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Platinum(II) complexes of fluorinated pyrrole carbothioamides: enhanced anticancer activity and overcoming cisplatin resistance

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A series of fluorinated pyrrole-derived thioamide ligands was synthesized via a solvent-free reaction of (substituted) pyrrole with various aryl isothiocyanates. Subsequent reactions of these ligands with *cis*-[PtCl₂(PPh₃)₂] afforded a set of charge-neutral platinum(II) complexes, featuring a variety of fluorine-containing substituents on the phenyl ring of the ligand. All compounds were characterized by NMR spectroscopy and electrospray ionization-mass spectrometry. Single-crystal X-ray diffraction analysis of a representative complex revealed that the ligand coordinated to the platinum center in a bidentate fashion through the deprotonated pyrrole nitrogen and the sulfur atom of the thioamide group, forming a five-membered chelate ring. The antiproliferative activity of selected ligands and their corresponding Pt(II) complexes was evaluated against HCT116, NCI-H460, A2780, and A2780cis human cancer cell lines, and significantly increased potency was found for a Pt complex as compared to its ligand.

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Introduction

Sulfur-nitrogen donor ligands are highly versatile and attractive due to their unique combination of soft and intermediate/hard donor characteristics, enabling coordination with a wide variety of metal centers in diverse binding modes.¹ Examples include natural compounds such as the thiols penicillamine and cysteine,^{2,3} the thioether methionine,^{4,5} and synthetic ligands incorporating pyridine and thioamide functionalities.^{6,7} Among these, pyridine-derived thioamide ligands have garnered significant attention for the ancillary ligand properties associated with the pyridine moiety, and with their coordination chemistry being extensively reviewed.^{8,9} Recently, organometallic complexes with *S,N*-chelating sulfonyl-substituted thiourea ligands were reported to show isomer-dependent coordination modes and exhibit moderate to promising antiproliferative activity against human cancer cell lines.¹⁰ Other *S,N*-coordinating ligands bound to metal centers yielded stable and anticancer-active complexes with interesting modes of action.^{11–16} The high stability even under strongly

acidic conditions allowed the development of orally active anti-cancer metallodrugs, such as of the plecstatin compound family,^{12,17,18} which could also be equipped with a variety of functionalities.^{14,17} Beyond ruthenium, recent advances in platinum-based systems have demonstrated that rational ligand design can profoundly alter the biological mechanism of action.^{19,20}

Fluorine is characterized by its exceptional reactivity and influence on molecular properties, and when incorporated into ligand structures further enhances their utility and those of the respective complexes.^{21–26} Fluorine-containing ligands and anions exhibit unmatched thermal and oxidative stability, volatility, and unique reactivity compared to their non-fluorinated analogs,²⁷ and some of these features can be exploited in anticancer drug development.²³ Additionally, fluorinated anions are among the weakest donors known,²⁸ which significantly impacts the coordination behavior.

Pyrrole carbothioamide ligands, structurally closely related to those found in the anticancer agent plecstatin-1, can be efficiently prepared by reacting pyrrole with an aryl isothiocyanate (RNCS).²⁹ In this work, we extended our studies to fluorinated pyrrole carbothioamide ligands and their platinum complexes and explored their biological activity in human cancer cells.

Results and discussion

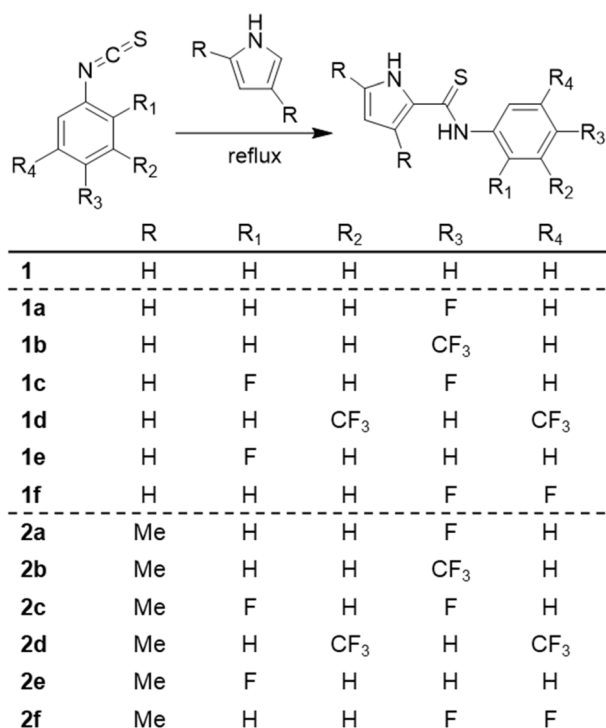
Using a strategy similar to that reported by Bullock and Abraham, which was also employed in the preparation of 1

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Scheme 1 Syntheses of fluorinated pyrrole-**1a–1f** and dimethylpyrrole-derived **2a–2f** thioamide ligands.

(Scheme 1),³⁰ the fluorinated compounds **1a–1f** and **2a–2f** were synthesized by refluxing the respective phenyl isothiocyanate with an excess of pyrrole or 2,4-dimethylpyrrole under solvent-free conditions. The reaction was monitored by thin-layer chromatography until the complete consumption of the starting pyrrole was confirmed. The resulting products were purified *via* silica gel chromatography, employing an eluent system composed of ethyl acetate, dichloromethane, and petroleum ether in a ratio of 1:3:5. When the solution volume was reduced to approximately 3 mL under vacuum, needle-like crystals of the compounds were observed to form in most cases.

All the pyrrole thioamide ligands showed multiplets in their ¹H NMR spectra in the range of δ 6.9–8.8 ppm which were assigned to the phenyl protons. Compared to the hydrogen atoms on the benzene ring, the chemical shifts of the hydrogen atoms on the two methyl groups attached to the pyrrole ring showed minimal variations in ligands **2a–2f**, and they appeared as two singlets around δ 2.5 and 2.3 ppm. In addition, these ligands gave two singlets in the regions of 9.4–9.8 and 8.4–8.9 ppm, which were assigned to the pyrrole NH and thioamide protons, respectively.²⁹ Compared to *N*-phenyl-1*H*-pyrrole-2-carbothioamide,²⁹ the thioamide proton resonance peak in compound **1b** shifted downfield from 8.78 to 8.83 ppm (CDCl₃). Additionally, the hydrogen atoms on the benzene ring adjacent to the trifluoromethyl group also exhibited downfield shifts. This behavior can be attributed to the strong electron-withdrawing nature of the trifluoromethyl group. However, for the *para*-substituted ligand **1a**, where a

hydrogen atom on the benzene ring was replaced with electron-withdrawing fluorine, the hydrogen atoms on the benzene ring near the fluorine shifted upfield when compared to the unsubstituted derivative. In the ¹⁹F{¹H} NMR spectra of all compounds except for **1f** and **2f**, a single peak was observed. Although **1d** and **2d** contain two trifluoromethyl groups, these groups share the same chemical environment, resulting in a single peak in their ¹⁹F{¹H} NMR spectra.

