Journal of Organometallic Chemistry 694 (2009) 3247–3253

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

# Synthesis and characterization of organometallic rhenium(I) and technetium(I) bile acid complexes

Liliang Huang [a,b], Hua Zhu [a,b], Xiaoping Xu [a,b], Chunchun Zhang [a,b], Yu-Mei Shen [a,*]

[a] Research Center of Radiopharmaceuticals, Shanghai Institute of Applied Physics, Chinese Academy of Sciences, Shanghai 201800, PR China
[b] Graduate School of the Chinese Academy of Sciences, Beijing 100049, PR China

ARTICLE INFO

*Article history:*
Received 25 December 2008
Received in revised form 9 June 2009
Accepted 11 June 2009
Available online 17 June 2009

*Keywords:*
Tricarbonyl rhenium
Tricarbonyl technetium
Bile acids

ABSTRACT

Eight bile acid derivatives have been synthesized with alkyl chains of various length based tridentate ligand chelating system. These derivatives have been reacted with the precursor $[Et_4N]_2[Re(CO)_3Br_3]$ and *fac*-$[M(CO)_3(H_2O)_3]^+$ (M = $^{99m}$Tc, Re) in ethanol or ethanol–aqueous media to form water-soluble and stable organometallic complexes in good yields. $^1$H NMR, $^{13}$C NMR, IR and elemental analysis or HRMS spectroscopic analyses confirmed the tridentate complexation of the metal–tricarbonyl fragment exclusively via the tridentate chelates. In addition, the corresponding radioactive technetium-99m complexes were prepared successfully and challenged for stability in physiological phosphate buffer at 37 °C for 24 h. No decomposition of the complexes could be detected under the condition proving the stability of these complexes.



## 1. Introduction

Malignant hepatobiliary diseases, liver tumor and intestinal cancer have been imperiled health of human being [1–3]. It is crucial for patients how to diagnose timely in initial stage. ECT (emission computed tomography) is a technology making use of the radioactivity nuclide to diagnose. The former radiopharmaceuticals for hepatobiliary scintigraphy have mainly $^{99m}$Tc-IDA, $^{99m}$Tc-IDA derivatives, $^{99m}$Tc-GH and $^{99m}$Tc-PMT [4–6]. Although these radiopharmaceuticals have exerted important role, some hepatobiliary diseases, liver tumor and intestinal cancer are still not diagnosed accurately because of the limitation of specificity and affinity of these radiopharmaceuticals to cancer cell. Therefore, new radiopharmaceuticals with higher specificity and affinity needs to be developed to increase imaging quality.

Metals accumulating in the liver will cause serious problems while metal chelating agents can facilitate to excrete by urinary system but causing damage to kidney. An alternative for excretion of such metals via bile and feces is to use bile acids or bile acid derivatives as chelating agents [7]. Natural ligands specifically recognized by liver are the bile acids. Bile acids are selectively taken up from portal blood into the liver. Many bile acid derivatives including bile acid radiopharmaceuticals were synthesized and evaluated [8–14], but $^{99m}$Tc-labeled bile acid derivatives are still not explored up to now.

The low-cost single photon emission computed tomography (SPECT) isotope technetium-99m shows almost ideal decay properties for diagnosis (Ec = 140 keV and $t1/2$ = 6.0 h). Because $^{99m}$Tc is readily available due to a $^{99}$Mo/$^{99m}$Tc generator system is still the mainstay in routine nuclear medicine [15–17]. Therefore, the development of new SPECT radiotracers based on this important isotope is still of high interest.

In this paper, a series of novel bile acid derivatives, rhenium(I)–tricarbonyl complexes and radioactive Tc-99m(I) analogues were synthesized and characterized, their stability in vitro is very good in physiological phosphate buffer.

## 2. Experimental

### 2.1. Materials and methods

All of the starting materials and reagents were commercially available and used directly without further purification. The organometallic precursor $[Et_4N]_2[Re(CO)_3Br_3]$ and the radioactive precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$ were prepared as reported [18,19]. $Na[^{99m}TcO_4]$ was eluted from a $^{99}$Mo/$^{99m}$Tc generator (Shanghai Yuanpu isotope technology. Co., Ltd.) using 0.9% saline. HPLC analyses of the rhenium and technetium-99m complexes were performed on a Dionex P680-system equipped with a tunable absorption detector and a PDA-100 photodiode array detector using a Hypersil BDS C-18 reversed phase column (5 μm, 250 × / 4.6 mm). HPLC solvents: MeOH (solvent A), aqueous TEAP (triethylammonium phosphate) buffer, pH 2.76 (solvent B). HPLC eluting condition: (0–3 min, 15% A), (3–6 min, 15–25% A), (6–9 min,

* Corresponding author. Tel.: +86 21 39194692; fax: +86 21 39194696.
*E-mail address:* shenyumei@sinap.ac.cn (Y.-M. Shen).

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doi:10.1016/j.jorganchem.2009.06.015

25–35% A), (9–22 min, 35–98% A), (22–25 min, 98–25% A), (25–30 min, 25–15% A). The flow rate was 1 mL $min^{-1}$. Melting points were determined on a WRS-IA apparatus and were uncorrected. IR spectra were recorded as KBr disks on a Nicolet AVATAR 370 FT-IR spectrophotometer. The NMR spectra were recorded on a Bruker AV-500 FT-NMR at 500 MHz for $^1H$ and 125 MHz for $^{13}C$, using TMS as internal standard. Chemical shifts are expressed in ppm ($\delta$) and coupling constants ($J$) in Hz. High-resolution mass spectra were obtained on a Thermo-MAT95XP mass spectrometer under electron impact ionization conditions. Elemental analysis was obtained Elementar Vario EL III.

### 2.2. Chemical synthesis

#### 2.2.1. Syntheses of compounds **1a**–**4a**

The syntheses of compounds **1a**–**4a** were performed according to the literature procedure [20,21] with minor modification. Compounds **1**–**4** (one equivalent) were dissolved in $CH_3OH$. Hydrochloric acid (2.5 equivalent) for compound **1** and compound **3**, *p*-toluenesulfonic acid (2.5 equivalent) for compound **2** or phosphoric acid (2.5 equivalent) for compound **4** was added. The resulting mixture was stirred for 10–15 h at room temperature. The formation of the active ester was monitored by TLC. After the reaction finished (monitored by TLC), the solution was neutralized with 2 N NaOH. Then most methanol was removed under reduced pressure and the residue was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed successively with saturated $NaHCO_3$ (20 mL), water (20 mL) and saturated NaCl (20 mL). After drying over anhydrous sodium sulfate, filtered, and concentrated to give an oil. The resulting crude product was purified by flash chromatography (dichloromethane/methanol, 8:1). *Analytical data for compound **1a**:* Yield: 95%; m.p. 155.1–155.9 °C (lit [20] 155–156 °C); $^1H$ NMR ($CDCl_3$): $\delta$ 0.71 (s, 3H, 18-$CH_3$), 0.92 (s, 3H, 19-$CH_3$), 1.00 (d, 3H, $J$ = 6.2 Hz, 21-$CH_3$), 1.03–1.16 (m, 1H), 1.30–1.43 (m, 5H), 1.51–2.16 (m, 17H), 2.15–2.25 (m, 3H), 2.27–2.39 (m, 1H), 3.46–3.49 (m, 1H, $C_3$-βH), 3.87 (s, 3H, –$OCH_3$), 3.88–3.89 (m, 1H, $C_7$-βH), 4.01 (br s, 1H, $C_{12}$-βH); IR (KBr): $\nu$ (O–H) 3403, $\nu$ (C=O) 1736, $\nu$ (C–O) 1074 $cm^{-1}$.

*Analytical data for compound **2a**:* Yield: 93%; m.p. 85.2–86.0 °C; $^1H$ NMR ($CDCl_3$): $\delta$ 0.66 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.93 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 0.94–1.01 (m, 1H), 1.08–1.22 (m, 3H), 1.23–1.53 (m, 12H), 1.60–1.74 (m, 3H), 1.76–1.87 (m, 3H), 1.88–1.94 (m, 1H), 1.95–2.03 (m, 2H), 2.18–2.25 (m, 2H), 2.33–2.38 (m, 1H), 3.44–3.50 (m, 1H, $C_3$-βH), 3.666 (s, 3H,–$OCH_3$), 3.82–3.86 (m, 1H, $C_7$-βH); IR (KBr): $\nu$ (O–H) 3416, $\nu$ (C=O) 1786, $\nu$ (C–O) 1074 $cm^{-1}$.

