# Supplementary Material for

Organocatalytic enantioselective conjugate addition of nitromethane to benzylidine-2-benzoyl acetate: Asymmetric synthesis of ABT – 627, an endothelin receptor antagonist

Saumen Hajra\* 1, Sk Mohammad Aziz<sup>2,3</sup>, Bibekananda Jana<sup>1,2</sup>, Sunit Hazra<sup>2,4</sup>

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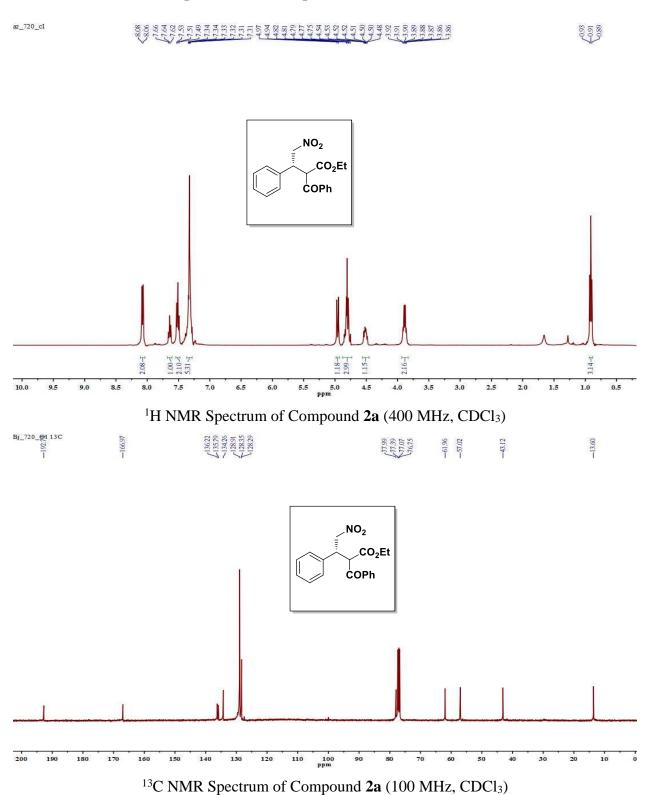
S1
51
S2-S19
S20-S35

<sup>&</sup>lt;sup>1</sup>Centre of Biomedical Research, Sanjay Gandhi Post-Graduate Institute of Medical Sciences Campus, Raebareli Road, Lucknow 226014, India

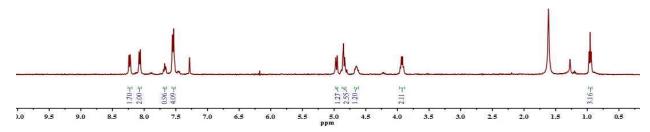
<sup>&</sup>lt;sup>2</sup>Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India <sup>3</sup>Present address: Department of Chemistry, Narajole Raj College, Narajole, West Midnapore 721211, India

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# <sup>1</sup>H NMR and <sup>13</sup>C NMR Spectra of all Compounds:



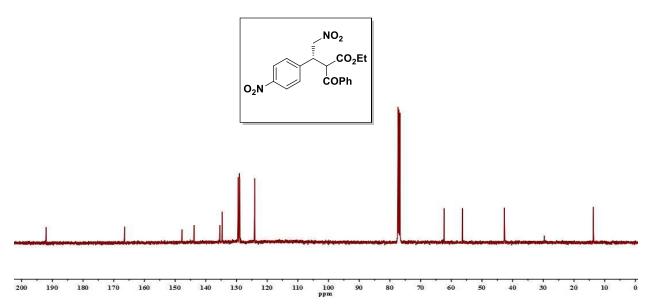




<sup>1</sup>H NMR Spectrum of Compound **2b** (400 MHz, CDCl<sub>3</sub>)

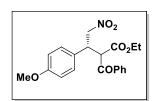
-147.79 -143.84 -135.42 -134.62 -129.04 -128.92 -124.08

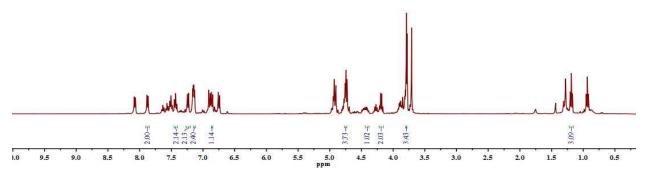
77.28 77.05 77.05 76.73 —-62.36 —-56.39 13.67



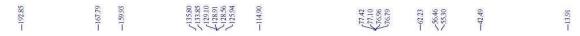
<sup>13</sup>C NMR Spectrum of Compound **2b** (100 MHz, CDCl<sub>3</sub>)

