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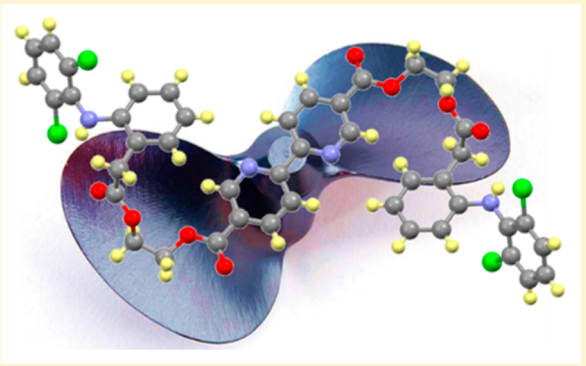
Nonsteroidal Anti-inflammatory—Organometallic Anticancer Compounds

Emilia Păunescu, Sarah McArthur, Mylène Soudani, Rosario Scopelliti, and Paul J. Dyson*

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Supporting Information

ABSTRACT: Compounds that combine metal-based drugs with covalently linked targeted organic agents have been shown, in some instances, to exhibit superior anticancer properties compared to the individual counterparts. Within this framework, we prepared a series of organometallic ruthenium(II)- and osmium(II)-*p*-cymene complexes modified with the nonsteroidal anti-inflammatory drugs (NSAIDs) indomethacin and diclofenac. The NSAIDs are attached to the organometallic moieties via monodentate (pyridine/phosphine) or bidentate (bipyridine) ligands, affording piano-stool Ru(II) and Os(II) arene complexes of general formula [M(η^6-*p*-cymene)Cl_2(*N*)], where *N* is a pyridine-based ligand, {2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetoxy)ethyl-3-(pyridin-3-yl)propanoate} or {2-(2-(2-((2,6-dichlorophenyl)amino)-phenyl)acetoxy)ethyl-3-(pyridin-3-yl)propanoate}, [M(η^6-*p*-cymene)Cl_2(*P*)], where *P* is a phosphine ligand, {2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetoxy)ethyl-4-(diphenylphosphanyl)benzoate} or {2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)ethyl-4-(diphenylphosphanyl)-benzoate, and [M(η^6-*p*-cymene)Cl(*N*,*N*′)][Cl], where *N*,*N*′ is a bipyridine-based ligand, (4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate), (4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate), (bis(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetoxy)-ethyl)[2,2′-bipyridine]-5,5′-dicarboxylate), or (bis(2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)ethyl)[2,2′-bipyridine]-5,5′-dicarboxylate). The antiproliferative properties of the complexes were assessed in human ovarian cancer cells (A2780 and A2780cisR, the latter being resistant to cisplatin) and nontumorigenic human embryonic kidney (HEK-293) cells. Some of the complexes are considerably more cytotoxic than the original drugs and also display significant cancer cell selectivity.



INTRODUCTION

Metal ions are an important building-block for the generation of chemical diversity in the search for novel therapeutic and diagnostic agents, especially anticancer drugs. Following the remarkable success of platinum-based chemotherapeutics,[1] ruthenium complexes have emerged as an encouraging class of anticancer agents, and two ruthenium compounds have been evaluated in the clinic. The compounds evaluated in clinical trials are imidazolium *trans*-[tetrachlorido(dimethyl sulfoxide)-(1*H*-imidazole)ruthenate(III)] (NAMI-A), which reduces the number and size of solid metastatic tumors[2−4] and which recently completed a phase II trial in combination with gemcitabine,[3] and indazolium *trans*-[tetrachloridobis(1*H*-indazole)ruthenate(III)] (KP1019) or its sodium salt KP1339, which are active against a number of primary human tumors (Figure 1).[5−7]

Organometallic ruthenium(II)-arene compounds offer a versatile platform for the design of novel anticancer agents, and for example, [Ru(II)(η^6-*p*-cymene)(PTA)Cl_2] (PTA = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane, RAPTA-C)[8−10] and [Ru(II)(η^6-biphenyl)(en)Cl][PF_6] (en = ethylenediamine, RM175)[11,12] (Figure 1) represent lead structures that have been extensively studied. RAPTA-C exerts antimetastatic,[8,9] antiangiogenic,[13] and antitumor effects.[10] These compounds have been extensively modified via derivatization of the η^6-arene moiety or with various mono- or bidentate leg ligands. Related osmium-based compounds, typically showing slower exchange kinetics than those of ruthenium analogues, have also been evaluated *in vitro*[14−19] and *in vivo*.[11,20−22] In this context, bioactive organic compounds tethered to the complexes have been shown to significantly modulate the activity and selectivity of the organometallic scaffold.[20,23−31] Indeed, the intramolecular combination of a ruthenium(II)-arene moiety with an organic drug can lead to substantial enhancements in antiproliferative activity.[14,23,24,26,32−36]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have recently been shown to exhibit chemo-preventive and anticancer effects,[37−44] and studies have shown that they can increase the activity of certain anticancer drugs when applied in combination.[45−52] Certain NSAIDS are even moderately effective against colorectal and ovarian cancers.[52−55]

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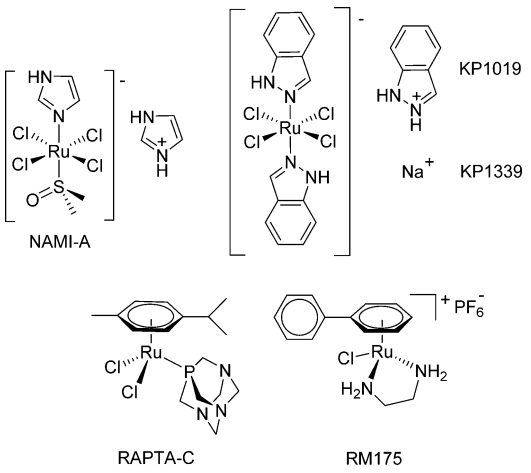

Figure 1. Structures of the ruthenium complexes NAMI-A, KP1019, KP1339, RAPTA-C, and RM175.

The anti-inflammatory effect of NSAIDs is mainly attributed to the inhibition of cyclooxygenase (COX)-mediated production of prostaglandins, although COX-independent mechanisms have also been considered.[56,57] COX-1 is commonly found in the kidney, stomach, and platelets, where it helps to maintain normal physiological function, i.e. control of renal parenchyma, gastric mucosa protection and gastric acid regulation, and platelet function, whereas COX-2 is mainly found in macrophages, leukocytes, and fibroblasts, where it produces the prostaglandins involved in inflammation and mitogenesis. The mechanism of action responsible for the antitumorigenic effects of NSAIDs remains unclear.[55,58−60] COX-independent mechanisms of cancer chemoprevention by anti-inflammatory drugs have been proposed.[41] Nonetheless, COXs are known to play a role in tumor growth, progression, migration, and angiogenesis,[61] which makes them interesting anticancer targets. For example, COX-2 is involved in tumorigenesis (especially of gastrointestinal and colorectal cancer),[43,62−65] and inhibitors of the enzyme are increasingly used as adjuvant modulators in anticancer therapies due to their synergistic effects with traditional chemotherapeutics (indomethacin and diclofenac are both cyclooxygenase inhibitors).[66−68]

Since various studies have established a relationship between inflammation and carcinogenesis, the development of new anticancer chemotherapeutics combining a metal unit with an anti-inflammatory drug represents an attractive approach. In this context, a cobalt(0) carbonyl complex with a pendant aspirin moiety shows promising antiproliferative and antiangiogenic properties[69,70] and silver(I) complexes modified with naproxen and salicilic acid show higher activity than cisplatin against leiomyosarcoma and breast cancer cells.[71,72] Other studies combine NSAIDs with essential metal ions such as Cu(II), Zn(II), and Co(II).[73−78] The dinuclear complex $[Cu_2(indomethacin)_4(DMF)_2]$ was shown to inhibit colorectal cancer growth in rats with only low levels of observed renal and gastrointestinal toxicity.[77,79] Pt(II) and Pt(IV) complexes with indomethacin or ibuprofen conjugates were found to overcome cisplatin resistance in COX-2-expressing triple negative breast cancer cells and ovarian adenocarcinoma cells (Figure 2).[80,81] Mixed valent Ru_2(II/III)-NSAID (ibuprofen, aspirin, naproxen, indomethacin, or ketoprofen) paddlewheel complexes have been reported.[82−84] Coordination to the Ru_2(II/III) core significantly increases the inhibition of C6 rat glioma tumor-cell proliferation compared to the organic compounds alone.

Ruthenium(II)-arene complexes with oxicam-derived ligands have been recently reported (Figure 2).[35] In these compounds the anti-inflammatory drug is directly complexed to the ruthenium(II) center. Based on these studies we decided to tether NSAID moieties to monodentate or bidentate ligands and then to coordinate them to ruthenium(II)- or osmium(II)-*p*-cymene units, thereby creating conjugates with possible new modes of action. Herein, we describe the synthesis and characterization of these compounds and also report on their promising biological properties.

RESULTS AND DISCUSSION

The two NSAIDS considered for this study, indomethacin (**1**, 2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid) and diclofenac (**2**, 2-(2,6-dichloranilino)-phenylacetic acid) (Figure 2), are efficient inflammation

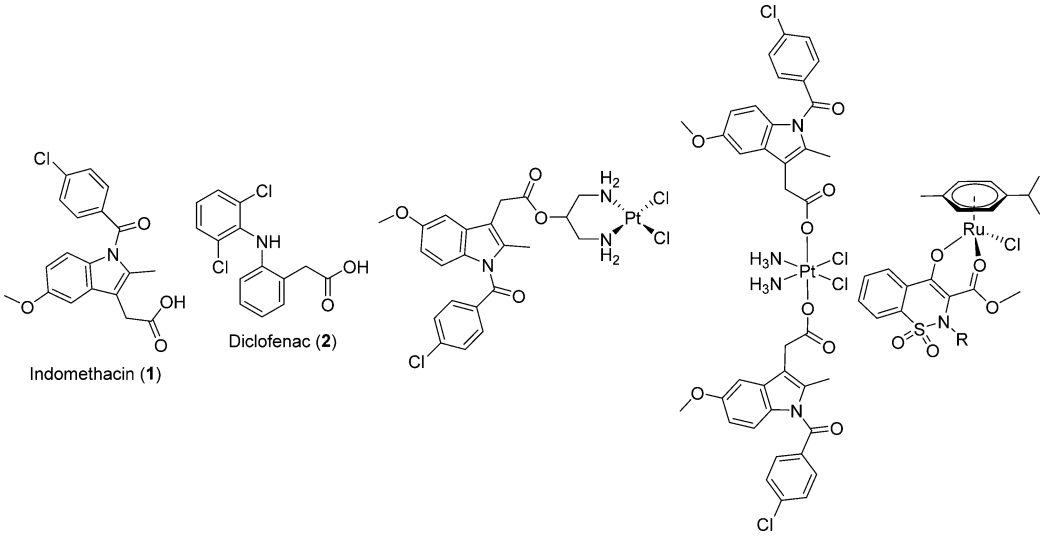

Figure 2. Structures of indomethacin (**1**), diclofenac (**2**), indomethacin Pt(II) and Pt(IV) conjugates, and a Ru(II)-*p*-cymene complex bearing an oxicam-derived ligand.

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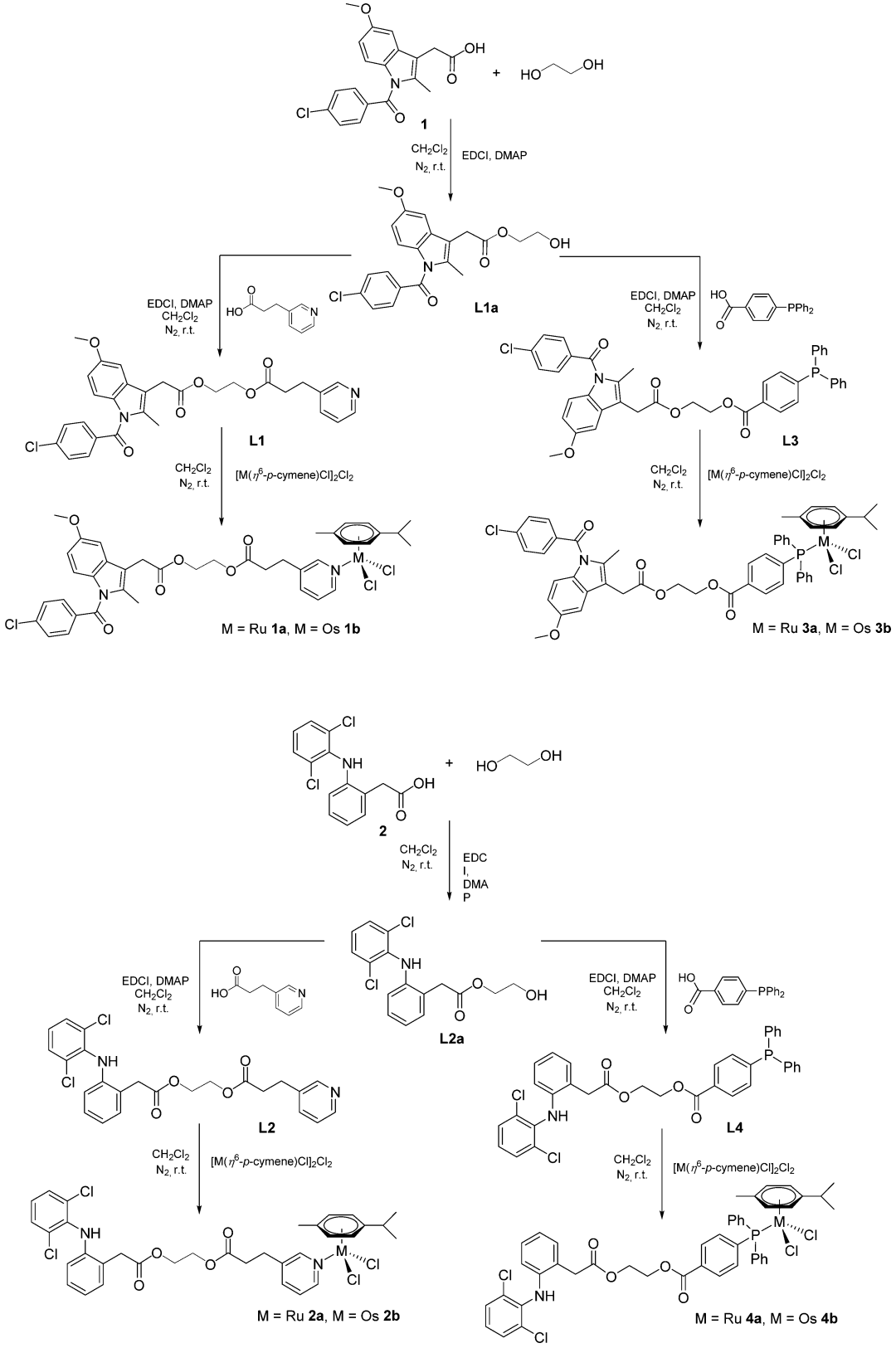
Scheme 1. Synthesis of the Indomethacin-Based Intermediate L1a; Pyridine Complexes 1a, 1b; Phosphine Complexes 3a, 3b (top); Diclofenac-Based Intermediate L2a; Pyridine Complexes 2a, 2b; and Phosphine Complexes 4a, 4b (bottom)



modulators used to treat painful conditions and are also shown to exhibit promising anticancer properties.[54,55,59,85−90] They are both classified as phenylalkanoic acids presenting an easy derivatizable carboxylic group. Previous reports indicate that modification of the carboxylic group does not impair biological activity.[91−93] Monodentate pyridine- and phosphine-based ligands modified with indomethacin and diclofenac were prepared as shown in Scheme 1. In the first step, indomethacin

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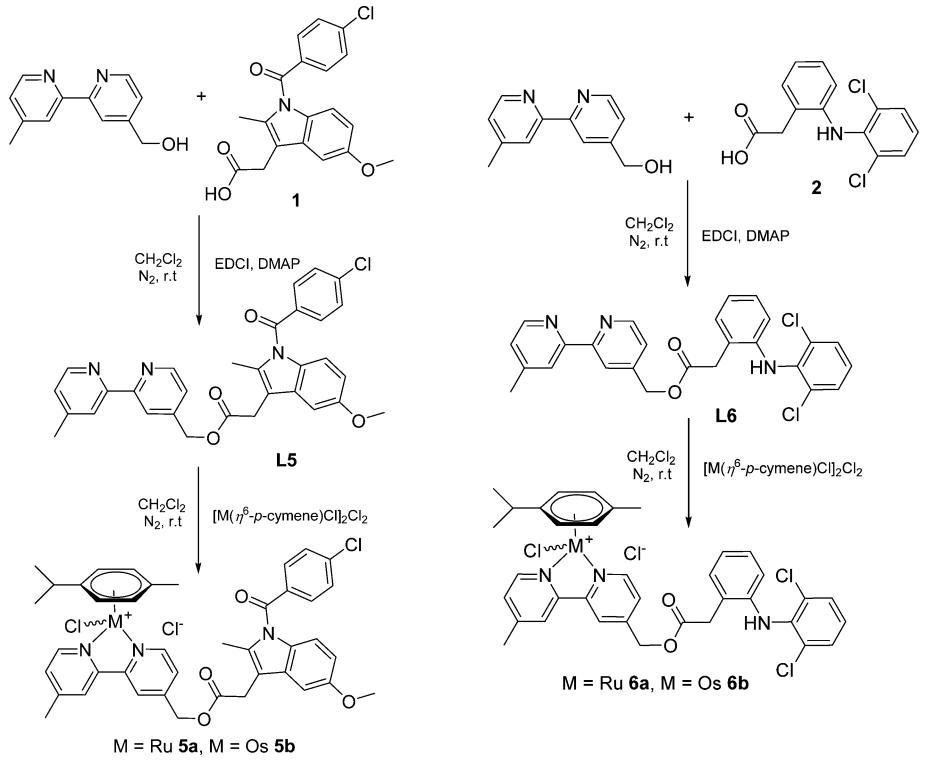
Scheme 2. Synthesis of the Indomethacin Ligand L5 and Complexes 5a, 5b (left) and the Diclofenac Ligand L6 and Complexes 6a, 6b (right)



or diclofenac are reacted with ethylene glycol, leading to intermediates **L1a** and **L2b**, respectively, which are further coupled with 3-(pyridin-3-yl)propanoic acid or 4-(diphenylphosphanyl)benzoic to obtain the pyridine ligands **L1** and **L2** and the phosphine ligands **L3** and **L4** in reasonable overall yields, with the coupling reactions being conducted in the presence of EDCI (1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide) as coupling agent and DMAP ((4-dimethylamino)pyridine) as catalyst. The ruthenium(II)-*p*-cymene complexes **1a**, **2a**, **3a**, and **4a** and osmium(II)-p-cymene complexes **1b**, **2b**, **3b**, and **4b** were obtained from the direct reaction of the appropriate ligands with the metal-dimers $[M(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (M = Ru and Os; Scheme 1). All compounds were characterized by ^1H, ^{31}P (when appropriate), and ^{13}C NMR spectroscopy, mass spectrometry, IR spectroscopy, and elemental analysis (see Experimental Section for full details).

The ^1H NMR spectra of ligands **L1** and **L2** differ from those of the complexes, with coordination to the ruthenium(II) ion, leading to the two protons in the α position to the pyridine nitrogen atom being observed at higher frequencies, by ca. $\Delta\delta_H \approx 0.5$ ppm. In the ^{13}C NMR spectra of **1a** and **2a** the corresponding C atoms α to the pyridine nitrogen are also observed at higher frequencies than in the ligands, $\Delta\delta_C \approx 5$ ppm. A similar, but slightly less pronounced effect, is observed in the ^1H and ^{13}C NMR spectra of the osmium(II) derivatives, **1b** and **2b** ($\Delta\delta_H \approx 0.4$ ppm and $\Delta\delta_C \approx 4$ ppm). The phosphine ligands **L3** and **L4** exhibit peaks at −4.96 and −5.01 ppm, respectively. Following coordination of the ruthenium(II) ion, these peaks are observed at 25.12 ppm for **3a** and 24.94 ppm for **4a**, and for the osmium(II) complexes, the corresponding signals appear at −12.31 ppm for **3b** and −12.50 ppm for **4b**. Coordination of the phosphine ligands results in the peaks corresponding to the *p*-cymene ligand shifting to lower frequencies, i.e. $\Delta\delta_H \approx 0.3$ ppm for **3a**, **3b** and $\Delta\delta_H \approx 0.9$ ppm for **4a**, **4b**. Electrospray ionization mass spectrometry (ESI-MS) corroborated the spectroscopic data with the ligands exhibiting molecular ion peaks corresponding to $[M + H]^+$ ions and the complexes as $[M - Cl]^+$ ions. Complexes **3a**, **3b** and **4a**, **4b** are stable in DMSO-d_6 at r.t. (see Figures S12−S15, Supporting Information), whereas **1a**, **1b** and **2a**, **2b** react over time, presumably involving substitution of the chloride ligands and possibly the pyridine ligand by DMSO-d_6. In water, in the absence of DMSO, the compounds are likely to be more stable.

Indomethacin and diclofenac were also conjugated to a bipyridine ligand. Ligands **L5** and **L6** were obtained in a single step by direct reaction with indomethacin or diclofenac with 4-hydroxymethyl-4′-methyl-2,2′-bipyridyl in the presence of EDCI/DMAP (Scheme 2). Ligands **L5** and **L6** were reacted with the metal dimers $[M(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (M = Ru and Os), affording complexes **5a**, **5b**, **6a**, and **6b** in good yield.

