

# Primary Amine-Catalyzed Biginelli Reaction for the Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

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## Supporting Information

### <sup>1</sup>H NMR Data and Spectra

**(*R*)-5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (11a):** White solid, yield 81%;  $[\alpha]_{\text{D}}^{23} = -62.0$  (c 0.52, MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.24 (s, 1H), 7.27-7.33 (m, 5H), 5.80 (s, 1H), 5.41 (d, *J* = 2.5, 1H), 4.06-4.11 (m, 2H), 2.35 (s, 3H), 2.86 (t, *J* = 7.0, 3H).

**(*R*)-5-Ethoxycarbonyl-6-methyl-4-(*p*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (11b):** White solid, yield 53%;  $[\alpha]_{\text{D}}^{23} = -63.3$  (c 0.57, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.27 (s, 1H), 7.22 (d, *J* = 4.5, 2H), 7.10 (d, *J* = 4.5, 2H), 5.80 (s, 1H), 5.36 (d, *J* = 2.7, 1H), 4.07 (q, *J* = 6.9, 2H), 2.33 (s, 3H), 2.32 (s, 3H), 1.18 (t, *J* = 6.9, 3H).

**(*R*)-5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (11c):** White solid, yield 71%;  $[\alpha]_{\text{D}}^{23} = -46.8$  (c 0.55, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.32 (s, 1H), 7.21-7.25 (m, 2H), 6.81-6.84 (m, 2H), 5.83 (s, 1H), 5.34 (d, *J* = 2.7, 1H), 4.03-4.11 (m, 2H), 3.78 (s, 3H), 2.33 (s, 3H), 1.18 (t, *J* = 6.9, 3H).

**(*R*)-5-Ethoxycarbonyl-6-methyl-4-(*o*-tolyl)-3,4-dihydropyrimidin-2(1*H*)-one (11d):** White solid, yield 53%;  $[\alpha]_{\text{D}}^{23} = -36.6$  (c 1.52, MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.77 (s, 1H), 7.11-7.16 (m, 3H), 7.25-7.27 (m, 1H), 6.13 (s, 1H), 5.64 (s, 1H), 3.99 (q, *J* = 7.0, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 1.06 (t, *J* = 7.0, 3H).

**(*R*)-5-Ethoxycarbonyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (11e):** White solid, yield 61%;  $[\alpha]_{\text{D}}^{23} = -66.9$  (c 0.52, MeOH); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.23 (s, 1H), 7.25-7.30 (m, 2H), 6.95-7.01 (m, 2H), 5.87 (s, 1H), 5.38 (d, *J* = 2.7, 1H), 4.03-4.11 (m, 2H), 2.34 (s, 3H), 1.17 (t, *J* = 7.2, 3H).

**(*R*)-5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (11f):** White solid, yield 63%;  $[\alpha]_{\text{D}}^{23} = -79.5$  (c 0.52, MeOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.52 (s, 1H), 7.24-7.29 (m, 4H), 6.20 (s, 1H), 5.37 (d, *J* = 2.5, 1H), 4.06-4.11 (m, 2H), 2.33 (s, 3H), 1.18 (t, *J* = 7.5, 3H).

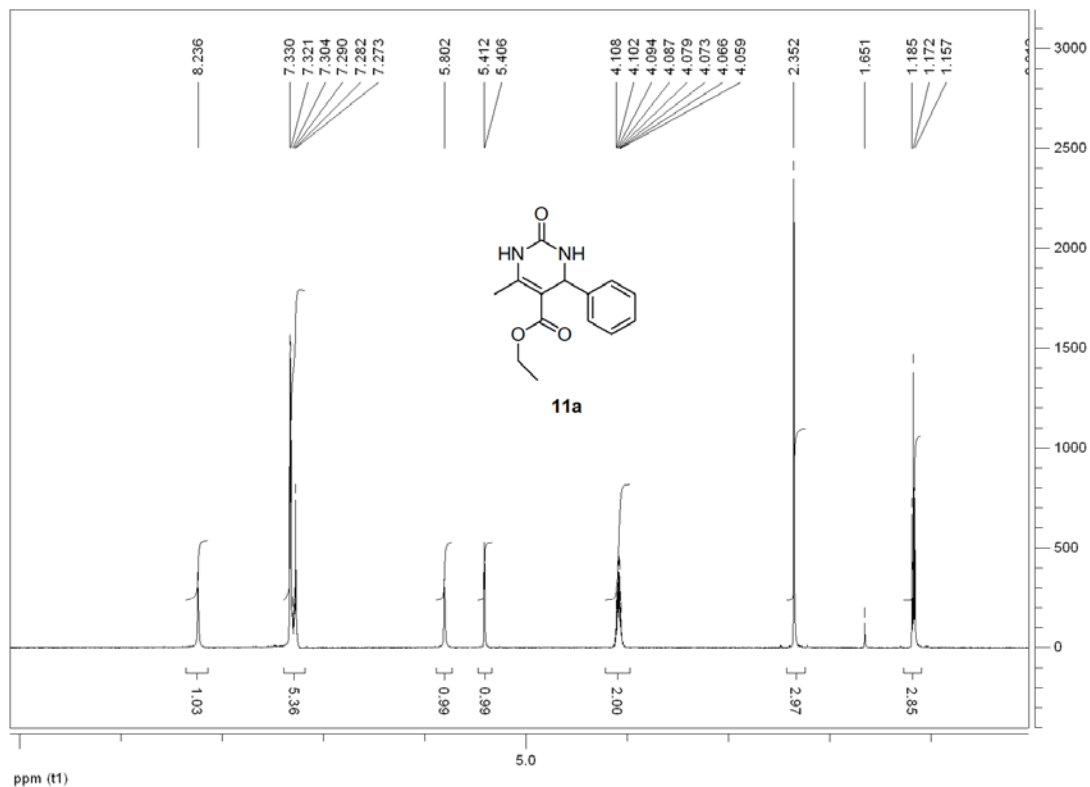
**(*R*)-4-(4-Bromophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (11g):**

Pale solid, yield 68%;  $[\alpha]_D^{23} = -70.6$  (c 0.57, MeOH);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.50 (s, 1H), 7.43 (d,  $J = 8.5$ , 2H), 7.19 (d,  $J = 8.5$ , 2H), 6.18 (s, 1H), 5.36 (d,  $J = 3.0$ , 1H), 4.06-4.11 (m, 2H), 2.32 (s, 3H), 1.18 (t,  $J = 7.0$ , 3H).

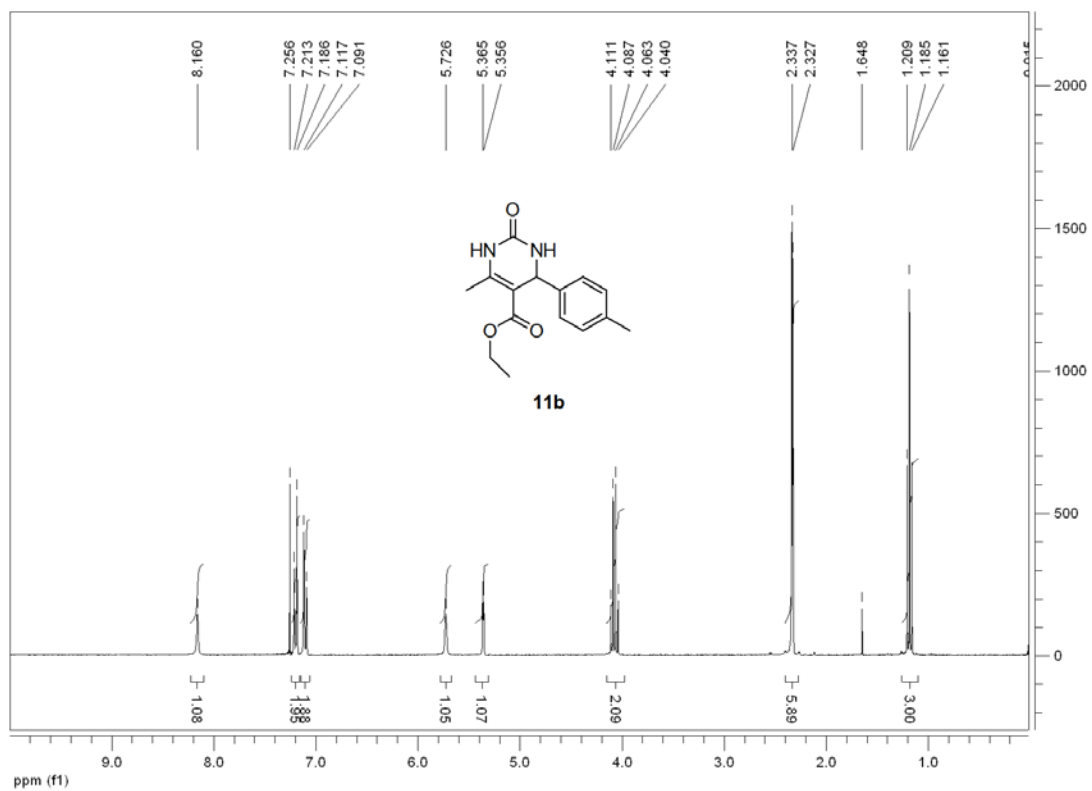
**(R)-4-(4-Cyanophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (11h):**  
White solid, yield 20%;  $[\alpha]_D^{23} = -85.5$  (c 0.71, MeOH);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.41 (s, 1H), 7.62 (d,  $J = 8.5$ , 2H), 7.44 (d,  $J = 8.5$ , 2H), 6.17 (s, 1H), 5.46 (d,  $J = 3.0$ , 1H), 4.06-4.13 (m, 2H), 2.34 (s, 3H), 1.18 (t,  $J = 7.5$ , 3H).

**(R)-5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (11i):**  
Pale yellow solid, yield 14%;  $[\alpha]_D^{23} = -52.6$  (c 0.375,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.32 (s, 1H), 8.18-8.20 (m, 2H), 7.87 (s, 1H), 7.47-7.50 (m, 2H), 5.26 (d,  $J = 3.3$ , 1H), 3.97 (q,  $J = 7.2$ , 1H), 2.58 (s, 3H), 1.09 (t,  $J = 7.2$ , 3H).

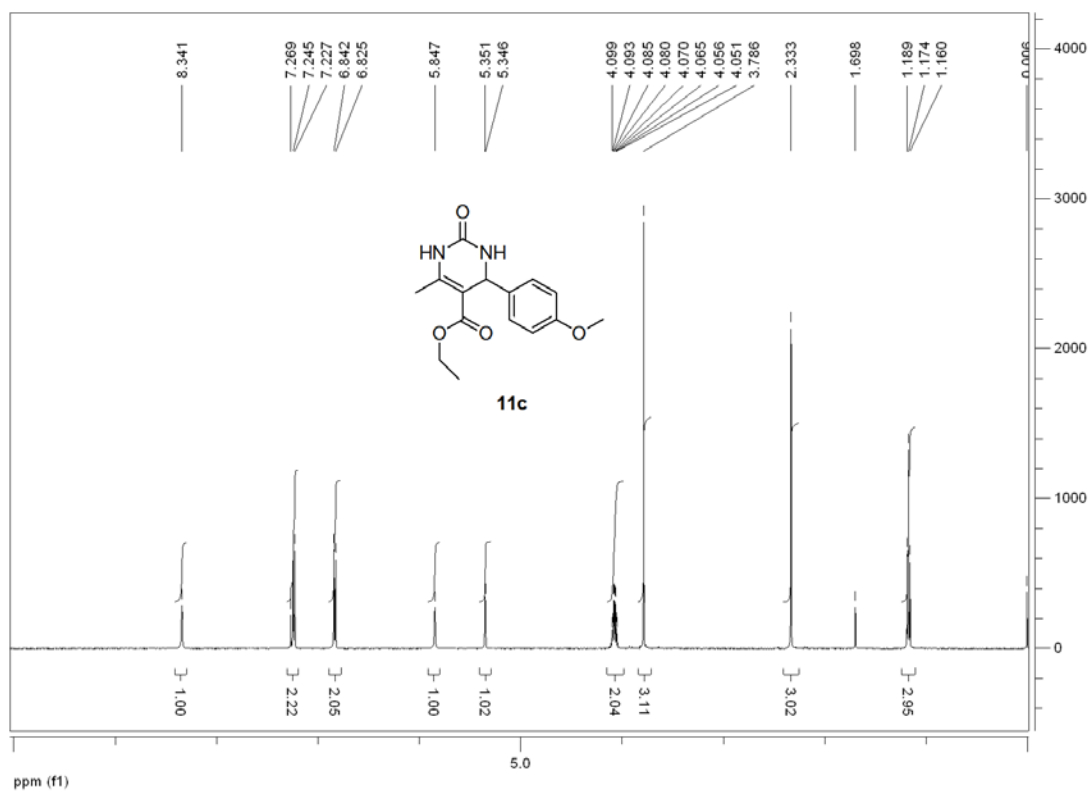
**(R)-5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (11j):**  
White solid, 21% yield;  $[\alpha]_D^{25} = -83.6$  (c 0.1,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (500 MHz,  $d_6$ -DMSO):  $\delta$  9.36 (s, 1H), 8.13 (dd,  $J = 1.3, 7.7$  Hz, 1H), 8.07 (s, 1H), 7.98 (br s, 1H), 7.70-7.61 (m, 2H), 5.30 (d,  $J = 3.3$  Hz, 1H), 3.99 (m, 2H), 2.27 (s, 3H), 1.10 (t,  $J = 7.3$  Hz, 1H).



