Asymmetric Aminolytic Kinetic Resolution of Racemic Epoxides Using Recyclable Chiral Polymeric Co(III)-Salen Complexes: A Protocol for Total Utilization of Racemic Epoxide in the Synthesis of (*R*)-Naftopidil and (*S*)-Propranolol

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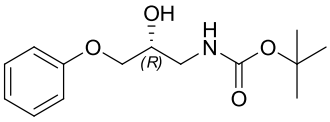
General Information

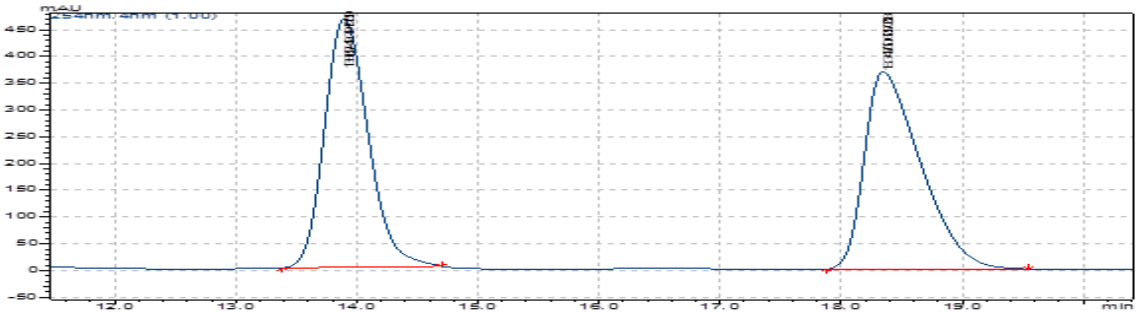
Racemic aryloxy/terminal epoxides, N-protected amines and other reagents were used as received. The solvents were dried by standard procedures, distilled and stored under nitrogen[1]. NMR spectra were obtained with (500/200 MHz and 125/50 MHz for ^{1}H and ^{13}C NMR respectively) and are referenced internally with TMS, Splitting patterns were reported as s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; br, broad. FTIR spectra were recorded using KBr window. Mass spectra were recorded with LC-MS(Q-TOFF). For the product purification flash chromatography was performed using silica gel 100-200 mesh. Enantiomeric excesses (*ee*) of the products were determined by HPLC using AD-H, OD and OJ, IA and IC chiral columns with 2-propanol/*n*-hexane as eluent, enantiomeric excesses (*ee*) of the aliphatic epoxides were determined by GC length of polymeric chain were determined by GPC with THF as eluent, optical rotations were measured with Automatic Polarimeter .

HPLC and GC profiles of products

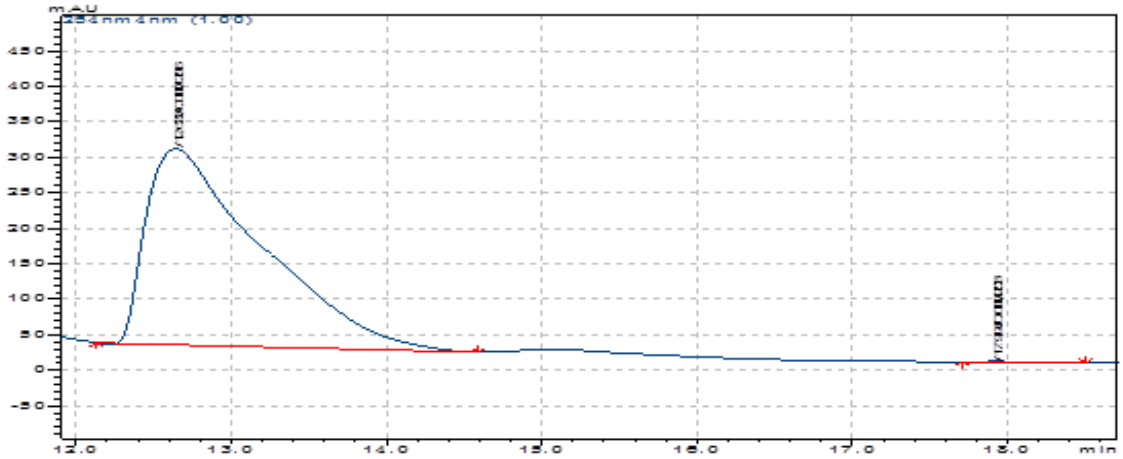
(*R*)-tert-butyl-2-hydroxy-3-phenoxypropylcarbamate (11a)



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 12.63 min (*R*, major) and 17.94 min (*S*, minor);

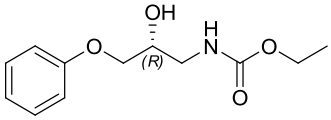


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	13.889	11619768	13.387	14.699	49.3914
2	18.343	11906108	17.877	19.552	50.6086

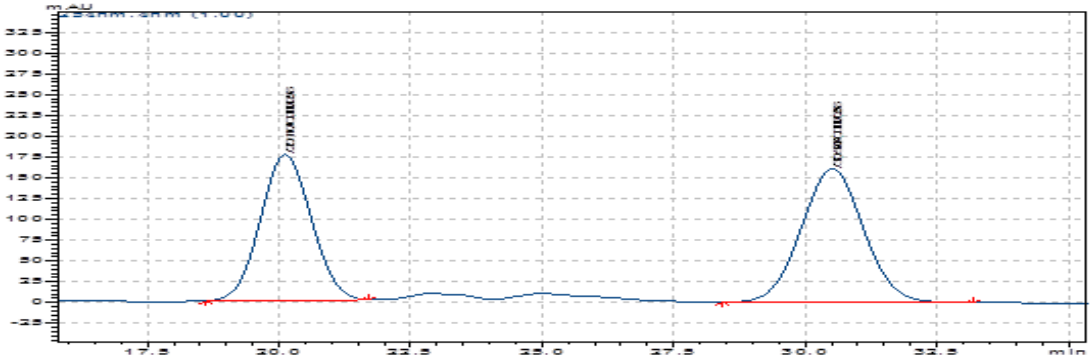


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	12.633	14174882	12.128	14.592	99.9107
2	17.904	12665	17.707	18.507	0.0893

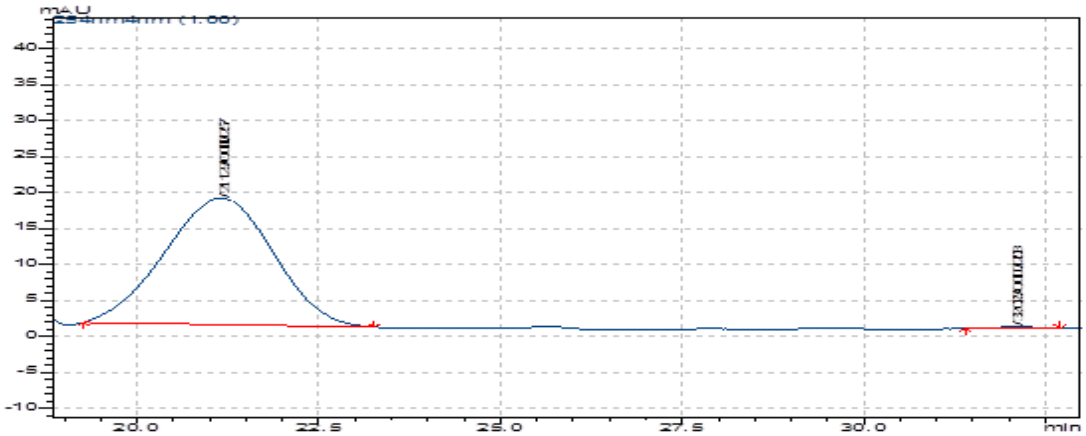
***(R)*-ethyl-2-hydroxy-3-phenoxypropylcarbamate (12a)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 21.12 min (*R*, major) and 32.02 min (*S*, minor);

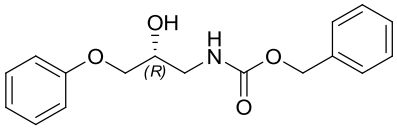


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	20.110	11799816	18.613	21.717	47.1971
2	30.506	13201356	28.427	33.205	52.8029

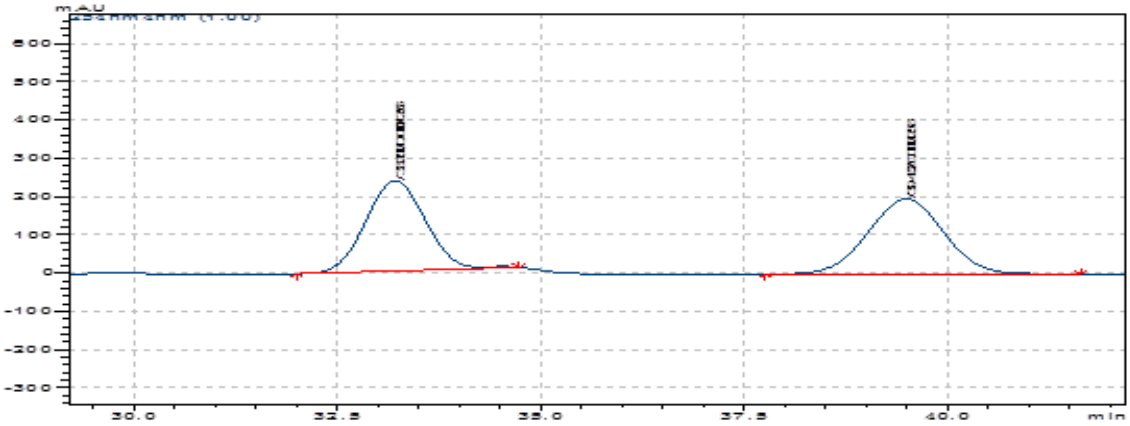


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	21.129	1873354	19.072	23.381	99.5408
2	32.023	8643	31.392	32.704	0.4592

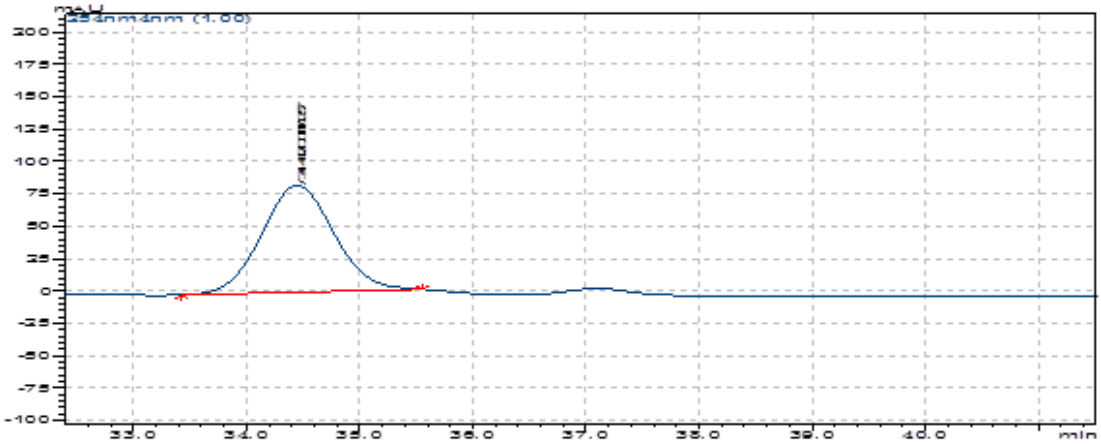
***(R)*-benzyl-2-hydroxy-3-phenoxypropylcarbamate (13a)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 34.44 min (*R*, major);

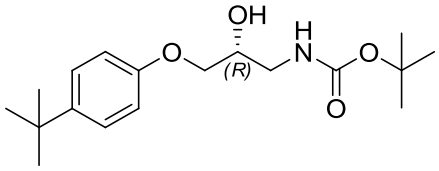


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	33.200	11954256	31.989	34.731	48.5718
2	39.482	12657249	37.749	41.632	51.4282

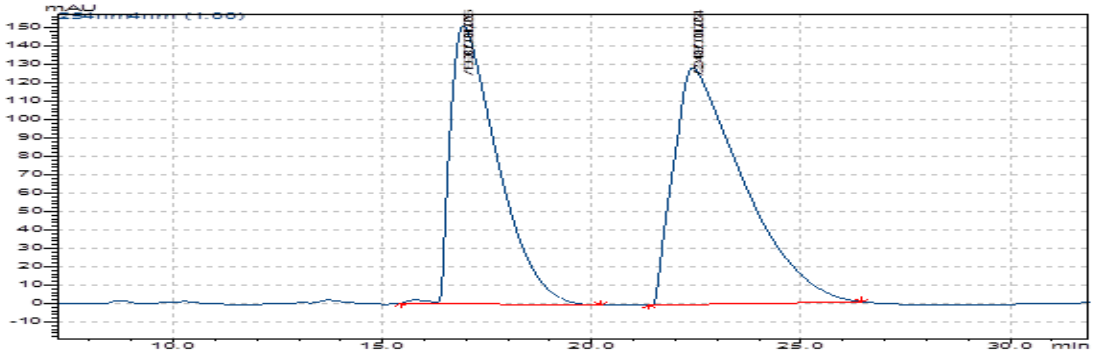


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	34.442	3653681	33.429	35.552	100.0000

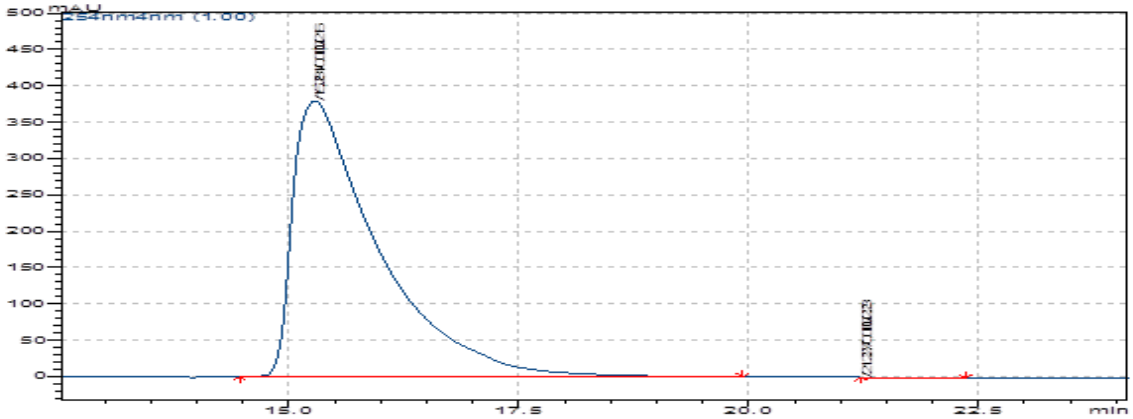
***(R)*-tert-butyl-3-(4-tert-butylphenoxy)-2-hydroxy propylcarbamate (11b)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 15.28 min (*R*, major) and 21.22 min (*S*, minor);

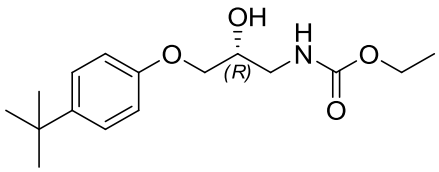


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	16.930	11796382	15.435	20.224	44.2253
2	22.408	14876974	21.365	26.464	55.7747

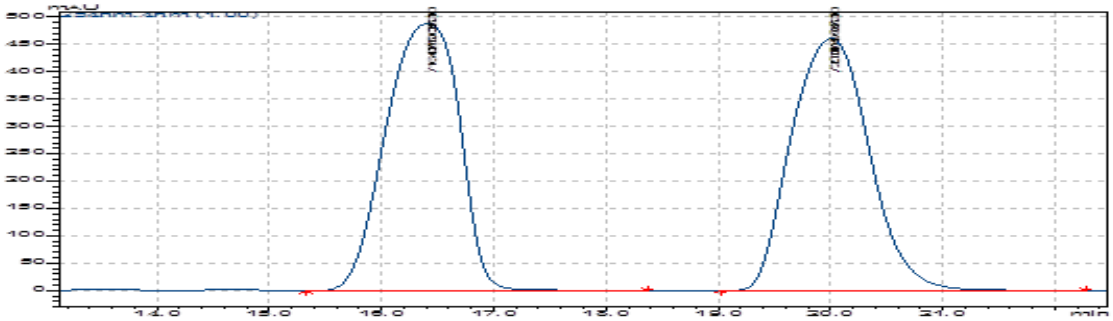


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	15.281	24586306	14.464	19.936	100.0039

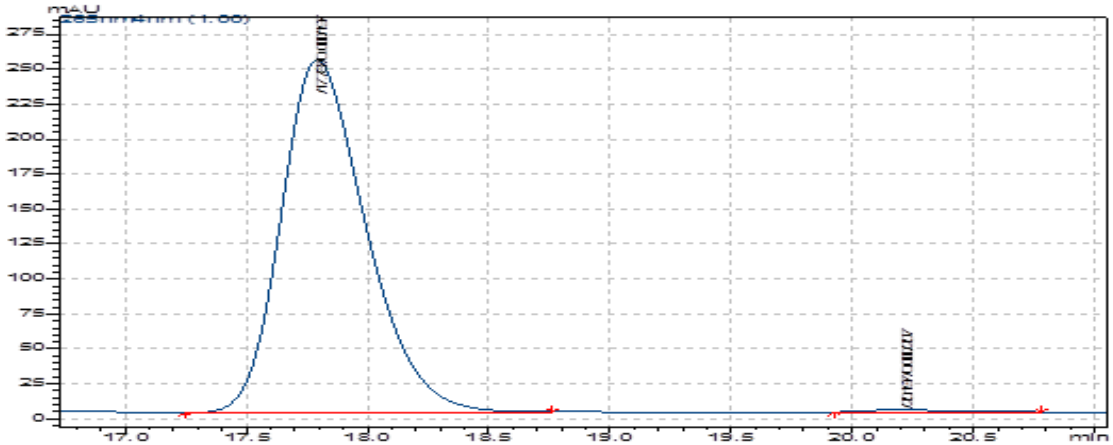
***(R)*-ethyl-3-(4-tert-butylphenoxy)-2-hydroxy propylcarbamate (12b)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 17.78 min (*R*, major) and 20.19 min (*S*, minor);

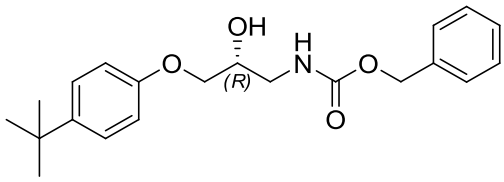


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	16.403	22296073	15.328	18.379	50.0353
2	20.000	22264630	19.019	22.283	49.9647

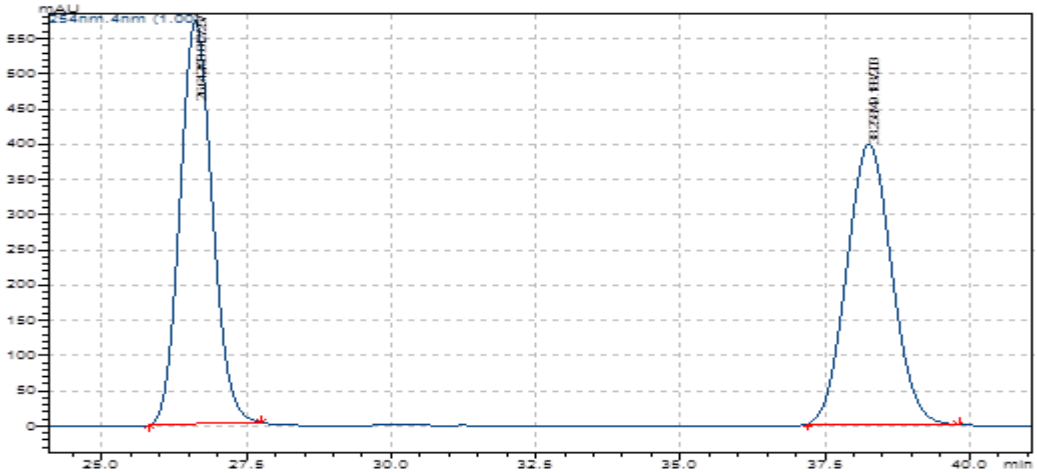


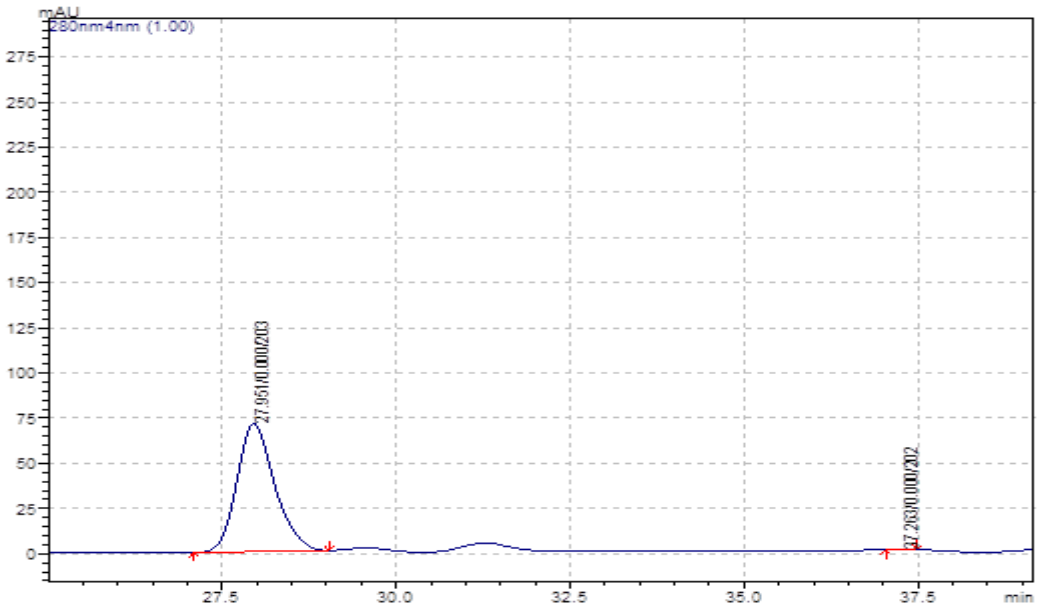
Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	17.787	6121003	17.248	18.763	99.2627
2	20.197	45465	19.925	20.779	0.7373

***(R)*-benzyl-3-(4-tert-butylphenoxy)-2-hydroxy propylcarbamate (13b)**

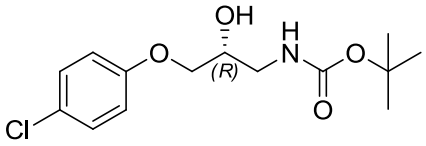


The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 27.95 min (*R*, major) and 32.26 min (*S*, minor);

