Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Applications of 3-aminolactams: design, synthesis, and biological evaluation of a library of HIV1-protease inhibitors

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Supplemetary material

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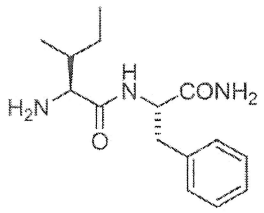
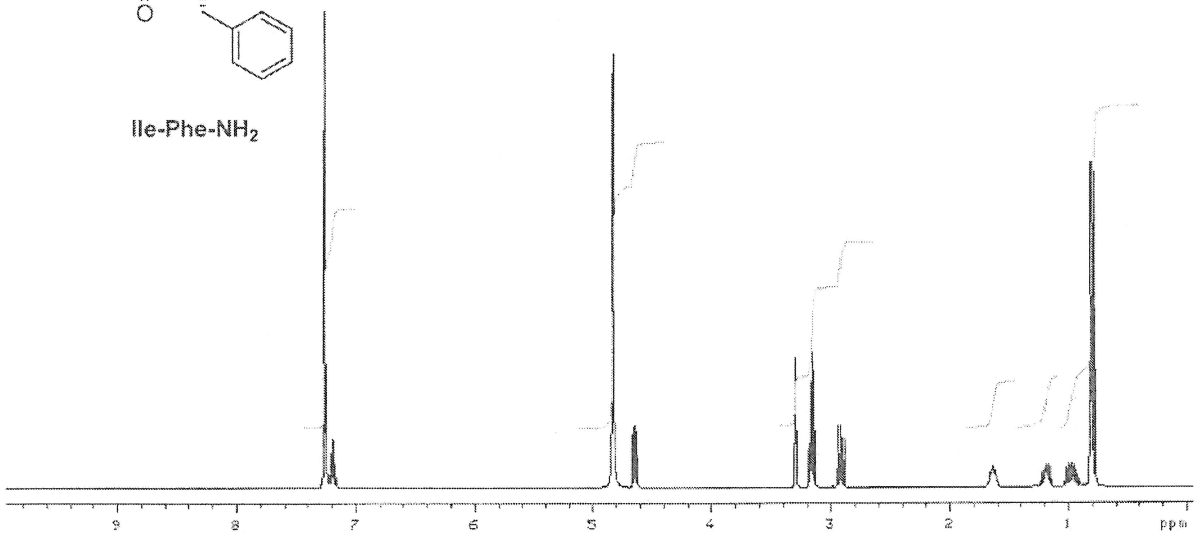
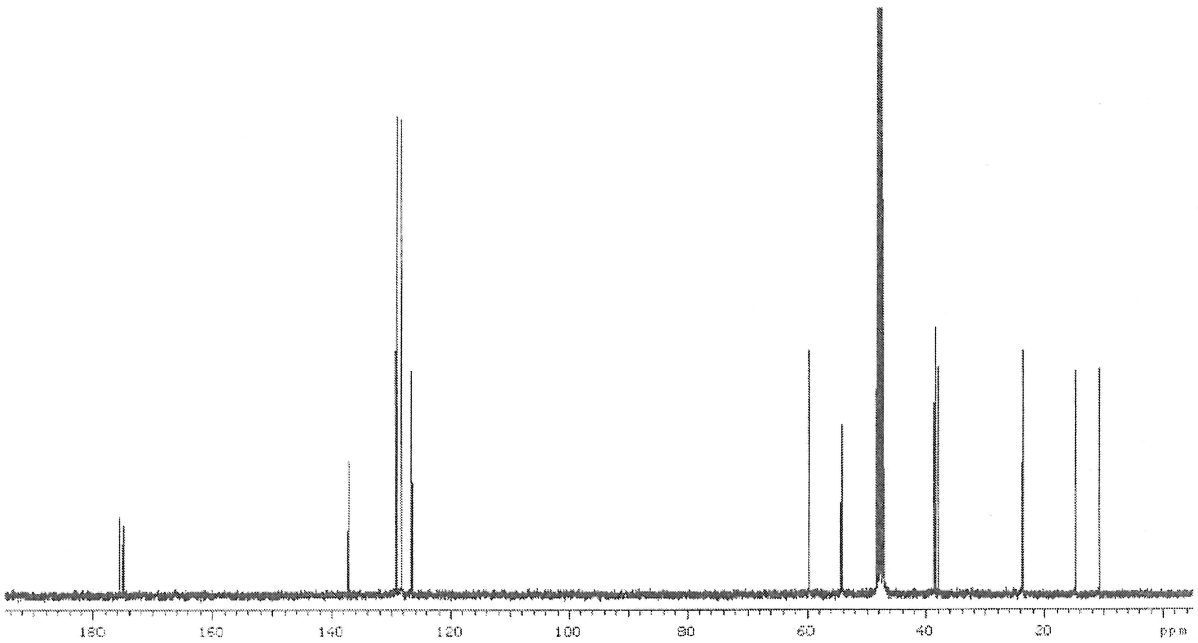
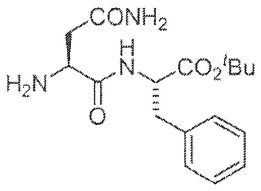


