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ARTICLE

Bis-cyclometalated Iridium Complexes Containing Modified Phenanthroline Ligands and Evaluation of their Cytotoxic Activities

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Dedicated to Prof. Thomas M. Klapötke on the Occasion of his 60th Birthday

Abstract. The synthesis and characterization of new bis-cyclometalated complex salts $[Ir(ptpy)_2(L_{phen})]PF_6$ with L_{phen} = 2,9-dimethyl-4,7-bis(pentyloxy)-1,10-phenanthroline (**1**) and L_{phen} = 2,9-dimethyl-4,7-bis(2-ethoxyethoxyl)-1,10-phenanthroline (**2**) are described. Compounds **1** and **2** were obtained by the reaction of the corresponding phenanthroline ligands with $[\{Ir(\mu\text{-}Cl)(ptpy)_2\}_2]$ in a refluxing CH_2Cl_2/MeOH mixture. The molecular structure of compound **2** was confirmed by single-crystal X-ray structure determination. Complex **2** was crystallized from dichloromethane/methanol/*iso*-hexane in the monoclinic space group $P2_1/c$. The biological activity of both new compounds was examined, and they exhibit significant cytotoxicity against human cancer cell lines with the IC_{50} values around 2 μM, significantly better than the established anticancer drug cisplatin under identical conditions.

Introduction

Metal complexes play an important role in modern medicinal inorganic chemistry approaches to discover and develop new pharmaceutical agents.[1] Amongst these compounds of potential candidates of metallodrugs, cyclometalated iridium(III) complexes are in the focus of studies devoted towards therapy of cancers due to the high cytotoxic activities of many of these compounds and due to the ability of these phosphorescent Ir complexes as cellular staining agents for biomedical molecular imaging.[2] Recently in one example, a selective recognition of DNA defects by cyclometalated Ir^{III} complexes was reported.[3] In earlier works we showed that a modification of the ancillary ligand in complexes $[M(C^\wedge N)_2(N^\wedge N)]^+$ (M = Rh, Ir; C^N = cyclometalated ligand; N^N = bidentate *N*-donor ligand) especially with 4,4′-dialkyl-bipyridines (R = Me, *n*Prop, But, *n*-nonyl) afforded good antiproliferative activities towards HT-29 and MCF-7 cell lines.[4a] The most active compounds in the latter study displayed IC_{50} values down to 120 nM, exhibiting them two orders of magnitude more active than the well-established anticancer drug cisplatin.

Inspired by these results, we were interested in the metal and substituent influence on the cytostatic activity of cyclometalated rhodium and iridium complexes containing substituted 1,10-phenanthrolines as the ancillary ligands.[4b] Currently we directed our studies on 1,10-phenanthrolines which are substituted in the 4,7-positions with enlarged substituents to investigate their corresponding biological activities. In this context we describe here the synthesis, characterization and the evaluation of the cytotoxic activities of two new cyclometalated iridium(III) compounds $[Ir(ptpy)_2(N^\wedge N)]PF_6$ with the co-ligands N^N = 2,9-dimethyl-4,7-bis(pentyloxy)-1,10-phenanthroline and N^N = 2,9-dimethyl-4,7-bis(2-ethoxyethoxyl)-1,10-phenanthroline.

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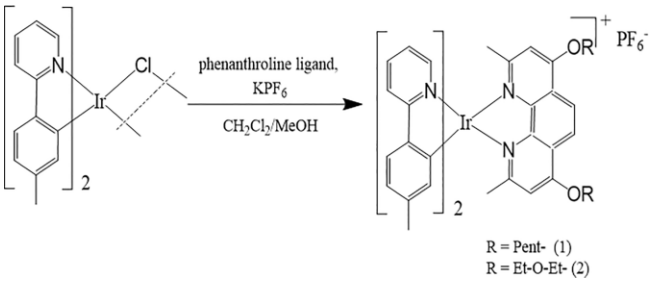
Results and Discussion

For the synthesis of the cationic mononuclear title complexes we used a bridge-splitting reaction starting from the dimeric precursor compound $[\{Ir(\mu\text{-}Cl)(ptpy)_2\}_2]$ (ptpy = 2-*p*-tolylpyridinato) by the corresponding chelating phenanthroline (phen) ligands in a mixture of dichloromethane/methanol under reflux conditions. The intermediate formed chloride salts $[M(ptpy)_2(N^\wedge N)]Cl$ yielded after metathesis with KPF_6 the corresponding hexafluoridophosphate salts (Scheme 1).



