ORGANOMETALLICS

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Neutral and Ionic Cycloruthenated 2-Phenylindoles as Cytotoxic Agents

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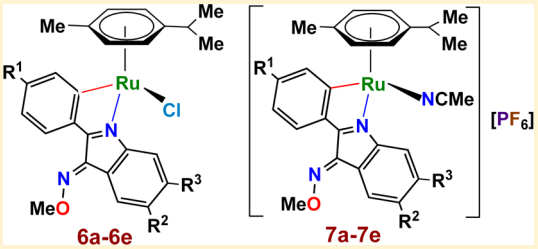
Supporting Information

ABSTRACT: The synthesis and characterization of two families of cyclometalated Ru(II) complexes with the new $(C_{sp^2},N_{indole})^-$ motif formed by activation of the C−H bonds of 2-phenylindole ligands of the general formula {(4′-R^1-C_6H_4)-3-NOMe-5-R^2-6-R^3-(C_6H_2N)} are presented. The novel ruthenacycles show a remarkable cytotoxic activity in MCF7 and MDA-MB231 breast cancer cell lines, which clearly exceeds those of the *trans* and *cis* isomers of [$PtCl_2$(L)(DMSO)] derived from the same ligands and even that of cisplatin.



Cancer is one of the main causes of death in developed countries.[1] The discovery of the cytotoxic properties of *cis*-[$PtCl_2(NH_3)_2$] (cisplatin) and its clinical use has marked the origin of fast and increasing interest in the chemistry of platinum(II).[2−5] Unfortunately, cisplatin and other Pt-based cytotoxic agents (i.e., carboplatin and oxaliplatin) display limited activity against certain types of cancers, trigger drug resistance, and provoke adverse effects (kidney toxicity, nausea, and bone marrow disruption).[5] Thus, the design of new antitumoral drugs with activity greater than that of cisplatin and lower adverse side effects is one of the main challenges of current research. Organometallic compounds with potent cytotoxic activities containing metallocenes, half-sandwiches, or cyclometalated rings have been described.[6]

Ruthenium compounds have attracted intense research interest as potential anticancer agents.[7] Recently new classes of neutral and cationic half-sandwich Ru(II)−arene compounds were found to have promising anticancer activity.[8] Representative examples of these organometallic compounds are RAPTA-C and RM175 (Figure 1). Furthermore, cycloruthenated complexes are scarce[9] and show great promise for the design of antitumoral drugs. RCD-11 (Figure 1) deserves special attention, with reduced neurotoxicity and good antitumor activity in vitro and in vivo using a wide panel of cell lines (including some cisplatin-resistant ones).[10]

Some 2-phenylindole derivatives (**1** and **2** in Figure 2) exhibit interesting antitumoral activity.[11,12] In addition, they are

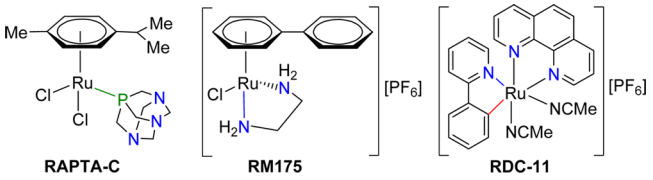


Figure 1. Main examples of highly cytotoxic organometallic ruthenium(II) complexes used for both in vitro and in vivo studies.

valuable reagents in coordination and organometallic chemistry.[13] Cyclopalladation of the 3-metoxyimino-2-phenylindoles (**3a,b** in Figure 2) has been described.[14] *trans* (**4**) and *cis* (**5**) isomers of [Pt(L)Cl_2(DMSO)] (L = **3a−c**) have also been prepared,[15,16] and most of them showed cytotoxic activity (IC_{50} = 2 μM) greater than that of cisplatin in the MCF7 cell line.[16] In view of the cytotoxic activity of the Pt(II) complexes **4a−c** and **5a−c** and the increasing interest in ruthenacycles as antitumoral agents, here we report two sets of cycloruthenated complexes (neutral (**6a−e**) and ionic (**7a−e**)) with the uncommon $(C_{sp^2},N_{indole})^-$ cyclometalation motif.

