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Structure-activity relations of Pd(II) and Pt(II) thiosemicarbazone complexes on different human glioblastoma cell lines

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Ten thiosemicarbazone ligands obtained by condensation of pyridine-2-carbaldehyde, quinoline-2-carbaldehyde, 2-acetylpyridine, 2-acetylquinoline, or corresponding 2-pyridyl ketones with thiosemicarbazides RNHC(S)NHNH$_2$ and R=CH$_3$, C$_6$H$_5$ were prepared in good yield. The reaction of [PdCl$_2$(cod)] with cod = 1,5-cyclooctadiene or K$_2$[PtCl$_4$] resulted in a total of 17 Pd(II) and Pt(II) complexes isolated in excellent purity, as demonstrated by ^{1}H, ^{13}C, and, where applicable, ^{195}Pt NMR spectroscopy combined with CHNS analysis. The cytotoxicity of the title compounds was studied on four human glioblastoma cell lines (GaMG, U87, U138, and U343). The most active compound, with a Pd(II) metal centre, a 2-quinolinyl ring, and methyl groups on both the proximal C and distal N atoms exhibited an EC$_{50}$ value of 2.1 μM on the GaMG cell lines, thus being slightly more active than cisplatin (EC$_{50}$ 3.4 μM) and significantly more potent than temozolomide (EC$_{50}$ 67.1 μM). Surprisingly, the EC$_{50}$ values were inversely correlated with the lipophilicity, as determined with the "shake-flask method", and decreased with the length of the alkyl substituents (C$_1$ > C$_8$ > C$_{10}$). Correlation with the different structural motifs showed that for the most promising anticancer activity, a maximum of two aromatic rings (either quinolinyl or pyridyl plus phenyl) combined with one methyl group are favoured and the Pd(II) complexes are slightly more potent than their Pt(II) analogues.

Introduction

Glioblastoma (GBM) is the most prevalent and most malignant primary brain tumour of adults. The median survival time of GBM patients ranges from 16 to 20 months, despite multidisciplinary treatment compromising surgery or biopsy followed by γ-irradiation with concomitant temozolomide and adjuvant temozolomide chemotherapy, which might be supplemented by tumour-treating fields (TTFields).[1] Recently, lomustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) has been added to the therapy of patients younger than 70 years having a methylated promoter of the O^6-methylguanine-DNA methyltransferase (MGMT) gene.[2] Nevertheless, developing new therapeutic means targeting this devastating malignancy is of the highest priority in biomedical research. Metal-based anticancer agents, in particular those of platinum(II), have been a mainstay of chemotherapeutic approaches of many malignancies and are in widespread clinical use, in particular against testicular, ovarian, colorectal, and bladder cancer.[3] In a recent study, it was reported that the three generally approved compounds cisplatin, carboplatin, and oxaliplatin were used in 25% of the evaluated chemotherapeutic protocols.[4] Cisplatin was also examined in the context of glioblastoma treatment and shown to be active *in vitro*, but in a clinical phase III study it did not improve median survival while at the same time showing more serious toxicity than standard therapy.[5] Further studies suggested that this might be due to the activity of atypical protein kinases C (PKCι and PKCζ), which are also thought to have a role in leukaemia cell chemoresistance. In particular, PKCι appears to be involved in the development of resistance to cisplatin in glioblastoma cells due to suppression of GMFβ-mediated enhancement of p38 MAP kinase signalling.[6] Against the common assumption that platinum(II) complexes show higher activity than their palladium(II) congeners due to slower ligand exchange kinetics,[7] significant anticancer potential has recently been demonstrated for various classes of palladium compounds.[8] In particular, in an interesting series of *N*-heterocyclic carbene (NHC) complexes derived from purine nucleobases, differential activity of isostructural and isoelectronic Pd(II) and Pt(II) compounds on U251 glioblastoma cells was observed.[9] Since most of the studies have focused on other malignancies so far, we were tempted to evaluate a family of Pd(II) and Pt(II) thiosemicarbazone complexes as potential new chemotherapeutic agents to tackle GBM and test their efficacy on the human GBM cell lines GaMG, U138, U343 and

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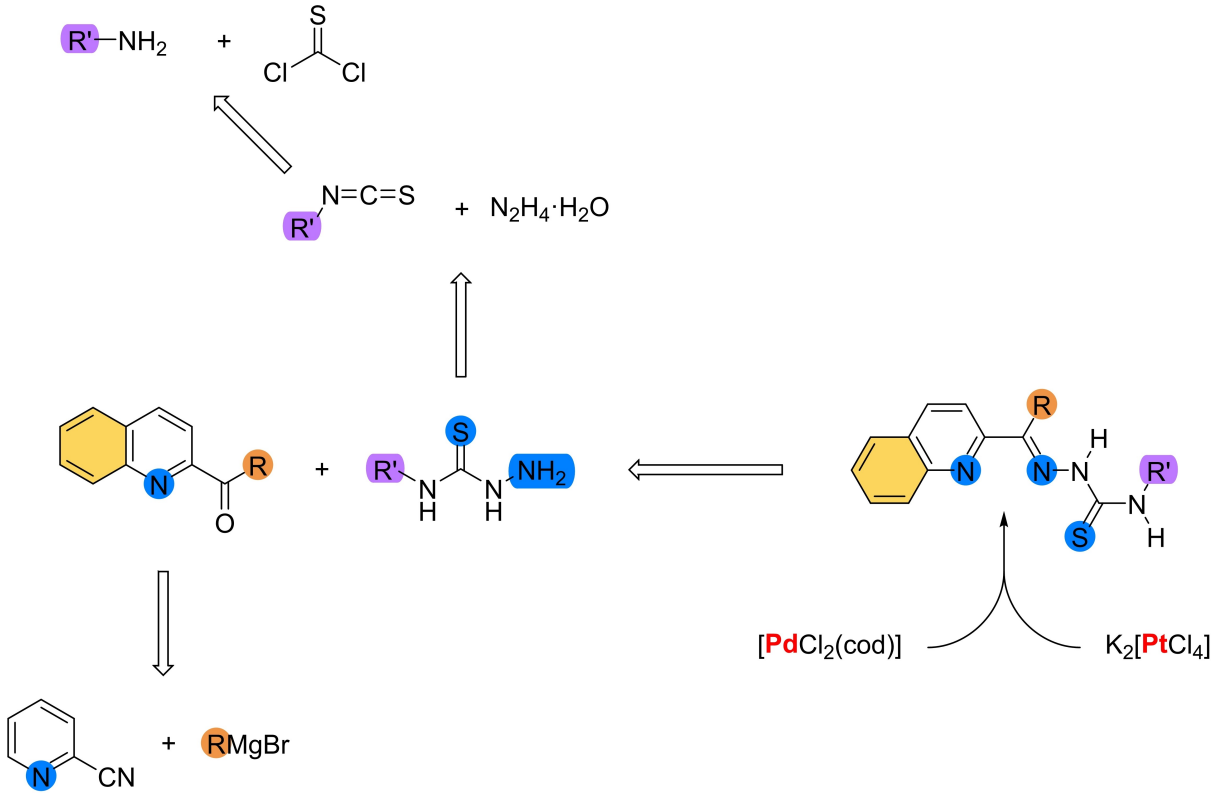
U87. While GaMG and U87 cells were established from 42 and 44-year old Caucasian females,[10] U138 and U343 originated from 47 and 54-year old Caucasian males, respectively.[10a,b, 11] These cells grow as adherent, large, spindle-like cells, except for U87, which displays a more three-dimensional shape and forms spheroid-like cell clusters on top of a monolayer. In addition, these cells retain inter-patient variability in terms of individual karyotypes and drug sensitivity.[12]