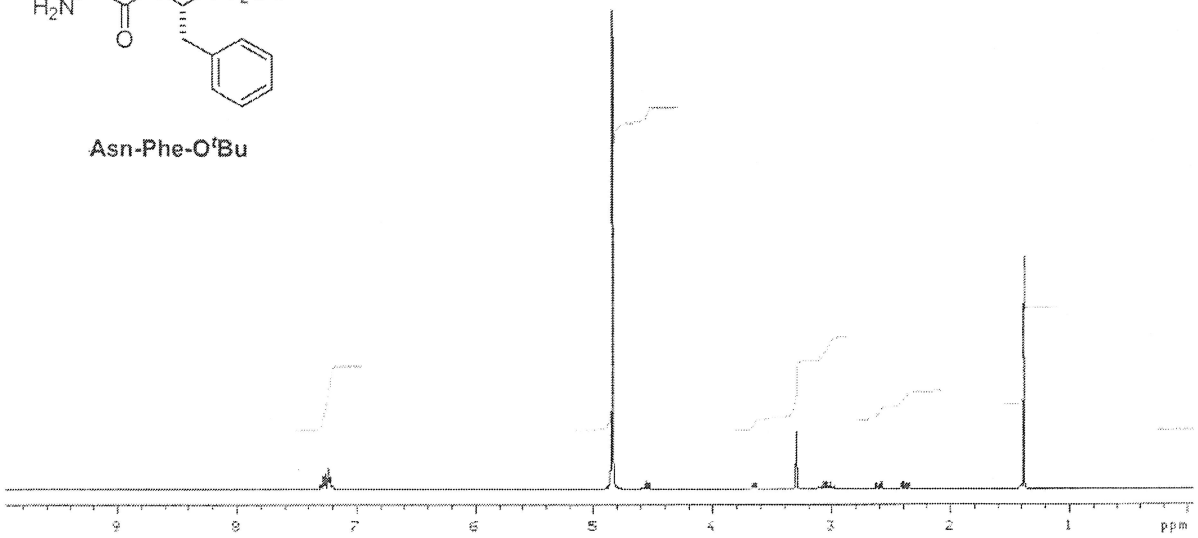
Ile-Phe-NH_2

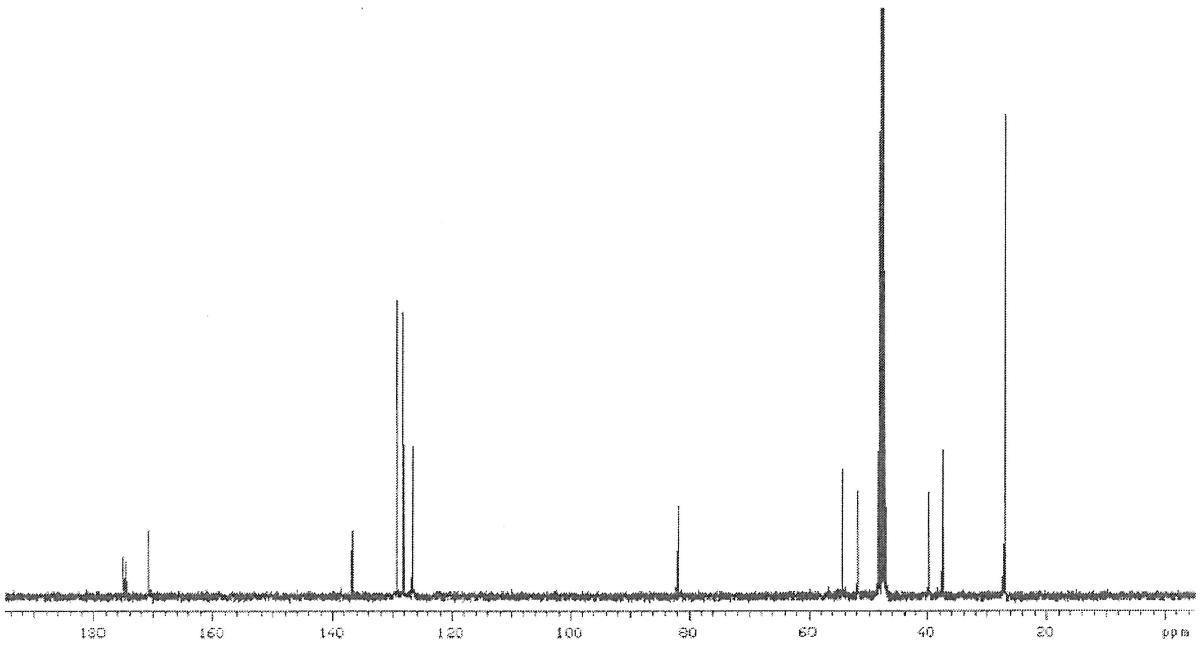


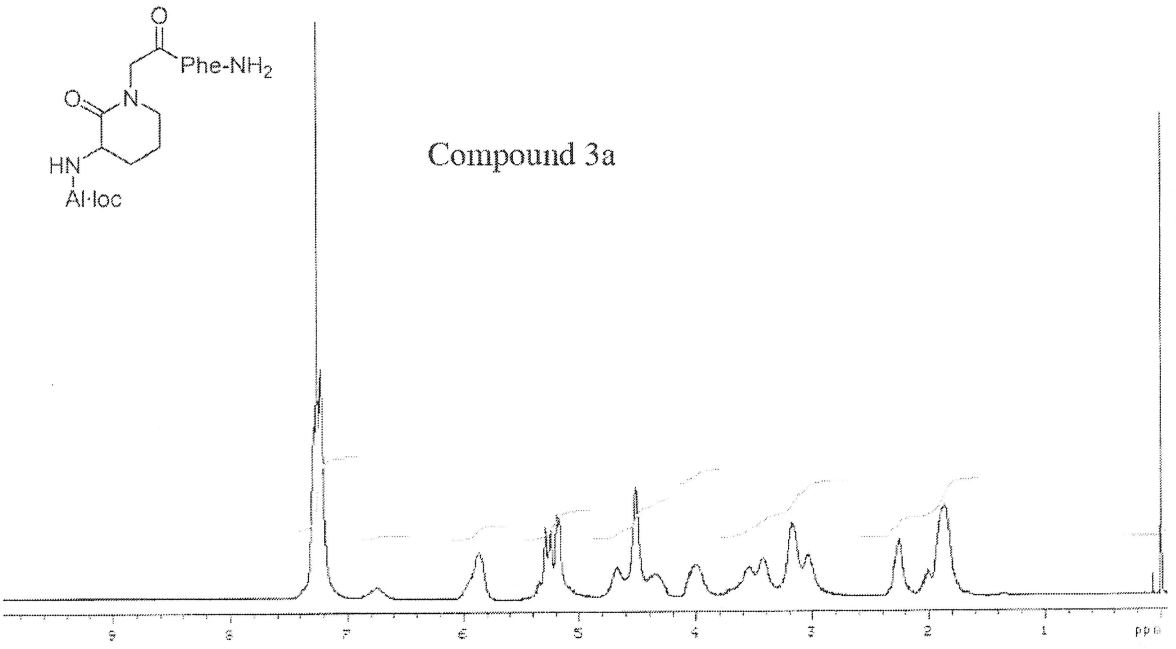


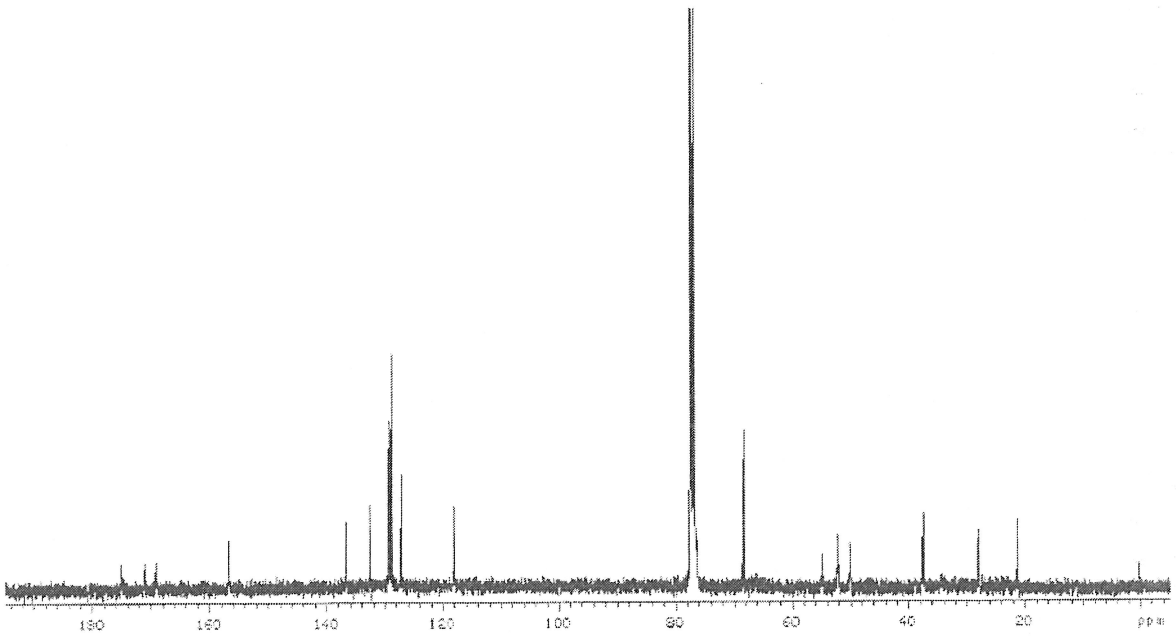


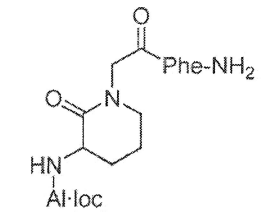
Asn-Phe-O^{t}Bu



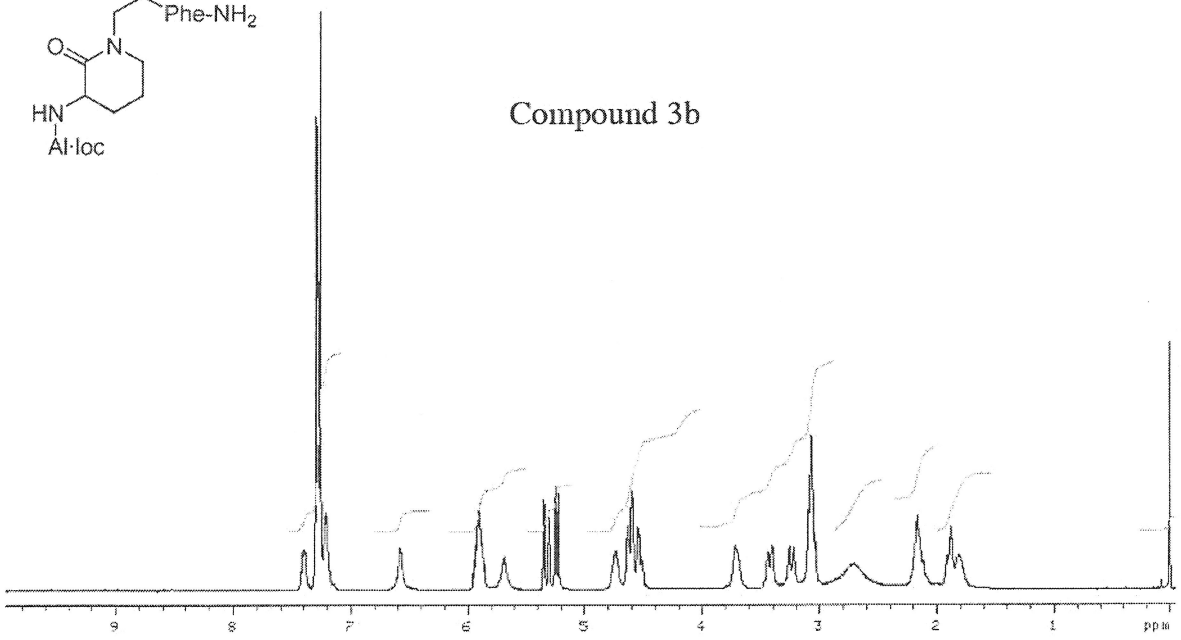


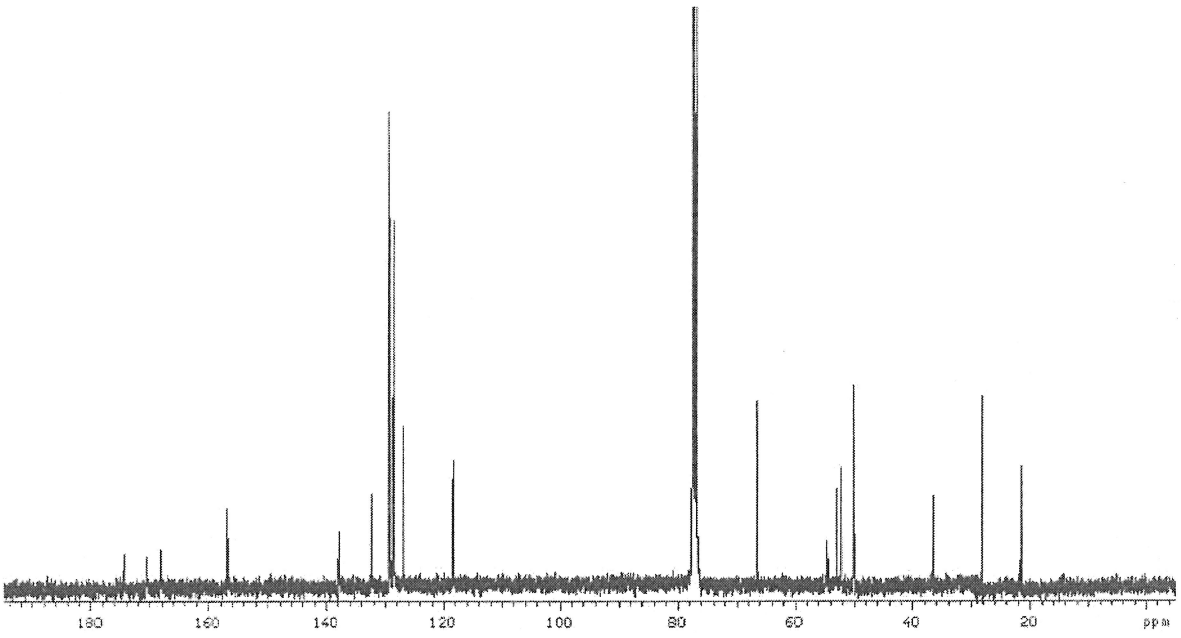


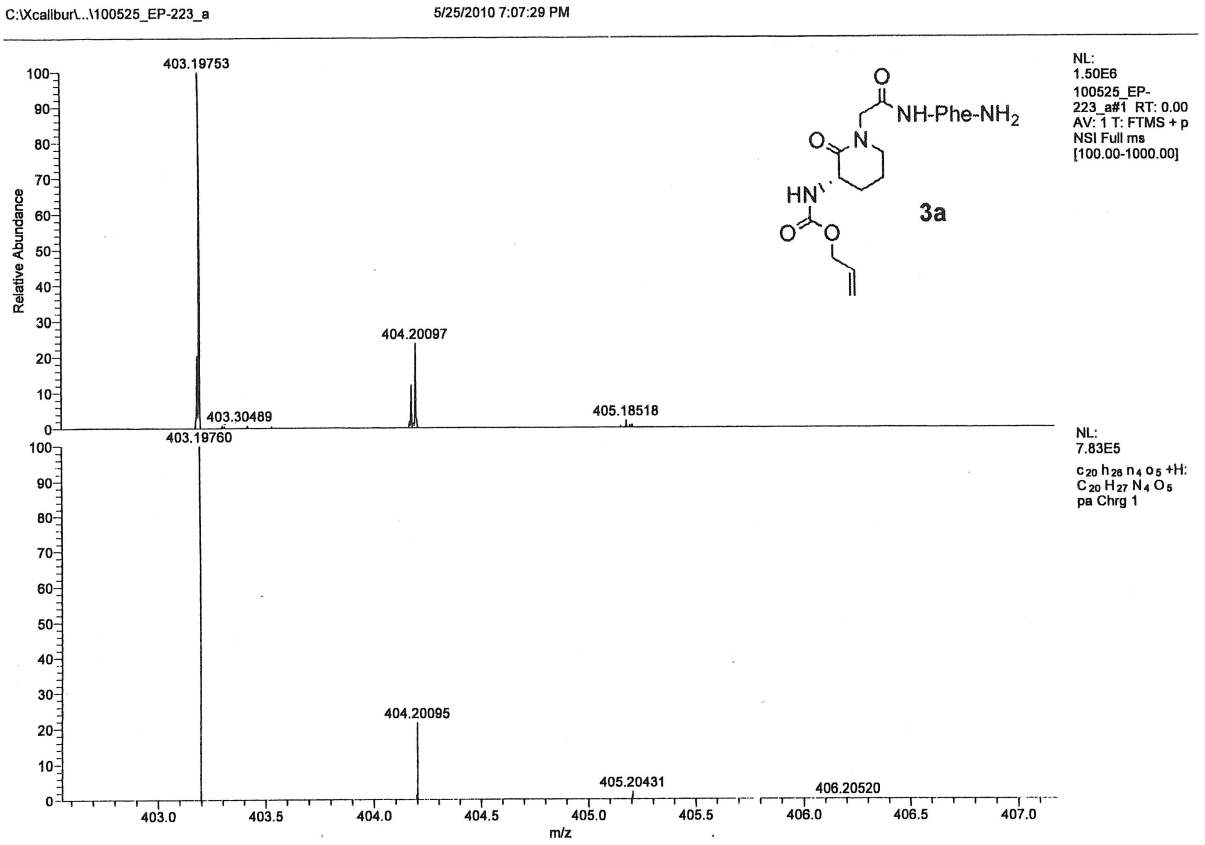


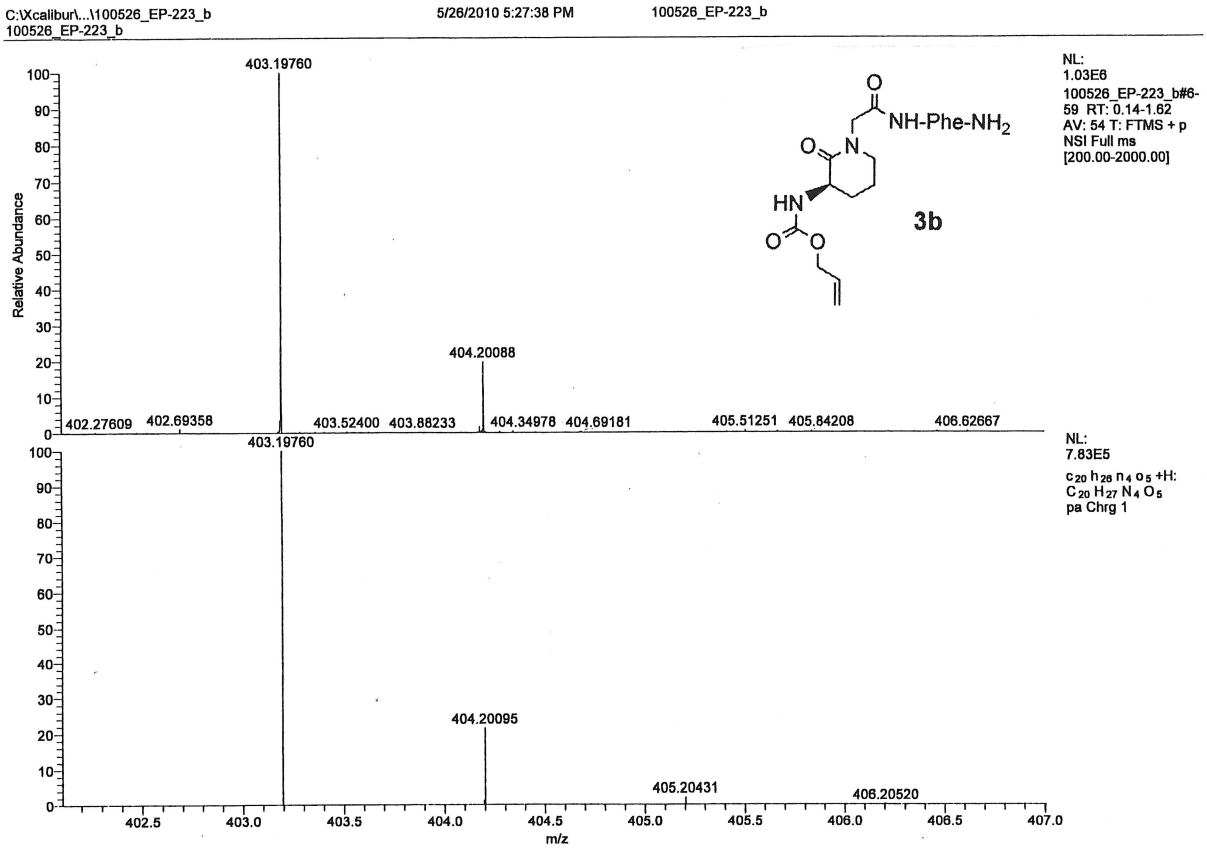


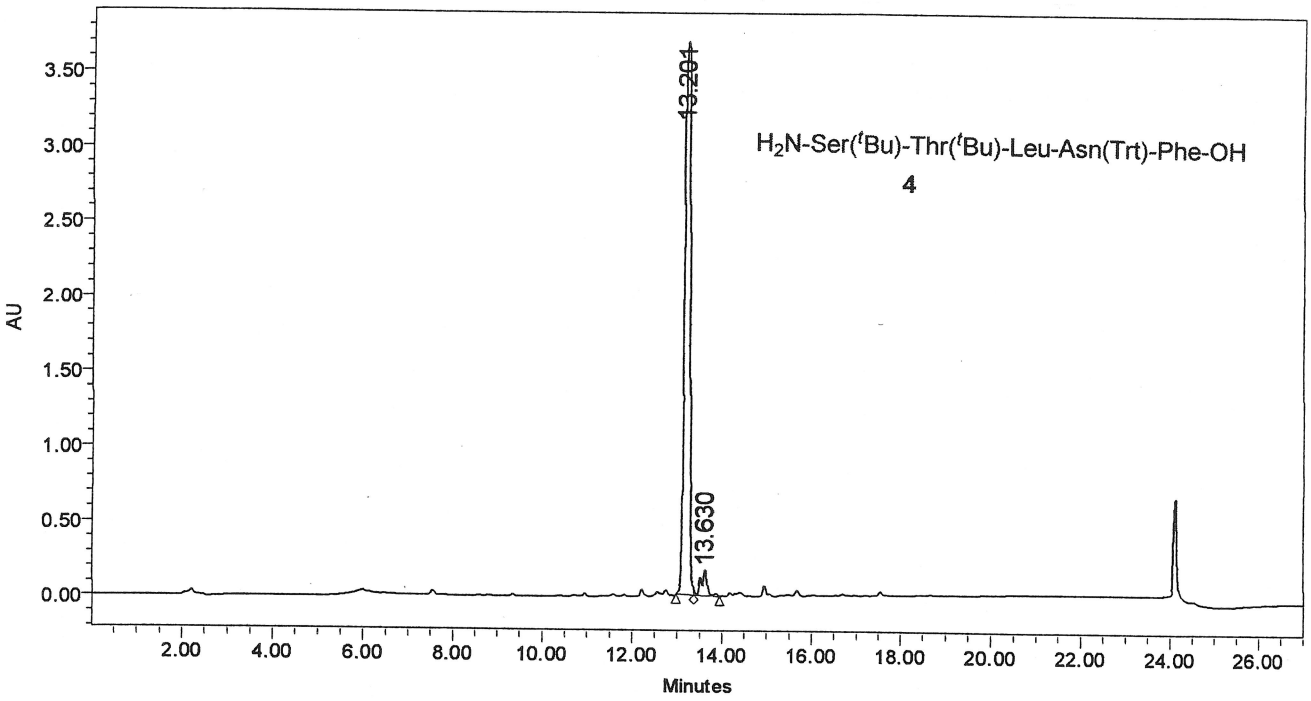
Compound 3b











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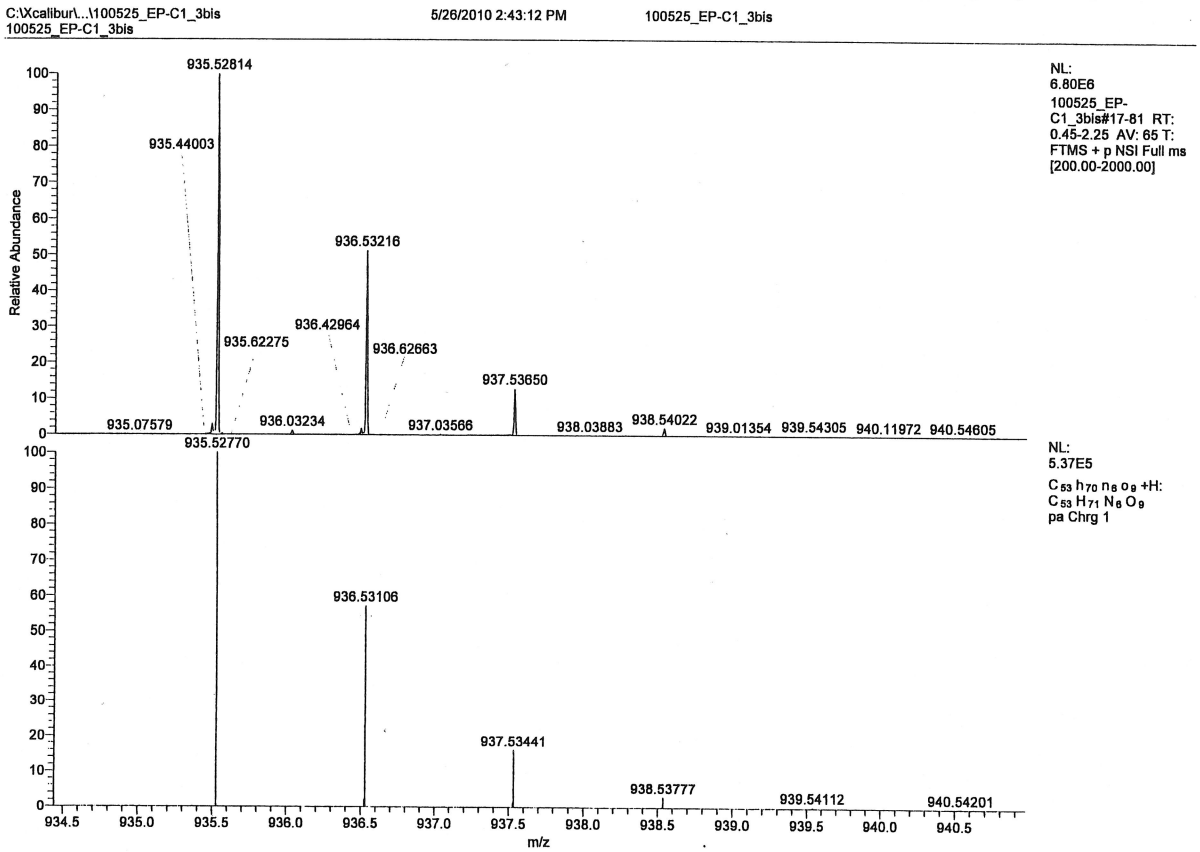

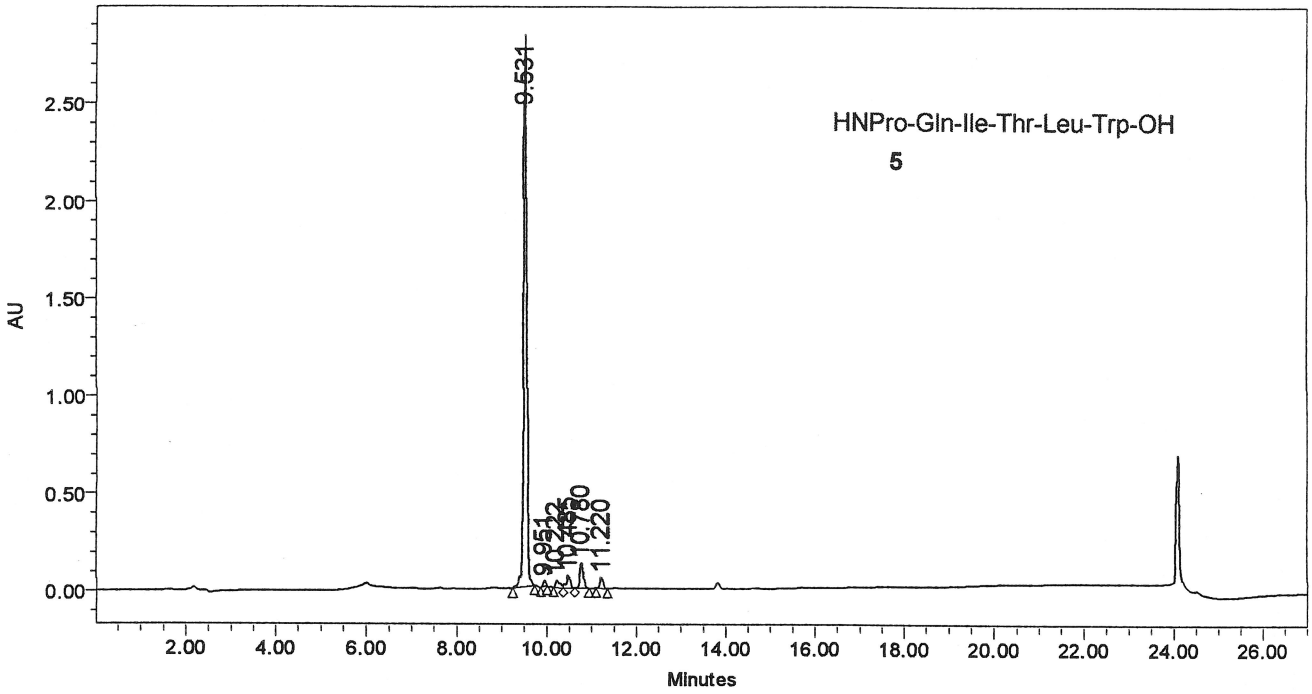

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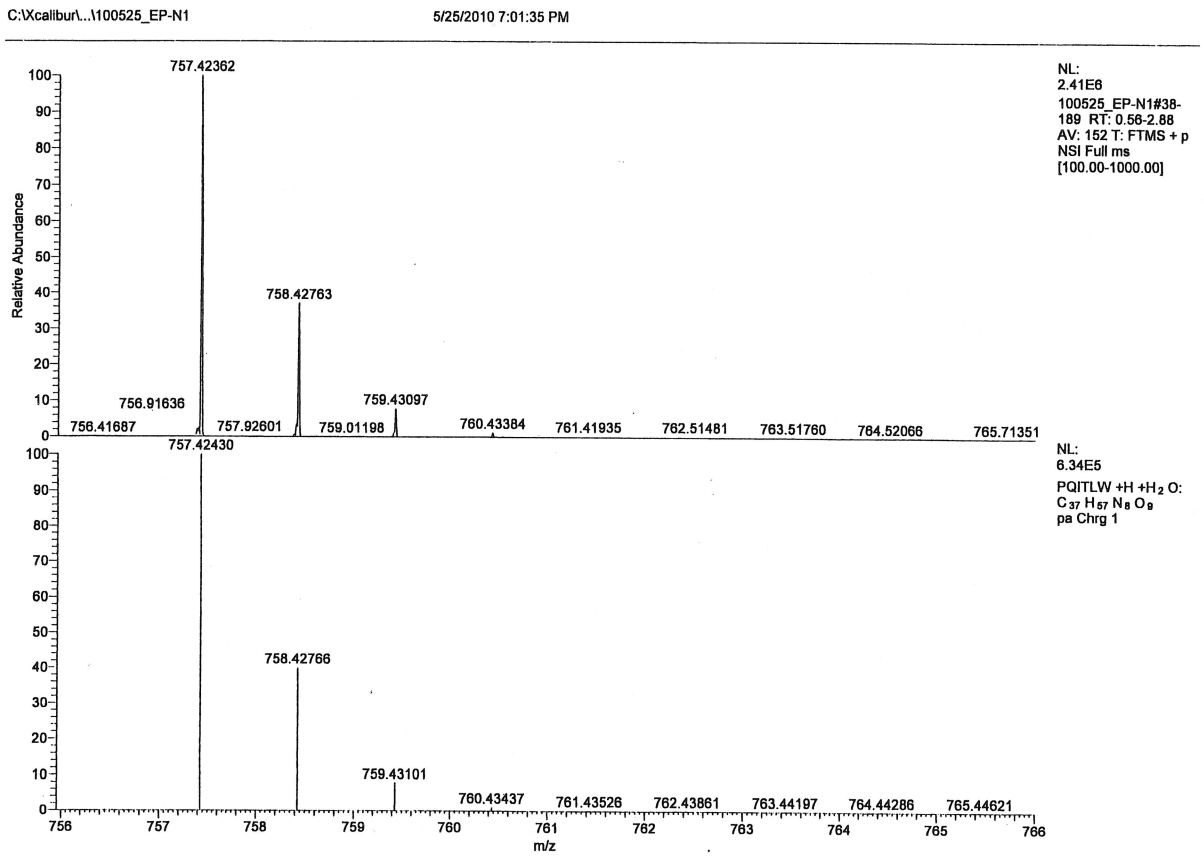
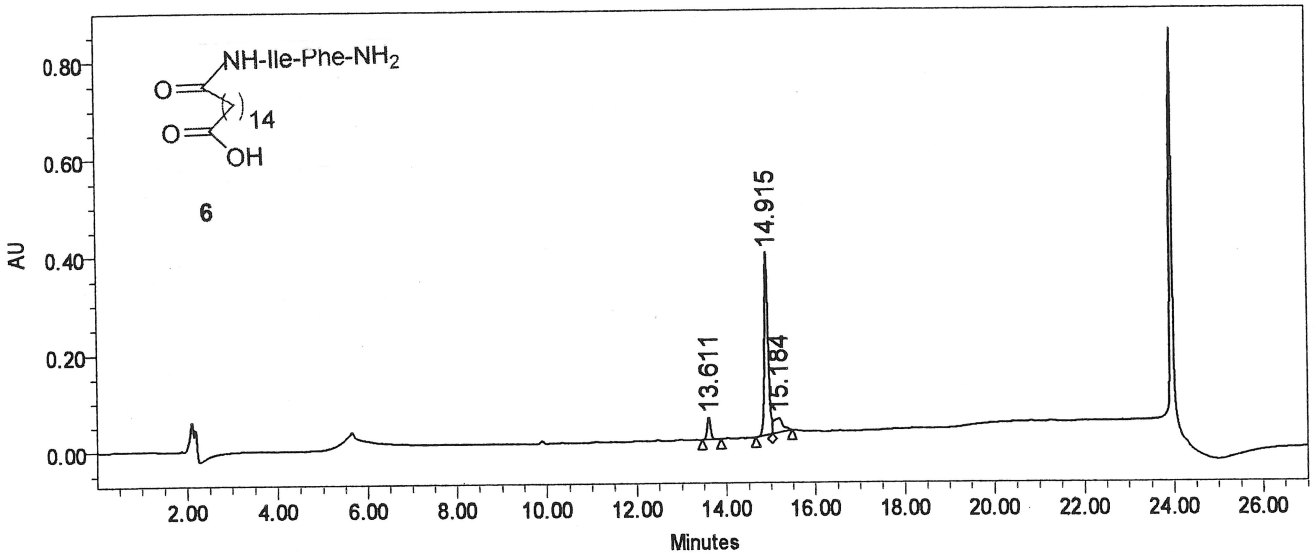
1	9.531	14155639	88.94	2853021	89.97
2	9.951	122610	0.77	28280	0.89
3	10.222	269670	1.69	37675	1.19
4	10.485	371147	2.33	64155	2.02
5	10.780	715466	4.50	129831	4.09
6	11.220	281291	1.77	58158	1.83





