

# Anticancer Activity of Self-Assembled Molecular Rectangles via Arene–Ruthenium Acceptors and a New Unsymmetrical Amide Ligand

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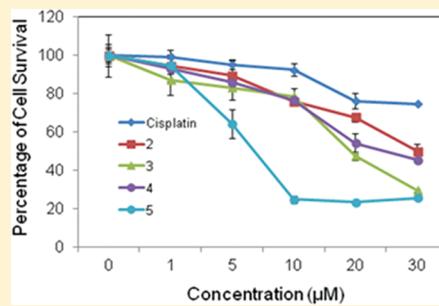
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## Supporting Information

**ABSTRACT:** Two new and large molecular rectangles **4** and **5** were synthesized from two different arene–ruthenium  $[\text{Ru}_2(\mu\text{-}\eta^4\text{-C}_2\text{O}_4)(\text{MeOH})_2(\eta^6\text{-}p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})_2][\text{O}_3\text{SCF}_3]_2$  (**2**) and  $[\text{Ru}_2(p\text{-cymene})_2(\text{donq})(\text{OH}_2)_2][\text{O}_3\text{SCF}_3]_2$  (**3**) acceptors and a new unsymmetrical *N*-(4-(pyridin-4-ylethynyl)phenyl) isonicotinamide (**1**) donor ligand. X-ray crystallography of **4** confirmed a molecular rectangle. The <sup>1</sup>H NMR spectra of both rectangles **4** and **5** showed a mixture of two structural, *head-to-tail* (HTT) and *head-to-head* (HTH), type isomers in a 1:1 ratio. The cytotoxicities of both rectangles have been established against Colo320 (colorectal cancer), A549 (lung cancer), MCF-7 (breast cancer), and H1299 (lung cancer) human cancer cell lines. The cytotoxicity of rectangle **5** was found to be considerably stronger against all cancer cell lines than that of the reference drug cisplatin.



## INTRODUCTION

In the last two decades, the metal-directed self-assembly of supramolecular architectures has attracted much attention, due to their promise for various applications, including molecular recognition,<sup>1</sup> separation materials,<sup>2</sup> catalysis,<sup>3</sup> host–guest chemistry,<sup>4</sup> and biology.<sup>5</sup> In particular, the coordination bonding motif of pyridyl-based ligands with metal acceptors has proven very useful for constructing a wide array of molecular architectures.<sup>6</sup> Most assemblies prepared to this date are highly symmetrical in nature as they are built from simple homodi- and tridentate pyridine-containing donors and metal acceptors.<sup>7</sup> A literature survey reveals that only a few unsymmetrical and ambidentate ligands have been successfully incorporated with discrete metallasupramolecules.<sup>8</sup> Among the several kinds of functionalities, the one that incorporates an ethynyl spacer in the backbone serves as an excellent substrate that endows interesting optical properties and rigidity to supramolecules.<sup>9</sup> Its rigid and  $\pi$ -conjugated structure makes the acetylene group an outstanding candidate for the construction of unsaturated molecular scaffolds.

The identification of new anticancer metal complexes is presently receiving a surge of interest due to their structural diversity and inimitable biological and medicinal properties arising from either covalent or noncovalent bindings/interactions with biomolecular cellular targets.<sup>10</sup> Metal–ligand coordination is a useful means to create bioactive molecules

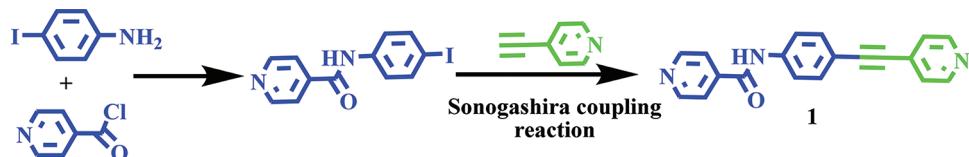
with structural complexity and functionalities by simple reactions. In these endeavors, ruthenium complexes are an attractive alternative to platinum-based anticancer agents because of their rich synthetic chemistry, variable oxidation states, accessibility under physiological conditions, selective antimetastatic properties, multiple mechanisms of action distinct from platinum-based drugs, and low systemic toxicity.<sup>11</sup> Two Ru(III) complexes, NAMI-A and KP1019, have successfully entered clinical trials for the treatment of metastatic solid tumors.<sup>12</sup> Therrien and co-workers have reported a half-sandwich ruthenium-based coordination cage that encapsulates the  $[\text{M}(\text{acac})_2]$  ( $\text{M} = \text{Pt}^{2+}, \text{Pd}^{2+}$ ) complexes with a synergic enhancement of their antitumor activity.<sup>13</sup> Recently, we have reported a new set of molecular rectangles constructed by the coordination-driven self-assembly approach and that were evaluated for in vitro anticancer activity.<sup>14</sup> The results suggested that larger rectangles show higher activity over small rectangles, in agreement with the hypothesis that large macromolecules are more retained inside cancer cells. Although a number of metallarectangles have been reported for host–guest chemistry or other properties,<sup>15</sup> only a few have been explored for their antitumor properties.<sup>14,16</sup>

