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Naphthalimide-Tagged Ruthenium–Arene Anticancer Complexes: Combining Coordination with Intercalation†

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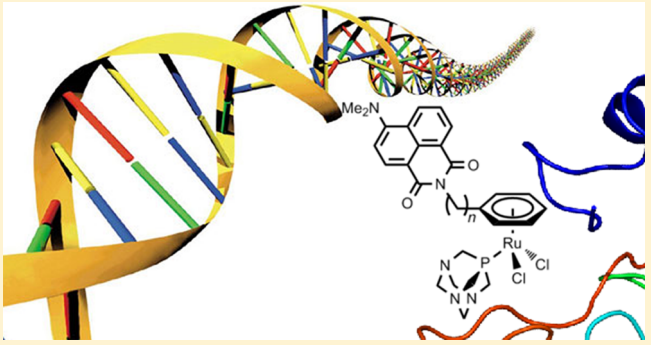
Supporting Information

ABSTRACT: Ruthenium(II) arene compounds have been modified with the naphthalimide group, tethered via the arene ligand, i.e. {dichloro[η^6-*N*-(phenylalkyl)(4-dimethylamino)-1,8-naphthalimide](pta)ruthenium(II)} (alkyl = methyl, ethyl, propyl, pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]-decane), or via an imidazole group, i.e. {dichloro(η^6-arene)-(*N*-[3-(imidazol-1-yl)propyl]-1,8-naphthalimide)ruthenium-(II)} (arene = *p*-cymene, toluene). All the compounds are reasonably cytotoxic (ca. 2–49 μM) toward cancer cells, and the arene-linked compounds also display selectivity in that they are less cytotoxic toward model healthy cells. Mechanistic studies show that the ruthenium center does not readily react with DNA but preferentially binds to proteins. In contrast, the naphthalimide group is a strong DNA intercalator, and combined, the complexes might be expected to simultaneously cross-link DNA and proteins.



INTRODUCTION

Organometallic chemistry has had a profound impact on medicinal chemistry, with the majority of pharmacologically active compounds employing organometallic reagents, catalysts, and intermediates in their synthesis.[1,2] In addition to this highly important application, organometallic compounds also display highly interesting medicinal traits in their own right, with properties somewhat intermediate between classical inorganic drugs and organic drug molecules.[3−5] A number of metallocenes were evaluated for anticancer activity shortly after the introduction of cisplatin into the clinic, and titanocene dichloride, Ti(η^5-C_5H_5)$_2$Cl$_2$, was identified as a promising drug candidate.[6] Indeed, Ti(η^5-C_5H_5)$_2$Cl$_2$ underwent extensive evaluation as an anticancer drug, in many different in vitro and in vivo models as well as on patients, but was finally not approved for clinical use.[7] Nevertheless, these studies inspired the search for anticancer drugs containing metal–carbon bonds and over the years many interesting and unique properties have emerged. Indeed, the influence of the metal type, oxidation state, ligands, and charge on anticancer activity has been studied, and mechanistic studies and rational ligand design have resulted in many different classes of organometallic anticancer compounds.[8−10]

In our own studies on the anticancer properties of organometallic compounds that began in the mid-1990s, we became interested in the application of ruthenium(II) arene compounds.[11] Such compounds are widely used as catalysts, which in combination with various ligands lead to a wide and diverse range of organic transformations.[12,13] However, at first it was not apparent that these compounds would also display remarkable chemotherapeutic properties. After struggling for some time, we discovered the so-called RAPTA complexes, the prototype being RAPTA-C, Ru(η^6-*p*-cymene)(pta)Cl$_2$, containing the phospha-adamantane ligand 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane, abbreviated pta.[14] Like cisplatin and titanocene dichloride, there are two chloride ligands that can potentially be hydrolyzed to give an "activated" complex that subsequently reacts with targets such as DNA—the classic (presumed) target of most metal-based anticancer drugs. Moreover, the amphiphilic pta ligand provides ideal properties for physiological environments, being soluble in water and organic solvents, and hence with the potential for facile transport in the body combined with the ability to cross lipophilic cell membranes. Finally, the arene ligand may be systematically modified to fine-tune the properties of the compound. It was subsequently shown that RAPTA-C exhibits antitumor,[15] antimetastatic,[16] and antiangiogenic[17] properties

†Invited award article: Paul Dyson was the recipient of the Centennial Memorial Sacconi Medal in 2011 for his contributions to organometallic chemistry. The award is given by the Italian Chemical Society on behalf of the Luigi Sacconi Foundation. Luigi Sacconi was a prolific inorganic/organometallic chemist whose research is an indispensable part of modern inorganic chemistry textbooks. He founded the highly reputed school of inorganic chemistry in Florence that today explores the frontiers of bioinorganic chemistry, material chemistry, and sustainable chemistry and catalysis.

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in vivo with negligible side effects observed. Nevertheless, in the same way that organometallic chemists working on catalysis modify the ligands to improve or modulate the catalytic properties of a complex (consider for example the kinetic, mechanistic, and synthetic studies that have seen the utility and scope of Grubbs's first-generation metathesis catalyst expand over the years),[18,19] we set out to enhance the efficacy of RAPTA-C on the basis of a mechanistic approach. Many of these studies are summarized in a relatively recent review.[20]

While many themes and variations have been developed, two main approaches show considerable potential and were, in part, inspired by the elegant studies of Jaouen, who showed that organometallic units tethered to biologically active organic molecules may exhibit new and enhanced anticancer properties.[21] Specifically, a ferrocene derivative of tamoxifen, a selective estrogen receptor modulator used to treat breast cancer, extends the activity of the molecule to highly invasive breast tumors. In our first approach,[22] biologically active groups are tethered to the η^6-arene via a suitable linker unit (Figure 1)—it should be noted that the role of both the ruthenium(II)

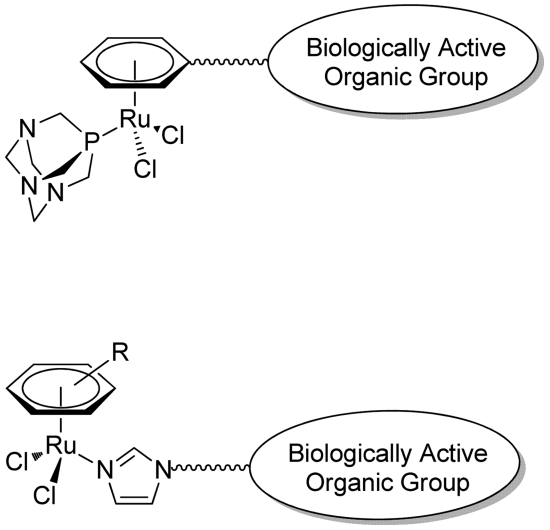

Figure 1. Illustration of the two approaches used to tether biologically active organic groups to the ruthenium(II) arene unit via either the η^6-arene (top) or an imidazole ligand in place of the pta (bottom).

arene unit and the selected biological groups are distinct from those of ferrocene and tamoxifen. Selection of the biological group requires a knowledge of both the mechanism of action of the ruthenium(II) arene unit and the organic molecule so that complementary functionalities can work together in a synergistic manner. Moreover, in cancer chemotherapy drug combinations are virtually always applied,[23,24] and in this sense the organometallic and organic components can be viewed as a covalently linked drug combination, with the added possible advantage that the compounds reach the tumor site simultaneously. In the second approach the biologically active organic group is attached to the ruthenium(II) arene unit via an imidazole ligand in place of pta (Figure 1).[25] This approach was in part motivated from the structure of NAMI-A, one of the two ruthenium(III) coordination complexes currently undergoing clinical trials, which contains an imidazole ligand among others.[26,27] The imidazole moiety is relatively stable but has also been shown to dissociate on binding to a zinc-containing enzyme, such that both the ruthenium ion and imidazole bind at different locations within the active site.[28]

In both the approaches described above, the role of the ruthenium(II) arene unit is quite broad, as it is potentially able to coordinate to many biomolecules and has been shown to bind to the histones in the nucleosome core in preference to the DNA.[29] In the compounds described to date, the tethered organic molecule has a much more selective function: e.g., inhibition of specific enzymes leading to synergies between the inorganic and organic subunits of the structure. On the basis of the observed histone binding we hypothesize that tethering a DNA intercalator to the ruthenium(II) arene unit may allow both histone binding and DNA intercalation, enhancing the cytotoxic effect of the compound. Such a mechanism differs from that of platinum-based anticancer compounds that potentially coordinate and intercalate with DNA alone.[30]

RESULTS AND DISCUSSION

Naphthalimides were first recognized as intercalating cytotoxic agents in the early 1980s,[31] and since then many derivatives have been evaluated for antitumor activity, with two examples of this class of compound (mitonafide and amonafide) entering clinical trials.[32,33] In addition to the biological activity of the group, the naphthalimide unit is an attractive intercalating unit to tether to the ruthenium structure, as it has rich and well-studied photophysical properties,[34,35] which can be exploited to probe interactions with DNA.[36,37]

Two types of napthalimide-tagged ruthenium(II) arene complexes were prepared using the methodologies depicted in Schemes 1 and 2. For the synthesis of the RAPTA-type complexes **5a**–**c**, in which the naphthalimide is tagged to the arene ligand via an aliphatic chain, the precursor cyclohexadiene ligands (**3a**–**c**) were synthesized by the reaction of *N*,*N*-dimethylnaphthalic anhydride **1a** with **2a**–**c** in refluxing toluene to afford the ligands as yellow solids in good yields. Subsequent reaction of **3a**–**c** with $RuCl_3 \cdot 3H_2O$ in refluxing acetone/water (5/1) produced the ruthenium(II) arene complexes **4a**–**c** as dark orange solids. The mononuclear RAPTA-type complexes were obtained by the reaction of the dimeric complexes **4a**–**c** with 2 equiv of pta in methanol/dichloromethane (Scheme 1).

