Eu^{II}-Containing Cryptates as Contrast Agents for Ultra-High Field Strength Magnetic Resonance Imaging

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Experimental Procedures

Commercially available chemicals were of reagent-grade purity or better and were used without further purification unless otherwise noted. Water was purified using a PURELAB Ultra Mk2 water purification system (ELGA). Dicholoromethane was dried using a solvent purification system (Vacuum Atmospheres Company) and degassed under vacuum. Triethylamine was distilled from CaH_2 under an atmosphere of Ar.[1] 4-Allylbiphenyl was prepared according to a published procedure.[2] Ozone was generated using an apparatus from Ozone Research and Equipment Corporation. For ozone generation, oxygen was passed through a column of anhydrous calcium sulfate before the ozone apparatus, and the oxygen flow rate and current were held constant at 1.0 L/min and 0.8 A, respectively. *p*-Toluenesulfonyl chloride was recrystallized prior to use.[1]

Flash chromatography was performed using silica gel 60, 230–400 mesh (EMD Chemicals).[3] Analytical thin-layer chromatography (TLC) was carried out on ASTM TLC plates precoated with silica gel 60 F_{254} (250 µm layer thickness). TLC visualization was accomplished using a UV lamp followed by charring with potassium permanganate stain (2 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% w/v aqueous NaOH, 300 mL H_2O).

^{1}H NMR spectra were obtained using a Varian Unity 400 (400 MHz) spectrometer, and ^{13}C NMR spectra were obtained using a Varian Unity 400 (101 MHz) spectrometer. Chemical shifts are reported relative to residual solvent signals (CD_3OD: ^{1}H: δ 3.30, ^{13}C: δ 49.00; CD_3CN: ^{1}H: δ 1.94, ^{13}C: δ 118.26 and 1.30). ^{1}H NMR data are assumed to be first order, and the apparent multiplicities are reported as "s" = singlet, "m" = multiplet, and "brs" = broad singlet. Italicized elements are those that are responsible for the shifts. High-resolution electrospray ionization mass spectra (HRESIMS) were obtained using an electrospray time-of-flight high-resolution Waters Micromass LCT Premier XE mass spectrometer.

Samples for inductively coupled plasma mass spectrometry (ICP–MS) were diluted with nitric acid (2% v/v, aqueous). Standard solutions were prepared by serial dilution of Eu, Gd, and Sr standards (High-Purity Standards). ICP–MS measurements were conducted on a PE Sciex Elan 9000 ICP–MS instrument with a cross-flow nebulizer and Scott-type spray chamber.

Susceptibility weighted imaging (SWI) was performed at 3 (Siemens TRIO at 19.8 ºC) and 7 (ClinScan at 19 ºC) Tesla (T). Volume coils were used at both field strengths. The acquisition parameters for SWI were as follows: $T_R = 37$ ms, $T_E = 5.68–31.18$ ms, and resolution = 0.5 × 0.5 × 2 mm^3 for 3 T; $T_R = 21$ ms, $T_E = 3.26–15.44$ ms, and resolution = 0.27 × 0.27 × 2 mm^3 for 7 T. Multiple flip angles (5, 10, 15, 20, 25, and 30°) were used in the SWI experiments to allow for the determination of longitudinal relaxation time, T_1.[4] MR images were processed using SPIN software (SVN Revision 1751).

Matlab (7.12.0.635 R2011a) was used to generate effective transverse relaxation time, T_2^*, and corrected T_1 maps. The T_1 values from the corrected T_1 maps were plotted vs the concentration of Gd or Eu in the samples to calculate longitudinal relaxivities, r_1. The Matlab codes for T_2* and T_1 (with T_2* correction) maps are shown below:

T_2*:

```
% function [T2map error_estimatemap]=flash_fit(fa,s,tr)
% s is the 3D matrix of # of slices equal to the number of flip angles.
clear all;

clc
format long;

h=msgbox(' --------Please enter the information Asked for ---------');

waitfor(h);
```

```
rows=input('Enter Matrix size # ROWS: ');

cols=input('Enter Matrix size # COLS: ');

echonumber=input('Enter number of echoes: ');

slices=input('Enter the number of slices in each echo images: ');

s.fpathname=[];

%%%%%%%%%% FILE INFORMATION INPUT
for i=1:echonumber
    disp(' ');disp(' ');disp(' ')
    display('Select the first file in the series you want to calculate T2*');
    [fname, path]=uigetfile('C:\Archives\Ang Doktorado\Projects\Imaging
Experiments\2011 05 20 Phantom Imaging 3T\DICOM\5-
11Echo_SWI_FA5_.5x.5x2\TEsorted\*.*');
    s(i).fpathname=strcat(path,fname)
    disp(' ');disp(' ');disp(' ');
    TE(i)=input('\n Please enter the Corresponding echo time (TE) : ');
end

mm=zeros(rows,cols);
mm1=zeros(rows,cols);

%%%%%%%%%%%%%%%%%% ACTUAL CALCULATION WITH ALPHA MAP COMPENSATION INCLUDED
for i=1:slices

    mat=zeros(rows,cols); % IMAGE MATRIX SIZE
    xmat=zeros(size(TE,2),rows,cols); % IMAGE MATRIX SIZE
    ymat=zeros(size(TE,2),rows,cols); % IMAGE MATRIX SIZE

    for j=1:echonumber

        if s(j).fpathname(size(s(j).fpathname,2)-7)=='-'
            firstnum=str2num(s(j).fpathname(size(s(j).fpathname,2)-
6))*100+str2num(s(j).fpathname(size(s(j).fpathname,2)-
5))*10+str2num(s(j).fpathname(size(s(j).fpathname,2)-4));

mat(:,:)=dicomread(strcat(s(j).fpathname(1,1:(size(s(j).fpathname,2)-
7)),num2str(firstnum+i-1),'.dcm'));
        elseif s(j).fpathname(size(s(j).fpathname,2)-6)=='-'
            firstnum=str2num(s(j).fpathname(size(s(j).fpathname,2)-
5))*10+str2num(s(j).fpathname(size(s(j).fpathname,2)-4));

mat(:,:)=dicomread(strcat(s(j).fpathname(1,1:(size(s(j).fpathname,2)-
6)),num2str(firstnum+i-1),'.dcm'));
        else s(j).fpathname(size(s(j).fpathname,2)-5)=='-'
            firstnum=str2num(s(j).fpathname(size(s(j).fpathname,2)-4));

mat(:,:)=dicomread(strcat(s(j).fpathname(1,1:(size(s(j).fpathname,2)-
5)),num2str(firstnum+i-1),'.dcm'));
        end

        ymat(j,:,:)=log(mat);
```

```
        xmat(j,:,:)=-TE(j);

        %          end
    end

    clear  mat tmps tmpt;

    num=echonumber*sum((xmat.*ymat),1)-(sum(xmat,1).*sum(ymat,1));
    din=echonumber*(sum(xmat.^2,1))-(sum(xmat,1)).^2;

    b1=num./din;

    b2=(1/echonumber)*(sum(ymat,1)-b1.*sum(xmat,1));

    T2map=(1./b1);
    %     T1map=-tr./(log(b1)); %%%%% TR OF THE EXPERIMENT

    mm(:,:)=T2map(1,:,:);
    clear T2map;
    T2map=mm;

%     mm(:,:)=echoimagemat(1,:,:);
%     mm1(:,:)=echoimagemat(2,:,:);
%
%     T2_error= (T2map/dTE).*sqrt( (sigma1./mm).^2 + (sigma2./mm1).^2 );

    curntfname=strcat(s(1).fpathname(1,(1:size(s(1).fpathname,2)-
7)),'T2_map_mult10-',num2str(i),'.ima');
    writeima(curntfname, T2map*100);
%     dicomwrite(T2map*100,curntfname);

%     curntfname=strcat(s(1).fpathname(1,(1:size(s(1).fpathname,2)-
7)),'T2_errmap_mult10-',num2str(i),'.dcm');
%     %     writeima(curntfname, T2_error*10);
%     dicomwrite(T2map,curntfname);
end
```

T_1 map (with T_2* correction):

```
% function [T1map error_estimatemap]=flash_fit(fa,s,tr)
% s is the 3D matrix of # of slices equal to the number of flip angles.
clear all;

clc
format long;

h=msgbox(' --------Please enter the information Asked for ---------');

waitfor(h);

rows=input('Enter Matrix size # ROWS: ');
```

```
cols=input('Enter Matrix size # COLS: ');

TE=input('Enter Echo-time: ');

fanumber=input('Enter number of flip angles: ');
slices=input('Enter the number of slices in the Flip angle images: ');

s.fpathname=[];

display('Please input the T2starcorrection file (.ima)');
[fnameT2star, pathT2star]=uigetfile('C:\Archives\Ang
Doktorado\Projects\Imaging Experiments\2011 05 20 Phantom Imaging
3T\DICOM\*.*');
fpathnameT2star=strcat(pathT2star,fnameT2star)
t2starcorrection=showima(fpathnameT2star);

%%%%%%%%%% FILE INFORMATION INPUT
for i=1:fanumber
    disp(' ');disp(' ');disp(' ')
    display('Select the first file in the series you want to calculate T1');
    [fname, path]=uigetfile('C:\Archives\Ang Doktorado\Projects\Imaging
Experiments\2011 05 20 Phantom Imaging 3T\DICOM\*.*');
    s(i).fpathname=strcat(path,fname)
    disp(' ');disp(' ');disp(' ');
    fa(i)=input('\n Please enter the Corresponding Flip angle:    ');
end

% disp(' ');disp(' ');
% disp('Select the corresponding first reference flip angle image for
normalization:');
% fa=(fa)*(pi/180);

% [fname, path]= uigetfile('E:\Data_OM\Rahul1.5T_LOW FA data\');
% str=strcat(path,fname);
%
% disp(' ');disp(' ');
% normfactor=input('Enter the normalization peak/mode/mean value from the
normalization image:  ');

tr=input('Enter TR of the experiment: ');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

mm=zeros(rows,cols);

% flag=input(' ENTER 1 for alpha map normalisation: OR 2 for normal T1 map
calculation: ');

fa=fa*(pi/180);

%%%%%%%%%%%%%%%%%% ACTUAL CALCULATION WITH ALPHA MAP COMPENSATION INCLUDED
for i=1:slices

    %     alphamap=zeros(rows,cols);% IMAGE MATRIX SIZE
    mat=zeros(rows,cols); % IMAGE MATRIX SIZE
```

```
    xmat=zeros(size(fa,2),rows,cols); % IMAGE MATRIX SIZE
    ymat=zeros(size(fa,2),rows,cols); % IMAGE MATRIX SIZE
    %     faimagemat=zeros(size(fa,2),rows,cols); % IMAGE MATRIX SIZE

    for j=1:fanumber

        if s(j).fpathname(size(s(j).fpathname,2)-5)=='-'
            firstnum=str2num(s(j).fpathname(size(s(j).fpathname,2)-4));

mat(:,:)=dicomread(strcat(s(j).fpathname(1,1:(size(s(j).fpathname,2)-
5)),num2str(firstnum+i-1),'.dcm'));
            mat(:,:)=mat./exp(-TE./t2starcorrection);
        else
            firstnum=str2num(s(j).fpathname(size(s(j).fpathname,2)-4))+10;

mat(:,:)=dicomread(strcat(s(j).fpathname(1,1:(size(s(j).fpathname,2)-
6)),num2str(firstnum+i-1),'.dcm'));
            mat(:,:)=mat./exp(-TE./t2starcorrection);
        end

        faimagemat(j,:,:)=mat;

        tmps=sin(fa(j));
        tmpt=tan(fa(j));
        ymat(j,:,:)=mat./tmps;
        xmat(j,:,:)=mat./tmpt;

    end
    clear  mat tmps tmpt;

    num=fanumber*sum((xmat.*ymat),1)-(sum(xmat,1).*sum(ymat,1));
    din=fanumber*(sum(xmat.^2,1))-(sum(xmat,1)).^2;

    b1=num./din;

    b2=(1/fanumber)*(sum(ymat,1)-b1.*sum(xmat,1));

    T1map=-tr./(log(b1)); %%%%% TR OF THE EXPERIMENT

    mm(:,:)=T1map(1,:,:);
    clear T1map;
    T1map=mm;

    % Error MATRIX calculation

    yestimate=zeros(size(fa,2),rows,cols); % IMAGE MATRIX SIZE

    for j=1:fanumber
        num=b2.*sin(fa(j));
        din=1-cos(fa(j)).*b1;
        yestimate(j,:,:)=num./din;
    end
    sigma_y_error_estimate=sqrt((1/(fanumber-2))*sum((yestimate-
faimagemat).^2,1));
```

```
    din=fanumber*(sum(xmat.^2,1))-(sum(xmat,1)).^2;

    error_b1=sigma_y_error_estimate.*sqrt(fanumber./din);

    mm(:,:)=zeros(rows,cols);
    mm(:,:)=din(1,:,:);
    clear din;
    din=mm;clear mm;

    T1_error=(tr*error_b1)./(b1.*(log(b1)).^2);

    rho_e2=b2./(1-b1);

    mm(:,:)=zeros(rows,cols);
    mm(:,:)=T1_error(1,:,:);
    clear T1_error error_b1;
    T1_error=mm;

    curntfname=strcat(s(1).fpathname(1,(1:size(s(1).fpathname,2)-7)),'T1_map-
',num2str(i),'.ima');
    writeima(curntfname, T1map);

    curntfname=strcat(s(1).fpathname(1,(1:size(s(1).fpathname,2)-
7)),'T1_errmap_mult10-',num2str(i),'.ima');
    writeima(curntfname, T1_error*10);

end
```

Inverse recovery experiments were performed using a Bruker mq 60 NMR Analyzer (1.4 T, 37 ºC) and a Varian-500S (11.7 T, 20 and 37 ºC) spectrometer for samples of GdDOTA, **1**, **2**, and **3** in degassed phosphate buffered saline (PBS, pH 7.4). The relaxivity of the complexes were calculated from the slopes of the linear plots of $1/T_1$ versus concentration.