The compounds were characterized by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, IR spectroscopy, and elemental analysis (see Experimental Section for full details). The ^1H NMR spectra of the ligands, **L5** and **L6**, with respect to the corresponding ruthenium(II) and osmium(II)-*p*-cymene complexes, **5a**, **5b**, **6a**, and **6b**, show trends similar to the pyridine complexes described above; that is, the α protons on the heterocycle shift to higher frequencies ($\Delta\delta_H$ 0.7−1.2 ppm), whereas the two protons in the β position to the N atoms are less affected ($\Delta\delta_H \approx 0.4$ ppm). The ^1H and ^{13}C NMR spectra of **5a**, **6a** and **5b**, **6b** reveal diastereotopic splitting for peaks corresponding to the *p*-cymene ring protons as well as to the *iso*-propyl group protons, and the corresponding carbon atoms, due to chirality at the metal center from loss of the 2-fold symmetry of the M(II)-*p*-cymene moiety.[18]

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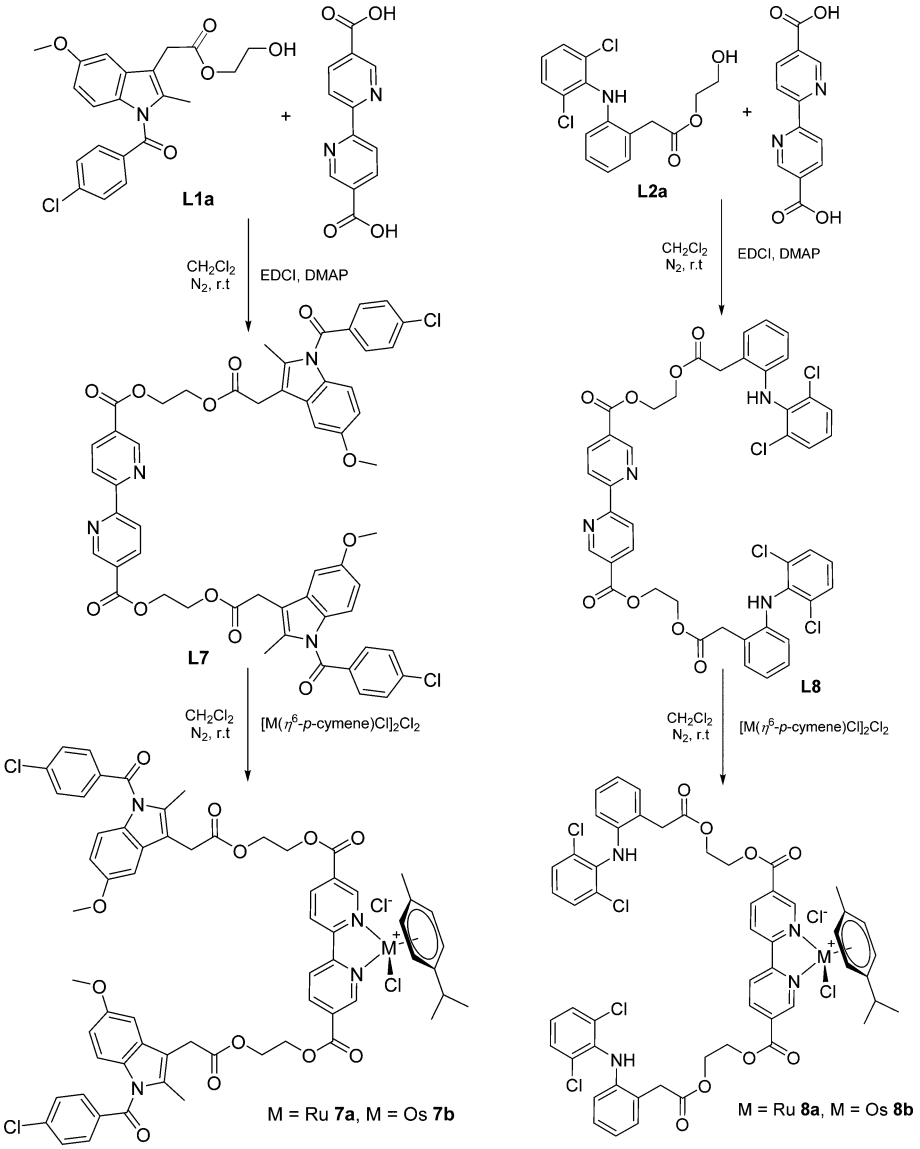
Scheme 3. Synthesis of the Indomethacin Ligand L7 and Complexes 7a, 7b (left) and the Diclofenac Ligand L8 and Complexes 8a and 8b (right)



Coordination of nonsymetrical *N,N*-ligands is accompanied in the ^{1}H NMR spectra by diastereotopic splitting of the signals corresponding to the η^6-bound *p*-cymene ring, i.e. four doublets for the aromatic ring protons and two doublets for the methyl groups of the *iso*-propyl moiety.[94−96] In addition, coordination of **L5** and **L6** to the ruthenium center in **5a** and **6a** is accompanied by a shift toward slightly higher frequencies with $\Delta\delta_H \approx 0.6-0.7$ ppm of the *p*-cymene ring peaks.

The bis-substituted bipyridine ligands **L7** and **L8** were also prepared from the reaction of [2,2′-bipyridine]-5,5′-dicarboxylic acid and the intermediates **L1a** and **L2a** (Scheme 3). Ligands **L7** and **L8** were subsequently reacted with the dimers $[M(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (M = Ru or Os) to afford **7a**, **7b**, **8a**, and **8b** in high yield.

Similar changes to those described above were observed in the ^{1}H NMR spectra of **L7** and **L8** and their corresponding complexes; that is, the protons in the α positions of the bipyridine ring system are shifted to higher frequency ($\Delta\delta_H \approx 0.4-0.5$). In keeping with **5a** and **6a**, the peaks corresponding to the *p*-cymene ring protons in **7a** and **8a** are observed at higher frequency than those observed in the spectra of the dimer in $CDCl_3$, $\Delta\delta_H \approx 0.5$ ppm (in $CDCl_3$ for $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$, the *p*-cymene arene protons appear at 5.33 and 5.46 ppm, while, for $[Os(\eta^6\text{-}p\text{-cymene})Cl_2]_2$, the equivalent protons appear at 6.01 and 6.17 ppm). The ESI-MS of **L5**−**L8** contain a parent ion peak attributable to the $[M + H]^+$ ion and complexes **5a**, **6a**, **5b**, **6b**, **7a**, **7b**, **8a**, and **8b** contain a strong peak corresponding to the $[M - Cl]^+$ ion. All the bipyridine-containing complexes are stable in DMSO-d_6 at r.t. (see Figures S16−S19, Supporting Information).

The solid state structure of **L4** containing the diclofenac moiety was established by single crystal X-ray diffraction analysis (Figure 3), confirming the expected molecular structure. The structure reveals a bifurcated intramolecular H-bond interaction between the diclofenac secondary amine N−H and the oxygen atom of the ester group (contact *D*−H···*A* corresponds to N−H···O) and one of the chlorine atoms of the dichlorophenyl unit (contact *D*−H···*A* corresponds to N−H···Cl) (parameters characterizing these interactions are provided in Tables 1 and 2).

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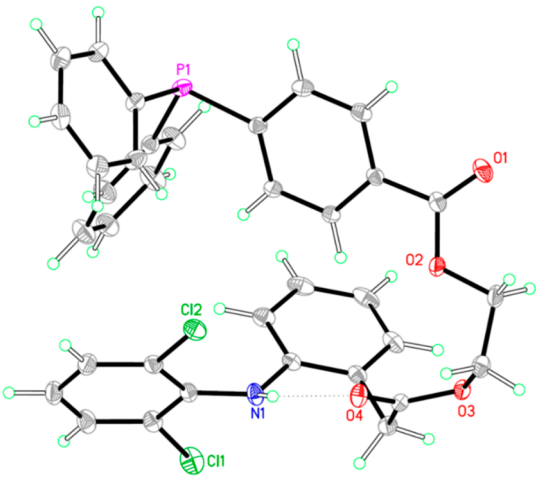

Figure 3. ORTEP representation of **L4** (thermal ellipsoids are 50% equiprobability envelopes, and H atoms are spheres of arbitrary diameter).

Table 1. Intramolecular H-Bonding Interactions (Contact *D*−H···*A* Corresponds to N−H···O) for Ligands L4, L6, and L8 and Complex 8a

	Distance, Å			Angle, deg
Compound	*D*−H	H···*A*	*D*···A	*D*−H···*A*
L4	0.872	2.212	2.995	149.32
L6	0.873	2.184	2.958	147.65
L8	0.893	2.518	3.220	135.93
	0.893	2.518	3.220	135.93
8b	0.966	2.428	3.057	122.41
	0.910	2.457	2.977	116.53

Table 2. Intramolecular H-Bonding Interactions (Contact *D*−H···*A* Corresponds to N−H···Cl) for Ligands L4, L6, and L8 and Complex 8a

	Distance, Å			Angle, deg
Compound	*D*−H	H···*A*	*D*···A	*D*−H···*A*
L4	0.872	2.664	3.004	104.50
L6	0.873	2.578	2.992	110.11
L8	0.893	2.526	3.005	114.27
	0.893	2.526	3.005	114.27
8b	0.966	2.504	3.032	114.26
	0.910	2.335	3.003	130.06

The solid state structure of **L6** was also determined (Figure 4), confirming the expected molecular structure, and as for **L4**, intramolecular H-bonds between the diclofenac secondary amine N−H and the oxygen atom of the C═O ester group are observed (see Tables 1 and 2). The two pyridine rings are coplanar (torsion angle N(1)−C−C−N(2) 176.20°) with a distance between the two nitrogen atoms N(1)···N(2) of 3.623 Å. The bipyridine unit is coplanar with the chloroarene moiety (Figure S4).

The solid state structures of ligand **L8** and its corresponding osmium complex **8b** were established by single crystal X-ray diffraction (Figure 5). In both structures bifurcated intramolecular H-bond interactions similar to those observed in **L4** and **L6** are present (Tables 1 and 2). The two pyridine rings in **L8** are coplanar with a N(1)−C−C−N(2) torsion angle of 180.00°, similar to the topology observed in **L6**. Complex **8b**

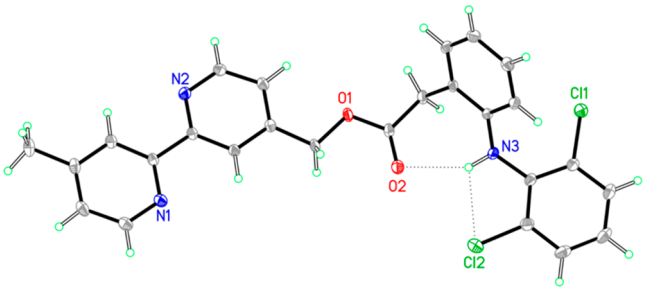

Figure 4. ORTEP representation of **L6** (thermal ellipsoids are 50% equiprobability envelopes, and H atoms are spheres of arbitrary diameter).

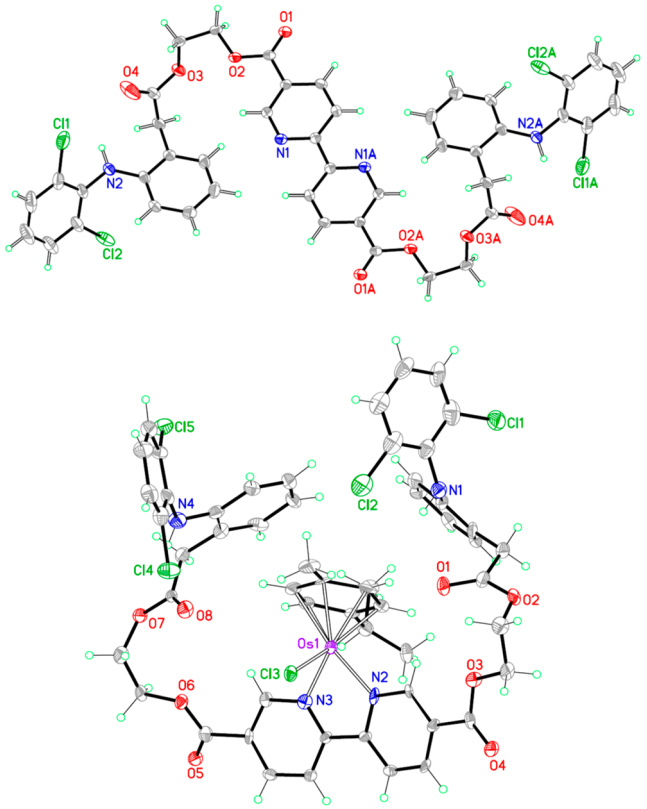

Figure 5. ORTEP representations of **L8** (top) and **8b** (bottom). Thermal ellipsoids are 50% and 30% equiprobability envelopes, respectively, for **L8** (top) and **8b** (bottom), and H atoms are spheres of arbitrary diameter. In the structure of **8b** the chloride counterion has been omitted for clarity.

adopts the familiar half-sandwich three-legged "piano-stool" geometry with the η^6-*p*-cymene ring forming the seat and the bipyridine and chloride ligands representing the legs of the stool. The more representative bond parameters around the Os-center that characterize **8b** in solid state include: the η^6-ring-Os centroid of 1.690 Å, and the Os−Cl 2.408(4) Å, Os−N distances 2.105(11) and 2.129(12) Å. The two rings of the bidentate ligand are almost coplanar with a distance between the two nitrogen atoms N(2)···N(3) of 2.601 Å and a torsion angle N(2)−C−C−N(3) 0(2)°. For all the compounds N−H···O and N−H···Cl intramolecular hydrogen bonding interactions are observed (Tables 1 and 2).

In vitro antiproliferative activity. The cytotoxicity of the ligands **L1**−**L8** and complexes **1a/b**−**8a/b** was assessed in the human ovarian carcinoma cell lines A2780 and A2780cisR, with

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the latter exhibiting acquired resistance to cisplatin, and human embryonic kidney (HEK-293) cells, used as a model for normal cells (Table 3 and Figure 6). The cytotoxicity values of indomethacin **1**, diclofenac **2**, and cisplatin were also evaluated as controls.

Table 3. IC_{50} Values (μM, 72 h) Determined for Indomethacin, Diclofenac, L1-L8, 1*a*/1b−8*a*/8b, and Cisplatin toward Human Ovarian A2780 and A2780R Cancer Cells and Human Embryonic Kidney HEK-293 Cells Using the MTT Assay[a]

Compound	A2780	A2780cisR	HEK-293
1	26.7 ± 1.4	112.3 ± 1.1	66.8 ± 0.6
2	202.3 ± 16.4	84.3 ± 2.6	186.4 ± 13.7
L1	79.4 ± 0.8	53.8 ± 1.4	49.7 ± 0.1
1a	34.2 ± 2.3	110.3 ± 7.1	60.7 ± 2.3
1b	48.7 ± 3.7	77.5 ± 1.1	89.2 ± 3.5
L2	36.6 ± 2.6	79.5 ± 0.6	76.5 ± 0.1
2a	20.0 ± 0.3	79.8 ± 3.5	70.9 ± 0.4
2b	25.1 ± 4.7	62.5 ± 2.1	53.7 ± 1.4
L3	>200	>200	>200
3a	43.5 ± 2.4	29.1 ± 3.5	22.4 ± 0.6
3b	60.2 ± 2.3	74.5 ± 2.8	48.7 ± 1.4
L4	>200	>200	>200
4a	3.1 ± 0.6	24.2 ± 1.3	4.3 ± 1.7
4b	4.8 ± 0.8	45.1 ± 0.8	34.3 ± 3.1
L5	6.8 ± 2.4	13.2 ± 2.4	0.3 ± 0.0
5a	7.8 ± 2.8	8.1 ± 3.5	19.9 ± 1.4
5b	15.5 ± 1.2	14.6 ± 1.9	20.1 ± 0.5
L6	6.2 ± 1.1	22.4 ± 4.9	24.6 ± 1.1
6a	10.2 ± 2.4	9.1 ± 1.7	28.2 ± 0.4
6b	13.6 ± 1.1	18.5 ± 1	23.5 ± 1.5
L7	>200	>200	>200
7a	4.8 ± 1.9	1.7 ± 0.1	4.0 ± 0.2
7b	2.1 ± 0.0	1.4 ± 0.1	4.9 ± 0.3
L8	>200	>200	>200
8a	2.5 ± 0.2	0.2 ± 0.0	4.1 ± 0.5
8b	5.8 ± 0.7	2.2 ± 0.3	9.9 ± 0.7
Cisplatin	0.95 ± 0.3	11.1 ± 0.5	16.5 ± 1.2

[a]Values are given as the mean ± SD.

Compounds **1** and **2** are slightly cytotoxic to the three cell lines, but do not display clinically useful cancer cell selectivity. Ligands **L3**, **L4**, **L7**, and **L8** are essentially nontoxic to any of the cell lines tested (>200 μM). However, there is a dramatic increase in activity when these ligands are coordinated to either the ruthenium(II)- or osmium(II)-*p*-cymene fragments (more than 2 orders of magnitude more cytotoxic in the case of **7a**, **7b** and **8a**, **8b**, reaching low micromolar IC_{50} values in the range of cisplatin and lower in the A2780cisR resistant cell line). For the related pairs, **3a**/**3b** and **4a**/**4b**, merely differing in the metal, i.e. ruthenium versus osmium, the osmium derivatives are the less cytotoxic of each pair. For these compounds, however, selectivity to cancerous cells is not observed. Compounds **1**, **L2**, **2a**, **2b**, **4b**, **5a**, **L6**, **6a**, and **7b** are at least two times more cytotoxic to A2780 cells relative to nontumorigenic HEK-293 cells, although none display the same extent of selectivity as cisplatin. In the case of the cisplatin resistant A2780cisR cancer cells, selectivity relative to nontumorgenic HEK-283 is observed with **2**, **5a**, **6a**, **7a**, **7b**, **8a**, and **8b**, all demonstrating greater selectivity than cisplatin, with **8a** even exceeding the selectivity of cisplatin for the cisplatin sensitive A2780 cell line.

Of the monodentate ligands, **L1** is slightly cytotoxic to all three cell lines tested, but **L3** shows no appreciable toxicity. On coordination to the organometallic fragment in complexes **1a**/**1b**, the selectivity is increased with toxicity toward A2870 also enhanced, whereas the toxicity toward the other two cell lines decreases. In contrast, coordination of **L3** to afford **3a**/**3b** increases the cytotoxicity observed in all three cell lines, but with no selectivity toward the tumor cell lines.

Ligand **L2** is more active against A2780 cells compared to the other two cell lines, and this property is preserved on coordination to the organometallic fragments, i.e. in complexes **2a** and **2b**. The cytotoxicity of **L4** increases considerably following coordination to the organometallic unit. Notably, **4a** and **4b**, incorporating the diclofenac-modified phosphine, are highly cytotoxic to A2780 cells (IC_{50} = 3.1 and 4.8 μM, respectively), and **4b** is also selective, being considerably less cytotoxic to HEK-293 cells (34.3 ± 3.1 μM), with a similar cytotoxicity profile to cisplatin.

The monofunctionalized bipyridine ligands **L5** and **L6** are reasonably cytotoxic, but they are not selective. Indeed, **L5** is at least an order of magnitude more cytotoxic to the HEK-293 cell line than the tumorgenic cell lines. When coordinated to the metal units as in **5a**/**5b** and **6a**/**6b**, the overall cytotoxicity changes relatively little. However, the relative selectivtiy toward the nontumorigenic HEK-293 cell line is reduced. For example, **L5** is the most cytotoxic of all the compounds to the nontumorigenic HEK-293 cells (IC_{50} = 0.3 μM), whereas the IC_{50} values of **5a** are 7.8 and 8.1 μM in the A2780 and A2780cisR cell lines and 19.9 μM in HEK-293 cells, thus showing a moderate degree of cancer cell selectivity combined with a lack of cross resistance on the A2780cisR cell line.

The bis-functionalized bipyridine modified ligands **L7** and **L8** are not cytotoxic to any of the cell lines, whereas their organometallic complexes are highly cytotoxic, with IC_{50} values ranging from 0.2 to 9.9 μM. Importantly, complex **8a** is more than 20-fold more cytotoxic toward A2870cisR than the HEK-293 cell line, which is on the same order of selectivity as cisplatin for the sensitive A2780 cell line and considerably more effective than cisplatin on A2780cisR cells. It is noteworthy that although the ligands with two bioactive moieties, i.e. **L7** and **L8**, are considerably less cytotoxic than the single NSAID equivalent (**L5** and **L6**, respectively), the organometallic complexes show the opposite profile, with the increased cytotoxicity ranging from 2- to 46-fold, with **7a** showing the least enhancement compared to its single NSAID analogue **5a**, whereas **8a** shows the largest enhancement compared to **6a**.

Cytotoxicity is a multifactorial process, and resistance to cisplatin in the A2870cisR cell line is attributed to decreased uptake, increased glutathione and glutathione S-transferase levels, and increased DNA repair (adduct removal), although other mechanism cannot be excluded.[97] Uptake may be correlated with Ctr1 transporter expression, with cisplatin resistant A2870cisR cells having lower levels compared to sensitive cell lines.[98] In addition, HEK-293 cells have a relatively high expression of this transporter which is linked to the side effect of nephrotoxicity caused by cisplatin treatment.[99] The toxicity profiles of the three most selective complexes for A2870cisR cells over HEK-293 cells (**8a** > **8b** > **7a**) also demonstrate a higher toxicity in A2870cisR cells compared to A2870 cells and therefore suggest a different mode of uptake compared to cisplatin. It should be noted that certain COX-2 inhibitors can overcome cross-drug resistance in multidrug-resistant (MDR) cells.[100] It has also been shown

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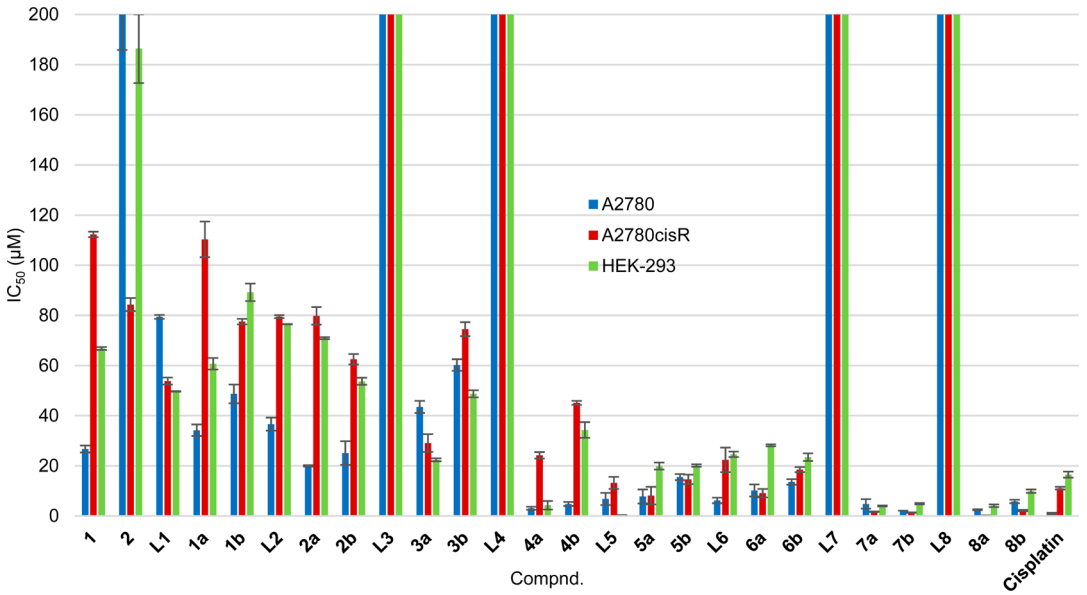

Figure 6. Comparison of the IC_{50} values for indomethacin, diclofenac, **L1-L8**, **1*a*/1b−8*a*/8b**, and cisplatin.

that platium(II) and platinum(IV) complexes modified with aspirin, a potent COX-1 inhibitor, are able to overcome cisplatin acquired drug resistance via a mechanism involving COX-1 pathway modulation.[101−104] Moreover, **1** has been shown to increase the cellular accumulation of dyes that are usually effluxed via multidrug resistant protein, thereby sensitizing formerly resistant cells to drugs such as vincristine,[105] and in other studies **1** has been shown to enhance the anticancer activity of chlorambucil.[106,107] Interestingly, **2** is suggested to be activated in a process involving glutathione conjugation,[108] also offering a mode of selectivity to the hybrid complexes.

■ CONCLUDING REMARKS

Combining organometallic fragments based on metal(II)-*p*-cymene (metal = ruthenium and osmium) with anti-inflammatory drug motifs, i.e. indomethacin and diclofenac, represents a promising strategy to generate cytotoxic, cancer cell selective compounds, which lack the cross-resistance problematic in cisplatin treatment. The relative ratio between the two active units, i.e. the metal fragment versus the bioactive organic drug moiety, is important, with the bis-functionalized compounds being the most cytotoxic and selective and also the most active against the cisplatin resistant A2780cisR cell line, and demonstrating higher cytotoxicity and selectivity than cisplatin against the A2870 cell line. Thus, combining established anti-inflammatory (NSAID) drugs with these organometallic fragments appears to be a promising approach to overcoming drug resistance mechanisms associated with cisplatin treatment.

