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# Synthesis and Study on Magnetic Resonance Imaging Performance of Gd(III)-DTPA-bisfuran-2-carbohydrazide as a Potential MRI Contrast Agent

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**Abstract**

One novel ligand, diethylenetriamine-N, N''-bi(acetyl-furan-2-carbohydrazide)-N, N′, N''-triacetic acid ($H_3L$) has been synthesized in high yield by the reaction of bicyclic anhydride of diethylenetraiaminepentaacetic acid (DTPA) with furan-2-carbohydrazide, it has three carboxylic groups, the corresponding non-ion complex of Gd(III)-L holding promise of magnetic resonance imaging (MRI) was obtained by treating these ligand with $Gd_2O_3$ in water. The efficacy of the contrast agent was assessed by measuring the longitudinal relaxivity ($r_1$) and $T_1$ weighted magnetic resonance imaging in vitro. The $r_1$ of Gd(III)-DTPA-bisfuran-2-carbohydrazide was up to 5.92 $mM^{-1}\cdot s^{-1}$, which was 1.27 times higher than that of the analogous MRI contrast agent Gd(III)-DTPA( 4.65 $mM^{-1}\cdot s^{-1}$) in clinical application. $T_1$ weighted magnetic resonance imaging in vitro showed that proton signal intensity increased with Gd(III) complex concentration and the imaging effect of

 

Gd(III)-DTPA-bisfuran-2-carbohydrazide was superior to that of Gd(III)-DTPA in the same condition.These results showed that the complex might be considered as a potential MRI contrast agent.

Keywords

furan, DTPA derivative, paramagnetic metal complex, MRI contrast agent, relaxivity

## 1. Introduction

It is well known that magnetic resonance imaging (MRI) has become a powerful tool in preclinical research and in the clinical diagnosis of various diseases, in comparison with other clinical imaging techniques, such as ultrasound, planar X-ray imaging and computed tomography (CT), single photon emission computed tomography (SPECT), positron emission tomography (PET), MRI is especially advantageous: due to its high spatial (<0.1 mm) and temporal resolutions, 3-dimensional anatomical images, non-invasive (lack of ionizing radiation), deep tissue penetration and excellent soft tissue contrast and multiple contrast mechanisms [1-3]. In MRI, image contrast can be generated by differences in tissue water content, water relaxation times, flow, or diffusion, but the image contrast is often insufficient for diagnostic purposes [4-5]. Unfortunately the image contrast is often insufficient for diagnostic purposes. In order to enhance the contrast in MRI, MRI contrast agents(CAs) was introduced to increase the relaxation rates of water protons in tissue in which the agent accumulates [6]. Therefore, many research groups around the world have been studying MRI contrast agents. To date, more than nine types of the ligand of paramagnetic metal ion-chelate complexes have been approved by Food and Drug Administration (FDA) for clinical application [7].

A vast body of literature exists describing ligands for Gd(III), and the majority are polyaminopolycarboxylate ligands, like Gd-DTPA (DTPA=diethylenetriamine pentaacetic acid), Gd-DOTA(DOTA=1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid),Gd(HP-DO3A)(HP-DO3A=10-(2-hydroxypropyl)-1,4,7,10-tetra-azacyclododecane-1,4,7-triacetic acid), etc [8-10]. However, most contrast agents were hindered by some drawbacks:

non-specific extracellular distribution, low relaxivity, low tissue specificity, and rapid clearance [11].

An effective way to obtain hepatobiliary excretion of low molecular weight contrast agents is to increase the lipophilicity of Gd-DTPA, for example, by adding aromatic rings to the diethylenetriamine backbone of DTPA [12]. The gadolinium complexes of two DTPA analogues, benzyloxy propionictetraacetate (BOPTA) and ethoxybenzyl-diethylenetriamine pentaaceticacid (EOB-DTPA) are clinically approved hepatobiliary agents [13-14].

Furan derivatives, both obtained from synthetic and natural sources, have been extensively investigated due to the interesting biological activities, such as antitumor properties and cytotoxic [15], as well as antimicrobial [16], antispasmodic [17], and several other potentially useful activities [18].

Considering the furan derivatives are widely used in the field of pharmaceutical, especially 1-(((5-nitro-2-furanyl)methylene)amino)-2,4-imidazolidinedione commercially known as nitrofurantoin, which is clinically used for the treatment of urinary tract infections caused by sensitive bacteria, such as pyelonephritis, urinary tract infection, cystitis, prostatitis, etc [19].

