inorganics

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Dibromo- and Dichlorotriphenylphosphino N-Acyclic Carbene Complexes of Platinum(II)—Synthesis and Cytotoxicity

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Abstract: Some new dichloro- and dibromotriphenylphosphino isonitrile and *N*-acyclic (NAC) carbene complexes of platinum(II) were synthesized, starting from suitable dinuclear precursors. The reaction of cyclohexylisonitrile with *trans*-[Pt(μ-X)X(PPh_3)]$_2$, followed by the addition of *N*,*N*-diethylamine afforded the corresponding N-acyclic carbene (NAC)derivatives *cis*-[PtX_2(PPh_3)(NAC)] in 61–64% isolated yield. The *cis* geometry was attributed based on the comparison with known structures. The stability of the complexes in pure DMSO, DMSO/H_2O, and DMSO/$NaCl_{aq}$ mixtures was evaluated. While pure DMSO, as well as DMSO/H_2O, did not affect the nature of either dichloro- or dibromo-compounds, dibromo derivatives were not stable in the presence of chloride ions. Since a high concentration of chloride ions is essential to perform in vitro cell assays, only dichlorocomplexes were tested as cytotoxic agents against HepG2 and human tumor cells. Among the tested complexes, NAC derivatives showed a moderate effect on MSTO-211H.

Keywords: Platinum(II) bromo- and chlorocomplexes; carbene ligands; triphenylphosphine; chloro-bromo metathesis; cytotoxicity

Citation: Farasat, A.; Labella, L.; Di Paolo, M.L.; Dalla Via, L.; Samaritani, S. Dibromo- and Dichlorotriphenylphosphino N-Acyclic Carbene Complexes of Platinum(II)—Synthesis and Cytotoxicity. *Inorganics* **2023**, *11*, 365. https://doi.org/10.3390/inorganics11090365

Academic Editor: Wolfgang Linert

Received: 27 July 2023
Revised: 28 August 2023
Accepted: 7 September 2023
Published: 8 September 2023

1. Introduction

Since the first discovery in 1964 of the anticancer activity of cisplatin [1] and its subsequent introduction into the drug market in the Seventies [2–5], hundreds of new metal-based drugs have been synthesized and studied. Limiting the bibliographic SciFinder© search to platinum-based anticancer agents that appeared in the literature in 2022, more than 150 reviews can be found, showing that cisplatin-derived metal drugs are still a hot subject. As a matter of fact, although cisplatin-based chemotherapy is very effective against some kinds of oncological diseases, it has many drawbacks in terms of undesired side effects [6,7]. Moreover, some cancer cells are intrinsically resistant or can develop acquired resistance to cisplatin [8–13]. The first structural analogues synthesized to overcome these limits strictly resembled cisplatin [14–17], and some of them are still commonly used to heal certain tumors. Afterwards, platinum complexes whose structures are significantly different in ligands, metal oxidation state, and geometry from that of the original drug, were prepared and their anticancer properties were described [18–33].

In recent years, we focused on the synthesis and biological studies of many platinum-based complexes endowed with antiproliferative properties [34–42]. Such investigations allowed us to conclude that the presence of a triphenylphosphine ligand can promote cell uptake and, in many cases, provide modes of action against cisplatin-resistant cancer cells. The *trans*-[$PtCl_2$(PPh_3)(L)] (L = *N*,*N*-dialkylamine) [36,42] and [PtCl(PPh_3)(L∧L´)]