Scheme 1. Synthesis of compounds **1** and **2**.

The new compounds were obtained as yellow crystals and characterized by elemental analysis, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy, mass spectrometry, and by infrared as well as by UV/Vis and emission spectroscopy. Moreover, for **2** a single-crystal X-ray diffraction study was undertaken. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of both new compounds confirmed the assumed molecular constitution (see Experimental Section).

Compounds **1** and **2** are strongly luminescent in diluted solutions. The UV/Vis absorption and emission spectra of **1** recorded in dichloromethane are shown in Figure 1. The spectra of compound **2** are almost identical.

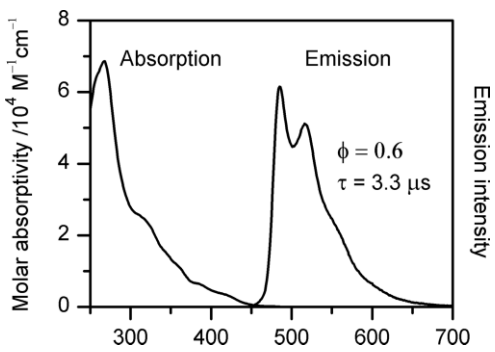


Figure 1. Ambient temperature UV/Vis absorption and photoluminescence spectra of **1** in dichloromethane (concentration of **1** ≈0.05 mM).

The absorption spectrum is characterized by strong bands peaking at 261 nm and a series of overlapping bands of lower intensity at longer wavelengths, up to 450 nm. In analogy to similar compounds,[5] the strong high-energy absorptions are assigned to π → π* excitations localized at the ptpy and phen ligands and the weak low-energy absorptions are due to mixed metal-to-ligand (d → π*, MLCT) and ligand-to-ligand [π(ptpy) → π*(phen), LLCT] charge and ligand centered [π(ptpy) → π*(ptpy), LC] character. In particular, according to results of DFT and TD-DFT computations, for the three lowest-energy singlet excited states, mixed ^{1}MLCT/LLCT character is inferred. (Table 1 and Figure 2)

The emission spectra of compounds **1** and **2** represent partly structured bands in the green-yellow spectral region with the maximum (first apparent peak of the vibronic progression) at 485 nm. The photoluminescence quantum yield ϕis 60 % in a degassed solution and about 3 % in air saturated solution, respectively. The decay time τ is 3.3 µs (3.5 µs for compound **2**) and 0.2 µs, respectively. The emitting state is identified as a mixed ^{3}MLCT/LLCT state with significant LC character contributions (cf. Table 1: The HOMO → LUMO+2 and HOMO-1 → LUMO+2 contributions in excited states T_1 and T_2, respectively, of >30 %). However, due to close proximity of the calculated vertical transitions (i.e. three lowest-energy triplet states within a range of as few as 0.1 eV) makes precise assignment of the (relaxed) emitting state difficult.

We were able to obtain yellow crystals of compound **2** suitable for X-ray diffraction. **2** crystallized from dichloromethane/methanol/*iso*-hexane in the monoclinic space group $P2_1/c$ with four molecules in the unit cell. The unit cell has void of around 22.1 % of the cell volume. The program routine SQUEEZE, contained in PLATON, was therefore used for the final refinement. A selected view of the molecular structure of the cationic complex of **2** in the crystal is shown in Figure 3, selected bond lengths and angles are given in the caption. The iridium complex exhibits two cyclometalated 2-(*p*-tolyl)pyridinato ligands and one 9-dimethyl-4,7-bis(2-ethoxyethoxyl-1,10-phenanthroline in a pseudooctahedral coordination sphere around the metal center. The Ir–C bond lengths in the cation of **2** range from 2.011(6) to 2.022(6) Å. The Ir–N bond lengths are in the range of 2.040(5) to 2.056(5) Å. The Ir–N(L) bond lengths are found to be 2.192(6) and 2.212(5) Å, respectively. Thus these Ir–N and Ir–C bond parameters within the cyclo-