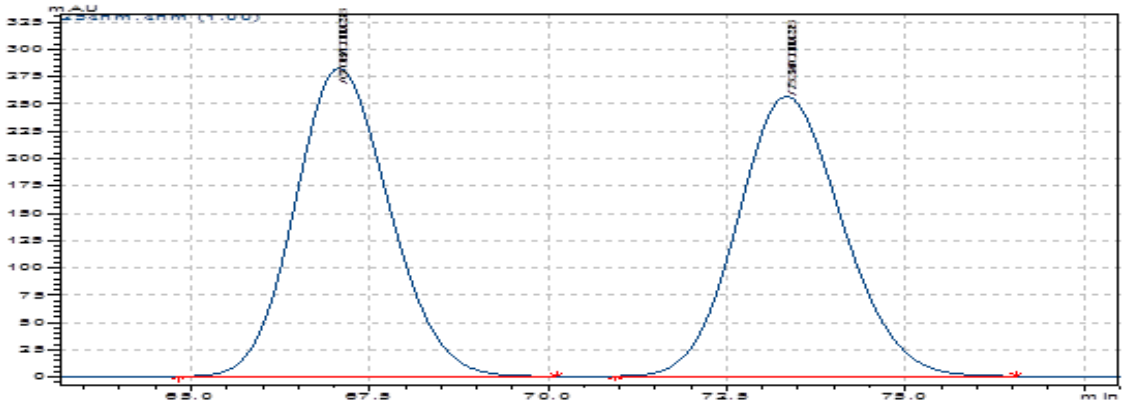




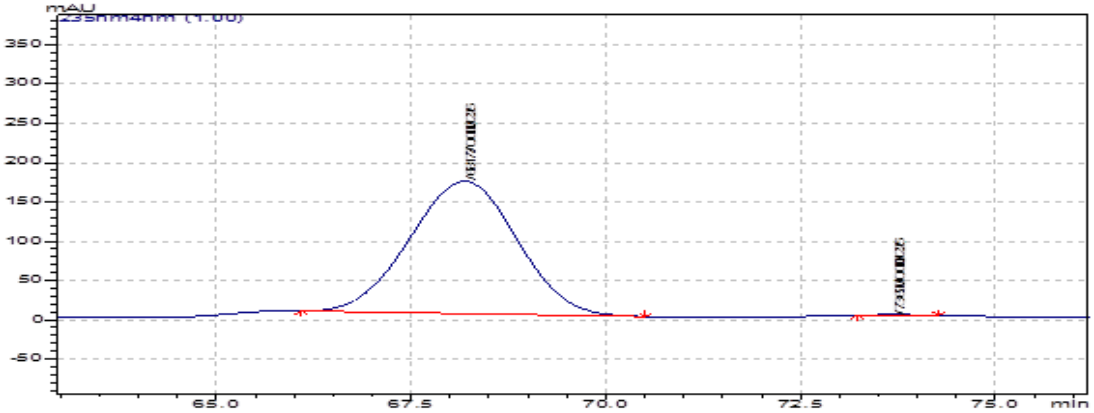
***(R)*-tert-butyl-3-(4-chlorophenoxy)-2-hydroxy propylcarbamate (11c)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 68.17 min (*R*, major) and 73.69 min (*S*, minor);

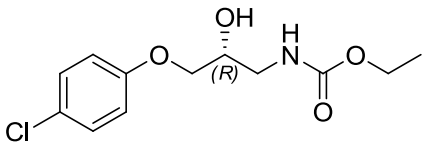


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	67.065	26043507	64.821	70.112	49.8090
2	73.334	26243191	70.933	76.555	50.1910

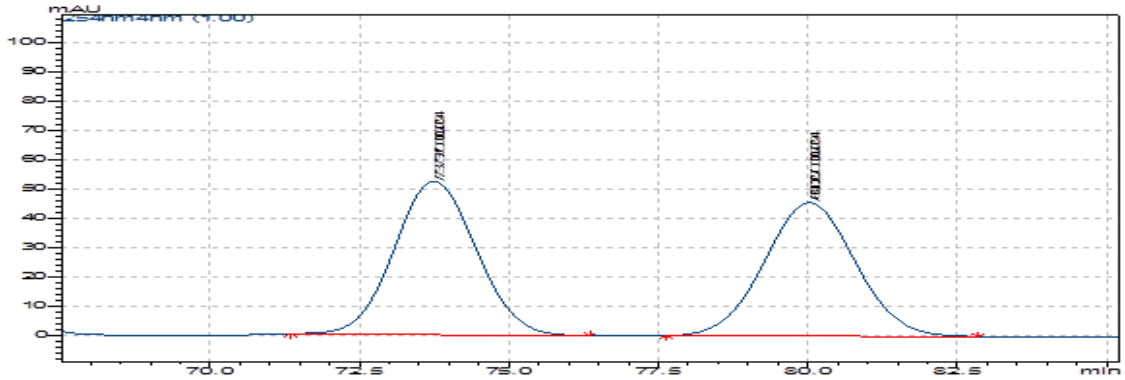


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	68.177	17485022	64.800	70.805	99.8708
2	73.690	22616	73.227	74.272	0.1292

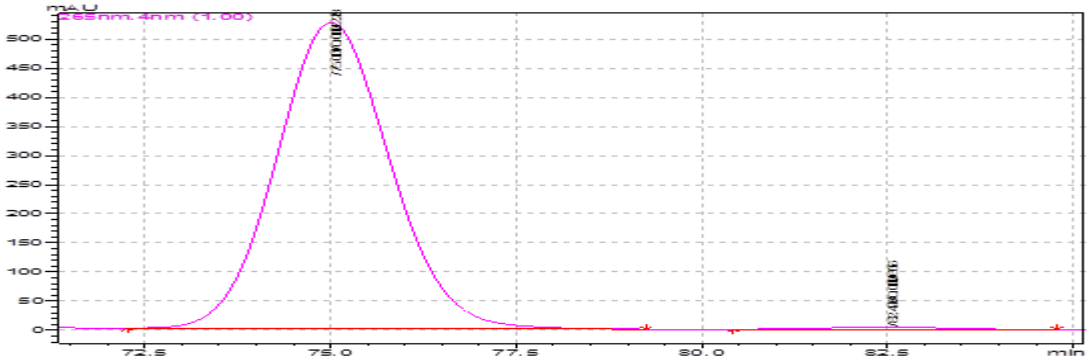
***(R)*-ethyl-3-(4-chlorophenoxy)-2-hydroxy propylcarbamate (12c)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 75.00 min (*R*, major) and 82.49 min (*S*, minor);

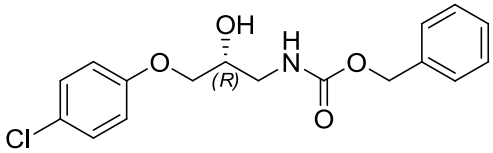


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	73.737	5013835	71.349	76.363	50.8671
2	80.020	4842894	77.632	82.848	49.1329

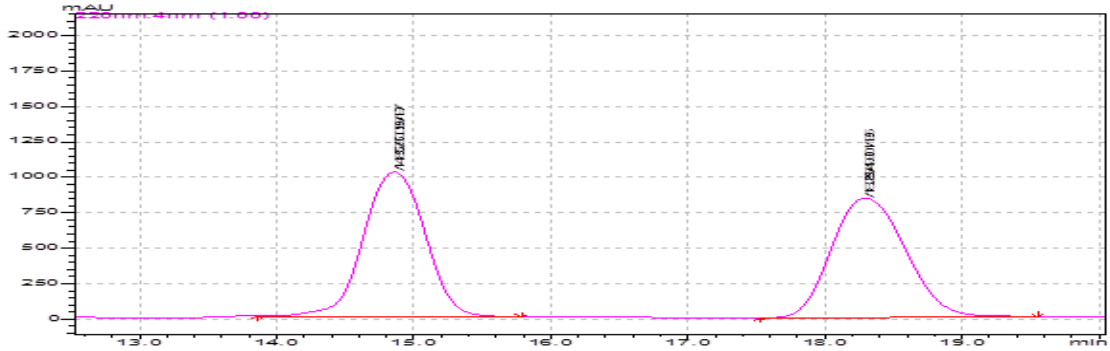


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	75.001	55935832	72.267	79.253	99.1787
2	82.498	463186	80.427	84.779	0.8213

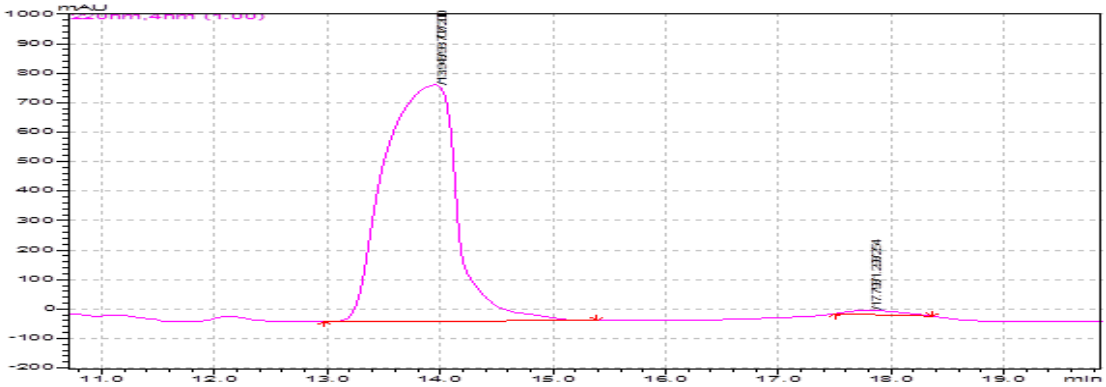
***(R)*-benzyl-3-(4-chlorophenoxy)-2-hydroxy propylcarbamate (13c)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 13.94 min (*R*, major) and 17.79 min (*S*, minor);

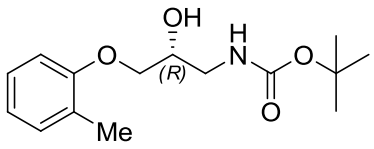


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	14.852	31740568	13.856	15.787	50.0989
2	18.289	31615195	17.525	19.552	49.9011

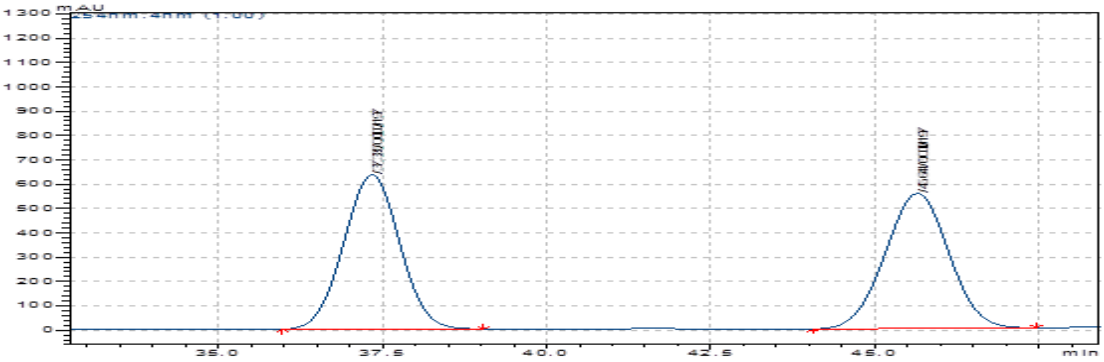


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	13.948	35771852	12.971	15.392	98.7074
2	17.793	468458	17.504	18.368	1.2926

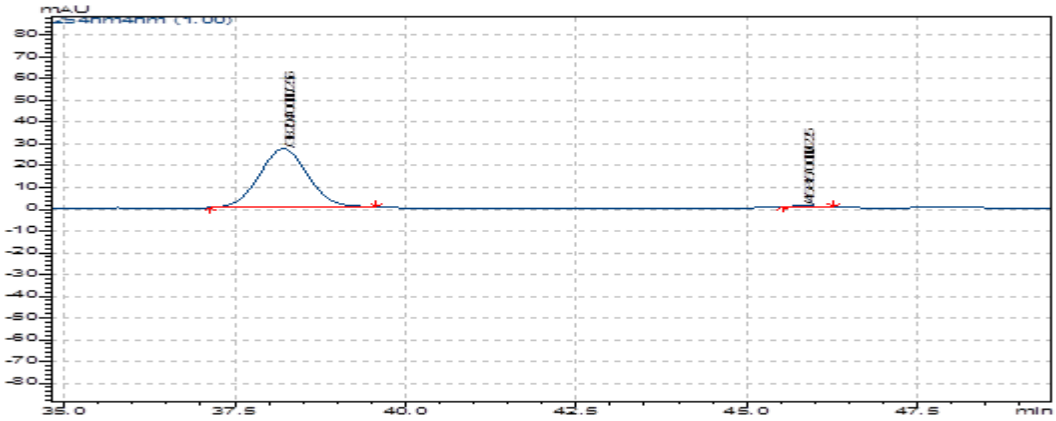
***(R)*-tert-butyl-2-hydroxy-3-(O-tolyloxy)propylcarbamate (11d)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 38.20 min (*R*, major) and 45.81 min (*S*, minor);

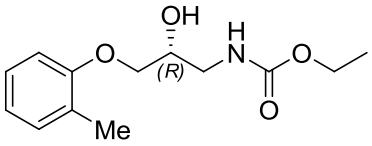


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	37.335	37638672	35.979	39.040	50.0888
2	45.641	37505166	44.064	47.456	49.9112

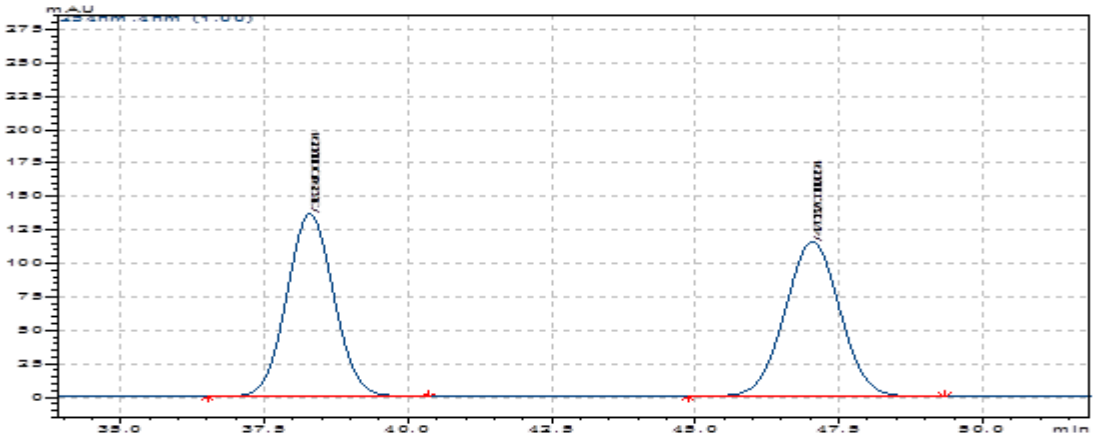


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	38.204	1334113	37.141	39.573	99.4223
2	45.815	7752	45.525	46.272	0.5777

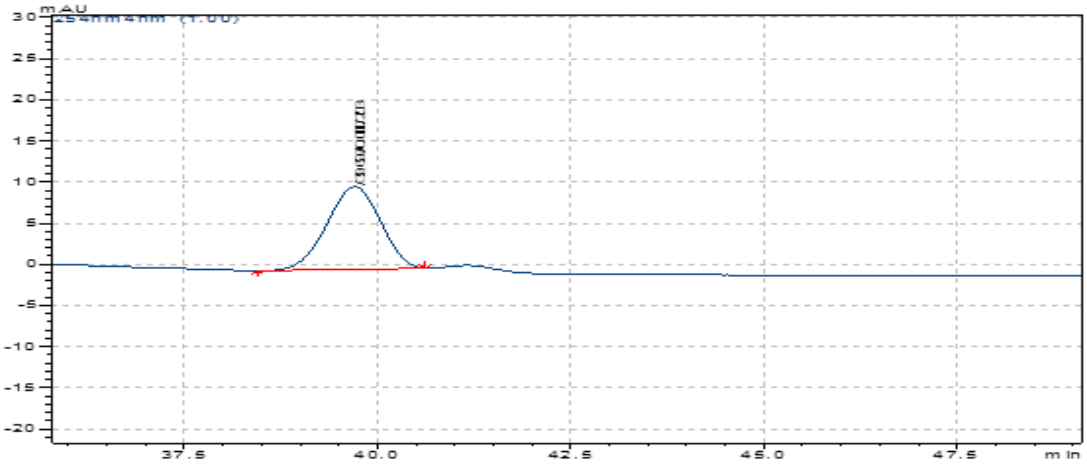
***(R)*-ethyl-2-hydroxy-3-(O-tolyloxy)propylcarbamate (12d)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 36.69 min (*R*, major);

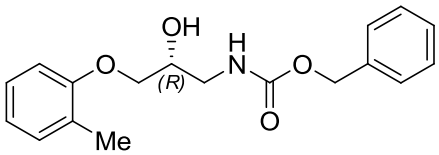


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	38.284	7807375	36.512	40.363	50.1011
2	47.032	7775867	44.875	49.344	49.8989

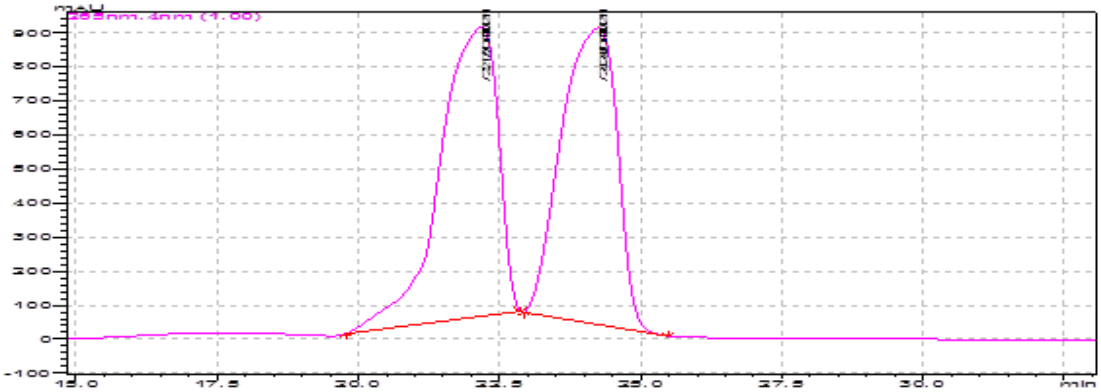


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	39.699	483735	38.453	40.619	100.0000

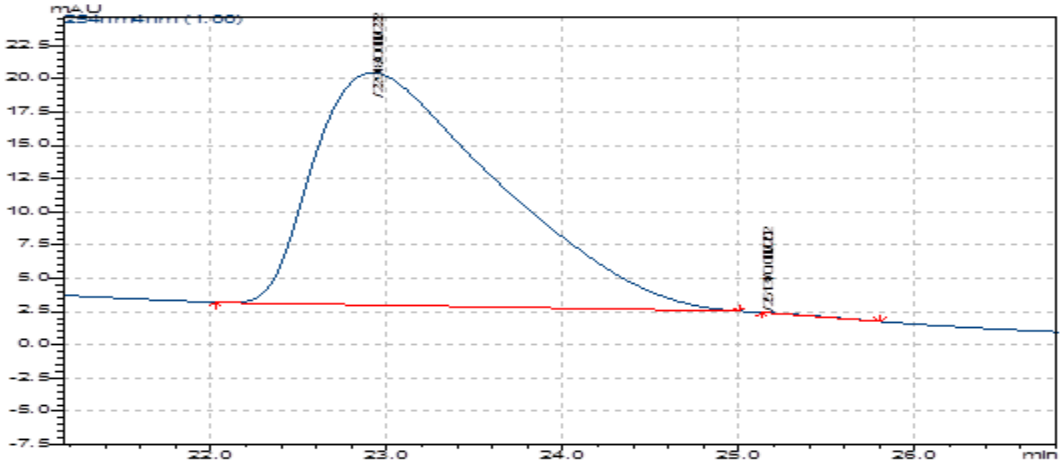
***(R)*-benzyl-2-hydroxy-3-(o-tolyloxy)propylcarbamate (13d)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 22.91 min (*R*, major) and 25.13 min (*S*, minor);

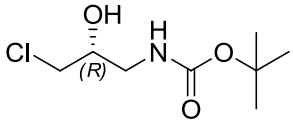


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	22.175	61092025	19.787	22.869	50.6321
2	24.244	59566648	22.923	25.483	49.3679

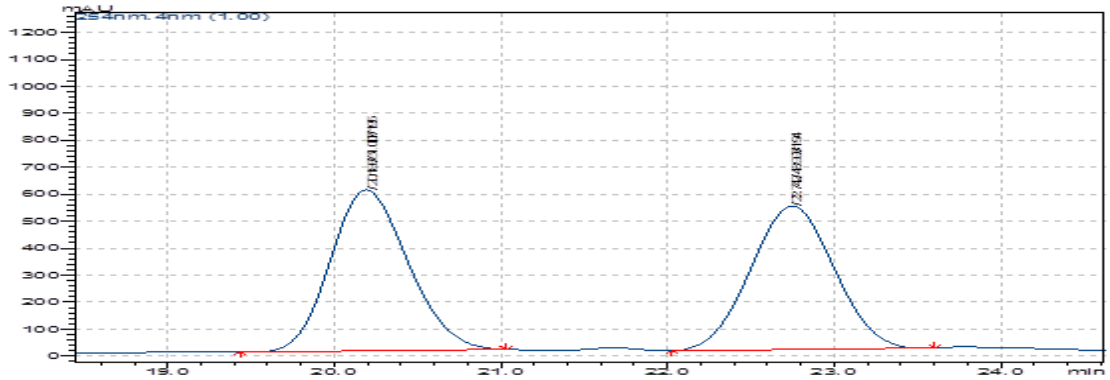


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	22.918	1260589	22.027	25.003	99.9380
2	25.131	781	25.131	25.803	0.0620

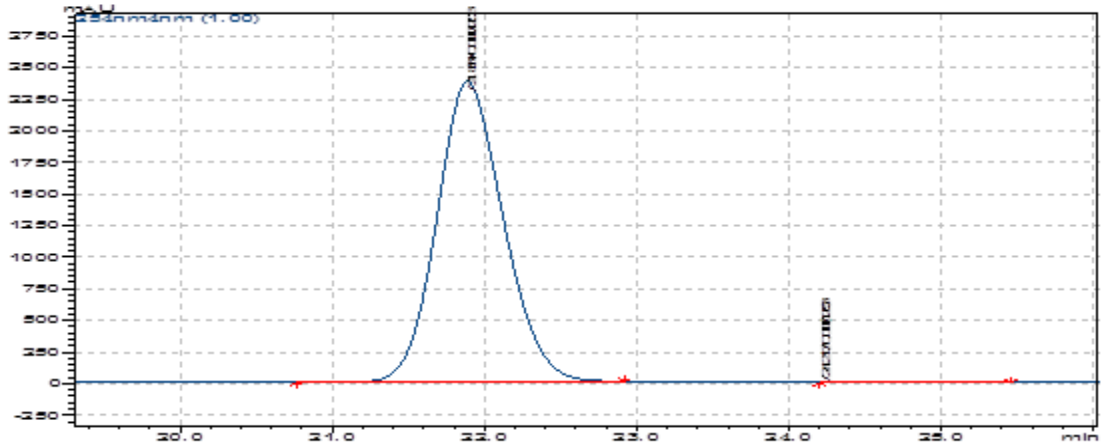
***(R)*-3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester (11e)**



The *ee* was determined by HPLC on the corresponding *O*-benzyl derivative[2] (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 21.88 min (*R*, major) and 24.21 min (*S*, minor);

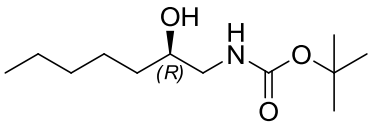


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	20.186	19280896	19.435	21.035	51.0070
2	22.742	18519630	22.027	23.605	48.9930

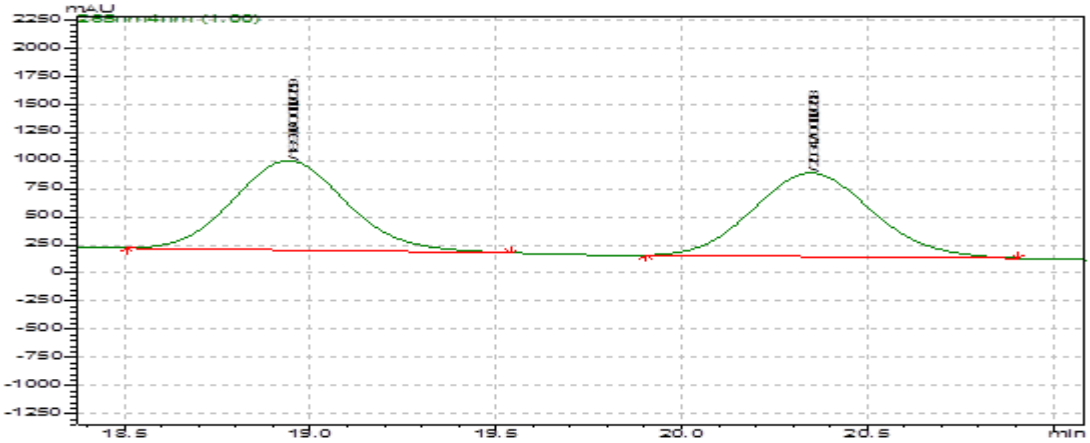


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	21.881	72102752	20.768	22.923	99.9875
2	24.213	9045	24.203	25.461	0.0125

