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Synthesis, characterization and biological evaluation of two cyclometalated iridium(III) complexes containing a glutathione S-transferase inhibitor

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ABSTRACT

The cyclometalated iridium(III) compounds have been intensively studied for health-related applications due to their outstanding luminescent properties and multiple anticancer modes of action. Herein, two iridium(III) compounds **Ir-1** and **Ir-3** containing glutathione S-transferase inhibitor (GSTi) were developed and studied together with two unfunctionalized compounds **Ir-2** and **Ir-4** as a comparison. Biological study indicated that GSTi-bearing complexes **Ir-1** and **Ir-3** exert a synergistic effect on the inhibition of cancer cells. The photophysical properties of **Ir-1** ~ **Ir-4** were investigated by UV/vis absorption and fluorescence spectroscopy and rationalized with TD-DFT calculations. As expected, GSTi-bearing complexes **Ir-1** and **Ir-3** exhibited considerable cytotoxicity against both A549 and cisplatin-resistant A549/cis cancer cells, much higher than the unfunctionalized iridium compounds **Ir-2** and **Ir-4**. Further study indicated that **Ir-1** and **Ir-3** mainly localize in the mitochondria of tumor cells, and exert their cytotoxicity *via* generating ROS and inhibiting GST activity. The flow cytometry investigations demonstrated that **Ir-1** and **Ir-3** can arrest the cell cycle in S phase and induce the cell death through apoptosis process. Overall, the complexation of GST inhibitors with cyclometalated iridium(III) agents provides an effective way for potentiating the cytotoxicity of iridium(III) anticancer agents and resensitizing the efficacy against cisplatin resistant cancer cells.

1. Introduction

The platinum-based anticancer drugs, cisplatin and its analogues have shown great success in the clinic for the treatment of a wide variety of cancers, which stimulates the development of non-platinum metal-based anticancer agents [1–4]. The diverse coordination modes, variable spatial structures, tunable kinetic reactivities, and rich photophysicochemical properties of the metal-based compounds provide more opportunities to design anticancer agents with ideal properties and functionalities [5–11]. To date, numerous non-platinum metal-based compounds have been designed and explored as potential anticancer agents, and several of them have successfully entered clinical trials for cancer treatment not only as chemotherapeutic agents but also as photosensitizer [12–15].

The cyclometalated octahedral iridium(III) compounds are a class of well-studied anticancer agents due to their limited side effects and facile modification, which display multiple modes of action such as mitochondria-mediated cell death pathway, inhibition of protein-protein interaction, and deregulation of the cellular redox balance [16–23]. Distinctly, the cyclometalated iridium(III) compounds are kinetically inert under physiological conditions, thereby exerting their anticancer activity through non-covalent interaction with the therapeutic targets [24,25], which is different from platinum agents that covalently bind to the DNA [26]. The irreversible interaction of the platinum drugs to biomolecules often cause serious side effects [27,28]. Consequently, the development of iridium(III) anticancer agents has the potential to overcome the limitations of the platinum drugs.

Glutathione S-transferase(s) (GSTs) are a class of xenobiotic metabolizing enzymes, which have a vital physiological function in detoxifying process *via* catalyzing the conjugation of glutathione (GSH) with detrimental electrophilic agents [29,30]. Notably, GSTs are highly overexpressed in many cancer cells, especially in drug-resistant cancer