Compounds **6a−e** were isolated by reaction of [Ru(η^6-*p*-cymene)Cl(μ-Cl)]$_2$ with Ag[PF_6] in acetone, followed by the addtion of the corresponding ligand **3a−e** (at 328 K for 24 h)

Received: September 21, 2013
Published: December 6, 2013

   dx.doi.org/10.1021/om400941b | *Organometallics* 2013, 32, 7264−7267

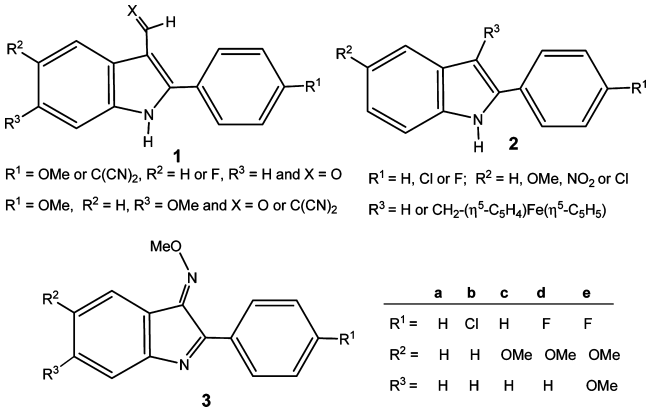
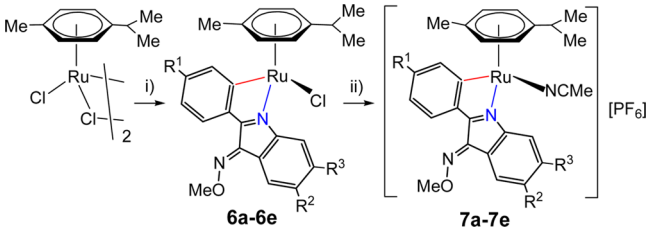


Figure 2. Relevant 2-phenylindole derivatives **1** and **2** with cytotoxic activity, reported previously, and the 3-methoxyimino derivatives **3** used in this work.

Scheme 1. Preparation of Compounds 6 and 7[a]



[a]Legend: (i) $Ag[PF_6]$ in acetone, removal of AgCl, treatment with the corresponding ligand **3** and SiO_2 column chromatography; (ii) $Ag[PF_6]$ in MeCN.

and subsequent workup by SiO_2 column chromatography (Scheme 1(i)). Further treatment of **6** with $Ag[PF_6]$ in acetonitrile produced the precipitation of AgCl and the ionic products (**7**) (Scheme 1(ii). In all cases, characterization data (Supporting Information) are consistent with the proposed formulas. Moreover, the crystal structures of **6b**·$^1/_2CH_2Cl_2$ and **6c**·H_2O (Figures 3 and 4)[17] confirmed the binding of the

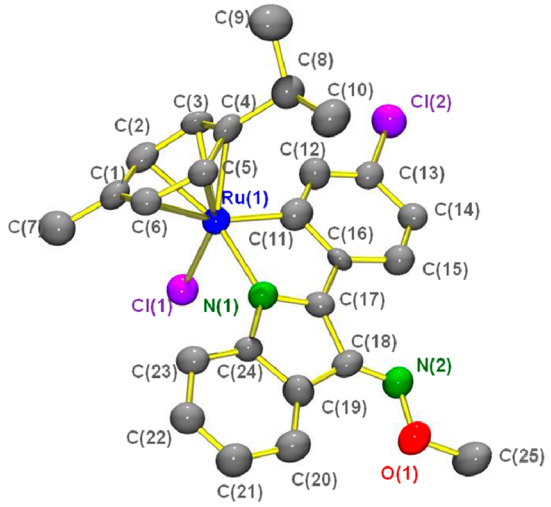


Figure 3. X-ray crystal structure of **6b**·$^1/_2CH_2Cl_2$. The molecule of solvation and hydrogen atoms have been omitted for clarity. Selected bond lengths (in Å) and angles (in deg): Ru(1)−C(11), 2.036(6); Ru(1)−N(1), 2.067(9); Ru(1)−Cl(1), 2.049(1); N(1)−Ru−C(11), 78.5(3); Cl(1)−Ru(1)−C(11), 88.53(15).

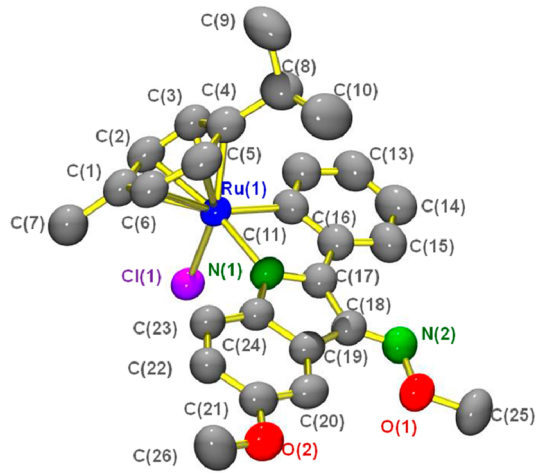


Figure 4. X-ray crystal structure of **6c**·H_2O. Hydrogen atoms have been omitted for clarity. Selected bond lengths (in Å) and angles (in deg): Ru(1)−N(1), 2.074(3); Ru(1)−C(11), 2.057(5); Ru(1)−Cl(1), 2.04858(11); N(1)−Ru(1)−C(11), 76.77(18); N(1)−Ru−Cl(1), 88.50(10); C(11)−Ru−Cl(1), 86.66(14).

heterocyclic ligands through the indole nitrogen and the C(11) atom of the phenyl ring. It should be noted that compounds **6** and **7** are the first examples of ruthenacycles with the $(C_{phenyl},N_{indole})^-$ motif.

