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Short communication

Organometallic binuclear Pd(II) complex: Synthesis, crystal structure and in-vitro antitumor activity study

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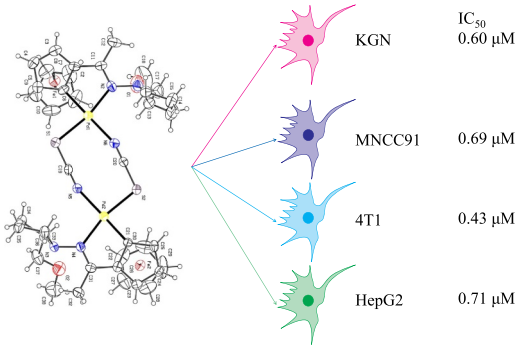
GRAPHICAL ABSTRACT



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ABSTRACT

A novel planar chiral ferrocene cyclopalladated compound (**C2**) was synthesized and fully characterized. The absolute configuration of **C2** has been determined by single-crystal X-ray analysis. The cytotoxic activities of **C2** and cisplatin were evaluated against liver (MHCC97 and HepG2), mouse breast (4 T1) and ovarian granulosa (KGN) cancer cell lines. **C2** was about 23 times more potent than cisplatin in the suppression of KGN cells.

Cancer seriously threatened human health, the reason of which may be the difficulty in developing new highly active anticancer drugs [1]. Synthesizing new compounds and using them as anticancer drug candidates was an effective way to solve this problem [1,2]. Platinum-based compounds like cisplatin, carboplatin and oxaliplatin play key roles in cancer therapeutics because of their high anticancer activity [3]. However, side effect and drug resistance limited their use in oncotherapy [4]. Under this consideration, palladium-based compounds attracted attention due to the similarly chemical characteristic of platinum and palladium.

Some cyclopalladated compounds were synthesized and their anticancer activities were evaluated [5–9]. Structure-activity relationship (SAR) study illustrated that the anticancer activity of cyclopalladated compounds was highly related to the C-N cycle, the N-group and the bridge anion [9–11]. Besides, the chirality part also plays a very important role in the anticancer ability of cyclopalladated compounds [8]. It has reported that some cyclopalladated compounds could oxidize the thiol-group of the proteins in organelle membrane and then induce cancer cell apoptosis [5,7]. However, the target of cyclopalladated compounds used as anticancer drug candidates is still unclear. As a result, more cyclopalladated compounds should be synthesized and further mechanization of them inducing cancer cell apoptosis should be studied.

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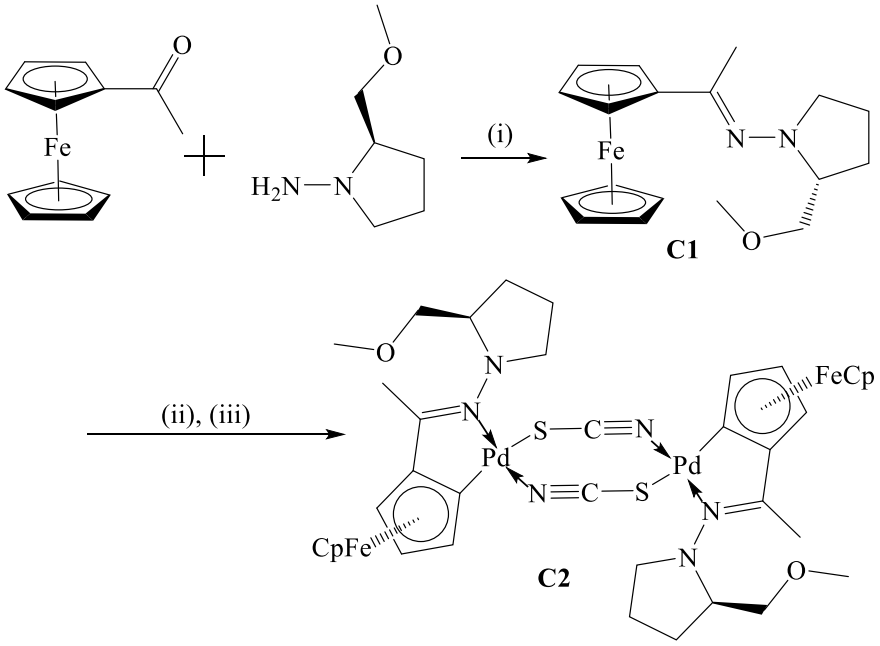

Scheme 1. Overview of synthesized compound **C2**. i) $C_6H_5CH_3$, 110 °C, 24 h. ii) $Pd(OAc)_2$, MeOH, r.t., 24 h. iii) KSCN, MeOH, r.t., 2 h.

