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Self-assembly of novel thiophene-based BODIPY Ru(II) rectangles: Potential antiproliferative agents selective against cancer cells

Gajendra Gupta,*[+][a] Abhishek Das,[+][b] Sourav Panja,[b] Ji Yeon Ryu,[c] Junseong Lee,[c] Nripendranath Mandal,*[b] and Chang Yeon Lee*[a,d]

Dedication ((optional))

Abstract: Novel Ru (2+2) rectangles were designed and synthesized by self-assembly of a new thiophene-functionalized dipyridyl BODIPY ligand, BDPS, and ruthenium (II) precursors. The complexes exhibited dose-dependent antiproliferative activities against cancer cells, where some compounds selectively kill cancer cells. The net fluorescence due to BODIPY allowed us to visualize their location inside cancer cells. Moreover, the metalla-rectangles displayed substantial propensity to bind with biomolecules.

Coordination-driven self-assembly is one of the most convenient and useful techniques to synthesize complex supramolecules, owing to its simplicity.[1] The reactions are easily performed using appropriate electron-donor ligands with different electron-deficient metal-centred precursors. Various metal-centred precursors are widely used to synthesize a library of supramolecules such as triangles, squares, rectangles, prisms, and cubes, among others.[2] In particular, arene-linked ruthenium metal supramolecules have been widely studied in the last decade owing to their interesting structures and vital applications in catalysis, drug-delivery, and host-guest chemistry.[1] Despite the popularity of platinum-containing drugs such as Cisplatin, Carboplatin, and Oxaliplatin, their use is highly restricted by their efficacy against only a limited range of cancers, owing to drug resistance and severe side effects, *viz*. nephrotoxicity, nausea, and bone marrow suppression.[3a] Other metal-based drugs such as ruthenium complexes, which exhibit ligand exchange kinetics akin to platinum drugs, are an intriguing avenue of research. Moreover, tailoring these drugs to increase cancer cell selectivity, minimize drug resistance, and reduce side effects would greatly improve drug efficacy and patients' quality of life. Ruthenium-based metal drugs are potential candidates owing to their low toxicity to normal cells and a dissimilar mode of action.[3b] In general, cationic metal complexes form crosslinks with DNA, causing hydrolysis and redox or photoreactions in living cells.[3c]

Boron dipyrromethene (BODIPY) is a class of fluorescent dyes used for many applications such as light harvesting, photodynamic therapy, imaging, and in solar cells.[4] Although a large number of BODIPY-based compounds have been synthesized and studied, metal-conjugated BODIPY supramolecules are understudied. Recently, BODIPY-based palladium, platinum, iron, and zinc supramolecules have been synthesized by self-assembly and analysed for their host-guest chemistry and biological properties.[5] Inspired by these properties of BODIPY-based supramolecules, we recently designed, synthesized, and studied the antiproliferative activities of new ruthenium and iridium metalla-rectangles.[6] Drugs containing thiophene moieties are quite popular among the practitioners due to their wide range of pharmacological efficacies.[7] In the field of anticancer drugs, medicines containing thiophene group have also been reported.[7a] Therefore, in order to further improve the biological activities of ruthenium based complexes, herein, we designed a new thiophene-functionalized BODIPY ligand, BDPS, and used this ligand to synthesize four new Ru (2+2) rectangles by self-assembly. To investigate their activities against cells *in vitro*, rectangles **1**-**4** were studied in different cell lines and the presence of these rectangles inside cancer cells was further demonstrated by confocal laser scanning microscopy.