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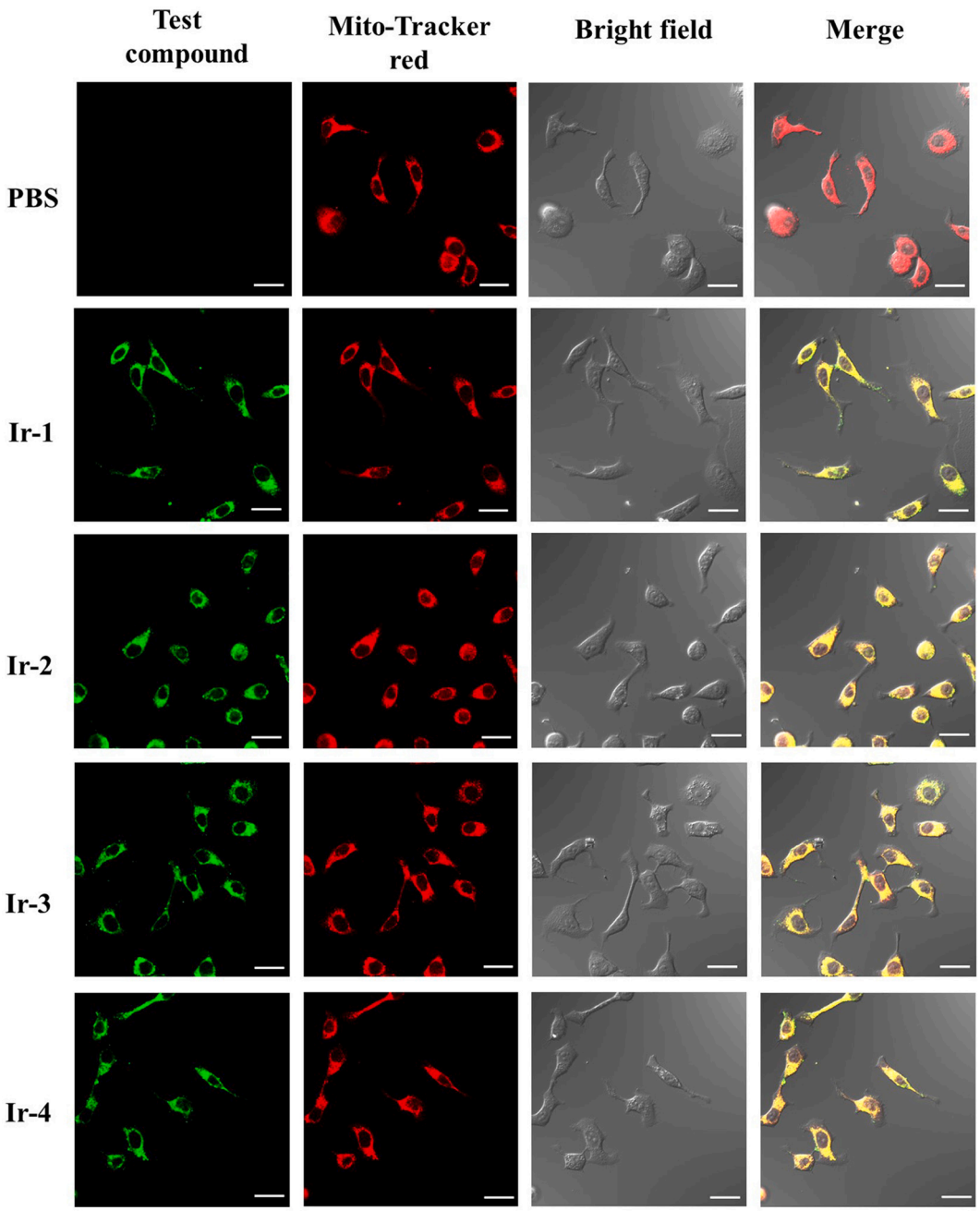

Fig. 3. Co-incubation of the iridium(III) compounds with Mito-Tracker Red in A549 cells. **Ir-1** and **Ir-3** were excited at 405 nm and emission was collected at 520 ± 20 nm. **Ir-2** and **Ir-4** were excited at 405 nm and emission was collected at 590 ± 20 nm. MTR was excited at 579 nm and the emission was collected at 599 nm. Scale bar: 20 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Cellular accumulation of complexes **Ir-1** ~ **Ir-4** (30 μM) in A549 cells after 6 h and 12 h incubation by ICP-MS.

