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Synthesis, structural characterisation and anti-proliferative activity of (κ^1-*C*)- and (κ^2-*C*,*S*)-Pt(II) complexes bearing thioether-functionalized N-heterocyclic carbenes

Julien Egly, Mathilde Bouché, Weighang Chen, Aline Maisse-François, Thierry Achard,* and Stéphane Bellemin-Laponnaz*[a]

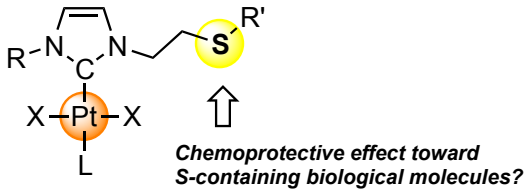
Abstract: A series of platinum(II) complexes, bearing thioether-functionalized N-heterocyclic carbene ligands has been synthesized and characterized. The hemilabile and reversible character (i.e. coordination/decoordination) of the sulfur moiety on these platinum complexes has been established by ligand displacement (addition of pyridine) or ligand abstraction (on silica gel). The chemical reactivity with glutathione has been investigated by NMR and mass spectrometry. Biological activities on various human cancer cells have been studied and these S-functionalized NHC-platinum complexes displayed moderate cytotoxicity activity.

Introduction

Despite all these years spent, cisplatin compound still remains the bestseller drug to fight several types of cancer (i.e. colorectal, head neck, lung, non-Hodgkin lymphoma, ovarian and testicular cancer).[1] Indeed, more than 50% of cancer tumours are currently cured with platinum-based drugs alone or with complementary treatment.[2,3] This includes few new platinum drugs (*e.g.* carboplatin, oxaliplatin) but their number is small compared to the thousands of Pt compound biologically tested so far.[4] Moreover, the main disadvantage of their therapeutic efficacy is the serious side effects and the potential emergence of cellular resistance.[5] Additionally, the undesired accumulation of platinum in organs is responsible of high level of nephrotoxicity, neurotoxicity and ototoxicity.[6] These toxicities are also amplified by the great affinity of platinum for sulfur containing molecule (cysteine, methionine, glutathione, metallothionein and albumin), which are highly abundant in the human body.[7]

Platinum-based drugs exert cytotoxic effects by binding the DNA through various mechanisms.[8] However, on the long way to first penetrate the targeted cell and then the nucleus, Pt complexes will inexorably meet potentially reactive functions including various sulfur-containing molecules.[7a] Consequently only a small quantity of Pt will finally reach the goal and induce cell death.[7b] In this purpose, cytoprotective sulfur-containing reagents/ligands have been largely investigated to reduce side effects.[9] For example, Borch and co-workers showed the chemoprotective effect of diethyldithiocarbamate sodium salt (NaDEDT) during cisplatin chemotherapeutic treatment.[10] The particularity of this ligand is to selectively remove platinum from thiol functionalities of different proteins but not from nucleotides involved in Pt-DNA adducts. Lately, platinum-drugs that include in their coordination sphere a S-donor ligand -that may act as chemoprotectant group- have been successfully investigated in chemotherapy and some of them showed promising results in clinical trials.[11] Oxaliplatin-like complexes containing bidentate hybrid N,S ligand, such as dichloro(2-methylthiomethylpyridine)Pt(II), were found to be promising cytotoxic agents.[12,13]

The necessity of discovering new metal-drugs with improved stability in physiological media is of importance. In this context, several groups highlighted the interest of N-heterocyclic ligands (NHCs) as new scaffold for drug design.[14] Various benefits were observed while using NHC ligands including: (i) the strong carbene–metal σ-bond enhances the stability of the NHC-metal complex, essential condition in physiological media, (ii) the stereoelectronic properties of the NHC may be finely tuned and (iii) high modularity is possible via simple synthetic pathways thus allowing the quick development of libraries of metal-NHC compounds.[15] The presence of the NHC also has a dramatic impact on the mode of action since several mechanistic studies suggest concurrent cell death mechanisms involving for example mitochondria in addition to classical cisplatin-based mechanisms.[16] Platinum NHC complexes of general formula [(NHC)PtX$_2$L] (X = halogen, L = nitrogen-containing ligand) have been highlighted as valuable candidate to fight cancer by Marinetti and co-workers in 2010.[17] Since then, numerous groups including us extended this family of compounds by introducing new substituents or functions through new synthetic strategies, with the aim of increasing efficiency, selectivity and reducing side effects of such Pt-NHC complexes.[18]



Scheme 1. General structure of the NHC Pt compounds.

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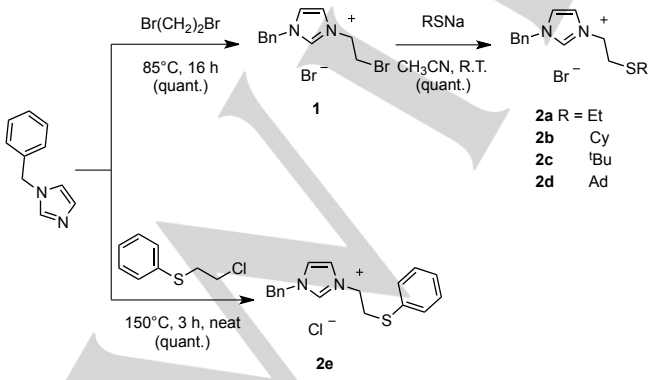
Interestingly, sulfur-containing NHC complexes have not been the subject of study in medicinal chemistry. Nevertheless, sulfur-functionalized NHC ligands (S-NHC) and their corresponding transition metal complexes have become a dynamic field of investigation. These studies are principally focused on their coordination chemistry and their use in catalysis and nothing is yet described for their use as a bioactive molecule.[19] In this paper, we report on the synthesis, characterisation and preliminary results on the biological effects of Pt complexes that contain thioether-functionalized NHCs (Scheme 1). These ligand systems are expected to bind tightly the platinum centre to stabilize the complex and on the other hand the labile thioether group is expected to provide a chemoprotective effect toward sulfur sites in biological media.

