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Dibromo–Isonitrile and N-acyclic Carbene Complexes of Platinum(II): Synthesis and Reactivity

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Abstract: A series of dibromo-N-acyclic (NAC) carbene complexes of platinum(II) were synthesized, starting from *trans*-[Pt(μ-Br)Br(PPh_3)]$_2$ and according to a protocol previously optimized for the preparation of analogous chlorinated compounds. In the first step of the synthesis, the ring opening of the dinuclear precursor was carried out using suitable isonitrile ligands, while the following step consisted of the addition of *N*,*N*-diethylamine to the products obtained in the first step. The two reactions were separately investigated, and attention was given to the differences between brominated and chlorinated systems.

Keywords: platinum(II) bromocomplexes; isocyanide ligands; carbene ligands; triphenylphosphine

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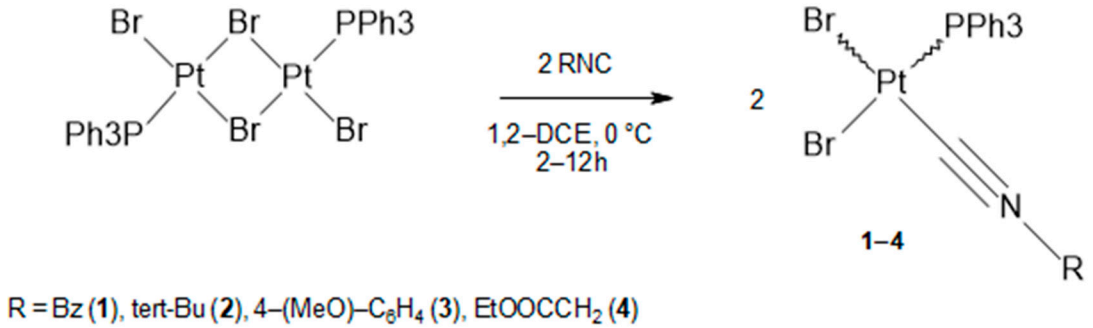
1. Introduction

In the context of our studies about platinum complexes with antiproliferative properties [1–6], we have been searching for new scaffolds to outline compounds capable of circumventing platinum resistance phenomena [7,8]. Among the complexes prepared, those bearing a triphenylphosphino ligand proved capable of affecting mitochondria, and their modes of action often proved effective on cisplatin resistant cell lines. This prompted us to design many [$PtCl_2$(PPh_3)(L)] complexes, where the PPh_3 ligand was maintained in the coordination sphere of the metal, while neutral ligands L were varied, affording libraries of compounds with modulable biological properties. We have recently prepared systems where L was a N-acyclic carbene (NAC) of platinum(II) [9]. The syntheses were carried out starting from the dinuclear precursor *trans*-[Pt(μ-Cl)Cl(PPh_3)]$_2$ [10], which was reacted with suitable isocyanide (RNC) ligands, affording *cis*-[$PtCl_2$(PPh_3)(CNR)] (R = 4-$MeOC_6H_4$, CH_2Ph). The isocyanido complex was then reacted with a secondary amine R_2NH, to afford the NAC product of addition to the coordinated isonitrile functional group. The reaction was chemoselective towards addition and stereoselective in both steps, since only *cis* carbene complexes were obtained. It was also shown that when particularly nucleophilic alicyclic amines (pyrrolidine, morpholine and piperidine) were used, ionic products were obtained, arising from the substitution of a chlorido ligand. The obtained derivatives showed a good solubility and stability in dimethylsulfoxide (DMSO) solution; thus, their antiproliferative properties are now under evaluation. In addition to the neutral ligands, the leaving groups as well can play an important role in modulating the properties of anticancer complexes [11,12]. Considering the wide applications described for carbene metal complexes in both bioinorganics [13–30] and catalysis [31–44], we hereby describe the synthesis of new [$PtBr_2$(PPh_3)(CNR)] and [$PtBr_2$(PPh_3)(NAC)] compounds, in order to compare their properties with those of their chlorinated counterparts.

2. Results and Discussion

2.1. Synthesis of Isocyanide Complexes [$PtBr_2(PPh_3)(CNR)$]

The preparation of isonitrile derivatives [$PtBr_2(PPh_3)(CNR)$] was carried out according to the reaction depicted in Scheme 1. The dinuclear brominated precursor was prepared according to a convenient reported procedure, starting from the easily available [$PtCl_2(NCMe)_2$] [45] (see Supplementary Material for the synthesis), while the chosen isonitrile ligands were commercially available.



Scheme 1. Synthesis of isonitrile complexes **1**–**4**.

The ring-opening reaction of the dinuclear precursor was carried out in 1,2-dichloroethane (1,2-DCE) and was followed by TLC or ^{31}P nuclear magnetic resonance (NMR) spectroscopy. The isonitrile ([ligand]/[Pt] = 2.0 molar ratio) was dissolved in 1,2-DCE and the addition was made at 0 °C to avoid any further substitution by the nucleophile. In all cases, the initially orange suspension turned into a light yellow, clear solution in a few hours and the chromatographic or spectroscopic analysis evidenced the disappearance of the precursor and the presence of products in solution. Only in the case of tert-butylisocyanide, a [ligand]/[Pt]= 3.0 molar ratio was necessary to obtain the complete conversion of the precursor, occurring anyway within a few hours at room temperature. The reaction is directed by the *trans* effect exerted by the phosphine ligand, so that the expected kinetic product is *trans*-[$PtBr_2(PPh_3)(CNR)$]. However, being both isonitrile and triphenylphosphine π-acid ligands, the initial formation of the kinetic product can be followed by a fast isomerization process in solution, to afford a mixture of isomers, where the *cis* complex is the most abundant [9]. Meanwhile, for the analogous chloro-complexes [9], we observed the complete conversion of the kinetic ring-opening products into *cis*-[$PtCl_2(PPh_3)(CNR)$]; in this case, a mixture of the two geometric isomers was obtained in most of the studied cases, both during the reaction and on the isolated samples, most likely for the higher steric hindrance of *cis* bromide ligands. Isolated yields in *cis*,*trans* complexes were quite good and the composition of the equilibrium mixtures could be conveniently studied using ^{31}P NMR spectroscopy.

Isolated yields and percentage compositions at equilibrium in solution are indicated in Table 1. *Cis*,*trans* percentages were calculated by integrating the corresponding ^{31}P NMR signals in $CDCl_3$ solution.

Table 1. Isolated yields and isomeric compositions ($CDCl_3$, equilibrium) of [$PtBr_2(PPh_3)(CNR)$].

Complex	R	% Yield	*cis*,*trans* % [a]
1	Bz	93	59/41
2	Tert-Bu	98	85/15
3	4-(MeO)C_6H_4	75	76/24
4	CH_2COOEt	83	100/0

[a] Calculated by integration of ^{31}P NMR signals in solution.

The coordination of isonitrile ligands to the platinum center was evidenced in ^{31}P NMR spectra by the presence of satellites, with $^{1}J_{P\text{-}Pt}$ coupling constants within 3310–3380 Hz for both isomers, in agreement with previous results [2,9,45]. In the ^{195}Pt NMR spectra, doublet signals were observed in the −4180−−4600 ppm spectral zone, with the same $^{1}J_{PPt}$ coupling constants measured in the ^{31}P NMR spectra. In comparing these values with those previously observed for the chlorinated counterparts [9], a shift towards high fields is evident, coherently with the substitution of chlorido ligands with bromido ones [46–52]. Coordination was evident in the infrared (IR) spectrum as well, where very strong absorption bands were observed around 2200–2240 cm^{-1}, with an hypsochromic shift of about 90–100 cm^{-1} from the position of the same band in the free ligand [53].

