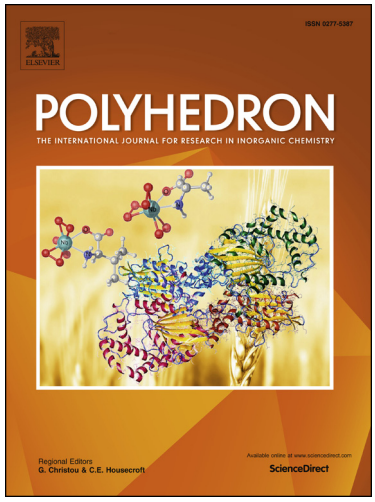

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Non-classical *N*-Metallated Pd(II) Pincer Complexes Featuring Amino Acid Pendant Arms: Synthesis and Biological Activity

Svetlana G. Churusova,[a] Diana V. Aleksanyan,*[a] Ekaterina Yu. Rybalkina,[b] Yulia V. Nelyubina,[a,c] Alexander S. Peregudov,[a] Zinaida S. Klemenkova,[a] Vladimir A. Kozlov[a]

[a]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, Moscow, 119991 Russia*

[b]*Institute of Carcinogenesis, N. N. Blokhin Russian Cancer Research Center, Kashirskoe sh. 24, Moscow, 115478 Russia*

[c]*Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninskii pr. 31, Moscow, 117901 Russia*

corresponding author: aleksanyan.diana@ineos.ac.ru

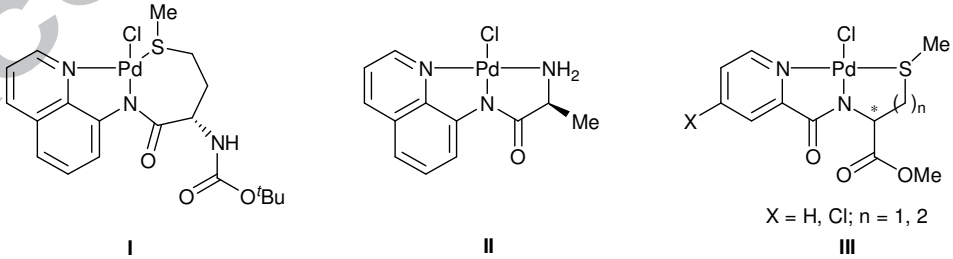
Abstract

A series of non-classical pincer ligands with the secondary amide central unit and amino acid pendant arms was obtained from 2-diphenylphosphanyl- and 2-methylsulfanylbenzoic acids and a range of amino acid derivatives (*S*-methyl-L-cysteine, L-methionine, and L-histidine methyl esters). In addition, the reactions of amino acid-functionalized chloroacetamides with *in situ* generated Ph_2PSK afforded their counterparts with an aliphatic ligand backbone. All the compounds obtained smoothly underwent direct cyclopalladation upon interaction with $PdCl_2(NCPh)_2$ under mild reaction conditions, resulting in *N*-metallated pincer complexes with 5,6- and 6,6-membered fused metallocycles. The realization of κ^3-*S,N,S*-, *S,N,N*- and *S,N,P*-coordination was unambiguously confirmed based on the IR and NMR spectroscopic data. In the case of the methionine-based thiophosphorylacetamide derivative, the unexpected selectivity in the formation of one complex diastereomer was observed in solution. The solid-state structures of some of the complexes obtained were also elucidated by X-ray crystallography. The preliminary investigations on cytotoxicity of the resulting palladocycles against HCT116, MCF7, and PC3 human cancer cell lines as well as HEK293 normal cells gave some insight into the structure–activity relationships for this relatively new type of potential anticancer agents. Some of the complexes demonstrated promising cytotoxic effects.

Key words: pincer complexes, palladium, functionalized amides, amino acids, cytotoxicity

1. Introduction

Nowadays pincer complexes featuring a specific tridentate monoanionic framework with multiple options for directed structural modifications comprise one of the most actively studied classes of organometallic and metal-organic compounds.[1,2] They attract continuous interest of researchers owing to enormous potential for use in organic synthesis, catalysis, materials science, and medicinal chemistry. The rapid development of pincer chemistry, especially, in recent years gave rise to a variety of non-classical structural scaffolds, which open up new horizons for investigations. One of these types of non-classical pincer ligands is formed by multidentate derivatives with the central secondary amide unit, furnishing upon metalation the covalent metal–nitrogen, in particular, Pd–N bond.[3] These ligands can be synthesized by modular assembling of readily available building blocks – functionalized amines and acids. Furthermore, their cyclopalladated complexes have been already recommended as efficient (pre)catalysts for different chemical reactions, including, the Suzuki and Heck cross-coupling, asymmetric allylic alkylation, *etc*.[4] Palladocycles based on functionalized carboxamides were also found to play a significant role as intermediates in various Pd-catalyzed C–H functionalization processes.[5] Recently, Pd(II) pincer complexes of carboxamides with amino acid residues showed promising inhibition activity against several human cancer cell lines (Fig. 1). Thus, *N,N,X*-palladocycles (X = S, N) derived from 8-aminoquinoline and L-alanine or L-methionine (**I**, **II**) exhibited significant *in vitro* cytotoxicity against human cervical (HeLa), breast (MCF7), and lung (A549) cancer.[6] Their counterparts based on picolinamides with L-cysteine and L- and D-methionine residues demonstrated pronounced cytotoxic effects on human colon (HCT116), breast (MCF7), and prostate (PC3) cancer cell lines, with IC_{50} values falling in the low micromolar range.[7] Noteworthy, complexes **I** and **III** with ancillary *S*-donor groups were found to be much more active than the reference – cisplatin. In general, cyclometallated complexes (including cyclopalladated derivatives) are very promising antitumor agents.[8,9]



I **II** **III**

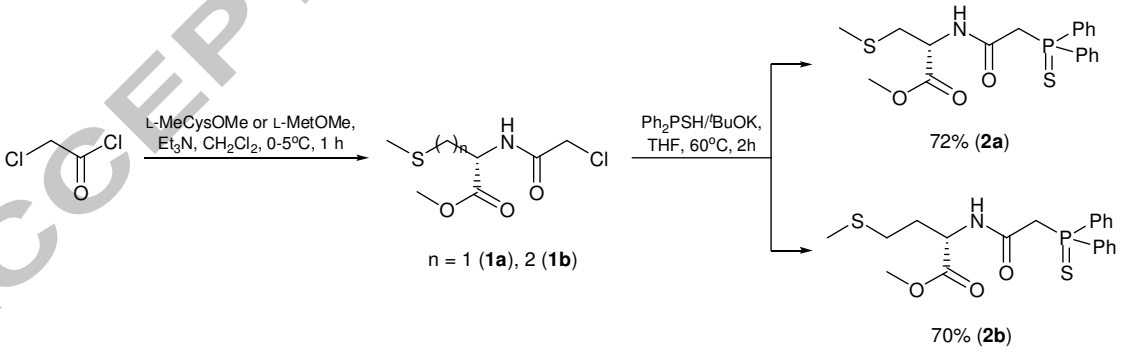
Fig. 1. Cytotoxic Pd(II) pincer complexes based on the amide ligands with amino acid pendant arms.

In continuation of these studies, it seemed interesting to broaden the range of Pd(II) pincer complexes based on amino acid-functionalized carboxamides in order to evaluate their potential as anticancer agents. Herein, we report on the synthesis of several new non-classical pincer ligands with the central amide unit featuring amino acid pendant arms and their cyclopalladated complexes, which were tested for *in vitro* cytotoxic activity.

2. Results and Discussion

The preliminary evaluation of cytotoxic properties of picolinamide derivatives **III** towards several human cancer and normal cell lines allowed us to outline some structure–activity regularities, which would be interesting to check for new representatives of this type of potential anticancer agents. Therefore, upon development of novel pincer ligands with the secondary amide central unit and amino acid pendant arms, it seemed reasonable to vary the structural parameters, such as rigidity of the ligand backbone, which would affect the conformational stability of the resulting complexes, and nature of auxiliary coordination sites (soft and/or hard donor centers), which would define their kinetic and thermodynamic stability.

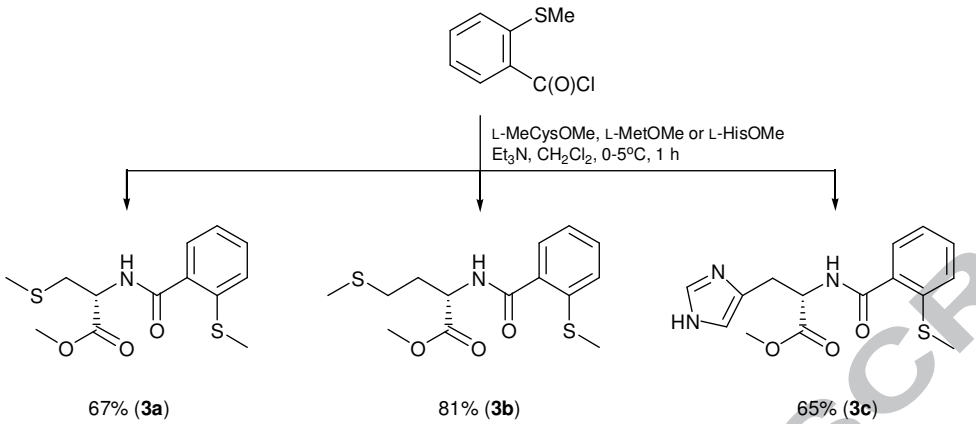
Convenient key precursors for the synthesis of novel pincer ligands with the aliphatic backbone were chloroacetamide derivatives **1a,b**, readily available from chloroacetyl chloride and cysteine or methionine methyl esters, *in situ* generated from the corresponding hydrochlorides (Scheme 1). Treatment of **1a,b** with Ph_2PSK afforded thiophosphoryl-functionalized carboxamides **2a,b** in good yields (Scheme 1). Note that the application of chiral amino acid predecessors allowed us to obtain the target ligands in enantiomerically pure forms.



Scheme 1. Synthesis of thiophosphorylacetamide ligands **2a,b**.

Functionalized carboxamide ligands with the more rigid backbone were derived from 2-methylthiosalicyl chloride and amino acids bearing ancillary *N*- and *S*-donor groups (*S*-methyl-L-cysteine, L-methionine, and L-histidine) (compounds **3a–c**, Scheme 2). Interestingly, in the case of L-histidine derivative, the reaction was complicated by further interaction of ligand **3c** with 2-

methylthiosalicyl chloride, giving rise to double acylation product **4**, which was isolated and fully characterized by spectroscopic methods and X-ray diffraction (Fig. 2).



Scheme 2. Synthesis of methylthiosalicylamide ligands **3a**–**c**.

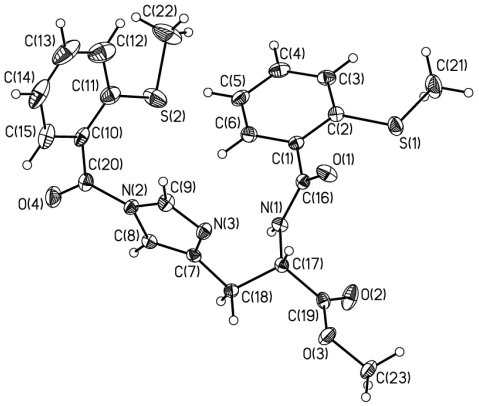
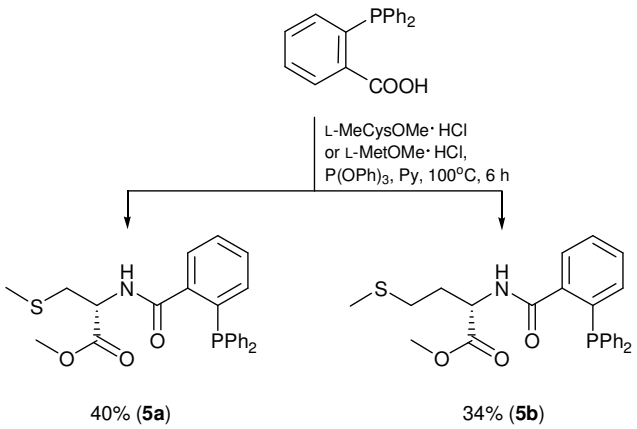


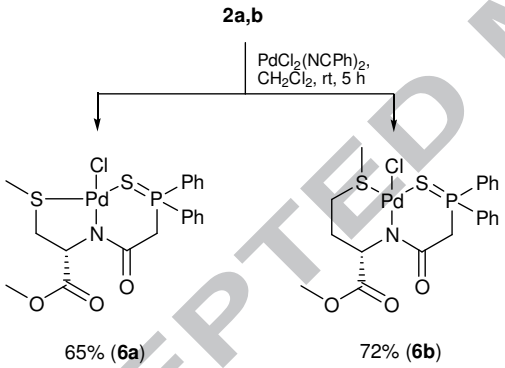
Fig. 2. General view of compound **4** in representation of atoms *via* thermal ellipsoids at 50% probability level.