Variable-temperature ^{17}O NMR measurements of degassed solutions of GdDOTA (20 mM); **1** (5.0 mM); **2** (0.50 mM); **3** (0.42 mM); and the Sr^{II} analogues of **1** (5.0 mM), **2** (0.50 mM), and **3** (0.42 mM) in phosphate buffered saline (PBS, pH = 7.4) as well as acidified water ($HClO_4$, pH 3.4) were obtained on a Varian–500S (9.4 T) spectrometer. ^{17}O-enriched water (10% $H_2{}^{17}O$, Cambridge Isotope Laboratories, Inc.) was added to samples to yield 1% ^{17}O enrichment. Line widths at half height were measured at 15, 20, 30, 40, 50, 60, and 70 °C. The Sr^{II} analogues of **1**, **2**, and **3** and the acidified water were used as diamagnetic references. $A/\hbar$, q, and ΔE were fixed to -3.8×10^{-6} rad/s, 2, and 2.5×10^{-11} J/mol, respectively, for Eu^{II}-containing cryptates. Data acquired from variable-temperature ^{17}O NMR experiments were fitted using sixty unique values of T_{1e}^{298} in the range of 10^{-8}–10^{-3} s, and the T_{1e}^{298} values that were associated with the best correlation coefficients were reported. The least-squares fits of the ^{17}O NMR relaxation data were calculated using Origin software (8.0951 B951) following published procedures.[5] The variable temperature ^{17}O NMR data and fits are presented below:

GdDOTA:

Temperature (°C)	**Linewidth (Hz)**	
	Acidified water	**GdDOTA**
70	33	97
60	39	137
50	50	197
40	68	249
30	99	281
20	137	256
15	160	241

Notes

Input Data

Parameters

		Value	Standard Error
1overT2P	T1e298	2.9E-8	0
	taum298	2.8731E-7	1.44761E-8
	deltaH	70278.52868	1737.2312
	deltaE	2.5E-11	0
	q	1	0
	Gd	0.02	0

Iterations Performed = 8
Total Iterations in Session = 8
Fit converged - tolerance criterion satisfied.
Some parameter values were fixed.

Statistics

	1overT2P
Number of Points	7
Degrees of Freedom	5
Reduced Chi-Sqr	355.87249
Residual Sum of Squares	1779.36246
Adj. R-Square	0.98372
Fit Status	Succeeded(100)

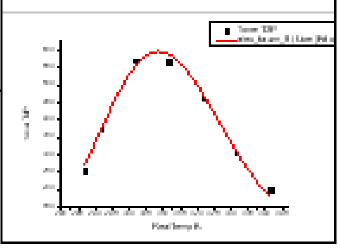
Fit Status Code :
100 : Fit converged

Summary

ANOVA

Fitted Curves Plot

1overT2P



Residual vs. Independent Plot

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Eu^II^-containing complex, 1:

Temperature (°C)	Linewidth (Hz)	
	Sr analog of 1	1
70	30	31
60	34	37
50	40	46
40	53	57
30	64	73
20	91	111
15	107	142

⊞ *Notes*

⊞ *Input Data*

⊟ *Parameters*

		Value	Standard Error
1overT2P	T1e298	1.2E-7	0
	taum298	3.0316E-9	3.61557E-10
	deltaH	60371.25707	8482.41449
	deltaE	2.5E-11	0
	q	2	0
	Eu	0.005	0

Iterations Performed = 5
Total Iterations in Session = 5
Fit converged - Chi-sqr no longer changed.
Some parameter values were fixed.

⊟ *Statistics*

	1overT2P
Number of Points	7
Degrees of Freedom	5
Reduced Chi-Sqr	51.7001
Residual Sum of Squares	258.50051
Adj. R-Square	0.96503
Fit Status	Succeeded(101)

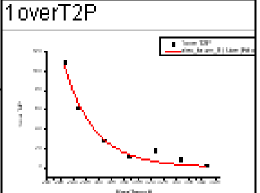
Fit Status Code :
101 : Fit converged

⊞ *Summary*

⊞ *ANOVA*

⊟ *Fitted Curves Plot*

1overT2P



⊞ *Residual vs. Independent Plot*

Eu^{II}-containing complex, 2:

Temperature (°C)	Linewidth (Hz)	
	Sr analog of 2	2
70	30	37
60	34	45
50	41	57
40	52	75
30	71	105
20	102	154
15	126	183

⊞ *Notes*
⊞ *Input Data*
⊟ *Parameters*

		Value	Standard Error
1overT2P	T1e298	4.1E-8	0
	taum298	1.16602E-8	2.57992E-10
	deltaH	33732.12485	1360.89106
	deltaE	2.5E-11	0
	q	2	0
	Eu	0.005	0

Iterations Performed = 6
Total Iterations in Session = 6
Fit converged - Chi-sqr no longer changed.
Some parameter values were fixed.

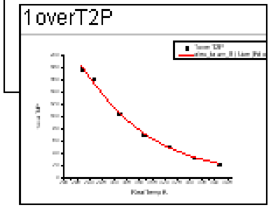
⊟ *Statistics*

	1overT2P
Number of Points	7
Degrees of Freedom	5
Reduced Chi-Sqr	19.20064
Residual Sum of Squares	96.0032
Adj. R-Square	0.99503
Fit Status	Succeeded(101)

Fit Status Code :
101 : Fit converged

⊞ *Summary*
⊞ *ANOVA*
⊟ *Fitted Curves Plot*

1overT2P



⊞ *Residual vs. Independent Plot*

Eu^{II}-containing complex, 3:

Temperature (°C)	Linewidth (Hz)	
	Sr analog of 3	3
70	29	30
60	33	35
50	39	43
40	48	55
30	63	75
20	90	108
15	112	134

⊞ *Notes*

⊞ *Input Data*

⊟ *Parameters*

		Value	Standard Error
1overT2P	T1e298	1.1E-6	0
	taum298	4.78533E-8	3.77746E-9
	deltaH	48872.87829	5457.16633
	deltaE	2.5E-11	0
	q	2	0
	Eu	4.2E-4	0

Iterations Performed = 11
Total Iterations in Session = 11
Fit converged - tolerance criterion satisfied.
Some parameter values were fixed.

⊟ *Statistics*

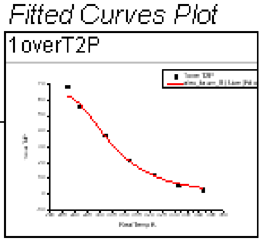
	1overT2P
Number of Points	7
Degrees of Freedom	5
Reduced Chi-Sqr	9.39458
Residual Sum of Squares	46.97288
Adj. R-Square	0.98571
Fit Status	Succeeded(100)

Fit Status Code :
100 : Fit converged

⊞ *Summary*

⊞ *ANOVA*

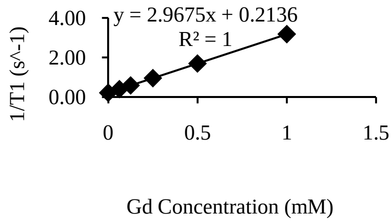
⊟ *Fitted Curves Plot*



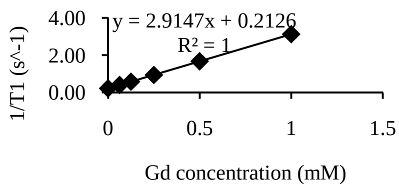
⊞ *Residual vs. Independent Plot*

GdDOTA (1.4 T, Temp = 37 °C)

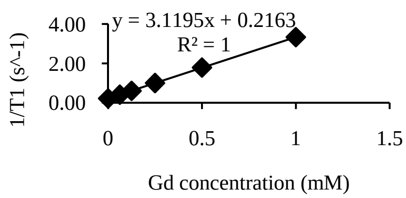
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.18	0.31
0.5	1.69	0.59
0.25	0.96	1.05
0.125	0.58	1.71
0.0625	0.40	2.51
0	0.22	4.63



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.13	0.32
0.5	1.67	0.60
0.25	0.93	1.07
0.125	0.58	1.74
0.0625	0.40	2.52
0	0.22	4.63

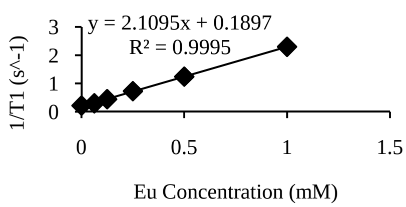


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.33	0.30
0.5	1.79	0.56
0.25	1.00	1.00
0.125	0.60	1.66
0.0625	0.41	2.45
0	0.22	4.63

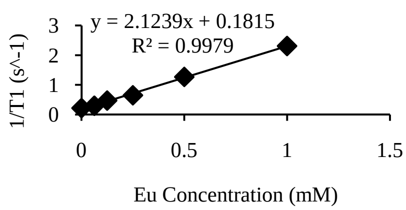


Cryptate **1** (1.4 T, Temp = 37 °C)

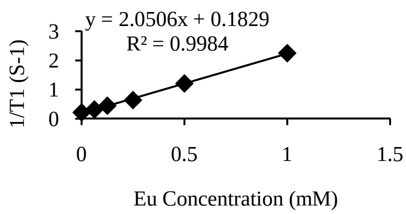
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	2.30	0.43
0.5	1.24	0.81
0.25	0.73	1.37
0.125	0.44	2.26
0.0625	0.30	3.38
0	0.22	4.63



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	2.31	0.43
0.5	1.27	0.79
0.25	0.65	1.54
0.125	0.47	2.13
0.0625	0.29	3.39
0	0.22	4.63

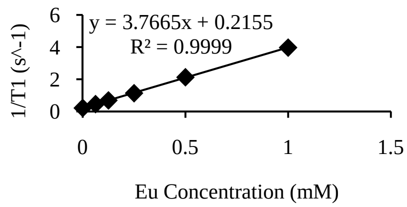


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	2.31	0.43
0.5	1.27	0.79
0.25	0.65	1.54
0.125	0.47	2.13
0.0625	0.29	3.39
0	0.22	4.63

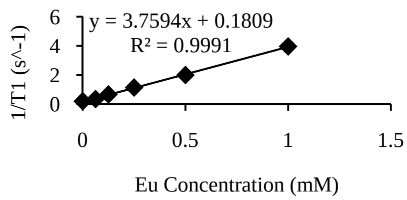


Cryptate **2** (1.4 T, Temp = 37 °C)

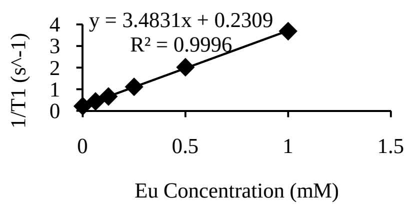
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.97	0.25
0.5	2.13	0.47
0.25	1.14	0.88
0.125	0.69	1.46
0.0625	0.45	2.21
0	0.22	4.63



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.96	0.25
0.5	2.00	0.50
0.25	1.15	0.87
0.125	0.68	1.48
0.0625	0.36	2.76
0	0.22	4.63

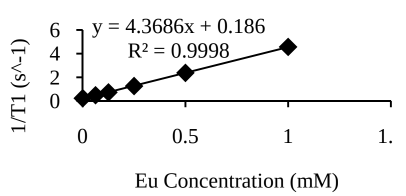


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.69	0.27
0.5	2.02	0.50
0.25	1.11	0.90
0.125	0.66	1.51
0.0625	0.44	2.30
0	0.22	4.63

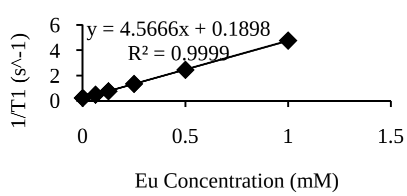


Cryptate **3** (1.4 T, Temp = 37 °C)

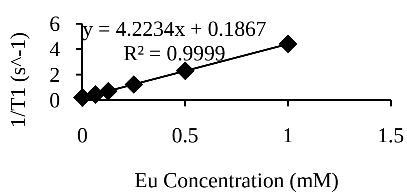
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.57	0.22
0.5	2.36	0.42
0.25	1.25	0.80
0.125	0.72	1.40
0.0625	0.47	2.14
0	0.22	4.63