Because of these properties of furan derivatives, furan ring was introduced into DTPA and diethylenetriamine-N, N''-bi(acetyl-furan-2-carbohydrazide)-N, N′, N''-triacetic acid ($H_3L$) and its Gd(III)-L complex were designed and synthesized( **Scheme 1** ). The efficacy of the contrast agent was assessed by measuring the longitudinal relaxivity ($r_1$) and $T_1$ weighted magnetic resonance imaging in vitro. The $r_1$ of Gd(III)-L was up to 5.92 $mM^{-1}\cdot s^{-1}$, which was 1.27 times higher than that of the analogous MRI contrast agent Gd(III)-DTPA(4.65 $mM^{-1}\cdot s^{-1}$) in clinical application. $T_1$ weighted magnetic resonance imaging in vitro showed that proton signal

intensity increased with Gd(III) complex concentration, and the imaging effect of Gd(III)-L was superior to that of Gd(III)-DTPA in the same condition. Water-solubility tests showed that the solubility of the Gd(III)-L complex in water is good and up to 1.0 g $mL^{-1}$ at room temperature . These results showed that the complex might be considered as a potential MRI contrast agent.



## 2. Experiment

### 2.1 General

Melting points were determined on a digital apparatus and are uncorrected. TLC analysis was performed on glass sheets coated with Merck silica gel 60 $F_{254}$. Compounds were visualized by $I_2$ steam or Uv-vis. $^1$H-NMR spectra were recorded on Bruker AV-400 spectrometers respectively. Chemical shifts($\delta$) were reported in parts per million from internal standard tetramethylsilane (TMS). Coupling constants (*J*) were measured in Hertz. Multiplicity was reported as follows: *s*(singlet), *d*(doublet), *t*(triplet), *m* (multiplet) and combination of these signals. Column chromatographies were performed on silica gel 60 (200-300 mesh). IR spectrometry recorded with a Nicolet 380 FT-IR. Elemental analyses were determined on a Vario EL Ⅲ(Elementar), Mass spectra were obtained on a Angilent6110 (Angilent Technologies, USA). The solvent longitudinal relaxation time ($T_1$) for gadolinium complexes in distilled water was determined by a standard inversion-recovery sequence on the MicroMR imaging & analyzing system at 32 °C and 0.5 T ( Niumag Technology Co., Ltd., Suzhou, China ). MARS5 microwave digestion system. RT1001-RT1002 ultarsonic cleaning machine.

All reagents and solvents were analytical grade from commercial suppliers and used without further treatments unless otherwise stated. Reactions were carried out under $N_2$ atmosphere, unless otherwise noted.

**2.2 Syntheses**

**2.2.1 Synthesis of ethyl-2-furoate (2)**

In a 50 mL round bottom flask were placed 16 mL anhydrous ethanol and 2-furic acid (5.5 g, 0.05 mol). While the mixture was cooled with ice with stirring, concentrated sulfuric acid (3 mL, 98 %) was added dropwise to the mixture. After the completion of the dripping, the resulting mixture in the flask was brought to room temperature. Then the resulting mixture was refluxed at 80 °C for about 4 h. The reaction progress was monitored by TLC using toluene:ethylacetate (*v:v*=75:25) as mobile phase. The resultant was brought to room temperature again. Then, the contents in the flask were introduced into ice water. The product was filtered, washed with water, and dried under vacuum to obtain the ethyl-2-furoate as a yellowish solid. Yield: 5.7 g (81 %); mp 32-33 ℃. FT-IR (KBr pellet): 3139, 2982, 2938, 2906, 1722, 1576, 1473, 1397, 1299, 1231,1118, 1077, 885 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, δ/ppm): 1.248(brs, 1H, NH, disappeared on $D_2O$ exchange), 3.835((s, 3H, $OCH_3$), 4.22(brs, 2H, $NH_2$, disappeared on $D_2O$ exchange), 6.916(dd, $J^3$=8.8 Hz, $J^4$=2.4 Hz 1H), 7.187(d, $J^4$=2.4 Hz 1H), 7.443(d, $J^3$=8.8 Hz 1H).