Results and Discussion

Synthesis of proligands ***2a-e*** *and the corresponding platinum complexes*

Several new S-functionalized imidazolium salts **2a-d** have been prepared starting from benzyl imidazole as displayed in Scheme 2. Reaction of benzyl imidazole in 1,2-dibromoethane at 85 °C gave the corresponding imidazolium salt precursor **1** in quantitative yield, which was next easily and quantitatively functionalized by reacting with the desired thiolate. The phenyl thioether imidazolium **2e** was synthesized in one step according to standard procedure. [20]

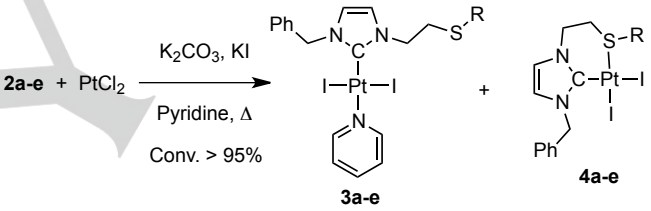
The NHC-platinum(II) complexes were readily prepared in a one-step process by reaction of the azolium precursor **2a-e** in the presence of one equivalent of $PtCl_2$ and excess of KI and K_2CO_3 in dry pyridine at 100 °C overnight (Scheme 3).[18g] [(NHC)PtI_2(pyridine)] complexes were obtained in moderate to good yield (47-71%) after purification by chromatography on silica gel. The formation of the (NHC)Pt-pyridine complexes **3a-e** was easily established by the disappearance of the resonances assigned to the 2*H*-imidazolium proton in the ^{1}H NMR spectrum and also by the appearance of a signal at δ 135–138 ppm in the ^{13}C NMR spectrum, which was assigned as the carbenic carbon.



Scheme 2. Synthesis of imidazolium precursors **2a-e**.

The analytical data (IR, HRMS, ^{1}H NMR) advocate for the coordination of NHC in a monodentate fashion. Indeed in the ^{1}H NMR spectrum both the methylene protons in α-position to N and S atom showed two sets of triplet signals in the vicinity of 3.3 and 4.4 ppm respectively, which is similar to those observed for free imidazolium salts **2a-e** in the range of 3.1 and 4.5 ppm. The structure of the pyridine complex was lately confirmed by X-ray diffraction studies (*vide infra*).

However, a meticulous analysis by proton NMR of the crude product before purification by column chromatography revealed the presence of a second platinum compound as minor product which was assigned as the (NHC)PtI_2 complex **4** with the carbene acting as a bidentate ligand. Indeed, ^{1}H NMR spectrum shows noticeable changes in signals of the thioether chain bound to the NHC and the complexity of the coupling pattern for both N-CH_2 and S-CH_2 protons suggests the coordination of the sulfur atom which renders those protons diastereotopic (see SI). The κ^2-*C,S* coordination mode was confirmed by X-ray analysis on suitable crystal (*vide infra*). The crude product ratio between **3** and **4** was 90:10 with the smallest thioether group (i.e., Et) whereas all other crudes contained less than 5 % of the minor compound **4**.



Product ratio (crude)

R = Et	90	:	10
R = Cy, tBu, Ad, Ph	>95	:	<5

Isolated yield:[a]

R = Et	47%	26%
Cy	63%	20%
*t*Bu	70%	<2%
Ad	71%	<2%
Ph	60%	<2%

Scheme 3. Synthesis of platinum thioether-functionalized NHC complexes **3**-**4** [a] isolated yield after purification by column chromatography on silica gel.

Interestingly, during the purification step, we have noticed that platinum complexes **3** partially decompose into complex **4** over silica. Indeed, the pyridine molecule is known to interact with acidic sites on the silica surface which occurs by a proton transfer from silanol to pyridine to form pyridinium species.[21] In our case, this protonation process coupled to the chelate effect might favour the coordination of the sulfur atom, which removes the pyridine from the metal center. The adsorption of pyridine through the silica gel makes then its displacement irreversible preventing any new coordination onto the platinum center. Thus, it was possible to isolate complexes **4a** and **4b** in 20-26% yield

as a white solid (Scheme 3). Both compounds were found to be poorly soluble in either $CDCl_3$ or DMSO-d_6 and only moderately soluble in acetone and dichloromethane. In the ^{13}C NMR spectra of the complexes, the resonance of the carbenic carbon is observed between 147 and 148 ppm which are in good agreement with literature values.[22] Here, the bulkiness of the thioether group plays a crucial role in the sulfur coordination to a metal center. In fact, larger groups, most likely because of their steric hindrance on sulfur atom, are less able to form the chelate in contrast to more flexible or smaller groups such as Cy or Et.
Curiously, after several hours in CD_2Cl_2, the solution of pure complexes **4a** (R = Et) evolved into a 1:1 mixture of complex **4a** and a new platinum specie as evidence by its ^1H and ^{13}C spectra. The ^1H NMR experiment performed after this time shows clearly new set of visible signals in several regions of the spectrum for CH_{imid} (doublet at 6.74 ppm, J = 2 Hz), CH_{2Benz} (singlet at 5.54 ppm) and CH_3 (triplet at 1.33 ppm J = 7 Hz) protons. It has been suggested that platinum thioether-functionalized NHC ligands exhibit dynamic hemilabile behaviour with multiple species coexisting in solution.[22] This character could involve a reversible de- and recoordination of the sulfur donor in a hemilabile fashion. The decoordination would result in the formation of a formally unsaturated metal center, which could be stabilized by dimerization. Additionally, the inversion at the sulfur atom could flip of the six-membered ring providing access to other chair- or boat-like conformations. Finally, the situation could be even more complicated due to the fact that the thioether function becomes a chiral center upon coordination. Consequently, it is not surprising to observe the formation of a new species after a few hours in CD_2Cl_2 solution for complex **4a**.

*X-ray diffraction studies of complexes **3c** and **4a**.*

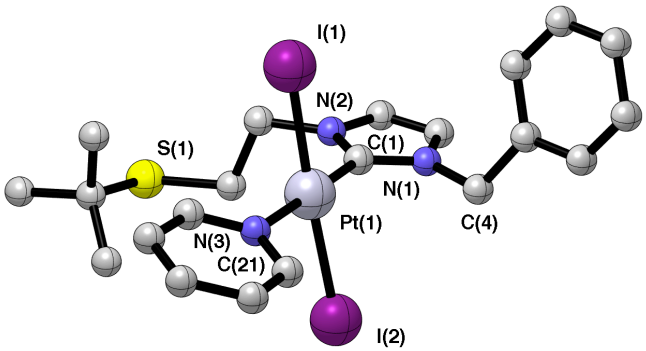


Figure 1. Molecular structure of the pyridine complex **3c**. Selected bond lengths [Å] and angles [°]: Pt(1)- C(1): 1.985(10); Pt(1)- I(1): 2.6041(8); Pt(1)-I(2): 2.6100(8); Pt(1)-N(3): 2.097(8); C(1)-Pt(1)-I(1): 90.0(3); C(1)-Pt(1)-I(2): 89.3(3); I(1)-Pt(1)-I(2): 177.30(2); C(1)-Pt(1)-N(3): 179.1(4); I(2)-Pt(1)-C(1)-N(1): -71.14; I(2)-Pt(1)-N(3)-C(21): 60.16.