■ EXPERIMENTAL SECTION

General experimental conditions. $RuCl_3{\cdot}3H_2O$ was obtained from Precious Metals Online and all other chemicals were purchased from Aldrich, AlfaAesar, Acros, ABCR Chemicals and Bachem and used without further purification. Reactions were performed under an inert atmosphere (N_2) using Schlenk techniques with solvents dried using drying-columns. The dimers $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ and $[Os(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ were prepared and purified according to literature procedures.[109] The complexation reactions were performed in the absence of light, as a precaution, although exclusion of light is not essential. ^1H (400.13 MHz), ^{13}C (100.62 MHz) and ^{31}P (161.97 MHz) NMR spectra were recorded on a Bruker Avance II 400 spectrometer at 298 K. The chemical shifts are reported in parts per million (ppm) and referenced to deuterated solvent residual peaks for ^1H and ^{13}C ($CDCl_3$: ^1H δ 7.26, ^{13}C δ 77.16 ppm, CD_3OD: ^1H δ 3.31, ^{13}C δ 49.00 ppm) and coupling constants (J) are reported in Hertz (Hz).[110,111] IR spectra were recorded on a PerkinElmer Spectrum One FT-IR Spectrometer at room temperature. Electrospray ionization mass spectra (ESI-MS) were obtained on a Thermo-Finnigan LCQ Deca XP Plus quadropole ion-trap instrument operated in positive-ion mode. Elemental analysis was carried out by the microanalytical laboratory at the Institute of Chemical Sciences and Engineering (EPFL). Melting points were determined using a SMP3 Stuart Melting Point Apparatus and are uncorrected. Reactions were monitored by TLC using Merck TLC silica gel coated aluminum sheets 60 F_{254}, and verified with a UV lamp at 254 nm and $KMnO_4$ stain. Purification of products was performed by column flash chromatography using silica gel (60A, 43−60 μm) using the elution systems indicated.

Synthesis of 2-hydroxyethyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (L1a). To a solution of indomethacin (0.702 g, 1 equiv) in CH_2Cl_2 (150 mL), EDCI (0.478 g, 1.25 equiv) ethylene glycol (0.44 mL, 4 equiv) and DMAP (0.048 g, 0.2 equiv) were added. The reaction mixture was stirred at r.t. for 24 h. The mixture was washed with H_2O (150 mL) and isolated organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using Hex/EtOAc elution mixture afforded the product as a pale-yellow solid (0.532 g, yield 70%). Mp (°C): 104−105; R_f (Hex/EtOAc: 5/5 (v/v)): 0.35; ^1H NMR ($CDCl_3$) δ_H, ppm: 7.66 (2H, m, 2xCl-(*Ar*)C−CH-C$\underline{H}$, $^3J_{H,H}$ = 8.7 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.47 (2H, m, 2xCl-(*Ar*)C−C$\underline{H}$-CH, $^3J_{H,H}$ = 8.7 Hz, $^4J_{H,H}$ = 2.3 Hz), 6.96 (1H, d, CH_3−O-(*Ar*)C−C$\underline{H}$-C, $^4J_{H,H}$ = 2.5 Hz), 6.86 (1H, d, CH_3−O-(*Ar*)C−CH-C$\underline{H}$-C, $^3J_{H,H}$ = 8.9 Hz), 6.67 (1H, dd, CH_3−O-(*Ar*)C−C$\underline{H}$-CH-C, $^3J_{H,H}$ = 8.9 Hz, $^4J_{H,H}$ = 2.5 Hz), 4.23−4.25 (2H, m, O−C$\underline{H_2}$-CH_2−OH), 3.83 (3H, s, C$\underline{H_3}$-O-(*Ar*)C−CH-C), 3.80−3.82 (2H, m, O−CH_2−C$\underline{H_2}$−OH), 3.71 (2H, s, CH_2−O-C$\underline{H_2}$-CH_2−OH), 2.39 (3H, s, (*Ar*)N−C−C$\underline{H_3}$); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 171.3 (1C, (*Ar*)C−CH_2−(C=O)-O-$(CH_2)_2$−OH), 168.4 (1C, Cl-(*Ar*)C−CH−CH-C-(C=O)), 156.2 (1C, CH_3−O-(*Ar*)C-CH-C), 139.5 (1C, Cl-(*Ar*)C-CH−CH), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 134.0 (1C, CH_3-(*Ar*)C-N-(C=O)), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 131.0 (1C, Cl-(*Ar*)C−CH−CH-C), 130.7 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 115.2 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.4 (1C, (*Ar*)C-CH_2−(C=O)-O), 111.8 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 101.4 (1C, CH_3−O-(*Ar*)C-CH−C), 66.7 (1C,

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(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−OH), 61.3 (1C, (*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−OH), 55.9 (1C, CH_3−O-(*Ar*)C), 30.4 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−OH), 13.5 (1C, (*Ar*)N−C-CH_3); IR (ν, cm^{-1}): 3448 (O−H); 2931 (C−H, CH_2, CH_3); 1731 (C═O, ester); 1676 (C═O, amide); 1589, 1476, 1355, 1313 (ring skeleton C═C, C−C, C═N, C−N); 1218, 1165, 1142 (C−O, ether, ester);831 (C−H, aromatic); ESI-MS(+): *m*/*z* 402.11 $[M + H]^+$, 424.09 $[M + Na]^+$, 825.18 $[2M+Na]^+$ calcd. for $C_{21}H_{20}ClNO_5$ 401.84, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{21}H_{20}ClNO$ C 62.77, H 5.02, N 3.49; found C 62.87, H 4.89, N 3.44.

Synthesis of 2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl-3-(pyridin-3-yl)propanoate (L1). To a suspension of 3-(pyridin-3-yl)propanoic acid (0.186 g, 1.1 equiv) in CH_2Cl_2 (100 mL), EDCI (0.263 g, 1.2 equiv), a solution of **L1a** (0.435 g, 1 equiv) in CH_2Cl_2 (50 mL) and DMAP (0.027 g, 0.2 equiv) were added. The reaction mixture was stirred at 40 °C for 2 h and then for further 24 h at r.t. The mixture was then washed with H_2O (100 mL) the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using Hex/EtOAc elution mixture afforded the product as a viscous pale yellow oil (0.463 g, yield 84%). R_f (Hex/EtOAc: 5/5 (v/v)): 0.49; ^1H NMR ($CDCl_3$) δ_H, ppm: 8.45 (2H, m, (*Py*)N−C*H*-C−CH, (*Py*)N−C*H*-CH−CH), 7.64 (2H, m, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.49 (1H, ddd overlapped, (*Py*)N−CH-CH-C*H*, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.8 Hz), 7.45 (2H, m, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.21 (1H, dd, (*Py*)N−CH-C*H*-CH, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 4.9 Hz), 6.96 (1H, d, CH_3−O-(*Ar*)C−C*H*-C, $^4J_{H,H}$ = 2.5 Hz), 6.84 (1H, d, CH_3−O-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 9 Hz), 6.64 (1H, dd, CH_3−O-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.5 Hz), 4.25−4.30 (4H, m, (*Ar*)C−CH_2−(C═O)−O-C*H*$_2$-CH_2−O, (*Ar*)C−CH_2−O−CH_2−C*H*$_2$-O), 3.80 (3H, s, C*H*$_3$-O-(*Ar*)C−CH-C), 3.67 (2H, s, (*Ar*)C−C*H*$_2$-O-$(CH_2)_2$−O), 2.87 (2H, t, (*Py*)N−CH-C-C*H*$_2$-CH_2−(C═O), $^3J_{H,H}$ = 7.6 Hz), 2.55 (2H, t, (*Py*)N−CH-C−CH_2−C*H*$_2$-(C═O), $^3J_{H,H}$ = 7.6 Hz), 2.38 (3H, s, C*H*$_3$-(*Ar*)C−N-(C═O)); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.1 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 170.7 (1C, (*Py*)N−CH-C-$(CH_2)_2$−(C═O)), 168.4 (1C, Cl-(*Ar*)C−CH−CH-C-(C═O)), 156.1 (1C, CH_3−O-(*Ar*)C-CH-C), 149.7 (1C, (*Py*)N-CH−C−CH), 147.8 (1C, (*Py*)N-CH−CH−CH), 139.4 (1C, Cl-(*Ar*)C-CH−CH), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 136.1 (1C, (*Py*)N−CH-CH-CH_2), 135.9 (1C, (*Py*)N−CH-C-CH), 134.0 (1C, CH_3-(*Ar*)C-N-(C═O)), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 130.9 (1C, Cl-(*Ar*)C−CH−CH-C), 130.7 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 123.6 (1C, (*Py*)N−CH-CH−CH_2), 115.0 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.3 (1C, (*Ar*)C-CH_2−(C═O)-O-$(CH_2)_2$−O-(*Py*)C), 111.6 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 101.6 (1C, CH_3−O-(*Ar*)C-CH−C), 62.7 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 62.3 (1C, (*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−O), 55.8 (1C, CH_3−O-(*Ar*)C−CH-C), 35.0 (1C, (*Py*)N−CH-C-CH_2−CH_2−(C═O)), 30.3 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O-(*Py*)C), 28.0 (1C, (*Py*)N−CH-C−CH_2−CH_2-(C═O)), 13.4 (1C, CH_3-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2932 (C−H, CH_2, CH_3); 1733 (C═O, ester); 1678 (C═O, amide); 1590, 1477, 1355, 1314 (ring skeleton C═C, C−C, C═N, C−N); 1220, 1140 (C−O, ether, ester); 832, 802, 754 (C−H aromatic); ESI-MS($^+$): *m*/*z* 535.50 $[M + H]^+$, calcd. for $C_{29}H_{27}ClN_2O_6$ 534.99, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{29}H_{27}ClN_2O_6$ C 65.11, H 5.09, N 5.24; found C 65.10, H 5.07, N 5.13.

Synthesis of 2-hydroxyethyl-2-(2-((2,6-dichlorophenyl)-amino)phenyl)acetate (L2a). To a solution of diclofenac (0.702 g, 1 equiv) in CH_2Cl_2 (150 mL), EDCI (0.478 g, 1.25 equiv), ethylene glycol (0.44 mL, 4 equiv) and DMAP (0.048 g, 0.2 equiv) were added. The reaction mixture was stirred at r.t. for 24 h. and then the mixture was washed with H_2O (150 mL), the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using Hex/EtOAc elution mixture afforded the product as colorless solid (0.532 g, yield 66%). Mp (°C): 70−71; R_f (Hex/EtOAc): 3/2 (v/v)): 0.34; ^1H NMR ($CDCl_3$) δ_H, ppm: 7.34 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.1 Hz), 7.24 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.4 Hz), 7.13 (1H, ddd overlapped, NH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.6 Hz), 7.00 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.1 Hz), 6.96 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.2 Hz), 6.84 (1H, s br, N*H*), 6.56 (1H, dd, NH-(*Ar*)C−C−C*H*-CH, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.0 Hz), 4.28−4.30 (2H, m, (*Ar*)C−CH_2−(C═O)−O-C*H*$_2$-CH_2−OH), 3.87 (2H, s, (*Ar*)C−C*H*$_2$-(C═O)-O-$(CH_2)_2$−OH), 3.84−3.87 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−C*H*$_2$−OH); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.8 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−OH), 142.9 (1C, NH-(*Ar*)C−C-Cl), 137.9 (1C, NH-(*Ar*)C-CH−CH−CH), 131.0 (1C, NH-(*Ar*)C−C*H*-CH−CH), 129.7 (2C, 2xCl-(*Ar*)C-CH−CH), 129.0 (2C, 2xCl-(*Ar*)C-CH−CH), 128.3 (1C, NH-(*Ar*)C−CH-CH−CH), 124.3 (1C, NH-(*Ar*)C-C-CH), 124.3 (1C, Cl-(*Ar*)C−CH-CH), 122.3 (1C, NH-(*Ar*)C−CH−CH-CH), 118.5 (1C, NH-(*Ar*)C−C-CH−CH), 67.0 (1C, (*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−OH), 61.3 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−OH), 38.6 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−OH); IR (ν, cm^{-1}): 3319 (O−H); 2953 (C−H, CH_2, CH_3); 1717 (C═O); 1577, 1503, 1450, (ring skeleton C═C, C−C); 1279, 1252, 1147, 1075 (C−O, ester); 882, 743 (C−H, aromatic); ESI-MS(+): *m*/*z* 341.07 $[M + H]^+$, calcd. for $C_{16}H_{15}Cl_2NO_3$ 340.20, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{16}H_{15}Cl_2NO_3$ C 56.49, H 4.44, N 4.12; found C 56.57, H 4.39, N 4.11.

Synthesis of 2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)-acetoxy)ethyl-3-(pyridin-3-yl)propanoate (L2). To a suspension of 3-(pyridin-3-yl)propanoic acid (0.386 g, 1.1 equiv) in CH_2Cl_2 (100 mL), EDCI (0.263 g, 1.2 equiv) a solution of **L2a** (0.435 g, 1 equiv) in CH_2Cl_2 (50 mL) and DMAP (0.027 g, 0.2 equiv) were added. The reaction mixture was stirred at 40 °C for 2 h and then for further 24 h at r.t. The mixture was washed with H_2O (100 mL), the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using Hex/EtOAc elution mixture afforded the product as a viscous yellow oil (0.463 g, yield 86%). R_f (CH_2Cl_2/MeOH: 4/1 (v/v)): 0.39; ^1H NMR ($CDCl_3$) δ_H, ppm: 8.45−8.46 (2H, m, (*Py*)N−C*H*-C−CH, (*Py*)N−C*H*-CH−CH), 7.48 (1H, ddd overlapped, (*Py*)N−CH-CH-C*H*, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.7 Hz), 7.33 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8 Hz), 7.22 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.5 Hz), 7.19 (1H, dd, (*Py*)N−CH-C*H*-CH, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 4.9 Hz), 7.11 (1H, ddd overlapped, NH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.5 Hz), 6.98 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8 Hz), 6.94 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.0 Hz), 6.84 (1H, s br, N*H*), 6.53 (1H, d, NH-(*Ar*)−C−C-C*H*-CH, $^3J_{H,H}$ = 8 Hz), 4.32−4.34 (2H, m, (*Ar*)C−CH_2−(C═O)−O-C*H*$_2$-CH_2−O), 4.29−4.31 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−C*H*$_2$-O), 3.83 (2H, s, (*Ar*)C−C*H*$_2$-(C═O)-O-$(CH_2)_2$−O), 2.89 (2H, t, (*Py*)N−CH-C−CH_2−C*H*$_2$-(C═O), $^3J_{H,H}$ = 7.6 Hz), 2.59 (2H, t, (*Py*)N−CH−C-C*H*$_2$-CH_2−(C═O), $^3J_{H,H}$ = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.21 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 172.15 (1C, (*Py*)N−CH-C-$(CH_2)_2$−(C═O)), 150.0 (1C, (*Py*)N-CH−C−CH), 148.0 (1C, (*Py*)N-CH−CH−CH), 142.8 (1C, NH-(*Ar*)C−C-Cl), 137.9 (1C, NH-(*Ar*)C-CH−CH−CH), 135.9 (1C, (*Py*)N−CH-CH-CH), 135.8 (1C, (*Py*)N−CH-C-CH), 131.0 (1C, NH-(*Ar*)C−C*H*-CH−CH), 129.7 (2C, 2xCl-(*Ar*)C-CH−CH), 129.0 (2C, 2xCl-(*Ar*)C-CH−CH), 128.2 (1C, NH-(*Ar*)C−CH-CH−CH), 124.3 (1C, NH-(*Ar*)C-C-CH−CH), 124.2 (1C, Cl-(*Ar*)C−CH-CH), 123.5 (1C, (*Py*)N−CH-CH−CH), 122.2 (1C, NH-(*Ar*)C−CH−CH-CH), 118.4 (1C, NH-(*Ar*)C−C-CH−CH), 62.9 (1C, (*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−O), 62.3 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 38.5 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 35.2 (1C, (*Py*)N−CH-C−CH_2−CH_2-(C═O)), 28.0 (1C, (*Py*)N−CH-C-CH_2−CH_2−(C═O)); ESI-MS(+): *m*/*z* 474.11 $[M + H]^+$, calcd. for $C_{24}H_{23}Cl_2N_2O_4$ 473.35, the isotopic pattern corresponds well to the calculated one; IR (ν, cm^{-1}): 3315 (N−H); 2958 (C−H, CH_2, CH_3); 1731 (C═O, ester); 1503, 1450, 1423 (ring skeleton C═C, C−C,

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C═N, C−N); 1278, 1251, 1141 (C−O, ester); 772, 745 (C−H aromatic); Elemental analysis (%): calcd. for $C_{24}H_{23}Cl_2N_2O_4$ C 60.90, H 4.68, N 5.92; found C 61.01, H 4.70, N 5.88.

Synthesis of 2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl-4-(diphenylphosphanyl)benzoate (L3). To a solution of 4-(diphenylphosphanyl)benzoic acid (0.493 g, 1.2 equiv) in CH_2Cl_2 (100 mL), EDCI (0.329 g, 1.25 equiv), **L1a** (0.520 g, 1.0 equiv) and DMAP (0.042 g, 0.3 equiv) were added. The reaction mixture was stirred at r.t. for 24 h, then the mixture was washed with H_2O (150 mL), the isolated organic phase has been further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using Hex/EtOAc as elution mixture afforded the product as a yellow solid (0.886 g, yield 87%). Mp (°C): 114−115; R_f (Hex/EtOAc: 7/3 (v/v)): 0.39; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 7.83 (2H, m, 2xO-(C═O)-(*Ar*)C−C*H*-CH−C-P, $^3J_{H,H}$ = 5.2 Hz, $^4J_{H,H}$ = 1.7 Hz), 7.61 (2H, m, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.4 Hz), 7.43 (2H, m, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.4 Hz), 7.25−7.40 (12H, m, 2xO-(C═O)-(Ar)C−CH-C*H*−C-P, 4xP-(*Ar*)C−C*H*-CH−CH, 4xP-(*Ar*)C−CH-C*H*-CH, 2xP-(*Ar*)C−CH−CH-C*H*), 6.96 (1H, d, CH_3−O-(*Ar*)C−C*H*-C, $^3J_{H,H}$ = 2.6 Hz), 6.79 (1H, d, CH_3−O-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 9.0 Hz), 6.55 (1H, dd, CH_3−O-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 2.6 Hz), 4.49−4.52 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O), 4.43−4.45 (2H, m, (*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O), 3.73 (3H, s, CH_3-O-(*Ar*)C−CH-C), 3.70 (2H, s, (*Ar*)C−CH_2-(C═O)-O-$(CH_2)_2$−O), 2.37 (3H, s, CH_3-(*Ar*)C−N); ^{31}P NMR ($CDCl_3$) δ_P, ppm: −4.96 (1P); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 170.6 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 168.2 (1C, Cl-(*Ar*)C−CH−CH-C-(C═O)), 166.0 (1C, O-(C═O)-(*Ar*)C−CH−CH−C-P), 156.1 (1C, CH_3−O-(*Ar*)C-CH-C), 144.5 (1C, O-(C═O)-(*Ar*)C−CH−CH-C-P, $^1J_{C,P}$ = 15 Hz), 139.3 (1C, Cl-(*Ar*)C-CH−CH), 136.2 (2C, 2xP-(*Ar*)C-CH−CH−CH, $^1J_{C-P}$ = 11 Hz), 136.1 (1C, CH_3−O-(*Ar*)C−CH-C), 134.1 (4C, 4xP-(*Ar*)C-CH−CH−CH, $^2J_{C,P}$ = 20 Hz), 133.9 (1C, CH_3-(*Ar*)C-N-(C═O)), 133.2 (2C, O-(C═O)-(*Ar*)C−CH-CH−C−P, $^2J_{C,P}$ = 19 Hz), 131.2 (2C, 2xCl-(*Ar*)C−CH-CH), 130.8 (1C, Cl-(*Ar*)C−CH−CH-C), 130.6 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.5 (1C, O-(C═O)-(*Ar*)C-CH−CH−C-P), 129.3 (2C, O-(C═O)-(*Ar*)C-CH−CH−C-P, $^3J_{C-P}$ = 6 Hz), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 129.2 (2C, 2xP-(*Ar*)C−CH−CH-CH), 128.7 (4C, 4xP-(*Ar*)C−CH-CH−CH, $^3J_{C,P}$ = 7 Hz), 114.9 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.3 (1C, (*Ar*)C-CH_2−(C═O)-O), 111.6 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 101.3 (1C, CH_3−O-(*Ar*)C-CH−C), 62.7 (1C, (*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−O), 62.6 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 55.6 (1C, CH_3−O-(*Ar*)C−CH-C), 30.3 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 13.4 (1C, CH_3-(*Ar*)C−N-(C═O)); IR (ν, cm-1): 2931 (C−H, CH_2, CH_3); 1730, (C═O, ester); 1714 (C═O, ester); 1678 (C═O, amide); 1594, 1469, 1353 (ring skeleton C═C, C−C, C═N, C−N); 1243, 1144, 1086 (C−O, ether, ester); 857, 745 (C−H aromatic); ESI-MS(+): *m/z* 690.42 $[M]^+$, calcd. for $C_{40}H_{31}ClNO_6P$ 690.13, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{40}H_{31}ClNO_6P$ C 69.62, H 4.82, N 2.03, found C 69.53, H 4.86, N 2.01.