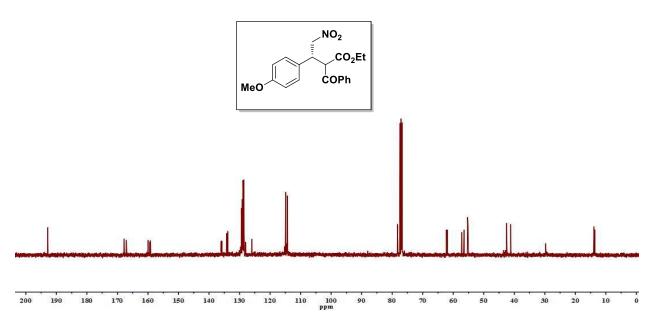
£119



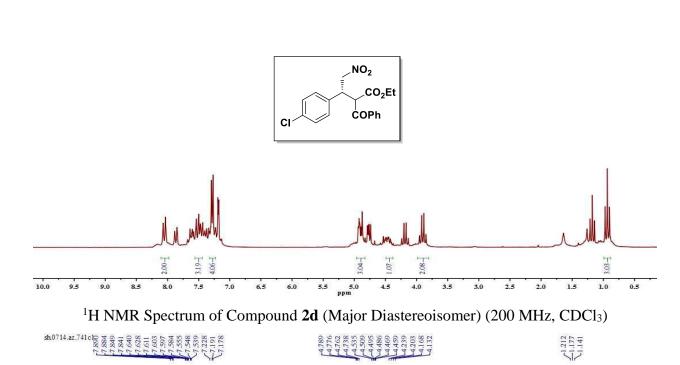


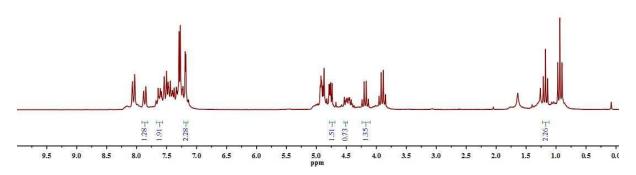
<sup>1</sup>H NMR Spectrum of Compound **2c** (400 MHz, CDCl<sub>3</sub>)



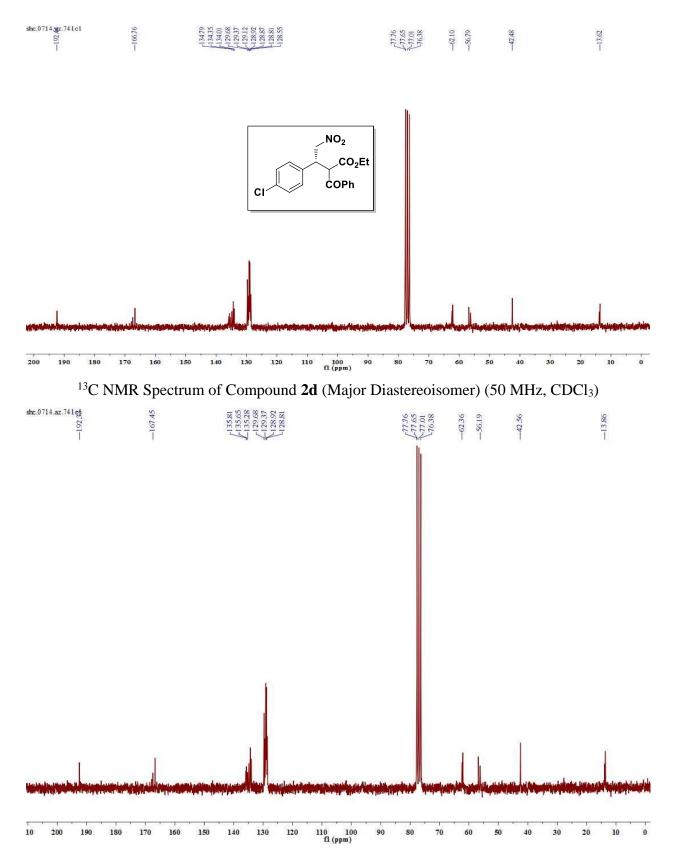


<sup>13</sup>C NMR Spectrum of Compound **2c** (100 MHz, CDCl<sub>3</sub>)





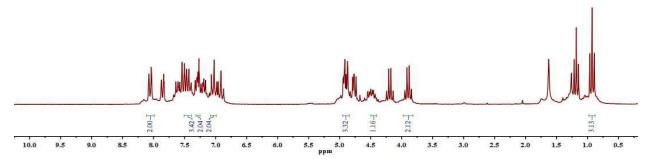
<sup>1</sup>H NMR Spectrum of Compound **2d** (Minor Diastereoisomer) (200 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C NMR Spectrum of Compound **2d** (Minor Diastereoisomer) (50 MHz, CDCl<sub>3</sub>)