By slow diffusion of diethyl ether into a chloroform solution of complex **3c** and by slow evaporation of a dichloromethane solution of **4a**, single crystals have been obtained and the molecular structures have been elucidated by X-ray diffraction analysis (Figures 1 and 2).[23] Pyridine complex **3c** displays the awaited coordination square-planar geometry where the pyridine ligand is *trans* to the N-heterocyclic carbene ligand. Both carbene-platinum and platinum-pyridine bond lengths are in accordance with literature reports with 1.985(10) and 2.6041(8) Å respectively.[18d, 18f-h, 18k-n, 24] The two iodide ligands adopt a *trans* geometry (I-Pt-I angle of 177.30°) and point perpendicularly toward the NHC ligand plane [Pt(1)-C(1)-N(1)-C(4), -0.3(14)°] or [Pt(1)-C(1)-N(1)-C(2), -179.8(8)°], a classical feature that has been observed in such complexes. [18d, 18f-h, 18k-n, 24]

For complex **4a**, the coordination geometry at the platinum center is distorted square planar. Coordination of the sulfur onto the metal generated a boat-shaped (Pt-C-N-C-C-S) chelate ring. The $C_{carbene}$–Pt bond length [Pt(1)-C(1) 1.976(12) Å] is within the range for such NHC–Pt(II) complexes. The Pt-S (Pt(1)-S(1) 2.290(3) Å) bond length is consistent with the average bond length of 2.27 Å reported by Hyun for various S-NHC platinum complexes derived from benzimidazole.[22] The strong *trans* influence of the NHC ligand is reflected in the lengthening of the Pt–I distance in *trans* disposition to the carbene ligand compared to the Pt–I distance *trans* to the S donor atom [2.6534(9) vs. 2.6127(9) Å].

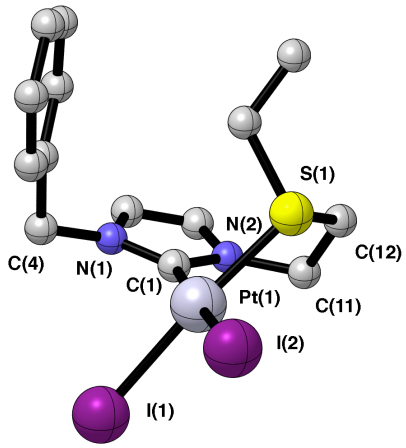
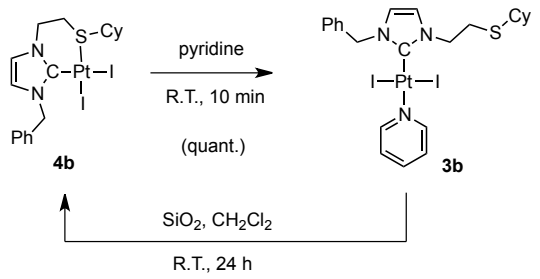


Figure 2. Molecular structure of (κ^2-*C,S*) complex **4a**. Selected bond lengths [Å] and angles [°]: Pt(1)-C(1): 1.976(12); Pt(1)-I(1): 2.6127(9); Pt(1)-I(2): 2.6534(9); Pt(1)-S(1): 2.290(3); C(1)-Pt(1)-S(1): 86.8(4); C(1)-Pt(1)-I(1): 91.5(3); C(1)-Pt(1)-I(2): 176.0(4); S(1)-Pt(1)-I(1): 174.20(10); S(1)-Pt(1)-I(2): 90.39(8); I(1)-Pt(1)-I(2): 91.63(3); N(2)-C(11)-C(12)-S(1): 52.3(13).

Reactivity of the platinum NHC complexes

The formation of the chelate from the pyridine complex demonstrates that the thioether moiety is able to displace one ligand from the coordination sphere. In order to get more insight into the labile character of the thioether, complex **4b** was dissolved in d_5-pyridine at 20 °C. The compound was quantitatively converted back to **3b** in less than 10 min as deduced from NMR data, (Scheme 4 and Fig S2) and no more evolution was then observed.[25] Interestingly, the bidentate complex **4b** could be regenerated in presence of SiO_2 in a

dichloromethane solution stirred for 24h; then, it is quantitatively recovered after filtration.



Scheme 4. Experiment on the lability of the Cy-S group in the presence of pyridine.

Glutathione (GSH), proteins and peptides that contain sulfur residue such as methionine or cysteine are considered as a major inactivation step for platinum-based drugs.[7a, 26] Numerous works have been done on its reaction with cisplatin showing in most cases its coordination to the complex through the thiol function.[27] The behaviour of the *S,C* chelate complex **4b** in presence of GSH was investigated by ^{1}H NMR in deuterated DMSO.[28] The platinum species was first dissolved in DMSO-d_6 and then the desired quantity of GSH was added to the solution and NMR spectra were recorded over the time. Interestingly, GSH can act as a monodentate ligand binding the platinum center via the cysteine thiolate but can also act as a bidentate ligand by binding the platinum through both the thiol and one of the amide nitrogen.[27d] Its ability allows the formation of a variety of possible GS-Pt adducts. Moreover, the presence of DMSO should increase the number of platinum species present in the mixture, but since DMSO is known to be easily displaced from the coordination sphere of platinum in the presence of a better donor ligand,[29] it is envisioned that glutathione will do

The initial reaction with GSH (1 equiv) took place rapidly (<30 min) to form a mixture of several species. The signals for the NH protons in the cysteine and glycine residues are shielded (8.35 and 8.23 ppm) with respect to free GSH (8.73 and 8.30 ppm, see SI, Fig. S1),[30] and no residual signals of free GSH are observed in this region (Fig. S3).

Both the chemical shift and the multiplicity of the cys-*β* protons are impacted in presence of the platinum complex (Fig. S4). Compared to free GSH the multiplet at 2.88 ppm may have shifted in be obscured by the large residual pick of water; in the same time the multiplet at 2.65 ppm seems to become a broad singlet at 2.7 ppm which might indicate a very different magnetic and chemical environment. In this region we observed as well a multiplet that would correspond to degraded complex **4b** in presence of dmso

The signal at 4.35 ppm corresponding to cys-*α* proton in free GSH was also shifted downfield, as well as the gly-*α* proton. The overall shift of GSH protons and more particularly those of cysteine residue advocate for coordination on the platinum center through the sulfur atom. The signals of the two protons from the NHC ring were also shifted downfield. At this stage it is difficult to conclude about which platinum species are present in solution since several scenarios could occur.[27a] It is noteworthy that no more evolution in the crude mixture was observed for the sample even after 72h of experiment.