Results and Discussion

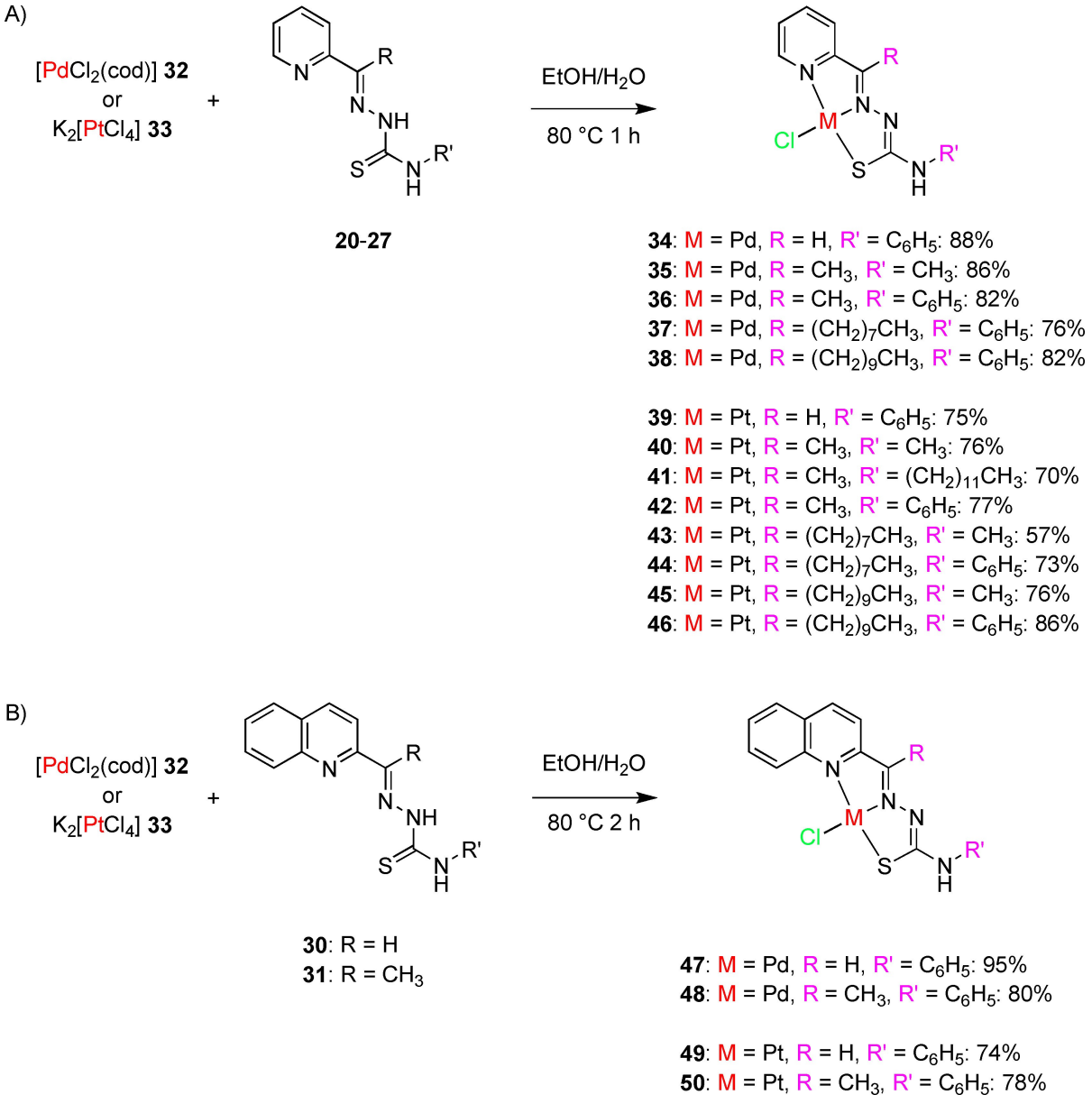
Synthesis

The targeted thiosemicarbazone ligands were prepared in a modular approach which enables wide and facile variation of the heteroaromatic ring as well as the substituents on the C=N carbon atom in α-position to the ring and the distal amino group, respectively (Scheme 1). In the key condensation of a carbonyl compound with a thiosemicarbazide, commercially available pyridine-2-carbaldehyde or quinoline-2-carbaldehyde were used to access ligands with R=H, while 2-acetylpyridine or 2-acetylquinoline lead to compounds with R=CH_3. Furthermore, to generate ligands with longer alkyl chains as the R group, two mixed pyridyl alkyl ketones were prepared by the reaction of 2-cyanopyridine with the corresponding alkyl Grignard reagents (Scheme 1 bottom left).[13] The thiosemicarbazide starting material was accessible by condensation of alkyl or phenyl isothiocyanates with hydrazine hydrate in isopropanol (Scheme 1 top centre). In cases where the isothiocyanates are not commercially available, they were prepared by reaction of thiophosgene with the corresponding primary amines (Scheme 1 top left),[14] which in turn can either be purchased or prepared from the alkyl bromides or alkyl alcohols, which also allows easy variation of the R′ substituent.

A total of ten ligands **20**–**27** and **30**–**31** were synthesized this way and then reacted with either a palladium(II) or platinum(II) precursor in a mixture of ethanol and water at reflux. In the latter case, potassium tetrachloroplatinate(II) was the starting material of choice, while synthesis of the Pd(II) analogue required use of [$PdCl_2$(cod)] with cod = 1,5-cyclo-octadiene instead. A total of 17 complexes were prepared based on this procedure in good to excellent yield of 57–95 % (Scheme 2). Since some of the compounds with R′=CH_3 showed unfavourable properties, not all of the potential metal-ligand combinations were explored (see below). Composition and purity of the title compounds **34**–**50** was established by ^{1}H and ^{13}C NMR spectroscopy as well as CHNS analysis. The latter confirmed an exceptionally high degree of purity, with an average deviation of calculated and experimental values of only



Scheme 1. Retrosynthesis of the targeted palladium(II) and platinum(II) thiosemicarbazone complexes with the precursors of the different functional groups highlighted in colour. The side chains R and R′ highlighted in orange and violet trace back to the primary amine used in the isothiocyanate synthesis (top left) and the alkyl Grignard reactant employed in the reaction with 2-cyanopyridine (bottom left), respectively.



Scheme 2. Synthesis of the palladium(II) and platinum(II) thiosemicarbazone complexes **34**–**50** by reflux of $[PdCl_2(cod)]$ **32** or $K_2[PtCl_4]$ **33** with ligands **20**–**27** (panel A) and **30**+**31** (panel B) in a mixture of ethanol and water for 1 h.

±0.12%. Also highly diagnostic of the ligand environment are the ^{195}Pt NMR shifts of **39**–**46** and **49**–**50**,[15] which differ by about 130 ppm for the pyridyl *vs.* quinolinyl complexes, with the former resonances further shifted to higher fields (average values −3160 *vs.* −3030 ppm). Interestingly, complexes with an alkyl group as the distal R′ substituent (either CH_3 or $(CH_2)_{11}CH_3$) showed an additional ^{195}Pt NMR signal at about −3100 ppm which was not present in the case of R′=phenyl. Since the elemental analysis results underscore the high purity of the complexes, this is possibly due to an isomerization taking place in solution, but for lack of a proper spectroscopic handle, the species involved could not be identified. A chlorido ligand exchange with DMSO solvent, on the other hand, can be ruled out since the [Pt(L)(DMSO)]OTf analogue of compound **42** shows a peak at −3650 ppm, shifted by around 540–550 ppm relative to the species observed here.[16]

Crystal structure analysis

Single crystals suitable for structure analysis using single-crystal X-ray diffraction were obtained for Pt(II) complex **45** with R=*n*-decyl and R′=CH_3 (Table 1). The metal centre is in a square-planar coordination environment with a Cl,N,N,S ligand sphere (Figure 1). While the N2–Pt1–Cl1 angle is near-linear at 176.98(9)° the N1–Pt1–S2 is somewhat more bent at 166.18(10)°. The methyl group on the distal nitrogen atom N4 is in a *trans* arrangement relative to the sulphur atom and the first

Table 1. Single-crystal X-ray diffraction data and refinement details of [PtCl($L_{py}^{(CH2)9CH3,CH3}$)].

Compound	**45**
CCDC number	2152499
Empirical formula	$C_{18}H_{29}ClN_4PtS$
Formula weight ($g \cdot mol^{-1}$)	564.05
Temperature (K)	100(2)
Radiation, λ (Å)	Mo-K_α, 0.71073
Crystal size (mm^3)	$0.47 \times 0.45 \times 0.21$
Crystal colour, habit	Red block
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	10.889(6)
b (Å)	10.493(7)
c (Å)	18.337(9)
α (°)	90.00(3)
β (°)	101.13(2)
γ (°)	90.00(3)
Volume ($Å^3$)	2056(2)
Z	4
Calculated density ($kg \cdot m^{-3}$)	1.822
Absorption coefficient (mm^{-1})	7.066
F(000)	1104
Theta range for collection (°)	2.264 to 26.020°
Reflections collected	19325
Independent reflections	4047
Minimum/maximum transmission	0.0692/0.1689
Refinement method	Full-matrix least-squares on F^2
Parameters	228
Goodness-of-fit on F^2	1.060
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0252$, $wR^2 = 0.0631$
R indices (all data)	$R_1 = 0.0298$, $wR^2 = 0.0653$
Max./min. residual electron density ($e \cdot Å^{-3}$)	3.221/−1.289

three carbon atoms of the *n*-decyl chain essentially point away from the ligand at a 90° angle. From the 3rd to the 4th carbon atom in the side-chain, however, there is a strong bent with an approx. 72° angle between the planes spanned by the 1st to 3rd and the 3rd to 10th carbon atoms, respectively. The further packing is dominated by intermolecular Cl···H–N hydrogen bonds with Cl···H distances of 2.461 Å, which leads to a "staircase" arrangement of the individual molecules and the long alkyl chains alternatingly pointing outwards. The *n*-decyl substituents of adjacent molecules are in an antiparallel orientation and the main planes of two complexes are in a parallel arrangement at approx. 3.3 Å distance. As far as we are aware of, this is the first structurally characterized example of a thiosemicarbazone metal complex with a long alkyl chain as the R group.

LogP values

In order to assess the effect of the substitution pattern on the lipophilicity of the title complexes, log*P* values were determined with the "shake flask" method (Table 2), excluding the compounds with R′ = alkyl, since the ^{195}Pt NMR showed that they are present as a mixture of two closely related species in solution and therefore no clear structural correlation can be made. Generally, comparing the Pd(II) and Pt(II) compounds with identical ligands, the latter show significantly higher log*P* values. However, this is not thought to reflect any significant structural differences of [MCl(L)] for Pd(II) *vs.* Pt(II), but might rather be due to faster chlorido to aqua ligand exchange rates for the Pd compounds compared to the Pt analogues, leading to fast formation of charged species in the palladium case, which are less lipophilic than the neutral compounds with the coordinated chlorido ligand.