Counterparts of ligands **3a,b** with an ancillary phosphine donor group were synthesized by the reaction of 2-diphenylphosphanylbenzoic acid with the corresponding amino acid hydrochlorides upon heating in pyridine using $P(OPh)_3$ as a coupling agent (compounds **5a,b**, Scheme 3).

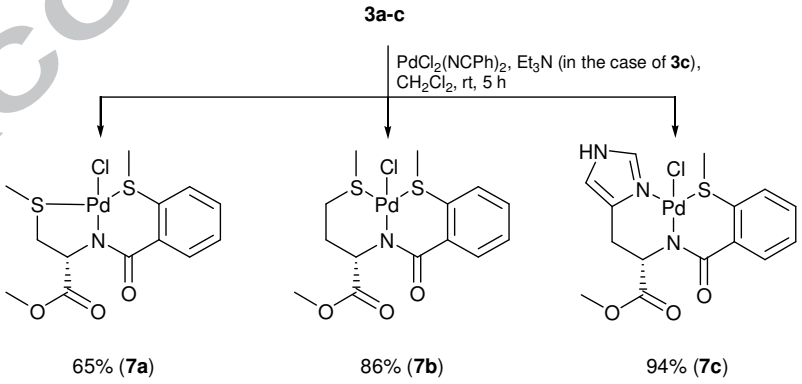


Scheme 3. Synthesis of diphenylphosphanylbenzamide ligands **5a,b**.

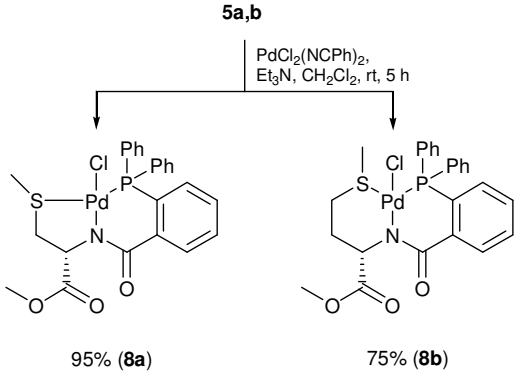
Independently of the length of coordination arms and nature of the ancillary donor groups, all the ligands derived readily underwent direct cyclopalladation upon interaction with $PdCl_2(NCPh)_2$ in dichloromethane solution at room temperature, giving rise to 5,6- and 6,6-membered pincer complexes **6–8** (Schemes 4–6). In some cases the reactions were found to proceed more efficiently in the presence of Et_3N, which obviates the adverse effect of HCl liberated upon metalation.



Scheme 4. Synthesis of complexes **6a,b**.



Scheme 5. Synthesis of complexes **7a–c**.



Scheme 6. Synthesis of complexes **8a,b**.

Complexes **6–8** are moisture- and air-resistant brightly colored crystalline solids. The realization of κ^3-*S,N,S*-, *S,N,N*- and *S,N,P*-coordination was unambiguously confirmed based on the IR and NMR spectroscopic data. Thus, the ^{1}H NMR spectra of all the complexes obtained lack the signals of the amide NH protons. Their IR spectra also did not show the absorption bands characteristic for the stretching and bending vibrations of the amide NH moiety. Furthermore, the C=O bond stretching vibrations of the amide group are strongly shifted to the lower frequencies relative to the corresponding absorption bands of the free ligands ($\Delta\nu$ = 36–122 cm^{-1}). All this clearly indicates the occurrence of metalation at the central secondary amide unit. The coordination of the ancillary sulfide donor groups in all the palladocycles under consideration (either in the acid or in the amine part of the ligands) is evident from the downfield shifts of the signals of SMe hydrogen and carbon nuclei in the ^{1}H and ^{13}C NMR spectra compared to those of the free ligands ($\Delta\delta_H$ = 0.26–0.68 ppm, $\Delta\delta_C$ = 2.45–11.35 ppm). The complexation of the imidazole moiety in compound **7c** is supported by strong downfield shifts of the NH proton signal and the signal of H(C9) proton, situated between two nitrogen centers ($\Delta\delta_H$ ~ 4.2 and 0.4 ppm, respectively). The coordination of the phosphorus-containing donor groups in complexes **6a,b** and **8a,b** is confirmed by downfield shifts of the phosphorus resonances in the ^{31}P NMR spectra relative to the spectra of the corresponding ligands, which comprise ~2.7–4.0 ppm in the case of thiophosphoryl-containing derivatives and reach up to 36.3 ppm for the phosphine-substituted counterparts. In addition, the coordination of the thiophosphoryl group in complexes **6a,b** is supported by a strong low-frequency displacement of the P=S stretching vibrations in the IR spectra ($\Delta\nu$ = 109 and 123 cm^{-1} for complexes **6a** and **6b**, respectively).

An important feature of the complexes under consideration, which merits special discussion, is their possibility to exist in different diastereomeric forms, which arises from the presence of the chiral carbon center and the coordinated thioether group. Earlier we have observed the formation of such diastereomers in solutions of the related picolinamide derivatives (complexes **III** in Fig. 1), which was expressed in a double set of signals in the ^{1}H and ^{13}C NMR

spectra.[7] The additional ROESY experiment confirmed that the isomers differed in the disposition of the methyl substituent at the sulfur atom and the substituents at the chiral carbon center relative to the main molecular plane. Similarly, the ^{1}H and ^{13}C NMR spectra of histidine-based *S,N,N*-complex **7c** also showed a double set of signals (well-resolved already at room temperature), which correspond to two diastereomers in approximately 3:1 ratio (see Experimental section). In the case of its *S,N,S*-counterparts **7a,b**, which have two different coordinated SMe groups, the expected spectral patterns must be essentially complicated due to possibility of the existence of four diastereomeric forms. While the ^{1}H NMR spectrum of 5,6-membered complex **7a** in $CDCl_3$ at room temperature contained broadened unresolved signals (Fig. S1 in Supplementary data), cooling to –30 °C indeed resulted in the resolution of the signals of all four possible isomers. Figure 3 presents the extended fragment of the ^{1}H NMR spectrum of **7a** at the lower temperature in the region of SMe proton signals of the amino acid pendant arm, which shows four distinct singlet signals of the isomers designated as A, B, C, and D. Figures S2–S10 in Supplementary data demonstrates the ^{1}H, ^{13}C, and HMQC NMR spectra of palladocycle **7a** in $CDCl_3$ at –30 °C. For 6,6-membered complex **7b** based on the methionine derivative, having more conformationally flexible structure, even cooling to –30 °C does not afford full resolution of the spectrum. Figure 4 depicts the extended fragment of the ^{1}H NMR spectrum of **7b** at –30 °C in the region of H(C6) proton signals (the signals of the proton situated in the *ortho*-position relative to the C(O)N moiety). It is obvious that only one of four diastereomers affords a resolved doublet signal. Therefore, the ^{1}H and ^{13}C NMR spectra of **7b** cannot be reliably assigned (see Figs. S11–S19 in Supplementary data). As for *S,N,P*-complex **8b**, the ^{1}H and ^{13}C NMR spectra at room temperature show one set of distinct, well-resolved signals, which testifies that the interconversion between its isomers is rapid on the NMR time scale at room temperature. In the case of its cysteine-based counterpart **8a**, such a dynamic transformation is slower, which is evident, for example, from the significantly broadened signals of the CH_2 protons, falling under the signals of SMe and OMe protons (Fig. S20 in Supplementary data). Furthermore, its ^{13}C NMR spectrum showed mainly the signals of the aromatic carbon nuclei, while most of the aliphatic carbon resonances (except for OMe group signal) were not observed (Fig. S21). The variable-temperature ^{1}H NMR studies in $CDCl_3$ revealed that heating to 50 °C essentially facilitates the interconversion of the isomers, but the resolution of the CH_2 proton signals is still limited (Fig. S22). In contrast, cooling to –30 °C afforded fully resolved signals of two diastereomers, which ratio composed ~3:2 (Figs. S23 and S24). Figures S25–S33 present the ^{1}H, ^{13}C, COSY, and HMQC NMR spectra of complex **8a** in $CDCl_3$ at –30 °C. The most interesting behavior was observed in the case of thiophosphoryl-functionalized complexes **6a,b**. Both of the complexes demonstrated two signals in the ^{31}P NMR

spectra in $CDCl_3$ at room temperature, however, only cysteine-based derivative **6a** afforded resolved signals in the ^{1}H and ^{13}C NMR spectrum (for the ^{31}P and ^{1}H NMR spectra of complex **6b** in $CDCl_3$ at room temperature see Fig. S34 in Supplementary data). Cooling of a solution of **6b** in $CDCl_3$ to –30 °C unexpectedly disclosed that the content of the minor component composes only 8% (Fig. S35), thus suggesting the preferential formation of one of the diastereomers. This property of Pd(II) pincer complexes based on functionalized carboxamide ligands can be further used in catalysis.

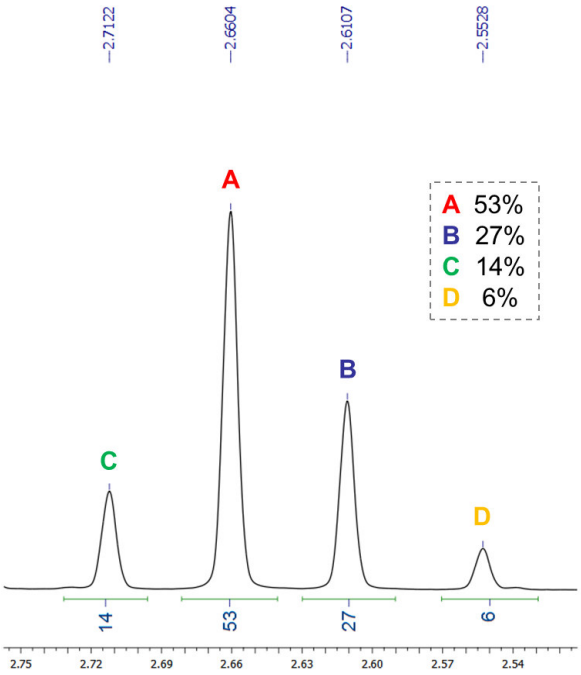


Fig. 3. Extended fragment of the ^{1}H NMR spectrum of complex **7a** in $CDCl_3$ at –30°C (AlkSMe proton region).

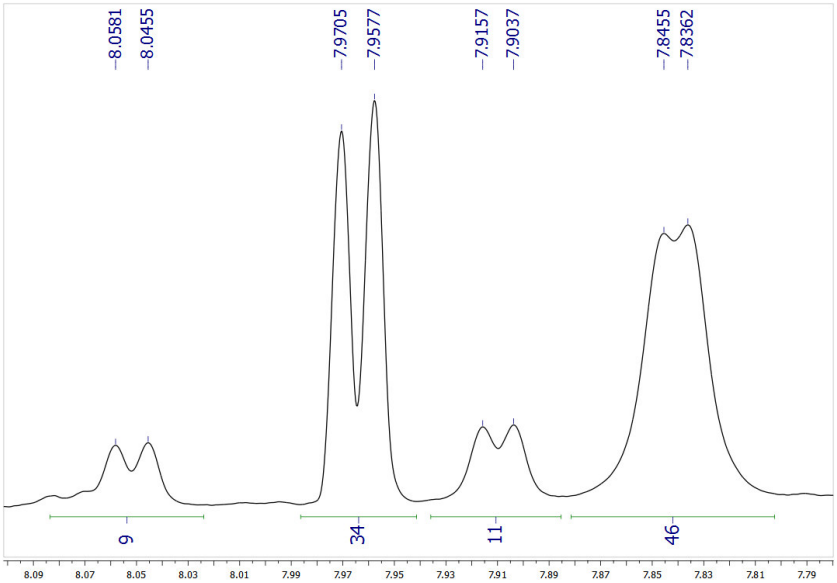


Fig. 4. Extended fragment of the ^{1}H NMR spectrum of complex **7b** in $CDCl_3$ at –30 °C (H(C6) proton region).