Compound	Ir (ng/10^6 cells)[a]	
	6 h	12 h
Ir-1	42.5 ± 3.8	50.6 ± 4.1
Ir-2	13.8 ± 1.5	18.6 ± 2.0
Ir-3	45.7 ± 4.0	55.3 ± 5.2
Ir-4	11.5 ± 1.3	17.4 ± 2.1

[a] Values represent the mean ± SD from three independent experiments.

2.7. Intracellular ROS level detection

It has been demonstrated that many metal-based anticancer agents have the potential to alter the cellular redox balance and elevate intracellular ROS levels, resulting in cancer cell death. Therefore, the intracellular ROS levels in A549 and A459/cis cells after treatment with **Ir-1** ~ **Ir-4** were investigated with 2′,7′-dichlorodihydrofluorescein diacetate (H_2DCF-DA) as an ROS-sensitive fluorescent probe. As shown in Fig. 4, **Ir-1** and **Ir-3** increased ROS levels in both A549 and A549/cis cells as evident by the green fluorescence, especially for **Ir-3** with relatively intense fluorescence, whereas **Ir-2** and **Ir-4**-treated A549 and A549/cis cells exhibited weak green fluorescence, demonstrating the low production of intracellular ROS. Taken together, **Ir-1** and **Ir-3** can exert a synergistic anticancer effect *via* generating ROS and inhibiting GST

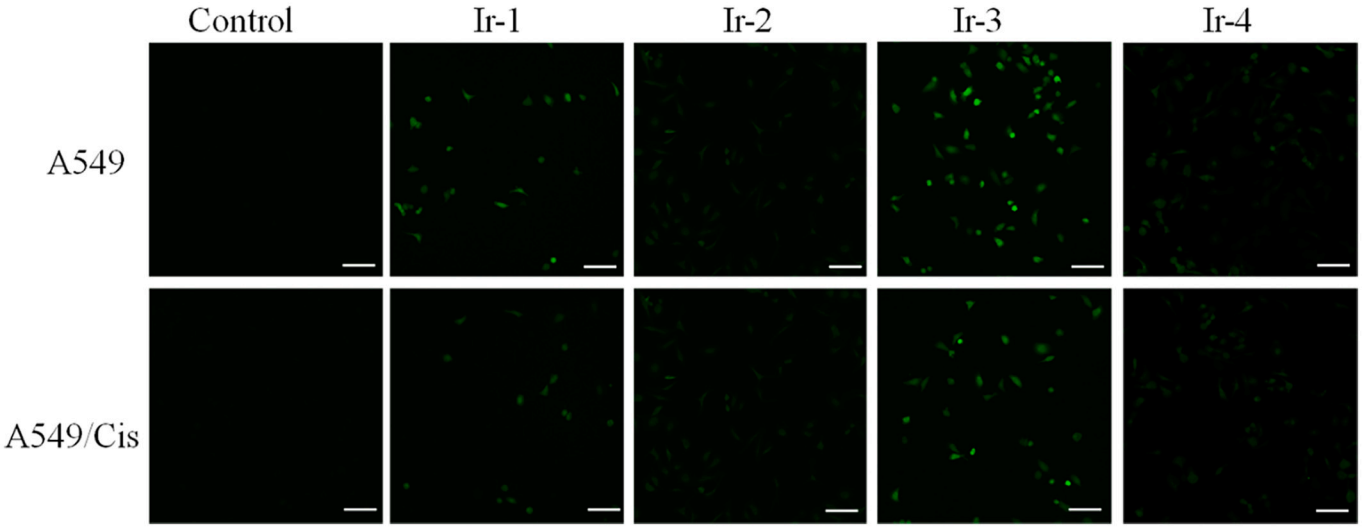

Fig. 4. Confocal fluorescence images of ROS production in A549 and A549/cis cells treated with **Ir-1** ~ **Ir-4** at a concentration of 20 μM. Scale bar: 60 μm.

activity.

