladium analogues.[9] Moreover, the introduction of a sulfur ancillary donor group into the ligand framework can facilitate improvement of the bioavailability of potential Pd(II) chemotherapeutics, which often suffers from the strong binding with sulfur-containing biomolecules such as glutathione.[41] As a confirmation of our rationale, the analogues of complexes **I** bearing histidine pendant arms with N-donor ancillary groups (compounds **II**, Figure 2) were shown to exhibit very low antiproliferative activity against several human cancer cell lines or even facilitated the growth of cancer cells.[6] Another avenue used to modify the ligand framework was the variation of an acid component (N-modification).[10] The resulting pincer complexes with S,N,S- and S,N,P-donor sets (compounds **III**–**V**) appeared to be inferior in cytotoxic activity to their S,N,N-counterparts **I** derived from picolinylamides.[6] Finally, palladium(II) pincer complexes that featured a complementary S,N,N-coordination but were deprived of amino acid residues (compounds **VI** and **VII**) also displayed lower cytotoxic effects in comparison to **I**.[11] To further explore the anticancer potential of these types of Pd(II) pincer complexes, it seemed reasonable to extend the structural motif of functionalized amide ligands to S-modified derivatives bearing various substituents at the sulfur donor center of the amino acid residue (S-modification of the ligand framework).

Herein, we report on the synthesis of new representatives of cytotoxic Pd(II) pincer complexes based on picolinylamides with amino acid pendant arms, where the latter are comprised by S-substituted cysteine derivatives or their homologues bearing an additional methylene unit—S-modified homocysteine residues. Although homocysteine is a nonproteinogenic amino acid, it plays a crucial role in methionine metabolism and serves as a source of cysteine in the body. The discussion of cytotoxic properties of the resulting complexes against several human cancer cell lines is supplemented by a deeper analysis of the action mode of these promising types of potential antitumor agents.

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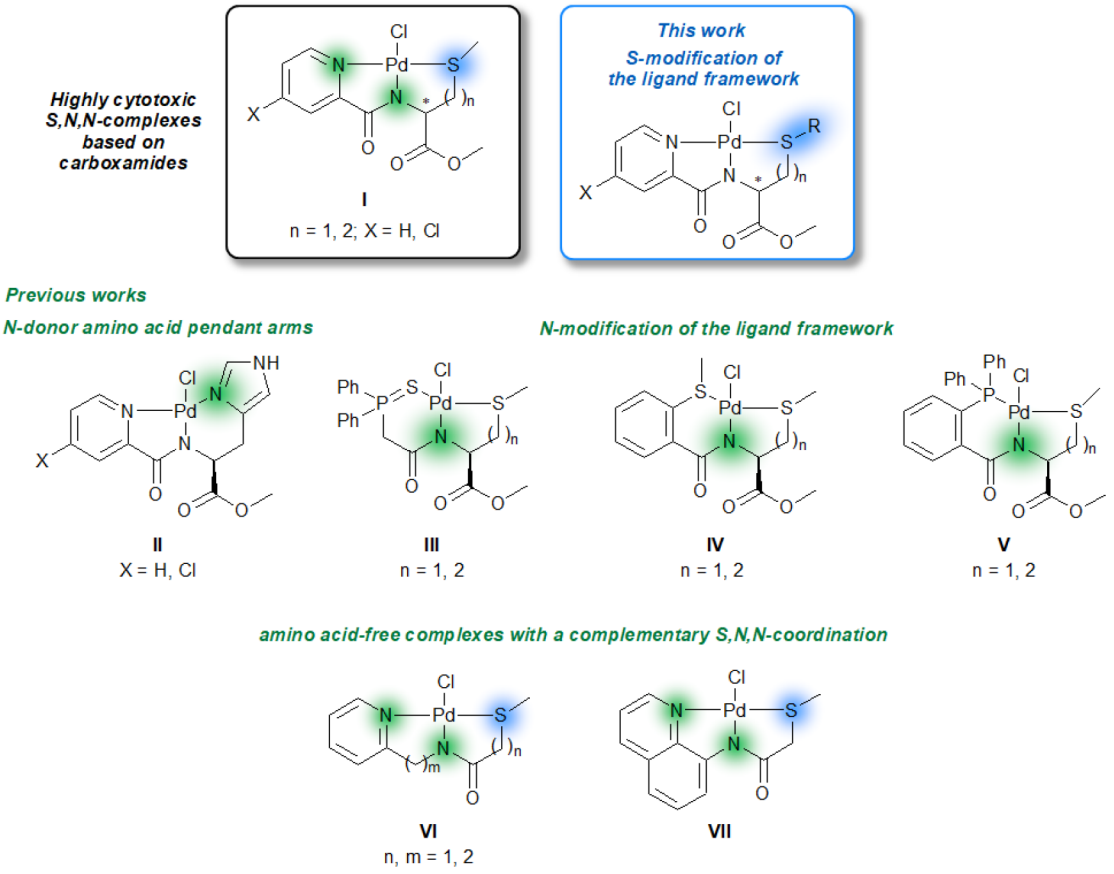
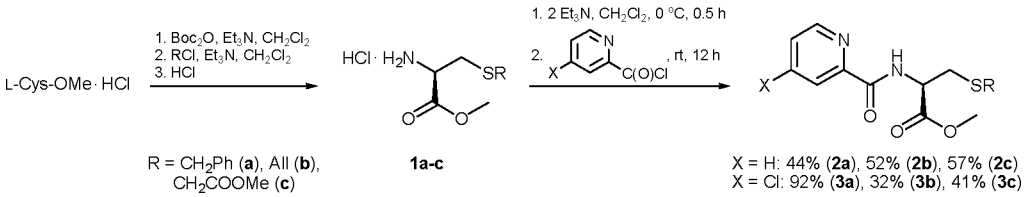
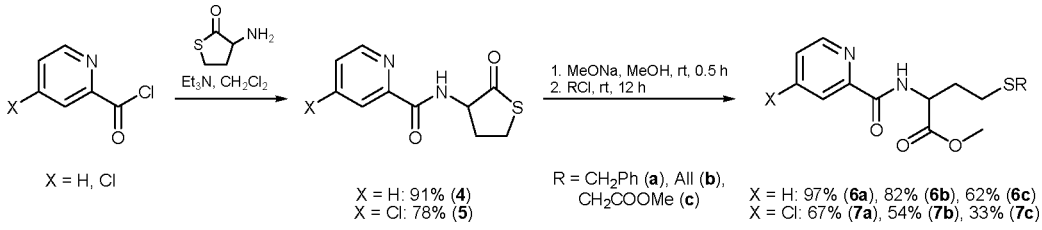


Figure 2. Nonclassical palladium(II) pincer complexes with functionalized carboxamide ligands: strategies for tuning cytotoxic properties.

Scheme 1. Synthesis of Cysteine-Based Ligands 2 and 3



Scheme 2. Synthesis of Homocysteine-Based Ligands 6 and 7



RESULTS AND DISCUSSION

Despite the ostensible similarity of the target compounds to the key prototypes, the synthesis of S-modified ligands required the development of new versatile approaches, especially in the case of functionalized carboxamides with elongated S-donor pendant arms.

For the synthesis of the target cysteine-based ligands, L-cysteine methyl ester hydrochloride was sequentially treated with di-*tert*-butyl dicarbonate and different alkyl halides followed by deprotection, which afforded S-modified cysteine derivatives **1a−c** bearing benzyl, allyl, and methoxycarbonyl-methyl substituents (Scheme 1). A short panel of the alkylating agents was chosen to endow the ancillary sulfur donor with different steric and electronic profiles. Obviously, this strategy is not restricted to these particular examples and can open the way to a great variety of S-modified cysteine derivatives, providing the proper choice of reaction conditions. The condensation of free amines generated *in situ* from hydrochlorides **1a−c** with picolinyl and 4-chloropicolinyl chlorides yielded functionalized amide ligands **2a−c** and **3a−c**, respectively (Scheme 1). It is noteworthy that in this study, owing to the application of selective synthetic approaches, the

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aforementioned acylating agents were used in the individual forms (see the Experimental Section).

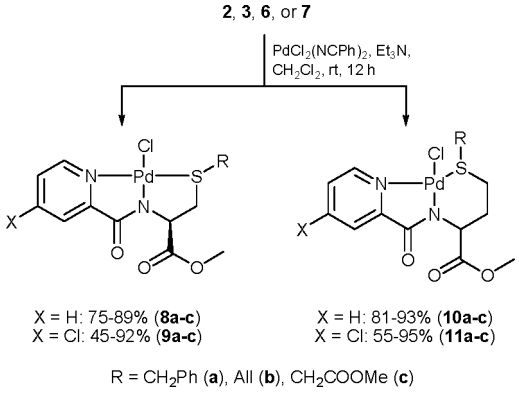
A convenient key precursor for the synthesis of ligands having elongated coordination arms with different substituents at the sulfur donor atom appeared to be D,L-homocysteine thiolactone. Its reactions with picolinyl and 4-chloropicolinyl chlorides smoothly afforded amides **4** and **5** (Scheme 2). Homocysteine derivatives **4** and **5** readily underwent the opening of a thiolactone ring under the action of MeONa. The *in situ* generated sodium salts of methyl homocysteinates were alkylated with different alkyl halides to afford S-modified homocysteine ligands **6a−c** and **7a−c** in generally good to high yields (Scheme 2). As in the case of the cysteine-based derivatives, the alkylating agents used were benzyl, allyl, and methoxycarbonylmethyl chlorides. Although the target S-modified homocysteine derivatives were obtained in the racemic forms, it is remarkable that the suggested approach can furnish a whole range of new pincer ligands from a single key precursor.

The identities of all the new compounds were supported by a combination of spectroscopic techniques and elemental analyses. The IR spectra of ligands **2**, **3**, **6**, and **7** show the characteristic absorption bands of the secondary amide units, associated mainly with C═O and N−H stretching in the ranges of 1676−1683 and 3373−3383 cm^{-1}, respectively, and in-plane N−H bending (amide II band) at ca. 1517 cm^{-1}. The C═O stretches of the ester groups are observed at 1739−1746 cm^{-1}. The ^1H NMR spectra of the functionalized amide ligands contain, among other signals, the expected downfield doublet resonances of NH protons (δ_H 8.46−8.74 ppm) with coupling constants of about 8.4 Hz, which arise from the interaction with methine protons. The latter appear as multiplets in the narrow range of 4.86−5.08 ppm. Note that in some cases the proton signals of prochiral methylene units give rise to separate signals. The hydrogen and carbon resonances of homocysteine derivatives **6a** and **7b**,**c** were unambiguously assigned on the basis of the 2D NMR experiments (COSY, HMBC, and HMQC or HSQC pulse sequences) (see, for example, Figures S1−S15 in the Supporting Information). In addition, the chemical shifts of the nitrogen nuclei in representative ligands **6a** and **7b** were defined from the $^1H-^{15}N$ HMBC correlation spectra (Figure S16 in the Supporting Information). The amide nitrogen resonances were readily identified due to the one-bond direct NH responses at about −275.0 ppm, whereas the pyrdine nitrogen nuclei appeared to be coupled with the nearest CH protons and gave rise to signals at −80.0 (**6a**) and −85.4 (**7b**) ppm.

The direct cyclopalladation of both cysteine- and homocysteine-based ligands was smoothly accomplished under mild reaction conditions and afforded desired pincer complexes **8−11** in generally good to high yields (Scheme 3). $PdCl_2(NCPh)_2$ was used as a convenient metalating agent. The reactions were performed in the presence of Et_3N to trap HCl liberated upon metalation and thus avoid potential deactivation of the pyridine pendant moiety.

Complexes **8−11** are moisture- and air-resistant crystalline solids, thermally stable at least to 120 °C. Their structures were unambiguously confirmed by the IR and NMR spectroscopic data. Thus, the deprotonation and coordination of the secondary amide unit were supported by the absence of NH stretching and bending vibrations in the IR spectra of all the complexes obtained along with a concomitant strong low-

Scheme 3. Cyclopalladation of the Picolinylamides with Cysteine and Homocysteine Pendant Arms



frequency shift of the amide group C═O stretches ($\Delta\nu$ = 37−48 and 52−62 cm^{-1} for the cysteine- and homocysteine-based derivatives, respectively). Furthermore, the ^1H NMR spectra also lacked the doublet signals of NH protons, whereas the ^{13}C NMR spectra revealed a significant downfield shift of the C(O)N carbon resonances, reaching up to 9.5 ppm. A noticeable shift of the amide nitrogen resonance from −275.0 ppm for ligand **6a** to −250.5 ppm for the corresponding complex (compound **10a**) was also consistent with the N-metalation of the central amide unit. In turn, a strong upfield shift of the signal of the pyridine nitrogen nucleus ($\Delta\delta_N$ = −78.7 ppm) clearly indicated the heterocycle complexation. In the other cases, the coordination of the pyridine moiety was deduced from a downfield shift of the proton resonances of the adjacent CH units (up to 0.53 ppm). The coordination of S-donor pendant arms was evidenced by the marked downfield shifts of both carbon and hydrogen resonances of the exo methylene units (CH_2 units of benzyl, allyl, and methoxycarbonyl substituents). For example, in the case of complex **10a**, the corresponding values of $\Delta\delta$ reached 7.75 and 0.81 ppm, respectively. Furthermore, the configurationally stabilized coordinated sulfur atom serves as the second stereocenter in the complex molecules, giving rise to spectroscopically distinguishable isomers. Thus, the ^1H and ^{13}C NMR spectra of cysteine-based derivatives **8a−c** and **9a−c** displayed a double set of signals, which correspond to two diastereomers resulting from a combination of the coordinated sulfur atom with a chiral carbon center of the L-amino acid residue. Depending on the nature of a substituent in the sulfide group, the ratio of diastereomers varied from ∼3/2 to 5/2. The signals of both major and minor isomers were readily assigned on the basis of the 2D NMR spectra (see the Experimental Section). In the case of the homocysteine-based derivatives, the complexation by the sulfur donor gave rise to four stereoisomers, since the amino acid precursor (homocysteine thiolactone) was used in a racemic form. Therefore, two sets of signals in the ^1H and ^{13}C NMR spectra of complexes **10a−c** and **11a−c** refer to two pairs of enantiomers. It should also be noted that the presence of six-membered chelate rings formed by the elongated S-coordination arms make these compounds more conformationally labile than their 5,5-membered cysteine counterparts. This resulted in broadened and unresolved signals; in particular, the room-temperature ^1H NMR spectra provided only limited information on the complex structures. However, cooling to −40 to −10 °C afforded resolution of almost all the signals, especially in the congested aliphatic

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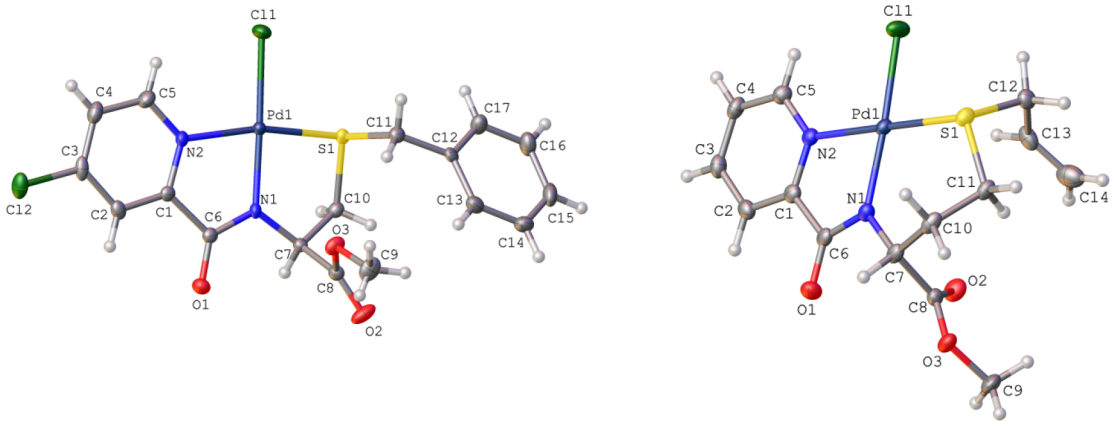

a *b*

Figure 3. Molecular structures of complexes **9a** (a) and **10b** (b) in representations of atoms via thermal ellipsoids at the 50% probability level.