Synthesis of 2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)-acetoxy)ethyl-4-(diphenylphosphanyl)benzoate (L4). To a solution of 4-(diphenylphosphanyl)benzoic acid (0.972 g, 1.2 equiv) in CH_2Cl_2 (100 mL), EDCI (0.647 g, 1.25 equiv), a solution of **L2a** (0.900 g, 1.0 equiv) in CH_2Cl_2 (50 mL) and DMAP (0.097 g, 0.3 equiv) were added. The reaction mixture was further stirred for 24 h at r.t., then the mixture was washed with H_2O (150 mL), the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using Hex/EtOAc elution mixture afforded the product as a white solid (0.784 g, yield 47%). Mp (°C): 115−116; R_f (Hex/EtOAc: 9/1 (v/v)): 0.692; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 7.84 (2H, m, 2xO-(C═O)-(*Ar*)C−C*H*-CH−C-P, $^3J_{H,H}$ = 8.4 Hz, $^4J_{H,H}$ = 1.4 Hz), 7.24−7.38 (12H, m, 2xO-(C═O)-(*Ar*)C−CH-C*H*−C-P, 4xP-(*Ar*)C−C*H*-CH−CH, 4xP-(*Ar*)C−CH-C*H*-CH, 2xP-(*Ar*)C−CH−CH-C*H*), 7.30 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8 Hz), 7.20 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$= 7.5 Hz, $^4J_{H,H}$ = 1.4 Hz), 7.02 (1H, ddd overlapped, NH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.5 Hz), 6.95 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8 Hz), 6.86 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.1 Hz), 6.86 (1H, s br, N*H*), 6.46 (1H, dd, NH-(*Ar*)C−C−C*H*-CH, $^3J_{H,H}$= 7.9 Hz, $^4J_{H,H}$ = 0.5 Hz), 4.51−4.54 (2H, m, (*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O), 4.47−4.50 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O), 3.84 (2H, s, (*Ar*)C−CH_2-(C═O)-O-$(CH_2)_2$−O); ^{31}P NMR ($CDCl_3$) δ_P, ppm: −5.01 (1P); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.2 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 166.1 (1C, O-(C═O)-(*Ar*)C−CH−CH−C-P), 144.4 (1C, d, O-(C═O)-(*Ar*)C−CH−CH-C-P, $^1J_{C,P}$ = 14 Hz), 142.8 (1C, NH-(*Ar*)C-C-Cl), 137.8 (1C, NH-(*Ar*)C-CH−CH), 136.2 (2C, d, 2xP-(*Ar*)C-CH−CH−CH, $^1J_{C,P}$ = 11 Hz), 134.1 (4C, d, 4xP-(*Ar*)C-CH−CH−CH, $^2J_{C,P}$ = 20 Hz), 133.2 (2C, d, 2xO-(C═O)-(*Ar*)C−CH-CH−C−P, $^2J_{C,P}$ = 19 Hz), 130.9 (1C, NH-(*Ar*)C−CH-CH−CH), 129.6 (2C, 2xCl-(*Ar*)C-CH−CH), 129.6 (1C, O-(C═O)-(*Ar*)C-CH−CH−C-P), 129.5 (2C, d, O-(C═O)-(Ar)C-CH−CH−C-P, $^3J_{C,P}$ = 6 Hz), 129.3 (2C, 2xP-(*Ar*)C−CH−CH-CH), 129.0 (2C, 2xCl-(*Ar*)C-CH−CH), 128.8 (4C, d, 4xP-(*Ar*)C−CH-CH−CH, $^3J_{C,P}$ = 7 Hz), 128.1 (1C, NH-(*Ar*)C−CH-CH−CH), 124.2 (1C, Cl-(*Ar*)C−CH-CH), 124.1 (1C, NH-(*Ar*)C-C-CH), 122.1 (1C, NH-(*Ar*)C−CH−CH-CH), 118.4 (1C, NH-(*Ar*)C−C-CH−CH), 62.9 (1C, (*Ar*)C-(C═O)-O-CH_2−CH_2−O), 62.7 (1C, (*Ar*)C-(C═O)-O−CH_2−CH_2−O), 38.5 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O); IR (ν, cm^{-1}): 3327 (N−H); 2960 (C−H, CH_2, CH_3); 1719 (C═O, ester); 1586, 1505, 1450, 1395 (ring skeleton C═C, C−C); 1285, 1266, 1232, 1124 (C−O); 743 (C−H aromatic); ESI-MS(+): *m/z* 629.10 $[M + H]^+$, 651.08 $[M + Na]^+$, calcd. for $C_{35}H_{28}Cl_2NO_4P$ 628.49, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{35}H_{28}Cl_2NO_4P$ C 66.89, H 4.49, N 2.23, found C 66.86, H 4.48, N 2.16;

Synthesis of (4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (L5). To a solution of indomethacin (0.643 g, 1.2 equiv) in CH_2Cl_2 (100 mL), EDCI (0.493 g, 1.4 equiv), 4′-methyl-[2,2′-bipyridin]-4-yl)methanol (0.300 g, 1 equiv) and DMAP (0.055 g, 0.3 equiv) were added. The reaction mixture was stirred at r.t. for 24 h, then the mixture was washed with H_2O (150 mL), the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography using CH_2Cl_2/MeOH elution mixture afforded the product as pale yellow solid (0.598 g, yield 74%). Mp (°C): 134.5−135.5; R_f (CH_2Cl_2/MeOH: 9.5/0.5 (v/v)): 0.339; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 8.59 (1H, d, O−CH_2−(*Py*)C−CH-C*H*-N, $^3J_{H,H}$ = 5.0 Hz), 8.48 (1H, d, CH_3-(*Py*)C−CH-C*H*-N, $^3J_{H,H}$ = 4.9 Hz), 8.34 (1H, s, CH_3-(*Py*)C−C*H*−C-N), 8.22 (1H, s, O−CH_2−(*Py*)C−C*H*−C-N), 7.61 (2H, m, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.41 (2H, m, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.16 (1H, dd, O−CH_2−(*Py*)C−C*H*-CH-N, $^3J_{H,H}$ = 5.0 Hz, $^4J_{H,H}$ = 1.5 Hz), 7.11 (1H, dd, CH_3-(*Py*)C−C*H*-CH-N, $^3J_{H,H}$ = 4.9 Hz, $^3J_{H,H}$ = 1.3 Hz), 6.95 (1H, d, CH_3−O-(*Ar*)C−C*H*-C, $^4J_{H,H}$ = 2.5 Hz), 6.85 (1H, d, CH_3−O-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 9 Hz), 6.64 (1H, dd, CH_3−O-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.5 Hz), 5.22 (2H, s, O−CH_2-(*Py*)C−CH−CH-N), 3.79 (2H, s, (*Ar*)C−CH_2-(C═O)-O−CH_2−(*Py*)C), 3.75 (3H, s, CH_3-O-(*Ar*)C−CH-C), 2.43 (6H, s, CH_3-(*Ar*)C−N-(C═O), CH_3-(*Py*)C−CH−CH-N); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 170.5 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 168.4 (1C, e), Cl-(*Ar*)C−CH−CH-C-(C═O), 156.8 (1C, O−CH_2−(*Py*)C−CH-C-N), 156.2 (1C, CH_3−O-(*Ar*)C-CH-C), 155.5 (1C, CH_3-(*Py*)C−CH-C-N), 149.4 (1C, O−CH_2−(*Py*)C−CH-C*H*-N), 149.0 (1C, CH_3-(*Py*)C−CH-C*H*-N), 148.4 (1C, O−CH_2−(*Py*)C-CH−CH-N), 145.8 (1C, CH_3-(*Py*)C-CH−CH-N), 139.3 (1C, Cl-(*Ar*)C-CH−CH), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 134.0 (1C, CH_3-(*Ar*)C-N-(C═O)), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 130.9 (1C, Cl-(*Ar*)C−CH−CH-C), 130.6 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.2 (2C, 2xCl-(*Ar*)C-CH−CH), 125.0 (1C, CH_3-(*Py*)C-CH−CH-N), 122.1 (1C, CH_3-(*Py*)C-CH−C−N), 121.8 (1C, O−CH_2−(*Py*)C-CH−CH-N), 119.4 (1C, O−CH_2−(*Py*)C-CH−C−N), 115.1 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.2 (1C, (*Ar*)C-CH_2−(C═O)-O−CH_2−(*Py*)C), 112.0 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 101.2 (1C,

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CH_3−O-(*Ar*)C-C̲H−C), 65.1 (1C, O-C̲H_2-(*Py*)C−CH−CH-N), 55.7 (1C, C̲H_3−O-(*Ar*)C−CH-C), 30.4 (1C, (*Ar*)C-C̲H_2-(C═O)-O−CH_2−(*Py*)C), 21.3 (1C, C̲H_3-(*Py*)C−CH-CH-N), 13.5 (1C, C̲H_3-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2927 (C−H, CH_3, CH_2); 1731 (C═O, ester); 1670, (C═O, amide); 1597, 1458, 1357, (ring skeleton C═C, C−C, C═N, C−N); 1214, 1171, 1148 (C−O, ester); 820, 755 (C−H aromatic); ESI-MS(+): *m*/*z* 540.20 $[M]^+$, calcd. for $C_{31}H_{26}ClN_3O_4$ 540.02, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{31}H_{26}ClN_3O_4$ C 68.95, H 4.85, N 7.78; found C 68.97, H 4.81, N 7.74;

Synthesis of (4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(2-((2,6-dichlorophenyl)amino) phenyl)acetate (L6). To a solution of diclofenac (0.714 g, 1.2 equiv) in CH_2Cl_2 (100 mL), EDCI (0.547 g, 1.4 equiv), 4′-methyl-[2,2′-bipyridin]-4-yl)methanol (0.400 g, 1 equiv) and DMAP (0.055 g, 0.3 equiv) were added. The reaction mixture was stirred at r.t for 24 h, then the mixture was washed with H_2O (150 mL), the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography using CH_2Cl_2/MeOH elution mixture afforded the product as pale pink solid (0.731 g, yield 77%). Mp (°C): 108−109; R_f (CH_2Cl_2/MeOH: 9.5/0.5 (v/v)): 0.51; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 8.63 (1H, d, O−CH_2−(*Py*)C−CH-CH̲-N, $^3J_{H,H}$ = 5.0 Hz), 8.54 (1H, d, CH_3-(*Py*)C−CH-CH̲-N, $^3J_{H,H}$ = 5.0 Hz), 8.38 (1H, s, CH_3-(*Py*)C−CH̲−C-N), 8.23 (1H, s, O−CH_2−(*Py*)C−CH̲−C-N), 7.31 (2H, d, 2xCl-(Ar)C−CH̲-CH, $^3J_{H,H}$ = 8.1 Hz), 7.28 (1H, dd, NH-(*Ar*)C−CH̲-CH−CH, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.1 Hz), 7.21 (1H, dd, O−CH_2−(*Py*)C−CH̲-CH-N, $^3J_{H,H}$ = 5 Hz, $^4J_{H,H}$ = 1.1 Hz), 7.16 (1H, dd, CH_3-(*Py*)C−CH̲-CH-N, $^3J_{H,H}$ = 5 Hz, $^3J_{H,H}$ = 1.1 Hz), 7.14 (1H, ddd overlapped, NH-(*Ar*)C−CH-CH̲, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.3 Hz), 6.97 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-CH̲, $^3J_{H,H}$ = 7.1 Hz, $^4J_{H,H}$ = 0.9 Hz), 6.96 (1H, t, Cl-(Ar)C−CH-CH̲, $^3J_{H,H}$ = 8.1 Hz), 6.79 (1H, s br, NH̲), 6.55 (1H, d, NH-(*Ar*)C−C−CH̲-CH, $^3J_{H,H}$ = 8.0 Hz), 5.30 (2H, s, O−C̲H_2-(*Py*)C−CH−CH-N), 3.94 (2H, s, (*Ar*)C−C̲H_2-(C═O)-O), 2.45 (3H, s, C̲H_3-(*Py*)C−CH−CH-N); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.0 (1C, (*Ar*)C−CH_2−(C̲═O)-O−CH_2−(*Py*)C), 156.6 (1C, O−CH_2−(*Py*)C−CH-C̲-N), 155.4 (1C, CH_3-(*Py*)C−CH-C̲-N), 149.6 (1C, O−CH_2−(*Py*)C−CH-CH̲-N), 149.0 (1C, CH_3-(*Py*)C−CH-CH̲-N), 148.6 (1C, O−CH_2−(*Py*)C̲-CH−CH-N), 145.8 (1C, CH_3-(*Py*)C̲-CH−CH-N), 142.9 (1C, NH-(*Ar*)C̲−C-Cl), 137.9 (1C, NH-(*Ar*)C̲-CH−CH), 131.1 (1C, NH-(*Ar*)C−CH̲-CH−CH), 129.6 (2C, 2xCl-(*Ar*)C̲-CH−CH), 129.0 (2C, 2xCl-(*Ar*)C-C̲H−CH), 128.3 (1C, NH-(*Ar*)C−CH-C̲H−CH), 125.1 (1C, CH_3-(*Py*)C−CH̲-CH-N), 124.2 (2C, NH-(*Ar*)C-C̲-CH, Cl-(*Ar*)C−CH-C̲H), 122.34 (1C, NH-(*Ar*)C−CH−CH-C̲H), 122.29 (1C, CH_3-(*Py*)C−CH̲−C-N), 122.0 (1C, O−CH_2−(*Py*)C-C̲H−CH-N), 119.7 (1C, O−CH_2−(*Py*)C-C̲H−C−N), 118.6 (1C, NH-(*Ar*)C−C-C̲H−CH), 65.3 (1C, O-C̲H_2-(*Py*)C−CH−CH-N), 38.6 (1C, (*Ar*)C-C̲H_2-(C═O)-O−CH_2−(*Py*)C), 21.4 (1C, C̲H_3-(*Py*)C−CH̲-CH-N); IR (ν, cm^{-1}): 3321 (N−H); 3009, 2923 (C−H, CH_2, CH_3); 1724 (C═O, ester); 1676 (C═O, ester); 1597, 1502, 1450 (ring skeleton C═C, C−C, C−N, C═N, C−N); 1277, 1233, 1142 (C−O); 821, 770, 747 (C−H aromatic); ESI-MS(+): *m*/*z* 478.13 $[M + H]^+$, calcd. for $C_{26}H_{21}Cl_2N_3O_2$ 477.10, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{26}H_{21}Cl_2N_3O_2$ C 65.28, H 4.42, N 8.78; found C 65.18, H 4.29, N 8.68;

Synthesis of bis(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl) [2,2′-bipyridine]-5,5′-dicarboxylate (L7). To a suspension of [2,2′-bipyridine]-5,5′-dicarboxylic acid (0.528 g, 1 equiv) in a mixture of CH_2Cl_2 (20 mL) and H(CO)-N(CH_3)$_2$, EDCI (0.996 g, 2.4 equiv), **L1a** (2.000 g, 2.3 equiv) and DMAP (0.159 g, 0.6 equiv) were added. The reaction mixture was stirred at r.t. for 48 h, then the mixture was concentrated under reduced pressure to dryness, the crude was solubilized in CH_2Cl_2 (150 mL) washed with H_2O (150 mL), then the isolated organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using first Hex/EtOAc elution mixture afforded the product as a pale yellow solid (1.133 g, yield 52%). Mp (°C): 117−119; R_f (Hex/EtOAc: 4/6 (v/v)): 0.702; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 9.17 (2H, d, 2xO-(C═O)-(*Py*)C−CH̲-N, $^4J_{H,H}$ = 2.1 Hz), 8.48 (2H, d, 2x(*Py*)N−C−CH̲-CH-C, $^3J_{H,H}$ = 8.3 Hz), 8.24 (2H, dd, 2x(*Py*)N−C−CH-CH̲-C, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 2.1 Hz), 7.62 (4H, m, 4xCl-(*Ar*)C−CH-CH̲, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.42 (4H, m, 4xCl-(*Ar*)C−CH̲-CH, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,H}$ = 2.3 Hz), 6.96 (2H, d, 2xCH_3−O-(*Ar*)C−CH̲-C, $^4J_{H,H}$ = 2.5 Hz), 6.77 (2H, d, 2xCH_3−O-(*Ar*)C−CH-CH̲-C, $^3J_{H,H}$ = 9 Hz), 6.58 (2H, dd, 2xCH_3−O-(*Ar*)C−CH̲-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.5 Hz), 4.56−4.61 (4H, m, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−C̲H_2-O), 4.48−4.53 (4H, m, 2x(*Ar*)C−CH_2−(C═O)−O-C̲H_2-CH_2−O), 3.78 (6H, s, 2xC̲H_3-O-(*Ar*)C−CH-C), 3.72 (4H, s, 2x(*Ar*)C−C̲H_2-(C═O)-O-$(CH_2)_2$−O), 2.40 (6H, s, 2xC̲H_3-(*Ar*)C−N); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 170.8 (2C, 2x(*Ar*)C−CH_2−(C̲═O)-O-$(CH_2)_2$−O), 168.3 (2C, 2xCl-(*Ar*)C−CH−CH-C-(C̲═O)), 164.9 (2C, 2x(*Py*)N−CH-C-(C̲═O)-O), 158.3 (2C, 2x(*Py*)N-C̲-CH−CH-C), 156.2 (2C, 2xCH_3−O-(*Ar*)C̲-CH−CH-C), 150.7 (2C, 2x(*Py*)N−C̲H-C-(C═O)), 139.4 (2C, 2xCl-(*Ar*)C̲-CH−CH), 138.3 (2C, 2x(*Py*)N−C−CH-C̲H-C), 136.3 (2C, 2xCH_3−O-(*Ar*)C−CH-C̲), 134.0 (2C, 2xCH_3-(*Ar*)C̲-N-(C═O)-O), 131.3 (4C, 4xCl-(*Ar*)C−CH-C̲H), 130.9 (2C, 2xCl-(*Ar*)C−CH−CH-C̲), 130.6 (2C, 2xCH_3−O-(*Ar*)C−CH−CH-C̲), 129.2 (4C, 4xCl-(*Ar*)C-C̲H−CH), 126.0 (2C, 2x(*Py*)N−CH-C̲-(C═O)-O), 121.5 (2C, 2x(*Py*)N−C−C̲H-CH-C), 115.1 (2C, 2xCH_3−O-(*Ar*)C−CH-C̲H−C), 112.3 (2C, 2x(*Ar*)C̲-(C═O)-O−CH_2), 111.6 (2C, 2xCH_3−O-(*Ar*)C-C̲H−CH-C), 101.5 (2C, 2xCH_3−O-(*Ar*)C-C̲H−C), 63.2 (2C, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−C̲H_2−O), 62.6 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-C̲H_2−CH_2−O), 55.8 (2C, 2xC̲H_3−O-(*Ar*)C), 30.4 (2C, 2x(*Ar*)C-C̲H_2-(C═O)-O-$(CH_2)_2$−O), 13.5 (2C, 2xC̲H_3-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2959 (C−H, CH_2, CH_3); 1722 (C═O, ester); 1661 (C═O, amide); 1592, 1457, 1363, (ring skeleton C═C, C−C, C═N, C−N); 1286, 1235 (C−O, ether, ester); 827, 753 (C−H aromatic); ESI-MS(+): *m*/*z* 1011.24 $[M + H]^+$, calcd. for $C_{54}H_{44}Cl_2N_4O_{12}$ 1011.86, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{54}H_{44}Cl_2N_4O_{12}$ C 64.10, H 4.38, N 5.54; found C 64.25, H 4.39, N 5.44;

Synthesis of bis(2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)-acetoxy)ethyl)[2,2′-bipyridine]-5,5′-dicarboxylate (L8). To a suspension of [2,2′-bipyridine]-5,5′-dicarboxylic acid (0.524 g, 1 equiv) in a mixture of CH_2Cl_2 (20 mL) and H(CO)-N(CH_3)$_2$ (40 mL), EDCI (0.987 g, 2.4 equiv), **L2a** (1.679 g, 2.3 equiv) and DMAP (0.157 g, 0.6 equiv) were added. The reaction mixture was stirred at r.t. for 48 h then the mixture was concentrated under reduced pressure to dryness, and the crude was solubilized in CH_2Cl_2 (150 mL) washed with H_2O (150 mL), then the isolated organic phase organic phase was further washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography using first Hex/EtOAc elution mixture afforded the product as a white solid (1.301 g, yield 68%). Mp (°C): 94−95; R_f (Hex/EtOAc: 6/4 (v/v)): 0.54; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 9.22 (2H, d, 2xO-(C═O)-(*Py*)C−CH̲-N, $^4J_{H,H}$ = 2.1 Hz), 8.49 (2H, d, 2x(*Py*)N−C−CH̲-CH-C, $^3J_{H,H}$ = 8.3 Hz), 8.31 (2H, dd, 2x(*Py*)N−C−CH-CH̲-C, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 2.1 Hz), 7.30 (2H, d, 2xCl-(*Ar*)C−CH̲-CH, $^3J_{H,H}$ = 8.1 Hz), 7.23 (2H, dd, 2xNH-(*Ar*)C−CH̲-CH−CH, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.2 Hz), 7.09 (2H, ddd overlapped, 2xNH-(*Ar*)C−CH-CH̲-CH, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.4 Hz), 6.93 (2H, t, 2xCl-(*Ar*)C−CH-CH̲, $^3J_{H,H}$ = 8.1 Hz), 6.92 (2H, ddd overlapped, 2xNH-(*Ar*)C−CH−CH-CH̲, $^3J_{H,H}$ = 7.3 Hz, $^4J_{H,H}$ = 0.9 Hz), 6.81 (2H, s br, 2xNH̲), 6.52 (2H, d, 2xNH-(*Ar*)C−C−CH̲-CH, $^3J_{H,H}$ = 8.0 Hz), 4.59−4.64 (4H, m, 2x(*Ar*)C−CH_2−(C═O)−O-C̲H_2-CH_2−O), 4.52−4.57 (4H, m, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−C̲H_2-O), 3.87 (4H, s, 2x(*Ar*)C−C̲H_2-(C═O)-O-$(CH_2)_2$−O); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.2 (2C, 2x(*Ar*)C−CH_2−(C̲═O)-O-$(CH_2)_2$−O), 165.0 (2C, 2x(*Py*)N−CH-C-(C̲═O)-O), 158.4 (2C, 2x(*Py*)N-C̲-CH−CH-C), 150.8 (2C, 2x(*Py*)N-C̲H−C-(C═O)), 142.8 (2C, 2xNH-(*Ar*)C̲-C-Cl), 138.3 (2C, 2x(*Py*)N−C−CH-C̲H−C), 137.9 (2C, 2xNH-(*Ar*)C̲-CH−CH), 131.0 (2C, 2xNH-(*Ar*)C-C̲H−CH−CH), 129.6 (4C, 4xCl-(*Ar*)C̲-CH−CH), 129.0 (4C, 4xCl-(*Ar*)C-C̲H−CH), 128.4 (2C, 2xNH-(*Ar*)C−CH-C̲H−CH), 126.0 (2C, 2x(*Py*)N−CH-C̲-(C═O)-O), 124.2 (2C, 2xNH-(*Ar*)C-C̲-CH), 124.1 (2C, 2xCl-(*Ar*)C−CH-C̲H), 122.2 (2C, 2xNH-(*Ar*)C−CH−

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CH-CH), 121.5 (2C, 2x(*Py*)N−C−CH-CH-C), 118.5 (2C, 2xNH-(*Ar*)C−C-CH−CH), 63.1 (2C, 2x(*Ar*)C−CH_2−(C=O)-O-CH_2−CH_2−O), 62.8 (2C, 2x(*Ar*)C−CH_2−(C=O)-O−CH_2−CH_2−O), 38.6 (2C, 2x(*Ar*)C-CH_2-(C=O)-O-$(CH_2)_2$−O); IR (ν, cm^{-1}): 3347 (N−H); 2954 (C−H, CH_2, CH_3); 1719 (C=O, ester); 1713 (C=O, ester); 1591, 1511, 1451 (ring skeleton C=C, C−C, C=N, C−N); 1288, 1242, 1139 (C−O, ester); 854, 742, 734 (C−H aromatic); ESI-MS(+): m/z 889.12 $[M + H]^+$, calcd. for $C_{44}H_{34}Cl_4N_4O_8$ 888.58, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{44}H_{34}Cl_4N_4O_8{\cdot}CH_2Cl_2$ 55.52; H, 3.73; N, 5.76; found C 55.44, H 3.79, N 5.58;

General procedure for the synthesis of the ruthenium(II)- and osmium(II)-p-cymene complexes. To a solution of the appropriate dimer, $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ or $[Os(\eta^6\text{-}p\text{-cymene})Cl_2]_2$, in CH_2Cl_2 (10 mL) a solution of the appropriate ligand in CH_2Cl_2 (25 mL) was added and the resulting mixture was stirred at r.t. in the dark for 24 h. The solvent was removed under reduced pressure and the crude was redissolved in CH_2Cl_2 (1 mL) and then successively washed with Et_2O (4 × 50 mL) and then with hexane (2 × 25 mL). The solvent was removed under reduced pressure and the resulting solid was dried under high vacuum.

