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Short communication

# Two novel platinum(II) complexes with sorafenib and regorafenib: Synthesis, structural characterization, and evaluation of in vitro antitumor activity

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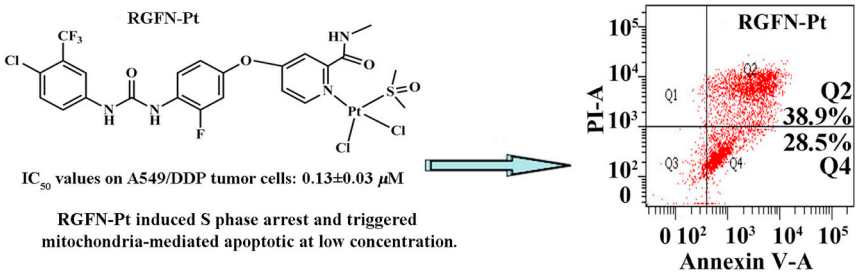
## GRAPHICAL ABSTRACT

**SRFN-Pt** and **RGFN-Pt** triggered mitochondria-mediated apoptotic at low concentration.

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## ABSTRACT

Two new Pt(II) complexes with sorafenib (SRFN) and regorafenib (RGFN), having the general formulae [Pt(SRFN)(DMSO)$Cl_2$] (**SRFN-Pt**) and [Pt(RGFN)(DMSO)$Cl_2$] (**RGFN-Pt**), were prepared and characterized by ESI-MS, IR, UV–Vis spectroscopy, elemental analyses, and $^1$H and $^{13}$C NMR, respectively. The anticancer activities of **SRFN-Pt** and **RGFN-Pt** were evaluated by MTT assay with NCI-H460 (human non-small cell lung cancer NCI-H460 cell line), SK-OV-3 (ovarian cancer cell line), SK-OV-3/DDP (cisplatin-resistant SK-OV-3 cell line), T-24 (human bladder cancer cell line), HeLa (cervical cancer cell line), A549/DDP (cisplatin-resistant A549/DDP non-small cell lung cancer cell line) cancer cells and in the normal HL-7702 cells. The results suggested that **SRFN-Pt** and **RGFN-Pt** were more effective against the A549/DDP tumor cells ($IC_{50}$ = 1.18 ± 0.15 μM and 0.13 ± 0.03 μM) than SRFN (45.03 ± 0.79 μM), RGFN (40.11 ± 2.15 μM), and cisplatin (97.63 ± 1.06 μM), respectively, and **RGFN-Pt** was more effective than **SRFN-Pt**. In addition, **SRFN-Pt** and **RGFN-Pt** induced G2/M and S phase arrest. Cytotoxic mechanism studies revealed that **SRFN-Pt** and **RGFN-Pt** triggered mitochondria-mediated apoptotic cell death at low concentration. **RGFN-Pt** exhibited obvious priority on the in vitro anti-tumor activity than **SRFN-Pt**, which should be undoubtedly correlated with the key roles of the fluoro

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substituted groups in the RGFN ligand of **RGFN-Pt**. The in vitro anti-tumor activity studies suggested that RGFN-Pt pointed to a new direction in developing Pt(II) drugs as anti-cancer agent.

To date, cisplatin (cDDP) and its derivatives still play a major role in tumor treatment [1–18]. Although drug resistance and cell toxicity have restricted their use [14–20]. Thus, the search for novel series of Pt (II/IV) compounds is of constant research interest [16,17,21–44]. For example, the Pt-c(RGDfK) conjugate as a Pt(IV) pro-drug increased the number of cancer cells that could be targeted. [1] Besides, a novel noncovalent polynuclear Pt complex, [{$Pt(NH_3)_3$}2-$\mu$-{trans-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}]$^{6+}$ (TriplatinNC-A), could work as a DNA condensing agent to bind regulatory proteins and initiate the onset of tumor cell apoptosis [44]. In addition, sixteen anticancer Pt(II) complexes, [PtCl(hq)(S-dmso)](**1a–8a**, hq = quinolinol derivatives) and [PtCl(hq)(pta)] (**1b–8b**, pta = 1,3,5-triaza-7-phosphaadamantane), could induce much stronger oxidative stress response in zebrafish than cisplatin [22]. They inhibited the growth of breast cancer (MDA-MB-231 cells) xenografts in mice via apoptosis induction and proteasome inhibition [38].