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.77	0.21
0.5	2.45	0.41
0.25	1.33	0.75
0.125	0.75	1.33
0.0625	0.47	2.12
0	0.22	4.63

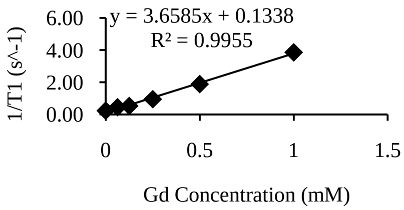


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.41	0.23
0.5	2.30	0.43
0.25	1.23	0.81
0.125	0.70	1.43
0.0625	0.44	2.27
0	0.22	4.63

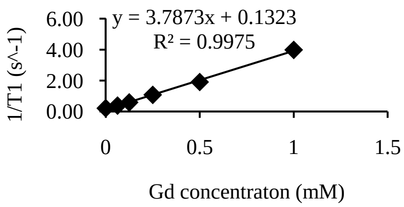


GdDOTA (3 T, Temp = 19.8 °C)

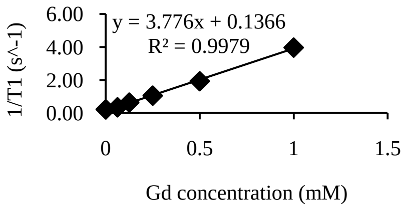
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.86	0.26
0.5	1.88	0.53
0.25	0.95	1.06
0.125	0.53	1.90
0.0625	0.45	2.24
0	0.23	4.36



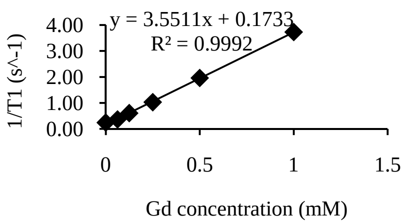
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.98	0.25
0.5	1.90	0.53
0.25	1.07	0.93
0.125	0.58	1.71
0.0625	0.38	2.65
0	0.21	4.78



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.97	0.25
0.5	1.93	0.52
0.25	1.05	0.95
0.125	0.63	1.58
0.0625	0.34	2.91
0	0.22	4.62

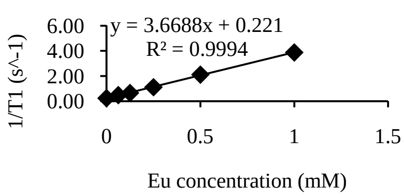


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.73	0.27
0.5	1.96	0.51
0.25	1.02	0.98
0.125	0.60	1.66
0.0625	0.36	2.78
0	0.24	4.19

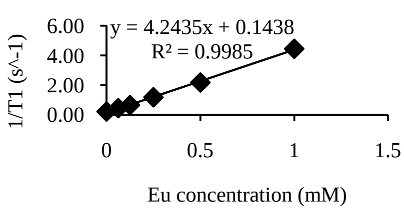


Cryptate **1** (3 T, Temp = 19.8 °C)

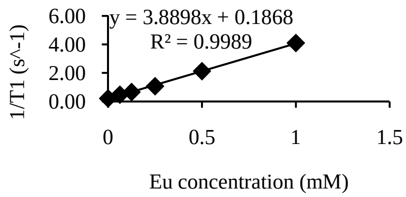
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	3.88	0.26
0.5	2.11	0.48
0.25	1.10	0.91
0.125	0.64	1.55
0.0625	0.47	2.11
0	0.23	4.36



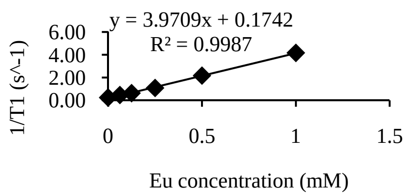
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.44	0.23
0.5	2.17	0.46
0.25	1.18	0.85
0.125	0.65	1.55
0.0625	0.44	2.27
0	0.21	4.78



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.10	0.24
0.5	2.13	0.47
0.25	1.07	0.93
0.125	0.66	1.51
0.0625	0.48	2.09
0	0.22	4.62

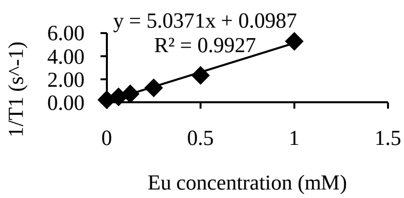


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.17	0.24
0.5	2.16	0.46
0.25	1.08	0.92
0.125	0.63	1.60
0.0625	0.46	2.18
0	0.24	4.19

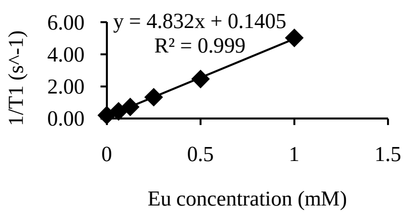


Cryptate **2** (3 T, Temp = 19.8 °C)

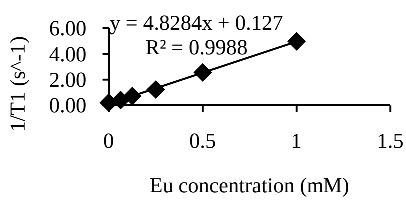
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	5.29	0.19
0.5	2.34	0.43
0.25	1.26	0.79
0.125	0.74	1.35
0.0625	0.48	2.07
0	0.23	4.36



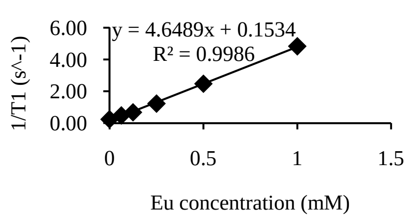
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	5.03	0.20
0.5	2.46	0.41
0.25	1.33	0.75
0.125	0.72	1.38
0.0625	0.45	2.22
0	0.21	4.78



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.98	0.20
0.5	2.56	0.39
0.25	1.23	0.81
0.125	0.73	1.38
0.0625	0.41	2.42
0	0.22	4.62

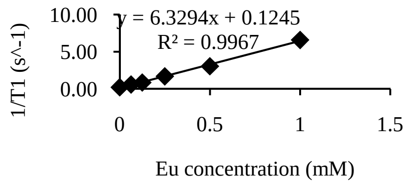


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.83	0.21
0.5	2.48	0.40
0.25	1.23	0.82
0.125	0.68	1.48
0.0625	0.48	2.08
0	0.24	4.19

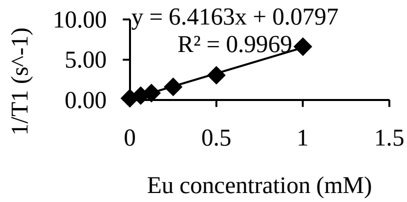


Cryptate **3** (3 T, Temp = 19.8 °C)

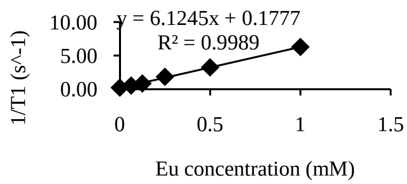
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	6.58	0.15
0.5	3.05	0.33
0.25	1.69	0.59
0.125	0.86	1.16
0.0625	0.60	1.68
0	0.23	4.36



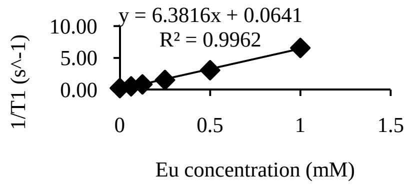
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	6.62	0.15
0.5	3.07	0.33
0.25	1.62	0.62
0.125	0.85	1.17
0.0625	0.54	1.85
0	0.21	4.78



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	6.29	0.16
0.5	3.24	0.31
0.25	1.83	0.55
0.125	0.83	1.20
0.0625	0.53	1.90
0	0.22	4.62

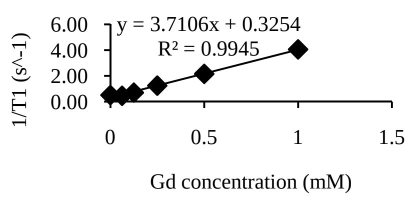


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	6.58	0.15
0.5	3.06	0.33
0.25	1.52	0.66
0.125	0.83	1.20
0.0625	0.52	1.93
0	0.24	4.19

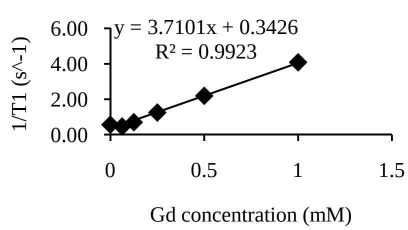


GdDOTA (7 T, Temp = 19 °C)

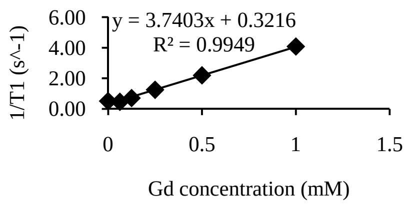
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.07	0.25
0.5	2.16	0.46
0.25	1.25	0.80
0.125	0.70	1.42
0.0625	0.46	2.20
0	0.51	1.96



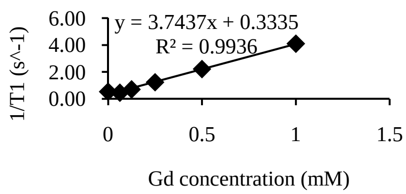
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.08	0.25
0.5	2.19	0.46
0.25	1.25	0.80
0.125	0.70	1.43
0.0625	0.46	2.18
0	0.56	1.77



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.08	0.25
0.5	2.19	0.46
0.25	1.24	0.80
0.125	0.70	1.43
0.0625	0.45	2.20
0	0.50	1.99

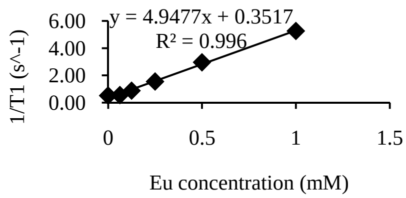


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	4.10	0.24
0.5	2.22	0.45
0.25	1.24	0.81
0.125	0.71	1.42
0.0625	0.46	2.17
0	0.54	1.86

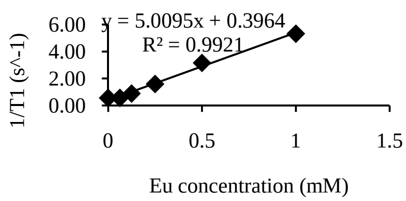


Cryptate **1** (7 T, Temp = 19 °C)

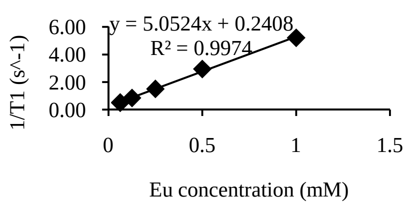
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	5.26	0.19
0.5	2.96	0.34
0.25	1.55	0.65
0.125	0.87	1.15
0.0625	0.55	1.83
0	0.51	1.96



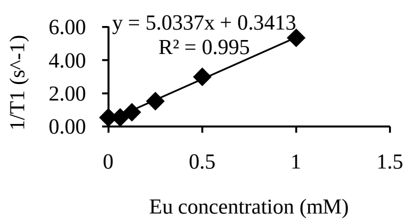
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	5.32	0.19
0.5	3.15	0.32
0.25	1.59	0.63
0.125	0.89	1.13
0.0625	0.57	1.77
0	0.56	1.77



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	5.32	0.19
0.5	3.15	0.32
0.25	1.59	0.63
0.125	0.89	1.13
0.0625	0.57	1.77
0	0.56	1.77

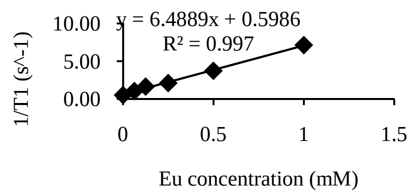


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	5.32	0.19
0.5	3.15	0.32
0.25	1.59	0.63
0.125	0.89	1.13
0.0625	0.57	1.77
0	0.56	1.77

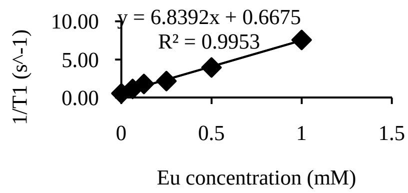


Cryptate **2** (7 T, Temp = 19 °C)

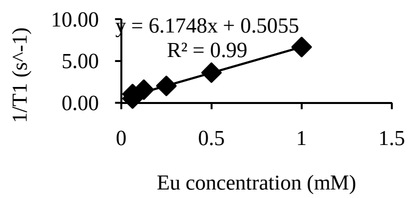
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.14	0.14
0.5	3.73	0.27
0.25	2.10	0.48
0.125	1.63	0.61
0.0625	1.04	0.96
0	0.51	1.96