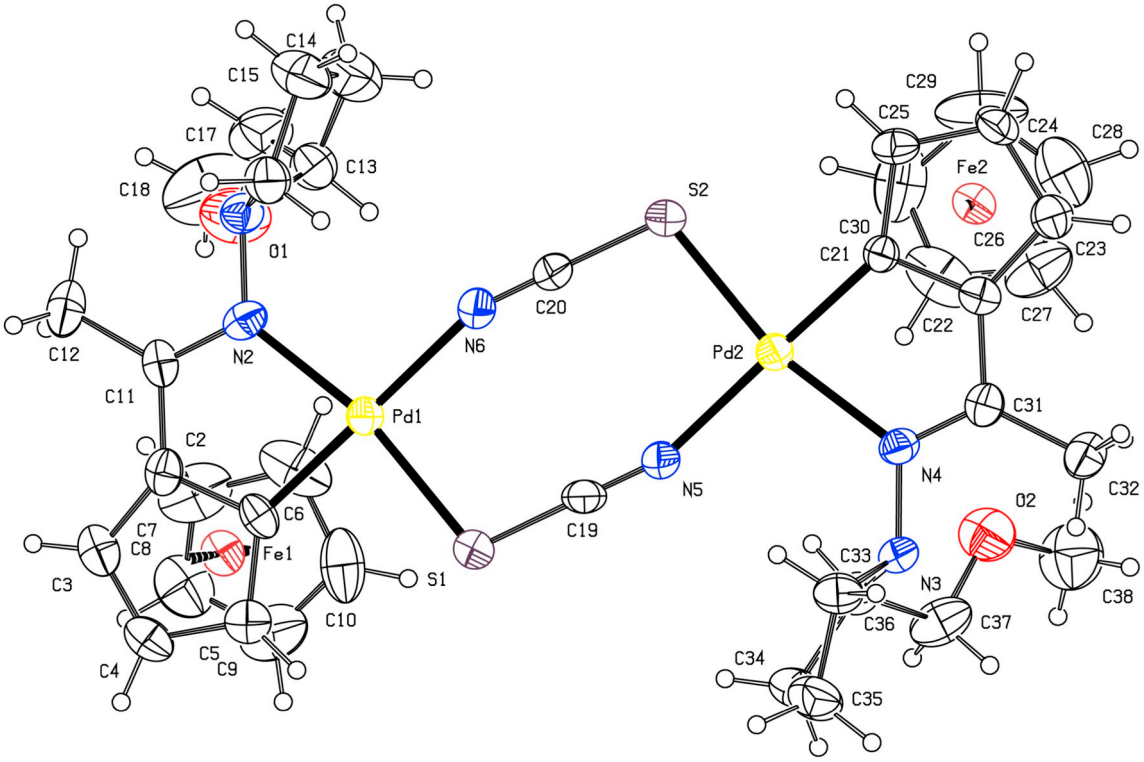

Fig. 1. X-ray crystal structures of C2 presented as ellipsoid models.

Ferrocene is an eye-catching modified group because of its unique three-dimensional (3D) structure and chemical property [9,12–14]. Some ferrocene cyclopalladated compounds were synthesized and their catalytic activities or anticancer activities were evaluated [8,9,15,16]. However, the involute structure of ferrocene cyclopalladated compounds limited their use. Consequently, synthesizing new ferrocene cyclopalladated compounds and clearing their 3D structures are needful for expanding their use.

Hence, a novel binuclear plane chirality ferrocene cyclopalladated **C2** was synthesized and fully characterized. The absolute configuration was tested by X-ray single crystal diffraction. The antiproliferation ability of **C2** on KGN, MHCC91, HepG2 and 4 T1 cancer cell lines was evaluated, taking cisplatin as a positive control.

The structural formulas and the numbering of the compounds under study are presented in Scheme 1. The compound **C2** was synthesized as a reported way [9]. In brief, **C1** was obtained from combing acetylferrocene and (+)-(*R*)-1-amino-2-(methoxymethyl)-pyrrolidine in dry toluene with a quite high yield. **C1** mixed with equivalent $Pd(OAc)_2$ in MeOH, stirred at 25 °C for 24 h and then excess KSCN was added. **C2** was obtained after separated with a column chromatography. **C2** was

Table 1
Crystal data and structures refinement for **C2**.