The structures of complexes **6b**, **7a**, **7b**, **8a**, and **8b** were also ascertained by X-ray diffraction analysis of their single crystals (Figs. 5a–e). Note that compound **8b** (Fig. 5e) actually represents a crystallosolvate with water, having two symmetry-independent molecules of the complex. According to the results obtained, the coordination environment of the palladium atom is almost square-planar in the phosphorus-containing derivatives **6b** and **8a,b**. At the same time, in *S,N,S*-complexes 7**a** and **7b** there is a slight bent along the S(1)…S(2) line with the corresponding angles being equal to 170.2 and 167.3°, respectively. This is likely to be explained by the less flexible structure of the six-membered metallocycle involving the thiosalicylamide fragment (in **7a,b**) compared to that formed by the thiophosphorylacetamide moiety (in **6b**), on the one hand, and the shorter length of the C(2)–S(2) bond in **7a,b** compared to the length of the C(2)–P(1) bond in complexes **8a,b**, on the other hand. The differences in the degree of flexibility of the ligand backbones are also reflected in conformations of the resulting metallocycles. In complexes **7a,b** and **8a,b**, the six-membered palladocycles formed by the aromatic acid components adopt twist conformations in all cases, although the atoms deviating the most differ depending on the ancillary donor atom (S *vs* P): S(2) (1.28–1.84 Å) and C(2) (0.41–0.86 Å) in **7a,b** and Pd(1) (up to 1.65 Å) and N(1) (0.31–0.50 Å) in **8a,b**. At the same time, the corresponding metal-containing ring in complex **6b** (involving $CH_2P(S)$ unit) adopts a boat conformation with the deviation of Pd(1) and C(1) atoms by 1.12 and 0.76 Å, respectively. The conformation of the second metallocycle, formed by the amino acid pendant arm, depends on its size and varies from an envelope (in the case of five-membered rings in **7a** and **8a** with atoms C(8) or N(1) deviating by 0.56 or 0.70 Å, respectively) to a twist (in the case of six-membered rings in complexes **6b**, **7b**, and **8b**). For the latter, the following pairs of atoms deviate the most: N(1) (0.79 Å) and C(9) (0.80 Å) in **7b**, N(1) (0.73 Å) and C(4)/C(5) (0.83/0.60 Å) in **6b** (depending on whether major or minor component of $MeS(CH_2)_2COOMe$ disordered moiety is considered), and S(1) (0.69–0.78 Å) and C(8)/C(10) (1.25–1.87 Å) in **8b** (the data for two symmetry-independent complex molecules featuring slightly different geometries).

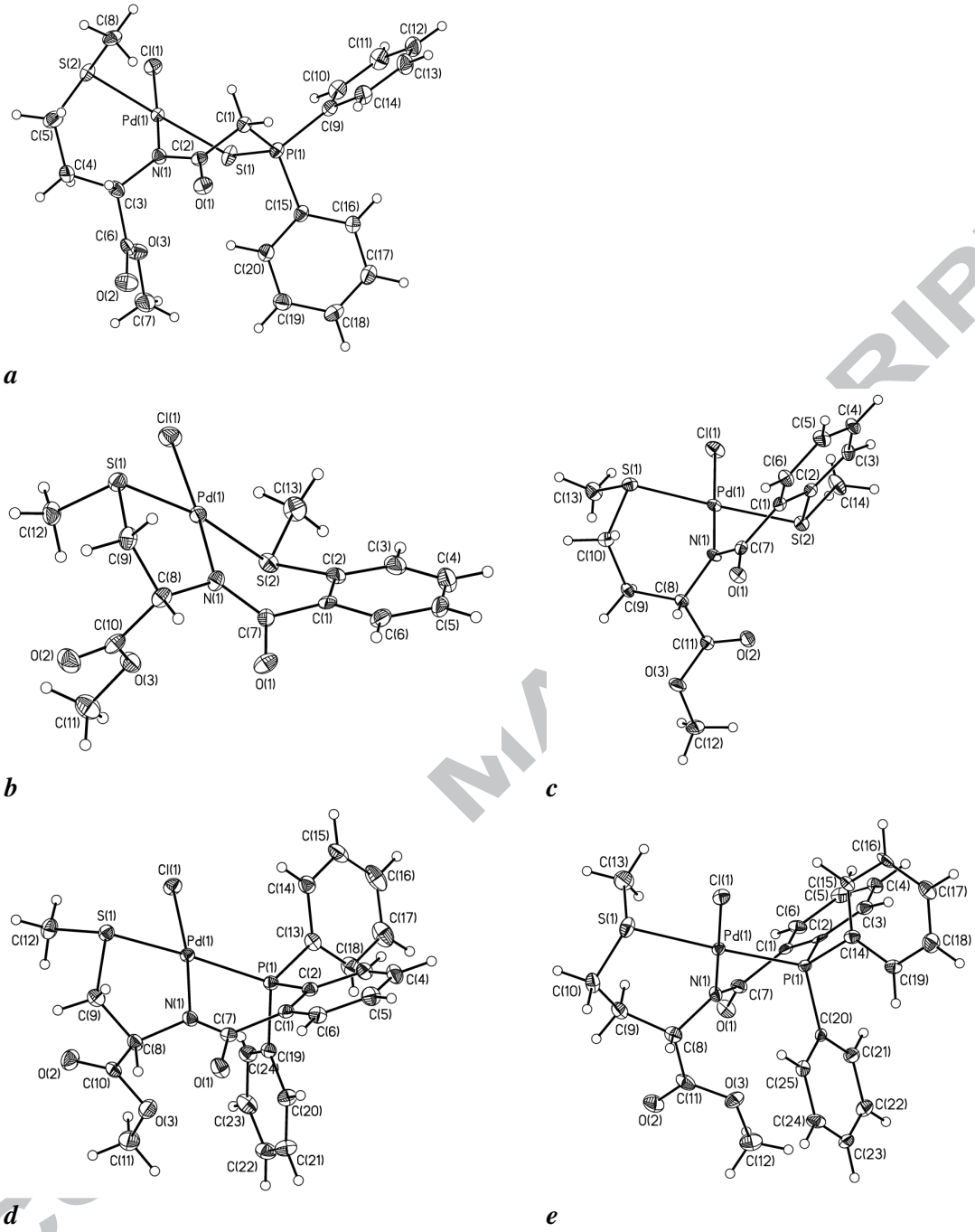


Fig. 5. General views of complexes **6b** (***a***), **7a** (***b***), **7b** (***c***), **8a** (***d***), and **8b** (***e***) in representation of atoms *via* thermal ellipsoids at 50% probability level.

The antiproliferative activity of the complexes obtained was tested against several human cancer cell lines as well as normal human embryonic kidney cells (HEK293) using the conventional method based on MTT reduction. Cisplatin from a commercial source served as a positive control. Table 1 presents the concentrations of the compounds required to inhibit the cellular survival fraction to 50% (IC_{50}) after exposure for 48 h. As can be seen, thiophosphoryl-functionalized complexes **6a,b** did not exhibit cytotoxic effects even at the concentration of 100

μM (Table 1, entries 1–2). Thiosalicylamide derivative **7c** based on L-histidine was also nontoxic at such a high concentration (entry 5). At the same time, its *S,N,S*-counterparts **7a,b** displayed moderate activity against HCT116 and PC3 cancer cells, exceeding in efficiency the reference (cisplatin). The differences observed in the activities of complexes **7a,b** and **7c** are in good agreement with our earlier assumption about a crucial role of amino acids bearing *S*-donor ancillary groups in the cytotoxicity of the related Pd(II) pincer complexes based on picolinamide derivatives (compounds **III** in Fig. 1). However, complexes **7a,b** demonstrated only low cytotoxicity towards MCF7 cancer lineage and markedly affected normal HEK293 cells. As for κ^3-*S,N,P*-palladocycles with the phosphine ancillary donor group, both of the complexes exhibited pronounced cytotoxic effects on all the cancer cell lines under consideration (Table 1, entries 6, 7). The values of IC_{50} achieved with these compounds fall within the low micromolar range, which make them commensurable with most of picolinamide derivatives **III**. In addition, these complexes essentially outperformed in activity the clinically used drug – cisplatin. Interestingly, the structure–activity relationships observed for palladocycles **III** were generally reproduced in the case of complexes **8a,b**. Thus, the latter also displayed higher cytotoxicity against colon cancer cells, indicating their selectivity towards this particular cancer lineage. As well as in the case of complexes **III**, a reduction in the size of one of the fused metallocycles (cysteine *vs* methionine derivatives) negatively influenced the cytotoxic activity against MCF7 and PC3 cancer cell lines, although had no effect on HCT116 cancer cells. It is also noteworthy that complexes **8a,b** were less toxic to normal cells (HEK293) than to HCT116 and PC3 cancer cell lines. Thus, *S,N,P*-complexes **8a,b** as well as their picolinamide counterparts **III** have potential value as anticancer agents. In summary it can be concluded that the nature of an acid component in the ligand backbone is of particular importance for the cytotoxic activity of Pd(II) pincer complexes based on carboxamides with amino acid pendant arms.

Table 1. Cytotoxic effects of the cyclopalladated complexes under consideration on some human cell lines (IC_{50}/μM)

Entry	Compound	Cancer cell lines			Normal cell line
		HCT116	MCF7	PC3	HEK293
1	**6a**	>100	>100	>100	>100
2	**6b**	>100	>100	>100	>100
3	**7a**	30 ± 4.2	90	26 ± 4	45 ± 7
4	**7b**	40 ± 6	100	46 ± 2	55 ± 5
5	**7c**	>100	>100	>100	>100
6	**8a**	2 ± 1	16 ± 4	5 ± 1.5	8 ± 1
7	**8b**	2 ± 0.5	30 ± 8	13.5 ± 1.5	25 ± 5
8	Cisplatin	400.0	25.0	120.0	28.0

3. Conclusions

To summarize the results presented, a series of non-classical pincer ligands based on functionalized carboxamides with amino acid pendant arms were prepared from readily available precursors. The direct cyclopalladation of the ligands obtained was accomplished under mild reaction conditions, leading to new representatives of *N*-metallated Pd(II) pincer complexes, featuring 5,6- and 6,6-membered fused metallocycles and ancillary *P*-, *N*- and *S*-donor groups. In the case of the methionine-based thiophosphorylacetamide derivative, the unexpected diastereoselectivity was observed in solution. The preliminary evaluation of cytotoxicity of the resulting complexes against several human cancer cell lines allowed us to confirm some structure–activity relationships observed previously for the related picolinamide derivatives with amino acid pendant arms. Some of the palladocycles from this study showed an appreciable level of cytotoxic efficiency. Therefore, further search for anticancer agents among this type of non-classical *N*-metallated Pd(II) pincer complexes seems to be reasonable.

4. Experimental

4.1. General remarks

Unless otherwise mentioned, all manipulations were carried out without taking precautions to exclude air and moisture. Dichloromethane was distilled over P_2O_5. Tetrahydrofuran was distilled over sodium benzophenone ketyl. *S*-Methyl-L-cysteine methyl ester hydrochloride was obtained from L-cysteine methyl ester hydrochloride *via* sequential treatment with di-*tert*-butyl dicarbonate,[10] methyl iodide,[11] and acetyl chloride.[12] L-Methionine methyl ester hydrochloride was prepared by the esterification of L-methionine under action of dimethylsulfite, *in situ* generated by the reaction of $SOCl_2$ with an excess of methanol at low temperature.[13] *N*-Chloroacetyl-L-methionine methyl ester **1b** was synthesized by the reaction of sodium salt of L-methionine with $ClCH_2C(O)Cl$[14] followed by the esterification with methanol using a catalytic amount of hydrochloric acid.[15] 2-(Methylsulfanyl)benzoyl chloride was derived from thiosalicylic acid *via* methylation with MeI[16] followed by treatment with $SOCl_2$.[17] 2-(Diphenylphosphanyl)benzoic acid was synthesized from 2-chlorobenzoic acid, PPh_3, and sodium.[18] All other chemicals and solvents were used as purchased.

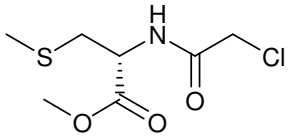
NMR spectra were recorded on Bruker AV-300, AV-400 and AV-600 spectrometers, and the chemical shifts (δ) were referenced internally by the residual solvent signals relative to tetramethylsilane (^1H, ^{13}C) or externally to H_3PO_4 (^{31}P). In most cases, $^{13}C\{^1H\}$ NMR spectra were registered using the *J*MODECHO mode; the signals for the C nuclei bearing odd and even numbers of protons have opposite polarities. The assignment of the NMR spectra of the

compounds obtained was carried out based on ^{1}H, $^{13}C\{^{1}H\}$, $^{1}H–^{1}H$-COSY and HMQC experiments and the data obtained previously for the related compounds.[4a,7]

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).