Solutions of the compounds in CH₃OH were analyzed with ESI-MS. The mass spectra gave abundant peaks that were assigned to [M + H]⁺ ions (Fig. 1 for compound **3d**). The *m/z* values supported the formation of the target compounds and errors relative to the calculated values were in the low ppm range. The isotope patterns were largely dominated by the presence of the Pt ion and the calculated patterns closely matched the calculated ones.

The needle-like crystals of **1b**, which were obtained during work up, were found suitable for single crystal X-ray diffraction analysis (Fig. S1). The pyrrole N1–C1 and N1–C4 bond lengths were determined to be 1.351(3) and 1.367(3) Å (Table 1), respectively, suggesting an influence from the thioamide group attached to the pyrrole ring. The C5–S1 distance in **1b**

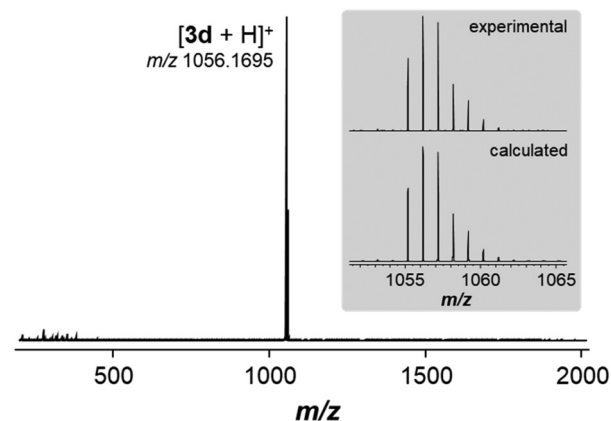


Fig. 1 ESI-mass spectrum of compound **3d**. The inset shows a comparison of the measured (top) and calculated (bottom) isotope patterns for the [3d + H]⁺ pseudomolecular ion.

Table 1 Selected bond lengths (Å) and angles (°) for **1b** in comparison to that of one of the two independent molecules of **3a** (esds in parentheses) and of the structurally-related pyridinecarbothioamide Ph-PCA and the Ru PCA complex plecstatin-1

Bond	Bond length (Å)			
	1b	3a	Ph-PCA ^a	Plecstatin-1 ^b
C5–S1	1.668(2)	1.775(2)	1.664(3)	1.687(3)
C5–N2	1.340(2)	1.297(3)	1.323(3)	1.314(4)
N2–C6	1.429(2)	1.406(3)	1.425(3)	1.424(4)
M–S1	—	Pt1 2.3280(5)	—	Ru 2.3413(9)
M–N1	—	Pt1 2.067(2)	—	Ru 2.095(3)

^a Taken from ref. 31. ^b Taken from ref. 12.

was measured at 1.668(2) Å and was slightly shorter than that observed in 4-ethyl-3,5-dimethyl-*N*-(4-nitrophenyl)-1*H*-pyrrole-2-carbothioamide [1.6775(17) Å]²⁵ but similar to that found for the structurally-related pyridinecarbothioamide Ph-PCA [Fig. S3; 1.664(3) Å].³¹ The average C–F bond length was approximately 1.291 Å, while the dihedral angle between the planes of the benzene and pyrrole rings was determined to be 68.062(2)°. The CF₃ group was found to be disordered.³² H bonds and π -interactions were observed between molecules of **1b** (Fig. S2).

The pyrrole-derived thiocarbamide ligands **1a–1f** and **2c–2f** were reacted with one molar equivalent of *cis*-[PtCl₂(PPh₃)₂] in methanol under reflux in the presence of trimethylamine to give **3a–3f** and **4c–4f**, respectively (Scheme 2). Due to the structural similarity of the employed ligands, complexes **4a** and **4b** were not prepared. Upon cooling of the reaction mixtures to room temperature, complexes **4c**, **4e** and **4f** were isolated by adding distilled water, whereas **3a–3f** and **4d** precipitated directly from methanol. The compounds were obtained in moderate to good yields (35–87%) and were found to be soluble in CHCl₃ and CH₂Cl₂ but exhibited low solubility in CH₃OH.

The absence of signals assignable to the pyrrole and thioamide NH protons in the ¹H NMR spectra of the platinum complexes suggests coordination either monodentately or in a bidentate coordination mode involving the nitrogen and/or sulfur donor atoms in the complexes. Complex formation induced an upfield shift in the ¹H NMR spectroscopy signals associated with the pyrrole CH protons.

To elucidate the coordination mode of the ligands to the Pt center, the molecular structure of **3a** (Fig. 2) was determined by X-ray diffraction analysis of a single crystal obtained by slow