*Analytical data for compound **3a**:* Yield: 88%; m.p. 58.4–58.6 °C; $^1H$ NMR ($CDCl_3$): $\delta$ 0.68 (s, 3H, 18-$CH_3$), 0.92 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 0.94 (s, 3H, 19-$CH_3$), 0.98–1.16 (m, 3H), 1.21–1.36 (m, 5H), 1.38–1.53 (m, 6H), 1.54–1.62 (m, 2H), 1.63–1.69 (m, 2H), 1.76–1.86 (m, 5H), 1.87–1.93 (m, 1H), 1.97–2.03 (m, 1H), 2.18–2.25 (m, 1H), 2.32–2.38 (m, 1H), 3.51–3.62 (m, 2H, $C_3$-βH and $C_7$-αH), 3.66 (s, 3H, –$OCH_3$); IR (KBr): $\nu$ (O–H) 3412, $\nu$ (C=O) 1786, $\nu$ (C–O) 1074 $cm^{-1}$.

*Analytical data for compound **4a**:* Yield: 86%; m.p. 66.8–67.6 °C; $^1H$ NMR ($CDCl_3$): $\delta$ 0.64 (s, 3H, 18-$CH_3$), 0.92 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 0.93–0.98 (m, 1H), 1.02 (s, 3H, 19-$CH_3$), 1.09–1.23 (m, 3H), 1.25–1.57 (m, 12H), 1.60–1.73 (m, 3H), 1.75–1.86 (m, 3H), 1.88–1.93 (m, 1H), 1.95–2.06 (m, 2H), 2.18–2.37 (m, 3H), 3.60–3.64 (m, 1H, $C_3$-βH), 3.67 (s, 3H, –$OCH_3$), 4.03–4.08 (m, 1H, $C_6$-βH); IR (KBr): $\nu$ (O–H) 3350, $\nu$ (C=O) 1743, $\nu$ (C–O) 1123 $cm^{-1}$.

#### 2.2.2. Syntheses of compounds **1b**–**4b** and **1b′**–**4b′**

Compounds **1b**–**4b** and **1b′**–**4b′** were prepared according to the literature procedure [22] with minor modification. Compounds **1a**–**4a** or **1a′**–**4a′** were dissolved in appropriate ethylenediamine or 1,6-hexanediamine and stirred at 73 °C for 16 h. The reaction solution was quenched with ice-water and extracted three times with trichloromethane. The organic layer was separated and washed successively with water and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo, which was purified by flash column chromatography ($CH_3OH$–$NH_3{\cdot}H_2O$, 85:1) to give **1b**–**4b** and **1b′**–**4b′**.

*Analytical data for compound **1b**.* Yield: 93%; m.p. 191.8–192.4 °C (lit [23] 192–194 °C); $^1H$ NMR ($CD_3OD$) : $\delta$ 0.70 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.94–0.98 (m, 1H), 1.02 (d, 3H, $J$ = 6.4 Hz, 21-$CH_3$), 1.06–1.13 (m, 1H), 1.25–1.47 (m, 7H), 1.51–1.66 (m, 7H), 1.71–1.97 (m, 9H), 2.08–2.15 (m, 1H), 2.22–2.31 (m, 4H), 2.76 (t, 2H, $J$ = 6.3 Hz, 2′-$CH_2$), 3.25 (t, 2H, $J$ = 6.3 Hz, 1′-$CH_2$), 3.33–3.39 (m, 1H, $C_3$-βH), 3.77–3.80 (m, 1H, $C_7$-βH), 3.94 (br s, 1H, $C_{12}$-βH); IR (KBr): $\nu$ (N–H and O–H) 3371, $\nu$ (C=O) 1638 $cm^{-1}$.

*Analytical data for compound **2b**:* Yield: 90%; m.p. 75.7–76.3 °C; $^1H$ NMR ($CD_3OD$): $\delta$ 0.68 (s, 3H,18-$CH_3$), 0.92 (s, 3H, 19-$CH_3$), 0.97 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.06–1.12 (m, 1H), 1.14–1.21 (m, 3H), 1.27–1.38 (m, 5H), 1.41–1.53 (m, 5H), 1.56–1.65 (m, 2H), 1.68–2.01 (m, 12H), 2.08–2.15 (m, 1H), 2.02–2.28 (m, 2H), 2.74 (t, 2H, $J$ = 6.4 Hz, 2′-$CH_2$), 3.24 (t, 2H, $J$ = 6.4 Hz, 1′-$CH_2$), 3.32–3.36 (m, 1H, $C_3$-βH), 3.71–3.79 (m, 1H, $C_7$-βH); IR (KBr): $\nu$ (N–H and O–H) 3358, $\nu$ (C=O) 1646 $cm^{-1}$.

*Analytical data for compound **3b**:* Yield: 91%; m.p. 223.9–224.2 °C; $^1H$ NMR ($CD_3OD$): $\delta$ 0.70 (s, 3H, 18-$CH_3$), 0.96 (s, 3H, 19-$CH_3$), 0.98 (d, 3H, $J$ = 2.9 Hz, 21-$CH_3$), 1.02–1.17 (m, 3H), 1.15–1.36 (m, 7H), 1.37–1.50 (m, 7H), 1.51–1.63 (m, 5H), 1.75–1.91 (m, 6H), 2.01–2.04 (m, 1H), 2.05–2.13 (m, 1H), 2.22–2.29 (m, 1H), 2.71 (t, 2H, $J$ = 6.4 Hz, 2′-$CH_2$), 3.22 (t, 2H, $J$ = 6.4 Hz, 1′-$CH_2$), 3.41–3.53 (m, 2H, $C_3$-βH and $C_7$-αH); IR (KBr): $\nu$ (N–H and O–H) 3411, $\nu$ (C=O) 1650 $cm^{-1}$.

*Analytical data for compound **4b**:* Yield: 85%; m.p. 116.8–117.2 °C; $^1H$ NMR (DMSO): $\delta$ 0.58 (s, 3H, 18-$CH_3$), 0.82 (s, 3H, 19-$CH_3$), 0.86 (d, 3H, $J$ = 7.0 Hz, 21-$CH_3$), 0.91–1.02 (m, 1H), 1.04–1.26 (m, 10H), 1.27–1.40 (m, 5H), 1.41–1.56 (m, 4H), 1.57–1.70 (m, 3H), 1.71–1.83 (m, 3H), 1.86–1.98 (m, 3H), 2.02–2.11 (m, 1H), 2.52 (d, 2H, $J$ = 8.0 Hz, 2′-$CH_2$), 2.99 (dd, 2H, $J_1$ = 16.0 Hz, $J_2$ = 8.0 Hz, 1′-$CH_2$), 3.27–3.32 (m, 1H, $C_3$-βH), 3.78–3.83 (m, 1H, $C_6$-βH), 7.712 (s, 1H, –NH); IR (KBr): $\nu$ (N–H and O–H) 3342, $\nu$ (C=O) 1642 $cm^{-1}$.

*Analytical data for compound **1b′**:* Yield:95%; m.p. 118.1–118.3 °C; $^1H$ NMR ($CD_3OD$): $\delta$ 0.70 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.92–0.97 (m, 1H), 1.02 (d, 3H, $J$ = 6.2 Hz, 21-$CH_3$), 1.06–1.16 (m, 1H), 1.25–1.46 (m, 10H), 1.48–1.68 (m, 13H), 1.71–2.03 (m, 9H), 2.08–2.13 (m, 1H), 2.18–2.27 (m, 3H), 2.75 (t, 2H, $J$ = 7.4 Hz, 6′-CH2), 3.15 (t, 2H, $J$ = 7.0 Hz, 1′-$CH_2$), 3.33–3.39 (m, 1H, $C_3$-βH), 3.73–3.79 (m, 1H, $C_7$-βH), 3.94 (br s, 1H, $C_{12}$-βH); IR (KBr): $\nu$ (N–H and O–H) 3350, $\nu$ (C=O) 1646 $cm^{-1}$.

*Analytical data for compound **2b′**:* Yield: 93%; m.p. 69.0–69.5 °C; $^1H$ NMR ($CD_3OD$): $\delta$ 0.68 (s, 3H, 18-$CH_3$), 0.92 (s, 3H, 19-$CH_3$), 0.96 (d, 3H, $J$ = 6.6 Hz, 21-$CH_3$), 1.01–1.21 (m, 5H), 1.22–1.40 (m, 11H), 1.46–1.56 (m, 10H), 1.57–1.68 (m, 2H), 1.68–2.02 (m, 8H), 2.05–2.12 (m, 1H), 2.18–2.27 (m, 2H), 2.703 (t, 2H, $J$ = 7.4 Hz, 6′-$CH_2$), 3.152 (t, 2H , $J$ = 7.0 Hz , 1′-$CH_2$), 3.33–3.39 (m, 1H, $C_3$-βH), 3.76–3.81 (m, 1H, $C_7$-βH); IR (KBr): $\nu$ (N–H and O–H) 3375, $\nu$ (C=O) 1646 $cm^{-1}$.