Table 1. Lowest-energy electronic transitions of **1** revealed by TD-DFT computations on the molecular ground state geometry at the PBE0/Def2-svp theory level.

Transition	Energy /eV	Oscilator strength	1-Electron configurations	Contributions
$S_0 \rightarrow S_1$	2.74	0.008	HOMO → LUMO	97 %
$S_0 \rightarrow S_2$	2.86	0.007	HOMO → LUMO+1	93 %
$S_0 \rightarrow S_3$	3.06	0.020	HOMO → LUMO+2	92 %
$S_0 \rightarrow T_1$	2.61	0	HOMO → LUMO	20 %
			HOMO → LUMO+1	15 %
			HOMO → LUMO+2	32 %
$S_0 \rightarrow T_2$	2.67	0	HOMO → LUMO	36 %
			HOMO → LUMO+3	27 %
			HOMO-1 → LUMO+2	32 %
$S_0 \rightarrow T_3$	2.69	0	HOMO → LUMO	28 %
			HOMO → LUMO+2	15 %
			HOMO → LUMO+3	24 %
			HOMO-1 → LUMO+2	6 %
			HOMO-1 → LUMO+3	7 %

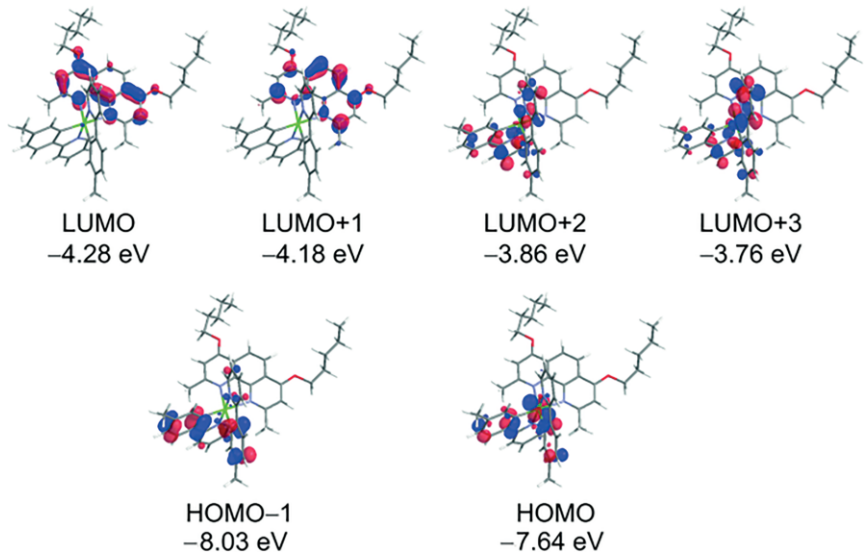


Figure 2. Molecular orbital contour plots and orbital energies of **1** resulting from DFT calculations at the PBE0/Def2-svp theory level.

metalated chelating rings show the usually observed values.[4,6] The two chelate rings containing the cyclometalating ligands are essentially planar. As a consequence of the two "*ortho*" methyl groups on the phenanthroline ligand, the chelate ring containing the two phenanthroline nitrogen atoms deviates significantly from planarity towards an envelope conformation on iridium. While the phenanthroline ligand remains essentially planar [torsion angle N3–C30–C41–N4–0.6(8)°], the chelate ring is twisted [torsion angle Ir–N3–C30–C41 20.0(6)°].