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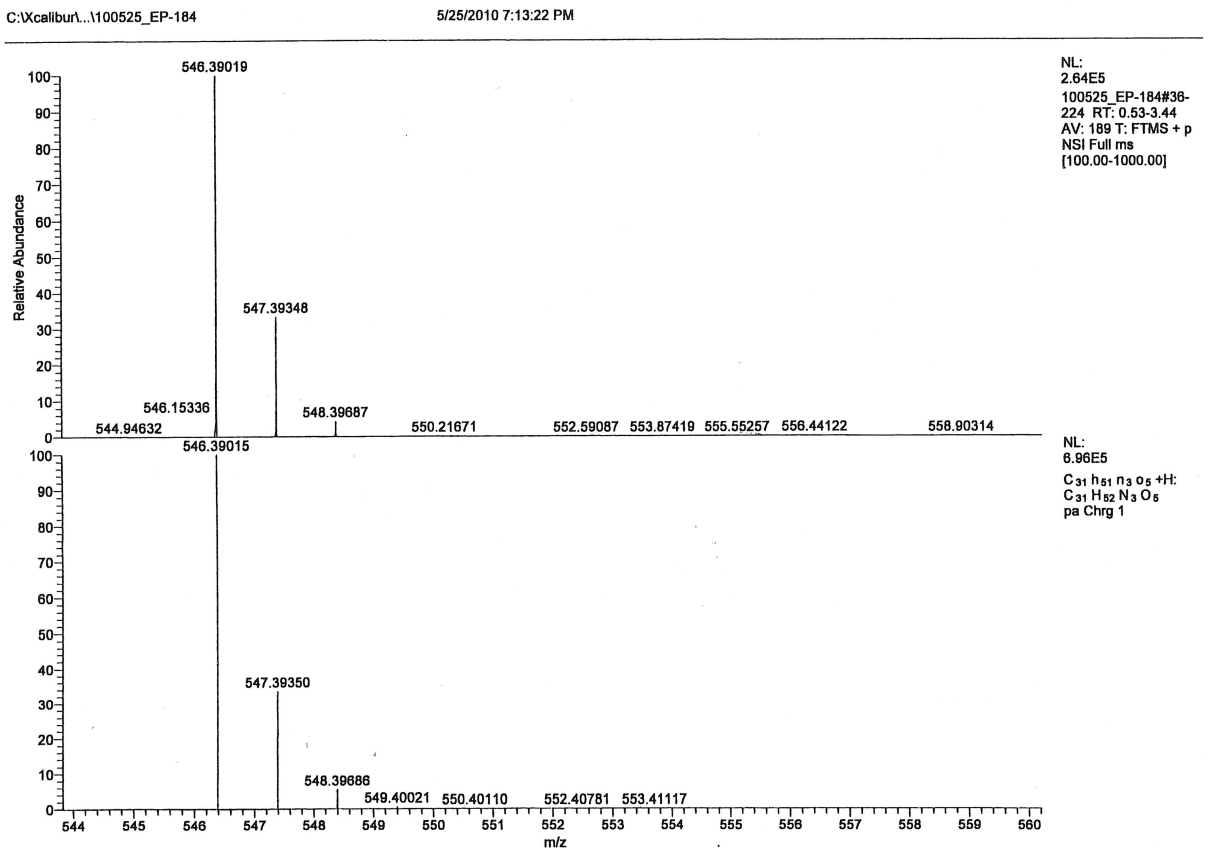
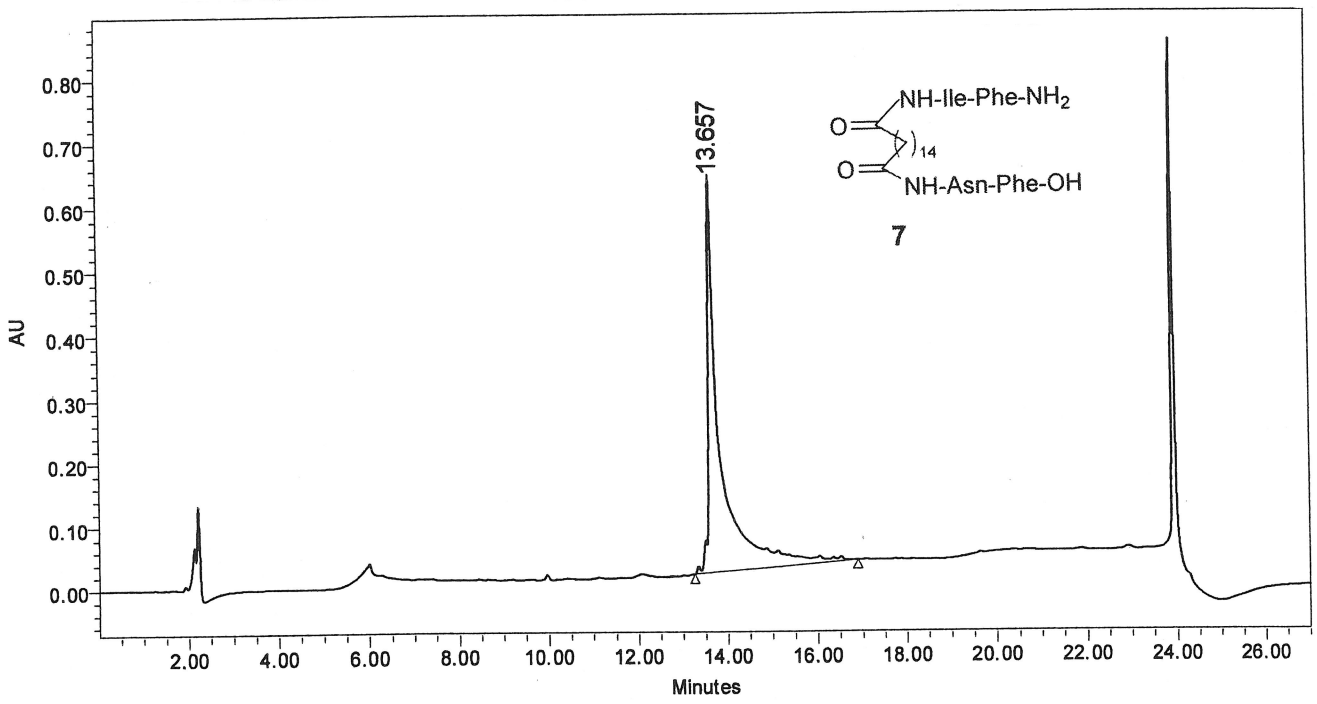
2	14.915	2162121	75.61	371125
3	15.184	448356	15.68	30124





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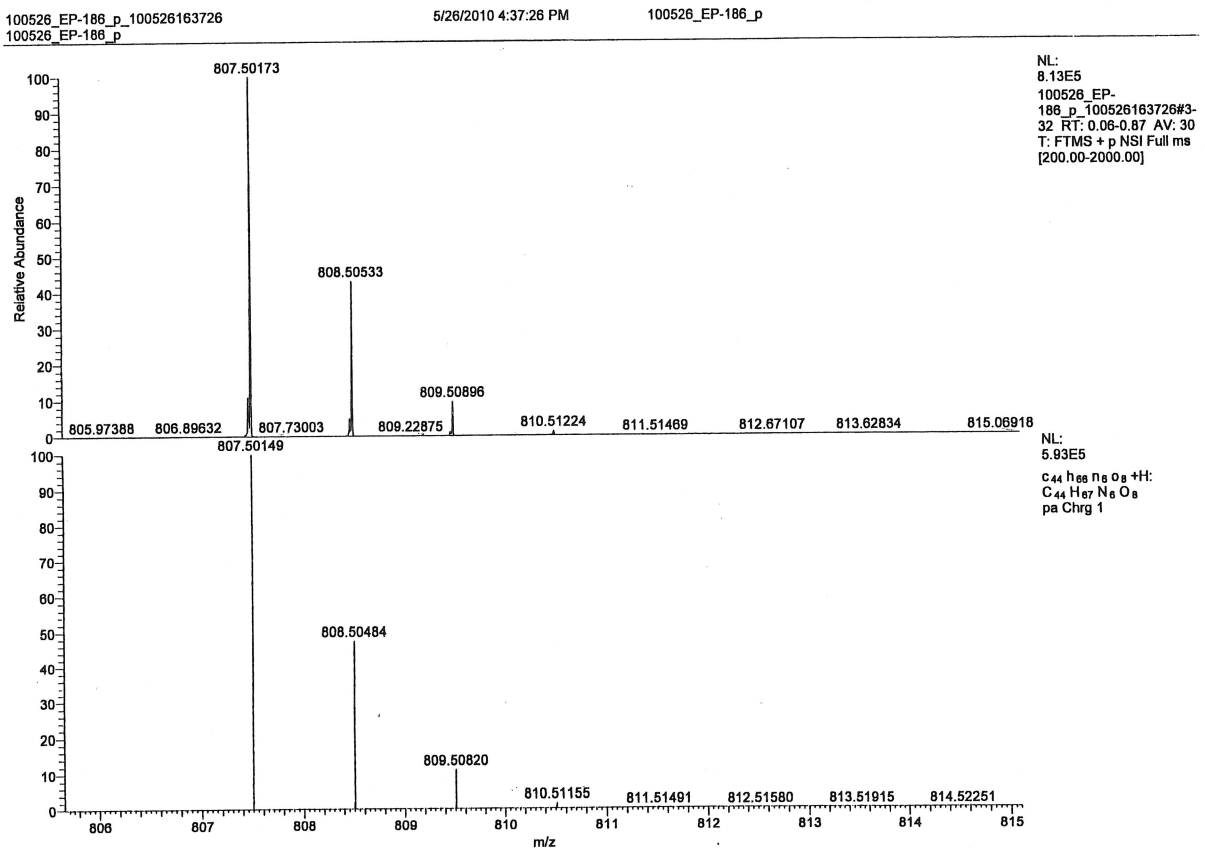

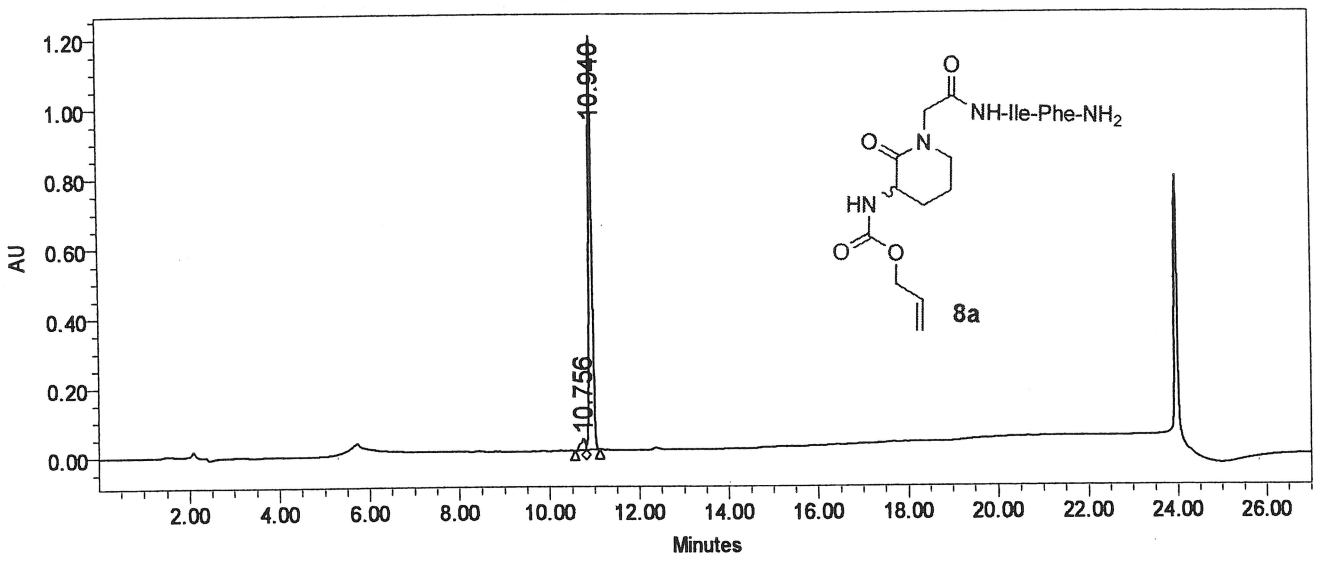

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1	10.756	245752	3.97	32751
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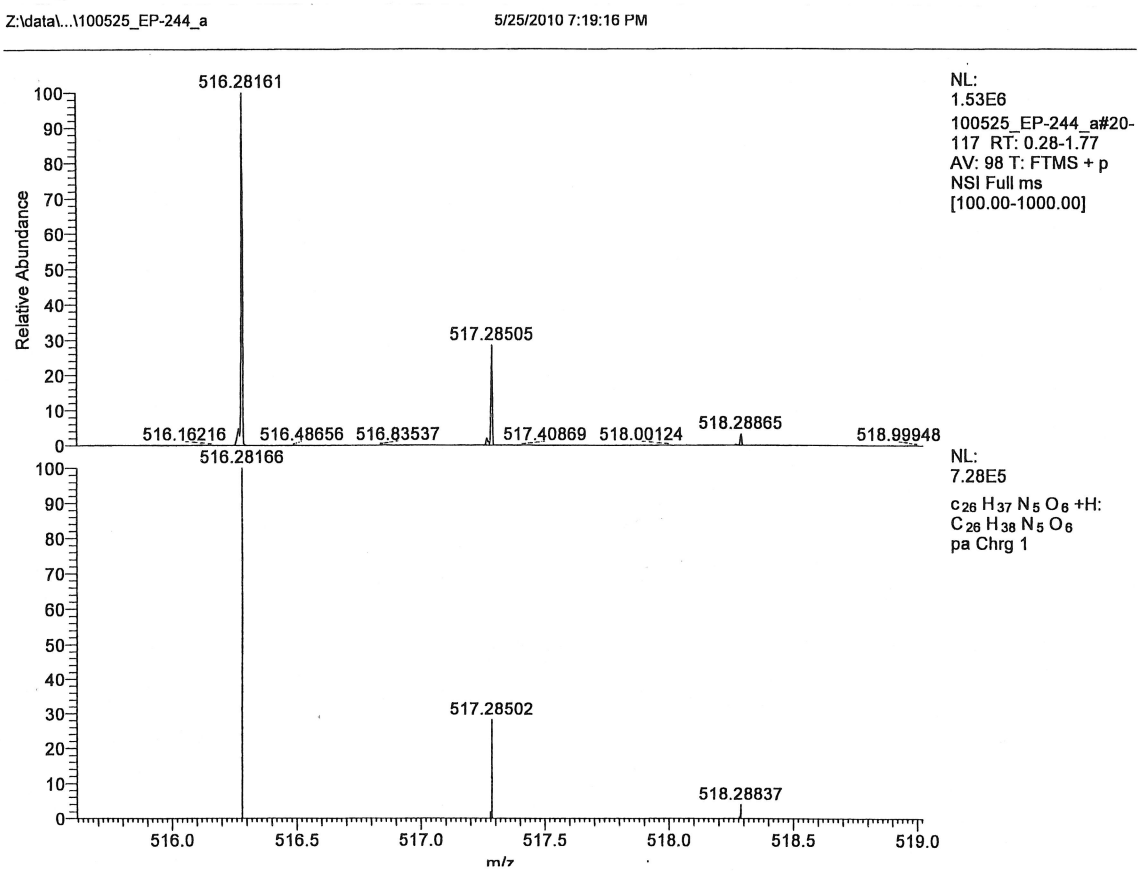