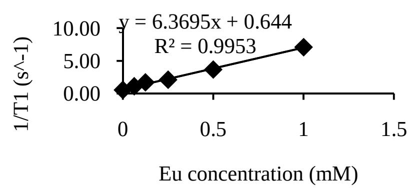
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.58	0.13
0.5	3.97	0.25
0.25	2.18	0.46
0.125	1.81	0.55
0.0625	1.16	0.86
0	0.56	1.77



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	6.67	0.15
0.5	3.60	0.28
0.25	2.01	0.50
0.125	1.56	0.64
0.0625	1.04	0.96
0	0.50	1.99

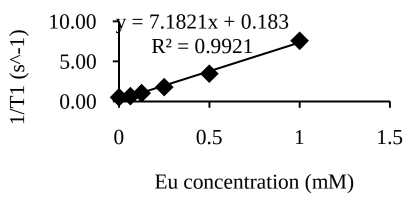


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.09	0.14
0.5	3.66	0.27
0.25	2.11	0.48
0.125	1.71	0.59
0.0625	1.10	0.91
0	0.54	1.86

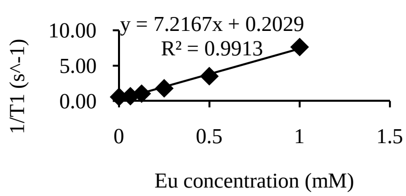


Cryptate **3** (7 T, Temp = 19 °C)

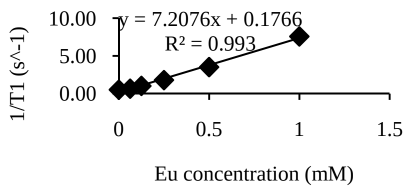
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.58	0.13
0.5	3.46	0.29
0.25	1.78	0.56
0.125	1.03	0.97
0.0625	0.65	1.54
0	0.51	1.96



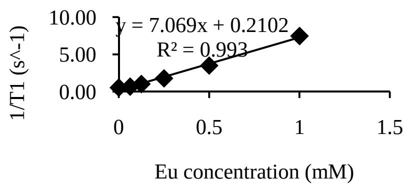
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.63	0.13
0.5	3.51	0.29
0.25	1.79	0.56
0.125	1.04	0.96
0.0625	0.67	1.49
0	0.56	1.77



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.58	0.13
0.5	3.51	0.29
0.25	1.79	0.56
0.125	1.01	0.99
0.0625	0.64	1.55
0	0.50	1.99

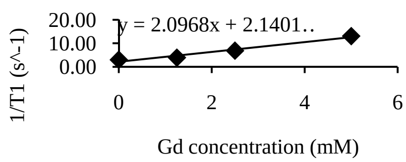


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
1	7.46	0.13
0.5	3.50	0.29
0.25	1.77	0.56
0.125	1.02	0.98
0.0625	0.67	1.50
0	0.54	1.86

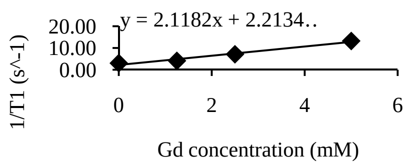


GdDOTA (11.7 T, Temp = 37 °C)

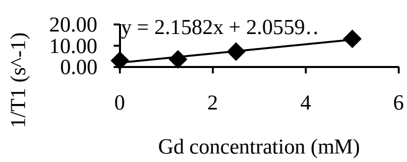
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
5	13.08	0.08
2.5	6.89	0.15
1.25	3.93	0.25
0	3.01	0.33



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
5	13.21	0.08
2.5	7.10	0.14
1.25	4.07	0.25
0	3.01	0.33

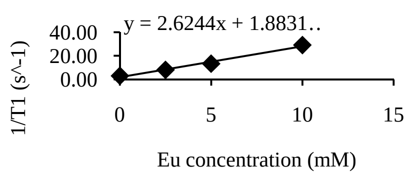


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
5	13.24	0.08
2.5	7.24	0.14
1.25	3.62	0.28
0	3.01	0.33

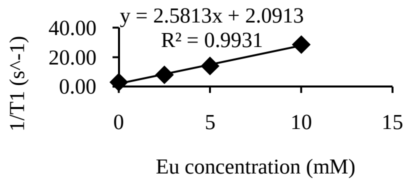


Cryptate **1** (11.7 T, Temp = 37 °C)

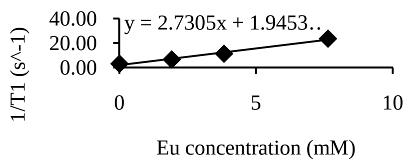
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	29.08	0.03
5	13.28	0.08
2.5	8.08	0.12
0	3.01	0.33



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	28.54	0.04
5	14.02	0.07
2.5	7.97	0.13
0	3.01	0.33

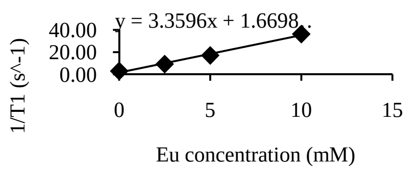


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
7.63	23.53	0.04
3.825	11.21	0.09
1.9125	6.52	0.15
0	3.01	0.33

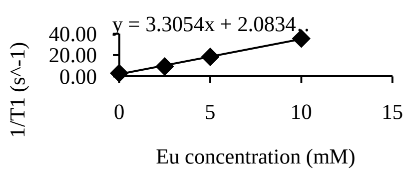


Cryptate **2** (11.7 T, Temp = 37 °C)

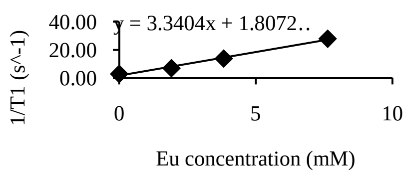
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	36.19	0.03
5	17.03	0.06
2.5	9.23	0.11
0	3.01	0.33



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	35.54	0.03
5	18.34	0.05
2.5	9.29	0.11
0	3.01	0.33

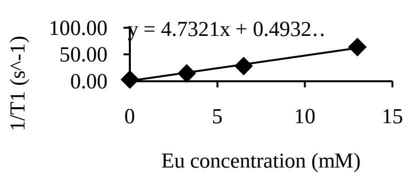


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
7.63	27.93	0.04
3.825	13.88	0.07
1.9125	7.05	0.14
0	3.01	0.33

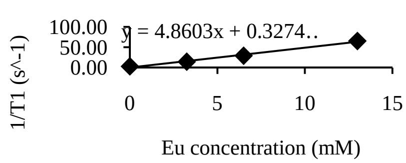


Cryptate **3** (11.7 T, Temp = 37 °C)

Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
13	63.86	0.02
6.5	28.23	0.04
3.25	14.52	0.07
0	3.01	0.33

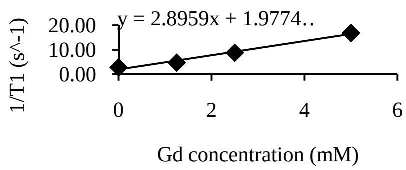


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
13	65.36	0.02
6.5	29.06	0.03
3.25	14.45	0.07
0	3.01	0.33

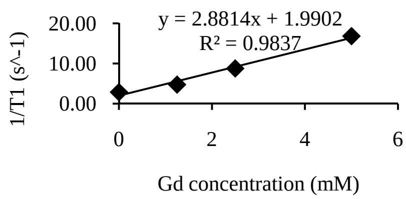


GdDOTA (11.7 T, Temp = 20 °C)

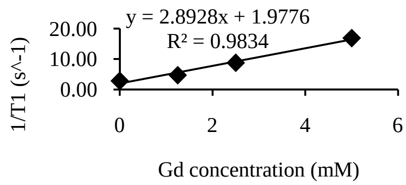
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
5	16.89	0.06
2.5	8.79	0.11
1.25	4.73	0.21
0	2.84	0.35



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
5	16.83	0.06
2.5	8.77	0.11
1.25	4.72	0.21
0	3.01	0.35

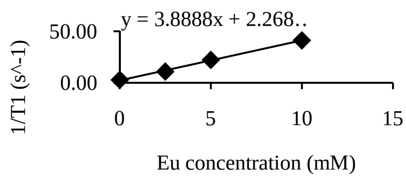


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
5	16.88	0.06
2.5	8.77	0.11
1.25	4.71	0.21
0	3.01	0.35

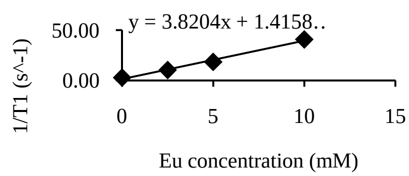


Cryptate **1** (11.7 T, Temp = 20 °C)

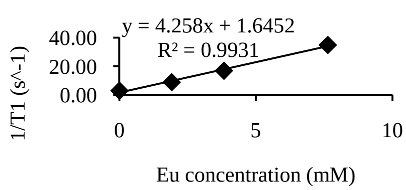
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	41.19	0.02
5	22.20	0.05
2.5	10.90	0.09
0	2.84	0.35



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	40.78	0.02
5	18.47	0.05
2.5	10.41	0.10
0	3.01	0.35

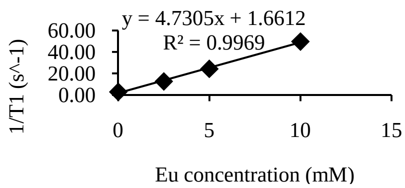


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
7.63	34.89	0.03
3.825	16.88	0.06
1.9125	8.87	0.11
0	3.01	0.35

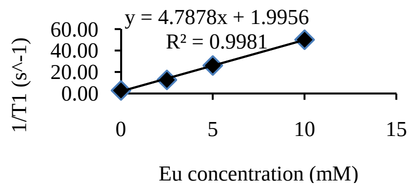


Cryptate **2** (11.7 T, Temp = 20 °C)

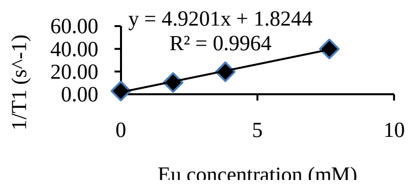
Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	49.70	0.02
5	24.30	0.04
2.5	12.57	0.08
0	2.84	0.35



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
10	50.10	0.02
5	26.12	0.04
2.5	12.70	0.08
0	3.01	0.35

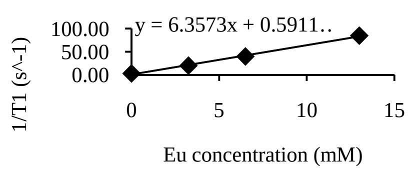


Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
7.63	39.98	0.03
3.825	19.83	0.05
1.9125	10.40	0.10
0	3.01	0.35

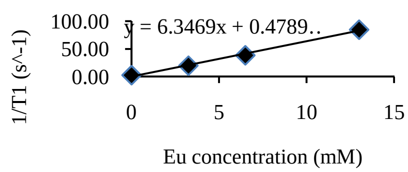


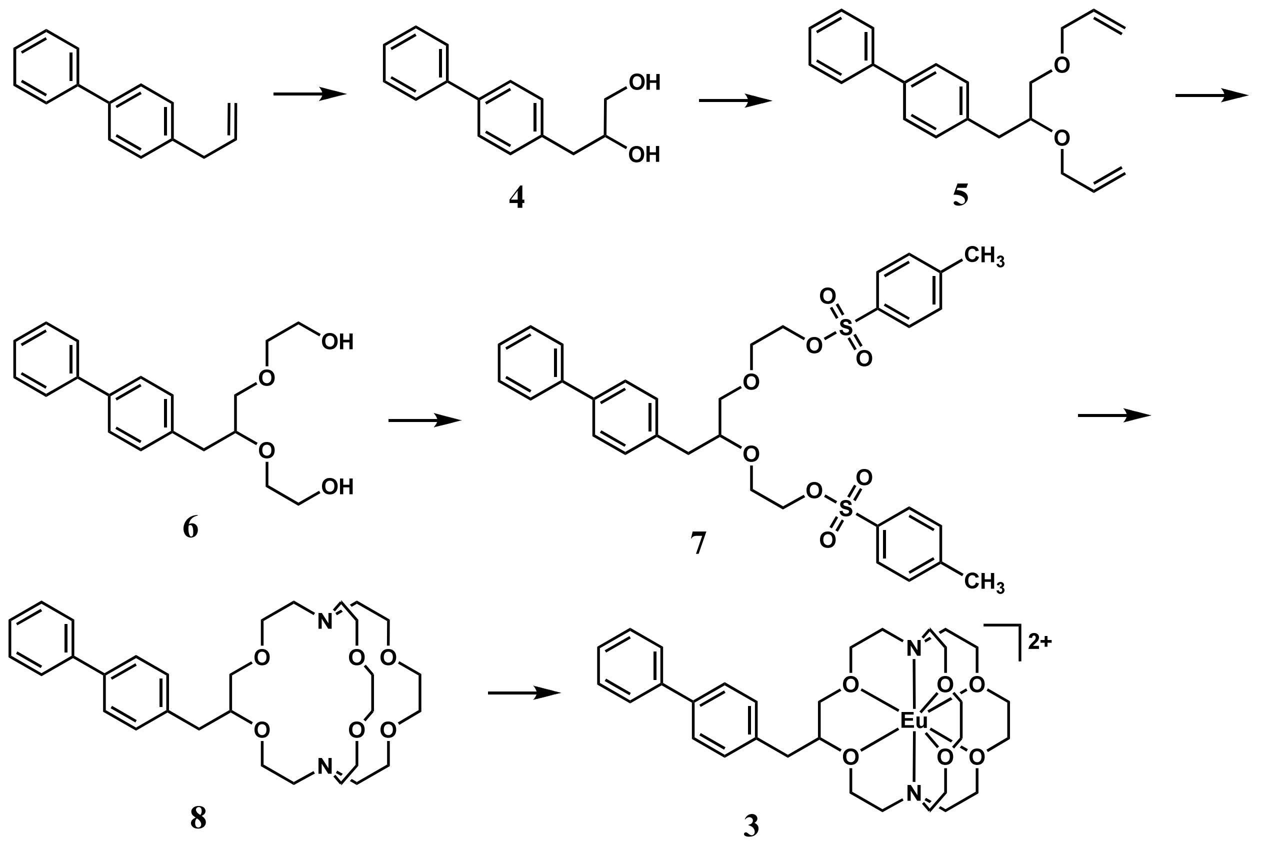
Cryptate **3** (11.7 T, Temp = 20 °C)

Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
13	84.75	0.01
6.5	39.64	0.03
3.25	19.77	0.05
0	2.84	0.35



Concn (mM)	$1/T_1$ (s^{-1})	T_1 (s)
13	84.82	0.01
6.5	38.62	0.03
3.25	20.01	0.05
0	3.01	0.35





3-(Biphenyl-4-yl)propane-1,2-diol (4): To a mixture of 4-allylbiphenyl (4.00 g, 20.6 mmol, 1 equiv), *t*-BuOH (150 mL), and H_2O (150 mL) was added sequentially $K_3Fe(CN)_6$ (20.3 g, 61.8 mmol, 3 equiv), $K_2CO_3 \cdot H_2O$ (9.65 g, 61.8 mmol, 3 equiv), and a solution of OsO_4 in *t*-BuOH (95.9 mM, 2.70 mL, 0.0129 equiv). The reaction mixture was stirred for 20 h at ambient temperature at which point Na_2SO_3 (7.79 g, 61.8 mmol, 3 equiv) was added, and stirring was continued for 4 h. The resulting solution was concentrated to dryness under reduced pressure, and the residue was extracted with Et_2O (6 × 50 mL). After removal of Et_2O under reduced pressure, purification was performed using silica gel chromatography (1:1 hexanes/ethyl acetate) to yield 4.25 g (90%) of **4** as white solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 2.66–2.90 (m, CH_2, 2H), 3.44–3.56 (m, CH_2, 2H), 3.81–3.89 (m, C*H*, 1H), 7.24–7.58 (m, C*H*, 9H); ^{13}C NMR (101 MHz, CD_3OD, δ): 40.5 (*C*H_2), 66.6 (*C*H_2), 74.4 (*C*H), 127.80 (*C*H), 127.81 (*C*H), 128.1 (*C*H), 129.8 (*C*H), 130.9 (*C*H), 139.3, 140.3, 142.2; TLC: R_f = 0.33 (1:1 hexanes/ethyl acetate); HRESIMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{15}H_{16}O_2Na$, 251.1048; found, 251.1046.

4-(1,2-Bis(allyloxy)ethyl)biphenyl (5): To a solution of **4** (3.10 g, 13.5 mmol, 1 equiv) in anhydrous dimethoxyethane (60 mL) under Ar at ambient temperature was added NaH (50% in oil, 2.53 g, 52.6 mmol, 4 equiv) followed by the dropwise addition of 1-bromoprop-2-ene (4.45 mL, 52.6 mmol, 4 equiv). The resulting reaction mixture was heated at reflux for 23 h and allowed to cool to ambient temperature before excess NaH was quenched with methanol (2 mL). Solvent was removed under reduced pressure; the resulting residue was extracted with ethyl acetate (3 × 20 mL); and the combined ethyl acetate solutions were washed with water (3 × 20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification was performed using silica gel chromatography (9:1 hexanes/ethyl acetate) to yield 3.85 g (95%) of **5** as a yellow oil. ^1H NMR (400 MHz, CD_3CN, δ): 2.79–2.91 (m, CH_2, 2H), 3.37–3.48 (m, CH_2, 2H), 3.68–3.76 (m, C*H*, 1H), 3.93–4.11 (m, CH_2, 4H), 5.04–5.32 (m, CH_2, 4H), 5.78–5.98 (m, C*H*, 2H), 7.28–7.66 (m, C*H*, 9H); ^{13}C NMR (101 MHz, CD_3CN, δ): 38.1 (CH_2), 72.3 (CH_2), 72.6 (CH_2), 79.8 (*C*H), 116.4 (CH_2), 116.7 (CH_2), 127.6 (*C*H), 127.7 (*C*H), 128.1 (*C*H), 129.8 (*C*H), 131.0 (*C*H), 136.2 (*CH*), 136.6 (*C*H), 139.2, 139.5, 141.6; TLC: R_f = 0.53 (9:1 hexanes/ethyl acetate); HRESIMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{21}H_{24}O_2Na$, 331.1674; found, 331.1669.

2,2'-(Propane-1,2-diylbisoxy-3-biphenyl-4-yl)-diethanol (6): Ozone was passed through a solution of **5** (4.00 g, 12.9 mmol, 1 equiv) in methanol (100 mL) at –50 °C until the starting compound was consumed (55 min). The resulting reaction mixture was purged with Ar, and $NaBH_4$ (4.87 g, 129 mmol, 10 equiv) was added. The mixture was stirred for 1 h, a mixture of HOAc/H_2O 1:10 (v/v) (18 mL) was added, and the resulting solution was stirred for 2 h. Volatile components were removed under reduced pressure, and the residue was extracted with ethyl acetate (6 × 20 mL). The extract was concentrated under reduced pressure, and purification was performed using silica gel chromatography (ethyl acetate) to yield 3.31 g (81%) of **6** as pale yellow oil. ^{1}H NMR (400 MHz, CD_3CN, δ): 2.75–2.90 (m, CH_2, 2H), 3.01 (brs, O*H*, 2H), 3.25–3.77 (m, C*H* and CH_2, 11H), 7.29–7.68 (m, C*H*, 9H); ^{13}C NMR (101 MHz, CD_3CN, δ): 38.1 (*C*H_2), 61.9 (*C*H_2), 62.2 (*C*H_2), 72.3 (*C*H_2), 73.3 (*C*H_2), 73.6 (*C*H_2), 80.8 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 128.2 (*C*H), 129.8 (*C*H), 131.0 (*CH*), 139.1, 139.6, 141.6; TLC: R_f = 0.44 (ethyl acetate); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{25}O_4$, 317.1753; found, 317.1745.

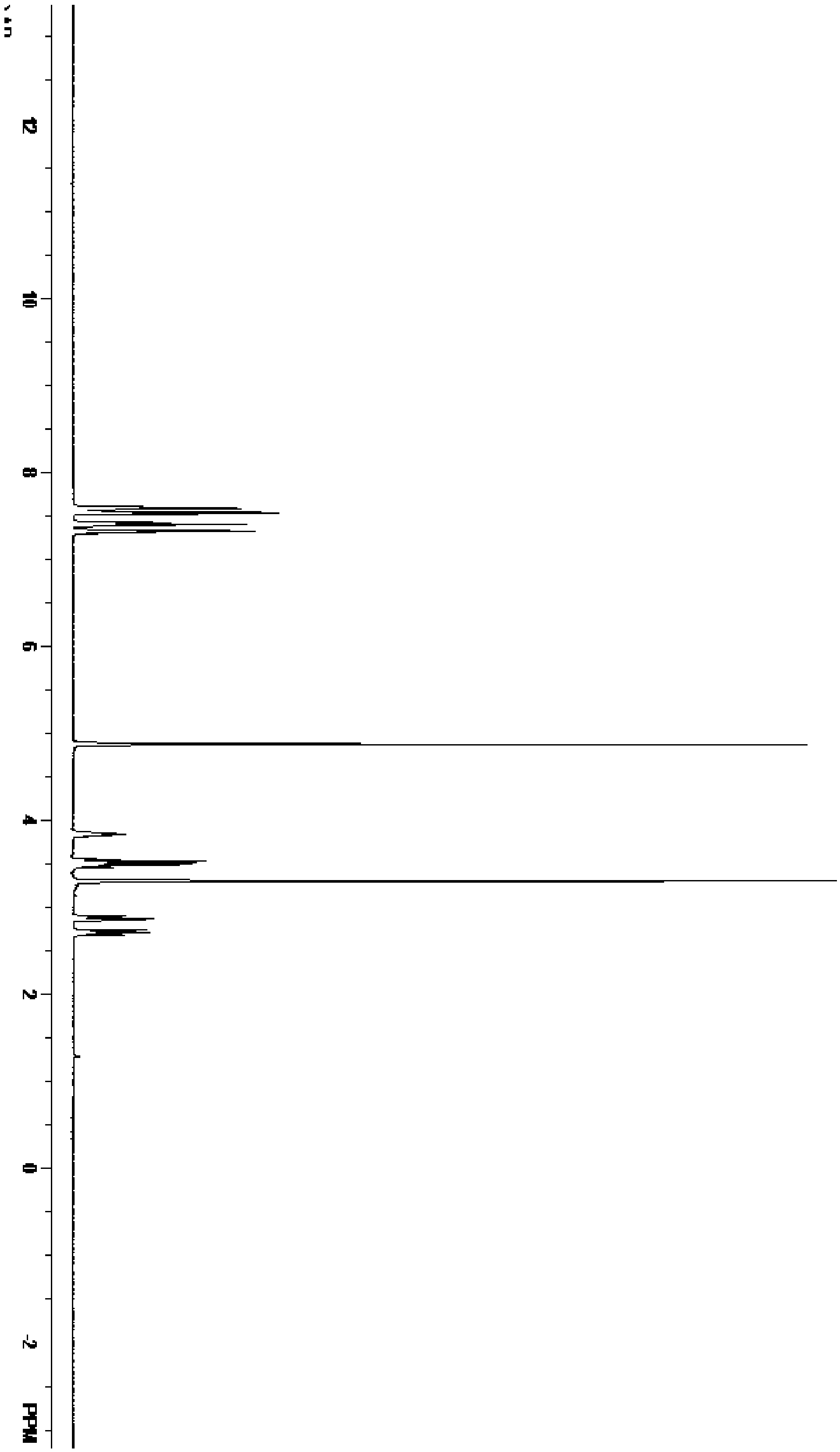
2,2'-(Propane-1,2-diylbisoxy-3-biphenyl-4-yl)-ditosylate (7): A solution of tosyl chloride (3.71 g, 19.5 mmol, 3 equiv) in CH_2Cl_2 (22 mL) was added in a dropwise manner to an ice-cooled solution of **6** (2.06 g, 6.51 mmol, 1 equiv), triethylamine (5.45 mL, 39.1 mmol, 6 equiv), and dimethylaminopyridine (0.030 mL, 0.25 mmol, 0.038 equiv) in CH_2Cl_2 (33 mL), and the resulting mixture was stirred for 24 h while warming to ambient temperature. The reaction mixture was washed sequentially with water (2 × 33 mL), saturated aqueous Na_2CO_3 (2 × 22 mL), and saturated aqueous citric acid (2 × 22 mL); dried over Na_2SO_4; and concentrated under reduced pressure. Purification was performed using silica gel chromatography (stepwise gradient of 3:1→1:1 hexanes/ethyl acetate) to yield 3.15 g (78%) of **7** as a light yellow oil. ^{1}H NMR (400 MHz, CD_3CN, δ): 2.37 (s, CH_3, 6H), 2.60–2.74 (m, CH_2, 2H), 3.20–3.35 (m, CH_2, 2H), 3.47–3.67 (m, C*H* and CH_2, 5H), 3.97–4.12 (m, CH_2, 4H), 7.18–7.81 (m, C*H*, 17H); ^{13}C NMR (101 MHz, CD_3CN, δ): 21.6 (*C*H_3), 37.7 (*C*H_2), 68.2 (*C*H_2), 69.3 (*C*H_2), 70.8 (*C*H_2), 71.1 (*C*H_2), 73.1 (*C*H_2), 80.7 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 128.2 (*C*H), 128.7 (*C*H), 129.8 (*CH*), 131.0 (*C*H), 133.8, 138.6, 139.5, 141.6, 146.3; TLC: R_f = 0.21 (3:1 hexanes/ethyl acetate); HRESIMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{33}H_{36}O_8S_2Na$, 647.1749; found, 647.1735.