4.2. Syntheses

*4.2.1. Methyl (2R)-2-[(chloroacetyl)amino]-3-(methylsulfanyl)propanoate **1a***



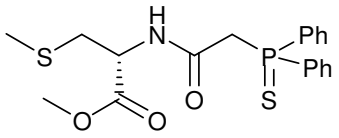
A solution of triethylamine (3.50 mL, 0.025 mol) in CH_2Cl_2 (6 mL) was added dropwise to a stirred suspension of *S*-methyl-L-cysteine methyl ester hydrochloride (1.86 g, 0.010 mol) in CH_2Cl_2 (25 mL) at –5 °C under an argon atmosphere. The reaction mixture was stirred for 30 min. Then, a solution of $ClCH_2C(O)Cl$ (1.35 g, 0.012 mol) in CH_2Cl_2 (5 mL) was added dropwise. The resulting mixture was stirred at 0–5 °C for 1 h and poured into distilled water (75 mL). The organic layer was separated, sequentially washed with a dilute aqueous solution of hydrochloric acid, saturated aqueous solution of $NaHCO_3$, 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 $CHCl_3$–MeOH (75:1)) to give 2.13 g of compound **1a** as a white crystalline solid. Yield: 94%. Mp: 65–67 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.15 (s, 3H, SMe), 3.01–3.04 (m, 2H, CH_2S), 3.81 (s, 3H, OMe), 4.13 (s, 2H, CH_2Cl), 4.82–4.88 (m, 1H, CH), 7.42 (br s, 1H, NH) ppm. Anal. Calcd for $C_7H_{12}ClNO_3S$: C, 37.25; H, 5.36; N, 6.21. Found: C, 37.35; H, 5.40; N, 6.14%.

*4.2.2. General procedure for the synthesis of ligands **2a,b***

A solution of $Ph_2P(S)H$ (0.50 g, 2.29 mmol) in THF (10 mL) was added dropwise to a stirred suspension of ^{t}BuOK (0.28 g, 2.50 mmol) in THF (10 mL) under an argon atmosphere. In 30 min, the reaction mixture was cooled to 10 °C, and then a solution of the corresponding chloroacetamide **1a,b** (2.29 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the resulting mixture was poured into distilled water (50 mL). The desired product was extracted with chloroform. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to dryness. The resulting residue was purified by column chromatography on silica gel (eluent: $CHCl_3$–MeOH (100:1)

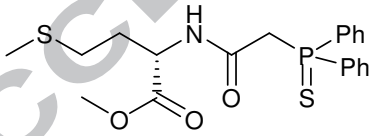
(**2a**), CH_2Cl_2 (**2b**)) to give the desired ligands as pinkish (**2a**) or white (**2b**) crystalline solids. Note that an analytically pure sample of compound **2a** was obtained after additional purification by thin-layer chromatography on silica gel plates (eluent Et_2O).

4.2.2.1. Methyl (2R)-2-{[(diphenylthiophosphoryl)acetyl]amino}-3-(methylsulfanyl)propanoate ***2a***



Yield: 0.67 g (72%). Mp: 100–102 °C. $^{31}P\{^1H\}$ NMR (121.49 MHz, $CDCl_3$): δ 37.56 ppm. ^1H NMR (300.13 MHz, $CDCl_3$): δ 2.07 (s, 3H, SMe), 2.88 (d, 2H, CH_2S, $^3J_{HH}$ = 5.8 Hz), 3.60–3.65 (m, 2H, $CH_2P(S)$), 3.71 (s, 3H, OMe), 4.75 (dt, 1H, CH, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.8 Hz), 7.52–7.60 (m, 6H, H_{Ar}), 7.87–7.96 (m, 4H, H_{Ar}), 8.05 (br d, 1H, NH, $^3J_{HH}$ = 7.3 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 15.79 (s, SMe), 35.70 (s, CH_2S), 41.54 (d, $CH_2P(S)$, $^1J_{CP}$ = 46.2 Hz), 51.90 and 52.05 (both s, OMe and CH), 128.51 (d, *m*-C in $P(S)Ph_2$, $^3J_{CP}$ = 12.8 Hz), 130.81 (d, *o*-C in P(S)Ph, $^2J_{CP}$ = 11.0 Hz), 130.97 (d, *o*-C in P(S)Ph, $^2J_{CP}$ = 10.6 Hz), 131.71 (d, *p*-C in P(S)Ph, $^4J_{CP}$ = 3.3), 131.76 (d, *p*-C in P(S)Ph, $^4J_{CP}$ = 3.3 Hz), 164.03 (d, C(O)NH, $^2J_{CP}$ = 4.0 Hz), 170.32 (s, C(O)OMe) ppm (the signals of *ipso*-C nuclei in $P(S)Ph_2$ were not observed). IR (KBr, ν/cm^{-1}): 445(vw), 485(w), 496(w), 577(w), 614(w), 628(w), 668(w), 693(m), 706(m) (νP=S), 736(w), 746(w), 805(w), 829(vw), 859(w), 897(vw), 974(vw), 1027(vw), 1107(m), 1139(w), 1168(w), 1213(m), 1250(vw), 1340(w), 1412(w), 1437(m), 1540(br, m) (C(O)NH), 1645(s) (νC=O in C(O)NH), 1738(m) (νC=O in C(O)OMe), 2907(vw), 2954(vw), 3052(vw), 3271(br, m) (νNH). Anal. Calcd for $C_{19}H_{22}NO_3PS_2$: C, 56.00; H, 5.44; N, 3.44. Found: C, 56.30; H, 5.41; N, 3.46%.

4.2.2.2. Methyl (2S)-2-{[(diphenylthiophosphoryl)acetyl]amino}-4-(methylsulfanyl)butanoate ***2b***



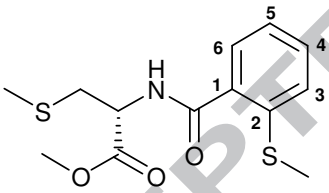
Yield: 0.68 g (70%). Mp: 98–100 °C. $^{31}P\{^1H\}$ (121.49 MHz, $CDCl_3$): δ 37.91 ppm. ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.93–2.09 (m, 2H, CH_2), 2.03 (s, 3H, SMe), 2.34 (t, 2H, CH_2S, $^3J_{HH}$ = 7.5 Hz), 3.51–3.69 (m, 2H, $CH_2P(S)$), 3.72 (s, 3H, OMe), 4.64–4.71 (m, 1H, CH), 7.51–7.61 (m, 6H, H_{Ar}), 7.83–7.99 (m, 5H, NH + H_{Ar}) ppm. $^{13}C\{^1H\}$ (75.47 MHz, $CDCl_3$): δ 15.16 (s, SMe), 29.50 (s, CH_2), 31.28 (s, CH_2S), 41.56 (d, $CH_2P(S)$, $^1J_{CP}$ = 45.6 Hz), 51.66 and 52.29 (both s, OMe and CH), 128.78 (d, *m*-C in $P(S)Ph_2$, $^3J_{CP}$ = 12.6 Hz), 130.75 (d, *o*-C in P(S)Ph, $^2J_{CP}$ = 11.0 Hz), 131.17 (d, *o*-C in P(S)Ph, $^2J_{CP}$ = 11.0 Hz), 131.94 (d, *p*-C in P(S)Ph, $^4J_{CP}$ = 2.7 Hz), 132.13 (d, *p*-C in P(S)Ph, $^4J_{CP}$ = 2.7 Hz), 163.92 (d, C(O)NH, $^2J_{CP}$ = 3.8 Hz), 171.50 (s,

C(O)OMe) ppm (the signals of *ipso*-C nuclei in $P(S)Ph_2$ were not observed). IR (KBr, ν/cm^{-1}): 487(w), 588(vw), 609(vw), 688(w), 707(m) (νP=S), 744(w), 802(vw), 844(w), 935(vw), 991(w), 1073(vw), 1104(w), 1140(w), 1172(w), 1196(w), 1213(m), 1353(m), 1406(w), 1435(m), 1556(br, m) (C(O)NH), 1636(s) (νC=O in C(O)NH), 1738(m) (νC=O in C(O)OMe), 2944(vw), 3055(vw), 3270(br, m) (νNH). Anal. Calcd for $C_{20}H_{24}NO_3PS_2$: C, 56.99; H, 5.74; N, 3.32. Found: C, 56.95; H, 5.55; N, 3.40%.

*4.2.3. General procedure for the synthesis of ligands **3a–c***

A solution of triethylamine (1.60 mL, 11.50 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred suspension of the corresponding amino acid methyl ester hydrochloride (3.75 mmol) in CH_2Cl_2 (10 mL) at –5 °C under an argon atmosphere. The reaction mixture was stirred for 30 min. Then, a solution of 2-(methylsulfanyl)benzoyl chloride (0.70 g, 3.75 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resulting mixture was stirred at 0–5 °C for 1 h and poured into distilled water (75 mL). The organic layer was separated, sequentially washed with a dilute aqueous solution of hydrochloric acid, saturated aqueous solution of $NaHCO_3$, 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) (**3a,b**), EtOAc–acetone (1:2) (**3c**)) to give ligands **3a**–**c** as white crystalline solids. In the case of histidine derivative **3c**, the product of double acylation (compound **4**) was also isolated.

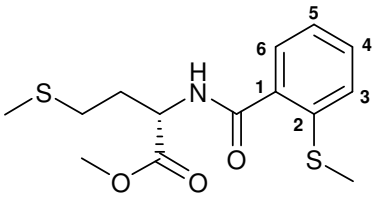
*4.2.3.1. Methyl (2R)-3-(methylsulfanyl)-2-{[2-(methylsulfanyl)benzoyl]amino}propanoate **3a***



Yield: 0.75 g (67%). Mp: 75–77 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.16 (s, 3H, AlkSMe), 2.49 (s, 3H, ArSMe), 3.04–3.18 (m, 2H, CH_2S), 3.81 (s, 3H, OMe), 5.03–5.08 (m, 1H, CH), 7.22 (dt, 1H, H(C4), $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz), 7.30 (br d, 1H, NH, $^3J_{HH}$ = 6.8 Hz), 7.34 (d, 1H, H(C3), $^3J_{HH}$ = 7.4 Hz), 7.40–7.44 (m, 1H, H(C5)), 7.65 (dd, 1H, H(C6), $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz) ppm. ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$): δ 16.19 and 16.63 (both s, AlkSMe and ArSMe), 36.29 (s, CH_2S), 52.04 and 52.53 (both s, OMe and CH), 125.01 (s, C5), 127.19 (s, C3), 128.54 (s, C6), 130.96 (s, C4), 133.60 (s, C1), 137.61 (s, C2), 167.38 (s, C(O)NH), 171.13 (s, C(O)OMe) ppm. IR (KBr, ν/cm^{-1}): 466(vw), 507(vw), 554(vw), 630(w), 697(w), 740(m), 915(w), 966(vw), 1000(w), 1044(vw), 1066(vw), 1110(vw), 1180(w), 1228(w), 1251(m), 1298(m), 1335(w), 1420(w), 1435(m), 1466(w), 1534(br, m) (C(O)NH), 1570(w), 1586(w), 1650(s) (νC=O in C(O)NH), 1728(sh, m) and 1737(s) (both νC=O in C(O)OMe),

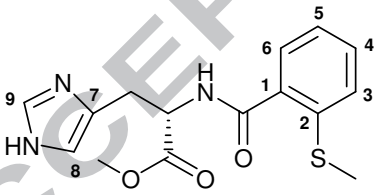
2916(w), 3281(br, m) (*ν*NH). Anal. Calcd for $C_{13}H_{17}NO_3S_2$: C, 52.15; H, 5.72; N, 4.68. Found: C, 52.25; H, 5.84; N, 4.70%.