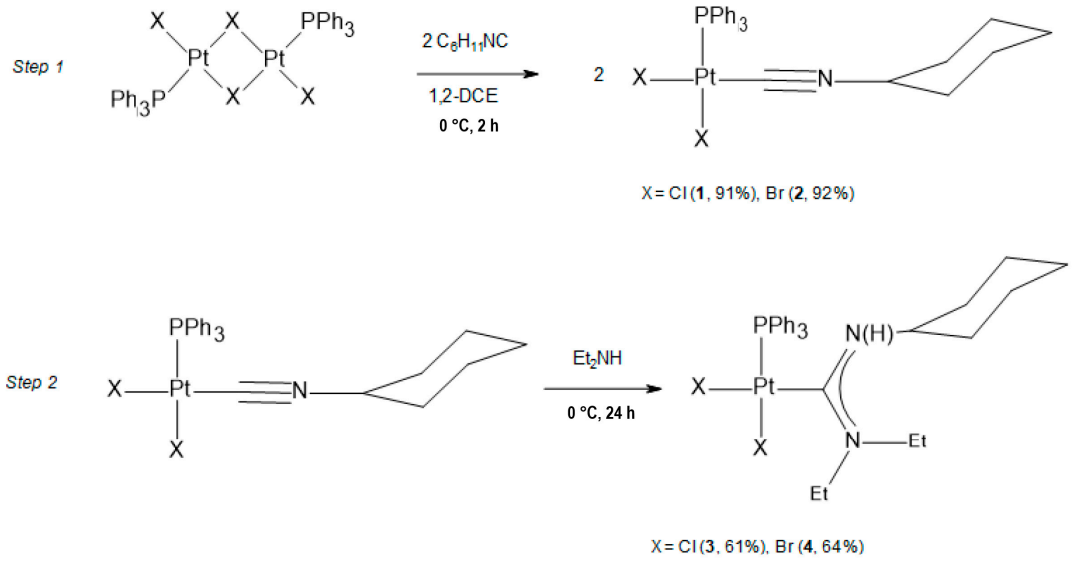
(L∧L´= chelating oxime ligand) [38,41] represent interesting examples of such complexes. More in detail, the mechanism of action of *trans*-[$PtCl_2(PPh_3)(L)$] (L = *N*,*N*-dialkylamine) was investigated [42] and the ability to interfere with the catalytic activity of topoisomerase II was evidenced. Since this enzyme is known to play an important role in the occurrence of resistance, the inhibitory effect observed was considered responsible for overcoming the resistance. Analogously, the study of the mode of action of [$PtCl(PPh_3)$(L∧L´)] (L∧L´= chelating oxime ligand) [38] on cisplatin-resistant cell lines evidenced the capacity to depolarize the transmembrane mitochondrial potential, as well as the ability to produce reactive oxygen species inside the cells. Interestingly, this behavior was observed for many metal complexes carrying triphenylphosphine and/or triphenylphosphonium residues and for some cationic lipophilic N-heterocyclic carbene platinum complexes [43,44]. More recently we have described the synthesis of some [$PtX_2(PPh_3)$(NAC)] complexes (NAC = N-Acyclic Carbene ligand; X = Cl, Br) [34,35], both stable in DMSO/H_2O solutions and thus good candidates for biological investigations. The interest of these systems arises from the observation that (i) carbene metal complexes have shown great potential in the field of anticancer compounds [45–47], thus an N-heterocyclic carbene (NAC) ligand and a triphenylphosphine ligand on the same platinum center could exert a synergistic effect and (ii) the availability of platinum(II) dihalocomplexes differing in the leaving group would allow a direct comparison of its role in the biological properties. Indeed; some examples are described [48,49] where changing the leaving group allows for modulation of the properties of the complex. We hereby describe the preparation of two novel [$PtX_2(PPh_3)$(NAC)] complexes; discuss their stability in the standard conditions for in vitro cell assays and evaluate their cytotoxic effect on human tumor cells.

2. Results and Discussion

2.1. Synthesis of Complexes [$PtX_2(PPh_3)(Et_2NCN(H)C_6H_{11})$]

The synthesis of the title compounds was carried out according to known procedures [34,35], in two steps (Scheme 1) starting from [Pt(μ-X)X(PPh_3)] [50]. Briefly, the suitable dinuclear precursor was reacted with cyclohexyl isocyanide, affording in all cases a single product, to which a *cis* geometry was assigned, in strict analogy with similar compounds [34,35]. *cis*-[$PtX_2(PPh_3)(CNC_6H_{11})$] (X= Cl, **1**; Br, **2**) were recovered, after the usual work-up procedures, in 91–92% yield (Scheme 1, step 1). In the IR spectra of **1** and **2** a strong absorption peak was observed around 2230 cm^{-1} for both compounds, indicating the coordinated isonitrile. Moreover, the nature of the intermediates was clear when observing the ^{13}C NMR spectra, where signals around 160 ppm were attributed to the isonitrile carbon atom. Finally, ^{31}P- and ^{195}Pt NMR spectra afforded for both compounds a single signal, with $^1J_{P\text{-}Pt}$ coupling constants of about 3330–3340 Hz. In the second step, *N*,*N*-diethylamine was added and the corresponding *cis*-NAC derivatives **3** (X = Cl) and **4** (X = Br) were obtained in a 61–64% yield (Scheme 1, step 2).

A complete spectroscopic characterization (Figures S1–S12) was carried out for all the unprecedented complexes prepared For ease of comparison, ^{31}P- and ^{195}Pt NMR main signals for complexes **1**–**4** are reported in Table 1. For both chloride- and bromido derivatives a very good agreement with data previously collected for similar compounds [34,35,51,52] was observed. The carbene nature of the obtained compounds was evident in the $^1J_{P\text{-}Pt}$ coupling constants (around 4000 Hz) observed in both ^{31}P- and ^{195}Pt NMR spectra. In the IR spectra, the strong absorption around 2230 cm^{-1} was no longer observed, while a typical absorption band around 1550 cm^{-1} appeared and was ascribed to the carbene functional group. The carbene carbon atom was observed, in the ^{13}C NMR spectrum, around 170 ppm.



Scheme 1. Synthesis of cyclo-Hexylisocyanide- and NAC complexes.

Table 1. The ^{31}P- and ^{195}Pt NMR data for complexes **1**–**4**.

Complex	^{31}P NMR δ ppm ($^{1}J_{P\text{-}Pt}$, Hz)	^{195}Pt NMR δ ppm ($^{1}J_{P\text{-}Pt}$, Hz)
1	8.4 (3410)	−4120 (3410)
2	9.0 (3346)	−4402 (3346)
3	8.3 (4092)	−4126 (4092)
4	9.3 (4020)	−4187 (4020)

As already noticed in the case of the analogous systems, since triphenylphosphine NAC complexes are characterized by a rigid backbone, most hydrogen atoms in the aliphatic portion of the molecule are not chemically equivalent and afford, in the ^{1}H NMR spectrum, a series of peculiar multiplet signals, each integrating as one hydrogen atom. As an example, the 5.1–1.3 ppm spectral zone of complex **4** ^{1}H NMR spectrum is reported in Figure 1.