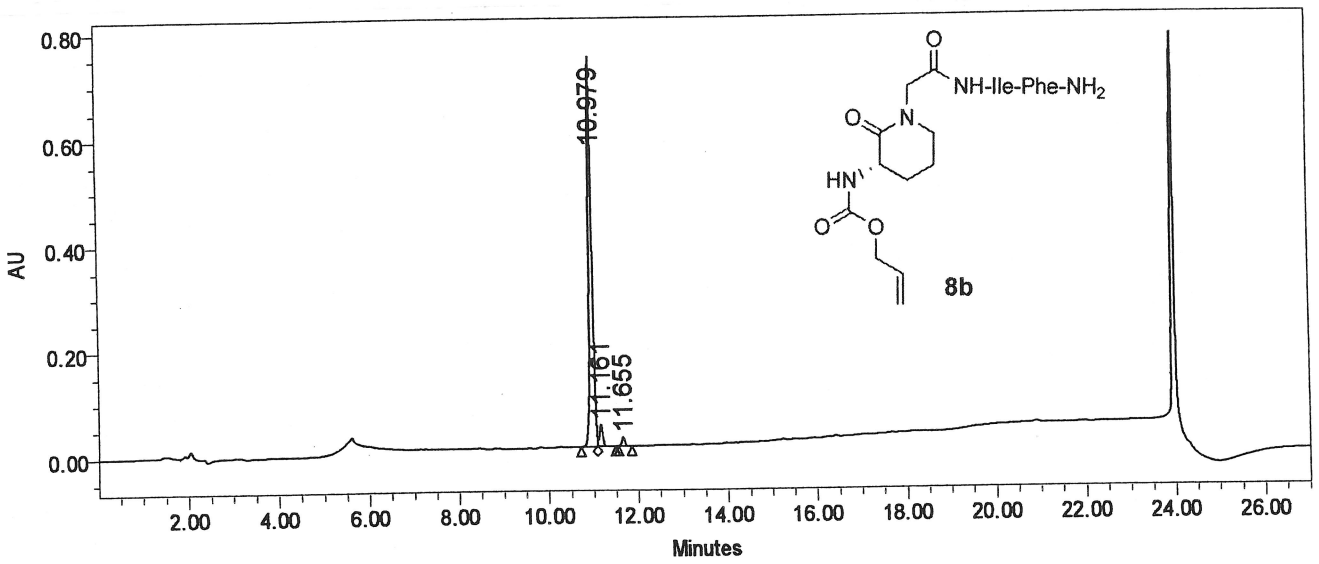

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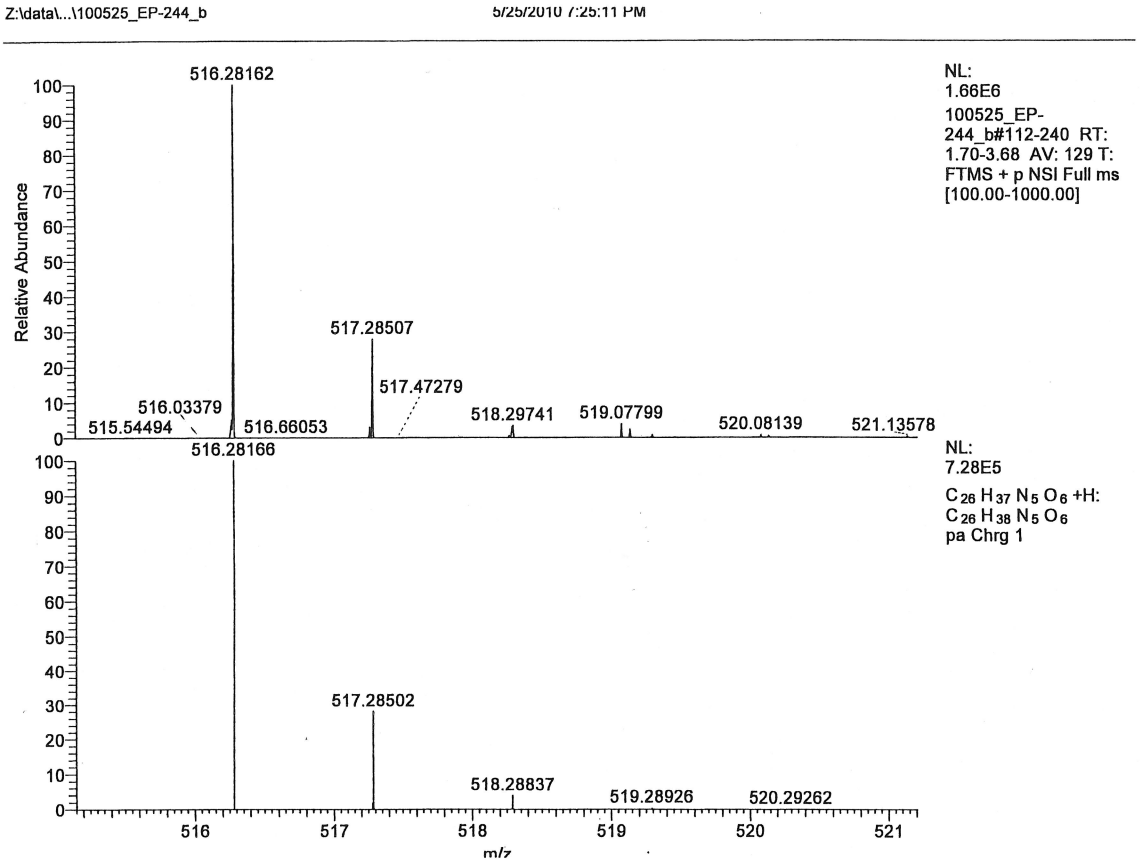
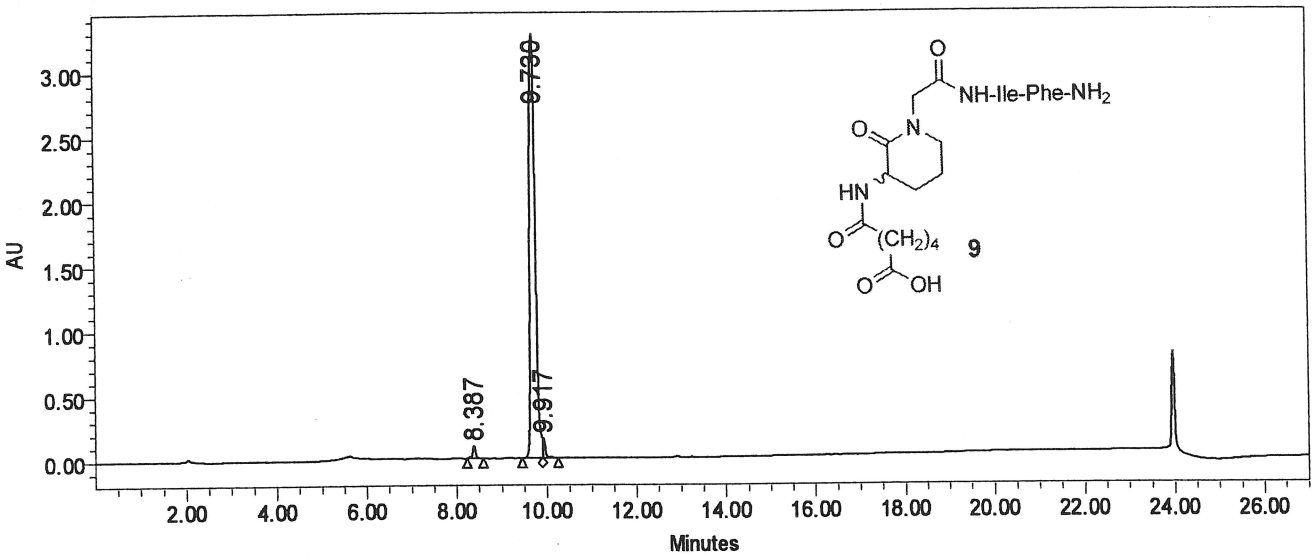
1	10.979	3815145	92.81	730575
2	11.161	217374	5.29	41231
3	11.655	78286	1.90	16480





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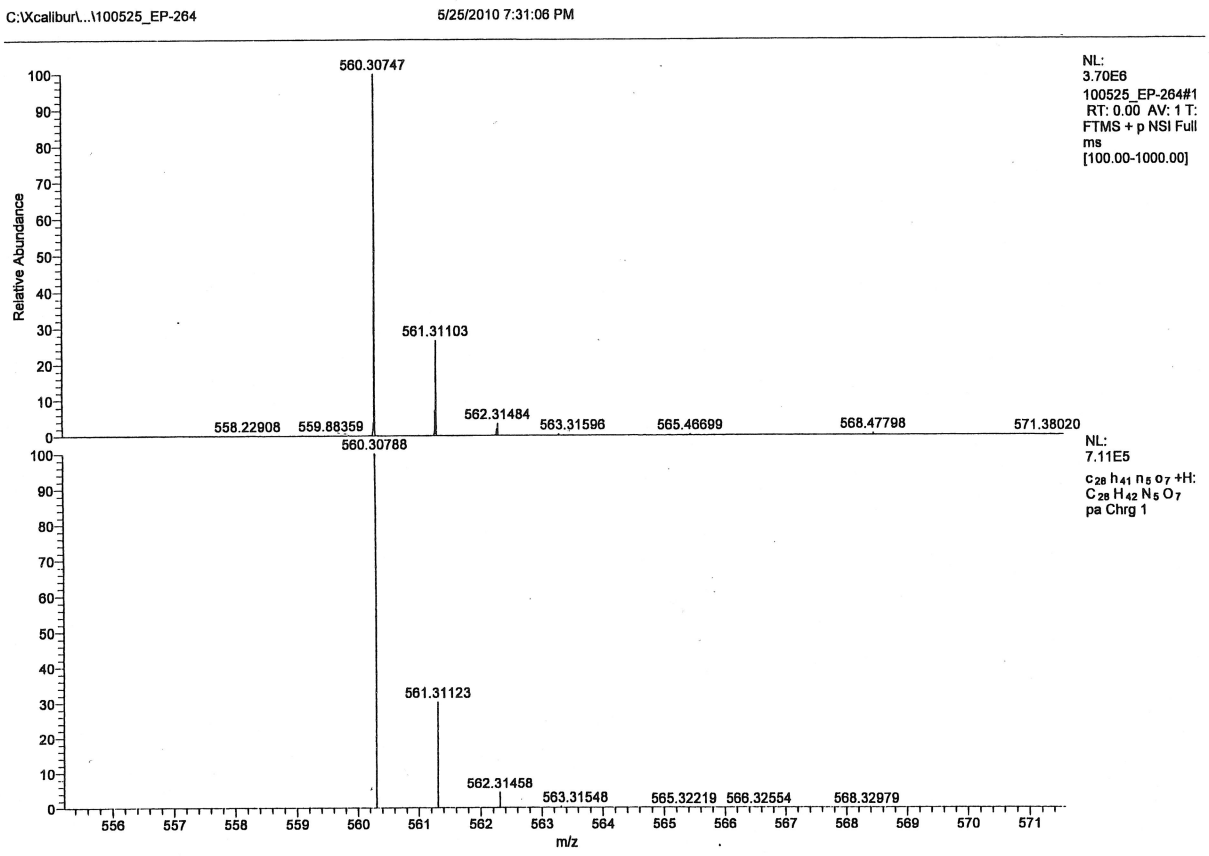
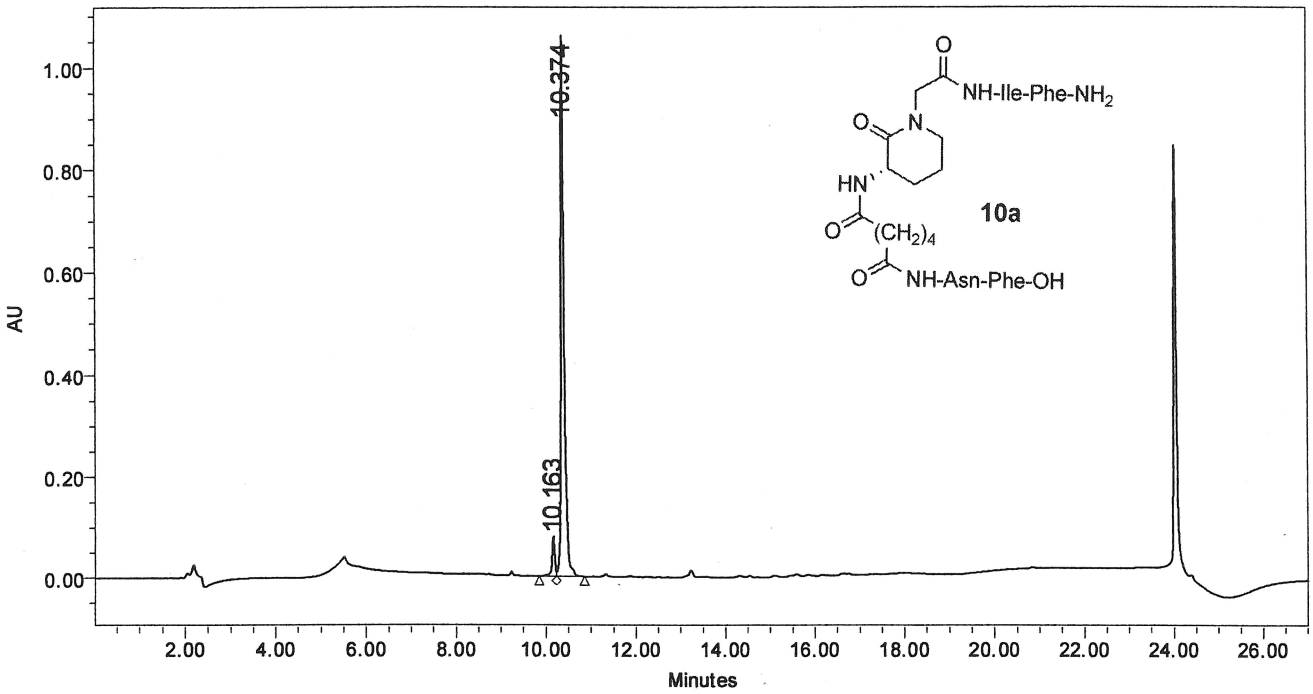
1	8.387	444367	1.54	94518
2	9.730	27827580	96.24	3284641
3	9.917	642270	2.22	154872





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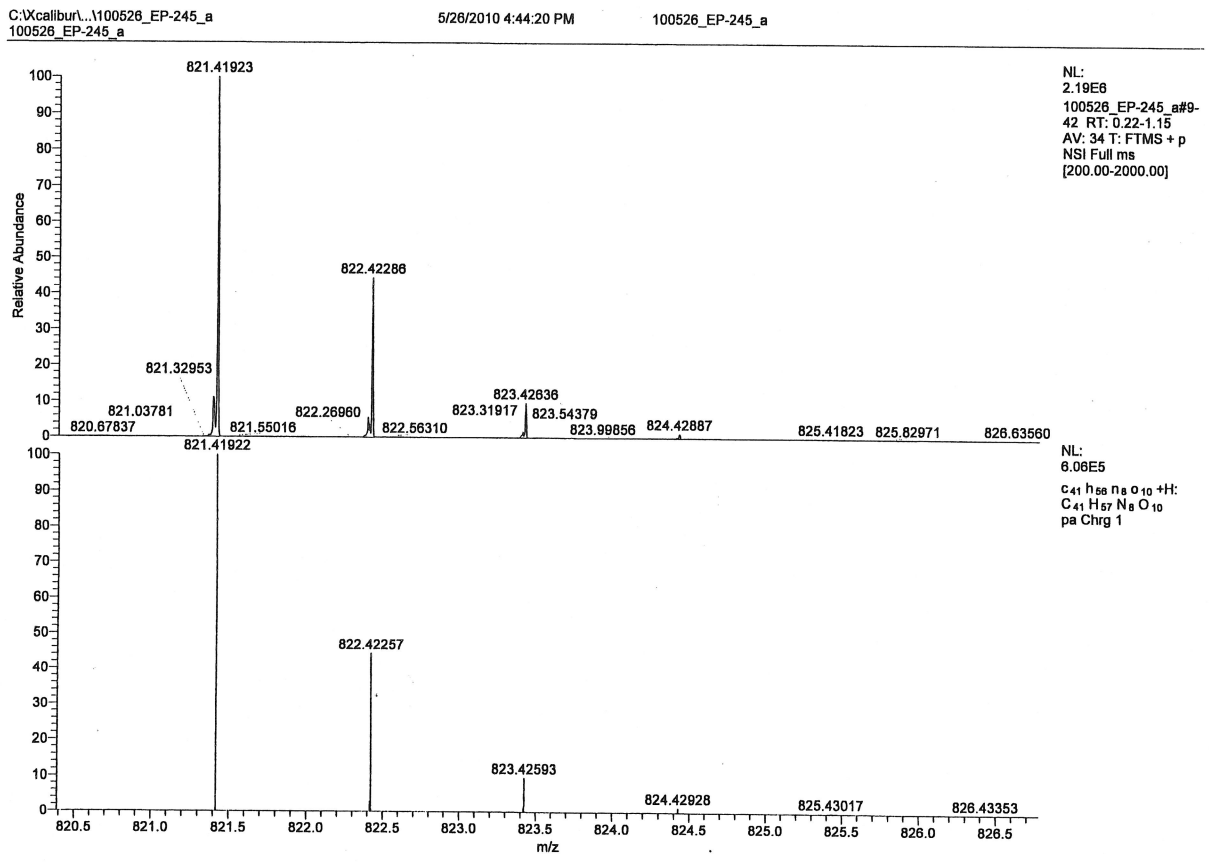
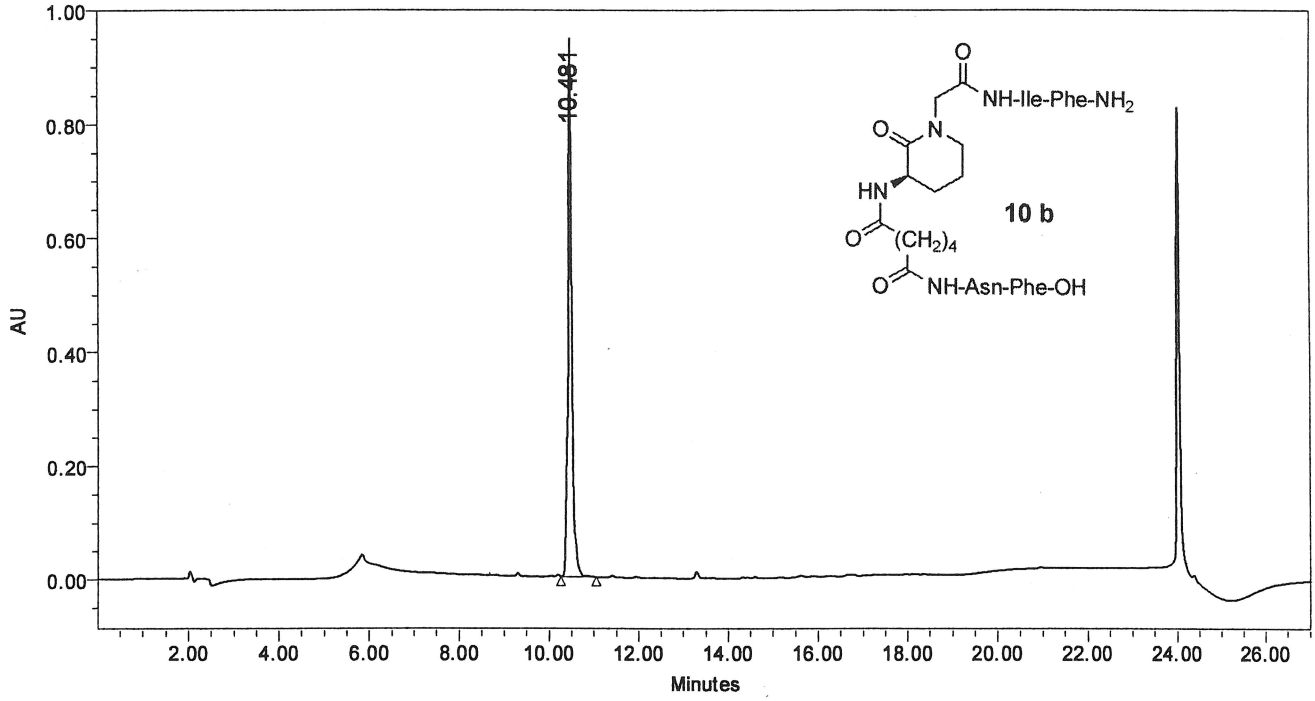
1	10.163	335501	5.79	77014	6.81
2	10.374	5455413	94.21	1054629	93.19





