Improved synthesis of miriplatin, an antitumor drug

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Key words: antitumor drug; miriplatin; improved synthesis

Abstract: Miriplatin, a novel lipophilic platinum complex has been developed to treat hepatocellular carcinoma. An improvd synthetic route was designed and used to prepare the target compound. $Pt(C_6H_{14}N_2)I_2$ was reacted with $CH_3(CH_2)_{12}COOAg$ in water subsequently product was separated from AgI by dissolved in ethanol. The structure of the target compound was identified by elemental analysis, ESI-MS, FT-IR, ^{1}H-NMR, the structure was consistent with the target compound.

Introduction

Miriplatin is a derivative of cisplatin containing myristates as a carrier ligand, which has been chemically designed to be a lipophilic platinum complex that can be easily suspended in Lipiodol. In vitro studies have shown that platinum compounds gradually released from miriplatin suspended in Lipiodol were incorporated into rat hepatoma cells including cisplatin-resistant cells and formed platinum DNA adducts. In several animal models, miriplatin/Lipiodol had sufficient antitumor effects on hepatic tumors after intrahepatic arterial administration. In a phase II study, 56% of patients achieved CR, The grade 3 toxicities were neutropenia (19%), total bilirubin elevation (19%), AST elevation (44%), and ALT elevation (19%), None of the patients showed grade 4 toxicities or episodes of renal dysfunction. Thus, TACE using miriplatin/Lipiodol is expected to have enhanced therapeutic effect on human HCC as well, and miriplatin/Lipiodol has been commercially available since 2010 in Japan.

MAEDA M et al[1] prepared miriplatin from $Pt(C_6H_{14}N_2)Cl_2$ through hydrolyzation with $AgNO_3$ and reacion with $CH_3(CH_2)_{12}COONa$, by this method the controllability of Ag^+ was high and the reaction rate was too high, therefore there was a large amount of $CH_3(CH_2)_{12}COONa$ still in the product. Tanno N et al[2] prepared miriplatin from $Pt(C_6H_{14}N_2)I_2$ and $CH_3(CH_2)_{12}COOAg$ in chloroform. However, the low solubility of the reagents in chloroform results in a long reaction period. Furthermore, the chloroform is harmful to human health. Yokoyama T et al[3] prepared miriplatin by using $Pt(C_6H_{14}N_2)Cl_2$ through hydrolyzation with $AgNO_3$ and reaction with $CH_3(CH_2)_{12}COOH$ in chloroform, by this method the controllability of Ag^+ was high and the harmful chloroform was used as well.Wang QK et al[4] prepared miriplatin from $Pt(C_6H_{14}N_2)I_2$ through hydrolyzation with $AgNO_3$ and reaction with $CH_3(CH_2)_{12}COONa$, by this method the controllability of Ag^+ was low but the reaction rate was too high, a large amount of $CH_3(CH_2)_{12}COONa$ was still in the product. Wang QK et al[5]. prepared miriplatin from $Pt(C_6H_{14}N_2)I_2$ with Ag_2SO_4 and $Ba(OH)_2$, it was subsequently reacted with $CH_3(CH_2)_{12}COOH$, in n-butanol. The water-normal butanol as the reaction medium can achieve a desirable reaction rate but the route was too long. Wang QK et al[6]. prepared miriplatin, the intermediate $Pt(C_6H_{14}N_2)(NO_3)_2$ solution was synthesized from $Pt(C_6H_{14}N_2)I_2$ and $AgNO_3$, and it was treated with the anion exchange resin to give the key intermediate $Pt(C_6H_{14}N_2)(OH)_2$, and subsequently

reacted with $CH_3(CH_2)_{12}COOH$, in n-butanol to give target compound.

In the paper, the method of synthesis miriplatin was improved, the product was prepared prepared miriplatin from $Pt(C_6H_{14}N_2)I_2$ and $CH_3(CH_2)_{12}COOAg$ in H_2O, subsequently product was separated from AgI by dissolved in ethanol. The improved method can control the rate of reaction easy, and the ethanol replace chloroform in order to reduced the harmful. The reaction route was shown in Fig.1.

Experimental section

Materials and characterizations. $Pt(C_6H_{14}N_2)I_2$, $AgNO_3$ were prepared by Gui Yan Pharmcceutical Co., Ltd, $CH_3(CH_2)_{12}COONa$(AR), ethanol. Elemental analysis was perpormed on a JY/T 017-1996 elemental analyzer(C, H, N), Mass spectra was performed on a API QSTAR time-of-flight Spectrometer and a VG Autospec-3000 speitrometer, Infrared spectrum was performed on a TJ270-30 infrared spectrometer, The ^{1}H-NMR data was obtained with a 500 MHz Bruker DMX spectrometer.