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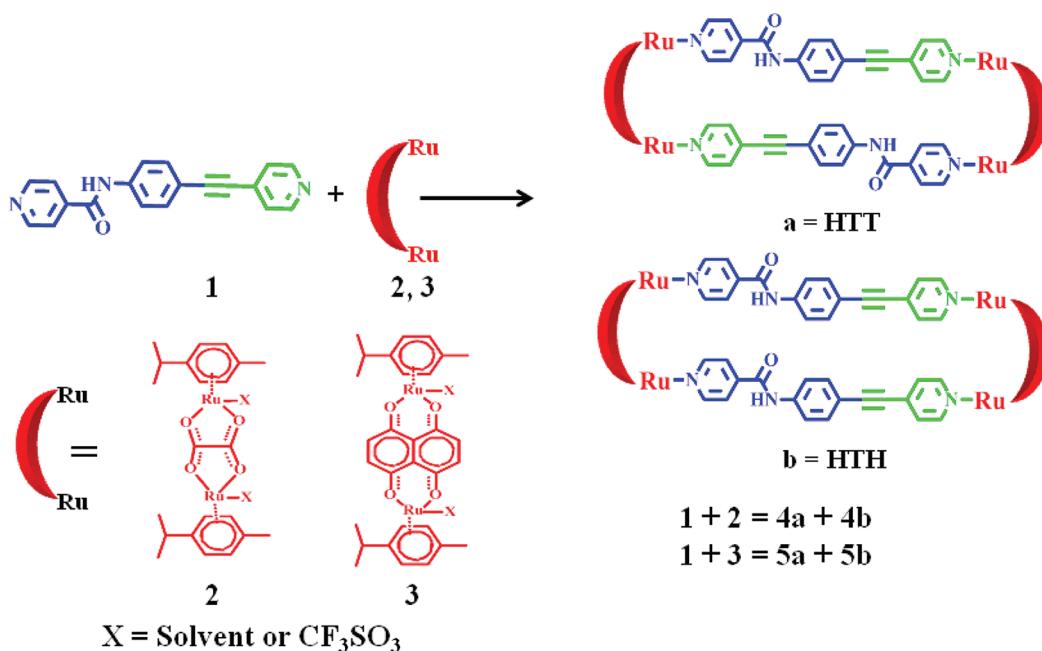
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Scheme 1. Synthesis of Unsymmetrical Amide Ligand 1



Scheme 2. Synthesis of Molecular Rectangles 4 and 5



In this paper, we report the synthesis and characterization of two new cationic molecular rectangles incorporating  $[\text{Ru}_2(\mu\text{-}\eta^4\text{-C}_2\text{O}_4)(\text{MeOH})_2(\eta^6\text{-}p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})_2][\text{O}_3\text{SCF}_3]_2$  (**2**) and  $[\text{Ru}_2(p\text{-cymene})_2(\text{donq})(\text{OH}_2)_2][\text{O}_3\text{SCF}_3]_2$  (donq = 5,8-dioxido-1,4-naphthaquinonato) (**3**) building blocks with a new *N*-(4-(pyridin-4-ylethynyl)phenyl) isonicotinamide (**1**) donor ligand and their cytotoxic activity against various cancer cell lines.

## RESULTS AND DISCUSSION

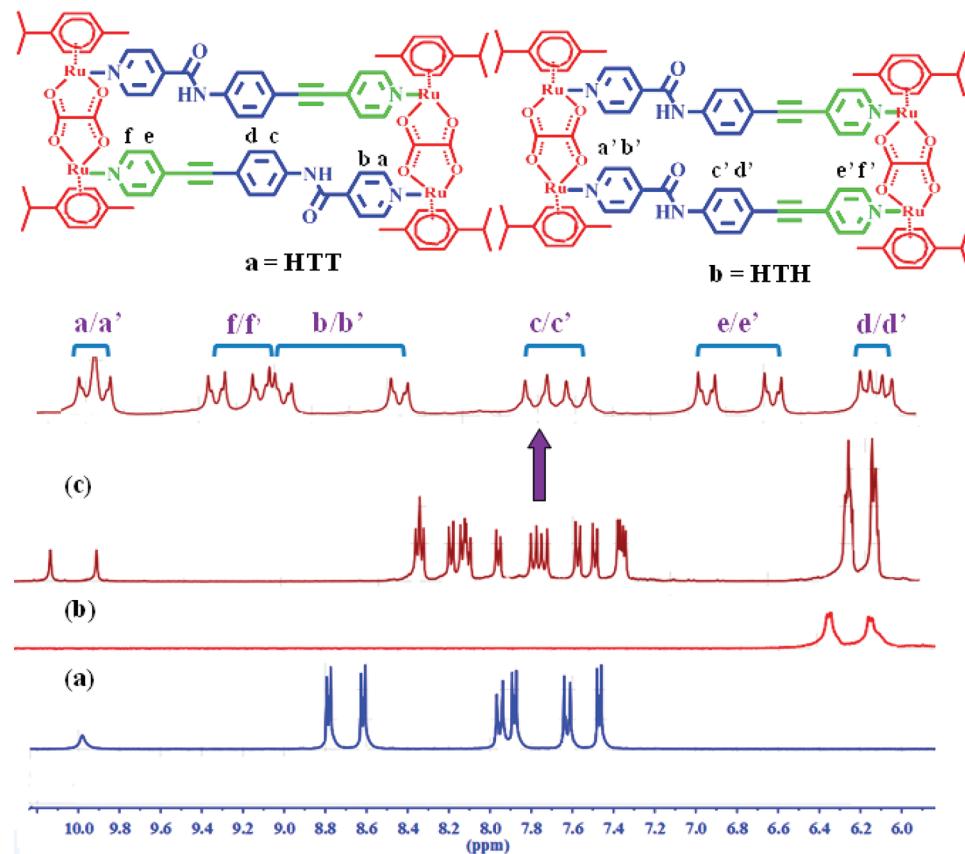
**Synthesis and Characterization of Ligand.** The starting ligand precursor (4-iodophenyl)-pyridine carbox-amide (PyI) was synthesized by coupling 4-iodo-aniline and isonicotinoyl chloride hydrochloride in  $\text{CH}_2\text{Cl}_2$  in the presence of triethylamine, followed by recrystallization from methanol/ $\text{H}_2\text{O}$  (yield 74%). The  $^1\text{H}$  NMR showed one sharp singlet for the NH at  $\delta$  10.67 in  $d_6\text{-DMSO}$ , and four aromatic resonances were found, indicating the presence of eight protons (Figure S1, Supporting Information). The ligand **1** was synthesized via Sonogashira coupling of (4-iodophenyl)pyridine carboxamide (PyI) and 4-ethynylpyridine in DMF solution (Scheme 1). In the IR spectrum of **1**, the NH and CO vibration stretching peaks for the amide linkage were observed at 3345 and 1650  $\text{cm}^{-1}$ , respectively, while the  $\text{C}\equiv\text{C}$  vibration stretching peak was obtained at 2245  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR showed one broad singlet for the NH at  $\delta$  9.97 in acetone- $d_6$ , and six aromatic resonances were found, indicating the presence of 12 protons (Figure S2, Supporting Information). The  $^{13}\text{C}$  NMR spectrum of the ligand was also simple, and all carbon centers were located easily (Figure S3, Supporting Information). The  $\text{C}\equiv\text{C}$

carbon peak was observed at 86 and 89 ppm, and the  $\text{C}=\text{O}$  peak was at 165 ppm.