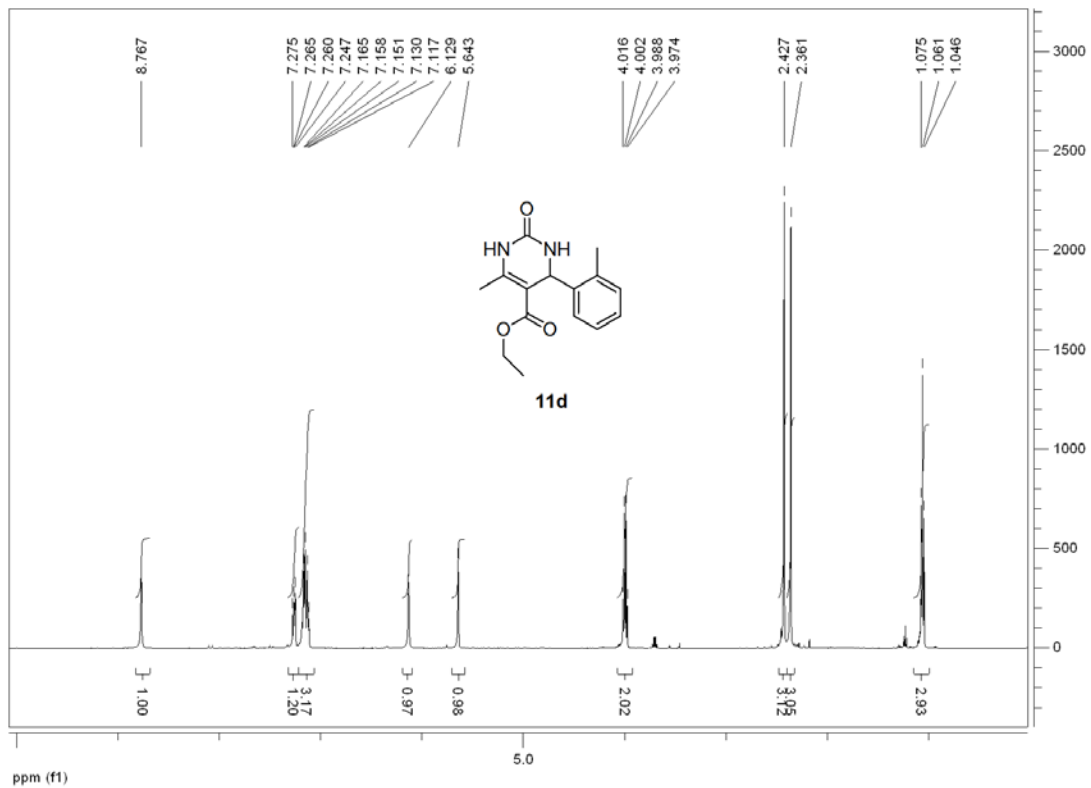
$^1\text{H NMR}$  of **11a**



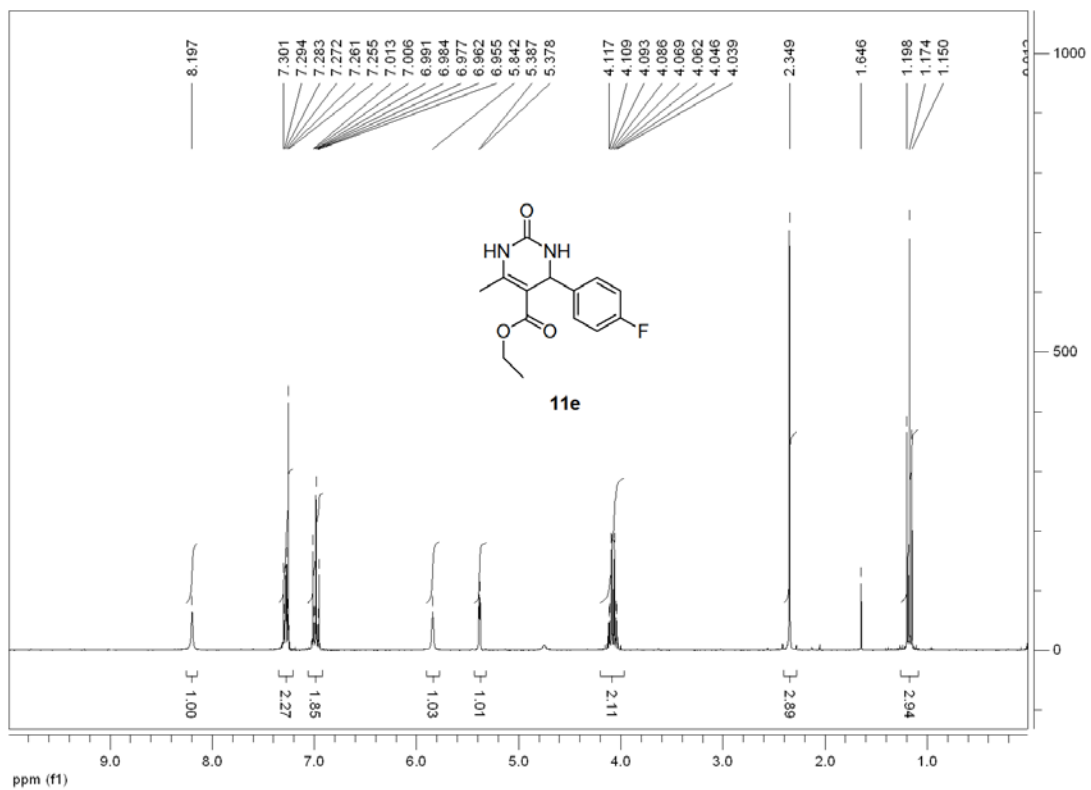
<sup>1</sup>H NMR of **11b**



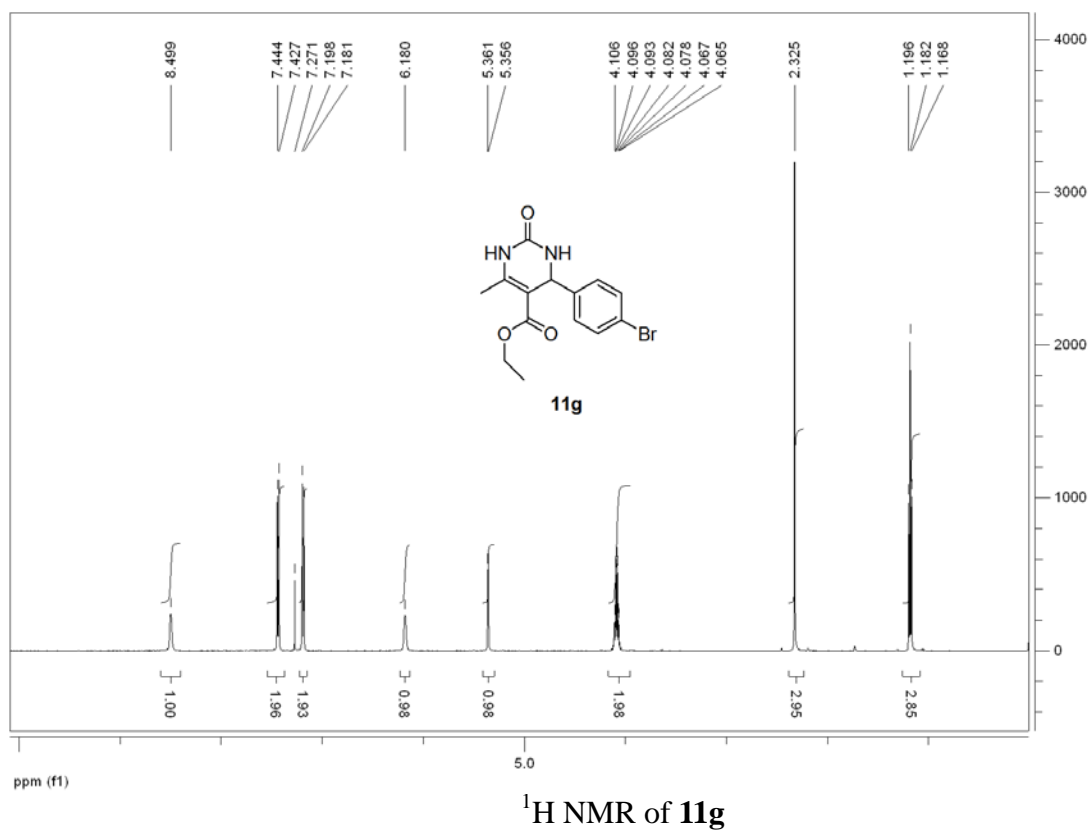
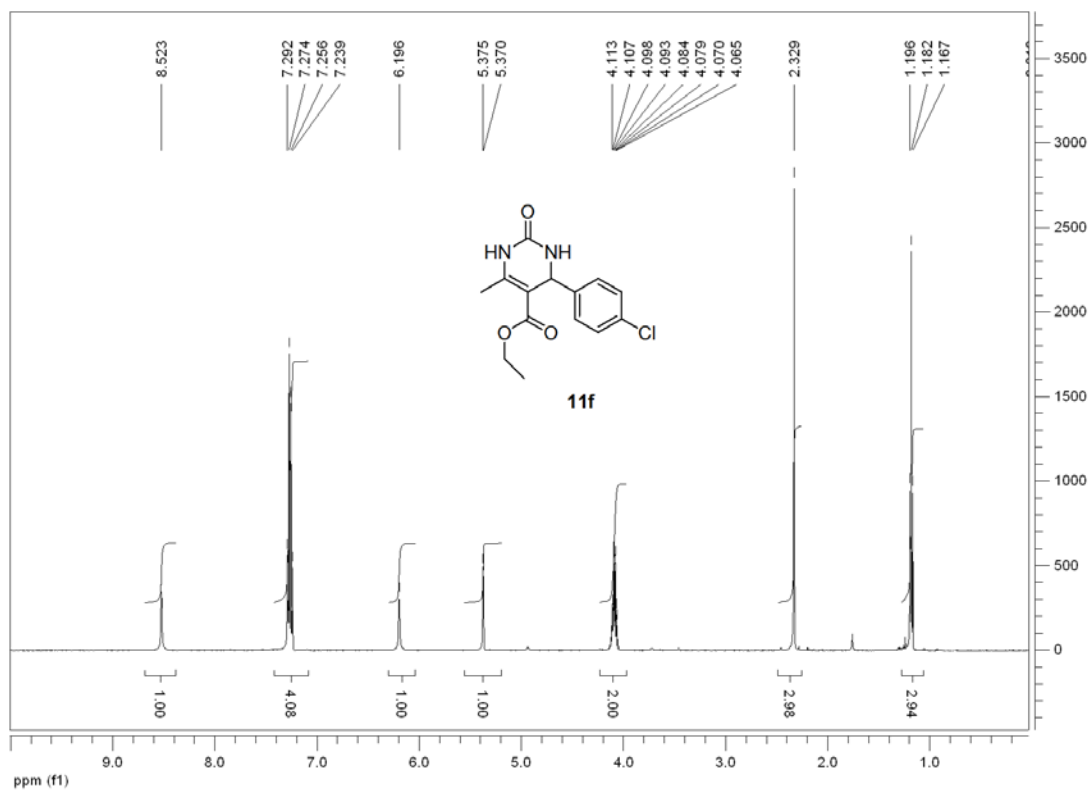
<sup>1</sup>H NMR of **11c**