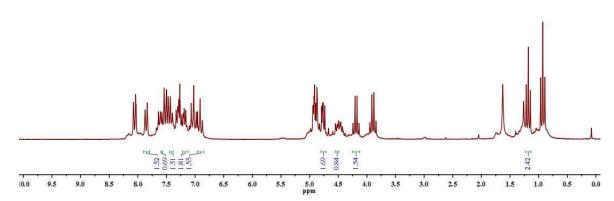




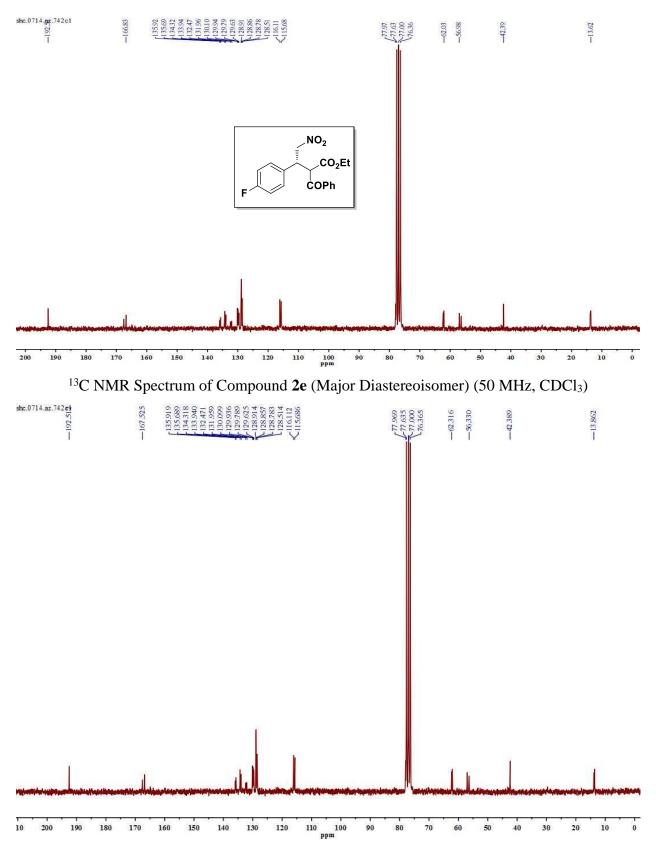
<sup>1</sup>H NMR Spectrum of Compound **2e** (Major Diastereoisomer) (200 MHz, CDCl<sub>3</sub>)



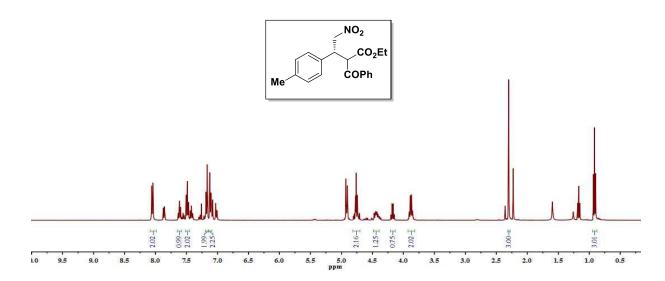




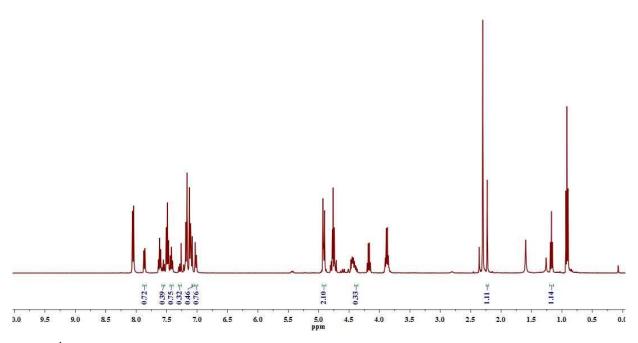
<sup>1</sup>H NMR Spectrum of Compound **2e** (Minor Diastereoisomer) (200 MHz, CDCl<sub>3</sub>)



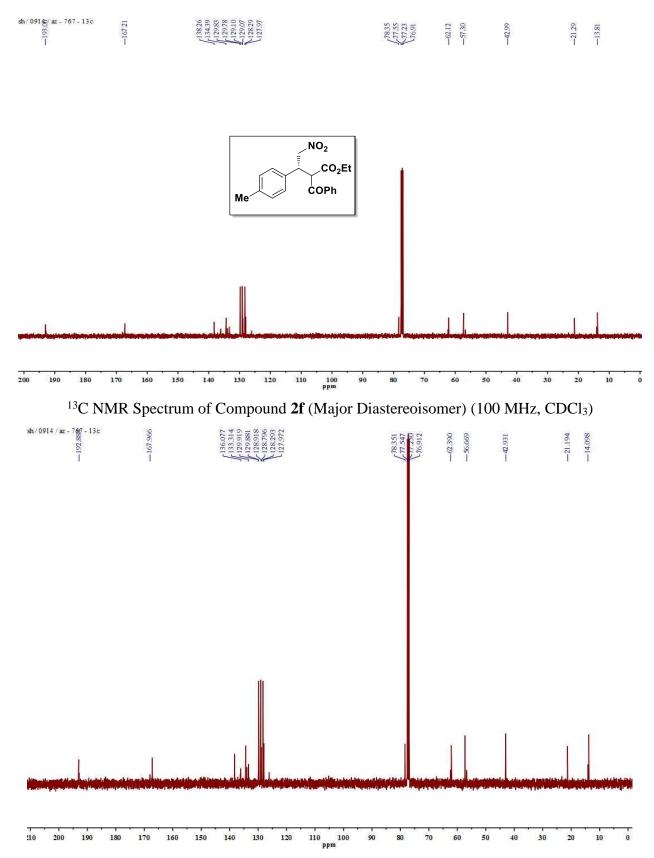
<sup>13</sup>C NMR Spectrum of Compound **2e** (Minor Diastereoisomer) (50 MHz, CDCl<sub>3</sub>)



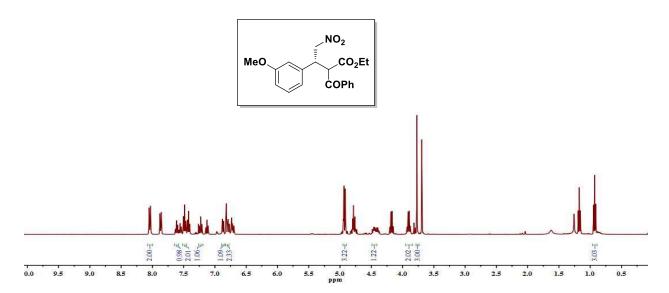
<sup>1</sup>H NMR Spectrum of Compound **2f** (Major Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