**Synthesis and Characterization of Molecular Rectangles.** Ligand **1** was stirred with the  $[\text{Ru}_2(\mu\text{-}\eta^4\text{-C}_2\text{O}_4)(\text{MeOH})_2(\eta^6\text{-}p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})_2][\text{O}_3\text{SCF}_3]_2$  (**2**) and  $[\text{Ru}_2(p\text{-cymene})_2(\text{donq})(\text{OH}_2)_2][\text{O}_3\text{SCF}_3]_2$  (donq = 5,8-dioxido-1,4-naphthaquinonato) (**3**) acceptors, respectively, in acetone at room temperature for 6 h to generate the  $[2 + 2]$  systems. Precipitation with diethyl ether furnishes **4** and **5** as analytically pure solids. Two isomeric molecular rectangles are possible, as depicted in Scheme 2.

The evidence for the formation of two structural isomeric products came from the  $^1\text{H}$  NMR spectra, which showed two types of proton nuclei. In the  $^1\text{H}$  NMR spectrum of **4**, two different signals of amidic NH protons ( $\delta$  10.19 and 9.96 ppm) and two sets of aromatic protons were observed in the ratio of 1:1, as shown in Figure 1. Two sets of doublets corresponding to the pyridyl-H, (highlighted in Figure 1) may be assigned to the two isomers, generally referred to as *head-to-tail* (HTT) and *head-to-head* (HTH) (Scheme 2), and the relative stabilities of these isomers were consistent with previous observations in related systems.<sup>17</sup> Moreover, we observed the 0.5 ppm upfield shift of  $\text{H}_a$  and  $\text{H}_f$  protons as compared to ligand **1** (Figure 1). This shift was most likely due to the enhanced electron density at the metal center and was more pronounced for the  $\text{H}_a$  and  $\text{H}_f$  protons than for the other *N*-pyridine protons. The  $^1\text{H}$  NMR spectrum of complex **5** was very similar to that of **4** (Figure S4, Supporting Information).

Electrospray ionization mass spectrometry (ESI-MS) of complexes **4** and **5** were obtained to provide additional



**Figure 1.** Comparison of representative <sup>1</sup>H NMR spectra showing the aromatic portion of (a) amide ligand **1**, (b) Ru acceptor **2**, and (c) the self-assembled [2 + 2] rectangle **4** in acetone-*d*<sub>6</sub>.

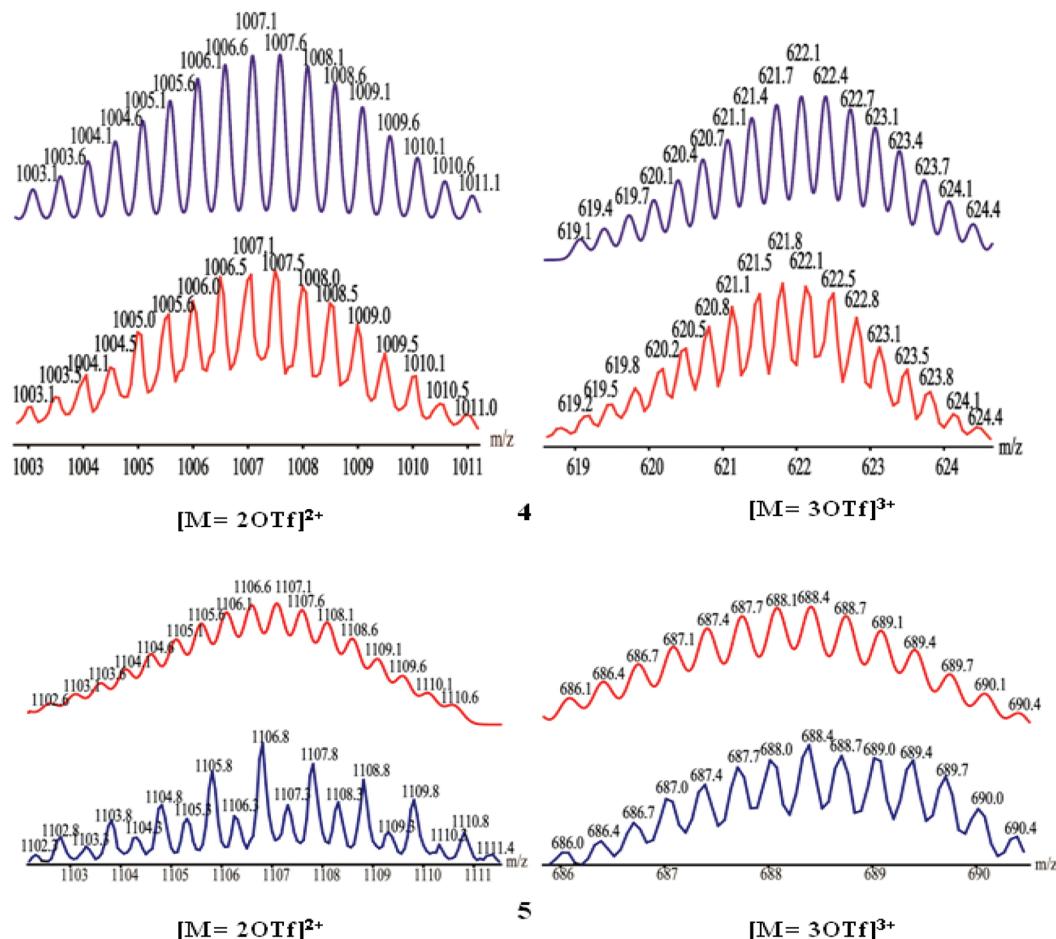
evidence for the formation of the molecular rectangles. The charged states for **4** at *m/z* = 1007.1 ([M - 2OTf]<sup>2+</sup>) and 621.8 ([M - 3OTf]<sup>3+</sup>) (Figure 2), and **5** at *m/z* = 1106.8 ([M - 2OTf]<sup>2+</sup>) and 688.4 ([M - 3OTf]<sup>3+</sup>) were clearly observed and isotopically resolved (Figure 2). These peaks matched well with the theoretical distributions.