2.8. Apoptosis study

Based on the results of cytotoxicity test, the apoptosis analysis of cisplatin, NBDHEX and **Ir-1** ~ **Ir-4** against A549 and A549/cis cells was performed by flow cytometry with Annexin-V FITC and propidium iodide (PI) staining. As shown in Figs. 5 and 6, four areas in the diagrams represent different cell states: necrotic cells (Q1), late apoptotic (Q2), living cells (Q3), and early apoptotic cells (Q4). In comparison with the untreated cells, both **Ir-1** ~ **Ir-4** treatment increased incidences of early- to late-stage apoptosis (14.2% - 36.2%) in A549 cancer cells. Besides, only 63.1% and 76.6% of the **Ir-1** and **Ir-3**-treated cells are intact, respectively, while 79.2% and 85.8% of A549 cells remain intact after treatment with **Ir-2** and **Ir-4**, respectively, demonstrating that **Ir-1** and **Ir-3** can produce significant impact on A549 cells. Notably, the population of apoptotic cells induced by **Ir-1** (36.2%) and **Ir-3** (23.3%) was much higher than that of NBDHEX (8.3%) and was superior and/or comparable to that of cisplatin (31.9%). Besides, cisplatin and NBDHEX can not only induce cell apoptosis, but also necrosis (11.6% and 18.4%). Moreover, **Ir-1** and **Ir-3** induced the apoptosis of A549/cis cells with apoptotic rates of 40.6% and 24.8%, respectively, confirming the considerable cytotoxicity against A549/cis cells. These results clearly demonstrating that the complexation with NBDHEX conferred the iridium(III) complexes with great potential for improving their cytotoxicity and overcoming the drug resistance.