Among the Pt(II) compounds, variation of the R group (H *vs.* CH_3) in α-position to the pyridine ring did not lead to any statistically significant differences in log*P*, but the *n*-octyl and particularly *n*-decyl substituents resulted in much more lipophilic compounds, in particular **44** and **46** (log*P* of 1.34 *vs.*

Table 2. Log*P* values determined with the "shake flask" method for selected metal complexes.

Complex	Metal	Ring	R group	R′ group	log*P*
34	Pd	2-pyridyl	H	C_6H_5	0.66 ± 0.09
35	Pd	2-pyridyl	CH_3	CH_3	n.d.
36	Pd	2-pyridyl	CH_3	C_6H_5	0.86 ± 0.17
37	Pd	2-pyridyl	$(CH_2)_7CH_3$	C_6H_5	1.59 ± 0.09
38	Pd	2-pyridyl	$(CH_2)_9CH_3$	C_6H_5	1.26 ± 0.61
39	Pt	2-pyridyl	H	C_6H_5	1.20 ± 0.16
40	Pt	2-pyridyl	CH_3	CH_3	n.d.
41	Pt	2-pyridyl	CH_3	$(CH_2)_{11}CH_3$	n.d.
42	Pt	2-pyridyl	CH_3	C_6H_5	1.12 ± 0.22
43	Pt	2-pyridyl	$(CH_2)_7CH_3$	CH_3	n.d.
44	Pt	2-pyridyl	$(CH_2)_7CH_3$	C_6H_5	1.34 ± 0.15
45	Pt	2-pyridyl	$(CH_2)_9CH_3$	CH_3	n.d.
46	Pt	2-pyridyl	$(CH_2)_9CH_3$	C_6H_5	1.90 ± 0.45
47	Pd	2-quinolinyl	H	C_6H_5	0.85 ± 0.07
48	Pd	2-quinolinyl	CH_3	CH_3	1.23 ± 0.07
49	Pt	2-quinolinyl	H	C_6H_5	1.06 ± 0.12
50	Pt	2-quinolinyl	CH_3	CH_3	1.45 ± 0.29

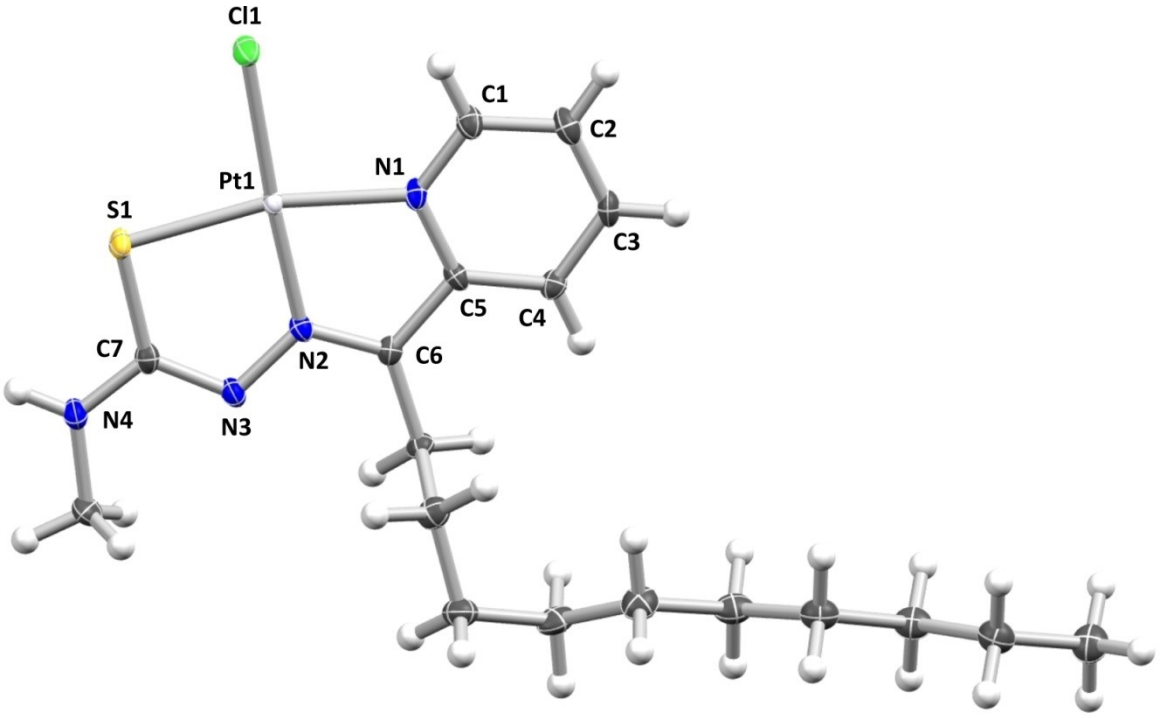


Figure 1. Solid state molecular structure of **45** determined by single-crystal X-ray diffraction at 100 K. Thermal ellipsoids are displayed at the 50% probability level. The sidechain carbon atoms are not labelled for clarity. Selected bond lengths [Å] and angles [°] for **45**: Pt1–Cl1 2.3057(15), Pt1–N1 2.033(3), Pt1–N2 1.952(3), Pt1–S1 2.2531(14), C5–C6 1.466(5), C6–N2 1.301(5), N2–N3 1.370(4), N3–C7 1.326(5), C7–S1 1.759(4), Cl1–Pt1–N2 176.98(9), N1–Pt1–S1 166.18(10), Cl1–Pt1–N1 96.41(11), N1–Pt1–N2 80.60(13), N2–Pt1–S1 85.61(10), Cl1–Pt1–S1 97.39(5), S1–C7–N3 125.3(3), C7–N3–N2 112.2(3), N3–N2–C6 119.2(3), N2–C6–C5 114.3(3).

1.90). The same trend also holds for the quinolinyl complexes, but the impact of the additional aromatic ring was less than extension of the R alkyl chain.

Anticancer activity

The anticancer activity of selected Pd(II) and Pt(II) complexes was evaluated with the MTT assay after 72 h of incubation. Complexes with R′ = alkyl were excluded from the study due to presence of two closely related species in solution and in some cases, only the representative GaMG cell line instead of the full panel was investigated to keep the number of experiments at a manageable scale. Cisplatin and temozolomide served as the references drugs studied under identical conditions, with all EC_{50} values reported in Table 3. In particular, for the GaMG and U138 cell lines, a significant number of metal complexes turned out to be significantly more active than the organic drug while in the case of the U343 cells, only cisplatin was about twice as active as temozolomide while all of the thiosemicarbazone complexes were less potent than even the organic drug (EC_{50} of 11.6–26.9 μM *vs.* 3.1 μM for cisplatin and 7.3 μM for temozolomide). Focusing the discussion on the GaMG cell line, some of the Pd(II) compounds were surprisingly active and with an EC_{50} of 2.1 μM, Pd(II) quinolinyl complex **48** with R=R′=CH_3 was identified as the most potent compound in the whole series, showing an activity slightly higher than that of cisplatin. Interestingly, the metal centre does not seem to be the determining factor here, as the Pt(II) analogue **50** was only marginally less potent, with an EC_{50} value of 3.6 μM, about the same as determined for cisplatin. Retaining the quinolinyl group but changing to R=H and R′ = phenyl however significantly reduced the activity independent of the metal, to 20–50 μM. Interestingly, among the Pd(II) compounds **34**–**38**, the EC_{50} values are inversely correlated with the lipophilicity and in particular decreased for R=CH_3 > $(CH_2)_7CH_3$ > $(CH_2)_9CH_3$ with 4.2 *vs.* 12.0 *vs.* 36.9 μM while keeping R′ = phenyl. Pd(II) complex **36** with R=CH_3 and R′=phenyl also retains an activity in the 4–12 μM range regardless of the cell line and thus seems to be the most generally applicable compound, which is also reflected in the activity of the Pt(II) analogue **42**, which is however somewhat less potent, in particular on the GaMG and U87 cell lines. Comparing the pyridyl and quinolinyl compounds, a maximum of two aromatic rings (either quinolinyl or pyridyl plus phenyl) combined with one methyl group give rise to the highest activity (**36** *vs.* **48**) and a slight advantage of Pd(II) *vs.* Pt(II).

Table 3. EC_{50} values determined with the MTT assay upon exposure of GaMG, U87, U138, and U343 brain cancer cells to selected metal complexes **34**–**50** for 72 h. Shown is the mean ± standard deviation of three independent experiments.