**2.2.2 Synthesis of Furan-2-carbohydrazide (3)**

A solution of ethyl-2-furoate (2 g, 14.3 mmol) and hydrazine monohydrate (6.9 mL, 143 mmol) in EtOH (10 mL) was refluxed overnight. After removal of bulk solvent under reduced pressure afforded the crude product, which was recrystallized from ethanol as a yellowish solid. Yield:

1.4 g (80 %); mp 78-80 ℃. FT-IR (KBr pellet): 3443, 3339, 1682, 1578, 1475, 1392, 1296, 1230,1115, 1072, 880cm$^{-1}$; Anal. Calcd. for $C_5H_6N_2O_2$ ($w_B$/%): C, 47.62; H, 4.80; N, 22.21; Found: C, 47.75; H, 4.72; N, 22.28.

**2.2.3 Synthesis of Diethylenetriamine-N,N″-bi(acetyl-Furan-2-carbohydrazide)-N,N′,N″-triacetic Acid ($H_3L$)**

Furan-2-carbohydrazide (1.008 g, 8 mmol) and triethylamine (1.11 mL, 8 mmol) were dissolved in N,N-dimethylformamide (DMF, 30 mL) and cooled to 0 ºC by the ice-salt bath. Diethylenetriaminepentaacetic dianhydrides (DTPAA, 1.428 g, 4 mmol) was added slowly to the solution of Furan-2-carbohydrazide in DMF with rapid stirring at the same temperature. The reaction was continued stirring for 8 h at 0 ºC and a further 48 h at room temperature. The resultant mixture was filtered and precipitated with anhydrous diethyl ether (90 mL). The precipitate was reprecipitated from DMF using diethyl ether, filtered and dried under vacuum to give $H_3L$ as a yellowish solid. Yield: 2.07g (85 %); mp 138-140 ℃. FT-IR (KBr pellet) 3446, 3045, 2920, 2851, 1710, 1658, 1473, 1385, 1230, 1133, 544 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$, δ/ppm): 2.870(t, 4H, 2×N-$CH_2$), 2.933(t, 4H, 2×N-$CH_2$ ), 3.127(s, 4H, 2×N-$CH_2$-CO-NH ) 3.368 (s, 4H, 2×N-$CH_2$-COOH ), 3.430 (s, 2H, N-$CH_2$-COOH ), 4.122 (brs, 2H, NH disappeared on $D_2O$exchange), 6.655-6.643(dd, 2H, J= 2.0, 3.2Hz, Ar-H), 7.220(d, 2H, J= 3.2 Hz, Ar-H), 7.882(2H, J= 2.0 Hz, Ar-H), 10.249 (brs, 3H, -COOH). $^{13}$C NMR (100 MHz, $CDCl_3$, δ/ppm) 46.6, 49.1, 50.1, 52.5, 54.1, 55.5, 56.9, 57.3, 112.2, 116.9, 144.3, 146.7, 159.4, 170.2, 170.7, 171.4, 174.5; Anal . calcd for $C_{24}H_{33}N_7O_{13}$ ($w_B$/%): C,45.93; H, 5.30; N, 15.62. found C, 45.63; H, 5.47; N, 15.57.

**2.2.4 Synthesis of Gd(III)-L complex**

To a suspension of 0.18 g $Gd_2O_3$ of in 20 mL of water was added 0.63 g of $H_3L$. after the resulting suspension was stirred at 80 ℃ for about 48 h all the material had dissolved. The solution was cooled to room temperature and then cold acetone was added dropwise to crystallize the complex, and dried under vacuum ($P_2O_5$) to obtain the complex as a white solid. Yield: 0.81g (95 %); mp > 300 ℃. FT-IR (KBr pellet) 3430, 3040 2921, 2851, 1610, 1464, 1408, 1386, 1232, 1125, 1092, 859, 610 $cm^{-1}$; Anal. calcd for $C_{24}H_{38}N_7GdO_{17}$($w_B$/%): C, 33.76; H, 4.49; N, 11.48. found C, 33.43; H, 4.47; N, 11.67.