The thiophene-functionalized dipyridine BODIPY ligand, BDPS, was synthesized in five steps by the Suzuki-Miyaura coupling reaction, which resulted in moderate yield (Scheme S1). The starting dinuclear arene-ruthenium precursors $[Ru_2(p\text{-}cymene)_2(L)Cl_2]$ (L = oxalato, 2,5-diydroxy-1,4-benzoquinone, 5,8-dihydroxy-1,4-naphthoquinone and 1,4-dihydroxyanthraquinone) were mixed with $AgCF_3SO_3$ in

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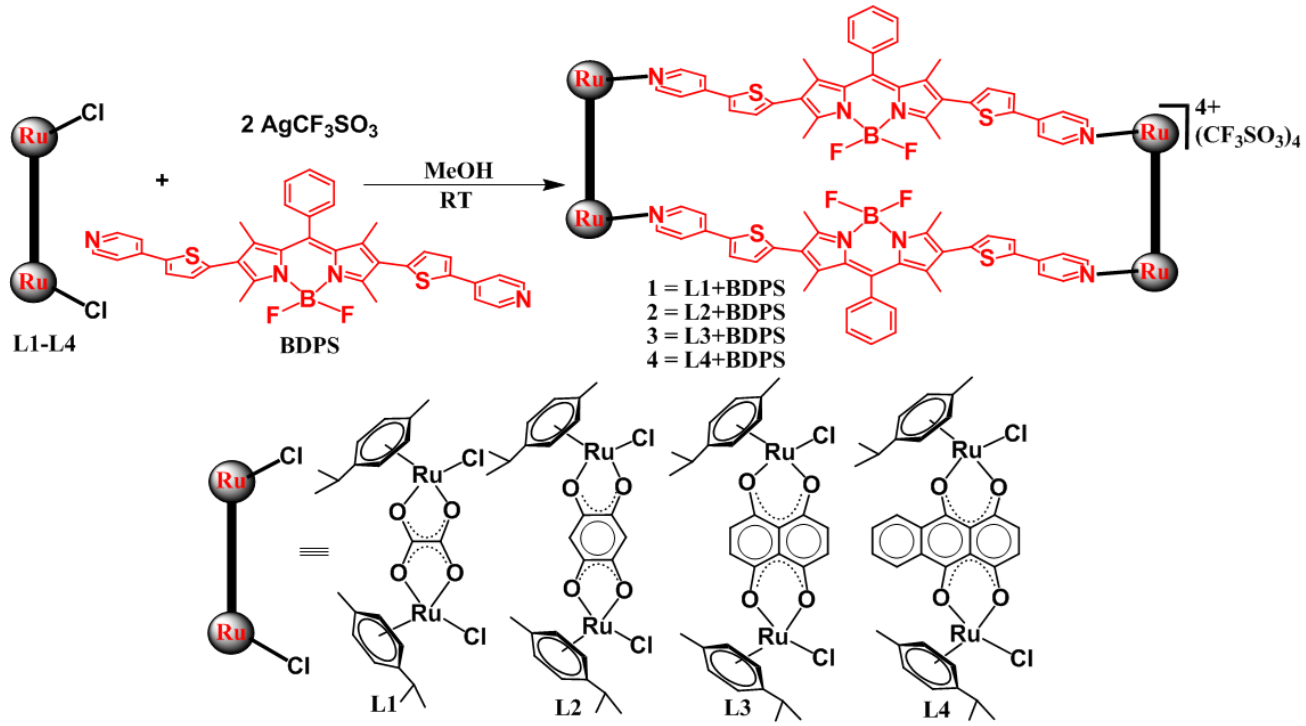

Scheme 1. Reaction scheme for the synthesis of metalla-rectangles **1**-**4**.

