Journal of Inorganic and General Chemistry
ZAAC
Zeitschrift für anorganische und allgemeine Chemie
www.zaac.wiley-vch.de
RESEARCH ARTICLE
DOI: 10.1002/zaac.202200382

Synthesis, Characterization and Cytotoxic Activities of Half-sandwich Pentamethylcyclopentadienyl Iridium(III) Complexes Containing 4,4'-substituted 2,2'-Bipyridine Ligands

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Dedicated to Professor Wolfgang Weigand on the occasion of his 65th birthday

The synthesis and characterization of six new organometallic half-sandwich iridium(III) compounds containing modified 4,4'-substituted 2,2'-bipyridines as the bidentate co-ligands were described. Thus the compounds $[Ir(\eta^5\text{-}C_5Me_5)(N\text{^}N)Cl]PF_6$ [N^N: 4,4'-bpy-Ph, **1**; 4,4'-bpy-Me, **2**; 4,4'-bpy-nonyl, **3**; 4,4'-bpy-CH_2OH, **4**; 4,4'-bpy-Cl, **5**; 4,4'-bpy-NH_2, **6** were obtained by bridge-splitting reactions from the precursor $[\{Ir(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2]$ with the corresponding bidentate bipyridines. The X-ray single-crystal structures of compounds **1**, **2**, **4** and **6** in the solid state were determined. To evaluate the cytotoxic properties of all six compounds, colorimetric assays (MTT assay) against two cancer cell lines, MCF-7 and HT-29, were performed. Most promising results were achieved for compounds **1** and **3** with nonpolar phenyl or nonyl group attached to the bipyridine ligand, while the substitution with less lipophilic groups led to the inactivation of the compound. The most remarkable biological activity showed compound **3** with an IC_{50} value in the low macromolecular range and >40-fold enhanced toxicity compared to cisplatin against both cell lines.

Introduction

The quest for alternative anticancer drugs to the well-known cisplatin and its derivatives is highly needed because of undesirable side effects and easily acquired drug resistance of the latter. In this light, organometallic complexes of transition metals other than platinum have been widely studied in the development of new anticancer metal-containing drugs.[1] Especially for the treatment of skin cancers, the development of such metallodrugs was reviewed very recently.[2] Cyclometalated iridium(III) complexes belong to compounds of potential candidates because they play a crucial role in studies of cancer therapy due to their high cytotoxic activities.[3] Thus, in the last years we investigated the biological activities of many derivatives bearing modified phenanthrolines and related bipyridines as the ancillary ligands.[4] Octahedral iridium(III) species of the investigated bis-cyclometalated type of complex are considered very inert towards ligand substitution reactions due to the low-spin $5d^6$ electron configuration. On the other hand, the introduction of a cyclopentadienyl ligand in iridium(III) complexes can increase the ligand exchange rate considerably.[5] This is an important feature that has been exploited for both inert and labile iridium(III) complexes as anticancer agents. Among these compounds, half-sandwich iridium(III) complexes containing bidentate N^N or cyclometalated C^N ligands received great attention even in light of the mechanism of actions which were found to be different from platinum-based anticancer drugs, *e.g.*.[6–9] More generally speaking, half-sandwich Ir(III) complexes have received significant attention as diagnostic or therapeutic agents in recent years.[10–18] Beside the properties of the cyclopentadienyl ligand, the electronic and steric features of the present bidentate co-ligand can show important effects on the biological activities.[8,9] In this context, effects of the functional groups within the N^N-chelated ligands in half-sandwich iridium(III) anticancer complexes has not been widely investigated.[19] Therefore, beside our current investigations on bis-cyclometalated octahedral iridium(III) complexes,[4] we are also interested to study the cancer cell cytotoxicity of half-sandwich iridium(III) complexes bearing modified neutral N^N-chelating ligands of 4,4'-substituted 2,2'-bipyridines. In this paper we describe the synthesis and characterization of six new half-sandwich iridium(III) com-