Table 1. Cytotoxic Effects of the Pd(II) Pincer Complexes under Investigation on Some Human Cell Lines

		$IC_{50} \pm SD$,[a] μM				
entry	compound	HCT116	MCF7	PC3	HEK293	NKE
1	**8a**	2.5 ± 0.5	12.5 ± 1.5	2.6 ± 0.4	8.2 ± 1.0	14.4 ± 2.4
2	**8b**	6.4 ± 1.4	17.5 ± 2.5	9.0 ± 2.5	9.0 ± 1.0	19.2 ± 2.6
3	**8c**	20.0 ± 2.5	70.0 ± 12.0	28.0 ± 3.6	27.0 ± 3.0	n/d
4	**9a**	2.2 ± 0.2	6.4 ± 0.4	23.6 ± 1.2	6.6 ± 0.4	15.5 ± 1.5
5	**9b**	5.0 ± 1.0	16.0 ± 4.0	11.0 ± 4.0	7.5 ± 1.5	n/d
6	**9c**	6.5 ± 1.0	25.0 ± 5.0	7.5 ± 2.5	12.0 ± 6.0	n/d
7	**10a**	10.5 ± 4.5	15.0 ± 5.0	18.0 ± 3.5	18.0 ± 7.0	n/d
8	**10b**	12.0 ± 4.0	37.0 ± 3.0	24.0 ± 4.0	15.0 ± 5.0	16.0 ± 2.0
9	**10c**	14.0 ± 4.0	26.0 ± 11.0	12.5 ± 2.5	19.5 ± 4.5	n/d
10	**11a**	3.5 ± 0.5	12.0 ± 2.5	6.6 ± 0.2	10.0 ± 1.5	12.5 ± 1.5
11	**11b**	8.0 ± 3.0	22.0 ± 4.0	9.0 ± 2.0	19.0 ± 8.0	15.2 ± 3.2
12	**11c**	2.6 ± 0.4	16.2 ± 2.0	3.0 ± 0.5	7.4 ± 0.8	n/d
13	cisplatin	18.0 ± 2.0	25.0 ± 4.0	16.0 ± 3.0	12.5 ± 1.5	n/d

[a]SD is the standard deviation of the value. n/d denotes not defined.

region (see, for example, the variable-temperature NMR spectra of complex **10a** in Figure S17 in the Supporting Information). Again, a complete and unambiguous assignment of the hydrogen and carbon resonances of homocysteine-based derivatives **10** and **11** was made using different 2D NMR techniques. Figures S18−S34 in the Supporting Information show the NMR spectra for complex **10a** used as a representative example.

The structures of complexes **9a** and **10b** were further corroborated by single-crystal X-ray diffraction (Figure 3). In both compounds, the coordination environment of the palladium atom was found to be slightly distorted square planar. The distortions are obviously caused by the heterodentate nature of the ligand: whereas the Pd−N bond lengths vary within a narrow range of 1.969(3)−2.049(3) Å for both the coordinated amide and pyridine units, the Pd−S bonds are longer and reach up to 2.2646(7) Å (in **10b**). In general, the observed bond lengths are within the expected norms for these types of complexes. Nevertheless, such a dissymmetry leads to a slight bend along the S1···N2 line in 5,5-membered complex **9a**, which almost disappears in its 5,6-membered counterpart **10b** (the corresponding angles are equal to 167.54(9) and 179.30(6)°, respectively). The presence of the fused metallocycles formed by the pendant arms with different donor centers and different lengths inevitably affects their conformations. Thus, the five-membered metal-containing ring involving both of the nitrogen coordination sites is flat (in complex **9a**) or adopts a flattened-envelope conformation (in **10b**, with Pd1 atom deviating by 0.248 Å). In turn, the conformation of the metallocycle formed by the amino acid pendant arm depends on its size and varies from an envelope (with atom C10 deviating by 0.464 Å) to a twist (in the case of the six-membered ring in complex **10b**, with C10 and C11 atoms deviating by 0.683 and 0.337 Å, respectively). It is noteworthy that slow crystallization of **9a** from CH_2Cl_2−hexane afforded a single diastereomer of this complex. Furthermore, the resulting single crystals of complex **10b** appeared to include only one pair of enantiomers instead of a mixture of the four possible isomeric forms; in both cases the ester group and allyl substituent adopt a *syn* arrangement relative to the Pd1N1N2Cl1S1 mean plane. This opens up interesting prospects for the separation of stereoisomers of these types of nonclassical pincer complexes.

The cytotoxic activities of complexes **8**−**11** were tested against several human cancer cell lines of different origins: colon (HCT116), breast (MCF7), and prostate (PC3) cancers. After 48 h exposure, the cell viability was determined by the conventional MTT assay. Cisplatin was used as a positive control. The resulting concentrations necessary to

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inhibit the cellular survival fraction to 50% are given in Table 1.

Most of the complexes obtained exhibited significant antiproliferative activity against all of the cancer cell lines explored. The only exception was complex **8c** (Table 1, entry 3), which demonstrated moderate or even low cytotoxicity and was inferior to the reference—cisplatin (entry 13). In most of the other cases, the compounds under consideration outperformed this widely used chemotherapeutic agent. In some cases, especially in the experiments with HCT116 and PC3 cells, the values of IC_{50} reached a low micromolar range (see, for example, entries 1, 4, 10, and 12). As a rule, MCF7 breast cancer cells appeared to be less sensitive to Pd(II) complexes **8**−**11**.

The S-modified cysteine-based complexes were found to be more active than their counterparts with elongated S-donor pendant arms against all the tested cancer cell lineages. The order of efficiency depending on the substituent at the ancillary sulfur donor group for the cysteine derivatives was as follows: CH_2Ph > All > CH_2COOMe (entries 1−6). For the homocysteine-based complexes, methoxycarbonylmethyl derivatives **10c** and **11c** appeared to be more efficient than their allyl analogues **10b** and **11b** (entries 9 and 12 vs entries 8 and 11). Nevertheless, in both series the highest cytotoxic effects were exerted by the S-modified complexes bearing benzyl substituents. Another general tendency observed for the S,N,N-complexes under investigation is that the introduction of a chlorine atom into the pyridine ring facilitated the improvement of cytotoxic activity: in some examples a difference of more than 4 times between the IC_{50} values of the corresponding 4-chloropicolinyl- and picolinylamide derivatives was observed (entries 4−6 vs entries 1−3, entries 10−12 vs entries 7−9). As in the case of prototypes **I**, the positive effect of chlorine substituents can be associated with an increase in the lipophilicity and a possibility of a nonbonding interaction of the chlorine atom in a binding site.[12] The cytotoxic activity of complexes **8**−**11** was also estimated against noncancer human embryonic kidney cells (HEK293) and kidney epithelial cells (NKE). Unfortunately, an appreciable level of selectivity in the case of HEK293 cells was observed only relative to the HCT116 cancer lineage, although for some complexes the selectivity indices were above 3.0. Slightly better results were achieved with the selected examples of S-modified cyclopalladated derivatives on NKE cells (the highest selectivity index was 7.0).

It is important to note that free ligands **2**, **3**, **6**, and **7** did not afford 50% cell growth inhibition even at a concentration as high as 200 μM, suggesting that the observed cytotoxic properties of the cyclopalladated complexes are determined by the coordination with palladium ions, as was the case with compounds **I**. In general, the S-modified derivatives obtained in this study provide comparable levels of cytotoxic activity and conform to the main structure−activity relationships observed for the *S*-methyl-L-cysteine and methionine prototypes. This confirms the value of pincer systems based on picolinylamides bearing S-donor amino acid pendant arms as a potentially interesting scaffold for the development of new antitumor agents and renders following research in this field very promising.

By the examples of complexes **11a**,**c**, it was demonstrated that the S-modified cyclopalladated derivatives, as well as compounds **I** bearing methyl substituents at the ancillary S-donor group, are stable both in neat DMSO and in DMSO−water and DMSO−PBS solutions: UV−vis spectroscopic studies confirmed the retention of a pincer structure in solution over a prolonged period of time (120 h), with the only conceivable change being the substitution of the auxiliary chloride ligand for DMSO (Figures S35−S39 in the Supporting Information).[6]

To further evaluate the anticancer potential of Pd(II) pincer complexes based on functionalized carboxamides with S-donor amino acid residues, we analyzed the effects of **8a**, **9a**, **11a**−**c**, and a representative example of compounds **I** on the proliferation of transformed breast cells HBL100 and doxorubicin-resistant subline HBL100/Dox (Table 2). All of the tested complexes provided almost the same level of growth inhibition in both native and resistant cells, while the reference, doxorubicin, exhibited more than a 130-fold drop in the activity on passing to HBL100/Dox cells. This indicates that these types of cytotoxic Pd(II) complexes can serve as the basis for new chemotherapeutic agents that would be able to overcome drug resistance.

Table 2. Cytotoxic Effects of the Pd(II) Pincer Complexes Based on Picolinylamides with S-Donor Amino Acid Pendant Arms on HBL100 and HBL100/Dox Cells

compound	IC_{50} ± SD, μM	
	HBL100	HBL100/Dox
8a	8.4 ± 1.4	9.4 ± 2.2
9a	9.4 ± 2.6	14.0 ± 3.5
11a	9.6 ± 2.2	7.8 ± 1.4
11b	11.5 ± 1.0	14.5 ± 1.5
11c	15.0 ± 0.5	20.5 ± 3.5
compound I (n = 2, X = Cl, L-methionine derivative)	10.2 ± 0.7	14.6 ± 2.2
doxorubicin	0.40 ± 0.14	53.0 ± 7.0

Currently, it is widely recognized that targeting apoptosis—a programmed cell death—ranks among the most successful nonsurgical strategies for cancer treatment. One of the earliest indicators of apoptosis is the externalization of phospholipid phosphatidylserine (PS). The exposed PS can readily be detected by the phospholipid-binding protein annexin V or its highly luminescent conjugates with fluorochromes such as phycoerythrin (PE). An Annexin V-PE staining assay was used to study the ability of the complexes obtained to induce apoptosis. The investigations were performed with some of the most active cysteine- and homocysteine-based derivatives—complexes **8a** and **11a**, respectively. For comparison, the apoptotic effects of selected representatives of other types of cytotoxic Pd(II) pincer complexes based on functionalized amide ligands (compounds **I**, **V**, and **VI** from Figure 2) were also evaluated. Acute monocytic leukemia cells (THP-1) were treated with the aforementioned compounds at concentrations of 10 μM for 20 h. The following analysis by flow cytometry (Figure 4) revealed that type **VI** S,N,N-complex lacking an amino acid residue and S,N,P-complex **V** with an L-methionine pendant arm provide almost the same percentages of apoptotic cells above 30% versus 3.7% in the control experiment but are considerably less effective in the efficiency than the S,N,N-counterparts derived from the functionalized picolinylamides. More importantly, the apoptotic efficiency increases on passing from key prototype **I** to S-modified analogues **8a** and **11a** obtained in this study: the percentages of apoptotic cells

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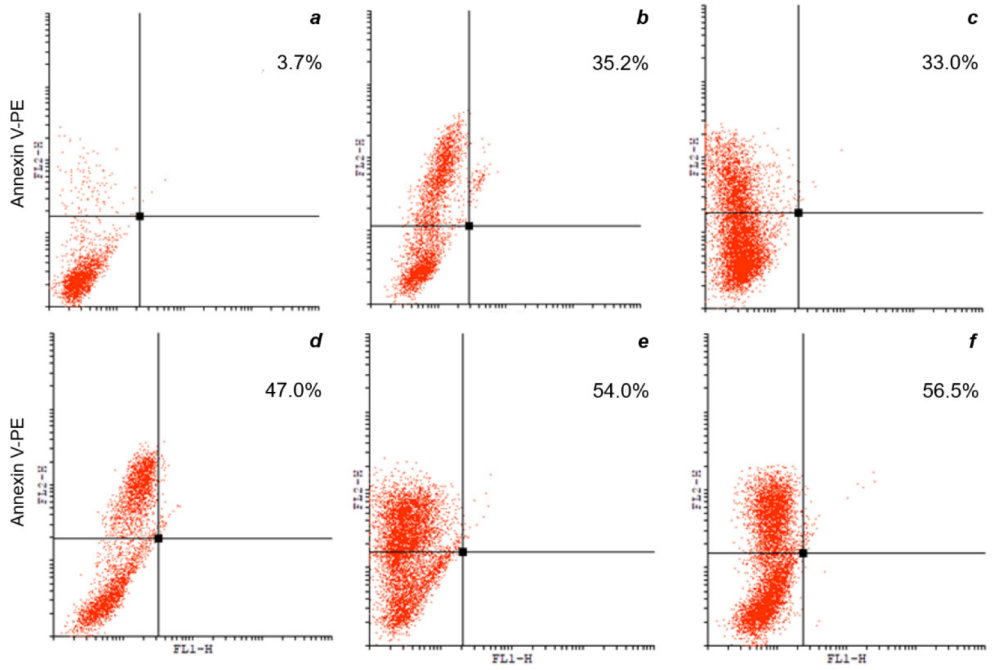

Figure 4. Percentages of apoptotic THP-1 cells in the control experiment (a) and after exposure to the complexes from the previous studies **VI** (n = 2, m = 1 (b)), **V** (n = 2 (c)), and **I** (n = 2, X = Cl, L-amino acid derivative (d)) and exposure to the complexes from the present study **8a** (e) and **11a** (f).

composed 47.0%, 54.0%, and 56.5%, respectively. Thus, the S-modification of the ligand framework can serve as a tool to improve apoptosis induction by this potent class of cytotoxic agents.

Interestingly, S-modified complexes **8a**−**11a** did not affect the mobility of supercoiled plasmid DNA pHOT1 (Topo-GEN) at concentrations up to 120 μM in agarose gel electrophoresis studies (Figure 5). The inhibition effect of

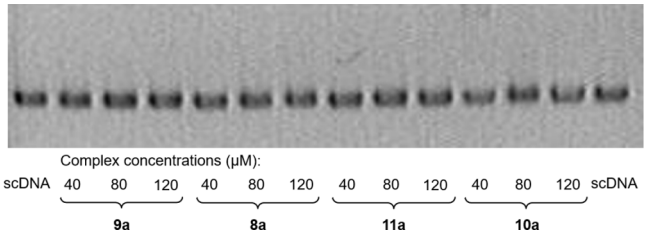

Figure 5. Gel electrophoresis diagram showing the effect of complexes **8a**−**11a** on supercoiled pHOT1 DNA.

most of the complexes from this study on human DNA topoisomerase I was manifested, as a rule, at concentrations above 10 μM (Figures 6a,b). Some changes in the DNA relaxation in the electrophoretic patterns obtained after treatment with the selected compounds at the lower concentrations were observed only for **9b** and **11c** starting from 2.5 μM (Figures 6c,d). These preliminary results on the binding ability with DNA and Topo I, often serving as the main targets for metal-based chemotherapeutics, may suggest different action modes of the S-modified complexes under consideration and their key prototypes **I** bearing methyl substituents at the ancillary sulfur-donor moieties.

To gain further insight into the biological effect of Pd(II) pincer complexes of picolinylamides with S-donor amino acid pendant arms on living cells, it seemed interesting to analyze their cellular uptake. This characteristic is of high importance for the application of compounds as therapeutic or diagnostic agents and is underexplored for the potential metal-based drugs. Unfortunately, neither complexes **8**−**11** nor their prototypes derived from the related ligands display photoluminescence properties. Therefore, we decided to obtain a fluorophore-conjugated analogue of these compounds. Functionalized carboxamide **12** bearing a fluorescein moiety was obtained according to the general method for the synthesis of S-modified homocysteine-based ligands **6** and **7**, starting from homocysteine thiolactone derivative **4** and using 2-chloro-*N*-fluoresceinylacetamide as the alkylating agent. The direct cyclopalladation of **12** under the action of $PdCl_2(NCPh)_2$ readily afforded target Pd(II) S,N,N-pincer complex **13** featuring favorable emission properties (for the experimental details and characterization of compounds **12** and **13**, including their luminescence spectra (Figure S40), see the Supporting Information). The structure of this complex is depicted in Figure 7. The fluorescence microscopy images of PC3 cells treated with compound **13** (Figure 7) show that it is accumulated mainly in the cytoplasm and, in some cases, additionally in certain subcellular zones (for the corresponding images of PC3 cells treated with free ligand **12**, see Figure S41 in the Supporting Information). Further studies by flow cytometry confirmed that compound **13** is indeed taken up inside PC3 cancer cells despite a large expanse of the ligand. Figure 8 illustrates its internalization in a time-dependent manner. It is also noteworthy that this complex is stable to the intracellular environment, since there is no loss in luminescence over time. Additionally, the stability of fluorophore-conjugated derivative **13**, in particular, in DMSO−PBS solution was also confirmed by UV−vis spectroscopic studies (see Figure S42 in the Supporting Information).