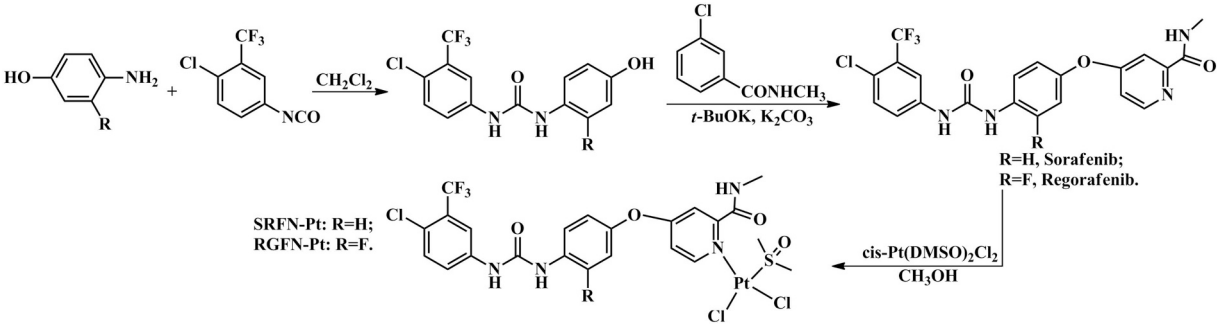
In addition, Sorafenib (SRFN) and regorafenib (RGFN) play important roles in the clinical treatment of gastrointestinal stromal tumor (GIST) and metastatic colorectal cancer (mCRC) [45,46]. To date, there have been no reports about the Pt(II) complexes with sorafenib (SRFN) and regorafenib (RGFN). In this work, we synthesized two new Pt(II) complexes with sorafenib (SRFN) and regorafenib (RGFN), denoted as [Pt(SRFN)(DMSO)$Cl_2$] (**SRFN-Pt**) and [Pt(RGFN)(DMSO)$Cl_2$] (**RGFN-Pt**). In addition, we explored the in vitro antitumor activity of **SRFN-Pt** and **RGFN-Pt** and evaluated their action mechanisms in human tumor cells.

Scheme 1 illustrates the synthesis of the sorafenib (SRFN) and regorafenib (RGFN) ligands, which were prepared according to reported procedures [46]. The synthesis of [Pt(SRFN)(DMSO)$Cl_2$] (**SRFN-Pt**) and [Pt(RGFN)(DMSO)$Cl_2$] (**RGFN-Pt**) was accomplished by mixing the respective ligand with *cis*-$Pt(DMSO)_2Cl_2$ in acetone (5.0 mL) and $CH_3OH$ (10.0 mL) at 65 °C for 24 h. Both **SRFN-Pt** and **RGFN-Pt** were characterized by ESI-MS, elemental analysis, IR, and $^1H$ and $^{13}C$ NMR (Figs. S1–S8). In addition to the corresponding SRFN or RGFN ligands, the Pt(II) complexes **SRFN-Pt** and **RGFN-Pt** were coordinated by two Cl ligands and one DMSO molecule coordinated via the S atom, respectively. Furthermore, the stability of **SRFN-Pt** and **RGFN-Pt** ($2.5 \times 10^{-5}$ M) in Tris-HCl buffer (10 mM, pH = 7.35) was analyzed by ESI-MS analysis [47,48]. At 0 h, the Pt(II) complexes showed base peaks at $m/z$ = 884.6 (**SRFN-Pt**, $[M - H + DMSO]^-$) and 902.1 (**RGFN-Pt**, $[M - H + DMSO]^-$), respectively, which remained unchanged in the original species after incubation for 48 h (Figs. S3 and S6). Hence, **SRFN-Pt** and **RGFN-Pt** were stable in Tris-HCl buffer solution at the concentration of $2.5 \times 10^{-5}$ M.

The in vitro anticancer activities of **SRFN-Pt** and **RGFN-Pt** complexes and the free sorafenib (SRFN) and regorafenib (RGFN) ligands were evaluated by MTT assay in NCI-H460 (human non-small cell lung cancer NCI-H460 cell line), SK-OV-3 (ovarian cancer cell line), SK-OV-3/DDP (cisplatin-resistant SK-OV-3 cell line), T-24 (human bladder cancer cell line), HeLa (cervical cancer cell line), A549/DDP (cisplatin-resistant A549/DDP non-small-cell lung cancer cell line) cancer cells and the normal HL-7702 cells [49], using cisplatin and *cis*-$Pt(DMSO)_2Cl_2$ as a positive control [50,51]. The free sorafenib (SRFN) and regorafenib (RGFN) ligands were more cytotoxic to NCI-H460, SK-OV-3, SK-OV-3/DDP, T-24, and HeLa cancer cell lines than the **SRFN-Pt**, cisplatin, **RGFN-Pt**, and *cis*-$Pt(DMSO)_2Cl_2$ complexes (Tables 1 and S1), indicating that the two platinum(II) complexes were not potent for these tumor cells [52–58]. Nevertheless, the two platinum(II) complexes were more cytotoxic than the ligands toward the A549/DDP tumor cells, giving low $IC_{50}$ values (1.18 ± 0.15 μM for **SRFN-Pt** and 0.13 ± 0.03 μM for **RGFN-Pt**) that corresponded to 47.90 and 501.38 times the cytotoxicity of the free SRFN and RGFN ligands and 103.86 and 1220.38 times the cytotoxicity of cisplatin, respectively. We were pleased to find that **SRFN-Pt** and **RGFN-Pt** were less cytotoxic against the normal live HL-7702 cells than the SRFN and RGFN ligands or cisplatin.