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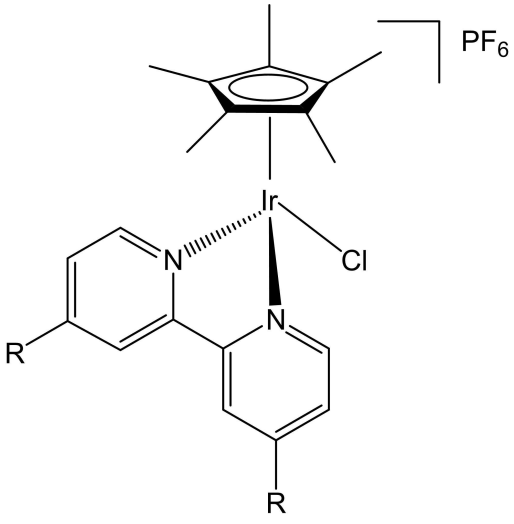
pounds of the type $[Ir(\eta^5\text{-}C_5Me_5)(N\hat{}N)Cl]PF_6$, including the determination of the molecular structure in the crystal of four representatives, where the bidentate N^N ligands have been chosen as modified 4,4'-substituted 2,2'-bipyridines. The anticancer activities of these compounds have been investigated towards the prominent cell lines MCF-7 (human breast adenocarcinoma) and HT-29 (colon adenocarcinoma) using the MTT assay and compared to the clinically used benchmark metallodrug cisplatin.

Results and Discussion

The preparation of the cationic mononuclear title complexes was realized by bridge-splitting reaction of the precursor $[\{Ir(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2]$ with the corresponding bidentate chelating 4,4'-substituted-2,2'-bipyridine ligands by stirring for one hour in methanol at room temperature. The primarily formed chloride salts yielded after metathesis with KPF_6 the corresponding hexafluoridophosphate compounds **1**–**6** (see Eq. 1 and Scheme 1 respectively).

$$[\{Ir(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2] + 2\ N\hat{}N + 2\ KPF_6 \rightarrow 2\ [Ir(\eta^5\text{-}C_5Me_5)(N\hat{}N)Cl]PF_6 + 2\ KCl \quad (1)$$

All compounds were obtained in yields in the range from 42 to 83 % and characterized by elemental analysis, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy as well as by mass spectrometry. Additionally, for compounds **1**, **2**, **4**, and **6** single-crystal X-ray diffraction studies were carried out to confirm its molecular structure in the crystal. The ^1H and $^{13}C\{^1H\}$ NMR spectra of all new compounds confirmed the assumed molecular constitution (see Experimental Section).



R = Ph (**1**), R = Me (**2**), R = nonyl (**3**),
R = CH_2OH (**4**), R = Cl (**5**), R = NH_2 (**6**)

Scheme 1. Graphical overview on compounds **1**–**6**.

Exemplarily, the data should be discussed on one selected compound. The proton NMR spectrum of **5** (400 MHz, acetone-d_6) showed a singlet at 1.74 ppm corresponding to five chemically equivalent methyl groups of the η^5-C_5Me_5 ligand. The aromatic protons of the bpy ligand resonated at 9.08 (d), 8.93 (d) and 8.00 (dd). These values and the corresponding coupling constants agree well with the reported ones for the ligand bpy-Cl in the closely related half-sandwich compound $[IrCp^{biph}(bpy\text{-}Cl)]PF_6$.[19] The $^{13}C\{^1H\}$ NMR spectrum of **5** (100 MHz, acetone-d_6) exhibited a singlet at 7.8 ppm indicating the carbon atoms of the methyl groups of the η^5-C_5Me_5 ligand. The aromatic carbon atoms of the latter resonated as singlet at 89.9 ppm, and finally, five singlets corresponding to the remaining aromatic carbon atoms of the bpy ligand between 125.2 and 156.1 ppm were found.