**2.2.5 Relaxation Measurements**

The solvent longitudinal relaxation time ( $T_1$ ) for gadolinium complex was carried out on a solution of gadolinium complex in distilled water at concentrations ranging from 0.0 to 2.0 mM (0.4, 0.8, 1.2, 1.6 and 2.0 mM) were measured by a standard inversion-recovery sequence( P90(us)=22, P180(us)=40.00, TD=1024, SW(KHz)=100, TR(ms)=2000, RG1=20, RG2=3, NS=4, DL1(ms)=1~2000, NTI=30 ) on the MesoMR23-060H-I imaging & analyzing system at 32 °C and 0.5 T ( Niumag Technology Co., Ltd., Suzhou, China ). Thus the relaxivity $r_1$ for gadolinium complex in distilled water can be calculated. This Gd(III)-L complex was compared with Magnevist ( Gd(III)-DTPA ) at the same condition.

**2.2.6 $T_1$-Weight imaging in vitro**

In vitro imaging effect of Gd(III)-L is visualized by FLASH images in phantoms. Multislice spin echo (MSE) sequence ( TR=15 ms, TE=0.55 ms, NS=32, Slice thickness=2.0 mm) on the MR23-060H-I imaging & analyzing system was employed for the acquisition of the in vitro imaging. The schematic drawing of a phantom was shown in **Fig. 1**. The center tube labeled as

0.0 mM contained water only. The surrounding five tubes were grouped together with the order of increasing concentrations (0.4, 0.8, 1.2, 1.6 and 2.0 mM) counterclockwise.

**3. Results and discussion**

As mentioned previously, because of the favorable pharmaceutical properties of Furan derivatives compounds, we have produced the corresponding DTPA analogues containing furan ring group. In addition, the synthesis of the ligand ($H_3L$) is efficient and convenient. DMF was used as solvent and $Et_3N$ as the scavenger of acid as well. The synthetic scheme of ligand ($H_3L$) is shown in **Scheme 1**.

The structure of ligand ($H_3L$) was characterized by FT-IR, ES-API-MS, $^1$H NMR, $^{13}$C NMR and elemental analysis. $^1$H NMR, $^{13}$C NMR and FT-IR were conformed with the structure of diethylenetriamine-N, N''-bi(acetyl-furan-2-carbohydrazide) - N, N′, N''-Triacetic acid ($H_3L$), the $^1$H NMR spectrum of the ligand ($H_3L$) was shown in **Fig. 2** and the $^{13}$C NMR spectrum of the ligand ($H_3L$) was shown in **Fig. 3.**

The ES-API-MS spectra(**Fig. 4**) revealed that the molecular ion peaks were in accordance with the given structure of it. ES-API-MS(positive mode): m/z $[M+H]^+$ Calcd. 610.20 Da; Obsd. 610.20 Da.

The Gd(III)-L complex is synthesized by the reaction of performed ligand $H_3L$ with stoichiometric amounts of the $Gd_2O_3$ in deionized water at 80-90 °C for 48 h. The absence of the uncomplexed Gd(III) ions is confirmed by testing the solution with xylenol orange. Gd(III)-L complex is neutral non-ionic chelates and soluble in water, DMSO, DMF, methanol, ethanol, and insoluble in ether. Water-solubility tests showed that the solubility of the Gd(III)-L complex in water is good and up to 1.0 g $mL^{-1}$ at room temperature. The Gd(III)-L complex is an

off-white solid with no clear melting point before decomposition. The complex is stable in air and not sensitive to light.

In the FT-IR spectra of the ligand(**Fig.5a**), strong and broad absorption peaks at 3434 $cm^{-1}$ were attributed to *v*(O-H) and *v*(N-H) vibration. The bands at 2920 and 2851 $cm^{-1}$ are assigned to the *v*(C-H) vibration of the methylene groups. The peaks at 1710 $cm^{-1}$ (A) and 1658 $cm^{-1}$ (B) , were attributed to *v*(COOH) and *v*(CONH-), respectively. The FT-IR spectra of Gd(III)-L complex(**Fig.5b**) shows a broad band at 3430$cm^{-1}$ assignable to the *v* (OH) and *v*(N-H) vibration, the band (A) disappeared in the complex, showing that the carboxyl proton dissociates and the oxygen atom was coordinated to metal. The band (B) was shifted to 1610 $cm^{-1}$, suggesting that the oxygen atom of the amide is coordinated to metal. The new peak at 859 $cm^{-1}$ was assigned to vibration of coordinative water. The rocking vibrational modes of coordinated water molecules appear at 610 $cm^{-1}$. The ligand provided three nitrogen atoms, five carboxyl oxygen atoms bonding to metal. At least, one water molecule takes part in coordination to metal.