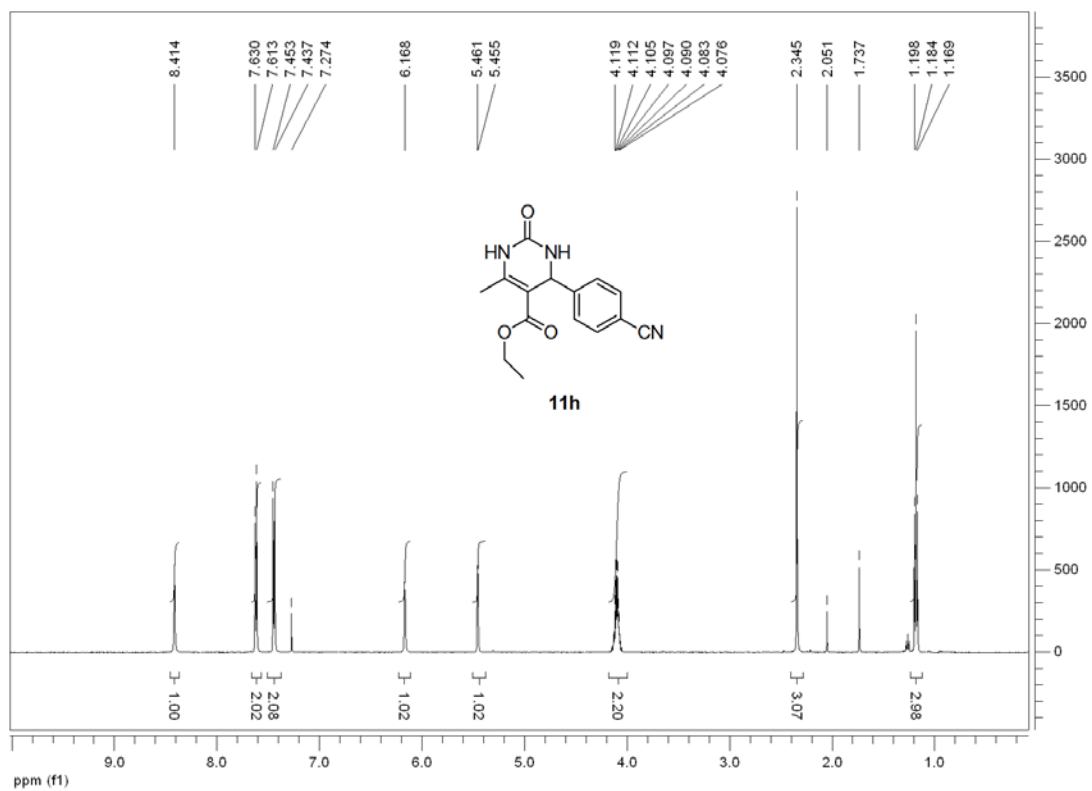


<sup>1</sup>H NMR of **11d**

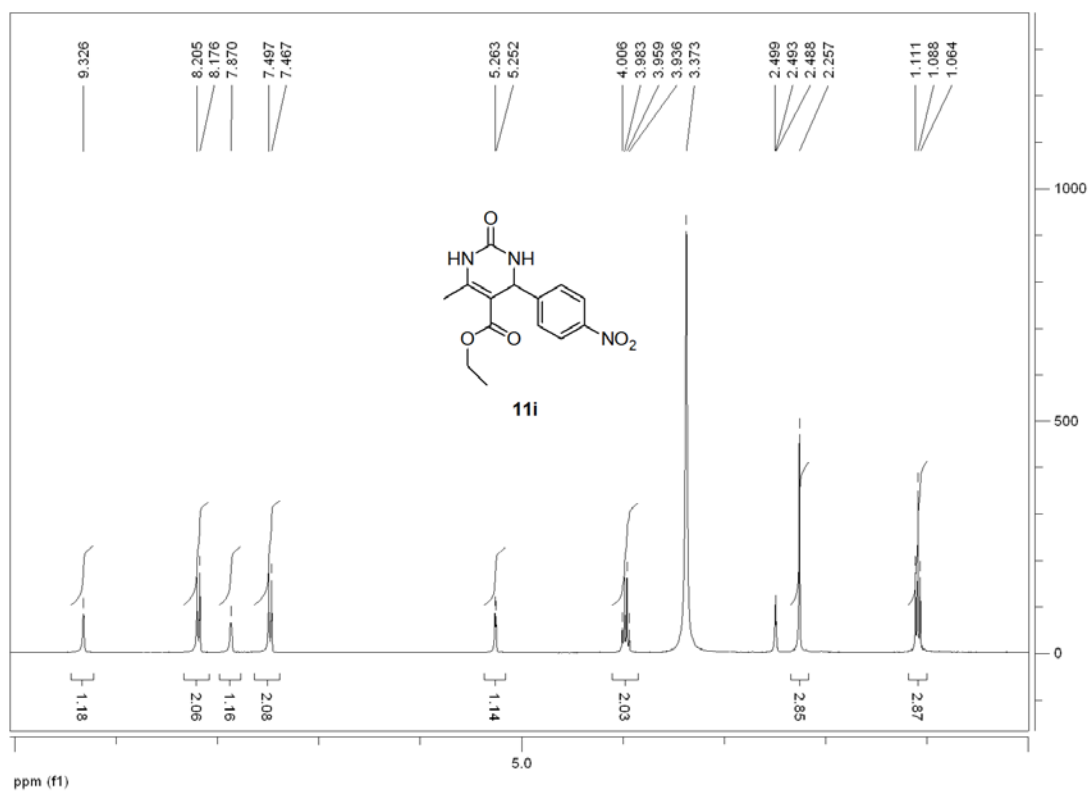


<sup>1</sup>H NMR of **11e**

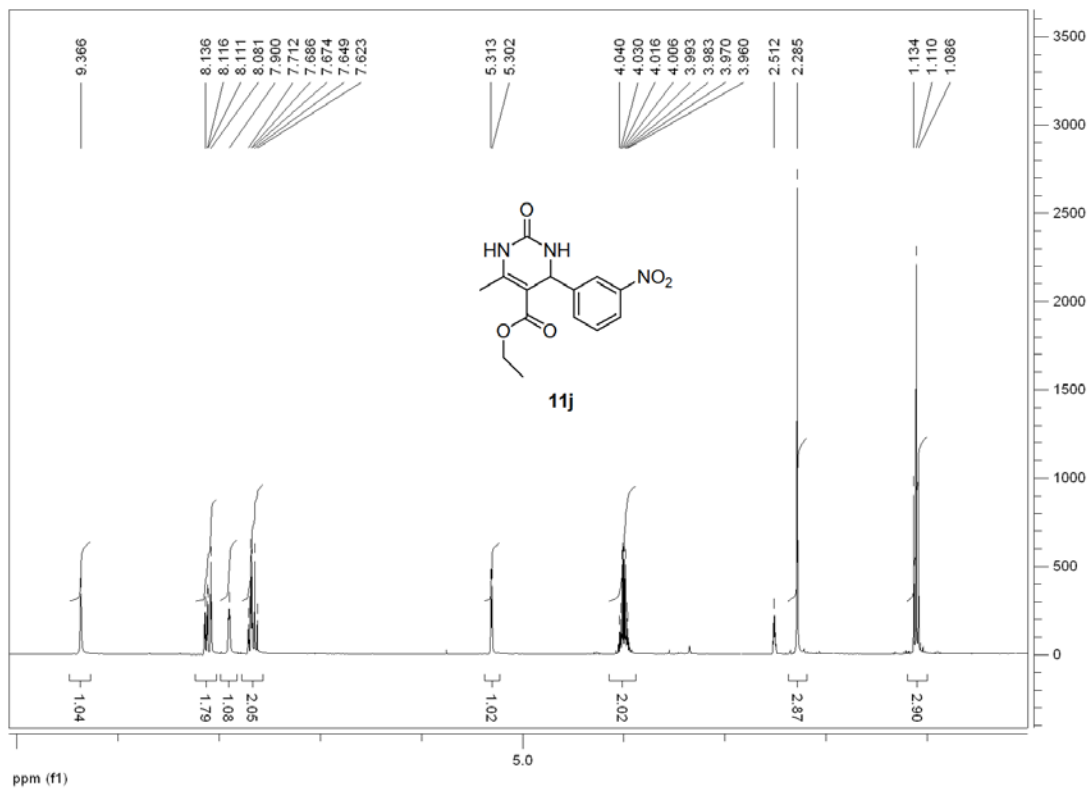




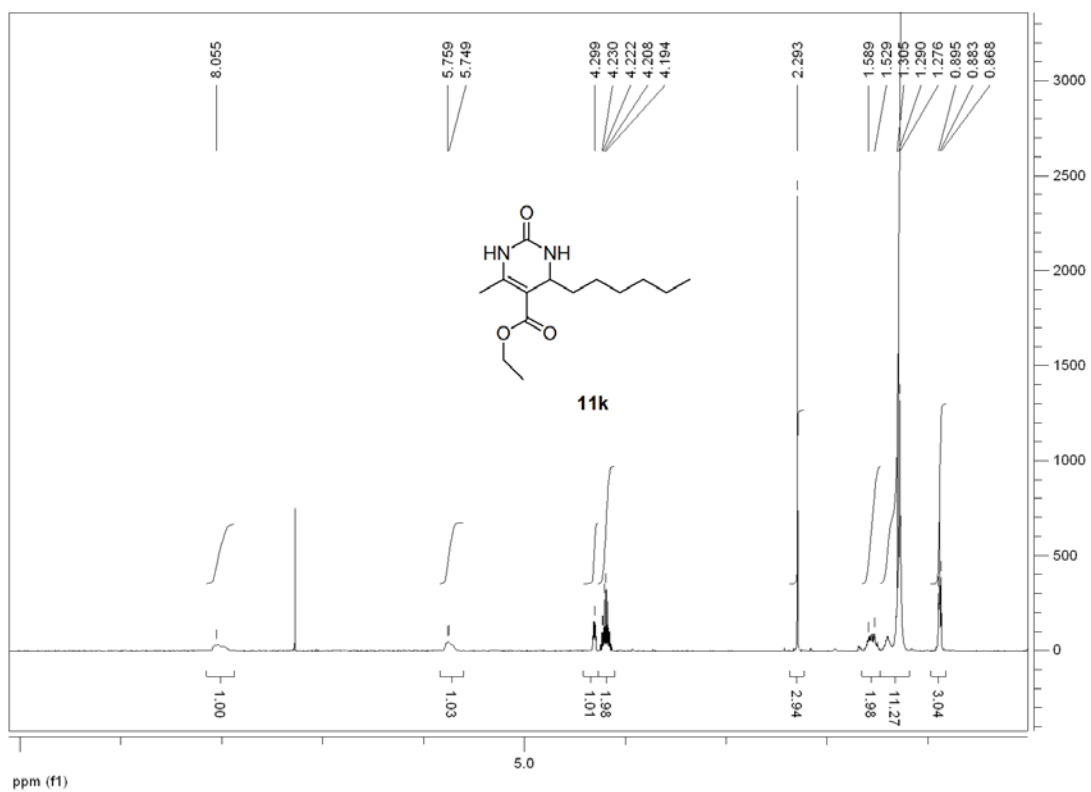
**<sup>1</sup>H NMR of 11h**



**<sup>1</sup>H NMR of 11i**

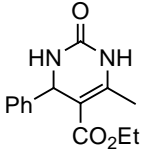
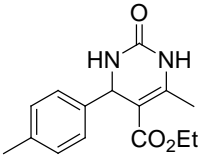
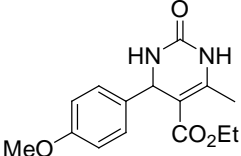
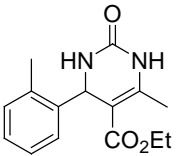
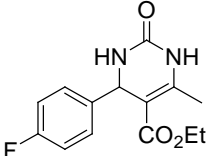
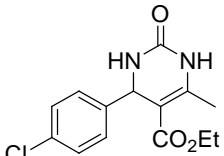
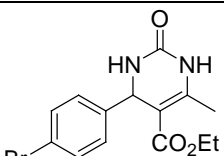
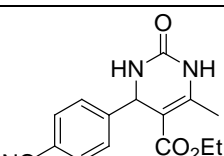
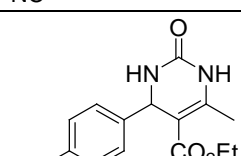


**<sup>1</sup>H NMR of 11j**

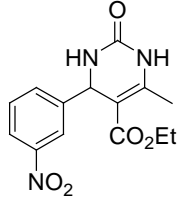
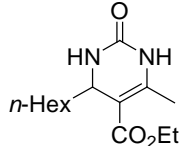


**<sup>1</sup>H NMR of 11k**

**Table 3. HPLC Conditions**

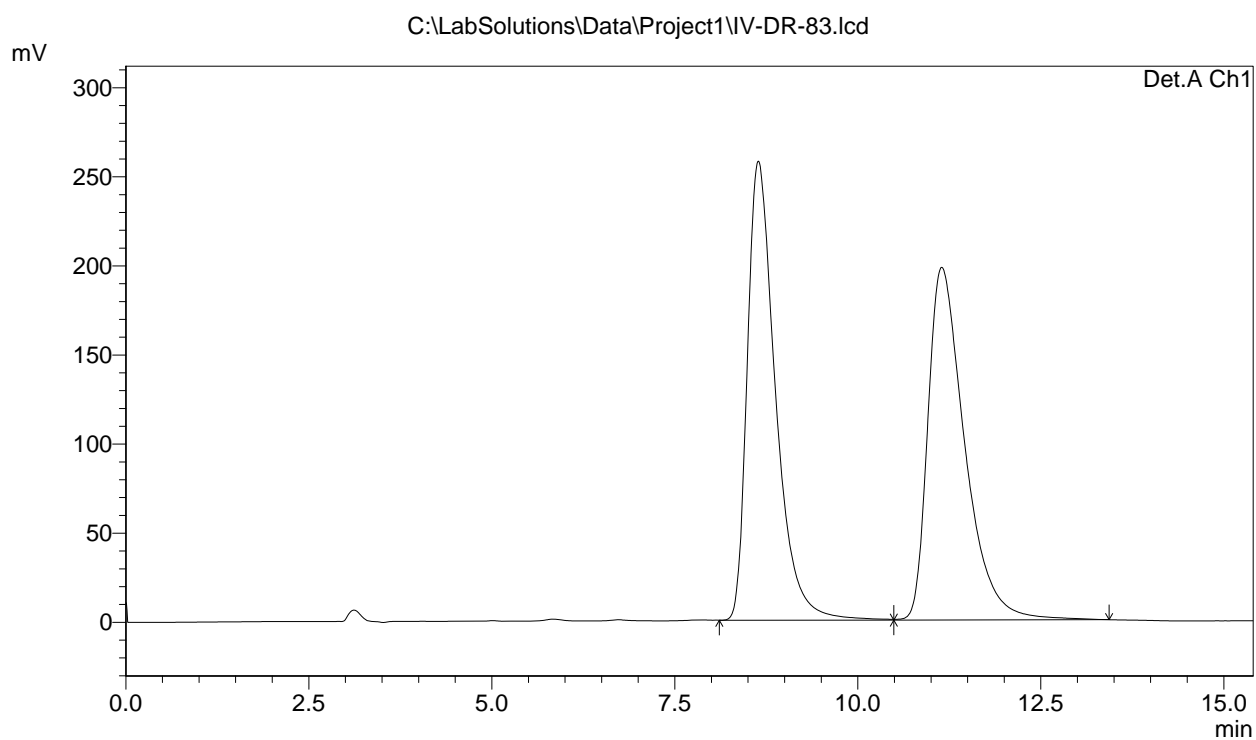
Compound	Column	<i>i</i> -PrOH/hexane	Flow rate (mL/min)	UV detection (nm)
	ChiralCel OD-H	15:85	1.0	254
	ChiralCel OD-H	15:85	1.0	254
	ChiralCel OD-H	15:85	1.0	254
	ChiralPak AD-H	20:80	1.0	254
	ChiralCel OD-H	15:85	1.0	254
	ChiralCel OD-H	15:85	1.0	254
	ChiralCel OD-H	15:85	1.0	254
	ChiralCel OD-H	15:85	1.0	254
	ChiralCel OD-H	15:85	1.0	254



 <p>Chemical structure: A chiral amide derivative. The central carbon is bonded to a p-nitrophenyl group, a methyl group, and a nitrogen atom. The nitrogen atom is part of a cyclic urea-like structure with a carbonyl group (=O) and another nitrogen atom. The second carbon of this ring is bonded to a methyl group and an ethyl ester group (-CO<sub>2</sub>Et).</p>	ChiralPak AD-H	10:90	1.0	254
 <p>Chemical structure: A chiral amide derivative. The central carbon is bonded to an n-hexyl group, a methyl group, and a nitrogen atom. The nitrogen atom is part of a cyclic urea-like structure with a carbonyl group (=O) and another nitrogen atom. The second carbon of this ring is bonded to a methyl group and an ethyl ester group (-CO<sub>2</sub>Et).</p>	ChiralCel OD-H	12:88	1.0	254

# ==== Shimadzu LCsolution LC Data Image ====

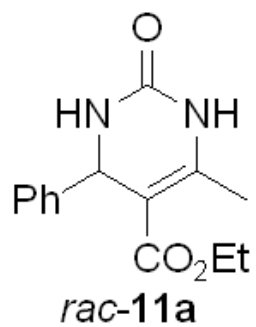
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PeakTable

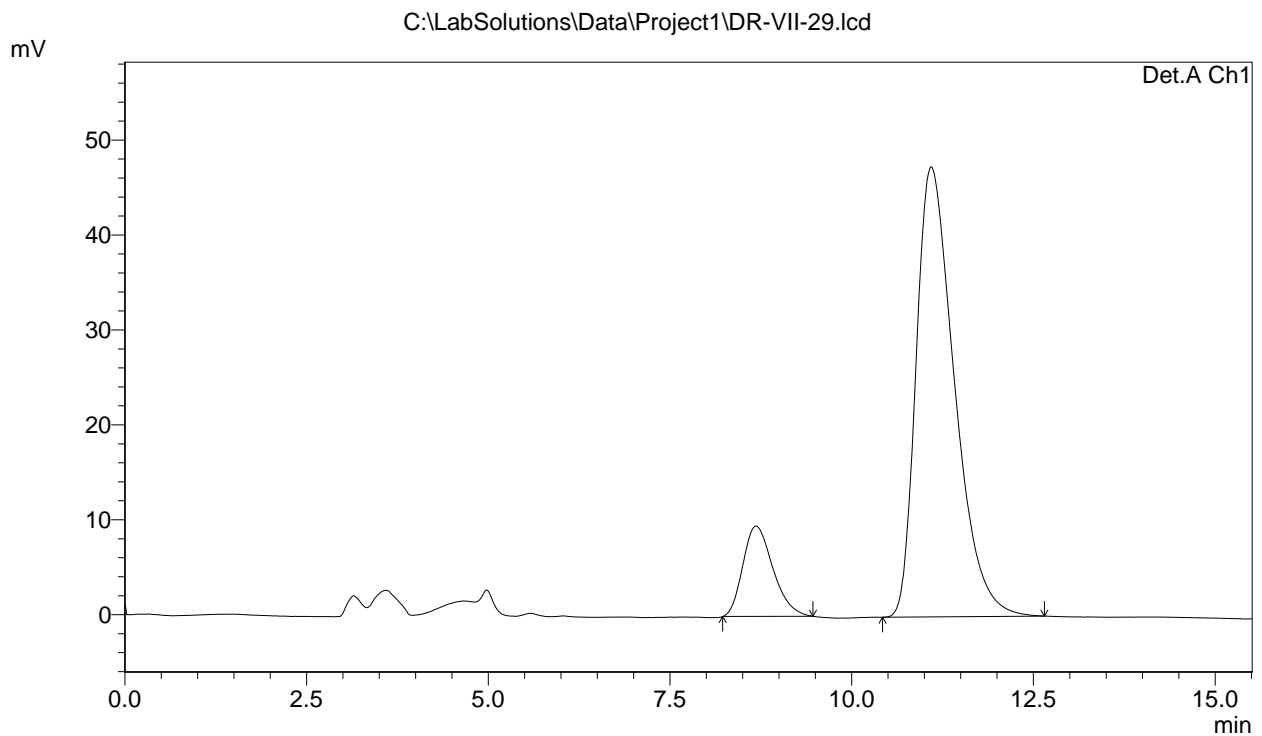
Detector A Ch1 226nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.637	6917814	257717	50.024	56.565
2	11.142	6911228	197899	49.976	43.435
Total		13829041	455617	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

