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# Cytotoxic Activity of Some Half-sandwich Rhodium(III) Complexes Containing 4,4'-disubstituted-2,2'-bipyridine Ligands

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Dedicated to Professor Ingo-Peter Lorenz on the occasion of his 80<sup>th</sup> birthday

The synthesis and characterization of three compounds [Rh( $\eta^{5}-C_{5}Me_{5}$ )Cl(N^N)]PF<sub>6</sub> (N^N = 4,4'-disubstituted-2,2'-bipyridines, 1– **3**) are described. The cationic complexes contain the bidentate ligands N^N = 4,4'-di-*tert*-butyl-2,2'-bipyridine (1), N^N = 4,4'-dinonyl-2,2'-bipyridine (2) and N^N = 4,4'-diamino-2,2'-bipyridine (3). The complex salts were obtained by the bridge-splitting reaction from the precursor [{Rh( $\eta^{5}-C_{5}Me_{5}$ )( $\mu$ -Cl)Cl}<sub>2</sub>] and subsequent salt metathesis affording their corresponding hexafluorido phosphate salts. All compounds were characterized by elemental analysis and spectroscopic means. Additionally, the molecular structure of compound **3** in the solid was

#### Introduction

The immense clinical success of cisplatin and its derivatives has inspired scientists to search for other transition metal compounds playing a more significant role with respect to human cancer therapy. In this light, targeting and drug resistance are still great problems which need to be solved for an effective transfer of novel metal complexes into clinical applications, *e.g.*<sup>[1-4]</sup> Considering organometallic transition metal compounds within the group of the other platinum elements, half-sandwich complexes have received more attention in this light during the

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determined by a single-crystal X-ray diffraction study. The cytotoxicity of all three compounds was examined by MTT assay against two cancer cell lines – HT-29 (colon adenocarcinoma) and MCF-7 (human breast adenocarcinoma) - and normal human fibroblast cells (GM5657T). Compound 1 has moderate cytotoxicity against both cell lines, while compound 2 is seven to nine times more cytotoxic than cisplatin against MCF-7 and HT-29, respectively. In contrast to cisplatin, both compounds are more active against cancer cells than fibroblasts, thus showing some cancer selectivity.

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last years, e.g.<sup>[5-12]</sup> Especially rhodium complexes as therapeutic agents were of interest in this field because they exhibit a greater kinetical lability in comparison with its iridium congeners.<sup>[13]</sup> Recently, a review article summarized halfsandwich rhodium(III) complexes covering the most important results on their biological activities in light of their use as possible anticancer agents.<sup>[14]</sup> Thus many rhodium(III) complexes show higher in vitro activity and different mechanism of action (MoA) in comparison to conventional anticancer metallodrugs (frequently cisplatin and derivatives thereof) or clinically studied ruthenium-based drug candidates (NAMI-A and related Ru complexes). Moreover, many organometallic rhodium(III) complexes showed the highest anticancer activities in comparison with their ruthenium, osmium and iridium analogues.<sup>[14]</sup> Whereas our research interests were focused over many years on octahedral bis-cyclometallated M(III) complexes (M = Rh, Ir) bearing modified phenanthroline (phen) or related bipyridine (bpy) ligands in light of their evaluation as promising anticancer agents,<sup>[15]</sup> we examined recently the cytotoxic activities of some half-sandwich iridium(III) complexes containing 4,4'-disubstituted-2,2'-bipyridine ligands,<sup>[16]</sup> and related M(III) complexes (M = Rh and Ir) bearing chloro-substituted bidentate-coordinated phenanthroline or terpyridine ligands.<sup>[17]</sup> To continue our efforts in this field we describe herein the synthesis and the characterization of three rhodium(III) half-sandwich complexes containing 4,4'-disubstituted-2,2'-bipyridine ligands including the evaluation of their cytotoxic activities towards the two prominent cancer cell lines HT-29 and MCF-7 respectively. During these investigations, the molecular structure of the new compound  $[Rh(\eta^5-C_5Me_5)Cl(N^N)]PF_6$   $(N^N=4,4'-diamino-2,2'-$ 



bipyridine, **3**) in the solid was determined and confirmed by a single-crystal X-ray diffraction study.