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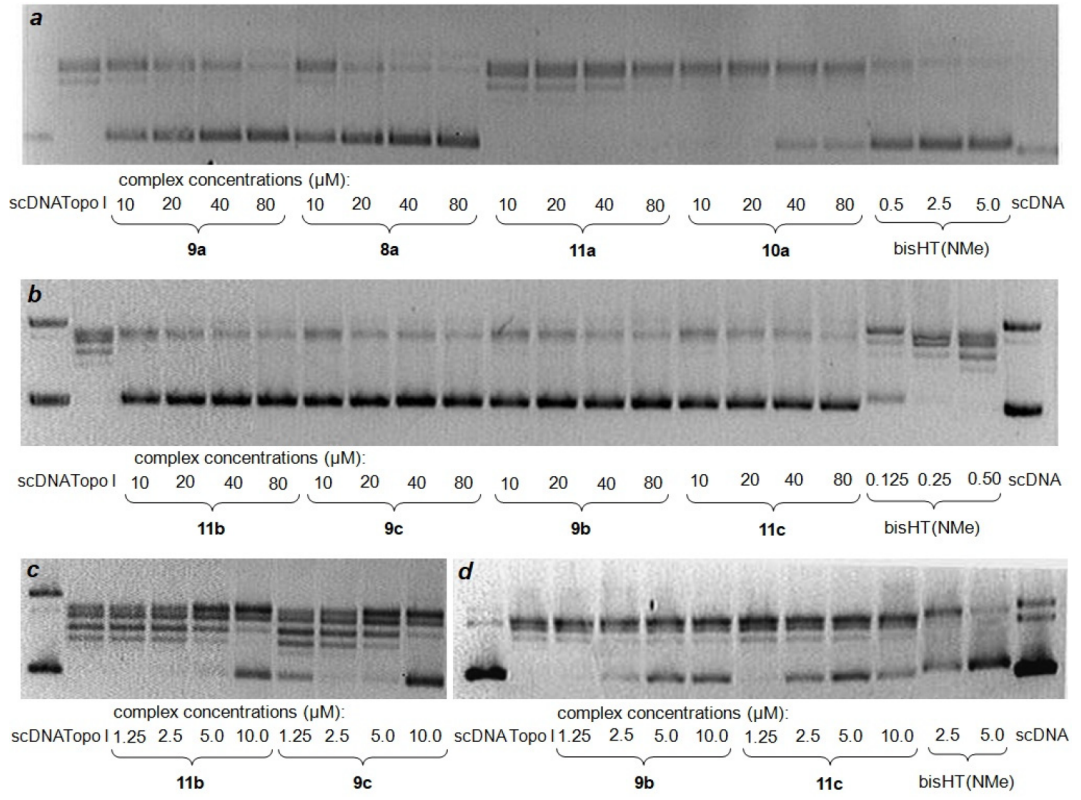

Figure 6. Gel electrophoresis diagrams showing the effect of complexes **8a**, **9a**–**c**, **10a**, and **11a**–**c** on human DNA topoisomerase I.

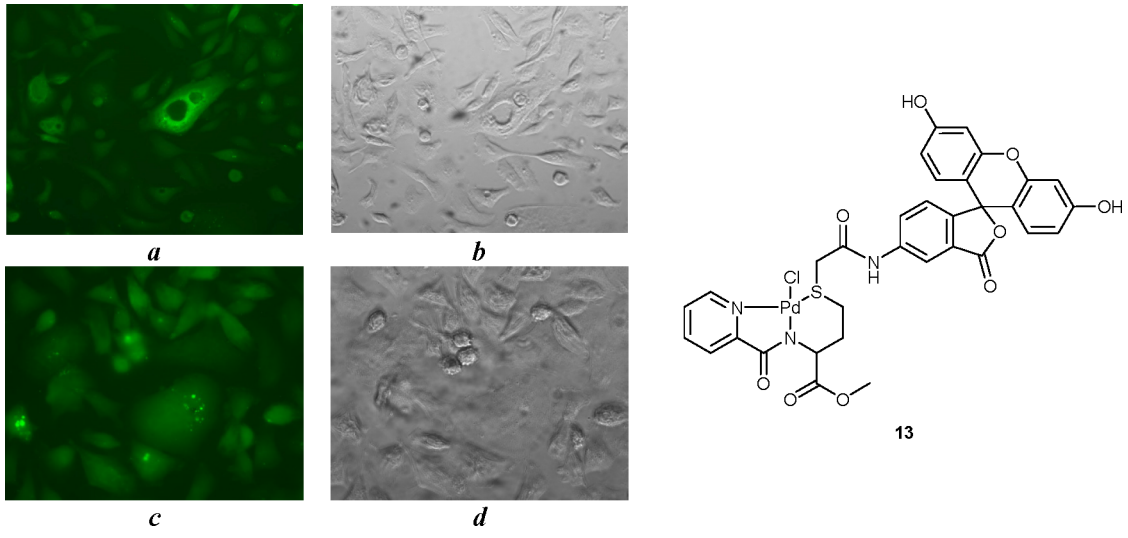

Figure 7. Fluorescence microscopy analysis of PC3 cells incubated with complex **13**: images showing the fluorescence of **13** in the cells obtained with a blue filter (a, c) and phase contrast images (b, d) at ×400 magnification.

There is sometimes an unpredictable interplay between the structural modifications and relevant properties. Thus, complex **13** appeared to be almost nontoxic toward the tested cancer lineages: the viabilities of HCT116, MCF7, and PC3 cells after 48 h exposure to this compound at a concentration as high as 60 μM were above 80%. Nevertheless, firm evidence for the uptake into the cellular interior of this particular representative of nonclassical Pd(II) pincer complexes based on functionalized carboxamides with amino acid residues is an important addition to the characteristics of the whole class of these potential antitumor agents. Our future efforts will be focused on the further modification of a ligand framework in order to obtain pincer–(pseudo)dipeptide conjugates.

CONCLUSIONS

A small library of new potential antitumor agents based on Pd(II) pincer complexes of functionalized carboxamides with S-modified cysteine and homocysteine residues has been synthesized and fully characterized. A preliminary evaluation of the cytotoxic activities of the resulting complexes against several human cancer cell lines revealed comparably high levels of efficiency and structure–activity relationships analogous to

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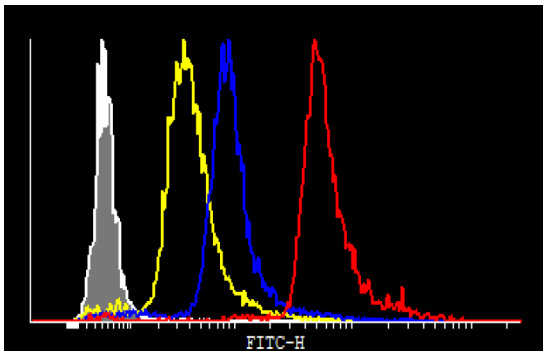


Figure 8. Flow cytometry analysis of PC3 cells incubated with complex **13** for 1 (yellow), 2 (blue), or 20 h (red) (the gray histogram denotes control cells).

those observed earlier for the related picolinylamide derivatives with *S*-methyl-L-cysteine and methionine residues. Furthermore, both the newly prepared and previous representatives of N-metalated Pd(II) pincer complexes with S-donor amino acid pendant arms displayed prominent cytotoxic effects on transformed breast cells HBL100 and their doxorubicin-resistant clones HBL100/Dox, opening the way for the creation of metal-based chemotherapeutics that would be able to overcome drug resistance. The supplemental mechanistic considerations revealed that the complexes obtained induce significant tumor cell death by apoptosis, exceeding their key prototypes in the activity, and unlike the latter did not exhibit high binding affinity to DNA. Hence, the S-modification of the ligand framework can serve as a tool to improve apoptosis induction ability and modify the action mode of potential antitumor agents based on these types of Pd(II) complexes. Finally, additional fluorescence microscopy and flow cytometry studies with a specially designed fluorescein-conjugated pincer complex also comprising the S-modified derivative discovered its efficient cellular uptake and stability to the intracellular environment, rendering non-classical Pd(II) pincer complexes based on picolinylamides with S-donor amino acid residues worthy of further studies as a highly potent class of therapeutic agents.

EXPERIMENTAL SECTION

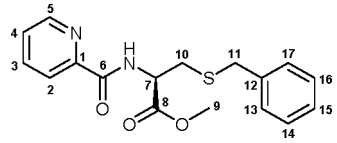
General Remarks. If not mentioned otherwise, all manipulations were carried out without taking precautions to exclude air and moisture. Dichloromethane was distilled from P_2O_5. Triethylamine was distilled from sodium. Methanol for the synthesis of ligands **6** and **7** was distilled over magnesium turnings activated with iodine. Picolinyl and 4-chloropicolinyl chlorides were synthesized by the reactions of picolinic acid with $SOCl_2$ in the presence of Et_3N[13] and NaBr,[14] respectively, and directly used in further steps without purification. Methyl *S*-benzyl-L-cysteinate,[15] methyl *S*-allyl-L-cysteinate,[16] and methyl *S*-(2-methoxy-2-oxoethyl)-L-cysteinate[17] hydrochlorides were obtained from methyl L-cysteinate hydrochloride by a sequential treatment with Boc_2O, the corresponding alkyl halide, and HCl. 2-Chloro-*N*-fluoresceinylacetamide used in the synthesis of ligand **12** was derived from 5-aminofluorescein and chloroacetyl chloride in the presence of sodium bicarbonate according to the published procedure.[18] For the synthesis and characterization of ligand **12** and its Pd(II) pincer complex **13**, see the Supporting Information. All other chemicals and solvents were used as purchased.

The NMR spectra were recorded on Bruker Avance 400, Avance 500, and Avance 600 spectrometers, and the chemical shifts (δ) were referenced internally by the residual (^{1}H) or deuterated (^{13}C) solvent signals relative to tetramethylsilane or externally to H_3PO_4 (^{31}P) or $MeNO_2$ (^{15}N). In most cases, the $^{13}C\{^1H\}$ NMR spectra were registered using the *J*MODECHO mode; the signals for the C nuclei bearing odd and even numbers of protons had opposite polarities. The ^{15}N chemical shifts were extracted from the $^1H-^{15}N$ HMBC spectra. The NMR peak assignments for the representative ligands and complexes were based on the analysis of $^1H-^1H-$COSY, $^1H-^{13}C$ HMBC, HMQC (**6a**, **7b**, **8a**, **9b**,**c**, **10a**−**c**, **11b**) and/or HSQC (**7c**, **9b**) spectra. Along with the previously reported data for the related compounds,[6] the results obtained were used to assign the NMR spectra of the other compounds from this study. The UV−vis spectra of complexes **11a**,**c** and **13** were registered on a Cary50 spectrometer in quartz cells with 10 mm path length. The fluorescence emission spectra of compounds **12** and **13** were recorded on a Cary Eclipse fluorescence spectrophotometer (λ_{ex} = 490 nm, 2.5 nm slit).

The IR spectra were recorded on a Nicolet Magna-IR750 FT spectrometer (resolution 2 cm^{-1}, 128 scans). The assignment of absorption bands in the IR spectra was made according to ref 19. Column chromatography was carried out using Macherey-Nagel silica gel 60 (MN Kieselgel 60, 70−230 mesh). Melting points were determined with an MPA 120 EZ-Melt automated melting point apparatus (Stanford Research Systems).

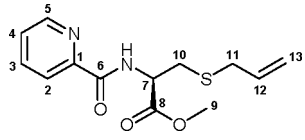
Syntheses. *General Procedure for the Synthesis of Ligands **2** and **3**.* A solution of Et_3N (0.76 g, 7.51 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred suspension of the corresponding S-substituted methyl L-cysteinate hydrochloride (3.00 mmol) in CH_2Cl_2 (10 mL) at −5 to 0 °C under an argon atmosphere. The resulting mixture was stirred at 0 °C for 30 min. Then, a suspension of picolinic or 4-chloropicolinic acid chloride (3.00 mmol) in CH_2Cl_2 (15 mL) was added at −5 to +2°C. The reaction mixture was stirred at room temperature for 12 h, poured into distilled water, sequentially washed with saturated aqueous $NaHCO_3$ and water, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH (75/1) (**2a**−**c**), CH_2Cl_2 (**3a**−**c**)) to give the target compounds as yellow (**3a**,**b**) or light yellow (**2a**−**c**, **3c**) viscous oils.

*Methyl S-Benzyl-N-(pyridin-2-ylcarbonyl)-L-cysteinate (**2a**).*



Yield: 0.44 g (44%). $[\alpha]_D^{20}$ = −26.6 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.95−3.07 (m, 2H, CH_2S), 3.79 (s, 2H, CH_2Ph), 3.80 (s, 3H, OMe), 5.02−5.07 (m, 1H, CH), 7.22−7.26 (m, 1H, H_{Ar}), 7.28−7.34 (m, 4H, H_{Ar}), 7.48 (ddd, 1H, H(C4), $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.1 Hz), 7.88 (dt, 1H, H(C3), $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.7 Hz), 8.19−8.22 (m, 1H, H(C2)), 8.63−8.65 (m, 1H, H(C5)), 8.74 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 33.39 and 36.63 (both s, CH_2S and CH_2Ph), 52.00 and 52.69 (both s, CH and OMe), 122.39 and 126.52 (both s, C2 and C4), 127.22 (s, C15), 128.58 and 129.02 (both s, C13 + C17 and C14 + C16), 137.35 (s, C3), 137.59 (s, C12), 148.42 (s, C5), 149.23 (s, C1), 164.17 (s, C(O)NH), 171.13 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 621(w), 702(m), 751(w), 820(vw), 998(w), 1028(vw), 1042(vw), 1072(vw), 1088(vw), 1178(w), 1212(br, m), 1239(w), 1294(w), 1312(w), 1356(w), 1435(m), 1454(w), 1466(w), 1515(br, s) (C(O)NH), 1570(w), 1591(w), 1678(br, s) (ν(C═O) in C(O)NH), 1746(br, s) (ν(C═O) in C(O)OMe), 2848(vw), 2924(vw), 2952(w), 3028(vw), 3060(vw), 3378(br, w) (ν(NH)). Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.42; H, 5.88; N, 8.13.

*Methyl S-Allyl-N-(pyridin-2-ylcarbonyl)-L-cysteinate (**2b**).*



Yield: 0.44 g (52%). $[\alpha]_D^{20}$ = −9.6 (*c* = 0.26, $CHCl_3$). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.95−3.20 (m, 2H, CH_2S + 2H, CH_2CH═

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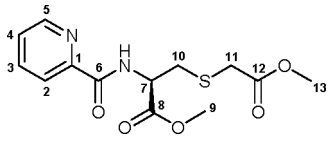
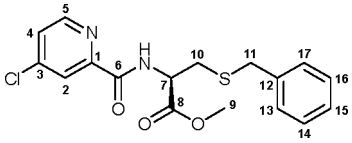
CH_2), 3.78 (s, 3H, OMe), 4.96−5.01 (m, 1H, CH), 5.06−5.11 (m, 2H, $CH_2CH{=}CH_2$), 5.68−5.78 (m, 1H, $CH_2CH{=}CH_2$), 7.42−7.45 (m, 1H, H(C4)), 7.83 (t, 1H, H(C3), $^3J_{HH}$ = 7.7 Hz), 8.15 (d, 1H, H(C2), $^3J_{HH}$ = 7.7 Hz), 8.58 (d, 1H, H(C5), $^3J_{HH}$ = 4.7 Hz), 8.70 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 32.49 and 35.08 (both s, CH_2S and $CH_2CH{=}CH_2$), 51.99 and 52.68 (both s, CH and OMe), 118.00 (s, $CH_2CH{=}CH_2$), 122.32 and 126.52 (both s, C2 and C4), 133.61 (s, $CH_2CH{=}CH_2$), 137.35 (s, C3), 148.40 (s, C5), 149.16 (s, C1), 164.11 (s, C(O)NH), 171.13 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 598(w), 621(m), 700(w), 751(m), 821(w), 887(vw), 922(w), 998(m), 1020(w), 1042(w), 1088(w), 1178(m), 1212(br, m), 1356(m), 1435(m), 1466(m), 1517(br, s) (C(O)NH), 1570(w), 1591(w), 1636(w), 1678(br, s) (ν(C=O) in C(O)NH), 1746(br, s) (ν(C=O) in C(O)OMe), 2855(vw), 2921(vw), 2953(w), 3008(vw), 3063(vw), 3383(br, w) (ν(NH)). Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found: C, 55.74; H, 5.87; N, 9.81.