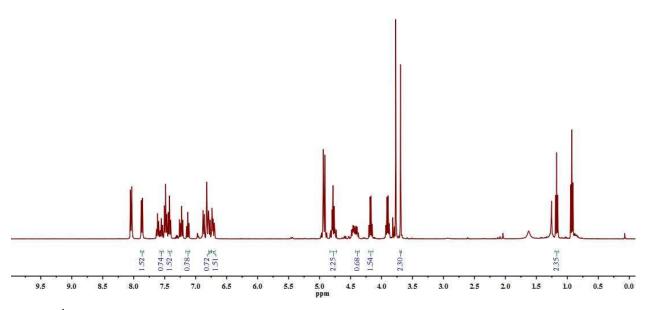
<sup>1</sup>H NMR Spectrum of Compound **2f** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



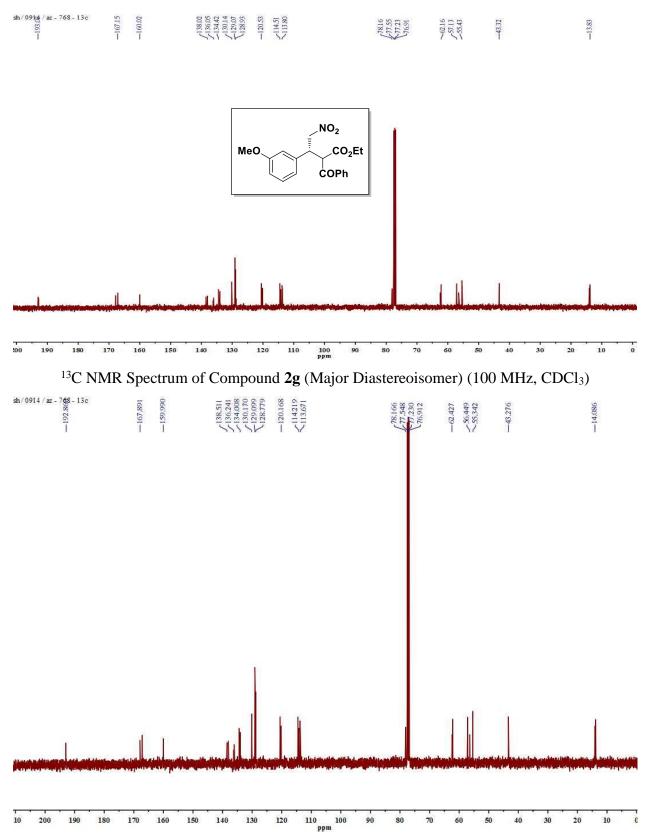
<sup>13</sup>C NMR Spectrum of Compound **2f** (Minor Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)



 $^1H$  NMR Spectrum of Compound 2g (Major Diastereoisomer) (400 MHz, CDCl3)  $^{\text{sh}/\text{0}}$  2 (Major Diastereoisomer) (400 MHz, CDCl3)  $^{\text{sh}/\text{0}}$  2 (Major Diastereoisomer) (400 MHz, CDCl3)

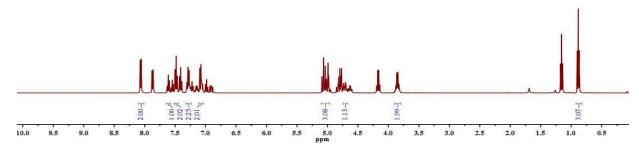


<sup>1</sup>H NMR Spectrum of Compound **2g** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



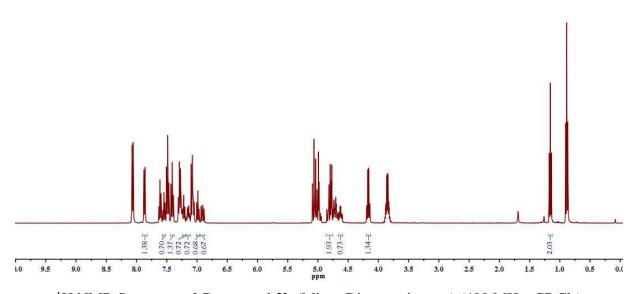
<sup>13</sup>C NMR Spectrum of Compound **2g** (Minor Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)



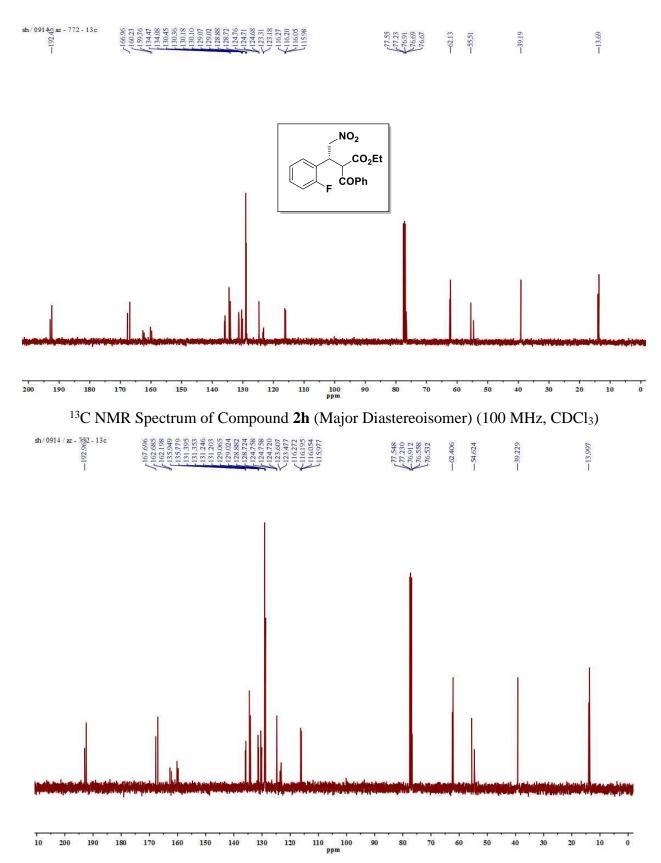


<sup>1</sup>H NMR Spectrum of Compound **2h** (Major Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)