methanol and stirred for 3 h. AgCl salt formed was removed by filtration. BDPS ligand was then added and the mixture stirred at room temperature for 24 h, yielding four new cationic, tetranuclear, metalla-rectangles **1**-**4** (scheme 1). The complexes were obtained as their triflate salts and are soluble in common organic solvents. Spectroscopic analyses confirmed the formation of the desired (2+2) metalla-rectangles **1**-**4**. The ^{1}H NMR spectra of the BDPS ligand and the rectangles showed well-defined peaks displaying the expected resonances for these complexes (Fig. S1 & S2). The ^{1}H NMR spectra of the free BDPS ligand indicated peaks at 8.59 and 7.46 ppm, which belong to the H_{α} and H_{β} protons of the pyridine group of this ligand, respectively. However, after metalation, the H_{α} protons had shifted upfield whereas the H_{β} protons shifted downfield in comparison to the free ligand. These data confirm the coordination of the ligands to the metal centres in these rectangles. Electrospray ionization mass spectrometry (ESI-MS) were further used to study the formation of these supramolecules **1**-**4**. The MS spectra confirmed the formation of these metalla-rectangles and showed di, tri, and tetracationic peaks corresponding to the loss of two, three, and four triflate anions: $[M\text{-}2CF_3SO_3]^{2+}$, $[M\text{-}3CF_3SO_3]^{3+}$, and $[M\text{-}4CF_3SO_3]^{4+}$, respectively (Fig. S3), where rectangles maintained good stability. The peaks at m/z = 600.15, 850.19, 1350.04 for **1**; 625.56, 883.92, 1400.04 for **2**; 650.69, 917.03, 1450.11 for **3** correspond to the loss of two, three and four triflate anions for complexes **1**-**3**, respectively. The peak at m/z 1501.11 correspond to the loss of four triflate anions for complex **4**. The peaks were isotopically resolved and matched well with its theoretical distributions (Fig. S3).

Single crystals suitable for X-ray diffraction studies were obtained for rectangles **1** and **2** by slow vapor diffusion of diethyl ether into a nitromethane solution of these complexes. The single crystal structures of both these complexes unequivocally confirmed the formation of (2+2) tetranuclear rectangular architectures (Fig. 1). The overall geometry around the ruthenium centre corresponds to the characteristic piano-stool configuration where metals are capped by *p*-cymene ligands. The BDPS ligands act as a bridge between the metal centres to form the rectangular structure. The phenyl groups of the BDPS ligands in these structures were directed away from each other, likely due to their steric bulkiness.

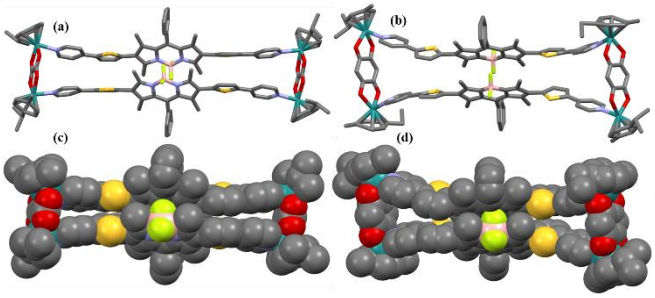

Figure 1. X-ray structures of metalla-rectangles (a) **1** and (b) **2** and their space-filling model (c) and (d).

The UV-Vis absorption and fluorescence spectroscopy of BDPS and rectangles **1**-**4** was studied using solvents of different polarities (Fig. 2 & Fig. S5). Interestingly, a

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bathochromic effect of up to 20 nm was observed upon insertion of the thiophene group in the BDPS ligand compared to the thiophene free ligand.[6] The visible region of rectangles **1**-**4** was dominated by an intense peak around 525 nm, which corresponded to the vibration band of the *π*-*π** transition localised on the BDPS chromophores of these complexes. A blue shift of up to 10 nm was observed in these complexes compared to the free BDPS ligand. In addition, two strong, high-energy absorption bands shouldered at approximately 402 and 318 nm were observed and could be assigned due to the combination of intra/intermolecular *π*-*π** transitions mixed with MLCT transitions. The emission spectra of the BDPS ligand and the rectangles were also measured in different solvents. The rectangles were highly fluorescent with an emission peak at approximately 630 nm corresponding to the BDPS chromophore. In dichloromethane, rectangles **1** and **2** showed an interesting red shift of approximately 25 nm in its emission spectra (Fig. 2). This behaviour was not observed using solvents with increased polarity. The absorption and emission spectra are summarised in Fig. S5.