## **Results and Discussion**

The preparation of the title compounds was realized using the well-known literature method by cleavage of the precursor [ $\{Rh(\eta^5-C_5Me_5)(\mu-Cl)Cl\}_2$ ] by addition of the corresponding bidentate chelating ligands in methanol at ambient temperature with stirring for one hour.<sup>[18]</sup> The salt metathesis using KPF<sub>6</sub> afforded finally the products **1–3** from the intermediate formed chloride compounds (see Eq. 1 and Scheme 1 respectively).

$$\begin{split} & [\{Rh(\eta^{5}\text{-}C_{5}Me_{5})(\mu\text{-}CI)CI\}_{2}]+2\,N^{\hat{}}N+2\,\,\text{KPF}_{6}\rightarrow \\ & 2\,\,[Rh(\eta^{5}\text{-}C_{5}Me_{5})CI(N^{\hat{}}N)]PF_{6}+2\,\,\text{KCI} \\ & 1-3 \end{split} \tag{1}$$

#### $(N^N = 4,4'-disubstituted-2,2'-bipyridines)$

Compounds 1–3 were obtained in yields ranging from 48 to 69% and fully characterized by elemental analysis, <sup>1</sup>H, <sup>13</sup>C[<sup>1</sup>H] NMR spectroscopy as well as by mass spectrometry. Additionally, the molecular structure of compound **3** in the crystal was confirmed by a single-crystal X-ray diffraction study (see below). Whereas the compound **1** was already reported in the literature,<sup>[19]</sup> compounds **2** and **3** are newly reported species. The NMR data of our compound **1** are in very good agreement with the corresponding reported ones for that species.<sup>[19]</sup> Thus, some NMR spectroscopic data of the new compounds **2** and **3** should be discussed here shortly. Compound **2** exhibits in the <sup>1</sup>H NMR spectrum (CD<sub>2</sub>Cl<sub>2</sub>) at room temperature resonances in the characteristic region of aromatic protons corresponding to



Scheme 1. General structure of compounds 1–3 ( $R = {}^{t}Bu$ , 1; R = non-yl, 2;  $R = NH_2$ , 3).

these ring protons at  $\delta = 8.62$  (d,  $J_{HH} = 5.6$  Hz, 2H), 8.01 (d,  $J_{HH} =$ 1.6 Hz, 2H), and 7.55 (dd,  $J_{HH} = 5.6$  Hz,  $J_{HH} = 1.6$  Hz, 2H). These data are comparable to the observed ones of our compound 1 and the related species described in the literature.<sup>[19]</sup> In the <sup>13</sup>C {<sup>1</sup>H} NMR spectrum (CD<sub>2</sub>Cl<sub>2</sub>) of **2** the characteristic resonance according to the  $\eta^5$ -C<sub>5</sub>Me<sub>5</sub>-ligand coordinated to rhodium was found at 97.0 ppm with the coupling  $J_{BhC} = 7.6$  Hz. Similar data were observed also for compound 3 (for more details see Experimental Section). It should be noted that a closely related compound to 3 was recently reported in the literature. Thus the same complex cation was described as the corresponding chloride salt  $[Rh(\eta^5-C_5Me_5)Cl(4,4'-NH_2-bpy)]Cl$  (obtained as dihydrate).<sup>[20]</sup> That compound was studied as a catalyst, beside other related type of complexes, dealing with the hydrogen evolution during photoreduction studies of carbon dioxide to formic acid. The reported NMR data of the latter species match well the collected ones for our compound 3. For example, the following <sup>13</sup>C{<sup>1</sup>H} NMR data for [Rh(η<sup>5</sup>-C<sub>5</sub>Me<sub>5</sub>)Cl(4,4'-NH<sub>2</sub>-bpy)]Cl recorded in dmso-d<sub>6</sub> were reported: 157.0, 154.8, 151.2, 112.3, 106.4 and 95.6 (d,  $J_{RhC} = 7.5$  Hz). The signal corresponding to the carbon atoms of the methyl groups of the pentamethylcyclopentadienyl ligand resonated at 8.9 ppm.<sup>[20]</sup> (For comparison purposes to compound 3 see Experimental Section.)