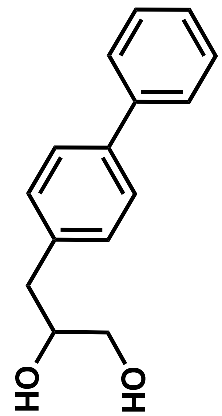
5-(Biphenyl-4-ylmethyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (8): Under an atmosphere of Ar, 4,13-diaza-18-crown-6-ether (0.177 g, 0.675 mmol, 1 equiv) was added to a suspension of Cs_2CO_3 (1.08 g, 3.33 mmol, 4.93 equiv) in anhydrous acetonitrile (37 mL). The mixture was heated to 60 °C, and a solution of **7** (0.478 g, 0.765, 1.13 equiv) in anhydrous acetonitrile (13 mL) was added. The reaction mixture was heated at reflux for 115 h, cooled to ambient temperature, and filtered through celite. Solvent was removed under reduced pressure, and purification was performed using silica gel chromatography (stepwise gradient of 20:1→10:1 CH_2Cl_2/methanol) to yield 73.6 mg (21%) of **8** as a pale yellow oil. ^{1}H NMR (400 MHz, CD_3CN, δ): 2.55–2.88 (m, CH_2, 10H), 3.03–3.11 (m, CH_2, 1H), 3.32–3.82 (m, C*H* and CH_2, 26H), 7.30–7.66 (m, C*H*, 9H); ^{13}C NMR (101 MHz, CD_3CN, δ): 38.4 (*C*H_2), 53.4 (*C*H_2), 53.5 (*C*H_2), 53.7 (*C*H_2), 53.8 (*C*H_2), 54.1 (*C*H_2), 54.3 (*C*H_2), 66.1 (*C*H_2), 68.0 (*C*H_2), 68.1 (*C*H_2), 68.57 (*C*H_2), 68.59 (*C*H_2), 68.8 (*C*H_2), 68.9 (*C*H_2), 69.2 (*C*H_2), 69.6 (*C*H_2), 71.4 (*C*H_2), 79.4 (*C*H), 126.7 (*C*H), 127.7 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 129.2 (*CH*), 129.9 (*C*H), 131.0 (*C*H), 138.4, 139.6, 141.5; TLC: R_f = 0.23 (10:1 CH_2Cl_2/methanol); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{31}H_{47}O_6N_2$, 543.3434; found, 543.3425.

General Procedure for the synthesis of Eu^{II}-containing cryptates (1–3): A degassed aqueous solution of $EuCl_2$ (1 equiv) was mixed with a degassed aqueous solution of a cryptand (2 equiv). The resulting mixture was stirred for 12 h at ambient temperature under Ar. Degassed PBS (10×) was added to make the entire reaction mixture 1× in PBS, and stirring was continued for 30 min. The concentration of Eu was verified by ICP-MS.

References

1. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals, Fifth Edition;* Elsevier: Burlington, MA, 2003.
2. Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008,** *130,* 12901−12903.
3. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43,* 2923–2925.
4. Haacke, E. M.; Brown, R. W.; Thompson, M. R.; Venkatesan, R. *Magnetic Resonance Imaging Physical Principles and Sequence Design;* John Wiley & Sons, Inc.: New York, 1999; p 654.
5. Urbanczyk-Pearson, L. M.; Femia, F. J.; Smith, J.; Parigi, G.; Duimstra, J. A.; Eckermann, A. L.; Luchinat, C.; Meade, T. J. *Inorg. Chem.* **2008,** *47,* 56–68.





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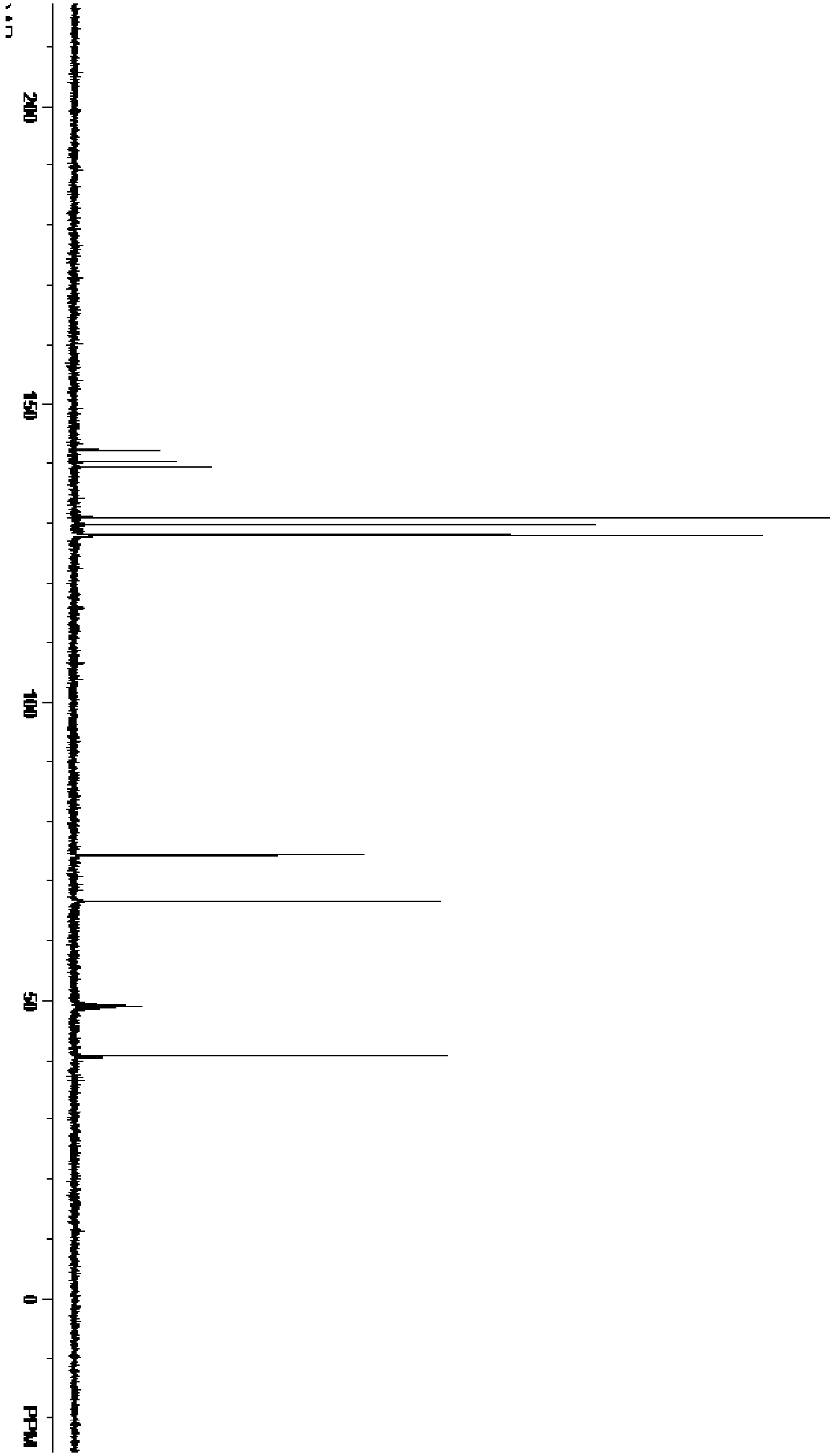

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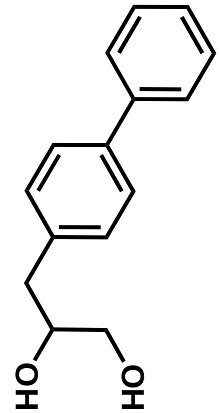

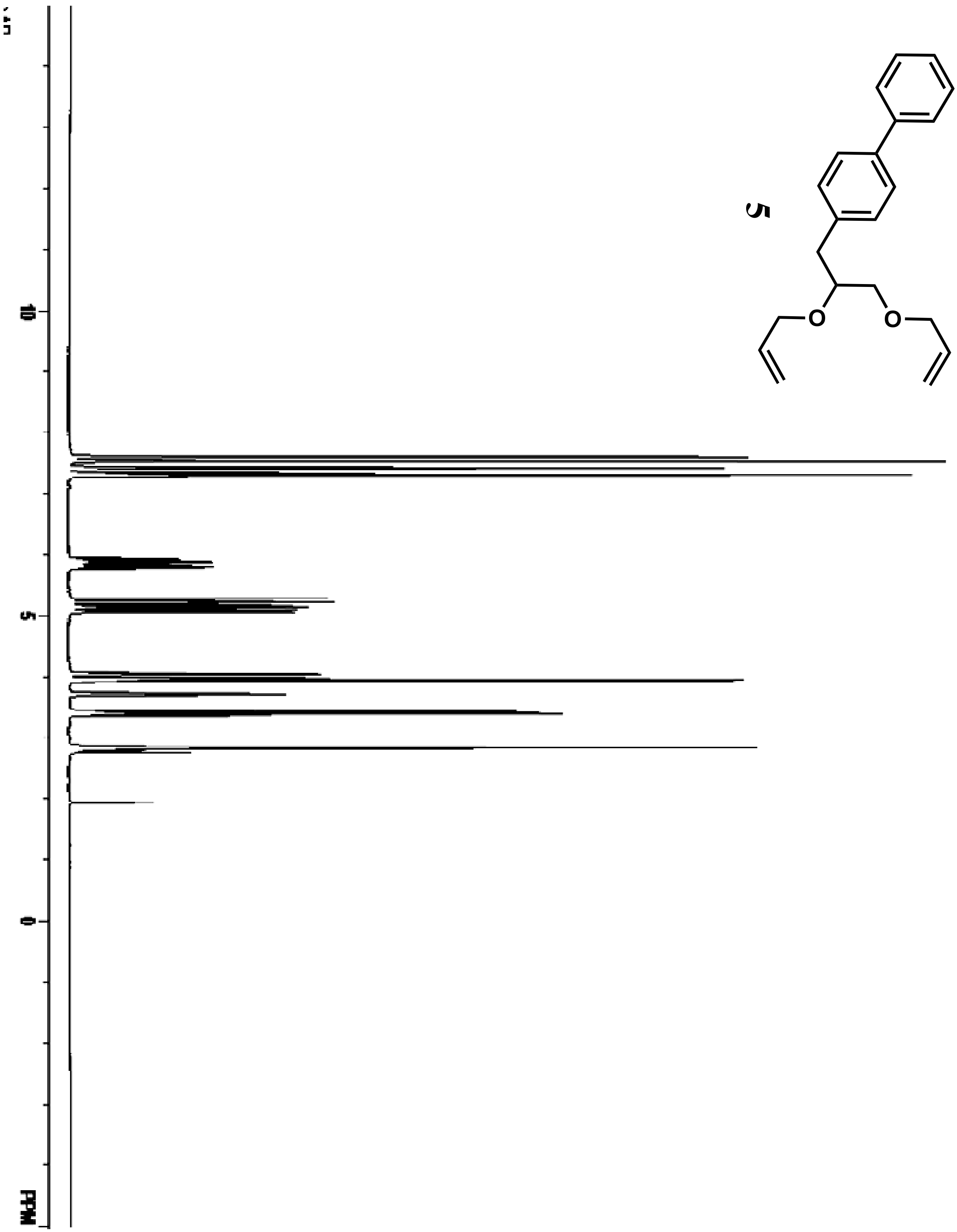
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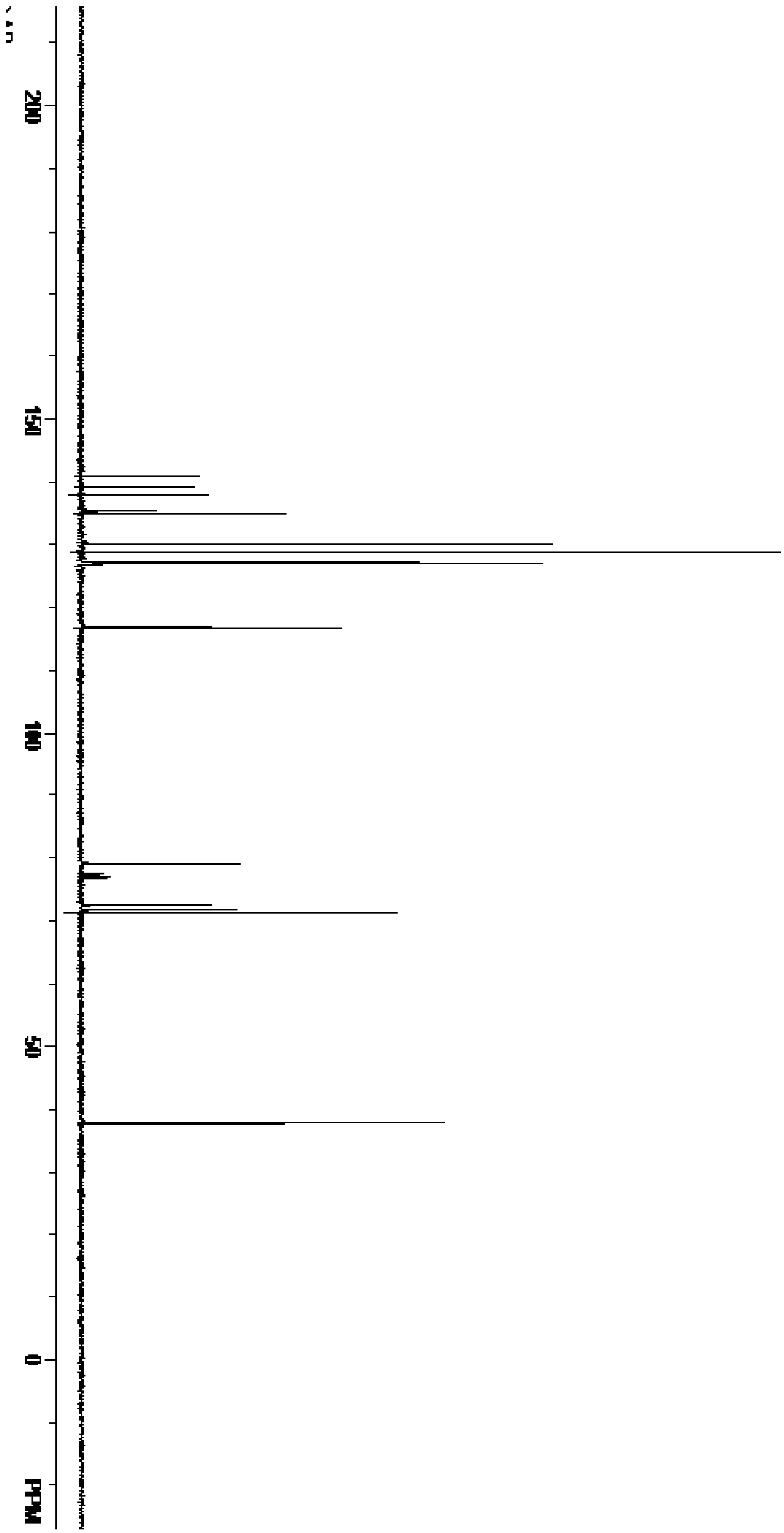