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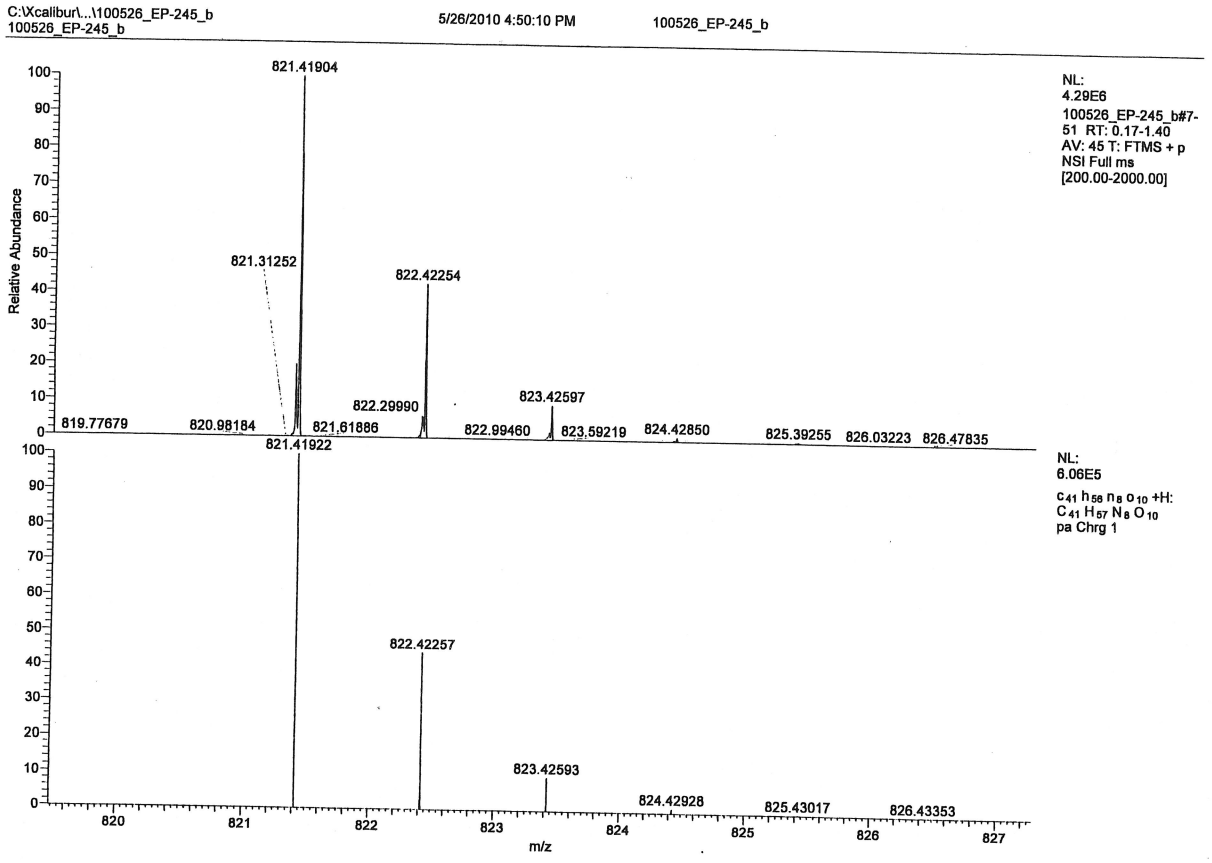
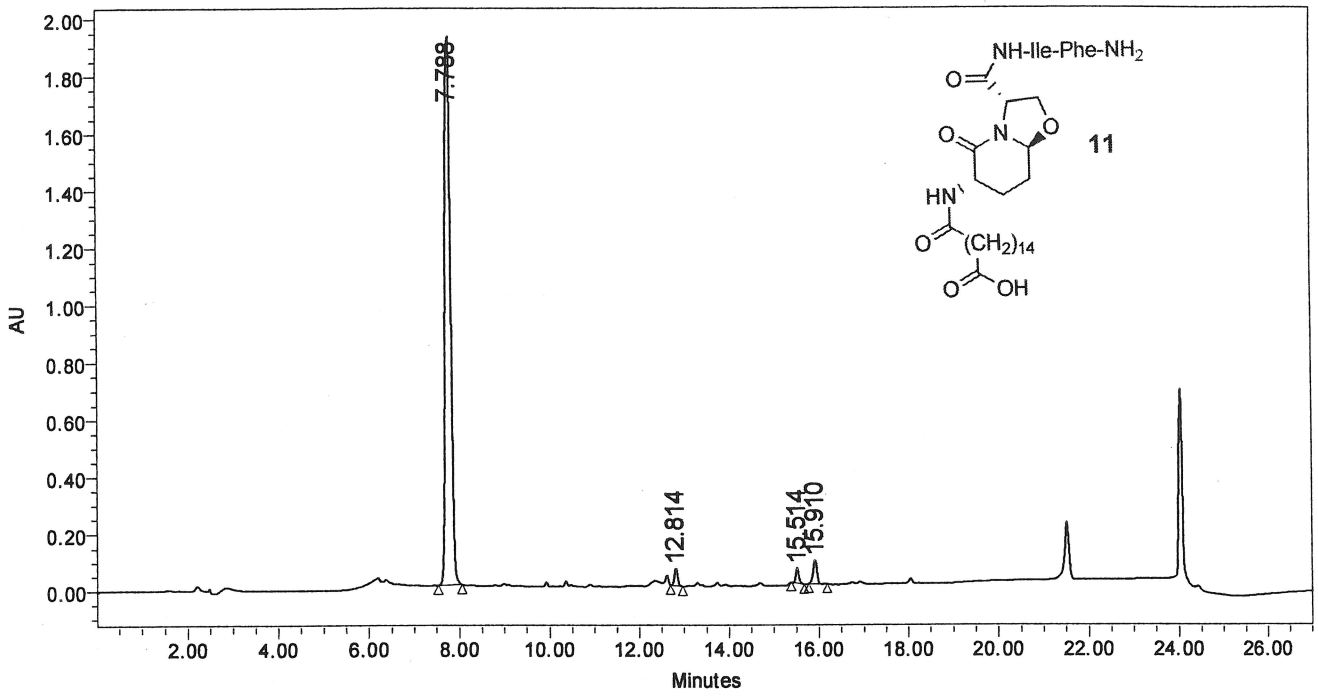
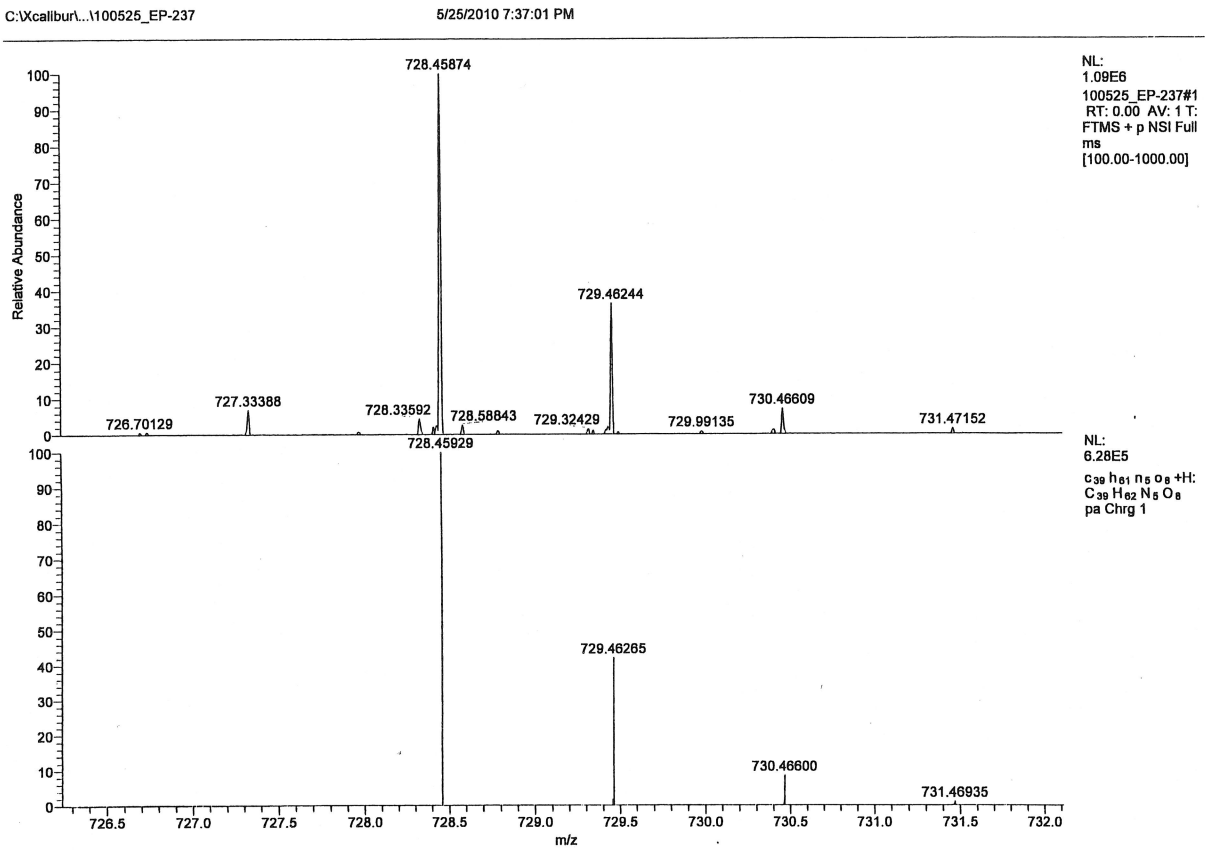
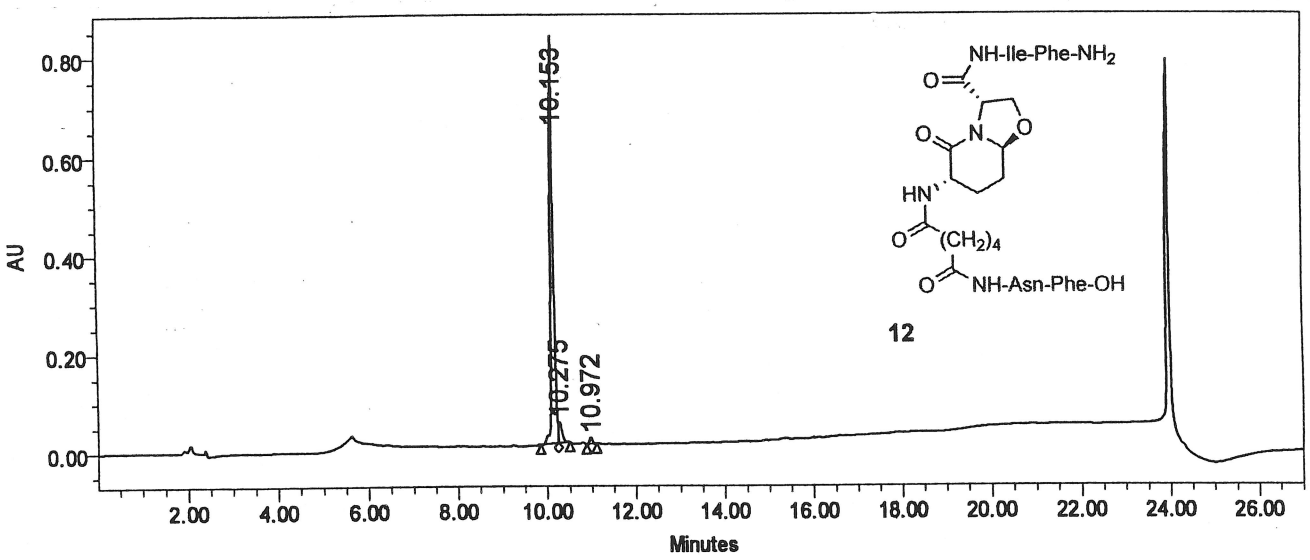




	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.788	16854006	94.17	1951498	90.88
2	12.814	299113	1.67	59479	2.77
3	15.514	246263	1.38	52268	2.43
4	15.910	497880	2.78	84106	3.92





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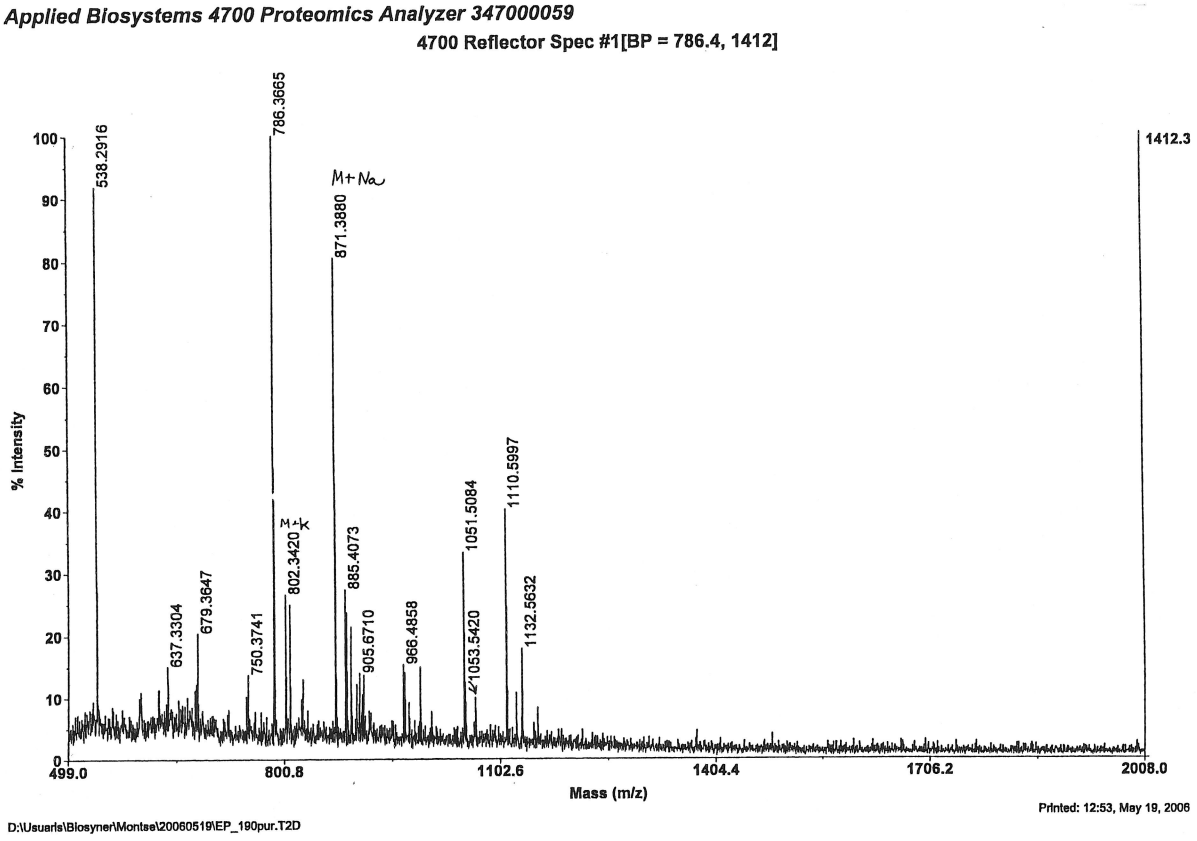
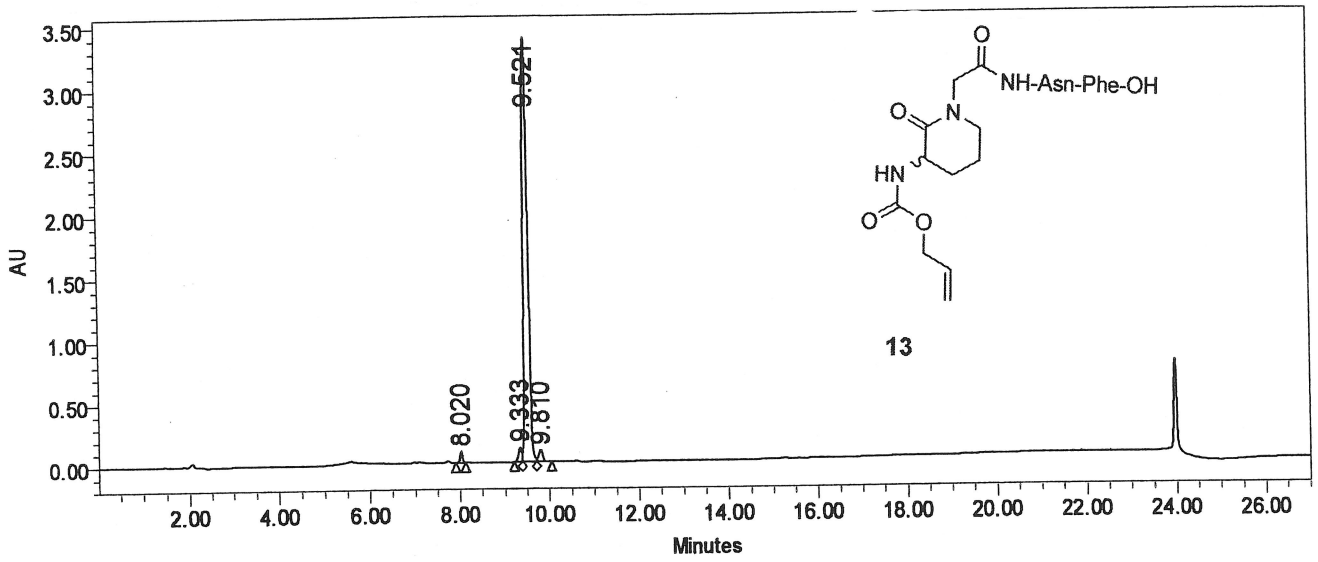
1	10.153	3791289	93.14	810276
2	10.275	218889	5.38	41451
3	10.972	60264	1.48	12799