Molecular Structure of Compounds 1, 2, 4 and 6

Single-crystals of compounds **1**, **2**, **4** and **6** were grown from dichloromethane/methanol/*iso*-hexane mixtures at room temperature and investigated by X-ray diffraction studies. The results affording information on the molecular structures are shown in Figures 1–4. All the investigated complexes showed the expected half-sandwich pseudo-octahedral "three-legged piano-stool" geometry with the iridium bound to a η^5-cyclopentadienyl, a chlorido and a chelating 4,4'-substituted 2,2'-bipyridine ligand, respectively. Compound **1** crystallized from the before-mentioned mixture in the monoclinic space group $P2_1/n$ with four molecules in the unit cell. An ORTEP view of the molecular cation of **1** is depicted in Figure 1, selected bond lengths are given in the caption.

In the literature, closely related molecular structures were reported, for example in the complex salts $[Ir(\eta^5\text{-}$

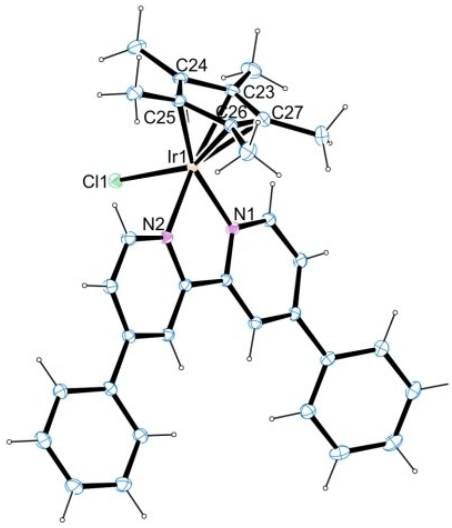


Figure 1. The molecular structure of the complex cation of compound **1** in the crystal (ORTEP drawing and atom labeling scheme with 50 % probability level). Selected bond lengths/Å: Ir1–N1, 2.090(2); Ir1–N2, 2.094(2); Ir1–Cl, 2.4037(6).

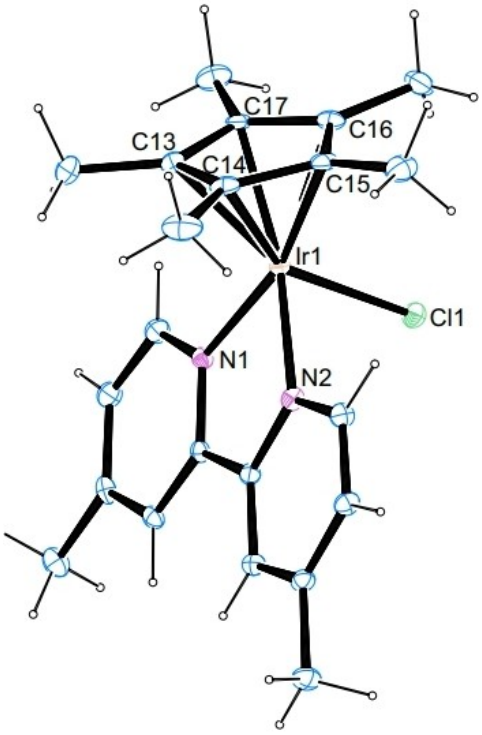


Figure 2. The molecular structure of the complex cation of compound **2** in the crystal (ORTEP drawing and atom labeling scheme with 50% probability level). Selected bond lengths/Å: Ir1–N1, 2.102(5); Ir1–N2, 2.090(5); Ir1–Cl, 2.385(1).