Complex	Metal	Ring	R group	R′ group	EC_{50} (μM) GaMG	EC_{50} (μM) U87	EC_{50} (μM) U138	EC_{50} (μM) U343
34	Pd	2-pyridyl	H	C_6H_5	7.6	n.d.	n.d.	n.d.
35	Pd	2-pyridyl	CH_3	CH_3	n.d.	n.d.	n.d.	n.d.
36	Pd	2-pyridyl	CH_3	C_6H_5	4.2	7.5	6.2	11.6
37	Pd	2-pyridyl	$(CH_2)_7CH_3$	C_6H_5	12.0	16.4	19.0	15.4
38	Pd	2-pyridyl	$(CH_2)_9CH_3$	C_6H_5	36.9	n.d.	33.8	16.8
39	Pt	2-pyridyl	H	C_6H_5	> 50	n.d.	n.d.	n.d.
40	Pt	2-pyridyl	CH_3	CH_3	n.d.	n.d.	n.d.	n.d.
41	Pt	2-pyridyl	CH_3	$(CH_2)_{11}CH_3$	n.d.	n.d.	n.d.	n.d.
42	Pt	2-pyridyl	CH_3	C_6H_5	9.1	11.9	17.3	12.6
43	Pt	2-pyridyl	$(CH_2)_7CH_3$	CH_3	n.d.	n.d.	n.d.	n.d.
44	Pt	2-pyridyl	$(CH_2)_7CH_3$	C_6H_5	13.0	30.4	32.7	26.9
45	Pt	2-pyridyl	$(CH_2)_9CH_3$	CH_3	n.d.	n.d.	n.d.	n.d.
46	Pt	2-pyridyl	$(CH_2)_9CH_3$	C_6H_5	6.0	17.3	30.6	13.3
47	Pd	2-quinolinyl	H	C_6H_5	18.0	n.d.	n.d.	n.d.
48	Pd	2-quinolinyl	CH_3	CH_3	2.1	n.d.	n.d.	n.d.
49	Pt	2-quinolinyl	H	C_6H_5	> 50	n.d.	n.d.	n.d.
50	Pt	2-quinolinyl	CH_3	CH_3	3.6	n.d.	n.d.	n.d.
cisplatin					3.4	3.4	1.8	3.1
temozolomide					67.1	n.d.	24.2	7.3

Conclusion

In a modular approach based on the condensation of pyridine-2-carbaldehyde or quinoline-2-carbaldehyde with different thiosemicarbazides to give thiosemicarbazone ligands with various substituents at the proximal C and distal N atoms, 17 palladium(II) and platinum(II) complexes were prepared in very good purity and studied for their cytotoxic potential on four different human glioblastoma cell lines (GaMG, U87, U138, and U343). The EC_{50} values determined were correlated with the log*P* values, nature of aromatic rings (quinolinyl *vs.* pyridyl), and type of metal (Pd(II) *vs.* Pt(II)). In particular, the GaMG and U138 cell lines were generally more responsive towards the metal complexes than temozolomide used as the organic reference compound. The most potent complex exhibited an EC_{50} value of 2.1 μM and although featuring a Pd(II) centre, was even slightly more active than cisplatin. Surprisingly, EC_{50} values were inversely correlated with the lipophilicity and decreased with the length of the alkyl substituents ($C_1 > C_8 > C_{10}$). In future mechanistic studies, it is planned to examine whether signalling pathways different from those of cisplatin are triggered which would indicate the potential for *in vivo* studies of the most promising title complex.

Experimental section

General remarks. Air- and moisture-sensitive compounds were handled in oven-dried Schlenk glassware under argon or nitrogen when necessary. All commercially available starting materials and solvents were obtained from Sigma-Aldrich, Strem, and Merck and used without purification. Diethyl ether was dried and stored over 3 Å molecular sieves. For purifications involving column chromatography, silica gel SC 60 from Merck was used. NMR spectra were recorded on Bruker Avance 200, DPX 300, DPX 400, Avance III 400 Nanobay, and Avance 500 instruments (^{1}H 199.93, 300.13, 400.40 und 500.13 MHz; ^{13}C 100.68 and 125.76 MHz, ^{195}Pt: 86.09 and 107.51 MHz). The chemical shift δ in ppm indicates a shift to lower field relative to tetramethylsilane (TMS) and was referenced to the proton or carbon signal of trace amounts of non-deuterated solvent.[17] The ^{195}Pt NMR chemical shifts are reported relative to 1.2 M $Na_2[PtCl_6]$ in D_2O.[18] Coupling constants *J* are given in Hz and peak multiplicities are indicated as follows: s = singlet, d = doublet, dd: doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, t = triplet, q = quartet, quin = quintet, and m = multiplet. IR spectra were recorded on pure solid samples using Nicolet 380 and Jasco FTIR spectrometers with an ATR accessory. Band positions are given in wavenumbers. The elemental analysis was carried out on an Elementar Vario Micro-Cube instrument from Elementar Analysensysteme or – for halogen-containing compounds – on a EA 3000 elemental analyser from HEKAtech. To obtain accurate results for the metal complexes, vanadium pentoxide was added to assist with complete combustion. UV/Vis spectra were collected on an Agilent 8453 diode array spectrophotometer in quartz cuvettes (d = 1 cm).

Synthesis of [PdCl($L_{py}^{H,Ph}$)] (34)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(pyridin-2-ylmethylen)hydrazin-1-carbothio-amide (135.4 mg, 0.53 mmol) was dissolved in ethanol (40 mL) with heating to 80 °C. Then, a solution of [$PdCl_2$(cod)] (149.7 mg, 0.52 mmol) in water (10 mL) was added and heating continued for 2 h. After cooling to room temperature, the resulting yellow precipitate was filtered off, washed with water (2 × 5 mL), ethanol (5 mL), and diethyl ether (2 × 5 mL) and dried under vacuum. Yield: 88 % (183.7 mg, 0.46 mmol). **IR** (ATR): $\tilde{\nu}$ = 3263, 2364, 1740, 1599, 1537, 1487, 1464, 1432, 1126, 749, 693 cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.34 (s, 1H, C_6H_5NH), 8.54–8.52 (m, 1H, H6), 8.26 (s, 1H, C*H*N), 8.18 (dt, 1H, ^3J = 7.8 Hz, ^4J = 1.6 Hz, H4), 7.83 (dd, 1H, ^3J = 8.0 Hz, ^3J = 1.2 Hz, H3), 7.67 (ddd, 1H, ^3J = 7.8 Hz, ^3J = 5.4 Hz, ^4J = 1.4 Hz, H5), 7.60 (d, 2H, ^3J = 8.7 Hz, H2′/H6′), 7.34–7.31 (m, 2H, H3′/H5′), 7.08–7.05 (m, 1H, H4′) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 157.52 (C2), 150.83 (*C*H=N), 148.33 (C6), 141.06 (C4),

140.01 (C1'), 128.67 (C3'/C5'), 126.29 (C5), 126.01 (C3), 123.66 (C4'), 120.43 (C2'/C6') ppm; **Elemental analysis** (%) calcd. for $C_{13}H_{11}ClN_4PdS$: C 39.31, H 2.79, N 14.11, S 8.07; found (%): C 39.33, H 2.66, N 14.04, S 7.77.

Synthesis of [PdCl($L_{py}^{CH3,CH3}$)] (35)[19]

In a 100 mL round-bottom flask, *N*-methyl-2-(1-(Pyridin-2-yl)ethyliden)hydrazin-1-carbo-thioamide (56.3 mg, 0.27 mmol) was dissolved in ethanol (10 mL) with heating to 80 °C. Then, a solution of sodium tetrachloropalladate(II) (79.8 mg, 0.27 mmol) in water (5 mL) was slowly added and heating continued for 1 h. After cooling to room temperature, the resulting yellow solid was filtered off, washed with water (1 mL), ethanol (2×2 mL), and diethyl ether (2×5 mL) and dried under vacuum. Yield: 86% (81.1 mg, 0.23 mmol). **IR** (ATR): $\tilde{\nu}$ = 3286 (NH), 1525 (C=N), 1503, 1462, 1438, 1402, 1373, 1255, 1190, 1163, 767 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 8.55 (d, 1H, ^3J = 4.7 Hz, H6), 8.16 (t, 1H, ^3J = 7.5 Hz, H4), 8.05 (s, 1H, CH_3NH), 7.83 (d, 1H, ^3J = 7.7 Hz, H3), 7.63 (t, 1H, ^3J = 7.4 Hz, H5), 2.87 (d, 3H, ^3J = 4.3 Hz, CH_3NH), 2.36 (s, 3H, C(CH_3)N) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 178.25 (*C*–S), 158.86 (*C*(CH_3)=N), 156.01 (C2), 148.12 (C6), 141.28 (C4), 126.45 (C5), 125.27 (C3), 33.68 (CH_3NH), 13.54 (C(CH_3)=N) ppm; **Elemental analysis** (%) calcd. for $C_9H_{11}ClN_4PdS$: C 30.96, H 3.18, N 16.05, S 9.13; found (%): C 30.89, H 3.20, N 15.89, S 8.82.

Synthesis of [PdCl($L_{py}^{CH3,Ph}$)] (36)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(pyridin-2-yl)ethyliden)hydrazin-1-carbothio-amide (71 mg, 0.26 mmol) was dissolved in ethanol (5 mL) with heating to 80 °C. Then, a solution of sodium tetrachloropalladate(II) (76.4 mg, 0.26 mmol) in water (5 mL) was added and heating continued for 1 h. After cooling to room temperature, the resulting yellow precipitate was filtered off, washed with ethanol (2×2 mL) and dried under vacuum. Yield: 82% (87.7 mg, 0.21 mmol). IR (ATR): $\tilde{\nu}$ = 3288 (NH), 1599, 1546, 1503, 1465, 1435, 1251, 1154 cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.21 (s, 1H, C_6H_5NH), 8.61 (d, 1H, ^3J = 5.1 Hz, H6), 8.21 (td, 1H, ^3J = 7.9 Hz, ^4J = 1.4 Hz, H4), 7.95 (d, 1H, ^3J = 8.0 Hz, H3), 7.70 (t, 1H, ^3J = 6.3 Hz, H5), 7.63 (d, 2H, ^3J = 8.4 Hz, H2'/H6'), 7.34 (t, 2H, ^3J = 7.7 Hz, H3'/H5'), 7.05 (t, 1H, ^3J = 7.3 Hz, H4'), 2.49 (s, 3H, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 174.61 (*C*–S), 159.14 (*C*(CH_3)=N), 157.99 (C2), 147.95 (C6), 141.01 (C1'), 140.31 (C4), 128.75 (C3'/C5'), 126.76 (C5), 125.66 (C3), 123.21 (C4'), 119.86 (C2'/C6'), 13.89 (CH_3) ppm; **Elemental analysis** (%) calcd. for $C_{14}H_{13}ClN_4PdS$: C 40.89, H 3.19, N 13.68, S 7.80; found (%): C 41.00, H 3.26, N 13.38, S 7.76.