#### Molecular Structure of Compound 3

As mentioned before, the molecular structure of compound 1 was already reported in the literature.<sup>[19]</sup> Considering compound 2, unfortunately we were unable to grow suitable single-crystals of that compound to confirm its molecular structure in the crystal. Contrary, suitable single-crystals of compound 3 were grown by the layering method from dichloromethane solution using methanol/*iso*-hexane as the antisolvent at ambient temperature. The crystals were examined by X-ray diffraction and the result of the molecular structure determination of the complex cation of 3 is shown in Figure 1. Selected bond lengths are given in the figure caption.

The complex cation of 3 exhibits the expected halfsandwich pseudo-octahedral "three-legged piano-stool" geometry. Many related molecular structures were reported in the literature exhibiting such a rhodium backbone with the  $\eta^{5}$ pentamethylcyclopentadienyl group and one chlorido ligand beside the bidentate N-donor ligand. For example, in the compound  $[Rh(\eta^5-C_5Me_5)CI(N^N)]BF_4$   $(N^N = Ph-terpy)^{[21]}$  the corresponding bonding parameters comparable to 3 were found: Rh1-N1, 2.086(3); Rh1-N2, 2.197(3) and Rh-Cl, 2.3984(1) Å. Furthermore, for  $[Rh(\eta^5-C_5Me_5)Cl(phen)]ClO_4$  the bond lengths Rh1-N1, 2.128(3); Rh1-N2, 2.109(3) and Rh-Cl, 2.386(1) Å were reported,<sup>[22]</sup> and for the complex  $[Rh_2(\eta^5 C_{s}Me_{s})_{2}Cl_{2}(\mu$ -bpym)]<sup>2+</sup> (bpym = 2,2'-bipyrimidine) the corresponding data were Rh1-N1, 2.134(5); Rh1-N2, 2.161(5) and Rh-Cl, 2.405(2) Å.<sup>[23]</sup> Finally, the observed bonding parameters of 3 are also in accordance with the observed ones for the closely related cationic complex [Rh(n<sup>5</sup>-C<sub>5</sub>Me<sub>5</sub>)Cl(4,7-dichloro-1,10-phenanthroline)]<sup>+</sup>: Rh1–N1, 2.1241(17); Rh1–N2, 2.1165(17) and Rh1–Cl, 2.405(2) Å,<sup>[17]</sup> as well as for  $[Rh(\eta^5-C_5Me_5)Cl(\kappa^2-N-1)]$ 





**Figure 1.** The molecular structure of the cationic complex of compound **3** in the crystal (ORTEP drawing and atom labeling scheme with 25% probability level). Solvent molecules are omitted for clarity. Selected bond lengths/Å: Rh1–N1, 2.094(3); Rh1–N2, 2.087(3); Rh1–Cl, 2.4281(8).

tppz)]<sup>+</sup>: Rh1–N1, 2.1418(19); Rh1–N2, 2.1245(18) and Rh1–Cl, 2.4127(6) Å [tppz=2,3,5,6-tetra(2'-pyridyl)pyrazine] reported by us recently.<sup>[24]</sup>