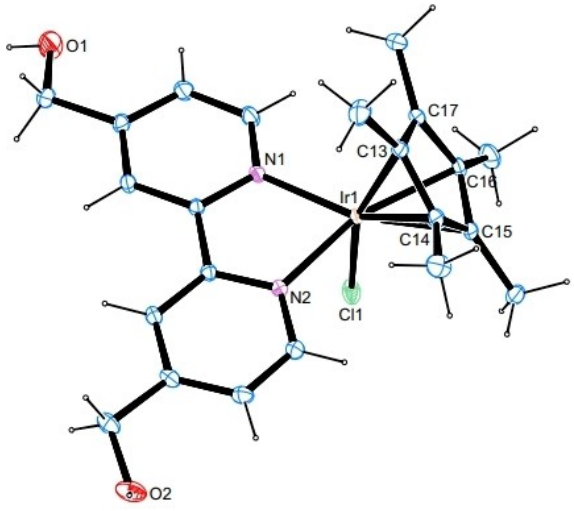


Figure 3. The molecular structure of the complex cation of compound **4** in the crystal (ORTEP drawing and atom labeling scheme with 50% probability level). Selected bond lengths/Å: Ir1–N1, 2.103(2); Ir1–N2, 2.093(2); Ir1–Cl, 2.4000(6).

C_5Me_5)(bpy)Cl]Cl,[20] or [Ir(η^5-C_5Me_5)(bpy-CF_3)Cl]Cl.[21] Furthermore, similar molecular structures were described by Sadler and co-workers in related compounds of the composition [Ir(η^5-C_5Me_4R)(bpy)Cl]PF_6 (R = several aromatic substituents), where

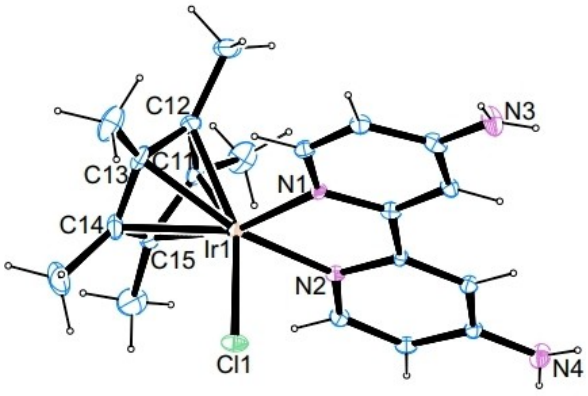


Figure 4. The molecular structure of the complex cation of compound **6** in the crystal (ORTEP drawing and atom labeling scheme with 50% probability level). Selected bond lengths/Å: Ir1–N1, 2.094(4); Ir1–N2, 2.082(4); Ir1–Cl, 2.4304(9).

the Ir–Cl and Ir–N bond lengths were reported ranging from 2.3840(14) to 2.3891(5) and from 2.083(6) to 2.1001(17) Å, respectively.[22] For comparison purposes of the corresponding bond lengths in the title compounds **1**, **2**, **4** and **6** see figure captions in Figures 1–4 affording a good agreement with the reported ones in the literature.[19–22] Compound **2** crystallized in the monoclinic space group $P2_1/c$ with four molecules in the unit cell. An ORTEP view of the molecular cation of **2** is depicted in Figure 2, selected bond lengths are given in the caption.

Compound **4** crystallized in the triclinic space group $P\bar{1}$ with two molecules in the unit cell. An ORTEP view of the molecular cation of **4** is depicted in Figure 3, selected bond lengths are given in the caption.

Compound **6** crystallized in the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell. An ORTEP view of the molecular cation of **6** is depicted in Figure 4, selected bond lengths are given in the caption.

In all crystallographically investigated compounds the pentamethylcyclopentadienyl ligand is symmetrically bound to the central iridium atom.

Biological Activity of Compounds 1–6

Many organometallic iridium(III) complexes show encouraging antiproliferative properties both *in vitro* and *in vivo*. For this reason, the antiproliferative activity of the six new compounds towards the cancer cell lines MCF-7 (human breast adenocarcinoma) and HT-29 (colon adenocarcinoma) has been determined. 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.