Synthesis of [PdCl($L_{py}^{(CH2)7CH3,Ph}$)] (37)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(pyridin-2-yl)nonyliden)hydrazin-1-carbo-thioamide (79.3 mg, 0.22 mmol) was dissolved in ethanol (5 mL) with heating to 80 °C. Then, a solution of sodium tetrachloropalladate(II) (64 mg, 0.22 mmol) in water (5 mL) was added and heating continued for 1 h. After cooling to room temperature, the resulting yellow precipitate was filtered off, washed with water (1 mL), ethanol (1 mL), and diethyl ether (1 mL) and dried under vacuum. Yield: 76% (82.9 mg, 0.16 mmol). **IR** (ATR): $\tilde{\nu}$ = 3269 (NH), 2923, 2855, 1599, 1544 (C=N), 1495, 1472, 1457, 1431, 1316, 1252, 1151, 752 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.24 (s, 1H, C_6H_5NH), 8.63–8.62 (m, 1H, H6), 8.20 (dt, 1H, ^3J = 7.9 Hz, ^4J = 1.0 Hz, H4), 7.98 (d, 1H, ^3J = 8.0 Hz, H3), 7.71–7.68 (m, 1H, H5), 7.62 (d, 2H, ^3J = 7.7 Hz, H2'/H6'), 7.30 (t, 2H, ^3J = 7.5 Hz, H3'/H5'), 7.04 (t, 1H, ^3J = 7.8 Hz, H4'), 2.92 (t, 2H, ^3J = 7.7 Hz, C(CH_2)N), 1.61–1.55 (m, 2H, C(CH_2CH_2)N), 1.45–1.39 (m, 2H, C($CH_2CH_2CH_2$)N), 1.30–1.22 (m, 8H, (CH_2)$_4$$CH_3$), 0.82 (t, 3H, ^3J = 6.8 Hz, CH_2CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 175.16 (*C*–S), 163.03 (*C*(CH_2)=N), 157.74 (C2), 148.79 (C6), 141.65 (C1'), 140.83 (C4), 129.05 (C3'/C5'), 127.03 (C5), 126.05 (C3), 123.68 (C4'), 120.18 (C2'/C6'), 31.63 ($CH_2CH_2CH_3$), 29.69 (CH_2(CH_2)$_4$$CH_3$), 29.09 ($CH_2$($CH_2$)$_3$$CH_3$), 27.62 (C($CH_2$)=N), 26.28 (C($CH_2CH_2$)=N), 22.51 ($CH_2CH_3$), 14.40 ($CH_3$) ppm; **Elemental analysis** (%) calcd. for $C_{21}H_{27}ClN_4PdS$: C 49.51, H 5.34, N 11.00, S 6.29; found (%): C 49.61, H 5.43, N 11.10, S 6.55.

Synthesis of [PdCl($L_{py}^{(CH2)9CH3,Ph}$)] (38)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(pyridin-2-yl)undecyliden)hydrazin-1-carbo-thioamide (99.9 mg, 0.25 mmol) was dissolved in ethanol (10 mL) with heating to 80 °C. Then, a solution of sodium tetrachloropalladate(II) (77.29 mg, 0.21 mmol) in water (10 mL) was added and heating continued for 1 h. After cooling to room temperature, the yellow solid which had precipitated was filtered off, washed with water (2×1 mL) and ethanol (2×1 mL) and dried under vacuum. Yield: 82% (110.5 mg, 0.21 mmol). **IR** (ATR): $\tilde{\nu}$ = 3335 (NH), 3280, 2954, 2923, 2852, 1599 1543, 1499 (C=N), 1472, 1457, 1431, 1317, 1251, 1152, 1104.51, 749 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.23 (s, 1H, C_6H_5NH), 8.63 (dd, 1H, ^3J = 5.3 Hz, ^4J = 1.6 Hz, H6), 8.20 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.6 Hz, H4), 7.98 (d, 1H, ^3J = 7.8 Hz, H3), 7.70 (ddd, 1H, ^3J = 7.7 Hz, ^3J = 5.5 Hz, ^4J = 1.1 Hz, H5), 7.63 (d, 2H, ^3J = 7.8 Hz, H2'/H6'), 7.30 (t, 2H, ^3J = 7.5 Hz, H3'/H5'), 7.04 (t, 1H, ^3J = 8.1 Hz, H4') 2.92 (t, 2H, ^3J = 7.1 Hz C(CH_2)N), 1.58 (quin, 2H, ^3J = 7.5 Hz, C($CH_2CH_2CH_2$)N), 1.41 (quin, 2H, ^3J = 7.2 Hz, C($CH_2CH_2CH_2$)N), 1.31–1.20 (m, 12H, (CH_2)$_6$$CH_3$), 0.83 (t, ^3J = 6.9 Hz, 3H, CH_2CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 174.70 (*C*–S), 162.55 (C(CH_2)=N), 157.28 (C2), 148.33 (C6), 141.18 (C1'), 140.37 (C4), 128.58 (C3'/C5'), 126.83 (C5), 125.58 (C3), 123.18 (C4'), 119.70 (C2'/C6'), 31.21 ($CH_2CH_2CH_3$), 29.21 (CH_2), 28.96 (CH_2), 28.87 (CH_2), 28.67 (CH_2), 28.64 (CH_2), 27.17 (CH_2), 25.81 (C(CH_2CH_2)=N), 22.09 (CH_2CH_3), 13.97 (CH_3) ppm; **Elemental analysis** (%) calcd. for $C_{23}H_{31}ClN_4PdS$: C51.40, H 5.81, N 10.42, S 5.97; found (%): C 51.72, H 5.78, N 10.46, S 5.78.

Synthesis of [PtCl($L_{py}^{H,Ph}$)] (39)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(pyridin-2-ylmethylen)hydrazin-1-carbothio-amide (94 mg, 0.37 mmol) was dissolved in ethanol (40 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (149.9 mg, 0.36 mmol) in water (10 mL) was added and heating continued for 2 h. After cooling to room temperature, the resulting red precipitate was filtered off, washed with water (2×5 mL), ethanol (5 mL), and diethyl ether (2×5 mL) and dried under vacuum. Yield: 75% (132 mg, 0.27 mmol). **IR** (ATR): $\tilde{\nu}$ = 3276, 1598, 1537, 1487, 1559, 1430, 1320, 1245, 1122, 1103, 756, 693 cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.42 (s, 1H, C_6H_5NH), 8.76–8.75 (m, 1H, H6), 8.66 (s, 1H, *CH*N), 8.18 (dt, 1H, ^3J = 7.8 Hz, ^4J = 1.5 Hz, H4), 8.44 (d, 1H, ^3J = 7.6 Hz, H3), 7.74 (ddd, 1H, ^3J = 7.8 Hz, ^3J = 5.6 Hz, ^4J = 1.4 Hz, H5), 7.60 (dd, 2H, ^3J = 8.6 Hz, ^4J = 1.0 Hz, H2'/H6'), 7.35–7.32 (m, 2H, H3'/H5'), 7.08–7.05 (m, 1H, H4') ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 180.05 (*C*–S), 159.02 (C2), 151.01 (*C*H=N), 146.89 (C6), 140.98 (C1'), 140.01 (C4), 128.62 (C3'/C5'), 126.96 (C3), 126.33 (C5) 123.83 (C4'), 120.70 (C2'/C6') ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ =-3153 ppm; **Elemental analysis** (%) calcd. for $C_{13}H_{11}ClN_4PtS$: C 32.14, H 2.28, N 11.53, S 6.60; found (%): C 32.26, H 2.32, N 11.14, S 6.24.

Synthesis of [PtCl($L_{py}^{CH3,CH3}$)] (40)[19]

In a 100 mL round-bottom flask, *N*-methyl-2-(1-(pyridin-2-yl)ethyliden)hydrazin-1-carbothio-amide (40.3 mg, 0.19 mmol) was dissolved in ethanol (5 mL) with heating to 80 °C. Then, a solution

of potassium tetrachloroplatinate(II) (80 mg, 0.19 mmol) in water (5 mL) was slowly added and heating continued for 1 h. After cooling to room temperature, the red solid that had precipitated was filtered off, washed with water (1 mL), ethanol (2×2 mL), and diethyl ether (2×5 mL), and dried under vacuum. Yield: 76% (64 mg, 0.15 mmol). **IR** (ATR): $\tilde{\nu}$ = 3306 (NH), 1524 (C=N), 1503, 1462, 1438, 1402, 1374, 1244, 1184, 765 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 8.79 (d, 1H, ^3J = 4.5 Hz, H6), 8.18–8.16 (m, 2H, H4, CH_3NH), 7.79–7.69 (m, 2H, H3, H5), 3.99 (d, 3H, ^3J = 3.3 Hz, $NHCH_3$), 2.33 (s, 3H, $C(CH_3)N$) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 182.83 (C–S), 160.18 ($C(CH_3)$=N), 155.79 (C2), 146.44 (C6), 140.90 (C4), 127.17 (C5), 125.78 (C3), 33.53 (CH_3NH), 13.69 ($C(CH_3)$=N) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3106, −3165 ppm; **Elemental analysis** (%): calcd. for $C_9H_{11}ClN_4PtS$: C 24.69, H 2.53, N 12.80, S 7.32; found (%): C 24.27, H 2.60, N 12.30, S 6.80.