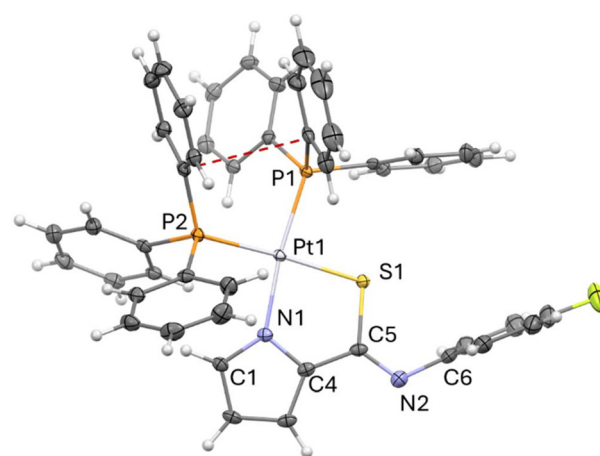
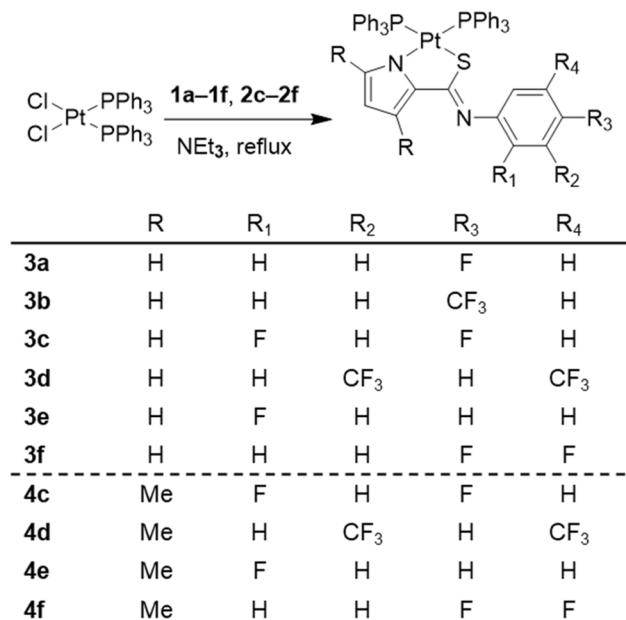


Fig. 2 Molecular structure of one of the two independent molecules of **3a** drawn at 50% probability level. The intramolecular π interaction between two phenyl groups of the two PPh₃ ligands is indicated as a red dashed line between the closest atoms of the two Ph groups (3.288 Å).

diffusion of diethyl ether into a dichloromethane solutions. The fluorinated pyrrole thioamide **1a** was found to coordinate to the platinum(II) center as a bidentate ligand through its sulfur and endocyclic nitrogen atoms, forming a five-membered ring, after deprotonation of the pyrrole NH. The preference for S coordination is consistent with the Hard and Soft Acids and Bases theory. Since Pt²⁺ is a soft acid, it preferentially interacts with soft donor atoms like sulfur. Compared to ligand **1b** (Table 1), the S1–C5 distance in one of the two independent molecules of **3a** was longer at 1.775(2) Å (1.668(2) Å in **1b**), suggesting that the S1–C5 bond transitions from a double bond in the ligand to having more single bond character upon coordination.^{33–36} Similarly, the N2–C5 bond length in compound **3a** was determined as 1.296(3) Å, compared to 1.340(2) Å in ligand **1b**, indicating the larger double bond character of the N2–C5 bond in the complex.^{37–40} A similar change in C–S and C–N bond characters was observed for some *N*-substituted 2-pyridinecarbothioamides (PCAs),^{41–43} while in other cases the effect of metal coordination on these bond lengths was less pronounced (Table 1).¹² This is related to the crystallization of the complexes as either charge-neutral complexes or as complex cations, as which they are isolated.^{12,17,43} Moreover, the *trans* effect of the S donor atoms resulted in significant lengthening of the Pt1–P2 bonds in *trans* position to the sulfur donor as compared to Pt1–P1 *trans* to the pyrrolo nitrogen.

The geometry index τ_4 is a parameter used to analyze the geometry of four-coordinate transition metal complexes.⁴⁴ Its values range from 0.00 for ideal square-planar geometry to 1.00 for a *T*_d geometry. The τ_4 value for complex **3a** was determined as 0.11, indicating a geometry that is slightly distorted from an ideal square planar arrangement. In order to provide a more accurate evaluation of geometrical distortion, the modified index τ'_4 , as proposed by Okuniewski *et al.*,⁴⁵ was also calculated. The resulting τ'_4 value of 0.09 further supports



Scheme 2 Syntheses of platinum(II) complexes of fluorinated pyrrole (**3a–3f**) and dimethyl-pyrrole (**4c–4f**) thioamide ligands.

the conclusion that the metal center adopts a predominantly square-planar coordination environment with minimal tetrahedral character. The interplanar angle between the C5–Pt1–S1 and C4–Pt1–N1 planes measured at 10.39°, while the S1–C5–C4–N2 torsion angle was 6.95°. The five-membered ring formed about the Pt center [Pt1–S1–C5–C4–N1] and the pyrrole ring were determined to be nearly co-planar.

The antiproliferative activity of the carbothioamide ligands **1a**, **1b** and **1d** and the respective platinum(II) complexes **3a**, **3b**, and **3d** was evaluated in human colorectal (HCT116), non-small cell lung (NCI-H460), ovarian (A2780), and cisplatin-resistant ovarian carcinoma (A2780cis) cells using the colorimetric SRB assay (Table 2), while compound **1** (Scheme 1) served as a control compound.²⁹ The limited aqueous solubility of compounds **3b** and **3d** did not allow the determination of an IC₅₀ value. Compound **1a** was the least potent ligand across all the cell lines but still more active than unsubstituted **1**. Increasing the number of fluoro substituents resulted in increased *in vitro* anticancer activity of the ligands with **1d** giving an IC₅₀ value as low as 3.1 μM in NCI-H460 cells. Compound **1d** was also more potent in HCT116 and NCI-H460 cells than structurally-related *p*-F-Ph-PCA (Fig. S3), the ligand found in the anticancer complex plecstatin-1.⁴⁶ However, the Pt complex of **1d** showed lower activity than the ligand, whereas upon coordination of **1a** to the platinum(II) center, the resultant compound **3a** was significantly more potent than its free ligand. Complex **3a** was especially effective in A2780 and A2780cis cells (IC₅₀ = 1.1 and 1.0 μM, respectively), indicating promising activity against cisplatin-resistant cancer cells as in their wildtype form. The very similar IC₅₀ values in these cell lines suggest that the compound does not show cross-resistance to cisplatin and implies a different mode of action. This is also underlined by the absence of leaving groups coordinated to the Pt center which are key for cisplatin to form DNA adducts. Notably, compound **3a** also demonstrated low micromolar antiproliferative activity in HCT116 and NCI-H460

cells, with activity comparable to that of Ru(η⁶-*p*-cymene) complexes derived from *N*-phenyl substituted pyridine-2-carbothioamides (PCAs), which have previously shown potent anticancer efficacy in the same cell lines.⁴⁶ Interestingly, it is also the *p*-fluoro substituted derivative that is the most potent in cancer cells, similar to the plecstatin compound family.¹² Overall, this suggests that the investigated molecular framework has potential for the development of anticancer agents.