We then examined the effects of **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM) on the progression of cell apoptosis and on the cell cycle phase arrest in A549/DDP cancer cells. The A549/DDP cancer cells were incubated with complexes for 24 h and stained with propidium iodide (PI) and/or annexin V fluorescein isothiocyanate (FITC), and then analyzed by flow cytometry to determine the DNA content [59,60]. Fig. S9 shows that **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM) caused cell cycle arrest at the G2/M and S phase in the A549/DDP cancer cells, which indicated the apoptosis of A549/DDP cells [59,60]. The A549/DDP cells treated with **RGFN-Pt** (0.13 μM) showed stronger apoptosis (ca. 67.4%) than those treated with **SRFN-Pt** (1.18 μM, ca. 48.6%) and cisplatin (97.63 μM, ca. 24.3%) (Figs. 1 and S10). The results indicated that the **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM) inhibited the proliferation of the A549/DDP cancer cells by inducing apoptosis.

Cellular uptake, flow cytometry, and Western blot assays were carried out for the A549/DDP cancer cells treated with **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM) to further study the anticancer activities of the complexes [61–71]. Tables S2 and S3 shows that, as expected, the cellular uptake and distribution of **RGFN-Pt** in the mitochondria were higher than those of **SRFN-Pt**. Next, the mitochondrial $Ca^{2+}$ fluctuation, mitochondria membrane potential (MMP), caspase-3/9 activation, and ROS generation in the A549/DDP cells were examined by appropriate assays. Figs. S10–S15 show that the A549/DDP cells




**Scheme 1.** Synthesis of Pt(II) complexes **SRFN-Pt** and **RGFN-Pt**. Reagents: (a) $CH_2Cl_2$, reflux, 6.0 h; (b) DMF, 90 °C, 3.0 h; (c) *cis*-$Pt(DMSO)_2Cl_2$, 5.0 mL acetone and 10.0 mL $CH_3OH$, 65 °C, 24 h.

**Table 1**
$IC_{50}$[a] values (μM) of SRFN, RGFN, cis-Pt(DMSO)$_2$Cl$_2$, **SRFN-Pt**, **RGFN-Pt**, and cisplatin against seven selected human cell lines.

| Compound | NCI-H460 | SK-OV-3 | SK-OV-3/DDP | T-24 | HeLa | A549/DDP | HL-7702 |
|---|---|---|---|---|---|---|---|
| SRFN | 6.95 ± 0.45 | 4.65 ± 1.09 | 30.12 ± 1.56 | 3.48 ± 1.18 | 7.38 ± 0.22 | 45.03 ± 0.79 | 37.02 ± 1.48 |
| **SRFN-Pt** | 13.43 ± 0.36 | 20.79 ± 0.74 | 39.37 ± 0.66 | 21.08 ± 0.58 | 49.20 ± 1.75 | 1.18 ± 0.15 | 75.03 ± 0.31 |
| RGFN | 2.10 ± 0.96 | 1.18 ± 0.24 | 25.06 ± 0.76 | 1.02 ± 0.46 | 0.84 ± 0.35 | 40.11 ± 2.15 | 37.46 ± 1.11 |
| **RGFN-Pt** | 10.81 ± 0.36 | 14.75 ± 1.33 | 28.12 ± 0.19 | 19.11 ± 1.49 | 35.66 ± 1.11 | 0.13 ± 0.03 | 85.06 ± 2.01 |
| *cis*-PtCl$_2$(DMSO)$_2$ | > 150 | > 150 | > 150 | > 150 | > 150 | > 150 | > 150 |
| Cisplatin[b] | 12.11 ± 1.06 | 14.23 ± 0.49 | 80.15 ± 0.93 | 15.44 ± 1.36 | 13.07 ± 1.93 | 97.63 ± 1.06 | 18.12 ± 0.54 |

[a] $IC_{50}$ values are presented as the mean ± SD (standard error of the mean) from five independent experiments.
[b] Cisplatin (1.0 mM) was dissolved in NaCl solution (0.154 M) [52–58].