Synthesis of [PtCl($L_{py}^{CH3,(CH2)11CH3}$)] (41)[19]

In a 100 mL round-bottom flask, *N*-methylhydrazine carbothioamide (70 mg, 0.19 mmol) was dissolved in ethanol (10 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (80.2 mg, 0.19 mmol) in water (5 mL) was added and heating continued for 1 h. After cooling to room temperature, chloroform (10 mL) was added to dissolve the sticky product which otherwise could not be removed from the flask. The combined solutions were then evaporated to dryness and the resulting red solid dried under vacuum. Yield: 70% (80 mg, 0.14 mmol). **IR** (ATR): $\tilde{\nu}$ = 3332, 3272, 2918, 2850, 1559, 1515, 1467, 1438, 1372, 1315, 1074, 763 cm^{-1}; **^{1}H NMR** (500.13 MHz, $CDCl_3$): δ = 8.99 (s, 1H, $C_{12}H_{25}NH$ or H6), 7.91 (t, 1H, ^3J = 7.3 Hz, H4), 7.40–7.36 (m, 2H, H3, H5), 3.51 (q, 2H, ^3J = 7.5 Hz, CH_2CH_2NH), 2.30 (s, 3H, $C(CH_3)N$), 1.60 (s, 2H, $CH_2(CH_2)_9CH_3$), 1.26 (s, 18H, $(CH_2)_9CH_3$), 0.88 (t, 3H, ^3J = 6.9 Hz, CH_3) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$, ppm):147.37 (($C(CH_3)$=N), 147.34 (C6), 139.54 (C4), 125.76 (C5), 123.89 (C3), 32.06 ($CH_2CH_2CH_3$), 29.79 (CH_2), 29.77 (CH_2), 29.73 (CH_2), 29.67 (CH_2), 29.49(CH_2), 29.41 (CH_2), 26.96 ((NH-$(CH_2)_2CH_2$), 22.83 (CH_2CH_3), 14.27 (CH_3), 13.46 ($C(CH_3)$=N), the peaks of *C*–S and py-C2 were not identified due to poor solubility; **^{195}Pt NMR** (107.5 MHz, $CDCl_3$): δ = -3102, −3150 ppm; **Elemental analysis** (%) calcd. for $C_{20}H_{33}ClN_4PtS$: C 40.57, H 5.62, N 9.46, S 5.42; found (%): C 40.41, H 5.55, N 9.30, S 5.11.

Synthesis of [PtCl($L_{py}^{CH3,Ph}$)] (42)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(pyridin-2-yl)ethyliden)hydrazin-1-carbothio-amide (52.1 mg, 0.19 mmol) was dissolved in ethanol (15 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (80.0 mg, 0.19 mmol) in water (5 mL) was added and heating continued for 1 h. After cooling to room temperature, the resulting red precipitate was filtered off, washed with ethanol (2×2 mL) and dried under vacuum. Yield: 77% (74 mg, 0.15 mmol). IR (ATR): $\tilde{\nu}$ = 3308 (NH), 1510 (C=N), 1502, 1494, 1472, 1457, 1434, 1375, 1313, 1247, 1151, 746 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.29 (s, 1H, C_6H_5NH), 8.83 (dd, 1H, ^3J = 5.5 Hz, ^4J = 1.0 Hz, H6), 8.21 (dt, 1H, ^3J = 7.9 Hz, ^4J = 1.6 Hz, H4), 7.89 (d, 1H, ^3J = 7.6 Hz, H3), 7.75 (ddd, 1H, ^3J = 7.6 Hz, ^3J = 5.5 Hz, ^4J = 1.3 Hz, H5), 7.63 (dd, 2H, ^3J = 7.7 Hz, ^4J = 0.9 Hz, H2'/H6'), 7.35 (t, 2H, ^3J = 7.3 Hz, H3'/H5'), 7.04 (m, 1H, H4'), 2.45 (s, 3H, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 177.70 (C–S), 159.24 ($C(CH_3)$=N), 159.11 (C2), 146.33 (C6), 140.70 (C1'), 140.33 (C4), 128.69 (C3'/C5'), 127.51 (C3), 126.23 (C5), 123.36 (C4'), 120.12 (C2'/C6'), 13.93 (CH_3) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3165 ppm; **Elemental analysis** (%) calcd for $C_{14}H_{13}ClN_4PtS$: C 33.83, H 2.62, N 11.21, S 6.41; found (%): C 33.52, H 2.71, N 11.07, S 6.26.

Synthesis of [PtCl($L_{py}^{(CH2)7CH3,CH3}$)] (43)[19]

In a 100 mL round-bottom flask, *N*-methyl-2-(1-(pyridin-2-yl)nonyliden)hydrazin-1-carbo-thioamide (59.2 mg, 0.19 mmol) was dissolved in ethanol (5 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (80.5 mg, 0.19 mmol) in water (5 mL) was slowly added and the solution heated to reflux for 1 h. After cooling to room temperature; the red solid which had precipitated was filtered off, washed with water (1 mL), ethanol (1 mL), and diethyl ether (1 mL) and then dried under vacuum. Yield: 57% (58.6 mg, 0.11 mmol). **IR** (ATR): $\tilde{\nu}$ = 3310 (NH), 2933, 2851, 1555, 1521 (C=N), 1501, 1472, 1461, 1437, 1420, 1399, 1356, 1247, 1180, 1157, 1100, 779 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 8.81 (d, 1H, ^3J = 4.8 Hz, H6), 8.16 (s, 2H, H4, CH_3NH), 7.79 (d, 1H, ^3J = 7.5 Hz, H3), 7.68 (t, 1H, ^3J = 6.7 Hz, H5), 2.98 (d, 3H, ^3J = 4.1 Hz, CH_3NH), 2.84 (t, 2H, ^3J = 7.4 Hz, $C(CH_2)$=N), 1.55 (quin, 2H, ^3J = 8.5 Hz, $CH_2CH_2CH_3$), 1.28–1.22 (m, 10H, $(CH_2)_5$), 0.82 (t, 3H, ^3J = 6.9 Hz, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 180.40 (C–S), 158.99 ($C(CH_2)$=N), 158.73 (C2), 146.27 (C6), 140.57 (C4), 126.68 (C5), 125.22 (C3), 32.94 ($CH_2CH_2CH_3$), 31.17 (CH_3), 28.61 (CH_2), 28.44 (CH_2), 26.10 ($C(CH_2)$=N), 25.17 ($C(CH_2CH_2)$=N), 22.02 (CH_2CH_3), 13.92 (CH_3) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3104, −3163 ppm; **Elemental analysis** (%): calcd. for $C_{16}H_{25}ClN_4PtS$: C 35.85, H 4.70, N 10.45, S 5.98; found (%): C 36.15, H 4.82, N 10.17, S 5.40.

Synthesis of [PtCl($L_{py}^{(CH2)7CH3,Ph}$)] (44)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(pyridin-2-yl)nonyliden)hydrazin-1-carbo-thioamide (71.50 mg, 0.19 mmol) was dissolved in ethanol (5 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (80.20 mg, 0.19 mmol) in water (5 mL) was added and heating continued for 1 h. After cooling to room temperature, the red solid which had precipitated was filtered off, washed with water (1 mL), ethanol (1 mL), and diethyl ether (1 mL), and dried under vacuum. Yield: 73% (84.70 mg, 0.14 mmol). **IR** (ATR): $\tilde{\nu}$ = 3323, 2923, 2853, 1599, 1542 (C=N), 1500, 1461, 1434, 1353, 1319, 1250, 1150, 1104, 751, 742 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.32 (s, 1H, C_6H_5NH), 8.86 (d, 1H, ^3J = 5.2 Hz, H6), 8.21 (td, 1H, ^3J = 7.9 Hz, ^4J = 1.2 Hz, H4), 7.92 (d, 1H, ^3J = 8.0 Hz, H3), 7.75 (t, 1H, ^3J = 6.8 Hz, H5), 7.64 (d, 2H, ^3J = 7.7 Hz, H2'/H6'), 7.31 (t, 2H, ^3J = 7.5 Hz, H3'/H5'), 7.04 (t, 1H, ^3J = 7.4 Hz, H4'), 2.93 (t, 2H, ^3J = 8.0 Hz, $C(CH_2)N$), 1.62–1.56 (m, 2H, $C(CH_2CH_2)N$), 1.44–1.39 (m, 2H, $C(CH_2(CH_2)_2)N$), 1.30–1.21 (m, 8H, $(CH_2)_4CH_3$), 0.82 (t, 3H, ^3J = 6.9 Hz, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 177.19 (C–S), 162.38 ($C(CH_2)$=N), 158.50 (C2), 146.71 (C6), 140.88 (C1'), 140.38 (C4), 128.51 (C3'/C5'), 127.55 (C5), 126.14 (C3), 123.36 (C4'), 119.96 (C2'/C6'), 31.15 ($CH_2CH_2CH_3$), 29.13 ($CH_2(CH_2)_4CH_3$), 28.63 ($CH_2(CH_2)_3CH_3$), 28.61($CH_2(CH_2)_2CH_3$), 27.19 ($C(CH_2CH_2)$=N), 25.61 ($C(CH_2)$=N), 22.04 (CH_2CH_3), 13.92 (CH_3) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3164 ppm; **Elemental analysis** (%) calcd. for $C_{21}H_{27}ClN_4PtS$: C 42.17, H 4.55, N 9.37, S 5.36; found (%): C 41.99, H 4.65, N 9.72, S 5.56.