X-ray crystallography unambiguously established the nanoscopic rectangular shape of the product **4**. Single crystals of **4** suitable for X-ray diffraction were grown at ambient temperature by vapor diffusion of diethyl ether into a concentrated acetone solution of the complex. The molecular structure of **4** is shown in Figure 3. However, only the head-to-tail isomer diffracted successfully. We were unable to crystallize the head-to-head isomer even after repeated recrystallization. X-ray analysis revealed that the two pyridine units bridge with two  $[(\text{Ru}_2(\mu-\eta^4-\text{C}_2\text{O}_4)(\eta^6-p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})_2)]^{4+}$  building blocks to form an M<sub>4</sub>L<sub>2</sub> rectangle. In the difference Fourier map, two independent structures were observed with similar geometries (Figure S6, Supporting Information). The bond distances of Ru1–N<sub>pyridine</sub> and Ru2–N<sub>pyridine</sub> are 2.13(2) and 2.10(1) Å, and the Ru3–N<sub>pyridine</sub> and Ru4–N<sub>pyridine</sub> distances are 2.12(1) and 2.06 (2) Å, respectively. The observed Ru–N and Ru–O distances are comparable to those found in oxalato-bridged tetracationic rectangles.<sup>14,15a</sup> Despite the head-to-tail fashion of ligand **1** binding to the Ru centers, the amide group carbonyl (–CO–) and NH moieties aligned in the opposite direction.

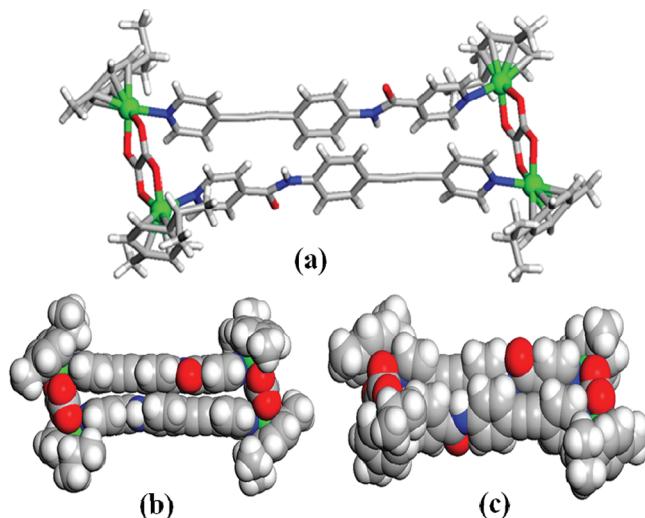
Electronic absorption spectra of **4** and **5**, along with their corresponding metal acceptors **2** and **3** and donor **1**, were also investigated. The absorption spectra of **4** and **5** in methanol solutions at  $1 \times 10^{-5}$  M concentration exhibit intense bands at

$\lambda_{\text{abs}} = 335$  and 337, 454 nm for **4** and **5** (Figure 4). The high-energy bands observed in both the rectangles **4** and **5** were also present in the spectra of the free ligand **1**. These bands are likely due to  $\pi \rightarrow \pi^*$  transitions of the ethynyl backbone, which are preserved upon self-assembly. The dinuclear arene–Ru acceptors exhibited energy absorption bands at 263, 319 and 320, 450 nm for **2** and **3**, respectively. These bands are likely a combination of intra/intermolecular  $\pi \rightarrow \pi^*$  transitions mixed with metal-to ligand charge-transfer transitions. As with the bands of the pyridyl donors, these arene–Ru-based bands are also preserved upon self-assembly, giving rise to strong absorption for **4** and **5**.<sup>6e</sup> The rectangle **4** gives a strong absorption band with respect to acceptor **2** red shifted by ~15 nm. Similar red shifts (~17 nm) are observed for the bands in **5**, which correspond to the absorption in donor **3**.

**In Vitro Anticancer Activity.** Metal-based drugs are widely used in clinical applications. Currently, organometallic arene–ruthenium(II) compounds are attracting considerable attention as antitumor agents.<sup>18–20</sup> To explore the potential biological effects of the interaction of these systems with biomolecules, we have evaluated ligand **1**, acceptors **2** and **3**, and metalarectangles **4** and **5** for their cytotoxicity against Colo320 (colorectal cancer), A549 (lung cancer), MCF-7 (breast cancer), and H1299 (lung cancer) cancer cell lines. All cancer cells were exposed for 24 h to increasing concentrations of the compounds, and their proliferation was determined using the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) cell proliferation assay. Cisplatin, a chemotherapeutic drug, was used as a control. On the basis of the results of the MTS assay, only one of the cell

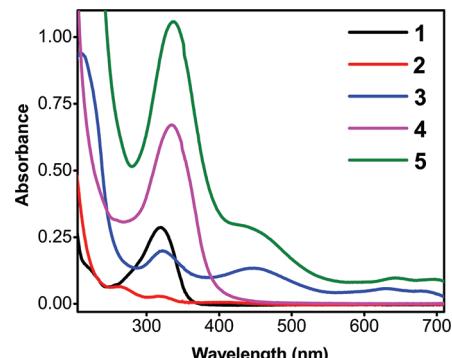


**Figure 2.** Theoretical (top) and experimental (bottom) ESI-MS results for self-assembled  $[2 + 2]$  rectangles 4 and 5.