Three of the tested compounds, namely **1**, **3** and **5** showed antiproliferative activity against at least one of the tested cell lines. The most active compounds **1** and **3** have higher activity compared to the commonly used chemotherapeutic cisplatin. **3**, with a long aliphatic chain, has an even five- to tenfold lower

Table 1. IC_{50} values in μM of **1**–**6** for the antiproliferative activity towards MCF-7 and HT-29 cells with cisplatin as control reference. MTT assay, 48 h incubation time, all values are reported as mean value ± SD from triplicate experiments with three independent repeats.

compound	MCF-7	HT-29
1	22.9 ± 2.0	10.5 ± 0.7
2	> 250	> 250
3	2.3 ± 0.3	2.0 ± 0.4
4	> 250	> 250
5	184.5 ± 16.0	> 250
6	> 250	> 250
Cisplatin	36.6 ± 1.2	84.1 ± 5.7

IC_{50} than **1**, which is phenylsubstituted. It is interesting to note the excellent activity of **3** in HT-29 cells (2 μM), which is 42-fold enhanced compared to cisplatin. For similar $Ir^{III}(\eta^5\text{-}C_5Me_5)$ complexes with bidentate ancillary coordinating ligands, the lipophilicity has a significant impact on the toxicity due to the cellular accumulation.[22,23] The above-mentioned compound $[Ir(\eta^5\text{-}C_5Me_5)(bpy)Cl]Cl$,[20] when investigated by Sadler and co-workers, showed up to 100 μM no cytotoxic activity while changing only one methyl group to a phenyl group of the $\eta^5\text{-}C_5Me_5$ ligand decreased the IC_{50} value to 15.86 μM.[22] Although we have not experimentally determined logP values or similar measures of lipophilicity in this work, we still feel that our results are qualitatively in agreement with previously reported trends in lipophilicity in this compound class. The chlorido-substituted compound **5** is likely more hydrophilic than e.g. **3**, but still showed slight antiproliferative activity against the MCF-7 cell line. The complexes are in the $5d^6$ electronic configuration, which is inert towards ligand exchange, but the $\eta^5\text{-}C_5Me_5$ could be able to increase the exchange rate similar to the cyclopentadienyl ligand.[5] The stability in DMSO-d_6 with small amounts of water was tested because the chlorido ligand could be substituted by DMSO or water during the MTT assay. In comparison to cisplatin, which is deactivated by DMSO,[24] iridium(III) complexes can be activated by hydrolysis.[22] The herein reported complexes are all stable against both solvents as evidenced by the fact that no change in the methyl group or aromatic proton regions is observable over incubation with a H_2O/DMSO mixture over 2–3 days. Only in compound **4**, an additional singlet at 5.83 ppm began to grow in after 24 h. However, the exact origin of this proton could not be clarified as the aromatic region of compound **4** showed no change whatsoever, and no other new signals were observed in the spectrum.

Conclusions

The bridge-splitting reaction of $[\{Ir(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2]$ with several bidentate chelating 4,4'-substituted-2,2'-bipyridine ligands resulted in formation of six new cationic complexes which were obtained as its corresponding hexafluoridophosphate salts. All the compounds have a "three-legged piano-stool" molecular geometry at the metal center, which was confirmed in four cases by single-crystal X-ray structure determination. All new compounds were investigated by colorimetric assays (MTT assay) against prominent cancer cell lines (MCF-7 and HT-29) to evaluate their cytotoxic properties. Only the two most lipophilic compounds **1** and **3** showed significant cytotoxicity within micromolar concentrations. This indicates lipophilicity as the main influence on the IC_{50} values. As expected for iridium compounds in the oxidation state +III, all compounds are kinetically inert for several days as shown by ^{1}H NMR experiments in a DMSO/water mixture. This behavior is unlike the hydrolysis observed for the clinically used anticancer compound cisplatin, and likely suggests a different mode of action for this compound class.