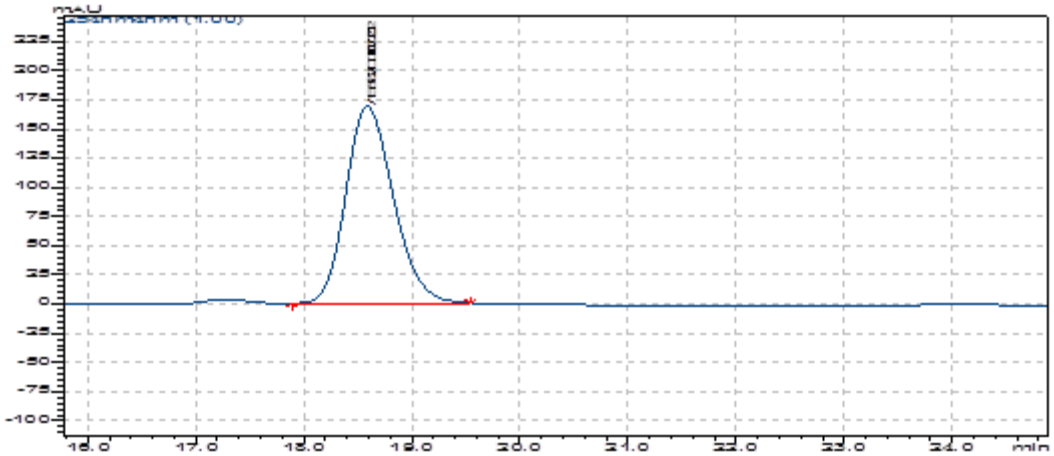
***((R)*-tert-butyl 2-hydroxyheptylcarbamate (11f)**



The *ee* was determined by HPLC the corresponding *O*-benzyl derivative[2] (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 18.58 min (*R*, major);

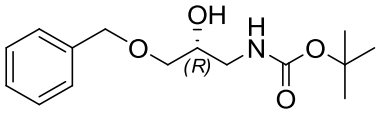


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	18.936	16891193	18.507	19.541	50.3810
2	20.342	16635717	19.904	20.907	49.6190

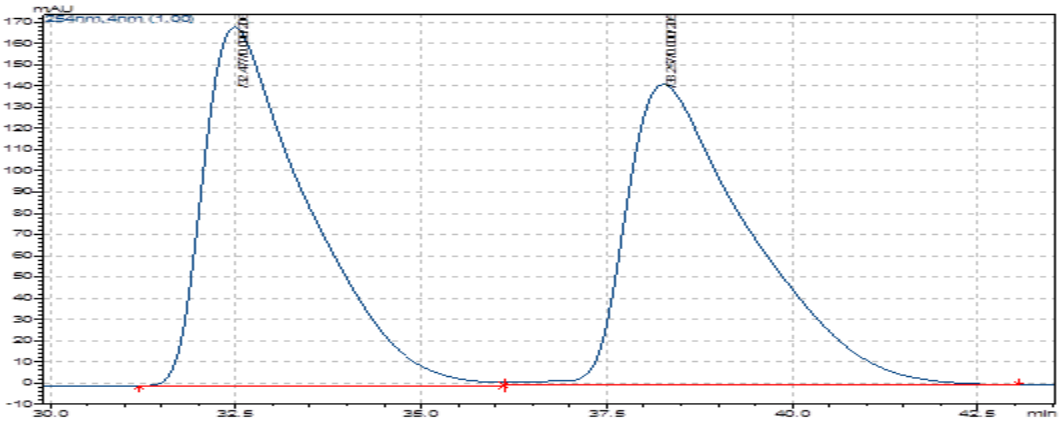


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	18.582	5152967	17.888	19.541	100.0000

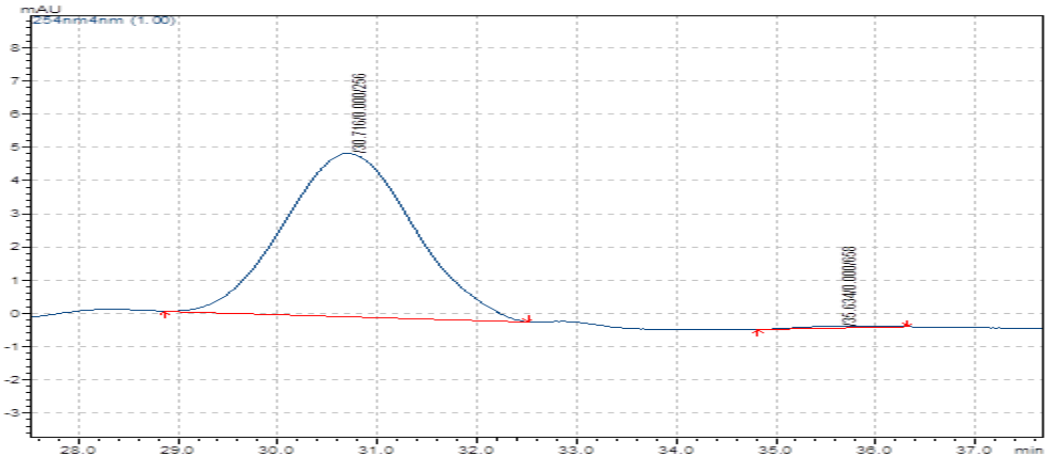
***(R)*-tert-butyl-3-(benzyloxy)-2-hydroxy propylcarbamate (11g)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 30.71 min (*R*, major) and 35.63 min (*S*, minor);

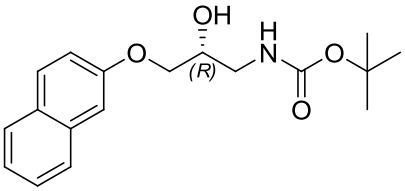


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	32.477	16460161	31.200	36.117	49.9548
2	38.257	16489976	36.117	43.061	50.0452

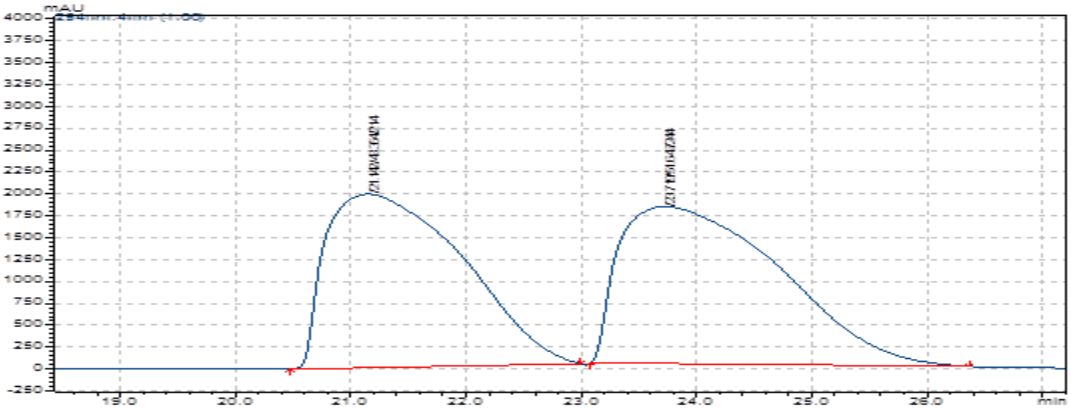


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	30.716	445971	28.864	32.512	99.2607
2	35.634	3321	34.816	36.320	0.7393

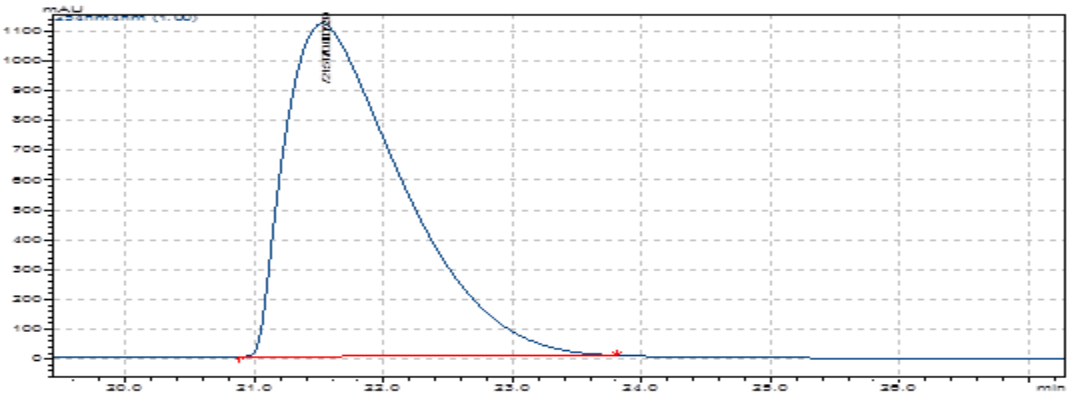
***(R)*-2-hydroxy-3-(naphthalen-1-yloxy)-propyl-carbamic acid tert-butyl ester (11h)**



The *ee* was determined by HPLC (Chiralpak AD-H column) mobile phase, 90/10 n-hexane/*i*-PrOH; flow rate 0.7 mL/min; t_R = 21.51 min (*R*, major)

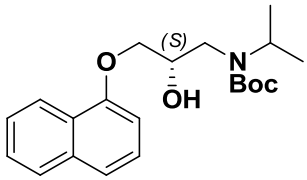


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	23.704	137963427	23.029	25.867	48.4906
2	26.812	146552648	26.037	29.429	51.5094

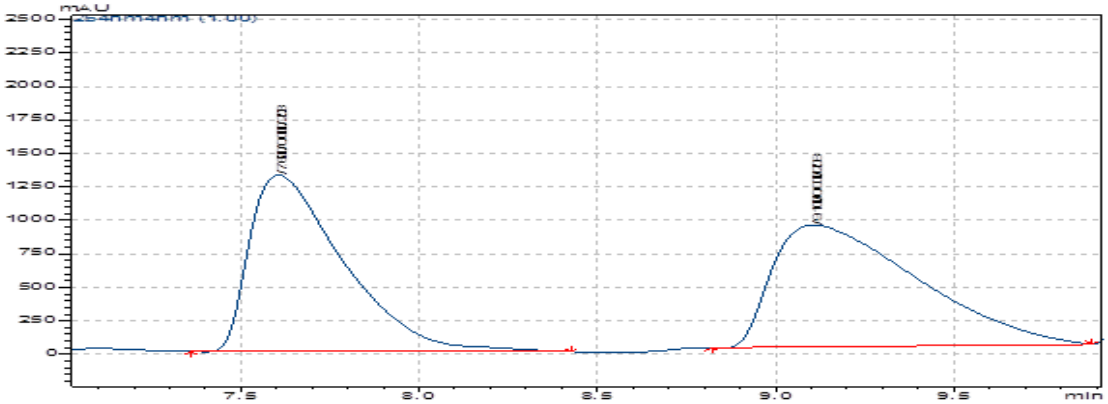


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	21.517	70560054	20.885	23.808	100.0000

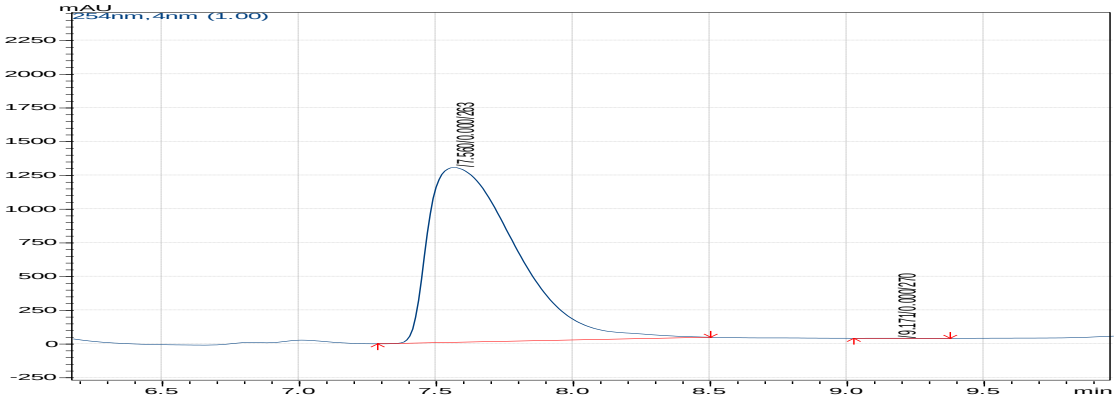
(*S*)-tert-butyl 2-hydroxy-3-(naphthalen-1-yloxy) propyl (isopropyl)carbamate 15



The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 8.72 min; t_S = 10.10 min).

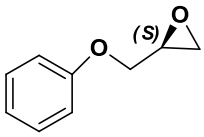


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	7.600	24046757	7.360	8.427	48.3799
2	9.100	25657217	8.821	9.888	51.6201

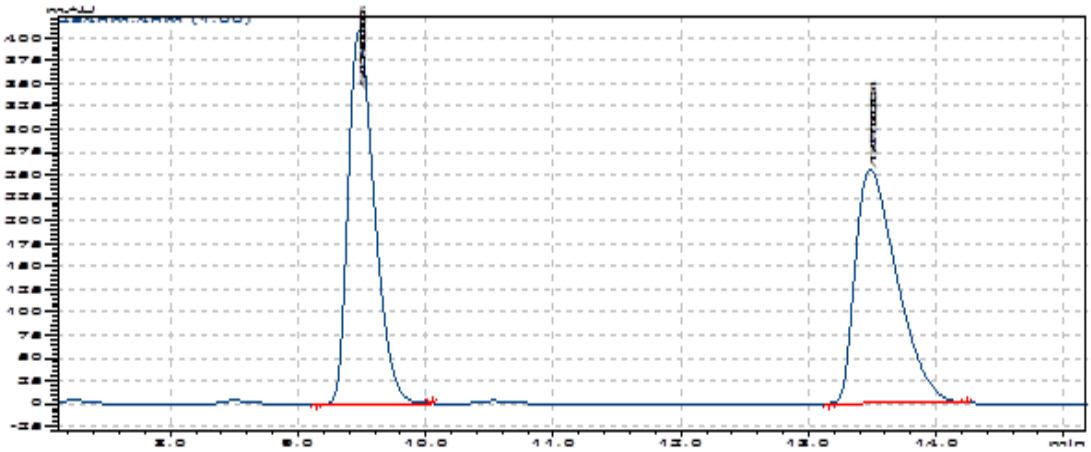


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	7.560	28824612	7.285	8.501	99.9813
2	9.171	5378	9.024	9.376	0.0187

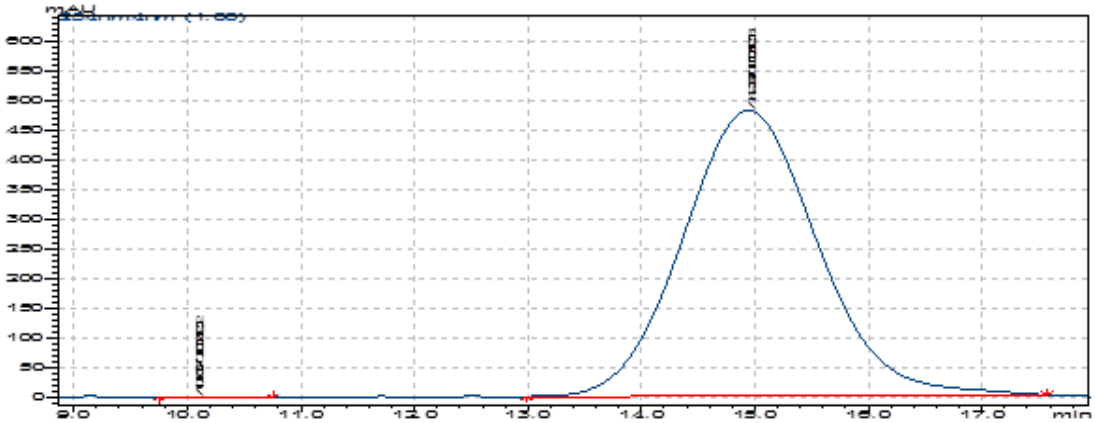
(*S*)-1,2-epoxy-3-phenoxy propane (9a')



The ee was determined by HPLC analysis using a Chiralpak OD column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 10.06 min; t_S = 14.93 min).

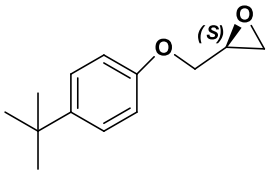


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	9.471	5822261	9.141	10.048	50.0838
2	13.477	5802772	13.163	14.240	49.9162

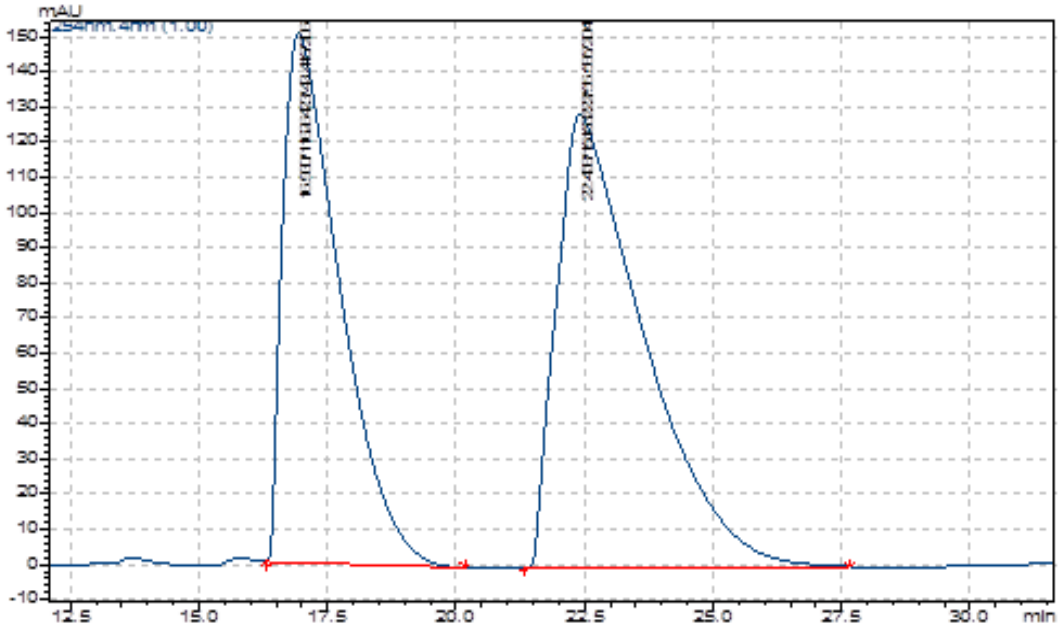


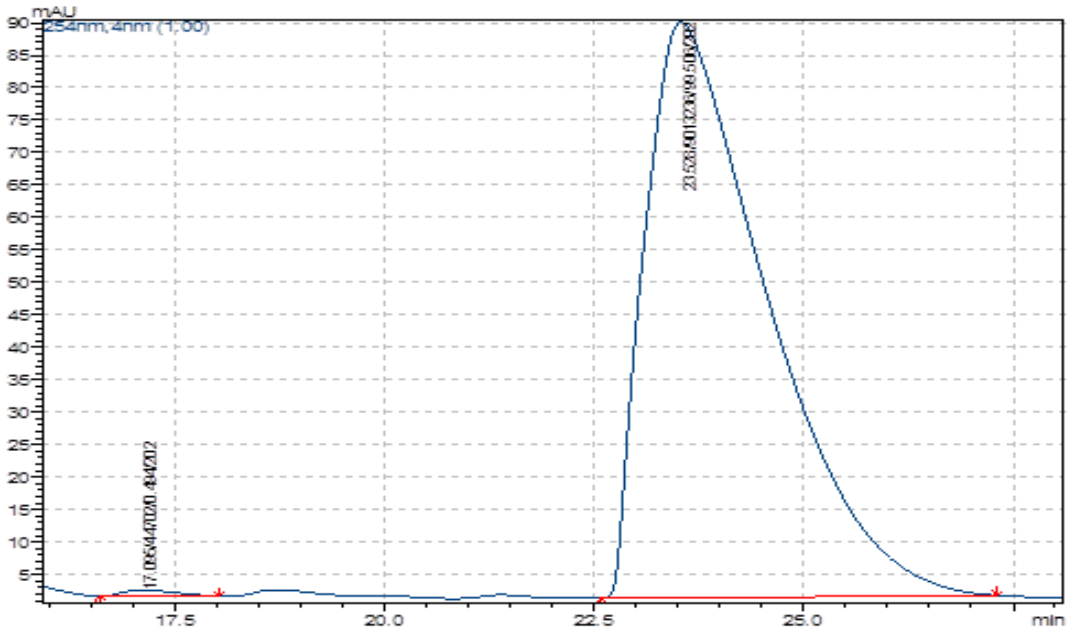
Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	10.067	3039	9.749	10.752	0.0077
2	14.939	39643169	12.992	17.579	99.9923

(*S*)-1,2-epoxy-3-(4-tert-butylphenoxy) propane **(9b')**

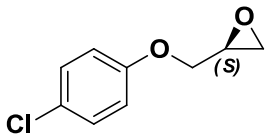


The ee was determined by HPLC analysis using a Chiralpak OD column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 17.09 min; t_S = 23.52 min).

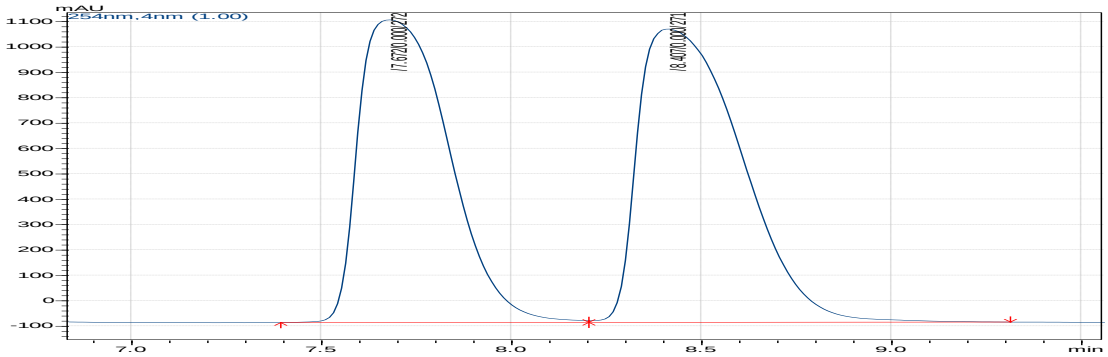




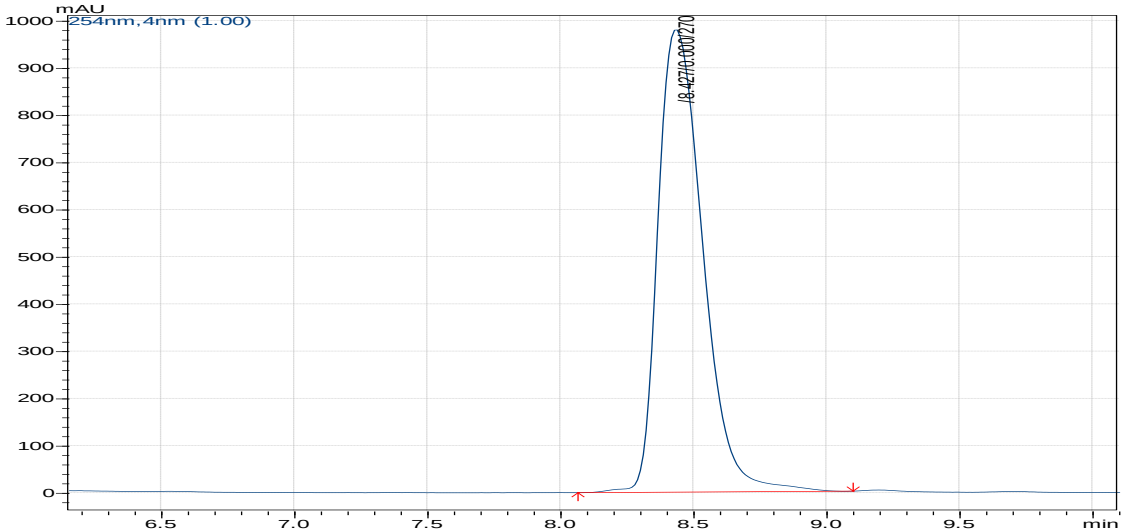
(*S*)-1,2-epoxy-3-(4-chlorophenoxy) propane (9c')



The ee was determined by HPLC analysis using a Chiralpak IC column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 8.72 min; t_S = 10.10 min).