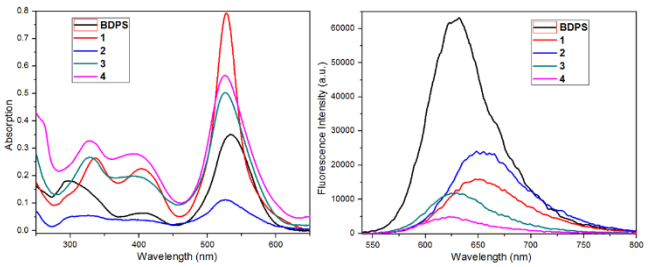

Figure 2. Absorption (left) and emission (right) spectra of BDPS and rectangles **1**-**4** in CH_2Cl_2.

The activities of complexes **1**-**4** against cancer cells were determined using cell lines of different origins, including breast (MCF-7), cervical (HeLa), and brain (U87) cancers, and results were compared with those of non-malignant WI38 cells. Complexes **1**-**4** were found to selectively kill MCF-7 cells while exhibiting relatively low toxicity in WI38 cells (Table 1; Fig. S7). Moreover, complexes **3** and **4** were more effective than cisplatin. Complex **3** showed selective toxicity at lower doses compared to the other compounds against U87 cells (Fig. S7). Overall, HeLa cells exhibited higher resistance against the compounds, although complexes **1** and **2** had lower IC_{50} values compared to that in WI38 cells. Thiophene compounds are activated chiefly by cytochrome P450 mediated oxidation which result in various electrophilic intermediates.[7b] Thiophene containing compounds have potent antioxidant activities.[8a] Now due to the anomalous mitochondrial function in the cancer cells owing to their increased production of reactive oxygen species (ROS) compared to that in normal cells that leads to oxidative stress,[8b] thiophene compounds further disrupt the redox balance particularly in cancer cells, which may aid to their selective action. Our previous studies measured the antiproliferative activities of BODIPY-based ruthenium and iridium rectangles, concluding that some complexes displayed varying degrees of selectivity in killing cancer cells over normal WI38 cells.[6] In this study, we incorporated a thiophene group into the BODIPY ligand with the aim of improving their selectivity. Our results are supported by the low cytotoxicity observed for rectangles **1** and **2** in normal WI38 cells (Table 1; Fig. S7). For same reason, such selectivity was also evident in the BDPS ligand against all cells although yielding high IC_{50} values in most cases. It may be noted that every complex has two BDPS ligands and therefore there is a fair possibility that the activity of BDPS itself has a major role to play in the toxicities of the complexes. Although, there is no sufficient evidence to ensure whether this activity is cumulative or synergistic. Additionally, we had tested the activities of **L1**-**L4** on proliferation of cancer cells (Table S1). Interestingly, Linker **L3** projected a comparatively higher IC_{50} value in all the cell lines than the other linkers. In U87 **L3** showed the highest activity, though it was still nearly 2.5 times lesser than that of its associating complex **3** (Table SI 1). Similar trend was evident in MCF-7 as well, but not HeLa. This imparts the fact that activity of complex **3** may be primarily attributed to **L3**.[1d]

Table 1. IC_{50} (μM) values of **1**-**4**, BDPS, and Cisplatin in different cell lines.

Compounds*	MCF-7	HeLa	U87	WI38
1	25.55 ± 1.82	215.77 ± 51.29	370.51 ± 47.18	936.67 ± 160.13
2	40.21 ± 1.30	374.13 ± 62.03	291.88 ± 40.50	> 2000
3	10.54 ± 0.72	44.96 ± 1.80	6.55 ± 0.35	17.86 ± 1.52
4	11.29 ± 0.59	644.11 ± 94.07	120.59 ± 25.69	92.12 ± 8.32
BDPS	39.47 ± 3.64	471.11 ± 88.89	441.41 ± 70.45	> 5000
CISPLATIN	16.13 ± 0.87	8.44 ± 0.98	6.06 ± 0.12	77.25 ± 7.28

* IC_{50} values of complexes **1**-**4** are inclusive of the effects of two BDPS molecules in each complex.