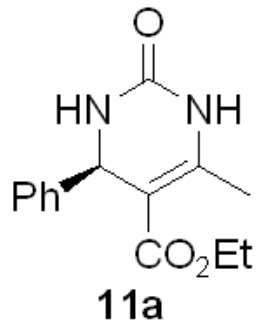
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PeakTable

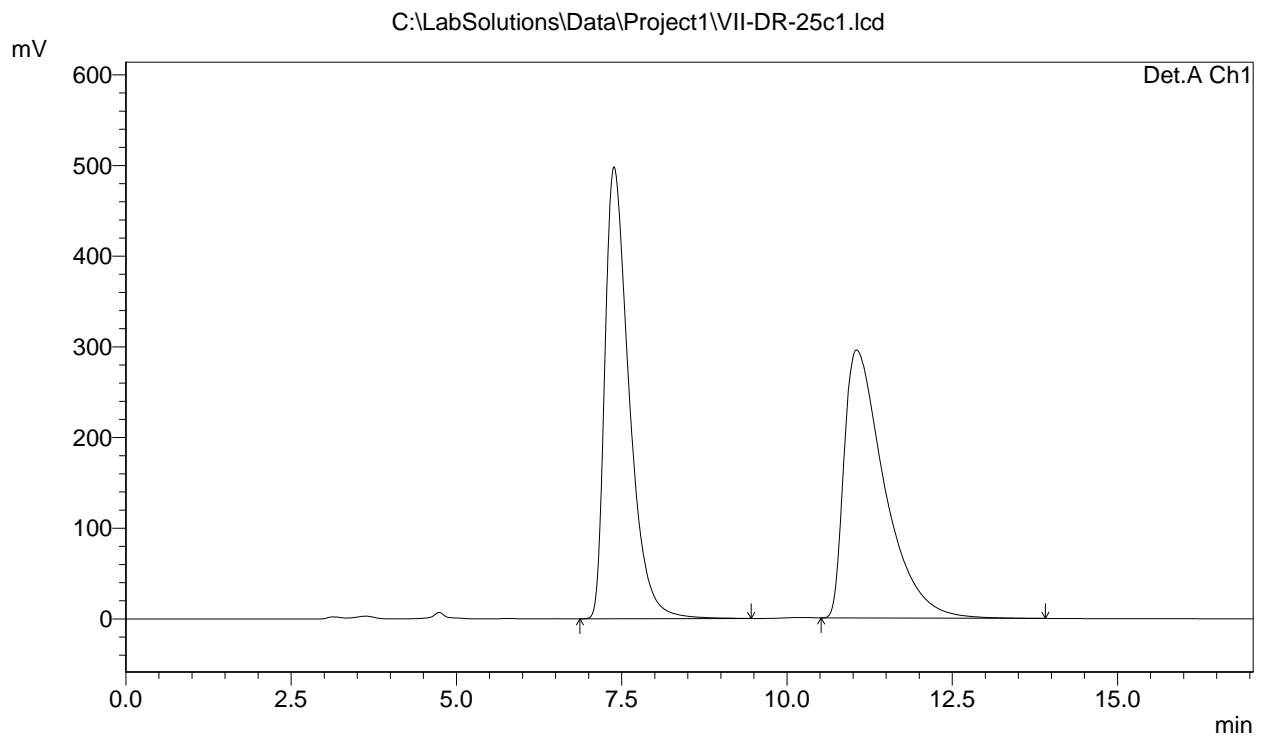
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.679	273312	9527	13.619	16.728
2	11.089	1733565	47425	86.381	83.272
Total		2006878	56952	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

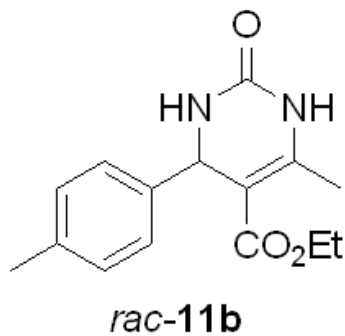
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PeakTable

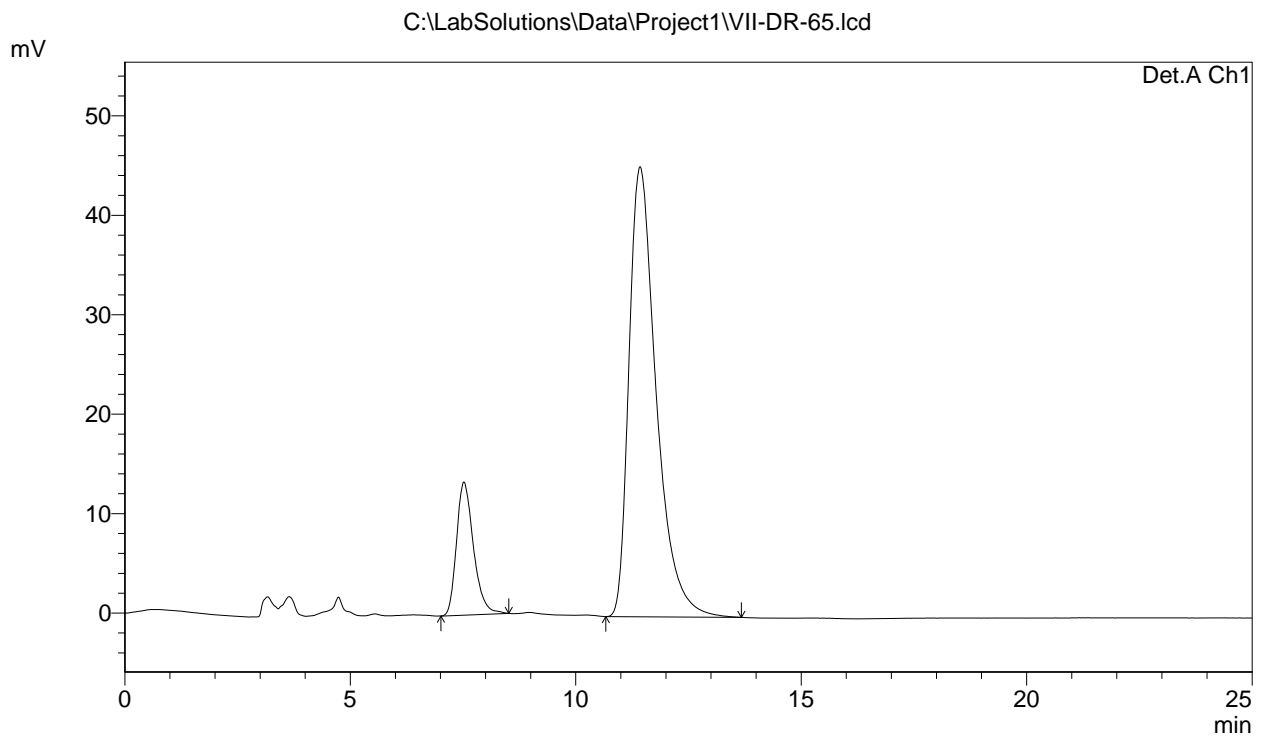
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.379	12676607	498461	50.212	62.779
2	11.049	12569519	295527	49.788	37.221
Total		25246126	793989	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

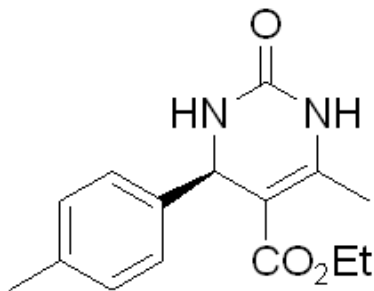
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PeakTable

Detector A Ch1 254nm

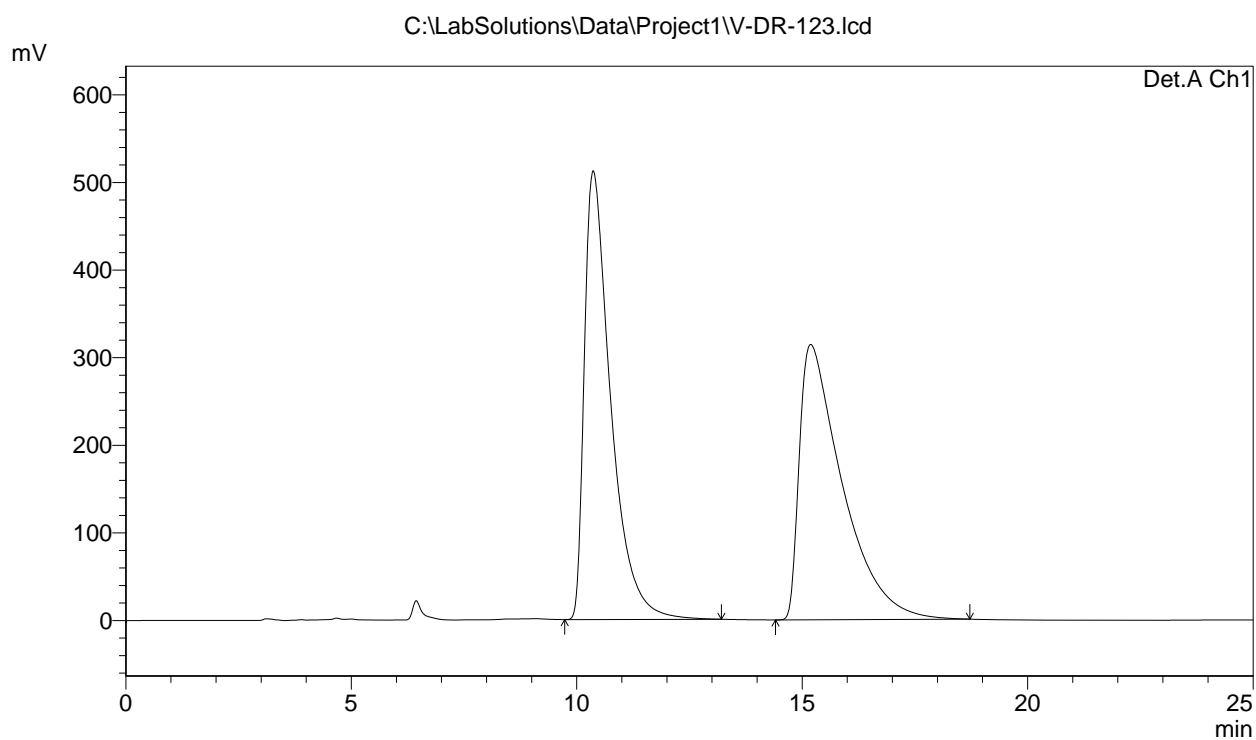
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.515	350827	13398	15.579	22.844
2	11.421	1901055	45252	84.421	77.156
Total		2251882	58650	100.000	100.000



**11b**

# ==== Shimadzu LCsolution LC Data Image ====

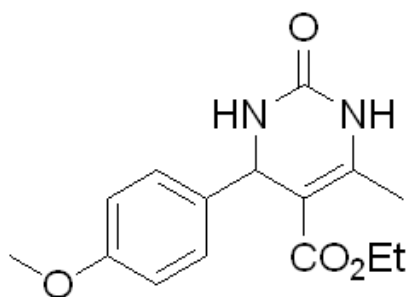
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PeakTable

Detector A Ch1 254nm

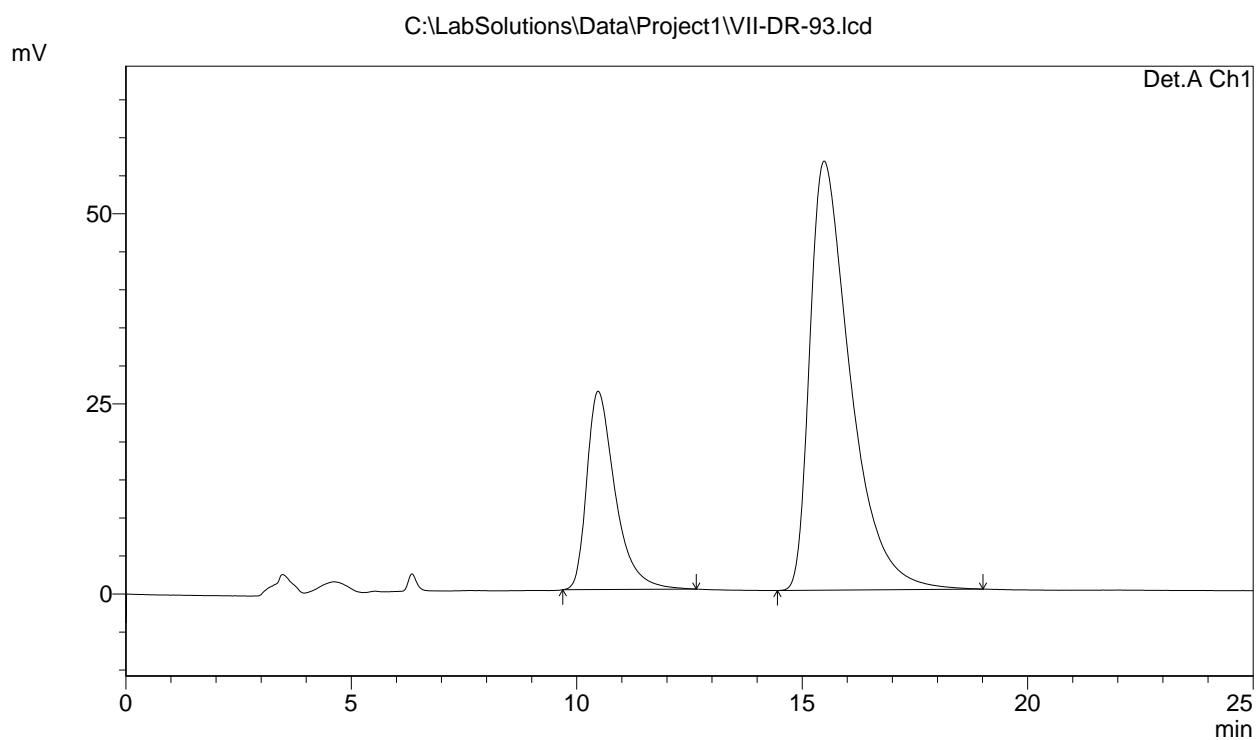
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.360	20828971	512289	50.069	61.970
2	15.184	20771242	314389	49.931	38.030
Total		41600213	826678	100.000	100.000