The effects of paramagnetic ions on the $T_1$ relaxation nuclear spins were first formulated by Bloembergen and Solomon [21-22] and subsequently extended by several authors. On the basis of this theory, the longitudinal relaxation time $T_1$ in the presence of Gd complex is given by **Eq. (1)**:

$$1/T_{1,\mathrm{obsd}} = 1/T_{1,\mathrm{d}} + r_1[\mathrm{M}] \quad \textbf{Eq. (1)}$$

where$T_{1,\mathrm{d}}$ is the $T_1$ relaxation time in the absence of gadolinium, [M] denotes the concentration of gadolinium ion in the measured solution, and $r_1$ is a constant defining the relaxivity of the contrast agent, which is the most important parameter in evaluating a contrast agent and was calculated from the slope of the plots of $(1/T_1)_{\mathrm{obsd}}$ versus the Gd concentrations. **Fig. 6** illustrates

that the relaxivity of gadolinium complex produced in our present work was 5.92 mM $^{-1}\cdot s^{-1}$, which was 1.27 times higher than that of the analogous MRI contrast agent Gd(III)-DTPA($r_1$ = 4.65 mM $^{-1}\cdot s^{-1}$) in commercial use at the same condition.

Possible explanations for increased relaxivity, relative to clinical contrast agent Gd(III)-DTPA, include: (a) increasing the molecule size by introducing an aromatic group causes a decrease in rotational correlation rate(relatively long rotational correlation time); (b) an increase in the number of outer sphere coordinated water molecules via hydrogen bonds to the oxygen atoms of the furan groups; (c) hydrophilic hydrazide group may be able to transmit water molecule from outer-sphere to the inner-sphere easily.

The **Fig.7** showed in vitro MR images prepared by Gd(III)-DTPA(left) and Gd(III)-L (right) solutions in phantoms. The intensity in the center tube that contained water only, was used as baseline intensity. It was seen that proton signal intensity increased with Gd(III) complex concentration. Besides, the imaging effect of Gd(III)-L was superior to that of Gd(III)-DTPA in the same condition.

**4. Conclusion**

Gd(III)-DTPA-bisfuran-2-carbohydrazide was synthesized by the incorporation of furan-2-carbohydrazide to DTPA and further chelation with $Gd_2O_3$. The longitudinal relativity ($r_1$) of this Gd(III)-L complex is higher than that of Gd(III)-DTPA, and the in vitro imaging effect of Gd(III)-L was superior to that of Gd(III)-DTPA in the same condition, which makes it possible to reduce the risk of the toxicity by lowering the dose of Gd(III) chelates. Thus Gd(III)-L might be considered as a potential MRI contrast agent.

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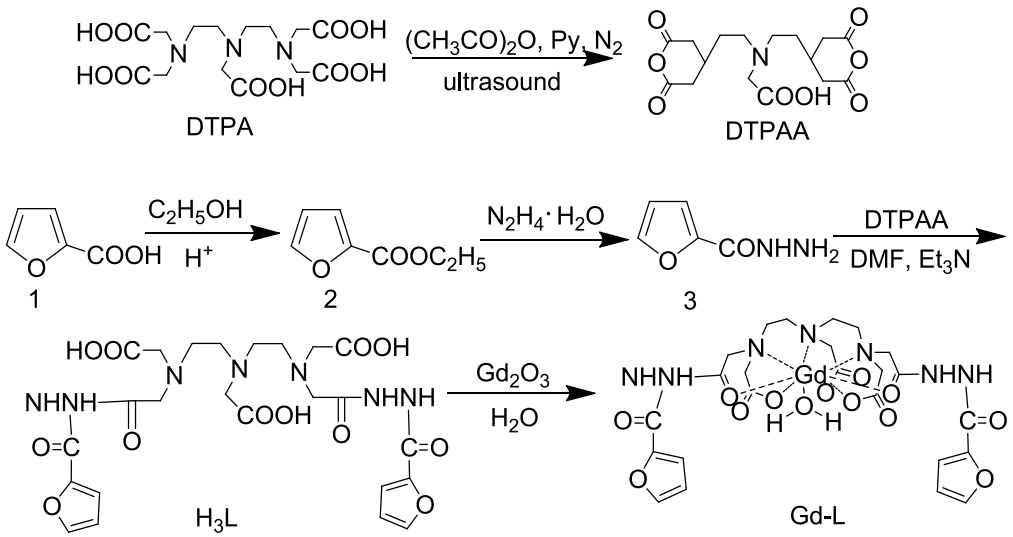