In the second series of compounds, where the naphthalimide group is tagged to the ruthenium(II) arene center via an imidazole ligand, complexes **8a**,**b** and **9a**,**b** were prepared by the reaction of either $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ or $[Ru(\eta^6\text{-toluene})Cl_2]_2$ with 2 equiv of the appropriate imidazole–naphthalimide ligand **7a**,**b** in dichloromethane (Scheme 2).

All new complexes were characterized by ^1H, $^{13}C\{^1H\}$, and (where appropriate) $^{31}P\{^1H\}$ NMR spectroscopy, HR-ESI mass spectrometry, IR spectroscopy, and elemental analysis. A distinctive spectroscopic feature of complexes **5a**–**c** is the singlet in the $^{31}P\{^1H\}$ NMR spectra at ca. −34 ppm, consistent with related complexes.[22] The ^1H NMR spectra of all the complexes contain peaks between 5 and 6 ppm that are characteristic of the η^6-coordinated arene. In **8a**,**b** and **9a**,**b** there is little change in position of the proton signals of the *p*-cymene and toluene rings in comparison to those observed in the parent dimers $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ and $[Ru(\eta^6\text{-toluene})Cl_2]_2$. The peaks for the imidazole protons are observed at higher frequencies in the complexes (**8a**,**b** and **9a**,**b**) relative to the free ligands (**7a**,**b**), confirming coordination to the ruthenium center via the imidazole N atom. In both sets of compounds the ^1H NMR signals of the

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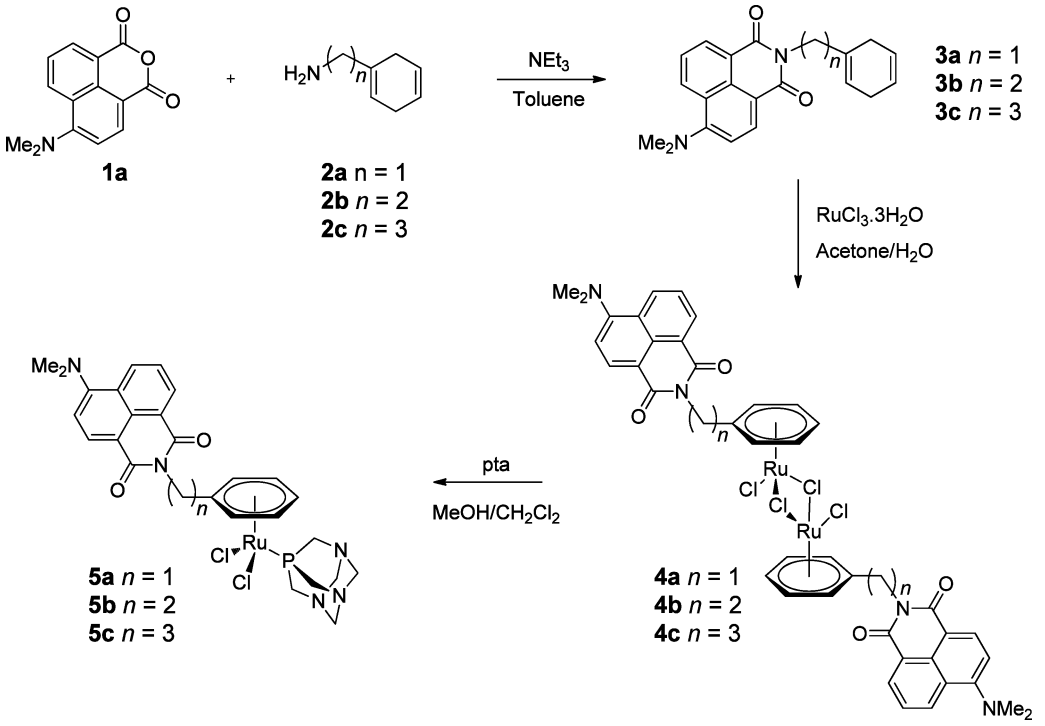
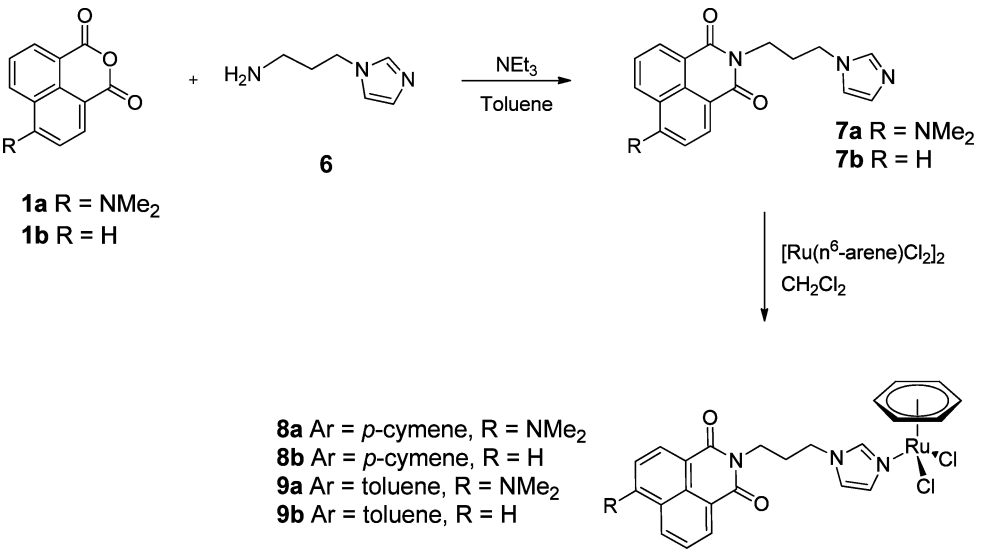
Scheme 1. Synthesis of Napthalimide-Tagged RAPTA-Type Complexes, 5a−c



Scheme 2. Synthesis of Naphthalimide-Tagged Complexes 8a,b and 9a,b



naphthalimide moiety remain essentially unchanged, indicating the naphthalimide does not interact with the ruthenium center and thus is free to interact with DNA.

The structure of the compounds was corroborated by HR ESI-MS. The most abundant peak observed in the spectra of the RAPTA-type complexes (**5a−c**) were those assigned to $[M + H]^+$ ions. Conversely, the spectra of the imidazole complexes (**8a,b**, **9a,b**) were dominated by species assigned to $[M - Cl]^+$ ions. Presumably, the difference in the spectra is due to the presence of the pta ligand in **5a−c**, which contains basic nitrogen atoms that are protonated under the experimental conditions employed.

The chloride ligands coordinated to ruthenium−arene complexes are known to undergo hydrolysis in aqueous solution, with the behavior of the prototype RAPTA complex, RAPTA-C, being the subject of in-depth studies.[38] To determine the influence of the pendant naphthalimide group on hydrolysis, and aquatic stability more generally, the aqueous stability of **5a−c** was evaluated using $^{31}P\{^1H\}$ NMR spectroscopy, as the chemical shift of the pta ligand can be used to monitor the extent of hydrolysis. Analogous to the case for RAPTA-C, the naphthalimide complexes **5a−c** undergo aquation in aqueous solution, characterized by a shift in the $^{31}P\{^1H\}$ NMR spectra from −32 to −28 ppm. Irrespective of the length of the linker between the η^6-arene and the naphthalimide, **5a−c** undergo complete conversion to the monoaquated form within 30 min. Exchange of both chloride ligands was not observed, even after 48 h. However, upon the

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addition of $AgBF_4$ to forcibly remove both chloride ligands, a peak appeared in the $^{31}P\{^1H\}$ NMR spectra, which we assign to be the doubly aquated species. This species was not observed in the absence of silver salts. Notably, over this time period, the ^1H NMR spectra indicated that the arene remained coordinated to the ruthenium center—signals for the free arene ligands were not observed.

Similar behavior was observed for the imidazole-linked compounds **8a,b** and **9a,b**. ^1H NMR spectroscopy indicated that in aqueous solution the imidazole (and hence the naphthalimide) remains coordinated to the ruthenium over 48 h. However, as with the pta complexes **5a−c**, hydrolysis of the chloride ligands takes place over 30 min, resulting in multiple peaks assigned to the imidazole (but always to higher frequency in comparison with the free ligands **7a,b**). The number of peaks present suggest that, in contrast to the pta complexes **5a−c**, both the mono- and diaquated species are formed with the imidazole complexes **8a,b** and **9a,b**.

Biological Studies. The cytotoxicities of the ligands and complexes were determined using the MTT assay in comparison to RAPTA-C on cisplatin-sensitive and -resistant human ovarian carcinoma (A2780 and A2780R, respectively) and human embryonic kidney cells (HEK, a model for healthy cells) (see Table 1 and Figure S19 (Supporting Information)).