Investigation of the Biological Activity of 1 and 2

Following the seminal work by *Barton* and co–workers on Ru and Rh complexes with diimine-type ligands (e.g. phenanthroline), their DNA interaction,[7] and cellular activity,[8] also organometallic Rh^{III} and Ir^{III} compounds attracted considerable attention as potential candidates for the rational design of novel anti-cancer metallodrugs in recent years.[9] In our collaborative work we demonstrated the potent in vitro cytotoxicity of related Ir and Rh complexes featuring the 2-(*p*-tolyl)pyridine ligand system containing different ancillary bidentate aromatic ligands.[6] To continue our investigations on these promising complexes, the in vitro antiproliferative activity of the novel compounds **1** and **2** was evaluated by an MTT-assay on the two malignant human cancer cell lines HT-29 (colorectal adenocarcinoma) and MCF-7 (breast adenocarcinoma). Both compounds were found to provide antiproliferative activity against both tested cell lines. The compounds **1** and **2** have higher cytotoxicity with IC_{50} values in the lower micromolar range. This corresponds to an approximately ten-fold increase in activity compared to cisplatin (see Table 2).

The bidentate ligand, 1,10-phenanthroline, is a widely favored ligand system, which has been reported to show solely a significant *anti*-proliferative activity against cancer cell lines, such as MCF-7, in a range of 4.73 μM.[10] Accordingly, metal complexes with derivatives of the 1,10-phenanthroline ligand have been intensively studied as potential anticancer agents, over the years. Methylation at the 5,6 position showed the low-

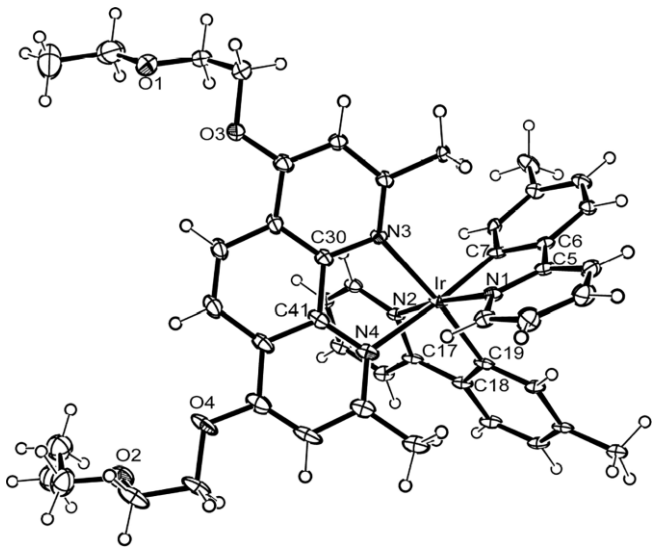


Figure 3. Molecular structure of the cation of **2** in the crystal (ORTEP drawing and atom labeling scheme with 50% probability level). Selected bond lengths /Å and angles /°: Ir–C(7), 2.019(6); Ir–C(19), 2.021(5); Ir–N(1), 2.040(5); Ir–N(2), 2.057(5); Ir–N(3), 2.192(5); Ir–N(4), 2.211(5). N(1)–Ir–N(2), 171.95(19); N(3)–Ir–C(19), 173.3(2); N(4)–Ir–C(7), 175.6(2); N(1)–Ir–C(7), 80.3(2); N(2)–Ir–C(19), 80.2(2); N(3)–Ir–N(4), 75.95(18).

Table 2. IC_{50} values in μM of **1** and **2** for the antiproliferative effects in MCF-7 and HT-29 cells. All data were measured in triplicates with 48 h incubation time. Cisplatin was used as a positive control, treated under identical conditions (with 0.5% final DMSO concentration in all cases).