*Analytical data for compound **3b′**:* Yield: 92%; m.p. 54.4–55.6 °C; $^1H$ NMR ($CD_3OD$): $\delta$ 0.69 (s, 3H, 18-$CH_3$), 0.95 (s, 3H, 19-$CH_3$), 0.96 (d, 3H, $J$ = 6.6 Hz, 21-$CH_3$), 0.98–1.10 (m, 1H), 1.14–1.36 (m, 15H), 1.38–1.51 (m, 10H), 1.55–1.63 (m, 4H), 1.75–1.91 (m, 6H), 2.01–2.12 (m, 2H), 2.18–2.23 (m, 1H), 2.62 (t, 2H, $J$ = 7.2 Hz, 2′-$CH_2$), 3.14 (t, 2H, $J$ = 7.0 Hz , 1′-$CH_2$), 3.40–3.51 (m, 2H, $C_3$-βH and $C_7$-αH); IR (KBr): $\nu$ (N–H and O–H) 3297, $\nu$ (C=O) 1650 $cm^{-1}$.

*Analytical data for compound **4b′**:* Yield: 86%; m.p. 115.0–116.2 °C; $^1H$ NMR (DMSO): $\delta$ 0.58 (s, 3H, 18-$CH_3$), 0.82 (s, 3H, 19-$CH_3$), 0.86 (d, 3H, $J$ = 7.5 Hz, 21-$CH_3$), 0.92–1.10 (m, 6H), 1.12–

1.26 (m, 10H), 1.26–1.39 (m, 10H), 1.40–1.53 (m, 3H), 1.58–1.67 (m, 3H), 1.71–1.82(m, 3H), 1.86–1.97 (m, 2H), 1.99–2.09 (m, 1H), 2.98 (dd, 2H, $J_1$ = 15.5 Hz, $J_2$ = 7.5 Hz, 6′-$CH_2$), 3.29 (m, 2H, 1′-$CH_2$), 3.55–3.60 (m, 1H, $C_3$-βH), 3.78–3.83 (m, 1H, $C_6$-βH), 7.71 (s, 1H, –NH); IR (KBr): $\nu$ (N–H and O–H) 3293, $\nu$ (C=O) 1646 $cm^{-1}$.

### 2.2.3. Syntheses of compounds 1c–4c and 1c′–4c′

Compounds **1c**–**4c** and **1c′**–**4c′** was prepared according to the literature procedure [23] with minor modification. Compounds **1b**–**4b** and **1b′**–**4b′** (1 equivalent) were dissolved in 15 mL 1,2-dichloroethane (DCE) and 2 mL methanol. Then 2-pyridine carboxaldehyde (2.2 equivalent) in 1,2-dichloroethane (5 mL) was slowly added. The reaction mixture was stirred at 21 °C for 3 h. Sodium triacetoxyborohydride (2.2 equivalent) was then added to the solution at 0 °C. After 1 h, the suspension was stirred at ambient temperature for 16 h. The reaction mixture was quenched with ice-water and extracted three times with dichloromethane. The organic layer was separated and washed successively with water and brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated to give an yellow oil, which was purified by flash column chromatography (dichloromethane/methanol, 20:1 and dichloromethane/methanol, 10:1) to give **1c**.

*Analytical data for compound **1c**:* Yield: 81%; m.p. 72.0–72.6 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.67 (s, 3H, 18-$CH_3$), 0.87 (s, 3H, 19-$CH_3$), 0.92–0.98 (m, 1H), 1.02 (d, 3H, $J$ = 5.9 Hz, 21-$CH_3$), 1.06–1.12 (m, 1H), 1.23–1.28 (m, 1H), 1.32–1.70 (m, 12H), 1.72–1.94 (m, 8H), 2.08–2.15 (m, 1H), 2.21–2.28 (m, 3H), 2.74 (t, 2H, $J$ = 5.6 Hz, 2′-$CH_2$), 3.34 (dd, 2H, $J_1$ = 10.4 Hz, $J_2$ = 4.8 Hz, 1′-$CH_2$), 3.41–3.44 (m, 1H, $C_3$-βH), 3.82–3.86 (m, 1H, $C_7$-βH), 3.87 (s, 4H, –N($CH_2$)$_2$), 3.97 (br s, 1H, $C_{12}$-βH), 7.17 (dd, 2H, $J_1$ = 7.3 Hz, $J_2$ = 5.0 Hz, δ-H , Py), 7.36 (d, 2H, $J$ = 5.6 Hz, β-H, Py), 7.55 (s, 1H, –NH), 7.63 (td, 2H, $J_1$ = 7.7 Hz, $J_2$ = 1.5 Hz, γ-H, Py), 8.54 (d, 2H, $J$ = 4.7 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3396, $\nu$ (C=O) 1650, $\nu$ (C=N) 1593 $cm^{-1}$; HRMS Calc. for $C_{38}H_{56}N_4O_4$ $[M+1]^+$ 633.4380. Found: 633.4380.

*Analytical data for compound **2c**:* Yield: 80%; m.p. 70.3–71.6 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.67 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.97 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.04–1.51 (m, 14H), 1.59–1.72 (m, 3H), 1.78–1.97 (m, 7H), 2.08–2.15 (m, 2H), 2.18–2.30(m, 2H), 2.75 (t, 2H, $J$ = 5.6 Hz, 2′-$CH_2$), 3.35 (dd, 2H, $J_1$ = 11.2 Hz, $J_2$ = 4.9 Hz, 1′-$CH_2$), 3.43–3.48 (m, 1H, $C_3$-βH), 3.80–3.85 (m, 1H, $C_7$-βH), 3.88 (s, 4H, –N($CH_2$)$_2$), 7.18 (ddd, 2H, $J_1$ = 7.4 Hz, $J_2$ = 5.0 Hz, $J_3$ = 0.9 Hz, δ-H, Py), 7.36 (d, 2H, $J$ = 7.8 Hz, β-H, Py), 7.48 (s, 1H, –NH), 7.63 (td, 2H, $J_1$ = 7.7 Hz, $J_2$ = 1.8 Hz, γ-H, Py), 8.56 (ddd, 2H, $J_1$ = 4.2 Hz, $J_2$ = 1.6 Hz, $J_3$ = 0.8 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3346, $\nu$ (C=O) 1646, $\nu$ (C=N) 1597 $cm^{-1}$; HRMS Calc. for $C_{38}H_{56}N_4O_3$ $[M+1]^+$ 617.4431. Found: 617.4424.

*Analytical data for compound **3c**:* Yield: 80%; m.p. 71.5–72.3 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.68 (s, 3H, 18-$CH_3$), 0.95 (s, 3H, 19-$CH_3$), 0.97 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.03–1.56 (m, 15H), 1.57–1.68 (m, 5H), 1.75–1.83 (m, 4H), 1.89–1.96 (m, 1H), 2.01–2.05(m, 1H), 2.10–2.16 (m, 1H), 2.25–2.32(m, 1H), 2.74 (t, 2H, $J$ = 5.6 Hz, 2′-$CH_2$), 3.34 (dd, 2H, $J_1$ = 10.9 Hz, $J_2$ = 5.0 Hz, 1′-$CH_2$), 3.53–3.62 (m, 2H, $C_3$-βH and $C_7$-αH), 3.87 (s, 4H, –N($CH_2$)$_2$), 7.18 (ddd, 2H, $J_1$ = 7.4 Hz, $J_2$ = 4.8 Hz, $J_3$ = 0.8 Hz, δ-H, Py), 7.35 (d, 2 H, $J$ = 7.8 Hz, β-H, Py),7.51 (s, 1H, –NH), 7.63 (td, 2H, $J_1$ = 7.7 Hz, $J_2$ = 1.8 Hz, γ-H, Py), 8.55 (dd, 2H, $J_1$ = 3.4 Hz, $J_2$ = 0.8 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3301, $\nu$ (C=O) 1646, $\nu$ (C=N) 1593 $cm^{-1}$; HRMS Calc. for $C_{38}H_{56}N_4O_3$ $[M+1]^+$ 617.4431. Found: 617.4419.

*Analytical data for compound **4c**:* Yield: 76%; m.p. 73.0–73.6 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.64 (s, 3H, 18-$CH_3$), 0.90 (s, 3H, 19-$CH_3$), 0.96 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.03–1.22 (m, 8H), 1.23–1.49 (m, 8H), 1.51–1.60 (m, 4H), 1.66–1.99 (m, 6H), 2.09–2.28 (m, 2H), 2.74 (t, 2H, $J$ = 5.6 Hz, 2′-$CH_2$), 3.34 (dd, 2H, $J_1$ = 10.9 Hz, $J_2$ = 5.0 Hz, 1′-$CH_2$), 3.60–3.65 (m, 1H, $C_3$-βH), 3.87 (s, 4H, –N($CH_2$)$_2$), 3.98–4.03 (m, 1H, $C_6$-βH),7.18 (ddd, 2H, $J_1$ = 7.3 Hz, $J_2$ = 5.0 Hz, $J_3$ = 0.7 Hz, δ-H, Py), 7.35 (d, 2H, $J$ = 7.8 Hz, β-H, Py), 7.53 (s, 1H, –NH), 7.63 (td, 2H, $J_1$ = 7.6 Hz, $J_2$ = 1.8 Hz, γ-H, Py), 8.55 (dd, 2H, $J_1$ = 4.7 Hz, $J_2$ = 0.7 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3321, $\nu$ (C=O) 1646, $\nu$ (C=N) 1589 $cm^{-1}$; HRMS Calc. for $C_{38}H_{56}N_4O_3$ $[M+1]^+$ 617.4431. Found: 617.4431.