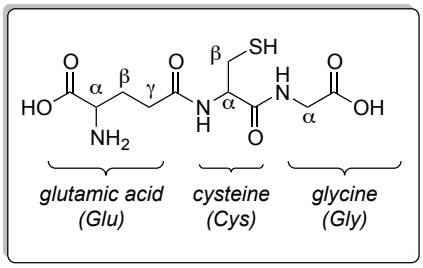
Interestingly, in the presence of an excess of glutathione (10 equiv.) the resulting H^1 NMR seems cleaner than previously observed with 1 equivalent (see SI, Fig. S5). Analysis of the resonance in the region of the cys-*α* protons suggests the formation of a new platinum species. A new NH gly-proton signal appeared as small doublet at 8.31 ppm, slightly deshielded compared to free GSH in solution (8.21 ppm). As observed previously, the two benzylic proton signals of the NHC are transformed in a large multiplet between 5.2 and 5.8 ppm (see SI, Fig. S6). Again, after 72h of experiment no notable evolution was observed for the sample.

MALDI-TOF experiments were conducted on **4b**/GSH (1/10 equiv) reaction in DMSO-d_6 after 72 hours of reaction, the mass spectrum display three peaks at *m/z* 1217.05, 1293.88 and 1473.09 (see SI, Fig. S7-10). Assignment was confirmed by isotopic distribution analysis (see SI, Fig. S11). The fragment ions correspond to a single species which is most likely a dinuclear complex of general formula $[\{(NHC)PtI\}_2(GSH)]^+$, thus confirming the GSH/Pt interaction (eq 1). Altogether, the analyses by NMR and mass spectrometry show that, despite the presence of a labile thioether group onto the NHC ligand, glutathione still displays a high affinity for the Pt center, most likely to generate Pt-S thiolate bond.

$$(NHC)PtI_2 + GSH \longrightarrow [(NHC)PtI]_2(GSH)^+ \quad \text{(eq 1)}$$

4b

GSH =



Antiproliferative effect

The cytotoxicity of complexes **3** and **4** on cancer cells was investigated on a panel of three human cancer cell lines namely HCT116 (human colorectal adenocarcinoma), PC3 (human prostate adenocarcinoma) and MCF7 (breast carcinoma). Half inhibitory concentrations (IC_{50}) induced by these compounds are displayed in Table 1. Cisplatin was used as reference for the studies.

Even though all determined IC_{50} values are higher than those measured for cisplatin, complexes **3-4** showed antiproliferative activities toward the three cell lines. The bulkiness of the substituent attached to the sulfur atom was found to influence the potency of the resulting complex. Increasing both the size and the lipophilicity of the thioether group increased the

cytotoxicity effect of the compound. Effectively, phenyl and adamantyl derivatives **3d** and **3e** showed the highest cytotoxic activity (IC_{50} up to 16 µM, Entry 6) for this series which are expected to promote greater cell uptake. These results are consistent with previous studies on platinum bearing bidentate O,S ligand.[32] The presence of adamantyl group so called "lipophilic bullet" onto platinum complex is known to be beneficial for cytotoxic activity.[33] This trend is verified in this platinum complexes series as S-Ad complex **3d** displayed better IC_{50} values than other alkyl groups.

Surprisingly, the monodentate complex **3c** containing the larger and more lipophilic group S-*t*Bu exhibited low cytotoxic activities (IC_{50} > 100 µM) compared to smaller and less lipophilic S-Et derivative **3a** (Entries 1 and 3).

The bidentate complex **4a** displayed a poor cytotoxic activity which is comparable to its corresponding monodentate derivative (with the exception of HCT116; Entries 1 & 2). Its poor cytotoxic activity does not appear to be related to the strength of the Pt-S bond as shown by the competition experiment but more surely might be due to low drug uptake induced by its low solubility rather than unduly stability of the Pt-S bond. Overall, the IC_{50} values do not vary massively, suggesting that the compounds could induce their cytotoxic effect through similar mechanisms.

Table 1. Half inhibitory concentrations (IC_{50} in µM) of the selected compounds against a range of cell lines.[a]

Entry	Complex	R	HCT116	MCF7	PC3
1	**3a**	**R = Et**	63.2 ± 0.1	130 ± 20	113 ± 9
2	**4a**	**R = Et**	118 ± 6	104 ± 1	161 ± 15
3	**3b**	**R = Cy**	37.3 ± 2.5	58.3 ± 2.0	43.5 ± 0.4
4	**3c**	**R = *t*Bu**	100.7 ± 0.1	172 ± 46	110 ± 3
5	**3d**	**R = Ad**	20 ± 2	52.4 ± 1.4	33.1 ± 3.7
6	**3e**	**R = Ph**	16.6 ± 1.3	44.5 ± 3.1	23.6 ± 0.6
cisplatin			3.7 ± 0.1	4.2 ± 0.7	3.1 ± 0.2

[a] After 72h of incubation; stock solutions in DMSO for all complexes; stock solutions in H_2O for *cisplatin*. MCF7 (breast carcinoma), HCT116 (colon cancer cells), PC3 (prostate adenocarcinoma).

Conclusions

A novel class of platinum(II) compounds based on bidentate thioether-functionalized NHC ligands κ^1-*C* or κ^2-*C,S* coordinated has been described and fully characterized. They have been prepared based on a straightforward synthesis that requires only three steps from the appropriate imidazole ring. Interestingly, the steric hindrance on the sulfur atom strongly influences its coordination mode to be monodentate κ^1-*C* when R group is large or bidentate κ^2-*C,S* when R group is small. The lability of the thioether moiety has been established by competition experiments which discarded an excessive protective effect on the platinum centre that could inhibit cytotoxic activity. Accordingly, the protective effect of the thioether moiety was not sufficiently robust to prevent the coordination of the GSH to the platinum center. These complexes displayed moderate cytotoxic activity although enhanced cytotoxicities were observed for more lipophilic compounds, which are expected to be linked to greater cellular uptake.