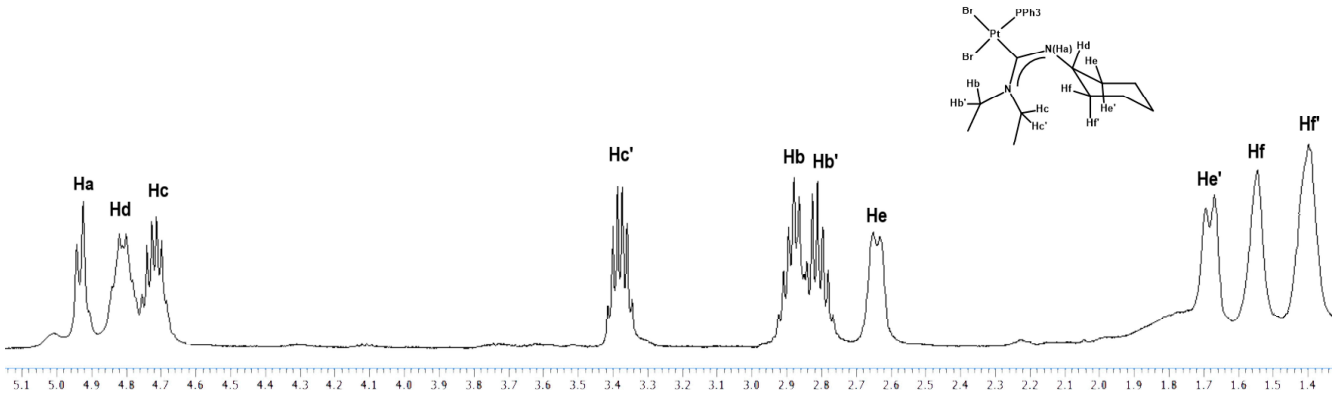


Figure 1. The ^{1}H NMR spectrum (expansion) of complex **4**.

The NH residue of NAC (Figure 1, Ha) and the methyne group of cyclohexyl moiety (Hd) afford two multiplets at 4.93 and 4.81 ppm, respectively, with a $^{3}J_{H\text{-}Pt}$ of 72 Hz for NH. The two methylene groups of diethylamine moiety and the two methylene groups of cyclohexyl residue close to Hd afford eight distinct multiplet signals, each integrating as one hydrogen atom (Hb-c and He-f in Figure 1). The remaining aliphatic hydrogen atoms of cyclohexyl moiety, as well as the two methyl groups of diethylamine residue, resonate in

the 1.30–0.88 ppm spectral zone, affording superimposed multiplet signals. The rigidity of the NAC derivatives was well evident in the ^{13}C NMR spectra as well, where a signal for each carbon atom of the N-acyclic carbene residue was observed. Elemental analysis was satisfactory for all the samples.

2.2. Stability of Complexes

DMSO/H_2O. Complexes **1**–**4** are not soluble in water or ethanol, but they are well soluble in dimethylsulfoxide (DMSO). Although DMSO is commonly used in biological studies to dissolve samples, its coordinating behavior towards many metal centers cannot be ignored. In the case of platinum(II), DMSO shows a very good affinity as a soft S-coordinating ligand towards the metal center, thus competition between DMSO and other ligands can be observed when it is used to dissolve complexes. The potential alteration of the complexes' nature and/or of their activity in DMSO and DMSO/water solutions [53,54], makes a stability check necessary each time DMSO is used. In the case of triphenylphosphine complexes **1**–**4**, the stability in DMSO and DMSO/H_2O mixtures can be conveniently checked by ^{31}P NMR spectroscopy since the complexes originating from the substitution of isonitrile or NAC ligands by DMSO (*cis*-[$PtX_2(PPh_3)$(DMSO)], X = Cl, Br) are known [50]. Complex **4** was chosen as representative of the prepared complexes and was used to carry out the stability tests. The maximum amount of water that can be added to a DMSO solution of **4** (10 mg in 1 mL) without precipitation of the complex was determined by subsequent additions of aliquots of water (20 µL) to the DMSO solution until the solid started to form (120 µL). For the stability tests, first, a solution of **4** (10 mg) in DMSO (1 mL) was inserted into an NMR tube and analyzed *via* ^{31}P NMR spectroscopy at different time spans (t = 0, 6, and 24 h). A single signal was always observed at 9.11 ppm, and no traces of the substitution byproducts were observed. In a further experiment, 60 µL of water were added to 1 mL of solution (10 mg of **4** in 1 mL DMSO) and spectra were registered after 0, 6, and 24 h. Again, a single signal was observed at 9.11 ppm, with no traces of decomposition nor substitution byproducts.