*Analytical data for compound **1c′**:* Yield: 78%; m.p. 84.1–84.6 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.67 (s, 3H, 18-$CH_3$), 0.87 (s, 3H, 19-$CH_3$), 0.92–0.97 (m, 1H), 0.98 (d, 3H, $J$ = 6.2 Hz, 21-$CH_3$), 1.03–1.13 (m, 1H), 1.20–1.30 (m, 5H), 1.34–1.61 (m, 13H), 1.62–1.96 (m, 11H), 2.02–2.09 (m, 1H), 2.15–2.27 (m, 3H), 2.55 (t, 2H, $J$ = 7.4 Hz, 6′-$CH_2$), 3.17 (dd, 2H, $J_1$ = 14.5 Hz, $J_2$ = 7.2 Hz, 1′-$CH_2$), 3.39–3.44 (m, 1H, $C_3$-βH), 3.78–3.82 (m, 1H, $C_7$-βH), 3.83 (s, 4H, –N($CH_2$)$_2$), 3.95 (br s, 1H, $C_{12}$-βH), 6.11 (s, 1H, –NH), 7.15 (dd, 2H, $J_1$ = 6.8 Hz, $J_2$ = 5.3 Hz, δ-H, Py), 7.53 (d, 2H, $J$ = 7.8 Hz , β-H, Py), 7.66 (td, 2H, $J_1$ = 7.6 Hz, $J_2$ = 1.7 Hz, γ-H, Py), 8.51(d, 2H, $J$ = 4.7 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3350, $\nu$ (C = O) 1646, $\nu$ (C=N) 1589 $cm^{-1}$; HRMS Calc. for $C_{42}H_{64}N_4O_4$ $[M+1]^+$ 689.5006. Found: 689.5009.

*Analytical data for compound **2c′**:* Yield: 75%; m.p. 68.7–69.3 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.65 (s, 3H, 18-$CH_3$), 0.90 (s, 3H, 19-$CH_3$), 0.92 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 0.93–0.99 (m, 1H), 1.08–1.19 (m, 3H), 1.21–1.56 (m, 19H), 1.60–2.06 (m, 11H), 2.16–2.25 (m, 2H), 2.54 (t, 2H, $J$ = 7.3 Hz, 6′-$CH_2$), 3.19 (dd, 2H, $J_1$ = 13.4 Hz, $J_2$ = 6.6 Hz, 1′-$CH_2$), 3.41–3.47 (m, 1H, $C_3$-βH), 3.81 (s, 4H, –N($CH_2$)$_2$), 3.80–3.85 (m, 1H, $C_7$-βH), 5.59 (s, 1H, –NH), 7.15 (m, 2H, δ-H, Py), 7.54 (d, 2H, $J$ = 7.8 Hz, β-H, Py), 7.66 (td, 2H, $J_1$ = 7.7 Hz, $J_2$ = 1.7 Hz, γ-H, Py), 8.52 (dd, 2H, $J_1$ = 4.7 Hz, $J_2$ = 0.7 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3354, $\nu$ (C=O) 1650, $\nu$ (C=N) 1593 $cm^{-1}$; HRMS Calc. for $C_{42}H_{64}N_4O_3$ $[M+1]^+$ 673.5057. Found: 673.5059.

*Analytical data for compound **3c′**:* Yield: 79%; m.p. 63.1–64.6 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.67 (s, 3H, 18-$CH_3$), 0.92 (s, 3H, 19-$CH_3$), 0.94 (d, 3H, $J$ = 3.5 Hz, 21-$CH_3$), 1.01–1.13 (m, 1H), 1.15–1.40 (m, 10H), 1.41–1.49 (m, 7H), 1.50–1.61 (m, 7H), 1.62–1.76 (m, 5H), 1.77–2.13 (m, 3H), 2.18–2.23 (m, 3H), 2.55 (t, 2H, $J$ = 9.3 Hz, 6′-$CH_2$), 3.19 (dd, 2H, $J_1$ = 13.0 Hz, $J_2$ = 8.0 Hz, 1′-$CH_2$), 3.51–3.60 (m, 2H, $C_3$-βH and $C_7$-αH), 3.83 (s, 4H, –N($CH_2$)$_2$), 5.51 (s, 1H, –NH), 7.15 (m, 2H, δ-H, Py), 7.54 (d, 2H, $J$ = 5.0 Hz, β-H, Py), 7.66(td, 2H, $J_1$ = 9.5 Hz, $J_2$ = 2.0 Hz, γ-H, Py), 8.52 (d, 2H, $J$ = 6.0 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3366, $\nu$ (C=O) 1646, $\nu$ (C=N) 1597 $cm^{-1}$; HRMS Calc. for $C_{42}H_{64}N_4O_3$ $[M+1]^+$ 673.5057. Found: 673.5045.

*Analytical data for compound **4c′**:* Yield: 71%; m.p. 70.4–72.3 °C; $^1$H NMR ($CDCl_3$): $\delta$ 0.63 (s, 3H, 18-$CH_3$), 0.90 (s, 3H, 19-$CH_3$), 0.92 (d, 3H, $J$ = 6.4 Hz, 21-$CH_3$), 0.98–1.20 (m, 7H), 1.21–1.49 (m, 15H), 1.50–1.77 (m, 7H), 1.82–1.96 (m, 5H), 2.00–2.08 (m, 2H), 2.18–2.23 (m, 1H), 2.54 (t, 2H, $J$ = 7.2 Hz, 6′-$CH_2$), 3.19 (dd, 2H, $J_1$ = 13.3 Hz, $J_2$ = 6.7 Hz, 1′-$CH_2$), 3.59–3.63 (m, 1H, $C_3$-βH), 3.81 (s, 4H, –N($CH_2$)$_2$), 4.02–4.07 (m, 1H, $C_6$-βH), 7.14 (dd, 2H, $J_1$ = 6.9 Hz, $J_2$ = 5.5 Hz, δ-H, Py), 7.53 (d, 2H, $J$ = 7.8 Hz, β-H, Py), 7.66 (td, 2H, $J_1$ = 7.7 Hz, $J_2$ = 1.7 Hz, γ-H, Py), 8.51(d, 2H, $J$ = 4.5 Hz, σ-H, Py); IR (KBr): $\nu$ (O–H) 3371, $\nu$ (C=O) 1642, $\nu$ (C=N) 1593 $cm^{-1}$; HRMS Calc. for $C_{42}H_{68}N_4O_3$ $[M+1]^+$ 673.5012. Found: 673.5032.

### 2.2.4. Syntheses of complexes 1d–4d and 1d′–4d′

Complexes **1d**–**4d** and **1d′**–**4d′** were synthesized according to the following general procedure: $(Et_4N)_2[Re(CO)_3Br_3]$ (1 equivalent) and the ligands **1c**–**4c** and **1c′**–**4c′** (1 equivalent) were solved in ethanol and stirred at room temperature till the disappearance of the starting material (monitored by TLC). The reaction mixture was evaporated to dryness. The residue was purified by chromatography on silica gel (first $CH_2Cl_2$–$CH_3OH$: 20:1, then $CH_2Cl_2$–$CH_3OH$: 15:1).

*Analytical data for complex **1d**:* Yield: 71%; m.p.125.7–127.4 °C; $^1$H NMR ($CD_3OD$): $\delta$ 0.70 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.92–0.98 (m, 1H), 1.05 (d, 3H, $J$ = 6.3 Hz, 21-$CH_3$), 1.10–1.17 (m, 1H), 1.22–1.30 (m, 2H), 1.33–1.46 (m, 5H), 1.51–1.68 (m, 6H), 1.71–2.08 (m, 8H), 2.20–2.38 (m, 4H), 3.32–3.40 (m, 1H, 3-CH), 3.75 (t, 2H, $J$ = 7.1 Hz, 2′-$CH_2$), 3.76–3.78 (s, 1H, 7-CH), 3.92–3.96 (m, 1H, 12-CH), 3.95 (t, 2H, $J$ = 4.3 Hz, 1′-$CH_2$), 4.90–5.06 (m, 4H,

–N($CH_2$)$_2$), 7.37 (t, 2H, $J$ = 6.6 Hz, δ-CH, Py), 7.58 (d, 2H, $J$ = 7.8 Hz, β-CH, Py), 7.95 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.5 Hz, γ-CH, Py), 8.32 (s, 1H, –NH), 8.85 (d, 2H, $J$ = 6.0 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 37.21 (C1), 31.5 (C2), 73.2 (C3), 40.8 (C4), 43.3 (C5), 36.8 (C6), 69.9 (C7), 41.3 (C8), 28.2 (C9), 36.2 (C10), 29.9 (C11), 74.3 (C12), 47.8 (C13), 43.5 (C14), 24.5 (C15), 29.1 (C16), 48.4 (C17), 13.3 (C18), 23.5 (C19), 36.9 (C20), 18.1 (C21), 34.4 (C22), 33.5 (C23), 177.7 (C24), 43.3 (C1′), 69.4 (C2′), 68.9 (2C, $PyCH_2$), 162.2 (2C, Py-αC), 127.3 (2C, Py-βC), 142.0 (2C, Py-γC), 125.0 (2C, Py-δC), 153.4 (2C, Py-σC), 197.4 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3316, ν (C=O) 2030, ν (C=O) 1920, ν (C=O) 1642 cm$^{-1}$; Anal. Calc. for $C_{41}H_{56}N_4O_7ReBr{\cdot}0.5CH_2Cl_2$: C, 48.61; H, 5.60; N, 5.46. Found: C, 48.46; H, 5.56; N, 5.61%.