Table 1. IC_{50} Values (μM) Determined by the MTT Assay after 72 h Exposure of the Compounds to A2780, A2780R, and HEK Cells

	A2780[a]	A2780R[b]	HEK[c]
5a	8.53 ± 1.41	6.89 ± 1.49	16.61 ± 1.13
5b	2.31 ± 0.1	2.25 ± 0.23	6.60 ± 0.21
5c	6.45 ± 0.46	9.09 ± 1.72	17.43 ± 0.33
7b	38 ± 3	49 ± 6	35.7 ± 0.8
8b	28.1 ± 0.8	36 ± 3	32 ± 3
9b	30 ± 3	48.3 ± 0.1	33 ± 4
7a	18.5 ± 0.3	26 ± 4	29.3 ± 3
8a	6.1 ± 1.1	7.8 ± 0.4	12.7 ± 0.2
9a	6.5 ± 1.5	8.6 ± 1.8	18.4 ± 1.3
RAPTA-C	230	270	>1000

[a]Human ovarian carcinoma, cisplatin-sensititve cells. [b]Human ovarian carcinoma, cisplatin-resistant cells. [c]Human embryonic kidney cells.

All the naphthalimide complexes are far more active than the prototype complex RAPTA-C, indicating that the naphthalimide moiety plays an important role in the cytotoxic mechanism. Furthermore, the compounds containing the unsubstituted naphthalimide group (**7b−9b**) are less active than the analogous compounds which contain the dimethylamino substituent group (**7a−9a**), which may indicate that DNA intercalation is playing a role in the cytotoxic mechanism, as it has been shown that the presence of an internal charge transfer in the napthalimide group (present in **7a−9a**, absent in **7b−9b**) enhances interaction with DNA.[39] The imidazole complexes (**8a,b** and **9a,b**) are slightly less active than the RAPTA-type complexes (**5a−c**), and importantly, the RAPTA-type complexes are consistently selective toward cancer cell lines (A2780/A2780R) over the HEK cells, supporting the previous observation that the pta ligand endows compounds with some degree of selectivity. This selectivity is somewhat lost when the naphthalimide moiety is tethered via the imidazole and the pta ligand is absent. Overall, the RAPTA-type complexes, **5a−c**, show the highest selectivity toward cancer cells and are also active against the cisplatin-resistant A2780R cell line (notably **5b**); therefore, only these complexes were studied further. It is noteworthy that **5b**, containing the ethyl linker, is the most active of the RAPTA-type series of compounds.

Naphthalimides are known to intercalate DNA, and consequently the interaction of **5b** with DNA was investigated initially by NMR spectroscopy, using the nucleoside guanosine as a model for DNA, as the N7 nitrogen is the usual binding site for ruthenium- and platinum-based compounds.[40,41] The frequency of the H8 proton (adjacent to N7 of guanosine) did not change following incubation with **5b** (1/1) in D_2O/d_6-DMSO (9/1). The ^1H NMR spectrum did reveal the presence of the hydrolysis product, and while the hydrolysis product is considered to be activated, direct reaction (coordination) with the isolated guanosine base was not observed. However, when the concentration of guanosine is increased, the frequency of the naphthalimide protons decreases, indicative of π-stacking interactions in solution and demonstrating that π-stacking is preferred over coordination of the ruthenium center (see the Supporting Information, Figure S15). After 24 h incubation, two new peaks appear in the $^{31}P\{^1H\}$ NMR spectrum at −29.5 and −29.7 ppm, assigned to the guanosine-coordinated diastereoisomers (see the Supporting Information, Figure S16). The presence of the guanosine adduct was additionally confirmed using HR-ESI MS (see the Supporting Information, Figure S17). It is noteworthy that these guanosine adducts were only observed after a significant incubation time, in the presence of an excess (5 equiv) of guanosine. These results differ significantly when compared with those for RAPTA-C, which is far more reactive toward the base (complete conversion to the guanosine adduct after 12 h, 1 equiv).[40]

It has previously been shown that the photophysical properties of the naphthalimide unit can be exploited to delineate interactions with DNA.[36,37] Thus, UV−vis spectrometry was used to monitor changes to **5b** as increasing amounts of ct-DNA were added to a phosphate-buffered solution of the complex (Figure 2a). A bathochromic shift of λ_{max} of the naphthalimide moiety of 10 nm (λ_{max} of free **5b** 445 nm, λ_{max} of bound **5b** 455 nm), accompanied by a decrease in intensity of the absorbance band at 445 nm of approximately 20%, was observed upon the addition of ct-DNA. These observations are consistent with those reported in the literature[36] and are indicative of a weak naphthalimide−DNA interaction; however, the results are not diagnostic for a particular type of binding, since both intercalated and externally bound drugs display the same changes to their UV−vis spectra on interacting with DNA.

In addition to the UV−vis absorption spectra, the steady-state emission spectra (excitation at 485 nm) of **5b** upon addition of increasing amounts of ct-DNA were recorded (Figure 2b). As expected, in phosphate-buffered solution the fluorescence of **5b** is essentially quenched,[34,35] but on addition of DNA the emission is enhanced by a factor of 5, along with a blue shift of λ_{max} of 4 nm (λ_{max} of free **5b** 548 nm, λ_{max} of bound **5b** 544 nm). These data are consistent with weak interactions with DNA, as an association with less polar binding sites of DNA would decrease the stability of the excited state.

Circular dichroism (CD) spectroscopy was also used to investigate the interaction of **5b** with ct-DNA (Figure 3). Upon addition of **5b** ([DNA]/[**5b**] = 0 → 20) to a solution of ct-DNA, the CD trace characteristic of B-DNA was significantly altered, especially at high drug concentrations ([DNA]/[**5b**] = 2). Specifically, a substantial decrease in the ellipticity of the

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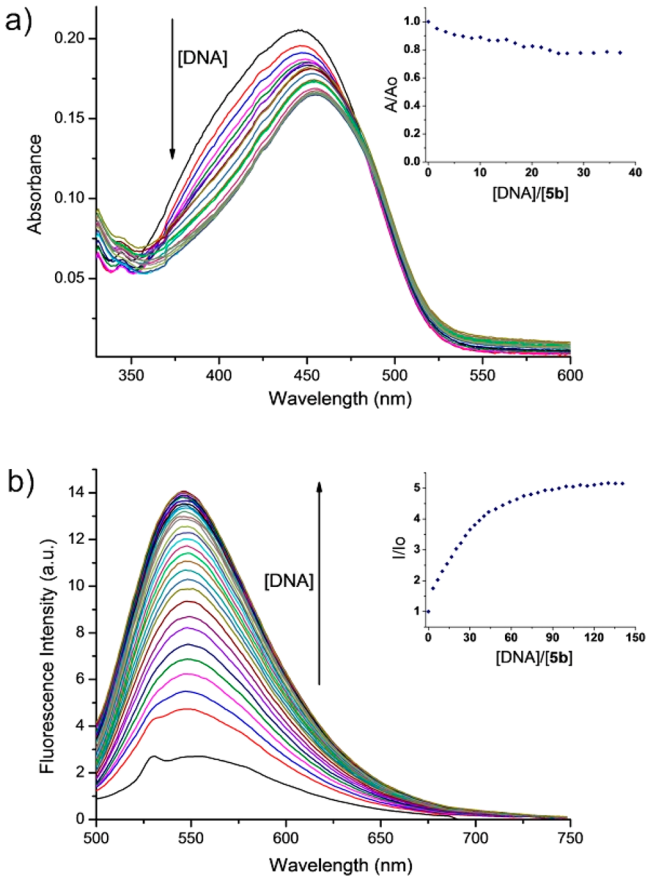

Figure 2. (a) UV−vis spectra (300 − 650 nm) of **5b** (0.02 mM, phosphate buffer, 10 mM, pH 7.4) in the presence of increasing concentrations of ct-DNA (0−0.7 mM). Inset: plot of A/A_0 vs [DNA]/[**5b**]. (b) Steady-state emission of **5b** (0.02 mM, phosphate buffer, 10 mM, pH 7.4) in the presence of increasing concentrations of ct-DNA (0−2.5 mM), λ_{ex} 485 nm. Inset: plot of I/I_0 vs [DNA]/[**5b**].

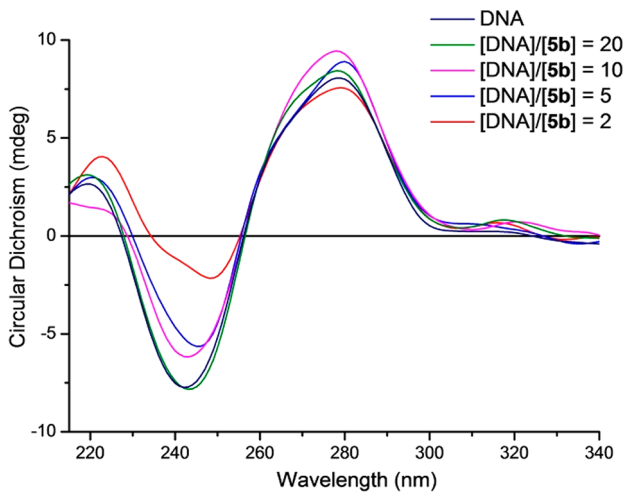

Figure 3. CD spectra (210−340 nm) of ct-DNA (150 mM, phosphate buffer, 10 mM, pH 7.4) in the presence of **5b** at varying [DNA]/[**5b**] ratios.

negative band (240 nm) was observed. Again, these results contrast with those obtained for RAPTA-C, which at the same concentrations has no effect on the secondary structure of DNA.[42]

Taken together, these data clearly indicate that the naphthalimide group is interacting with DNA. Although the results do not explicitly confirm this interaction is via intercalation, the secondary structure of B-DNA is significantly altered. However, in comparison with data obtained for known naphthalimide intercalators, it is not unreasonable to suggest that the ruthenium conjugates also interact with DNA via intercalation. These noncovalent naphthalimide/DNA interactions appear to dominate over Ru−DNA binding interactions, which are slow in comparison to those for RAPTA-C, which may bind to DNA without altering the secondary structure.