7 288 7 7 882 7 882 7 88

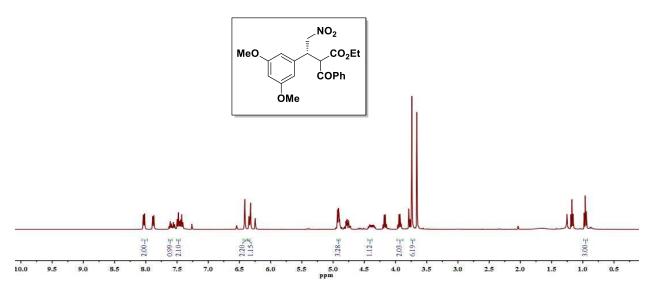


<sup>1</sup>H NMR Spectrum of Compound **2h** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)

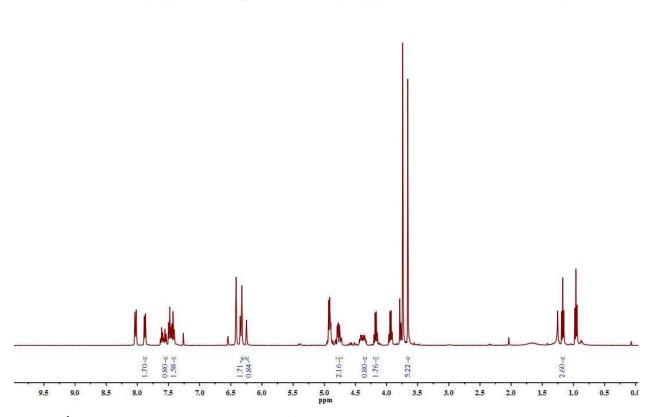


<sup>13</sup>C NMR Spectrum of Compound **2h** (Minor Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)

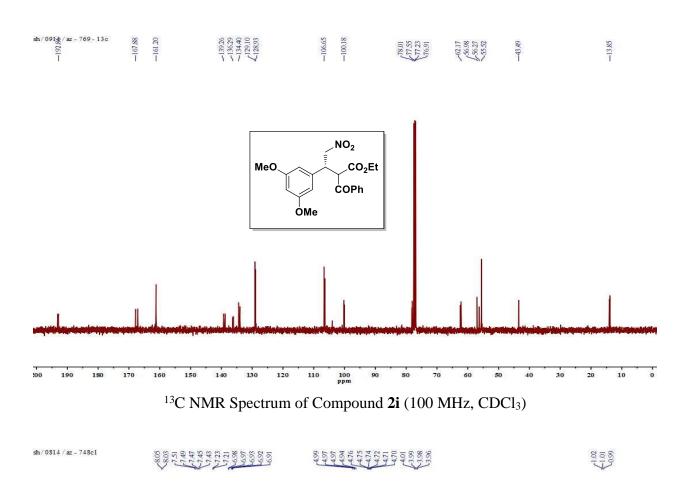
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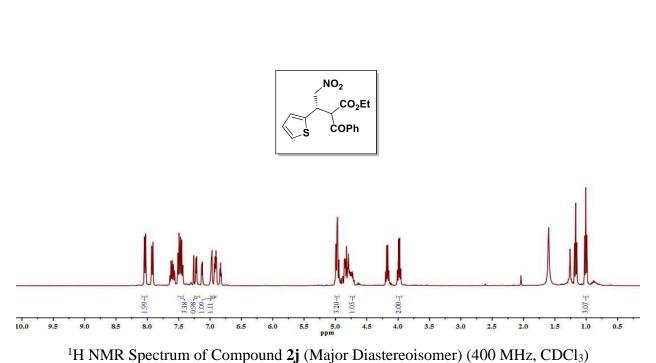


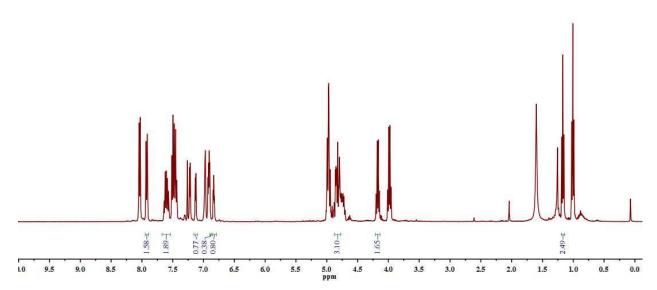
<sup>1</sup>H NMR Spectrum of Compound **2i** (Major Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