*rac-11c*

# ==== Shimadzu LCsolution LC Data Image ====

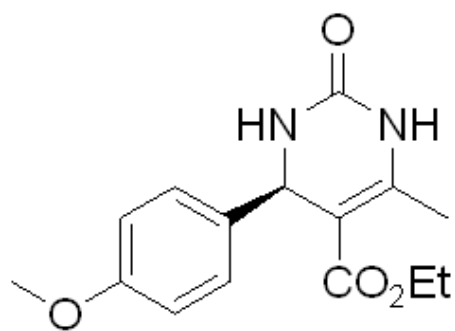
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PeakTable

Detector A Ch1 254nm

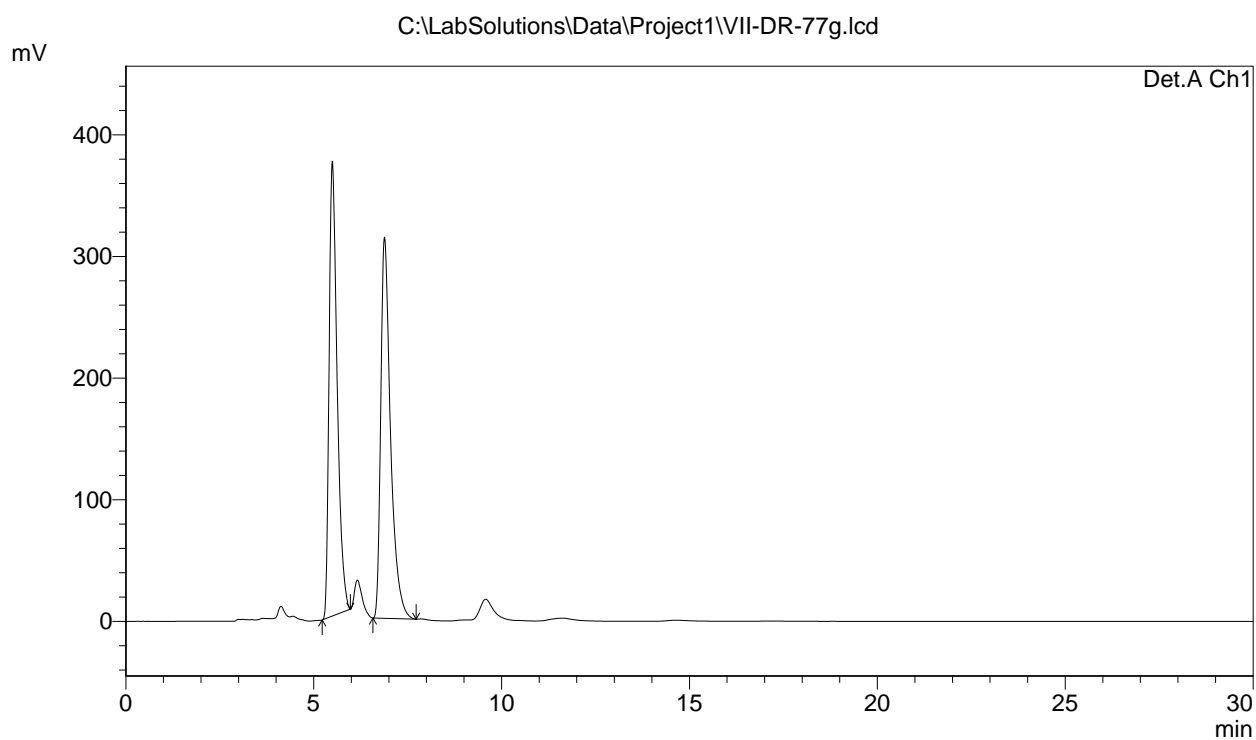
Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.471	1139510	26096	24.409	31.623
2	15.483	3528985	56426	75.591	68.377
Total		4668495	82522	100.000	100.000



**11c**

# ==== Shimadzu LCsolution LC Data Image ====

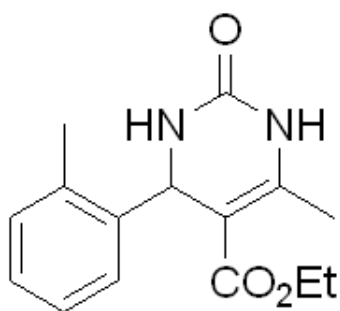
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PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.490	5584650	374144	49.576	54.415
2	6.880	5680197	313437	50.424	45.585
Total		11264847	687581	100.000	100.000

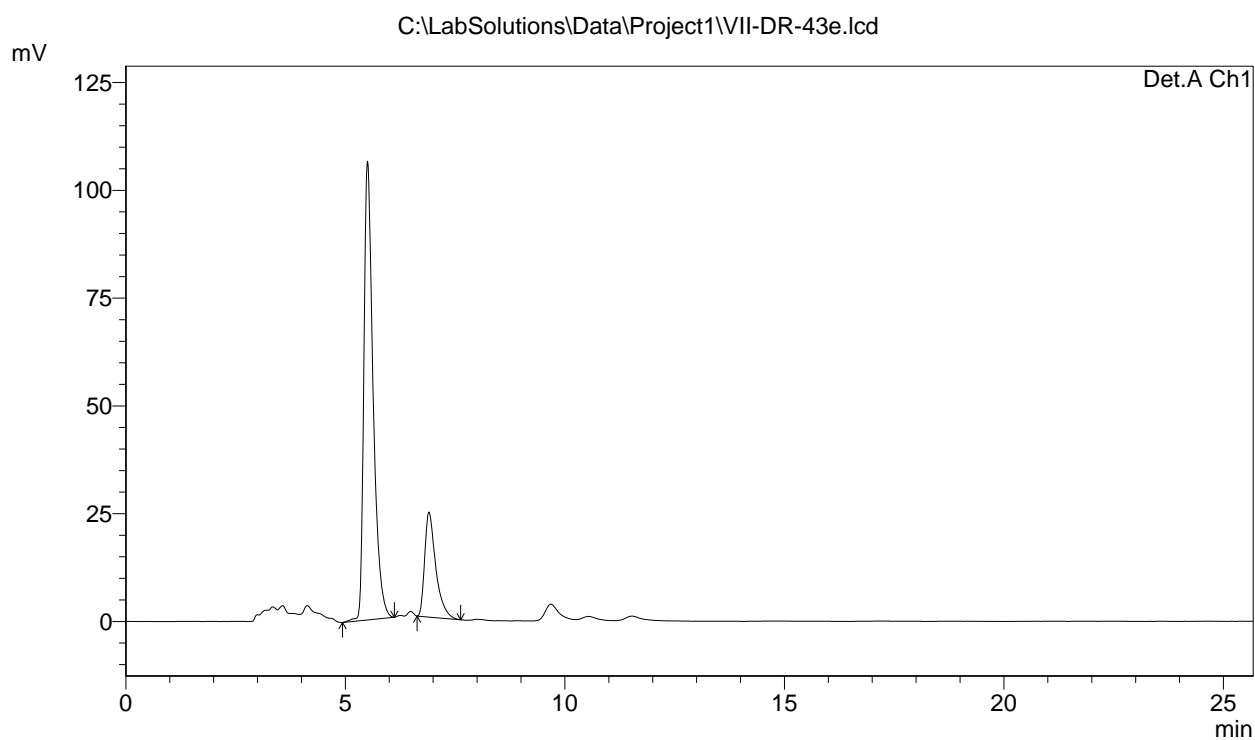


*rac-11d*



# ==== Shimadzu LCsolution LC Data Image ====

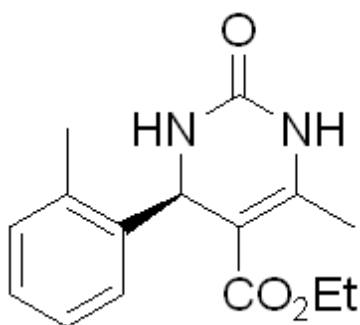
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PeakTable

Detector A Ch1 254nm

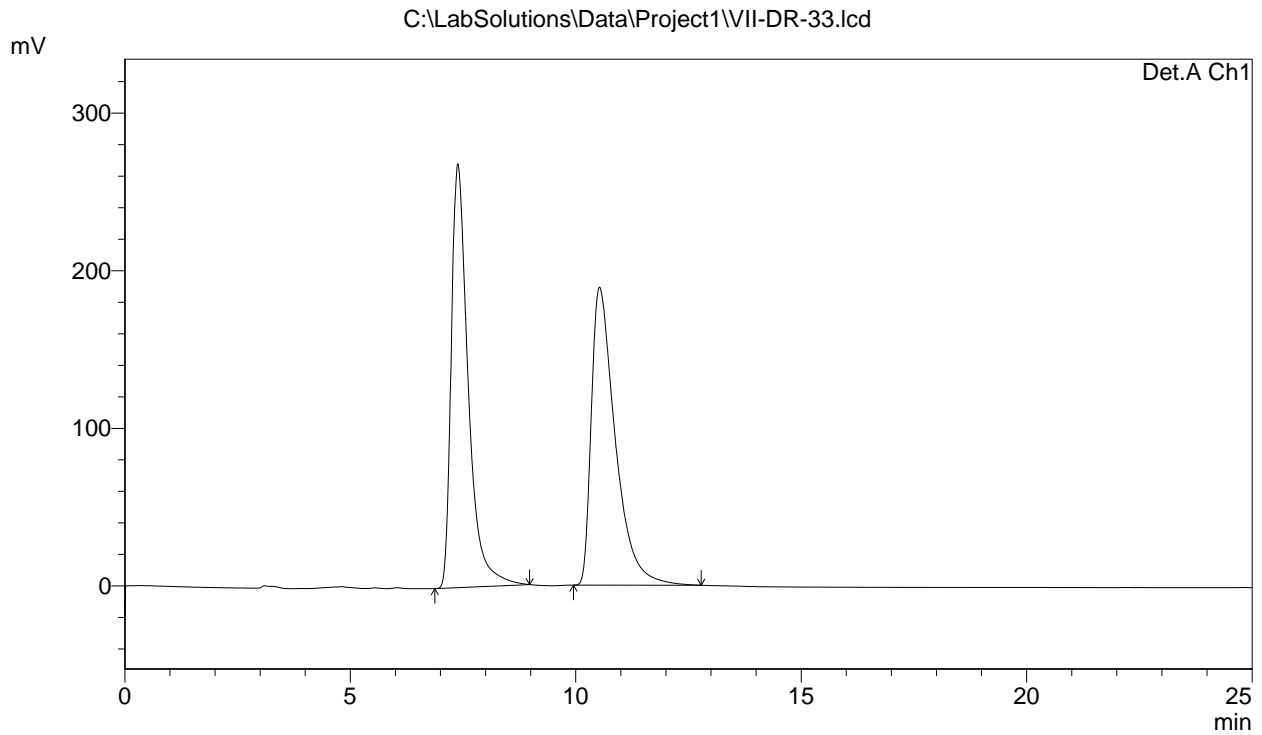
Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.500	1561298	106368	78.581	81.377
2	6.899	425559	24342	21.419	18.623
Total		1986858	130710	100.000	100.000



**11d**

# ==== Shimadzu LCsolution LC Data Image ====

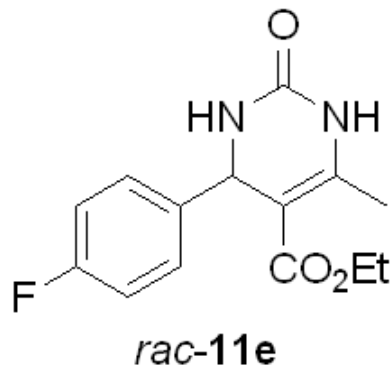
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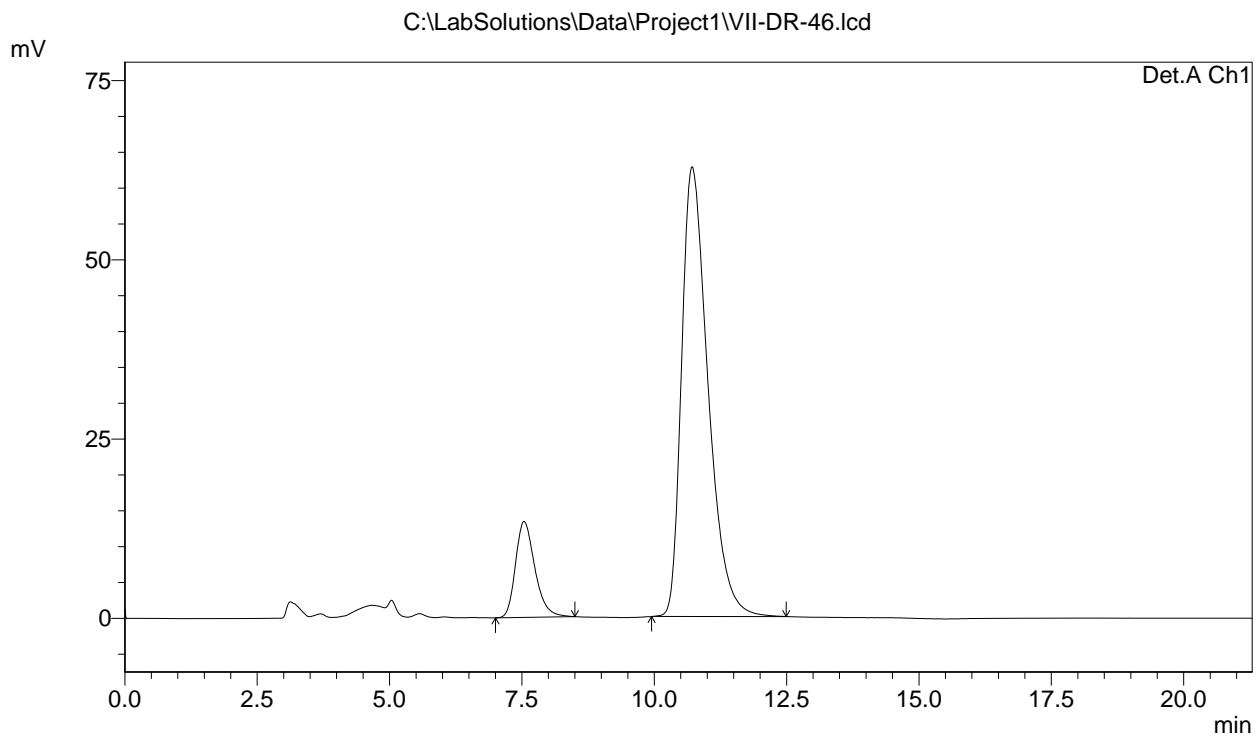
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.379	7043586	269018	50.242	58.721
2	10.524	6975699	189111	49.758	41.279
Total		14019285	458130	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