4.2.3.2. Methyl (2S)-4-(methylsulfanyl)-2-{[2-(methylsulfanyl)benzoyl]amino}butanoate ***3b***



Yield: 0.95 g (81%). Mp: 86–88 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.07–2.16 (m, 1H, CH_2), 2.12 (s, 3H, AlkSMe), 2.27–2.36 (m, 1H, CH_2), 2.48 (s, 3H, ArSMe), 2.58–2.69 (m, 2H, CH_2S), 3.79 (s, 3H, OMe), 4.91–4.96 (m, 1H, CH), 7.12 (br d, 1H, NH, $^3J_{HH}$ = 7.2 Hz), 7.21 (dt, 1H, H(C4), $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.0 Hz), 7.32 (d, 1H, H(C3), $^3J_{HH}$ = 7.6 Hz), 7.39–7.43 (m, 1H, H(C5)), 7.60 (d, 1H, H(C6), $^3J_{HH}$ = 7.6 Hz) ppm. ^{13}C{^{1}H} (100.61 MHz, $CDCl_3$): δ 15.32 and 16.54 (both s, AlkSMe and ArSMe), 29.84 (s, CH_2), 31.64 (s, CH_2S), 51.86 and 52.42 (both s, OMe and CH), 125.00 (s, C5), 126.98 (s, C3), 128.48 (s, C6), 130.84 (s, C4), 133.94 (s, C1), 137.15 (s, C2), 167.42 (s, C(O)NH), 172.14 (s, C(O)OMe) ppm. IR (KBr, *ν*/cm^{-1}): 469(vw), 546(vw), 658(w), 709(vw), 736(w), 784(vw), 888(vw), 928(vw), 958(vw), 1017(w), 1044(w), 1066(vw), 1155(w), 1218(w), 1235(m), 1259(w), 1296(w), 1313(w), 1332(m), 1352(vw), 1433(m), 1443(sh, w), 1464(vw), 1529(br, s) (C(O)NH), 1568(vw), 1585(w), 1633(s) (*ν*C=O in C(O)NH), 1739(s) (*ν*C=O in C(O)OMe), 2841(vw), 2916(w), 2947(w), 2972(w), 3301(br, m) (*ν*NH). Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.65; H, 6.11; N, 4.47. Found: C, 53.59; H, 6.14; N, 4.44%.

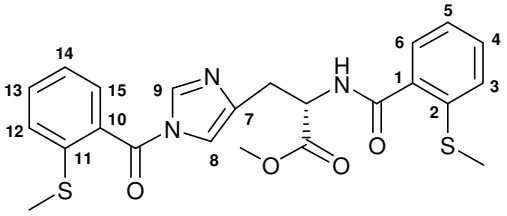
4.2.3.3. Methyl (2S)-3-(1H-imidazol-4-yl)-2-{[2-(methylsulfanyl)benzoyl]amino}propanoate ***3c***



Yield: 0.78 g (65%). Mp: 122–124 °C (EtOAc). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.44 (s, 3H, SMe), 3.25 (d, 2H, CH_2, $^3J_{HH}$ = 5.1 Hz), 3.74 (s, 3H, OMe), 4.99–5.05 (m, 1H, CH), 6.84 (s, 1H, H(C8)), 7.16–7.21 (m, 1H, H(C4)), 7.29–7.32 (m, 2H, H(C3) + NH), 7.40 (t, 1H, H(C5), $^3J_{HH}$ = 7.7 Hz), 7.53 (s, 1H, H(C9)), 7.57 (d, 1H, H(C6), $^3J_{HH}$ = 7.7 Hz), 7.74 (br d, 1H, NHC(O), $^3J_{HH}$ = 7.7 Hz) ppm. ^{13}C{^{1}H} (75.47 MHz, $CDCl_3$): δ 16.28 (s, SMe), 29.03 (s, CH_2), 52.39 and 52.77 (both s, OMe and CH), 116.38 (s, C8), 124.73 (s, C5), 126.46 (s, C3), 128.12 (s, C6), 130.84 (s, C4), 133.66 (s, C1 + C7), 135.00 (s, C9), 138.10 (s, C2), 167.98 (s, C(O)NH), 171.75 (s, C(O)OMe) ppm. IR (KBr, *ν*/cm^{-1}): 520(vw), 545(vw), 625(m), 647(w), 747(m), 757(w),

810(w), 920(vw), 985(vw), 1033(w), 1064(w), 1172(m), 1219(m), 1256(m), 1290(w), 1317(w), 1351(w), 1433(m), 1467(w), 1528(br, s) (C(O)NH), 1569(vw), 1586(w), 1648(s) (*ν*C=O in C(O)NH), 1743(s) (*ν*C=O in C(O)OMe), 2915(w), 3102(w), 3313(s) (*ν*NH). Anal. Cacld for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16. Found: C, 56.62; H, 5.30; N, 13.24%.

4.2.3.4. Methyl (2S)-2-{[2-(methylsulfanyl)benzoyl]amino}-3-{1-[2-(methylsulfanyl)benzoyl]-1H-imidazol-4-yl}propanoate ***4***



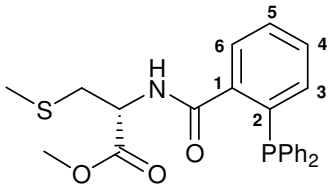
Yield: 0.18 g (20%). Mp: 160–162 °C ($CHCl_3$–Et_2O). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.49 and 2.50 (both s, 3H + 3H, SMe), 3.31 (d, 2H, CH_2, $^3J_{HH}$ = 5.0 Hz), 3.83 (s, 3H, OMe), 5.16 (dt, 1H, CH, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 5.0 Hz), 7.24 (t, 1H, H_{Ar}), 7.30–7.37 (m, 2H, H_{Ar}), 7.43–7.49 (m, 3H, H_{Ar} + H(C8)), 7.57–7.66 (m, 4H, H_{Ar} + NH), 7.86 (s, 1H, H(C9)) ppm. ^{13}C{^{1}H} (100.61 MHz, $CDCl_3$): δ 16.34 and 16.54 (both s, SMe), 29.65 (s, CH_2), 52.06 and 52.36 (both s, OMe and CH), 114.90 (s, C8), 124.65 and 124.98 (both s, C5 and C14), 126.57 and 127.69 (both s, C3 and C12), 128.16 and 128.70 (both s, C6 and C15), 130.67 (s, C4), 131.72 (s, C1 or C10), 132.10 (s, C13), 133.82 (s, C10 or C1), 138.01 and 138.83 (both s, C2 and C11), 139.51 (s, C7), 164.79 (s, C(O)N), 167.48 (s, C(O)NH), 171.45 (s, C(O)OMe) ppm (the signal of C9 carbon nucleus was not observed). IR (KBr, *ν*/cm^{-1}): 465(vw), 646(vw), 715(vw), 742(w), 754(m), 867(vw), 901(m), 969(w), 1021(w), 1065(vw), 1100(vw), 1135(w), 1179(w), 1218(m), 1241(m), 1286(m), 1309(w), 1362(w), 1383(m), 1435(m), 1464(w), 1488(w), 1544(br, m) (C(O)NH), 1586(m), 1657(s) (*ν*C=O in C(O)N and C(O)NH), 1715(s) and 1747(s) (both *ν*C=O in C(O)OMe), 2843(vw), 2921(vw), 3047(vw), 3130(w), 3233(br, w) (*ν*NH). Anal. Calcd for $C_{23}H_{23}N_3O_4S_2$: C, 58.83; H, 4.94; N, 8.95. Found: C, 58.58; H, 4.74; N, 8.86%.

4.2.4. General procedure for the synthesis of ligands ***5a,b***

Triphenylphosphite (2.25 g, 7.25 mmol) was added portionwise to a stirred mixture of the corresponding amino acid methyl ester hydrochloride (7.15 mmol), 2-(diphenylphosphanyl)benzoic acid (2.19 g, 7.15 mmol), and pyridine (30 mL) at 100 °C under an argon atmosphere. The reaction mixture was stirred at this temperature for 6 h. The excess of pyridine was removed under vacuum. The resulting residue was dissolved in chloroform, washed with water (3 times), saturated aqueous solution of $NaHCO_3$ (3 times), and again with water (2 times). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to

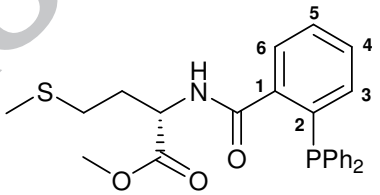
dryness. The resulting residue was purified by column chromatography on silica gel (eluent EtOAc–hexane (1:2)) to give ligands **5a,b** as white crystalline solid.

4.2.4.1. Methyl (2R)-2-{[2-(diphenylphosphanyl)benzoyl]amino}-3-(methylsulfanyl)propanoate ***5a***



Yield: 1.25 g (40%). Mp: 105–108 °C. $^{31}P\{^{1}H\}$ (121.49 MHz, $CDCl_3$): δ –9.31 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.11 (s, 3H, SMe), 2.93 (d, 2H, CH_2, $^{3}J_{HH}$ = 5.0 Hz), 3.79 (s, 3H, OMe), 4.92 (dt, 1H, CH, $^{3}J_{HH}$ = 7.6 Hz, $^{3}J_{HH}$ = 5.0 Hz), 6.87 (br d, 1H, NH, $^{3}J_{HH}$ = 7.6 Hz), 7.02 (ddd, 1H, H(C3), $^{3}J_{HH}$ = 7.7 Hz, $^{3}J_{HP}$ = 4.0 Hz, $^{4}J_{HH}$ = 0.8 Hz), 7.29–7.39 (m, 11H, H_{Ar}), 7.43 (dt, 1H, H(C5), $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.2 Hz), 7.70 (ddd, 1H, H(C6), $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HP}$ = 3.8 Hz, $^{4}J_{HH}$ = 1.2 Hz) ppm. $^{13}C\{^{1}H\}$ NMR (100.61 MHz, $CDCl_3$): δ 16.33 (s, SMe), 36.45 (s, CH_2S), 52.04 and 52.64 (both s, OMe and CH), 127.66 (d, C3, $^{2}J_{CP}$ = 4.6 Hz), 128.53 (d, *m*-C in PPh, $^{3}J_{CP}$ = 6.9 Hz), 128.58 (d, *m*-C in PPh, $^{3}J_{CP}$ = 6.8 Hz), 128.62 (s, C4 or C5), 128.75 and 128.78 (both s, *p*-C in PPh_2), 130.60 (s, C5 or C4), 133.79 (d, *o*-C in PPh, $^{2}J_{CP}$ = 3.8 Hz), 133.99 (d, *o*-C in PPh, $^{2}J_{CP}$ = 3.7 Hz), 134.45 (s, C6), 137.09 (d, C2, $^{1}J_{CP}$ = 22.2 Hz), 137.28 (d, *ipso*-C in PPh, $^{1}J_{CP}$ = 11.3 Hz), 137.33 (d, *ipso*-C in PPh, $^{1}J_{CP}$ = 11.0 Hz), 140.15 (d, C1, $^{2}J_{CP}$ = 24.3 Hz), 168.37 (s, C(O)NH), 171.26 (s, C(O)OMe) ppm. IR (KBr, ν/cm^{-1}): 498(w), 518(w), 697(m), 749(s), 999(vw), 1027(vw), 1090(w), 1126(vw), 1159(w), 1176(w), 1214(m), 1258(w), 1311(w), 1434(m), 1459(w), 1479(w), 1520(br, m) (C(O)NH), 1560(vw), 1584(w), 1649(s) (νC=O in C(O)NH), 1744(s) (νC=O in C(O)OMe), 2850(vw), 2917(w), 2950(w), 3051(w), 3295(br, w) (νNH). Anal. Calcd for $C_{24}H_{24}NO_3PS$: C, 65.89; H, 5.53; N, 3.20. Found: C, 66.03; H, 5.49; N, 3.14%.