### Biological Activity of Compounds 1-3

Sadler and co-workers investigated numerous organometallic rhodium complexes of the general type  $[Rh(\eta^5-C_5Me_5)Cl(N^N)]^+$ as anticancer agents especially in light of C-H bond activation on the methyl groups.<sup>[25]</sup> They showed that a new activation mechanism is possible and facile for certain rhodium(III) cyclopentadienyl complexes containing chelated  $\pi$ -acceptor diamine ligands such as bpy or phen. These findings inspired us to investigate the compounds 1-3 with respect to their biological activity. For this reason, the antiproliferative activity of the three complexes towards the cancer cell lines MCF-7 (human breast adenocarcinoma) and HT-29 (colon adenocarcinoma) has been determined. In addition, selectivity towards cancer cells was checked against normal human fibroblasts cells (GM5657T). The cytotoxicity was evaluated using the MTT assay, which measures the mitochondrial metabolism in the entire cell. The resulting  $IC_{50}$  values are shown in Table 1.

The antiproliferative activity shows a significant difference between the three complexes. Complex **3**, which is diaminosubstituted in the 4,4'-position, is not active. However, complex **1**, bearing *tert*-butyl groups in 4,4'-position, shows moderate cytotoxicity against MCF-7 and HT-29 cancer cells with 69.4  $\mu$ M and 59.7  $\mu$ M, respectively. In contrast, complex **2**, with the large nonyl groups, has IC<sub>50</sub> values about six times lower than complex **1**. Moreover, the cytotoxicity of **2** is significantly improved compared to cisplatin, with 7.1  $\mu$ M against MCF-7 and 10.4  $\mu$ M against HT-29. In comparison, the non-derivatized **Table 1.** IC<sub>50</sub> values in  $\mu$ M of 1–3 for the antiproliferative activity towards MCF-7 and HT-29 cells. MTT assay, 48 h incubation time, total concentration of DMSO was 0.5% in all samples including cisplatin control. Results are mean values of three independent measurements, +/- standard deviation.

| compound  | MCF-7          | HT-29           | GM5657T          |
|-----------|----------------|-----------------|------------------|
| 1         | $69.4 \pm 3.2$ | $59.7 \pm 2.6$  | $160.9 \pm 15.5$ |
| 2         | $7.1 \pm 1.5$  | $10.4 \pm 0.5$  | 21.0 $\pm$ 0.9   |
| 3         | > 250          | > 250           | > 250            |
| Cisplatin | $48.9 \pm 8.8$ | $94.3 \pm 12.3$ | 19.7 $\pm$ 4.5   |

bpy complex  $[Rh(\eta^5-C_5Me_5)Cl(bpy)]Cl$ , published by Sheldrick and co-workers, shows no cytotoxicity against MCF-7 and HT-29 up to 100  $\mu$ M. The complex undergoes a Cl<sup>-</sup>/water exchange,<sup>[26]</sup> typical for complexes bearing the Rh<sup>III</sup>(η<sup>5</sup>-C₅Me₅)Cl backbone.<sup>[18]</sup> The formed dicationic species is only marginally taken up by cells, leading to low activity.<sup>[27]</sup> Therefore, we tested the stability of our complexes in water/DMSO, simulating our assay conditions. The stability was monitored by <sup>1</sup>H NMR spectroscopy, recording spectra between 5 minutes to 72 hours after dissolution (compare the ESI of this article). During this time, neither the compound signals changed nor an additional, shifted water or DMSO signal appeared. As compounds 1-3 behave similarly, the difference in activity needs to arise from the residues. For larger aromatic systems, the uptake and cytotoxicity are improved by increasing the  $\pi$ -system, but the addition of charged groups leads to activity loss.<sup>[27]</sup> This observation fits our findings that NH<sub>2</sub> derivatization (3, protonated under physiological conditions) leads to activity loss, while the alkyl chains <sup>t</sup>Bu (1) and nonyl (2) show moderate and good activity, respectively.

As anticancer drugs should be selective towards cancer cells, cytotoxicity was tested additionally against normal human fibroblast cells (GM5657T). Here, the approved drug cisplatin is two to five times more toxic against GM5657T than against MCF-7 or HT-29, respectively. This finding is in agreement with the known and massive side effects of cisplatin treatment. In contrast, our active compounds 1 and 2 show improved selectivity towards cancer cells as they are two times more active against both tested cell lines than against the non-cancerous human fibroblast cells. As noted before, compound 3 is not active against all tested cell lines.