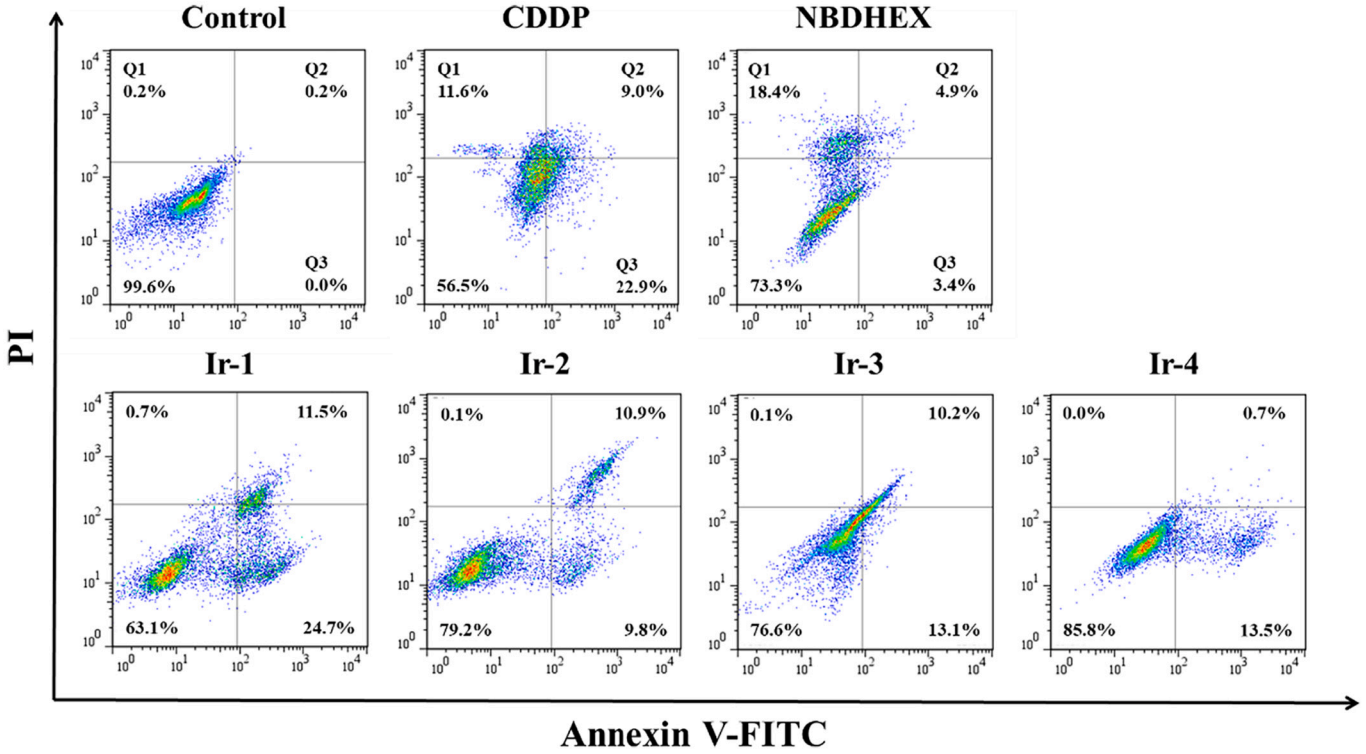

Fig. 5. Apoptosis analysis of A549 cells treated with cisplatin (CDDP), NBDHEX, **Ir-1** ~ **Ir-4** at the concentrations of IC_{50} values for 48 h.