In the case of complex **3**, well-shaped single crystals were obtained by slow diffusion of pentane vapors into a chloroform solution of the compound, and the molecular structure was determined using single crystal X-ray diffraction. The structure of **3** is reported in Figure 1, while the most significant bond lengths and angles are listed in Table 2. The compound crystallized in the triclinic *P*-1 space group, and two independent molecules were observed in the unit cell, together with a molecule of chloroform. The coordination is square planar around the metal and the configuration is *cis*, with small deviations from ideality. The structure is in very good agreement with that previously described [9] for the chlorinated analogue *cis*-[$PtCl_2(CNC_6H_4(OCH_3))(PPh_3)$], where the most important differences in bond lengths have been ascribed to the larger size of bromido ions.

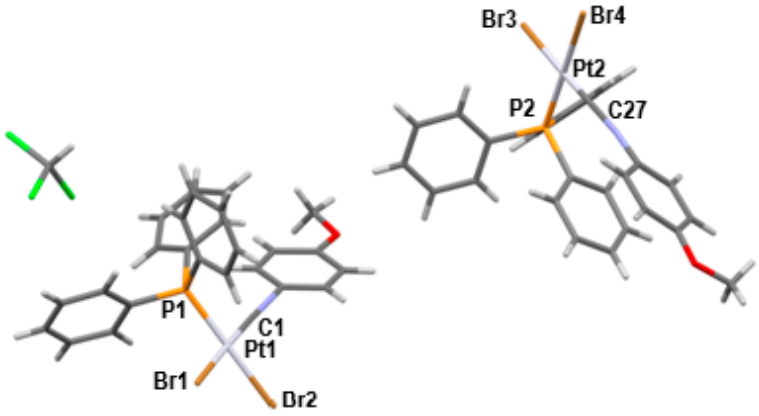


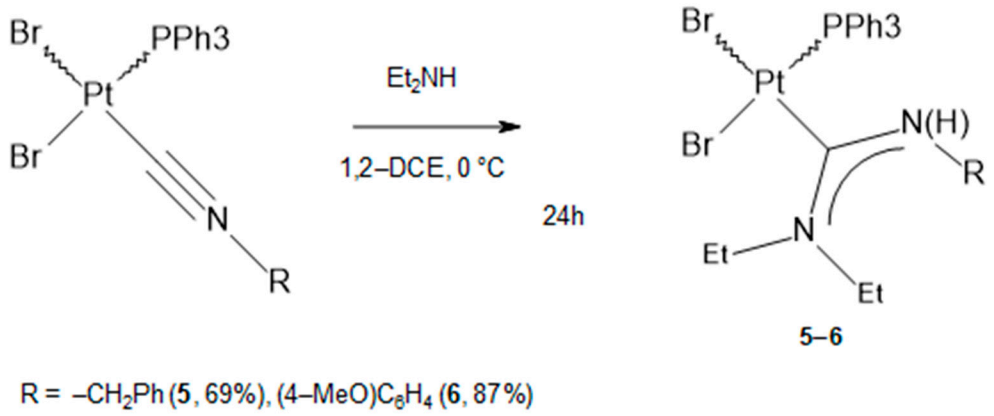
Figure 1. Structure of complex **3**. Dark gray: carbon; Light gray: hydrogen; Green: chlorine; Brown: Bromine; Yellow: phosphorus; White: platinum; Blue: nitrogen; Red: oxygen.

Table 2. Most significant bond lengths and angles for complex **3**.

Bond lengths (Å)			
Pt1-C1	1.910 (5)	Pt1-P1	2.2563 (12)
Pt1-Br2	2.4317 (6)	Pt1-Br1	2.4886 (6)
Pt2-C27	1.897 (5)	Pt2-P2	2.2536 (10)
Pt2-Br3	2.4358 (5)	Pt2-Br4	2.4754 (5)
Bond angles (°)			
P1-Pt1-Br2	89.77 (3)	P1-Pt1-Br1	179.32 (3)
C1-Pt1-P1	92.48 (16)	C1-Pt1-Br2	177.19 (17)
C1-Pt1-Br1	86.88 (16)	C1-N1-C2	179.4 (6)
C27-Pt2-Br4	88.43 (13)	C27-Pt2-Br3	177.91 (14)
C27-Pt2-P2	91.74 (13)	C27-N2-C28	172.5 (5)
P2-Pt2-Br4	179.69 (3)	P2-Pt2-Br3	88.86 (3)
Br3-Pt2-Br4	90.986 (19)	Br2-Pt1-Br1	90.86 (3)

2.2. Synthesis of Carbene Complexes [$PtBr_2(PPh_3)(Et_2N(H)CNR)$]

The synthesis of the NAC derivatives was carried out in 1,2-DCE solution, according to an experimental procedure previously applied to the successful preparation of chlorinated models. In each experiment, the chosen isocyanide complex was dissolved in 1,2-DCE and treated with a solution of *N*,*N*-diethylamine in the same solvent (Scheme 2) at 0 °C, following the reaction spectroscopically (^{31}P NMR). When complexes one and three were used, the reaction proceeded smoothly to afford the expected NAC product in a good, isolated yield.



Scheme 2. Synthesis of NAC derivatives **5** and **6**.

The unprecedented **5** and **6** bromocomplexes were spectroscopically characterized. In the attenuated total reflectance IR spectra, the strong absorption band due to the stretching of isonitrile functional group was no longer observable, while a typical absorption band appeared, in both cases, around 1550 cm^{-1}, which could be ascribed to NCN stretching. In the ^{31}P NMR spectra, the disappearance of signals due to the isocyanido precursors was accompanied by the presence of new signals with satellites ($J_{P\text{-}Pt} \approx 4000$ Hz), which could be ascribed to the carbene species. In the case of benzyl derivative **5,** a single signal was observed both in ^{31}P- and ^{195}Pt NMR spectra, indicating the stereoselectivity of the process towards the formation of a single isomer, to which a *cis* geometry was assigned for analogy with the analogous chlorinated system [9]. In the case of the 4-methoxyphenyl derivative **6,** a mixture of carbene products was observed, as indicated by the presence of two distinct signals with satellites in the ^{31}P NMR spectrum and of two doublet signals in the ^{195}Pt NMR one. The equilibrium composition of the mixture was 80/20 and it seems reasonable to assign the *cis* geometry to the main component of the mixture, taking into account the complete stereoselectivity observed in the synthesis of the analogous chlorinated compound [9]. The ^{1}H NMR spectra of the carbene complexes **5** and **6** were quite typical of rigid systems, with non-equivalent hydrogen atoms affording distinct signals. As an example, we report the ^{1}H NMR spectrum of complex **5** (Figure 2).