Propidium iodide (PI) binding to DNA can be used to determine the amount of DNA in G1, S, and G2/M cell cycle phases as well as post-apoptotic, fragmented nuclear DNA (as a sub-G1 peak) when analysed by flow cytometry.[9] Cell cycle-dependent distributions of only those compounds that exhibited selectivity for U87 and MCF-7 cells were measured using this technique and the same were considered for further experiments. **1** and **2** were not considered for analyses with U87 cells due to their comparatively many folds higher IC_{50} values than those with MCF-7 cells (Table 1), even though they had showed selectivity. Although an exception has been made in case of HeLa cells. We speculated that, despite comparatively higher IC_{50} values, it would have been interesting to observe the behaviour of the complexes against HeLa cells, as previously a similar ruthenium complex was found to be the only example with which we had observed nuclear localization in these cells under a confocal microscope.[6] Dose ranges for compounds were determined based on their cytotoxicity results. At 30 μM, complexes **1** and **2** substantially compromised the cell-cycle distribution, and at 50 μM, 23.62% and 34.26% of cells were observed in the sub-G1 population, respectively (Fig. S8; A-D). Complex **3** exhibited a dose-dependent increase

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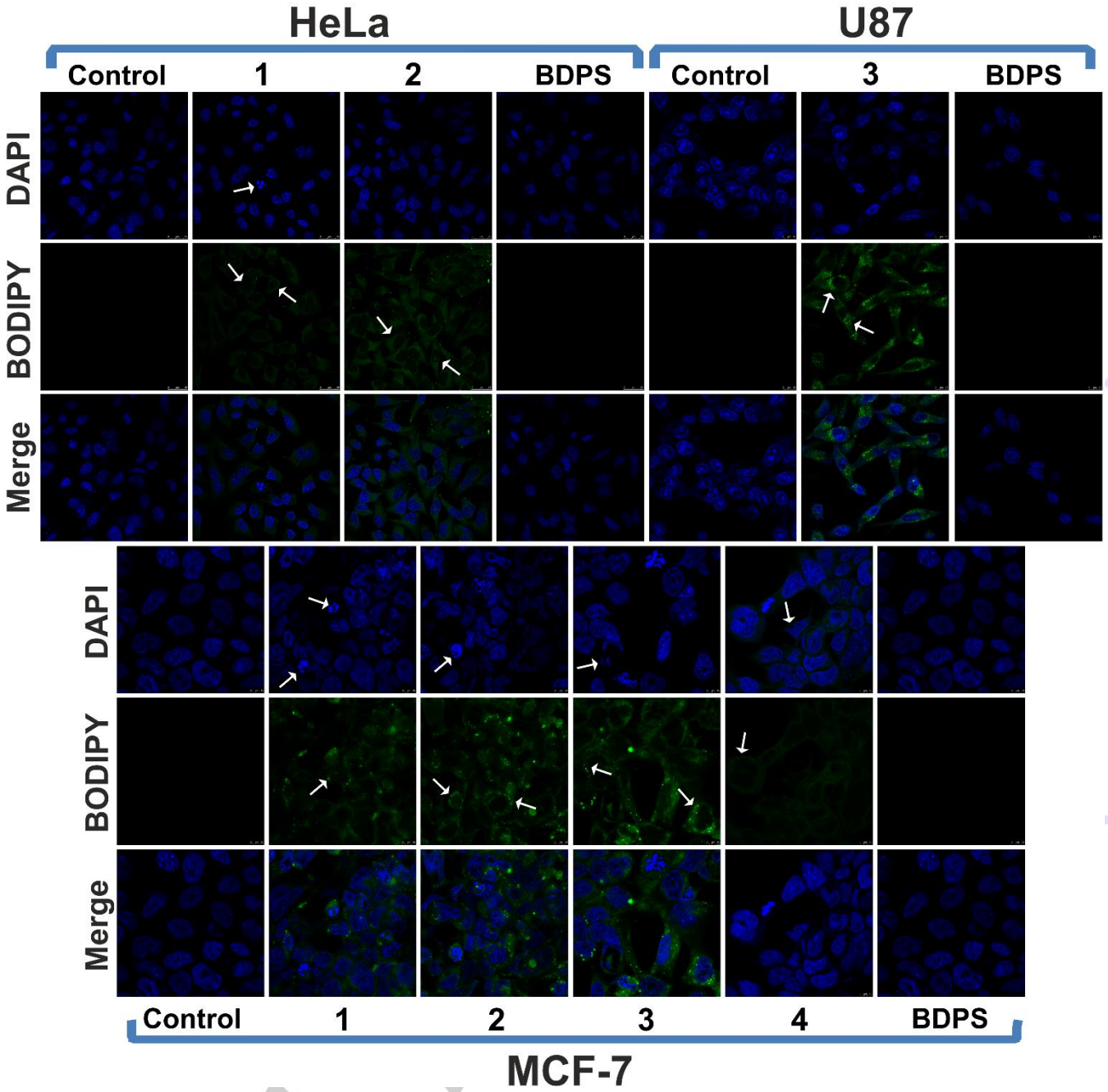