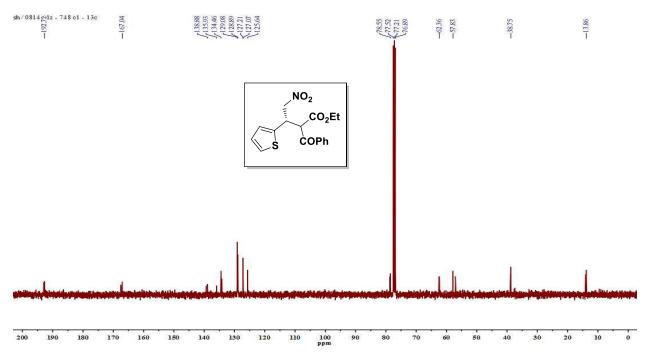
<sup>1</sup>H NMR Spectrum of Compound **2i** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



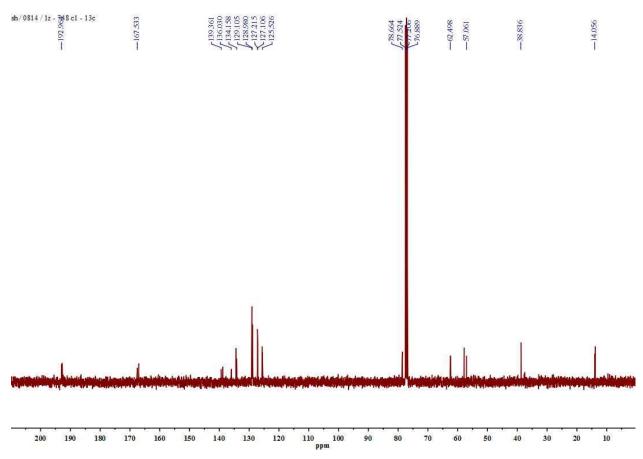




<sup>1</sup>H NMR Spectrum of Compound **2j** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



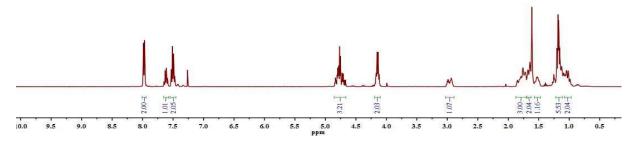
<sup>13</sup>C NMR Spectrum of Compound **2j** (Major Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)



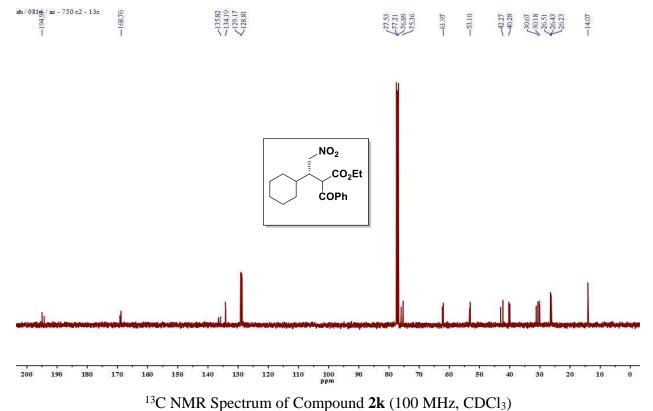
<sup>13</sup>C NMR Spectrum of Compound **2j** (Minor Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)

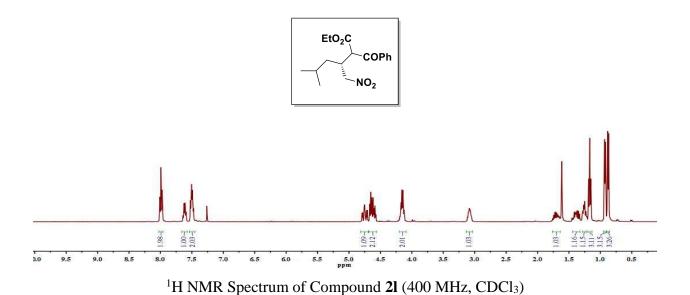


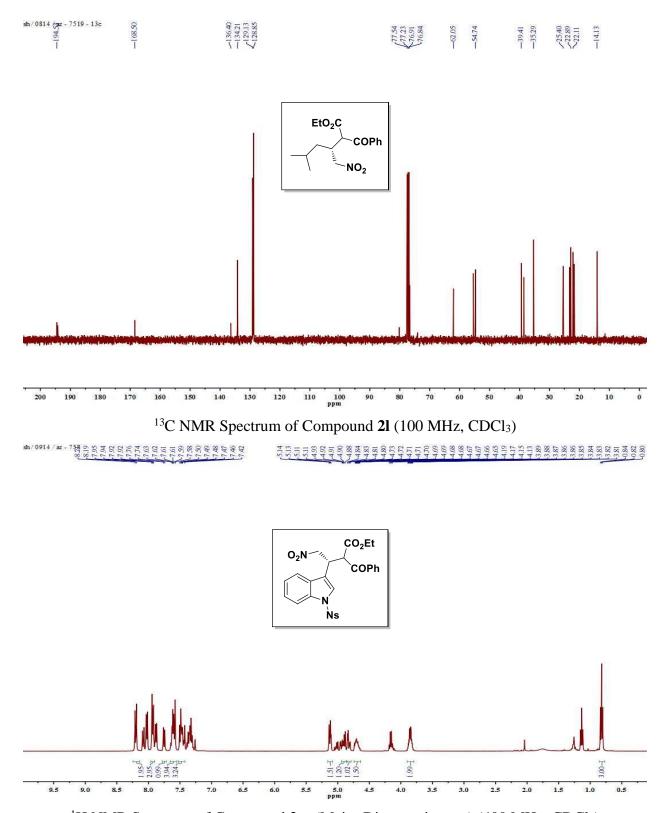




 $^{1}H$  NMR Spectrum of Compound 2k (400 MHz, CDCl<sub>3</sub>)