**Figure 3.** (a) X-ray crystal structure of 4 showing the two  $\text{Ru}^{2+}$  ions (green) coordinated with four pyridine N atoms in head-to-tail mode. (b) and (c) side views are shown by the CPK model.

lines, Colo320, was found to be sensitive to cisplatin and the other three cell lines, such as A549, MCF-7, and H1299, were resistant to it. The comparative cytotoxicity of the ligand 1 and arene–ruthenium acceptors 2 and 3 with tetranuclear molecular rectangles 4 and 5 are presented in Table 1.



**Figure 4.** UV-visible spectra of 1–5 in methanol ( $1 \times 10^{-5}$  M) solution.

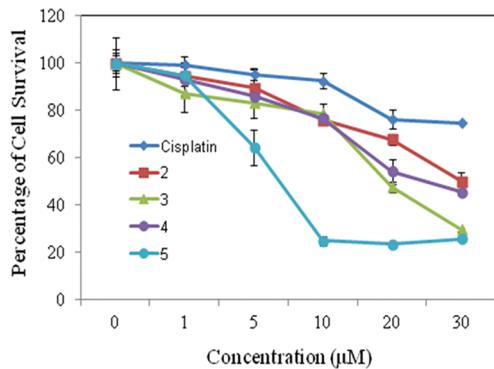
Interestingly, all four cell lines used in this study were highly sensitive to the rectangle 5, and their growths were effectively inhibited at a very low concentration (Table 1 and Figure 5). In particular, the rectangle 5 was found to inhibit the proliferation of H1299 cells with an  $\text{IC}_{50}$  of  $3.62 \mu\text{M}$ , whereas the rectangle 4, donor 1, and both arene–ruthenium acceptors 2 and 3 did not have any cytotoxic effect, as shown in Figure 5 and Table 1.

To determine the ability of rectangle 5 to induce apoptosis in cancer cells, H1299 cells were treated with  $10 \mu\text{M}$  rectangle 5 and cisplatin, respectively, for 12 h, after which they were stained with TUNEL and examined by FACS analysis. Whereas cisplatin caused apoptosis in 25% of H1299 cells, rectangle 5

**Table 1. Cytotoxicity of the Compounds 1–5 in Human Cancer Cells**

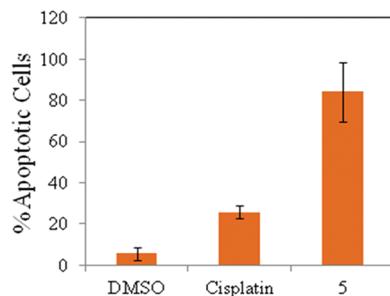
compound	<sup>a</sup> IC <sub>50</sub> (μM)			
	Colo320	A549	H1299	MCF7
cisplatin	38.6	>100	>100	>100
<b>1</b>	>100	70.98	>100	>100
<b>2</b>	51.01	40.94	>100	>100
<b>3</b>	12.95	18.05	>100	63.97
<b>4</b>	>100	38.86	>100	80.91
<b>5</b>	0.33	10.18	3.62	<0.1

<sup>a</sup>IC<sub>50</sub>: drug concentration necessary for 50% inhibition of cell viability.



**Figure 5.** Comparative cytotoxic effects of **2**, **3**, **4**, and **5** with cisplatin on the H1299 cancer cell line.

led to apoptosis in 84% of the cell population (Figure 6). This result suggested that the inhibitory effect of rectangle **5** on the



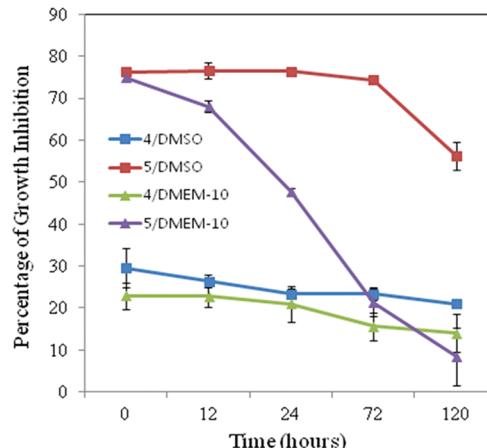
**Figure 6.** Analysis of rectangle-induced apoptosis of H1299 cells by TUNEL assay. DMSO and cisplatin were used as controls. Data represent means  $\pm$  SD of three independent experiments.

growth of cancer cells was obtained from the induction of apoptosis.

This result indicated that rectangle **5** was much more effective than cisplatin in the inhibition of cancer cell growth and might be a candidate for the development of a chemotherapeutic drug against cisplatin-resistant cancer cells. Although both rectangles have a mixture of two structural isomers, rectangle **5** was more cytotoxic than rectangle **4** in all the cancer cell lines. The reason for the enhanced cytotoxicity of **5** is not clear, but it can be related to the presence of extended aromaticity in the dhnq ligand.

Our next goal was to determine the stability of the growth-inhibitory activity of the rectangles in the cell culture medium. This was tested by preincubating 20 μM rectangle **4** or **5** in the culture medium with 10% FBS (DMEM-10) at 37 °C for

various times before adding them to H1299 cell cultures. As a control, the rectangles were preincubated in DMSO at 37 °C for the same times. As shown in Figure 7, a 50% loss in growth-



**Figure 7.** Loss of growth-inhibitory activity of the rectangles preincubated in culture medium. Rectangles **4** and **5** at 20 μM were preincubated in a cell culture medium containing 10% FBS and 100 μg of penicillin-streptomycin (DMEM-10) at 37 °C for indicated times before being added to cultures of H1299 cells. DMSO was used as a control.

inhibitory activity of the rectangle **5** was observed around 24 h of preincubation in the cell culture medium. On the contrary, in DMSO, its growth-inhibitory activity was stable until 72 h of preincubation. In the case of the rectangle **4**, consistent with the data shown in Figure 5, its growth-inhibitory activity was very low and we could not determine whether the preincubation affected its activity. It would be expected that the loss of growth-inhibitory activity parallels the loss of the rectangles from the medium, suggesting that the rectangle **5** may be stable for 24 h of preincubation in the cell culture medium. In addition, for stability studies, molecular rectangle **5** was dissolved in DMSO, and the sample was analyzed by <sup>1</sup>H NMR spectroscopy immediately after dissolution and after 48 h. No change was observed even after 48 h, thus attesting to the stability of the molecular rectangles in DMSO (Figure S5, Supporting Information).