Experimental Section

Materials and methods. All manipulations were carried out using standard Schlenk techniques unless stated otherwise. Reagents were purchased from commercial chemical suppliers (mainly Acros, Aldrich, Alfa Aesar, TCI Europe and Strem) and used without further purification. Solvents were dried according to standard procedures. Pyridine employed during complexation reactions was distilled over calcium hydride and carefully stored under argon. Metal complexes were synthesized using distilled solvents. ^{1}H, ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 spectrometer. ^{13}C assignments were confirmed when necessary with the use of DEPT-135 experiments. ^{1}H and ^{13}C-NMR spectra were referenced using the residual solvent peak ($CDCl_3$: δ H = 7.26 ppm; δ C = 77.16 ppm; CD_2Cl_2: δ H = 5.32 ppm; δ C = 53.84 ppm;DMSO-d_6: δ H = 2.50 ppm; δ C = 39.52 ppm) at 295K. Chemical shifts δ are given in ppm whereas coupling constants J are stated in Hertz (Hz). The following abbreviations are used to classify the multiplicity of the observed signals: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, dd = doublet from doublet, dt = doublet from triplet, m = complex multiplet or broad signal, pyr = pyridine proton, imid = NHC alkene proton, Ar = aromatic protons. Positive mode electrospray ionization mass spectra (ESI-MS) were recorded on microTOF, Bruker Daltonics. Because of possible platinum carbide formation during combustion, Pt complexes such as those reported in this study are not easily amenable to accurate elemental analysis. X-Ray diffraction studies were carried out by Dr. Corinne Bailly at Institut de Chimie X-ray Facility of the University of Strasbourg. Crystal data were collected at 173 K using a MoKα graphite monochromated (λ = 0.71073 Å) radiation on a Nonius KappaCCD diffractometer. The structures were solved using direct methods with SHELXS97552 and refined against F2 using the SHELXL97 software.[34] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated according to stereochemistry and refined using a riding model in SHELXL97. CCDC 1570177 (for **3c**) to CCDC 1570178 (for **4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Synthesis of imidazolium salts precursors

1-benzyl-3-(2-bromoethyl)-1H-imidazol-3-ium bromide (1):

Precursor **1** was synthesized according to the procedure reported in literature and all data correspond to previously reported material.[35] A mixture of 1-benzylimidazole (3 g, 0.037 mmol) and 1,2-dibromobutane (40 mL) was heated at 85 °C for 15h. After cooling at room temperature, two phases were observed. The excess of 1,2-dibromobutane is removed under vacuum giving a white residue which was extracted with 40 ml of CH_2Cl_2 and filtered through celite. The solvent was removed to

give an egg shell solid. Yield: 98%. **^{1}H NMR** (300MHz, DMSO-d_6): δ 3.96 (t, *J* = 6 Hz, 2H, CH_2Br), 4.64 (t, *J* = 6 Hz, 2H, NCH_2), 5.48 (s, 2H, CH_2), 7.4 (m, 5H, CH_{benz}), 7.87 (m, 2H, CH_{imid}) and 9.4 (s, 1H, CH_{imid}) ppm.

1-benzyl-3-(2-(ethylthio)ethyl)-1*H*-imidazol-3-ium bromide (2a):

Precursor **1** (2 g, 5.8 mmol, 1 equiv) was dissolved in distillated acetonitrile (60 mL). Sodium ethanethiolate (0.5 g, 5.8 mmol, 1 equiv) was added, and stirring was continued for 15 hours at ambient temperature under argon. After this time, the volatiles were removed under reduced pressure. The solid residue was suspended in CH_2Cl_2 and filtered through celite. Volatiles were removed under reduced pressure and the resulting orange/brown oil is passed through a silica plug, first with dichloromethane (to remove traces of unreacted thiolate) and then with 90/10 DCM/MeOH mixture. The solvent was removed under reduced pressure to give an orange/brown oil. Yield: 99%. δ **^{1}H NMR** (300 MHz, $CDCl_3$) 1.24 (t, *J* = 7.4 Hz, 3H), 2.62 (q, *J* = 7.4 Hz, 2H, CH_2S), 3.06 (t, *J* = 6.3 Hz, 2H, CH_2S), 4.61 (t, *J* = 6.3 Hz, 1H, NCH_2), 5.54 (s, 2H, NCH_2), 7.13 (s, 1H, CH_{imid}), 7.50-7.36 (m, 6H, CH_{imid} + CH_{benz}) and 10.89 (s, 1H, CH_{imid}) ppm. **^{13}C NMR** (75MHz, $CDCl_3$) : δ 14.8 (CH_3), 26.3 (SCH_2), 32.1 (CH_2S), 49.5 ($PhCH_2$), 53.5 (NCH_2), 121.6 (CH_{imid}), 123 (CH_{imid}), 129 (2xCH_{benz}), 129.45 (3xCH_{benz}), 133.2 (C_{benz}) and 137.4 (CH_{imid}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 3439br, 3100m, 3000s, 2850m, 1559s, 1493w, 1455s, 1260w, 1146vs, 1080w, 864w, 713vs, 640m. **HRMS** (positive ESI) *m/z*, calcd for $[C_{14}H_{19}N_2S]^+$ calculated 247.1295, found 247.1263.

1-benzyl-3-(2-(cyclohexylthio)ethyl)-1*H*-imidazol-3-ium bromide (2b) :

Cyclohexanethiol (0.1 g, 0.86 mmol, 1.5 equiv), was dissolved in dry acetonitrile (7 mL). Sodium hydroxide (37 mg, 0.9 mmol, 1.5 equiv) in water (0.5 mL) was added, and the resulting mixture was stirred for 30 minutes at room temperature under argon. Then **1** (0.2 g, 0.58 mmol, 1 equiv) was added, and the solution was stirred for 15 hours at room temperature. After this time, the solvent was removed under vacuum and the solid residue was suspended in dichloromethane and filtered through celite. Volatiles were removed under reduced pressure and the resulting orange/brown oil is passed through a silica plug, first with dichloromethane (to remove traces of unreacted thiolate) and then with 90/10 DCM/MeOH mixture. Compound is obtained as orange oil after being concentrated. Yield: 99%. **^{1}H NMR** (300MHz, DMSO-d_6) : δ 1.86-1.1 (m, 10H, CH_2), 2.64 (m, 1H, SCH), 3.00 (t, *J* = 7 Hz, 2H, CH_2S), 4.35 (t, *J* = 7 Hz, 2H, NCH_2), 5.45 (s, 2H, $PhCH_2$), 7.83 (s, 1H, CH_{imid}), 7.84 (s, 1H, CH_{imid}) and 9.34 (s, 1H, CH_{imid}) ppm. **^{13}C NMR** (300MHz, $CDCl_3$) : δ 25.6 (CH_2), 25.8 (2xCH_2), 30.4 (2xCH_2), 33.6 (SCH), 44.0 (SCH_2), 50.0 (NCH_2), 53.6 ($PhCH_2$), 121 (CH_{imid}), 122.6 (CH_{imid}), 128.9 (2xCH_{benz}), 129.43 (3xCH_{benz}), 132.7 (C_{benz}) and 137.7 (CH_{imid}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 2900m, 1557s, 1447s, 1209m, 1163s, 757s, 713vs, 698vs, 611s, 465m. **MS** (ESI): m/z, $[M-Br]^+$ 301.17 (100).