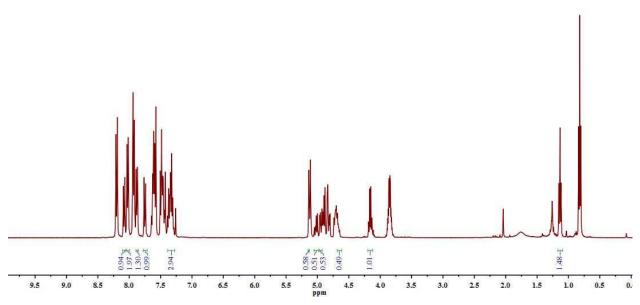




<sup>1</sup>H NMR Spectrum of Compound **2m** (Major Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)

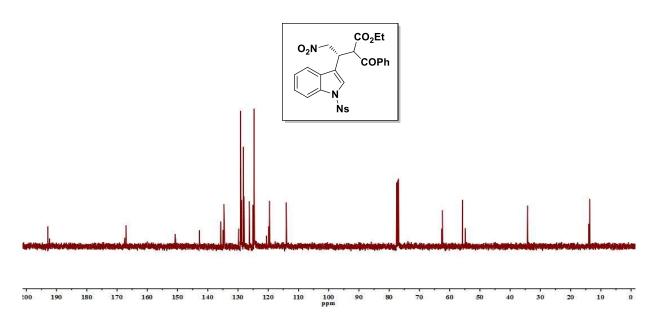




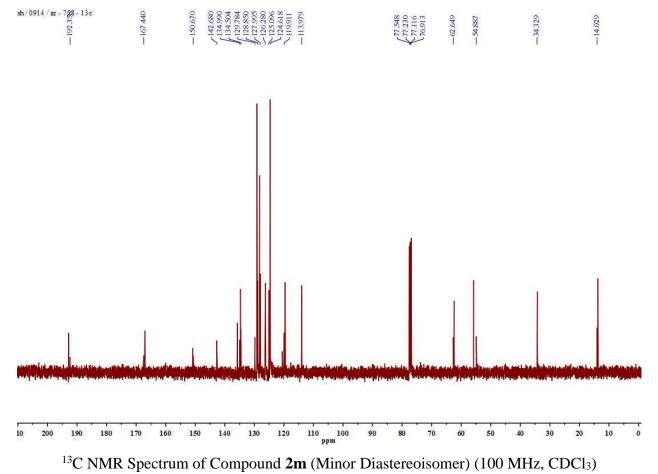


<sup>1</sup>H NMR Spectrum of Compound **2m** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)

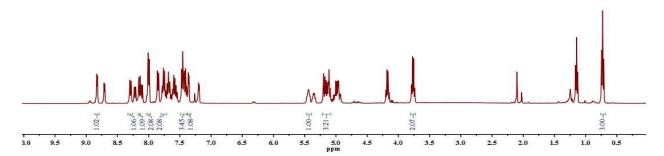




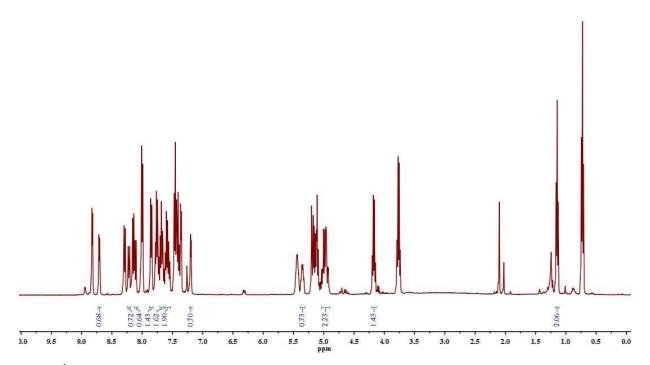
<sup>13</sup>C NMR Spectrum of Compound **2m** (Major Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)