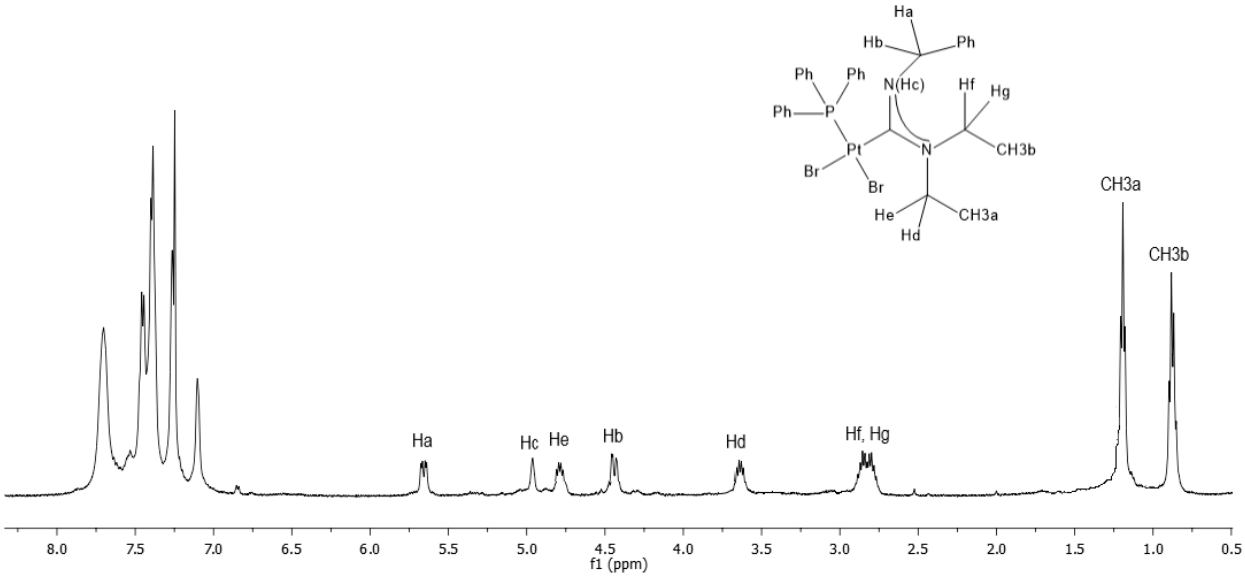


Figure 2. ^{1}H NMR spectrum ($CDCl_3$) of complex **5**.

In the aliphatic portion of the spectrum, benzyl hydrogen atoms H_a and H_b originate two distinct double doublet signals at 5.65 and 4.44 ppm, where a typical geminal coupling constant (12 Hz) can be measured. Analogously, each of the four methylene hydrogen atoms of the diethylamino moiety ($H_{d\text{-}g}$) gives rise to a distinct multiplet signal (at 4.79, 3.64, 2.85 and 2.80 ppm). Finally, two triplet signals are observable at 1.19 and 0.88 ppm, which can be attributed to the two methyl groups of the diethylamino residue. The non-equivalence of the ethyl groups of the diethylamino residue is well observable in the ^{13}C NMR spectrum as well, where each carbon atom originates a distinct signal. A very similar spectral profile, although complicated by the presence of two geometric isomers, was observed in the NMR spectra of complex **6**.

The reaction of tert-butylisocyano derivative **2** with *N*,*N*-diethylamine did not afford the expected products. Indeed, ^{31}P NMR analyses carried out on samples of the reaction mixture at different time spans revealed only the presence of the precursor. A greater excess of the nucleophile was added and the mixture was refluxed longer; nonetheless, the composition of the solution did not change and the precursor was recovered after the usual work-up procedures. It seems reasonable to ascribe this different behavior to the steric hindrance of the tert-butyl group. As a matter of fact, a sample of *cis*-[$PtCl_2(PPh_3)$(CNtert-Bu)], prepared in this work (see Supplementary Material for the synthesis) showed the same reactivity as the bromo complex.

Attempts were made to prepare the diethylamino NAC carbene of functionalized isocyano derivative **4**. Unfortunately, repeated experiments afforded complex mixtures that could not be purified. It has to be noted that **4** is characterized by the presence of enolizable hydrogen atoms, in alfa position to diethyl carboxylate group. Indeed, this ligand is a synthetic equivalent of glycine and it has been used successfully to synthesize complex aminoacidic derivatives in experimental procedures based mostly upon the acidity of hydrogen atoms in alfa position to the ester group [54]. It is likely that, in the presence of *N*,*N*-diethylamine, enolization equilibria are established, leading to the formation of byproducts. The same behavior was observed when a sample of *cis*-[$PtCl_2(PPh_3)(CNCH_2COOEt)$] (see Supplementary Material for the synthesis) was reacted with *N*,*N*-diethylamine.

2.3. Stability of Complexes in DMSO

As anticipated, one of the possible applications of the prepared carbene complexes concerns their possible activity as anticancer agents. In view of the study of their antiprolif-

erative properties in vitro, the stability of the derivatives in media used for the biological tests is mandatory. The compounds here prepared are not soluble in water or ethanol and are well soluble in DMSO; however, it is well known [55] that the coordination properties of DMSO towards platinum can severely affect the nature of the tested compounds. Indeed, the coordination of this solvent to the metal center can be competitive with certain ligands, displacing them or, in the presence of traces of water, assisting metal-halogen hydrolysis processes [56,57]. The occurrence of these side reactions is often enhanced by the presence of strongly *trans*-directing ligands. Thus, the behavior of derivatives **1**–**6** in DMSO was studied spectroscopically. In particular, the stability of the complexes was conveniently checked by ^{31}P NMR, as the possible substitution product of the isonitrile or NAC ligand by DMSO (*cis*-[$PtBr_2(PPh_3)(SOMe_2)$]) is known to afford a signal at 17.2 ppm in d_6-DMSO ($^1J_{P\text{-}Pt}$ = 3730 Hz) [45]. In a typical experiment, a sample of the NAC complex **5** (about 10 mg) was dissolved in d_6-DMSO and analyzed at different time spans (t = 0, 24 and 72 h). A single signal was observed in the freshly prepared sample (8.59 ppm, $^1J_{P\text{-}Pt}$ = 4084 Hz, Figure S1), well in agreement with the ^{31}P NMR characterization previously registered in $CDCl_3$. Analogously, in the ^{1}H NMR, all the signals attributed to **5** were present (Figure S2). No changes were observed in the spectra registered on the same sample after 24 and 72 h (Figures S3–S6). Other complexes afforded analogous results, thus proving their stability in DMSO.

3. Conclusions

The synthetic protocol previously used for the preparation of [$PtCl_2(PPh_3)(CNR)$] and [$PtCl_2(PPh_3)(NAC)$] derivatives proved suitable for the synthesis of the analogous brominated systems. Starting from *trans*-[$Pt(\mu\text{-}Br)Br(PPh_3)]_2$, the corresponding isonitrile complexes [$PtBr_2(PPh_3)(CNR)$] (R = Bz (**1**), tert-Bu (**2**), 4-$MeOC_6H_4$ (**3**) and CH_2COOEt (**4**)) were obtained with very good yields (75–98%), although the reaction was not as stereoselective as for the chlorinated counterparts and mixtures of geometric isomers, generally enriched in the *cis* isomer, were observed in chloroform solution. This behavior can be reasonably ascribed to the steric hindrance of bromido ligands. In the case of R = 4-$MeOC_6H_4$ (**3**), the *cis* isomer was crystallized, and its molecular structure was determined using single crystal X-ray diffraction. The reaction of the isonitrile derivatives **1** and **3** with *N*,*N*-diethylamine afforded the desired NAC compounds in good yields (69–87%), while the reaction failed when substrates **2** and **4** were used. In the case of complex **2**, the complete lack of reactivity observed seems to have been caused by the steric hindrance exerted by the tert-butyl residue on the isonitrile functional group, which makes it scarcely accessible by the attacking *N*,*N*-diethylamine. As for complex **4**, it is reasonable to ascribe the side reactions observed to the high reactivity of hydrogen atoms in alfa position to the ethyl carboxylate group in a basic environment. Indeed, the easily enolizable hydrogen atoms of ethyl-2-isocyanoacetate are commonly exploited to synthetize glycine derivatives [54]. Finally, both isonitrile and NAC complexes proved stable in DMSO solution, where they are all well soluble; thus, their antiproliferative properties will be investigated in vitro and compared with their chlorido counterparts.