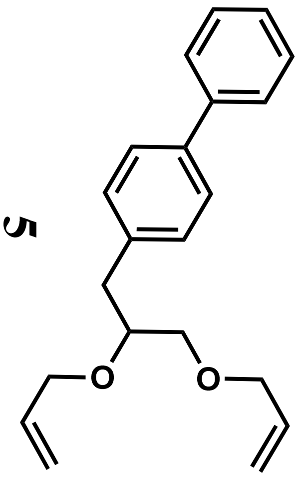

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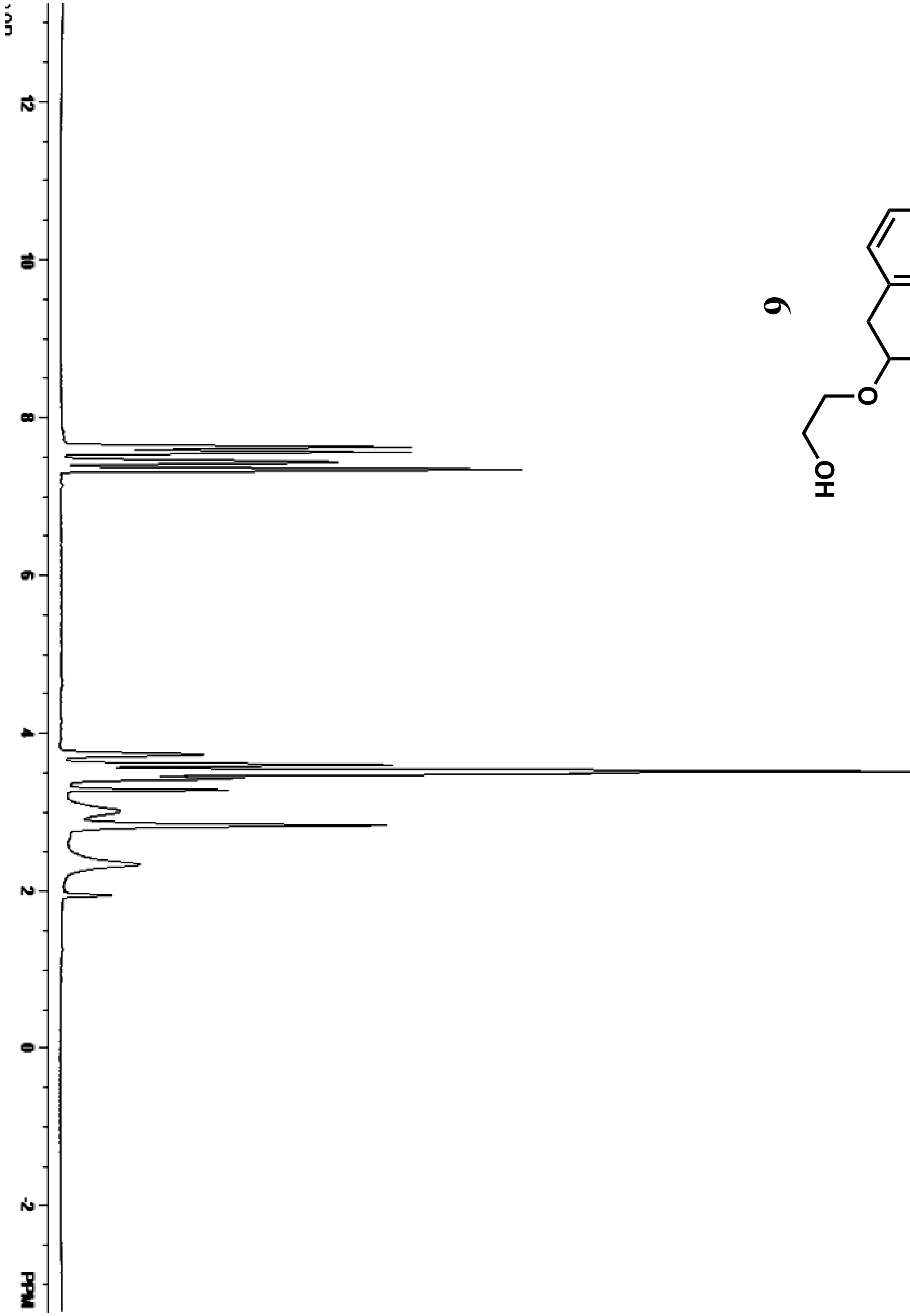

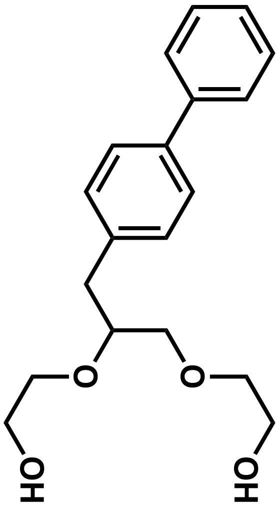

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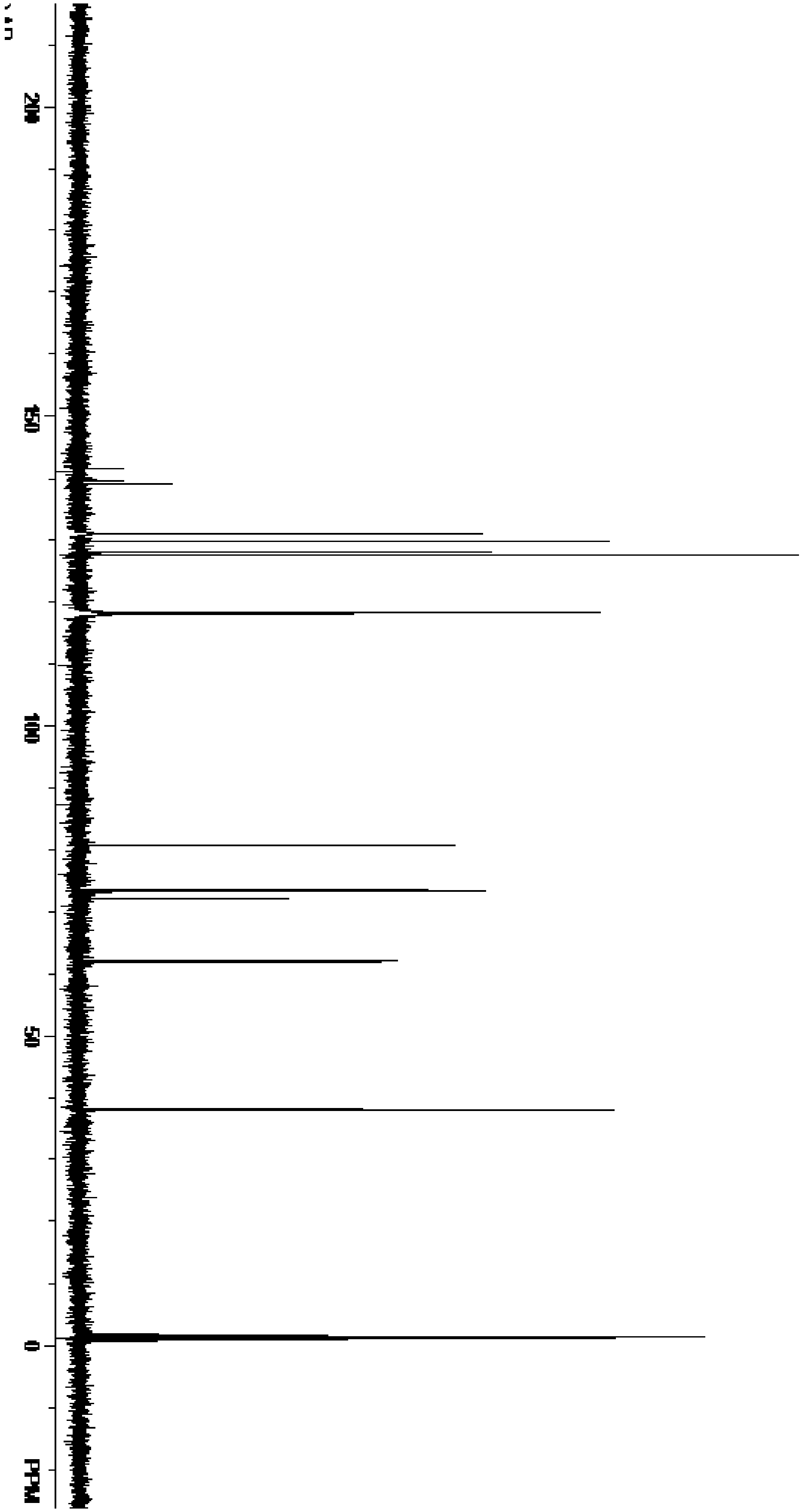
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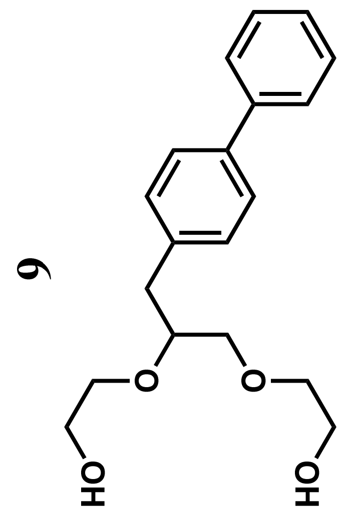