Scheme 1. Synthesis of ligand($H_3L$) and complex(Gd(III)-L)

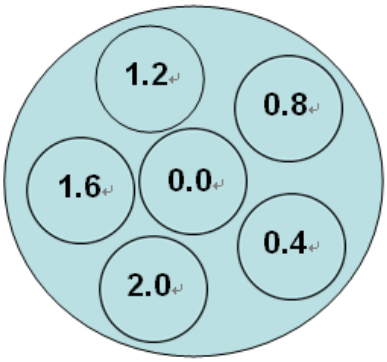


Fig. 1. Schematic drawing of a phantom assembled with six tubes consisting of a concentration series of Gd(III)-L or Gd(III)-DTPA solutions. Numbers indicated in tubes showed the concentrations of Gd(III)-L or Gd(III)-DTPA ( mM ). The center tube contained water only. The larger circle surrounding the six tubes is the outer tube, filled with 0.2 % $CuSO_4$ solution. The six-tube phantom was immersed in the solution to reduce artifacts.

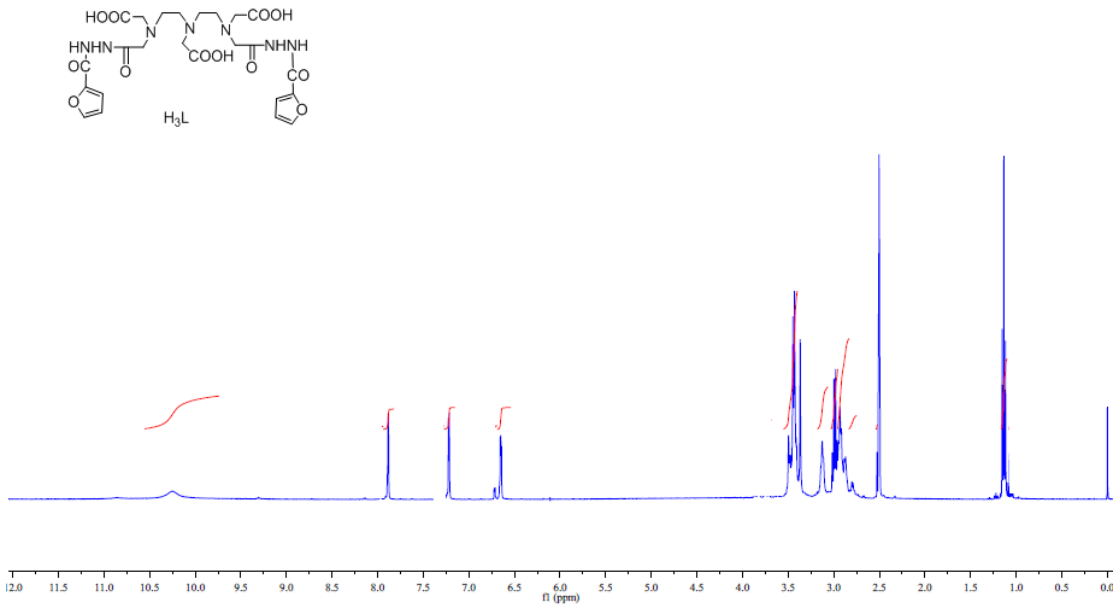


Fig. 2. $^{1}$H NMR (400 MHz, DMSO-$d_6$ δ/ppm) spectrum of the ligand ($H_3L$)