*Methyl S-(2-Methoxy-2-oxoethyl)-N-(pyridin-2-ylcarbonyl)-L-cysteinate (**2c**).*



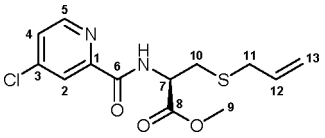
Yield: 0.53 g (57%). $[\alpha]_D^{20}$ = −11.5 (*c* = 0.33, $CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.17 (dd, 1H, CH_2S, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 6.3 Hz), 3.26−3.37 (m, 1H, CH_2S + 2H, $CH_2C(O)OMe$), 3.71 (s, 3H, OMe), 3.80 (s, 3H, OMe), 5.03−5.08 (m, 1H, CH), 7.44−7.47 (m, 1H, H(C4)), 7.85 (t, 1H, H(C3), $^3J_{HH}$ = 7.7 Hz), 8.17 (d, 1H, H(C2), $^3J_{HH}$ = 7.7 Hz), 8.60 (d, 1H, H(C5), $^3J_{HH}$ = 4.7 Hz), 8.74 (br d, 1H, NH, $^3J_{HH}$ = 8.5 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 33.63 and 34.58 (both s, CH_2S and $CH_2C(O)OMe$), 51.79, 52.51, and 52.82 (three s, CH and OMe in C(O)OMe and $CH_2C(O)OMe$), 122.38 and 126.57 (both s, C2 and C4), 137.36 (s, C3), 148.41 (s, C5), 149.10 (s, C1), 164.25 (s, C(O)NH), 170.43 and 170.95 (both s, C(O)OMe and $CH_2C(O)OMe$) ppm. IR (thin film, ν/cm^{-1}): 621(w), 701(vw), 752(m), 821(vw), 998(m), 1173(br, m), 1214(m), 1281(br, m), 1356(w), 1436(m), 1466(w), 1517(br, s) (C(O)NH), 1570(w), 1591(w), 1676(br, s) (ν(C=O) in C(O)NH), 1740(br, s) (ν(C=O) in C(O)OMe), 2850(vw), 2954(w), 3007(vw), 3375(br, w) (ν(NH)). Anal. Calcd for $C_{13}H_{16}N_2O_5S$: 49.99; H, 5.16; N, 8.97. Found: C, 49.63; H, 5.26; N, 8.86.

*Methyl S-Benzyl-N-[(4-chloropyridin-2-yl)carbonyl]-L-cysteinate (**3a**).*



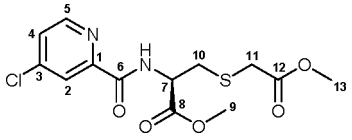
Yield: 1.01 g (92%). $[\alpha]_D^{20}$ = −10.6 (*c* = 0.53, $CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.95−3.07 (m, 2H, CH_2S), 3.77 (s, 2H, CH_2Ph), 3.80 (s, 3H, OMe), 4.99−5.04 (m, 1H, CH), 7.22−7.32 (m, 5H, H_{Ar}), 7.48 (dd, 1H, H(C4), $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 2.1 Hz), 8.20 (d, 1H, H(C2), $^4J_{HH}$ = 2.1 Hz), 8.53 (d, 1H, H(C5), $^3J_{HH}$ = 5.2 Hz), 8.66 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 33.34 and 36.62 (both s, CH_2S and CH_2Ph), 52.02 and 52.77 (both s, CH and OMe), 123.06 and 126.67 (both s, C2 and C4), 127.26 (s, C15), 128.60 and 129.00 (both s, C13 + C17 and C14 + C16), 137.51 (s, C12), 145.88 (s, C3), 149.32 (s, C5), 150.68 (s, C1), 163.02 (s, C(O)NH), 170.94 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 526(w), 565(vw), 705(m), 749(m), 781(w), 843(w), 901(vw), 994(vw), 1028(vw), 1072(vw), 1097(w), 1130(w), 1178(m), 1215(br, m), 1312(w), 1350(m), 1437(m), 1454(m), 1516(br, s) (C(O)NH), 1557(m), 1579(m), 1680(br, s) (ν(C=O) in C(O)NH), 1746(br, s) (ν(C=O) in C(O)OMe), 2952(vw), 3028(vw), 3060(vw), 3379(br, w) (ν(NH)). Anal. Calcd for $C_{17}H_{17}ClN_2O_3S$: C, 55.96; H, 4.70; N, 7.68. Found: C, 55.58; H, 4.60; N, 7.51.

*Methyl S-Allyl-N-[(4-chloropyridin-2-yl)carbonyl]-L-cysteinate (**3b**).*



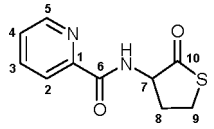
Yield: 0.30 g (32%). $[\alpha]_D^{20}$ = −5.0 (*c* = 0.50, CH_2Cl_2). ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.97−3.22 (m, 2H, CH_2S + 2H, $CH_2CH{=}CH_2$), 3.81 (s, 3H, OMe), 4.97−5.02 (m, 1H, CH), 5.09−5.13 (m, 2H, $CH_2CH{=}CH_2$), 5.70−5.81 (m, 1H, $CH_2CH{=}CH_2$), 7.47 (dd, 1H, H(C4), $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 2.0 Hz), 8.19 (d, 1H, H(C2), $^4J_{HH}$ = 2.0 Hz), 8.52 (d, 1H, H(C5), $^3J_{HH}$ = 5.2 Hz), 8.64 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 32.35 and 34.97 (both s, CH_2S and $CH_2CH{=}CH_2$), 51.89 and 52.62 (both s, CH and OMe), 117.93 (s, $CH_2CH{=}CH_2$), 122.88 and 126.52 (both s, C2 and C4), 133.43 (s, $CH_2CH{=}CH_2$), 145.73 (s, C3), 149.18 (s, C5), 150.52 (s, C1), 162.84 (s, C(O)NH), 170.82 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 526(w), 692(w), 749(m), 781(w), 842(w), 921(w), 994(w), 1019(w), 1097(w), 1178(m), 1215(br, m), 1312(w), 1350(m), 1437(m), 1462(m), 1517(br, s) (C(O)NH), 1558(m), 1579(m), 1636(w), 1678(br, s) (ν(C=O) in C(O)NH), 1746(br, s) (ν(C=O) in C(O)OMe), 2849(vw), 2954(w), 3082(vw), 3373(br, w) (ν(NH)). Anal. Calcd for $C_{13}H_{15}ClN_2O_3S$: C, 49.60; H, 4.80; N, 8.90. Found: C, 49.50; H, 4.87; N, 8.97.

*Methyl N-[(4-Chloropyridin-2-yl)carbonyl]-S-(2-methoxy-2-oxoethyl)-L-cysteinate (**3c**).*



Yield: 0.43 g (41%). $[\alpha]_D^{20}$ = −2.6 (*c* = 0.70, $CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.18 (dd, 1H, CH_2S, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 6.3 Hz), 3.29 and 3.36 (ABq, 2H, $CH_2C(O)OMe$, J_{AB} = 15.0 Hz), 3.31 (dd, 1H, CH_2S, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 5.0 Hz), 3.74 (s, 3H, OMe), 3.83 (s, 3H, OMe), 5.06 (ddd, 1H, CH, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 5.0 Hz), 7.48 (dd, 1H, H(C4), $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 2.1 Hz), 8.20 (d, 1H, H(C2), $^4J_{HH}$ = 2.1 Hz), 8.52 (d, 1H, H(C5), $^3J_{HH}$ = 5.2 Hz), 8.68 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 33.63 and 34.54 (both s, CH_2S and $CH_2C(O)OMe$), 51.85, 52.56, and 52.90 (three s, CH and OMe in C(O)OMe and $CH_2C(O)OMe$), 123.07 and 126.72 (both s, C2 and C4), 145.91 (s, C3), 149.33 (s, C5), 150.59 (s, C1), 163.13 (s, C(O)NH), 170.40 and 170.78 (both s, C(O)OMe and $CH_2C(O)OMe$) ppm. IR (thin film, ν/cm^{-1}): 527(w), 626(br, vw), 692(w), 748(w), 782(w), 845(w), 904(vw), 995(w), 1009(w), 1135(w), 1175(br, w), 1217(br, m), 1283(br, m), 1350(w), 1437(m), 1462(w), 1517(br, s) (C(O)NH), 1557(m), 1579(w), 1679(br, s) (ν(C=O) in C(O)NH), 1740(br, s) (ν(C=O) in C(O)OMe), 2847(vw), 2954(w), 3003(vw), 3059(vw), 3373(br, w) (ν(NH)). Anal. Calcd for $C_{13}H_{15}ClN_2O_5S$: C, 45.02; H, 4.36; N, 8.08. Found: C, 44.94; H, 4.34; N, 7.91.

*N-(2-Oxotetrahydro-3-thienyl)pyridine-2-carboxamide (**4**).*



A solution of Et_3N (2.12 g, 21.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred suspension of DL-homocysteine thiolactone hydrochloride (1.54 g, 10.0 mmol) in CH_2Cl_2 (10 mL) at −5 to 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Then, a suspension of picolinic acid chloride (1.42 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was added at −5 to +2 °C. The reaction mixture was poured into distilled water, washed with saturated aqueous $NaHCO_3$ and water, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The resulting residue was purified by column

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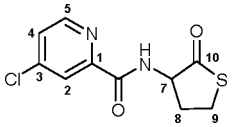
chromatography on silica gel (eluent: CH_2Cl_2/MeOH (75/1)) followed by recrystallization from EtOAc to give compound **4** as grayish crystals. Yield: 2.03 g (91%). Mp: 138−139 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.10−2.21 (m, 1H, CH_2), 2.92−2.98 (m, 1H, CH_2), 3.29−3.33 (m, 1H, CH_2S), 3.39−3.47 (m, 1H, CH_2S), 4.75−4.82 (m, 1H, CH), 7.45 (dd, 1H, H(C4), $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 4.8 Hz), 7.83−7.88 (m, 1H, H(C3)), 8.17 (d, 1H, H(C2), $^3J_{HH}$ = 7.8 Hz), 8.45 (br d, 1H, NH, $^3J_{HH}$ = 7.2 Hz), 8.56 (d, 1H, H(C5), $^3J_{HH}$ = 4.8 Hz) ppm. ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$): δ 27.59 and 31.74 (both s, CH_2 and CH_2S), 59.29 (s, CH), 122.35 and 126.63 (both s, C2 and C4), 137.42 (s, C3), 148.32 (s, C5), 149.07 (s, C1), 164.84 (s, C(O)NH) ppm (the signal of C(O)S carbon nucleus was not observed). IR (KBr, ν/cm^{-1}): 564(w), 588(w), 621(w), 704(vw), 757(m), 826(vw), 841(vw), 930(m), 997(w), 1016(w), 1041(w), 1091(vw), 1148(vw), 1277(vw), 1314(w), 1436(w), 1465(w), 1512(s) (C(O)NH), 1567(w), 1590(w), 1668(s) (ν(C═O) in C(O)NH), 1703(s) (ν(C═O) in C(O)S), 2889(vw), 2942(vw), 2995(vw), 3098(vw), 3381(m) (ν(NH)). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.94; H, 4.46; N, 12.64.

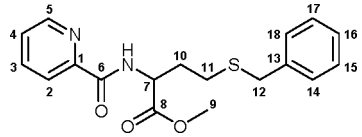
*4-Chloro-N-(2-oxotetrahydro-3-thienyl)pyridine-2-carboxamide (**5**).*



A solution of Et_3N (2.12 g, 21.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred suspension of DL-homocysteine thiolactone hydrochloride (1.54 g, 10.0 mmol) in CH_2Cl_2 (10 mL) at −5 to 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Then, a suspension of 4-chloropicolinic acid chloride (1.76 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was added at 0 °C. The reaction mixture was poured into distilled water, washed with saturated aqueous $NaHCO_3$ and water, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The resulting residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH (100/1)) to give compound **5** as light beige crystals. Yield: 2.01 g (78%). Mp: 134−136 °C (EtOAc/hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.09−2.20 (m, 1H, CH_2), 2.97−3.04 (m, 1H, CH_2), 3.32−3.37 (m, 1H, CH_2S), 3.42−3.50 (m, 1H, CH_2S), 4.74−4.81 (m, 1H, CH), 7.48 (dd, 1H, H(C4), $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 2.1 Hz), 8.20 (d, 1H, H(C2), $^4J_{HH}$ = 2.1 Hz), 8.36 (br d, 1H, NH, $^3J_{HH}$ = 6.9 Hz), 8.49 (d, 1H, H(C5), $^3J_{HH}$ = 5.2 Hz) ppm. ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$): δ 27.59 and 31.66 (both s, CH_2 and CH_2S), 59.35 (s, CH), 123.00 and 126.78 (both s, C2 and C4), 145.95 (s, C3), 149.23 (s, C5), 150.51 (s, C1), 163.69 (s, C(O)NH), 204.64 (s, C(O)S) ppm. IR (KBr, ν/cm^{-1}): 528(w), 557(w), 623(vw), 666(w), 688(w), 716(w), 785(w), 843(w), 899(w), 927(m), 978(w), 1018(vw), 1058(w), 1234(vw), 1300(w), 1351(w), 1520(s) (C(O)NH), 1555(m), 1578(m), 1656(s) (ν(C═O) in C(O)NH), 1692(s) and 1702(s) (both ν(C═O) in C(O)S), 2856(vw), 2926(vw), 3062(vw), 3093(vw), 3327(m) and 3362(m) (both ν(NH)). Anal. Calcd for $C_{10}H_9ClN_2O_2S$: C, 46.79; H, 3.53; N, 10.91. Found: C, 46.64; H, 3.58; N, 10.67.

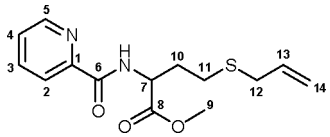
*General Procedure for the Synthesis of Ligands **6** and **7**.* The corresponding homocysteine thiolactone derivative (compound **4** or **5**, 1.74 mmol) was added portionwise to a stirred solution of sodium methoxide obtained *in situ* from sodium (0.04 g, 1.74 mmol) and methanol (20 mL) at room temperature under an argon atmosphere. The resulting mixture was stirred at room temperature for 30 min. Then, a solution of the corresponding chloride (1.92 mmol) in MeOH (5 mL) was added dropwise. The reaction mixture was stirred for 12 h. The solvent was removed under vacuum. A solution of the resulting residue in CH_2Cl_2 was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue obtained was purified by column chromatography on silica gel (eleuent: CH_2Cl_2/MeOH (75/1)) to give the target compounds as light brown (**6b,c**) or light yellow (**7a−c**) viscous oils or a beige crystalline solid (in the case of ligand **6a** after treatment of the resulting yellow viscous oil with hexane).

*Methyl S-Benzyl-N-(pyridin-2-ylcarbonyl)homocysteinate (**6a**).*



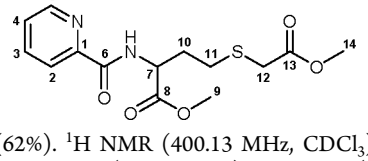
Yield: 0.58 g (97%). Mp: 42−43 °C. ^{1}H NMR (600.22 MHz, $CDCl_3$): δ 2.07−2.13 (m, 1H, CH_2), 2.24−2.30 (m, 1H, CH_2), 2.47−2.55 (m, 2H, CH_2S), 3.73 (s, 2H, CH_2Ph), 3.77 (s, 3H, OMe), 4.89−4.92 (m, 1H, CH), 7.19−7.21 (m, 1H, H(C16)), 7.24−7.27 (m, 2H, H(C15) + H(C17)), 7.28−7.30 (m, 2H, H(C14) + H(C18)), 7.47 (ddd, 1H, H(C4), $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.2 Hz), 7.88 (dt, 1H, H(C3), $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz), 8.19 (dd, 1H, H(C2), $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.2 Hz), 8.53 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz), 8.61 (dd, 1H, H(C5), $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.7 Hz) ppm. ^{13}C{^{1}H} NMR (150.93 MHz, $CDCl_3$): δ 26.95 (s, CH_2S), 32.24 (s, CH_2), 36.04 (s, CH_2Ph), 51.60 (s, CH), 52.53 (s, OMe), 122.36 (s, C2), 126.45 (s, C4), 127.00 (s, C16), 128.49 (s, C15 and C17), 128.90 (s, C14 and C18), 137.34 (s, C3), 138.05 (s, C13), 148.29 (s, C5), 149.33 (s, C1), 164.18 (s, C(O)NH), 172.09 (s, C(O)OMe) ppm. ^{15}N NMR (60.85 MHz, $CDCl_3$): δ −275.0 (C(O)NH), −80.0 (Py) ppm. IR (thin film, ν/cm^{-1}): 565(vw), 621(w), 702(m), 751(w), 820(vw), 998(w), 1028(vw), 1042(vw), 1072(vw), 1088(vw), 1174(m), 1224(br, m), 1271(w), 1362(w), 1434(m), 1453(m), 1466(m), 1516(br, s) (C(O)NH), 1570(w), 1591(w), 1678(br, s) (ν(C═O) in C(O)NH), 1742(br, s) (ν(C═O) in C(O)OMe), 2849(vw), 2920(w), 2952(w), 3028(vw), 3060(vw), 3378(br, w) (ν(NH)). Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.61; H, 5.88; N, 8.04.

