Synthesis of A Novel Ferrocene Derivative and Cytotoxicity to A549, HCT116 and MCF-7 Cell Lines

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Abstract

Based on our previous results, a ferrocene derivative 1 was synthesized in this study and characterized by 1H NMR, 13C NMR, MS and XRD methods. And then, the cytotoxicity to A549, HCT116 and MCF-7 cell lines was evaluated using the MTT method. The results showed that this compound exhibited good cytotoxicity to A549, HCT116 and MCF-7 cell lines.

Keywords: Ferrocene derivative; Synthesis; Reaction mechanism; Antitumor activity

Introduction

Cancer is a major health problem worldwide. The death caused by cancer mainly is lung cancer, breast cancer, liver cancer, carcinoma of colon and rectum. Some small molecule anticancer agents have been approved by the U.S. Food and Drug Administration (FDA) in clinics and some are currently in clinical trials [1,2]. However, cancer chemotherapy is still highly inadequate. Thus, it is urgent to discover novel anticancer agents.

Ferrocene is a potential pharmacophore for drug design and drug discovery, for it is a neutral, chemically stable and nontoxic molecule [3]. Some ferrocene derivatives are potential metal-based anticancer agents [4].

In recent years, our researching group is devoted to design and synthesize the small molecule libraries for the development of anticancer agents [5,6]. We have reported some ferrocene derivatives containing isoxazole moiety and their in vitro anticancer activity against A549, HCT16 and MCF-7 cell lines [7]. In our previous work, we synthesized a novel structure of ferrocene derivative and evaluated its anticancer activity against A549, HCT16 and MCF-7 cell lines [8].

To find the most potent anticancer agents based on the ferrocene core, another new structure of ferrocene derivative 1 was synthesized in present work. The synthetic route was outlined in Figure 1. The target compound was confirmed by 1H NMR, 13C NMR, MS and XRD methods. And then, the cytotoxicity to A549, HCT116 and MCF-7 cell lines was preliminarily evaluated.

Experimental

General methods

Melting point was determined on XT-5 (Benjing Keyecopti Instrument Factory) apparatus equipped with a microscope and value is uncorrected. 1H and 13C NMR spectra was recorded on a 400 MHz Bruker AVANCE III spectrometer in CDCl3, the chemical shifts are expressed in ppm relative to tetramethylsilane (TMS) as the internal standard; ESI-MS was performed on a DECAX-30000 LCQ Deca XP (70 eV). The reaction was monitored by thin layer chromatography (TLC) on silica gel plates at 254 nm under a UV lamp using petroleum or ethyl acetate as eluent. Column chromatography separation were obtained on silica gel (100-200 mesh). All solvents were of analytical grade and used without further purification unless specially stated.

The process for the preparation of the target compound 1

Ferrocenemethanol (0.864 g, 4 mmol) was added into a 50 mL one-necked round-bottom flask with 10 mL dry THF, the mixture was stirred in a cold bath, cyanuric chloride(TCT) (0.184 g, 1 mmol) in 10 mL dry THF was slowly added to the reaction system using a syringe, the mixture was stirred in the cold bath for 30min. Subsequently, DMAP (0.366 g, 3 mmol) in 10 mL dry THF was also slowly added to the reaction system using a syringe, the mixture was stirred in the cold bath for an additional 30 min. Then, temperature naturally rose to room temperature for 8 h. The completion of the reaction was indicated by simple TLC analysis, the solvent was evaporated under the reduced pressure, and the residue was directly purified by column.
chromatography (Petroleum ether/EtOAc: 5:1→2:1) to obtain the target compound 1. 0.663 g, light yellow solid, yield, 80%, Mp.: 121-123°C, 1H NMR (400 MHz, CDCl$_3$) δ (ppm): 4.12 (s, 10H, 2 × C$_5$H$_5$), 4.14 (s, 4H, 2 × CH$_2$), 4.23 (s, 4H, 2 × 2H of C$_5$H$_4$), 4.27 (s, 4H, 2 × 2H of C$_5$H$_4$); 13C NMR (100MHz, CDCl$_3$) δ (ppm): 68.5, 69.4, 76.7, 77.0, 77.4; ESI-MS( m/e, 100%) 415([M+1]$^+$, 100); Anal.calcd. for C$_{22}$H$_{22}$Fe$_2$O: C63.77; H5.31; Found C63.75; H5.36.

The cytotoxicity to A549, HCT116 and MCF-7 cell lines

The cytotoxicity to A549, HCT116 and MCF-7 cell lines of compound 1 was evaluated using the MTT method. The cancer cell lines were cultured in Dulbecco's Modified Essential Medium (DMEM) supplemented with 10% fetal bovine serum and 1.5% antibiotic/antimycotic (Life Technologies, Invitrogen, USA) and maintained in CO$_2$ incubator at 37°C, at 5% CO$_2$ and 95% atmospheric humidity. The mixture of DMSO, PBS and DMEM was used as a negative control and gefitinib was used as the positive control. The detailed process see the reference [7].

Results and Discussion

Chemistry

In our previous study, we added the ferrocenemethanol to the cyanuric chloride solution in THF, we obtained a novel structure of ferrocene derivative (Figure 2), and we have proposed the reaction mechanism of forming this compound [8].

But in current study, we added the cyanuric chloride to the ferrocenemethanol solution in THF, we obtained another novel ferrocene derivative 1. From this result, we can propose the reaction mechanism for forming this new ferrocene derivative 1 (Figure 3): Firstly, the ferrocenemethanol and cyanuric chloride formed the intermediate 2. Then, another ferrocenemethanol molecule reacted with the intermediate 2 by SN2-type reaction to form intermediate 3, the intermediate 3 was neutralized with DMAP to obtain the target compound 1.

X-Ray crystallographic study

X-ray diffraction data for the ferrocene derivative 1 was collected on a Siemens Smart CCD diffractometer equipped with a graphite-monochromated CuKa radiation($\lambda=1.54178\,\AA$). The structure was solved by direct method using the program SHELXL-97 and refined by...
full-matrix least-squares techniques on F^2 with SHELXL-97 program package [9]. The molecular structure showed in Figure 5 (CCDC Number: 1487772).

Figure 5: Crystal structure of ferrocene derivative 1.

The cytotoxicity to A549, HCT116 and MCF-7 cell lines

The cytotoxicity to A549, HCT116 and MCF-7 cell lines of the compound 1 was evaluated using the MTT method. The anticancer efficacy was comparable with the reference drug gefitinib, and the results were summarized in Table 1. It can be seen from the Table 1 that this compound exhibited good cytotoxicity to A549, HCT116 and MCF-7 cell lines.

<table>
<thead>
<tr>
<th>Compd.</th>
<th>IC_{50} (μM)</th>
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<tr>
<td>Ferrocene derivative 1</td>
<td>455.8</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>17.9</td>
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</tbody>
</table>

Table 1: The cytotoxicity to A549, HCT116 and MCF-7 cell lines of ferrocene derivative 1.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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Disclosure

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