Synthesis of $[Ru(\eta^6\text{-p-cymene})Cl_2]$\{(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl-3-(pyridin-3-yl)propanoate\} (1a). Complex **1a** was prepared following the general procedure starting from $[Ru(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (0.123 g, 1 equiv) and ligand **L1** (0.237 g, 2.2 equiv)), to afford a yellow-orange solid (0.321 g, yield 86%). Mp (°C): 84−85.5; ^{1}H NMR ($CDCl_3$) δ, ppm: 8.90 (1H, d, (*Py*)N−CH-C−CH, $^4J_{H,H}$ = 2 Hz), 8.87 (1H, dd, (*Py*)N−CH-CH−CH, $^3J_{H,H}$ = 5.7 Hz, $^4J_{H,H}$ = 1 Hz), 7.66 (2H, m, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.49 (1H, ddd overlapped, (*Py*)N−CH-CH-CH, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 2 Hz), 7.47 (2H, m, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.5 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.20 (1H, dd, (*Py*)N−CH-CH-CH, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 5.7 Hz), 6.96 (1H, d, CH_3−O-(*Ar*)C−CH-C, $^4J_{H,H}$ = 2.5 Hz), 6.86 (1H, d, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz), 6.66 (1H, dd, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.5 Hz), 5.43 (2H, d, 2xCH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6.0 Hz), 5.20 (2H, d, 2xCH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6.0 Hz), 4.25−4.32 (4H, m, (*Ar*)C−CH_2−(C=O)−O-CH_2-CH_2−O, (*Ar*)C−CH_2−O−CH_2−CH_2-O), 3.82 (3H, s, CH_3-O-(*Ar*)C−CH-C), 3.69 (2H, s, (*Ar*)C−CH_2-O-$(CH_2)_2$−O), 2.95 (1H, sept, (*Ar*)C−CH−CH−C-$CH(CH_3)_2$, $^3J_{H,H}$ = 6.9 Hz), 2.88 (2H, t, (*Py*)N−CH-C−CH_2−CH_2-(C=O), $^3J_{H,H}$ = 7.2 Hz), 2.55 (2H, t, (*Py*)N−CH−C-CH_2-CH_2−(C=O), $^3J_{H,H}$ = 7.2 Hz), 2.38 (3H, s, CH_3-(*Ar*)C−N), 2.07 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.29 (6H, d, (*Ar*)C−CH−CH-C−CH(CH_3)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 171.8 (1C, (*Ar*)C−CH_2−(C=O)-O-$(CH_2)_2$−O), 170.7 (1C, (*Py*)N−CH-C-$(CH_2)_2$−(C=O)), 168.4 (1C, Cl-(*Ar*)C−CH−CH-C-(C=O)), 156.2 (1C, CH_3−O-(*Ar*)C-CH-C), 155.1 (1C, (*Py*)N-CH−C−CH), 153.0 (1C, (*Py*)N-CH−CH−CH), 139.5 (1C, Cl-(*Ar*)C-CH−CH), 137.7 (1C, (*Py*)N−CH-CH-CH), 137.1 (1C, (*Py*)N−CH-C-CH), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 134.0 (1C, CH_3-(*Ar*)C-N-(C=O)), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 131.0 (1C, Cl-(*Ar*)C−CH−CH-C), 130.7 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 124.2 (1C, (*Py*)N−CH-CH−CH,), 115.1 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.4 (1C, (*Ar*)C-CH_2−(C=O)-O-$(CH_2)_2$−O), 111.6 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 103.6 (1C, CH_3-(*Ar*)C−CH−CH-C), 101.6 (1C, CH_3−O-(*Ar*)C-CH−C), 97.2 (1C, CH_3-(*Ar*)C-CH−CH-C), 83.0 (2C, 2xCH_3-(*Ar*)C−CH-CH−C), 82.3 (2C, 2xCH_3-(*Ar*)C-CH−CH-C), 62.6 (1C, (*Ar*)C−CH_2−(C=O)-O−CH_2−CH_2−O), 62.5 (1C, (*Ar*)C−CH_2−(C=O)-O-CH_2−CH_2−O), 55.9 (1C, CH_3−O-(*Ar*)C−CH-C), 34.5 (1C, (*Py*)N−CH-C-CH_2−CH_2−(C=O)), 30.8 (1C, (*Ar*)CH−CH-C-CH(CH_3)$_2$), 30.3 (1C, (*Ar*)C-CH_2-(C=O)-O-$(CH_2)_2$−O, 27.7 (1C, (*Py*)N−CH-C−CH_2−CH_2-(C=O)), 22.4 (2C, (*Ar*)CH−CH-C−CH(CH_3)$_2$), 18.3 (1C, CH_3-(*Ar*)C−CH−CH), 13.5 (1C, CH_3-(*Ar*)C−N-(C=O)); IR (ν, cm^{-1}): 2925 (C−H, CH_2, CH_3); 1733 (C=O, ester); 1676, (C=O, amide); 1589, 1476, 1356, 1317 (ring skeleton C=C, C−C, C=N, C−N); 1221, 1141, (C−O, ether, ester); 834, 803, 754 (C−H, aromatic); ESI-MS(+): m/z 805.14 $[M-Cl]^+$, calcd. for $C_{39}H_{41}Cl_2N_2O_6Ru^+$ 805.73, the isotopic pattern corresponds well to the calculated one; Elemental Analysis (%): calcd. for $C_{39}H_{41}Cl_3N_2O_6Ru$ C 55.69, H 4.91, N 3.33; found C 55.69, H 4.93, N 3.33.

Synthesis of $[Os(\eta^6\text{-p-cymene})Cl_2]$\{(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl-3-(pyridin-3-yl)propanoate\} (1b). Complex **1b** was prepared following the general procedure starting from $[Os(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (0.235 g, 1 equiv) and ligand **L1** (0.350 g, 2.2 equiv), to afford a yellow-orange solid (0.297 g, yield 54%). Mp (°C): 83−85; ^{1}H NMR ($CDCl_3$) δ, ppm: 8.78−8.81 (2H, m, (*Py*)N−CH-C−CH, (*Py*)N−CH-CH−CH), 7.65 (2H, m, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.4 Hz), 7.43−7.49 (3H, m, 2xCl-(*Ar*)C−CH-CH, (*Py*)N−CH-CH-CH, $^3J_{H,H}$ = 8.4 Hz), 7.17 (1H, dd, (*Py*)N−CH-CH-CH, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 5.7 Hz), 6.96 (1H, d, CH_3−O-(*Ar*)C−CH-C, $^4J_{H,H}$ = 2.5 Hz), 6.87 (1H, d, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz), 6.65 (1H, dd, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.5 Hz), 5.80 (2H, d, 2xCH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 5.4 Hz), 5.55 (2H, d, 2xCH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 5.4 Hz), 4.24−4.32 (4H, m, (*Ar*)C−CH_2−(C=O)−O-CH_2-CH_2−O, (*Ar*)C−CH_2−O−CH_2−CH_2-O), 3.81 (3H, s, CH_3-O-(*Ar*)C−CH-C), 3.68 (2H, s, (*Ar*)C−CH_2-(C=O)-O-$(CH_2)_2$−O), 2.85 (2H, t, (*Py*)N−CH-C−CH_2−CH_2-(C=O), $^3J_{H,H}$ = 7.2 Hz), 2.81 (1H, sept, (*Ar*)C−CH−CH−C-CH(CH_3)$_2$, $^3J_{H,H}$ = 6.9 Hz), 2.55 (2H, t, (*Py*)N−CH−C-CH_2-CH_2−(C=O), $^3J_{H,H}$ = 7.2 Hz), 2.37 (3H, s, CH_3-(*Ar*)C−N-(C=O)), 2.04 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.28 (6H, d, (*Ar*)C−CH−CH-C−CH(CH_3)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 171.8 (1C, (*Ar*)C−CH_2−(C=O)-O-$(CH_2)_2$−O), 170.7 (1C, (*Py*)N−CH-C-$(CH_2)_2$−(C=O)), 168.4 (1C, Cl-(*Ar*)C−CH−CH-C-(C=O)), 156.2 (1C, CH_3−O-(*Ar*)C-CH-C), 154.5 (1C, (*Py*)N-CH−C−CH), 152.5 (1C, (*Py*)N-CH−CH−CH), 139.5 (1C, Cl-(*Ar*)C-CH−CH), 137.9 (1C, (*Py*)N−CH-CH-CH), 137.1 (1C, (*Py*)N−CH-C-CH_2), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 134.0 (1C, CH_3-(*Ar*)C-N-(C=O)), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 131.0 (1C, Cl-(*Ar*)C−CH−CH-C), 130.7 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 124.3 (1C, (*Py*)N−CH-CH−CH), 115.1 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.4 (1C, (*Ar*)C-CH_2−(C=O)-O-$(CH_2)_2$−O), 111.6 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 101.7 (1C, CH_3−O-(*Ar*)C-CH−C), 93.8 (1C, CH_3-(*Ar*)C−CH−CH-C), 88.8 (1C, CH_3-(*Ar*)C-CH−CH-C), 75.1 (2C, 2xCH_3-(*Ar*)C−CH-CH−C), 73.1 (2C, 2xCH_3-(*Ar*)C-CH−CH-C), 62.6 (1C, (*Ar*)C−CH_2−(C=O)-O−CH_2−CH_2−O), 62.5 (1C, (*Ar*)C−CH_2−(C=O)-O-CH_2−CH_2−O), 55.9 (1C, CH_3−O-(*Ar*)C−CH-C), 34.4 (1C, (*Py*)N−CH-C-CH_2−CH_2−(C=O)), 31.0 (1C, (*Ar*)CH−CH-C-CH(CH_3)$_2$), 30.3 (1C, *Ar*)C-CH_2-(C=O)-O-$(CH_2)_2$−O), 27.7 (1C, (*Py*)N−CH-C−CH_2−CH_2-(C=O)), 22.7 (2C, (*Ar*)CH−CH-C−CH(CH_3)$_2$), 18.2 (1C, CH_3-(*Ar*)C−CH−CH), 13.5 (1C, CH_3-(*Ar*)C−N-(C=O)); IR (ν, cm^{-1}): 2960 (C−H, CH_2, CH_3); 1731 (C=O, ester); 1676, (C=O, amide); 1590, 1477, 1356, 1317, (ring skeleton C=C, C−C, C=N, C−N); 1221, 1142 (C−O, ether, ester); 832, 803, 754 (C−H, aromatic); ESI-MS(+): m/z 894.20 $[M-Cl]^+$, calcd. for $C_{39}H_{41}Cl_2N_2O_6Os^+$ 894.90, the isotopic pattern corresponds well to the calculated one; Elemental Analysis (%): calcd. for $C_{39}H_{41}Cl_3N_2O_6Os$ C 50.35, H 4.44, N 3.01; found C 50.32, H 4.43, N 3.07.

Synthesis of $[Ru(\eta^6\text{-p-cymene})Cl_2]$\{2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)ethyl-3-(pyridin-3-yl)-propanoate\} (2a). Complex **2a** was prepared following the general procedure starting from $[Ru(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (0.206 g, 1 equiv) and ligand **L2** (0.350 g, 2.2 equiv), to afford an orange solid (0.413 g, yield80%). Mp (°C): 89.5−90.5; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 8.90 (1H, d, (*Py*)N−CH-C−CH, $^4J_{H,H}$ = 1.9 Hz), 8.88 (1H, dd, (*Py*)N−CH-CH−CH, $^3J_{H,H}$ = 5.6 Hz, $^4J_{H,H}$ = 1.1 Hz), 7.52 (1H, ddd overlapped, (*Py*)N−CH-CH-CH, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.8 Hz), 7.34 (2H, d, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8 Hz), 7.23 (1H, dd, NH-(*Ar*)C−CH-CH−CH, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.4 Hz), 7.20 (1H, dd, (*Py*)N−CH-CH-CH, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 5.6 Hz), 7.12 (1H, ddd overlapped, NH-(*Ar*)C−CH-CH-CH, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.5 Hz), 6.98 (1H, t, Cl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8 Hz), 6.95 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-CH, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 0.9 Hz), 6.82 (1H, s br, NH), 6.53 (1H, d, NH-(*Ar*)−C−C-CH-CH, $^3J_{H,H}$ = 8.0 Hz), 5.43 (2H, d, 2xCH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6 Hz), 5.20 (2H,

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d, 2xCH$_3$-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 6 Hz), 4.33−4.37 (2H, m, (*Ar*)C−CH$_2$−(C=O)−O-C*H*$_2$-CH$_2$−O), 4.28−4.32 (2H, m, (*Ar*)C−CH$_2$−(C=O)-O−CH$_2$−C*H*$_2$-O), 3.84 (2H, s, (*Ar*)C−C*H*$_2$-(C=O)-O-(CH$_2$)$_2$−O), 2.97 (1H, sept, (*Ar*)C−CH−CH−C-C*H*(CH$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz), 2.89 (2H, t, (*Py*)N−CH-C−CH$_2$−C*H*$_2$-(C=O), $^3J_{H,H}$ = 7.2 Hz), 2.60 (2H, t, (*Py*)N−CH−C-C*H*$_2$-CH$_2$−(C=O), $^3J_{H,H}$ = 7.2 Hz), 2.06 (3H, s, C*H*$_3$-(*Ar*)C−CH−CH-C), 1.29 (6H, d, (*Ar*)C−CH−CH-C−CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{13}C NMR (CDCl$_3$) δ, ppm: 172.2 (1C, (*Ar*)C−CH$_2$−(*C*=O)-O-(CH$_2$)$_2$−O), 171.8 (1C, (*Py*)N−CH-C-(CH$_2$)$_2$−(*C*=O)), 155.1 (1C, (*Py*)N-*C*H−C−CH), 153.0 (1C, (*Py*)N-*C*H−CH−CH), 142.8 (1C, NH-(*Ar*)*C*−C-Cl), 137.8 (1C, NH-(*Ar*)*C*-CH−CH−CH), 137.7 (1C, (*Py*)N−CH-CH-*C*H), 137.0 (1C, (*Py*)N−CH-*C*-CH), 131.0 (1C, NH-(*Ar*)C−C*H*-CH−CH), 129.6 (2C, 2xCl-(Ar)*C*-CH−CH), 129.0 (2C, 2xCl-(Ar)C-*C*H−CH), 128.2 (1C, NH-(*Ar*)C−CH-*C*H−CH), 124.3 (1C, NH-(*Ar*)C-*C*-CH−CH), 124.2 (1C, Cl-(Ar)C−CH-*C*H), 124.2 (1C, (*Py*)N−CH-*C*H−CH), 122.2 (1C, NH-(*Ar*)C−CH−CH-*C*H), 118.4 (1C, NH-(*Ar*)C−C-*C*H−CH), 103.5 (1C, CH$_3$-(*Ar*)C−CH−CH-*C*), 97.2 (1C, CH$_3$-(*Ar*)*C*-CH−CH-C), 83.0 (2C, 2xCH$_3$-(*Ar*)C−CH-*C*H−C), 82.3 (2C, 2xCH$_3$-(*Ar*)C-*C*H−CH-C), 62.9 (1C, (*Ar*)C−CH$_2$−(C=O)-O-*C*H$_2$−CH$_2$−O), 62.5 (1C, (*Ar*)C−CH$_2$−(C=O)-O−CH$_2$−*C*H$_2$−O), 38.5 (1C, (*Ar*)C-*C*H$_2$-(C=O)-O-(CH$_2$)$_2$−O), 34.6 (1C, (*Py*)N−CH-C-*C*H$_2$−CH$_2$−(C=O)), 30.7 (1C, (*Ar*)CH−CH-C-*C*H(CH$_3$)$_2$), 27.7 (1C, (*Py*)N−CH-C−CH$_2$−*C*H$_2$-(C=O)), 22.4 (2C, (*Ar*)CH−CH-C−CH(*C*H$_3$)$_2$), 18.2 (1C, *C*H$_3$-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3317 (N−H); 2959 (C−H, CH$_2$, CH$_3$); 1729 (C=O, ester); 1501, 1450 (ring skeleton C=C, C−C, C−N, C=N); 1145 (C−O, ester); 776, 746 (C−H aromatic); ESI-MS(+): *m*/*z* 744.08 [M-Cl]$^+$, calcd. for $C_{34}H_{36}Cl_3N_2O_4Ru^+$ 744.09, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{34}H_{36}Cl_4N_2O_4Ru$ C 52.39, H 4.66, N 3.59; found C 52.31, H 4.65, N 3.50.

Synthesis of [Os(η^6-p-cymene)Cl$_2$]{2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)ethyl-3-(pyridin-3-yl)-propanoate} (2b). Complex **2b** was prepared following the general procedure starting from [Os(η^6-*p*-cymene)Cl]$_2$Cl$_2$ (0.266 g, 1 equiv) and ligand **L2** (0.350 g, 2.2 equiv), to afford an orange solid (0.316 g, yield 54%).

Mp (°C): 74−76; ^{1}H NMR (CDCl$_3$) δ_H, ppm: 8.81 (1H, d, (*Py*)N−C*H*-C−CH, $^4J_{H,H}$ = 1.6 Hz), 8.79 (1H, dd, (*Py*)N−C*H*-CH−CH, $^3J_{H,H}$ = 5.8 Hz, $^4J_{H,H}$ = 1.2 Hz), 7.47 (1H, ddd overlapped, (*Py*)N−CH-CH-C*H*, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.6 Hz), 7.33 (2H, d, 2xCl-(Ar)C−C*H*-CH, $^3J_{H,H}$ = 8.1 Hz), 7.23 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.3 Hz), 7.16(1H, dd, (*Py*)N−CH-C*H*-CH, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 5.8 Hz), 7.12 (1H, ddd overlapped, NH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.4 Hz), 6.98 (1H, t, Cl-(Ar)C−CH-C*H*, $^3J_{H,H}$ = 8.1 Hz), 6.95 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.1 Hz), 6.82 (1H, s br, N*H*), 6.53 (1H, d, NH-(*Ar*)−C−C-C*H*-CH, $^3J_{H,H}$ = 8.0 Hz), 5.80 (2H, d, 2xCH$_3$-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 5.6 Hz), 5.55 (2H, d, 2xCH$_3$-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 5.6 Hz), 4.33−4.37 (2H, m, (*Ar*)C−CH$_2$−(C=O)−O-C*H*$_2$-CH$_2$), 4.28−4.32 (2H, m, (*Ar*)C−CH$_2$−(C=O)-O−CH$_2$−C*H*$_2$), 3.83 (2H, s, (*Ar*)C−C*H*$_2$-(C=O)-O-(CH$_2$)$_2$−O), 2.87 (2H, t, (*Py*)N−CH-C−CH$_2$−C*H*$_2$-(C=O), $^3J_{H,H}$ = 7.3 Hz), 2.80 (1H, sept, (*Ar*)C−CH−CH−C-C*H*(CH$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz), 2.59 (2H, t, (*Py*)N−CH−C-C*H*$_2$-CH$_2$−(C=O), $^3J_{H,H}$ = 7.3 Hz), 2.04 (3H, s, C*H*$_3$-(*Ar*)C−CH−CH-C), 1.29 (6H, d, (*Ar*)C−CH−CH-C−CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{13}C NMR (CDCl$_3$) δ, ppm: 172.2 (1C, (*Ar*)C−CH$_2$−(*C*=O)-O-(CH$_2$)$_2$−O), 171.8 (1C, (*Py*)N−CH-C-(CH$_2$)$_2$−(*C*=O)), 154.5 (1C, (*Py*)N-*C*H−C−CH), 152.5 (1C, (*Py*)N-*C*H−CH−CH), 142.8 (1C, NH-(*Ar*)*C*−C-Cl), 137.9 (2C, NH-(*Ar*)*C*-CH−CH, (*Py*)N−CH-*C*-CH), 137.2 (1C, (*Py*)N−CH-CH-*C*H), 131.0 (1C, NH-(*Ar*)C−C*H*-CH−CH), 129.6 (2C, 2xCl-(*Ar*)*C*-CH−CH), 129.1 (2C, 2xCl-(*Ar*)C-*C*H−CH), 128.3 (1C, NH-(*Ar*)C−CH-*C*H−CH), 124.3 (2C, Cl-(*Ar*)C−CH-*C*H, NH-(*Ar*)C-*C*-CH−CH), 124.2 (1C, (*Py*)N−CH-*C*H−CH), 122.2 (1C, NH-(*Ar*)C−CH−CH-*C*H), 118.5 (1C, NH-(*Ar*)C−C-*C*H−CH), 93.8 (1C, CH$_3$-(*Ar*)C−CH−CH-*C*), 88.8 (1C, CH$_3$-(*Ar*)*C*-CH−CH-C), 75.1 (2C, 2xCH$_3$-(*Ar*)C−CH-*C*H−C), 73.1 (2C, 2xCH$_3$-(*Ar*)C-*C*H−CH-C), 62.9 (1C, (*Ar*)C−CH$_2$−(C=O)-O-*C*H$_2$−CH$_2$−O), 62.5 (1C, (*Ar*)C−CH$_2$−(C=O)-O−CH$_2$−*C*H$_2$−O), 38.5 (1C, (*Ar*)C-*C*H$_2$-(C=O)-O-(CH$_2$)$_2$−O), 34.5 (1C, (*Py*)N−CH-C-*C*H$_2$−CH$_2$−(C=O)), 31.0 (1C, (*Ar*)CH−CH-C-*C*H(CH$_3$)$_2$), 27.7 (1C, (*Py*)N−CH-C−CH$_2$−*C*H$_2$-(C=O)), 22.8 (2C, (*Ar*)CH−CH-C−CH-(*C*H$_3$)$_2$), 18.2 (1C, *C*H$_3$-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3322 (N−H); 3066, 2960 (C−H, CH$_3$, CH$_2$); 1729 (C=O, ester); 1506, 1450 (ring skeleton C=C, C−C, C−N, C=N); 1144 (C−O, ester); 774, 745 (C−H, aromatic); ESI-MS(+): *m*/*z* 833.13 [M-Cl]$^+$, calcd. for $C_{34}H_{36}Cl_3N_2O_4Os^+$ 833.25, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{34}H_{36}Cl_4N_2O_4Os$ C 47.01, H 4.18, N 3.22; found C 47.03, H 4.22, N 3.28.

Synthesis of [Ru(η^6-p-cymene)Cl$_2$]{2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl-4-(diphenylphosphanyl)benzoate} (3a). Complex **3a** was prepared following the general procedure strating from [Ru(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.133 g, 1 equiv) and ligand **L3** (0.300 g, 2 equiv), to afford an orange solid (0.267 g, yield 98%).

Mp (°C): 107−108; ^{1}H NMR (CDCl$_3$) δ_H, ppm: 7.79−7.90 (8H, m, 2xO-(C=O)-(*Ar*)C−C*H*-CH−C-P, 2xO-(C=O)-(*Ar*)C−CH-C*H*−C-P, 4xP-(*Ar*)C−C*H*-CH−CH), 7.62 (2H, m, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.44 (2H, m, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.3 Hz), 7.37−7.47 (6H, m, 4xP-(*Ar*)C−CH-C*H*-CH, 2xP-(*Ar*)C−CH−CH-C*H*), 6.94 (1H, d, CH$_3$−O-(*Ar*)C−C*H*-C, $^3J_{H,H}$ = 2.5 Hz), 6.81 (1H, d, CH$_3$−O-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 9.0 Hz), 6.54 (1H, dd, CH$_3$−O-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 2.5 Hz), 5.22 (2H, d, 2xCH$_3$-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 6.2 Hz), 4.98 (2H, d, 2xCH$_3$-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 6.2 Hz), 4.45−4.49 (2H, m, (*Ar*)C−CH$_2$−(C=O)-O−CH$_2$−C*H*$_2$-O), 4.38−4.42 (2H, m, (*Ar*)C−CH$_2$−(C=O)−O-C*H*$_2$-CH$_2$−O), 3.72 (3H, s, C*H*$_3$-O-(*Ar*)C−CH-C), 3.68 (2H, s, (*Ar*)C−C*H*$_2$-(C=O)-O-(CH$_2$)$_2$−O), 2.86 (1H, sept, (*Ar*)C−CH−CH−C-C*H*(CH$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz), 2.34 (3H, s, C*H*$_3$-(*Ar*)C−N-(C=O)), 1.85 (3H, s, C*H*$_3$-(*Ar*)C−CH−CH-C), 1.11 (6H, d, (*Ar*)C−CH−CH-C−CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{31}P NMR (CDCl$_3$) δ_P, ppm: 25.12 (1P); ^{13}C NMR (CDCl$_3$) δ_C, ppm: 170.7 (1C, (*Ar*)C−CH$_2$−(*C*=O)-O-(CH$_2$)$_2$−O), 168.3 (1C, Cl-(*Ar*)C−CH−CH-C-(*C*=O)), 165.9 (1C, O-(*C*=O)-(*Ar*)C−CH−CH−C-P), 156.2 (1C, CH$_3$−O-(*Ar*)*C*-CH-C), 139.5 (1C, O-(C=O)-(*Ar*)C−CH−CH-*C*-P, $^1J_{C,P}$ = 44 Hz), 139.3 (1C, Cl-(*Ar*)*C*-CH−CH), 136.1 (1C, CH$_3$−O-(*Ar*)C−CH-*C*), 134.6 (2C, O-(C=O)-(*Ar*)C−CH-*C*H−C−P, $^2J_{C,P}$ = 9 Hz), 134.4 (4C, 4xP-(*Ar*)C-*C*H−CH−CH, $^2J_{C,P}$ = 10 Hz), 134.0 (1C, CH$_3$-(*Ar*)*C*-N-(C=O)), 133.5 (2C, 2xP-(*Ar*)*C*-CH−CH−CH, $^1J_{C,P}$ = 45 Hz), 131.3 (2C, 2xCl-(*Ar*)C−CH-*C*H), 130.9 (1C, Cl-(*Ar*)C−CH−CH-*C*), 130.8 (1C, CH$_3$−O-(*Ar*)C−CH−CH-*C*), 130.7 (2C, 2xP-(*Ar*)C−CH−CH-*C*H, $^4J_{C,P}$ = 2 Hz), 130.7 (1C, O-(C=O)-(*Ar*)*C*-CH−CH−C-P), 129.2 (2C, 2xCl-(*Ar*)C-*C*H−CH), 128.7 (2C, O-(C=O)-(*Ar*)C-*C*H−CH−C-P, $^3J_{C,P}$ = 10 Hz), 128.3 (4C, 4xP-(*Ar*)C−CH-*C*H−CH, $^3J_{C,P}$ = 10 Hz), 115.0 (1C, CH$_3$−O-(*Ar*)C−CH-*C*H−C), 112.4 (1C, O-(C=O)−CH$_2$−(Ar)*C*), 111.8 (1C, CH$_3$−O-(*Ar*)C-*C*H−CH-C), 111.6, 111.7 (1C, CH$_3$-(*Ar*)C−CH−CH-*C*), 101.4 (1C, CH$_3$−O-(*Ar*)C-*C*H−C), 96.4 (1C, CH$_3$-(*Ar*)*C*-CH−CH-C), 89.03 (1C, CH$_3$-(*Ar*)C−CH-*C*H−C), 89.0 (1C, CH$_3$-(*Ar*)C−CH-*C*H−C), 87.52 (1C, CH$_3$-(*Ar*)C-*C*H−CH-C), 87.47 (1C, CH$_3$-(*Ar*)C-*C*H−CH-C), 62.9 (1C, (*Ar*)C−CH$_2$−(C=O)-O-*C*H$_2$−CH$_2$−O), 62.8 (1C, (*Ar*)C−CH$_2$−(C=O)-O−CH$_2$−*C*H$_2$−O), 55.8 (1C, *C*H$_3$−O-(*Ar*)C−CH-C), 30.4 (1C, O-(C=O)-*C*H$_2$-(*Ar*)C), 30.3 (1C, (*Ar*)CH−CH-C-*C*H(CH$_3$)$_2$), 22.0 (2C, (*Ar*)CH−CH-C−CH(*C*H$_3$)$_2$), 17.9 (1C, *C*H$_3$-(*Ar*)C−CH−CH), 13.5 (1C, *C*H$_3$-(*Ar*)C−N-(C=O)); IR (ν, cm^{-1}): 2961 (C−H, CH$_2$, CH$_3$); 1721 (C=O, ester); 1679 (C=O, amide); 1597, 1476, 1434, 1356 (ring skeleton C=C, C−C, C=N, C−N); 1259, 1221, 1086 (C−O, ether, ester); 799, 752 (C−H aromatic); ESI-MS(+): *m*/*z* 1035.09 [M+K]$^+$, 960.15 [M-Cl]$^+$, calcd. for $C_{50}H_{47}Cl_3NO_6PRu$ 996.32, calcd. for $C_{50}H_{47}Cl_2NO_6PRu^+$ 960.87, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{50}H_{47}Cl_3NO_6PRu$ C 60.28; H 4.76; N 1.41; O; found C 60.38, H 4.83, N 1.36.