Identification code	**C2**
Empirical formula	$C_{38}H_{46}Fe_2N_6O_2Pd_2S_2$
Formula weight	1007.43
Temperature/K	293.15
Crystal system	triclinic
Space group	P1
a/Å	10.6199(4)
b/Å	11.1823(4)
c/Å	19.9004(8)
α/°	93.488(3)
β/°	95.138(3)
γ/°	97.897(3)
Volume/Å^3	2325.04(15)
Z	2
ρ_{calc}g/cm^3	1.439
μ/mm$^-$1	1.498
F(000)	1016.0
Crystal size/mm^3	0.35 × 0.3 × 0.25
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.866 to 52.746
Index ranges	−13 ≤ h ≤ 12, −13 ≤ k ≤ 13, −24 ≤ l ≤ 22
Reflections collected	19,193
Independent reflections	13,548[R_{int} = 0.0243. R_{sigma} = 0.0522]
Data/restraints/parameters	13,548/6/927
Goodness-of-fit on F^2	0.997
Final R indexes [$I \geq 2\sigma$ (I)]	R_1 = 0.0406, wR_2 = 0.0930
Final R indexes [all data]	R_1 = 0.0500, wR_2 = 0.0990
Largest diff. Peak/hole / e Å^{-3}	0.63/−0.43
Flack parameter	−0.002(15)

fully characterized by ^{1}H NMR, ^{13}C NMR, optical rotation, elemental analysis and high resolution mass spectrum.

Single crystal of **C2** (CCDC 1909320, Fig. 1) was obtained by slowly evaporation of the solvents from dichloromethane/*n*-hexane. The crystal and experimental data of C2 were summarized in Table 1. Selected bond distances and angles for C2 were showed in Table 2. X-ray analysis shows that the complex exhibits a triclinic form with the space group *P*1. The pair of coordinating N atoms bear a *trans* relationship, and each palladium atom in the metallacycle is slightly distorted square-planar coordination environment. The two palladium atoms are bond to two thiocyanato groups. The two thiocyanato groups respectively adopts nearly linear configuration [the angle of N(5)-C(19)-S(1) and N(6)-C(20)-S(2): 179.7(10) and 179.5(9)°]. The two palladacycles are approximately co-planar, the relevant dihedral angle being 173.06. All bonds are normal except the Pd−C bond lengths, Pd(1)-C(6) and Pd (2)-C(21) are slightly longer than those of the other dimers, but substantially shorter than the predicted value of 2.05 Å due to the metal-to-ligand back-bonding [17–19].

Taking cisplatin as a positive control, Mouse breast cancer cell line 4 T1, human liver cancer cell lines HepG2 and MHCC97, human ovarian granulosa cell line KGN were used to evaluate the antiproliferation

Table 2
Selected bond distances and angles for **C2**.

Bond distance (Å)			
Pd1-S1	2.314(3)	Pd2-S2	2.318(2)
Pd1-N2	2.081(7)	Pd2-N4	2.088(7)
Pd1-N6	2.097(8)	Pd2-N5	2.106(8)
Pd1-C6	1.986(8)	Pd1-C21	1.947(8)
Bond angle (°)			
N2-Pd1-S1	167.4(2)	N4-Pd2-S2	166.4(2)
N2-Pd1-N6	99.0(3)	N4-Pd2-N5	99.7(3)
N6-Pd1-S1	93.5(2)	N5-Pd2-S2	93.6(2)
C1-Pd1-S1	87.3(3)	C21-Pd2-S2	87.3(2)
C1-Pd1-N2	80.1(4)	C21-Pd2-N4	79.4(3)
C1-Pd1-N6	177.8(3)	C21-Pd2-N5	178.2(3)

Table 3
IC_{50} values of **C2** and cisplatin against HepG2, MHCC97, 4T1 and KGN cell lines.

Cell lines	IC_{50} [μM] value ± SD[a]	
	Cisplatin[b]	C2
HepG2	4.6 ± 1.8	0.71 ± 0.2
MHCC97	5.6 ± 0.2	0.69 ± 0.03
4T1	4.85 ± 0.5	0.43 ± 0.07
KGN	14 ± 0.3	0.60 ± 0.07

[a] The values are shown as the mean values of more than two experiments in triplicate; the cells were incubated with **C2** or cisplatin for 72 h.
[b] Cisplatin was used as a positive control.

activity of **C2** [20,21]. The CCK8 assay was used to measure the cell viability after treated by **C2** or cisplatin respectively. As shown in Table 3, **C2** illustrated different antiproliferation to different cancer cell lines, and the IC_{50} to these 4 cancer cell lines were lower than 1 μM. Besides, the IC_{50} of **C2** to these 4 cancer cell lines was much lower than the positive control cisplatin, which meaned that **C2** shows high potential as an anticancer drug candidate. The reason for the high antiproliferation ability of **C2** showed in CCK8 assay may be the co-working of the palladium part and the ferrocene part with different antiproliferation mechanisms [6,7,22,23].

In conclusion, a novel planar chiral ferrocene cyclopalladated compound **C2** was synthesized and fully characterized. The absolute configuration of **C2** was confirmed by X-ray single crystal diffraction. The X-ray analysis showed that **C2** exhibits a triclinic form with the space group *P*1. The antiproliferative activity assays showed that **C2** were antiproliferative to four cancer cell lines with different potencies. The mechanism of **C2** against tumor cells is proceeding.

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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.2019.05.017.

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