4.2.4.2. Methyl (2S)-2-{[2-(diphenylphosphanyl)benzoyl]amino}-4-(methylsulfanyl)butanoate ***5b***



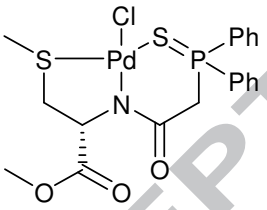
Yield: 1.10 g (34%). Mp: 74–75 °C (Et_2O). $^{31}P\{^{1}H\}$ NMR (121.49 MHz, $CDCl_3$): δ –9.89 ppm. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.89–2.02 (m, 1H, CH_2), 2.12 (s, 3H, SMe), 2.12–2.22 (m, 1H, CH_2), 2.46–2.56 (m, 2H, CH_2S), 3.79 (s, 3H, OMe), 4.81–4.87 (m, 1H, CH), 6.74 (d, 1H, NH, $^{3}J_{HH}$ = 7.3 Hz), 7.03 (ddd, 1H, H(C3), $^{3}J_{HH}$ = 7.5 Hz, $^{3}J_{HP}$ = 4.0 Hz, $^{4}J_{HH}$ = 1.0 Hz),

7.29–7.48 (m, 12H, H_{Ar}), 7.71 (ddd, 1H, H(C6), $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HP}$ = 3.6 Hz, $^{4}J_{HH}$ = 1.3 Hz) ppm. $^{13}C\{^{1}H\}$ (100.61 MHz, $CDCl_3$): δ 15.37 (s, SMe), 29.81 (s, CH_2), 31.79 (s, CH_2S), 51.91 and 52.44 (both s, OMe and CH), 127.85 (d, C3, $^{2}J_{CP}$ = 4.8 Hz), 128.47 (d, *m*-C in PPh, $^{3}J_{CP}$ = 7.0 Hz), 128.61 (d, *m*-C in PPh, $^{3}J_{CP}$ = 7.0 Hz), 128.69 and 128.72 (both s, *p*-C in PPh_2), 128.85 and 130.40 (both s, C4 and C5), 133.66 (d, *o*-C in PPh, $^{2}J_{CP}$ = 4.0 Hz), 133.86 (d, *o*-C in PPh, $^{2}J_{CP}$ = 4.0 Hz), 134.20 (s, C6), 136.12 (d, C2, $^{1}J_{CP}$ = 21.3 Hz), 136.81 (d, *ipso*-C in PPh, $^{1}J_{CP}$ = 11.0 Hz), 136.90 (d, *ipso*-C in PPh, $^{1}J_{CP}$ = 11.0 Hz), 140.51 (d, C1, $^{2}J_{CP}$ = 25.3 Hz), 168.46 (s, C(O)NH), 172.12 (s, C(O)OMe) ppm. IR (KBr, *ν*/cm^{-1}): 501(w), 698(m), 746(m), 857(vw), 998(vw), 1027(vw), 1069(vw), 1092(w), 1171(m), 1215(m), 1306(w), 1338(w), 1434(s), 1478(w), 1539(br, m) (C(O)NH), 1584(w), 1638(s) and 1654(sh, m) (both *ν*C=O in C(O)NH), 1741(s) (*ν*C=O in C(O)OMe), 2916(w), 2949(w), 3053(w), 3294(br, m) (*ν*NH). Anal. Calcd for $C_{25}H_{26}NO_3PS$: C, 66.50; H, 5.80; N, 3.10. Found: C, 66.57; H, 5.84; N, 3.09%.

*4.2.5. General procedure for the synthesis of Pd(II) complexes **6–8***

A solution of $PdCl_2(NCPh)_2$ (71 mg, 0.185 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of the corresponding ligand (0.185 mmol) and, in the case of ligands **3c**, **5a,b**, triethylamine (26 μL, 0.185 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 5 h and then purified by column chromatography on silica gel (eluent CH_2Cl_2–MeOH (50:1)) to give complexes **6–8** as yellow crystalline solids.

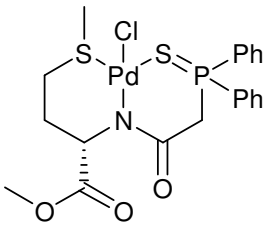
*4.2.5.1. Complex [κ^3-S,N,S-(L)Pd(II)Cl] **6a***



Yield: 66 mg (65%). Mp: >200 °C (dec.). $^{31}P\{^{1}H\}$ NMR (121.49 MHz, $CDCl_3$, major isomer (M) 65%, minor isomer (m) 35%): δ 40.84 (m), 41.49 (M) ppm. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.32 (dd, 1H, CH_2S (m), $^{2}J_{HH}$ = 11.4 Hz, $^{3}J_{HH}$ = 5.3 Hz), 2.67 (s, 3H, SMe (m)), 2.75 (s, 3H, SMe (M)), 2.79 (dd, 1H, CH_2S (M), $^{2}J_{HH}$ = 13.6 Hz, $^{3}J_{HH}$ = 5.8 Hz), 2.95 (d, 1H, CH_2S (M), $^{2}J_{HH}$ = 13.6 Hz), 3.19 (d, 1H, CH_2S (m), $^{2}J_{HH}$ = 11.4 Hz), 3.33 (s, 3H, OMe (m)), 3.38 (s, 3H, OMe (M)), 3.76 (dd, 1H, $CH_2P(S)$ (M), $^{2}J_{HH}$ = 14.7 Hz, $^{2}J_{HP}$ = 8.5 Hz), 3.84 (dd, 1H, $CH_2P(S)$ (m), $^{2}J_{HH}$ = 15.0 Hz, $^{2}J_{HP}$ = 8.8 Hz), 4.09 (dd, 1H, $CH_2P(S)$ (M), $^{2}J_{HH}$ = 14.7 Hz, $^{2}J_{HP}$ = 19.1 Hz), 4.13 (dd, 1H, $CH_2P(S)$ (m), $^{2}J_{HH}$ = 15.0 Hz, $^{2}J_{HP}$ = 18.5 Hz), 5.51 (d, 1H, CH (m), $^{3}J_{HH}$ = 5.3 Hz), 5.56 (d, 1H, CH (M), $^{3}J_{HH}$ = 5.8 Hz), 7.51–7.57 (m, 2H, H_{Ar} (M) + 2H, H_{Ar} (m)), 7.62–7.76 (m, 6H, H_{Ar} (M) + 6H, H_{Ar} (m)), 8.02–8.13 (m, 2H, H_{Ar} (M) + 2H, H_{Ar} (m)) ppm. $^{13}C\{^{1}H\}$ NMR (75.47 MHz, $CDCl_3$): δ 22.78 (s, SMe (M)), 24.66 (s, SMe (m)), 37.69 (s, CH_2S

(M)), 40.86 (s, CH_2S (m)), 44.21 (d, $CH_2P(S)$ (m), $^1J_{CP}$ = 45.7 Hz), 44.48 (d, $CH_2P(S)$ (M), $^1J_{CP}$ = 44.7 Hz), 52.33 (s, OMe (m)), 52.42 (s, OMe (M)), 64.55 (s, CH (m)), 67.17 (s, CH (M)), 125.47 (d, *ipso*-C in $P(S)Ph_2$ (M+m), $^1J_{CP}$ = 82.2 Hz), 127.28 (d, *ipso*-C in $P(S)Ph_2$ (M+m), $^1J_{CP}$ = 81.9 Hz), 128.98 (d, *m*-C in P(S)Ph (M+m), $^3J_{CP}$ = 13.3 Hz), 129.25 (d, *m*-C in P(S)Ph (M+m), $^3J_{CP}$ = 12.8 Hz), 131.23 (d, *o*-C in P(S)Ph (M+m), $^2J_{CP}$ = 10.6 Hz), 132.03 (d, *o*-C in P(S)Ph (m), $^2J_{CP}$ = 9.4 z), 132.16 (d, *o*-C in P(S)Ph (M), $^2J_{CP}$ = 10.5 Hz), 133.08 (d, *p*-C in P(S)Ph (M+m), $^4J_{CP}$ = 2.6 Hz), 133.17 (d, *p*-C in P(S)Ph (M+m), $^4J_{CP}$ = 2.6 Hz), 165.96 (d, C(O)N (M), $^2J_{CP}$ = 6.2 Hz), 166.25 (d, C(O)N (m), $^2J_{CP}$ = 6.2 Hz), 171.18 (s, C(O)OMe (m)), 172.28 (s, C(O)OMe (M)) ppm. IR (KBr, ν/cm^{-1}): 413(vw), 451(vw), 480(vw), 511(m), 570(vw), 597(w) (νP=S), 620(vw), 691(m), 724(w), 748(m), 788(vw), 811(vw), 856(w), 998(vw), 1026(w), 1107(m), 1170(w), 1214(m), 1265(w), 1314(vw), 1369(m), 1437(s), 1484(vw), 1593(br, s) (νC=O in C(O)N), 1725(s) (νC=O in C(O)OMe), 2923(w). Anal. Calcd for $C_{19}H_{21}ClNO_3PPdS_2$: C, 41.62; H, 3.86; N, 2.55. Found: C, 41.80; H, 4.15; N, 2.39%.

4.2.5.2. Complex [κ^3-S,N,S-(L)Pd(II)Cl] ***6b***

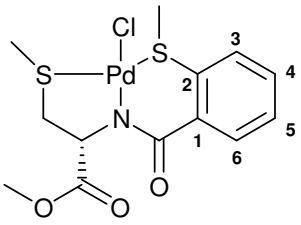


Yield: 75 mg (72%). Mp: >195 °C (dec.). $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$, major isomer (M) 84%, minor isomer (m) 16%): δ 40.56 (m), 41.20 (M) ppm. ^1H NMR (600.22 MHz, $CDCl_3$, 243 K, major isomer):[1] δ 2.52–2.57 (m, 1H, CH_2 + 1H, CH_2S), 2.60 (s, 3H, SMe), 2.62–2.68 (m, 1H, CH_2 + 1H, CH_2S), 3.52(s, 3H, OMe), 3.90–3.94 (m, 1H, $CH_2P(S)$), 4.39–4.44 (m, 1H, $CH_2P(S)$), 4.79 (dd, 1H, CH, $^3J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 5.8 Hz), 7.57–7.60 (m, 2H, H_{Ar}), 7.64–7.68 (m, 3H, H_{Ar}), 7.72–7.74 (m 1H, H_{Ar}), 7.90 (dd, 2H, *o*-H in P(S)Ph, $^3J_{HP}$ = 13.7 Hz, $^3J_{HH}$ = 7.6 Hz), 8.00 (dd, 2H, *o*-H in P(S)Ph, $^3J_{HP}$ = 14.0 Hz, $^3J_{HH}$ = 7.6 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$, 243 K, major isomer): δ 21.17 (s, SMe), 29.80 (s, CH_2), 31.80 (s, CH_2S), 48.49 (d, $CH_2P(S)$, $^1J_{CP}$ = 43.9 Hz), 52.33 (s, OMe), 53.18 (s, CH), 126.95 (d, *ipso*-C in P(S)Ph, $^1J_{CP}$ = 82.8 Hz), 127.88 (d, *ipso*-C in P(S)Ph, $^1J_{CP}$ = 82.5 Hz), 129.46 (d, *m*-C in P(S)Ph, $^3J_{CP}$ = 13.1 Hz), 129.67 (d, *m*-C in P(S)Ph, $^3J_{CP}$ = 13.1 Hz), 132.08 (d, *o*-C in P(S)Ph, $^2J_{CP}$ = 11.2 Hz), 132.20 (d, *o*-C in P(S)Ph, $^2J_{CP}$ = 11.3 Hz), 133.39 (s, *p*-C in P(S)Ph), 133.63 (s, *p*-C in P(S)Ph), 167.23 (d, C(O)N, $^2J_{CP}$ = 6.2 Hz), 172.71 (s, C(O)OMe) ppm. IR (KBr, ν/cm^{-1}): 464(vw),

[1] The content of the minor isomer at 243 K composes only 8%; therefore, only the signals of the major isomer were reliably assigned.

485(m), 562(w), 584(m) (*ν*P=S), 691(m), 744(m), 752(m), 797(vw), 834(w), 997(w), 1012(w), 1034(w), 1106(m), 1125(w), 1166(w), 1203(m), 1251(w), 1279(w), 1320(w), 1353(m), 1373(m), 1437(m), 1481(vw), 1600(br, s) (*ν*C=O in C(O)N), 1737(s) (*ν*C=O in C(O)Me), 2911(w), 2951(vw), 3052(vw). Anal. Calcd for $C_{20}H_{23}ClNO_3PPdS_2$: C, 42.71; H, 4.12; N, 2.49. Found: C, 42.26; H, 4.41; N, 2.05.