In addition to interactions with DNA, ESI MS was utilized to investigate the binding of **5b** to the protein ubiquitin (Ub). Compound **5b** readily binds to the protein, as after only 1 h incubation (**5b**/Ub 1/5) the ruthenium adduct [Ub+**5b**-Cl_2] is observed (see the Supporting Information, Figure S18). Over time, the intensity of this peak increases, and the appearance of a new peak arising from further loss of the pta ligand is observed. Importantly, in all the ruthenium/Ub adducts, the arene−naphthalimide units remain coordinated to the ruthenium center. Thus, it is not unreasonable to propose that the naphthalimide group may intercalate DNA with the ruthenium unit simultaneously coordinating to a protein.

CONCLUSIONS

Two series of ruthenium(II) arene complexes were prepared with pendant naphthalimide (DNA intercalating) moieties—one in which the naphthalimide is connected via the arene unit and in the other an imidazole linker. In both series of complexes the naphthalimide increases the cytotoxicity of the ruthenium(II) arene unit. The greatest selectivity toward cancer cells over model healthy HEK cells is observed for the former series, which are also active against the cisplatin-resistant cells. Subsequent studies suggest that intercalation of the naphthalimide group is the dominant interaction with DNA, whereas the ruthenium center prefers to bind to proteins. As such, it is possible that these compounds have a double-action mechanism, which could be responsible for the increased activity in comparison with RAPTA-C and also for overcoming cisplatin acquired drug resistance. Further studies are required to fully delineate the mechanism of action at a cellular level. It should also be noted that the approach used here not only extends our own studies but builds on an impressive body of research on anticancer organometallic compounds.

EXPERIMENTAL SECTION

1,3,5-Triaza-7-phosphatricyclo[3.3.1.1]decane (PTA)[43] and the aminoalkyl-cyclohexadienes **2a**,[44] **2b**,[45] and **2c**[46] were synthesized using literature procedures; all other reagents and solvents were obtained from commercial sources and used without further purification. ^{1}H (400.13 MHz), ^{31}P{^{1}H} (161.98 MHz), and ^{13}C{^{1}H} (100.62 MHz) NMR spectra were recorded at 25 °C on a Bruker Avance II 400 spectrometer and referenced to residual solvent peaks ($CDCl_3$ ^{1}H 7.26, ^{13}C{^{1}H} 77.16; CD_2Cl_2 ^{1}H 5.30, ^{13}C{^{1}H} 53.84; d_6-DMSO ^{1}H 2.50, ^{13}C{^{1}H} 39.52) or reported relative to 85% H_3PO_4. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer, and melting points were determined on an SMP3 Stuart melting point apparatus and are uncorrected. Elemental analysis was carried out by the microanalytical laboratory at EPFL. HR-ESI MS were obtained on a ThermFinnigan LCQ Deca XP Plus Quadrupole ion-trap instrument in the positive ion mode. UV−vis experiments were conducted on a Jasco V-550 spectrometer, Fluorescence spectra were acquired on a Varian Cary Eclipse spectrofluorimeter, and circular dichroism

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experiments were conducted on a Jasco J-810 spectropolarimeter with 10 accumulations per spectra. All photochemistry spectra were acquired using quartz cells (Helma Analytics) with a path length of 1 cm.

Synthesis. *4-N,N-Dimethylaminonaphthalene-1,8-dicarboximide (**1a**).* Dimethylamine (10 mL, 40% aqueous solution, excess) and $CuSO_4{\cdot}5H_2O$ (5 mol %) were added to a suspension of 4-bromonaphthalene-1,8-dicarboximide (5.00 g) in DMF (30 mL). The mixture was refluxed for 3 h, after which time the solvent was removed under vacuum. The product was crystallized from hot methanol to give a yellow solid. Yield: 3.84 g (88%). Mp: 206 °C. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.46; H, 4.54; N, 5.87. IR ν (cm^{-1}): 1748, 1713, 1581, 1563, 1391, 1340, 1308, 1081, 1016, 989, 779, 753, 721, 467, 494. NMR ($CDCl_3$): ^1H, δ 8.57 (dd, J = 7.3, 1.1 Hz, 1H, Ar-*H*), 8.51 (dd, J = 8.4, 1.1 Hz, 1H, Ar-*H*), 8.47 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.69 (dd, J = 8.4, 7.3 Hz, 1H, Ar-*H*), 7.13 (d, J = 8.0 Hz, 1H, Ar-*H*), 3.18 (s, 6H, N-C*H*$_3$); $^{13}C\{^1H\}$, δ 161.8 (*C*═O), 160.8 (*C*═O), 158.0 (Ar-*C*-NMe$_2$), 135.0 (Ar-*C*), 133.0 (Ar-*C*), 132.9 (Ar-*C*), 132.9 (Ar-*C*), 124.9 (Ar-*C*), 124.8 (Ar-*C*), 119.3 (Ar-*C*), 113.3 (Ar-*C*), 109.6 (Ar-*C*), 44.7 (N-CH_3). HR ESI-MS: m/z 242.081 ([M + H]$^+$, calcd for $C_{14}H_{12}NO_3$ 242.082).

*General Procedure for Preparation of Naphthalimide Ligands **3a**−**c** and **7a**,**b**.* Under an atmosphere of nitrogen, the 1,8-dicarboximide **1a**,**b** (1 equiv), the appropriate amine **2a**−**c** or **6** (1.4 equiv), and dry NEt_3 (2 equiv) were refluxed over molecular sieves in toluene (150 mL) for 2−3 days. While hot, the solution was filtered through Celite and the filter cake washed with hot toluene (2 × 25 mL). The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL), and brine (50 mL) and dried over $NaSO_4$. After evaporation, the residue was crystallized from hot MeOH and dried in vacuo.

*N-[1-(Cyclohexa-1,4-dienyl)methyl](4-dimethylamino)-1,8-naphthalimide (**3a**).* (4-Dimethylamino)naphthalene-1,8-dicarboximide (**1a**; 1.50 g, 6.2 mmol, 1 equiv), (cyclohexa-1,4-dienyl)methylamine (**2a**; 0.93 g, 8.7 mmol), and NEt_3 (1.73 mL, 12.4 mmol, 2 equiv) were reacted in toluene (110 mL) for 2 days. Workup as described above, followed by crystallization from hot MeOH, gave 1.22 g (60%) of **3a** as a yellow solid. Mp: 145 °C. Anal. Calcd for $C_{21}H_{20}N_2O_2{\cdot}H_2O$: C, 71.97; H, 6.33; N, 8.00. Found: C, 71.87; H, 6.05; N, 7.38. IR ν (cm^{-1}): 1686, 1650, 1587, 1575, 1377, 1341, 1240, 779, 761, 652, 504, 495, 466, 458. NMR ($CDCl_3$): ^1H, δ 8.59 (dd, J = 7.3, 0.9 Hz, 1H, Ar-*H*), 8.46 (d, J = 8.2 Hz, 1H, Ar-*H*), 8.44 (dd, J = 8.5, 0.9 Hz, 1H, Ar-*H*), 7.67 (dd, J = 7.3, 8.5 Hz, 1H, Ar-*H*), 7.13 (d, J = 8.2 Hz, 1H, Ar-*H*), 5.61 (m, 3H, diene C-*H*), 4.71 (s, 2H, C*H*$_2$), 3.11 (s, 6H, N-C*H*$_3$), 2.71 (m, 4H, diene C-*H*$_2$); $^{13}C\{^1H\}$, δ 164.7 (*C*═O), 164.1 (*C*═O), 156.9 (Ar-*C*-NMe$_2$), 132.9 (Ar-*C*), 131.3 (Ar-*C*), 131.3 (Ar-*C*), 130.4 (Ar-*C*), 130.3 (Ar-*C*), 125.5 (Ar-*C*), 125.1 (Ar-*C*), 124.1 (Ar-*C*), 123.1 (Ar-*C*), 123.2 (Ar-*C*), 120.3 (Ar-*C*), 115.2 (Ar-*C*), 113.5 (Ar-*C*), 45.0 (N-*C*H$_3$), 44.9 (N-*C*H$_2$), 27.9 (*C*H$_2$), 26.6 (*C*H$_2$). HR ESI-MS: m/z 333.160 ([M + H]$^+$, calcd for $C_{21}H_{19}N_2O_2$ 333.160).