Synthesis of [Os(η^6-p-cymene)Cl$_2$]{2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl-4-(diphenylphosphanyl)benzoate} (3b). Complex **3b** was prepared

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following the general procedure starting from [Os(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.444 g, 1 equiv) and ligand **L3** (1.370 g, 3.5 equiv) to afford an orange solid (1.430 g, yield 65%). Mp (°C): 115−116; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 7.84−7.86 (4H, m, 2xO-(C═O)-(*Ar*)C−C*H*-CH−C-P, 2xO-(C═O)-(*Ar*)C−CH-C*H*−C-P), 7.71−7.76 (4H, m, 4xP-(*Ar*)C−C*H*-CH−CH), 7.62 (2H, m, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.1 Hz), 7.45 (2H, m, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.6 Hz, $^4J_{H,H}$ = 2.1 Hz), 7.38−7.46 (6H, m, 4xP-(*Ar*)C−CH-C*H*-CH, 2xP-(*Ar*)C−CH−CH-C*H*), 6.94 (1H, d, CH_3−O-(*Ar*)C−C*H*-C, $^3J_{H,H}$ = 2.5 Hz), 6.81 (1H, d, CH_3−O-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 9.0 Hz), 6.54 (1H, dd, CH_3−O-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 2.5 Hz), 5.42 (2H, d, 2xCH_3-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 5.8 Hz), 5.15 (2H, d, 2xCH_3-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 5.8 Hz), 4.46−4.50 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−C*H*$_2$-O), 4.39−4.44 (2H, m, (*Ar*)C−CH_2−(C═O)−O-C*H*$_2$-CH_2−O), 3.72 (3H, s, C*H*$_3$-O-(*Ar*)C−CH-C), 3.68 (2H, s, (*Ar*)C−C*H*$_2$-(C═O)-O-$(CH_2)_2$−O), 2.75 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^3J_{H,H}$ = 6.9 Hz), 2.34 (3H, s, C*H*$_3$-(*Ar*)C−N), 1.96 (3H, s, C*H*$_3$-(*Ar*)C−CH−CH-C), 1.16 (6H, d, (*Ar*)C−CH−CH-C−CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{31}P NMR ($CDCl_3$) δ_P, ppm: −12.31 (1P); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 170.7 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 168.3 (1C, Cl-(*Ar*)C−CH−CH-C-(C═O)), 165.9 (1C, O-(C═O)-(*Ar*)C−CH−CH−C-P), 156.1 (1C, CH_3−O-(*Ar*)C-CH-C), 139.3 (1C, Cl-(*Ar*)C-CH−CH), 139.2 (1C, O-(C═O)-(*Ar*)C−CH−CH-C-P, $^1J_{C,P}$ = 50 Hz), 136.1 (1C, CH_3−O-(*Ar*)C−CH-C), 134.8 (2C, O-(C═O)-(*Ar*)C−CH-CH−C−P, $^2J_{C,P}$ = 11 Hz), 134.6 (4C, 4xP-(*Ar*)C-CH−CH−CH, $^2J_{C,P}$ = 10 Hz), 134.0 (1C, CH_3-(*Ar*)C-N-(C═O)), 132.9 (2C, 2xP-(*Ar*)C-CH−CH−CH, $^1J_{C,P}$ = 52 Hz), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 130.8 (2C, Cl-(*Ar*)C−CH−CH-C, CH_3−O-(*Ar*)C−CH−CH-C,), 130.7 (2C, 2xP-(*Ar*)C−CH−CH-CH, $^4J_{C,P}$ = 2 Hz), 130.8 (1C, O-(C═O)-(*Ar*)C-CH−CH−C-P), 129.2 (2C, 2xCl-(*Ar*)C-CH−CH), 128.6 (2C, 2xO-(C═O)-(*Ar*)C-CH−CH−C-P, $^3J_{C,P}$ = 10 Hz), 128.2 (4C, 4xP-(*Ar*)C−CH-CH−CH, $^3J_{C,P}$ = 10 Hz), 115.0 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.4 (1C, (Ar)C-CH_2−(C═O)-O), 111.8 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 103.95, 103.99 (1C, CH_3-(*Ar*)C−CH−CH-C), 101.3 (1C, CH_3−O-(*Ar*)C-CH−C,), 89.0 (1C, CH_3-(*Ar*)C-CH−CH-C), 80.44 (1C, CH_3-(*Ar*)C−CH-CH−C), 80.41 (1C, CH_3-(*Ar*)C−CH-CH−C), 80.30 (1C, CH_3-(*Ar*)C-CH−CH-C), 80.25 (1C, CH_3-(*Ar*)C-CH−CH-C), 62.9 (1C, (*Ar*)C−CH_2−(C═O)-O-C*H*$_2$−CH_2−O), 62.8 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−C*H*$_2$−O), 55.8 (1C, C*H*$_3$−O-(*Ar*)C−CH-C), 30.3 (1C, (*Ar*)CH−CH-C-C*H*$(CH_3)_2$), 30.2 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 22.3 (2C, (*Ar*)CH−CH-C−CH(C*H*$_3$)$_2$), 18.0 (1C, C*H*$_3$-(*Ar*)C−CH−CH), 13.5 (1C, C*H*$_3$-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2960 (C−H, CH_2, CH_3); 1719 (C═O, ester); 1680 (C═O, amide); 1597, 1476, 1356, 1315 (ring skeleton C═C, C−C, C═N, C−N); 1259, 1222, 1086 (C−O, ester, ether); 799, 753 (C−H aromatic); ESI-MS(+): *m*/*z* *m*/*z* 1124.14 [M+K]$^+$, 1050.21 [M-Cl]$^+$, calcd. for $C_{50}H_{47}Cl_3NO_6OsP$ 1085.48, calcd. for $C_{50}H_{47}Cl_2NO_6OsP^+$ 1050.03, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{50}H_{47}Cl_3NO_6OsP$ C 55.33, H 4.36, N 1.29; found C 55.29, H 4.36, N 1.24.

Synthesis of [Ru(η^6-p-cymene)Cl$_2$]{2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)ethyl-4-(diphenylphosphanyl)benzoate} (4a). Complex 4a was prepared following the general procedure starting from [Ru(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.098 g, 1 equiv) and ligand **L4**_(0.200 g, 2 equiv) to afford an orange solid (0.096 g, yield 59%).

Mp (°C): 92−93; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 7.77−7.89 (8H, m, 2xO-(C═O)-(*Ar*)C−C*H*-CH−C-P, 2xO-(C═O)-(*Ar*)C−CH-C*H*−C-P, 4xP-(*Ar*)C−C*H*-CH−CH), 7.36−7.49 (6H, m, 4xP-(*Ar*)C−CH-C*H*-CH, 2xP-(*Ar*)C−CH−CH-C*H*), 7.29 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8 Hz), 7.20 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.3 Hz), 7.02 (1H, ddd overlapped, NH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.4 Hz), 6.94 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8 Hz), 6.87 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.1 Hz), 6.83 (1H, s br, N*H*), 6.45 (1H, dd, NH-(*Ar*)C−C−C*H*-CH, $^3J_{H,H}$ = 8.0 Hz), 5.21 (2H, d, 2xCH_3-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 6.1 Hz), 4.97 (2H, d, 2xCH_3-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 6.1 Hz), 4.86−4.54 (2H, m, (*Ar*)C−CH_2−(C═O)−O-C*H*$_2$-CH_2−O), 4.43−4.47 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−C*H*$_2$-O), 3.83 (2H, s, (*Ar*)C−C*H*$_2$-(C═O)-O-$(CH_2)_2$−O), 2.86 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^3J_{H,H}$ = 6.9 Hz), 1.85 (3H, s, C*H*$_3$-(*Ar*)C−CH−CH-C), 1.11 (6H, d, (*Ar*)C−CH−CH-C−CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{31}P NMR ($CDCl_3$) δ_P, ppm: 24.94 (1P); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.2 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 165.7 (1C, O-(C═O)-(*Ar*)C−CH−CH−C-P), 142.6 (1C, NH-(*Ar*)C−C-Cl), 139.4 (1C, d, O-(C═O)-(*Ar*)C−CH−CH-C-P, $^1J_{C,P}$ = 45 Hz), 137.7 (1C, NH-(*Ar*)C-CH−CH), 134.4 (2C, d, 2xO-(C═O)-(*Ar*)C−CH-CH−C−P, $^2J_{C,P}$ = 8 Hz), 134.3 (4C, d, 4xP-(*Ar*)C-CH−CH−CH, $^2J_{C,P}$ = 10 Hz), 133.4 (2C, d, 2xP-(*Ar*)C-CH−CH−CH, $^1J_{C,P}$ = 45 Hz), 130.9 (1C, NH-(*Ar*)C−C*H*-CH), 130.8 (1C, d, O-(C═O)-(*Ar*)C-CH−CH−C-P, $^4J_{C,P}$ = 2 Hz), 130.6 (2C, d, 2xP-(*Ar*)C−CH−CH-CH, $^4J_{C,P}$ = 2 Hz), 129.5 (2C, 2xCl-(*Ar*)C-CH−CH), 128.9 (2C, 2xCl-(*Ar*)C-CH−CH), 128.7 (2C, d, 2xO-(C═O)-(*Ar*)C-CH−CH−C-P, $^3J_{C,P}$ = 10 Hz), 128.2 (4C, d, 4xP-(*Ar*)C- CH−CH−CH, $^3J_{C,P}$ = 10 Hz), 128.1 (1C, NH-(*Ar*)C−CH-CH−CH), 124.1 (1C, Cl-(Ar)C−CH-CH), 124.0 (1C, NH-(*Ar*)C-C-CH), 122.1 (1C, NH-(*Ar*)C−CH−CH-CH), 118.2 (1C, NH-(*Ar*)C−C-CH−CH), 111.5, 111.6 (1C, CH_3-(*Ar*)C−CH−CH-C), 96.3 (1C, CH_3-(*Ar*)C-CH−CH-C), 89.99 (1C, CH_3-(*Ar*)C−CH-CH−C), 88.96 (1C, CH_3-(*Ar*)C−CH-CH−C), 87.4 (1C, CH_3-(*Ar*)C-CH−CH-C), 87.3 (1C, CH_3-(*Ar*)C-CH−CH-C), 62.8 (1C, (*Ar*)C-(C═O)-O-C*H*$_2$−CH_2−O), 62.7 (1C, (*Ar*)C-(C═O)-O−CH_2−C*H*$_2$−O), 38.4 (1C, (*Ar*)C-C*H*$_2$-(C═O)-O-$(CH_2)_2$−O), 30.3 (1C, (*Ar*)CH−CH-C-CH-$(CH_3)_2$), 21.9 (2C, (*Ar*)CH−CH-C−CH(C*H*$_3$)$_2$), 17.8 (1C, C*H*$_3$-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3322 (N−H); 2960 (C−H, CH_3, CH_2); 1717 (C═O, ester); 1588, 1502, 1450, 1395 (ring skeleton C═C, C−C); 1285, 1272, 1229 (C−O); 853, 745 (C−H aromatic); ESI-MS(+): *m*/*z* 899.10 [M-Cl]$^+$, calcd. for $C_{45}H_{42}Cl_3NO_4PRu^+$ 899.23, the isotopic pattern coresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{45}H_{42}Cl_4NO_4PRu$ C 57.83, H 4.53, N 1.50, found C 57.73, H 4.62, N 1.42.

Synthesis of [Os(η^6-p-cymene)Cl$_2$]{2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetoxy)ethyl-4-(diphenylphosphanyl)benzoate} (4b). Complex 4b was prepared following the general procedures starting from [Os(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.220 g, 1 equiv) and ligand **L4** (0.461 g, 3.5 equiv) to afford an orange solid (0.126 g, yield 33%).

Mp (°C): 108−109; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 7.80−7.88 (4H, m, 2xO-(C═O)-(*Ar*)C−C*H*-CH−C-P, 2xO-(C═O)-(*Ar*)C−CH-C*H*−C-P), 7.70−7.76 (4H, m, 4xP-(*Ar*)C−C*H*-CH−CH), 7.37−7.44 (6H, m, 4xP-(*Ar*)C−CH-C*H*-CH, 2xP-(*Ar*)C−CH−CH-C*H*), 7.29 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8 Hz), 7.20 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.4 Hz), 7.02 (1H, ddd overlapped, NH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.4 Hz), 6.95 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8 Hz), 6.87 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1 Hz), 6.84 (1H, s br, N*H*), 6.45 (1H, dd, NH-(*Ar*)C−C−C*H*-CH, $^3J_{H,H}$ = 8.0 Hz), 5.40 (2H, d, 2xCH_3-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 5.8 Hz), 5.15 (2H, d, 2xCH_3-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 5.8 Hz), 4.89−4.53 (2H, m, (*Ar*)C−CH_2−(C═O)−O-C*H*$_2$-CH_2−O), 4.44−4.48 (2H, m, (*Ar*)C−CH_2−(C═O)-O−CH_2−C*H*$_2$-O), 3.83 (2H, s, (*Ar*)C−C*H*$_2$-(C═O)-O-$(CH_2)_2$−O), 2.75 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^3J_{H,H}$ = 6.9 Hz), 1.96 (3H, s, C*H*$_3$-(*Ar*)C−CH−CH-C), 1.16 (6H, d, (*Ar*)C−CH−CH-C−CH(C*H*$_3$)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{31}P NMR ($CDCl_3$) δ, ppm: −12.50 (1P); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.3 (1C, (*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 165.8 (1C, O-(C═O)-(*Ar*)C−CH−CH−C-P), 142.7 (1C, NH-(*Ar*)C−C-Cl), 139.3 (1C, d, O-(C═O)-(*Ar*)C−CH−CH-C-P, $^1J_{C,P}$ = 49 Hz), 137.8 (1C, NH-(*Ar*)C-CH−CH), 134.7 (2C, d, 2xO-(C═O)-(*Ar*)C−CH-CH−C−P, $^2J_{C,P}$ = 9 Hz), 134.6 (4C, d, 4xP-(*Ar*)C-CH−CH−CH, $^2J_{C,P}$ = 9 Hz), 133.0 (2C, d, 2xP-(*Ar*)C-CH−CH−CH, $^1J_{C,P}$ = 52 Hz), 131.0 (1C, NH-(*Ar*)C−C*H*-CH−CH), 130.9 (1C, d, O-(C═O)-(*Ar*)C-CH−CH−C-P, $^4J_{C,P}$ = 2 Hz), 130.7 (2C, d, 2xP-(*Ar*)C−CH−CH-CH, $^4J_{C,P}$ = 2 Hz), 129.6 (2C, 2xCl-(*Ar*)C-CH−CH), 129.0 (2C, 2xCl-(*Ar*)C-CH−CH), 128.7 (2C, d, O-(C═O)-(*Ar*)C-CH−CH−C-P, $^3J_{C,P}$ = 10 Hz), 128.3 (4C, d, 4xP-(*Ar*)C−CH-CH−CH, $^3J_{C,P}$ = 10 Hz), 128.2 (1C, NH-(*Ar*)C−CH-CH−CH), 124.2 (1C, Cl-(Ar)C−CH-CH), 124.1 (1C, NH-(*Ar*)C-C-CH), 122.2 (1C, NH-(*Ar*)C−CH−

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CH-CH), 118.3 (1C, NH-(*Ar*)C−C-CH−CH), 103.9, 114.0 (1C, CH_3-(*Ar*)C−CH−CH-C), 89.0 (1C, CH_3-(*Ar*)C-CH−CH-C), 80.51 (1C, CH_3-(*Ar*)C−CH-CH−C), 80.48 (1C, CH_3-(*Ar*)C−CH-CH−C), 80.3 (1C, CH_3-(*Ar*)C-CH−CH-C), 80.2 (1C, CH_3-(*Ar*)C-CH−CH-C), 62.9 (1C, (*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2), 62.8 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2), 38.5 (1C, (*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 30.2 (1C, (*Ar*)CH−CH-C-CH$(CH_3)_2$), 22.3 (2C, (*Ar*)CH−CH-C−CH$(CH_3)_2$), 18.0 (1C, CH_3-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3315 (N−H); 2960 (C−H, CH_2, CH_3); 1719 (C═O, ester); 1588, 1503, 1451, 1395 (ring skeleton C═C, C−C); 1272 (C−O, ester); 855, 743 (C−H aromatic); ESI-MS(+): *m*/*z* 1046.11 $[M + Na]^+$, 988.15 $[M\text{-}Cl]^+$, calcd. for $C_{45}H_{42}Cl_3NO_4POs^+$ 988.39, calcd. for $C_{45}H_{42}Cl_4NO_4POs$ 1023.84, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{45}H_{42}Cl_4NO_4POs$ C 52.79, H 4.14, N 1.37; found C 52.69, H 4.02, N 1.30.

Synthesis of {[Ru(η^6-p-cymene)Cl](4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate)}Cl (5a). Complex **5a** was prepared following the general procedures starting from $[Ru(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (0.198 g, 1 equiv) and ligand **L5** (0.350 g, 2 equiv), to afford an orange solid (0.485 g, yield 88%). Mp (°C): 133−134 with decomp.; ^1H NMR ($CDCl_3$) δ_H, ppm: 9.75 (1H, d, O−CH_2−(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.7 Hz), 9. 55 (1H, d, CH_3-(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.7 Hz), 8.23 (1H, s, O−CH_2−(*Py*)C−CH−C-N), 8.04 (1H, s, CH_3-(*Py*)C−CH−C-N), 7.62 (2H, m, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.4 Hz), 7.59 (1H, d, O−CH_2−(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.7 Hz), 7.50 (1H, d, CH_3-(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.7 Hz), 7.44 (2H, m, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.4 Hz), 6.95 (1H, d, CH_3−O-(*Ar*)C−CH-C, $^4J_{H,H}$ = 2.4 Hz), 6.88 (1H, d, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz), 6.63 (1H, dd, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.4 Hz), 6.19 (1H, m, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6.1 Hz), 6.17 (1H, m, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6.1 Hz), 6.05 (1H, m, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6.1 Hz), 6.01 (1H, m, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 6.1 Hz), 5.29 (2H, s, O−CH_2-(*Py*)C−CH−CH-N), 3.81 (2H, s, (*Ar*)C−CH_2-(C═O)-O−CH_2−(*Py*)C), 3.73 (3H, s, CH_3-O-(*Ar*)C−CH-C), 2.63 (1H, sept, (*Ar*)C−CH−CH−C-CH$(CH_3)_2$, $^3J_{H,H}$ = 6.8 Hz), 2.51 (3H, s, CH_3-(*Py*)C−CH−CH-N), 2.35 (3H, s, CH_3-(*Ar*)C−N-(C═O)), 2.22 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.01 (3H, d, (*Ar*)C−CH−CH-C−CH-CH_3, $^3J_{H,H}$ = 6.8 Hz), 0.99 (3H, d, (*Ar*)C−CH−CH-C−CH-CH_3, $^3J_{H,H}$ = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 170.3 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−(*Py*)C), 168.4 (1C, Cl-(*Ar*)C−CH−CH-C-(C═O)), 156.8 (1C, O−CH_2−(*Py*)C−CH-C-N), 156.2 (1C, CH_3−O-(*Ar*)C-CH-C), 155.8 (1C, CH_3-(*Py*)C−CH-C-N), 154.7 (1C, O−CH_2−(*Py*)C−CH-CH−N), 153.9 (1C, CH_3-(*Py*)C−CH-CH−N), 152.2 (1C, O−CH_2−(*Py*)C-CH−CH-N), 149.1 (1C, CH_3-(*Py*)C-CH−CH-N), 139.6 (1C, Cl-(*Ar*)C-CH−CH), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 133.7 (1C, CH_3-(*Ar*)C-N-(C═O)), 131.3 (2C, 2xCl-(*Ar*)C−CH-CH), 130.9 (1C, Cl-(*Ar*)C−CH−CH-C), 130.6 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 129.2 (1C, CH_3-(*Py*)C−CH-CH-N), 126.0 (1C, CH_3-(*Py*)C−CH−C-N), 124.5 (1C, O−CH_2−(*Py*)C-CH−CH-N), 121.3 (1C, O−CH_2−(*Py*)C-CH−C−N), 115.1 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.0 (1C, (*Ar*)C-CH_2−(C═O)-O−CH_2−(*Py*)C), 111.9 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 104.7 (1C, CH_3-(*Ar*)C−CH−CH-C), 104.2 (1C, CH_3-(*Ar*)C-CH−CH-C), 101.5 (1C, CH_3−O-(*Ar*)C-CH−C), 87.3 (1C, CH_3-(*Ar*)C−CH-CH-C), 87.2 (1C, CH_3-(*Ar*)C−CH-CH-C), 84.6 (1C, CH_3-(*Ar*)C−CH-CH-C), 84.4 (1C, CH_3-(*Ar*)C−CH-CH-C), 64.0 (1C, O-CH_2-(*Py*)C−CH−CH-N), 56.0 (1C, CH_3−O-(*Ar*)C−CH-C), 31.2 (1C, (*Ar*)CH−CH-C-CH$(CH_3)_2$), 30.2 (1C, (*Ar*)C-CH_2-(C═O)-O−CH_2−(*Py*)C), 22.31 (1C, (*Ar*)CH−CH-C−CH-CH_3), 22.25 (1C, (*Ar*)CH−CH-C−CH-CH_3), 21.5 (1C, CH_3-(*Py*)C−CH−CH-N), 19.1 (1C, CH_3-(*Ar*)C−CH−CH), 13.6 (1C, CH_3-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2963 (C−H, CH_3, CH_2); 1737 (C═O, ester); 1676 (C═O, amide); 1618, 1476, 1456, 1356, 1316 (ring skeleton C═C, C−C, C═N); 1218, 1140, 1086 (C−O, ester, ether); 828, 803, 754 (C−H aromatic); ESI-MS(+): *m*/*z* 810.13 $[M\text{-}Cl]^+$, calcd. for $C_{41}H_{40}Cl_2N_3O_4Ru^+$ 810.76, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{41}H_{40}Cl_3N_3O_4Ru$ C 58.20, H 4.76, N 4.97; found C, 58.08, H, 4.81, N, 4.84.