## Conclusions

The synthesis and the characterization of three rhodium compounds of the type  $[Rh(\eta^5-C_5Me_5)Cl(N^N)]PF_6$  (N^N=4,4'-disubstituted-2,2'-bipyridines, 1–3) were described. During these investigations the molecular structure of compound 3 was determined by an X-ray diffraction study. The antiproliferative activity of complex 1 is moderate against the MCF-7 and HT-29 cancer cell lines, while 2 shows promising activity in the low  $\mu$ M range. Unlike the established anticancer drug cisplatin, both compounds show some selectivity towards cancer cells

over normal, non-cancerous cells like human fibroblasts. It can be speculated that an increased lipophilicity of **2** leads to higher cell uptake, and hence higher activity of the compound. This is also in line with the observation that the amino-substituted compound **3** is inactive. A similar trend was observed for the medicinal activity of metalated or lipidated antimicrobial peptides, where an C<sub>8</sub> chain (octyl group) proved to be optimal<sup>[28]</sup> – similar to the nonyl group used here. Interestingly, substitution with a metallocene (ferrocene or ruthenocene) proved to have an effect comparable to this octyl substitution,<sup>[29]</sup> so related investigations for bimetallic compounds may be an interesting future direction for the work described herein.

# **Experimental Section**

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**General:** All manipulations were performed under an atmosphere of dry nitrogen using conventional Schlenk techniques. Solvents were dried with standard procedures and stored under nitrogen. The corresponding 4,4'-disubstituted-2,2'-bipyridines were purchased from Aldrich and used as received. The starting complex [{Rh( $\eta^{5}$ -C<sub>5</sub>Me<sub>5</sub>)( $\mu$ -Cl)Cl}<sub>2</sub>] was prepared by the literature method.<sup>[30]</sup> NMR spectra were recorded in CD<sub>2</sub>Cl<sub>2</sub> or acetone-d<sub>6</sub> using a Jeol Eclipse 400 instrument operating at 400 MHz (<sup>1</sup>H) and 100 MHz (<sup>13</sup>C) respectively. The <sup>1</sup>H NMR stability tests were recorded in DMSO-d<sub>6</sub> using a Bruker Aviii 300 (300 MHz). Chemical shifts are given in ppm, referenced to the solvent signals. Mass spectra were measured using a JeolMstation JMS 700 instrument. Elemental analyses (C, H, N) were performed by the Microanalytical Laboratory of the Department of Chemistry, LMU Munich, using a Heraeus Elementar Vario EL instrument.

## **Biological activities**

MCF-7, HT-29 and GM5657T cells were grown in Dulbecco's Modified Eagle's Medium (DMEM), containing 10% fetal calf serum, 1% penicillin and streptomycin. For harvesting, the cells were detached from the wells with trypsin and EDTA, centrifugated and resuspended in the cell culture medium. 96 well plates were prepared with 6000 cells per well for both cell lines and incubated for 24 h at 37 °C with 10% CO<sub>2</sub>. Afterwards, the cells were treated with the compounds with a final DMSO concentration of 0.5%/well. For comparison, the growth medium with 0.5% DMSO was used as a negative control. After incubation for 48 h, 50  $\mu$ L MTT (2.5 mg/mL) was added and further incubated for 2 h. The medium was removed, the formazan dye was dissolved in DMSO, and the absorption was measured at 550 nm, using 620 nm as a reference wavelength. All tests were carried out in triplicates in three independent experiments for each cell line.