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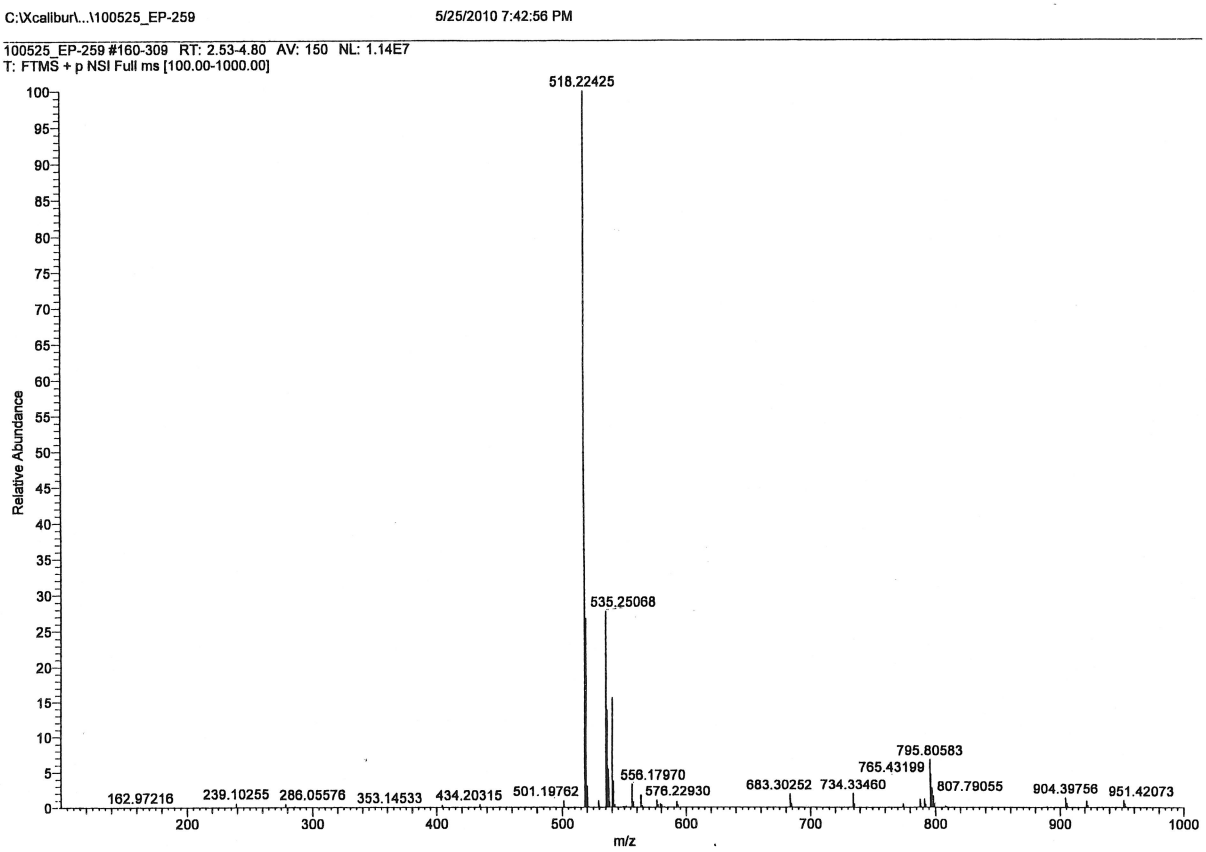
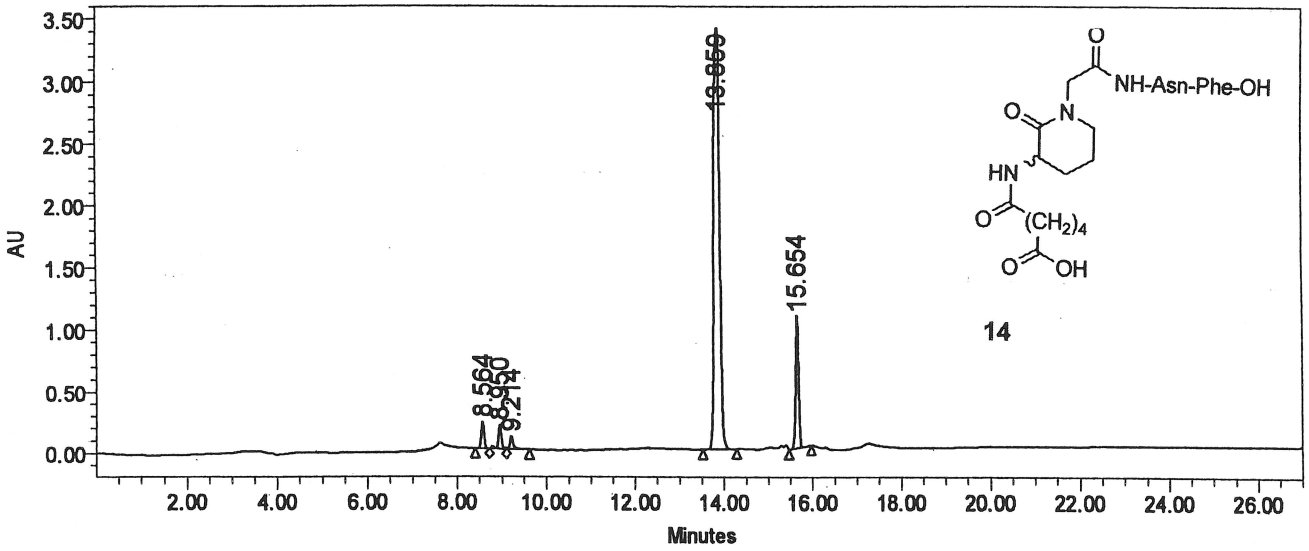
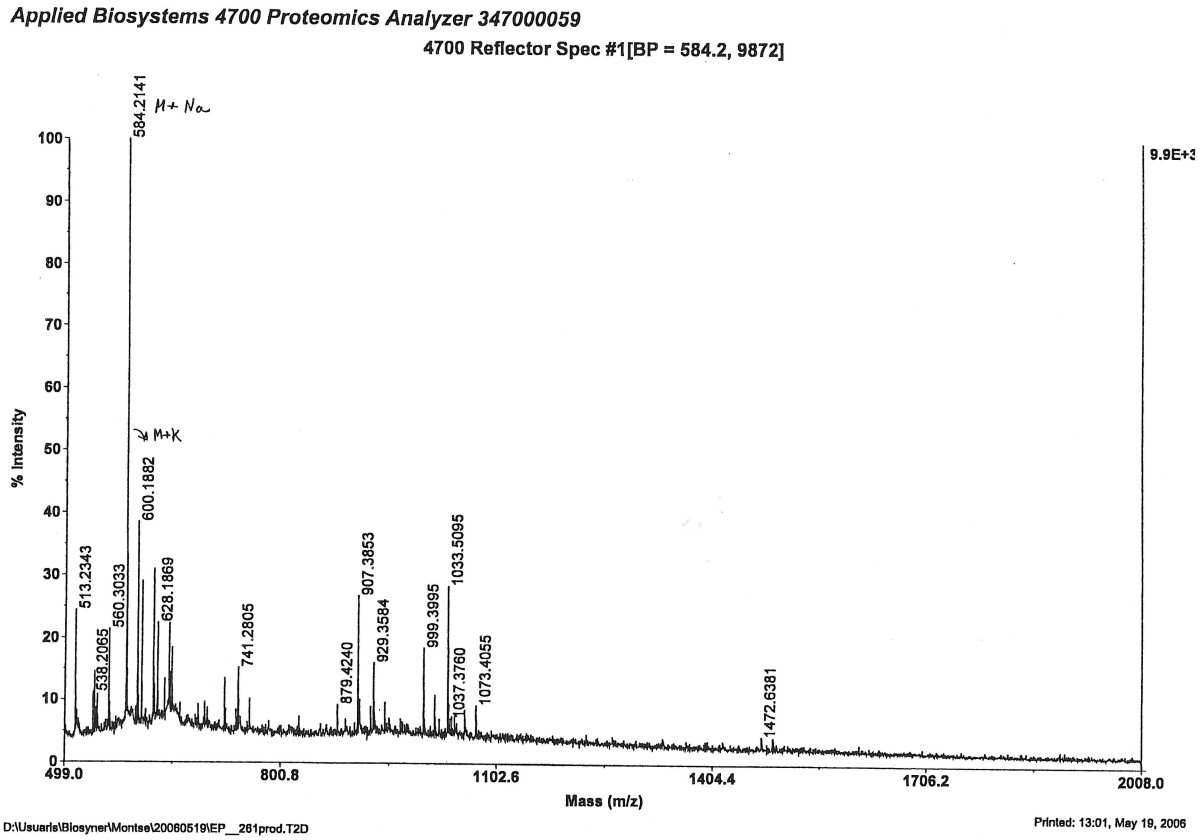
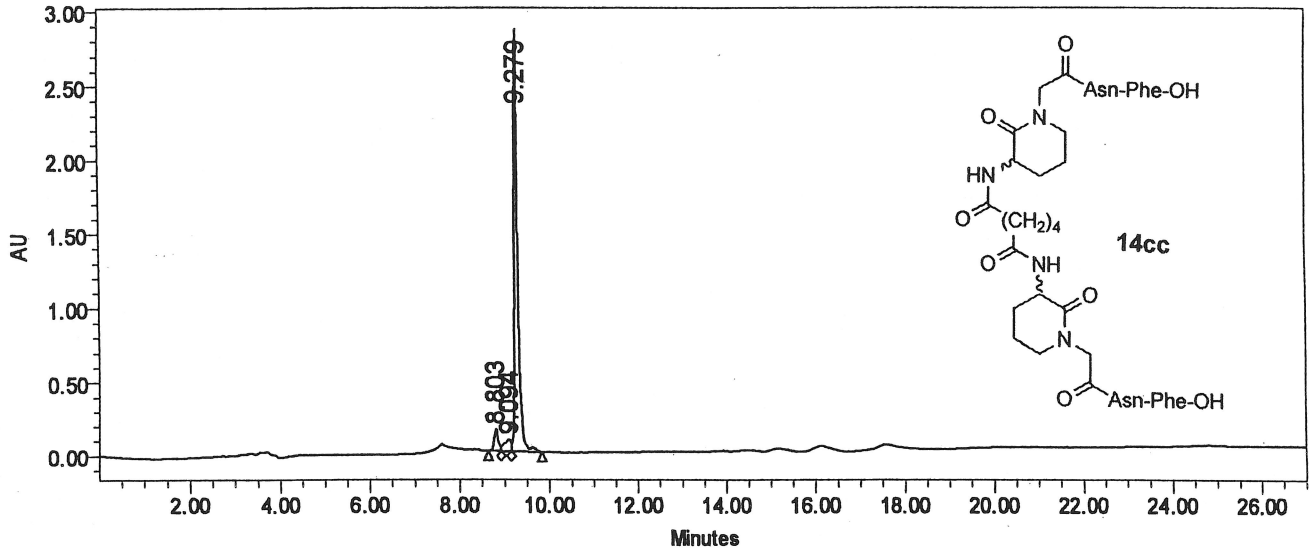
1	8.020	344923	1.28	86578
2	9.333	580780	2.16	112660
3	9.521	25350726	94.38	3396601
4	9.810	583583	2.17	95411



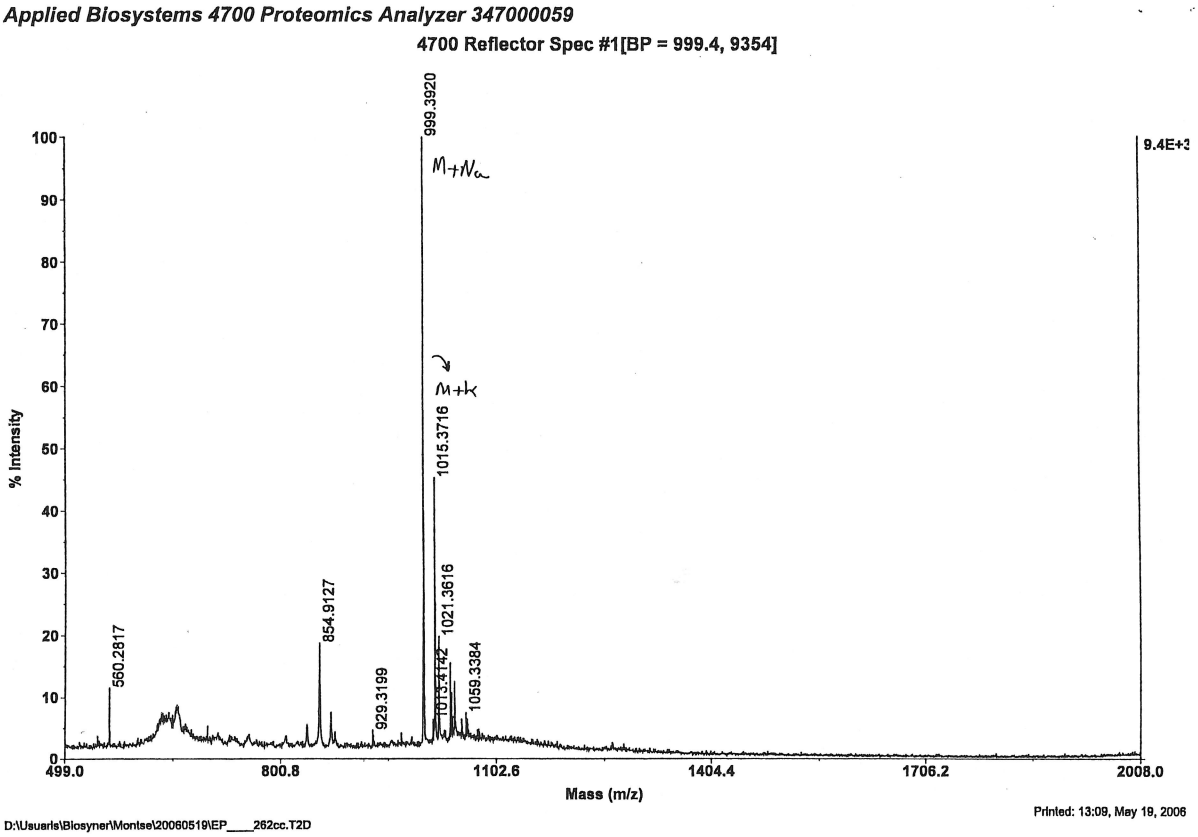


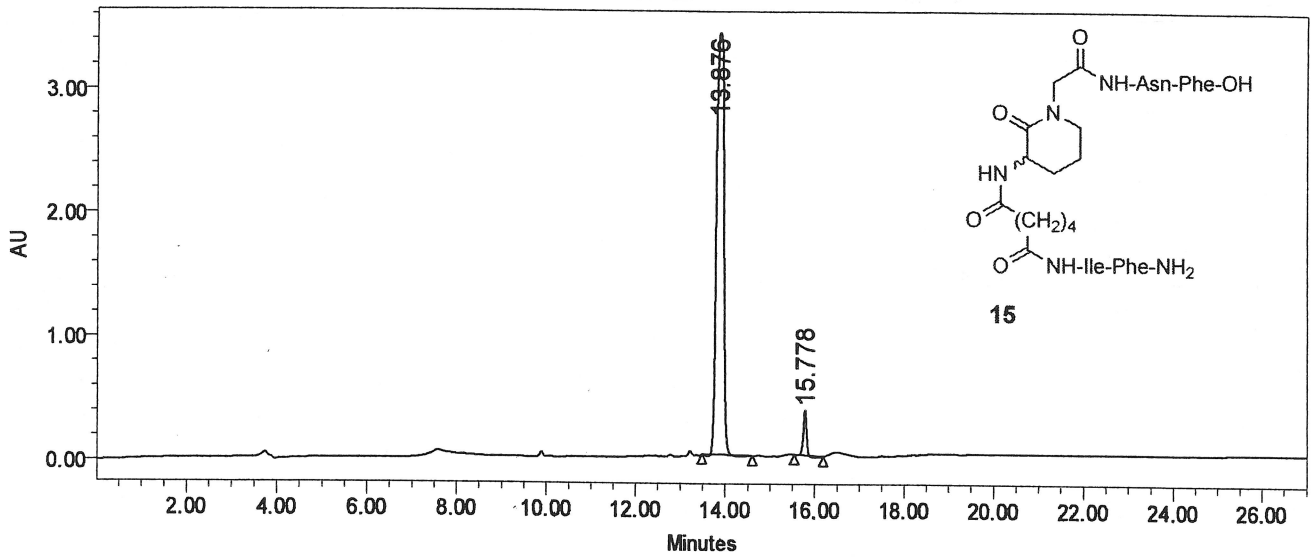
	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	8.564	940600	2.42	213587
2	8.950	938482	2.42	186957
3	9.214	533721	1.37	101471
4	13.859	31460676	81.00	3410503
5	15.654	4967638	12.79	1063396





	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	8.803	928054	5.29	146927
2	9.094	813905	4.64	81326
3	9.279	15806622	90.07	2850049