Synthesis of {[Os(η^6-p-cymene)Cl](4′-methyl-[2,2′-bipyridin]-4-yl)methylene-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate)}Cl (5b). Complex **5b** was prepared following the general procedure starting from $[Os(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (0.200 g, 1 equiv) and ligand **L5** (0.273 g, 2 equiv), to afford a yellow-orange solid (0.188 g, yield 79%). Mp (°C): 174.5−175.5 with decomp.; ^1H NMR ($CDCl_3$) δ_H, ppm: 9.61 (1H, d, O−CH_2−(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 4.8 Hz), 9.40 (1H, d, CH_3-(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.3 Hz), 8.41 (1H, s, O−CH_2−(*Py*)C−CH−C-N), 8.23 (1H, s, CH_3-(*Py*)C−CH−C-N), 7.64 (2H, d, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.4 Hz), 7.54 (1H, d, O−CH_2−(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 4.8 Hz), 7.45−7.47 (2H, m, CH_3-(*Py*)C−CH-CH-N, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.4 Hz), 6.97 (1H, d, CH_3−O-(*Ar*)C−CH-C, $^4J_{H,H}$ = 2.2 Hz), 6.91 (1H, d, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz), 6.66 (1H, dd, CH_3−O-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 2.2 Hz), 6.37 (1H, d, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 5 Hz), 6.32 (1H, d, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 5 Hz), 6.15 (1H, d, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 5 Hz), 6.09 (1H, d, CH_3-(*Ar*)C−CH-CH-C, $^3J_{H,H}$ = 5 Hz), 5.38 (2H, s, O−CH_2-(*Py*)C−CH−CH-N), 3.84 (2H, s, (*Ar*)C−CH_2-(C═O)-O−CH_2−(*Py*)C), 3.78 (3H, s, CH_3-O-(*Ar*)C−CH-C), 2.61 (3H, s, CH_3-(*Py*)C−CH−CH-N), 2.49 (1H, sept, (*Ar*)C−CH−CH−C-CH$(CH_3)_2$, $^3J_{H,H}$ = 6.8 Hz), 2.37 (3H, s, CH_3-(*Ar*)C−N-(C═O)), 2.29 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 0.96 (6H, d, (*Ar*)C−CH−CH-C−CH$(CH_3)_2$, $^3J_{H,H}$ = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 170.3 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−(*Py*)C), 168.4 (1C, Cl-(*Ar*)C−CH−CH-C-(C═O)), 156.5 (1C, O−CH_2−(*Py*)C−CH-C-N), 156.2 (1C, CH_3−O-(*Ar*)C-CH-C), 155.7 (1C, CH_3-(*Py*)C−CH-C-N), 155.6 (1C, O−CH_2−(*Py*)C−CH-CH-N), 154.7 (1C, CH_3-(*Py*)C−CH-CH-N), 152.4 (1C, O−CH_2−(*Py*)C-CH−CH-N), 149.3 (1C, CH_3-(*Py*)C-CH−CH-N), 139.5 (1C, Cl-(*Ar*)C-CH−CH), 136.2 (1C, CH_3−O-(*Ar*)C−CH-C), 133.7 (1C, CH_3-(*Ar*)C-N-(C═O)), 131.2 (2C, 2xCl-(*Ar*)C−CH-CH), 130.9 (1C, Cl-(*Ar*)C−CH−CH-C), 130.6 (1C, CH_3−O-(*Ar*)C−CH−CH-C), 129.8 (1C, CH_3-(*Py*)C−CH-CH-N), 129.3 (2C, 2xCl-(*Ar*)C-CH−CH), 126.7 (1C, CH_3-(*Py*)C−CH−C-N), 124.8 (1C, O−CH_2−(*Py*)C-CH−CH-N), 121.7 (1C, O−CH_2−(*Py*)C-CH−C−N), 115.1 (1C, CH_3−O-(*Ar*)C−CH-CH−C), 112.0 (1C, (*Ar*)C-CH_2−(C═O)-O−CH_2−(*Py*)C), 111.9 (1C, CH_3−O-(*Ar*)C-CH−CH-C), 101.5 (1C, CH_3−O-(*Ar*)C-CH−C), 97.5 (1C, CH_3-(*Ar*)C−CH−CH-C), 95.5 (1C, CH_3-(*Ar*)C-CH−CH-C), 78.7 (1C, CH_3-(*Ar*)C−CH-CH-C), 78.6 (1C, CH_3-(*Ar*)C−CH-CH-C), 74.6 (1C, CH_3-(*Ar*)C−CH-CH-C), 74.3 (1C, CH_3-(*Ar*)C−CH-CH-C), 63.9 (1C, O-CH_2-(*Py*)C−CH−CH-N), 56.0 (1C, CH_3−O-(*Ar*)C−CH-C), 31.3 (1C, (*Ar*)CH−CH-C-CH$(CH_3)_2$), 30.2 (1C, (*Ar*)C−C-CH_2-(C═O)-O−CH_2), 22.6 (1C, (*Ar*)CH−CH-C−CH-CH_3), 22.5 (1C, (*Ar*)CH−CH-C−CH-CH_3), 21.5 (1C, CH_3-(*Py*)C−CH−CH-N), 19.0 (1C, CH_3-(*Ar*)C−CH−CH), 13.6 (1C, CH_3-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2963 (C−H, CH_2, CH_3); 1739 (C═O, ester); 1676 (C═O, amide); 1621, 1589, 1476, 1356, 1314 (ring skeleton C═C, C−C, C═N, C−N); 1220, 1140 (C−O, ether, ester); 828 (C−H aromatic); ESI-MS(+): *m*/*z* 899.19 $[M\text{-}Cl]^+$, calcd. for $C_{41}H_{40}Cl_2N_3O_4Os^+$ 899.92; the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{41}H_{40}Cl_3N_3O_4Os$ C 54.72, H 4.48, N 4.67; found C 54.83, H 4.67, N 4.57;

Synthesis of {[Ru(η^6-p-cymene)Cl](4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(2-((2,6-dichlorophenyl)amino)phenyl)-acetate)}Cl (6a). Complex **6a** was prepared following the general procedure starting from $[Ru(\eta^6\text{-}p\text{-cymene})Cl]_2Cl_2$ (0.141 g, 1 equiv) and ligand **L6** (0.221 g, 2 equiv), to afford a yellow-orange solid (0.237 g, yield 65%). Mp (°C): 199−200.5 with decomp.; ^1H NMR (CD_3OD) δ_H, ppm: 9.35 (1H, d, O−CH_2−(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.9 Hz), 9.25 (1H, d, CH_3-(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.8 Hz), 8.29 (1H, s, CH_3-(*Py*)C−CH−C-N), 8.16 (1H, s, O−CH_2−(*Py*)C−CH−C-N), 7.64 (1H, dd, O−CH_2−(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.9 Hz, $^4J_{H,H}$ = 1.4 Hz), 7.58 (1H, dd, CH_3-(*Py*)C−CH-CH-N, $^3J_{H,H}$ = 5.8 Hz, $^3J_{H,H}$ = 1.1 Hz), 7.38 (2H, d, 2xCl-(*Ar*)C−CH-CH, $^3J_{H,H}$ = 8.1 Hz), 7.32 (1H, dd, NH-(*Ar*)C−CH-CH−CH, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.2 Hz), 7.11 (1H, ddd overlapped, NH-(*Ar*)C−CH-CH-CH, $^3J_{H,H}$ = 7.7 Hz,

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$^{4}J_{H,H}$ = 1.4 Hz), 7.09 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^{3}J_{H,H}$ = 8.1 Hz), 6.96 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^{3}J_{H,H}$ = 7.4 Hz, $^{4}J_{H,H}$ = 1.2 Hz), 6.39 (1H, d, NH-(*Ar*)C−C−C*H*-CH, $^{3}J_{H,H}$ = 8.0 Hz), 6.06 (1H, m, CH_3-(*Ar*)C−CH-C*H*-C, $^{3}J_{H,H}$= 7.2 Hz), 6.04 (1H, m, CH_3-(*Ar*)C−CH-C*H*-C, $^{3}J_{H,H}$= 7.2 Hz), 5.82 (1H, m, CH_3-(*Ar*)C−C*H*-CH-C, $^{3}J_{H,H}$= 7.2 Hz), 5.80 (1H, m, CH_3-(*Ar*)C−C*H*-CH-C, $^{3}J_{H,H}$= 7.2 Hz), 5.46 (2H, s, O−CH_2-(*Py*)C−CH−CH-N), 4.03 (2H, s, (*Ar*)C−CH_2-(C═O)-O), 2.59 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^{3}J_{H,H}$ = 6.9 Hz), 2.59 (3H, s, CH_3-(*Py*)C−CH−CH-N), 2.25 (3H, s, CH_3-(*Ar*)C−CH−CH), 1.03 (3H, d, (*Ar*)C−CH−CH-C−CH-CH_3, $^{3}J_{H,H}$ = 6.9 Hz), 1.01 (3H, d, (*Ar*)C−CH−CH-C−CH-CH_3, $^{3}J_{H,H}$ = 6.9 Hz); ^{13}C NMR (CD_3OD) δ_C, ppm: 173.0 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−(*Py*)C), 156.53 (1C, O−CH_2−(*Py*)C−CH-CH−N), 156.46 (1C, O−CH_2−(*Py*)C−CH-C-N), 156.0 (1C, CH_3-(*Py*)C−CH-CH−N), 155.5 (1C, CH_3-(*Py*)C−CH-C-N), 154.1 (1C, O−CH_2−(*Py*)C-CH−CH-N), 151.8 (1C, CH_3-(*Py*)C-CH−CH-N), 144.2 (1C, NH-(*Ar*)C−C-Cl), 138.9 (1C, NH-(*Ar*)C-CH−CH), 132.2 (1C, NH-(*Ar*)C-CH−CH−CH), 131.6 (2C, 2xCl-(*Ar*)C-CH−CH), 130.1 (2C, 2xCl-(*Ar*)C-CH−CH), 129.8 (1C, NH-(*Ar*)C−CH-CH−CH), 129.3 (1C, CH_3-(*Py*)C−CH-CH-N), 126.4 (1C, NH-(*Ar*)C-C-CH), 126.2 (2C, Cl-(*Ar*)C−CH-CH), 125.6 (1C, NH-(*Ar*)C−CH−CH-CH), 125.0 (1C, CH_3-(*Py*)C−CH−C-N), 122.8 (1C, O−CH_2−(*Py*)C-CH−CH-N), 122.3 (1C, O−CH_2−(*Py*)C-CH−C−N), 118.4 (1C, NH-(*Ar*)C−C-CH−CH), 105.8 (1C, CH_3-(*Ar*)C−CH−CH-C), 105.6 (1C, CH_3-(*Ar*)C-CH−CH-C), 88.03 (1C, CH_3-(*Ar*)C−CH-CH-C), 87.97 (1C, CH_3-(*Ar*)C−CH-CH-C), 85.4 (1C, CH_3-(*Ar*)C−CH-CH-C), 85.3 (1C, CH_3-(*Ar*)C−CH-CH-C), 65.0 (1C, O-CH_2-(*Py*)C−CH−CH-N), 38.6 (1C, (*Ar*)C-CH_2-(C═O)-O−CH_2−(*Py*)C), 32.3 (1C, (*Ar*)CH−CH-C-CH$(CH_3)_2$), 22.3 (1C, (*Ar*)CH−CH-C−CH-CH_3), 22.2 (1C, (*Ar*)CH−CH-C−CH-CH_3),21.3 (1C, CH_3-(*Py*)C−CH−CH-N), 19.0 (1C, CH_3-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3228 (N−H); 3047−2921 (C−H, CH_2, CH_3); 1741 (C═O, ester); 1619, 1511, 1450 (ring skeleton C═C, C−C, C═N, C−N); 1143 (C−O, ester); 775, 751 (C−H aromatic); ESI-MS(+): *m*/*z* 750.08 $[M\text{-}Cl]^+$, calcd. for $C_{36}H_{35}Cl_3N_3O_2Ru^+$ 749.12, the isotopic pattern coresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{36}H_{35}Cl_4N_3O_2Ru$ C 55.11, H 4.50, N 5.36, found C 55.07, H 4.51, N 5.26;

Synthesis of {[Os(η^6-p-cymene)Cl](4′-methyl-[2,2′-bipyridin]-4-yl)methyl-2-(2-((2,6-dichlorophenyl)amino)phenyl) acetate)}Cl (6b). Complex **6b** was prepared following the general procedure starting from [Os(η^6-*p*-cymene)Cl]$_2$$Cl_2$ (0.241 g, 1 equiv) and ligand **L6** (0.200 g, 2 equiv), to afford a yellow-orange solid (0.351 g, yield 80%). Mp (°C): 203−204.5 with decomp.; ^{1}H NMR (CD_3OD) δ_H, ppm: 9.31 (1H, d, O−CH_2−(*Py*)C−CH-C*H*-N, $^{3}J_{H,H}$ = 6 Hz), 9.20 (1H, d, CH_3-(*Py*)C−CH-C*H*-N, $^{3}J_{H,H}$ = 6 Hz), 8.37 (1H, s, O−CH_2−(*Py*)C−C*H*−C-N), 8.24 (1H, s, CH_3-(*Py*)C−C*H*−C-N), 7.60 (1H, dd, O−CH_2−(*Py*)C−C*H*-CH-N, $^{3}J_{H,H}$ = 6 Hz, $^{4}J_{H,H}$ = 1.6 Hz), 7.53 (1H, dd, CH_3-(*Py*)C−C*H*-CH-N, $^{3}J_{H,H}$ = 6 Hz, $^{3}J_{H,H}$ = 1.2 Hz), 7.37 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^{3}J_{H,H}$ = 8.1 Hz), 7.32 (1H, dd, NH-(*Ar*)C−C*H*-CH−CH, $^{3}J_{H,H}$ = 7.5 Hz, $^{4}J_{H,H}$ = 1.3 Hz), 7.09 (1H, ddd overlapped, NH-(*Ar*)C−CH-CH-C*H*-CH, $^{3}J_{H,H}$ = 7.8 Hz, $^{4}J_{H,H}$ = 1.5 Hz), 7.07 (1H, t, Cl-(*Ar*)C−CH-C*H*, $^{3}J_{H,H}$ = 8.1 Hz), 6.95 (1H, ddd overlapped, NH-(*Ar*)C−CH−CH-C*H*, $^{3}J_{H,H}$ = 7.4 Hz, $^{4}J_{H,H}$ = 1.1 Hz), 6.39 (1H, dd, NH-(*Ar*)C−C−C*H*-CH, $^{3}J_{H,H}$ = 8.0 Hz, $^{4}J_{H,H}$ = 0.9 Hz), 6.28 (1H, m, CH_3-(*Ar*)C−CH-CH-C*H*-C), 6.26 (1H, m, CH_3-(*Ar*)C−CH-CH-C*H*-C), 5.98 (1H, m, CH_3-(*Ar*)C−C*H*-CH-C), 5.97 (1H, m, CH_3-(*Ar*)C−C*H*-CH-C), 5.50 (2H, s, O−CH_2-(*Py*)C−CH−CH-N), 4.04 (1H, d, (*Ar*)C−C*H*-(C═O)-O−CH_2−(*Py*)C, $^{1}J_{H,H}$ = 15.0 Hz), 4.01 (1H, d, (*Ar*)C−C*H*-(C═O)-O−CH_2−(*Py*)C, $^{1}J_{H,H}$ = 15.0 Hz), 2.63 (3H, s, CH_3-(*Py*)C−CH−CH-N), 2.45 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^{3}J_{H,H}$ = 6.9 Hz), 2.31 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 0.94 (3H, d, (*Ar*)C−CH−CH-C−CH-CH_3, $^{3}J_{H,H}$ = 6.9 Hz), 0.96 (3H, d, (*Ar*)C−CH−CH-C−CH-CH_3, $^{3}J_{H,H}$ = 6.9 Hz); ^{13}C NMR (CD_3OD) δ_C, ppm: 173.0 (1C, (*Ar*)C−CH_2−(C═O)-O−CH_2−(*Py*)C), 157.2 (1C, O−CH_2−(*Py*)C−CH-CH−N), 156.5 (1C, O−CH_2−(*Py*)C−CH-C-N), 156.2 (1C, CH_3-(*Py*)C−CH-CH−N), 156.0 (1C, CH_3-(*Py*)C−CH-C-N), 154.2 (1C, O−CH_2−(*Py*)C-CH−CH-N), 151.7 (1C, CH_3-(*Py*)C-CH−CH-N), 144.2 (1C, NH-(*Ar*)C−C-Cl), 138.9 (1C, NH-(*Ar*)C-CH−CH), 132.2 (1C, NH-(*Ar*)C-CH−CH−CH), 131.6 (2C, 2xCl-(*Ar*)C-CH−CH), 130.5 (1C, NH-(*Ar*)C−CH-CH−CH), 130.1 (2C, 2xCl-(*Ar*)C-CH−CH), 129.3 (1C, CH_3-(*Py*)C−C*H*-CH-N), 127.2 (1C, NH-(*Ar*)C-C-CH), 126.3 (2C, Cl-(*Ar*)C−CH-CH), 125.7 (1C, NH-(*Ar*)C−CH−CH-CH), 125.0 (1C, CH_3-(*Py*)C−CH−C-N), 122.9 (1C, O−CH_2−(*Py*)C-CH−CH-N), 122.4 (1C, O−CH_2−(*Py*)C-CH−C−N), 118.4 (1C, NH-(*Ar*)C−C-CH−CH), 98.7 (1C, CH_3-(*Ar*)C−CH−CH-C), 96.6 (1C, CH_3-(*Ar*)C-CH−CH-C), 79.49 (1C, CH_3-(*Ar*)C−CH-CH-C), 79.45 (1C, CH_3-(*Ar*)C−CH-CH-C), 75.4 (1C, CH_3-(*Ar*)C−CH-CH-C), 75.2 (1C, CH_3-(*Ar*)C−CH-CH-C), 65.0 (1C, O-CH$_2$-(*Py*)C−CH−CH-N), 38.6 (1C, (*Ar*)C-CH$_2$-(C═O)-O−CH_2−(*Py*)C), 32.5 (1C, (*Ar*)CH−CH-C-CH$(CH_3)_2$), 22.7 (1C, (*Ar*)CH−CH-C−CH-CH_3), 22.6 (1C, (*Ar*)CH−CH-C−CH-CH_3), 21.3 (1C, CH_3-(*Py*)C−CH−CH-N), 18.9 (1C, CH_3-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 2968−3004 (C−H, CH_2, CH_3); 1742 (C═O, ester); 1622, 1511, 1450 (ring skeleton C═C, C−C, C−N, C═N); 1143 (C−O, ester); 779, 750 (C−H aromatic); ESI-MS(+): *m*/*z* 838.16 $[M\text{-}Cl]^+$, calcd. for $C_{36}H_{35}Cl_3N_3O_2Os^+$ 838.28, the isotopic pattern coresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{36}H_{35}Cl_4N_3O_2Os$ C 49.49, H 4.04, N 4.81; found C 49.56, H 3.93, N 4.70.