*N-[2-(Cyclohexa-1,4-dienyl)ethyl](4-dimethylamino)-1,8-naphthalimide (**3b**).* (4-Dimethylamino)naphthalene-1,8-dicarboximide (**1a**; 1.52 g, 6.3 mmol, 1 equiv), (cyclohexa-1,4-dienyl)ethylamine (**2b**; 1.09 g, 8.8 mmol), and NEt_3 (1.75 mL, 12.6 mmol, 2 equiv) were reacted in toluene (120 mL) for 2 days. The hot solution was filtered through Celite and the filter cake washed with hot toluene (2 × 25 mL). The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL), and brine (50 mL) and dried over $NaSO_4$. After evaporation, the residue was crystallized from hot MeOH and dried in vacuo to give 1.29 g (59%) of **3b** as an orange solid. Mp: 132 °C. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.06; H, 6.42; N, 8.01. IR ν (cm^{-1}): 1685, 1640, 1572, 1383, 1352, 786, 757. NMR ($CDCl_3$): ^1H, δ 8.57 (dd, J = 7.2, 1.1 Hz, 1H, Ar-*H*), 8.44 (d, J = 8.2 Hz, 1H, Ar-*H*), 8.42 (dd, J = 8.5, 1.1 Hz, 1H, Ar-*H*), 7.65 (dd, J = 8.5, 7.2 Hz, 1H, Ar-*H*), 7.11 (d, J = 8.2 Hz, 1H, Ar-*H*), 5.72 (m, 2H, diene C-*H*), 5.52 (br s, 1H, diene C-*H*), 4.26 (t, J = 7.7 Hz, 2H, N-C*H*$_2$), 3.10 (s, 6H, N-C*H*$_3$), 2.80 (m, 2H, diene C*H*$_2$), 2.65 (m, 2H, diene C*H*$_2$), 2.37 (t, J = 7.7 Hz, 2H, C*H*$_2$); $^{13}C\{^1H\}$, δ 164.6 (*C*═O), 164.0 (*C*═O), 157.0 (Ar-*C*-NMe$_2$), 132.7 (Ar-*C*), 132.5 (Ar-*C*), 131.2 (Ar-*C*), 131.0 (Ar-*C*), 130.3 (Ar-*C*), 125.4 (Ar-*C*), 125.0 (Ar-*C*), 124.5 (Ar-*C*), 124.1 (Ar-*C*), 123.2 (Ar-*C*), 120.7 (Ar-*C*), 115.2 (Ar-*C*), 113.4 (Ar-*C*), 44.9 (N-CH_3), 38.9 (*C*H$_2$), 35.9 (*C*H$_2$), 29.1 (*C*H$_2$), 26.9 (*C*H$_2$). HR ESI-MS: m/z 347.175 ([M + H]$^+$, calcd for $C_{22}H_{23}N_2O_2$ 347.176).

*N-[3-(Cyclohexa-1,4-dienyl)propyl](4-dimethylamino)-1,8-naphthalimide (**3c**).* (4-Dimethylamino)naphthalene-1,8-dicarboximide (**1a**; 1.50 g, 6.2 mmol, 1 equiv), (cyclohexa-1,4-dienyl)propylamine (**2c**; 1.18 g, 8.7 mmol), and NEt_3 (1.73 mL, 12.4 mmol, 2 equiv) were reacted in toluene (110 mL) for 3 days. Workup as for **3b** gave 1.50 g (66%) of **3c** as a yellow solid. Mp: 104 °C. Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.49; H, 6.69; N, 7.84. IR ν (cm^{-1}): 1690, 1645, 1574, 1348, 778, 758, 658, 469. NMR ($CDCl_3$): ^1H, δ 8.58 (d, J = 7.5 Hz, 1H, Ar-*H*), 8.48 (m, 2H, Ar-*H*), 7.67 (m, 1H, Ar-*H*), 7.14 (d, J = 8.1 Hz, Ar-*H*), 5.68 (m, 2H, diene C-*H*), 5.50 (br s, 1H, diene C-*H*), 4.16 (t, J = 7.6 Hz, 2H, N-C*H*$_2$), 3.11 (s, 6H, N-C*H*$_3$), 2.64 (br s, 4H, diene C*H*$_2$), 2.12 (t, J = 7.8 Hz, 2H, C*H*$_2$), 1.88 (m, 2H, C*H*$_2$); $^{13}C\{^1H\}$, 164.7 (*C*═O), 164.2 (*C*═O), 156.8 (Ar-*C*-NMe$_2$), 134.3 (Ar-*C*), 132.6 (Ar-*C*), 131.2 (Ar-*C*), 131.1 (Ar-*C*), 130.3 (Ar-*C*), 125.4 (Ar-*C*), 125.1 (Ar-*C*), 124.5 (Ar-*C*), 124.3 (Ar-*C*), 123.3 (Ar-*C*), 118.7 (Ar-*C*), 115.4 (Ar-*C*), 113.6 (Ar-*C*), 45.0 (N-*C*H$_3$), 40.3 (*C*H$_2$), 35.1 (*C*H$_2$), 29.0 (*C*H$_2$), 26.9 (*C*H$_2$), 25.7 (*C*H$_2$). HR ESI-MS: m/z 361.191 ([M + H]$^+$, calcd for $C_{23}H_{25}N_2O_2$ 361.192).

*N-[3-(Imidazol-1-yl)propyl](4-dimethylamino)-1,8-naphthalimide (**7a**).* (4-Dimethylamino)naphthalene-1,8-dicarboximide (**1a**; 1.00 g, 4.14 mmol, 1 equiv), 1-(3-aminopropyl)imidazole (**6**; 0.73 g, 5.80 mmol, 1.4 equiv), and NEt_3 (0.83 g, 8.24 mmol, 2 equiv) were refluxed in dry toluene (100 mL) over molecular sieves for 48 h to give 1.18 g (82%) of **7a** as an orange-yellow solid. Mp: 118−119 °C. Anal. Calcd for $C_{20}H_{20}N_4O_2{\cdot}0.5MeOH$: C, 67.55; H, 6.09; N, 15.38. Found: C 67.96; H, 5.57; N, 15.07. IR ν (cm^{-1}): 1692, 1644, 1587, 1360, 1349, 1225, 1073, 1052, 777, 758, 736, 661. NMR ($CDCl_3$): ^1H, δ 8.54 (d, J = 7.3 Hz, 1H, Ar-*H*), 8.43 (m, 2H, Ar-*H*), 7.64 (m, 1H, Ar-*H*), 7.54 (s, 1H, Im-*H*), 7.09 (d, J = 8.1 Hz, 1H, Ar-*H*), 7.03 (s, 1H, Im-*H*), 7.00 (s, 1H, Im-*H*), 4.21 (t, J = 6.9 Hz, 2H, N-C*H*$_2$-CH$_2$), 4.05 (t, J = 7.4 Hz, 2H, CH$_2$-C*H*$_2$-Im), 3.10 (s, 6H, N-C*H*$_3$), 2.24 (m, 2H, CH$_2$-C*H*$_2$-CH$_2$); $^{13}C\{^1H\}$, δ 164.8 (*C*═O), 164.2 (*C*═O), 157.3 (Ar-*C*-NMe$_2$), 137.3 (Im-*C*), 133.0 (Ar-*C*), 131.6 (Ar-*C*), 131.3 (Ar-*C*), 130.4 (Im-*C*), 129.6 (Ar-*C*), 125.3 (Ar-*C*), 125.0 (Ar-*C*), 122.8 (Ar-*C*), 118.8 (Im-*C*), 114.5 (Ar-*C*), 113.4 (Ar-*C*), 45.1 (*C*H$_2$), 44.9 (N-*C*H$_3$), 37.6 (*C*H$_2$), 29.9 (*C*H$_2$). HR ESI-MS: m/z 349.167 ([M + H]$^+$, calcd for $C_{20}H_{21}N_4O_2$ 349.166).

*N-[3-(Imidazol-1-yl)propyl]-1,8-naphthalimide (**7b**).* 1,8-Naphthalic anhydride (**1b**; 1.69 g, 8.6 mmol, 1 equiv), 1-(3-aminopropyl)-imidazole (1.50 g, 12.0 mmol, 1.4 equiv), and NEt_3 (1.74 g, 17.2 mmol, 2 equiv) were refluxed in dry toluene (150 mL) over molecular sieves for 3 days. The hot solution was filtered through Celite and the filter cake washed with hot toluene (2 × 25 mL). The solvent was removed under reduced pressure and the residue taken up in CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL), H_2O (2 × 50 mL), and brine (50 mL) and dried over $NaSO_4$. After evaporation, the residue was crystallized from hot MeOH and dried in vacuo to give 1.04 g (40%) of **7b** as white crystals. Mp: 166−168 °C. Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.62; H, 5.06; N, 13.69. IR ν (cm^{-1}): 1688, 1647, 1623, 1583, 1440, 1384, 1340, 1235, 1081, 1049, 1037, 907, 844, 778, 765, 726, 670. NMR ($CDCl_3$): ^1H, 8.61 δ (d, J = 7.3 Hz, 2H, Ar-*H*), 8.23 (d, J = 7.8 Hz, 2H, Ar-*H*), 7.77 (m, 2H, Ar-*H*), 7.56 (s, 1H, Im-*H*), 7.04 (s, 1H, Im-*H*), 7.01 (s, 1H, Im-*H*), 4.25 (t, J = 6.7 Hz, 2H, N-C*H*$_2$-CH$_2$), 4.08 (t, J = 7.1 Hz, 2H, CH$_2$-C*H*$_2$-Im), 2.27 (m, 2H, CH$_2$-C*H*$_2$-CH$_2$); $^{13}C\{^1H\}$, δ 164.3 (*C*═O), 137.3 (Im-*C*), 134.5 (Ar-*C*), 131.7 (Ar-*C*), 131.5 (Ar-*C*), 129.7 (Im-*C*), 128.2 (Ar-*C*), 127.1 (Ar-*C*), 122.5 (Ar-*C*), 118.8 (Im-*C*), 45.1 (*C*H$_2$), 37.8 (*C*H$_2$), 29.8 (*C*H$_2$). HR ESI-MS: m/z 306.125 ([M + H]$^+$, calcd for $C_{18}H_{16}N_3O_2$ 306.124).