Conclusions

In this work, a range of platinum complexes is reported which were synthesized from fluorinated pyrrole thioamide-derived ligands, and characterized by NMR, elemental analysis and MS methods. Single crystal X-ray structure determination of the platinum complex **3a** confirmed that the Pt(PPh₃)₂ moiety was coordinated to the ligand *via* the endocyclic pyrrole nitrogen atom after its deprotonation, as well as the sulfur atom of the deprotonated thioamide. This coordination mode resulted in charge-neutral Pt complexes that were investigated for their antiproliferative activity. While limited aqueous solubility complicated the determination of IC₅₀ values for some derivatives, transformation of ligand **1a** into complex **3a** resulted in potent activity, with IC₅₀ values as low as 1.0 μM in cisplatin-resistant A2780cis cells. This demonstrates that the compound class may be able to overcome the limitations of cisplatin, in particular with regard to drug resistance of cancer cells. Future work will focus on exploring the cellular uptake behavior, biological mechanisms, and structure–activity relationships across this ligand family to further understand their differences from cisplatin.

Experimental

Materials and instrumentation

The following materials were used as supplied from Sigma Aldrich: *cis*-[PtCl₂(PPh₃)₂], trimethylamine, 1*H*-pyrrole, phenyl isothiocyanate, 1-fluoro-2-isothiocyanatobenzene, 1-isothiocyanato-4-(trifluoromethyl)benzene, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene, 2,4-difluoro-1-isothiocyanatobenzene, 1,2-difluoro-4-isothiocyanatobenzene, 1-fluoro-2-isothiocyanatobenzene. 2,4-Dimethylpyrrole was used as supplied from Tokyo Chemical Industries (TCI). All solvents were AR grade, and petroleum spirits refers to the fraction of boiling range 60–90 °C.

All reactions were carried out without any attempts to exclude air or moisture. Thin-layer chromatography (TLC) plates were purchased from Aldrich. Elemental analyses were conducted on a Vario EL cube (Elementar Analysensysteme GmbH, Hanau, Germany). ESI-mass spectra were recorded in methanol on a Bruker micrOTOF-QII mass spectrometer in positive electrospray ionization (ESI) mode. NMR spectra were recorded in CDCl₃ on a Bruker AVIII 400 instrument using

Table 2 *In vitro* anticancer activity of **1**, **1a**, **1b**, **1d**, **3a**, **3b** and **3d** in comparison to *p*-F-Ph-PCA and cisplatin in human colorectal (HCT116), non-small cell lung (NCI-H460), ovarian (A2780), and cisplatin-resistant ovarian carcinoma (A2780cis) cell lines determined with the SRB assay after 72 h exposure

Compound	IC ₅₀ /μM			
	HCT116	NCI-H460	A2780	A2780cis
1	130 ± 12	175 ± 13	31 ± 1	118 ± 45
<i>p</i> -F-Ph-PCA ^a	16 ± 6	7.8 ± 1.8	—	—
1a	57 ± 7	92 ± 7	12 ± 1	78 ± 2
1b	18 ± 6	13 ± 3	6.8 ± 1.3	21 ± 3
1d	3.9 ± 0.6	3.1 ± 0.2	1.3 ± 0.1	3.3 ± 0.8
3a	3.4 ± 0.4	11 ± 1	1.1 ± 0.2	1.0 ± 0.1
3b ^c	>10	>10	>10	>10
3d ^c	>25	>25	>25	>25
Cisplatin ^b	2.9 ± 0.5	1.2 ± 0.2	1.3 ± 0.1	15 ± 1

^a Taken from ref. 46. ^b Taken from ref. 47. ^c “>” indicates that 50% growth inhibition was not reached at the highest tested concentration (10 or 25 μM).

Topspin 3.0 software; signals were reported *versus* SiMe₄ and referenced relative to residual non-deuterated solvent peaks.

Single-crystal X-ray diffraction studies on **3a** were carried out using a Rigaku Oxford Diffraction XtaLAB-Synergy-S diffractometer, which was equipped with a PILATUS 200K hybrid pixel array detector and utilizes Cu K α radiation (λ = 1.54184 Å; Table S3), while single crystals of **1b** were analyzed on a Rigaku XtaLAB Pro II single crystal X-ray diffractometer equipped with an AFC12 kappa goniometer (λ = 1.54184 Å; Table S3). The collected data were processed using the SHELX2018/3 and Olex2 1.3 software packages.^{48–50} All non-hydrogen atoms were refined anisotropically, while hydrogen atoms were positioned at calculated sites and refined either using a riding model or without additional restraints.

General procedure for the synthesis of fluorinated pyrrole thioamide ligands **1a–1f** and **2a–2f**

The respective isothiocyanate (1 equivalent) was added in a single portion to stirred 1H-pyrrole or 2,4-dimethylpyrrole (2.5–36 equivalents). The reaction mixture was refluxed for 19 hours until TLC analysis with ethyl acetate/dichloromethane/*n*-hexane (1:20:20) as the eluent confirmed consumption of the isothiocyanate. The crude product was purified by column chromatography on silica gel using a solvent mixture of ethyl acetate/dichloromethane/petroleum ether (1:3:5) as the eluent. The combined fractions were evaporated under reduced pressure, and the resulting solid was recrystallized from ethyl acetate/petroleum ether to afford the target compound in pure form.

Synthesis of *N*-(4-fluorophenyl)-1H-pyrrole-2-carbothioamide **1a.** A mixture of 1-fluoro-4-isothiocyanatobenzene (1.00 g, 0.007 mol) and 1H-pyrrole (2.63 g, 0.039 mmol) gave a light-yellow powder (0.41 mg, 28%). Found: C, 60.17; H, 4.18; N, 13.01%. C₁₁H₉FN₂S requires C, 59.98; H, 4.12; N, 12.72%. ¹H NMR (CDCl₃): δ (ppm) 9.79 (s, 1H), 8.76 (s, 1H), 7.59 (m, 2H), 7.11 (m, 3H), 6.69 (s, 1H), 6.33 (m, 1H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –114.1 (s, 1F). ESI MS⁺: [M + H]⁺, m/z 221.0544, calculated m/z 221.0543.