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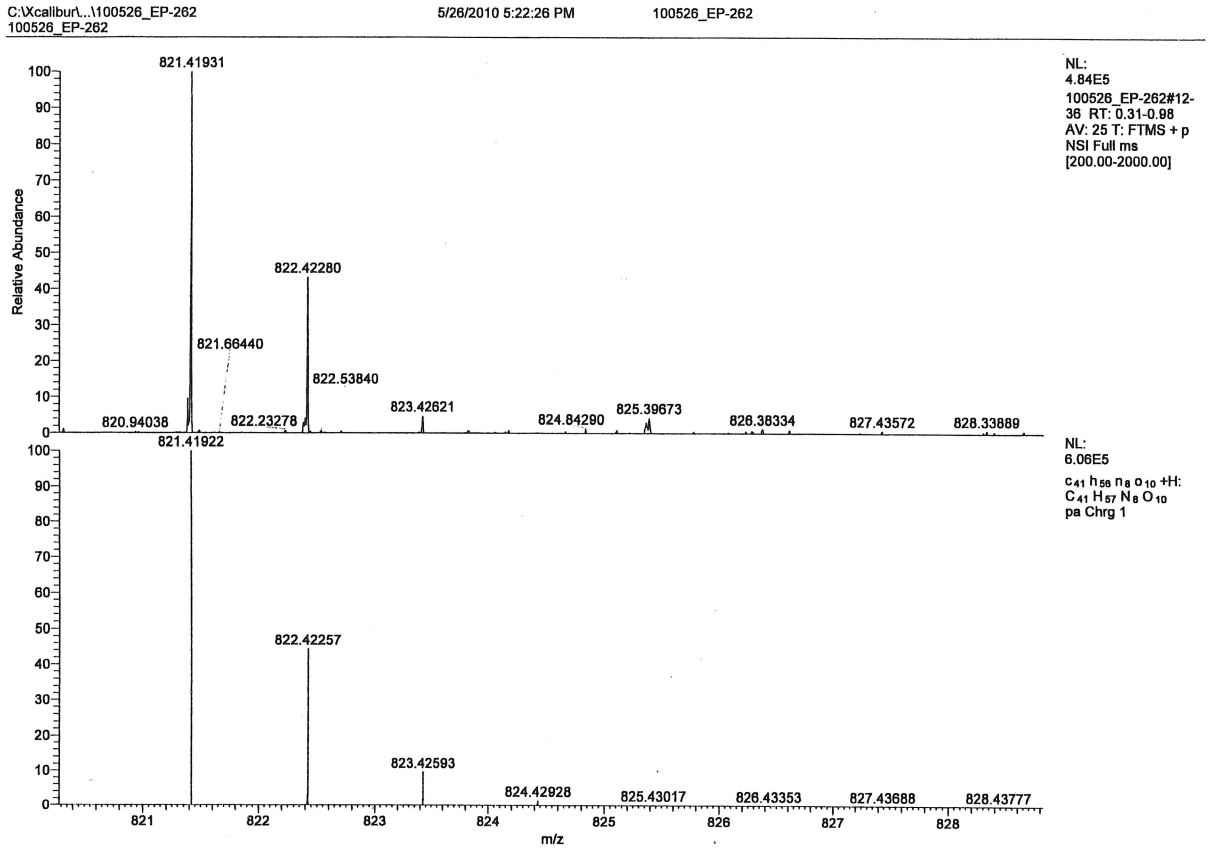
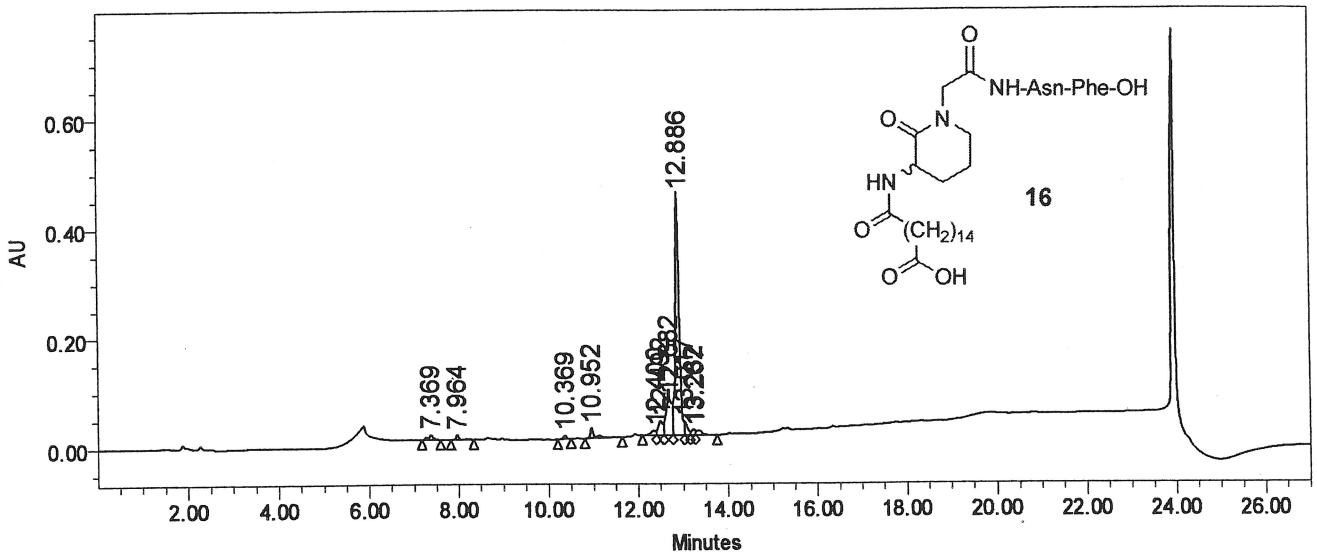
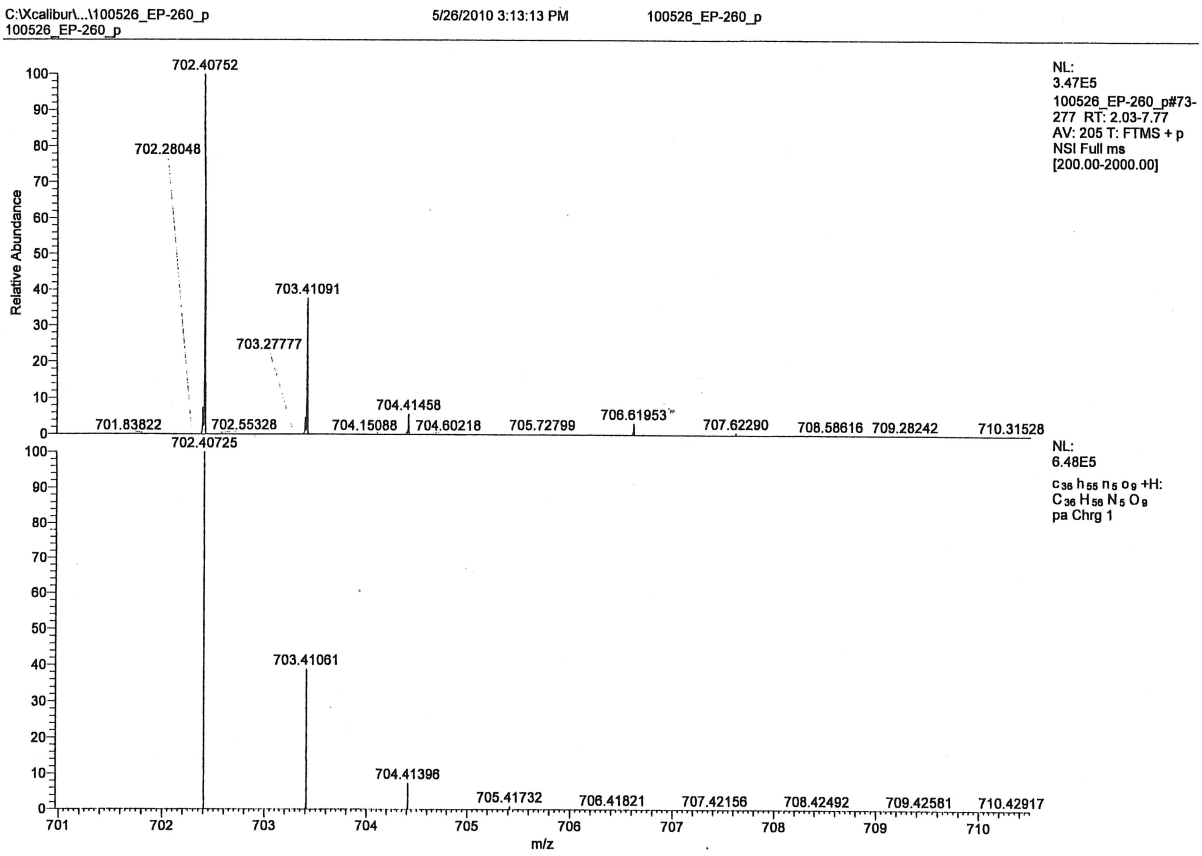
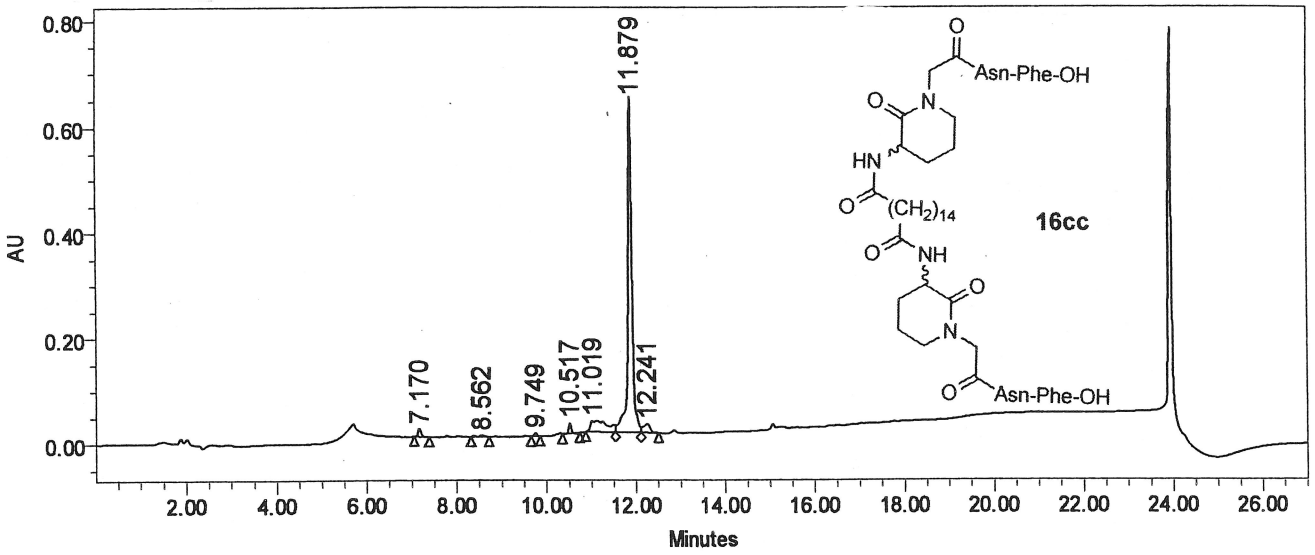
1	13.876	39063716	95.09	3410341
2	15.778	2015687	4.91	361998



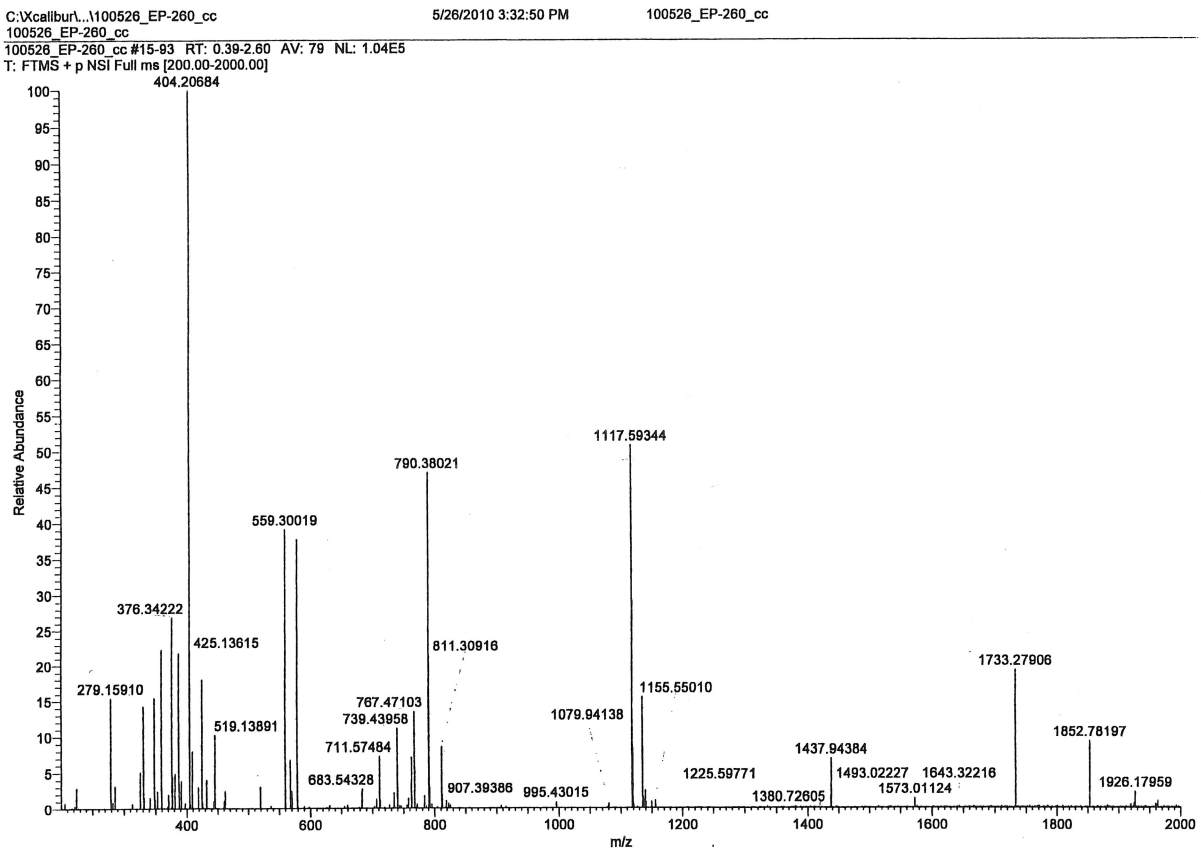


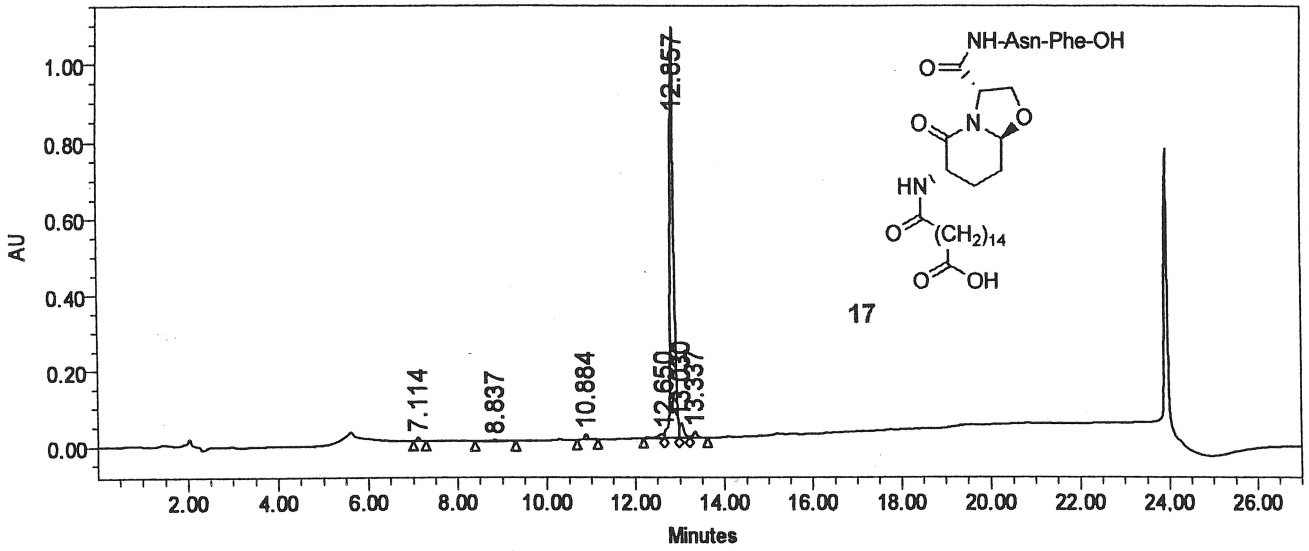
	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	7.369	68498	1.71	9446
2	7.964	46975	1.17	9402
3	10.369	31016	0.77	6386
4	10.952	117645	2.93	18285
5	12.400	60922	1.52	7479
6	12.492	186115	4.64	25165
7	12.682	612315	15.26	66415
8	12.886	2645553	65.94	440895
9	13.017	116966	2.92	24354
10	13.232	55672	1.39	10255
11	13.267	70288	1.75	7911





	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	7.170	73452	1.44	15522
2	8.562	34060	0.67	3191
3	9.749	24905	0.49	6372
4	10.517	86506	1.70	19420
5	11.019	580013	11.37	21407
6	11.879	4119101	80.73	632868
7	12.241	184316	3.61	16971