*Methyl S-Allyl-N-(pyridin-2-ylcarbonyl)homocysteinate (**6b**).*



Yield: 0.42 g (82%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.07−2.16 (m, 1H, CH_2), 2.24−2.33 (m, 1H, CH_2), 2.51−2.63 (m, 2H, CH_2S), 3.16 (d, 2H, CH_2CH═CH_2, $^3J_{HH}$ = 7.2 Hz), 3.81 (s, 3H, OMe), 4.90−4.96 (m, 1H, CH), 5.05−5.10 (m, 2H, CH_2CH═CH_2), 5.72−5.82 (m, 1H, CH_2CH═CH_2), 7.47 (ddd, 1H, H(C4), $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.2 Hz), 7.86−7.90 (m, 1H, H(C3)), 8.20 (d, 1H, H(C2), $^3J_{HH}$ = 7.8 Hz), 8.56 (br d, 1H, NH, $^3J_{HH}$ = 8.4 Hz), 8.61 (d, 1H, H(C5), $^3J_{HH}$ = 4.8 Hz) ppm. ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$): δ 26.21 (s, CH_2S), 32.27 (s, CH_2), 34.55 (s, CH_2CH═CH_2), 51.58 and 52.58 (both s, CH and OMe), 117.26 (s, CH_2CH═CH_2), 122.35 and 126.48 (both s, C2 and C4), 134.08 (s, CH_2CH═CH_2), 137.37 (s, C3), 148.31 (s, C5), 149.29 (s, C1), 164.21 (s, C(O)NH), 172.18 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 621(w), 700(w), 751(m), 821(vw), 921(w), 998(m), 1042(vw), 1088(vw), 1173(m), 1222(br, m), 1271(w), 1292(w), 1362(w), 1434(m), 1466(m), 1518(br, s) (C(O)NH), 1570(w), 1591(w), 1635(vw), 1677(br, s) (ν(C═O) in C(O)NH), 1743(br, s) (ν(C═O) in C(O)OMe), 2850(vw), 2919(w), 2952(w), 3008(vw), 3058(vw), 3378(br, w) (ν(NH)). Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found: C, 57.32; H, 6.44; N, 9.60.

*Methyl S-(2-Methoxy-2-oxoethyl)-N-(pyridin-2-ylcarbonyl)-homocysteinate (**6c**).*



Yield: 0.35 g (62%). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.12−2.21 (m, 1H, CH_2), 2.30−2.39 (m, 1H, CH_2), 2.75−2.78 (m, 2H, CH_2S), 3.27 (s, 2H, CH_2COOMe), 3.73 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.93−4.99 (m, 1H, CH), 7.48 (dd, 1H, H(C4), $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ =

https://doi.org/10.1021/acs.inorgchem.1c01138
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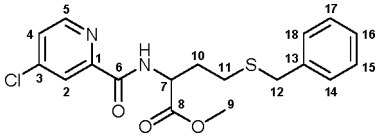
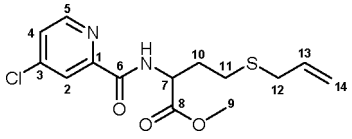
4.8 Hz), 7.86−7.90 (m, 1H, H(C3)), 8.20 (d, 1H, H(C2), $^3J_{HH}$ = 7.8 Hz), 8.58 (br d, 1H, NH, $^3J_{HH}$ = 8.5 Hz), 8.62 (d, 1H, H(C5), $^3J_{HH}$ = 4.8 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 28.41, 31.84, and 33.13 (three s, CH_2S, CH_2 and $CH_2C(O)OMe$), 51.27, 52.28, and 52.52 (three s, CH and OMe in C(O)OMe and $CH_2C(O)OMe$), 122.25 and 126.39 (both s, C2 and C4), 137.26 (s, C3), 148.20 (s, C5), 149.13 (s, C1), 164.16 (s, C(O)NH), 170.61 and 171.91 (both s, C(O)OMe and $CH_2C(O)OMe$) ppm. IR (thin film, ν/cm^{-1}): 621(w), 700(w), 752(w), 821(vw), 998(m), 1042(w), 1089(w), 1172(br, m), 1215(br, m), 1280(br, m), 1362(w), 1435(m), 1466(m), 1517(br, s) (C(O)NH), 1570(w), 1591(w), 1677(br, s) (ν(C═O) in C(O)NH), 1739(br, s) (ν(C═O) in C(O)OMe), 2849(vw), 2953(w), 3002(vw), 3058(vw), 3373(br, w) (ν(NH)). Anal. Calcd for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.56; N, 8.58. Found: C, 51.63; H, 5.96; N, 8.20.

*Methyl S-Benzyl-N-[(4-chloropyridin-2-yl)carbonyl]-homocysteinate (**7a**).*



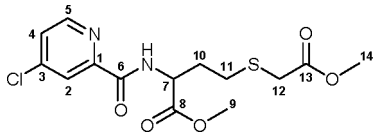
Yield: 0.44 g (67%). ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.05−2.14 (m, 1H, CH_2), 2.21−2.30 (m, 1H, CH_2), 2.43−2.55 (m, 2H, CH_2S), 3.73 (s, 2H, CH_2Ph), 3.78 (s, 3H, OMe), 4.86−4.92 (m, 1H, CH), 7.19−7.31 (m, 5H, H_{Ar}), 7.48 (dd, 1H, H(C4), $^3J_{HH}$ = 5.2 Hz, $^4J_{HH}$ = 2.1 Hz), 8.20 (d, 1H, H(C2), $^4J_{HH}$ = 2.1 Hz), 8.46 (br d, 1H, NH, $^3J_{HH}$ = 8.3 Hz), 8.51 (d, 1H, H(C5), $^3J_{HH}$ = 5.2 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 26.83 (s, CH_2S), 32.07 (s, CH_2), 36.00 (s, CH_2Ph), 51.66 and 52.64 (both s, CH and OMe), 123.02 and 126.63 (both s, C2 and C4), 127.03 (s, C16), 128.51 and 128.90 (both s, C15 + C17 and C14 + C18), 137.97 (s, C13), 145.90 (s, C3), 149.20 (s, C5), 150.73 (s, C1), 163.01 (s, C(O)NH), 171.94 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 527(w), 565(vw), 702(m), 743(w), 783(w), 843(vw), 902(vw), 994(vw), 1072(vw), 1096(w), 1175(m), 1223(br, m), 1305(w), 1356(w), 1438(m), 1453(m), 1518(br, s) (C(O)NH), 1557(m), 1579(m), 1680(br, s) (ν(C═O) in C(O)NH), 1743(br, s) (ν(C═O) in C(O)OMe), 2851(vw), 2921(w), 2952(w), 3028(vw), 3060(vw), 3379(br, w) (ν(NH)). Anal. Calcd for $C_{18}H_{19}ClN_2O_3S$: C, 57.06; H, 5.05; N, 7.39. Found: C, 57.45; H, 5.40; N, 7.08.

*Methyl S-Allyl-N-[(4-chloropyridin-2-yl)carbonyl]-homocysteinate (**7b**).*



Yield: 0.31 g (54%). ^1H NMR (600.22 MHz, $CDCl_3$, 253 K): δ 2.06−2.12 (m, 1H, CH_2), 2.23−2.29 (m, 1H, CH_2), 2.47−2.56 (m, 2H, CH_2S), 3.14 (d, 2H, $CH_2CH═CH_2$, $^3J_{HH}$ = 7.3 Hz), 3.80 (s, 3H, OMe), 4.90−4.94 (m, 1H, CH), 5.03−5.07 (m, 2H, $CH_2CH═CH_2$), 5.69−5.76 (m, 1H, $CH_2CH═CH_2$), 7.49−7.50 (m, 1H, H(C4)), 8.19 (s, 1H, H(C2)), 8.52 (d, 1H, H(C5), $^3J_{HH}$ = 5.2 Hz), 8.54 (br d, 1H, NH, $^3J_{HH}$ = 8.5 Hz) ppm. $^{13}C\{^1H\}$ NMR (150.93 MHz, $CDCl_3$, 253 K): δ 25.56 (s, CH_2S), 31.78 (s, CH_2), 34.26 (s, $CH_2CH═CH_2$), 51.48 (s, CH), 53.04 (s, OMe), 117.70 (s, $CH_2CH═CH_2$), 123.08 (s, C2), 126.91 (s, C4), 133.87 (s, $CH_2CH═CH_2$), 145.96 (s, C3), 149.34 (s, C5), 150.36 (s, C1), 163.15 (s, C(O)NH), 172.23 (s, C(O)OMe) ppm. ^{15}N NMR (60.85 MHz, $CDCl_3$, 253 K): δ −273.8 (C(O)NH), −85.4 (Py) ppm. IR (thin film, ν/cm^{-1}): 527(w), 693(w), 743(m), 783(w), 843(w), 919(w), 994(w), 1097(w), 1175(m), 1221(br, m), 1259(w), 1305(w), 1356(m), 1438(m), 1462(m), 1519(br, s) (C(O)NH), 1557(m), 1579(m), 1634(w), 1679(br, s) (ν(C═O) in C(O)NH), 1743(br, s) (ν(C═O) in C(O)OMe), 2850(vw), 2918(w), 2952(w), 3080(vw), 3379(br, w) (ν(NH)). Anal. Calcd for $C_{14}H_{17}ClN_2O_3S$: C, 51.14; H, 5.21; N, 8.52. Found: C, 51.04; H, 5.27; N, 8.34.

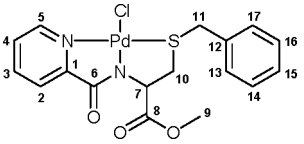
*Methyl N-[(4-Chloropyridin-2-yl)carbonyl]-S-(2-methoxy-2-oxoethyl)homocysteinate (**7c**).*



Yield: 0.21 g (33%). ^1H NMR (500.13 MHz, $CDCl_3$): δ 2.13−2.20 (m, 1H, CH_2), 2.30−2.37 (m, 1H, CH_2), 2.71−2.80 (m, 2H, CH_2S), 3.26 (s, 2H, CH_2COOMe), 3.74 (s, 3H, OMe in $CH_2C(O)OMe$), 3.82 (s, 3H, OMe in C(O)OMe), 4.92−4.96 (m, 1H, CH), 7.48 (dd, 1H, H(C4), $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 2.1 Hz), 8.16 (d, 1H, H(C2), $^4J_{HH}$ = 2.1 Hz), 8.49−8.52 (m, 2H, NH + H(C5)) ppm. $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): δ 28.47 (s, CH_2S), 31.86 (s, CH_2), 33.24 (s, CH_2COOMe), 51.49 (s, CH), 52.43 (s, OMe in $CH_2C(O)OMe$), 52.72 (s, OMe in C(O)OMe), 123.05 (s, C2), 126.67 (s, C4), 145.94 (s, C3), 149.22 (s, C5), 150.70 (s, C1), 163.12 (s, C(O)NH), 170.69 (s, $CH_2C(O)OMe$), 171.86 (s, C(O)OMe) ppm. IR (thin film, ν/cm^{-1}): 527(w), 693(w), 743(w), 783(w), 814(w), 844(w), 901(vw), 1009(w), 1134(m), 1160(m), 1220(br, m), 1281(br, m), 1355(m), 1393(w), 1436(m), 1520(br, s) (C(O)NH), 1557(m), 1579(m), 1683(br, s) (ν(C═O) in C(O)NH), 1739(br, s) (ν(C═O) in C(O)OMe), 2849(vw), 2953(w), 3060(vw), 3374(br, w) (ν(NH)). Anal. Calcd for $C_{14}H_{17}ClN_2O_5S$: C, 46.60; H, 4.75; N, 7.76. Found: C, 46.61; H, 4.71; N, 7.69.

*General Procedure for the Synthesis of Pd(II) Pincer Complexes **8**−**11**.* A solution of $PdCl_2(NCPh)_2$ (76 mg, 0.198 mmol) in 3 mL of dichloromethane was added dropwise to a solution of the corresponding ligand (0.198 mmol) and Et_3N (28 μL, 0.201 mmol) in 6 mL of CH_2Cl_2. The reaction mixture was left under ambient conditions for 12 h and then purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH (100/1)) to give the target Pd(II) pincer complexes as yellow (**8a**−**c**, **9a**−**c**, **10b**,**c**, **11a**,**c**), light yellow (**10a**), or dark yellow (**11b**) crystalline solids.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**8a**).*



Yield: 70 mg (75%). Mp: 185−187 °C. ^1H NMR (500.13 MHz, $CDCl_3$, major isomer (M) 66%, minor isomer (m) 34%): δ 2.99 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 6.5 Hz), 3.13−3.22 (m, 1H, CH_2S (M) + 2H, CH_2S (m)), 3.74 (s, 3H, OMe (M)), 3.88 (s, 3H, OMe (m)), 4.33 and 4.36 (ABq, 2H, CH_2Ph (m), J_{AB} = 13.8 Hz), 4.38 and 4.40 (ABq, 2H, CH_2Ph (M), J_{AB} = 13.8 Hz), 4.71 (dd, 1H, CH (m), $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 3.4 Hz), 4.74 (dd, 1H, CH (M), $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 2.1 Hz), 7.36−7.44 (m, 1H, H(C15) (M) + 1H, H(C15) (m) + 2H, H(C14) + H(C16) (M) + 2H, H(C14) + H(C16) (m) + 2H, H(C13) + H(C17) (m)), 7.50−7.52 (m, 2H, H(C13) + HC(17) (M)), 7.55−7.60 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.90−7.93 (m, 1H, H(C2) (M) + 1H, H(C2) (m)), 8.04−8.08 (m, 1H, H(C3) (M) + 1H, H(C3) (m)), 8.89 (d, 1H, H(C5) (M), $^3J_{HH}$ = 5.2 Hz), 8.91 (d, 1H, H(C5) (m), $^3J_{HH}$ = 5.2 Hz) ppm. $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): δ 40.96 (s, CH_2Ph (m)), 41.01 (s, CH_2S (m)), 42.54 (s, CH_2Ph (M)), 43.92 (s, CH_2S (M)), 52.98 (s, OMe (M)), 53.04 (s, OMe (m)), 59.36 (s, CH (M)), 61.58 (s, CH (m)), 125.84 (s, C2 (m)), 125.90 (s, C2 (M)), 127.21 (s, C4 (M)), 127.34 (s, C4 (m)), 128.96 (s, C15 (m)), 129.10 (s, C15 (M)), 129.32 (s, C14 + C16 (m)), 129.40 (s, C14 + C16 (M)), 129.57 (s, C13 + C17 (m)), 129.87 (s, C13 + C17 (M)), 132.41 (s, C12 (M)), 132.68 (s, C12 (m)), 140.32 (s, C3 (M)), 140.41 (s, C3 (m)), 147.85 (s, C5 (m)), 147.94 (s, C5 (M)), 155.61 (s, C1 (M + m)), 169.42 (s, C(O)N (M)), 169.86 (s, C(O)N (m)), 170.22 (s, C(O)OMe (M)), 171.71 (s, C(O)OMe (m)) ppm. IR (KBr, ν/cm^{-1}): 504(w), 658(vw), 688(m), 706(m), 758(m), 811(vw), 991(vw), 1020(w), 1049(w), 1072(vw), 1096(w), 1172(m), 1213(m), 1292(m), 1389(s), 1435(w), 1453(w), 1477(w), 1494(w), 1569(w), 1600(s), 1630(s) (ν(C═O) in C(O)N),

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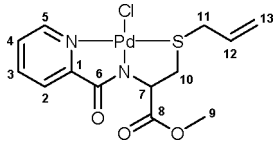
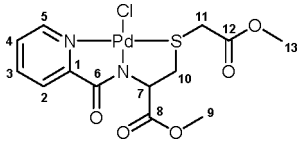
1738(s) (ν(C=O) in C(O)OMe), 2934(w), 2992(vw), 3056(w). Anal. Calcd for $C_{17}H_{17}ClN_2O_3PdS$: C, 43.33; H, 3.64; N, 5.94. Found: C, 43.31; H, 3.69; N, 5.98.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**8b**).*