*Analytical data for complex* ***2d****:* Yield: 76%, m.p. 166.8–168.6 °C; $^1$H NMR ($CD_3OD$): δ 0.68 (s, 3H, 18-$CH_3$), 0.92 (s, 3H, 19-$CH_3$), 0.99 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.03–1.13 (m, 1H), 1.15–1.22(m, 2H), 1.28–1.39 (m, 7H), 1.41–1.56 (m, 6H), 1.57–1.67 (m, 2H), 1.71–1.78 (m, 1H), 1.82–1.89 (m, 4H), 1.90–2.01 (m, 3H), 2.18–2.36 (m, 3H), 3.33–3.40 (m, 1H, 3-CH), 3.74 (t, 2H, $J$ = 7.0 Hz, 2′-$CH_2$), 3.72–3.79 (s, 1H, 7-CH),3.94 (t, 2H, $J$ = 7.1 Hz, 1′-$CH_2$), 4.90–5.03 (m, 4H, –N($CH_2$)$_2$), 7.37 (t, 2H, $J$ = 6.5 Hz, δ-CH,Py), 7.56 (d, 2H, $J$ = 7.9 Hz, β-CH, Py), 7.94 (t, 2H, $J$ = 7.8 Hz,γ-CH, Py), 8.85 (d, 2H, $J$ = 5.5 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 37.2(C1), 31.7 (C2), 73.2 (C3), 40.8 (C4), 43.5 (C5), 36.5 (C6), 69.9 (C7), 41.1 (C8), 36.2 (C9), 36.9 (C10), 22.1 (C11), 41.4 (C12), 44.0 (C13), 51.9 (C14), 24.9 (C15), 29.6 (C16), 57.6 (C17), 12.5 (C18), 23.7 (C19), 37.2 (C20), 19.2 (C21), 34.4 (C22), 33.5 (C23), 177.6 (C24), 44.0 (C1′), 69.3 (C2′), 68.9 (2C, PyCH2), 162.2 (2C, Py-αC), 127.3 (2C, Py-βC), 142.0 (2C, Py-γC), 124.9 (2C, Py-δC), 153.4 (2C, Py-σC), 197.4 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3316, ν (C=O) 2030, ν (C=O) 1916, ν (C=O) 1646 cm$^{-1}$; Anal. Calc. for $C_{41}H_{56}N_4O_6R$-eBr·0.5$CH_2Cl_2$: C, 49.37; H, 5.69; N, 5.55. Found: C, 49.30; H, 6.02; N, 5.53%.

*Analytical data for complex* ***3d****:* Yield: 73%, m.p. 226.7–228.3 °C; $^1$H NMR ($CD_3OD$): δ 0.70 (s, 3H, 18-$CH_3$), 0.96 (s, 3H, 19-$CH_3$), 0.99 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.01–1.05 (m, 1H), 1.08–1.38 (m, 10H), 1.39–1.49 (m, 6H), 1.50–1.61 (m, 4H), 1.77–1.90 (m, 5H), 2.01–2.07 (m, 1H), 2.15–2.22 (m, 1H), 2.31–2.37 (m, 1H), 3.40–3.50 (m, 2H, 3-CH and 7-CH), 3.74 (t, 2H, $J$ = 7.0 Hz, 2′-$CH_2$), 3.94 (t, 2H, $J$ = 7.1 Hz, 1′-$CH_2$), 4.90–5.05 (m, 4H, –N($CH_2$)$_2$), 7.37 (t, 2H, $J$ = 6.6 Hz, δ-CH, Py), 7.57 (d, 2H, $J$ = 8.0 Hz, β-CH, Py), 7.94 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.4 Hz, γ-CH, Py, 8.85 (d, 2H, $J$ = 5.4 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 38.3 (C1), 31.3 (C2), 72.4 (C3), 38.9 (C4), 44.3 (C5), 36.4 (C6), 72.3 (C7), 41.0 (C8), 35.5 (C9), 36.8 (C10), 22.7 (C11), 41.9 (C12), 44.8 (C13), 56.9 (C14), 28.2 (C15), 30.0 (C16), 57.8 (C17), 12.9 (C18), 24.2 (C19), 37.1 (C20), 19.3 (C21), 34.4 (C22), 33.5 (C23), 177.6 (C24), 45.1 (C1′), 69.9 (C2′), 68.9 (2C, $PyCH_2$), 162.2 (2C, Py-αC), 127.3 (2C, Py-βC), 141.9 (2C, Py-γC), 124.9 (2C, Py-δC), 153.4 (2C, Py-σC), 197.3 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3319, ν (C=O) 2026, ν (C=O) 1920, ν (C=O) 1650 cm$^{-1}$; Anal. Calc. for $C_{41}H_{56}N_4O_6ReBr{\cdot}1.5CH_2Cl_2$: C, 46.64; H, 5.43; N, 5.11. Found: C, 46.32; H, 5.80; N, 5.01%.

*Analytical data for complex* ***4d****:* Yield: 68%, m.p. 220.4–222.1 °C; $^1$H NMR ($CD_3OD$): δ 0.68 (s, 3H, 18-$CH_3$), 0.92 (s, 3H, 19-$CH_3$), 0.99 (d, 3H, $J$ = 6.4 Hz, 21-$CH_3$), 1.02–1.26 (m, 7H), 1.27–1.50 (m, 10H), 1.56–1.65 (m, 4H), 1.73–1.92 (m, 4H), 1.94–2.03 (m, 1H), 2.18–2.28 (m, 1H), 2.30–2.38 (m, 1H), 3.49–3.53 (m, 1H, 3-CH), 3.75 (t, 2H, $J$ = 7.1 Hz, 2′-$CH_2$), 3.94 (t, 2H, $J$ = 6.7 Hz, 1′-$CH_2$), 3.97–4.02 (m, 1H, 6-CH),4.90–5.05 (m, 4H, –N($CH_2$)$_2$), 7.37 (t, 2H, $J$ = 6.6 Hz, δ-CH,Py), 7.56 (t, 2H, $J$ = 7.7 Hz, β-CH, Py), 7.94 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.5 Hz, γ-CH, Py), 8.85 (d, 2H, $J$ = 5.5 Hz, σ-CH, Py; $^{13}$C NMR ($CD_3OD$): δ 36.8 (C1), 30.3 (C2), 72.7 (C3), 35.9 (C4), 44.3 (C5), 69.9 (C6), 36.5 (C7), 33.4 (C8), 34.3 (C9), 37.1 (C10), 22.2 (C11), 37.2 (C12), 41.6 (C13), 50.2 (C14), 24.4 (C15), 25.6 (C16), 57.7 (C17), 12.8 (C18), 19.3 (C19), 36.8 (C20), 19.2 (C21), 29.6 (C22), 31.4 (C23), 177.6 (C24), 44.3 (C1′), 57.9 (C2′), 68.9 (2C, $PyCH_2$), 162.2 (2C, Py-αC), 127.3 (2C, Py-βC), 142.0 (2C, Py-γC), 124.9 (2C, Py-δC), 153.4 (2C, Py-σC), 197.5 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3319, ν (C=O) 2030, ν (C=O) 1916, ν (C=O) 1650 cm$^{-1}$; Anal. Calc. for $C_{41}H_{56}N_4O_6ReBr{\cdot}2CH_2Cl_2$: C, 45.43; H, 5.31; N, 4.92. Found: C, 45.21; H, 5.51; N, 4.97%.