	RT (min)	Area (µV*sec)	% Area	Height (µV)
1	7.114	49238	0.72	10024
2	8.837	35795	0.52	4135
3	10.884	81793	1.19	14433
4	12.650	111827	1.63	12277
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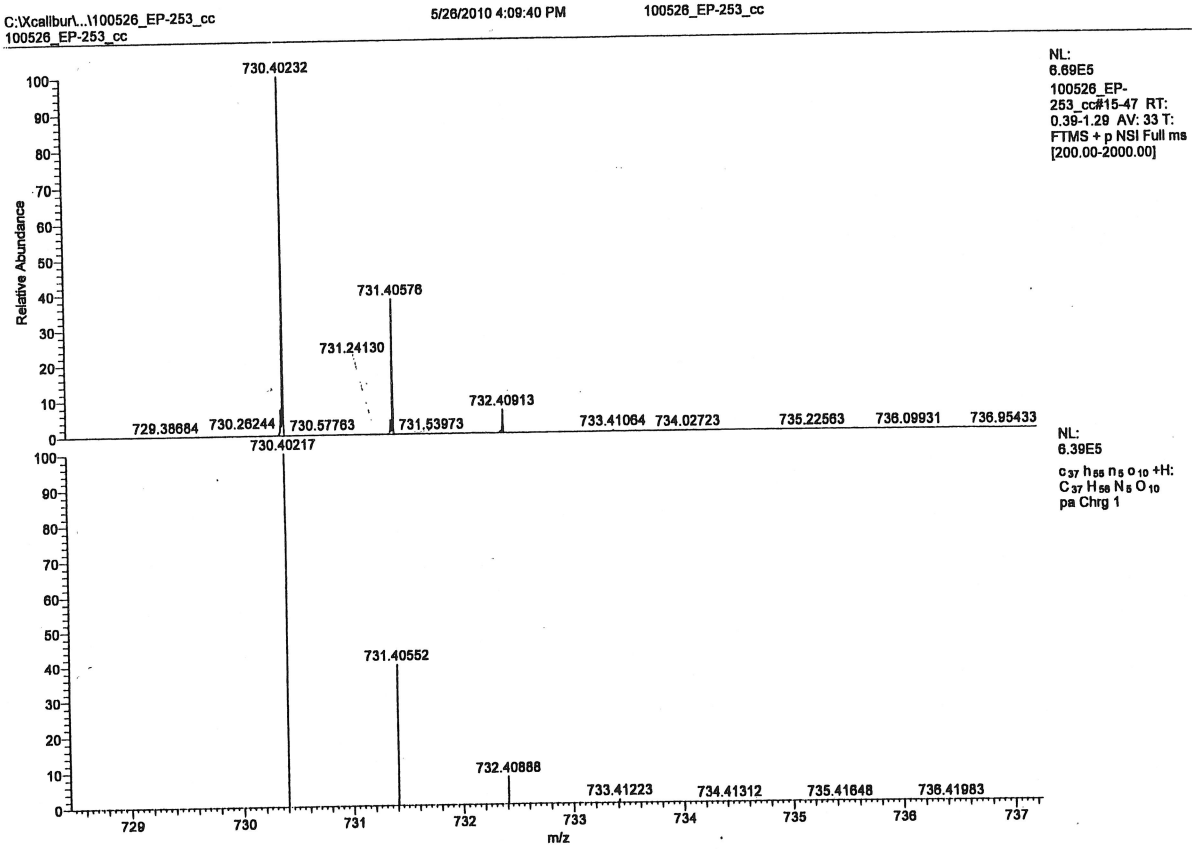
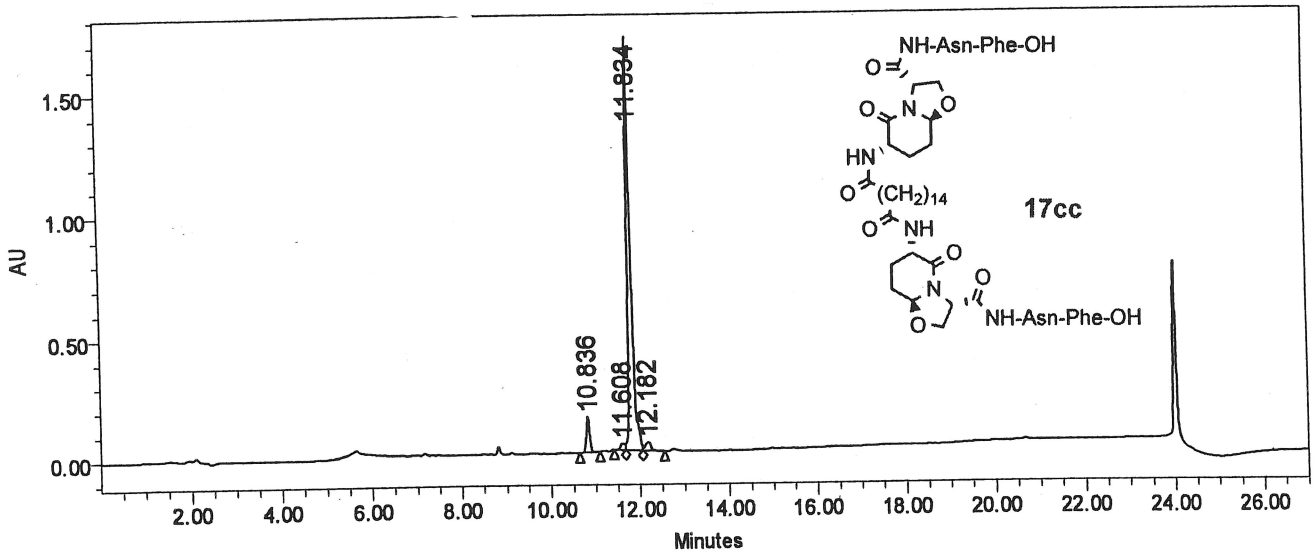
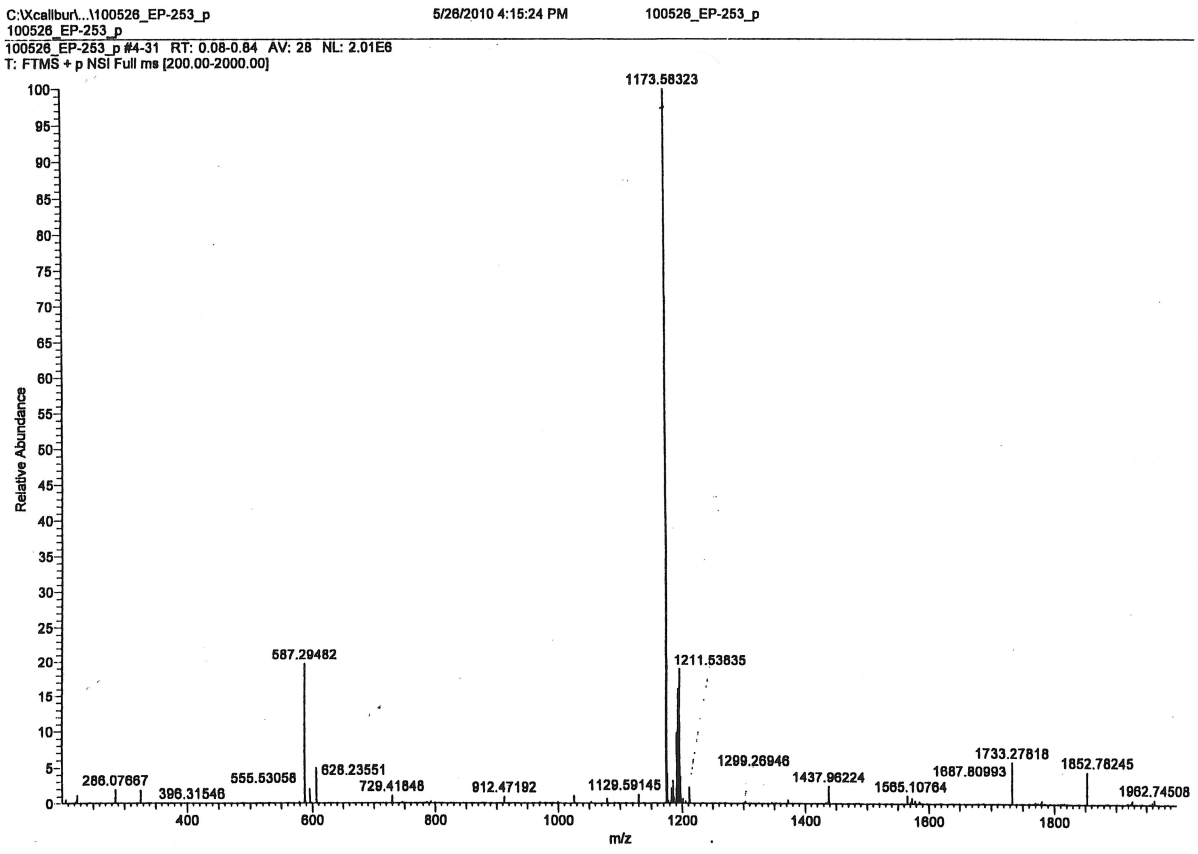
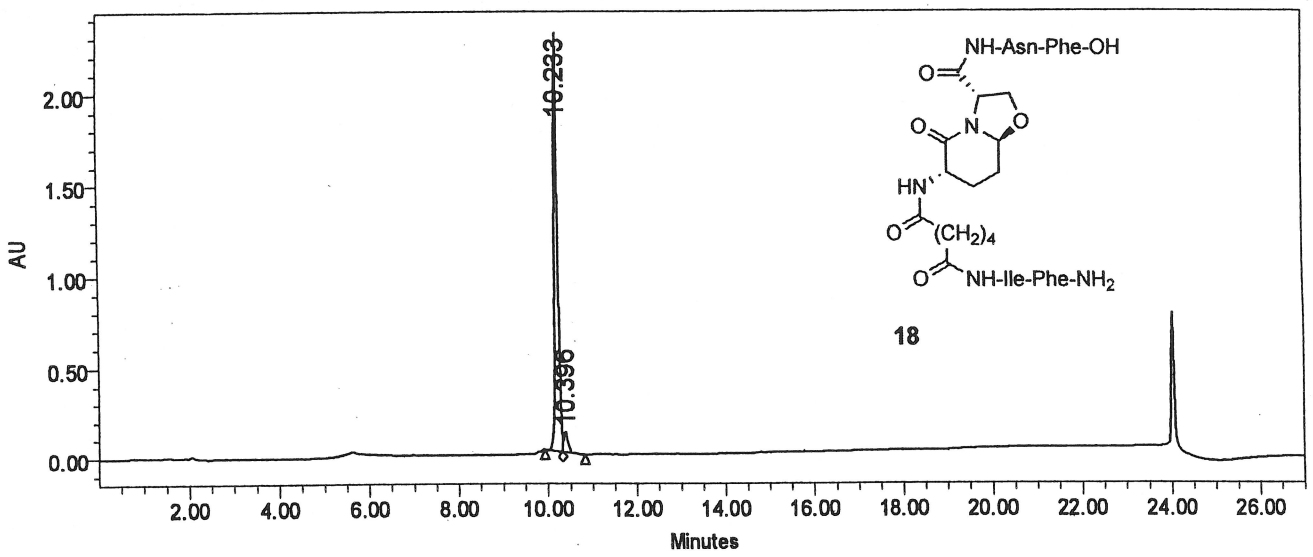
6	13.030	263182	3.83	39124
7	13.337	107980	1.57	16410



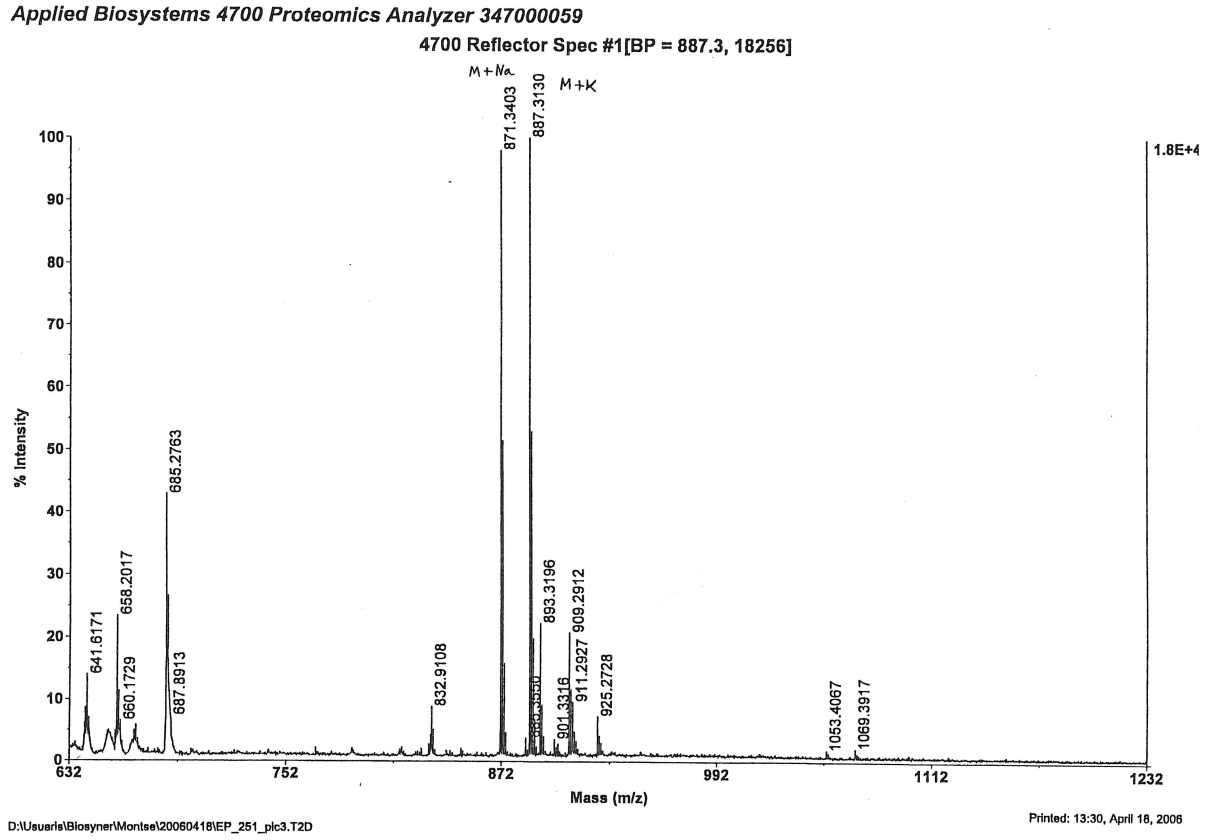


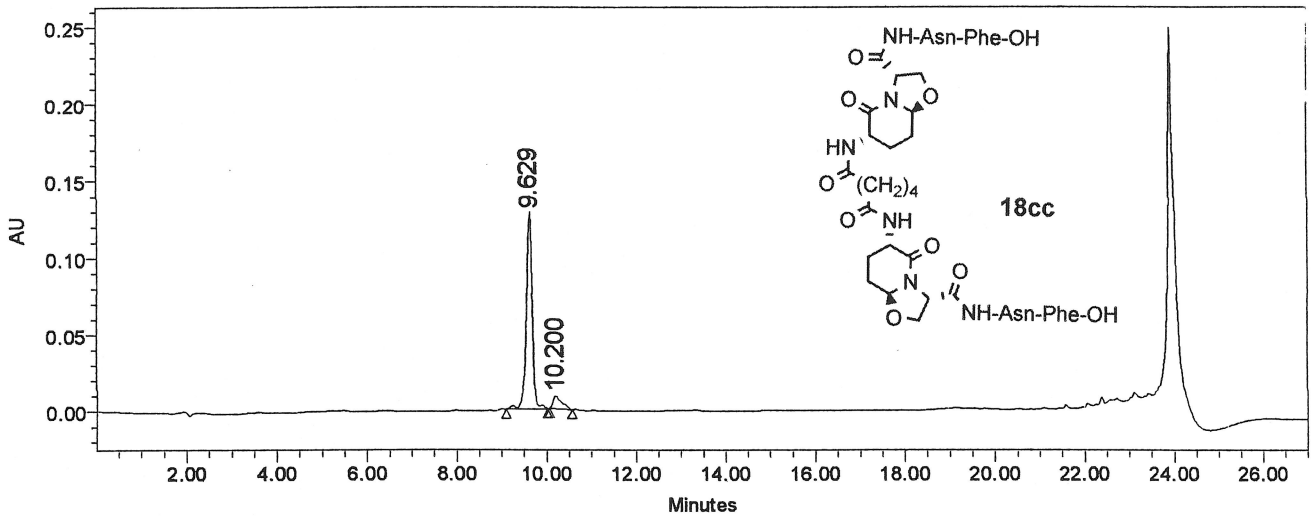
	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	10.836	746301	6.73	145566
2	11.608	204316	1.84	27445
3	11.834	9830308	88.63	1679777
4	12.182	309911	2.79	35082



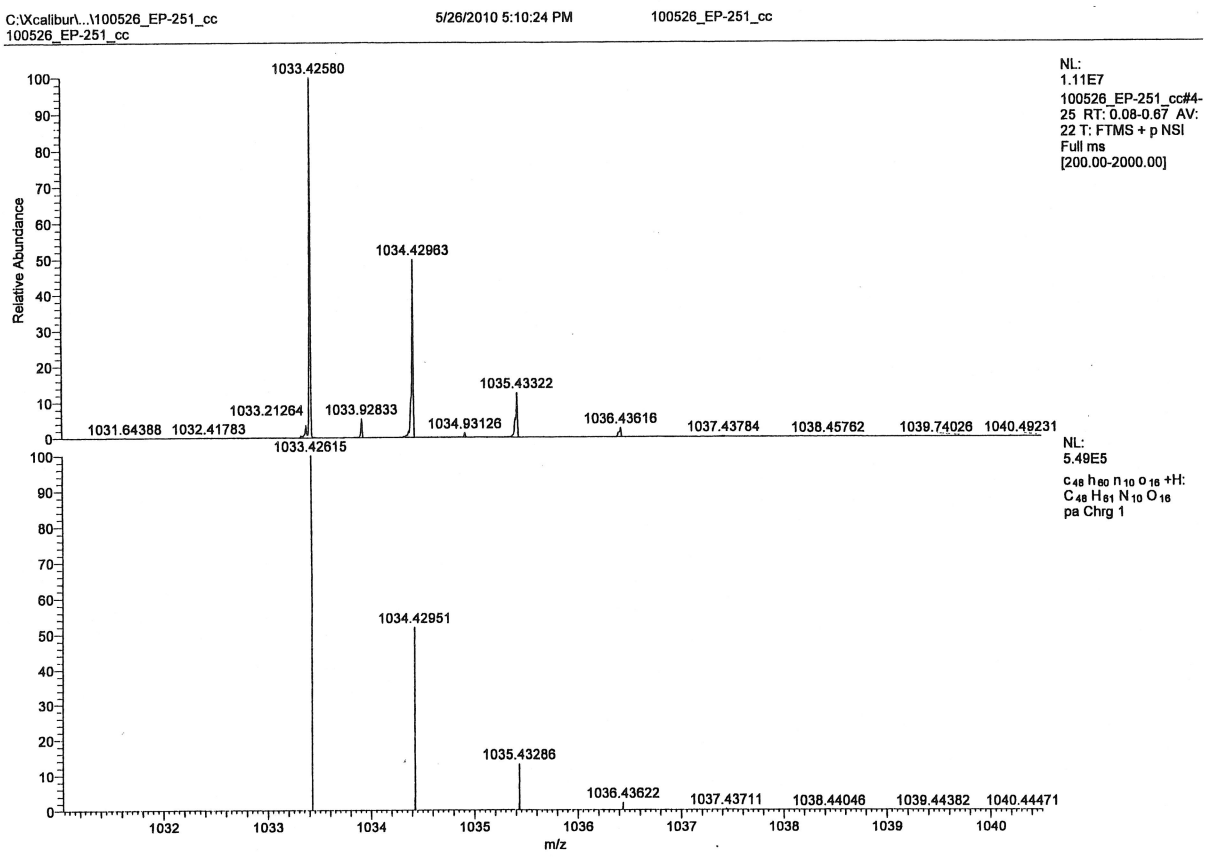


	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	10.233	12315684	94.33	2281723
2	10.396	740102	5.67	113089





	RT (min)	Area (μV*sec)	% Area	Height (μV)
1	9.629	1156513	91.41	128055
2	10.200	108729	8.59	8175



Anti-HIV activity in cell culture[1] (EC_{50})

All compounds were tested in cultures cells infected with wild type HIV1 virus. The four most potent compounds were then tested on cells infected with the multidrug resistant HIV1 strain IRLL98DPRO.[2] The test was based on the MTT colorimetric method that measures cellular proliferation,[3] specifically applied to HIV1-PR inhibitors.[4] The screening allowed determination of the 50% effective concentration (EC_{50}) of the compounds as well as their 50% cytotoxic concentration (CC_{50}). The results (Table 1) showed that four of our compounds (**6**, **14**, **15** and **16cc**) had antiviral activity on the wild type virus at the micromolar scale.

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(1) These tests were carried out at the IrsiCaixa AIDS Research Institute, Hospital Universitari Germans Trias i Pujol, Badalona (Spain).

(2) Moncunill, G.; Armand-Ugon, M.; Clotet-Codina, I.; Pauls, E.; Ballana, E.; Llano, A.; Romagnoli, B.; Vrijbloed, J. W.; Gombert, F. O.; Clotet, B.; De Marco, S.; Esté, J. A.. Anti-HIV activity and resistance profile of the CXC chemokine receptor 4 antagonist POL3026. *Mol. Pharmacol.* **2008**, *73*, 1264-73.

(3) a. Gonzalez-Ortega, E., Ballana, E., Badia, R., Clotet, B., and Este, J. A. (2011) *Antiviral Res* **92**, 479-483. b. Mosmann, T.; Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **1983**, *65*, 55-63. c. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; SChols, D.; Herdewijn, P.; Desmyter, J.; DeClerq, E. Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds. *J. Virol. Methods* **1988**, *20*, 309-321.

(4) Davis, D.A.; Brown, C.A.; Singer, K.E.; Wang, V.; Kaufman, J.; Stahl, S.J.; Wingfield, P. Maeda, K. Harada, S.; Yoshimura, K.; Kosalaraksa, P.; Mitsuya, H.; Yarchoan, R. Inhibition of HIV-1 replication by a peptide dimerization inhibitor of HIV-1 protease. *Antiviral Res.* **2006**, *72*, 89-99.

Name	**Activity**	**MW** (g/mol)	**CC50** (μg/mL)	**EC50** (wild type)	**EC50** (mutant22)	Fold Resistance "**R**"
AZT	Reverse transcriptase inhibitor	276.24	>1	1.09 nM	2.90 nM	2.6[a]
AMD 3100	Fusion inhibitor	502.78	>5	2.00 nM	8.00 nM	4[a]
Ritonavir	Protease inhibitor	720.94	>1	47.16 nM	>1 μg/ml	19
Indinavir	Protease inhibitor	613.79	>1.2	8.15 nM	0.85 μM	104
6	Protease inhibitor	573.76	>125	97.17 μM	132 μM	1,36
14	Protease inhibitor	561.58	>125	2.96 μM	>125 μg/ml	-
15	Protease inhibitor	820.93	>125	2.23 μM	>125 μg/ml	-
16cc	Protease inhibitor	1117.29	>125	87.04 μM	>125 μg/ml	-

a. AZT and AMD3100 are scarcely affected by the mutation of the protease, since they have different targets.

Table 1. Cell culture activity against native HIV1 and resistant mutant IRLL98DPRO.