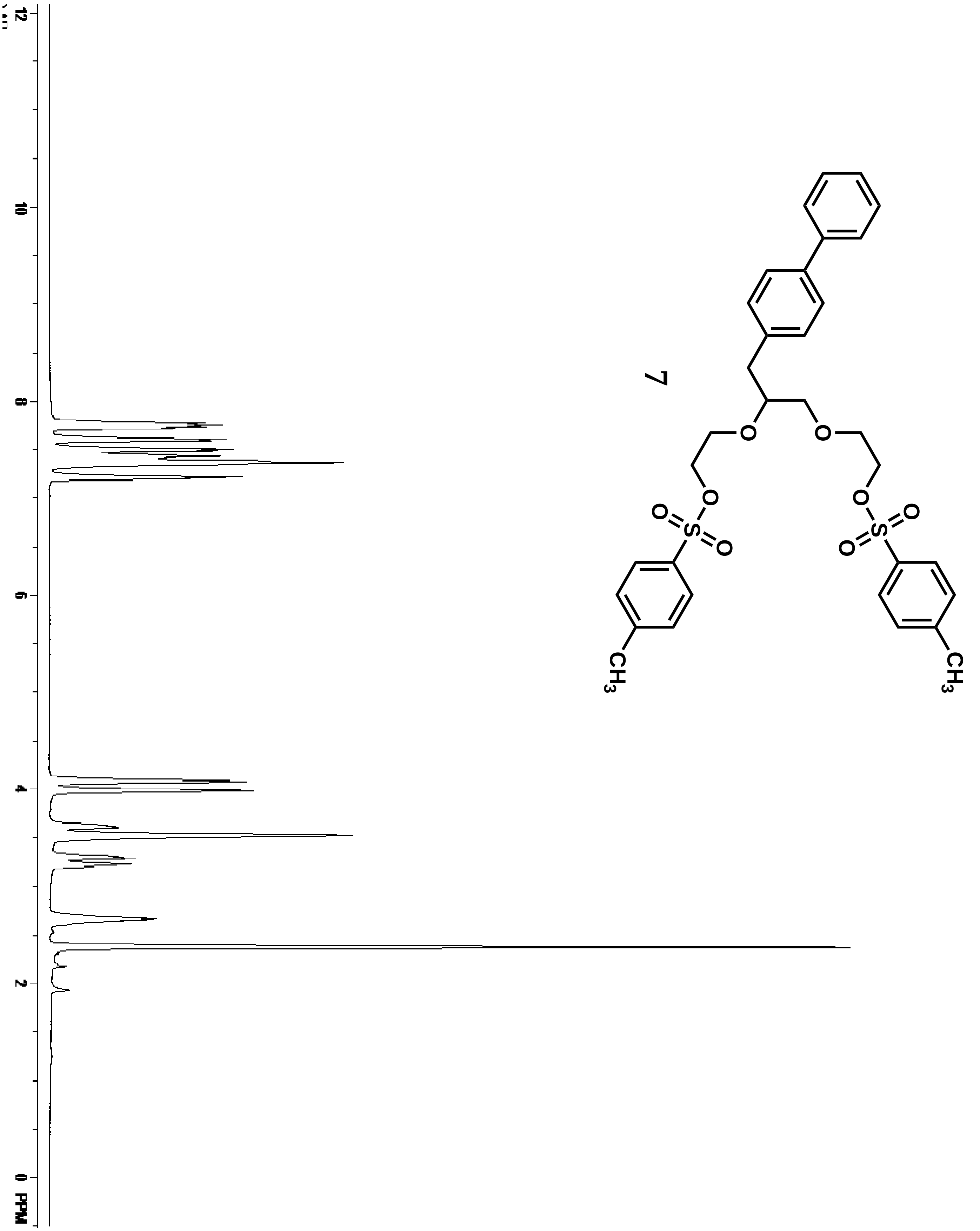

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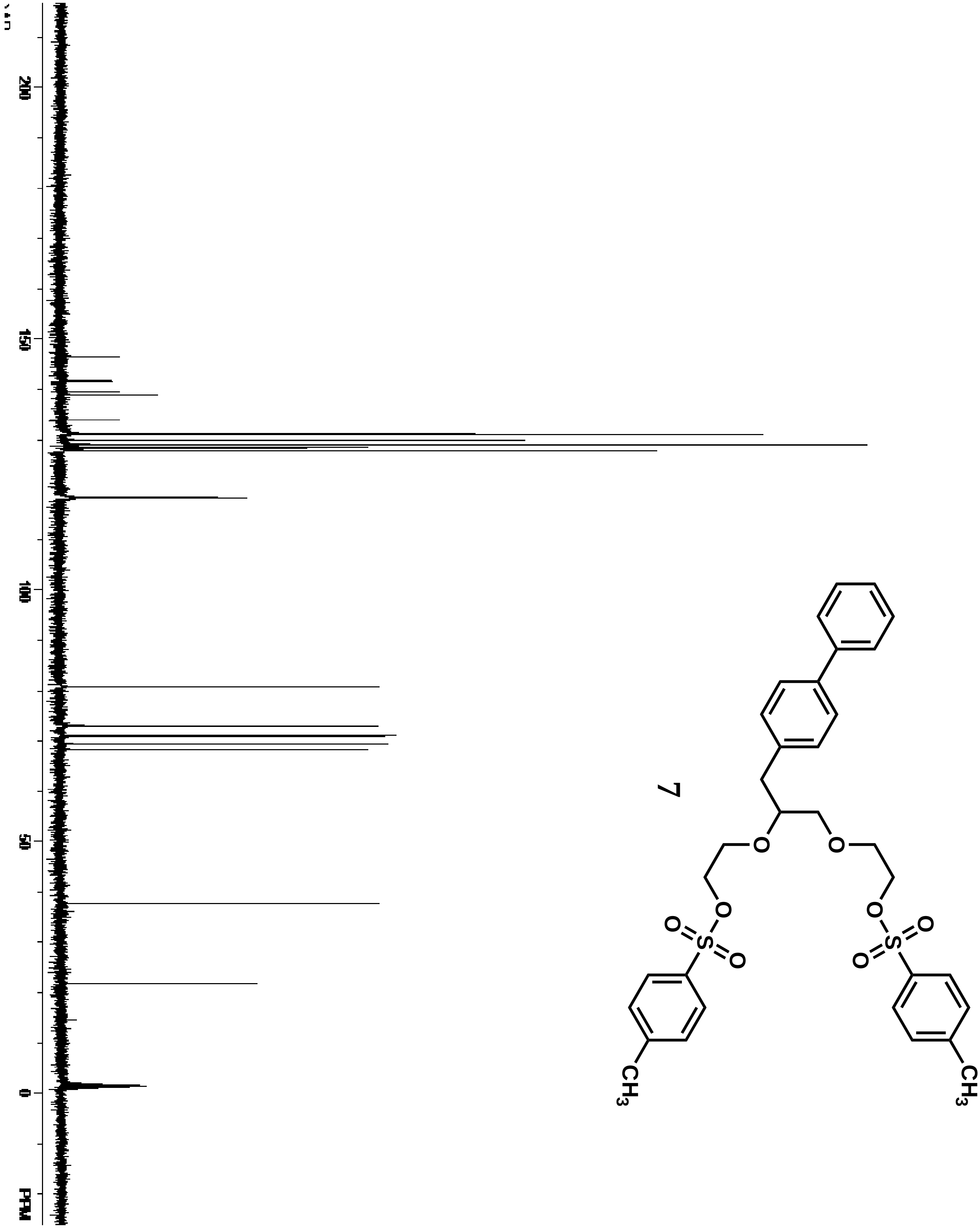

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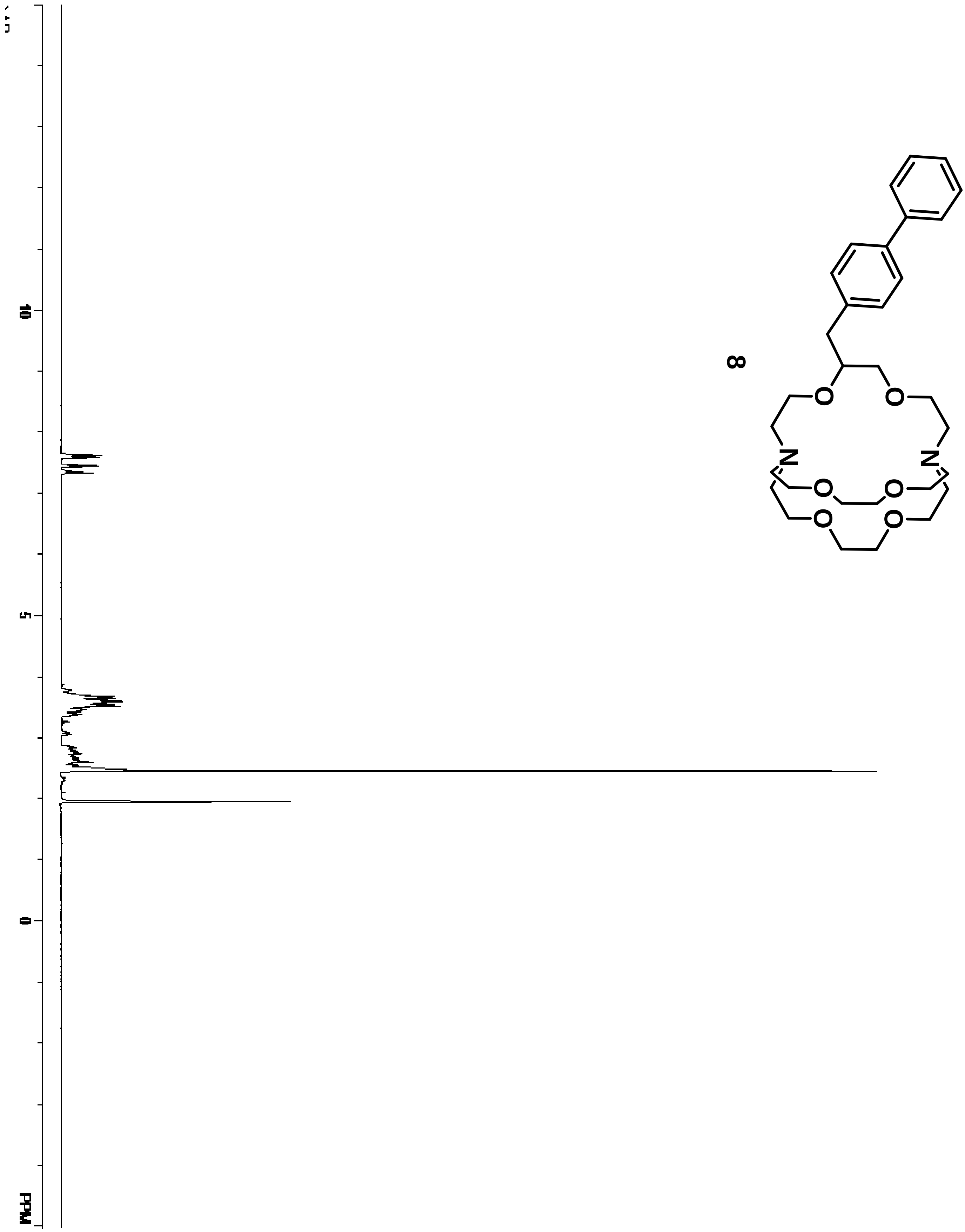

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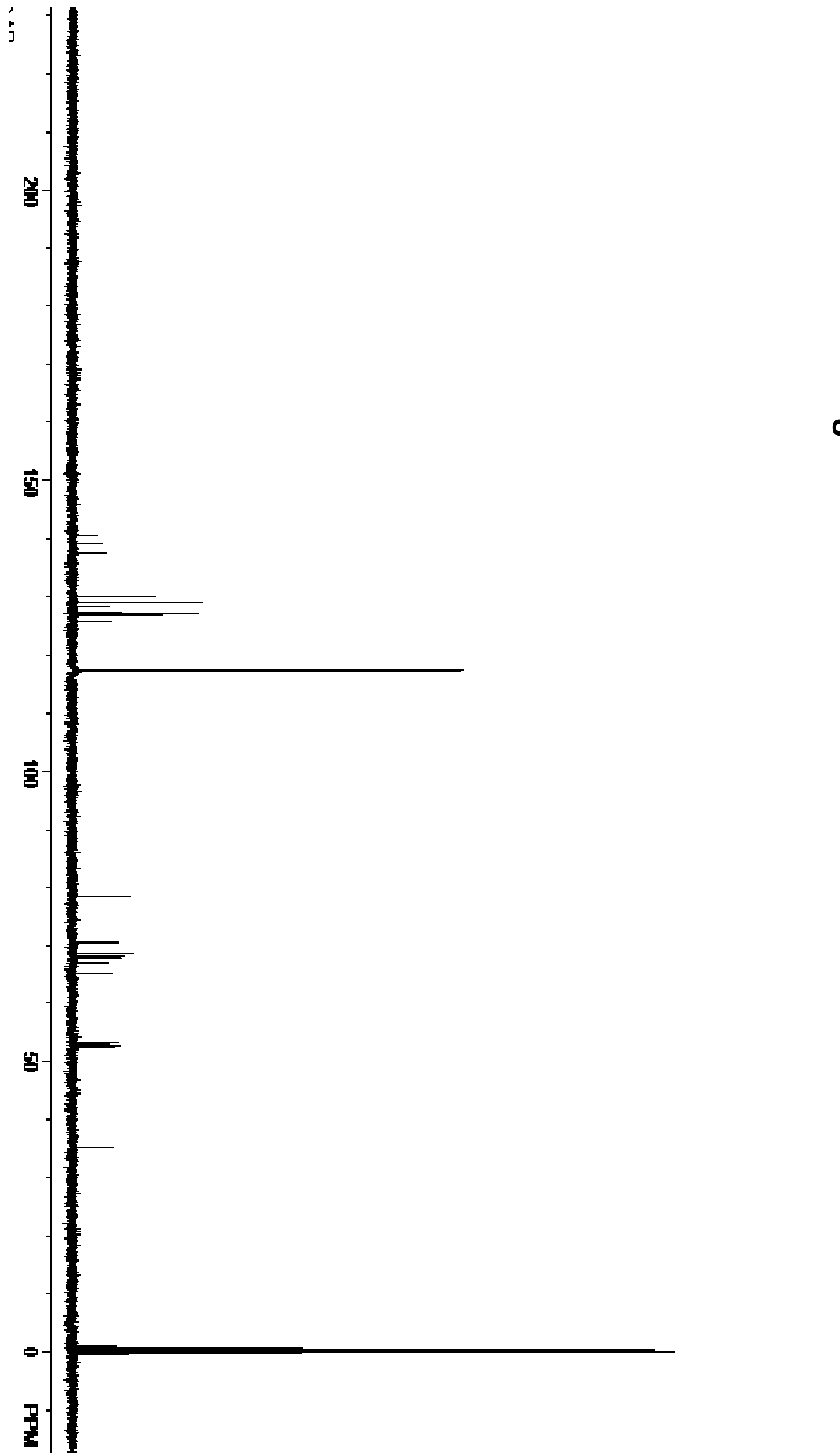

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