DMSO/H_2O/NaCl. The concentration of chloride ions in culture media commonly used to grow cells for in vitro biological tests is usually very high. As an example, MEM and RPMI culture media, used in the biological tests of the present work, contain chloride ions about 125 and 109 mM, respectively. Since metal complexes are tested usually in a concentration range between 1 and 20 µM, a chloride/substance molar ratio of at least 545 can be estimated. Considering the coordinating properties of chloride ions and their high affinity towards platinum, in the case of bromocomplexes, it is necessary to test their behavior in the presence of chloride ions, to exclude metathesis reactions that would change the nature of tested substances. Preliminarily, a solubility test was carried out as previously described above for water, using a 1 M NaCl aqueous solution instead of pure water. In these conditions, precipitation was observed after adding 100 µL of solution. The sample for NMR was then prepared by adding 80 µL of NaCl solution to 1 mL of a DMSO solution of **4** (10 mg). In these conditions, NaCl concentration was 80 mM and the concentration of the metal complex was 12.5 mM, with a [Cl^-]/[4] molar ratio of 6.4. ^{31}P NMR spectra registered after 0, 6, and 24 h are reported in Figure 2.

As can be easily seen in Figure 2, the signal attributed to **4**, initially observed at 9.11 ppm, slowly disappears, while two new signals are observed at 8.57 and 8.29 ppm. After 24 h the original signal at 9.11 ppm is no longer present, while the signal at 8.57 ppm is the main one. This last signal was ascribed to *cis*-[$PtCl_2(PPh_3)(Et_2NCN(H)C_6H_{11})$] (**3**), by comparison with a standard sample in the same mixture of solvents. The experiment showed that [$PtBr_2(PPh_3)$(NAC)] complexes are not stable in the presence of chloride ions, even when [Cl^-]/[$PtBr_2(PPh_3)$(NAC)] molar ratio is much lower than that commonly used in in vitro tests. On the basis of these results, only dichloro derivatives were used to test their cytotoxicity.

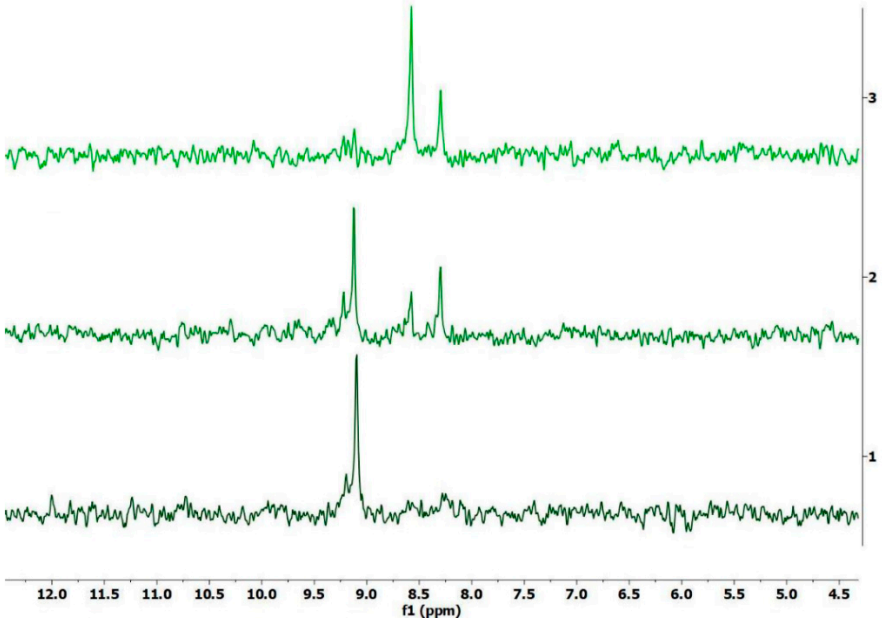


Figure 2. The ^{31}P NMR spectra of DMSO/H_2O/NaCl solution of **4** after 0 (dark green), 6 (green), and 24 h (light green). Satellite signals for $^{1}J_{P\text{-}Pt}$ are omitted.

2.3. Cytotoxic Effect

The isocyanide and carbene platinum(II) dichlorocomplexes **1** and **3** were tested for their cytotoxicity against two human tumor cell lines, HepG2 (hepatocarcinoma) and MSTO-211H (biphasic mesothelioma), along with the structurally related **5**–**8** [35]. All assayed complexes are reported in Figure 3. Cisplatin was taken as a reference drug.