*Bis{dichloro[η^6-N-(phenylmethyl)(4-dimethylamino)-1,8-naphthalimide]ruthenium(II)} (**4a**).* **3a** (253 mg, 0.77 mmol, 4 equiv) and $RuCl_3{\cdot}3H_2O$ (50 mg, 0.19 mmol, 1 equiv) were refluxed in acetone/water (5/1, 30 mL) for 18 h, during which time an orange-

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brown precipitate formed. While hot, the solid was isolated by filtration, washed with diethyl ether (3 × 10 mL), and dried in vacuo. The solid was used in the next step without further purification. Yield: 69 mg (71%). NMR (d_6-DMSO): ^{1}H, δ 8.53 (d, J = 8.6 Hz, 1H, Ar-*H*), 8.48 (d, J = 7.0 Hz, 1H, Ar-*H*), 8.36 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.76 (m, 1H, Ar-*H*), 7.22 (d, J = 8.3 Hz, 1H, Ar-*H*), 6.04 (m, 4H, Ru-Ar-*H*), 5.83 (t, J = 5.4 Hz, 1H, Ru-Ar-*H*), 5.03 (s, 2H, CH_2), 3.11 (s, 6H, N-CH_3).

*Bis{dichloro[η^6-N-(phenylethyl)(4-dimethylamino)-1,8-naphthalimide]ruthenium(II)} (**4b**).* **3b** (265 mg, 0.77 mmol, 4 equiv) and $RuCl_3 \cdot 3H_2O$ (50 mg, 0.19 mmol, 1 equiv) were refluxed in acetone/water (5/1, 30 mL) for 4 h. While hot, the solution was filtered to remove a black solid and the filtrate was evaporated to dryness. The residue was suspended in hot EtOH (50 mL), and the undissolved solid was isolated by filtration, washed with diethyl ether (3 × 10 mL), and dried in vacuo. The solid was used in the next step without further purification. Yield: 36 mg (37%). NMR (d_6-DMSO): ^{1}H, δ 8.52 (d, J = 8.6 Hz, 1H, Ar-*H*), 8.43 (d, J = 6.9 Hz, 1H, Ar-*H*), 8.31 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.75 (m, 1H, Ar-*H*), 7.21 (d, J = 8.3 Hz, 1H, Ar-*H*), 5.93 (m, 2H, Ru-Ar-*H*), 5.80 (d, J = 6.0 Hz, 2H, Ru-Ar-*H*), 5.72 (t, J = 5.5 Hz, 1H, Ru-Ar-*H*), 4.35 (t, J = 6.5 Hz, 2H, CH_2), 3.10 (s, 6H, N-CH_3), 2.78 (t, J = 6.5 Hz, 2H, CH_2).

*Bis{dichloro[η^6-N-(phenylpropyl)(4-dimethylamino)-1,8-naphthalimide]ruthenium(II)} (**4c**).* **3c** (548 mg, 1.53 mmol, 4 equiv) and $RuCl_3 \cdot 3H_2O$ (100 mg, 0.38 mmol, 1 equiv) were refluxed in acetone/water (5/1, 60 mL) for 2 h. While hot, the solution was filtered to remove a black solid and the filtrate was evaporated to dryness. The residue was suspended in hot EtOH (50 mL) and the undissolved solid isolated by filtration, washed with diethyl ether (3 × 10 mL), and dried in vacuo. The solid was used in the next step without further purification. Yield: 88 mg (44%). NMR (d_6-DMSO): ^{1}H, δ 8.52 (d, J = 8.8 Hz, 1H, Ar-*H*), 8.47 (d, J = 6.9 Hz, 1H, Ar-*H*), 8.35 (d, J = 8.3 Hz, 1H, Ar-*H*), 7.76 (m, 1H, Ar-*H*), 7.23 (d, J = 8.3 Hz, 1H, Ar-*H*), 5.96 (m, 2H, Ru-Ar-*H*), 5.81 (d, J = 5.9 Hz, 2H, Ru-Ar-*H*), 5.71 (t, J = 5.5 Hz, 1H, Ru-Ar-*H*), 4.11 (t, J = 6.9 Hz, 2H, CH_2), 3.10 (s, 6H, N-CH_3), 3.05, (m, 2H, CH_2), 1.99 (m, 2H, CH_2).

*General Procedure for the Preparation of {Dichloro[η^6-N-(phenylalkyl)(4-dimethylamino)-1,8-naphthalimide](pta)-ruthenium(II)} (**5a–c**).* PTA (2 equiv) was added to a solution of the appropriate ruthenium dimer **4a–c** (1 equiv) in CH_2Cl_2/MeOH (2/1) and the solution was stirred at room temperature under N_2, with the extent of the reaction being monitored by ^{31}P{^{1}H} NMR spectroscopy. When deemed complete (by disappearance of free PTA at ca. −90 ppm), the solution was filtered and evaporated to dryness. The solid was redissolved in a minimum amount of CH_2Cl_2 and precipitated with Et_2O at −18 °C.

*{Dichloro[η^6-N-(phenylmethyl)(4-dimethylamino)-1,8-naphthalimide](pta)ruthenium(II)} (**5a**).* A solution of **4a** (50 mg, 0.05 mmol, 1 equiv) and PTA (16 mg, 0.10 mmol, 2 equiv) in CH_2Cl_2/MeOH (60 mL, 2/1) was reacted for 3 h. Workup gave **5a** as an orange-brown solid (50 mg, 73%). Mp: 225 °C dec. Anal. Calcd for $C_{27}H_{30}N_5O_2PCl_2Ru \cdot 2.5H_2O$: C, 46.02; H, 5.01; N, 9.94. Found: C, 46.03; H, 4.56; N, 9.85. IR ν (cm^{-1}): 1684, 1642, 1578, 1376, 1336, 1013, 970, 945, 777, 755, 742, 574. NMR (CD_2Cl_2): ^{1}H, δ 8.54 (d, J = 7.3 Hz, 1H Ar-*H*), 8.46 (m, 2H, Ar-*H*), 7.67 (m, 1H, Ar-*H*), 7.12 (d, J = 8.3 Hz, 1H, Ar-*H*), 6.10 (d, J = 6.2 Hz, 2H, Ru-Ar-*H*), 5.61 (m, 2H, Ru-Ar-*H*), 5.21 (t, J = 5.3 Hz, 1H, Ru-Ar-*H*), 4.94 (s, 2H, CH_2), 4.56 (s, 6H, PTA), 4.38 (s, 6H, PTA), 3.12 (s, 6H, N-CH_3); ^{31}P{^{1}H}, δ −34.12; ^{13}C{^{1}H}, δ 165.3 (*C*═O), 164.5 (*C*═O), 158.1 (Ar-*C*-NMe$_2$), 133.5 (Ar-*C*), 132.5 (Ar-*C*), 131.8 (Ar-*C*), 131.0 (Ar-*C*), 128.8 (Ar-*C*), 125.7 (Ar-*C*), 125.3 (Ar-*C*), 123.2 (Ar-*C*), 114.2 (Ar-*C*), 113.7 (Ar-*C*), 97.3 (d, J = 2 Hz, Ru-*C*), 91.6 (d, J = 5 Hz, Ru-*C*), 86.6 (d, J = 5 Hz, Ru-*C*), 83.5 (Ru-*C*), 74.0 (J = 7 Hz, N-CH$_2$–N, PTA), 45.1 (N-CH$_3$), 42.8 (CH$_2$) (second PTA signal under solvent, ca. 54 ppm). HR ESI-MS: m/z 660.063 ([M + H]$^+$, calcd for $C_{27}H_{31}N_5O_2PCl_2Ru$ 660.067).