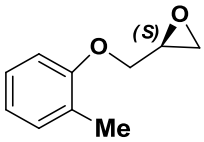


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	7.672	19589755	7.392	8.203	47.4663
2	8.407	21681072	8.203	9.312	52.5337

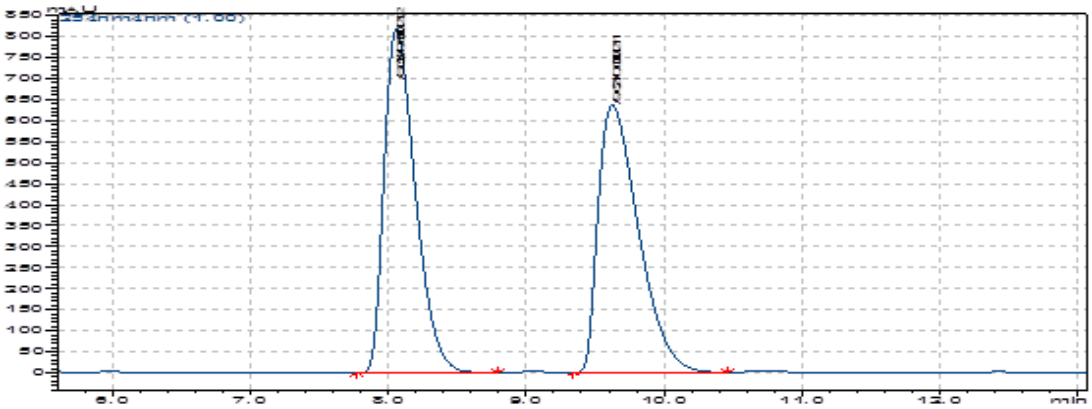


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	8.427	11483081	8.064	9.099	100.0000

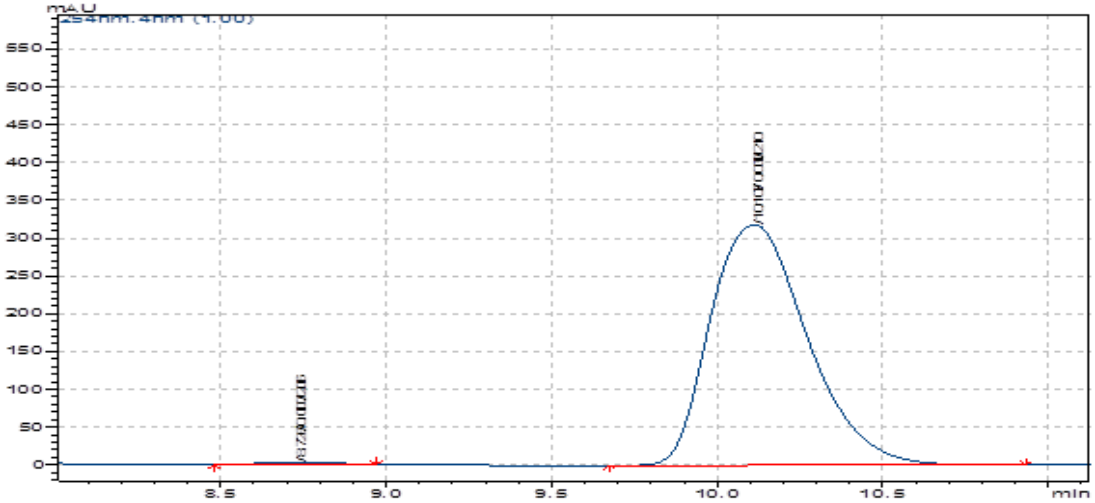
(*S*)-1,2-epoxy-3-(2-methylphenoxy) propane (9d')



The ee was determined by HPLC analysis using a Chiralpak IA column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 8.72 min; t_S = 10.10 min).

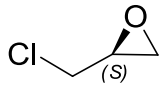


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	8.055	12841917	7.776	8.800	49.8692
2	9.621	12909278	9.344	10.464	50.1308

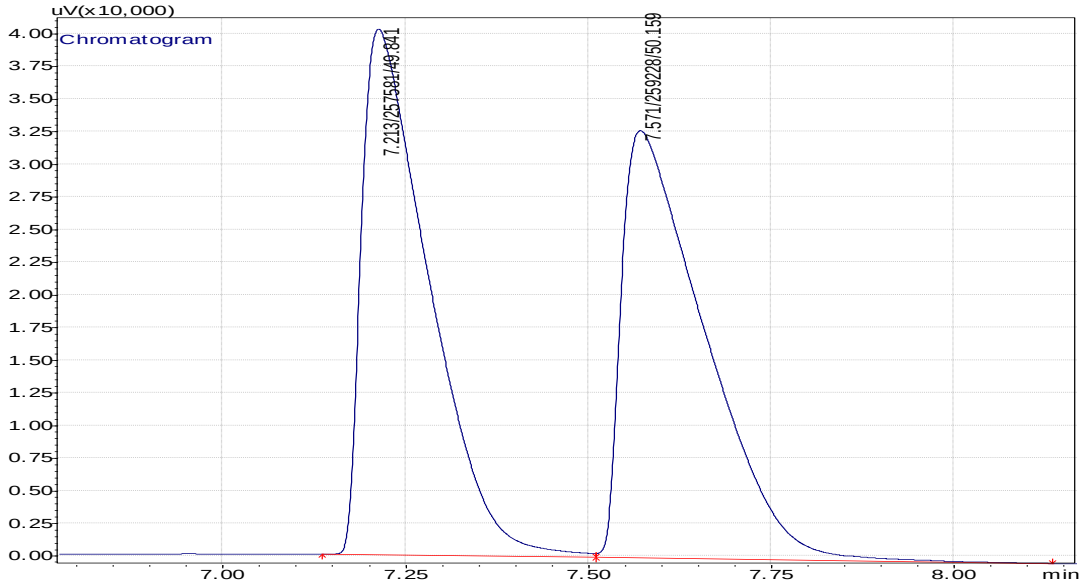


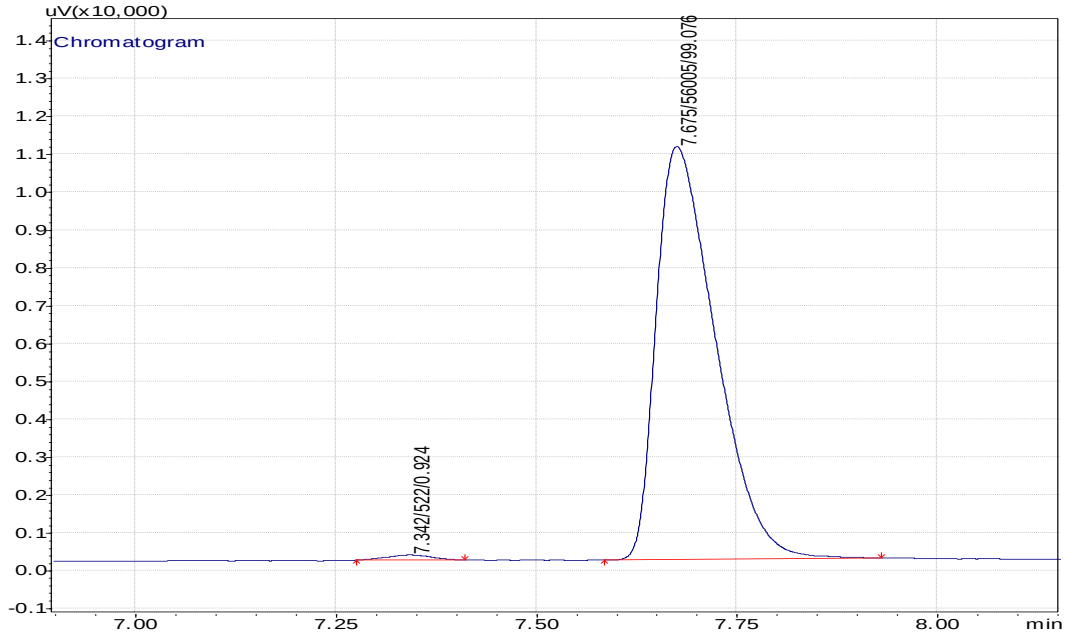
Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	8.726	55285	8.480	8.971	0.8474
2	10.107	6468582	9.675	10.933	99.1526

(*S*) Epichlorohydrin (9e')

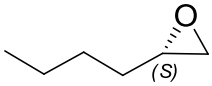


The ee was determined by GC analysis using a chiral BTA column. Column temperature ,70-140 ^{o}C, detector and injector temperature 200 ^{o}C.

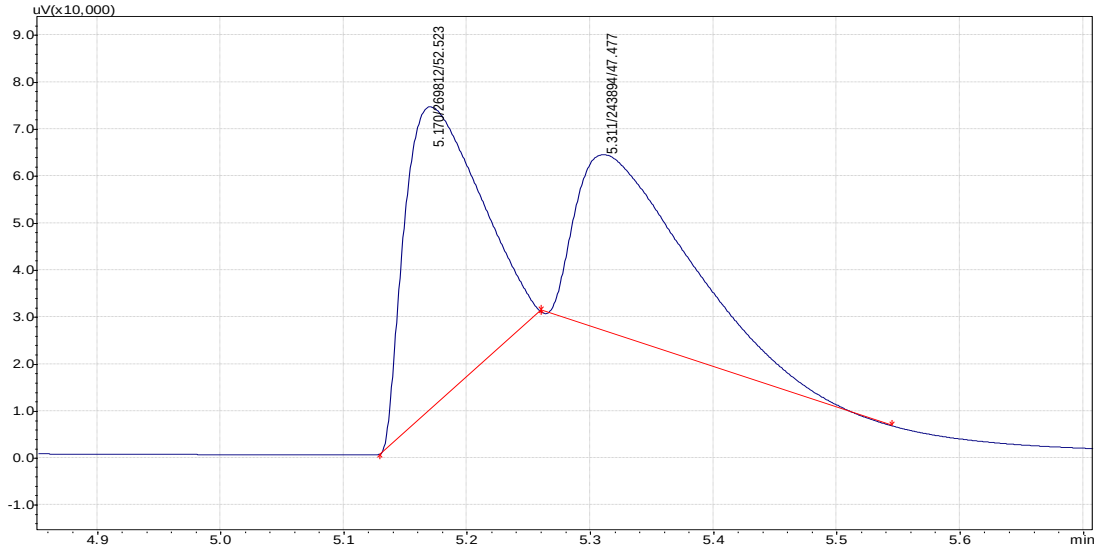


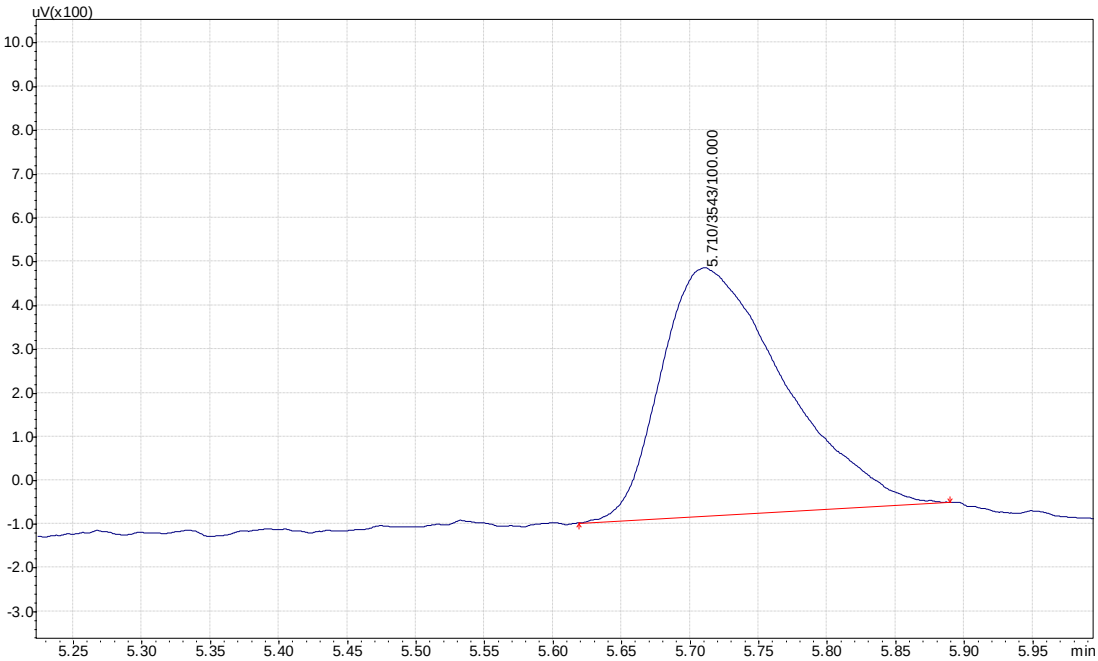


(*S*)1,2-epoxy hexane **(9f')**

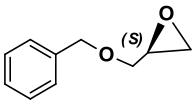


The ee was determined by GC analysis using a chiral BTA column. Column temperature ,50 ^{o}C isotherm, detector and injector temperature 200 ^{o}C.

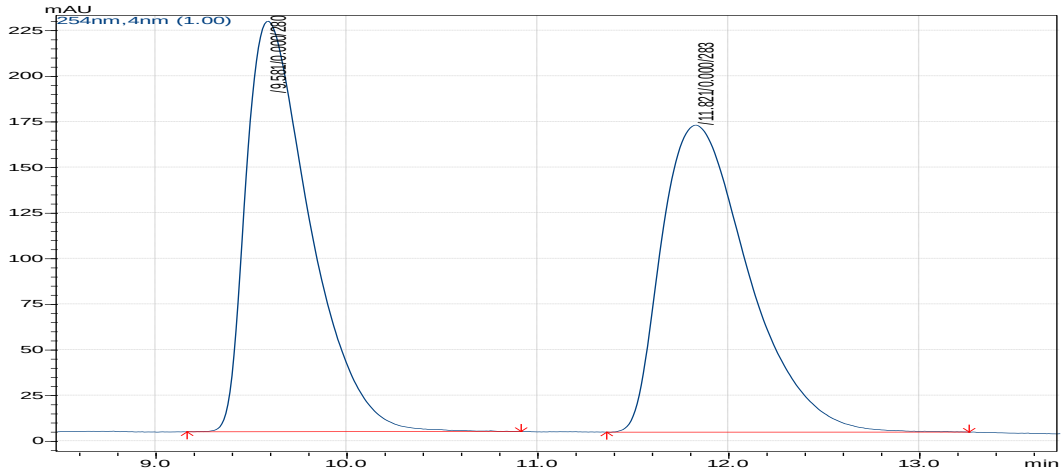




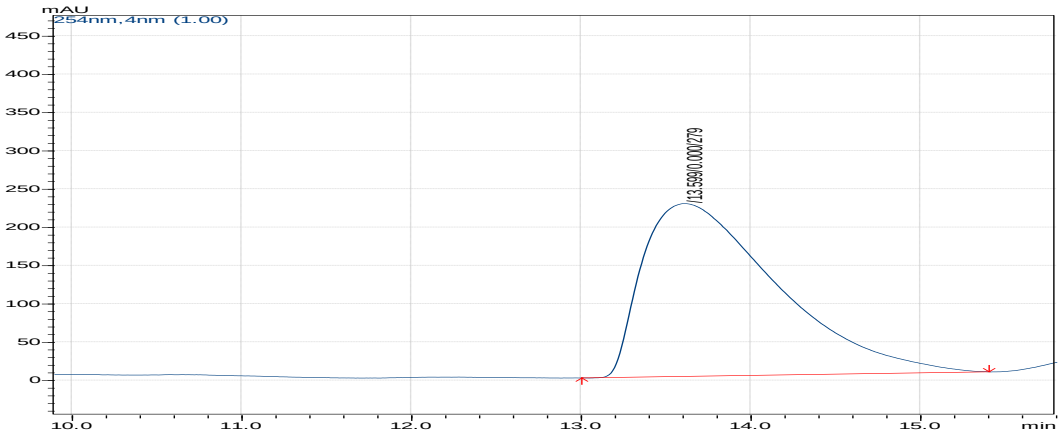
(*S*)-Benzylglycidyl ether (9g')



The ee was determined by HPLC analysis using a Chiralpak OD column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 8.72 min; t_S = 10.10 min).

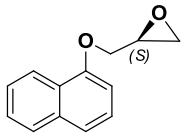


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	9.581	5223788	9.163	10.912	49.5096
2	11.821	5327269	11.360	13.259	50.4904

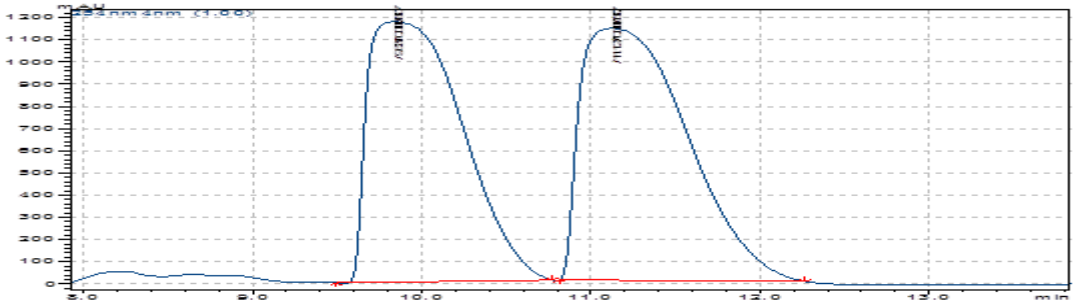


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	13.599	12456258	13.003	15.403	99.9857

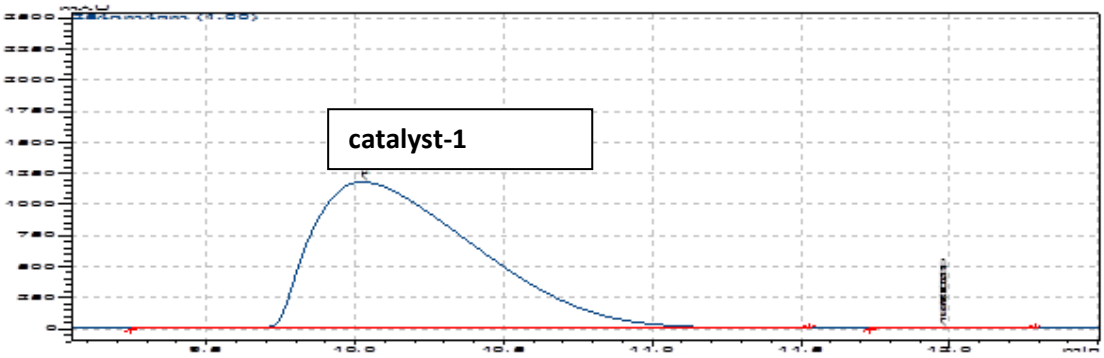
(*S*)-Naphthylglycidyl ether (9h′)

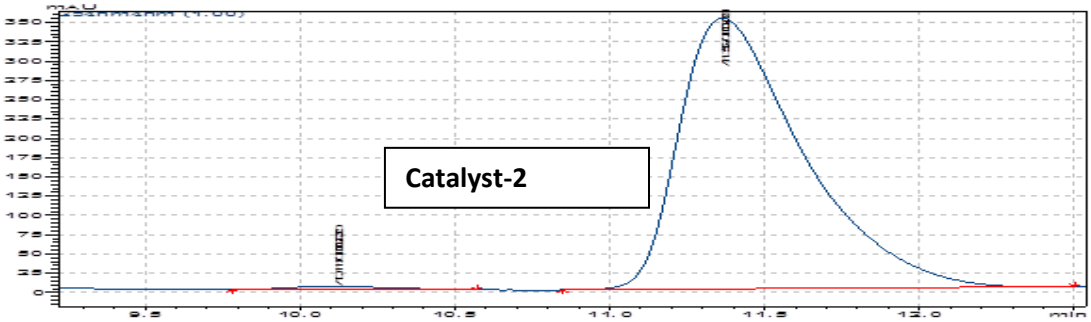


The ee was determined by HPLC analysis using a Chiralpak OD column (80/20 hexane/*i*-PrOH; flow rate 0.8 mL/min; t_R = 8.72 min; t_S = 10.10 min).



Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	9.831	45433743	9.493	10.773	47.8010
2	11.127	49613955	10.816	12.267	52.1990

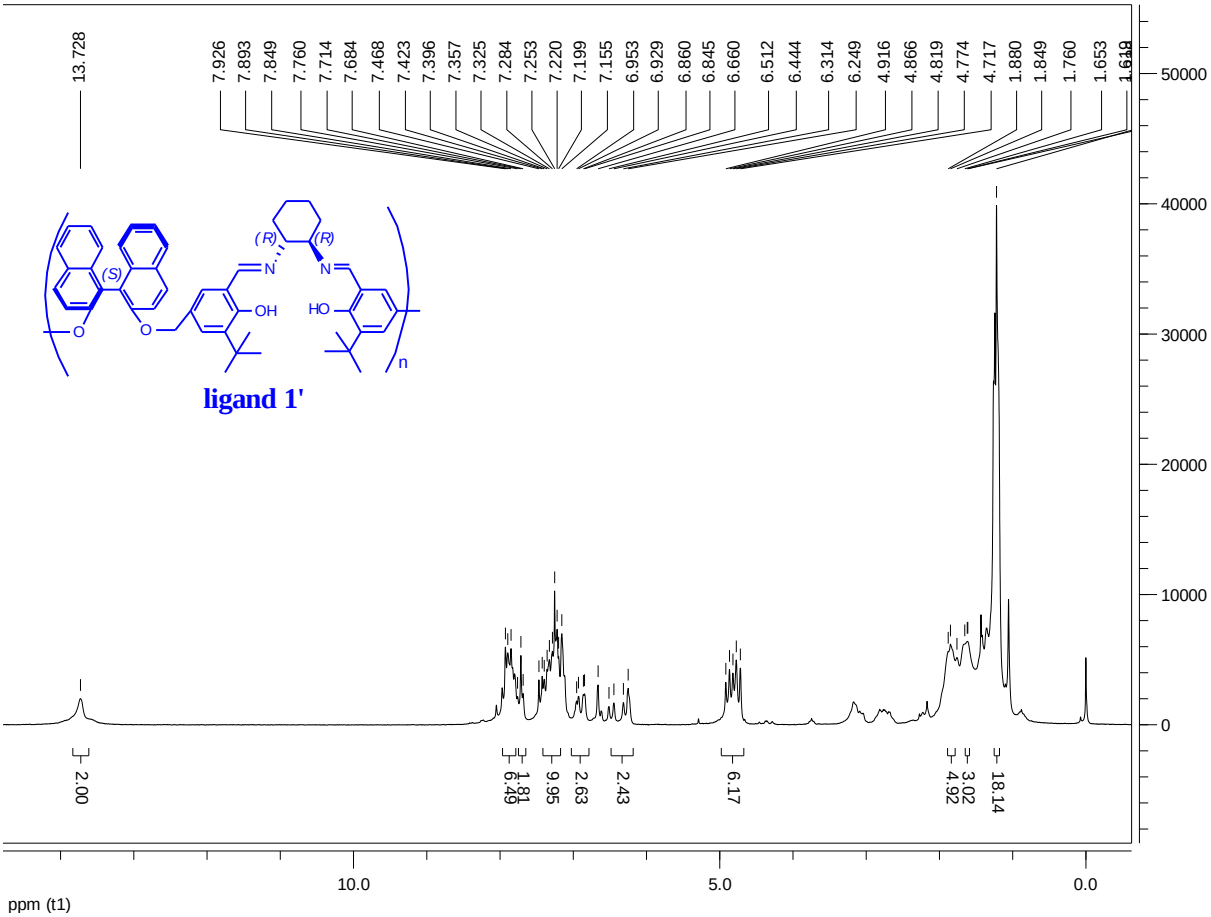


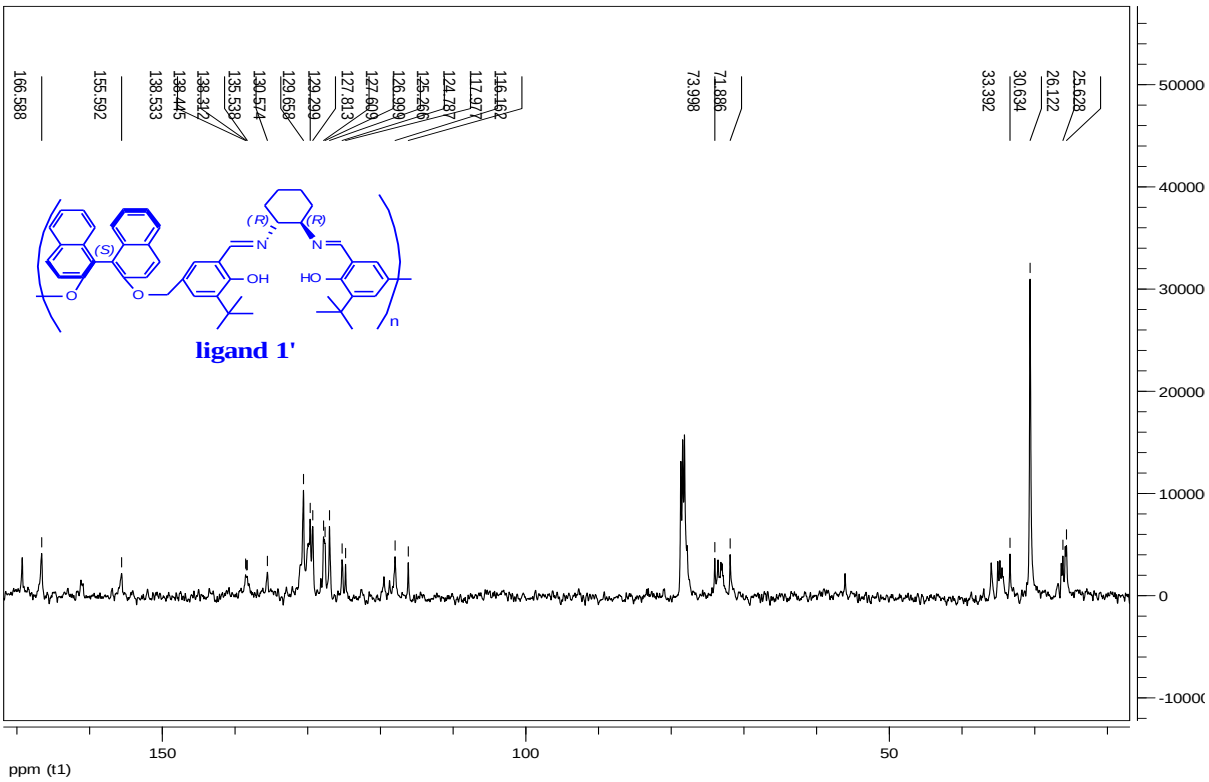


Peak#	Ret. Time	Area	Peak Start	Peak End	Area%
1	10.111	94545	9.781	10.571	0.9655
2	11.359	9697548	10.848	12.501	99.0345

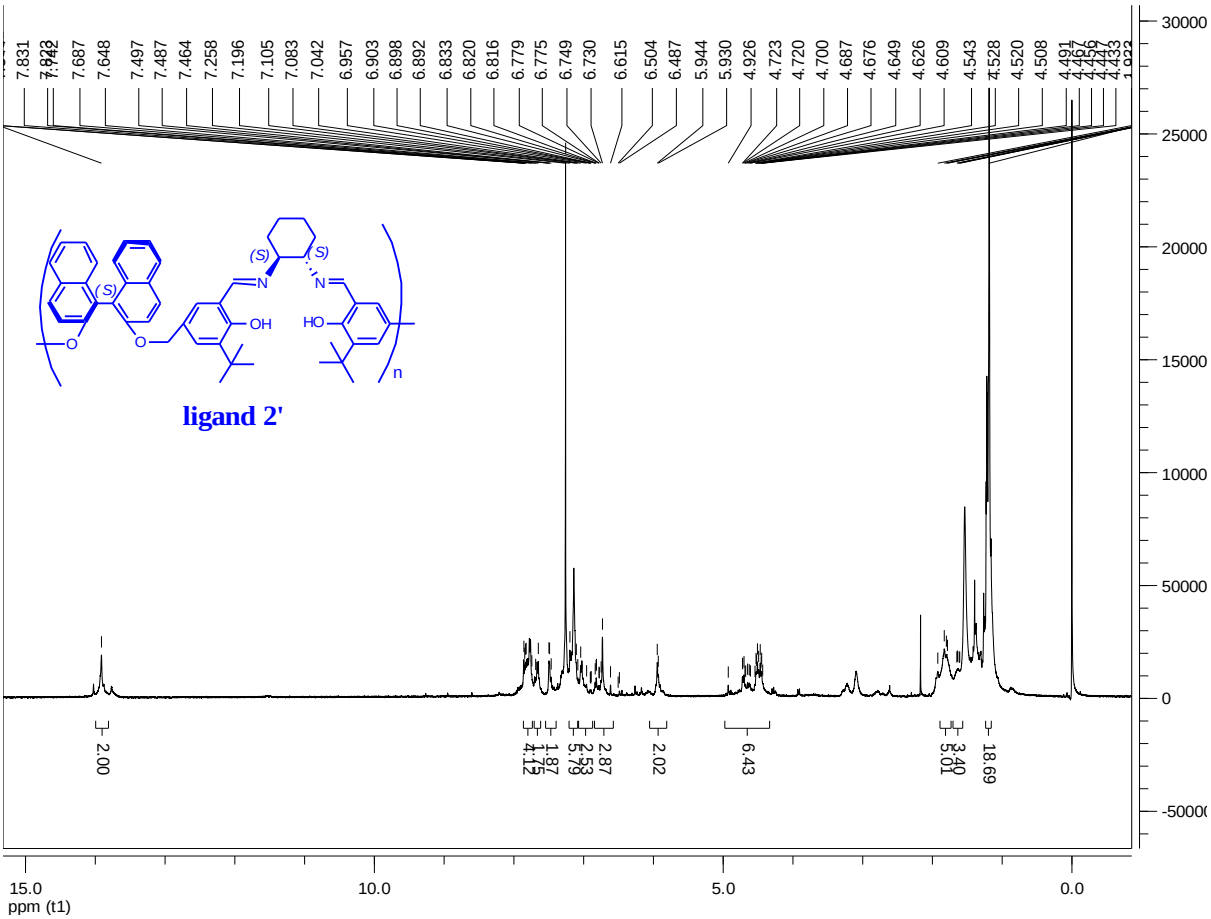
^{1}H and ^{13}C NMR Spectra of ligands and products

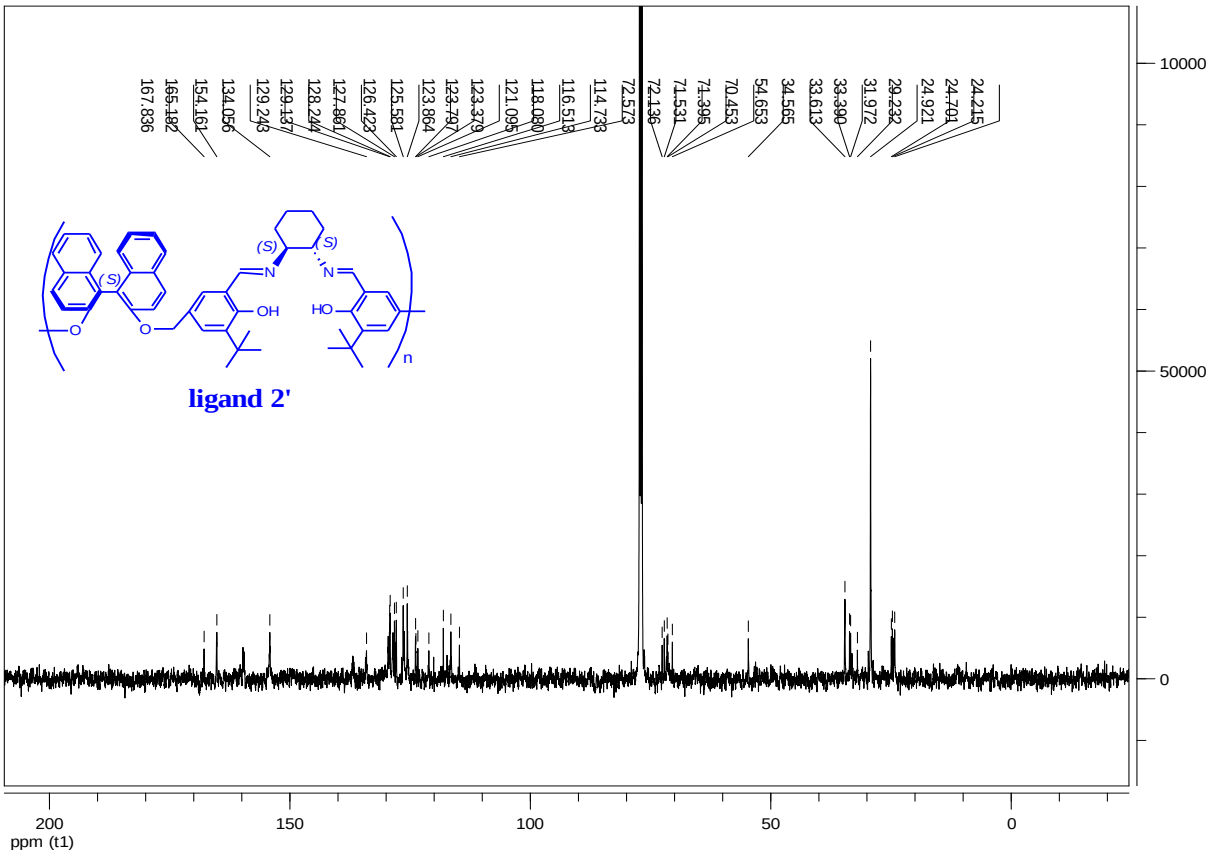
Polymeric salen ligand 1'



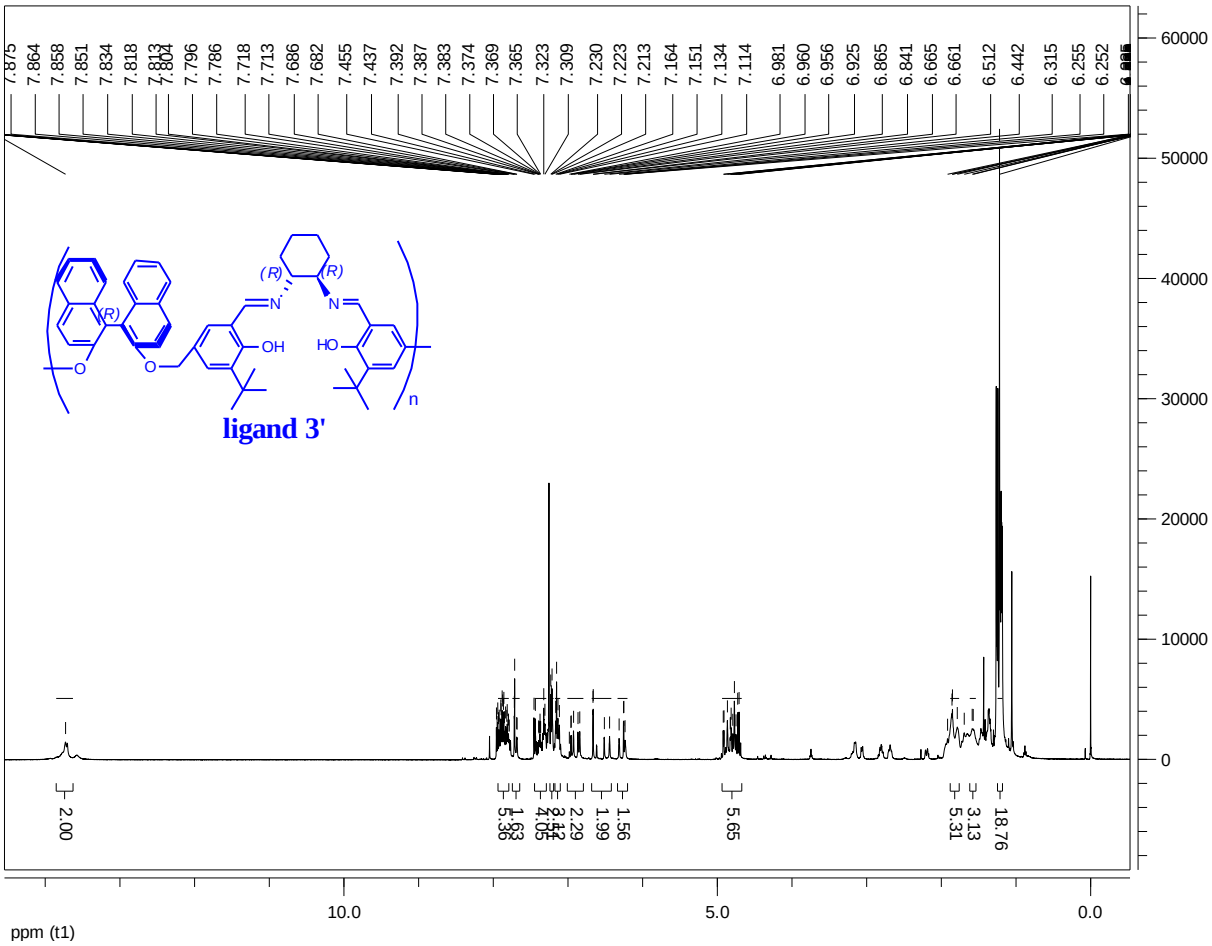


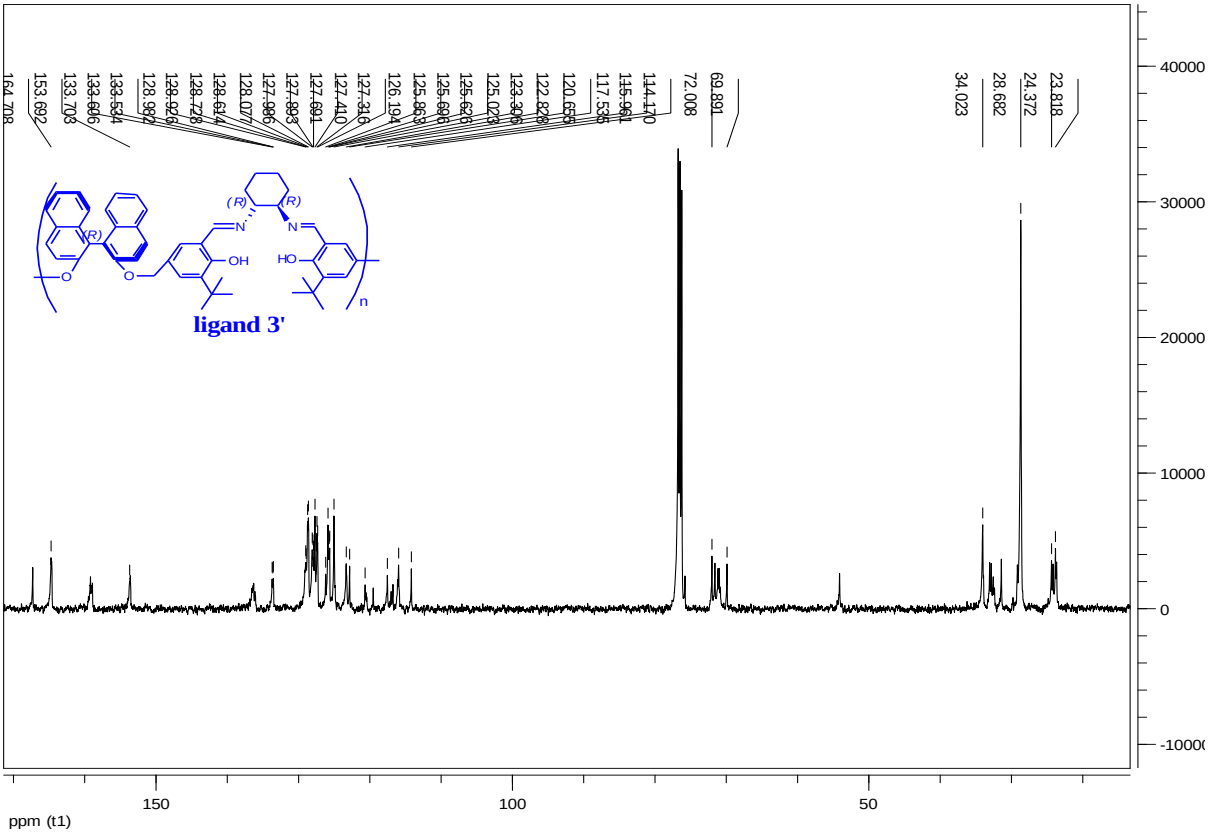
Polymeric salen ligand 2'



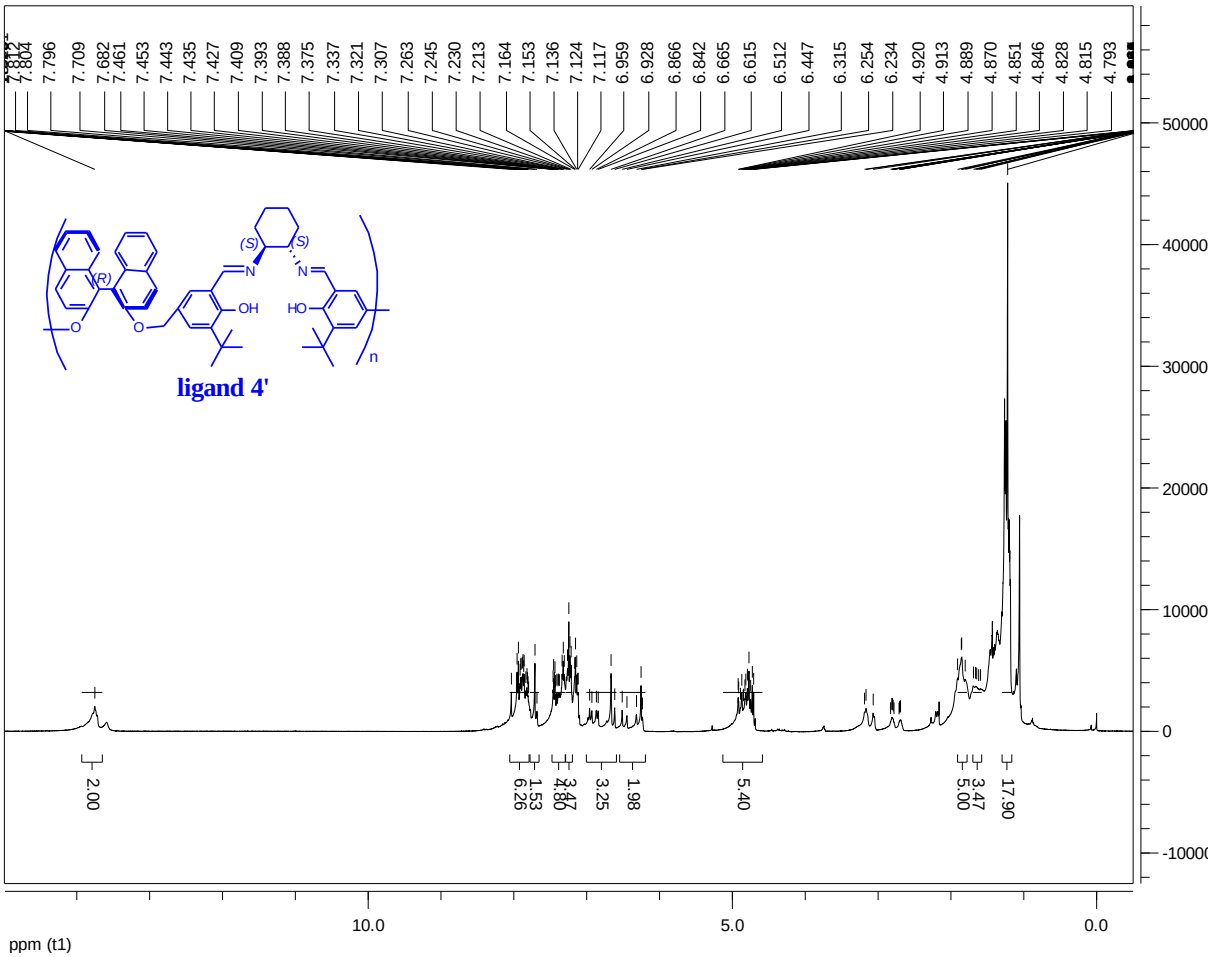


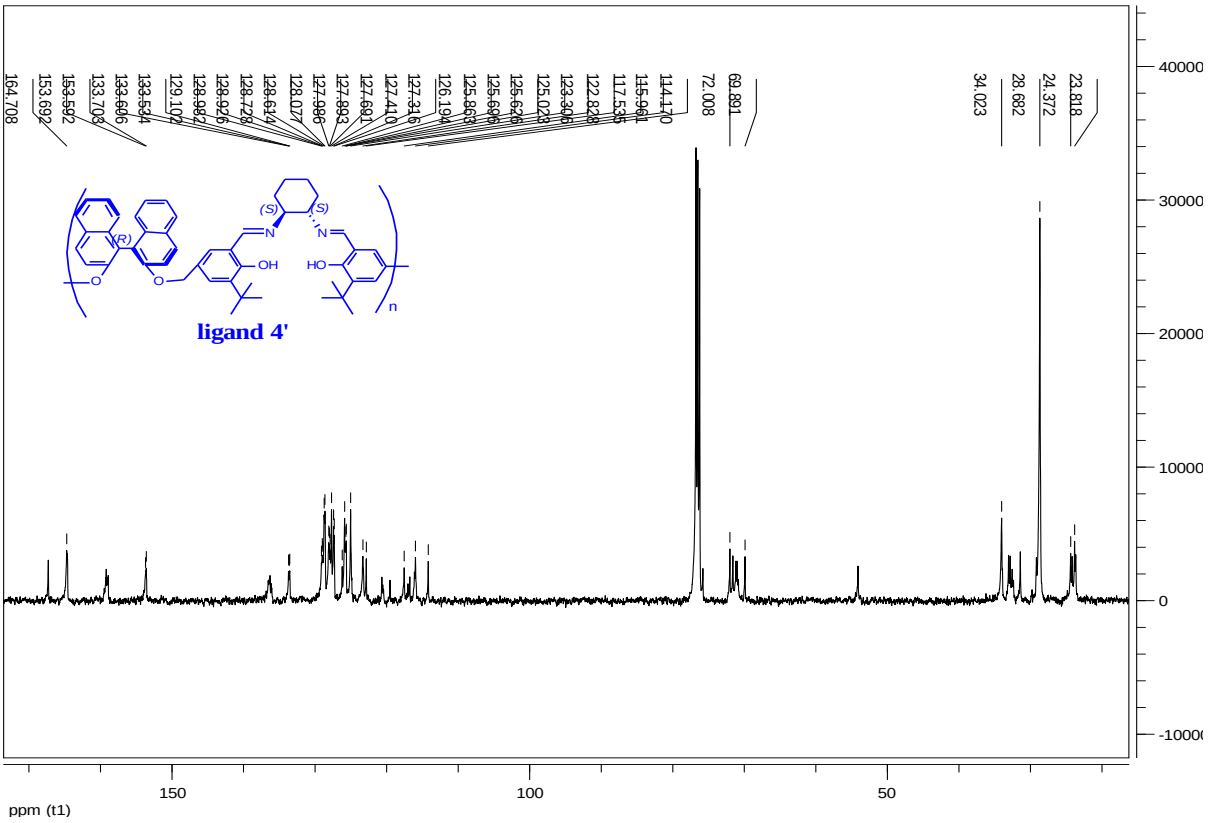
Polymeric salen ligand 3'