4. Materials and Methods

General. All manipulations were carried out under inert (Ar) atmosphere, if not otherwise stated. Usual procedures were followed to purify and dry solvents [58,59]. Solid, commercially available reagents were used with no further purification. Samples of [$PtBr_2(NCMe)_2$] [45], *trans*-[$Pt(\mu\text{-}Br)Br(PPh_3)]_2$ [45], *trans*-[$Pt(\mu\text{-}Cl)Cl(PPh_3)]_2$ [10] were prepared according to reported procedures. Samples of 4-methoxyphenylisocyanide, benzylisocyanide, tert-butylisocyanide and ethyl isocyanoacetate were 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 recorded on an Agilent "Cary 630" spectrometer, equipped with an ATR accessory; absorption peak ($\widetilde{\nu}$, cm^{-1}) intensities and

shapes were described by the following abbreviations: s = strong, m = medium, w = weak, br = broad and sh = shoulder. ^{1}H-, ^{13}C-, ^{31}P- and ^{195}Pt NMR spectra were recorded on JEOL YH 400 MHz and JEOL CZR 500 MHz spectrometers, in $CDCl_3$ solution (™Deutero GmbH, stored over Ag) if not otherwise stated. When samples of the reaction mixtures were analyzed using ^{31}P NMR in non-deuterated solvents, a sealed capillary containing C_6D_6 was inserted into the sample to lock the instrument. Chemical shifts (δ ppm) referred to: $Si(CH_3)_4$ for ^{1}H and ^{13}C, H_3PO_4 (85% in D_2O) for ^{31}P and H_2PtCl_6 for ^{195}Pt. The observed signals were described according to the following abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quadruplet and m = multiplet.

4.1. General Procedure for the Synthesis of [$PtBr_2(PPh_3)(CNR)$]

In a Schlenk tube equipped with a magnetic stirrer, an orange suspension of *trans*-[$Pt(\mu\text{-}Br)Br(PPh_3)]_2$ [45] (0.200–0.400 g) in 1,2-DCE (10–15 mL) was cooled (0 °C) and treated, under stirring, with a solution of the suitable isocyanide in the same solvent ([isocyanide]/[Pt] = 2.0 molar ratio). The temperature was raised (25 °C) and a clear, light yellow solution was obtained (2–12 h). The proceeding of the reaction was checked by TLC and/or ^{31}P NMR. The mixture was stirred until the maximum conversion of the precursor was obtained; then, the solution was concentrated under a vacuum up to a quarter of the original volume and treated with n-heptane (20–30 mL). A waxy–oily solid precipitated, which turned into a colorless powder upon prolonged stirring (3–12 h). The product was filtered, washed with n-heptane (2 × 3 mL) and dried under a vacuum. For each complex, the used isocyanide ligand, the yield, the elemental analysis and the spectroscopic (IR and NMR) characterizations are reported.

Cis,trans-[$PtBr_2(CNCH_2Ph)(PPh_3)$] (**1**). Benzylisocyanide, 0.293 g (93%). NMR analysis showed the presence of two geometric *cis,trans* isomers in a 41/59 molar ratio.

El. Anal. Calcd $C_{26}H_{22}$ Br_2NPPt, %: C 42.5, H 3.0 and N 1.9. Found, %: C 42.2, H 3.2 and N 2.2.

IR (ATR, $\widetilde{\nu}$, cm^{-1}): 3053 w, 2957 w, 2933 w, 2919 w, 2234 s (stretching C≡N), 2146 m, 1964 w, 1896 w, 1816 w, 1670 w, 1603 w, 1480 m, 1435 s, 1345 w, 1310 w, 1230 w, 1182 w, 1160 w, 1099 s, 999 w, 739 s and 691 s.

^{1}H NMR (mixture of isomers): 7.75–7.07 (m, Harom), 4.42(s, CH_2, 41%) and 4.31(s, CH_2, 59%).

^{31}P NMR (mixture of isomers): 9.45 ($^{1}J_{P\text{-}Pt}$ = 3330 Hz, 59%) and 7.14 ($^{1}J_{P\text{-}Pt}$ = 3310 Hz, 41%).

^{195}Pt NMR (mixture of isomers): −4600($^{1}J_{P\text{-}Pt}$ = 3330Hz, 41%) and −4402 ($^{1}J_{P\text{-}Pt}$ =3310Hz, 59%).

Cis,trans-[$PtBr_2(CNC(CH_3)_3)(PPh_3)$] (**2**). Tert-Butylisocyanide, (tert-Butylisocyanide]/[Pt] = 3.0 molar ratio), 0.384 g (98%). NMR analysis showed the presence of two geometric *cis,trans* isomers in a 85/15 molar ratio.

El. Anal. Calcd $C_{23}H_{24}Br_2NPPt$·DCE, % C 37.6, H 3.5 and N 1.8. Found, % C 37.6, H 3.2% and N 2.2%.

IR (ATR, $\widetilde{\nu}$, cm^{-1}): 3047 w, 2981 w, 2226 s (stretching C≡N), 2143 w, 1982 w, 1900 w, 1828 w, 1773 w, 1479 m, 1432 s, 1401 w, 1372 m, 1310 m, 1185 s, 1096 s, 995 m, 930 w, 880 w, 75 3s and 693 s.

^{31}P NMR(mixture of isomers): 9.94 (3397 Hz, 15%) and 9.30 ($^{1}J_{P\text{-}Pt}$ = 3375 Hz, 85%).

^{195}Pt NMR (mixture of isomers): −4259 $^{1}J_{P\text{-}Pt}$ = ($^{1}J_{P\text{-}Pt}$ = 3397 Hz, 15%) and −4397 ($^{1}J_{P\text{-}Pt}$ = 3375 Hz, 85%).

Cis,trans-[$PtBr_2(CNC_6H_4(OCH_3))(PPh_3)$] (**3**). 4-Methoxyphenylisocyanide, 0.353 g (75%). NMR analysis showed the presence of two geometric *cis,trans* isomers in a 76/24 molar ratio.

El. Anal. $C_{26}H_{22}Br_2NOPPt$ Calcd, % C 41.6, H 3.0, N 1.9. Found, C 42.0, H 3.3 and N 1.8%.

IR (ATR, $\widetilde{\nu}$, cm^{-1}): 3058 w, 3005 w, 2935 w, 2839 w, 2206 s (stretching C≡N), 1991 w, 1889 w, 1815 w, 1761 w, 1673 w, 1600 m, 1503 s, 1433 s, 1301 m, 1252 s, 1165 m, 1099 s, 1024 m, 833 s, 746 s and 691 s.

^{31}P NMR (mixture of isomers): 10.2 ($^{1}J_{P\text{-}Pt}$ = 3339 Hz, 24%) and 9.5 ($^{1}J_{P\text{-}Pt}$ = 3313 Hz, cis 76%).

^{195}Pt NMR (mixture of isomers): −4187 $^{1}J_{P\text{-}Pt}$ = ($^{1}J_{P\text{-}Pt}$ = 3339 Hz, 24%) and −4358 ($^{1}J_{P\text{-}Pt}$ = 3313 Hz, 76%).

Cis-[$PtBr_2(CNCH_2COOEt)(PPh_3)$] (**4**). ethyl isocyanoacetate, 0.246 g, (83%).

El. Anal. $C_{23}H_{22}Br_2NO_2PPt$, Calcd, %: C 37.8, H 3.0 and N 1.9. Found, %: C 37.5, H 2.6 and N 2.2.

IR (ATR, $\widetilde{\nu}$, cm^{-1}): 3055 w, 2978 w, 2952 w, 2905 w, 2240 s (stretching C≡N), 1748 s (stretching C=O), 1482 m, 1435 m, 1373 w, 1341 w, 1279 w, 1245 w, 1219 s, 1159 w, 1094 s, 1027 m, 994 m, 937 w, 857 w, 748 m, 709 m and 692 s.