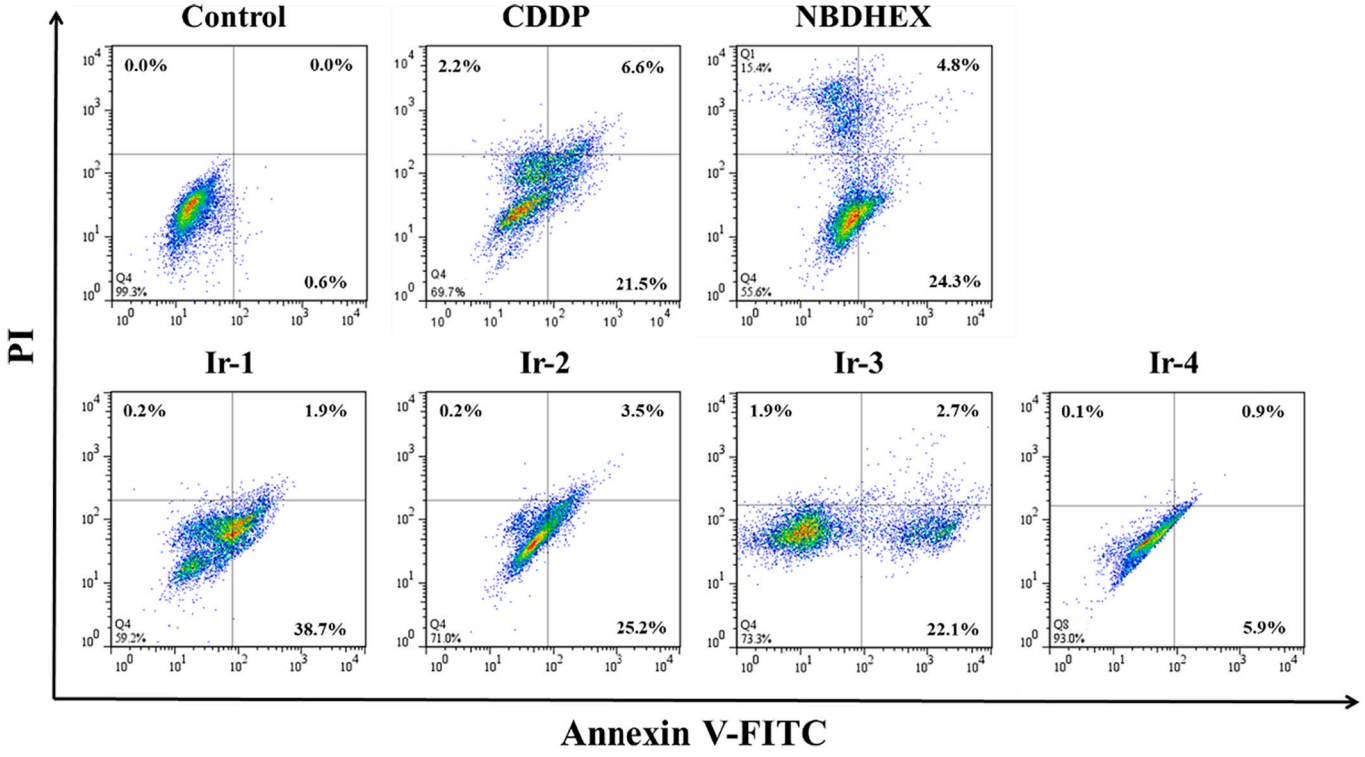

Fig. 6. Apoptosis analysis of A549/cis cells treated with cisplatin (CDDP), NBDHEX, **Ir-1** ~ **Ir-4** at the concentrations of IC_{50} values for 48 h.

2.9. Cell cycle arrest analysis

The perturbation effects of **Ir-1** ~ **Ir-4**, cisplatin and NBDHEX on cell cycle distribution in A549 cells were analyzed by flow cytometry. As shown in Fig. S18, exposure of A549 cells to cisplatin led to a moderate accumulation of cells mainly at S phase along with a minor G2/M phase of the cell cycle. Besides, NBDHEX arrested A549 cells mainly in the S phase of the cell cycle, which is in line with the previous literature [51] that S or G2/M phases arrest were observed for most of the anticancer drugs in current use due to the DNA binding or interaction with target proteins. However, both **Ir-2** and **Ir-4** arrest the cell cycle at G0-G1 phase compared to the untreated control, while **Ir-1** and **Ir-3** blocked