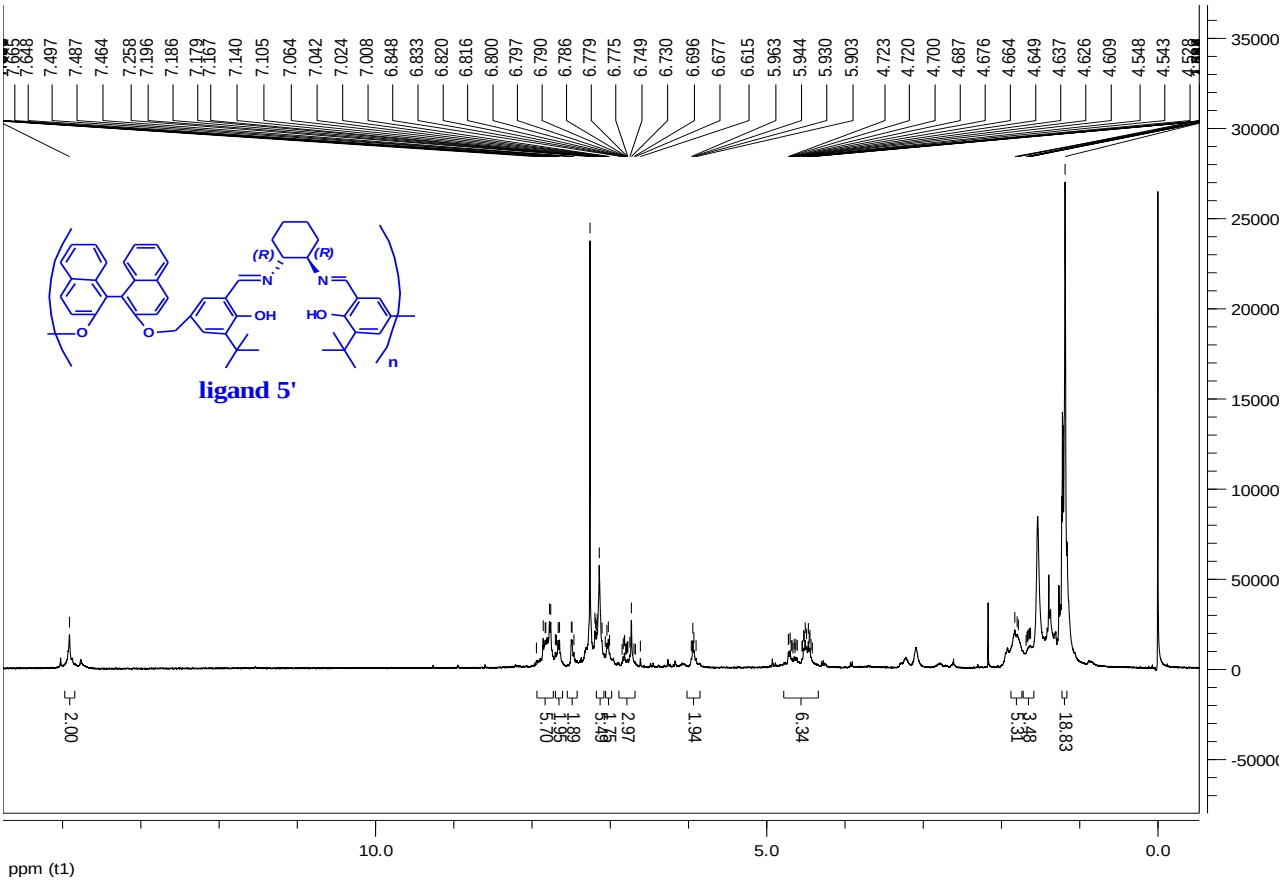


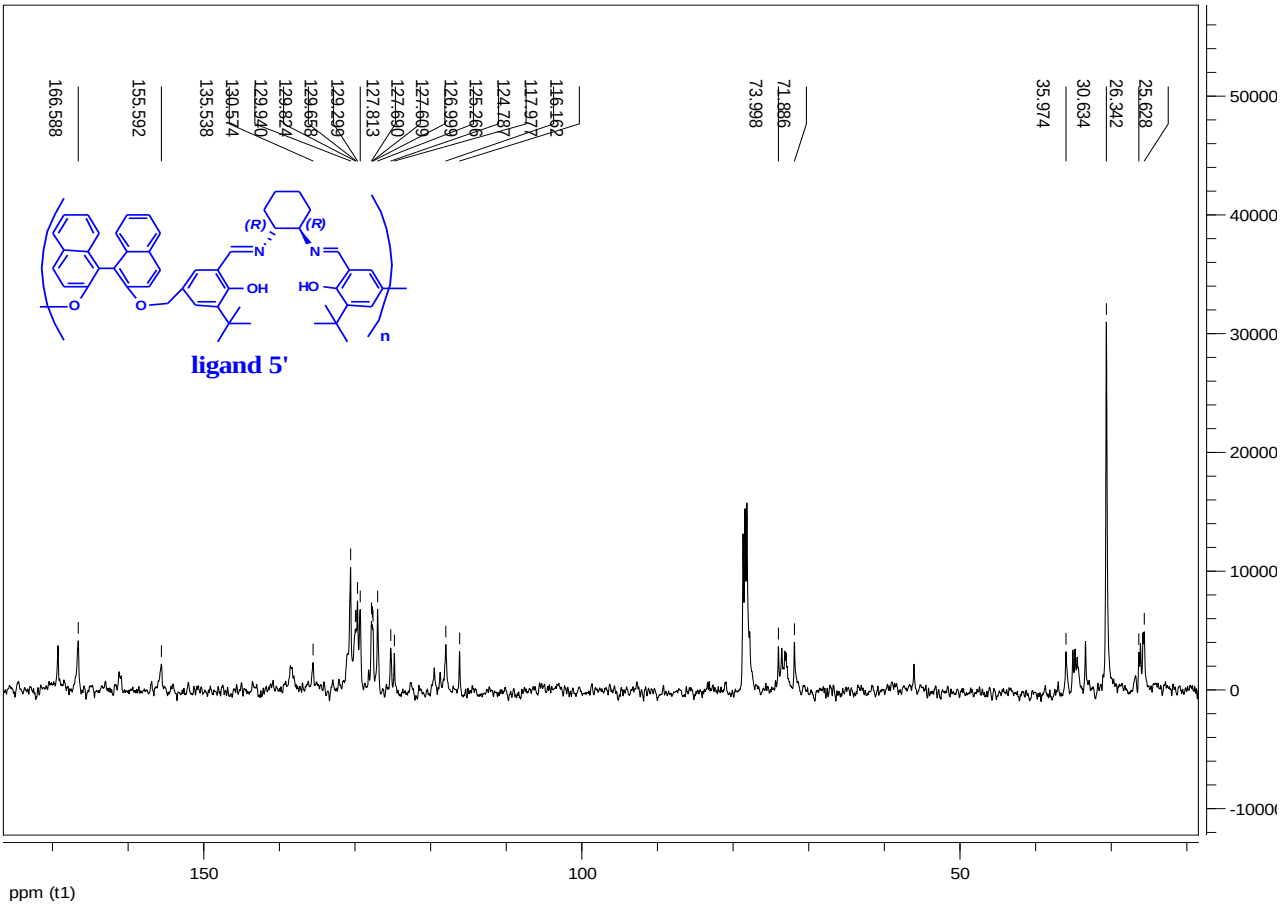
Polymeric salen ligand 4'



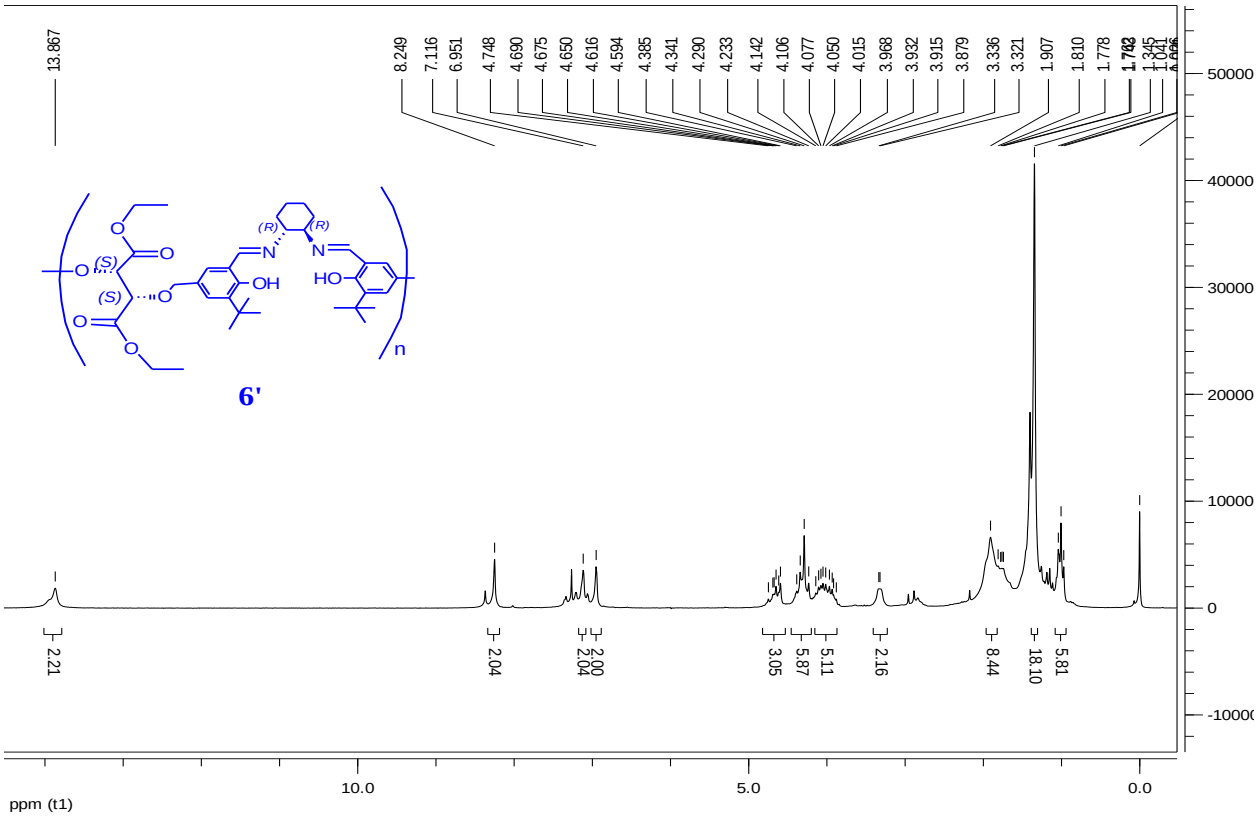


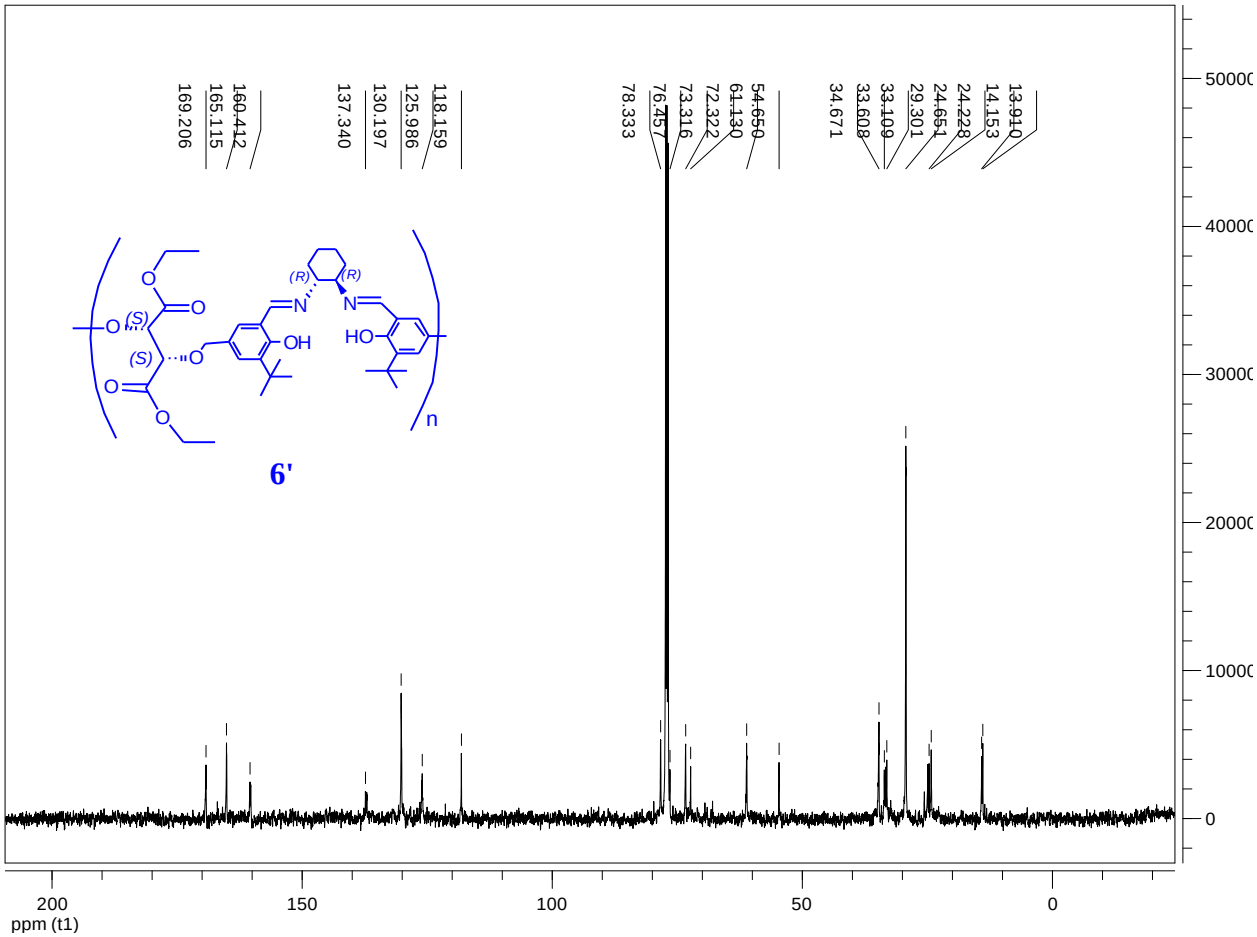
Polymeric salen ligand 5'



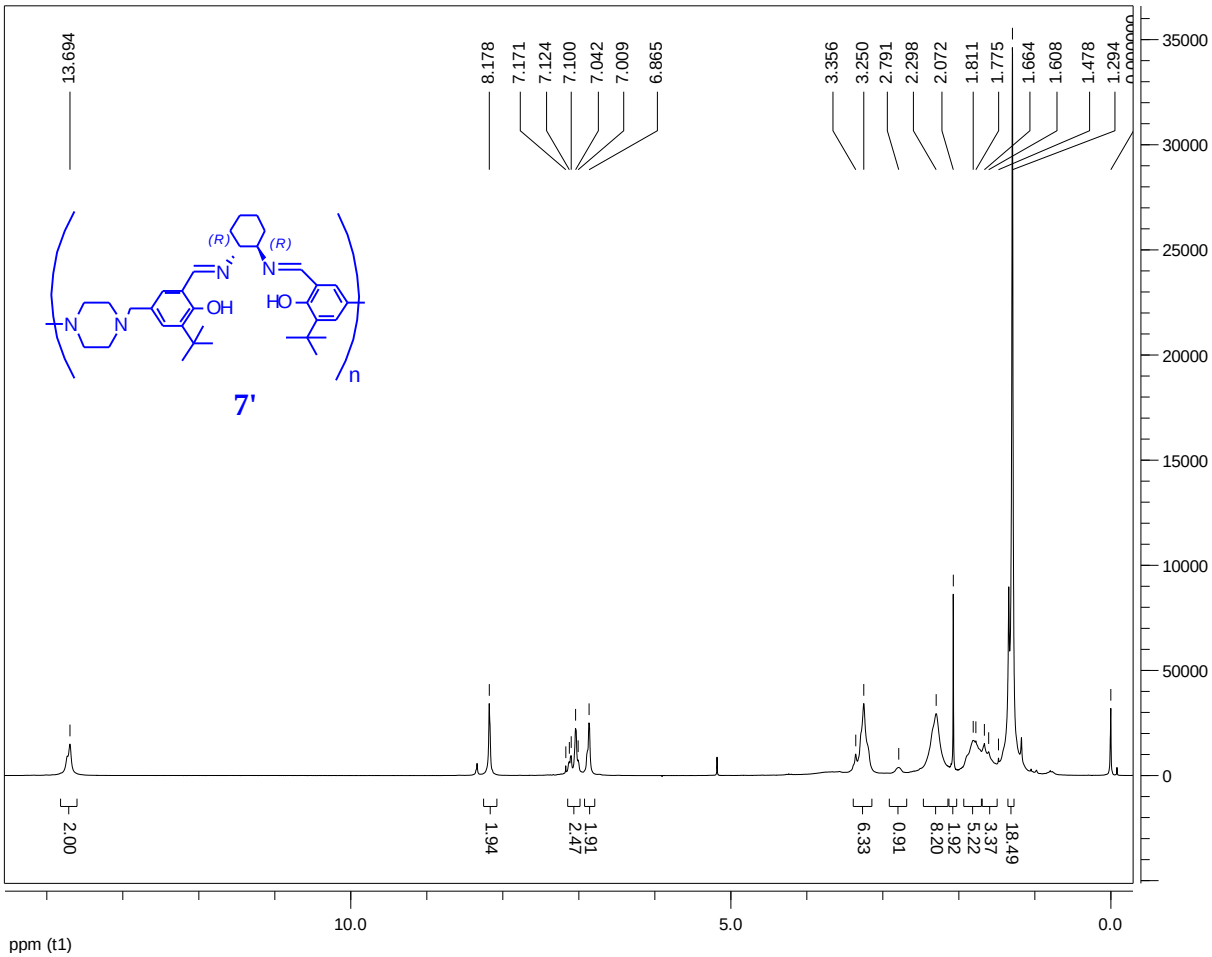


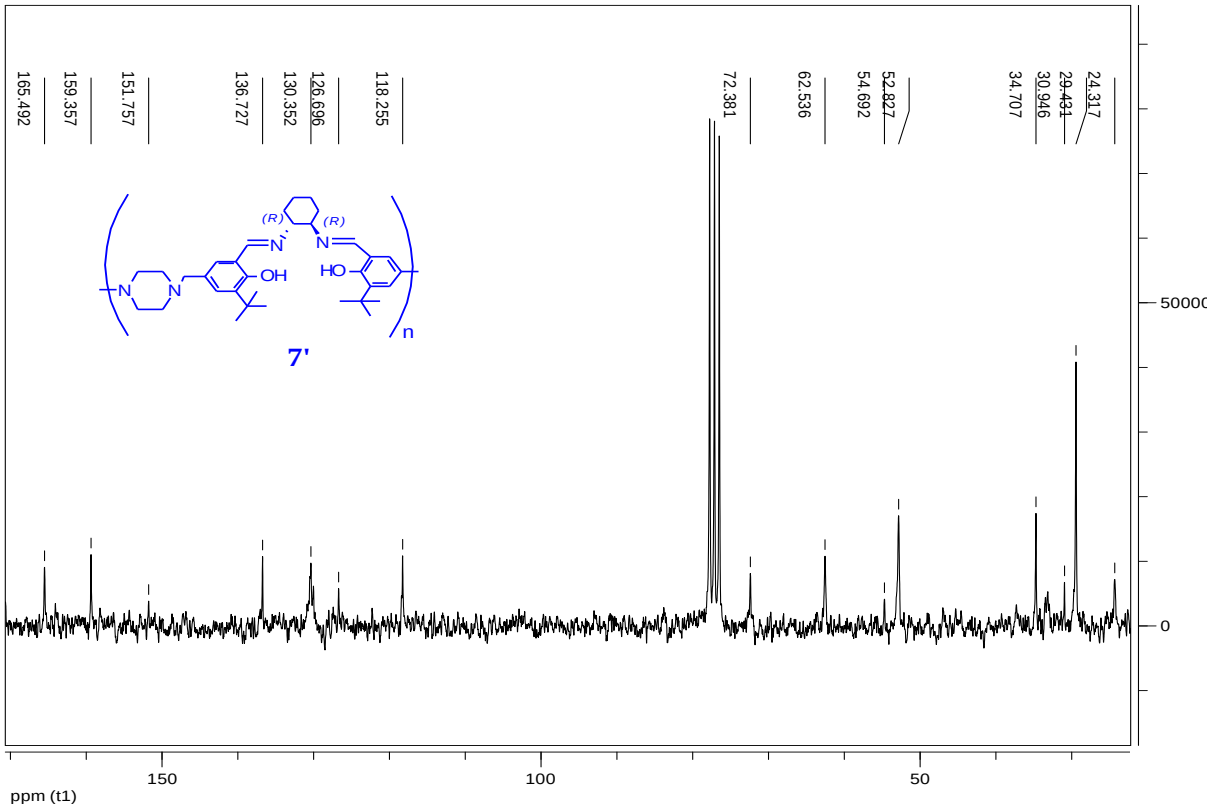
Polymeric salen ligand 6'