4.2.5.3. Complex [κ³-S,N,S-(L)Pd(II)Cl] ***7a***

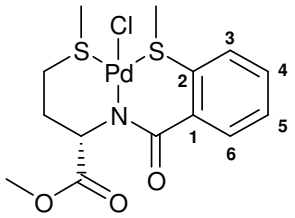


Yield: 53 mg (65%). Mp: 135–138 °C (dec.). ^{1}H NMR (600.22 MHz, $CDCl_3$, 243 K, content of the isomers: 53% (A), 27% (B), 14% (C), 6% (D)): δ 2.27 (dd, 1H, CH_2S (D), $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 5.5 Hz), 2.36 (dd, 1H, CH_2S (B), $^2J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 5.5 Hz), 2.55 (s, 3H, AlkSMe (D)), 2.61 (s, 3H, AlkSMe (B)), 2.66 (s, 3H, AlkSMe (A)), 2.71 (s, 3H, AlkSMe (C)), 2.78 (dd, 1H, CH_2S (C), $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 6.0 Hz), 2.82–2.85 (m, 1H, CH_2S (A) + 3H, ArSMe (B)), 2.88 (br s, 3H, ArSMe (A) + 3H, ArSMe (C) + 3H, ArSMe (D)), 3.06 (br d, 1H, CH_2S (A) +1H, CH_2S (C), $^2J_{HH}$ = 14.0 Hz), 3.35 (d, 1H, CH_2S (D), $^2J_{HH}$ = 11.5 Hz), 3.42 (d, 1H, CH_2S (B), $^2J_{HH}$ = 11.5 Hz), 5.96–6.00 (m, 1H, CH (A) + 1H, CH (B) + 1H, CH (C) + 1H, CH (D)), 3.80 (s, 3H, OMe (B)), 3.83 (s, 3H, OMe (D)), 3.85 (s, 3H, OMe (A)), 3.89 (s, 3H, OMe (C)), 7.26 (d, 1H, H(C3) (C), $^3J_{HH}$ = 7.9 Hz), 7.43–7.54 (m, 1H, H_{Ar} (A) + 2H, H_{Ar} (B) + 1H, H_{Ar} (C)), 7.59–7.65 (m, 2H, H_{Ar} (A) + 1H, H_{Ar} (B) + 1H, H_{Ar} (C) + 3H, H_{Ar} (D)), 8.08 (d, 1H, H(C6) (C), $^3J_{HH}$ = 7.6 Hz), 8.19–8.21 (m, 1H, H(C6) (A) + 1H, H(C6) (D)), 8.31 (d, 1H, H(C6) (B), $^3J_{HH}$ = 7.8 Hz) ppm. ^{13}C{^{1}H} NMR (150.93 MHz, $CDCl_3$, 243K):[2] δ 21.71 (s, AlkSMe (A)), 23.80 (s, AlkSMe (B)), 27.48 (s, ArSMe (A)), 27.98 (s, ArSMe (B)), 37.14 (s, CH_2S (A)), 39.81 (s, CH_2S (B)), 53.18 (s, OMe (A)), 53.22 (s, OMe (B)), 65.48 (s, CH (B)), 67.90 (s, CH (A)), 125.55 (s, C2 (B)), 125.70 (s, C2 (A)), 130.70 (s, C3 (A)), 130.84 (s, C3 (B)), 131.89–131.91 (m, overlapping signals of C4 (A), C5 (A), and C4 (B) or C5 (B)), 132.18 (s, C4 or C5 (B)), 134.00 (s, C6 (A)), 134.24 (s, C6 (B)), 140.26 (s, C1 (B)), 140.46 (s, C1 (A)), 165.78 (s, C(O)N (B)), 166.29 (s, C(O)N (A)), 171.30 (s, C(O)OMe (B)), 172.54 (s, C(O)OMe (A)) ppm. IR (KBr, *ν*/cm^{-1}): 504(vw), 695(w), 749(m), 787(w), 837(vw), 871(vw), 968(w), 1020(w), 1092(w), 1171(m), 1211(m), 1252(w), 1315(w), 1366(m), 1418(w), 1435(w), 1462(w), 1550(s) (*ν*C=O in

[2] The signals of C and D isomers were observed only for several carbon nuclei and cannot be reliably assigned (see Figs. S5–S10 in Supplementary data).

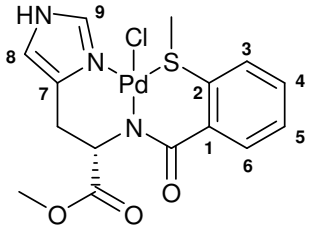
C(O)N), 1584(s), 1735(m) (*ν*C=O in C(O)OMe), 2853(vw), 2925(w), 2948(w), 3000(vw), 3059(vw). Anal. Calcd for $C_{13}H_{16}ClNO_3PdS_2$: C, 35.46; H, 3.66; N, 3.18. Found: C, 35.41; H, 3.89; N, 3.00%.

4.2.5.4. Complex [κ³-S,N,S-(L)Pd(II)Cl] ***7b***



Yield: 72 mg (86%). Mp: 195–200 °C (dec).[3] IR (KBr, *ν*/cm^{-1}): 524(vw), 582(vw), 691(w), 742(m), 770(w), 816(w), 901(vw), 976(w), 1046(w), 1066(w), 1107(m), 1173(m), 1198(m), 1225(w), 1286(w), 1320(m), 1368(m), 1418(w), 1442(m), 1559(m) (*ν*C=O in C(O)N), 1583(s), 1591(s), 1655(w), 1735(s) (*ν*C=O in C(O)OMe), 2922(w). Anal. Cacld for $C_{14}H_{18}ClNO_3PdS_2$: C, 37.01; H, 3.99; N, 3.08. Found: C, 37.25; H, 4.03; N, 2.92%.

4.2.5.5. Complex [κ³-S,N,N-(L)Pd(II)Cl] ***7c***

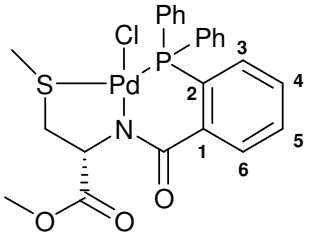


Yield: 80 mg (94%). Mp: 225–230 °C (dec.). ^{1}H NMR (400.13 MHz, $CDCl_3$, major isomer (M) 77%, minor isomer (m) 23%): 2.70 (s, 3H, SMe (m)), 2.87 (s, 3H, SMe (M)), 3.13 (dd, 1H, CH_2 (M), $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 3.4 Hz), 3.24 (dd, 1H, CH_2 (m), $^2J_{HH}$ =15.1 Hz, $^3J_{HH}$ = 3.6 Hz), 3.34–3.43 (m, 1H, CH_2 (M) + 1H, CH_2 (m)), 3.75 (s, 3H, OMe (m)), 3.77 (s, 3H, OMe (M)), 4.42 (dd, 1H, CH (m), $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 3.6 Hz), 4.54 (dd, 1H, CH (M), $^3J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 3.4 Hz), 6.86 (br s, 1H, H(C8) (m)), 6.88 (br s, 1H, H(C8) (M)), 7.27–7.29 (m, 1H, H(C4) (m)), 7.38 (dt, 1H, HC(4) (M), $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.4 Hz), 7.41–7.44 (m, 2H, H(C3) + H(C5) (m)), 7.51–7.58 (m, 2H, H(C3) + H(C5) (M)), 7.87 (br s, 1H, H(C9) (m)), 7.90–7.93 (m, 1H, H(C6) (m)), 7.93 (br s, 1H, H(C9) (M)), 8.06 (dd, 1H, H(C6) (M), $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz), 11.51 (br s, 1H, NH (M+m)) ppm. ^{13}C{^{1}H} NMR (100.61 MHz, $CDCl_3$): δ 18.73 (s, SMe (m)), 24.43 (s, SMe (M)), 29.50 (s, CH_2 (m)), 29.84 (s, CH_2 (M)), 52.01 (s, OMe (M)), 52.14 (s, OMe (m)), 57.16 (s, CH (M+m)), 112.78 (s, C8 (M)), 113.00 (s, C8 (m)), 125.27 (s, C2 (M)), 127.17 (s, C2 (m)), 128.97 (s, C3 (m)), 130.23 (s, C3 (M)), 130.42 (s, C4 (M)), 130.98 (s, C4 (m)),

[3] ^{1}H, ^{13}C{^{1}H} and HMQC NMR spectra of complex **7b** in $CDCl_3$ at –30 °C are presented in Supplementary data (Figs. S11–19).

131.31 (s, C5 (M)), 131.92 (s, C5 (m)), 133.06 (s, C6 (M+m)), 133.50 (s, C7 (M)), 133.79 (s, C7 (m)), 138.45 (s, C1 (m)), 140.85 (s, C1 (M)), 166.74 (s, C(O)N (M)), 167.04 (s, C(O)N (m)), 172.84 (s, C(O)OMe (m)), 173.46 (s, C(O)OMe (M)) ppm (the signal of C9 carbon nucleus was not observed). IR (KBr, ν/cm^{-1}): 455(w), 629(w), 704(vw), 757(m), 783(w), 827(w), 895(vw), 980(w), 1040(w), 1093(w), 1174(m), 1197(m), 1239(w), 1275(w), 1349(w), 1385(m), 1433(w), 1506(m), 1526(s) (νC=O in C(O)N), 1574(m), 1729(m)/1735(m) (both νC=O in C(O)OMe), 2662(w), 2753(w), 2852(w), 3030(w), 3138(w) (νNH). Anal. Calcd for $C_{15}H_{16}ClN_3O_3PdS$: C, 39.14; H, 3.50; N, 9.13. Found: C, 39.39; H, 3.78; N, 8.90%.

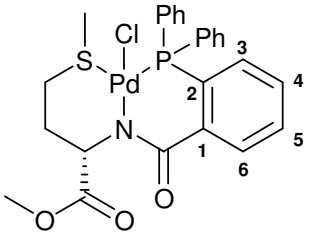
4.2.5.6. Complex [κ^3-S,N,P-(L)Pd(II)Cl] ***8a***



Yield: 102 mg (95%). Mp: >180 °C (dec.). ^{31}P{^{1}H} NMR (121.49 MHz, $CDCl_3$): δ 26.99 ppm. ^{1}H NMR (600.22 MHz, $CDCl_3$, 243 K, major isomer (M) 61%, minor isomer (m) 39%): δ 2.19 (dd, 1H, CH_2S (m), $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 4.6 Hz), 2.62 (d, 3H, SMe (m), $^4J_{HP}$ = 4.4 Hz), 2.66 (d, 3H, SMe (M), $^4J_{HP}$ = 4.3 Hz), 2.70 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 5.6 Hz), 2.96 (s, 3H, OMe (M)), 3.00 (s, 3H, OMe (m)), 3.11 (dd, 1H, CH_2S (M), $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 3.1 Hz), 3.42 (dd, 1H, CH_2S (m), $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 6.2 Hz), 6.19–6.21 (m, 1H, CH (M) + 1H, CH (m)), 6.71 (dd, 1H, H(C3) (M), $^3J_{HP}$ = 11.3 Hz, $^3J_{HH}$ = 8.0 Hz), 6.77 (dd, 1H, H(C3) (m), $^3J_{HP}$ = 11.6 Hz, $^3J_{HH}$ = 7.9 Hz), 7.37–7.63 (m, 11H, H_{Ar} (M) + 11H, H_{Ar} (m)), 7.66–7.71 (m, 1H, H(C5) (M) + 1H, H(C5) (m)), 8.47 (dd, 1H, H(C6) (M), $^3J_{HH}$ = 7.8 Hz, $^4J_{HP}$ = 3.9 Hz), 8.56 (dd, 1H, H(C6) (m), $^3J_{HH}$ = 7.7 Hz, $^3J_{HP}$ = 3.9 Hz) ppm. ^{13}C{^{1}H} NMR (150.93 MHz, $CDCl_3$, 243 K): δ 20.50 (s, SMe (M)), 22.83 (s, SMe (m)), 34.16 (s, CH_2S (M)), 37.57 (s, CH_2S (m)), 52.70 (s, OMe (m)), 52.80 (s, OMe (M)), 65.76 (s, CH (m)), 68.63 (s, CH (M)), 122.62 (d, C2 (M), $^1J_{CP}$ = 51.9 Hz), 122.65 (d, C2 (m), $^1J_{CP}$ = 51.6 Hz), 125.99 (d, *ipso*-C in PPh (m), $^1J_{CP}$ = 60.2 Hz), 127.09 (d, *ipso*-C in PPh (M), $^1J_{CP}$ = 60.5 Hz), 127.42 (d, *ipso*-C in PPh (M), $^1J_{CP}$ = 55.5 Hz), 127.56 (d, *ipso*-C in PPh (m), $^1J_{CP}$ = 56.4 Hz), 128.60–128.76 (m, *m*-C in PPh (M+m)), 129.33–129.46 (m, *m*-C in PPh (M+m)), 130.32 (d, C4 (M), $^3J_{CP}$ = 8.2 Hz), 130.40 (d, C4 (m), $^3J_{CP}$ = 9.1 Hz), 131.86 (s, *p*-C in PPh (M+m)), 132.11 (s, *p*-C in PPh (M+m)), 132.45 (s, C5 (M+m)), 132.86–132.94 (m, C3 (M+m) + C6 (M)), 133.14 (d, C6 (m), $^3J_{CP}$ = 11.4 Hz), 133.33 (d, *o*-C in PPh (M), $^2J_{CP}$ = 11.5 Hz), 133.52 (d, *o*-C in PPh (m), $^2J_{CP}$ = 12.0 Hz), 134.61 (d, *o*-C in PPh (m), $^2J_{CP}$ = 10.0 Hz), 134.65 (d, *o*-C in PPh (M), $^2J_{CP}$ = 10.6 Hz), 142.47 (d, C1 (m), $^2J_{CP}$ = 14.0 Hz), 142.74 (d, C1 (M), $^2J_{CP}$ = 14.4 Hz), 166.43 (d, C(O)N (m), $^3J_{CP}$ = 9.3 Hz), 166.95 (d, C(O)N,

$^3J_{CP}$ = 9.2 Hz), 171.98 (s, C(O)OMe (m)), 173.04 (s, C(O)OMe (M)) ppm. IR (KBr, ν/cm^{-1}): 438(vw), 510(m), 551(m), 693(m), 714(w), 737(w), 750(m), 791(vw), 865(vw), 970(vw), 998(vw), 1026(w), 1101(m), 1126(w), 1170(w), 1184(w), 1209(w), 1252(w), 1287(w), 1314(w), 1360(br, m), 1436(m), 1461(vw), 1482(w), 1548(s) (νC=O in C(O)N), 1579(s), 1593(m), 1724(m) (νC=O in C(O)OMe), 2854(vw), 2926(w), 2952(w), 3055(w). Anal. Calcd for $C_{24}H_{23}ClNO_3PPdS$: C, 49.84; H, 4.01; N, 2.42. Found: C, 49.84; H, 4.03; N, 2.38%.