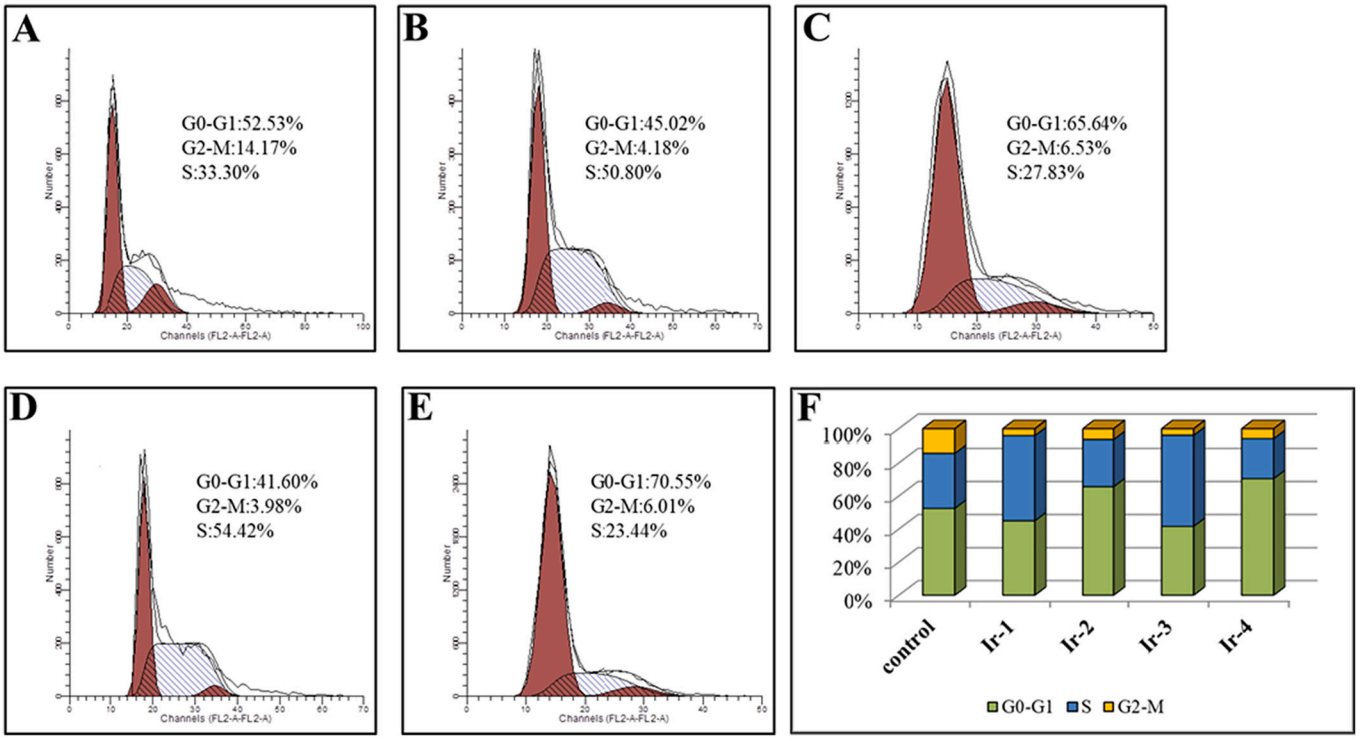

Fig. 7. Flow cytometry analysis on cell cycle distributions in A549 cells treated with **Ir-1** ~ **Ir-4** (30 μM) for 24 h (A: control; B: **Ir-1**; C: **Ir-2**; D: **Ir-3**; E: **Ir-4**).

the cell cycle at S phase (Fig. 7), indicating that **Ir-1** and **Ir-3** have the potential to inhibit DNA synthesis. In addition, no sub-G1 population was observed, suggesting that **Ir-1** ~ **Ir-3** might not induce apoptosis in this condition. Overall, **Ir-1** and **Ir-3** have different modes of action compared with **Ir-2** and **Ir-4** due to the synergistic effect of iridium(III) complexes and NBDHEX.

3. Conclusion

In this study, two novel iridium(III)-NBDHEX conjugates were designed and prepared to improve the biological and pharmacological activities of cyclometalated iridium(III)-based anticancer agents. The chemical structures and photophysical properties of **Ir-1** ~ **Ir-4** were well characterized by different techniques. *In vitro* cytotoxicity study indicated that the iridium(III) conjugates **Ir-1** and **Ir-3** displayed considerable cytotoxicity against A549 cells, superior to their unfunctionalized complexes **Ir-2** and **Ir-4**, suggesting that the GST inhibitor NBDHEX can effectively improve the anticancer activity of the iridium (III) complexes. Moreover, **Ir-1** and **Ir-3** also showed high cytotoxicity to A549/cis cells with similar IC_{50} values to A549 cells, respectively, implying that **Ir-1** and **Ir-3** lack the cross-resistance to cisplatin. Remarkably, **Ir-1** and **Ir-3** were about 3–4 folds less cytotoxic than cisplatin against normal LO2 cells. Further mechanism study indicated that the ability of **Ir-1** and **Ir-3** to generate ROS and inhibit GST activity probably be the major cause of cell apoptosis through the inhibition of DNA synthesis and arresting cell cycle at S phase. Overall, the intramolecular combination cyclometalated iridium(III) complexes with GST inhibitors appears to be a reasonable approach for developing high-efficacy and low-toxic iridium(III)-based anticancer agents.

Author statement

Synthesis and characterization: Ya Gao, Weiyu He.

In vitro cytotoxic activity: Ya Gao, Wei Wang.

GST inhibition activity: Weiwei Hu, Weiyu He.

Cellular uptake and ROS level detection: Jian Zhao, Yanyan Sun.

Electrostatic potential surfaces, Apoptosis and Cell cycle arrest analysis: Jian Zhao, Ya Gao.

Drafting of the manuscript: All authors.

Supervision of the final version of the manuscript: Yanyan Sun, Jian Zhao, Weiwei Hu.

All authors have commented on the manuscript and approved the manuscript to be submitted to JIB.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Experimental methods for synthesis and characterization; biological assays; ^{1}H, ^{13}C NMR and ESI-MS spectra for target compounds; other supplementary results. Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2022.112050.

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