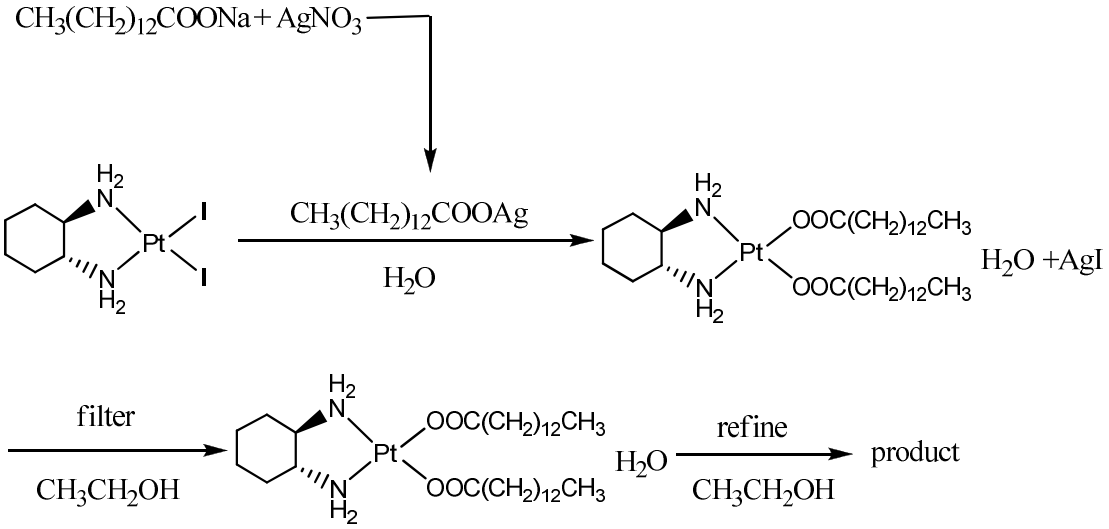

Fig.1. The reaction route of miriplatin

Synthesis of $CH_3(CH_2)_{12}COOAg$. $CH_3(CH_2)_{12}COONa$(5g, 20mmol) dissolved in 100ml H_2O at 60℃, $AgNO_3$ was dissolved in a 50ml, and added to the $CH_3(CH_2)_{12}COONa$ solution, and the mixture was stirred 0.5h at 60℃, the white precipitate was filtered off, washed with water and ethanol and dried at 60 to yield 5.8g of white precipitate.

Synthesis of miriplatin. $Pt(C_6H_{14}N_2)I_2$(2.8g, 5mmol) suspension was added to the $CH_3(CH_2)_{12}COOAg$(3.35g 10mmol) suspension in 100ml of H_2O, and the mixture was stirred 24h at room temperature, the precipitate was filtered off, washed with H_2O and ethanol and dried at 60℃. the precipitate was stired in 200ml of ethanol at 80℃, after 15min the AgI was filtered off, and 50ml of H_2O was added to the filtrate, the white precipitate was filtered off, washed with ethanol and dried at 60℃ to yield 3.4g(4.3mmol) of white precipitate, the production rate was about 87%, and 2.9g white precipitate was obtained by recrystallization with ethanol.

Results and discussion

Elemental Analysis. The result of the elemental analysis was listed in table 1. There was good agreement between the caculated and found values.

Tab.1 Element analysis result of the miriplatin

item	C	H	N
calcd(%)	52.17	3.58	8.95
found(%)	52.01	3.65	9.03

ESI-MS. As listed in Table2, the title compound have peaks of $[Pt(C_6N_2H_{14})(C_{14}H_{27}O_2)]^+$ and $[M\text{-}H_2O+Na]^+$.

Tab.2 ESI-MS data of the compound(Da with relative abumdance, %)

Comound	$[Pt(C_6N_2H_{14})(C_{14}H_{27}O_2)]^+$	$[M\text{-}H_2O+Na]^+$.
$PtC_{34}N_2H_{68}O_4 \cdot H2O$	536(56%)	787(100%)

IR. IR (KBr, cm^{-1}): 3416(m); 3199(m); 2928(s); 2856(m); 1616(vs); 1456(m); 1376(s); 720(w); 619(w)。

A strong C=O absorption appeared in 1616,1620cm^{-1}, which proved that the carboxylate anion was combined with the metal atom. The values of $\triangle V_{COO}^{-1}$（$Vas_{(COO)}$- $s_{(COO)}$）of the complexes were in the range of 238~318cm^{-1}, which were greater than $\triangle V_{COO}^{-1}$ of the coresponding sodium carboxylates so we may suggest that the carboxylate group was monodentate coordinated through oxygen atoms.

^{1}H NMR(DMSO, 500MHz). The ^{1}H NMR testing data of the title compound was listed in Table 3. ^{1}H NMR spectral peaks of compounds were compatible to the related molecular structure.

Tab.3 ^{1}H NMR data of the title compound

Chemical shiftδ/ppm	ascription
0.84~0.87	m, 6H, $2CH_2C\underline{H}_3$
1.12~1.14	d, 40H, $2CH_2(C\underline{H}_2)_{10}CH_2CH_3$
1.28~1.31	m, 4H, $CH_2C\underline{H}_2C\underline{H}_2CH_2$ of DACH
1.48~1.50	d, 2H, $C\underline{H}HCH_2CH_2C\underline{H}H$ of DACH
1.72~1.77	m, 4H, $2CH_2C\underline{H}_2(CH_2)_{10}$
2.12~2.15	d, 2H, $CH\underline{H}CH_2CH_2CH\underline{H}$ of DACH
2.44~2.47	m, 4H, $2O_2CC\underline{H}_2CH_2$
3.06	s, 2H, $2C\underline{H}NH_2$
5.01	s, 2H, $\underline{H}_2O$
7.31-7.33	d, 4H, $2N\underline{H}_2$

Conclusions

An improved synthetic route was designed and used to prepare the miriplatin, The water as the reaction medium can achieve a desirable reaction rate. The structure of the target compound was identified by elemental analysis，ESI-MS，FT-IR，^{1}H-NMR， and the structure was consistent with the target compound.

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