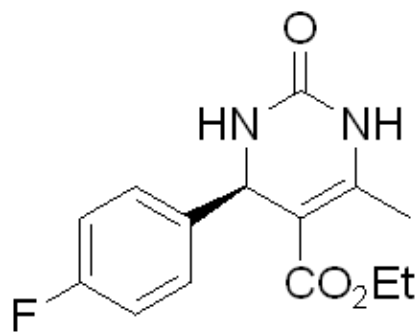
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PeakTable

Detector A Ch1 254nm

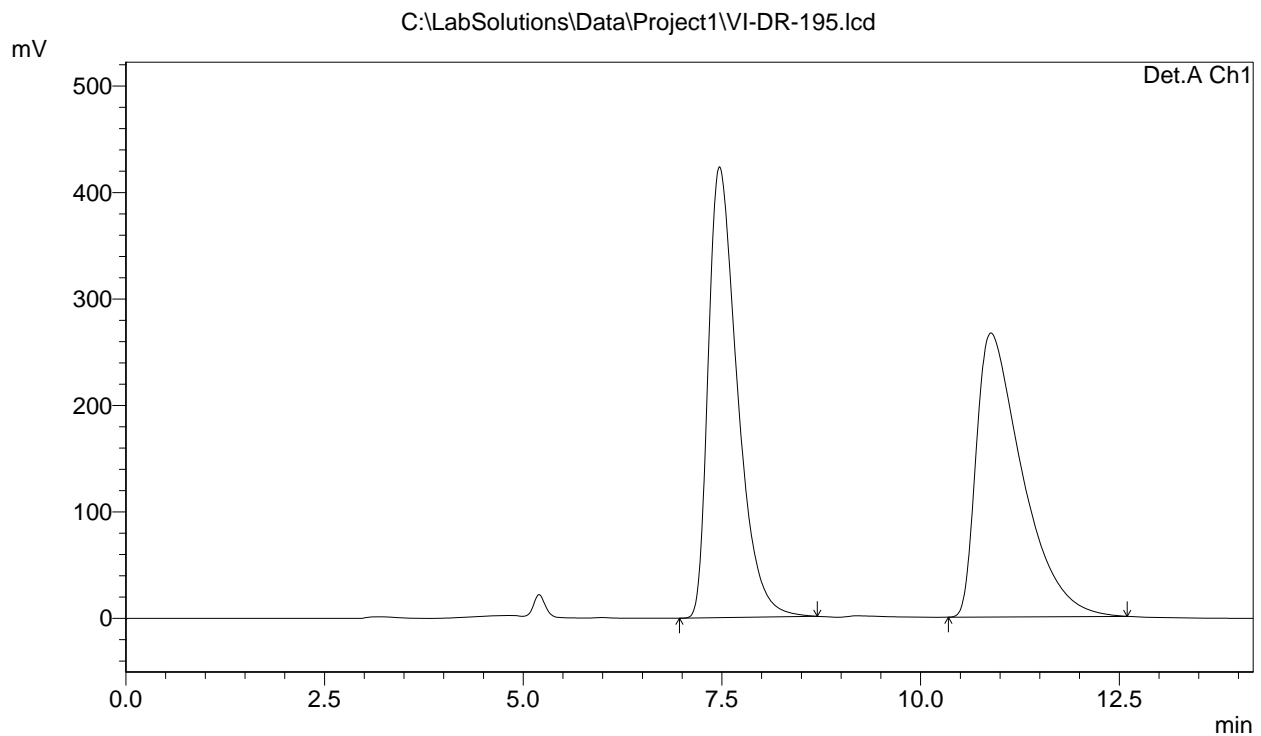
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.535	340677	13406	13.539	17.607
2	10.711	2175503	62736	86.461	82.393
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**11e**

# ==== Shimadzu LCsolution LC Data Image ====

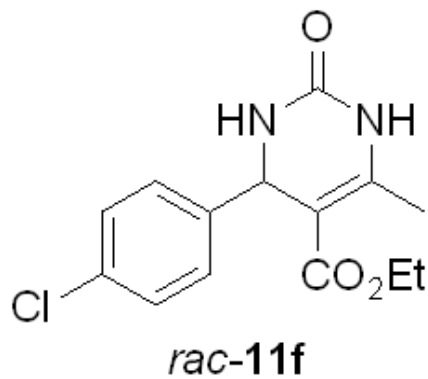
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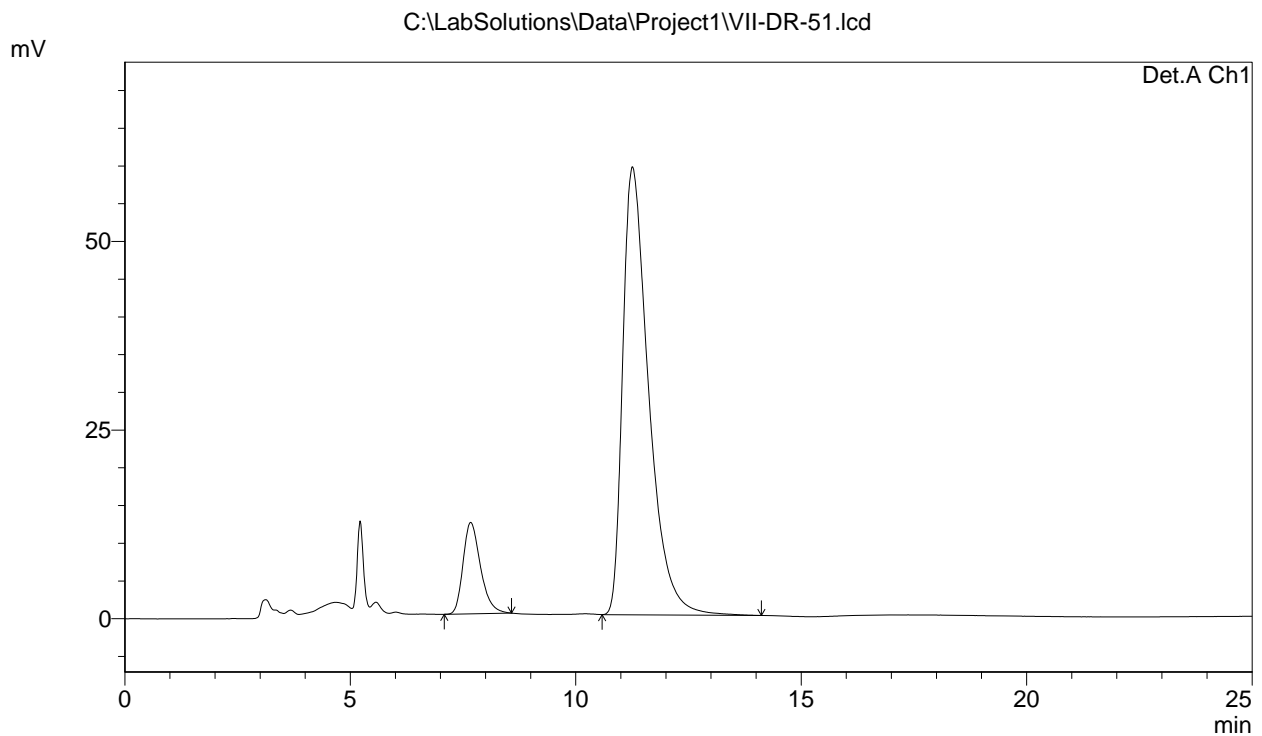
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.465	10778505	423554	50.100	61.347
2	10.880	10735360	266864	49.900	38.653
Total		21513865	690418	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

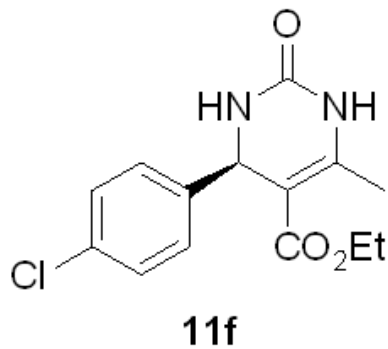
## <Chromatogram>



PeakTable

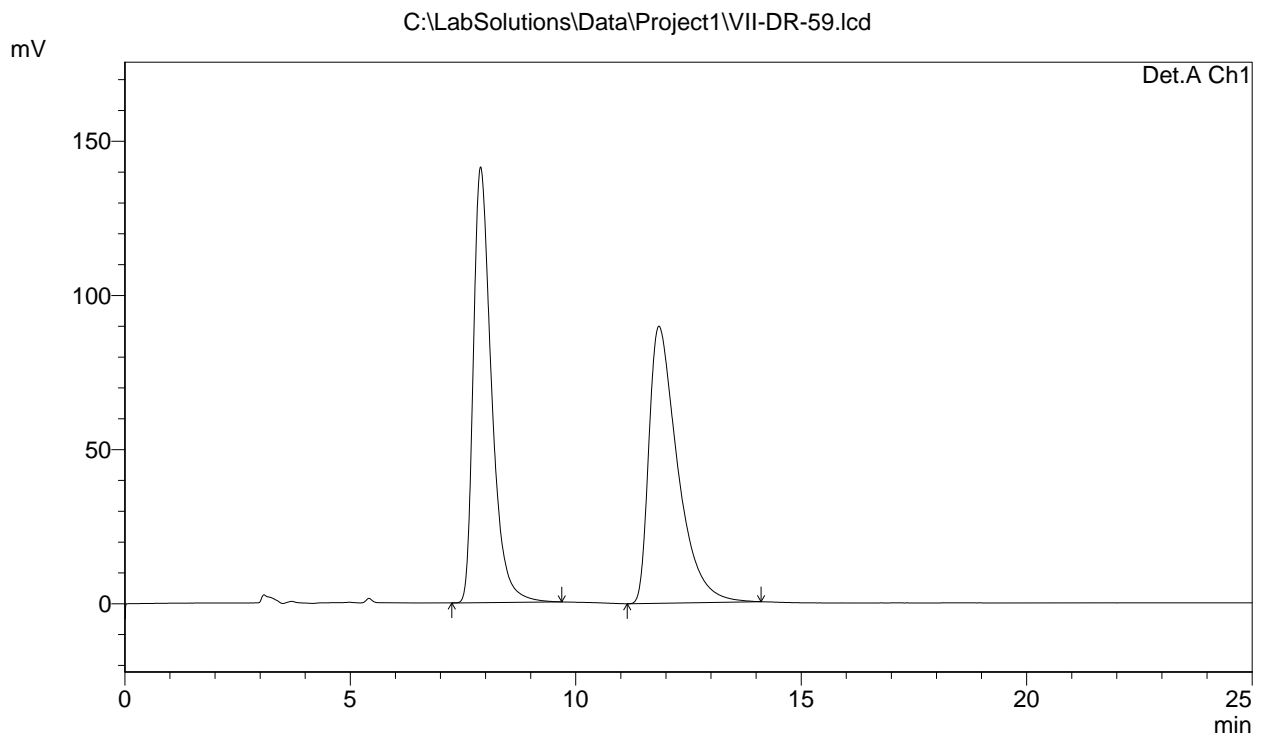
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.665	325950	12121	12.067	16.954
2	11.252	2375262	59376	87.933	83.046
Total		2701212	71497	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

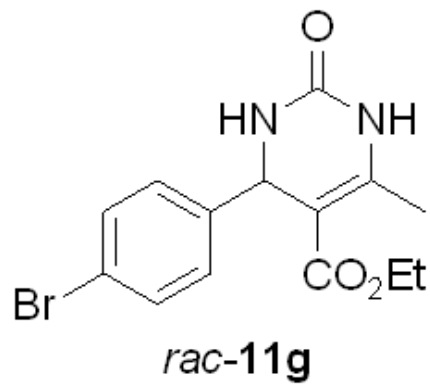
## <Chromatogram>



PeakTable

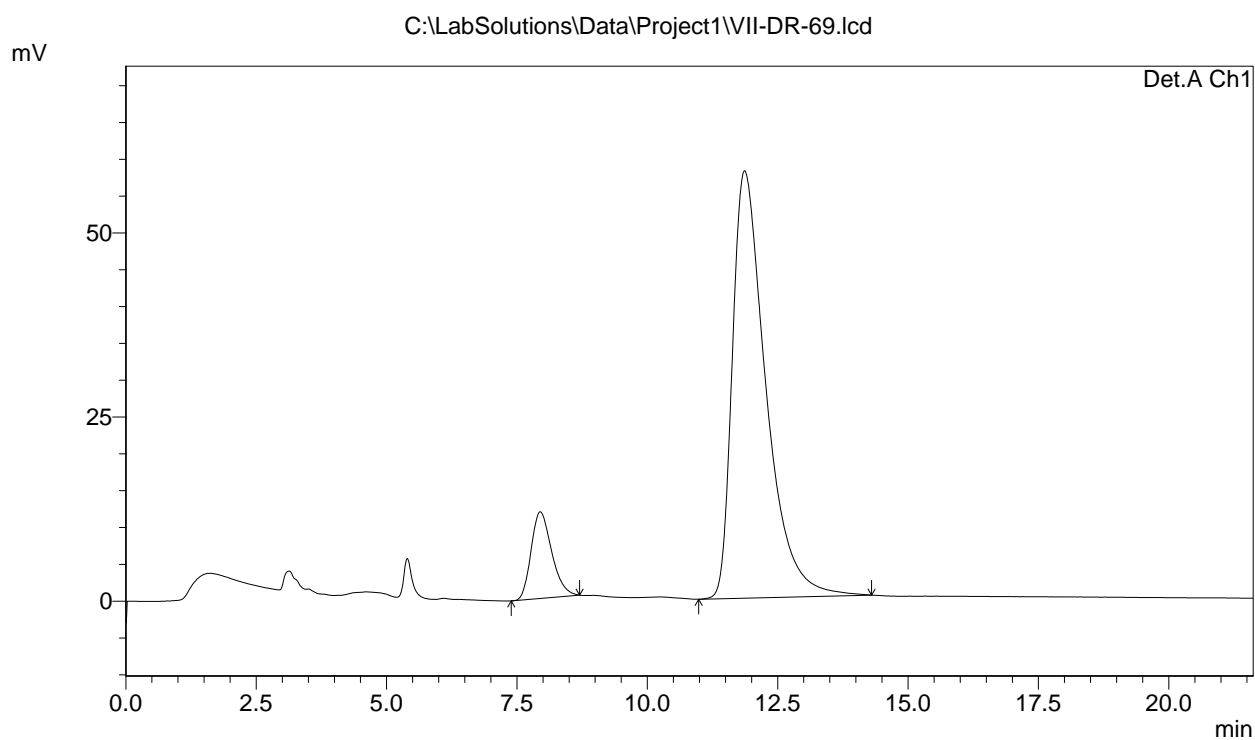
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.885	3967603	141385	49.965	61.129
2	11.841	3973178	89903	50.035	38.871
Total		7940781	231289	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