**Stability of Rectangle 5 in the Presence of Thiol (GSH).** Previous work has shown that some complexes were reactive with glutathione, and other small molecular weight thiols.<sup>21</sup> To gain insight into the potential reactivity of the thiol group with **5**, its stability in the presence of thiol was investigated by using <sup>1</sup>H NMR spectroscopy. The <sup>1</sup>H NMR spectrum of **5** was unaffected by the addition of reduced glutathione (GSH) up to 24 h in a DMSO/H<sub>2</sub>O mixed solvent. There was no change in the characteristic chemical shifts of **5**, and the resonance peaks remained sharp, even in the presence of excess GSH. This result suggested that the thiol did not bind to the complex or displace the coordination sphere, thus attesting to the stability of the molecular rectangles in the presence of 10 equiv of thiol (Figure S5, Supporting Information).

## CONCLUSION

In conclusion, we report the synthesis of two new large molecular rectangles via self-assembly of a new unsymmetrical amide ligand and two different lengths of arene-ruthenium

acceptors. Both rectangles **4** and **5** were characterized by <sup>1</sup>H NMR and ESI-MS analysis. The solid-state structure of **4** was determined by a single-crystal X-ray diffraction study, confirming the rectangular structure assigned to these complexes. The <sup>1</sup>H NMR spectra of both rectangles showed a mixture of two structural isomers in a 1:1 ratio. The new self-assembled rectangles were further screened for in vitro anticancer activity, and the antitumor efficacy of rectangle **5** was found to be considerably stronger against all cell lines than that of cisplatin.

## EXPERIMENTAL SECTION

**Materials and Methods.** All chemicals used in this work were purchased from commercial sources and used without further purification. The starting acceptors [Ru<sub>2</sub>(μ-η<sup>4</sup>-C<sub>2</sub>O<sub>4</sub>)(MeOH)<sub>2</sub>](η<sup>6</sup>-p-Pr<sup>i</sup>C<sub>6</sub>H<sub>4</sub>Me)<sub>2</sub>][O<sub>3</sub>SCF<sub>3</sub>]<sub>2</sub> (**2**)<sup>15a</sup> and [Ru<sub>2</sub>(*p*-cymene)<sub>2</sub>(dmg)-(OH<sub>2</sub>)<sub>2</sub>][O<sub>3</sub>SCF<sub>3</sub>]<sub>2</sub> (**3**)<sup>20</sup> were prepared by reported procedures. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in a Bruker 300 MHz spectrometer. The chemical shifts ( $\delta$ ) in the <sup>1</sup>H NMR spectra are reported in parts per million relative to tetramethylsilane (Me<sub>4</sub>Si) as an internal standard (0.0 ppm). The infrared spectra (either as KBr pellets or as a mull in mineral oil) were recorded using a Varian 2000 FTIR spectrometer. Mass spectra were recorded on a Micromass Quattro II triple-quadrupole mass spectrometer using electrospray ionization (ESI) with a MassLynx operating system. Elemental analyses were performed by using the Elemental GmbH Vario EL-3 instrument.

**X-ray Diffraction Data for **4**.** Single crystals suitable for X-ray diffraction study of **4** were obtained by the vapor diffusion of diethyl ether to a acetone solution of the compound. A single crystal of rectangle **4** was mounted on a loop, and data were collected at 100 K on an ADSC Quantum 210 CCD diffractometer with a synchrotron radiation ( $\lambda = 1.00000 \text{ \AA}$ ) at Macromolecular Crystallography Beamline 6B1, Pohang Accelerator Laboratory (PAL), Pohang, Korea. The raw data were processed and scaled using the program HKL2000. The structure was solved by direct methods, and the refinements were carried out with full-matrix least-squares on  $F^2$  with appropriate software implemented in the SHELLXTL program package. The contributions of the disordered solvent molecules were removed from the diffraction data using the SQUEEZE routine of PLATON software (c.a. 876 e/u.c), and then final refinements were carried out. X-ray data for **4**: C<sub>83</sub>H<sub>82</sub>F<sub>3</sub>N<sub>6</sub>O<sub>13</sub>Ru<sub>4</sub>S,  $M = 1864.89$ , monoclinic,  $P2_1/c$  (No. 14),  $a = 34.156(7) \text{ \AA}$ ,  $b = 10.371(2) \text{ \AA}$ ,  $c = 27.318(6) \text{ \AA}$ ,  $\beta = 98.05(3)^\circ$ ,  $V = 9581(3) \text{ \AA}^3$ ,  $Z = 4$ ,  $T = 90 \text{ K}$ ,  $\mu(\text{synchrotron}) = 1.736 \text{ mm}^{-1}$ ,  $\rho_{\text{calc}} = 1.293 \text{ g}\cdot\text{cm}^{-3}$ , 18 743 reflections measured, 5913 unique ( $R_{\text{int}} = 0.0443$ ),  $R_1 = 0.0946$  ( $I > 2\sigma(I)$ ),  $wR_2 = 0.2883$  (all data), GOF = 1.190, 992 parameters and 852 restraints.