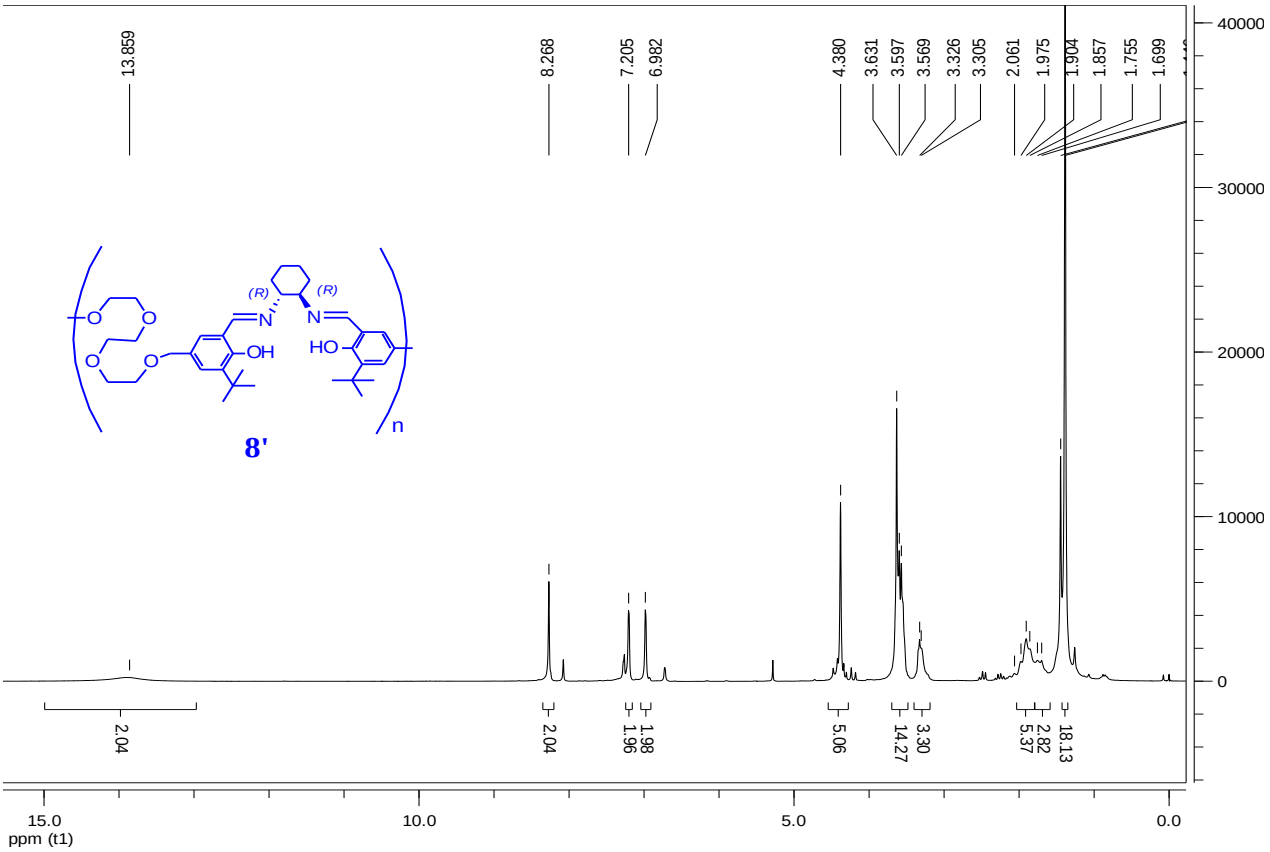


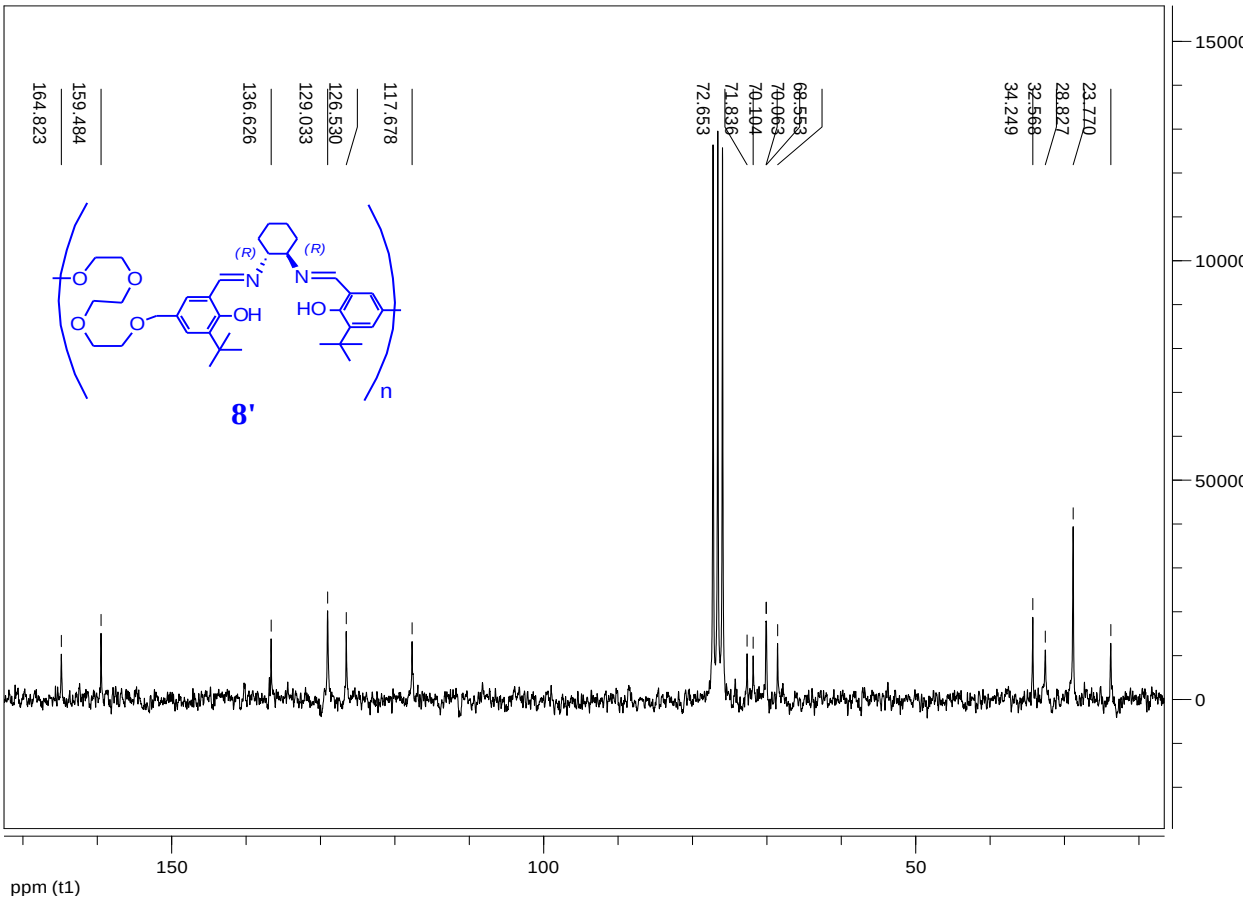
Polymeric salen ligand 7’



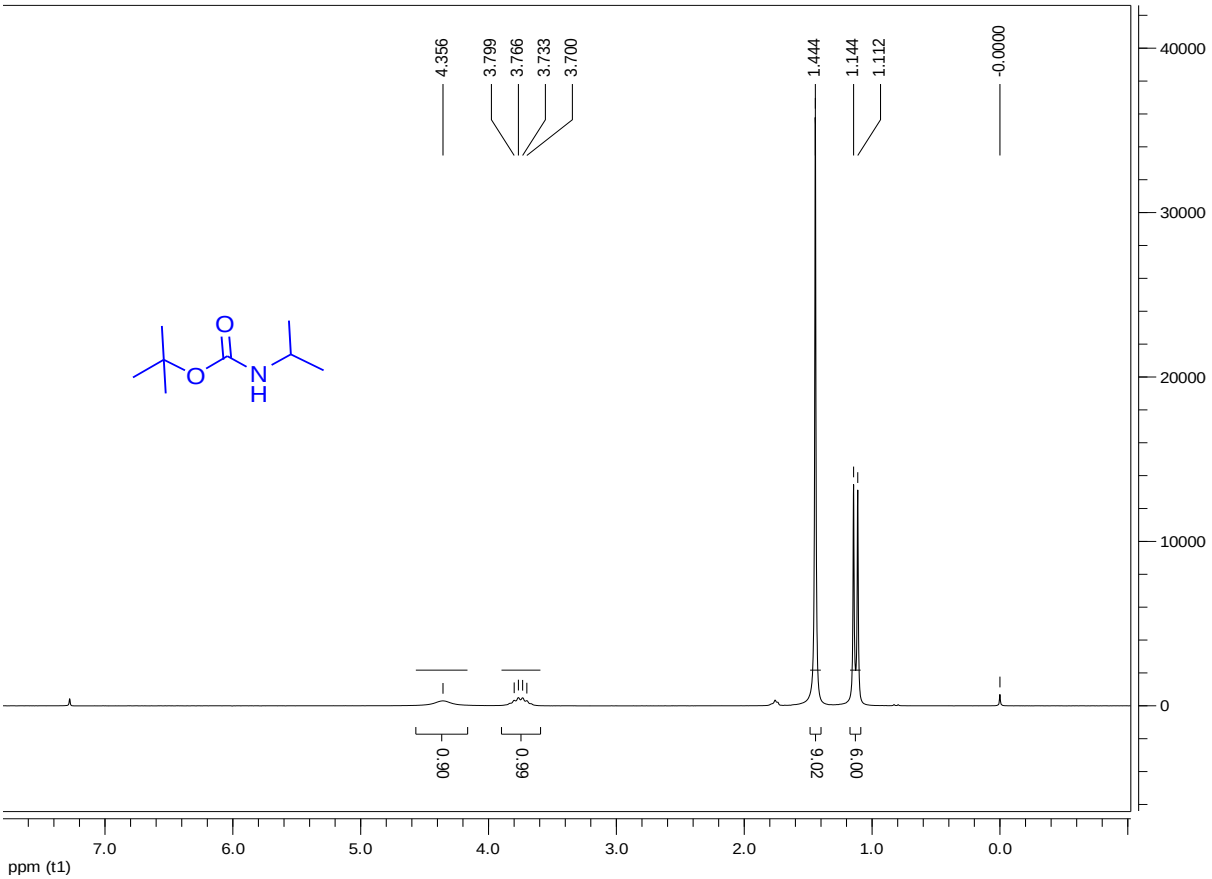


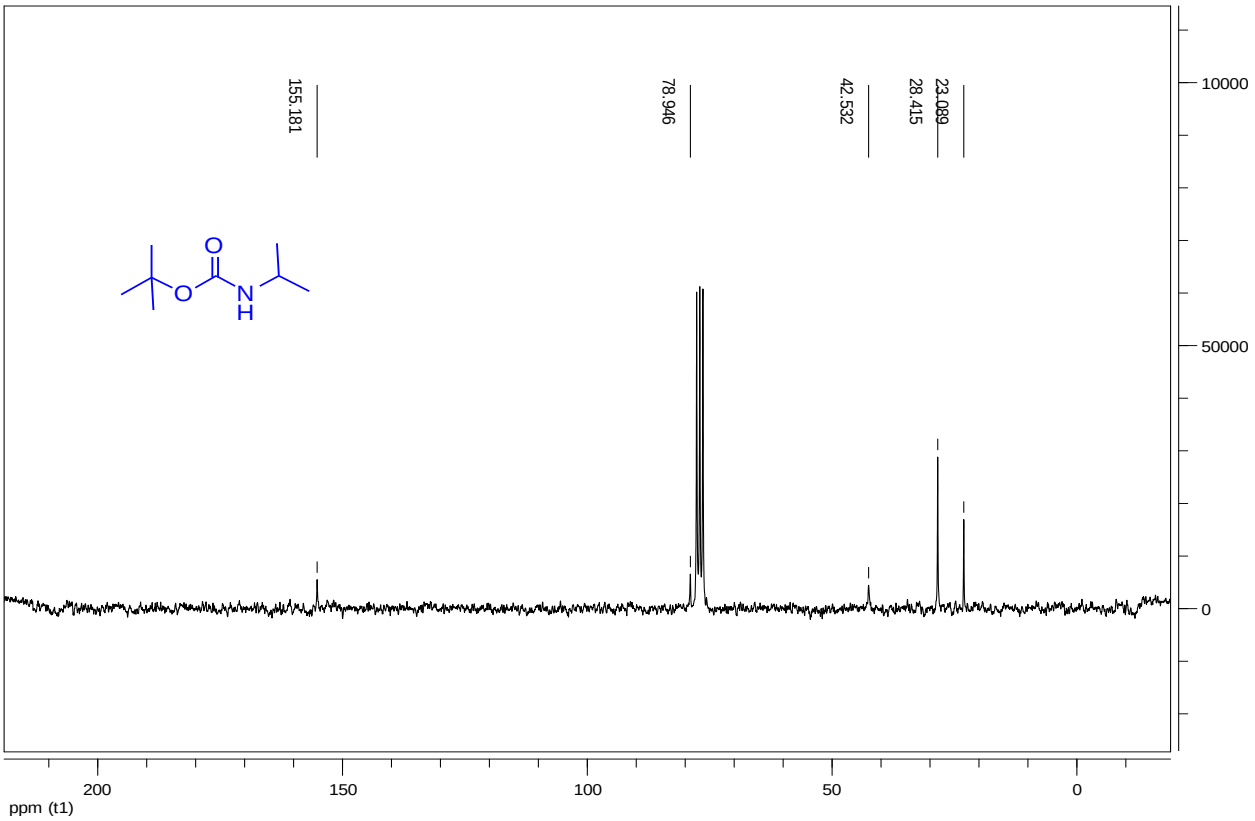
Polymeric salen ligand 8'