	IC_{50} [μM] HT-29	IC_{50}[μM] MCF-7
1	2.38 ± 0.1	2.68 ± 0.1
2	2.43 ± 0.2	2.67 ± 0.2
Cisplatin	27.4 ± 6.4	10.5 ± 1.0

est IC_{50} value of 1.5 μM, in a series of experiments comparing different methylated 1,10-phenanthroline ligands in platinum(II) complexes against the cancer cell line L1210 (mouse lymphocytic leukemia).[11] By comparison, methylation in other positions showed significant higher IC_{50} values (> 50μM). In the light of this, our finding that methyl substitution at the 2 and 9 positions as in compounds **1** and **2** yields highly active compounds seems quite remarkable. Moreover, it is likely that the six-atom chains on the 4 and 7 positions increase lipophilicity and hence cellular uptake and activity. It is interesting to see that the exact nature of the substitution in this position does not play a significant role in biological activity. The comparison of various methylated 1,10-phenanthroline derivatives, differing in position and number of methyl groups, provided insight into the relation between chemical structure and biological activity, especially focused on DNA binding.[10] We assume that also compounds **1** and **2** cause DNA interaction and thus low IC_{50} values. According to the determined IC_{50} values, it is highly recommended to further investigate on these phenanthroline based ligand systems to optimize potential anti-cancer agents in their cytotoxicity and to reveal further insight in the coherence between the chemical structure and bioactivity.

Conclusions

The synthesis and characterization of the new bis-cyclometalated complex salts $[Ir(ptpy)_2(L_{phen})]PF_6$ [L_{phen} = 2,9-dimethyl-4,7-bis(pentyloxy)-1,10-phenanthroline] (**1**) and $[Ir(ptpy)_2(L_{phen})]PF_6$ [L_{phen} = 2,9-dimethyl-4,7-bis(2-ethoxyethoxyl)-1,10-phenanthroline] (**2**) were reported and the crystal and molecular structure of compound **2** was confirmed by single-crystal X-ray structure determination. Both complexes are highly luminescent in diluted solutions at ambient temperature. The green-yellow emission with quantum yields of 60 % measured in degassed samples is subject to oxygen quenching. However, even in air saturated samples the emission is not quenched completely. Furthermore, their biological activities towards cancer cell lines were investigated. The compounds exhibit cytotoxic effects towards two cell lines (HT29 and MCF-7). For **1** and **2** high activities were observed, both providing very similar IC_{50} values in the low micromolar range and an approximately tenfold increase in activity compared to cisplatin.

Experimental Section

General: All manipulations were performed in an atmosphere of dry nitrogen using conventional Schlenk techniques. The starting complex $[\{Ir(\mu\text{-}Cl)(ptpy)_2\}_2]$ was prepared by a modified literature method.[12] NMR spectra were usually recorded in CD_2Cl_2 using a Jeol Eclipse 400 instrument operating at 400 MHz (^1H) and 100 MHz (^{13}C) respectively. Chemical shifts are given in ppm, referenced to the solvent signals. Mass spectra were measured using a JeolMstation JMS 700 spectrometer. IR spectra were recorded as KBr pellets on a Bruker IFS 66v/S spectrometer. 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. UV/Vis absorption spectra were measured using a Varian Cary 300 double-beam spectrometer with the sample held in a quartz cuvette of path length 1 cm. The spectra were recorded against a pure solvent in an optically matched cuvette. Emission spectra were measured with a Jobin Yvon Fluorolog-3 steady-state fluorescence spectrometer. Photoluminescence quantum yields were determined with a Hamamatsu C9920–02 system. The emission decay times were measured with a PicoBright PB-375 pulsed diode laser (λ_{exc} = 378 nm, pulse width 100 ps) as an excitation source was. The PL signal was detected with a cooled photomultiplier attached to a FAST ComTec multichannel scalar PCI card with a time resolution of 250 ps.

DFT and TD-DFT Calculations: Quantum mechanical computations were carried out using the NWChem. 6.6 computer program package.[13] The ground state molecular structure was optimized using the PBE0 functional and Def2-SVP atomic basis set for all atoms except Ir, for which Def2-TZVP basis set with appropriate effective core potentials was used.[14] For these ground state geometries 20 singlet and triplet excitations were calculated using the same functional and atomic basis sets, respectively.