*Analytical data for complex* ***1d′****:* Yield: 75%, m.p. 137.6–138.3 °C; $^1$H NMR ($CD_3OD$): δ 0.71 (s, 3H, 18-$CH_3$), 0.90 (s, 3H, 19-$CH_3$), 0.92–0.98 (m, 1H), 1.03 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.05–1.13 (m, 1H), 1.21–1.65 (m, 19H), 1.66–1.98 (m, 10H), 2.08–2.13 (m, 1H), 2.20–2.30 (m, 3H), 3.20 (t, 2H, $J$ = 6.7 Hz, 6′-$CH_2$), 3.33–3.39 (m, 1H, 3-CH), 3.77–3.79 (m, 2H, 1′-$CH_2$), 3.79–3.81 (m, 1H, 7-CH), 3.95 (br s, 1H, 12-CH), 4.83–4.91 (m, 4H, –N($CH_2$)$_2$), 7.37 (t, 2H, $J_1$ = 6.6 Hz, δ-CH , Py), 7.58 (d, 2H, $J$ = 7.8 Hz , β-CH, Py), 7.94 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.5 Hz, γ-CH, Py), 7.98 (br s, 1H, –NH), 8.85 (d, 2H, $J$ = 5.5 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 37.2 (C1), 31.5 (C2), 73.2 (C3), 40.8 (C4), 43.3 (C5), 36.8 (C6), 72.1 (C7), 41.3 (C8), 28.2 (C9), 36.2 (C10), 29.9 (C11), 74.3 (C12), 47.8 (C13), 43.5 (C14), 24.5 (C15), 29.0 (C16), 48.4 (C17), 13.3 (C18), 23.5 (C19),37.2 (C20), 18.1 (C21), 34.6 (C22), 33.8 (C23), 177.1 (C24),40.4 (C1′), 30.5 (C2′), 26.6 (C3′), 27.7 (C4′), 27.9 (C5′), 69.3 (C6′), 69.1 (2C, PyCH2), 162.5 (2C, Py-αC), 127.2 (2C, Py-βC), 141.9 (2C, Py-γC), 124.9 (2C, Py-δC), 153.4 (2C, Py-σC), 197.6 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3436, ν (C=O) 2026, ν (C=O) 1916, ν (C=O) 1634 cm$^{-1}$; Anal. Calc. for $C_{45}H_{64}N_4O_7ReBr{\cdot}2CH_2Cl_2$: C, 46.69; H, 5.66; N, 4.63. Found: C, 46.79; H, 5.26; N, 5.01%.

*Analytical data for complex* ***2d′****:* Yield: 78%, m.p. 213.2–215.4 °C; $^1$H NMR ($CD_3OD$): δ 0.68 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.92–0.96 (m, 1H), 0.97 (d, 3H, $J$ = 6.5 Hz, 21-$CH_3$), 1.06–1.21 (m, 3H), 1.23–1.38 (m, 6H), 1.41–1.62 (m, 14H), 1.66–2.02 (m, 10H), 2.08–2.14 (m, 1H), 2.20–2.29 (m, 2H), 3.19 (t, 2H, $J$ = 6.5 Hz, 6′-$CH_2$), 3.30–3.40 (m, 1H, 3-CH), 3.78–3.80 (m, 2H, 1′-$CH_2$), 3.81–3.83 (m, 1H, 7-CH),4.83–4.89 (m, 4H, –N($CH_2$)$_2$), 7.37 (t, 2H, $J$ = 6.7 Hz, δ-CH, Py), 7.56 (d, 2H, $J$ = 7.9 Hz, β-CH, Py), 7.94 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.4 Hz, γ-CH, Py), 8.85 (d, 2H, $J$ = 5.4 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 37.2 (C1), 31.7(C2), 73.1 (C3), 40.4 (C4), 41.4 (C5), 36.2 (C6), 72.2 (C7), 40.8 (C8), 34.5 (C9), 36.8 (C10), 22.1 (C11), 41.1 (C12), 43.5(C13), 51.8 (C14), 24.9 (C15), 29.6 (C16), 57.7 (C17), 12.5 (C18), 23.7 (C19),36.5 (C20),19.2 (C21), 34.4 (C22), 33.7 (C23), 177.6 (C24), 44.0 (C1′), 30.6 (C2′), 26.5 (C3′), 27.7 (C4′), 27.9 (C5′), 69.3 (C6′), 69.1 (2C, PyCH2), 162.5 (2C, Py-αC), 127.2 (2C, Py-βC), 141.9 (2C, Py-γC), 124.9 (2C, Py-δC), 153.5 (2C, Py-σC), 197.5 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3419, ν (C=O) 2026, ν (C=O) 1916, ν (C = O) 1650 cm$^{-1}$; Anal. Calc. for $C_{45}H_{64}N_4O_6ReBr{\cdot}1.5CH_2Cl_2$: C, 48.54; H, 5.86; N, 4.87. Found: C, 48.16; H, 5.69; N, 5.21%.

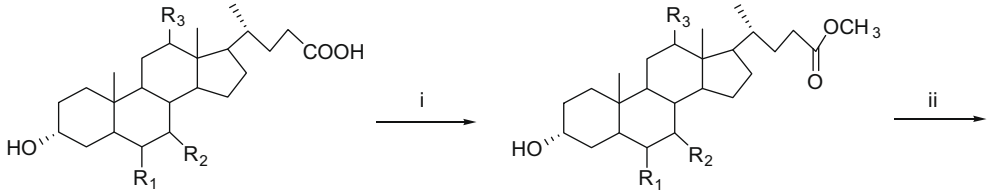
*Analytical data for complex* ***3d′****:* Yield: 65%, m.p. 225.6–226.5 °C; $^1$H NMR ($CD_3OD$): δ 0.71 (s, 3H, 18-$CH_3$), 0.95 (s, 3H, 19-$CH_3$), 0.97 (d, 3H, $J$ = 6.6 Hz, 21-$CH_3$), 1.01–1.08 (m, 2H), 1.10–1.33 (m, 7H), 1.36–1.44 (m, 11H), 1.51–1.62 (m, 6H), 1.78–2.10 (m, 10H), 2.21–2.25 (m, 1H), 3.20 (t, 2H, $J$ = 6.8 Hz, 6′-$CH_2$), 3.42–3.51 (m, 2H, 3-CH and 7-CH), 3.73–3.82 (m, 2H, 1′-$CH_2$), 4.83–4.87 (m, 4H, –N($CH_2$)$_2$), 7.36 (t, 2H, $J$ = 6.5 Hz, δ-CH, Py), 7.55 (dd, 2H, $J_1$ = 7.9 Hz, $J_2$ = 2.5 Hz, β-CH, Py), 7.93 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.4 Hz, γ-CH, Py), 8.85 (d, 2H, $J$ = 5.4 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 38.9 (C1), 31.4 (C2), 72.4 (C3), 40.4 (C4), 44.3 (C5), 36.4 (C6), 72.3 (C7), 41.0 (C8), 35.5 (C9), 37.2 (C10), 22.7 (C11), 41.9 (C12), 44.8 (C13), 56.9 (C14), 28.3 (C15), 30.0 (C16), 57.8 (C17), 12.9 (C18), 24.2 (C19), 38.3 (C20), 19.3 (C21), 34.5 (C22), 33.8(C23), 177.1 (C24), 45.1 (C1′), 30.6 (C2′), 26.5 (C3′), 27.7 (C4′), 27.9 (C5′), 72.2 (C6′), 69.1 (2C, $PyCH_2$), 162.5 (2C, Py-αC), 127.2 (2C, Py-βC), 141.9 (2C, Py-γC), 124.9 (2C, Py-δC), 153.5 (2C, Py-σC), 197.9 (3C, *fac*-Re(CO)$_3$); IR (KBr): ν (O–H) 3416, ν (C=O) 2026, ν (C=O) 1920, ν (C=O) 1642 cm$^{-1}$; Anal. Calc. for $C_{45}H_{64}N_4O_6ReBr$: C, 52.82; H, 6.31; N, 5.47. Found: C, 52.44; H, 6.17; N, 5.56%.

*Analytical data for complex* ***4d′****:* Yield: 73%, m.p. 214.8–215.6 °C; $^1$H NMR ($CD_3OD$): δ 0.67 (s, 3H, 18-$CH_3$), 0.91 (s, 3H, 19-$CH_3$), 0.95