Experimental Section

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 4,4'-substituted 2,2'-bipyridine ligands were purchased from Aldrich and used as received. The starting complex $[\{Ir(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2]$ was prepared following the literature method.[25] NMR spectra were recorded using a Jeol Eclipse 400 instrument operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) respectively. Chemical shifts are given in ppm, referenced to the solvent signals of dichloromethane at δ = 5.36 (^{1}H) and 53.5 ppm (^{13}C). 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

Dulbecco's Modified Eagle's Medium (DMEM) was used as the growth medium, containing 10% fetal calf serum and 1% penicillin/streptomycin. Detachment of MCF-7 and HT-29 cells was done with trypsin and EDTA, afterwards, the cells were harvested by centrifugation, resuspended in the cell culture medium, and plated out on 96 well plates with 6000 cells/well for both cell lines. The cells were treated with compounds **1**–**6** (DMSO concentrations of 0.5%) with a final volume of 200 μL/well, after an incubation time of 24 h at 37 °C and 10% CO_2. The DMSO concentration was except for the highest constant at 0.5%, therefore as the negative control, a set of cells was only treated with 0.5% DMSO. 48 h were the cells incubated with the compounds, then MTT (2.5 mg/mL) was added and further incubated for 2 h. The medium was removed, and the formazan dye was dissolved in 200 μM DMSO. Using a 620 nm reference wavelength, the absorption of the formazan was measured at 550 nm. For each compound, the test was repeated in triplicates and three independent experiments for each cell line. Stability measurements were performed by periodical ^{1}H NMR measurements using a *Bruker Avii 300* (300 MHz). DMSO-d_6 (2.50 ppm) containing water was used as solvent.

Synthesis of compounds 1–6: To a solution of $[\{Ir(\eta^5\text{-}C_5Me_5)(\mu\text{-}Cl)Cl\}_2]$ (0.15 mmol) in 25 mL of MeOH the 4,4'-substituted 2,2'-bipyridine ligands (0.3 mmol) was added and the mixture was stirred for 1 h at room temperature. KPF_6 (0.4 mmol) was added and the mixture stirred for additional 30 min. During this time the products were obtained as yellow powders which were collected by filtration. The solids were washed twice with cold methanol and

Table 2. Crystal data and structure refinements details for compounds **1**, **2**, **4**, and **6**.

Compound	**1**	**2**	**4**	**6**
Empirical formula	$C_{32}H_{31}ClF_6IrN_2P$	$C_{22}H_{27}ClF_6IrN_2P$	$C_{22}H_{27}ClF_6IrN_2O_2P$	$C_{22}H_{33}ClF_6IrN_4O_2P$
M/g·mol^{-1}	816.21	692.07	724.07	758.14
Temperature/K	173(2)	173(2)	173(2)	173(2)
Crystal system	monoclinic	monoclinic	triclinic	orthorhombic
Space group	$P2/n$	$P2_1/c$	$P\bar{1}$	$P2_1\,2_1\,2_1$
a /Å	7.9868(4)	14.836(3)	8.0421(3)	12.8299(16)
b/Å	24.0582(11)	13.952(3)	11.5442(4)	13.6789(17)
c/Å	16.1474(8)	11.530(2)	14.3415(5)	15.741(2)
α/°	90	90	104.0720(10)	90
ß/°	101.177(3)	98.9860(10)	93.1670(10)	90
γ /°	90	90	107.1180(10)	90
V/Å^3	3043.8(3)	2355.6(7)	1122.69(8)	2762.5(6)
Z	4	4	2	4
$\rho_{calcd.}$/g·cm^3	1.781	1.952	1.967	1.823
μ/mm^{-1}	4.589	5.911	5.704	5.055
θ range for data collection/°	2.707–28.282	3.236–26.371	2.874–30.507	2.978–28.280
Reflections observed	7077	4339	6949	6566
Reflections in refinement	7551	4702	7443	6835
S	1.123	1.098	1.057	1.075
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0222$, w$R_2 = 0.0491$	$R_1 = 0.0278$, w$R_2 = 0.0682$	$R_1 = 0.0206$, w$R_2 = 0.0453$	$R_1 = 0.0194$, w$R_2 = 0.0462$
$\Delta\rho_{fin}$ (max/min)/e·Å^{-3}	0.734/−0.758	1.103/−1.313	1.031/−0.568	0.914/−0.835

dried in vacuo. At this point the products were obtained in an analytically pure form.