Synthesis of *N*-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbothioamide **1b.** A mixture of 1-isothiocyanato-4-(trifluoromethyl)benzene (1.00 g, 0.005 mol) and 1H-pyrrole (9.69 g, 0.144 mol) gave a yellow powder (1.10 g, 80%). Found: C, 53.40; H, 3.40; N, 10.64%. C₁₂H₉F₃N₂S requires C, 53.33; H, 3.36; N, 10.36%. ¹H NMR (CDCl₃): δ (ppm) 9.77 (s, 1H), 8.83 (s, 1H), 7.89 (d, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H), 7.09 (m, 1H), 6.73 (m, 1H), 6.36 (m, 1H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –62.2 (s, 3F).

Synthesis of *N*-(2,4-difluorophenyl)-1H-pyrrole-2-carbothioamide **1c.** A mixture of 2,4-difluoro-1-isothiocyanatobenzene (0.50 g, 0.003 mol) and 1H-pyrrole (4.85 g, 0.072 mol) gave a yellow-green powder (0.51 g, 74%). Found: C, 55.63; H, 3.64; N, 11.64%. C₁₁H₈F₂N₂S requires C, 55.45; H, 3.38; N, 11.76%. ¹H NMR (CDCl₃): δ (ppm) 9.74 (s, 1H), 8.65 (s, 1H), 8.32 (m, 1H), 7.08 (m, 1H), 6.95 (m, 2H), 6.73 (s, 1H), 6.35 (m, 1H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –110.7 (s, 1F), –120.8 (s, 1F). ESI MS⁺: [M + H]⁺, m/z 239.0477, calculated m/z 239.0449.

Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrrole-2-carbothioamide **1d.** A mixture of 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (1.00 g, 0.004 mol) and 1H-pyrrole (9.68 g, 0.144 mol) gave a light yellow powder (0.78 g, 62%). Found: C, 46.28; H, 3.01; N, 8.47%. C₁₃H₈F₆N₂S requires C, 46.16; H, 2.38; N, 8.28%. ¹H NMR (CDCl₃): δ (ppm) 9.74 (s, 1H), 8.85 (s, 1H), 8.27 (s, 2H), 7.73 (s, 1H), 7.11 (m, 1H), 6.77 (m, 1H), 6.37 (m, 1H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –62.8 (s, 6F). ESI MS⁺: [M + H]⁺, m/z 339.0396, calculated m/z 339.0385.

Synthesis of *N*-(2-fluorophenyl)-1H-pyrrole-2-carbothioamide **1e.** A mixture of 1-fluoro-2-isothiocyanatobenzene (0.66 g, 0.004 mol) and 1H-pyrrole (7.75 g, 0.115 mol) gave a yellow powder (0.70 g, 74%). Found: C, 59.88; H, 4.33; N, 12.55%. C₁₁H₉FN₂S requires C, 59.98; H, 4.12; N, 12.72%. ¹H NMR (CDCl₃): δ (ppm) 9.75 (s, 1H), 8.83 (s, 1H), 8.48 (m, 1H), 7.18 (m, 3H), 7.05 (m, 1H), 6.71 (s, 1H), 6.33 (m, 1H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –126.4 (s, 1F). ESI MS⁺: [M + H]⁺, m/z 221.0544, calculated m/z 221.0543.

Synthesis of *N*-(3,4-difluorophenyl)-1H-pyrrole-2-carbothioamide **1f.** A mixture of 1,2-difluoro-4-isothiocyanatobenzene (0.64 g, 0.004 mol) and 1H-pyrrole (7.75 g, 0.115 mol) gave a light yellow powder (0.56 g, 63%). Found: C, 55.41; H, 3.45; N, 12.01%. C₁₁H₈F₂N₂S requires C, 55.45; H, 3.38; N, 11.76%. ¹H NMR (CDCl₃): δ (ppm) 9.75 (s, 1H), 8.68 (s, 1H), 7.77 (m, 1H), 7.29 (m, 1H), 7.20 (m, 1H), 7.08 (m, 1H), 6.69 (s, 1H), 6.35 (m, 1H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –134.9 (d, J = 20.8 Hz, 1F), –138.8 (d, J = 20.8 Hz, 1F). ESI MS⁺: [M + H]⁺, m/z 239.0448, calculated m/z 239.0449.

Synthesis of *N*-(4-fluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamide **2a.** A mixture of 1-fluoro-4-isothiocyanatobenzene (0.60 g, 0.003 mol) and 2,4-dimethyl-1H-pyrrole (1.11 g, 0.012 mol) gave a light yellow powder (0.85 g, 88%). ¹H NMR (CDCl₃): δ (ppm) 9.49 (s, 1H), 8.47 (s, 1H), 7.59 (m, 2H), 7.09 (m, 2H), 5.89 (d, J = 2.7 Hz, 1H), 2.44 (s, 3H), 2.26 (s, 3H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –114.9 (s, 1F). ESI MS⁺: [M + H]⁺, m/z 249.0858, calculated m/z 249.0862.

Synthesis of 3,5-dimethyl-*N*-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbothioamide **2b.** A mixture of 1-isothiocyanato-4-(trifluoromethyl)benzene (1.00 g, 0.005 mol) and 2,4-dimethyl-1H-pyrrole (5.00 g, 0.053 mol) gave an orange powder (1.11 g, 75%). Found: C, 56.29; H, 4.68; N, 9.06%. C₁₄H₁₃F₃N₂S requires C, 56.36; H, 4.39; N, 9.39%. ¹H NMR (CDCl₃): δ (ppm) 9.48 (s, 1H), 8.60 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 5.90 (d, J = 3.0 Hz, 1H), 2.46 (s, 3H), 2.27 (s, 3H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –62.1 (s, 3F). ESI MS⁺: [M + H]⁺, m/z 299.0823, calculated m/z 299.0824.

Synthesis of *N*-(2,4-difluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamide **2c.** A mixture of 2,4-difluoro-1-isothiocyanatobenzene (0.60 g, 0.004 mol) and 2,4-dimethyl-1H-pyrrole (1.00 g, 0.01 mol) gave a light yellow powder (0.67 g, 72%). Found: C, 58.62; H, 4.58; N, 10.87%. C₁₃H₁₂F₂N₂S requires C, 58.63; H, 4.54; N, 10.52%. ¹H NMR (CDCl₃): δ (ppm) 9.49 (s, 1H), 8.54 (m, 2H), 6.93 (m, 2H), 5.90 (d, J = 3.0 Hz, 1H), 2.47 (s, 3H), 2.27 (s, 3H). ¹⁹F{¹H} NMR (CDCl₃): δ (ppm) = –111.7 (s, 1F), –122.2 (s, 1F). ESI MS⁺: [M + H]⁺, m/z 267.0764, calculated m/z 267.0762.

Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-3,5-dimethyl-1*H*-pyrrole-2-carbothioamide 2d. A mixture of 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.55 g, 0.002 mol) and 2,4-dimethyl-1*H*-pyrrole (4.62 g, 0.049 mol) gave a light yellow powder (0.39 g, 53%). Found: C, 49.56; H, 3.50; N, 7.35%. $C_{15}H_{12}F_6N_2S$ requires C, 49.18; H, 3.30; N, 7.65%. 1H NMR ($CDCl_3$): δ (ppm) 9.48 (s, 1H), 8.58 (s, 1H), 8.22 (s, 2H), 7.71 (s, 1H), 5.93 (d, J = 3.0 Hz, 1H), 2.50 (s, 3H), 2.29 (s, 3H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -62.8 (s, 6F). ESI MS^+ : $[M + H]^+$, m/z 367.0693, calculated m/z 367.0698.

Synthesis of *N*-(2-fluorophenyl)-3,5-dimethyl-1*H*-pyrrole-2-carbothioamide 2e. A mixture of 1-fluoro-2-isothiocyanatobenzene (0.52 g, 0.003 mol) and 2,4-dimethyl-1*H*-pyrrole (5.54 g, 0.058 mol) gave a light yellow powder (0.35 g, 41%). Found: C, 62.91; H, 5.29; N, 11.37%. $C_{13}H_{13}FN_2S$ requires C, 62.88; H, 5.28; N, 11.28%. 1H NMR ($CDCl_3$): δ (ppm) 9.52 (s, 1H), 8.74 (m, 2H), 7.18 (m, 3H), 5.90 (d, J = 3.0 Hz, 1H), 2.48 (s, 3H), 2.27 (s, 3H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -127.9 (s, 1F). ESI MS^+ : $[M + H]^+$, m/z 249.0855, calculated m/z 249.0856.

Synthesis of *N*-(3,4-difluorophenyl)-3,5-dimethyl-1*H*-pyrrole-2-carbothioamide 2f. A mixture of 1,2-difluoro-4-isothiocyanatobenzene (0.56 g, 0.003 mol) and 2,4-dimethyl-1*H*-pyrrole (5.81 g, 0.061 mol) gave a yellow powder (0.34 g, 39%). Found: C, 58.81; H, 4.60; N, 10.88%. $C_{13}H_{12}F_2N_2S$ requires C, 58.63; H, 4.54; N, 10.52%. 1H NMR ($CDCl_3$): δ (ppm) 9.47 (s, 1H), 8.44 (s, 1H), 7.76 (m, 1H), 7.20 (m, 2H), 5.89 (d, J = 3.0 Hz, 1H), 2.44 (s, 3H), 2.27 (s, 3H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -135.2 (d, J = 20.8 Hz, 1F), -139.4 (d, J = 20.8 Hz, 1F). ESI MS^+ : $[M + H]^+$, m/z 267.0762, calculated m/z 267.0762.

General procedure for the synthesis of $[(PPh_3)_2(N\text{-substituted } 2\text{-pyrrolecarbothioamidato})platinum(II)]$ complexes 3a–3f

A suspension of $cis\text{-}[PtCl_2(PPh_3)_2]$ (1 equivalent) in methanol (10 mL) was added in one portion to a stirred solution of *N*-substituted 2-pyrrolecarbothioamide (1.1 equivalents) in methanol (10 mL), and the mixture was heated to 50 °C. Aqueous triethylamine (5 drops, excess) was added and the reaction mixture was refluxed for 5 h. A solid precipitated out after 10–20 min of reaction time. The product was collected by filtration, washed with methanol (3 mL) and water (3 mL) and dried under vacuum.

Synthesis of $[(PPh_3)_2(N\text{-}(4\text{-fluorophenyl})\text{-}1H\text{-pyrrole-}2\text{-carbothioamidato})platinum(II)]$ 3a. $cis\text{-}[PtCl_2(PPh_3)_2]$ (70 mg, 0.089 mmol) with *N*-(4-fluorophenyl)-1*H*-pyrrole-2-carbothioamide 1a (23 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow green powder (38 mg, 46%). Found: C, 59.97; H, 4.04; N, 2.82%. $C_{47}H_{37}FN_2P_2PtS$ requires C, 60.19; H, 3.98; N, 2.99%. 1H NMR ($CDCl_3$): δ (ppm) 7.48 (m, 6H), 7.39 (m, 6H), 7.29 (m, 6H), 7.12 (m, 12H), 6.90 (m, 2H), 6.76 (m, 2H), 6.71 (m, 1H), 6.00 (s, 1H), 5.70 (m, 1H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -123.6 (s, 1F). $^{31}P\{^1H\}$ NMR: δ (ppm) 19.4 [d, $^1J(PtP)$ 3528 Hz], 13.3 [d, $^1J(PtP)$ 3920 Hz]. ESI MS^+ : $[M + H]^+$, m/z 938.1809, calculated m/z 938.1861.

Synthesis of $[(PPh_3)_2(N\text{-}(4\text{-trifluoromethyl})phenyl)\text{-}1H\text{-pyrrole-}2\text{-carbothioamidato})platinum(II)]$ 3b. $cis\text{-}[PtCl_2(PPh_3)_2]$

(70 mg, 0.089 mmol) with *N*-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-2-carbothioamide 1b (26 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow powder (63 mg, 72%). Found: C, 58.21; H, 3.81; N, 2.77%. $C_{48}H_{37}F_3N_2PtS$ requires C, 58.36; H, 3.77; N, 2.84%. 1H NMR ($CDCl_3$): δ (ppm) 7.46 (m, 6H), 7.39 (m, 6H), 7.30 (m, 8H), 7.12 (m, 12H), 7.01 (m, 2H), 6.75 (s, 1H), 6.01 (m, 1H), 5.72 (m, 1H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -61.4 (s, 1F). $^{31}P\{^1H\}$ NMR: δ (ppm) 19.1 [d, $^1J(PtP)$ 3544 Hz], 12.7 [d, $^1J(PtP)$ 3916 Hz]. ESI MS^+ : $[M + H]^+$, m/z 988.1801, calculated m/z 988.1829.