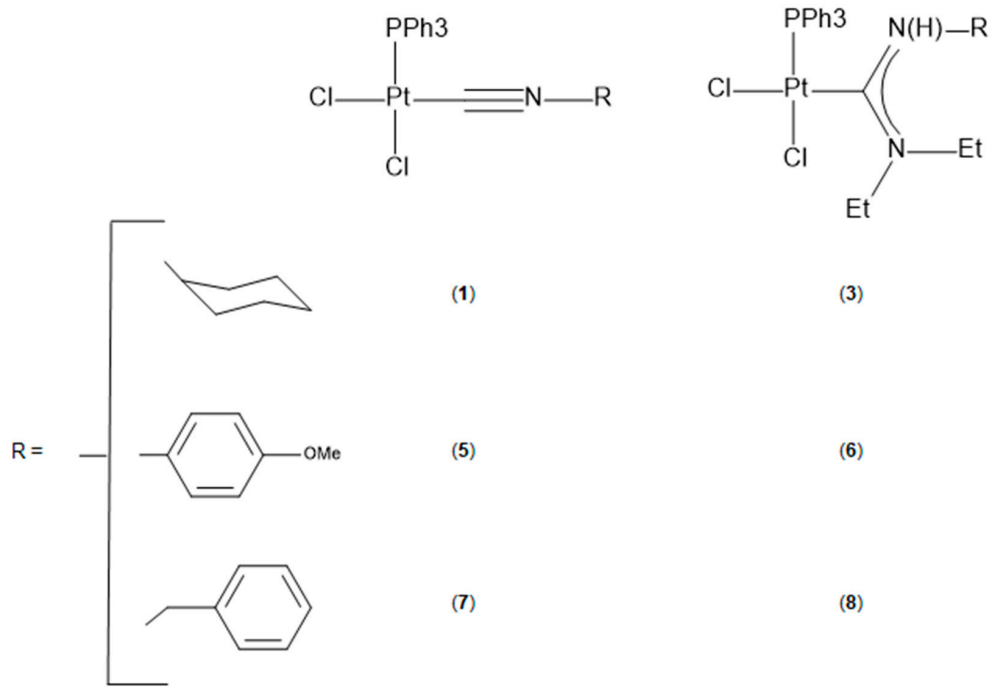


Figure 3. [$PtCl_2(PPh_3)$(CNR)] and [$PtCl_2(PPh_3)$(NAC)] complexes tested for their cytotoxic effect on human cell lines.

The percentage of cell viability after incubation for 72 h in the presence of 20 μM test compound was calculated, with respect to untreated control culture.

The obtained results (Table 2) indicate a higher sensitivity towards the test derivatives of MSTO-211H than HepG2 cells. Interestingly, in both cell lines, the viability in the presence of **3**, **6,** and **8** appears lower than that observed in cells treated with the corresponding **1**, **5,** and **7**, thus suggesting the carbene moiety is more effective than isocyanide in inducing a cytotoxic effect.

Table 2. Cell viability after 72 h of incubation in the presence of 20 μM **1,3,5–8**.

Compound	Cell Viability (% at 20 μM) [a]	
	HepG2	MSTO-211H
1	99 ± 1	54 ± 6
3	57 ± 12	2.6 ± 1.8 (4.0 ± 0.9) [b]
5	93 ± 6	87 ± 11
6	79 ± 15	24 ± 4 (9.4 ± 1.5) [b]
7	64 ± 9	43 ± 1
8	59 ± 7	38 ± 10
cisplatin	(0.6 ± 0.1) [b]	(1.4 ± 0.1) [b]

[a] Data are expressed as a percentage of viable cells with respect to untreated control culture. [b] GI_{50} values, that is, the concentration (μM) of the compound able to cause 50% cell death with respect to a control untreated cell culture. The values are the mean ± SD of at least three independent experiments in duplicate.

For the most cytotoxic **3** and **6**, the GI_{50} value, i.e., the concentration able to induce 50% cell death, was further obtained by incubating the most sensitive MSTO-211H cells in the presence of different concentrations of test compounds. Interestingly, the calculated values, shown in the bracket in Table 2, are both in the low micromolar range, even if they are significantly higher than those observed for the reference drug, pointing to a moderate cell effect for the tested complexes.

3. Conclusions

Following a simple synthetic protocol four novel complexes $[PtX_2(PPh_3)(CNC_6H_{11})]$ (X = Cl,**1**; Br, **2**) and $[PtX_2(PPh_3)(NAC)]$ complexes (X = Cl, **3**; Br, **4**) were prepared starting from suitable dinuclear derivatives. The complexes were characterized and their stability was evaluated under experimental conditions similar to those usually used to carry out biological tests in vitro. While all the complexes were stable in the presence of pure DMSO and DMSO/H_2O mixtures, bromo derivatives underwent halide substitution in the presence of chloride ions. The Cl/Br metathesis was complete in 24 h, even when chloride ion concentration was about tenfold lower than that usually employed during the in vitro tests. These data prompted us to investigate solely the chlorocomplexes for the cytotoxicity on human cell lines. It has to be underlined that, while the stability in DMSO and/or water is commonly described in works dealing with the biological activity of halometal complexes [48,49,55], the stability in the presence of chloride ions is not frequently discussed [56,57]. Since in physiological conditions as well as in vitro cell assays a high concentration of chloride ions cannot be avoided, our results suggest always testing the halocomplexes' stability towards chloride ions before studying their biological properties. The carbene derivatives were found capable of inducing a higher cytotoxic effect than the corresponding isocyanides.