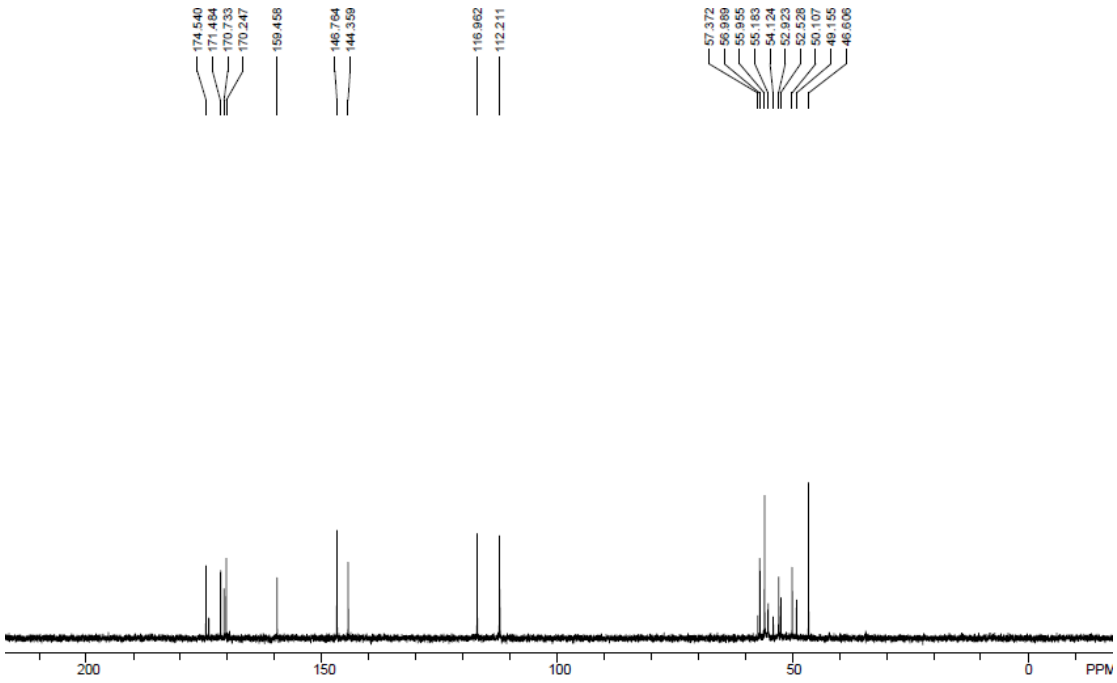


Fig. 3. $^{13}C$ NMR (100 MHz, $CDCl_3$, δ/ppm) spectrum of the ligand ($H_3L$)

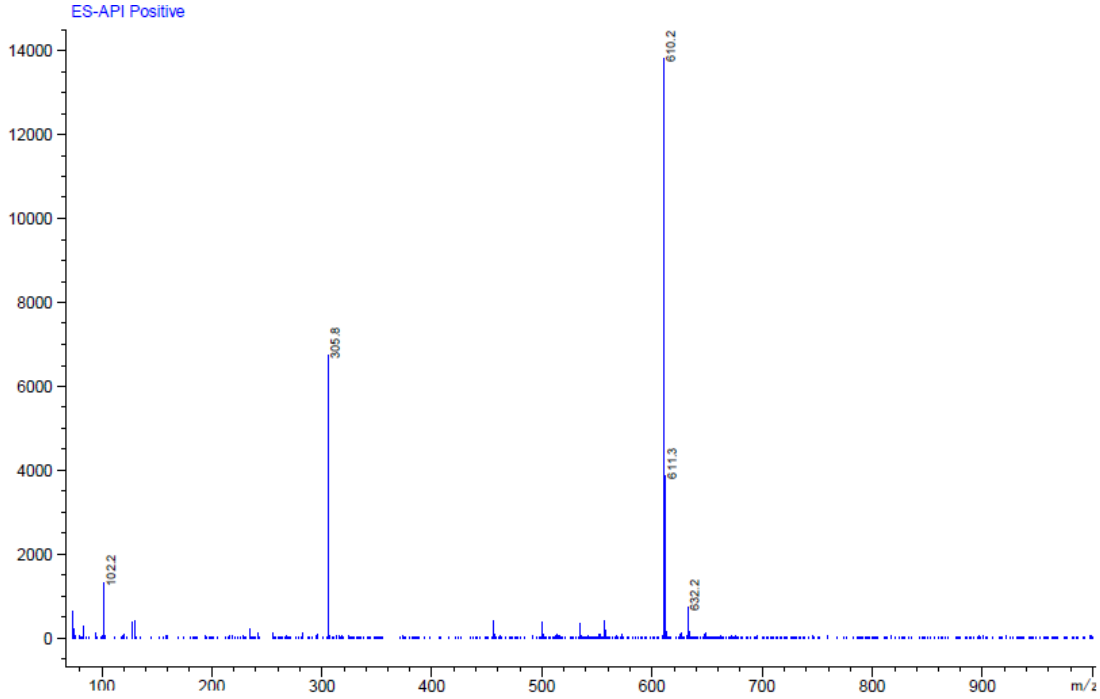


Fig. 4. MS(API, positive mode) spectra of the ligand ($H_3L$)