Figure 3. Intracellular localization of rectangles **1-4**. Nuclei stained with DAPI in the presence or absence of compound treatment were observed using confocal microscope (excited at 488 nm). MCF-7 cells were treated with rectangles **1** (1 μM), **2** (0.5 μM), **3** (1 μM) and **4** (3 μM); HeLa cells were treated with 3 μM of rectangles **1** and **2**; U87 cells treated with 1 μM of rectangle **3**.

in mortality of U87 cells, with 16.68% cell death at the highest concentration (Fig. S8, E-F). When compounds **1**-**3** were studied against the MCF-7 breast cancer cells, it was found that the percentage of apoptotic cells increased in a dose-dependent manner. Also, there was a gradual decrease in the G1 peak, suggesting cell death was predominantly occurring during G1 phase (Fig. S9) Cellular uptake of many ruthenium complexes is mediated by transferrin, an 80-kDa iron transport protein.[10] The localisation of these thiophene-based, BDPS-ruthenium rectangles was easily determined by confocal laser scanning microscopy by exploiting the intrinsic, green fluorescent characteristic of the BODIPY (excitation at 488 nm). Cells were also stained with DAPI to determine nuclear morphology. Control cells had well-defined nuclear regions and no green fluorescence throughout (Fig. 3). All rectangles were found to localise predominantly in the cytoplasmic region both uniformly as well as in the form of nano-aggregates (arrows indicate both forms in BODIPY panels). For comparison, the fate of BDPS only, was also checked in all the cell lines. Despite showing

some amounts of loss in cellular integrity in case of MCF-7 cells (DAPI panel of BDPS+MCF-7 in Fig. 3), no green fluorescence or aggregation was observed in any of the cancer cells. This proves that the green fluorescence results only when the rectangles carrying BDPS enter the cells and undergo aggregation under hypoxic conditions (Fig. 3). Nuclear disintegration, an indicator for apoptosis, was largely observed in MCF-7 and HeLa cells (specified with arrows in the DAPI panels, Fig. 3). Additionally, many pyknotic cells were observed, mostly in breast and brain cancer cells. These observations further supported the substantial rise in sub-G1 peak from the cell-cycle results. Unlike our previously established rectangles that showed both nuclear and cytoplasmic locations,[6] rectangles **1**-**4** predominantly localised in the cytoplasm. On the basis of this, along with observations like nuclear disintegration and occurrence of pyknotic cells, we postulate that their mechanism of selective anti-proliferative activities and induction of apoptosis may be mainly governed extranuclearly. Although to state anything affirmatively, in depth studies must follow.