Synthesis of [PtCl($L_{py}^{(CH2)9CH3,CH3}$)] (45)[19]

In a 100 mL round-bottom flask, *N*-methyl-2-(1-(pyridin-2-yl)undecyliden)hydrazin-1-carbo-thioamide (78.80 mg, 0.24 mmol) was dissolved in ethanol (7 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (99.80 mg, 0.24 mmol) in water (7 mL) was slowly added and the mixture heated to reflux for 1 h. After cooling to room temperature, the red solid which had precipitated was filtered off, washed with water (2×2 mL) and ethanol (2×2 mL) and dried under vacuum. Yield: 76% (101 mg, 0.18 mmol). **IR** (ATR): $\tilde{\nu}$ = 3328, 2950, 2921, 2852, 1559, 1513 (C=N), 1462, 1438, 1420, 1399, 1350, 1248, 1183, 1165, 1155, 777 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 8.82 (d, 1H, ^3J = 5.2 Hz,

H6), 8.19–8.16 (m, 2H, H4, CH_3NH), 7.80 (d, 1H, ^3J = 7.9 Hz, H3), 7.68 (t, 1H, ^3J = 6.1 Hz, H5), 2.98 (d, 3H, ^3J = 3.6 Hz, CH_3NH), 2.85 (t, 3H, ^3J = 7.8 Hz, C(CH_2CH$_2$)N), 1.93 (quin, 2H, ^3J = 6.7 Hz, CH$_2$$CH_2CH_2$), 1.22 (s, 14H, ($CH_2$)$_7$), 0.84 (t, 3H, ^3J = 6.9 Hz, CH$_2$$CH_3$) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 180.54 (*C*–S), 159.10 (*C*(CH$_2$)=N), 158.73 (C2), 146.35 (C6), 140.59 (C4), 126.72 (C5), 125.26 (C3), 33.00 (CH_2), 31.30 (CH_3NH), 28.94 (CH_2), 28.84 (CH_2), 28.69 (CH_2), 28.54 (CH_2), 26.17 (C(CH_2CH$_2$)=N), 25.23 C(CH_2)=N), 22.10 (CH_2CH$_3$), 13.98 (CH$_2$$CH_3$) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3098, −3157 ppm; **Elemental analysis** (%) calcd. for $C_{29}H_{52}ClN_4PtS$: C 38.33, H 5.18, N 9.93, S 5.68; found (%): C 37.20, H 5.11, N 9.60, S 5.27.

Synthesis of [PtCl(L$_{py}^{(CH2)9CH3,Ph}$)] (46)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(Pyridin-2-yl)undecyliden)hydrazin-1-carbo-thioamide (79.7 mg, 0.20 mmol) was dissolved in ethanol (7 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (87.8 mg, 0.21 mmol) in water (7 mL) was slowly added and the mixture heated to reflux for 1 h. After cooling to room temperature, the resulting red precipitate was filtered off, washed with water (2×1 mL) and ethanol (2×1 mL) and dried under vacuum. Yield: 86% (107.7 mg, 0.17 mmol). **IR** (ATR): $\tilde{\nu}$ = 3325 (NH), 2922, 2852, 1597, 1542, 1499 (C=N), 1461, 1433, 1356, 1317, 1250, 1190, 1156, 773, 750 (C–S) cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.33 (s 1H, C_6H_5NH), 8.86 (d, 1H, ^3J = 5.6 Hz, H6), 8.20 (t, 1H, ^3J = 7.8 Hz, H4), 7.92 (d, 1H, ^3J = 7.8 Hz, H3), 7.75 (t, 1H, ^3J = 7.7 Hz, H5), 7.63 (d, 2H, ^3J = 7.9 Hz, H2'/H6'), 7.33–7.30 (t, 2H, ^3J = 7.8 Hz, H3'/H5'), 7.03 (t, 1H, ^3J = 7.4 Hz, H4') 2.92 (t, 2H, ^3J = 7.4 Hz, C(CH_2)N), 1.57 (quin, 2H, ^3J = 8.0 Hz, C(CH$_2$$CH_2CH_2$)N)), 1.41 (quin, 2H, ^3J = 6.3 Hz, C(CH$_2$$CH_2CH_2CH_2$)N)), 1.30–1.20 (m, 12H, (CH_2)$_6$CH$_3$), 0.83 (t, 3H, ^3J = 7.0 Hz, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 177.79 (*C*–S), 162.39 (*C*(CH$_2$)=N), 158.51 (C2), 146.71 (C6), 140.88 (C1'), 140.39 (C4), 128.51 (C3'/C5'), 127.55 (C5), 126.14 (C3), 123.33 (C4'), 119.95 (C2'/C6'), 31.26 (CH$_2$CH$_2$CH$_3$), 29.12 (CH_2), 28.96 (CH_2), 28.86 (CH_2), 28.66 (CH_2), 28.63 (CH_2), 27.21 (CH_2), 25.60 (C(CH_2CH$_2$)=N), 22.08 (CH_2CH$_3$), 13.96 (CH_3) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3164 ppm; Elemental analysis (%) calcd. for $C_{23}H_{31}ClN_4PtS$: C 44.12, H 4.99, N 8.95, S 5.12; found (%): C 43.90, H 4.88, N 9.01, S 5.20.

Synthesis of [PdCl(L$_{quin}^{H,Ph}$)] (47)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(quinolin-2-ylmethylen)hydrazin-1-carbothio-amide (210.4 mg, 0.687 mmol) was dissolved in ethanol (40 mL) with heating to 80 °C. Then, a solution of [PdCl$_2$(cod)] (195.9 mg, 0.686 mmol) in water (15 mL) was added and heating continued for 2 h. After cooling to room temperature, the resulting red precipitate was filtered off, washed with water (2× 10 mL) and ethanol (2×10 mL) and dried under vacuum. Yield: 95% (292 mg, 0.65 mmol). **IR** (ATR): $\tilde{\nu}$ = 1481, 1429, 1116, 874, 744, 649 cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.48 (s, 1H, C_6H_5NH), 9.54 (d, 1H, ^3J = 8.9 Hz, H3), 8.78 (d, 1H, ^3J = 8.4 Hz, H4), 8.47 (s, 1H, C*H*N), 8.08 (d, 1H, ^3J = 8.1 Hz, H8), 7.94 (d, 1H, ^3J = 8.4 Hz, H5), 7.88 (t, 1H, ^3J = 8.5 Hz, H6), 7.74 (t, 1H, ^3J = 8.5 Hz, H7), 7.61 (d, 2H, ^3J = 7.8 Hz, H2'/H6'), 7.36 (t, 2H, ^3J = 8.0 Hz, H3'/H5'), 7.10 (t, 1H, ^3J = 7.4 Hz, H4') ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 158.65 (C2), 147.63 (C8a), 141.59 (C4), 139.81 (C1'), 132.56 (C6), 129.15 (C7), 128.75 (C3'/C5'), 128.52 (C8), 127.08 (C3), 123.88 (C4'), 122.19 (C5), 120.53 (C2'/C6') ppm; **Elemental analysis** (%) calcd. for $C_{17}H_{13}N_4ClPdS{\cdot}2(H_2O)$: C 42.25, H 3.55, N 11.59, S 6.63; found (%):C 42.61, H 3.36, N 11.20, S 6.25.

Synthesis of [PdCl(L$_{quin}^{CH3,Ph}$)] (48)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(quinolin-2-yl)ethyliden)hydrazin-1-carbo-thioamide (70 mg, 0.22 mmol) was dissolved in ethanol (20 mL) with heating to 80 °C. Then, a solution of [PdCl$_2$(cod)] (63 mg, 0.22 mmol) in water (5 mL) was added and heating continued for 2 h. After cooling to room temperature, the brown solid which had precipitated was filtered off, washed with water (2×10 mL) and ethanol (2×10 mL) and dried under vacuum. Yield: 80% (81 mg, 0.18 mmol). **IR** (ATR): $\tilde{\nu}$ = 3298, 1600, 1543, 1493, 1437, 1251, 1167, 1071, 824, 744, 683 cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.31 (s, 1H, C_6H_5NH), 9.63 (d, 1H, ^3J = 8.2 Hz, H3), 8.82 (d, 1H, ^3J = 8.5 Hz, H4), 8.11 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.5 Hz, H8), 8.09 (d, 1H, ^3J = 8.7 Hz, H5), 7.87 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 6.8 Hz, ^4J = 1.5 Hz, H6), 7.74 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 6.8 Hz, ^4J = 1.0 Hz, H7), 7.62 (dd, 2H, ^3J = 8.7 Hz, ^4J = 0.9 Hz, H2'/H6'), 7.37–7.34 (m, 2H, H3'/H5'), 7.08–7.05 (m, 1H, H4'), 2.59 (s, 3H, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 160.24 (*C*(CH$_3$)=N), 159.09 (C2), 147.24 (C8a), 141.58 (C4), 140.10 (C1'), 132.42 (C6), 129.42 (C4a), 128.80 (C7), 128.59 (C3'/C5'), 128.36 (C8), 127.73 (C3), 123.36 (C4'), 121.72 (C5), 119.91 (C2'/C6'), 15.02 (CH_3) ppm; **Elemental analysis** (%) calcd. for $C_{18}H_{15}ClN_4PdS$: C46.87, H 3.28, N 12.15, S 6.95; found (%): C 46.07, H 3.29, N 12.38, S 6.93.