**Synthesis of compounds 1–3**: To a suspension of  $[\{Rh(\eta^5-C_5Me_5)(\mu-Cl)Cl\}_2]$  (0.15 mmol) in 25 mL of MeOH the corresponding 4,4'-disubstituted-2,2'-bipyridine (0.3 mmol) was added and the mixture stirred for 1 h resulting in a clear orange solution. Then KPF<sub>6</sub> (0.4 mmol) was added and the mixture stirred for additional 30 min. At this point the products were dissolved in methanol. To the resulting solution diethyl ether (30 mL) was added in each case and the mixtures stored at -28 °C overnight. Thus, the products precipitated as yellows powders which were separated by filtration, washed twice with diethyl ether and dried in vacuo affording analytically pure products.

[**Rh**(η<sup>5</sup>-**C**<sub>5</sub>**Me**<sub>3</sub>)**Cl**(4,4'-(**Bu**<sup>1</sup>)<sub>2</sub>-2,2'-**bpy**)]**PF**<sub>6</sub> (1): Yield: 110 mg (53.4%). *Anal.* C<sub>28</sub>H<sub>39</sub>ClF<sub>6</sub>N<sub>2</sub>PRh (686.95): calcd. C, 48.96; H, 5.72; N, 4.08. Found: C, 48.71; H, 5.98; N, 3.89%. **MS** (FAB<sup>+</sup>): m/z=541.2 [M<sup>+</sup>] complex cation. <sup>1</sup>**H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 8.67 (d, J<sub>HH</sub> = 6.0 Hz, 2H), 8.11 (d, J<sub>HH</sub> = 2.0 Hz, 2H), 7.74 (dd, J<sub>HH</sub> = 6.0 Hz, J<sub>HH</sub> = 2.0 Hz, 2H), 1.68 (s, 15H, Cp<sup>\*</sup>-CH<sub>3</sub>), 1.44 (s, 18H, tert-C<sub>4</sub>H<sub>9</sub>). <sup>13</sup>C{<sup>1</sup>H} **NMR** (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 165.3, 154.1, 151.0, 125.8, 120.3, 97.1 (J<sub>RhC</sub> = 8.6 Hz, Cp<sup>\*</sup>-CCH<sub>3</sub>), 35.7 (CMe<sub>3</sub>), 30.0 (C-CH<sub>3</sub>), 8.8 (Cp<sup>\*</sup>-CH<sub>3</sub>).

[**Rh**(η<sup>5</sup>-**C**<sub>5</sub>**Me**<sub>5</sub>)**Cl**(4,4'-(nonyl)<sub>2</sub>-2,2'-bpy)]**PF**<sub>6</sub> (2): Yield: 120 mg (48.4 %). *Anal.* C<sub>38</sub>H<sub>59</sub>ClF<sub>6</sub>N<sub>2</sub>PRh (827.23): calcd. C, 55.17; H, 7.19; N, 3.39. Found: C, 55.00; H, 7.16; N, 3.28 %. **MS** (FAB<sup>+</sup>): m/z=682.3 [M<sup>+</sup>] complex cation. <sup>1</sup>**H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =8.62 (d, J<sub>HH</sub>= 5.6 Hz, 2H), 8.01 (d, J<sub>HH</sub>=1.6 Hz, 2H), 7.55 (dd, J<sub>HH</sub>=5.6 Hz, J<sub>HH</sub>= 1.6 Hz, 2H), 2.68 (m, 8H, H<sub>non</sub>), 1.68 (m, 8H, H<sub>non</sub>), 1.32 (m, 10H, H<sub>non</sub>), 1.26 (m, 6H, H<sub>non</sub>), 0.86 (t, J<sub>HH</sub>=7.0 Hz, 6H), 1.67 (s, 15H, Cp\*-CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H} **NMR** (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =157.6, 154.0, 150.7, 128.4, 123.5, 97.0 (J<sub>RhC</sub>=7.6 Hz), 35.5, 31.9, 30.2, 29.5, 29.4, 29.3, 29.2, 22.7, 13.9, 8.8 (Cp\*-CH<sub>3</sub>).