^{1}H NMR: 7.8–7.7 (m, 6H, H_{arom}), 7.5–7.4 (m, 9H, H_{arom}), 4.1 (q, J = 7.0 Hz, 2H, $COOCH_2$), 3.9 (s, 2H, $^{1}J_{PPt}$ = 17 Hz, CH_2CO) and 1.28 (t, J = 7.0 Hz, 3H, CH_3).

^{31}P NMR: 8.8 ($^{1}J_{PPt}$ = 3300 Hz).

^{195}Pt NMR: −4400 ($^{1}J_{PPt}$ = 3300 Hz).

4.2. General Procedure for the Synthesis of [$PtBr_2(PPh_3)(Et_2N(H)CNR)$]

In a Schlenk tube equipped with a magnetic stirrer, a solution of the suitable [$PtBr_2(PPh_3)$ (CNR)] (0.180–0.400 g) in 1,2-DCE (10–15 mL) was cooled (0 °C) and a solution of N,N-diethylamine (Et_2NH) in 2 mL of the same solvent ([Et_2NH]/[Pt] = 2.0 molar ratio) was added dropwise under stirring over 1 h. The temperature was slowly raised (25 °C) and the solution was stirred for 24 h. The proceeding of the reaction was followed by ^{31}P NMR, checking the disappearance of the precursor's signals. When the maximum conversion of the precursor was obtained, the solution was concentrated under a vacuum up to a quarter of the original volume, cooled (0 °C) and treated with n-heptane (20–30 mL). A waxy solid precipitated, which turned into a colorless powder upon prolonged stirring (3–12 h). The product was filtered, washed with n-heptane (2 × 3 mL) and dried under a vacuum. For each NAC derivative, the isocyanide complex used, the yield, the elemental analysis and the spectroscopic (IR and NMR) characterizations are reported.

Cis-[$PtBr_2(PPh_3)C(NHCH_2Ph)(NEt_2)$] (**5**). [$PtBr_2(PPh_3)(CNCH_2Ph)$], 0.196 g (69%).

El. Anal. Calcd $C_{30}H_{33}Br_2N_2PPt$, % C 44.6, H 4.1 and N 3.5. Found, % C 45.0, H 4.0% and N 3.7%.

IR (ATR, ν, cm^{-1}): 3056 w, 2982 w, 2928 w, 1554 s (stretching C=N), 1434 s, 1379 w, 1095 m, 998 m, 749 m and 691 s.

^{31}P NMR: 9.22 ($^{1}J_{P\text{-}Pt}$ = 4010 Hz).

^{1}H NMR: 7.70–7.10 (2 m, 20H, H_{arom}), 5.65 (dd, 1H, J = 13.0 Hz, J' = 4 Hz, PhC$\underline{H}$H), 4.96 (bm, 1H, $^{3}J_{H\text{-}Pt}$ = 80 Hz, NH), 4.79 (m, 1H, $CH_3C\underline{H}HN$), 4.44 (dd, 1H, J = 13.0 Hz, J' = 4.0 Hz, PhCH$\underline{H}$), 3,64 (m, 1H, $CH_3CH\underline{H}N$), 2.83 (m, 2H,$CH'_3C\underline{H}'_2N$), 1.19 (t, 3H, J = 6.0 Hz, $C\underline{H}_3CH_2N$) and 0.89 (t, 3H, J = 6.0 Hz, $C\underline{H}'_3CH'_2N$).

^{13}C NMR: 162.7, 134.8, 134.7, 134.6, 131.2, 129.0, 128.5, 128.3, 128.2, 53.7, 53.0, 43.3, 13.0 and 12.2.

^{195}Pt NMR: −4159 ($^{1}J_{P\text{-}Pt}$ = 4010 Hz).

[$PtBr_2(PPh_3)C(NHC_6H_4(OCH_3))(NEt_2)$] (**6**)**.** [$PtBr_2(CNC_6H_4(OCH_3))(PPh_3)$], 0.235 g (87%). Mixture of isomers.

El. Anal. Calcd $C_{30}H_{33}Br_2N_2OPPt$, % C 43.8, H 4.0 and N 3.4. Found, % C 43.9, H 3.8% and N 3.3%.

IR (ATR, ν, cm^{-1}): 3059 w, 2932 w, 1611 w, 1545 s (stretching C=N), 1508 s, 1435 s, 1337 m, 1250 s, 1173 w, 1094 m, 1032 m, 833 m and 753 m.

^{31}P NMR: 8.36 ($^{1}J_{P\text{-}Pt}$ = 4076 Hz, 80%) and 8.56 ($^{1}J_{P\text{-}Pt}$ =4045 Hz, 20%).

^{1}H NMR: Isomer A (selected signals): 7.80–7.00 (m, 17H, H_{arom}), 6.88–6.63 (m, 3H, H_{arom} + NH), 4.76 (m, 1H, $NC\underline{H}HCH_3$), 4.15 (m, 1H, $NCH\underline{H}CH_3$), 3.84 (s, 3H, OCH_3), 3.20 (m, 2H, $NC\underline{H}'_2CH_3$), 1.23 (t, 3H, $NCH_2C\underline{H}_3$) and 1.07 (t, 3H, $NCH'_2C\underline{H}'_3$).

Isomer B (selected signals): 7.80–7.00 (m, 17H, H_{arom}), 6.88–6.63 (m, 3H, H_{arom} + NH), 4.84 (m, 1H, $NC\underline{H}HCH_3$), 4.02 (m, 1H, $NCH\underline{H}CH_3$), 3.84 (s, 3H, OCH_3), 2.97 (m, 2H, $NC\underline{H}'_2CH_3$), 1.40 (t, 3H, $NCH_2C\underline{H}_3$) and 0.86 (t, 3H, $NCH'_2C\underline{H}'_3$).

^{13}C NMR (mixture of isomers): 158.2, 157.5, 134.9, 134.7, 134.6 (2C), 134.5 (2C), 132.4, 132.3, 130.9 (2C), 128.1, 128.0 (2C), 127.9, 127.8, 113.5 (2C), 55.6, 53.6, 44.7 (2C), 41.9, 22.7, 22.3, 12.8 and 12.3.

^{195}Pt NMR (only the most abundant isomer was observed): −4130 ($^1J_{P\text{-}Pt}$ = 4076 Hz).

5. Single-Crystal X-ray Diffraction

Single-crystal X-ray diffraction was performed with a Bruker D8 Venture instrument equipped with microfocus Mo source (Kα radiation, λ = 0.71073 Å) and a 2D Photon III detector. The main experimental details regarding the determination of the structure of **3** by single-crystal X-ray diffraction are reported in Table 3. In detail, a specimen of $C_{53}H_{45}Br_4Cl_3N_2O_2P_2Pt_2$, approximate dimensions 0.100 mm × 0.200 mm × 0.400 mm, was used for the X-ray crystallographic analysis. The integration of the data using a triclinic unit cell yielded a total of 100,548 reflections to a maximum θ angle of 28.27° (0.75 Å resolution), of which 13,634 were independent (average redundancy 7.375, completeness = 98.4%, R_{int} = 5.02%, R_{sig} = 3.59%) and 12,364 (90.69%) were greater than 2σ(F2). The final cell constants of *a* = 10.6145(3) Å, *b* = 14.8776(4) Å, *c* = 18.7841(4) Å, *α* = 103.8190(10)°, *β* = 103.3390(10)°, *γ* = 90.3250(10)° and volume = 2796.98(13) Å^3 are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.1400 and 0.4980. The final anisotropic full-matrix least-squares refinement on F2 with 615 variables converged at R1 = 3.67% for the observed data and wR2 = 11.14% for all data. The goodness-of-fit was 1.099. The largest peak in the final difference electron density synthesis was 1.183 e$^-$/Å^3 and the largest hole was −2.282 e$^-$/Å^3 with an RMS deviation of 0.199 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.924 g/cm^3 and F(000), 1540 e$^-$.