 

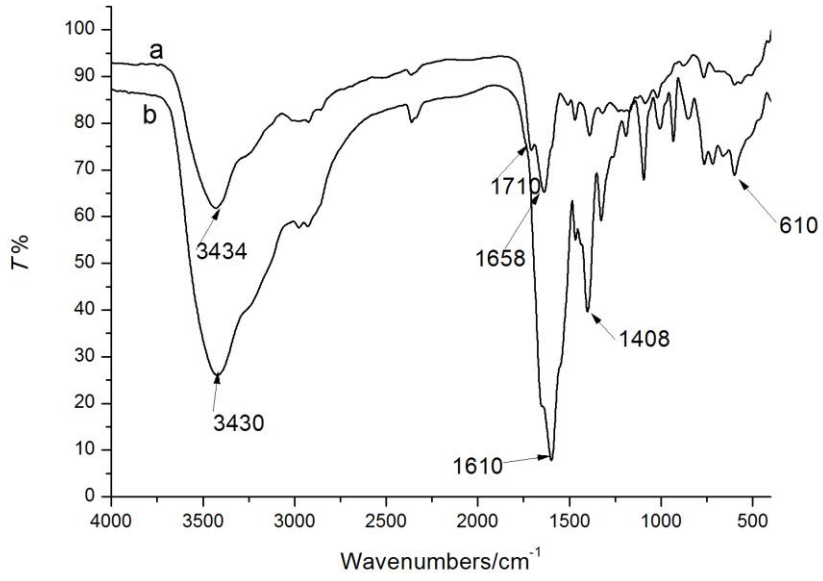


Fig. 5. FT-IR of $H_3L$ (a) and Gd(III)-L complex (b)



 

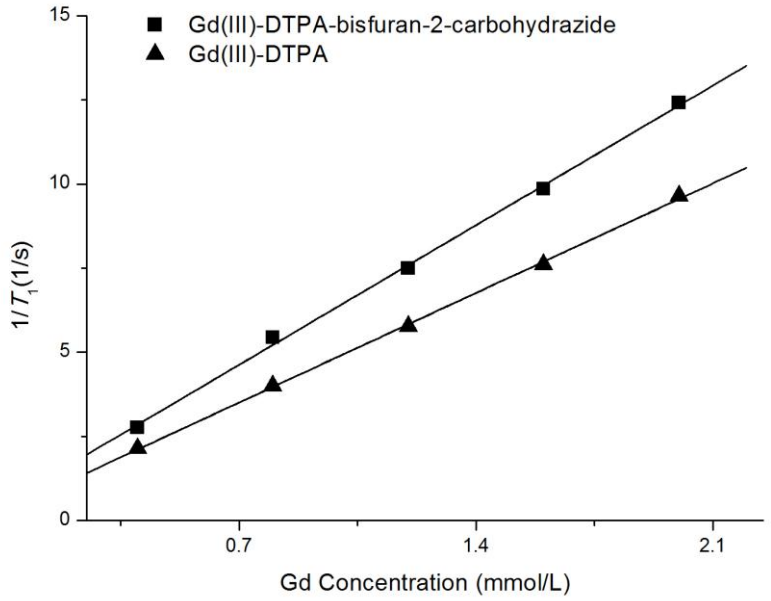


Fig. 6. Plots of $1/T_1$ vs the Gd concentrations of Gd(III)-L complex as well as Gd(III)-DTPA in water solution

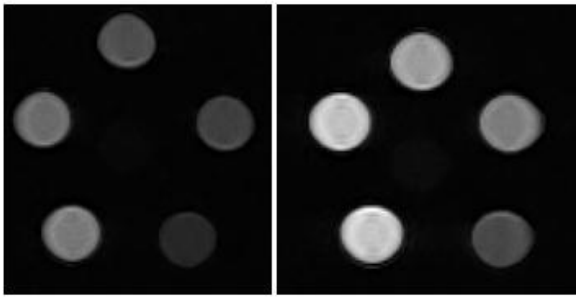

Fig.7. MR images of Gd-DTPA(left) and Gd(III)-L (right)



 