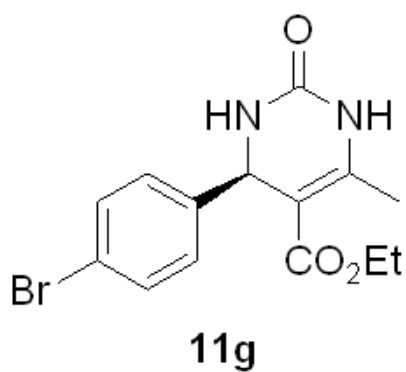
## <Chromatogram>



PeakTable

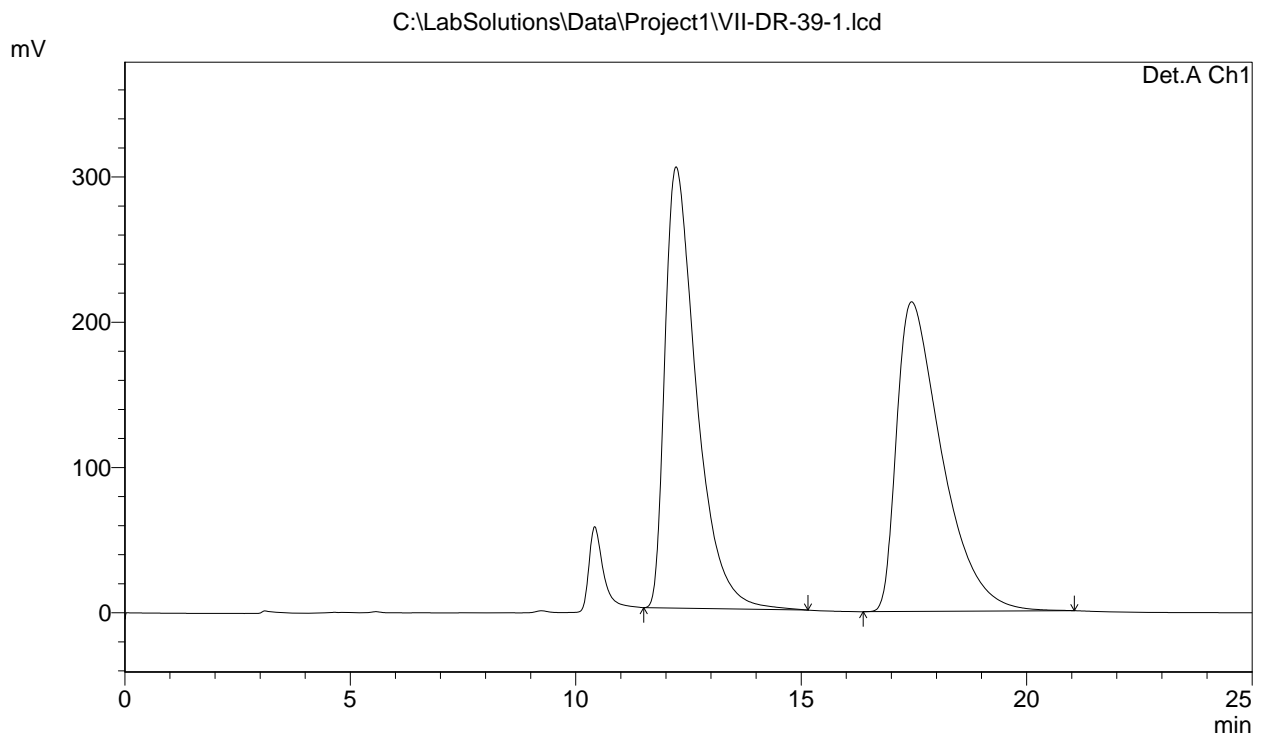
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.942	323339	11778	11.084	16.868
2	11.861	2593748	58046	88.916	83.132
Total		2917087	69823	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

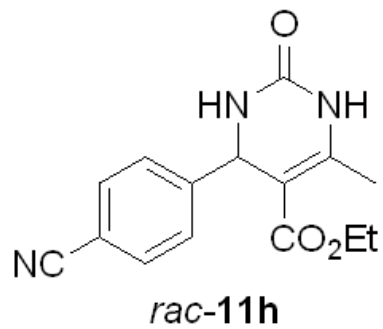
## <Chromatogram>



PeakTable

Detector A Ch1 254nm

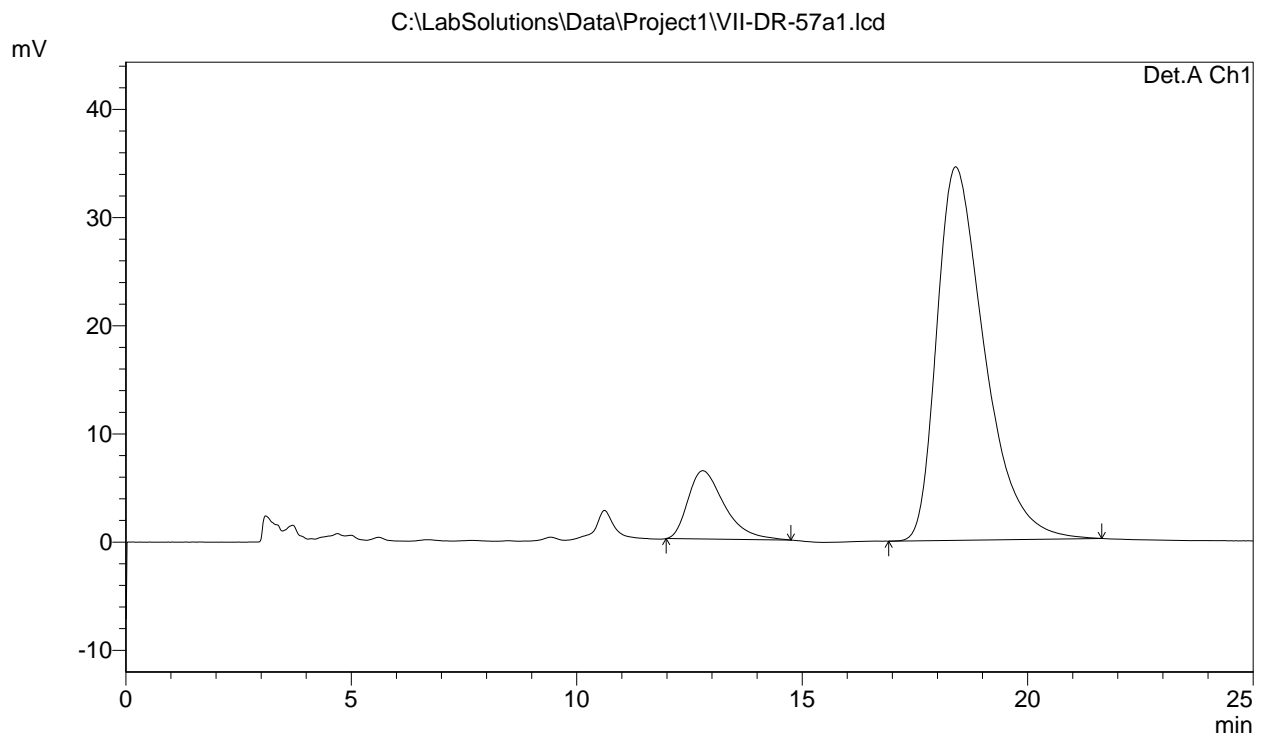
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.221	14737923	303815	49.799	58.768
2	17.444	14856830	213161	50.201	41.232
Total		29594753	516976	100.000	100.000





# ==== Shimadzu LCsolution LC Data Image ====

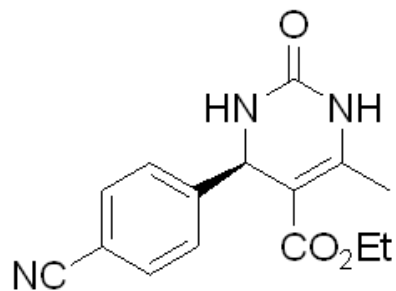
## <Chromatogram>



PeakTable

Detector A Ch1 254nm

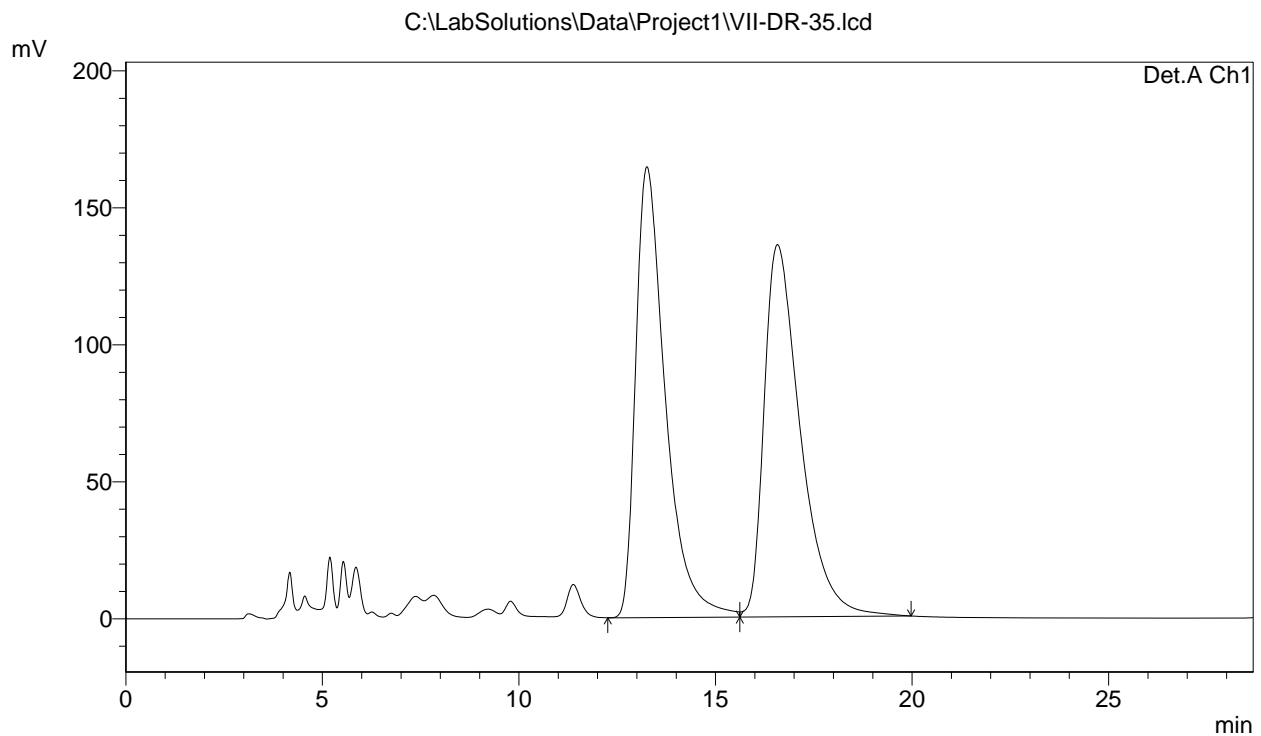
Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.789	353274	6312	12.203	15.452
2	18.400	2541605	34539	87.797	84.548
Total		2894879	40851	100.000	100.000



**11h**

# ==== Shimadzu LCsolution LC Data Image ====

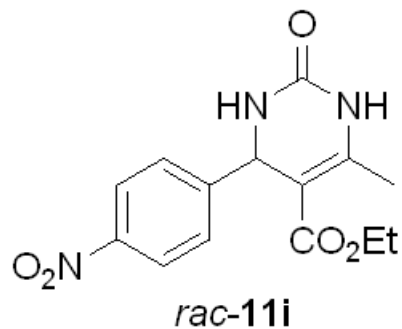
## <Chromatogram>



PeakTable

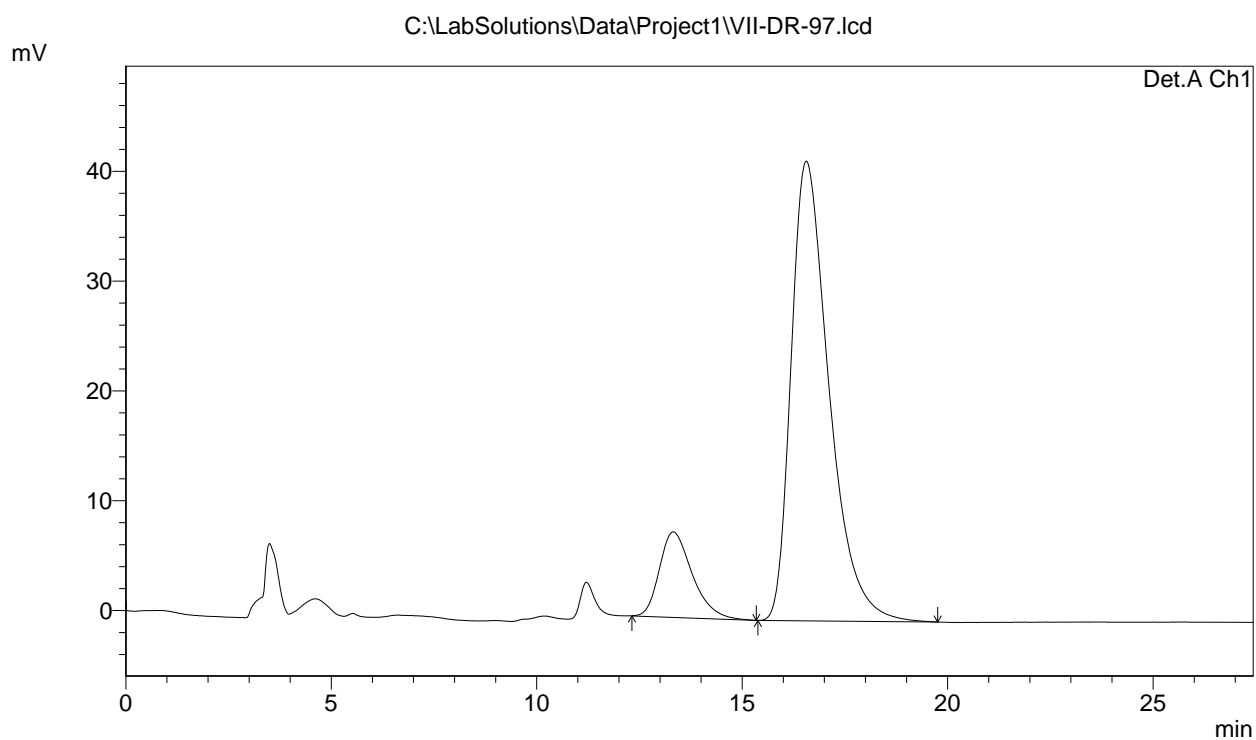
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.251	8637524	164534	49.817	54.769
2	16.572	8701094	135878	50.183	45.231
Total		17338618	300413	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