Table 3. Crystal data for *cis*-[$PtBr_2(PPh_3)(CNC_6H_4OMe)$] (**3**).

Identification code	CP9	
Empirical formula	$C_{53}H_{45}Br_4Cl_3N_2O_2P_2Pt_2$	
Formula weight	1620.02 g/mol	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*-1	
Unit cell dimensions	*a* = 10.6145(3)Å	*α* = 103.8190(10)°
	b = 14.8776(4) Å	*β* = 103.3390(10)°
	c = 18.7841(4)Å	*γ* = 90.3250(10)°
Volume	2796.98(13) Å^3	
Z	2	
Density (calculated)	1.924 g/cm^3	
Absorption coefficient	8.93 mm^{-1}	
F(000)	1540	
Theta range for data collection	1.98 to 28.27°	
Index ranges	$-14 \leq h \leq 14$, $-19 \leq k \leq 19$, $-25 \leq l \leq 24$	
Reflections collected	100,548	
Independent reflections	13,634 [R(int) = 0.0502]	
Max. and min. transmission	0.4980 and 0.1400	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	13,634/0/615	
Goodness-of-fit on F2	1.099	
Final R indices	12,364 data; I > 2σ(I)	R1 = 0.0367, wR2 = 0.1041
	all data	R1 = 0.0406, wR2 = 0.1114
Weighting scheme	w = 1/[σ2(Fo2) + (0.0675P)2 + 3.3100P]	
Largest diff. peak and hole	1.183 and −2.282 eÅ^{-3}	

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/inorganics11040137/s1: synthesis of *cis*-[$PtCl_2(PPh_3)(CNtert\text{-}Bu)$], *cis*-[$PtCl_2(PPh_3)(CNCH_2COOEt)$], [$PtBr_2(NCMe)_2$] and *trans*-[$Pt(\mu\text{-}Br)Br(PPh_3)]_2$; Figures S1–S6: spectroscopic study (^{1}H- and ^{31}P NMR) of the stability of complex **5** in DMSO-d^6; and Figures S7–S28: IR, ^{1}H-, ^{31}P-, ^{13}C- and ^{195}Pt NMR spectra of complexes **1**–**6**. CCDC 2244083 for *cis*-[$PtBr_2(PPh_3)(CNC_6H_4OMe)$] (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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

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References

1. Hyeraci, M.; Agnarelli, L.; Labella, L.; Marchetti, F.; Di Paolo, M.L.; Samaritani, S.; Dalla Via, L. Trans-Dichloro(Triphenylarsino)(*N*,*N*-Dialkylamino)Platinum(II) Complexes: In Search of New Scaffolds to Circumvent Cisplatin Resistance. *Molecules* **2022**, *27*, 644. [CrossRef] [PubMed]
2. Hyeraci, M.; Scalcon, V.; Folda, A.; Labella, L.; Marchetti, F.; Samaritani, S.; Rigobello, M.P.; Dalla Via, L. New Platinum(II) Complexes Affecting Different Biomolecular Targets in Resistant Ovarian Carcinoma Cells. *Chemmedchem* **2021**, *16*, 1956–1966. [CrossRef] [PubMed]
3. Scalcon, V.; Hyeraci, M.; Folda, A.; Labella, L.; Samaritani, S.; Dalla Via, L.; Rigobello, M.P. Insights into the Redox Activity of Platinum(II) Complexes Bearing a Mitochondriotropic Ligand in Cisplatin-Resistant Ovarian Cancer Cell Lines. *Free Rad. Biol. Med.* **2020**, *159*, S60–S61. [CrossRef]
4. Hyeraci, M.; Colalillo, M.; Labella, L.; Marchetti, F.; Samaritani, S.; Scalcon, V.; Rigobello, M.P.; Dalla Via, L. Platinum(II) Complexes Bearing Triphenylphosphine and Chelating Oximes: Antiproliferative Effect and Biological Profile in Resistant Cells. *Chemmedchem* **2020**, *15*, 1464–1472. [CrossRef]
5. Bondi, R.; Biver, T.; Dalla Via, L.; Guarra, F.; Hyeraci, M.; Sissi, C.; Labella, L.; Marchetti, F.; Samaritani, S. DNA Interaction of a Fluorescent, Cytotoxic Pyridinimino Platinum(II) Complex. *J. Inorg. Biochem.* **2020**, *202*, 7. [CrossRef] [PubMed]
6. Belli Dell' Amico, D.; Colalillo, M.; Dalla Via, L.; Dell' Acqua, M.; García-Argáez, A.N.; Hyeraci, M.; Labella, L.; Marchetti, F.; Samaritani, S. Synthesis and Reactivity of Cytotoxic Platinum(II) Complexes of Bidentate Oximes: A Step towards the Functionalization of Bioactive Complexes. *Eur. J. Inorg. Chem.* **2018**, *2018*, 1589–1594. [CrossRef]
7. Pokhriyal, R.; Hariprasad, R.; Kumar, L.; Hariprasad, G. Chemotherapy Resistance in Advanced Ovarian Cancer Patients. *Biomark. Cancer* **2019**, *11*, 1179299X19860815. [CrossRef]
8. Galluzzi, L.; Vitale, I.; Michels, J.; Brenner, C.; Szabadkai, G.; Harel-Bellan, A.; Castedo, M.; Kroemer, G. Systems Biology of Cisplatin Resistance: Past, Present and Future. *Cell Death Dis.* **2014**, *5*, e1257. [CrossRef]
9. Farasat, A.; Labella, L.; Marchetti, F.; Samaritani, S. Addition of Aliphatic, Secondary Amines to Coordinated Isonitriles. N-Acyclic Carbene (NAC) Platinum(II) Complexes from Trans-$[Pt(\mu\text{-}Cl)Cl(PPh_3)]_2$. *Inorg. Chim. Acta* **2022**, *540*, 121062. [CrossRef]
10. Belli, D.; Labella, L.; Marchetti, F.; Samaritani, S. A Convenient Route to Dinuclear Chloro-Bridged Platinum(II) Derivatives via Nitrile Complexes. *Dalton Trans.* **2012**, *41*, 1389–1396. [CrossRef]
11. Marzo, T.; Bartoli, G.; Gabbiani, C.; Pescitelli, G.; Severi, M.; Pillozzi, S.; Michelucci, E.; Fiorini, B.; Arcangeli, A.; Quiroga, A.G.; et al. Cisplatin and Its Dibromido Analogue: A Comparison of Chemical and Biological Profiles. *BioMetals* **2016**, *29*, 535–542. [CrossRef] [PubMed]
12. Tolbatov, I.; Marzo, T.; Cirri, D.; Gabbiani, C.; Coletti, C.; Marrone, A.; Paciotti, R.; Messori, L.; Re, N. Reactions of Cisplatin and Cis-$[PtI_2(NH_3)_2]$ with Molecular Models of Relevant Protein Sidechains: A Comparative Analysis. *J. Inorg. Biochem.* **2020**, *209*, 111096. [CrossRef] [PubMed]
13. Zhao, S.; Yang, Z.; Jiang, G.; Huang, S.; Bian, M.; Lu, Y.; Liu, W. An Overview of Anticancer Platinum N-Heterocyclic Carbene Complexes. *Coord. Chem.* **2021**, *449*, 214217. [CrossRef]