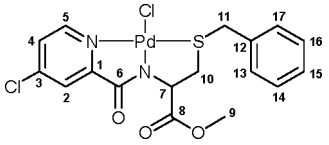
Yield: 68 mg (82%). Mp: 142−144 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, major isomer (M) 72%, minor isomer (m) 28%): δ 3.16 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.7 Hz), 3.26−3.38 (m, 1H, CH_2S (M) + 2H, CH_2S (m)), 3.48 (dd, 1H, CH_2CH=CH_2 (M), $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 8.1 Hz), 3.66 (dd, 1H, CH_2CH=CH_2 (m), $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 5.9 Hz), 3.77−3.88 (m, 1H, CH_2CH=CH_2 (M) + 1H, CH_2CH=CH_2 (m)), 3.78 (s, 3H, OMe (M)), 3.82 (s, 3H, OMe (m)), 4.70 (dd, 1H, CH (m), $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 3.8 Hz), 4.85 (dd, 1H, CH (M), $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 1.7 Hz), 5.36 (d, 1H, CH_2CH=CH_2 (m), $^3J_{HH}$ = 17.1 Hz), 5.38 (d, 1H, CH_2CH=CH_2 (M), $^3J_{HH}$ = 17.0 Hz), 5.45 (d, 1H, CH_2CH=CH_2 (m), $^3J_{HH}$ = 10.1 Hz), 5.49 (d, 1H, CH_2CH=CH_2 (M), $^3J_{HH}$ = 10.1 Hz), 5.89−5.99 (m, 1H, CH_2CH=CH_2 (m)), 6.18−6.28 (m, 1H, CH_2CH=CH_2 (M)), 7.54−7.59 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.90 (dd, 1H, H(C2) (m), $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz), 7.93 (dd, 1H, H(C2) (M), $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.6 Hz), 8.03−8.08 (m, 1H, H(C3) (M) + 1H, H(C3) (m)), 8.85−8.88 (m, 1H, H(C5), (M) + 1H, H(C5) (m)) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 39.47 (s, CH_2CH=CH_2 (m)), 40.43 (s, CH_2CH=CH_2 (M)), 40.93 (s, CH_2S (m)), 42.78 (s, CH_2S (M)), 53.00 (s, OMe (m)), 53.04 (s, OMe (M)), 59.37 (s, CH (M)), 61.50 (s, CH (m)), 122.90 (s, CH_2CH=CH_2 (M)), 123.13 (s, CH_2CH=CH_2 (m)), 125.84 (s, C2 (m)), 125.88 (s, C2 (M)), 127.23 (s, C4 (M)), 127.34 (s, C4 (m)), 129.20 (s, CH_2CH=CH_2 (m)), 130.14 (s, CH_2CH=CH_2 (M)), 140.32 (s, C3 (M)), 140.43 (s, C3 (m)), 147.77 (s, C5 (m)), 147.85 (s, C5 (M)), 155.59 (s, C1 (m)), 155.64 (s, C1 (M)), 169.45 (s, C(O)N (M)), 169.81 (s, C(O)N (m)), 170.39 (s, C(O)OMe (M)), 171.40 (s, C(O)OMe (m)) ppm. IR (KBr, ν/cm^{-1}): 499(w), 685(w), 767(w), 945(w), 1010(w), 1093(w), 1164(m), 1212(m), 1292(w), 1330(w), 1382(m), 1431(w), 1602(s), 1641(s) (ν(C=O) in C(O)N), 1752(s) (ν(C=O) in C(O)OMe), 2951(vw), 2994(vw), 3075(vw). Anal. Calcd for $C_{13}H_{15}ClN_2O_3PdS$: C, 37.07; H, 3.59; N, 6.65. Found: C, 36.93; H, 3.88; N, 6.75.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**8c**).*



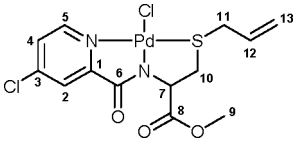
Yield: 80 mg (89%). Mp: 136−138 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, major isomer (M) 64%, minor isomer (m) 36%): δ 3.42 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 6.5 Hz), 3.52 (dd, 1H, CH_2S (m), $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 7.0 Hz), 3.65 (dd, 1H, CH_2S (m), $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 3.0 Hz), 3.75 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 1.9 Hz), 3.80 (s, 3H, OMe (M)), 3.81 (s, 3H, OMe (m)), 3.83 (s, 3H, OMe (m)), 3.84 (s, 3H, OMe (M)), 3.85−3.89 (m, 1H, $CH_2C(O)OMe$ (m)), 4.11 and 4.15 (ABq, 2H, $CH_2C(O)OM$ (M), J_{AB} = 16.4 Hz), 4.23 (d, 1H, $CH_2C(O)OMe$ (m), $^2J_{HH}$ = 16.4 Hz), 4.74 (dd, 1H, CH (m), $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 3.0 Hz), 4.83 (dd, 1H, CH (M), $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 1.9 Hz), 7.51−7.59 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.87−7.90 (m, 1H, H(C2) (m)), 7.94−7.96 (m, 1H, H(C2) (M)), 8.03−8.08 (m, 1H, H(C3) (M) + 1H, H(C3) (m)), 8.74 (d, 1H, H(C5) (M), $^3J_{HH}$ = 5.4 Hz), 8.84 (d, 1H, H(C5) (m), $^3J_{HH}$ = 5.9 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 37.23 (s, $CH_2C(O)OMe$ (m)), 40.03 (s, $CH_2C(O)OMe$ (M)), 43.49 (s, CH_2S (m)), 46.93 (s, CH_2S (M)), 53.10 (s, OMe (M)), 53.13 (s, OMe (m)), 53.38 (s, OMe (m)), 53.43 (s, OMe (M)), 59.66 (s, CH (M)), 61.25 (s, CH (m)), 125.98 (s, C2 (m)), 126.16 (s, C2 (M)), 127.24 (s, C4 (M)), 127.44 (s, C4 (m)), 140.55 (s, C3 (m + M)), 147.86 (s, C5 (m)), 147.91 (s, C5 (M)), 155.49 (s, C1 (M)), 155.52 (s, C1 (m)), 166.28 (s, $CH_2C(O)OMe$ (m)), 166.58 (s, $CH_2C(O)OMe$ (M)), 169.41 (s, C(O)N (M)), 169.72 (s, C(O)N (m)), 170.07 (s, C(O)OMe (M)), 171.59 (s, C(O)OMe (m)) ppm. IR (KBr, ν/cm^{-1}): 505(vw), 659(vw), 683(w), 759(w), 809(vw), 887(vw), 1015(w), 1094(w), 1170(m), 1202(m), 1274(m), 1291(m), 1308(m), 1386(m), 1435(m), 1601(s), 1636(s) (ν(C=O) in C(O)N), 1741(s) (ν(C=O) in C(O)OMe), 2853(vw), 2953(w). Anal. Calcd for $C_{13}H_{15}ClN_2O_5PdS$: C, 34.45; H, 3.34; N, 6.18. Found: C, 34.48; H, 3.41; N, 6.31.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**9a**).*



Yield: 91 mg (91%). Mp: 151−153 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, major isomer (M) 64%, minor isomer (m) 36%): δ 2.97 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 6.5 Hz), 3.13−3.24 (m, 1H, CH_2S (M) + 2H, CH_2S (m)), 3.75 (s, 3H, OMe (M)), 3.89 (s, 3H, OMe (m)), 4.30−4.42 (m, 2H, CH_2Ph (M) + 2H, CH_2Ph (m)), 4.70−4.75 (m, 1H, CH (M) + 1H, CH (m)), 7.35−7.45 (m, 1H, H(C15) (M) + 1H, H(C15) (m) + 2H, H(C14) + H(C16) (M) + 2H, H(C14) + H(C16) (m) + 2H, H(C13) + H(C17) (m)), 7.50−7.53 (m, 2H, H(C13) + H(C17) (M)), 7.55−7.59 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.90 (d, 1H, H(C2) (m), $^4J_{HH}$ = 2.4 Hz), 7.91 (d, 1H, H(C2) (M), $^4J_{HH}$ = 2.4 Hz), 8.81 (d, 1H, H(C5) (M), $^3J_{HH}$ = 5.9 Hz), 8.82 (d, 1H, H(C5) (m), $^3J_{HH}$ = 5.9 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 41.01 and 41.05 (both s, CH_2Ph (m) and CH_2S (m)), 42.57 (s, CH_2Ph (M)), 43.93 (s, CH_2S (M)), 53.04 (s, OMe (M)), 53.10 (s, OMe (m)), 59.45 (s, CH (M)), 61.75 (s, CH (m)), 126.30 (s, C2 (m)), 126.35 (s, C2 (M)), 127.35 (s, C4 (M)), 127.47 (s, C4 (m)), 129.03 (s, C15 (m)), 129.19 (s, C15 (M)), 129.36 (s, C14 + C16 (m)), 129.44 (s, C14 + C16 (M)), 129.57 (s, C13 + C17 (m)), 129.89 (s, C13 + C17 (M)), 132.22 (s, C12 (M)), 132.52 (s, C12 (m)), 148.46 (s, C5 (m)), 148.54 (s, C5 (M)), 149.12 (s, C3 (M)), 149.22 (s, C3 (m)), 156.73 (s, C1 (M + m)), 168.31 and 169.98 (both s, C(O)N (M) and C(O)OMe (M)) ppm (the signals of C(O)N (m) and C(O)OMe (m) carbon nuclei were not observed). IR (KBr, ν/cm^{-1}): 533(w), 702(m), 767(m), 843(w), 912(vw), 1021(w), 1107(w), 1171(m), 1202(m), 1252(w), 1364(m), 1422(m), 1454(w), 1495(w), 1553(w), 1595(s), 1641(s) (ν(C=O) in C(O)N), 1742(s) (ν(C=O) in C(O)OMe), 2951(w), 3030(vw), 3065(vw). Anal. Calcd for $C_{17}H_{16}Cl_2N_2O_3PdS$: C, 40.38; H, 3.19; N, 5.54. Found: C, 40.51; H, 3.28; N, 5.44.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**9b**).*



Yield: 83 mg (92%). Mp: 141−143 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$, major isomer (M) 73%, minor isomer (m) 27%): δ 3.15 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.6 Hz), 3.26−3.31 (m, 1H, CH_2S (M) + 1H, CH_2S (m)), 3.37 (dd, 1H, CH_2S (m), $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 3.6 Hz), 3.47 (dd, 1H, CH_2CH=CH_2 (M), $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 8.1 Hz), 3.66 (dd, 1H, CH_2CH=CH_2 (m), $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 5.9 Hz), 3.77−3.87 (m, 1H, CH_2CH=CH_2 (M) + 1H, CH_2CH=CH_2 (m)), 3.79 (s, 3H, OMe (M)), 3.83 (s, 3H, OMe (m)), 4.72 (dd, 1H, CH (m), $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 3.6 Hz), 4.84 (dd, 1H, CH (M), $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 1.7 Hz), 5.37 (d, 1H, CH_2CH=CH_2 (m), $^3J_{HH}$ = 17.1 Hz), 5.39 (d, 1H, CH_2CH=CH_2 (M), $^3J_{HH}$ = 17.0 Hz), 5.46 (d, 1H, CH_2CH=CH_2 (m), $^3J_{HH}$ = 10.1 Hz), 5.51 (d, 1H, CH_2CH=CH_2 (M), $^3J_{HH}$ = 10.0 Hz), 5.89−5.98 (m, 1H, CH_2CH=CH_2 (m)), 6.19−6.27 (m, 1H, CH_2CH=CH_2 (M)), 7.54−7.57 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.90 (d, 1H, H(C2) (m), $^4J_{HH}$ = 2.1 Hz), 7.93 (d, 1H, H(C2) (M), $^4J_{HH}$ = 2.2 Hz), 8.78 (d, 1H, H(C5) (M), $^3J_{HH}$ = 5.7 Hz), 8.79 (d, 1H, H(C5)

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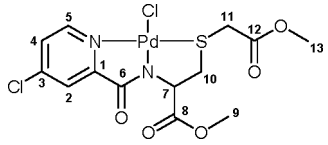
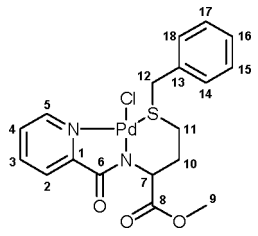
(m), $^{3}J_{HH}$ = 5.0 Hz) ppm. $^{13}C\{^{1}H\}$ NMR (125.76 MHz, $CDCl_3$): δ 39.56 (s, $CH_2CH{=}CH_2$ (m)), 40.52 (s, $CH_2CH{=}CH_2$ (M)), 40.98 (s, CH_2S (m)), 42.83 (s, CH_2S (M)), 53.05 (s, OMe (m)), 53.09 (s, OMe (M)), 59.49 (s, CH (M)), 61.67 (s, CH (m)), 123.04 (s, $CH_2CH{=}CH_2$ (M)), 123.27 (s, $CH_2CH{=}CH_2$ (m)), 126.32 (s, C2 (m)), 126.36 (s, C2 (M)), 127.32 (s, C4 (M)), 127.43 (s, C4 (m)), 129.05 (s, $CH_2CH{=}CH_2$ (m)), 130.04 (s, $CH_2CH{=}CH_2$ (M)), 148.38 (s, C5 (m)), 148.45 (s, C5 (M)), 149.10 (s, C3 (M)), 149.22 (s, C3 (m)), 156.74 (s, C1 (m)), 156.80 (s, C1 (M)), 168.33 (s, C(O)N (M)), 168.71 (s, C(O)N (m)), 170.15 (s, *C*(O)OMe (M)), 171.18 (s, C(O)OMe (m)) ppm. IR (KBr, ν/cm^{-1}): 516(w), 541(w), 741(w), 767(m), 856(w), 934(w), 991(w), 1033(w), 1110(m), 1166(w), 1202(m), 1251(w), 1348(sh, m), 1359(m), 1416(m), 1456(w), 1551(w), 1595(s), 1640(s) (ν(C=O) in C(O)N), 1741(s) (ν(C=O) in C(O)OMe), 2935(w), 3085(vw). Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_3PdS$: C, 34.27; H, 3.10; N, 6.15. Found: C, 34.41; H, 3.19; N, 6.28.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**9c**).*



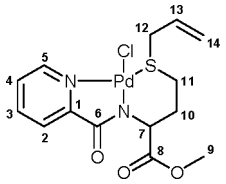
Yield: 43 mg (45%). Mp: 123−125 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$, major isomer (M) 61%, minor isomer (m) 39%): δ 3.37 (br s, 1H, CH_2S (M)), 3.49 (dd, 1H, CH_2S (m), $^{2}J_{HH}$ = 13.9 Hz, $^{3}J_{HH}$ = 6.9 Hz), 3.65−3.68 (m, 1H, CH_2S (m)), 3.75 (br d, 1H, CH_2S (M), $^{3}J_{HH}$ = 10.3 Hz), 3.80 (s, 3H, OMe in C(O)OMe (M)), 3.81 (s, 3H, OMe in C(O)OMe (m)), 3.84 (s, 3H, OMe in $CH_2C(O)OMe$ (m)), 3.85 (s, 3H, OMe in $CH_2C(O)OMe$ (M)), 3.85−3.88 (m, 1H, $CH_2C(O)OMe$ (m)), 4.00 (d, 1H, $CH_2C(O)OMe$ (M), $^{2}J_{HH}$ = 16.3 Hz), 4.13 (d, 1H, $CH_2C(O)OMe$ (M), $^{2}J_{HH}$ = 16.3 Hz), 4.22 (d, 1H, $CH_2C(O)OMe$ (m), $^{2}J_{HH}$ = 16.4 Hz), 4.75−4.77 (m, 1H, CH (m)), 4.85 (br s, 1H, CH (M)), 7.54 (dd, 1H, H(C4) (M), $^{3}J_{HH}$ = 5.9 Hz, $^{4}J_{HH}$ = 2.1 Hz), 7.56 (dd, 1H, H(C4) (m), $^{3}J_{HH}$ = 5.9 Hz, $^{4}J_{HH}$ = 2.2 Hz), 7.89 (d, 1H, H(C2) (m), $^{4}J_{HH}$ = 2.2 Hz), 7.93 (d, 1H, H(C2) (M), $^{4}J_{HH}$ = 2.1 Hz), 8.74 (d, 1H, H(C5) (M), $^{3}J_{HH}$ = 5.9 Hz), 8.77 (d, 1H, H(C5) (m), $^{3}J_{HH}$ = 5.9 Hz) ppm. $^{13}C\{^{1}H\}$ NMR (100.61 MHz, $CDCl_3$): δ 37.26 (s, $CH_2C(O)OMe$ (m)), 39.97 (s, $CH_2C(O)OMe$ (M)), 43.50 (s, CH_2S (m)), 47.00 (s, CH_2S (M)), 53.16 (s, OMe (M)), 53.20 (s, OMe (m)), 53.42 (s, OMe (m)), 53.49 (s, OMe (M)), 59.71 (s, CH (M)), 61.41 (s, CH (m)), 126.42 (s, C2 (m)), 126.51 (s, C2 (M)), 127.41 (s, C4 (M)), 127.54 (s, C4 (m)), 148.46 (s, C5 (m)), 148.55 (s, C5 (M)), 149.29 (s, C3 (M)), 149.38 (s, C3 (m)), 156.67 (s, C1 (m + M)), 166.15 (s, $CH_2C(O)OMe$ (m)), 166.42 (s, $CH_2C(O)OMe$ (M)), 168.29 (br s, C(O)N (M)), 168.63 (br s, C(O)N (m)), 169.85 (s, *C*(O)OMe (M)), 171.39 (s, C(O)OMe (m)) ppm. IR (KBr, ν/cm^{-1}): 534(w), 696(vw), 767(w), 846(w), 912(vw), 1015(w), 1033(w), 1107(w), 1170(m), 1202(m), 1273(br, m), 1308(m), 1365(m), 1423(m), 1435(m), 1553(w), 1596(s), 1640(s) (ν(C=O) in C(O)N), 1741(s) (ν(C=O) in C(O)OMe), 2849(vw), 2953(w), 3000(vw), 3087(vw). Anal. Calcd for $C_{13}H_{14}Cl_2N_2O_5PdS$: C, 32.02; H, 2.89; N, 5.74. Found: C, 32.07; H, 2.91; N, 5.49.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**10a**).*