Biological Activities: Dulbecco's Modified Eagle's Medium (DMEM), containing 10 % fetal calf serum, 1 % penicillin and streptomycin, was used as growth medium. MCF-7 and HT-29 cells were detached from the wells with trypsin and EDTA, harvested by centrifugation and resuspended again in the cell culture medium. The assays were carried out on 96 well plates with 6000 (3000) cells per well for MCF-7 (HT-29, respectively). After 24 h of incubation at 37 °C and 10 % CO_2, the cells were treated with the compounds **1** and **2** (with DMSO concentrations of 0.5 %) with a final volume of 200 μL per well. For a negative control, one series of cells was left untreated. The cells were incubated for 48 h followed by adding 50 μL MTT (2.5 mg·mL^{-1}). After an incubation time of 2 h, the medium was removed and 200 μL DMSO were added. The formazan crystals were dissolved, and the absorption was measured at 550 nm, using a reference wavelength of 620 nm. Each test was repeated in quadruplicates in two independent experiments for each cell line.

Synthesis of the Modified Phenanthroline Ligands: 2,9-Dimethyl-4,7-bis(pentyloxy)-1,10-phenanthroline and 2,9-dimethyl-4,7-bis(2-ethoxyethoxyl)-1,10-phenanthroline were prepared according to a known procedure by reaction of pentanol and ethoxyethanol, respectively, with sodium hydride and 4,7-dichloro-2,9-dimethyl-1,10-phenanthroline.[15]

Synthesis of 1 and 2: To a solution of $[\{Ir(\mu\text{-}Cl)(ptpy)_2\}_2]$ (0.15 mmol) in 25 mL of a mixture of CH_2Cl_2/MeOH (3:1) the corresponding L_{phen} co-ligand (0.3 mmol) was added and the mixture refluxed with stirring for 2 h. After cooling to room temperature KPF_6 (0.5 mmol) was added and stirred for 20 minutes. The solvent was removed to dryness in vacuo and the residue dissolved in dichloromethane and chromatographed on alumina with CH_2Cl_2/acetone (9:1) as the eluent. The resulting solution was evaporated to dryness and the residue was redissolved in 5 mL of dichloromethane and the product precipitated by slow diffusion with a methanol/*iso*-hexane mixture.

$[Ir(ptpy)_2$(2,9-dimethyl-4,7-bis(pentyloxy)-1,10-phenanthroline)$]PF_6$ (1): Yield: 140 mg (44.3 %). $C_{48}H_{52}F_6IrN_4O_2P$: calcd. C, 54.69; H, 4.97; N, 5.31 %; found: C, 54.53; H, 4.80; N, 5.37 %. **MS** (FAB$^+$): *m/z* = 909.3 [M$^+$] complex cation. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 8.25 (s, 2 H), 7.85 (d, J = 8 Hz, 2 H), 7.69 (m, 2 H), 7.51 (m, 4 H), 6.85 (s, 2 H), 6.78 (m, 4 H), 5.93 (s, 2 H), 4.24 (m, 4 H), 2.04 (s, 6 H), 2.00 (s, 6 H), 1.93 (m, 4 H), 1.47 (m, 8 H), 0.95 (t, $^3J_{HH}$ = 6.8 Hz, 6 H). **^{13}C{^{1}H} NMR** (100 MHz, CD_2Cl_2): δ = 168.1, 166.0, 162.8,

149.7, 149.2, 148.5, 140.6, 140.2, 137.6, 132.3, 124.6, 123.0, 122.5, 121.9, 119.7, 119.2, 107.4, 70.0, 28.4, 28.1, 27.9, 22.4, 21.5, 13.9. **IR** (KBr): $\tilde{\nu}$ = 3446 w,br, 2955 w,br, 2931 w,br, 2868 w,br, 1624 w, 1591 s, 1560 m, 1508 m, 1478 m, 1453 m, 1427 m, 1419 m, 1361 m, 1332 m, 1303 w, 1255 m, 1224 m, 1187 w, 1162 m, 1075 s, br, 1011 w, 972 w, 874 m, 841 vs,br, 773 m, 752 w, 728 w, 679 w, 630 w, 607 w, 579 s, 557 w, 432 w. **UV/Vis** 0.05 mM, CH_2Cl_2 (nm): 261 (51.480), 324 (23.440), 364 (11.020), 386 (7000) 424 (3260) cm^{-1}.