14. Bellemin-Laponnaz, S. N-Heterocyclic Carbene Platinum Complexes: A Big Step Forward for Effective Antitumor Compounds. *Eur. J. Inorg. Chem.* **2020**, *2020*, 10–20. [CrossRef]
15. Porchia, M.; Pellei, M.; Marinelli, M.; Tisato, F.; Del Bello, F.; Santini, C. New Insights in Au-NHCs Complexes as Anticancer Agents. *Europ. J. Med. Chem.* **2018**, *146*, 709–746. [CrossRef] [PubMed]
16. Scattolin, T.; Pessotto, I.; Cavarzerani, E.; Canzonieri, V.; Orian, L.; Demitri, N.; Schmidt, C.; Casini, A.; Bortolamiol, E.; Visentin, F.; et al. Indenyl and Allyl Palladate Complexes Bearing N-Heterocyclic Carbene Ligands: An Easily Accessible Class of New Anticancer Drug Candidates. *Eur. J. Inorg. Chem.* **2022**, *2022*, e202200103. [CrossRef]
17. Marichev, K.O.; Patil, S.A.; Patil, S.A.; Heras Martinez, H.M.; Bugarin, A. N-Heterocyclic Carbene Metal Complexes as Therapeutic Agents: A Patent Review. *Expert Opin. Ther. Pat.* **2022**, *32*, 47–61. [CrossRef] [PubMed]
18. Tolbatov, I.; Marzo, T.; Coletti, C.; La Mendola, D.; Storchi, L.; Re, N.; Marrone, A. Reactivity of Antitumor Coinage Metal-Based N-Heterocyclic Carbene Complexes with Cysteine and Selenocysteine Protein Sites. *J. Inorg. Biochem.* **2021**, *223*, 111533. [CrossRef]
19. Guarra, F.; Pratesi, A.; Gabbiani, C.; Biver, T. A Focus on the Biological Targets for Coinage Metal-NHCs as Potential Anticancer Complexes. *J. Inorg. Biochem.* **2021**, *217*, 111355. [CrossRef] [PubMed]
20. Tong, K.-C.; Hu, D.; Wan, P.-K.; Lok, C.-N.; Che, C.-M. Chapter Three—Anti-Cancer Gold, Platinum and Iridium Compounds with Porphyrin and/or N-Heterocyclic Carbene Ligand(s). In *Advances in Inorganic Chemistry*; Sadler, P.J., van Eldik, R., Eds.; Academic Press: Cambridge, MA, USA, 2020; Volume 75, pp. 87–119. ISBN 0898-8838.
21. APatil, S.; PHoagland, A.; APatil, S.; Bugarin, A. N-Heterocyclic Carbene-Metal Complexes as Bio-Organometallic Antimicrobial and Anticancer Drugs, an Update (2015–2020). *Future Med. Chem.* **2020**, *12*, 2239–2275. [CrossRef]
22. Hu, D.; Yang, C.; Lok, C.-N.; Xing, F.; Lee, P.-Y.; Fung, Y.M.E.; Jiang, H.; Che, C.-M. An Antitumor Bis(N-Heterocyclic Carbene)Platinum(II) Complex That Engages Asparagine Synthetase as an Anticancer Target. *Angew. Chem. Int. Ed.* **2019**, *58*, 10914–10918. [CrossRef] [PubMed]
23. Harlepp, S.; Chardon, E.; Bouché, M.; Dahm, G.; Maaloum, M.; Bellemin-Laponnaz, S. N-Heterocyclic Carbene-Platinum Complexes Featuring an Anthracenyl Moiety: Anti-Cancer Activity and DNA Interaction. *Int. J. Mol. Sci.* **2019**, *20*, 4198. [CrossRef] [PubMed]
24. Annunziata, A.; Cucciolito, M.E.; Esposito, R.; Imbimbo, P.; Petruk, G.; Ferraro, G.; Pinto, V.; Tuzi, A.; Monti, D.M.; Merlino, A.; et al. A Highly Efficient and Selective Antitumor Agent Based on a Glucoconjugated Carbene Platinum(Ii) Complex. *Dalton Trans.* **2019**, *48*, 7794–7800. [CrossRef] [PubMed]
25. Zou, T.; Lok, C.-N.; Wan, P.-K.; Zhang, Z.-F.; Fung, S.-K.; Che, C.-M. Anticancer Metal-N-Heterocyclic Carbene Complexes of Gold, Platinum and Palladium. *Curr. Opin. Chem. Biol.* **2018**, *43*, 30–36. [CrossRef] [PubMed]
26. Liu, W.; Gust, R. Update on Metal N-Heterocyclic Carbene Complexes as Potential Anti-Tumor Metallodrugs. *Coord. Chem. Rev.* **2016**, *329*, 191–213. [CrossRef]
27. Dahm, G.; Bailly, C.; Karmazin, L.; Bellemin-Laponnaz, S. Synthesis, Structural Characterization and In Vitro Anti-Cancer Activity of Functionalized N-Heterocyclic Carbene Platinum and Palladium Complexes. *J. Organomet. Chem.* **2015**, *794*, 115–124. [CrossRef]
28. Liu, W.; Gust, R. Metal N-Heterocyclic Carbene Complexes as Potential Antitumor Metallodrugs. *Chem. Soc. Rev.* **2013**, *42*, 755–773. [CrossRef] [PubMed]
29. Cisnetti, F.; Gautier, A. Metal/N-Heterocyclic Carbene Complexes: Opportunities for the Development of Anticancer Metallodrugs. *Angew. Chem. Int. Ed.* **2013**, *52*, 11976–11978. [CrossRef]
30. Skander, M.; Retailleau, P.; Bourrié, B.; Schio, L.; Mailliet, P.; Marinetti, A. N-Heterocyclic Carbene-Amine Pt(II) Complexes, a New Chemical Space for the Development of Platinum-Based Anticancer Drugs. *J. Med. Chem.* **2010**, *53*, 2146–2154. [CrossRef]
31. Mikhaylov, V.N.; Balova, I.A. Alternative Transformations of N-Heterocyclic Carbene Complexes of the Group 11 Metals in Transmetalation Reactions (A Review). *Russ. J. Gen. Chem.* **2021**, *91*, 2194–2248. [CrossRef]
32. Baczewska, P.; Śniady, K.; Kośnik, W.; Michalak, M. Acenaphthene-Based N-Heterocyclic Carbene Metal Complexes: Synthesis and Application in Catalysis. *Catalysts* **2021**, *11*, 972. [CrossRef]
33. Wang, Z.; Tzouras, N.V.; Nolan, S.P.; Bi, X. Silver N-Heterocyclic Carbenes: Emerging Powerful Catalysts. *Trends Chem.* **2021**, *3*, 674–685. [CrossRef]
34. Voloshkin, V.A.; Tzouras, N.V.; Nolan, S.P. Recent Advances in the Synthesis and Derivatization of N-Heterocyclic Carbene Metal Complexes. *Dalton Trans.* **2021**, *50*, 12058–12068. [CrossRef] [PubMed]
35. Bołt, M.; Mermela, A.; Żak, P. Influence of Bis-NHC Ligand on Platinum-Catalyzed Hydrosilylation of Internal Alkynes. *Eur. J. Inorg. Chem.* **2023**, *26*, e202200622. [CrossRef]
36. Strausser, S.L.; Jenkins, D.M. Synthesis of D10 N-Heterocyclic Carbene Complexes with a Perimidine Scaffold. *Organometallics* **2021**, *40*, 1706–1712. [CrossRef]
37. Koy, M.; Bellotti, P.; Das, M.; Glorius, F. N-Heterocyclic Carbenes as Tunable Ligands for Catalytic Metal Surfaces. *Nat. Catal.* **2021**, *4*, 352–363. [CrossRef]
38. Pertschi, R.; Hatey, D.; Pale, P.; de Frémont, P.; Blanc, A. Synthesis, Characterization, and Catalytic Activity of Chiral NHC Platinum(II) Pyridine Dihalide Complexes. *Organometallics* **2020**, *39*, 804–812. [CrossRef]
39. Maliszewski, B.P.; Tzouras, N.V.; Guillet, S.G.; Saab, M.; Beliš, M.; Van Hecke, K.; Nahra, F.; Nolan, S.P. A General Protocol for the Synthesis of Pt-NHC (NHC = N-Heterocyclic Carbene) Hydrosilylation Catalysts. *Dalton Trans.* **2020**, *49*, 14673–14679. [CrossRef] [PubMed]