Yield: 90 mg (90%). Mp: >250 °C. ^{1}H NMR (600.22 MHz, $CDCl_3$, 263 K, major isomers (M) 59%, minor isomers (m) 41%): δ 1.81−1.86 (m, 1H, CH_2 (m)), 1.90−1.95 (m, 1H, CH_2 (M)), 1.98−2.07 (m, 1H, CH_2S (M) + 1H, CH_2S (m)), 2.13 (dd, 1H, CH_2S (M), $^{2}J_{HH}$ = 14.5 Hz, $^{3}J_{HH}$ = 5.2 Hz), 2.27 (dd, 1H, CH_2S (m), $^{2}J_{HH}$ = 13.0 Hz, $^{3}J_{HH}$ = 6.8 Hz), 2.53−2.58 (m, 1H, CH_2 (m)), 2.60−2.64 (m, 1H, CH_2 (M)), 3.71 (s, 3H, OMe (M + m)), 4.24 (d, 1H, CH_2Ph (M), $^{2}J_{HH}$ = 13.6 Hz), 4.30 (d, 1H, CH_2Ph (m), $^{2}J_{HH}$ = 13.6 Hz), 4.53 (d, 1H, CH_2Ph (m), $^{2}J_{HH}$ = 13.6 Hz), 4.54 (d, 1H, CH_2Ph (M), $^{2}J_{HH}$ = 13.6 Hz), 4.57−4.58 (m, 1H, CH (m)), 4.67−4.68 (m, 1H, CH (M)), 7.38−7.46 (m, 5H, H_{Ar} (M) + 5H, H_{Ar} (m)), 7.56−7.58 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.99−8.01 (m, 1H, H(C2) (M) + 1H, H(C2) (m)), 8.05−8.07 (m, 1H, H(C3) (M) + 1H, H(C3) (m)), 9.13 (d, 1H, H(C5) (M + m), $^{3}J_{HH}$ = 5.5 Hz) ppm. $^{13}C\{^{1}H\}$ NMR (150.93 MHz, $CDCl_3$, 263 K): δ 21.62 (s, CH_2S (M)), 24.11 (s, CH_2S (m)), 30.53 (s, CH_2 (m)), 30.69 (s, CH_2 (M)), 41.64 (s, CH_2Ph (M)), 43.79 (s, CH_2Ph (m)), 52.57 (s, OMe (M + m)), 52.73 (s, CH (M)), 53.61 (s, CH (m)), 125.59 (s, C2 (M + m)), 126.92 (s, C4 (M + m)), 128.85 (s, C16 (m)), 129.00 (s, C16 (M)), 129.28 (s, C15 + C17 (m)), 129.43 (s, C15 + C17 (M)), 129.82 (s, C14 + C18 (m)), 129.94 (s, C14 + C18 (M)), 133.01 (s, C13 (M)), 133.33 (s, C13 (m)), 140.44 (s, C3 (m)), 140.49 (s, C3 (M)), 147.87 (s, C5 (m)), 147.93 (s, C5 (M)), 153.21 (s, C1 (M + m)), 172.28 (s, *C*(O)OMe (M)), 172.79 (s, *C*(O)OMe (m)), 173.15 (s, C(O)N (m)), 173.20 (s, C(O)N (M)) ppm. ^{15}N NMR (60.85 MHz, $CDCl_3$, 295 K): δ −250.5 (C(O)N), −158.7 (Py) ppm. IR (KBr, ν/cm^{-1}): 497(vw), 571(vw), 660(vw), 689(w), 708(m), 755(w), 783(m), 810(vw), 845(vw), 874(vw), 969(vw), 1017(w), 1055(w), 1067(w), 1116(w), 1215(m), 1253(m), 1280(w), 1295(w), 1380(m), 1419(w), 1436(w), 1481(w), 1570(w), 1597(s), 1625(s) (ν(C=O) in C(O)N), 1718(s) (ν(C=O) in C(O)OMe), 2851(vw), 2937(vw), 3027(vw). Anal. Calcd for $C_{18}H_{19}ClN_2O_3PdS \cdot 0.2\ CH_2Cl_2$: C, 43.52; H, 3.89; N, 5.58. Found: C, 43.33; H, 4.14; N, 5.66.

*Complex [κ^3-S,N,N-(L)Pd^{II}Cl] (**10b**).*



Yield: 70 mg (81%). Mp: 152−154 °C. ^{1}H NMR (600.22 MHz, $CDCl_3$, 263 K, major isomers (M) 51%, minor isomers (m) 49%): δ 1.83−1.88 (m, 1H, CH_2 (M)), 2.03−2.07 (m, 1H, CH_2 (m)), 2.14−2.20 (m, 1H, CH_2S (M) + 1H, CH_2S (m)), 2.38 (dd, 1H, CH_2S (m), $^{2}J_{HH}$ = 14.5 Hz, $^{3}J_{HH}$ = 5.3 Hz), 2.46 (dd, 1H, CH_2S (M), $^{2}J_{HH}$ = 12.8 Hz, $^{3}J_{HH}$ = 6.5 Hz), 2.61−2.70 (m, 1H, CH_2 (M) + 1H, CH_2 (m)), 3.46 (dd, 1H, $CH_2CH{=}CH_2$ (M), $^{2}J_{HH}$ = 13.5 Hz, $^{3}J_{HH}$ = 8.0 Hz), 3.74 (s, 3H, OMe (m)), 3.75 (s, 3H, OMe (M)), 3.74−3.79 (m, 1H, $CH_2CH{=}CH_2$ (m)), 3.82−3.85 (m, 1H, $CH_2CH{=}CH_2$ (m)), 3.90 (dd, 1H, $CH_2CH{=}CH_2$ (M), $^{2}J_{HH}$ = 13.5 Hz, $^{3}J_{HH}$ = 6.9 Hz), 4.63−4.64 (m, 1H, CH (M)), 4.66−4.67 (m, 1H, CH (m)), 5.27 (d, 1H, $CH_2CH{=}CH_2$ (M), $^{3}J_{HH}$ = 16.9 Hz), 5.34 (d, 1H, $CH_2CH{=}CH_2$ (m), $^{3}J_{HH}$ = 16.9 Hz), 5.39−5.42 (m, 1H, $CH_2CH{=}CH_2$ (M) + 1H, $CH_2CH{=}CH_2$ (m)), 5.95−6.02 (m, 1H, $CH_2CH{=}CH_2$ (m)), 6.14−6.21 (m, 1H, $CH_2CH{=}CH_2$ (M)), 7.53−7.56 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.97−7.99 (m, 1H, H(C2) (M) + 1H, H(C2) (m)), 8.03−8.06 (m, 1H, H(C3) (M) + 1H, H(C3) (m)), 9.06−9.08 (m, 1H, H(C5) (M) + 1H, H(C5) (m)) ppm. $^{13}C\{^{1}H\}$ NMR (150.93 MHz, $CDCl_3$, 263 K): δ 22.11 (s, CH_2S (m)), 23.09 (s, CH_2S (M)), 30.41 (s, CH_2 (M)), 31.24 (s, CH_2 (m)), 41.18 (s, $CH_2CH{=}CH_2$ (m)), 42.07 (s, $CH_2CH{=}CH_2$ (M)), 52.57 (s, OMe (M)), 52.61 (s, OMe (m)), 52.69 (s, CH (m)), 53.11 (s, CH (M)), 122.10 (s, $CH_2CH{=}CH_2$ (M)), 122.70 (s, $CH_2CH{=}CH_2$ (m)), 125.56 (s, C2 (M + m)), 126.91 (s, C4 (M + m)), 130.57 (s, $CH_2CH{=}CH_2$ (m)), 130.95 (s, $CH_2CH{=}CH_2$ (M)), 140.44 (s, C3 (M)), 140.49 (s, C3 (m)), 147.74 (s, C5 (m)), 147.84 (s, C5 (M)), 153.03 (s, C1 (M)), 153.17 (s, C1 (m)), 172.35 (s, *C*(O)OMe (m)), 172.60 (s, *C*(O)OMe (M)), 173.14 (br s, C(O)N (M + m)) ppm. IR (KBr, ν/cm^{-1}): 500(w), 659(vw), 683(w), 759(w), 809(vw), 933(w), 991(vw), 1053(w), 1073(w), 1094(w), 1121(w), 1171(m), 1199(m), 1293(w), 1376(m), 1426(w), 1440(w), 1481(vw), 1571(w), 1599(s), 1621(s) (ν(C=O) in C(O)N), 1743(m) (ν(C=O) in C(O)OMe), 2849(vw), 2949(w), 2975(w), 3077(vw). Anal. Calcd for

https://doi.org/10.1021/acs.inorgchem.1c01138
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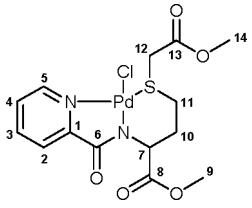
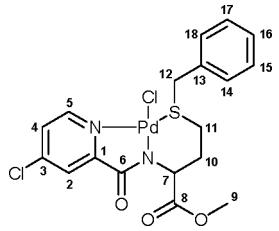
$C_{14}H_{17}ClN_2O_3PdS$: C, 38.63; H, 3.94; N, 6.44. Found: C, 38.70; H, 3.71; N, 6.53.

*Complex [κ³-S,N,N-(L)Pd^{II}Cl] (**10c**).*



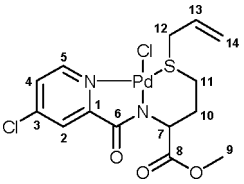
Yield: 86 mg (93%). Mp: 159−161 °C. ^{1}H NMR (600.22 MHz, $CDCl_3$, 233 K, major isomers (M) 51%, minor isomers (m) 49%): δ 1.83−1.89 (m, 1H, CH_2 (m)), 2.09−2.14 (m, 1H, CH_2 (M)), 2.24−2.34 (m, 1H, CH_2S (M) + 1H, CH_2S (m)), 2.65−2.74 (m, 1H, CH_2 (M) + 1H, CH_2 (m) + 1H, CH_2S (m)), 2.99 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 6.4 Hz), 3.76 (s, 3H, OMe in C(O)OMe (m)), 3.79 (s, 3H, OMe in C(O)OMe (M)), 3.82 (s, 3H, OMe in $CH_2C(O)OMe$ (M)), 3.83 (s, 3H, OMe in $CH_2C(O)OMe$ (m)), 3.97 (d, 1H, $CH_2C(O)OMe$ (m), $^2J_{HH}$ = 16.6 Hz), 4.01 (d, 1H, $CH_2C(O)OMe$ (M), $^2J_{HH}$ = 16.7 Hz), 4.20−4.26 (m, 1H, $CH_2C(O)OMe$ (M) + 1H, $CH_2C(O)OMe$ (m)), 4.63−4.65 (m, 1H, CH (m)), 4.67−4.68 (m, 1H, CH (M)), 7.54−7.58 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.97−7.99 (m, 1H, H(C2) (M) + 1H, H(C2) (m)), 8.06−8.09 (m, 1H, H(C3) (M) + 1H, H(C3) (m)), 9.01 (d, 1H, H(C5) (m), $^3J_{HH}$ = 5.5 Hz), 9.04 (d, 1H, H(C5) (M), $^3J_{HH}$ = 5.6 Hz) ppm. $^{13}C\{^1H\}$ NMR (150.93 MHz, $CDCl_3$, 233 K): δ 24.58 (s, CH_2S (m)), 26.66 (s, CH_2S (M)), 30.86 (s, CH_2 (M + m)), 38.16 (s, $CH_2C(O)OMe$ (m)), 41.42 (s, $CH_2C(O)OMe$ (M)), 52.68 (s, CH (M)), 52.98 (br s, OMe in C(O)OMe (M + m)), 53.07 (s, CH (m)), 53.86 (br s, OMe in $CH_2C(O)OMe$ (M + m)), 125.75 (s, C2 (m)), 125.79 (s, C2 (M)), 127.20 (s, C4 (M + m)), 140.76 (s, C3 (M)), 140.85 (s, C3 (m)), 147.91 (s, C5 (M + m)), 152.79 (s, C1 (m)), 152.85 (s, C1 (M)), 167.17 (s, $CH_2C(O)OMe$ (m)), 167.30 (s, $CH_2C(O)OMe$ (M)), 172.37 (s, C(O)OMe (m)), 172.96 (s, C(O)OMe (M)), 173.28 (s, C(O)N (M + m)) ppm. IR (KBr, ν/cm^{-1}): 496(vw), 685(w), 755(w), 972(vw), 1013(w), 1054(vw), 1117(w), 1170(w), 1213(m), 1264(m), 1294(m), 1380(m), 1436(m), 1481(vw), 1570(w), 1597(s), 1625(s) (ν(C═O) in C(O)N), 1718(s) and 1734(s) (both ν(C═O) in C(O)OMe), 2843(vw), 2929(w), 2950(w), 2999(vw). Anal. Calcd for $C_{14}H_{17}ClN_2O_5PdS$: C, 35.99; H, 3.67; N, 6.00. Found: C, 36.14; H, 3.71; N, 5.91.

*Complex [κ³-S,N,N-(L)Pd^{II}Cl] (**11a**).*



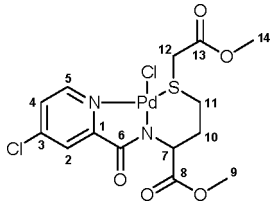
Yield: 85 mg (83%). Mp: 208−210 °C dec. ^{1}H NMR (500.13 MHz, $CDCl_3$, 253 K, major isomers (M) 59%, minor isomers (m) 41%): δ 1.80−2.05 (m, 1H, CH_2 (M) + 1H, CH_2 (m) + 1H, CH_2S (M) + 1H, CH_2S (m)), 2.12 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 5.3 Hz), 2.27 (dd, 1H, CH_2S (m), $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.3 Hz), 2.53−2.59 (m, 1H, CH_2 (m)), 2.60−2.65 (m, 1H, CH_2 (M)), 3.70 (s, 3H, OMe (m)), 3.71 (s, 3H, OMe (M)), 4.24 (d, 1H, CH_2Ph (M), $^2J_{HH}$ = 13.6 Hz), 4.29 (d, 1H, CH_2Ph (m), $^2J_{HH}$ = 13.5 Hz), 4.48−4.55 (m, 1H, CH_2Ph (M) + 1H, CH_2Ph (m) + 1H, CH (m)), 4.64−4.65 (m, 1H, CH (M)), 7.38−7.45 (m, 5H, H_{Ar} (M) + 5H, H_{Ar} (m)), 7.54−7.56 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.98 (d, 1H, H(C2) (m), $^4J_{HH}$ = 2.4 Hz), 7.98 (d, 1H, H(C2) (M), $^4J_{HH}$ = 2.4 Hz), 9.03 (dd, 1H, H(C5) (M), $^3J_{HH}$ = 6.0 Hz), 9.04 (dd, 1H, H(C5) (m), $^3J_{HH}$ = 6.4 Hz) ppm. $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$, 253 K): δ 21.58 (s, CH_2S (M)), 24.05 (s, CH_2S (m)), 30.42 (s, CH_2 (m)), 30.61 (s, CH_2 (M)), 41.70 (s, CH_2Ph (M)), 43.75 (s, CH_2Ph (m)), 52.69−52.73 (m, overlapping signals of OMe (M and m) and CH (M)), 53.64 (s, CH (m)), 126.05 (s, C2 (M + m)), 127.06 (s, C4 (M + m)), 128.95 (s, C16 (m)), 129.10 (s, C16 (M)), 129.33 (s, C15 + C17 (m)), 129.49 (s, C15 + C17 (M)), 129.85 (s, C14 + C18 (m)), 129.96 (s, C14 + C18 (M)), 132.82 (s, C13 (M)), 133.14 (s, C13 (m)), 148.50 (s, C5 (m)), 148.57 (s, C5 (M)), 149.09 (s, C3 (m)), 149.14 (s, C3 (M)), 154.13 (s, C1 (m)), 154.25 (s, C1 (M)), 172.03 (s, C(O)OMe or C(O)N (m)), 172.07 (s, C(O)OMe or C(O)N (M)), 172.09 (s, C(O)OMe or C(O)N (M)), 172.57 (s, C(O)OMe or C(O)N (m)) ppm. IR (KBr, ν/cm^{-1}): 571(vw), 658(vw), 708(m), 763(m), 783(m), 849(w), 900(vw), 945(vw), 967(vw), 1015(w), 1065(w), 1115(w), 1196(m), 1216(m), 1254(m), 1298(w), 1325(w), 1359(m), 1423(m), 1494(vw), 1557(w), 1597(s), 1618(s) and 1628(s) (both ν(C═O) in C(O)N), 1717(s) (ν(C═O) in C(O)OMe), 2851(vw), 2953(vw), 3028(vw), 3075(vw). Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_3PdS$: C, 41.60; H, 3.49; N, 5.39. Found: C, 41.43; H, 3.66; N, 5.48.