**Cancer Cell Growth Inhibition Assay (MTS Assay).** Human cancer cell lines, Colo320, A549, H1299, and MCF7, were purchased from the Korean Cell Line Bank (KCLB-Seoul, Korea). The cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat inactivated fetal bovine serum (FBS) and 100 μg of penicillin-streptomycin at 37 °C in a humidified atmosphere of 5% CO<sub>2</sub>. For the MTS cell proliferation assay, cells were plated in triplicate at 5.0 × 10<sup>4</sup> cells/well in 96-well culture plates in RPMI 1640 medium. Compounds **1–5** were preincubated in DMEM-10 or DMSO for the indicated times and added to the cells. After 24 h of incubation, MTS (CellTiter 96 Aqueous One Solution reagent, Promega, USA) was added to each well according to the manufacturer's instructions. Absorbance at 490 nm was determined for each well using a Victor 1420 multilabel counter (EG&G Wallac, Turku, Finland). The percentage of surviving cells was calculated from the ratio of absorbance of treated to untreated cells. The IC<sub>50</sub> values were obtained by fitting values to sigmoidal dose-response curves using the routines provided in GraphPad Prism.

**TUNEL Staining.** TUNEL staining was conducted using an in situ cell death detection kit, TMR Red, according to the protocol supplied by the manufacturer (Roche Molecular Biochemicals). Briefly, cells

were plated in 60 mm dishes at 2 × 10<sup>5</sup> cells/mL DMEM. The following day, the cells were treated with 10 μM cisplatin or 10 μM rectangle **5**, harvested, and fixed with 2% paraformaldehyde solution and permeabilized with 0.1% Triton X-100 in 0.1% sodium citrate. After washing twice with PBS (137 mM NaCl; 2.7 mM KCl; 4.3 mM Na<sub>2</sub>HPO<sub>4</sub>·7H<sub>2</sub>O; 1.4 mM KH<sub>2</sub>PO<sub>4</sub>; pH 7.2), cells were incubated in a TUNEL reaction mixture containing terminal deoxynucleotidyl transferase and tetramethyl-rhodamine-dUTP. Cells were analyzed for fluorescence intensity using a FACS flow cytometer (Becton Dickinson, Inc.).

**Reaction of **5** with L-Glutathione Reduced (GSH).** Aliquots of a solution of **5** in DMSO were added to solutions containing 2 or 10 equiv of GSH in D<sub>2</sub>O to give final millimolar concentrations in DMSO/D<sub>2</sub>O (1:1, v/v). <sup>1</sup>H NMR spectra were recorded at 1 and 24 h of reaction time.

**Synthesis of (4-Iodophenyl)pyridine Carboxamide (Pyl).** A solution of isonicotinoyl chloride hydrochloride (1.00 g, 5.60 mmol) and triethylamine (1.5 mL) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> was prepared and chilled at 0 °C in an ice bath for 5 min; then, 4-iodo aniline (1.35 g, 6.16 mmol) was added slowly to the cold solution over a period of 15 min. The reaction mixture was stirred at room temperature overnight. The resulting precipitate was collected on a frit, recrystallized with MeOH/H<sub>2</sub>O, and dried in a vacuum oven to afford a dark powder.

Yield: ca. 78% (1.45 g). Anal. Calcd for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O: C, 44.4; H, 2.80; N, 8.64; O, 4.94. Found: C, 44.35; H, 2.70; N, 8.63%; O, 5.11. <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO, 300 MHz, δ, ppm): 10.58 (s, 1H, CONH), 8.78 (d, 2H,  $J = 4.8 \text{ Hz}$ , H<sub>a</sub>), 7.84 (d, 2H,  $J = 5.1 \text{ Hz}$ , H<sub>b</sub>), 7.72 (d, 2H,  $J = 8.7 \text{ Hz}$ , H<sub>c</sub>), 7.62 (d, 2H,  $J = 8.7 \text{ Hz}$ , H<sub>d</sub>).

**Synthesis of N-(4-(Pyridin-4-ylethynyl)phenyl)-isonicotinamide(HL) 1.** In a flame-dried Schlenk flask, 4-ethynylpyridine hydrochloride (0.388 g, 2.77 mmol) and triethylamine (3 mL) were vigorously stirred for 20 min. During this time, a white precipitate formed. Thereafter, DMF (15 mL), Pd(PPh<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> (0.063 g, 0.09 mmol), CuI (0.012 g, 0.062 mmol), PPh<sub>3</sub> (0.016 g, 0.062 mmol), and (4-iodophenyl)pyridine-carboxamide (0.600 g, 1.851 mmol) were successively added. The Schlenk flask was wrapped in aluminum foil to keep the reaction mixture in the dark, and the mixture was refluxed for 24 h. The resulting brown precipitate was collected on a frit, washed several times with water, and was recrystallized with CH<sub>3</sub>OH/H<sub>2</sub>O (1:1). The yellow compound was filtered and dried under vacuum.

Yield: ca. 72% (0.4 g). Anal. Calcd for C<sub>19</sub>H<sub>13</sub>N<sub>3</sub>O: C, 76.24; H, 4.38%; N, 14.04; O, 5.35. Found: C, 76.35; H, 4.40; N, 14.13; O, 5.31. FT-IR spectrum (KBr, ν, selected peaks): 3345 (NH), 2250 (C≡C), 1650 (C=O) cm<sup>-1</sup>. <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone, 300 MHz, δ, ppm): 9.97 (s, 1H, CONH), 8.78 (d, 2H,  $J = 4.2 \text{ Hz}$ , H<sub>a</sub>), 8.61 (d, 2H,  $J = 4.2 \text{ Hz}$ , H<sub>f</sub>), 7.92 (d, 2H,  $J = 8.7 \text{ Hz}$ , H<sub>b</sub>), 7.88 (d, 2H,  $J = 8.7 \text{ Hz}$ , H<sub>c</sub>), 7.62 (d, 2H,  $J = 4.2 \text{ Hz}$ , H<sub>e</sub>), 7.46 (d, 2H,  $J = 4.2 \text{ Hz}$ , H<sub>d</sub>). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 300 MHz, δ, ppm): 164.23 (C=O, C<sub>4</sub>), 150.33 (C<sub>13</sub>), 149.36 (C<sub>1</sub>), 142.23 (C<sub>3</sub>), 140.10 (C<sub>5</sub>), 132.51 (C<sub>7</sub>), 130.26 (C<sub>11</sub>), 125.32 (C<sub>12</sub>), 122.10 (C<sub>6</sub>), 120.28 (C<sub>2</sub>), 116.60 (C<sub>8</sub>), 94.05 (C<sub>9</sub>), 86.56 (C<sub>10</sub>).