The ability of ruthenium to bind biomolecules, similar to iron, makes ruthenium-based metalla-rectangles a promising avenue for developing novel anticancer strategies. Anticancer drugs primarily target and damage DNA, leading to an obstruction of cell division and subsequent cell death.[11] Therefore, we further investigated the interaction between these complexes and genomic DNA by UV spectroscopy. A prominent peak typical of genomic DNA was observed close to 260 nm, using Salmon sperm DNA (Fig. S10). Addition of compounds (5-25 μM) resulted in dose-dependent hyperchromicity, where complexes **2**-**4** exhibited equal DNA-binding abilities (Fig. S10, A-E). BDPS alone showed least activity, even at its highest concentration. No hypochromicity or bathochromicity were observed in any of the conditions. Ruthenium-complexes are known to be mutagenic and induce SOS repair, inhibit DNA replication, and inhibit RNA synthesis by binding genomic DNA. These observations complement *in vivo* studies of ruthenium-compounds binding with DNA.[3b] Moreover, they are also known to intercalate mainly within the major grooves of DNA.[12] To investigate the nature of the DNA-compound interaction, mixtures were heated at 95°C for 15 min. Single-stranded DNA (ssDNA) showed a slight hyperchromic shift compared to its native double-stranded (dsDNA) form (Fig. S10, F-I). However, none of the compounds exhibited any substantial decrease in absorbance, excluding the possibility of intercalation. We postulate that electrostatic interactions between exposed bases of ssDNA as well as some non-covalent interactions mediate DNA-compound binding.

Next, we investigated the interaction between our metalla-rectangle drugs with the model protein, bovine serum albumin (BSA), owing to its high homology with human serum albumin.[13] A peak at 340 nm was observed using a fluorimeter, consistent with that for free BSA. Increasing concentrations of compound (5-25 μM) resulted in a decrease in peak intensity. The largest changes in peak intensity were observed for compounds **3** and **4**. Compound **1** exhibited the least peak intensity change, possibly due to the absence of aromatic rings between the two metal cores. These results were further confirmed by UV spectrometry (Fig. S11, F-I). Static quenching may be considered as one of the methods of interaction as no significant shift from the normal spectra was observed.

In conclusion, we report the synthesis of novel thiophene-based BDPS Ru (II) rectangles **1**-**4**, where introduction of the thiophene group in the BODIPY ligand significantly improved its selectivity for cancer cells. All compounds showed selective antiproliferative activities against breast cancer cells, **1** and **2** exhibited activity against cervical cancer cells, and all except compound **4** worked against glioblastoma cells. This dose-dependent inhibition of cell growth was further confirmed by cell-cycle analyses. Confocal laser scanning microscopy studies suggested that the compounds use a cytoplasmic mechanism of action in causing cell death. Additionally, binding studies revealed the ability of compounds **1**-**4** to substantially interact with DNA and protein. Therefore, these compounds could be useful for further studies on the biological activity of BODIPY-based metal supramolecules.

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Keywords: self-assembly • metalla-rectangles • bodipy • antiproliferative activities • anticancer • confocal microscopy

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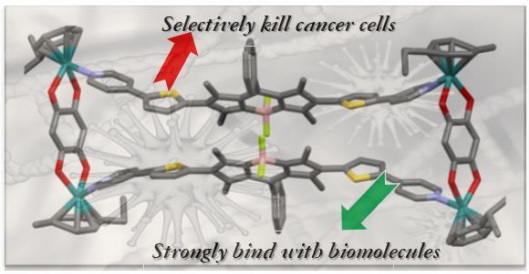
A new thiophene-based BODIPY ligand, BDPS, has been designed and utilized to successfully synthesize four new Ru (2+2) rectangles. The presence of thiophene group in these rectangles has significantly improved its biological activities.



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