Synthesis of [PtCl(L$_{quin}^{H,Ph}$)] (49)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(quinolin-2-ylmethylene)hydrazin-1-carbothio-amide (147.9 mg, 0.48 mmol) was dissolved in ethanol (25 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (199.9 mg, 0.48 mmol) in water (15 mL) was added and the mixture heated to reflux for 2 h. After cooling to room temperature, the precipitated material was filtered off, washed with water (2×10 mL) and ethanol (2×10 mL) and dried under vacuum to obtain the product as a black solid. Yield: 74% (150 mg, 0.36 mmol). **IR** (ATR): $\tilde{\nu}$ = 3349, 3077, 1598, 1476, 1430, 1111, 736, 688 cm^{-1} ; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.53 (s, 1H, C_6H_5NH), 9.72 (d, 1H, ^3J = 8.7 Hz, H3), 8.97 (s, 1H, C*H*N), 8.80 (d, 1H, ^3J = 8.4 Hz, H4), 8.07 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.1 Hz, H8), 7.90–7.87 (m, 2H, H5, H6), 7.74–7.71 (m, 1H, H7), 7.60 (d, 2H, ^3J = 7.7 Hz, H2'/H6'), 7.37–7.34 (m, 2H, H3'/H5'), 7.09 (t, 1H, ^3J = 7.4 Hz, H4') ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 160.18 (C2), 152.66 (*C*HN), 148.32 (C8a), 142.04 (C4), 139.72 (C1'), 132.80 (C6), 130.13 (C4a), 128.76 (C7), 128.66 (C3'/C5'), 128.48 (C8), 126.52 (C3), 124.06 (C4'), 121.89 (C5), 120.87 (C2'/C6') ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3021 ppm; **Elemental analysis** (%) calcd. for $C_{17}H_{13}ClN_4PtS{\cdot}0.5(C_2H_6O)$: C 38.68, H 2.89, N 10.02, S 5.74; found (%): C 38.45, H 2.94, N 9.62, S 5.50.

Synthesis of [PtCl(L$_{quin}^{CH3,Ph}$)] (50)[19]

In a 100 mL round-bottom flask, *N*-phenyl-2-(1-(quinolin-2-yl)ethyliden)hydrazin-1-carbo-thioamide (96.7 mg, 0.30 mmol) was dissolved in ethanol (25 mL) with heating to 80 °C. Then, a solution of potassium tetrachloroplatinate(II) (121 mg, 0.29 mmol) in water (10 mL) was added and heating continued for 2 h. After cooling to room temperature, the resulting black solid was filtered off, washed with water (10 mL) and ethanol (5 mL) and dried under vacuum. Yield: 78% (124.7 mg, 0.23 mmol). **IR** (ATR): $\tilde{\nu}$ = 1492, 1431, 1065, 818, 744, 7683 cm^{-1}; **^{1}H NMR** (500.13 MHz, DMSO-d_6): δ = 10.40 (s, 1H, C_6H_5NH), 9.80 (d, 1H, ^3J = 8.8 Hz, H3), 8.87 (d, 1H, ^3J = 8.6 Hz, H4), 8.11 (d, 1H, ^3J = 8.6 Hz, H8), 8.03 (d, 1H, ^3J = 8.4 Hz, H5), 7.90 (ddd, 1H, ^3J = 8.5 Hz, ^3J = 6.8 Hz, ^4J = 1.8 Hz, H6), 7.74 (ddd, 1H, ^3J = 8.5 Hz, ^3J = 6.6 Hz, ^4J = 1.0 Hz, H7), 7.62 (dd, 2H, ^3J = 8.6 Hz, ^4J = 0.9 Hz, H2'/H6'), 7.39–7.35 (m, 2H, H3'/H5'), 7.08–7.05 (m, 1H, H4'), 2.54 (s, 3H, CH_3) ppm; **^{13}C NMR** (125.76 MHz, DMSO-d_6): δ = 161.25 (*C*(CH$_3$)=N), 147.87 (C8a), 141.74 (C4), 140.05 (C1'), 132.62 (C6), 130.42 (C4a),

128.73 (C7), 128.70 (C3'/C5'), 128.56 (C8), 127.24 (C3), 123.57 (C4'), 121.81 (C5), 120.26 (C2'/C6'), 15.11 (CH_3) ppm; **^{195}Pt NMR** (107.51 MHz, DMSO-d_6): δ = -3045 ppm; **Elemental analysis** (%) calcd. for $C_{18}H_{15}N_4ClPtS$: C 39.31, H 2.75, N 10.19, S 5.83; found (%):C 38.77, H 2.65, N 10.39, S 5.97.

Determination of the n–octanol/water partition coefficient[20]

The *n*-octanol/water partition coefficient log*P* was determined by the "shake flask" method. Equal amounts of PBS buffer (10 mM, pH 7.4) and *n*-octanol were mixed in a conical flask and then stirred for 72 h, followed by separation of the two phases. Then, stock solutions of the metal complexes (approx. 1 mg in 200 µL of solvent) were prepared in DMSO and 10 µL thereof mixed with 750 µL of either the water or octanol phase. After mixing on a vortexer for 15 min, the vials were centrifuged at 3000 rpm for 5 min, the two phases separated and the absorbance measured on an Agilent 8453 UV/Vis diode array spectrophotometer. Log*P* values were then calculated using eq. 1:

$$logP = log\frac{A_{Octanol\ (300\ nm)}}{A_{PBS(300\ nm)}} \quad (1)$$

Single-crystal X-ray diffraction

A crystal suitable for single-crystal X-ray diffraction was selected, coated in perfluoropolyether oil, and mounted on a MiTeGen sample holder. Diffraction data of **45** was collected on a Bruker X8-APEX II 4-circle diffractometer with a CCD area detector using graphite monochromated Mo-K_α radiation. The crystal was cooled using an Oxford Cryostreams low-temperature device. Data was collected at 100 K. The images were processed and corrected for Lorentz-polarization effects and absorption as implemented in the Bruker software packages. The structure was solved using the intrinsic phasing method of ShelXT and Fourier expansion technique.[21] All non-hydrogen atoms were refined in anisotropic approximation, with hydrogen atoms 'riding' in idealized positions, by full-matrix least squares against F^2 of all data, using SHELXL[21] and the SHELXLE graphical user interface.[22] Crystal data and experimental details are listed in Table 1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-2152499. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Biological methods

Culture of glioblastoma cell lines

All experiments were performed with glioblastoma cell lines U87, U138, U343 (CLS) and GaMG (DSMZ), cultured as a monolayer in 75 cm^3 flasks (Corning) containing 15–20 mL Dulbecco's modified eagle's medium (DMEM), 10% heat inactivated fetal calf serum (FCS), 2% non-essential amino acids, 1000 U/L penicillin and 100 mg/mL streptomycin (all from Gibco) at 37 °C, 5% CO_2 and 95% humidity. Reaching 80% confluency, the cell culture medium was removed, the cells were washed with 5 mL phosphate buffered saline (PBS, Sigma-Aldrich) and incubated for 8 min with 2 mL Trypsin/EDTA (Carl Roth) for passaging. Cell detachment was controlled using a microscope (Leica Microsystems). The reaction was terminated by adding 8 mL of cell culture medium. The cell number was quantified utilising cell counter systems Scepter (Millipore) or Countess II FL (ThermoFisher). The detached cells were used for further cultivation or for experiments as outlined below.

MTT Assay

To determine EC_{50} values, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays were performed utilising the Cell Proliferation KIT I (Roche) following the manufacturer's instructions. Briefly, 3×10^3 cells per cell line contained in 100 µL medium were plated into each well of a 96-well plate (Corning) and incubated for 24 h as described above. Metal complexes were dissolved in dimethyl sulfoxide (DMSO, Sigma-Aldrich) and diluted in medium. The medium in the 96-well plate was replaced by 100 µL of medium containing the metal complexes, cisplatin and temozolomide, respectively. The concentrations ranged from 0.25 to 50 µM. The cells were incubated for 72 h (37 °C, 5% CO_2, 95% humidity). Next, 10 µL MTT solution was added, cells were incubated for another 4 h and finally the reaction was stopped by adding 10 µL of the kits' stop-solution. At the following day, the colour change was quantified at a wavelength of 540 nm using an ELISA reader (Tecan). EC50 values were calculated with GraphPad Prism 8 (GraphPad Software).

Supporting Information

Synthetic procedures for ligands and metal complex precursors; spectral data for all compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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