1-benzyl-3-(2-(tert-butylthio)ethyl)-1H-imidazol-3-ium bromide (2c):

It was prepared following the same procedure of **2a** : Precursor **1** (2 g, 5.8 mmol, 1 equiv), was dissolved in distillated acetonitrile (60 mL). Sodium 2-methylpropane-2-thiolate (0.972 g, 8.66 mmol, 1.5 equiv) was added, and stirring was continued for 24 hours at ambient temperature under argon. After this time, the volatiles were removed under reduced pressure. The solid residue was suspended in CH_2Cl_2 and filtered through celite. Volatiles were removed under reduced pressure and the resulting orange/brown oil is passed through a silica plug, first with dichloromethane (to remove traces of unreacted thiolate) and then with 90/10 DCM/MeOH mixture. The solvent was removed under reduced pressure to give an orange/brown oil. Yield: 98%. **^{1}H NMR** (300MHz, $CDCl_3$) : δ 1.28 (s, 9H, CH_3), 3.09 (t, *J* = 6 Hz, 2H, CH_2S), 4.57 (t, *J* = 6 Hz, 2H, NCH_2), 5.56 (s, 2H, CH_2), 7.2 (s, 1H, CH_{imid}), 7.45-7.39 (m, 6H, CH_{imid}, CH_{benz}) and 10.79 (s, 1H, CH_{imid}) ppm. **^{13}C NMR** (75MHz, $CDCl_3$) : δ 29 (CH_2S), 26.3 (3xCH_3), 43.7 (SC), 50.5 ($PhCH_2$), 53.6 (NCH_2), 121.4 (CH_{imid}), 122.9 (CH_{imid}), 129 (2xCH_{benz}), 129.6 (2xCH_{benz}), 129.7 (CH_{benz}), 133 (C_{benz}) and 137.5 (CH_{imid}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 2900m, 1559s, 1456s, 1364s, 1208m, 1152s, 754w, 714s, 698vs, 643m. **HRMS** (positive ESI) *m/z*, calcd for $[C_{16}H_{23}N_2S]^+$calculated 275.1600, found 275.1576.

3-(2-(((1*R*,3*s*)-adamantan-1-yl)thio)ethyl)-1-benzyl-1*H*-imidazol-3-ium bromide (2d):

It was prepared following the same procedure of **2d:** Adamantane-1-thiol (0.73 g, 4.34 mmol, 1.5 equiv) dry acetonitrile (30 mL), Sodium hydroxide (0.17g, 4.34 mmol, 1.5 equiv) stirring for 48 hours at ambient temperature under argon. Orange/brown oil was obtained. Yield: 99%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.60 (br, 6H), 1.70 (br, 6H), 1.95 (br, 3H), 2.99 (t, *J* = 6 Hz, 2H, C*H*$_2$S), 4.48 (t, *J* = 6 Hz, 2H, NC*H*$_2$), 5.55 (s, 2H, PhC*H*$_2$), 7.32-7.39 (m, 4H, C*H*$_{benz}$, C*H*$_{imid}$), 7.45 (m, 2H, C*H*$_{benz}$), 7.57 (s, 1H, C*H*$_{imid}$) and 10.36 (s, 1H, C*H*$_{imid}$) ppm. **^{13}C NMR** (75MHz, $CDCl_3$) : δ 26.4 (C_{ad}), (3xC_{ad}), 29.6, 36 (3xC_{ad}), 43.4 (SC_{ad}), 46.7 (CH_2S), 50.7 (NCH_2), 53.42 ($PhCH_2$), 121.4 (CH_{imid}), 123 (CH_{imid}), 129 (2xCH_{benz}), 129.5 (2xCH_{benz}), 129.6 (CH_{benz}), 133 (C_{benz}) and 137.5 (CH_{imid}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 3500br, 3000s, 2870s, 1557m, 1498w, 1445m, 1163s, 1105m, 1039s, 815m, 745m, 706vs, 650s, 606m. **MS** (ESI): m/z, $[M-Br]^+$ 343.2 (100).

1-benzyl-3-(2-(phenylthio)ethyl)-1H-imidazol-3-ium chloride (2e):

Pure 1-Benzylimidazole (1.43 g, 9.06 mmol, 1 equiv) and 2-chloroethyl phenyl sulfide (1.34 ml, 9.06 mmol, 1 equiv) were placed in a Schlenk. The mixture was heated for 3 hours at 130 °C under argon, during this time the colorless mixture turned brown. After cooling, the brown oil was washed two times with 40 ml THF, which provoke its precipitation as a soft pale flesh solid. The pure product was obtained after chromatography (silica gel, CH_2Cl_2/CH_3OH 95:5) Yield: 97% **^{1}H NMR** (300MHz, DMSO-d_6) : δ 3.5 (t, *J* =7 Hz, 2H, CH_2), 4,39 (t, *J* =7 Hz, 2H, CH_2), 5.4 (s, 2H, CH_2), 7.43-7.23 (m, 10H, CH_{benz}), 7.77 (m, 1H, H_{imid}), 7.81 (m, 1H, CH_{imid}) and 9.32 (m, 1H, CH_{imid}) ppm. **^{13}C NMR** (75MHz, DMSO-d_6) : δ 32.2 (CH_2S), 48.4 ($PhCH_2$), 51.9 (NCH_2), 122.5 (CH_{imid}), 122.9 (CH_{imid}), 128.2 (CH_{benz}), 128.6 (2xCH_{benz}), 128.7 (CH_{benz}), 128.9 (4xCH_{benz}), 129(2xCH_{benz}), 134 (C_{benz}), 134.8 (C_{benz}) and 136.7 (CH_{imid}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}:3000m, 1559s, 1440m, 1352w, 1156s, 1117m, 1027m, 742vs, 713vs, 691vs, 487s. **MS** (ESI): m/z, $[M-Cl]^+$ 295.13(100).

General Procedure for the Synthesis of the Pyridine/NHC-S platinum complexes 3

The ligand precursor (Imidazolium halide, 1.1 equiv), $PtCl_2$ (1 equiv), NaI (10 equiv) and K_2CO_3 (10 equiv) were suspended under argon in anhydrous pyridine (10 mL). The mixture was sonicated during 10 minutes, heated overnight at 100 °C, then concentrated under reduced pressure, dissolved in CH_2Cl_2 and filtered through a celite plug. The residue was purified by a silica gel chromatography (gradient CH_2Cl_2/pentane 1/1, CH_2Cl_2) affording the complex as a yellow solid.