Synthesis of {[Ru(η^6-p-cymene)Cl](bis(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl) [2,2′-bipyridine]-5,5′-dicarboxylate)}Cl (7a). Complex **7a** was prepared following the general procedure starting from [Ru(η^6-*p*-cymene)Cl]$_2$$Cl_2$ (0.064 g, 1 equiv) and ligand **L7** (0.210 g, 2 equiv), to afford yellow solid (0.258 g, yield 94%). Mp (°C): 119−121 with decomp.; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 9.69 (2H, s, 2xO-(C═O)-(*Py*)C−C*H*-N), 9.15 (2H, d, 2x(*Py*)N−C−CH-C*H*-C, $^{3}J_{H,H}$ = 7.3 Hz), 8.54 (2H, d, 2x(*Py*)N−C−C*H*-CH-C, $^{3}J_{H,H}$ = 7.3 Hz), 7.63 (4H, m, 4xCl-(*Ar*)C−CH-C*H*, $^{3}J_{H,H}$ = 8.5 Hz, $^{4}J_{H,H}$ = 2.1 Hz), 7.45 (4H, m, 4xCl-(*Ar*)C−C*H*-CH, $^{3}J_{H,H}$ = 8.5 Hz, $^{4}J_{H,H}$ = 2.1 Hz), 6.96 (2H, d, 2xCH_3−O-(*Ar*)C−C*H*-C, $^{4}J_{H,H}$ = 2.4 Hz), 6.86 (2H, d, 2xCH_3−O-(*Ar*)C−CH-C*H*-C, $^{3}J_{H,H}$ = 9 Hz), 6.62 (2H, dd, 2xCH_3−O-(*Ar*)C−C*H*-CH-C, $^{3}J_{H,H}$ = 9 Hz, $^{4}J_{H,H}$ = 2.4 Hz), 5.95 (2H, d, 2xCH_3-(*Ar*)C−CH-C*H*-C, $^{3}J_{H,H}$ = 5.1 Hz), 5.84 (2H, d, 2xCH_3-(*Ar*)C−C*H*-CH-C, $^{3}J_{H,H}$ = 5.1 Hz), 4.50−4.72 (8H, m, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O, 2x(*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O), 3.79 (6H, s, 2xCH_3-O-(*Ar*)C−CH-C), 3.77 (4H, s, 2x(*Ar*)C−CH_2-(C═O)-O-$(CH_2)_2$−O), 2.82 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^{3}J_{H,H}$ = 6.9 Hz), 2.37 (6H, s, 2xCH_3-(*Ar*)C−N), 2.17 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.19 (6H, d, (*Ar*)C−CH−CH-C−CH$(CH_3)_2$, $^{3}J_{H,H}$ = 6.9 Hz);

^{13}C NMR ($CDCl_3$) δ_C, ppm: 171.1 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 168.4 (2C, 2xCl-(*Ar*)C−CH−CH-C-(C═O)), 162.3 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 157.2 (2C, 2x(*Py*)N-C-CH−CH-C), 156.2 (2C, 2xCH_3−O-(*Ar*)C-CH−CH-C), 155.9 (2C, 2x(*Py*)N−CH-C-(C═O)),140.9 (2C, 2x(*Py*)N−C−CH-CH-C), 139.5 (2C, 2xCl-(*Ar*)C-CH−CH), 136.2 (2C, 2xCH_3−O-(*Ar*)C−CH-C), 133.8 (2C, 2xCH_3-(*Ar*)C-N-(C═O)-O), 131.3 (4C, 4xCl-(*Ar*)C−CH-CH), 130.9 (2C, 2xCl-(*Ar*)C−CH−CH-C), 130.6 (2C, 2xCH_3−O-(*Ar*)C−CH−CH-C), 129.4 (2C, 2x(*Py*)N−C−CH-CH-C), 129.3 (4C, 4xCl-(*Ar*)C-CH−CH), 126.9 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 115.1 (2C, 2xCH_3−O-(*Ar*)C−CH-CH−C), 112.2 (2C, (*Ar*)C-(C═O)-O−CH_2), 111.6 (2C, 2xCH_3−O-(*Ar*)C-CH−CH-C), 106.3 (1C, CH_3-(*Ar*)C−CH−CH-C), 102.5 (1C, CH_3-(*Ar*)C-CH−CH-C), 101.8 (2C, 2xCH_3−O-(*Ar*)C-CH−C), 87.2 (2C, 2xCH_3-(*Ar*)C−CH-CH-C), 85.5 (2C, 2xCH_3-(*Ar*)C−CH-CH-C), 64.9 (2C, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 62.4 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−O), 56.1 (2C, 2xCH_3−O-(*Ar*)C), 31.3 (1C, (*Ar*)CH−CH-C-CH$(CH_3)_2$), 30.5 (2C, 2x(*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 22.3 (2C, (*Ar*)CH−CH-C−CH$(CH_3)_2$), 18.8 (1C, CH_3-(*Ar*)C−CH−CH), 13.6 (2C, 2xCH_3-(*Ar*)C−N-(C═O)); IR (ν, cm^{-1}): 2960 (C−H, CH_2, CH_3); 1728 (C═O, ester); 1676 (C═O, amide); 1589, 1477, 1356 (ring skeleton C═C, C−C, C═N, C−N); 1285, 1219, 1133, (C−O, ether, ester); 830, 753 (C−H aromatic); ESI-MS(+): *m*/*z* 1282.22 $[M\text{-}Cl]^+$, calcd. for $C_{64}H_{58}Cl_3N_4O_{12}Ru^+$ 1282.60, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{64}H_{58}Cl_4N_4O_{12}Ru$ C 58.32, H 4.44, N 4.25; found C 58.29, H 4.47, N 4.13;

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Synthesis of {[Os(η^6-p-cymene)Cl](bis(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetoxy)ethyl)[2,2′-bipyridine]-5,5′-dicarboxylate)}Cl (7b). Complex 7b was prepared following the general procedure starting from [Os(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.093 g, 1 equiv) and ligand **L7** (0.250 g, 2.1 equiv), to afford a red solid (0.300 g, yield 90%). Mp (°C): 94−96; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 9.58 (4H, m, 2xO-(C═O)-(*Py*)C−C*H*-N, 2x(*Py*)N−C−CH-C*H*-C), 8.56 (2H, m, 2x(*Py*)N−C−C*H*-CH-C), 7.62 (4H, m, 4xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.3 Hz), 7.44 (4H, m, 4xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.3 Hz), 6.93 (2H, d, 2xCH_3−O-(*Ar*)C−C*H*-C, $^4J_{H,H}$ = 1.8 Hz), 6.85 (2H, d, 2xCH_3−O-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 9 Hz), 6.61 (2H, dd, 2xCH_3−O-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 9 Hz, $^4J_{H,H}$ = 1.8 Hz), 6.10 (2H, m, 2xCH_3-(*Ar*)C−CH-C*H*-C), 5.93 (2H, m, 2xCH_3-(*Ar*)C−C*H*-CH-C), 4.46−4.68 (8H, m, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O, 2x(*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O), 3.77 (6H, s, 2xCH_3-O-(*Ar*)C−CH-C), 3.75 (4H, s, 2x(*Ar*)C−CH_2-O-$(CH_2)_2$−O), 2.56−2.67 (1H, m, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$), 2.35 (6H, s, 2xCH_3-(*Ar*)C−N), 2.21 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.08 (6H, d, (*Ar*)C−CH−CH-C−CH(CH_3)$_2$, $^3J_{H,H}$ = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 171.0 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 168.4 (2C, 2xCl-(*Ar*)C−CH−CH-C-(C═O)), 162.1 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 158.0 (2C, 2x(*Py*)N-C-CH−CH-C), 156.2 (2C, 2xCH_3−O-(*Ar*)C-CH−CH-C), 155.6 (2C, 2x(*Py*)N−C*H*-C-(C═O)), 140.9 (2C, 2x(*Py*)N−C−CH-C*H*-C), 139.5 (2C, 2xCl-(*Ar*)C-CH−CH), 136.2 (2C, 2xCH_3−O-(*Ar*)C−CH-C), 133.9 (2C, 2xCH_3-(*Ar*)C-N-(C═O)-O), 131.3 (4C, 4xCl-(*Ar*)C−CH-CH), 130.9 (2C, 2xCl-(*Ar*)C−CH−CH-C), 130.6 (2C, 2xCH_3−O-(*Ar*)C−CH−CH-C), 130.0 (2C, 2x(*Py*)N−C−C*H*-CH-C), 129.3 (4C, 4xCl-(*Ar*)C-CH−CH), 127.3 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 115.1 (2C, 2xCH_3−O-(*Ar*)C−CH-CH−C), 112.2 (2C, 2x(*Ar*)C-CH_2−(C═O)-O), 111.6 (2C, 2xCH_3−O-(*Ar*)C-CH−CH-C), 101.8 (2C, 2xCH_3−O-(*Ar*)C-CH−C), 97.1 (1C, CH_3-(*Ar*)C−CH−CH-C), 95.4 (1C, CH_3-(*Ar*)C-CH−CH-C), 78.7 (2C, 2xCH_3-(*Ar*)C−CH-C*H*-C), 75.8 (2C, 2xCH_3-(*Ar*)C−C*H*-CH-C), 64.9 (2C, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O), 62.3 (2C, 2x(*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O), 56.0 (2C, 2xCH_3−O-(*Ar*)C), 31.4 (1C, (*Ar*)CH−CH-C-C*H*$(CH_3)_2$), 30.4 (2C, 2x(*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 22.5 (2C, (*Ar*)CH−CH-C−CH(CH_3)$_2$), 18.7 (1C, CH_3-(*Ar*)C−CH−CH), 13.6 (2C, 2xCH_3-(*Ar*)C−N-(C═O)); ESI-MS(+): *m*/*z* 1371.27 [M-Cl]$^+$, calcd. for $C_{64}H_{58}Cl_3N_4O_{12}Os^+$ 1371.76, the isotopic pattern corresponds well to the calculated one; IR (ν, cm^{-1}): 2961 (C−H, CH_2, CH_3); 1729 (C═O, ester); 1677 (C═O, amide); 1589, 1476, 1356 (ring skeleton C═C, C−C, C═N); 1286, 1134 (C−O, ether, ester); 833, 753 (C−H, aromatic); Elemental analysis (%): calcd. for $C_{64}H_{58}Cl_4N_4O_{12}Os \cdot 3CH_2Cl_2$ C, 48.42; H, 3.88; N, 3.37; found C 48.49, H 3.78, N 3.31;

Synthesis of {[Ru(η^6-p-cymene)Cl](bis(2-(2-(2-((2,6-dichlorophenyl)amino)phenyl) acetoxy)ethyl)[2,2′-bipyridine]-5,5′-dicarboxylate)}Cl (8a). Complex **8a** was prepared following the bgeneral procedure starting from [Ru(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.083 g, 1equiv) and ligand **L8** (0.240 g, 2 equiv), to afford a yellow solid (0.302 g, yield 94%). Mp (°C): 107−109 with decomp; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 9.69 (2H, s, 2xO-(C═O)-(*Py*)C−C*H*-N), 9.22 (2H, d, 2x(*Py*)N−C−CH-C*H*-C, $^3J_{H,H}$ = 7.4 Hz), 8.61 (2H, d, 2x(*Py*)N−C−C*H*-CH-C, $^3J_{H,H}$ = 7.4 Hz), 7.32 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8.1 Hz), 7.25 (2H, dd, 2xNH-(*Ar*)C−C*H*-CH−CH, $^3J_{H,H}$= 7.4 Hz, $^4J_{H,H}$ = 1.1 Hz), 7.09 (2H, ddd overlapped, 2xNH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.2 Hz), 6.97 (2H, t, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8.1 Hz), 6.92 (2H, ddd overlapped, 2xNH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 7.4 Hz), 6.69 (2H, s br, 2xN*H*), 6.51 (2H, d, NH-(*Ar*)C−C−C*H*-CH, $^3J_{H,H}$ = 8.0 Hz), 5.94 (2H, d, 2xCH_3-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 5.1 Hz), 5.83 (2H, d, 2xCH_3-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 5.1 Hz), 4.59−4.74 (8H, m, 2x(*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O), 3.92 (2H, d, 2x(*Ar*)C−C*H*-(C═O)-O-$(CH_2)_2$−O, $^1J_{H,H}$ = 15.1 Hz), 3.88 (2H, d, 2x(*Ar*)C−C*H*-(C═O)-O-$(CH_2)_2$−O, $^1J_{H,H}$= 15.1 Hz), 2.80 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^3J_{H,H}$ = 6.9 Hz), 2.18 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.18 (6H, d, (*Ar*)C−CH−CH-C−CH(CH_3)$_2$, $^3J_{H,H}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.6 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 162.3 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 157.3 (2C, 2x(*Py*)N-C-CH−CH-C), 155.8 (2C, 2x(*Py*)N-CH−C-(C═O)), 142.8 (2C, 2xNH-(*Ar*)C−C-Cl), 141.0 (2C, 2x(*Py*)N−C−CH-CH−C), 137.8 (2C, 2xNH-(*Ar*)C-CH−CH), 131.2 (2C, 2xNH-(*Ar*)C-CH−CH−CH), 129.6 (4C, 4xCl-(*Ar*)C-CH−CH), 129.5 (2C, 2x(*Py*)N−C-CH−CH-C), 129.1 (4C, 4xCl-(*Ar*)C-CH−CH), 128.4 (2C, 2xNH-(*Ar*)C−CH-CH−CH), 127.1 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 124.4 (2C, 2xCl-(*Ar*)C−CH-CH), 124.2 (2C, 2xNH-(*Ar*)C-C-CH), 122.5 (2C, 2xNH-(*Ar*)C−CH−CH-CH), 118.5 (2C, 2xNH-(*Ar*)C−C-CH−CH), 106.1 (1C, CH_3-(*Ar*)C−CH−CH-C), 102.9 (1C, CH_3-(*Ar*)C-CH−CH-C), 87.4 (2C, 2xCH_3-(*Ar*)C−CH-CH−C), 85.2 (2C, 2xCH_3-(*Ar*)C-CH−CH-C), 64.9 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−O), 62.5 (2C, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 38.7 (2C, 2x(*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 31.4 (1C, (*Ar*)CH−CH-C-C*H*$(CH_3)_2$), 22.4 (2C, (*Ar*)CH−CH-C−CH(CH_3)$_2$), 19.0 (1C, CH_3-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3335 (N−H); 2963 (C−H, CH_2, CH_3); 1725 (C═O, ester); 1667 (C═O, ester); 1503, 1450 (ring skeleton C═C, C−C, C═N, C−N); 1283, 1253, 1134 (C−O); 863, 774, 753 (C−H aromatic); ESI-MS(+): *m*/*z* 1159.10 [M-Cl]$^+$, calcd. for $C_{54}H_{48}Cl_5N_4O_8Ru^+$ 1159.32, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{54}H_{48}Cl_6N_4O_8Ru$ C 54.29, H 4.05, N 4.69; found C 54.35, H 4.11, N 4.82;

Synthesis of {[Os(η^6-p-cymene)Cl](bis(2-(2-(2-((2,6-dichlorophenyl)amino)phenyl) acetoxy)ethyl)[2,2′-bipyridine]-5,5′-dicarboxylate)}Cl (8b). Complex **8b** was prepared following the general procedure starting from [Os(η^6-*p*-cymene)-Cl]$_2$Cl$_2$ (0.093 g, 1 equiv) and ligand **L8** (0.210 g, 2 equiv), to afford a red solid (0.284 g, yield 94%). Mp (°C): 112−114 with decomp.; ^{1}H NMR ($CDCl_3$) δ_H, ppm: 9.77 (2H, d, 2x(*Py*)N−C−CH-C*H*-C, $^3J_{H,H}$ = 6.9 Hz), 9.56 (2H, s, 2xO-(C = O)-(*Py*)C−C*H*-N), 8.64 (2H, d, 2x(*Py*)N−C−C*H*-CH-C, $^3J_{H,H}$ = 6.9 Hz), 7.32 (2H, d, 2xCl-(*Ar*)C−C*H*-CH, $^3J_{H,H}$ = 8 Hz), 7.24 (2H, m, 2xNH-(*Ar*)C−C*H*-CH−CH), 7.10 (2H, dd overlapped, 2xNH-(*Ar*)C−CH-C*H*-CH, $^3J_{H,H}$ = 7.3 Hz), 6.98 (2H, t, 2xCl-(*Ar*)C−CH-C*H*, $^3J_{H,H}$ = 8 Hz), 6.92 (2H, dd overlapped, 2xNH-(*Ar*)C−CH−CH-C*H*, $^3J_{H,H}$ = 6.8 Hz), 6.67 (2H, s br, 2xN*H*), 6.52 (2H, d, NH-(*Ar*)C−C−C*H*-CH, $^3J_{H,H}$ = 7.8 Hz), 6.05 (2H, d, 2xCH_3-(*Ar*)C−CH-C*H*-C, $^3J_{H,H}$ = 3.8 Hz), 5.98 (2H, d, 2xCH_3-(*Ar*)C−C*H*-CH-C, $^3J_{H,H}$ = 3.8 Hz), 4.54−4.77 (8H, m, 2x(*Ar*)C−CH_2−(C═O)−O-CH_2-CH_2−O, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2-O), 3.93 (2H, d, 2x(*Ar*)C−C*H*-(C═O)-O-$(CH_2)_2$−O, $^1J_{H,H}$ = 14.8 Hz), 3.88 (2H, d, 2x(*Ar*)C−C*H*-(C═O)-O-$(CH_2)_2$−O, $^1J_{H,H}$ = 14.8 Hz), 2.59 (1H, sept, (*Ar*)C−CH−CH−C-C*H*$(CH_3)_2$, $^3J_{H,H}$ = 5.9 Hz), 2.24 (3H, s, CH_3-(*Ar*)C−CH−CH-C), 1.06 (6H, d, (*Ar*)C−CH−CH-C−CH(CH_3)$_2$, $^3J_{H,H}$ = 5.9 Hz); ^{13}C NMR ($CDCl_3$) δ_C, ppm: 172.5 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-$(CH_2)_2$−O), 162.1 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 158.1 (2C, 2x(*Py*)N-C-CH−CH-C), 155.5 (2C, 2x(*Py*)N-CH−C-(C═O)), 142.8 (2C, 2xNH-(*Ar*)C−C-Cl), 141.2 (2C, 2x(*Py*)N−C−CH-CH−C), 137.8 (2C, 2xNH-(*Ar*)C-CH−CH), 131.2 (2C, 2xNH-(*Ar*)C-CH−CH−CH), 130.0 (2C, 2x(*Py*)N−C-CH−CH-C), 129.5 (4C, 4xCl-(*Ar*)C-CH−CH), 129.1 (4C, 4xCl-(*Ar*)C-CH−CH), 128.4 (2C, 2xNH-(*Ar*)C−CH-CH−CH), 127.7 (2C, 2x(*Py*)N−CH-C-(C═O)-O), 124.4 (2C, 2xCl-(*Ar*)C−CH-CH), 124.1 (2C, 2xNH-(*Ar*)C-C-CH), 122.5 (2C, 2xNH-(*Ar*)C−CH−CH-CH), 118.5 (2C, 2xNH-(*Ar*)C−C-CH−CH), 96.8 (1C, CH_3-(*Ar*)C−CH−CH-C), 96.1 (1C, CH_3-(*Ar*)C-CH−CH-C), 78.9 (2C, 2xCH_3-(*Ar*)C−CH-CH−C), 75.3 (2C, 2xCH_3-(*Ar*)C-CH−CH-C), 64.9 (2C, 2x(*Ar*)C−CH_2−(C═O)-O-CH_2−CH_2−O), 62.5 (2C, 2x(*Ar*)C−CH_2−(C═O)-O−CH_2−CH_2−O), 38.7 (2C, 2x(*Ar*)C-CH_2-(C═O)-O-$(CH_2)_2$−O), 31.4 (1C, (*Ar*)CH−CH-C-C*H*$(CH_3)_2$), 22.6 (2C, (*Ar*)CH−CH-C−CH(CH_3)$_2$), 18.9 (1C, CH_3-(*Ar*)C−CH−CH); IR (ν, cm^{-1}): 3334 (N−H); 2960 (C−H, CH_2, CH_3); 1725 (C═O, ester); 1503, 1450 (ring skeleton C═C, C−C, C═N, C−N); 1284, 1134 (C−O); 863, 775, 753 (C−H aromatic); ESI-MS(+): *m*/*z* 1248.15 [M-Cl]$^+$, calcd. for $C_{54}H_{48}Cl_5N_4O_8Os^+$ 1248.48, the isotopic pattern corresponds well to the calculated one; Elemental analysis (%): calcd. for $C_{54}H_{48}Cl_6N_4O_8Os$ C 50.52, H 3.77, N 4.36; found C 50.46, H 3.70, N 4.39.

X-ray structure determination for L4, L6, L8, and 8b. Diffraction data of **L4**, **L6**, **L8**, and **8b** were measured at 100(2) K

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Table 4. Crystal Data and Structure Refinement for L4, L6, L8, and 8b[a]

	L4	L6	L8	8b
	$C_{35}H_{28}Cl_2NO_4P$	$C_{26}H_{21}Cl_2N_3O_2$	$C_{44}H_{34}Cl_4N_4O_8$	$C_{54}H_{48}Cl_6N_4O_8Os{\cdot}C_6H_5Cl{\cdot}H_2O$
F.W. ($g{\cdot}mol^{-1}$)	628.45	478.36	888.55	1414.43
Temperature (K)	100(2)	100(2)	100(2)	100(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/c$
Unit cell dimensions				
a (Å)	11.1554(11)	7.7313(4)	22.264(2)	26.219(9)
b (Å)	11.5216(12)	19.2204(19)	4.6639(4)	13.193(7)
c (Å)	12.7533(11)	15.4838(14)	23.386(2)	20.409(8)
α (deg)	94.419(9)	90	90	90
β (deg)	90.632(8)	92.174(6)	93.066(7)	112.12(3)
γ (deg)	110.452(7)	90	90	90
V (Å^3)	1530.0(3)	2299.2(3)	2424.9(4)	6540(5)
Z	2	4	2	4
D_{calcd} ($g{\cdot}cm^3$)	1.364	1.382	1.217	1.437
μ (mm^{-1})	0.305	0.312	0.295	2.290
F(000)	652	992	916	2840
Crystal size	0.43 × 0.34 × 0.29	0.31 × 0.28 × 0.22	0.553 × 0.179 × 0.112	0.277 × 0.217 × 0.122
Θ range for data collection (deg)	1.60 to 33.50	1.69 to 31.10	1.744 to 26.395	1.996 to 24.097
Index ranges				
h	−17/17	−11/10	−27/27	−30/30
k	−17/17	−27/27	−5/5	−14/15
l	−19/19	−22/22	−29/29	−20/23
Measd. reflns.	36699	38402	24310	66063
Independent reflns	11782 [R(int) = 0.0167]	7317 [R(int) = 0.0310]	4856 [R(int) = 0.0602]	10315 [R(int) = 0.1431]
Completeness to Θ (%)	98.20 (Θ = 33.50°)	98.90 (Θ = 31.10°)	98.10 (Θ = 25.242°)	99.30 (Θ = 24.097°)
Absorption correction	Semiempirical from equivalents	Semiempirical from equivalents	Semiempirical from equivalents	Semiempirical from equivalents
Max. and min transmission	0.7466 and 0.6988	0.7462 and 0.6807	0.7454 and 0.5493	0.6211 and 0.2755
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	11782/0/392	7317/0/303	4856/1/275	10315/0/739
GooF^2	1.109	1.107	1.048	1.111
R1 [$I > 2\sigma(I)$]	0.0334	0.0366,	0.0649	0.0913
wR2	0.0825	0.0809	0.1294	0.2037
R1 (all data)	0.0455	0.0533	0.1160	0.1481
wR2	0.0918	0.0914	0.1565	0.2400
Largest diff. peak and hole (Å^{-3})	0.481 and −0.248 e	0.436 and −0.247 e	0.334 and −0.365 e	2.638 and −2.737 e

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$; GooF = $\{\sum[w(F_o^2 - F_c^2)^2]/n - p\}^{1/2}$, where n is the number of data and p is the number of parameters refined.

using Mo Kα radiation on a Bruker APEX II CCD diffractometer equipped with a kappa geometry goniometer (Table 4). The data sets were reduced by EvalCCD[111] and then corrected for absorption.[112] The solutions and refinements were performed with SHELX.[113] The crystal structures were refined using full-matrix least-squares based on F^2 with all non-hydrogen atoms anisotropically defined. Hydrogen atoms were placed in calculated positions by means of the "riding" model. Additional electron density found in the difference Fourier map of compound **L6** and **8b** was treated using the SQUEEZE algorithm of PLATON.[114]

Cell culture. Human A2780 and A2780cisR ovarian carcinoma cells were obtained from the European Centre of Cell Cultures (ECACC, UK). The resistance of the A2780cisR cells was maintained by a monthly treatment with cisplatin (2 μM/one 4 days passage). Nontumorigenic HEK-293 cells were provided by the Institute of Pathology, CHUV, Lausanne, Switzerland. A2780 and A2780cisR were grown in RPMI 1640 medium supplemented with GlutaMAX (Gibco) and HEK-293 cells were grown in DMEM medium, all containing heat-inactivated fetal calf serum (FCS, Sigma, USA) (10%) and antibiotics (Penicillin (100 U/mL): Streptomycin (100 μg/mL), working concentration 1:100, Life Technologies, Gibco) at 37 °C and CO_2 (5%).

Antiproliferative activity in vitro. Cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide). Cells were seeded in 96-well plates as monolayers with 100 μL of cell solution per well and preincubated for 24 h in the cell medium. Compounds were freshly prepared as DMSO solution that were rapidly dissolved in the culture medium and serially diluted to the appropriate concentration to give a final DMSO concentration of 0.5% (all compounds were soluble at the concentrations employed). 100 μL of the drug solution was added to each well and the plates were incubated for another 72 h. Subsequently, MTT (5 mg/mL solution) was added to the cells and the plates were incubated for further 4 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in

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DMSO. The optical density, directly proportional to the number of surviving cells, was quantified at 590 nm using a multiwell plate reader and the fraction of surviving cells was calculated from the absorbance of untreated control cells. Evaluation is based on means from two independent experiments, each comprising four microcultures per concentration level.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b02690.

Packing diagrams of the X-ray structures with relevant bond parameters, and ^{1}H and ^{31}P spectra (when appropriate) NMR spectra of the complexes and ligands in DMSO-d_6 at r.t. Full crystallographic information is available free of charge via the Internet on the ACS Publications Web site http://pubs.acs.org/journal/inocaj and on the Cambridge Crystallographic Data Centre Web site under the deposition numbers CCDC 1450285-1450288. (PDF)

Cif data for **L4** $C_{35}H_{28}Cl_2NO_4P$ (CIF)

Cif data for **L6** $C_{26}H_{21}Cl_2N_3O_2$ (CIF)

Cif data for **L8** $C_{44}H_{34}Cl_4N_4O_8$ (CIF)

Cif data for **L8b** $C_{60}H_{55}Cl_7N_4O_9Os$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +41-21-6939854. Fax: +41-21-6939853. E-mail: paul.dyson@epfl.ch.

Notes

The authors declare no competing financial interest.

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