4. Materials and Methods

General chemical syntheses were carried out under an inert (Ar) atmosphere, if not otherwise stated. The solvents used were purified and dried following usual procedures [58,59]. Solid, commercially available reagents were used with no further purification. Dinuclear precursors *trans*-$[Pt(\mu\text{-}X)X(PPh_3)]_2$ (X = Cl, Br) were prepared according to described procedures. [50] Samples of **5–8** were prepared according to the described procedures [35]. Cyclohexyl isocyanide was purchased from ™Merck and used without further purification. *N*,*N*-Diethylamine was distilled over KOH and filtered over dry alumina immediately before use. An elemental analyzer "vario MICRO CUBE" CHNOS was used for elemental

analysis. IR spectra were acquired on an Agilent "Cary 630" spectrometer, equipped with an ATR accessory. The following abbreviations were used to describe absorption peak ($\tilde{\nu}$, cm^{-1}) intensities and shapes: s = strong; m = medium; w = weak; br = broad; sh = shoulder. ^{1}H-, $^{13}C\{^{1}H\}$-, $^{31}P\{^{1}H\}$-, and $^{195}Pt\{^{1}H\}$ NMR spectra were recorded on JEOL YH 400 MHz and JEOL CZR 500 MHz spectrometers; $CDCl_3$ solutions were used (™Deutero GmbH, stored over Ag), if not otherwise stated. When ^{31}P NMR spectra were registered in non-deuterated solvents, a sealed capillary containing C_6D_6 was inserted into the sample to allow instrumental lock. Chemical shifts (δ ppm) are referred to $Si(CH_3)_4$ for ^{1}H, H_3PO_4 (85% in D_2O) for ^{31}P and H_2PtCl_6 for ^{195}Pt. The following abbreviations were used to describe observed signals: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quadruplet, and m = multiplet.

4.1. Synthesis of [$PtX_2(PPh_3)(CN\,C_6H_{11})$] (X = Cl, Br)

In a Schlenk tube equipped with a magnetic stirrer a cooled (0 °C) suspension of *trans*-[Pt(μ-X)X$(PPh_3)]_2$ [50] (0.200–0.500 g) in 1,2-DCE (10–15 mL) was treated, under stirring, with a solution of cyclohexyl isocyanide in the same solvent ([*c*-HexNC]/[Pt] = 2.0 molar ratio). The mixture was warmed (25 °C) and a clear, yellow solution was obtained (2 h). The reaction was followed by ^{31}P NMR. As soon as a clear solution was obtained, two signals were observed at 12.3 ppm ($^{1}J_{PPt}$ = 2980 Hz, 22%) and 8.41 ppm ($^{1}J_{PPt}$ = 3424 Hz, 78%), with the less intense one slowly converting into the other (12 h). Most of the solvent was removed under vacuum and the residue was treated with *n*-heptane (25–30 mL). A waxy-oily solid precipitated, which turned into a colorless powder after cooling (0 °C) and stirring (12 h). The solid was recovered by filtration in air, washed with *n*-heptane (2 × 3 mL), and dried at reduced pressure. For each complex the yield, the elemental analysis, and the spectroscopic (IR and NMR) characterizations are reported.

***Cis*-[$PtCl_2(PPh_3)(CNC_6H_{11})$] (1)**. 0.243 g ($3.81 \times 10^{-4}$ mol, 91%). El. Anal. Calcd $C_{25}H_{26}Cl_2NPPt$, %: C 47.1, H 4.1, N 2.2, Found, %: C 46.8, H 3.8, N 2.1. I.R. (ATR, $\tilde{\nu}$, cm^{-1}): 3055 w, 2930 w, 2860 w, 2231 s (stretching N≡C), 1482 m, 1436 s, 1321 w, 1257 w, 1184 w, 1097 s, 998 m, 927 w, 864 w, 747 m, 709 m, 692 s. ^{1}H NMR: 7.86–7.37 (m, 15H, H_{arom}), 3.38 (m, 1H, $CH_2C\underline{H}CH_2$), 2.02–1.17 (m, 10H, cyclohexyl). ^{13}C NMR: 160.1, 134.6 (d, J = 11 Hz), 131.6, 131.2 (d, J =60 Hz), 128.6 (d, J = 12 Hz), 55.1, 31.3, 24.6, 22.5. ^{31}P NMR: 8.4 ($^{1}J_{PPt}$ = 3410 Hz). ^{195}Pt NMR: −4120 ($^{1}J_{PPt}$ = 3410 Hz).

***Cis*-[$PtBr_2(PPh_3)(CNC_6H_{11})$] (2)**. 0.600g ($8.27 \times 10^{-4}$ mol, 92%). El. Anal. Calcd $C_{25}H_{26}Br_2NPPt$, % C 41.3, H 3.6, N 1.9; Found, % C 40.9, H 3.6, N 1.9. IR (ATR, $\tilde{\nu}$, cm^{-1}): IR (ATR, ν, cm^{-1}): 3590–3283 w, 3046w, 2929 m, 2856 w, 2675 w, 2578 w, 2502 w, 2225 s (stretching N≡C), 1772 w, 1652 w, 1559 w, 1480 m, 1434 s, 1313 w, 1183 w, 1098 s, 996 w, 920 w, 863 w, 746 s, 691 s. ^{1}H NMR: 7.73–7.69 (m, 6H, H_{arom}), 7.50–7.42 (m, 9H, H_{arom}), 3.31 (m, 1H, CNCH), 1.63–1.53 (m, 4H cyclohexyl), 1.35–1.20 (m, 6H cyclohexyl). ^{13}C NMR: 162.0, 134.7 (d, J = 11 Hz), 131.7, 129.2 (d, J =60 Hz), 128.5 (d, J = 12 Hz),55.0, 31.3, 24.7, 22.5. ^{31}P-NMR: 9.0 ($J_{P\text{-}Pt}$ = 3346 Hz). ^{195}Pt NMR: −4402 ($J_{P\text{-}Pt}$ = 3346 Hz).