An evaluation of the cytotoxic activity of the new products in MCF7 and MDA-MB231 breast cancer cell lines (Table 1) reveals that the Ru(II) complexes **6** and **7** are more active than their free ligands, cisplatin, and even the *trans* and *cis* isomers of $[Pt(3)Cl_2(DMSO)]$[16] (Figure 5). Moreover, most of them showed $IC_{50} < 2$ μM and the ionic products are more effective than their parent neutral derivatives.

Table 1. Cytotoxic Activities of the Free Ligands 3a−e, the Cycloruthenated Complexes 6a−e and 7a−e, and Cisplatin on MCF7 and MDA-MB231 Breast Cancer Cell Lines

				IC_{50} (μM)	
	R^1	R^2	R^3	MCF7	MDA-MB231
Free Ligands[a]					
3a	H	H	H	~100	80
3b	Cl	H	H	~100	~100
3c	H	OMe	H	34 ± 15	~100
3d	F	OMe	H	~100	12.4 ± 4.2
3e	F	OMe	OMe	~100	~100
Neutral Ru(II) Complexes					
6a	H	H	H	2.1 ± 0.4	1.1 ± 0.44
6b	Cl	H	H	1.1 ± 2.7	0.45 ± 0.4
6c	H	OMe	H	1.9 ± 0.2	1.3 ± 0.23
6d	F	OMe	H	5.4 ± 0.5	3.5 ± 0.5
6e	F	OMe	OMe	3.7 ± 0.4	3.2 ± 0.3
Ionic Ru(II) Complexes					
7a	H	H	H	1.5 ± 0.2	1.4 ± 0.1
7b	Cl	H	H	0.66 ± 0.03	0.57 ± 0.03
7c	H	OMe	H	2.4 ± 0.3	1.9 ± 0.2
7d	F	OMe	H	0.91 ± 0.1	0.87 ± 0.04
7e	F	OMe	OMe	1.7 ± 0.2	1.5 ± 0.2
Cisplatin					
				19 ± 4.5	6.5 ± 2.4

[a]Data for ligands **3a−c** were reported previously.[16]

dx.doi.org/10.1021/om400941b | *Organometallics* 2013, 32, 7264−7267

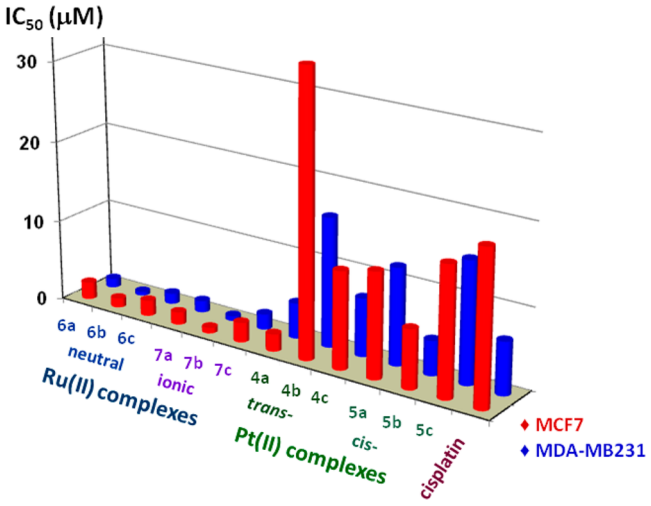


Figure 5. Comparative study of the cytotoxic activity (IC_{50} in μM) of the Ru(II) complexes **6a−c** and **7a−c**, the *trans* (**4a−c**) and *cis* (**5a−c**) isomers of $[Pt(L)Cl_2(DMSO)]$ (L = **3a−c**), and cisplatin on MCF7 and MDA-MB231 breast cancer cell lines.

Among all of the products tested **7b**, and to a lesser extent also **7d**, are especially outstanding. They exhibited IC_{50} values in the submicromolar level in the MCF7 and MDA-MB231 cell lines (i.e., for **7b** IC_{50} = 0.66 ± 0.03 and 0.57 ± 0.03 μM, respectively). In order to get further information on the mode of action of the Ru(II) complexes, additional experiments were carried out.