[Ir(η^5-C$_5$Me$_5$)(4,4'-bpy-Ph)Cl]PF$_6$ (1): Yield: 150 mg (61.2 %). *Anal.* $C_{32}H_{31}ClF_6IrN_2P$ (816.25): C 47.12 (calcd. 47.09), H 3.69 (3.83), N 3.36 (3.43) %. **MS** (FAB$^+$): $m/z = 671.2$ [M$^+$] complex cation. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 8.81 (d, J = 5.6 Hz, 2H), 8.51 (d, J = 1.6 Hz, 2H), 7.95 (dd, J = 2.0 Hz, J = 6.0 Hz, 2H), 7.83 (m, 4H), 7.60 (m 6H), 1.73 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, CD_2Cl_2): δ = 155.5, 152.7, 151.1, 135.2, 131.2, 129.8 (2C), 127.6 (2C), 126.6, 121.5, 89.6, 8.50.

[Ir(η^5-C$_5$Me$_5$)(4,4'-bpy-Me)Cl]PF$_6$ (2): Yield: 173 mg (83.3 %). *Anal.* $C_{22}H_{27}ClF_6IrN_2P$ (692.1): C 38.11 (calcd. 38.18), H 3.98 (3.93), N 3.89 (4.05) %. **MS** (FAB$^+$): $m/z = 547.1$ [M$^+$] complex cation. **^{1}H NMR** (400 MHz, acetone-d$_6$): δ = 8.90 (d, J = 5.6 Hz, 2H), 8.54 (m, 2H), 7.71 (m, 2H), 2.66 (s, 6H), 1.74 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-d$_6$): δ = 155.2, 152.9, 151.3, 129.5, 124.6, 89.1, 20.4, 7.90.

[Ir(η^5-C$_5$Me$_5$)(4,4'-bpy-nonyl)Cl]PF$_6$ (3): Yield: 120 mg (43.6 %). *Anal.* $C_{38}H_{59}ClF_6IrN_2P$ (916.54): C 49.88 (calcd. 49.80), H 6.27 (6.49), N 2.94 (3.06) %. **MS** (FAB$^+$): $m/z = 771.4$ [M$^+$] complex cation. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 8.61 (d, J = 6.0 Hz, 2H), 8.05 (d, J = 1.2 Hz, 2H), 7.53 (dd, J = 1.2 Hz, J = 4.0 Hz, 2H), 3.39 (m, 8H), 1.69 (m, 8H), 1.65 (s, 15H), 1.53 (m, 8H), 1.26 (m, 8H), 0.88 (t, J = 7.2 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, CD_2Cl_2): δ = 157.6, 155.0, 150.4, 128.8, 123.7, 89.1, 35.5, 31.9, 30.2, 29.5, 29.4, 29.3 (2C), 22.7, 13.9, 8.5.

[Ir(η^5-C$_5$Me$_5$)(4,4'-bpy-CH$_2$OH)Cl]PF$_6$ (4): Yield: 120 mg (69.1 %). *Anal.* $C_{22}H_{27}ClF_6IrN_2O_2P$ (579.1): C 36.49 (calcd. 36.49), H 3.62 (3.76), N 3.58 (3.87) %. **MS** (FAB$^+$): $m/z = 547.1$ [M$^+$] complex cation. **^{1}H NMR** (400 MHz, acetone-d$_6$): δ = 9.01 (d, J = 5.6 Hz, 2H), 8.64 (m, 2H), 7.86 (m, 2H), 5.00 (s, 4H), 3.28 (s, 2H), 1.74 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-d$_6$): δ = 157.2, 155.3, 151.5, 125.8, 120.8, 89.2, 61.7, 7.8.