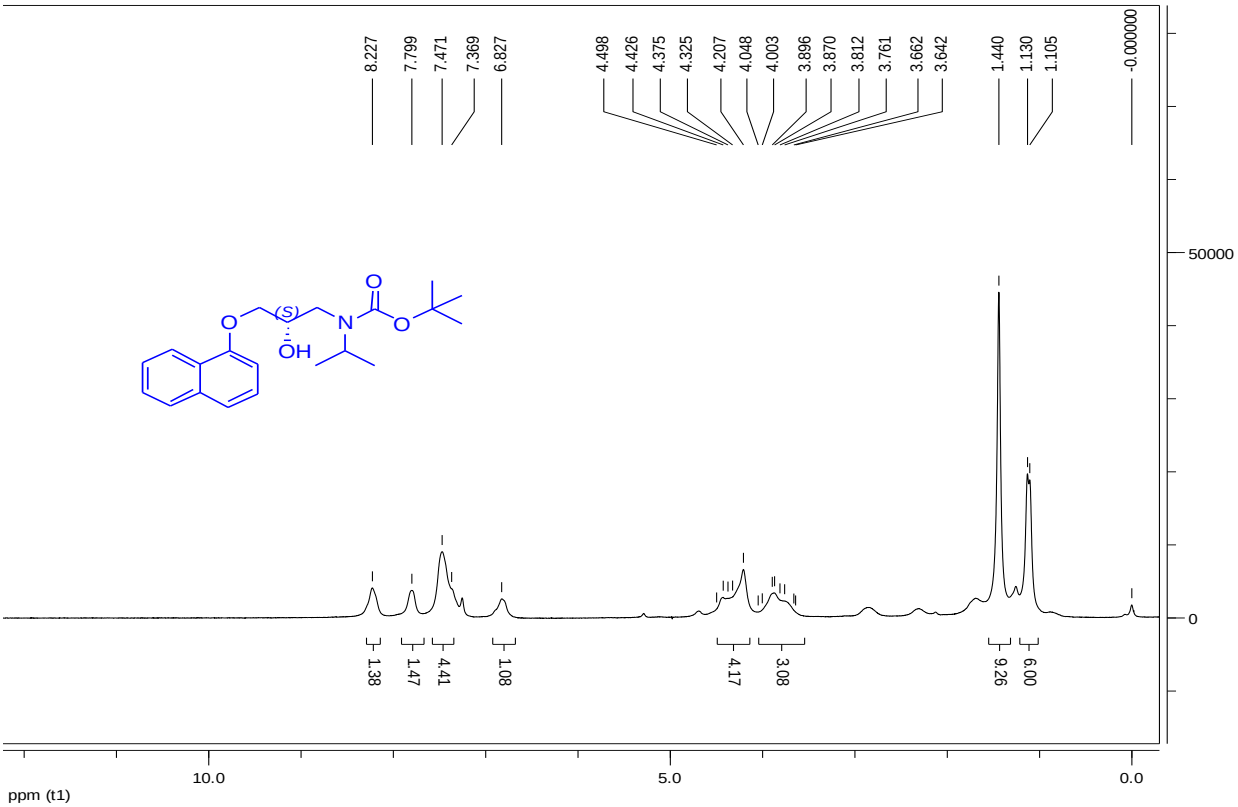


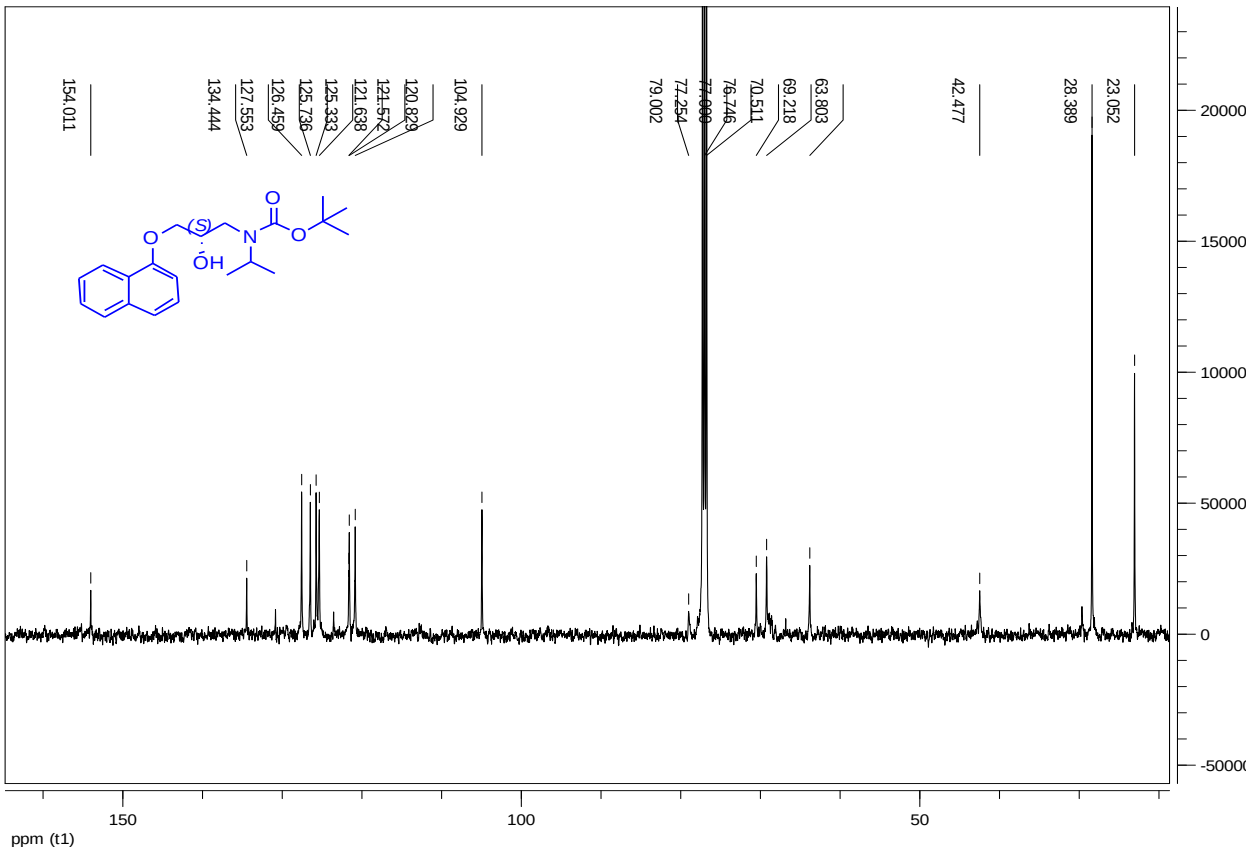
tert-butyl isopropylcarbamate 14





(*S*)-tert-butyl 2-hydroxy-3-(naphthalen-1-yloxy)propyl(isopropyl)carbamate 15





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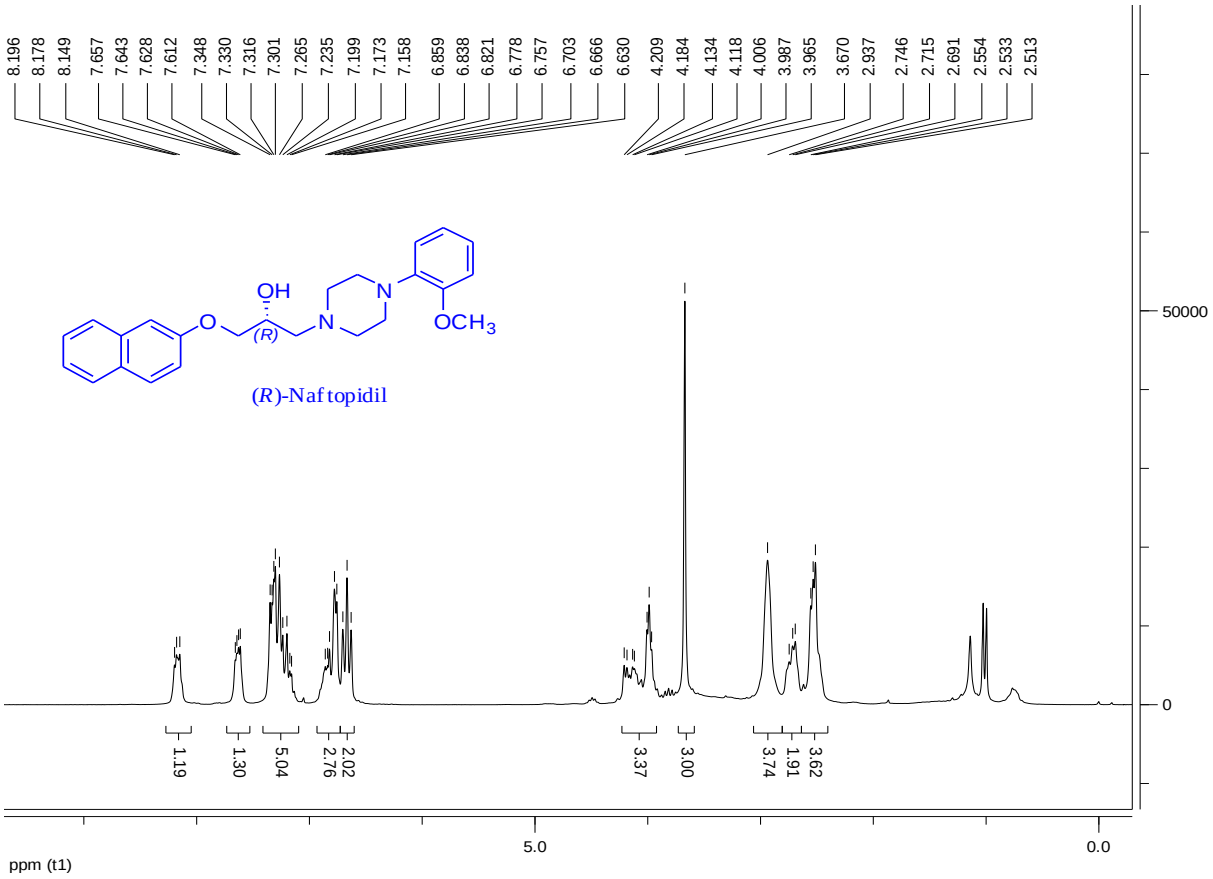
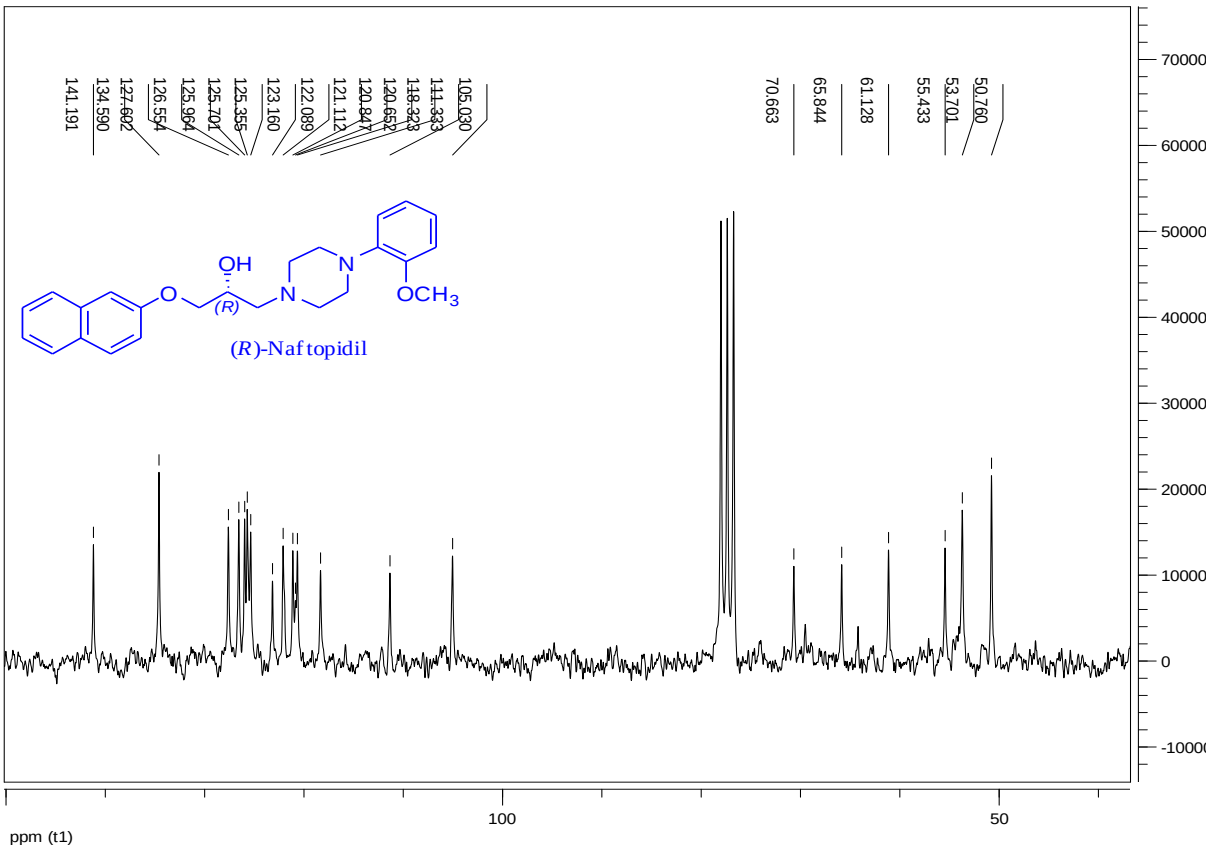
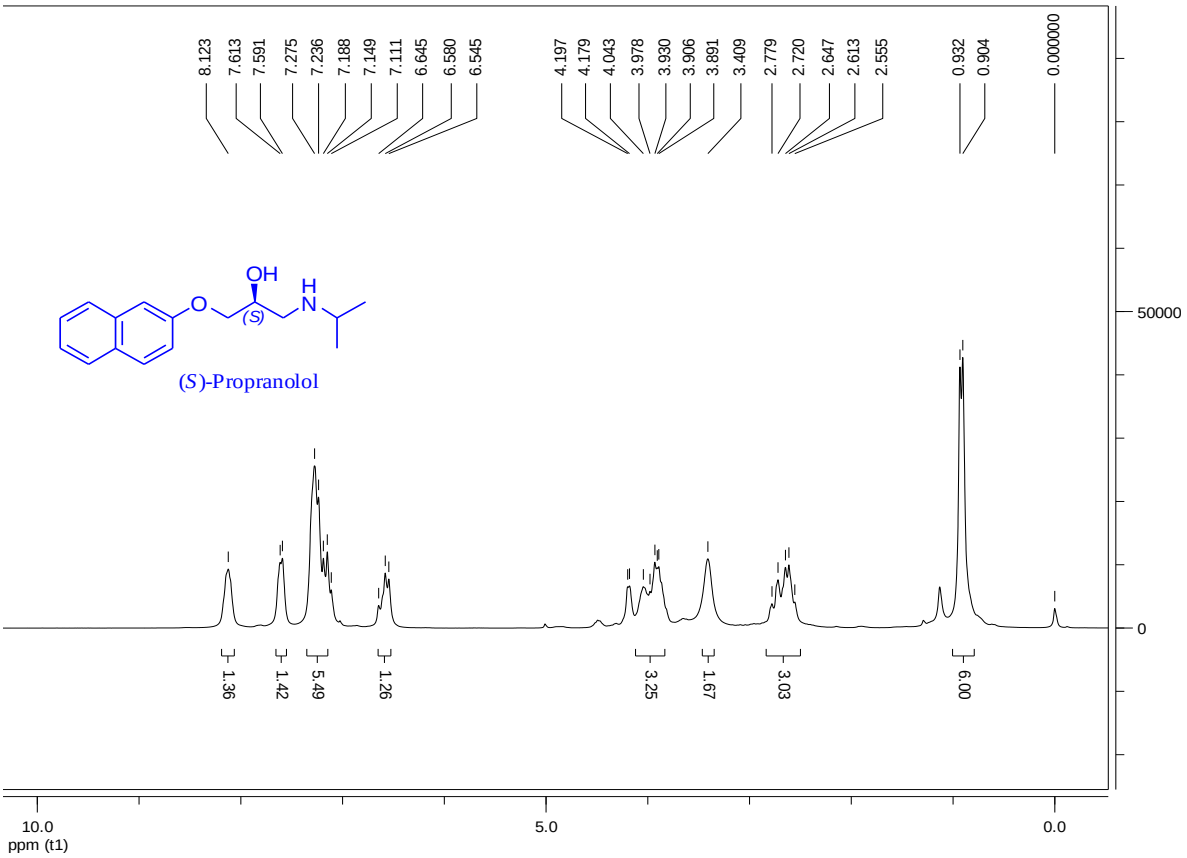
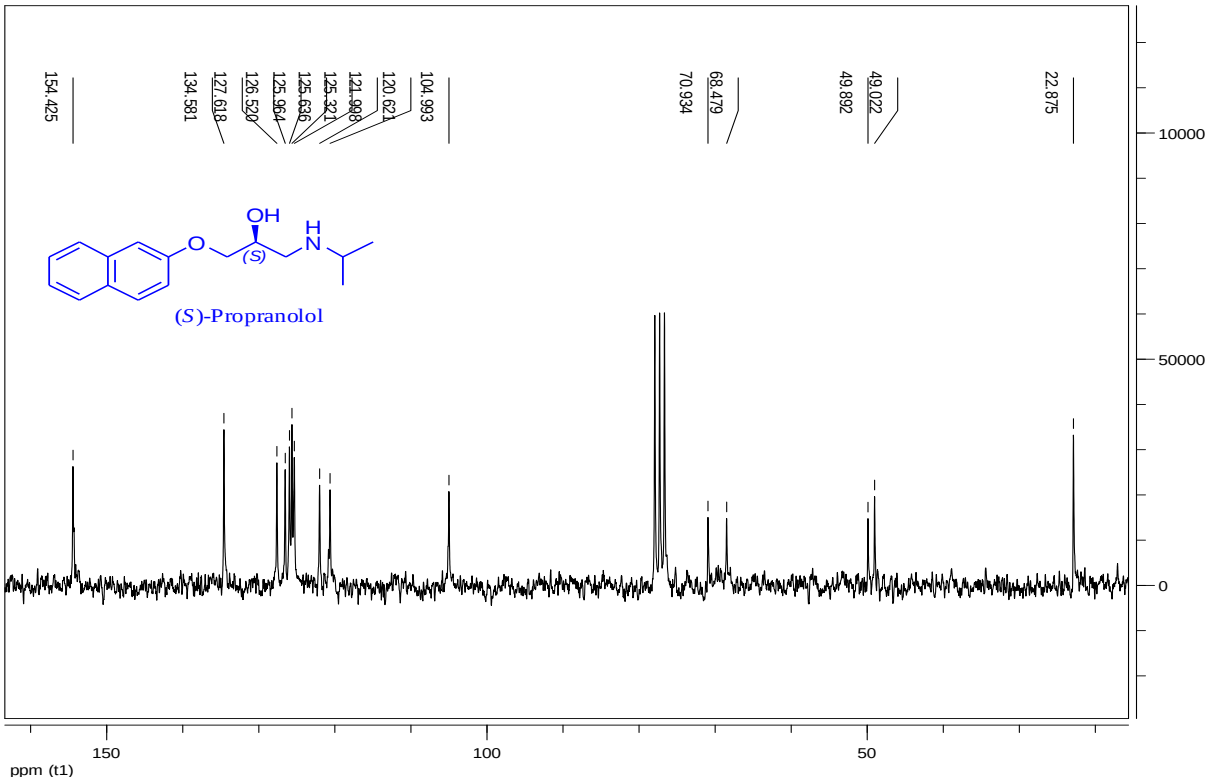




(*S*)-Propranolol 17





GPC Spectra of polymeric ligands

Polymeric salen ligand 1'

Empower 2 software

CSMCRI_GPC

SAMPLE INFORMATION

Sample Name:	biond	Acquired By:	CSMCRI
Sample Type:	Broad Unknown	Sample Set Name:	UDAY
Vial:	25	Acq. Method Set:	POLY STY_THF_HR5_HR4E
Injection #:	2	Processing Method:	POLY STYRENE _44000 TO 410
Injection Volume:	50.00 ul	Channel Name:	
Run Time:	80.0 Minutes	Proc. Chnl. Descr.:	
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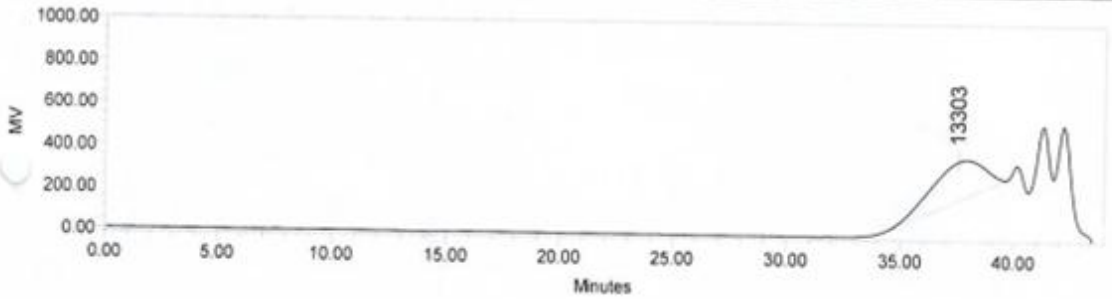
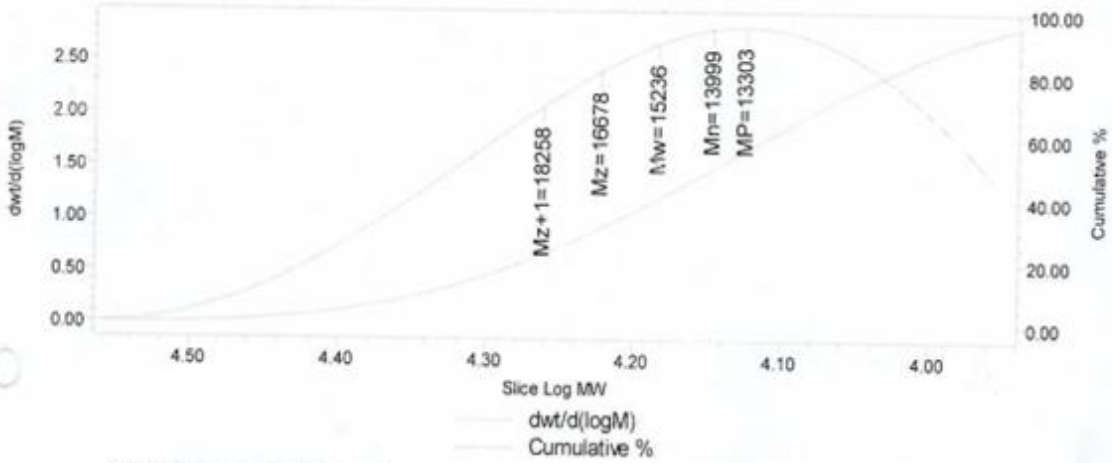
Date Processed:	4/7/2010 6:14:21 PM IST		





GPC Sample Results

	Retention Time	Mn	Mw	MP	Mz	Poly-dispersity
1	37.547	13999	15236	13303	16678	1.088

Mp: 13303 Name: Peak2

	RT	Mol Wt	Log Mol Wt	Area	Cumulative %
1	34.775	31797	4.502390	96325	0.232

	RT	Mol Wt	Log Mol Wt	Area	Cumulative %
2	35.233	27530	4.439811	477427	1.761

Polymeric salen ligand 2'

Empower 2 software

CSMCRI_GPC

SAMPLE INFORMATION

Sample Name:	bipoxy	Acquired By:	CSMCRI
Sample Type:	Broad Unknown	Sample Set Name:	UDAY
Vial:	26	Acq. Method Set:	POLY STY_THF_HR5_HR4E
Injection #:	2	Processing Method:	POLY STYRENE _44000 TO
Injection Volume:	50.00 ul	Channel Name:	410
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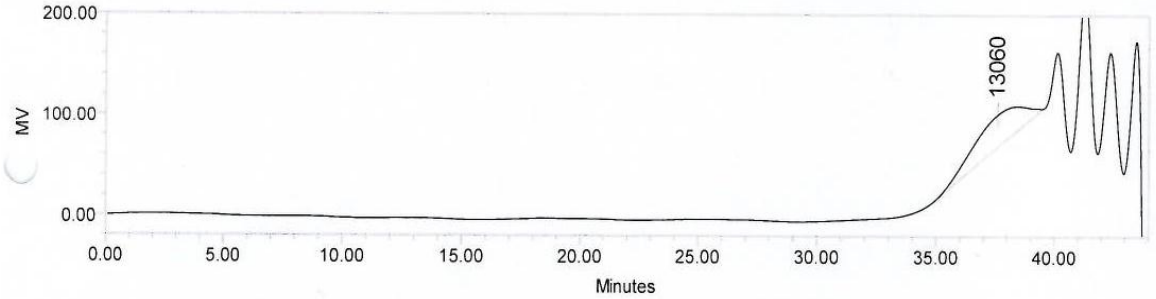
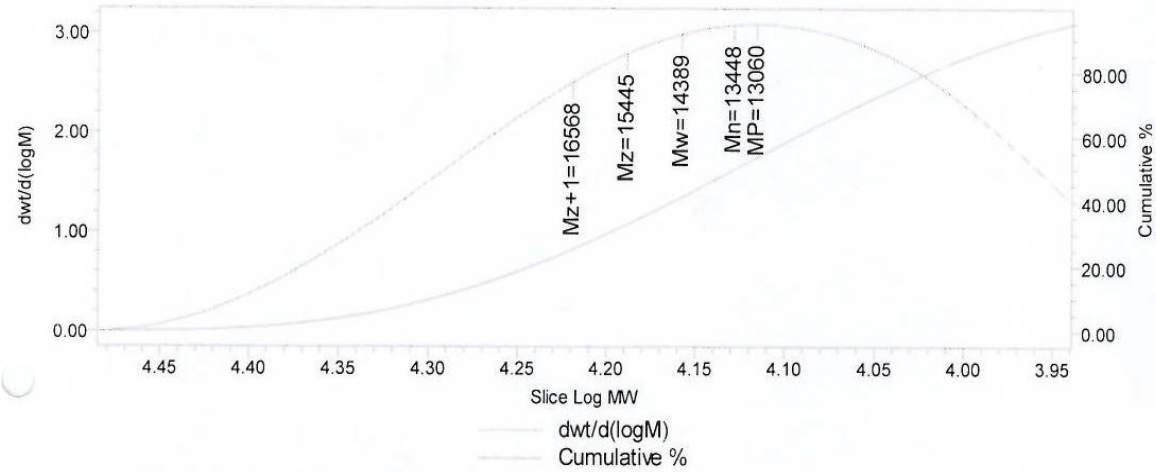




GPC Sample Results

	Retention Time	Mn	Mw	MP	Mz	Poly-dispersity
1	37.605	13448	14389	13060	15445	1.070

Mp: 13060 Name: Peak2

	RT	Mol Wt	Log Mol Wt	Area	Cumulative %
1	35.300	26959	4.430708	19843	0.298

	RT	Mol Wt	Log Mol Wt	Area	Cumulative %
2	35.700	23774	4.376094	94409	2.172

Polymeric salen ligand 6'

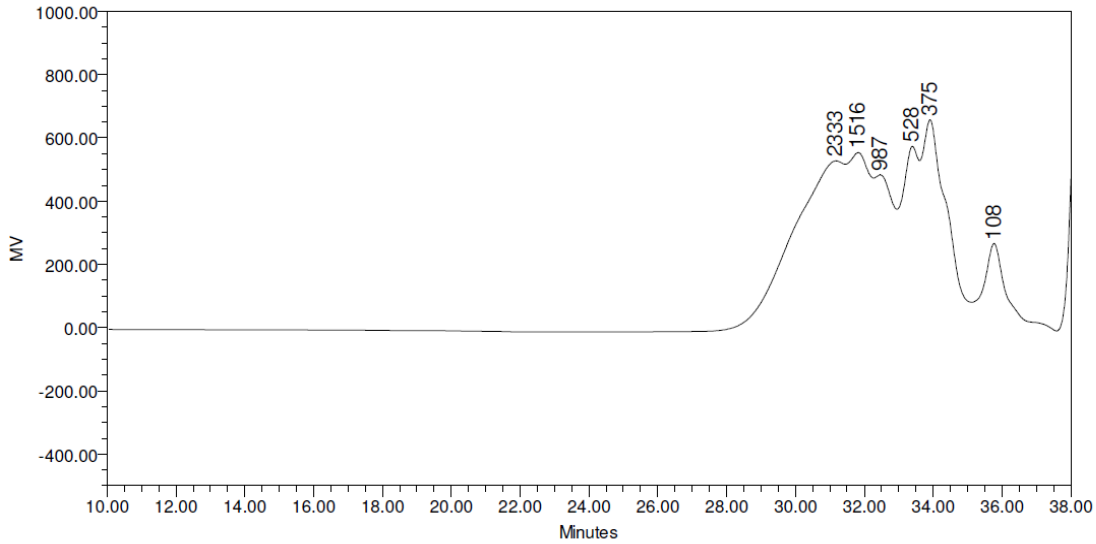
Empower 2 software

GPC

SAMPLE INFORMATION

Sample Name:	det poly	Acquired By:	CSMCRI
Sample Type:	Broad Unknown	Sample Set Name:	130213
Vial:	6	Acq. Method Set:	PS HR 5_4E_05_ THF all
Injection #:	1	Processing Method:	130213
Injection Volume:	80.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	2/13/2013 6:24:00 PM IST		
Date Processed:	2/19/2013 12:15:27 PM IST		

Auto-Scaled Chromatogram



GPC Results

	Mn	Mw	MP	Mz	Mz+1	Polydispersity
1	3466	4374	2333	5928	8307	1.262175
2	1470	1507	1516	1544	1581	1.025284
3	899	915	987	930	946	1.017776
4	557	566	528	576	585	1.016351
5	312	330	375	347	361	1.059363
6	116	119	108	122	126	1.024585

Reported by User: CSMCRI (CSMCRI)
Report Method: GPC
Report Method ID: 3003
Page: 1 of 1

Project Name: POLY STYRENE THF
Date Printed:
2/19/2013
12:17:36 PM Asia/Calcutta

Polymeric salen ligand 7'

Empower 2 software

GPC

SAMPLE INFORMATION

Sample Name:	S BN SS CHDA	Acquired By:	CSMCRI
Sample Type:	Broad Unknown	Sample Set Name:	LOW TEMP
Vial:	34	Acq. Method Set:	PS THF ALL LOW TEMP
Injection #:	1	Processing Method:	PS THF ALL LOW TEMP
Injection Volume:	80.00 ul	Channel Name:	410
Run Time:	35.0 Minutes	Proc. Chnl. Descr.:	
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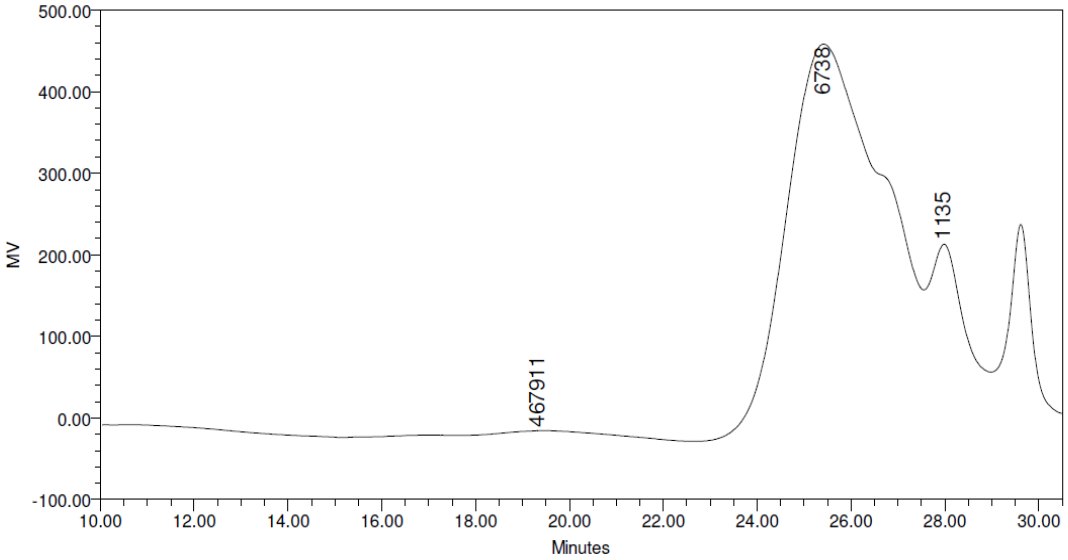
Date Processed:	10/12/2012 4:19:16 PM IST		

Auto-Scaled Chromatogram



GPC Results

	Mn	Mw	MP	Mz	Mz+1	Polydispersity
1			467911			
2	4529	6444	6738	8729	11049	1.422827
3	1284	1294	1135	1305	1315	1.008032

Reported by User: CSMCRI (CSMCRI)
Report Method: GPC
Report Method ID: 2704
Page: 1 of 1

Project Name: POLY STYRENE THF
Date Printed:
10/12/2012
4:20:07 PM Asia/Calcutta

Polymeric salen ligand 8'

Empower 2 software

GPC

SAMPLE INFORMATION

Sample Name:	frigol poly	Acquired By:	CSMCRI
Sample Type:	Broad Unknown	Sample Set Name:	130213
Vial:	1	Acq. Method Set:	PS HR 5_4E_05_ THF all
Injection #:	2	Processing Method:	130213
Injection Volume:	80.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
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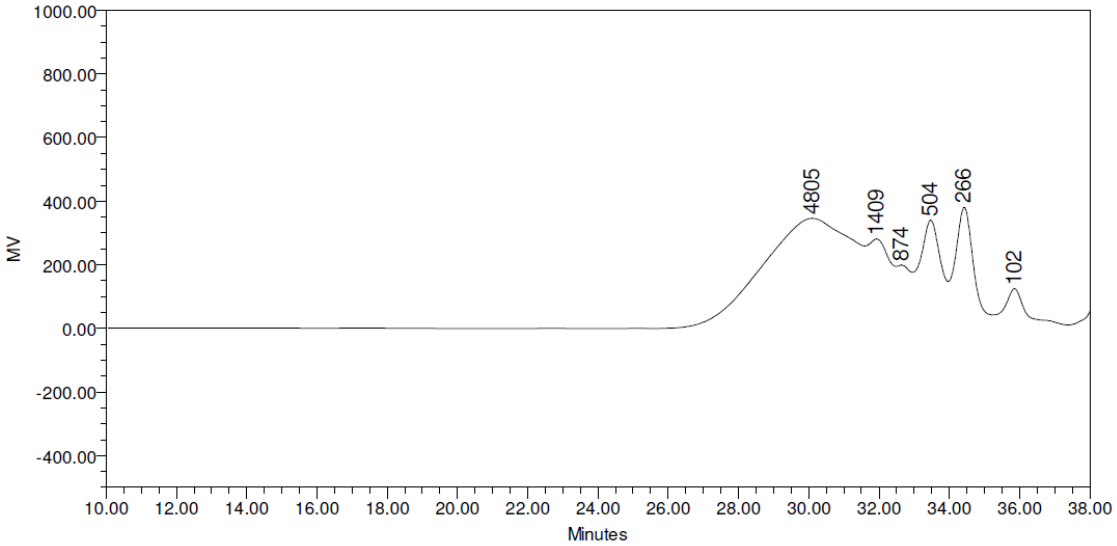
Date Processed:	2/19/2013 12:15:26 PM IST		

Auto-Scaled Chromatogram



GPC Results

	Mn	Mw	MP	Mz	Mz+1	Polydispersity
1	4543	7584	4805	13538	21921	1.669311
2	1315	1352	1409	1389	1425	1.028486
3	834	841	874	848	855	1.008566
4	502	518	504	534	550	1.031312
5	257	265	266	273	280	1.032447
6	111	113	102	115	118	1.017974

Reported by User: CSMCRI (CSMCRI)
Report Method: GPC
Report Method ID: 3003
Page: 1 of 1

Project Name: POLY STYRENE THF
Date Printed:
2/19/2013
12:17:55 PM Asia/Calcutta

References:

1. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals;*Pergamon: New York, 1981.

2. Bartoli G.; Bosco M.; Carlone A.; Locatelli M.; Melchiorre P.; Sambri L. *Org. Lett.* **2004**, 6, 3973.