*{Dichloro[η^6-N-(phenylethyl)(4-dimethylamino)-1,8-naphthalimide](pta)ruthenium(II)} (**5b**).* A solution of **4b** (50 mg, 0.05 mmol, 1 equiv) and PTA (15 mg, 0.10 mmol, 2 equiv) in CH_2Cl_2/MeOH (60 mL, 2/1) was reacted for 3 h. Workup gave **5b** as an orange-brown solid (37 mg, 57%). Mp: 178 °C dec. Anal. Calcd for $C_{28}H_{32}N_5O_2PCl_2Ru \cdot 0.5H_2O$: C, 49.26; H, 4.88; N, 10.27. Found: C, 49.24; H, 4.91; N, 10.33. IR ν (cm^{-1}): 1685, 1644, 1582, 1385, 1355, 1013, 970, 947, 780, 758, 576. NMR (CD_2Cl_2): ^{1}H, δ 8.49 (dd, J = 7.2, 1.1 Hz, 1H, Ar-*H*), 8.45 (dd, J = 8.5, 1.1 Hz, 1H, Ar-*H*), 8.41 (d, J = 8.2 Hz, 1H, Ar-*H*), 7.66 (dd, J = 8.5, 7.2 Hz, 1H, Ar-*H*), 7.11 (d, J = 8.4 Hz, 1H, Ar-*H*), 5.56 (m, 4H, Ru−Ar-*H*), 5.17 (t, J = 5 Hz, 1H, Ru-Ar-*H*), 4.51 (s, 6H, PTA), 4.47 (t, J = 7.3 Hz, 2H, Ar-CH_2), 4.28 (s, 6H, PTA), 3.11 (s, 6H, N-CH_3), 2.80 (t, 2H, J = 7.3 Hz); ^{31}P{^{1}H}, δ −34.15; ^{13}C{^{1}H}, δ 164.9 (*C*═O), 164.2 (*C*═O), 157.9 (Ar-*C*-NMe$_2$), 133.2 (Ar-*C*), 132.1 (Ar-*C*), 131.5 (Ar-*C*), 130.9 (Ar-*C*), 125.8 (Ar-*C*), 125.3 (Ar-*C*), 123.4 (Ar-*C*), 114.8 (Ar-*C*), 113.7 (Ar-*C*), 105.8 (d, J = 4 Hz, Ru-*C*), 88.8 (d, J = 6 Hz, Ru-*C*), 86.7 (d, J = 3 Hz, Ru-*C*), 80.1 (Ru-*C*), 73.93 (d, J = 7 Hz, N-CH$_2$-N, PTA), 45.2 (N-CH$_3$), 40.3 (CH$_2$), 32.9 (CH$_2$ (second PTA signal under solvent, ca. 54 ppm)). HR ESI-MS: m/z 674.079 ([M + H]$^+$, calcd for $C_{28}H_{33}N_5O_2PCl_2Ru$ 674.082).

*{Dichloro[η^6-N-(phenylpropyl)(4-dimethylamino)-1,8-naphthalimide](pta)ruthenium(II)} (**5c**).* A solution of **4a** (50 mg, 0.05 mmol, 1 equiv) and PTA (15 mg, 0.09 mmol, 2 equiv) in CH_2Cl_2/MeOH (60 mL, 2/1) were reacted for 3 h. Workup gave **5a** as an orange-brown solid (54 mg, 83%): Mp: 159 °C dec. Anal. Calcd for $C_{29}H_{34}N_5O_2PCl_2Ru \cdot 1.5H_2O$: C, 48.73; H, 5.22; N, 9.80. Found: C, 48.67; H, 5.04; N, 9.79. IR ν (cm^{-1}): 1684, 1643, 1581, 1386, 1360, 1241, 1013, 971, 947, 779, 757, 578. NMR (CD_2Cl_2): ^{1}H, δ 8.53 (d, J = 7.1 Hz, 1H Ar-*H*), 8.45 (m, 2H, Ar-*H*), 7.67 (m, 1H, Ar-*H*), 7.13 (d, J = 8.1 Hz, 1H, Ar-*H*), 5.54 (m, 4H, Ru-Ar-*H*), 5.10 (br t, 1H, Ru-Ar-*H*), 4.52 (s, 6H, PTA), 4.28 (s, 6H, PTA), 4.22 (t, J = 7.0 Hz, 2H, Ar-CH_2), 3.11 (s, 6H, N-CH_3), 2.57 (t, J = 7.2 Hz, 2H, CH_2), 2.06 (m, 2H, CH_2); ^{31}P{^{1}H}, δ −34.34; ^{13}C{^{1}H}, δ 165.1 (*C*═O), 164.5 (*C*═O), 157.7 (Ar-*C*-NMe$_2$), 133.1 (Ar-*C*), 132.0 (Ar-*C*), 131.4 (Ar-*C*), 130.9 (Ar-*C*), 128.9 (d, J = 9 Hz, Ru-*C*), 125.8 (Ar-*C*), 125.4 (Ar-*C*), 123.6 (Ar-*C*), 115.2 (Ar-*C*), 113.8 (Ar-*C*), 88.1 (Ru-*C*), 88.0 (Ru-*C*), 87.4 (Ru-*C*), 79.7 (Ru-*C*), 73.7 (br, N-CH$_2$-N, PTA), 52.6 (d, J = 17 Hz, P-CH$_2$, PTA), 45.2 (N-CH$_3$), 39.8 (CH$_2$), 30.9 (CH$_2$), 28.1 (CH$_2$). HR ESI-MS: m/z 688.095 ([M + H]$^+$, calcd for $C_{29}H_{35}N_5O_2PCl_2Ru$ 688.095).

*General Procedure for the Preparation of {Dichloro(η^6-arene)(N-[3-(imidazol-1-yl)propyl]-1,8-naphthalimide)ruthenium(II)} (**8a,b** and **9a,b**).* To a solution of either [Ru(η^6-*p*-cymene)Cl$_2$]$_2$ or [Ru(η^6-toluene)Cl$_2$]$_2$ (1 equiv) in CH_2Cl_2 (100 mL) the appropriate imidazole-linked naphthalimide **7a,b** (2 equiv) was added and the solution stirred at room temperature for 18 h. The solution was reduced in volume (ca. 10 mL) and filtered through a plug of Celite. Addition of diethyl ether to the filtrate resulted in the precipitation of a yellow or orange solid which was isolated by filtration, washed with diethyl ether (3 × 10 mL), and dried in vacuo.

*{Dichloro(η^6-*p*-cymene)(N-[3-(imidazol-1-yl)propyl](4-dimethylamino)-1,8-naphthalimide)ruthenium(II)} (**8a**).* [Ru(η^6-*p*-cymene)Cl$_2$]$_2$ (88 mg, 0.14 mmol, 1 equiv) and **7a** (100 mg, 0.29 mmol, 2 equiv) gave **8a** as an orange solid. Yield: 158 mg (84%). Mp: 174–175 °C. Anal. Calcd for $C_{30}H_{34}N_4O_2C_{l2}Ru \cdot 1.5H_2O$: C, 52.85; H, 5.47; N, 8.22. Found: C, 52.86; H, 5.28; N, 7.70. IR ν (cm^{-1}): 1691, 1647, 1576, 1391, 1370, 1358, 1245, 778, 158, 743, 662. NMR ($CDCl_3$): ^{1}H, δ 8.57 (d, J = 7.6 Hz, 1H, Ar-*H*), 8.47 (m, 2H, Ar-*H*), 7.70 (s, 1H, Im-*H*) 7.67 (m, 1H, Ar-*H*), 7.33 (s, 1H, Im-*H*), 7.13 (d, J = 8.2 Hz, 1H, Ar-*H*), 7.02 (s, 1H, Im-*H*), 5.45 (d, J = 6.0 Hz, 2H, Ar-*H*), 5.27 (d, J = 6.0 Hz, 2H, Ar-*H*), 4.21 (t, 2H, J = 6.7 Hz, N-CH_2-CH$_2$), 4.01 (t, J = 7.3 Hz, 2H, CH$_2$-CH_2-Im), 3.13 (s, 6H, N-CH_3), 2.99 (spt, J = 7.1 Hz, 1H, Ar-C*H*), 2.25 (m, 2H, CH$_2$-CH_2-CH$_2$), 2.18 (s, 3H, Ar-CH_3), 1.28 (d, J = 7.1 Hz, 6H, CH_3); ^{13}C{^{1}H}, δ 164.8 (*C*═O), 164.2 (*C*═O), 157.5 (Ar-*C*-NMe$_2$), 140.1 (Im-*C*), 133.1 (Ar-*C*), 132.2 (Im-*C*), 131.8 (Ar-*C*), 131.4 (Ar-*C*), 130.5 (Ar-*C*), 125.4 (Ar-*C*), 125.0 (Ar-*C*). 122.8 (Ar-*C*), 119.5 (Im-*C*), 114.5 (Ar-*C*), 113.5 (Ar-*C*), 102.8 (Ru-*C*), 97.4 (Ru-*C*), 82.7 (Ru-*C*), 81.7 (Ru-*C*), 46.1 (CH$_2$), 44.9 (N-CH$_3$), 37.1 (CH$_2$), 30.8 (Ar-CH-Me$_2$), 29.4 (CH$_2$), 22.5 (C-CH$_3$), 18.6 (Ar-CH$_3$). HR ESI-MS: m/z 619.139 ([M − Cl]$^+$, calcd for $C_{30}H_{34}N_4O_2ClRu$ 619.142).