[Ir(ptpy)$_2$(2,9-dimethyl-4,7-bis(2-ethoxyethoxyl-1,10-phenanthroline)]PF_6 (2): Yield: 142 mg (44.8%). $C_{46}H_{48}F_6IrN_4O_4P$: calcd. C, 52.22; H, 4.57; N, 5.30%; found: C, 52.13; H, 4.45; N, 5.12%. **MS** (FAB$^+$): *m/z* = 913.3 [M$^+$] complex cation. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ = 8.28 (s, 2 H), 7.85 (d, J = 8 Hz, 2 H), 7.69 (m, 2 H), 7.51 (m, 4 H), 6.91 (s, 2 H), 6.81 (m, 4 H), 5.93 (s, 2 H), 4.38 (m, 4 H), 3.92 (m, 4 H), 3.62 (q, $^3J_{HH}$ = 6.8 Hz, 4 H), 2.04 (s, 6 H), 2.00 (s, 6 H), 1.21 (t, $^3J_{HH}$ = 6.8 Hz, 6 H). **^{13}C{^{1}H} NMR** (100 MHz, CD_2Cl_2): δ = 168.1, 166.1, 162.7, 149.6, 149.2, 148.5, 140.6, 140.2, 137.7, 132.3, 124.6, 123.1, 122.5, 122.0, 119.8, 119.2, 107.7, 69.5, 68.2, 66.9, 27.8, 22.4, 21.5, 15.0. **IR** (KBr): $\tilde{\nu}$ = 3446 w,br, 2972 w,br, 2929 w,br, 2869 w,br, 1622 w, 1591 s, 1561 m, 1507 m, 1478 m, 1450 m, 1428 m, 1421 m, 1364 m, 1347 m, 1331 w, 1257 m, 1225 m, 1188 w, 1162 m, 1123 w, br, 1072 s, br, 1034 w, 869 w, 843 vr, br, 775 m, 754 w, 729 w, 678 w, 632 w, 609 w, 579 s, 557 w, 432 w. **UV/Vis** 0.05 mM, CH_2Cl_2 (nm): 260 (43.780), 324 (23.100), 365 (11.260), 387 (6880), 424 (3540) cm^{-1}.

Crystal Structure Determination and Refinement: A suitable crystal for X-ray diffraction of **2** was obtained from dichloromethane/MeOH/*iso*-hexane solution. The crystal was selected by means of a polarization microscope, mounted on the tip of a glass fiber, and investigated at 100 K with a Bruker D8 venture TXS diffractometer using Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXT)[16] and refined by full-matrix least-squares calculations on F^2 (SHELXL-2014/7).[17] Anisotropic collection, structure solution, and refinement parameters of compound **2** are summarized in Table 3.

Table 3. Experimental details of the crystal structure determination of **2**.

	2
Empirical formula	$C_{46}H_{48}F_6IrN_4O_4P$
Formula weight	1058.05
Temperature /K	106(2)
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a /Å	16.092(10)
b /Å	11.4658(6)
c /Å	28.1586(16)
β /°	98.9010(109
Volume /Å^3	10265.9(10)
Z	4
ρ calcd. /g·cm^{-3}	1.369
μ /mm^{-1}	2.695
θ range /°	2.245–27.955
Reflections, collected	74312
Reflections, independent	12259
R_{int}	0.0420
wR_2 (all data)	0.1247
R_1	0.0579
S	1.268
$\Delta\rho_{fin}$ (max / min) /e·Å^{-3}	2.557 / –2.604

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 on quoting the depository number CCDC-1949235 for compound **2** (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk)

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Keywords: Bioorganometallic chemistry; Cyclometalated complexes; Iridium; Organometallic anticancer drugs

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