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



Yield: 82 mg (75%). Mp: >170 °C (dec.). $^{31}P\{^1H\}$ NMR (121.49 MHz, $CDCl_3$): δ 25.00 ppm. ^1H NMR (400.13 MHz, $CDCl_3$): δ 2.30–2.36 (m, 1H, CH_2), 2.46 (d, 3H, SMe, $^4J_{HP}$ = 4.2 Hz), 2.63–2.69 (m, 1H, CH_2), 2.84–2.88 (m, 1H, CH_2S), 2.93–2.99 (m, 1H, CH_2S), 3.15 (s, 3H, OMe), 4.24–4.27 (m, 1H, CH), 6.76 (dd, 1H, H(C3), $^3J_{HP}$ = 11.4 Hz, $^3J_{HH}$ = 7.7 Hz,), 7.32 (t, 1H, H_{Ar}, $^3J_{HH}$ = 7.5 Hz), 7.41–7.47 and 7.51–7.64 (both m, 6H + 5H, H_{Ar}), 8.29 (dd, 1H, H(C6), $^3J_{HH}$ = 7.5 Hz, $^4J_{HP}$ = 3.8 Hz) ppm. $^{13}C\{^1H\}$ NMR (100.61 MHz, $CDCl_3$): δ 19.07 (s, SMe), 26.77 (s, CH_2), 32.59 (s, CH_2S), 51.58 (s, OMe), 57.88 (s, CH), 123.20 (d, C2, $^1J_{CP}$ = 53.5 Hz), 125.33 (d, *ipso*-C in PPh, $^1J_{CP}$ = 55.7 Hz), 127.23 (d, *ipso*-C in PPh, $^1J_{CP}$ = 59.1 Hz), 128.34 (d, *m*-C in PPh, $^3J_{CP}$ = 11.7 Hz), 128.53 (d, *m*-C in PPh, $^3J_{CP}$ = 12.1 Hz), 129.95 (d, C4, $^3J_{CP}$ = 8.8 Hz), 131.36 (d, C3, $^2J_{CP}$ = 4.4 Hz), 131.46 (d, *p*-C in PPh, $^4J_{CP}$ = 2.6 Hz), 131.59 (d, *p*-C in PPh, $^4J_{CP}$ = 2.9 Hz), 131.99 (d, C5, $^4J_{CP}$ = 2.6 Hz), 132.16 (d, C6, $^3J_{CP}$ = 10.3 Hz), 134.13 (d, *o*-C in PPh, $^2J_{CP}$ = 11.4 Hz), 134.37 (d, *o*-C in PPh, $^2J_{CP}$ = 11.0 Hz), 142.28 (d, C1, $^2J_{CP}$ = 12.8 Hz), 165.78 (d, C(O)N, $^3J_{CP}$ = 9.2 Hz), 171.88 (s, C(O)OMe) ppm. IR (KBr, ν/cm^{-1}): 439(w), 515(m), 549(m), 693(m), 713(w), 759(w), 802(w), 964(w), 998(w), 1048(w), 1103(m), 1126(w), 1162(m), 1170(m), 1286(w), 1332(m), 1355(m), 1366(m), 1435(m), 1481(w), 1552(s) (νC=O in C(O)N), 1575(m), 1590(m), 1739(s) (νC=O in C(O)OMe), 2917(w), 3057(w). Anal. Calcd for $C_{25}H_{25}ClNO_3PPdS$: C, 50.69; H, 4.25; N, 2.36. Found: C, 50.64; H, 4.19; N, 2.34%.

4.3. X-ray diffraction

Single crystals of compounds **4**, **6b**, **7a,b**, and **8a,b** suitable for X-ray diffraction analysis were obtained by slow recrystallization from $CHCl_3$–CH_2Cl_2–hexane (**4**), CH_2Cl_2–hexane (**6b**), $CHCl_3$–hexane (**7a,b**), Et_2O (**8a**), and MeCN–Et_2O–hexane (**b**). X-ray diffraction experiments were carried out with a Bruker APEX2 CCD diffractometer (for **4** and **8a,b**) and with a Bruker

APEX2 DUO CCD diffractometer (for **6b** and **7a,b**), using the graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, ω-scans) at 120 K. The structures were solved by direct method and refined by full-matrix least-squares techniques against F^2 in anisotropic approximation for non-hydrogen atoms. Hydrogen atom of the NH group in **4** was located from difference Fourier synthesis; the positions of the H(C) atoms were calculated. All hydrogen atoms were then refined in isotropic approximation in a riding model. Crystal data and structure refinement parameters for the compounds explored are given in Table 2. All calculations were performed using the SHELXTL software.[20]

Table 2. Crystal data and structure refinement parameters for **4**, **6b**, **7a,b**, and **8a,b**.

	4	**6b**	**7a**	**7b**	**8a**	**8b**
Empirical formula	$C_{23}H_{23}N_3O_4S_2$	$C_{20}H_{23}ClNO_3PPdS_2$	$C_{13}H_{16}ClNO_3PdS_2$	$C_{14}H_{18}ClNO_3PdS_2$	$C_{24}H_{23}ClNO_3PPdS$	$C_{100}H_{106}Cl_4N_4O_{15}P_4Pd_4S_4$
Formula weight	469.56	562.33	440.24	454.26	578.31	2423.40
Crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic	Monoclinic	monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_1$
Z	4	4	4	4	2	1
a, Å	9.3848(6)	9.4734(7)	5.9307(5)	8.5526(6)	9.3913(4)	8.9345(5)
b, Å	11.9291(7)	14.0294(10)	13.0337(11)	8.6465(5)	10.2354(4)	10.0505(6)
c, Å	20.7382(14)	16.5481(12)	20.3502(17)	21.8056(14)	12.6889(5)	27.8717(18)
β, °	90	90	90	90	103.897(1)	93.4040(10)
V, Å^3	2321.7(3)	2199.3(3)	1573.0(2)	1612.53(18)	1184.00(8)	2498.4(3)
D_{calc} (g cm^{-1})	1.343	1.698	1.859	1.871	1.622	1.611
Linear absorption, μ (cm^{-1})	2.64	12.5	16.22	15.85	10.79	10.29
F(000)	984	1136	880	912	584	1230
$2\Theta_{max}$, °	58	58	56	58	58	58
Reflections measured	18382	26962	12160	13346	23849	20148
Independent reflections	6139	5846	3796	4275	6284	12603
Observed reflections [$I > 2\sigma(I)$]	5073	5621	3160	4034	6224	11344
Parameters	292	284	193	202	291	617
R_1	0.0464	0.0191	0.0388	0.0260	0.0143	0.0459
wR_2	0.1006	0.0473	0.0726	0.0589	0.0369	0.0884
Goodness-of-fit (GOF)	1.042	1.009	1.004	1.003	0.996	1.038
$\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	0.281/–0.291	0.488/–0.403	0.692/–0.709	0.890/–0.774	0.295/–0.178	0.544/–1.058

4.4. Cytotoxicity assays

The cytotoxicities of Pd(II) complexes **6**–**8** were tested against human colon cancer cell line HCT116, human breast cancer cell line MCF7, human prostate cancer cell line PC3, and normal human embryonic kidney cells HEK293. 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) or DMEM (in the other cases) media supplemented with 10% FBS, 100 units/L penicillin, and 100 μg/mL streptomycin in a humidified incubator with 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 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 addition of MTT solution (Sigma) (20 μL, 5 mg/mL). The cells were incubated at 37 °C for further 3 h; then the culture medium was removed, and formazan crystals were dissolved in DMSO (70 μL). The absorbance of the resulting solutions was measured on a multi-well plate reader (Uniplan, Picon, Russia) at 590 nm to determine the percentage of surviving cells. The reported values of IC_{50} are the averages of three independent experiments (Table 1). Cisplatin from a commercial source was used as a positive control.

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The X-ray diffraction data were obtained using the equipment of Center for molecule composition studies of INEOS RAS.

Appendix A. Supplementary data

CCDC 1557198 (for **8a**), 1557199 (for **7a**), 1557200 (for **4**), 1557201 (for **6b**), 1557202 (for **8b**), and 1557203 (for **7b**) contain the supplementary crystallographic data. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Appendix B. Supplementary data

^1H, $^{13}C\{^1H\}$, ^1H–^1H COSY and HMQC spectra of complexes **6b**, **7a,b**, and **8a** in $CDCl_3$ at different temperatures.

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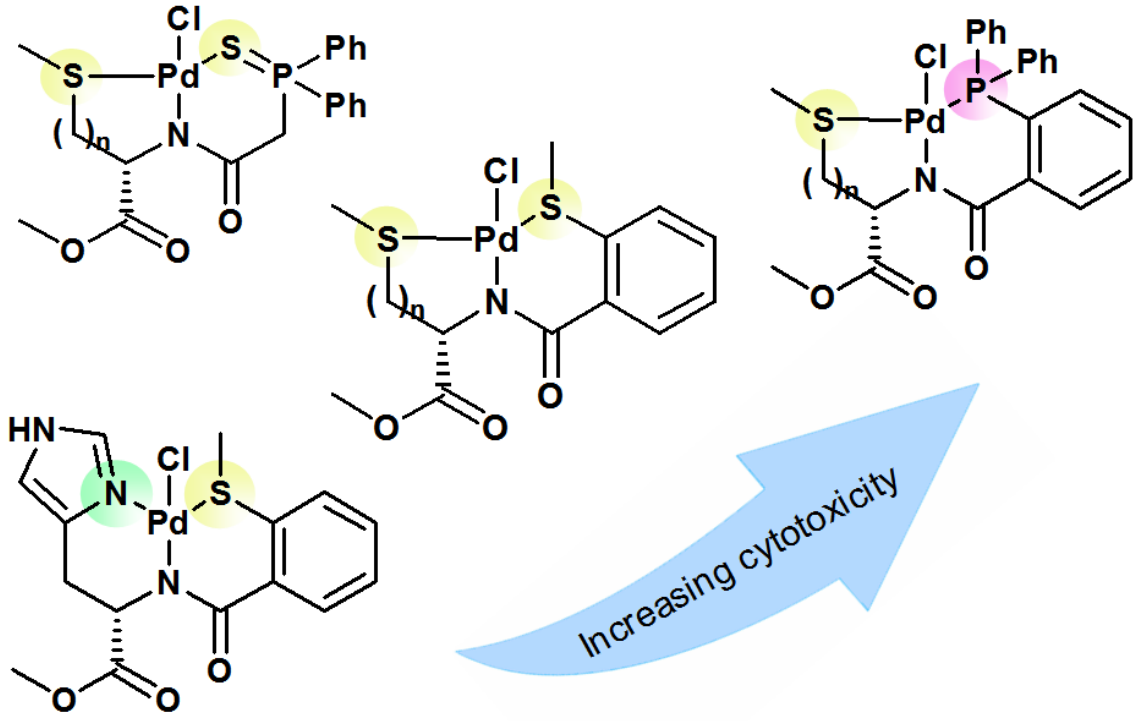

Non-classical *N*-metallated Pd(II) pincer complexes with amino acid pendant arms are synthesized and tested for cytotoxic activity as a new type of potential anticancer agents.