*Complex [κ³-S,N,N-(L)Pd^{II}Cl] (**11b**).*



Yield: 88 mg (95%). Mp: 146−148 °C. ^{1}H NMR (600.22 MHz, $CDCl_3$, 253 K, isomers A 50%, isomers B 50%): δ 1.81−1.87 (m, 1H, CH_2 (A)), 2.01−2.06 (m, 1H, CH_2 (B)), 2.11−2.16 (m, 1H, CH_2S (A) + 1H, CH_2S (B)), 2.36 (dd, 1H, CH_2S (B), $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 5.4 Hz), 2.45 (dd, 1H, CH_2S (A), $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 6.5 Hz), 2.60−2.68 (m, 1H, CH_2 (A) + 1H, CH_2 (B)), 3.41 (dd, 1H, $CH_2CH{=}CH_2$ (A), $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 8.0 Hz), 3.72 and 3.73 (both s, 3H + 3H, OMe (A and B)), 3.72−3.83 (m, 2H, $CH_2CH{=}CH_2$ (B)), 3.87 (dd, 1H, $CH_2CH{=}CH_2$ (A), $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 6.8 Hz), 4.58−4.59 (m, 1H, CH (A)), 4.61−4.63 (m, 1H, CH (B)), 5.26 (d, 1H, $CH_2CH{=}CH_2$ (A), $^3J_{HH}$ = 16.8 Hz), 5.33 (d, 1H, $CH_2CH{=}CH_2$ (B), $^3J_{HH}$ = 16.9 Hz), 5.38−5.42 (m, 1H, $CH_2CH{=}CH_2$ (A) + 1H, $CH_2CH{=}CH_2$ (B)), 5.92−5.99 (m, 1H, $CH_2CH{=}CH_2$ (B)), 6.12−6.19 (m, 1H, $CH_2CH{=}CH_2$ (A)), 7.51−7.52 (m, 1H, H(C4) (A) + 1H, H(C4) (B)), 7.93−7.95 (m, 1H, H(C2) (A) + 1H, H(C2) (B)), 8.94−8.96 (m, 1H, H(C5) (A) + 1H, H(C5) (B)) ppm. $^{13}C\{^1H\}$ NMR (150.93 MHz, $CDCl_3$, 253 K): δ 22.02 (s, CH_2S (B)), 23.01 (s, CH_2S (A)), 30.29 (s, CH_2 (A)), 31.11 (s, CH_2 (B)), 41.22 (s, $CH_2CH{=}CH_2$ (B)), 42.06 (s, $CH_2CH{=}CH_2$ (A)), 52.67−52.70 (m, overlapping signals of OMe (A and B) and CH (B)), 53.12 (s, CH (A)), 122.32 (s, $CH_2CH = CH_2$ (A)), 122.97 (s, $CH_2CH{=}CH_2$ (B)), 125.98 (s, C2 (A + B)), 127.05 (s, C4 (A + B)), 130.36 (s, $CH_2CH{=}CH_2$ (B)), 130.81 (s, $CH_2CH{=}CH_2$ (A)), 148.37 and 148.47 (both s, C5 (A and B), 149.04 and 149.10 (both s, C3 (A and B)), 154.06 and 154.19 (both s, C1 (A and B), 172.00 (br s, C(O)N (A and B)), 172.13 (s, C(O)OMe (B)), 172.38 (s, C(O)OMe (A)) ppm. IR (KBr, ν/cm^{-1}): 503(vw), 536(w), 698(vw), 739(w), 758(m), 785(w), 833(w), 945(vw), 961(vw), 1010(w), 1035(vw), 1071(vw), 1112(w), 1125(w), 1160(m), 1174(m), 1197(m), 1254(w), 1329(w), 1353(m), 1427(m), 1435(w), 1557(w), 1595(s), 1619(s) (ν(C═O) in C(O)N), 1747(m) (ν(C═O) in C(O)OMe), 2948(w), 3072(vw). Anal. Calcd for $C_{14}H_{16}Cl_2N_2O_3PdS$: C, 35.80; H, 3.43; N, 5.96. Found: C, 36.12; H, 3.75; N, 5.62.

*Complex [κ³-S,N,N-(L)Pd^{II}Cl] (**11c**).*



Yield: 55 mg (55%). Mp: 168−170 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$, 253 K, major isomers 53%, minor isomers 47%): δ 1.81−1.88

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Table 3. Crystal Data and Structure Refinement Parameters for 9a and 10b

	9a	10b
empirical formula	$C_{17}H_{16}Cl_2N_2O_3PdS$	$C_{14}H_{17}ClN_2O_3PdS$
formula wt	505.68	435.20
cryst syst	orthorhombic	monoclinic
space group	$P2_12_12_1$	$C2/c$
Z	4	8
a, Å	8.8569(6)	12.5700(16)
b, Å	11.2668(7)	15.674(2)
c, Å	18.4710(11)	17.247(3)
β, deg	90	90
V, Å^3	90	109.428(3)
D_{calc}, g cm^{-3}	1.822	1.804
linear absorption μ, cm^{-1}	14.3	14.67
$F(000)$	1008	1744
$2\theta_{max}$, deg	58	58
no. of rflns measd	22435	13115
no. of indep rflns	4898	4257
no. of obsd rflns ($I > 2\sigma(I)$)	4694	3550
no. of params	236	200
R1	0.0262	0.0305
wR2	0.0567	0.0725
GOF	1.110	1.017
$\Delta\rho_{max}/\Delta\rho_{min}$, e Å^{-3}	1.013/−0.517	0.629/−0.647

(m, 1H, CH_2 (m)), 2.06−2.13 (m, 1H, CH_2 (M)), 2.27−2.38 (m, 1H, CH_2S (M) + 1H, CH_2S (m)), 2.66−2.73 (m, 1H, CH_2 (M) + 1H, CH_2 (m) + 1H, CH_2S (m)), 2.96 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 6.5 Hz), 3.76 (s, 3H, OMe in C(O)OMe (m)), 3.79 (s, 3H, OMe in C(O)OMe (M)), 3.83 (s, 3H, OMe in $CH_2C(O)OMe$ (M)), 3.84 (s, 3H, OMe in $CH_2C(O)OMe$ (m)), 3.93 (d, 1H, CH_2C(O)OMe (m), $^2J_{HH}$ = 16.4 Hz), 4.00 (d, 1H, CH_2C(O)OMe (M), $^2J_{HH}$ = 16.7 Hz), 4.17−4.23 (m, 1H, CH_2C(O)OMe (M) + 1H, $CH_2C(O)OMe$ (m)), 4.64−4.65 (m, 1H, CH (M)), 4.67−4.68 (m, 1H, CH (m)), 7.52−7.54 (m, 1H, H(C4) (M) + 1H, H(C4) (m)), 7.97−7.98 (m, 1H, H(C2) (M) + 1H, H(C2) (m)), 8.96 (d, 1H, H(C5) (m), $^3J_{HH}$ = 6.1 Hz), 8.97 (d, 1H, H(C5) (M), $^3J_{HH}$ = 6.1 Hz) ppm. $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$, 253 K): δ 24.79 (s, CH_2S (m)), 26.65 (s, CH_2S (M)), 30.86 (s, CH_2 (M)), 30.96 (s, CH_2 (m)), 38.34 (s, $CH_2C(O)OMe$ (m)), 41.28 (s, $CH_2C(O)OMe$ (M)), 52.67 (s, CH (m)), 52.81 (br s, OMe in C(O)OMe (M + m)), 53.02 (s, CH (M)), 53.68 (s, OMe in $CH_2C(O)OMe$ (M)), 53.71 (s, OMe in $CH_2C(O)OMe$ (m)), 126.11 (s, C2 (M)), 126.13 (s, C2 (m)), 127.10 (s, C4 (M + m)), 148.52 (s, C5 (M)), 148.57 (s, C5 (m)), 149.22 (s, C3 (M)), 149.30 (s, C3 (m)), 154.09 (s, C1 (M)), 154.16 (s, C1 (m)), 166.96 (s, $CH_2C(O)OMe$ (m)), 167.07 (s, $CH_2C(O)OMe$ (M)), 172.01−172.04 (m, overlapping signals of C(O)OMe (M and m) and C(O)N (M or m)), 172.57 (s, C(O)N (m or M)) ppm. IR (KBr, ν/cm^{-1}): 517(vw), 537(vw), 754(w), 786(w), 841(vw), 942(vw), 979(vw), 1011(vw), 1034(vw), 1121(w), 1173(m), 1207(m), 1232(w), 1291(m), 1355(m), 1388(w), 1433(m), 1558(w), 1594(s), 1626(s) (ν(C═O) in C(O)N), 1725(s) and 1737(s) (both ν(C═O) in C(O)OMe), 2953(vw), 3061(vw). Anal. Calcd for: $C_{14}H_{16}Cl_2N_2O_5SPd$: C, 33.52; H, 3.21; N, 5.58. Found: C, 33.76; H, 3.38; N, 5.85.

X-ray Diffraction. Single crystals of compounds **9a** and **10b** were obtained by slow crystallization from CH_2Cl_2/hexane. X-ray diffraction experiments were carried out with a SMART APEX2 DUO CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å, ω-scans) at 120 K. The structures were solved by the direct method and refined by full-matrix least squares against F^2 in the anisotropic approximation for non-hydrogen atoms. The positions of hydrogen atoms were calculated and refined in the isotropic approximation in a riding model. The crystal data and structure refinement parameters for the complexes explored are given in Table 3. All calculations were performed using the SHELXTL software.[20] CCDC 1887955 and 1887957 contain the supplementary crystallographic data for **10b** and **9a**, respectively.

Cytotoxicity Assays. The cytotoxicities of ligands **2**, **3**, **6**, and **7** and complexes **8**−**11** were explored against human colon (HCT116), breast (MCF7), and prostate (PC3) cancer cell lines, as well as noncancerous human embryonic kidney cells (HEK293) and kidney epithelial cells (NKE). In the case of complexes **8a**,**b** and **11a**−**c**, additional experiments were carried out with the transformed breast cell line HBL100 and its doxorubicin-resistant subline HBL100/Dox. RPMI-1640 and DMEM media were obtained from Gibco. Fetal bovine serum (FBS) was purchased from HyClone. Cells were cultured in RPMI-1640 (in the case of PC3 and HBL100) or DMEM (in the other cases) media supplemented with 10% FBS and 50 μg/mL of gentamicin in a humidified incubator with a 5% CO_2 atmosphere. The effect of the compounds on cell viability was evaluated by the standard MTT assay (ICN Biomedicals, Germany). Cells were seeded in triplicate at a cell density of 5 × 10^3/well in 96-well plates in 100 μL of complete medium and preincubated for 24 h. The tested compounds were initially dissolved in DMSO. Then the compounds at various concentrations were added to the media. The well plates were incubated for 48 h followed by the addition of MTT solution (Sigma; 20 μL, 5 mg/mL). The cells were incubated at 37 °C for a further 3 h; then the culture medium was removed, and formazan crystals were dissolved in DMSO (70 μL). The absorbances of the resulting solutions were measured on a multiwell plate reader (Multiskan FC, Thermo scientific) at 530 nm to determine the percentage of surviving cells. The reported values of IC_{50} are the averages of three independent experiments (Tables 1 and 2). Cisplatin (in the initial form of an infusion concentrate in natural saline solution) and doxorubicin from commercial sources were used as the references.

DNA Binding Experiments. The DNA binding abilities of the selected complexes from this study were investigated by agarose gel electrophoresis. In each experiment, a solution of 0.15 μg of supercoiled pHOT1 plasmid DNA (TopoGEN) in water and the aforementioned amount of the complex (used as a stock solution in DMSO; the final concentration of the complexes ranged from 40 to 120 μM) was incubated in the dark at 37 °C for 30 min. The samples of free DNA were used as controls. After incubation, 10 μL aliquots of the resulting solutions were loaded onto 0.8% agarose gel. The

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electrophoresis was carried out at 1.5−2.0 V/cm for 8−10 h in TAE buffer. The gels were stained with ethidium bromide (0.5 μg/mL) and visualized under UV light.

Topoisomerase I Activity Inhibition Studies. The modulation of topoisomerase I activity by the selected complexes from this study was explored using a TopoGEN Topoisomerase I Drug Screening Kit. In the experiments, each specified complex and one unit of the purified topoisomerase from calf thymus (Fermentas, Lithuania) were incubated with 0.13 μg of supercoiled pHOT1 plasmid DNA (TopoGEN) in a reaction buffer (10 mM Tris-HCl, pH 7.9, 1 mM EDTA, 0.15 M NaCl, 0.1% BSA, 0.1 mM spermidine, 5% glycerol) for 30 min at 37 °C. The reactions were stopped with SDS. After digestion with proteinase K (50 μg/mL, 30−60 min at 37 °C), the samples were mixed with a DNA loading buffer and loaded onto 0.9% agarose gel. The electrophoresis was performed at the maximum voltage of 2−3 V/cm in a TAE buffer (2 M Tris base, 0.05 M EDTA, 1.56 M acetic acid). The gels were stained with ethidium bromide (0.5 μg/mL) and visualized via UV fluorescence at wavelengths in the range of 240−360 nm using a GelDoc-It TS imaging system. In the absence of inhibitors, topoisomerase I relaxed scDNA through the formation of a series of topoisomers. Topoisomerase I inhibition was revealed by the ability of the complexes under investigation to retard scDNA relaxation, which was observed as a decrease in the amount of topoisomers and a retention of scDNA.

Apoptosis Induction Assay. To define the ability of the complexes explored to promote apoptosis, acute monocytic leukemia cells THP-1, preincubated overnight in a CO_2 incubator at 37 °C, were cultured in a medium containing 10 μM of **8a** or **11a** for 20 h. After exposure, the cells were washed with cold PBS and incubated with annexin V-PE (BD PharMingen) according to the supplier's protocol for 15 min at room temperature in the dark. The apoptotic rates of the resulting cell samples were analyzed on a FACScan flow cytometer (Becton Dickinson, USA) using CellQuest software. For comparison, the apoptotic activities of representative examples of cytotoxic complexes **I**, **V**, and **VI** were also evaluated under the same conditions.

Cell Uptake Studies. PC3 cells were seeded on glass plates in the culture medium and incubated for 24 h under the standard conditions. Then, complex **13** was added at a concentration of 6×10^{-5} μM. This is a subtoxic concentration that leads to less than 10% cell death. The cells were incubated in the presence of the aforementioned compound for 24 h. Then, the plates were washed twice with the neat medium and observed under an Axioplan 2 fluorescence microscope (Zeiss).

For the flow cytometry analysis, PC3 cells were seeded on Petri dishes and cultured for 24 h under the standard conditions. Then, complex **13** was added to a final concentration of 6×10^{-5} M, and the resulting samples were incubated for the specified time spans. After the required period of time, the cells were detached by trypsinization (with Trypsin-Versene) and analyzed on a FACSCanto II flow cytometer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c01138.

Synthesis and characterization of fluorescein-conjugated derivatives **12** and **13**, NMR (^{1}H, ^{13}C{^{1}H}, and different 2D NMR) spectra of ligand **6a** and complex **10a**, UV−vis spectra of complexes **11a**,**c** and **13**, luminescence spectra of compounds **12** and **13**, and fluorescence microscopic images of PC3 cells treated with ligand **12** (PDF)

Accession Codes

CCDC 1887955 and 1887957 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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