[Ir(η^5-C$_5$Me$_5$)(4,4'-bpy-Cl)Cl]PF$_6$ (5): Yield: 165 mg (79.5 %). *Anal.* $C_{20}H_{21}Cl_3F_6IrN_2P$ (692.1): C 32.32 (calcd. 32.77, H 2.83 (2.89), N 3.54 (3.82) %. **MS** (FAB$^+$): $m/z = 587.0$ [M$^+$] complex cation. **^{1}H NMR** (400 MHz, acetone-d$_6$): δ = 9.08 (d, J = 6.0 Hz, 2H), 8.93 (d, J = 2.4 Hz, 2H), 8.00 (dd, J = 2.4 Hz, J = 6.0 Hz, 2H), 1.74 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-d$_6$): δ = 156.1, 152.9, 148.0, 129.5, 125.2, 89.9, 7.8.

[Ir(η^5-C$_5$Me$_5$)(4,4'-bpy-NH$_2$)Cl]PF$_6$ (6): Yield: 90 mg (43.2 %). *Anal.* $C_{20}H_{25}ClF_6IrN_4P$ (694.1): C 34.46 (calcd. 34.61), H 3.82 (3.63), N 8.02 (8.07) %. **MS** (FAB$^+$): $m/z = 549.1$ [M$^+$] complex cation. **^{1}H NMR** (400 MHz, acetone-d$_6$): δ = 8.33 (d, J = 6.4 Hz, 2H), 7.39 (d, J = 2.4 Hz, 2H), 6.92 (dd, J = 2.4 Hz, J = 6.4 Hz, 2H), 6.62 (s, br, 4H), 1.74 (s, 15H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-d$_6$): δ = 156.6, 155.9, 150.8, 112.3, 106.8, 87.4, 7.8.

X-ray Crystal Structure Determination: Crystals of **1**, **2**, **4**, and **6** suitable for X-ray diffraction studies 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-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXT)[26] and refined by full-matrix least-squares calculations on F^2 (SHELXL-2014/7).[27] The figures have been drawn at the 50% ellipsoid probability level using ORTEP.[28] All C-bound hydrogen atoms have been calculated in ideal geometry riding on their parent atoms. In **4** and **6**, the N- and O-bound hydrogen atoms have been refined freely. In **1**, the complete disorder of the PF_6^- ion has been described by a split model considering two moieties. The ratio of site occupation factors of the two disordered moieties was refined to 0.62/0.38. All P–F bonds have been restrained to be equal within a standard deviation of 0.01 Å. SIMU and ISOR restraints have been applied for several F atoms in order to improve the anisotropic displacement parameters. The structure of **2** has been refined as a 2-component twin (BASF refined to 0.25). The disorder of PF_6^- has been described by a split model. The ratio of site occupation factors of the three disordered parts was refined to 0.35, 0.35 and 0.3. Split atoms have been refined isotropically. The structure of **6** has been refined as an inversion twin (BASF refined to 0.034). The N–H distances as well as the O–H distances have each been restrained to be equal within a standard deviation of 0.01 Å. The ISOR restraint has been applied for four F atoms. Details of the crystal data, data collection, structure solution, and refinement parameters of compound **1**, **2**, **4**, and **6** are summarized in Table 2. Crystallographic data (excluding structure factors) for the structures 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-2211181 (**1**), CCDC-2211182 (**2**), CCDC-2211183 (**4**), and CCDC-2211184 (**6**) (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

Acknowledgements

The authors are grateful to the Department of Chemistry of the Ludwig-Maximilians-Universität Munich for financial support. J. O. is supported by a PhD grant from the DFG-funded GRK2341 (MiCon). Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Bidentate *N*-donor ligands · Cytotoxic activity · Half-sandwich complexes · Iridium

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Manuscript received: December 16, 2022
Revised manuscript received: January 20, 2023