40. Jalal, M.; Hammouti, B.; Touzani, R.; Aouniti, A.; Ozdemir, I. Metal-NHC Heterocycle Complexes in Catalysis and Biological Applications: Systematic Review. *Mater. Today Proc.* **2020**, *31*, S122–S129. [CrossRef] [PubMed]
41. Afanasenko, A.M.; Chulkova, T.G.; Boyarskaya, I.A.; Islamova, R.M.; Legin, A.A.; Keppler, B.K.; Selivanov, S.I.; Vereshchagin, A.N.; Elinson, M.N.; Haukka, M. C,N-Chelated Diaminocarbene Platinum(II) Complexes Derived from 3,4-Diaryl-1H-Pyrrol-2,5-Diimines and Cis-Dichlorobis(Isonitrile)Platinum(II): Synthesis, Cytotoxicity, and Catalytic Activity in Hydrosilylation Reactions. *J. Organomet. Chem.* **2020**, *923*, 121435. [CrossRef]
42. Correa, A.; Nolan, S.P.; Cavallo, L. N-Heterocyclic Carbene Complexes of Au, Pd, and Pt as Effective Catalysts in Organic Synthesis. In *Computational Mechanisms of Au and Pt Catalyzed Reactions*; Soriano, E., Marco-Contelles, J., Eds.; Springer: Berlin/Heidelberg, Germany, 2011; pp. 131–155. ISBN 978-3-642-21083-9.
43. Hashmi, A.S.K.; Lothschütz, C.; Böhling, C.; Hengst, T.; Hubbert, C.; Rominger, F. Carbenes Made Easy: Formation of Unsymmetrically Substituted N-Heterocyclic Carbene Complexes of Palladium(II), Platinum(II) and Gold(I) from Coordinated Isonitriles and Their Catalytic Activity. *Adv. Synth. Catal.* **2010**, *352*, 3001–3012. [CrossRef]
44. Brissy, D.; Skander, M.; Retailleau, P.; Frison, G.; Marinetti, A. Platinum(II) Complexes Featuring Chiral Diphosphines and N-Heterocyclic Carbene Ligands: Synthesis and Evaluation as Cycloisomerization Catalysts. *Organometallics* **2009**, *28*, 140–151. [CrossRef]
45. Fioco, D.; Belli Dell'Amico, D.; Labella, L.; Marchetti, F.; Samaritani, S. A Sound Sequence to Triphenylphosphino Dibromoplatinum(II) Complexes—Solvothermal Preparation of Trans-$[PtBr(\mu\text{-}Br)(PPh_3)]_2$. *Eur. J. Inorg. Chem.* **2019**, *2019*, 3970–3974. [CrossRef]
46. Priqueler, J.R.L.; Butler, I.S.; Rochon, F.D. An Overview of ^{195}Pt Nuclear Magnetic Resonance Spectroscopy. *Appl. Spectrosc. Rev.* **2006**, *41*, 185–226. [CrossRef]
47. Pregosin, P.S. Platinum-195 Nuclear Magnetic Resonance. *Coord. Chem. Rev.* **1982**, *44*, 247–291. [CrossRef]
48. Bouché, M.; Vincent, B.; Achard, T.; Bellemin-Laponnaz, S. N-Heterocyclic Carbene Platinum(IV) as Metallodrug Candidates: Synthesis and 195Pt NMR Chemical Shift Trend. *Molecules* **2020**, *25*, 3148. [CrossRef]
49. Sarju, J.; Arbour, J.; Sayer, J.; Rohrmoser, B.; Scherer, W.; Wagner, G. Synthesis and Characterisation of Mixed Ligand Pt(Ii) and Pt(Iv) Oxadiazoline Complexes. *Dalton Trans.* **2008**, 5302–5312. [CrossRef]
50. Still, B.M.; Kumar, P.G.A.; Aldrich-Wright, J.R.; Price, W.S. 195Pt NMR—Theory and Application. *Chem. Soc. Rev.* **2007**, *36*, 665–686. [CrossRef]
51. Gudat, D.; Dogan, A.; Kaim, W.; Klein, A. Multinuclear NMR Study of Some Organoplatinum Complexes Containing Multifunctional Azines as Chelating Ligands. *Magn. Reson. Chem.* **2004**, *42*, 781–787. [CrossRef] [PubMed]
52. Bret, J.-M.; Castan, P.; Commenges, G.; Laurent, J.-P. NMR (195Pt and 13C) Contribution to the Study of Some Pt(II), Pt(IV) and Mixed-Valence Thioamido Complexes. *Polyhedron* **1983**, *2*, 901–905. [CrossRef]
53. Silverstein, R.M.; Webster, F.X.; Kiemle, D.J.; Brice, D.L. *Spectrometric Identification of Organic Compounds*, 8th ed.; John Wiley Sons: Hoboken, NJ, USA, 2015; ISBN 978-1-119-09306-0.
54. Kotha, S.H.; Somnath, H. Ethyl Isocyanoacetate as a Useful Glycine Equivalent. *Synlett* **2010**, *2010*, 337–354. [CrossRef]
55. Hall, M.D.; Telma, K.A.; Chang, K.-E.; Lee, T.D.; Madigan, J.P.; Lloyd, J.R.; Goldlust, I.S.; Hoeschele, J.D.; Gottesman, M.M. Say No to DMSO: Dimethylsulfoxide Inactivates Cisplatin, Carboplatin, and Other Platinum Complexes. *Cancer Res.* **2014**, *74*, 3913–3922. [CrossRef] [PubMed]
56. Varbanov, H.P.; Ortiz, D.; Höfer, D.; Menin, L.; Galanski, M.S.; Keppler, B.K.; Dyson, P.J. Oxaliplatin Reacts with DMSO Only in the Presence of Water. *Dalton Trans.* **2017**, *46*, 8929–8932. [CrossRef] [PubMed]
57. Karmakar, S.; Purkait, K.; Chatterjee, S.; Mukherjee, A. Anticancer Activity of a Cis-Dichloridoplatinum(II) Complex of a Chelating Nitrogen Mustard: Insight into Unusual Guanine Binding Mode and Low Deactivation by Glutathione. *Dalton Trans.* **2016**, *45*, 3599–3615. [CrossRef] [PubMed]
58. Armarego, W.L.F.; Chai, C. Chapter 4—Purification of Organic Chemicals. In *Purification of Laboratory Chemicals*, 7th ed.; Armarego, W.L.F., Chai, C., Eds.; Butterworth-Heinemann: Boston, MA, USA, 2013; pp. 103–554. ISBN 978-0-12-382161-4.
59. Armarego, W.L.F.; Chai, C. Chapter 5—Purification of Inorganic and Metal-Organic Chemicals. In *Purification of Laboratory Chemicals*, 7th ed.; Armarego, W.L.F., Chai, C., Eds.; Butterworth-Heinemann: Boston, MA, USA, 2013; pp. 555–661. ISBN 978-0-12-382161-4.