[**Rh**(η<sup>5</sup>-**C**<sub>5</sub>**Me**<sub>5</sub>)**Cl**(4,4'-(**NH**<sub>2</sub>)<sub>2</sub>-2,2'-**bpy**)]**PF**<sub>6</sub> (3): Yield: 125 mg (68.9%). *Anal.* C<sub>20</sub>H<sub>25</sub>ClF<sub>6</sub>N<sub>4</sub>PRh (604.77): calcd. C, 39.72; H, 4.17; N, 9.26. Found: C, 39.64; H, 4.17; N, 9.16%. **MS** (FAB<sup>+</sup>): m/z=459.1 [M<sup>+</sup>] complex cation. <sup>1</sup>**H NMR** (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 8.06 (d, J<sub>HH</sub> = 6.4 Hz, 2H), 7.22 (d, J<sub>HH</sub> = 2.8 Hz, 2H), 6.75 (dd, J = 2.8 Hz, J = 6.8 Hz, 2H), 5.11 (s, br, 4H, NH<sub>2</sub>), 1.61 (s, 15H, Cp<sup>\*</sup>-CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H} **NMR** (acetoned<sub>6</sub>):  $\delta$  = 156.8, 155.1, 151.1, 112.2, 106.7, 95.6 (J<sub>RhC</sub> = 7.6 Hz), 8.1 (Cp<sup>\*</sup>-CH<sub>3</sub>).

X-ray Crystal Structure Determination: Crystals of 3 suitable for an X-ray diffraction study were obtained by crystallization from dichloromethane/methanol/iso-hexane mixtures at ambient temperature. Crystals were selected by means of a polarization microscope, mounted on a MiTeGen MicroLoop, and investigated with a Bruker D8 Venture TXS diffractometer using Mo-K $\alpha$  radiation ( $\lambda$  = 0.71073 Å). The frames were integrated with the Bruker SAINT software package.<sup>[31]</sup> All C-bound hydrogen atoms have been calculated in ideal geometry riding on their parent atoms. The Nand O-bound hydrogen atoms have been refined freely. The N-Hdistances have been restrained to be equal within a standard deviation of 0.01 Å. The ISOR restraint has been applied for one F atom. The structure has been refined as a 2-component inversion twin (BASF 0.02). Data were corrected for absorption effects using the Multi-Scan method (SADABS).<sup>[32]</sup> The structure was solved by direct methods and refined by full-matrix least-squares calculations on  $F^2$  using the Bruker SHELXTL Software package.<sup>[33]</sup> The figures have been drawn at the 25% ellipsoid probability level using ORTEP.<sup>[34]</sup> The H atoms, the methanol molecules and the hexafluoridophosphate anion respectively, in the Figure 1 have been omitted for more clarity. Details of the crystal data, data collection, structure solution, and refinement parameters of compound 3 are summarized in Table 2.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge upon quoting the depository number CCDC-2289088 (3) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

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| Table 2. Crystal data and structurepound 3.  | refinement details of com-   |
|--|--|
| Compound<br>Empirical formula<br>$M/g  mol^{-1}$<br>Temperature/K<br>Crystal system<br>Space group<br>a/Å<br>b/Å<br>c/Å<br>a/°<br>B/°<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>$\gamma/°$<br>Reflections observed<br>Reflections in refinement<br>$\gamma$<br>$\gamma(\gamma)$ | <b>3</b><br>$C_{20}H_{25}CIF_6N_4PRh \cdot 2 MeOH$<br>668.85<br>173(2)<br>orthorhombic<br>$P2_12_12_1$<br>12.7951(5)<br>13.6276(5)<br>15.8246(5)<br>90<br>90<br>90<br>90<br>90<br>90<br>90<br>90<br>90<br>90 |
| $\Delta \varrho_{fin}$ (max/min)/e Å <sup>-3</sup>   | 0.623/-0.556   |

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# **Conflict of Interest**

The authors declare no conflict of interest.

# **Data Availability Statement**

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

**Keywords:** Bidentate *N*-donor ligands · Crystal structure · Cytotoxic activity · Half-sandwich complexes · Rhodium

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