(d, 3H, $J$ = 8.4 Hz, 21-$CH_3$), 1.12–1.22 (m, 7H), 1.23–1.57 (m, 14H), 1.58–1.68 (m, 7H), 1.75–1.82 (m, 2H), 1.84–2.03 (m, 5H), 2.07–2.14 (m, 1H), 2.20–2.26 (m, 1H), 2.02–2.11 (m, 1H), 3.20 (t, 2H, $J$ = 6.9 Hz, 6′-$CH_2$), 3.48–3.53 (m, 1H, 3-CH), 3.78–3.81 (m, 2H, 1′-$CH_2$), 3.98–4.03 (m, 1H, 6-CH),4.84–4.88 (m, 4H, –$N(CH_2)_2$), 7.36 (t, 2H, $J$ = 6.3 Hz, δ-CH, Py), 7.55 (d, 2H, $J$ = 7.9 Hz, β-CH, Py), 7.94 (td, 2H, $J_1$ = 7.8 Hz, $J_2$ = 1.4 Hz, γ-CH, Py), 8.86 (d, 2H, $J$ = 5.4 Hz, σ-CH, Py); $^{13}$C NMR ($CD_3OD$): δ 37.1 (C1), 30.3 (C2), 72.7 (C3), 35.9 (C4), 44.3 (C5), 72.2 (C6), 36.5 (C7), 33.7 (C8), 34.5 (C9), 37.2 (C10), 22.2 (C11), 37.2 (C12), 41.6 (C13), 50.2 (C14), 24.4 (C15), 25.6 (C16), 57.7 (C17), 12.8 (C18), 19.3 (C19), 40.4 (C20), 19.2 (C21), 29.5 (C22), 31.4 (C23), 177.0 (C24), 57.9 (C1′), 30.6 (C2′), 26.5 (C3′), 27.7 (C4′), 27.9 (C5′), 68.9 (C6′), 69.1 (2C, PyCH2), 162.5 (2C, Py-αC), 127.2 (2C, Py-βC), 141.9 (2C, Py-γC), 124.9 (2C, Py-δC), 153.5 (2C, Py-σC), 197.6 (3C, *fac*-$Re(CO)_3$); IR (KBr): $\nu$ (O–H) 3428, $\nu$ (C=O) 2030, $\nu$ (C=O) 1924, $\nu$ (C=O) 1634 $cm^{-1}$; Anal. Calc. for $C_{45}H_{64}N_4O_6ReBr$: C, 52.82; H, 6.30; N, 5.47. Found: C, 52.61; H, 6.00; N, 5.64%.

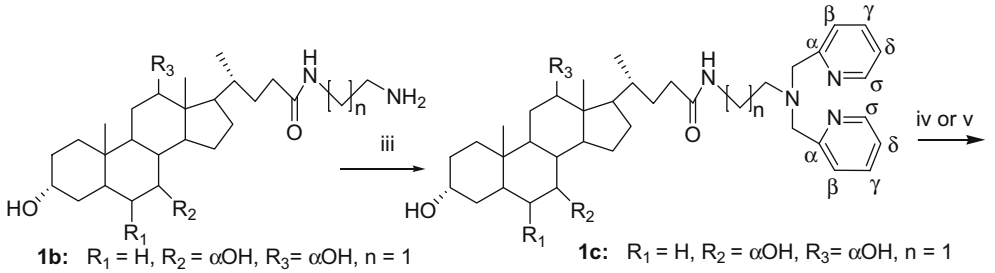
### 2.2.5. Preparation of $[^{99m}Tc(CO)_3(H_2O)_3$-ligand$]^+$

The technetium-99m complexes were prepared according to the following general procedure: 900 μL of a solution of *fac*-



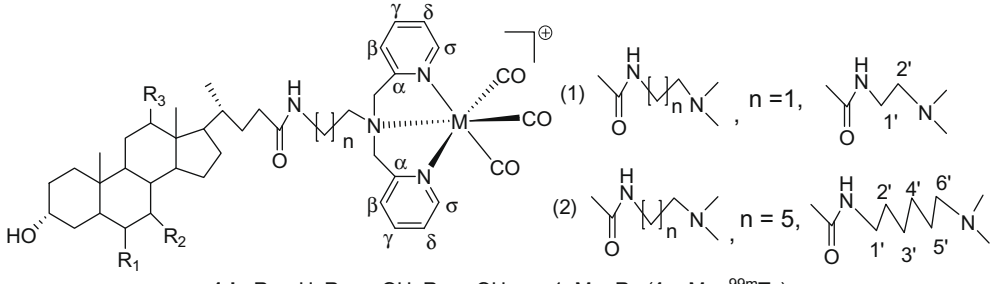

**1:** $R_1$ = H, $R_2$ = αOH, $R_3$ = αOH
**2:** $R_1$ = H, $R_2$ = αOH, $R_3$ = H
**3:** $R_1$ = H, $R_2$ = βOH, $R_3$ = H
**4:** $R_1$ = αOH, $R_2$ = H, $R_3$ = H

**1a:** $R_1$ = H, $R_2$ = αOH, $R_3$ = αOH
**2a:** $R_1$ = H, $R_2$ = αOH, $R_3$ = H
**3a:** $R_1$ = H, $R_2$ = βOH, $R_3$ = H
**4a:** $R_1$ = αOH, $R_2$ = H, $R_3$ = H




**1b:** $R_1$ = H, $R_2$ = αOH, $R_3$= αOH, n = 1
**1b':** $R_1$ = H, $R_2$= αOH , $R_3$= αOH, n = 5
**2b:** $R_1$ = H, $R_2$= αOH, $R_3$= H, n = 1
**2b':** $R_1$ = H, $R_2$= αOH, $R_3$= H, n = 5
**3b:** $R_1$ = H, $R_2$= βOH, $R_3$= H, n = 1
**3b':** $R_1$ = H, $R_2$= βOH, $R_3$= H, n = 5
**4b:** $R_1$ = αOH, $R_2$ = H, $R_3$= H, n = 1
**4b':** $R_1$ = αOH , $R_2$= H, $R_3$= H, n = 5

**1c:** $R_1$ = H, $R_2$ = αOH, $R_3$= αOH, n = 1
**1c':** $R_1$ = H, $R_2$= αOH , $R_3$= αOH, n = 5
**2c:** $R_1$ = H, $R_2$= αOH, $R_3$= H, n = 1
**2c':** $R_1$ = H, $R_2$= αOH, $R_3$= H, n = 5
**3c:** $R_1$ = H, $R_2$= βOH, $R_3$= H, n = 1
**3c':** $R_1$ = H, $R_2$= βOH, $R_3$= H, n = 5
**4c:** $R_1$ = αOH, $R_2$ = H, $R_3$= H, n = 1
**4c':** $R_1$ = αOH , $R_2$= H, $R_3$= H, n = 5




**1d:** $R_1$ = H, $R_2$ = αOH, $R_3$= αOH, n = 1; M = Re (**1e:** M = $^{99m}$Tc)
**1d':** $R_1$ = H, $R_2$= αOH, $R_3$ = αOH, n = 5; M = Re (**1e':** M = $^{99m}$Tc)
**2d:** $R_1$ = H, $R_2$ = αOH, $R_3$= H, n = 1; M = Re (**2e:** M = $^{99m}$Tc)
**2d':** $R_1$= H, $R_2$ = αOH, $R_3$= H, n = 5; M = Re (**2e':** M = $^{99m}$Tc)
**3d:** $R_1$ = H, $R_2$ = βOH, $R_3$= H, n = 1; M = Re (**3e:** M = $^{99m}$Tc)
**3d':** $R_1$= H, $R_2$ = βOH, $R_3$ = H, n = 5; M = Re (**3e':** M = $^{99m}$Tc)
**4d:** $R_1$= αOH, $R_2$ = H, $R_3$= H, n = 1; M = Re (**4e:** M = $^{99m}$Tc)
**4d':** $R_1$= αOH, $R_2$ = H, $R_3$= H, n = 5; M = Re (**4e':** M = $^{99m}$Tc)

**Scheme 1.** (i) $CH_3OH$, HCl or *p*-$CH_3C_6H_4SO_3H$ or 85% $H_3PO_4$, room temperature; (ii) $NH_2(CH_2)_2NH_2$ or $NH_2(CH_2)_2NH_2$; (iii) DCE, $CH_3OH$, pyridine-2-aldehyde and $NaHB(OAc)_3$; (iv) $(NEt_4)_2[Re(CO)_3Br_3]$, $CH_3CH_2OH$, r.t; (v) $[^{99m}Tc(CO)_3(H_2O)_3]^+$, ethanol/aqueous (v/v = 1:3), 75 °C.

$[^{99m}Tc(H_2O)_3(CO)_3]^+$ (pH 7.4) and 100 μL of $10^{-4}$ M solution of the corresponding ligands in ethanol–aqueous were placed in a 10 mL glass vial under nitrogen. The vial was sealed and the reaction heated to 80 °C for 30 min and cooled on an ice bath. The reaction was checked by HPLC (γ-trace). The complexes were characterized by comparison with the corresponding rhenium complexes (UV; 254 nm).

## 3. Results and discussion

The chemistry of technetium(V) and rhenium(V) are always received great interest due to the importance of nuclear medicine purposes for the two isomers of $^{99m}$Tc and $^{188}$Re [24,25]. In former research, technetium(V) and rhenium(V) are studied more because this oxidation state is easily accessible by reduction of $[MO_4]^-$ ion (M = Tc, Re) in pharmaceutical kits. However, nuclear medicine chemists are also trying to develop new radiopharmaceuticals in relation to technetium(I) and rhenium(I) since scientists synthesized labeled intermediate *fac*-$[M(CO)_3(H_2O)_3]^+$ (M = Tc, Re) under general pressure condition [26,27]. The $^{99m}Tc(CO)_3$ core possesses many excellent features, such as its small volume and kinetic inertness, and the three coordinated water in this complex could be easily replaced by other ligands. So a series of chelate agents were synthesized and found those chelate agents with imidazole and pyridine groups are able to easily coordinate with *fac*-$[M(CO)_3(H_2O)_3]^+$ (M = Tc, Re) [28,29]. They also found that the model compound of tridentate chelate agents have better biological behavior than that of bidentate chelate agents. Furthermore, the coordinating ability of these tridentate chelate agents is: N–N–N > N–N–O > N–S–S. MÜller C et al. [30] made use of folic acid synthesized tridentate chelate agents verified above conclusion. Organometallic complexes with various alkyl chain length can affect the biological affinity of complexes in vitro and in vivo [15,31]. So we choosed the chelate system with various alkyl chain length which contained N–N–N tridentate agents with excellent coordinating ability.