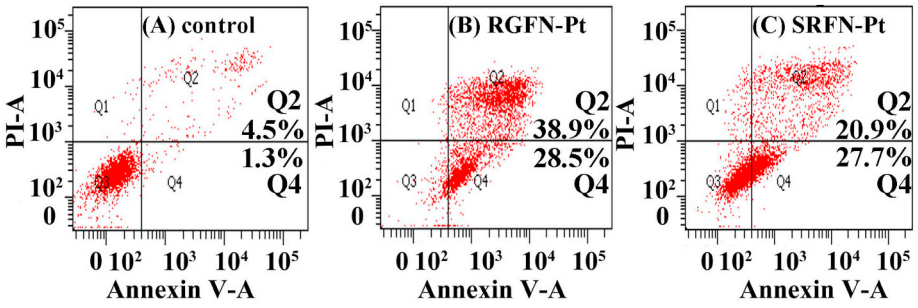



**Fig. 1.** Cell apoptosis (A–C) of A549/DDP cancer cells treated with **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM).

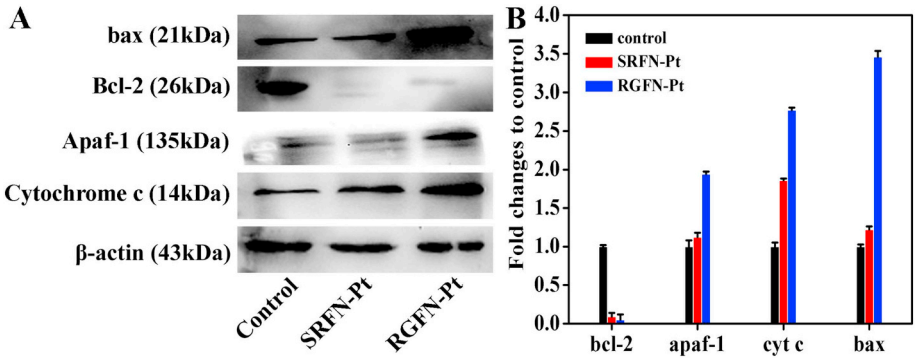



**Fig. 2.** (A) Western blot assay of apoptosis proteins in the A549/DDP cancer cells treated with **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM); (B) relative expression of each band, determined by dividing the density of each band by the density of the actin band; mean and SD were calculated from three independent measurements.

treated with **SRFN-Pt** (1.18 μM), cisplatin (97.63 μM) and **RGFN-Pt** (0.13 μM), more evidently the cells treated with **RGFN-Pt**, induced the activation of caspase-3/9, increased the mitochondrial $Ca^{2+}$ level, triggered ROS generation, and disrupted the MMP. Western blot analyses showed that after the cells were treated with **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM), the expression of apaf-1, cytochrome *c* (cyt c), and bax increased but the expression of bcl-2 decreased (Fig. 2). These findings demonstrated that **SRFN-Pt** (1.18 μM) and **RGFN-Pt** (0.13 μM) probably induced the mitochondrial death pathway (Figs. 2, S9 and S10).

In conclusion, [Pt(RGFN)(DMSO)Cl$_2$] (**RGFN-Pt**) and [Pt(SRFN)(DMSO)Cl$_2$] (**SRFN-Pt**) showed significantly enhanced cytotoxicities than cisplatin against the A549/DDP cancer cells. They effectively induced cell apoptosis by activating the corresponding apoptotic pathways and by inducing G2/M and S phase arrest according to in vitro cytotoxicity, flow cytometry, cellular uptake, and Western blot assays. The $IC_{50}$ value of **RGFN-Pt** was lower (0.13 μM) than that of **SRFN-Pt** (1.18 μM). A fluoro substituent might promote its effect on the cell intake, which had also been proven in our study by examining the platinum(II) intake and distribution of **SRFN-Pt** and **RGFN-Pt** using the ICP-MS method. This may be the most rational explanation for the better anticancer effect/activity of **RGFN-Pt** compared to **SRFN-Pt** till now based on the present results. Therefore, **RGFN-Pt** may have the potential for further development into safe and effective anticancer agents.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inoche.2019.03.031. These data include synthesis, materials and methods of **SRFN-Pt** and **RGFN-Pt** described in this article.

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