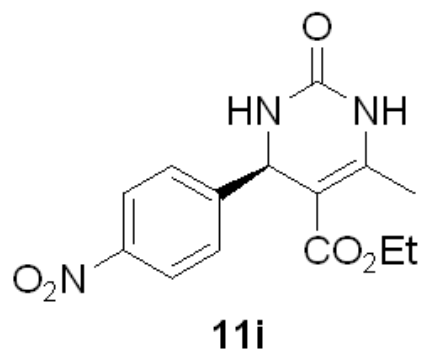
## <Chromatogram>



PeakTable

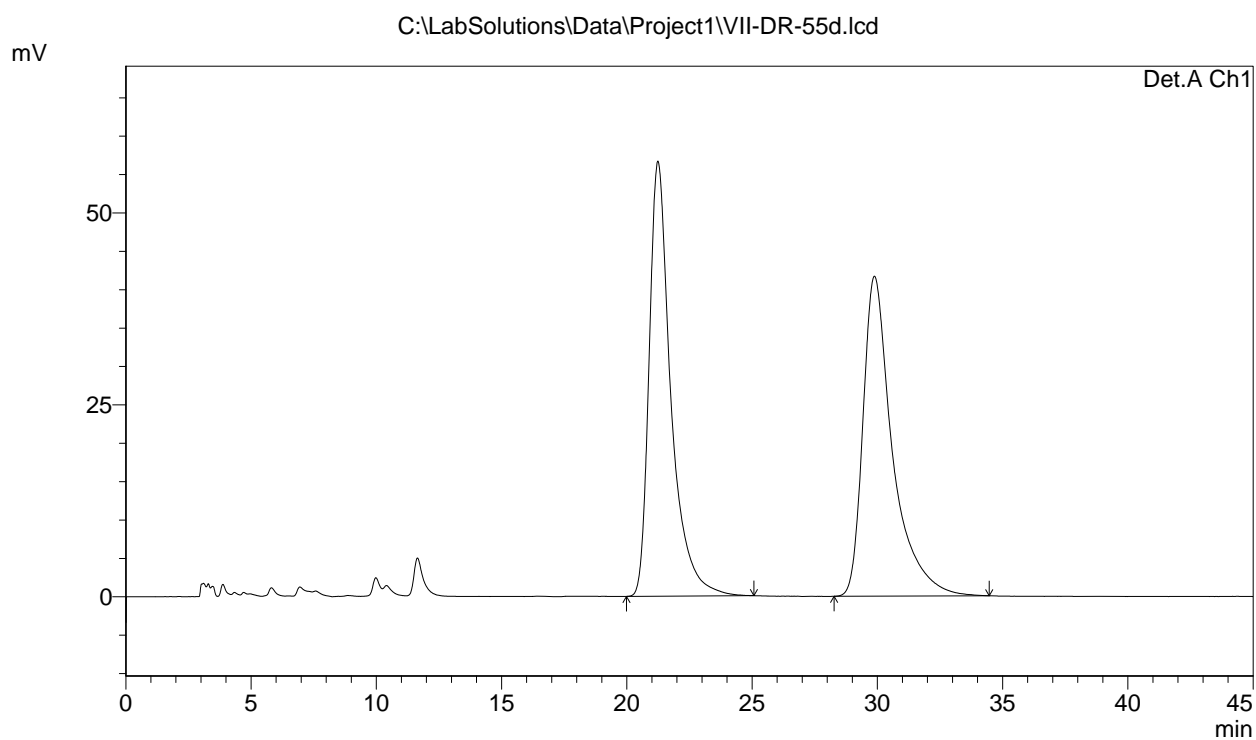
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.314	433929	7798	13.912	15.699
2	16.555	2685188	41876	86.088	84.301
Total		3119117	49675	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

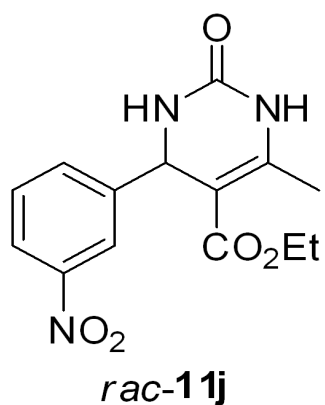
## <Chromatogram>



PeakTable

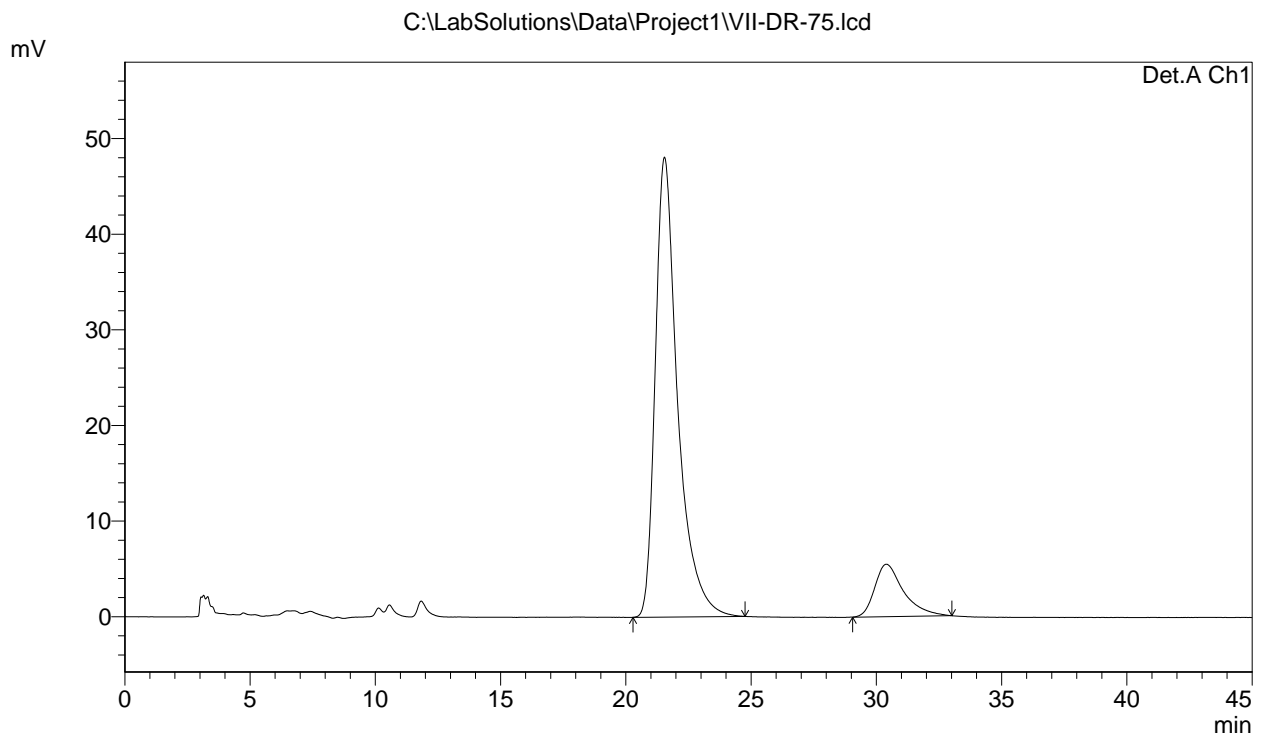
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.234	3417436	56680	50.047	57.620
2	29.879	3411064	41690	49.953	42.380
Total		6828500	98370	100.000	100.000



# ==== Shimadzu LCsolution LC Data Image ====

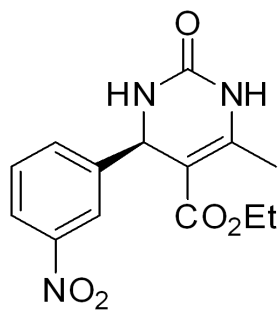
## <Chromatogram>



PeakTable

Detector A Ch1 254nm

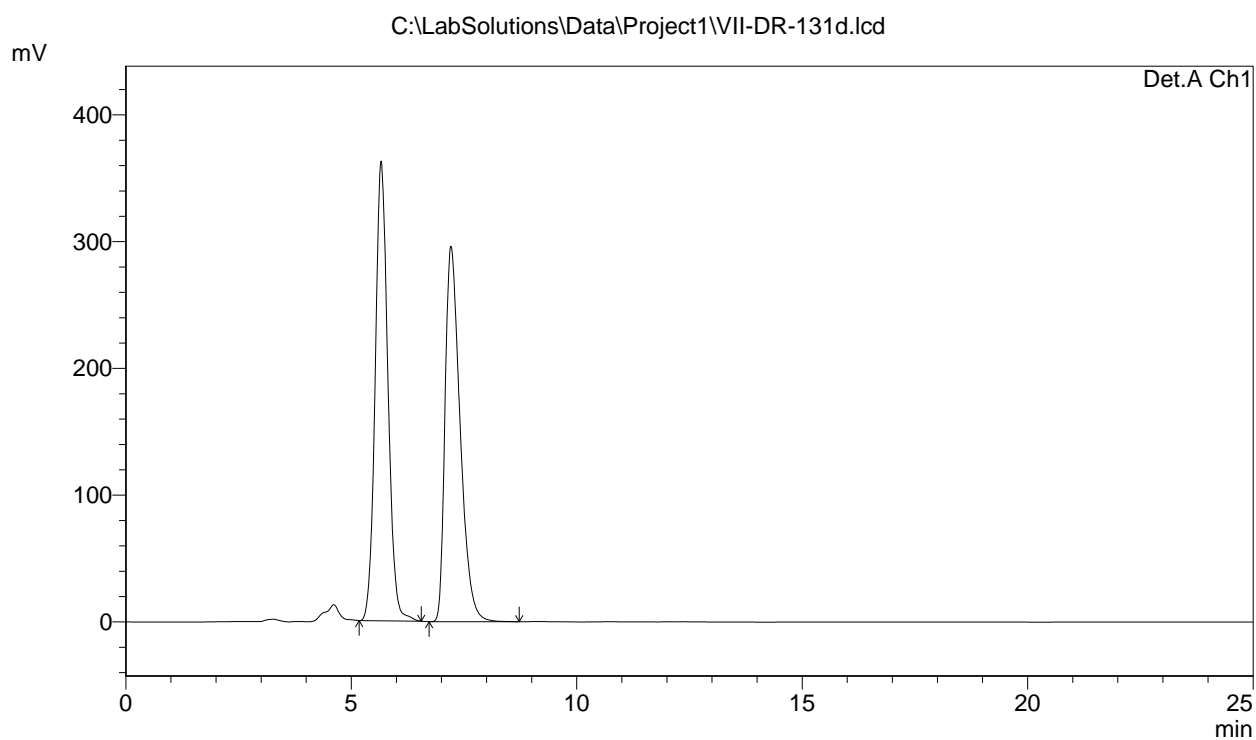
Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.537	2987651	48103	87.147	89.753
2	30.397	440644	5492	12.853	10.247
Total		3428294	53595	100.000	100.000



11j

# ==== Shimadzu LCsolution LC Data Image ====

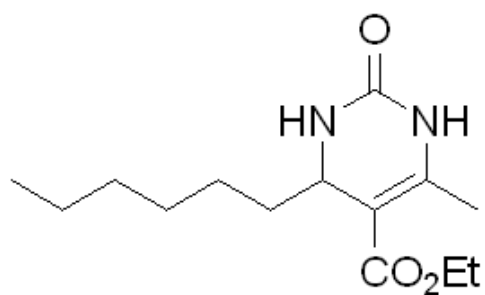
## <Chromatogram>



PeakTable

Detector A Ch1 254nm

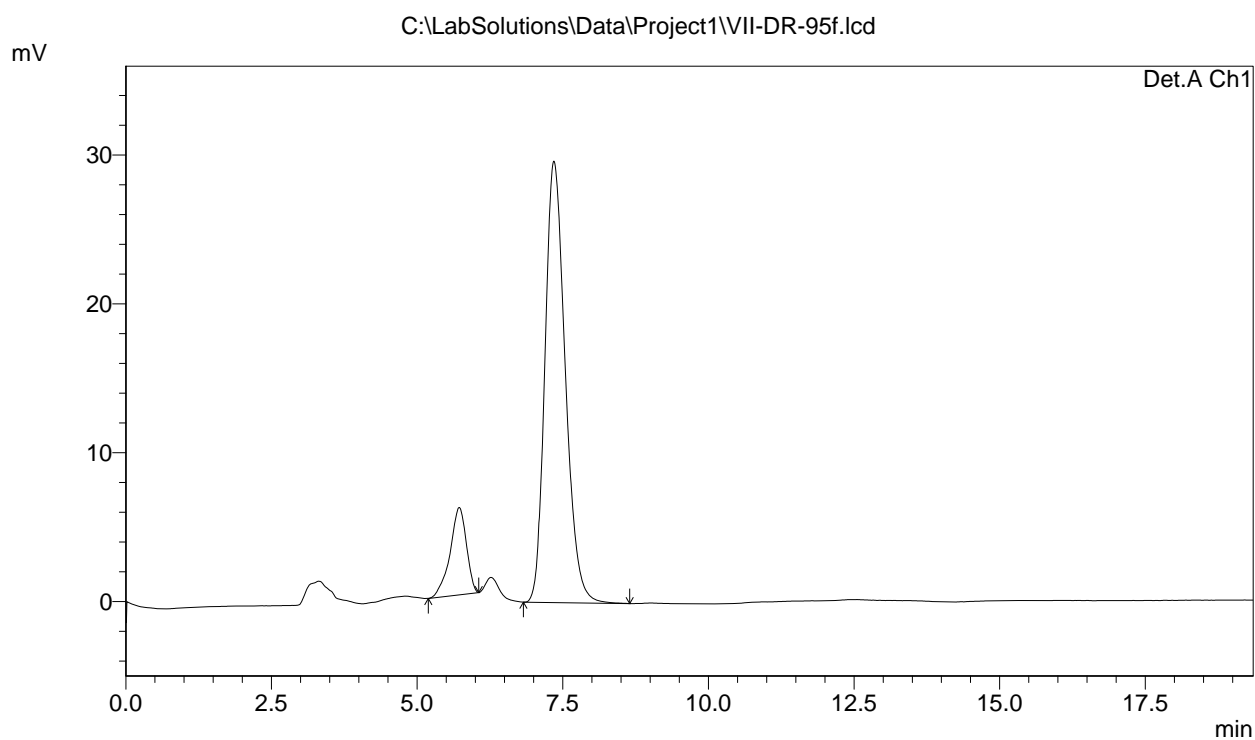
Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.657	7104171	362655	50.831	55.041
2	7.205	6871956	296220	49.169	44.959
Total		13976127	658875	100.000	100.000



*rac-11k*

# ==== Shimadzu LCsolution LC Data Image ====

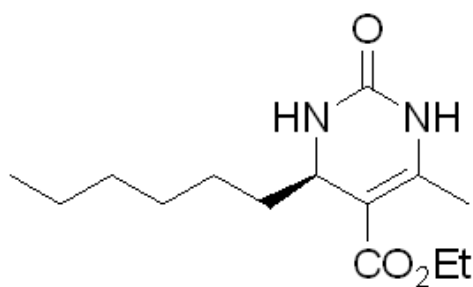
## <Chromatogram>



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.718	114802	5877	13.773	16.535
2	7.344	718716	29666	86.227	83.465
Total		833518	35542	100.000	100.000



11k