The preparations of eight cationic rhenium and technetium complexes are shown in Scheme 1. $[^{99m}Tc(CO)_3(H_2O)_3]^+$ was prepared with high labeling yield and radiochemical purity (RCP > 95%) measured by TLC and HPLC.

Compounds **1a**–**4a**, **1b**–**4b** and **1b′**–**4b′** have been characterized by IR and $^1$H NMR. The tridentate ligands **1c**–**4c** and **1c′**–**4c′** have been characterized by IR, $^1$H NMR and high-resolution mass spectroscopy. The rhenium complexes **1d**–**4d** and **1d′**–**4d′** have been unambiguously characterized by IR, $^1$H NMR, $^{13}$C NMR and elemental analysis.

The infrared spectra of complexes **1d**–**4d** and **1d′**–**4d′** exhibit a sharp, strong band in the 2026–2030 $cm^{-1}$ range and a broad, intense absorption in the 1916–1924 $cm^{-1}$ range, attributed to $\nu$(C–O) of the *fac*-{$Re(CO)_3$} unit [32–34]. The absorptions are significantly blue shifted compared to the starting material $[Re(CO)_3Br_3]^{2-}$ (1998 and 1871 $cm^{-1}$). The complexes and the ligands show strong absorption peaks between 1634 and 1650 $cm^{-1}$, corresponding to the asymmetric vibration of C=O groups of the amide units [35].

The high-resolution mass spectra of the ligands are consistent with the formulations from the spectroscopic evidence.

NMR spectra provide additional evidence for the proposed composition and molecular structure of the ligands and the corresponding rhenium complexes.

The $^1$H NMR spectrum 1′-$CH_2$- of ligands **1c**–**4c** shows a double doublets in the range of 3.3–3.4 ppm with coupling constants ($J_1$ = 10.4–11.2 Hz, $J_2$ = 4.8–5.0 Hz). The $^1$H NMR spectrum 1′-$CH_2$- of rhenium complexes **1d**–**4d** show a triplet peak in the range of 3.9 ppm with coupling constants ($J$ = 6.7–7.1 Hz). The chemical shifts of 1′-$CH_2$- of ligands **1c**–**4c** severally show a triplet peak in 2.8 ppm. Those of rhenium complexes **1d**–**4d** are also a triplet peak in 3.8 ppm. The protons of the methylene groups adjacent to the pyridines are equivalent by virtue of their symmetry for the ligands **1c**–**4c**. Their chemical shifts are all 3.9 ppm. After ligands **1c**–**4c** have been coordinated to rhenium, the splitting pattern of these methylene protons becomes more complicated, resulting in multiplets in the 4.9–5.1 ppm range. The pyridine proton signals also show an downfield shift. All the conditions show that rhenium core of lacking for electron make entire molecular electric field move towards rhenium core. So many proton signals show an downfield shift. As for ligands **1c′**–**4c′** and rhenium complexes **1d′**–**4d′**,they are similar to those of ligand **1c**–**4c** and rhenium complex **1d**–**4d**.

The $^{13}$C NMR spectrum of eight rhenium complexes show chemical shifts of three carbonyl peaks among {*fac*-$Re(CO)_3$} exhibiting in the range of 197.3–197.9 ppm. These features indicate the tridentate coordination mode of ligand **1c**, **2c**, **3c**, **4c** via the tertiary amine and the two pyridine nitrogens.

The corresponding radioactive technetium-99m complexes **1e**–**4e** and **1e′**–**4e′** have been almost quantitatively prepared in ethanol–aqueous media at ligand concentrations of $10^{-4}$ M after 30 min at 75 °C. The characterization of the complexes was accomplished by comparison of the retention time observed in the γ-trace with those of the UV-trace of the corresponding rhenium complexes. HPLC chromatograms for trace of complexes **1d′** and γ-trace of the radioactive complexes **1e′** were showed in Fig. 1. The chromatogram of γ-trace of the radioactive complexes **1e′** was shown in Fig. 2 for stability in physiological phosphate buffer at 37 °C for 24 h. The HPLC chromatogram retention time of other rhenium complexes and corresponding radioactive technetium complexes is respectively as followed: **1d** (23.8 min) and **1e**

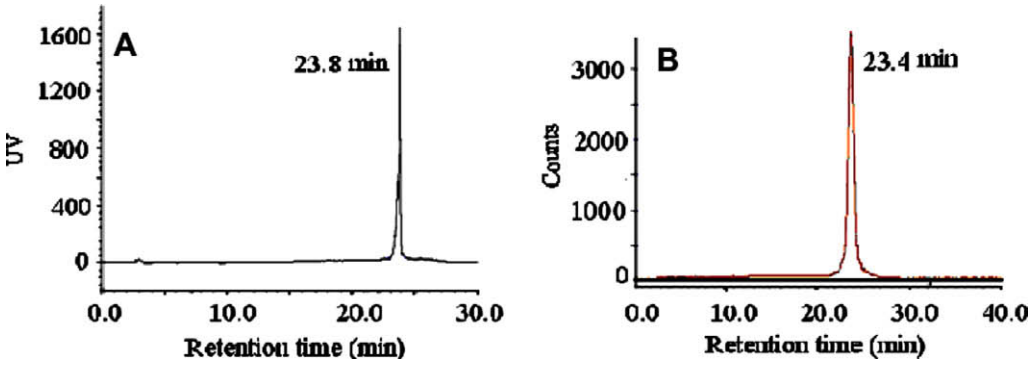



**Fig. 1.** (A) The HPLC chromatogram of the complex **1d′**, retention time: 23.8 min (254 nm). (B) The HPLC chromatogram of the radioactive complex **1e′**, retention time: 23.4 min (254 nm).

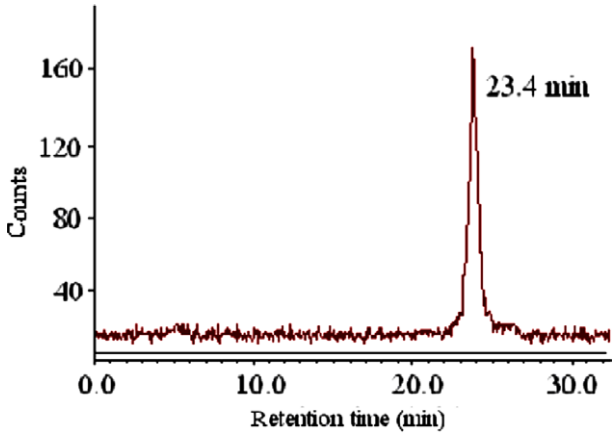



**Fig. 2.** The HPLC chromatogram of the complex **1e′** (radioactivity) for stability in physiological phosphate buffer at 37 °C for 24 h, retention time: 23.4 min (254 nm).

(23.4 min); **1d′** (23.8 min) and **1e′** (23.4 min); **2d** (24.5 min) and **2e** (24.3 min); **2d′** (24.5 min) and **2e′** (24.3 min); **3d** (23.1 min) and **3e** (22.9 min); **3d′** (23.1 min) and **3e′** (22.9 min); **4d** (23.1 min) and **4e** (22.9 min); **4d′** (23.3 min) and **4e′** (23.1 min).

The $^{99m}$Tc-complexes were purified via HPLC for stability testing. The organometallic $^{99m}$Tc-complexes were challenged in PBS buffer for 24 h at 37 °C. Decomposition or dissociation of the complexes to either $[^{99m}TcO_4]^-$ or other side products was not found for all complexes under the condition, which is tolerable for potential nuclear medical applications.

## 4. Conclusion

Eight tridentate ligands deriving from bile acids has been developed. The ligands react with $[NEt_4]_2[Re(CO)_3Br_3]$ in high yields to give complexes of the type [Re–$(CO)_3$ (ligand)]Br. The complexes provide novel potential radiopharmaceuticals for hepatobiliary diseases, liver tumor and intestinal cancer, endowing them with suitable properties for diagnostic applications. Ligands **1c**–**4c** and **1c′**–**4c′** that reacted with the radioactive precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$ obtained good radiochemical yields. Biological evaluations relating to this research are currently under investigation.

## Acknowledgements

This work was supported by the Hundred Talent Program of Chinese Academy of Sciences (No. 26200601) and the foundation of Innovation Project of the Chinese Academy of Sciences (No. 55200701).

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