Synthesis of $[(PPh_3)_2(N\text{-}(2,4\text{-difluorophenyl})\text{-}1H\text{-pyrrole-}2\text{-carbothioamidato})platinum(II)]$ 3c. $cis\text{-}[PtCl_2(PPh_3)_2]$ (70 mg, 0.089 mmol) with *N*-(2,4-difluorophenyl)-1*H*-pyrrole-2-carbothioamide 1c (23 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow green powder (69 mg, 81%). Found: C, 58.66; H, 3.86; N, 2.78%. $C_{47}H_{36}F_2N_2P_2PtS$ requires C, 59.05; H, 3.80; N, 2.93%. 1H NMR ($CDCl_3$): δ (ppm) 7.47 (m, 6H), 7.39 (m, 6H), 7.29 (m, 6H), 7.12 (m, 12H), 6.90 (m, 1H), 6.70 (m, 1H), 6.66–6.50 (m, 2H), 6.00 (s, 1H), 5.70 (m, 1H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -120.1 (s, 1F), -120.7 (s, 1F). $^{31}P\{^1H\}$ NMR: δ (ppm) 19.3 [d, $^1J(PtP)$ 3548 Hz], 12.9 [d, $^1J(PtP)$ 3916 Hz]. ESI MS^+ : $[M + H]^+$, m/z 956.1709, calculated m/z 956.1767.

Synthesis of $[(PPh_3)_2(N\text{-}(3,5\text{-bis(trifluoromethyl)phenyl})\text{-}1H\text{-pyrrole-}2\text{-carbothioamidato})platinum(II)]$ 3d. $cis\text{-}[PtCl_2(PPh_3)_2]$ (50 mg, 0.063 mmol) with *N*-(3,5-bis(trifluoromethyl)phenyl)-1*H*-pyrrole-2-carbothioamide 1d (24 mg, 0.070 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow green powder (23 mg, 35%). Found: C, 55.94; H, 3.95; N, 2.52%. $C_{49}H_{36}F_6N_2P_2PtS$ requires C, 55.74; H, 3.44; N, 2.65%. 1H NMR ($CDCl_3$): δ (ppm) 7.46 (m, 6H), 7.38 (m, 8H), 7.29 (m, 6H), 7.25 (m, 1H), 7.12 (m, 12H), 6.67 (m, 1H), 6.03 (s, 1H), 5.71 (m, 1H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -62.6 (s, 6F). $^{31}P\{^1H\}$ NMR: δ (ppm) 19.3 [d, $^1J(PtP)$ 3576 Hz], 12.2 [d, $^1J(PtP)$ 3896 Hz]. ESI MS^+ : $[M + H]^+$, m/z 1056.1695, calculated m/z 1056.1703.

Synthesis of $[(PPh_3)_2(N\text{-}(2\text{-fluorophenyl})\text{-}1H\text{-pyrrole-}2\text{-carbothioamidato})platinum(II)]$ 3e. $cis\text{-}[PtCl_2(PPh_3)_2]$ (55 mg, 0.069 mmol) with *N*-(2-fluorophenyl)-1*H*-pyrrole-2-carbothioamide 1e (17 mg, 0.076 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow green powder (30 mg, 46%). 1H NMR ($CDCl_3$): δ (ppm) 7.43 (m, 12H), 7.33–7.22 (m, 6H), 7.11 (m, 12H), 6.96 (m, 1H), 6.90–6.77 (m, 3H), 6.71 (m, 1H), 5.99 (s, 1H), 5.70 (m, 1H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -124.6 (s, 1F). $^{31}P\{^1H\}$ NMR: δ (ppm) 19.3 [d, $^1J(PtP)$ 3536 Hz], 13.0 [d, $^1J(PtP)$ 3920 Hz]. ESI MS^+ : $[M + H]^+$, m/z 938.1808, calculated m/z 938.1784.

Synthesis of $[(PPh_3)_2(N\text{-}(3,4\text{-difluorophenyl})\text{-}1H\text{-pyrrole-}2\text{-carbothioamidato})platinum(II)]$ 3f. $cis\text{-}[PtCl_2(PPh_3)_2]$ (70 mg, 0.089 mmol) with *N*-(3,4-difluorophenyl)-1*H*-pyrrole-2-carbothioamide 1f (28 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow green powder (74 mg, 87%). Found: C, 58.85; H, 3.87; N, 2.78%. $C_{47}H_{36}F_2N_2P_2PtS$ requires C, 59.05; H, 3.80; N, 2.93%. 1H NMR ($CDCl_3$): δ (ppm) 7.49 (m, 6H), 7.39 (m, 6H), 7.31 (m, 6H), 7.13 (m, 12H), 6.91–6.75 (m, 2H), 6.65 (m, 2H), 6.01 (s, 1H), 5.71 (m, 1H). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ (ppm) = -139.5 (d, J = 20.9

Hz, 1F), -148.2 (d, $J = 20.9$ Hz, 1F). $^{31}\text{P}\{^1\text{H}\}$ NMR: δ (ppm) 19.3 [d, $^1J(\text{PtP})$ 3548 Hz], 12.9 [d, $^1J(\text{PtP})$ 3912 Hz]. ESI MS $^+$: $[\text{M} + \text{H}]^+$, m/z 956.1764 , calculated m/z 956.1767 .

General procedure for the synthesis of $[(\text{PPh}_3)_2(\text{N-substituted 3,5-dimethyl-pyrrole carbothioamidato})\text{platinum(II)}]$ complexes **4c–4f**

A suspension of *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$ (1 equivalent) in methanol (10 mL) was added in one portion to a stirred solution of *N*-substituted 3,5-dimethyl-pyrrole carbothioamide (1.1 equivalent) in methanol (10 mL), and the mixture was heated to 50°C . Aqueous triethylamine (5 drops, excess) was added and the reaction mixture was refluxed for 5 h. After cooling to room temperature, water (2 mL) was added, resulting in precipitation of a light yellow solid. A solid precipitated out after 10–20 min reaction. The product was collected by filtration, washed with *n*-hexane, and dried under vacuum.