Compound 3a: Starting from 1-benzyl-3-(2-(ethylthio)ethyl)-1H-imidazol-3-ium bromide **2a** (100 mg, 0.305 mmol). Yield 66 mg (47%). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7 Hz, 3H), 2.70 (q, *J* = 7 Hz, 2H, S-CH_2), 3.25-3.28 (m, 2H, S-CH_2), 4.67-4.70 (m, 2H, N-CH_2), 5.73 (s, 2H), 6.61 (s, 1H_{imid}), 6.95 (s, 1H_{imid}), 7.31-7.39 (m, 6H), 7.50 (d, *J* = 7 Hz, 2H), 7.73 (t, *J* = 8 Hz, 1H) and 9.03 (d, *J* = 6 Hz, 2H_{Pyr}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.4 (*C*H_3), 26.4 (S-*C*H_2), 30.9 (S-*C*H_2), 51.0 (N-*C*H_2), 55.0 (N-*C*H_2), 120.2 (*C*H_{imid}), 121.8 (*C*H_{imid}), 125.1 (2 x *C*H_{pyr}), 128.5 (2 x *C*H_{pyr}), 129.00 (2 x *C*H_{Ar}), 129.37 (2 x *C*H_{Ar}), 135.4 (*C*$_{Ar}$), 136.5 (*C*-Pt), 137.6 (*C*H_{pyr}) and 153.90 (2 x *C*H_{pyr}). **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1603, 1456, 1445, 1419, 1222, 1069, 796, 721 and 687 cm^{-1}. **HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{19}H_{23}IN_3PtS$: 647.0301, found 647.0242.

Compound 3b: Starting from 1-benzyl-3-(2-(cyclohexylthio)ethyl)-1H-imidazol-3-ium bromide **2b** (100 mg, 0.262 mmol). Yield 136 mg (63 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.46-1.19 (m, 6H), 1.64-1.58 (m, 1H), 1.81-1.72 (m, 2H), 2.15-2.05 (m, 2H), 2.75-2.80 (m, 1H), 3.29-3.20 (t, *J* = 7 Hz, 2H, S-CH_2), 4.67 (t, *J* = 7 Hz, 2H, N-CH_2), 5.72 (s, 2H, N-CH_2), 6.60 (d, *J* = 2 Hz, 1H_{imid}), 6.96 (d, *J* = 2 Hz, 1H_{imid}), 7.43-7.29 (m, 5H), 7.50 (d, *J* = 7 Hz, 2H), 7.73 (t, *J* = 8 Hz, 1H) and 9.04 (d, *J* = 5 Hz, 2H_{pyr}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.8 (2 x *C*H_2), 26.3 (2 x *C*H_2), 29.5 (S-*C*H_2), 34.1 (2 x *C*H_2), 44.1 (*C*H), 51.6 (N-*C*H_2-*C*H_2-S), 55.0 (N-*C*H_2), 120.1 (*C*H_{imid}), 121.9 (*C*H_{imid}), 125.1 (2 x *C*H_{pyr}), 128.52 (*C*H_{Ar}), 128.99 (2 x *C*H_{Ar}), 129.36 (2 x *C*H_{Ar}), 135.5 (*C*$_{Ar}$), 136.1 (*C*-Pt), 137.6 (*C*H_{pyr}) and 153.9 (2 x *C*H_{pyr}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1606, 1445, 1421, 1224, 1067, 761, 727 and 689 cm^{-1}. **HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{23}H_{29}IN_3PtS$ 701.0771, found 701.0711.

Compound 3c: Starting from 1-benzyl-3-(2-(tert-butylthio)ethyl)-1H-imidazol-3-ium bromide **2c** (100 mg, 0.281 mmol). Yield 160 mg (71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.31-3.17 (m, 2H, S-CH_2), 3.96 (s, 2H, N-CH_2), 4.67-4.56 (m, 2H, N-CH_2), 6.84 (d, *J* = 2 Hz, 1H_{imid}), 6.94 (d, *J* = 2 Hz, 1H_{imid}), 7.38-7.27 (m, 1H), 7.73 (t, *J* = 8 Hz, 1H) and 9.03 (d, *J* = 5.0 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.4 (S-*C*H_2), 31.5 (3 x CH_3), 43.6 (*C*-*t*Bu), 51.6 (N-*C*H_2), 55.0 (N-*C*H_2), 120.2 (*C*H_{imid}), 121.8 (*C*H_{imid}), 125.1 (2 x *C*H_{pyr}), 128.5 (*C*H_{pyr}), 128.99 (2 x *C*H_{Ar}), 129.36 (2 x *C*H_{Ar}), 135.4 (*C*$_{Ar}$), 136.4 (*C*-Pt), 137.61 (*C*H_{Ar}), 153.90 (2 x *C*H_{pyr}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1606, 1448, 1420, 1224, 1153, 1069, 761, 740, 724 and 689 cm-1;**HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{21}H_{27}IN_3PtS$: 675.0614, found 675.0656.

Compound 3d: Starting from 3-(2-(((3s,5s,7s)-adamantan-1-yl)thio)ethyl)-1-benzyl-1H-imidazol-3-ium bromide **2d** (50 mg, 0.115 mmol). Yield 71 mg (70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.69 (m, 6H), 2.03 (m, 9H), 3.27-3.17 (m, 2H, S-CH_2), 4.66-4.59 (m, 2H, N-CH_2), 5.72 (s, 2H, N-CH_2), 6.59 (d, *J* = 2 Hz, 1H_{imid}), 6.92 (d, *J* = 2 Hz, 1H_{imid}), 7.42-7.27 (m, 5H), 7.50 (d, *J* = 7 Hz, 2H), 7.73 (t, *J* = 8 Hz, 1H) and 9.04 (d, *J* = 7 Hz, 2H_{pyr}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.9 (S-*C*H_2), 30.0 (3 x *C*H), 36.3 (3 x *C*H_2), 43.7 (3 x *C*H_2), 45.8 (*C*H), 52.2 (N-*C*H_2-*C*H_2-S), 54.9 (N-*C*H_2), 120.2 (*C*H_{imid}), 121.7 (*C*H_{imid}), 125.0 (2 x *C*H_{pyr}), 128.5 (*C*H_{Ar}), 128.98 (2 x *C*H_{Ar}), 129.4 (2 x *C*H_{Ar}), 135.4 (*C*$_{Ar}$), 136.3 (*C*-Pt), 137.6 (*C*H_{pyr}), 153.93 (2 x *C*H_{pyr}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1605, 1445, 1420, 1222, 1067, 761, 727 and 689 cm^{-1}. **HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{27}H_{33}IN_3PtS$: 753.1084, found 753.1068.