First of all, we studied the effect produced by the presence of 9-methylguanine (9MeG) on a solution of **7b** in a DMSO-d_6/D_2O (1/4) mixture. As shown in Figure S1 (Supporting Information), the ^{1}H NMR spectrum of the freshly prepared solution changed with time (t). After 20 h the spectrum showed two sets of signals, one of them due to **7b** and the other suggesting the formation of a new species, **8b**. The molar ratio **8b**:**7b** increased with time. For t = 100 h, the NMR spectrum suggested the presence of small amounts of **7b**; this indicates that the reaction is slow. The set of resonances attributed to **8b** showed a singlet at δ 8.69 ppm (consistent with the binding of 9MeG to the Ru(II) atom) and the typical pattern of the signals of the *p*-cymene and metalated ligands. In view of these findings, we tentatively postulate that **8b** may arise from the replacement of the MeCN ligand of **7b** by 9MeG.

We also compared the effect induced by complex **7b** on the electrophoretic mobility of pBluescript SK^+ plasmid DNA with those of cisplatin and 9-aminoacridine (9-AA) (Figure S2, Supporting Information). The results revealed that compound **7b** did not produce any significant change in the DNA mobility, for any of the assayed concentrations. The effect of **7b** is markedly different from that of cisplatin, but it resembles that of 9-AA, which is a typical intercalator.

For comparison purposes, we also evaluated the activity of **7b** with the HCT116 colon cell line. Interestingly, it was more potent (IC_{50} = 1.51 ± 0.07 μM) than cisplatin (24 ± 4 μM) and even than RDC-11 (IC_{50} = 3 ± 2 μM).[9] On this basis, the new Ru(II) complexes with $[C_{sp^2}$(phenyl),N(indole)$]^-$, and especially **7b,** are among the most active organometallic cytotoxic agents reported so far.

The results summarized here are the first stages of further studies centered on (a) the synthesis of a large variety of 2-phenylindole derivatives with electron-donating and/or -withdrawing groups on any of the positions of the aromatic rings and (b) their subsequent use as ligands to give both neutral and ionic cycloruthenated complexes.

The new products **6a−e** and **7a−e** are also attractive in view of their use in other relevant fields.[19] Examples of the utility of cycloruthenated compounds with $[C_{sp^2}$ (phenyl),N$]^-$ ligands as precursors in synthesis, in catalytic processes, or as components of dye sensitized solar cells (DSSC) have been recently reported.[18,19]

In summary, in this contribution we have introduced the 2-phenylindole skeleton as a novel type of cyclometalated ligand for Ru(II) and proved that these products have a promising future in the development of antitumoral drugs. The study of their biological activity with a wider panel of cell lines and their toxicity on normal cells and additional work in order to elucidate their mechanism of action will be actively pursued in the future. Complex **7b** also appears to be an excellent candidate for in vivo assays.

■ ASSOCIATED CONTENT

Supporting Information

Text giving experimental procedures and characterization data (elemental analyses, MS, melting (for **3d,e**) or decomposition (for **6** and **7**) points, IR, UV−vis, and NMR), Figures S1 and S2 (showing the variation of the ^{1}H NMR spectrum of the solution containing **7b** and 9MeG with time and photographs obtained from the electrophoretic studies, respectively), and CIF files giving the crystal structures of **6b**·$^1/_2CH_2Cl_2$ and **6c**·H_2O. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministerio de Ciencia e Innovación of Spain (Grant No. CTQ2009-11501).

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(17) Crystal data for **6b**·$^1/_2CH_2Cl_2$: formula $(C_{25}H_{54}Cl_2N_2ORu)_2 \cdot CH_2Cl_2$, FW = 1165.79; monoclinic, $P2_1/c$; a = 11.07(5) Å, b = 30.339(17) Å, c = 7.947(6) Å; β = 98.07(4)°; V = 2643(12) Å^3; Z = 2, D_{calcd} = 1.465 Mg/m^3, μ = 0.916 mm^{-1}; $F(000)$ = 1180; final R indices ($I > 2\sigma(I)$) R1 = 0.0434, wR2 = 0.0825; final R indices (all data) R1 = 0.1444, wR2 = 0.0996. Crystal data for **6c**·H_2O: formula $C_{26}H_{27}ClN_2O_2Ru \cdot H_2O$, FW = 554.03; trigonal, $R\bar{3}$; a = 28.202(4) Å, b = 28.202(4) Å, c = 16.5790(10) Å, γ = 120°; V = 11420(2) Å^3, Z = 18, D_{calcd} = 1.450 Mg/m^3; μ = 0.752 mm^{-1}; $F(000)$ = 5112; final R indices ($I > 2\sigma(I)$) R1 = 0.0626, wR2 = 0.1743; final R indices (all data) R1 = 0.0693 and wR2 = 0.1791. CCDC reference codes: CCDC 934130 and 934131.
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