4.2. Synthesis of [$PtX_2(PPh_3)(Et_2NCN(H)C_6H_{11})$] (X = Cl, Br)

In a Schlenk tube equipped with a magnetic stirrer a solution of the suitable [$PtX_2(PPh_3)$(CNR)] (0.180–0.400 g) in 1,2-DCE (10–15 mL) was cooled (0 °C) and slowly treated with a solution of *N*,*N*-diethylamine (Et_2NH) in 2 mL of the same solvent ([Et_2NH]/[Pt] = 2.0 molar ratio), under stirring. The temperature was slowly raised (25 °C) and stirring was maintained for 24 h. The reaction was followed by ^{31}P NMR, checking the disappearance of the precursor's signal and the appearance of a new signal, generally characterized by a bigger $^{1}J_{P\text{-}Pt}$ coupling constant (4000 Hz). After concentrating the solution under vacuum, *n*-heptane (20–30 mL) was added at 0 °C, under vigorous stirring. A waxy solid precipitated, which was converted into a colorless powder upon prolonged stirring (12 h). The suspension was filtered under vacuum in air, the solid was washed with *n*-heptane (2 × 3 mL) and dried under vacuum. For each complex the yield, the elemental analysis, and the spectroscopic (IR and NMR) characterizations are reported.

***Cis*-[$PtCl_2(PPh_3)(Et_2NCN(H)C_6H_{11})$]** (**3**) 0.151 g ($2.02 \times 10^{-4}$ mol, 61%). El. Anal. Cald. $C_{29}H_{37}Cl_2N_2PPt{\cdot}2H_2O$,%: C 46.7, H 5.5, N 3.7, Found: C 46.7, H 5.4, N 3.5. I.R. (ATR, $\widetilde{\nu}$, cm^{-1}): 3297 w, 3055 w, 2929 m, 2853 w, 2223 m, 1552 s (stretching C = N), 1482 w, 1435 s, 1378 w, 1260 w, 1206 w, 1157 w, 1096 s, 998 w, 892 w, 801 w, 746 s, 692 s. ^{1}H NMR: 7.81–7.26 (m,15H, H_{arom}), 5.09 (s,1H, $^3J_{H\text{-}Pt}$ = 60 Hz, NH), 4.76 (m, 2H, J = 6.9 Hz, $CH_2C\underline{H}CH_2$+ $CH_3C\underline{H}HNH$), 3.38(m, 1H, J = 6.9 Hz, $CH_3CH\underline{H}NH$), 2.92 (m, 2H, J = 6.9 Hz, $CH_3C\underline{H}'_2NH$), 2.65(m, 1H, J = 6.9 Hz, $CH_2CHC\underline{H}H$), 1.94 (m, 1H, $CH_2CHCH\underline{H}$), 1.68(m, 1H, $C\underline{H}'H'CHCH_2$), 1.63–0.80 (m, 13H, $CH'\underline{H}'(C\underline{H}_2)_3$ + CH_3). ^{13}C-NMR: 173.4, 134.5 (broad), 131.1, 128.2 (d, $J_{C\text{-}P}$ = 12 Hz), 130.3 (d, $^1J_{C\text{-}P}$ = 70 Hz), 58.4, 53.0, 41.5, 33.9, 33.4, 25.3, 25.2, 25.1, 13.2, 12.4.^{31}P NMR: 8.3 ($^1J_{PPt}$= 4092 Hz). ^{195}Pt NMR: −4126($^1J_{PPt}$ = 4092 Hz).