Compound 3e: Starting from 1-benzyl-3-(2-(phenylthio)ethyl)-1H-imidazol-3-ium bromide **2e** (50 mg, 0.151 mmol). Yield 78 mg (60 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.68 (t , *J* = 8 Hz, 2H, S-CH_2), 4.70 (t , *J* = 8 Hz, 2H, N-CH_2), 5.71 (s, 2H, N-CH_2), 6.58 (d, *J* = 2 Hz, 1H, CH_{imid}), 6.87 (d, *J* = 2 Hz, 1H, CH_{imid}), 7.20-7.24 (m, 1H), 7.42-7.27 (m, 7H), 7.50 (d, *J* = 7 Hz, 2H), 7.55 (d, *J* = 7 Hz, 2H) , 7.73 (t, *J* = 8 Hz, 1H) and 8.94 (d, *J* = 5.1 Hz, 2H_{pyr}) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* 32.8 (S-*C*H_2), 50.3 (N-*C*H_2-*C*H_2-S), 55.0 (N-*C*H_2), 120.3 (*C*H_{imid}), 121.8 (*C*H_{imid}), 125.0 (2 x *C*H_{pyr}), 126.6 (*C*H_{Ar}), 128.55 (*C*H_{Ar}), 129.0 (2 x *C*H_{Ar}), 129.33 (2 x *C*H_{Ar}), 129.39 (2 x *C*H_{Ar}), 130.05 (2 x *C*H_{Ar}), 134.9 (*C*$_{Ar}$), 135.3 (*C*$_{Ar}$), 136.8 (*C*-Pt), 137.6 (*C*H_{pyr}) and 153.94 (2 x *C*H_{pyr}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1604, 1446, 1419, 1227, 1071, 758, 726 and 686 cm^{-1}.**HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{23}H_{23}IN_3PtS$ 695.0301, found 695.0309.

General Procedure for the Synthesis of the (*κ*^{2}-*S,C*)NHC-platinum complexes 4

Complex **4** were obtained as byproduct during the synthesis of complex **3** and had been isolated by chromatography on silicagel in a DCM/MeOH mixture.

Compound 4a: Starting from 1-benzyl-3-(2-(ethylthio)ethyl)-1H-imidazol-3-ium bromide **2a** (100 mg, 0.305 mmol). Yield 55 mg (25%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 1.04 (br, 3H, CH_3), 2.12 (br, 3H, S-CH_2 + S-CH_2-CH_3), 3.04 (br, 1H, S-CH_2), 4.20 (br, 1H, N-CH_2), 4.50 (br, , N-CH_2), 5.35 (overlapped with solvent signal, N-CH_2), 6.02 (br, 1H, N-CH_2), 6.95-7.02 (m, 2H, CH_{imid}), 7.30-7.540 (m, 5H, CH_{Ar}) and 7.53-7.42 (m, 2H, CH_{Ar}) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1559, 1454, 1419, 1234, 1216, 1051, 724, 727 and 688 cm^{-1}. **HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{14}H_{18}IN_2PtS$: 567.9879, found 567.9834.

Compound 4b: Starting from 1-benzyl-3-(2-(cyclohexylthio)ethyl)-1H-imidazol-3-ium bromide **2b** (100 mg, 0.262 mmol). Yield 40 mg (20%). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 1.48-1.06 (m, 6H) peak overlap with grease, 2.01-1.61 (m, 4H), 2.22 (td, *J* = 13 and 3 Hz, 1H, S-CH_2), 2.38-2.26 (m, 1H, S-C*H*), 3.08-2.89 (m, 1H, S-CH_2), 4.24-4.18 (dt, *J* = 15 and 3 Hz, 1H, N-CH_2), 4.51 (ddd, *J* = 15, 13 and 3 Hz, 1H, N-CH_2), 5.58 (d, *J* = 15 Hz, 1H, N-CH_2), 5.78 (d, *J* = 15 Hz, 1H, N-CH_2), 6.84 (d, *J* = 2 Hz, 1H, CH_{imid}), 7.01 (d, *J* = 2 Hz, 1H, CH_{imid}) and 7.43-7.33 (m, 5H) ppm. **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 25.5 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 30.3 (CH_2) 31.0 (CH_2), 32.2 (S-CH_2), 33.8 (S-CH), 49.9 (N-CH_2), 56.5 (N-CH_2), 121.0 (CH_{imid}), 121.8 (CH_{imid}), 129.15(CH_{Ar}), 129.32(2 x CH_{Ar}), 129.53(2 x CH_{Ar}), 135.68 (C$_{Ar}$) and 148.27 (C-Pt) ppm. **FTIR**: ν max(pure, diamond orbit)/cm^{-1}: 1458, 1444, 1419, 1261, 1234, 1218, 1077, 1057, 1027, 800, 724, 715 and 688 cm^{-1}. **HRMS** (positive ESI) *m/z* [M-I]: calculated for $C_{18}H_{24}IN_2PtS$: 622.03473, found 622.03776.

In vitro cytotoxic activity. These tests were performed at Institut de Chimie des Substances Naturelles CNRS – UPR2301, Gif-Sur-Yvette, France. Samples were prepared by dissolution of the compounds in DMSO at stock concentration of 10 mM. Cells were plated in 96-well tissue culture plates in 200 µL complete medium at a density of 1000-2500 cells per well and treated 24 hours later with 2 µL of compounds using a Biomek 3000 automation workstation (Beckman-Coulter). Controls received the same volume of the appropriate vehicle (DMSO, 1% final volume). After 72 hours exposure, MTS reagent (CellTiter 96 Aqueous One, Promega) was added and incubated for 3 hours at 37 °C: the absorbance was monitored at 490 nm and results expressed as the inhibition of cell proliferation calculated as the ratio [(1 - (OD490 treated/OD490control)) x 100] in triplicate experiments after subtraction of the blank without cells. Positive controls (cells incubated with a reference drug at its IC_{50} concentration) were routinely added to check the responsiveness of cells. For IC_{50} determination [50% inhibition of cell proliferation], cells were incubated for 72 hours following the same protocol with compound concentrations ranging 5 nM to 100 µM in separate duplicate experiments.

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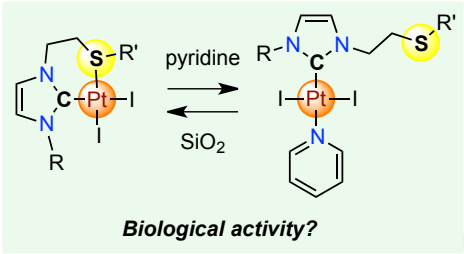
Entry for the Table of Contents

FULL PAPER

Platinum(II) complexes, bearing thioether-functionalized N-heterocyclic carbene ligands, have been synthesized and characterized. The effect of thioether on the biological activities of the platinum centre has been investigated on various cancer cell lines.



NHC complexes

J. Egly, M. Bouché, W. Chen, A. Maisse-François, T. Achard, and S. Bellemin-Laponnaz**

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Synthesis, structural characterisation and anti-proliferative activity of (κ^1-*C*)- and (κ^2-*S,C*)-Pt(II) complexes bearing thioether-functionalized N-heterocyclic carbenes