Synthesis of $[(\text{PPh}_3)_2(\text{N-(2,4-difluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamidato})\text{platinum(II)}]$ **4c.** *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$ (70 mg, 0.089 mmol) with *N*-(2,4-difluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamide **2c** (26 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a light yellow solid (67 mg, 77%). Found: C, 60.25; H, 4.38; N, 2.51%. $\text{C}_{49}\text{H}_{40}\text{F}_2\text{N}_2\text{P}_2\text{PtS}$ requires C, 59.81; H, 4.10; N, 2.85%. ^1H NMR (CDCl_3): δ (ppm) 7.53 (m, 6H), 7.34 – 7.14 (m, 18H), 7.09 (m, 6H), 6.74 (m, 1H), 6.63 (m, 1H), 6.49 (m, 1H), 2.46 (s, 3H), 1.46 (s, 3H). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3): δ (ppm) -120.6 (s, 1F), -121.1 (s, 1F). $^{31}\text{P}\{^1\text{H}\}$ NMR: δ (ppm) 15.7 [d, $^1J(\text{PtP})$ 3796 Hz], 7.3 [d, $^1J(\text{PtP})$ 3824 Hz]. ESI MS $^+$: $[\text{M} + \text{H}]^+$, m/z 984.2000 , calculated m/z 984.2080 .

Synthesis of $[(\text{PPh}_3)_2(\text{N-(3,5-bis(trifluoromethyl)phenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamidato})\text{platinum(II)}]$ **4d.** *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$ (70 mg, 0.089 mmol) with *N*-(3,5-bis(trifluoromethyl)phenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamide **2d** (36 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow green powder (60 mg, 62%). Found: C, 56.34; H, 3.72; N, 2.54%. $\text{C}_{51}\text{H}_{40}\text{F}_6\text{N}_2\text{P}_2\text{PtS}$ requires C, 56.51; H, 3.72; N, 2.58%. ^1H NMR (CDCl_3): δ (ppm) 7.49 (m, 6H), 7.36 (s, 2H), 7.28 (m, 13H), 7.17 (m, 6H), 7.08 (m, 6H), 5.42 (d, $J = 3.5$ Hz, 1H), 2.41 (s, 3H), 1.46 (s, 3H). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3): δ (ppm) -62.6 (s, 6F). $^{31}\text{P}\{^1\text{H}\}$ NMR: δ (ppm) 15.2 [d, $^1J(\text{PtP})$ 3792 Hz], 6.3 [d, $^1J(\text{PtP})$ 3840 Hz]. ESI MS $^+$: $[\text{M} + \text{H}]^+$, m/z 1084.2012 , calculated m/z 1084.2016 .

Synthesis of $[(\text{PPh}_3)_2(\text{N-(2-fluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamidato})\text{platinum(II)}]$ **4e.** *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$ (70 mg, 0.089 mmol) with *N*-(2-fluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamide **2e** (24 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a yellow powder (71 mg, 83%). Found: C, 60.56; H, 4.34; N, 2.89%. $\text{C}_{49}\text{H}_{41}\text{FN}_2\text{P}_2\text{PtS}$ requires C, 60.93; H, 4.28; N, 2.90%. ^1H NMR (CDCl_3): δ (ppm) 7.54 (m, 6H), 7.30 (m, 9H), 7.24 (m, 3H), 7.16 (m, 6H), 7.08 (m, 6H), 6.92 – 6.76 (m, 4H), 5.38 (m, 1H), 2.46 (s, 3H), 1.46 (s, 3H). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3): δ (ppm) -125.1 (s, 1F). $^{31}\text{P}\{^1\text{H}\}$ NMR: δ (ppm) 15.7 [d, $^1J(\text{PtP})$ 3788 Hz], 7.3 [d, $^1J(\text{PtP})$ 3828 Hz]. ESI MS $^+$: $[\text{M} + \text{H}]^+$, m/z 966.2099 , calculated m/z 966.2174 .

Synthesis of $[(\text{PPh}_3)_2(\text{N-(3,4-difluorophenyl)-3,5-dimethyl-1H-pyrrole-2-carbothioamidato})\text{platinum(II)}]$ **4f.** *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$ (70 mg, 0.089 mmol) with *N*-(4-fluorophenyl)-1H-pyrrole-2-carbothioamide **2f** (26 mg, 0.097 mmol) and triethylamine (5 drops, excess) in methanol (20 mL) gave a light yellow powder (60 mg, 69%). Found: C, 59.84; H, 4.31; N, 2.56%. $\text{C}_{49}\text{H}_{40}\text{F}_2\text{N}_2\text{P}_2\text{PtS}$ requires C, 59.81; H, 4.10; N, 2.85%. ^1H NMR (CDCl_3): δ (ppm) 7.50 (m, 6H), 7.25 – 7.17 (m, 12H), 7.09 (m, 6H), 6.79 (m, 1H), 6.67 (m, 1H), 6.51 (m, 1H), 5.41 (d, $J = 3.7$ Hz, 1H), 2.43 (s, 3H), 1.46 (s, 3H). $^{19}\text{F}\{^1\text{H}\}$ NMR (CDCl_3): δ (ppm) -139.5 (d, $J = 20.9$ Hz, 1F), -149.0 (d, $J = 20.9$ Hz, 1F). $^{31}\text{P}\{^1\text{H}\}$ NMR: δ (ppm) 15.8 [d, $^1J(\text{PtP})$ 3780 Hz], 7.4 [d, $^1J(\text{PtP})$ 3816 Hz]. ESI MS $^+$: $[\text{M} + \text{H}]^+$, m/z 984.2075 , calculated m/z 984.2080 .

Author contributions

Haiming Tang conceived and designed the study, performed the synthesis and characterization, curated the data, and wrote the original draft. Chen Chen contributed to methodology, validation, and experimental investigations. Yuhang Fu carried out ligand and complex synthesis and assisted with data collection. Tong Sun participated in experimental work and data curation. Li Yin performed validation, and Mingyuan He contributed to formal analysis. Qin Fu and Qin Li assisted with data collection and experiments. Yu Liu contributed to visualization, and Ziyun Chen assisted with data curation. Stephen M. F. Jamieson provided analytical resources and contributed to data interpretation. Tilo Söhnle supported methodology development and formal analysis. Christian G. Hartinger supervised the project, acquired funding, and contributed to conceptualization and manuscript drafting.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available and contains X-ray crystallographic data, experimental details on the antiproliferative activity studies, and the calculation of the geometry index τ_4 . See DOI: <https://doi.org/10.1039/d5dt02290h>.

Any additional details are available on request from the corresponding author.

CCDC 2474202 and 2474203 contain the supplementary crystallographic data for this paper.^{51a,b}

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