***Cis*-[$PtBr_2(PPh_3)(Et_2N(H)CNC_6H_{11})$]** (**4**) 0.142 g ($1.46 \times 10^{-4}$ mol, 64%). El. Anal. Cald. $C_{29}H_{37}Br_2N_2PPt{\cdot}2C_2H_4Cl_2$, %: C 39.7, H 4.6, N 2.8. Found: C 39.6, H 4.3, N 3.1. IR (ATR, ν, cm^{-1}): 3478 w, 3306 w, 3057 w, 2927 m, 2852 m, 1972 w, 1899 w, 1826 w, 1550 s (stretching C = N), 1434 s, 1376 m, 1158 w, 1096 s, 997 m, 893 w, 746 s, 694 s. ^{1}H-NMR: 7.80–7.25 (m, 15H, H_{arom}), 4.93 (m, 1H, $^3J_{H\text{-}Pt}$ = 72 Hz, NH), 4.81 (m, 1H, J = 6.9 Hz, $CH_2C\underline{H}CH_2$), 4.71(m, 1H, J = 6.9 Hz, $NC\underline{H}HCH_3$), 3.39 (m, 1H, J = 6.9 Hz, $NCH\underline{H}CH_3$), 2.92–2.73 (2m, 2H, $NC\underline{H}'_2CH_3$), 2.63 (m, 1H, J = 6.9 Hz, $C\underline{H}HCHCH_2$), 1.70 (m, 1H, $CH\underline{H}CHCH_2$), 1.54 (m, 1H, $CH_2CHC\underline{H}'H'$), 1.40 (m, 1H, $CH_2CHCH'\underline{H}'$), 1.24 (m, 2H, c-Hex), 1.11 (t, 3H, NCH_2CH_3), 1.01 (m, 4H, c-Hex), 0.94 (t, 3H, $NCH'_2CH'_3$). ^{13}C-NMR: 174.6, 134.8 (d, J = 11 Hz), 131.04, 128.2 (d, $J_{C\text{-}P}$ = 12 Hz), 130.5 (d, $^1J_{C\text{-}P}$ = 66 Hz), 58.0, 52.9, 41.4, 33.7, 33.5, 25.3, 25.1, 25.0, 13.0, 12.3.^{31}P NMR: 9.3 ($^1J_{P\text{-}Pt}$ = 4020 Hz). ^{195}Pt NMR: −4187 ($^1J_{Pt\text{-}P}$ = 4020 Hz).

4.3. Biological Evaluation

4.3.1. Cell Cultures

HepG2 (human hepatocarcinoma, ATCC, HB-8065) were grown in MEM (Merck M0894) containing 2.2 g/L $NaHCO_3$. MSTO-211H (human biphasic mesothelioma, ATCC, CRL-2081) were grown in RPMI 1640 (Merck R6504) containing 1.5 g/L $NaHCO_3$ and supplemented with 2.38 g/L Hepes, 0.11 g/L pyruvate sodium, and 2.5 g/L glucose.

A 10% heat-inactivated fetal bovine serum (Merck F7524), 100 U/mL penicillin, 100 µg/mL streptomycin, and 0.25 µg/mL amphotericin B (Merck A5955) were added to the media. Cells were maintained at 37 °C in a humid atmosphere of 5% carbon dioxide in the air.

4.3.2. Inhibition Growth Assay

To evaluate the percentage of viability, cells were seeded in 24-well plates at a density of 3–4 × 10 ^{4} and cultured at 37 °C in standard conditions. After 24 h, 20 µM concentration of the tested compound was added, and cells were cultured for a further 72 h. To evaluate the GI_{50} values, defined as the concentration (µM) of complex able to induce 50% cell death with respect to a control untreated culture, after 24 h of cell growth in standard conditions, different concentrations of tested compound (0.5, 1, 5, 10, 15, and 20 µM) or cisplatin (0.05–5 µM) were added and cells were incubated for 72 h. The GI50 values were obtained by non-linear regression analysis, fitting the standard four-parameter logistic curve to the data, by using the Sigma Plot version 9.0 (Jandel Scientific, San Rafael, CA, USA).

Cell viability was determined by trypan blue exclusion assay. All experiments were performed in duplicate and repeated for at least three times.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/inorganics11090365/s1, Figure S1: ^{1}H NMR spectrum of complex **1**; Figure S2: ^{31}P NMR spectrum of complex **1**; Figure S3: ^{195}Pt NMR spectrum of complex **1**; Figure S4: ^{1}H NMR spectrum of complex **2**; Figure S5: ^{31}P NMR spectrum of complex **2**; Figure S6: ^{195}Pt NMR spectrum of complex **2**; Figure S7: ^{1}H NMR spectrum of complex **3**; Figure S8: ^{31}P NMR spectrum of complex **3**; Figure S9: ^{195}Pt NMR spectrum of complex **3**; Figure S10: ^{1}H NMR spectrum of complex **4**; Figure S11: ^{31}P NMR spectrum of complex **4**; Figure S12: ^{195}Pt NMR spectrum of complex **4**.

Author Contributions: Conceptualization, S.S., L.L. and L.D.V.; methodology, A.F. and M.L.D.P.; data analysis and evaluation data, L.L., S.S., L.D.V. and M.L.D.P.; writing—original draft preparation, L.L., S.S. and L.D.V.; writing—review and editing, L.L., S.S. and L.D.V.; supervision, L.L., S.S. and L.D.V.; funding acquisition, L.L., S.S. and L.D.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Pisa University, Fondi di Ateneo 2022 and 2023 and by University of Padova, Dotazione Ordinaria Ricerca (DOR) 2022.

Data Availability Statement: The data presented in this study are available in Supplementary Materials.

Acknowledgments: Pisa University (Fondi di Ateneo 2022 and 2023) and Consorzio Interuniversitario di Ricerca in Chimica dei Metalli nei Sistemi Biologici (CIRCMSB) are gratefully acknowledged. Thanks are due to Chiara Palestini for preliminary experiments.

Conflicts of Interest: The authors declare no conflict of interest.

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