**Synthesis of Molecular Rectangle **4**.** The ligand **1** (0.006 g, 0.020 mmol) and solid [Ru<sub>2</sub>(μ-η<sup>4</sup>-C<sub>2</sub>O<sub>4</sub>)(MeOH)<sub>2</sub>](η<sup>6</sup>-p-Pr<sup>i</sup>C<sub>6</sub>H<sub>4</sub>Me)<sub>2</sub> [**2**] (0.018 g, 0.020 mmol) were suspended in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH (1:1, 1 mL), and the resulting mixture was then stirred for 6 h at room temperature. The reaction mixture was filtered, followed by the removal of the solvent under reduced pressure, and the product was washed with diethyl ether. The crude product thus obtained was redissolved in acetone and subjected to vapor diffusion of diethyl ether. This resulted in the highly crystalline product within a day. The product was filtered and dried under vacuum. Yield: ca. 92% (0.022 g). Anal. Calcd for C<sub>86</sub>H<sub>86</sub>F<sub>12</sub>N<sub>6</sub>O<sub>22</sub>Ru<sub>4</sub>S<sub>4</sub>: C, 44.60; H, 3.74; N, 3.63. Found: C, 44.80; H, 3.72; N, 3.60. FT-IR spectrum (KBr, ν, selected peaks): 3340 (NH), 2245 (C≡C), 1620 (C=O) cm<sup>-1</sup>. MS (ESI) calcd for [M - 3OTf]<sup>2+</sup> *m/z* 1007.1, found 1007.1; calcd for [M - 3OTf]<sup>3+</sup> *m/z* 622.1, found 622.1. <sup>1</sup>H NMR (*d*<sub>6</sub>-acetone, 300 MHz, δ, ppm): 10.18 (s, H, CONH), 9.94 (s, H, CONH), 8.30–8.20 (m, 8H, H<sub>a</sub>/H<sub>a'</sub>), 8.13–8.08 (m, 8H, H<sub>f</sub>/H<sub>f'</sub>), 8.02–7.89 (m, 8H, H<sub>b</sub>/H<sub>b'</sub>), 7.70–7.62 (m, 8H, H<sub>c</sub>/H<sub>c'</sub>), 7.47–7.39 (m, 8H, H<sub>e</sub>/H<sub>e'</sub>), 7.26–7.23 (m, 2H, H<sub>d</sub>/H<sub>d'</sub>), 6.10 (m, 16H; -C<sub>6</sub>H<sub>4</sub>), 5.94 (m, 16H, -C<sub>6</sub>H<sub>4</sub>), 2.86

(m, 8H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.28–2.27 (m, 24H;  $-\text{CH}_3$ ), 1.39–1.36 (m, 48H;  $-\text{CH}(\text{CH}_3)_2$ ).

**Synthesis of Rectangle 5.** The synthesis was performed as described for rectangle 4 except that the  $[\text{Ru}_2(p\text{-cymene})_2(\text{donq})(\text{OH}_2)_2][\text{O}_3\text{SCF}_3]_2$  (donq = 5,8-dioxyo-1,4-naphthaquinonato) (3) acceptor was used, and the product was isolated as a green crystalline solid.

Yield: ca. 91%. Anal. Calcd for  $\text{C}_{80}\text{H}_{86}\text{F}_{12}\text{N}_6\text{O}_{22}\text{Ru}_4\text{S}_4$ : C, 48.76; H, 3.61; N, 3.35. Found: C, 48.80; H, 3.72; N, 3.40. FT-IR spectrum (KBr,  $\nu$ , selected peaks): 3342 (NH), 2247 ( $\text{C}\equiv\text{C}$ ), 1633 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ . MS (ESI) calcd for  $[\text{M} - 3\text{OTf}]^{3+}$   $m/z$  755.4, found 755.6.  $^1\text{H}$  NMR ( $d_6$ -acetone, 300 MHz,  $\delta$ , ppm): 10.04 (s, H, CONH), 10.01 (s, H, CONH), 8.72–8.68 (m, 8H,  $\text{H}_a/\text{H}'_a$ ), 8.55–8.53 (m, 8H,  $\text{H}_b/\text{H}'_b$ ), 7.93–7.85 (m, 8H,  $\text{H}_c/\text{H}'_c$ ), 7.83–7.78 (m, 8H,  $\text{H}_d/\text{H}'_d$ ), 7.51–7.48 (m, 8H,  $\text{H}_e/\text{H}'_e$ ), 7.43–7.40 (m, 8H,  $\text{H}_f/\text{H}'_f$ ), 7.31–7.30 (d, 16H,  $\text{H}_{ar}$ ), 6.02 (m, 16H;  $-\text{C}_6\text{H}_4$ ), 5.82 (m, 16H,  $-\text{C}_6\text{H}_4$ ), 3.08 (m, 8H,  $-\text{CH}(\text{CH}_3)_2$ ), 2.28 (m, 24H;  $-\text{CH}_3$ ), 1.49–1.35 (m, 48H;  $-\text{CH}(\text{CH}_3)_2$ ).

## ASSOCIATED CONTENT

### Supporting Information

Supporting Information available:  $^1\text{H}$  NMR spectra of starting PyI and ligand 1,  $^{13}\text{C}$  NMR spectrum of ligand 1,  $^1\text{H}$  NMR spectrum of 5 in acetone- $d_6$ , comparative  $^1\text{H}$  NMR spectrum of 5 with and without GSH, X-ray crystal structure of rectangle 4 with two independent molecules, and table of bond lengths and angles for 4. 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.

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