*{Dichloro(η^6-*p*-cymene)(N-[3-(imidazol-1-yl)propyl]-1,8-naphthalimide)ruthenium(II)} (**8b**).* [Ru(η^6-*p*-cymene)Cl$_2$]$_2$ (100 mg,

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0.23 mmol, 1 equiv) and **7b** (100 mg, 0.7 mmol, 2 equiv) gave **8b** as an orange-yellow solid. Yield: 170 mg (85%). Mp: 163−164 °C. Anal. Calcd for $C_{28}H_{29}N_3O_2Cl_2Ru·H_2O$: C, 53.41; H, 4.97; N, 6.68. Found: C, 53.16; H, 4.96; N, 6.34. IR ν (cm^{-1}): 1697, 1656, 1588, 1439, 1387, 1346, 1234, 1093, 1056, 833, 779, 739. NMR ($CDCl_3$): ^1H, δ 8.61 (d, J = 7.4 Hz, 2H, Ar-*H*), 8.26 (d, J = 8.0 Hz, 2H, Ar-*H*), 8.01 (s, 1H, Im-*H*), 7.79 (m, 2H, Ar-*H*), 7.35 (s, 1H, Im-*H*), 7.02 (s, 1H, Im-*H*), 5.45 (d, J = 5.9 Hz, 2H, Ar-*H*), 5.27 (d, J = 5.9 Hz, 2H, Ar-*H*), 4.23 (t, J = 6.9 Hz, 2H, N-C*H*$_2$-CH$_2$), 4.03 (t, J = 7.1 Hz, 2H, CH$_2$-C*H*$_2$-Im), 2.99 (spt, J = 7.3 Hz, 1H, Ar-C*H*), 2.26 (m, 2H, CH$_2$-C*H*$_2$-CH$_2$), 2.19 (s, 3H, Ar-C*H*$_3$), 1.29 (d, J = 7.3 Hz, 6H, C*H*$_3$); $^{13}C\{^1H\}$, δ 164.4 (*C*═O), 140.1 (Im-*C*), 134.6 (Ar-*C*), 132.3 (Im-*C*), 131.8 (Ar-*C*), 131.7 (Ar-*C*), 128.3 (Ar-*C*), 127.2 (Ar-*C*), 122.4 (Ar-*C*), 119.5 (Im-*C*), 102.8 (Ru-*C*), 97.4 (Ru-*C*), 82.7 (Ru-*C*), 81.7 (Ru-*C*), 46.1 (*C*H$_2$), 37.4 (*C*H$_2$), 30.8 (Ar-*C*H-Me$_2$), 29.3 (*C*H$_2$), 22.4 (C-*C*H$_3$), 18.7 (Ar-*C*H$_3$). HR ESI-MS: m/z 576.097 ([M − Cl]$^+$, calcd for $C_{28}H_{29}N_3O_2ClRu$ 576.099).

*{Dichloro(η^6-toluene)(N-[3-(imidazol-1-yl)propyl](4-dimethylamino)-1,8-naphthalimide)ruthenium(II)} (**9a**).* [Ru(η^6-toluene)Cl$_2$]$_2$ (76 mg, 0.14 mol, 1 equiv) and **7a** (100 mg, 0.29 mmol, 2 equiv) gave **9a** as a yellow solid. Yield: 148 mg (84%). Mp: 140−141 °C. Anal. Calcd for $C_{27}H_{28}N_4O_2Cl_2Ru·1.5H_2O$: C, 50.70; H, 4.89; N, 8.76. Found: C, 50.62; H, 4.67; N, 8.16. IR ν (cm^{-1}): 1683, 1638, 1581, 1389, 1357, 844, 779, 757, 736, 659, 619. NMR ($CDCl_3$): ^1H, δ 8.57 (d, J = 7.2 Hz, 1H, Ar-*H*), 8.46 (m, 2H, Ar-*H*), 8.01 (s, 1H, Im-*H*), 7.68 (m, 1H, Ar-*H*), 7.35 (s, 1H, Im-*H*), 7.12 (d, J = 8.1 Hz, 1H, Ar-*H*), 7.03 (s, 1H, Im-*H*), 5.66 (m, 2H, Ar-*H*), 5.55 (t, J = 5.3 Hz, 1H, Ar-*H*), 5.33 (d, J = 5.7 Hz 2H, Ar-*H*), 4.21 (t, J = 6.8 Hz, 2H, N-C*H*$_2$-CH$_2$), 4.01 (t, J = 7.2 Hz, 2H, CH$_2$-C*H*$_2$-Im), 3.13 (s, 6H, N-C*H*$_3$), 2.27 (m, 2H, CH$_2$-C*H*$_2$-CH$_2$), 2.22 (s, 3H, Ar-C*H*$_3$); $^{13}C\{^1H\}$, δ 165.2 (*C*═O), 164.5 (*C*═O), 157.8 (Ar-*C*-NMe$_2$), 140.7 (Im-*C*), 133.4 (Ar-*C*), 132.6 (Im-*C*), 132.1 (Ar-*C*), 131.7 (Ar-*C*), 130.8 (Ar-*C*), 125.6 (Ar-*C*), 125.4 (Ar-*C*), 123.1 (Ar-*C*), 119.9 (Im-*C*), 114.7 (Ar-*C*), 113.7 (Ar-*C*), 99.9 (Ru-*C*), 86.6 (Ru-*C*), 80.1 (Ru-*C*), 79.8 (Ar-*C*), 46.4 (*C*H$_2$), 44.9 (N-*C*H$_3$), 37.4 (*C*H$_2$), 29.7 (*C*H$_2$), 19.5 (Ar-*C*H$_3$). HR-ESI MS: m/z 577.094 ([M − Cl]$^+$, calcd for $C_{27}H_{28}N_4O_2ClRu$ 577.095).

*{Dichloro(η^6-toluene)(N-[3-(imidazol-1-yl)propyl]-1,8-naphthalimide)ruthenium(II)} (**9b**).* [Ru(η^6-toluene)Cl$_2$]$_2$ (86 mg, 0.16 mmol, 1 equiv) and **7b** (100 mg, 0.33 mol, 2 equiv) gave **9b** as an orange-yellow solid. Yield: 157 mg (84%). Mp: 216 °C. Anal. Calcd for $C_{25}H_{23}N_3O_2Cl_2Ru·H_2O$: C, 51.10; H, 4.29; N, 7.16. Found: C, 51.46; H, 4.02; N, 7.03. IR ν (cm^{-1}): 1698, 1654, 1586, 1519, 1439, 1341, 1245, 1232, 1169, 1090, 1052, 897, 848, 779, 739, 653, 629, 540. NMR ($CDCl_3$): ^1H, δ 8.62 (d, J = 7.5 Hz, 2H, Ar-*H*), 8.26 (d, J = 8.6 Hz, 2H, Ar-*H*), 8.01 (s, 1H, Im-*H*), 7.79 (m, 2H, Ar-*H*), 7.36 (s, 1H, Im-*H*), 7.04 (s, 1H, Im-*H*), 5.67 (m, 2H, Ar-*H*), 5.56 (t, J = 5.4 Hz, 1H, Ar-*H*), 5.34 (d, J = 5.8 Hz, 2H, Ar-*H*), 4.24 (t, J = 6.8 Hz, 2H, N−C*H*$_2$-CH$_2$), 4.03 (t, J = 7.2 Hz, 2H, CH$_2$-C*H*$_2$-Im), 2.28 (m, 2H, CH$_2$-C*H*$_2$-CH$_2$), 2.24 (s, 3H, Ar-C*H*$_3$); $^{13}C\{^1H\}$, δ 164.4 (*C*═O), 140.4 (Im-*C*), 134.5 (Ar-*C*), 132.4 (Im-*C*), 131.8 (Ar-*C*), 131.7 (Ar-*C*), 128.3 (Ar-*C*), 127.2 (Ar-*C*), 122.4 (Ar-*C*), 119.6 (Im-*C*), 99.6 (Ru-*C*), 86.3 (Ru-*C*), 81.5 (Ru-*C*), 79.8 (Ru-*C*), 46.1 (*C*H$_2$), 37.4 (*C*H$_2$), 29.3 (*C*H$_2$), 19.2 (Ar-*C*H$_3$). HR ESI-MS: m/z 534.050 ([M − Cl]$^+$, calcd for $C_{25}H_{23}N_3O_2ClRu$ 534.052).

Photophysical Experiments with DNA. Freshly prepared solutions of ct-DNA (Sigma Aldrich) were used for all experiments. The DNA concentration (based on the nucleotide bases) was determined spectrophotometrically using an ε_{260} value of 6600 M^{-1} cm^{-1}. A solution of DNA in phosphate buffer (pH 7.4, 10 mM) gave a ratio of UV absorbance at 260 and 280 nm of ≥1.8, indicating the DNA was sufficiently free of protein contamination.

Cell Culture and Evaluation of the Anticancer Activity. The human A2780 and A2780cisR ovarian carcinoma and HEK (human embryonic kidney) cells were obtained from the European Collection of Cell Cultures (Salisbury, U.K.). A2780 and A2780R cells were grown routinely in RPMI-1640 medium, while HEK cells were grown with DMEM medium, with 10% fetal calf serum (FCS) and antibiotics at 37 °C and 5% CO_2. Cytotoxicity was determined using the MTT assay (MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide). Cells were seeded in 96-well plates as monolayers with 100 μL of cell solution (approximately 20 000 cells) per well and preincubated for 24 h in medium supplemented with 10% FCS. Compounds were prepared as DMSO solutions and then dissolved in the culture medium and serially diluted to the appropriate concentration, to give a final DMSO concentration of 0.5%. A 100 μL portion 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 a further 2 h. The culture medium was aspirated, and the purple formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in 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 three microcultures per concentration level.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR and HR-ESI MS spectra of selected compounds. 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.

Biography

Since 2008 Paul Dyson has been the chairman of the Institute of Chemical Sciences and Engineering at the Swiss Federal Institute of Technology in Lausanne (Ecole Polytechnique Fédérale de Lausanne, EPFL), having moved to the EPFL in 2002 to head the Laboratory of Organometallic and Medicinal Chemistry. He grew up in the U.K., completing his doctoral thesis in transition-metal carbonyl cluster chemistry at the University of Edinburgh. Prior to his appointment at the EPFL he held positions at the Imperial College of Science, Technology and Medicine (1994−1998) and the University of York (1998−2002) as a Royal Society University Research Fellow.

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