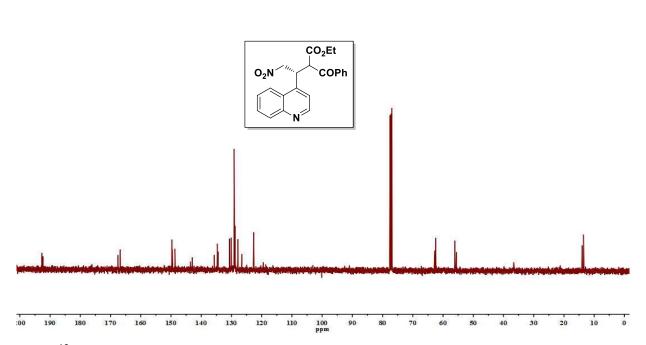




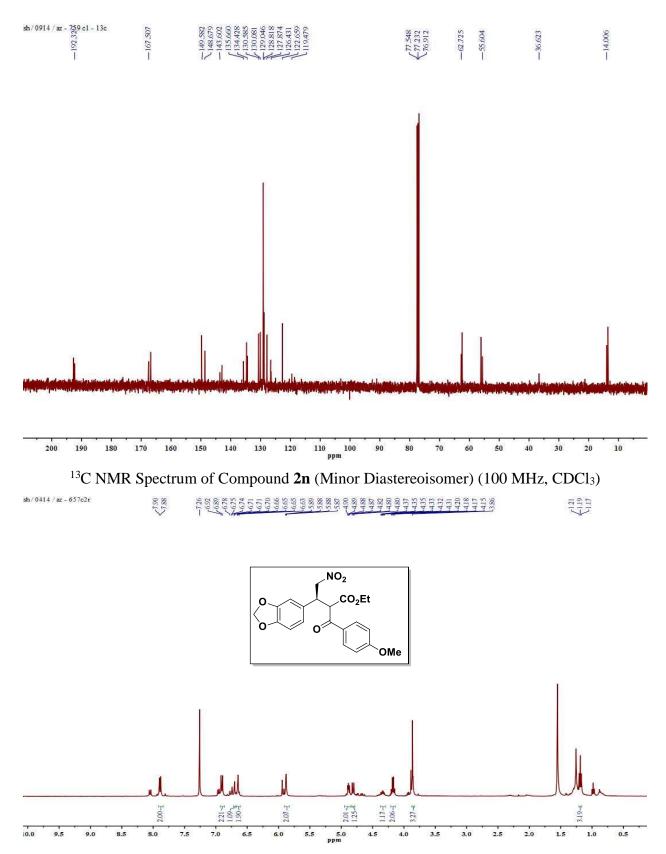
<sup>1</sup>H NMR Spectrum of Compound **2n** (Major Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



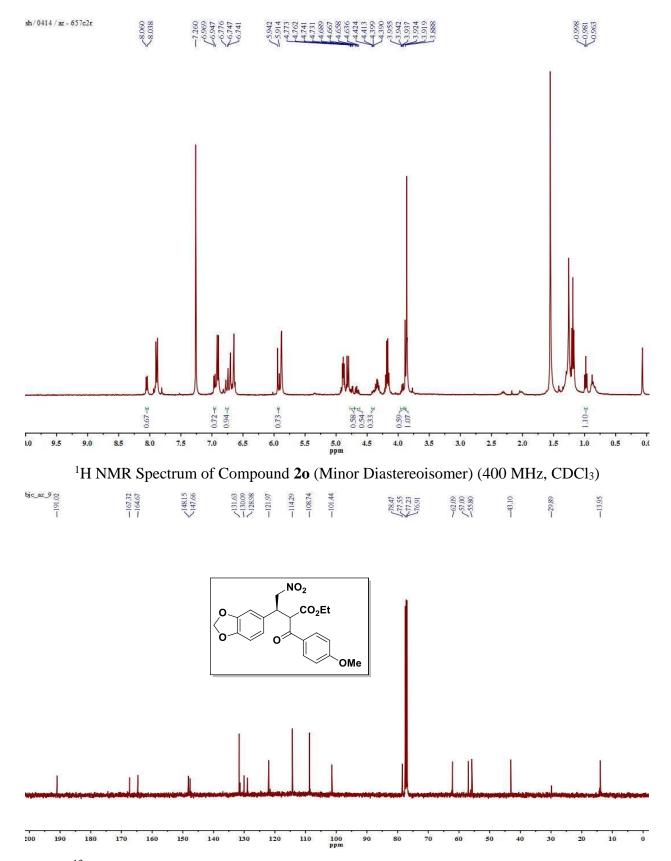
 $^{1}$ H NMR Spectrum of Compound **2n** (Minor Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)  $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sp}}$   $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sp}}$   $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sp}}$   $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sp}}$   $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sp}}$   $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sp}}$   $^{\text{sh/09l}+/\text{az}-759\,\text{cl}-13c}$   $^{\text{sh/09l}+/\text{az}-759\,\text{$ 



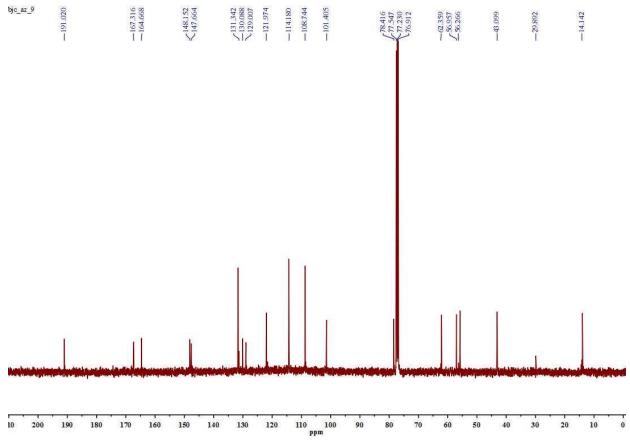
<sup>13</sup>C NMR Spectrum of Compound **2n** (Major Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)



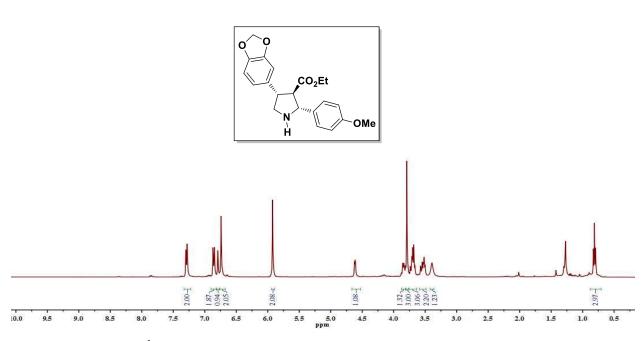
<sup>1</sup>H NMR Spectrum of Compound **20** (Major Diastereoisomer) (400 MHz, CDCl<sub>3</sub>)



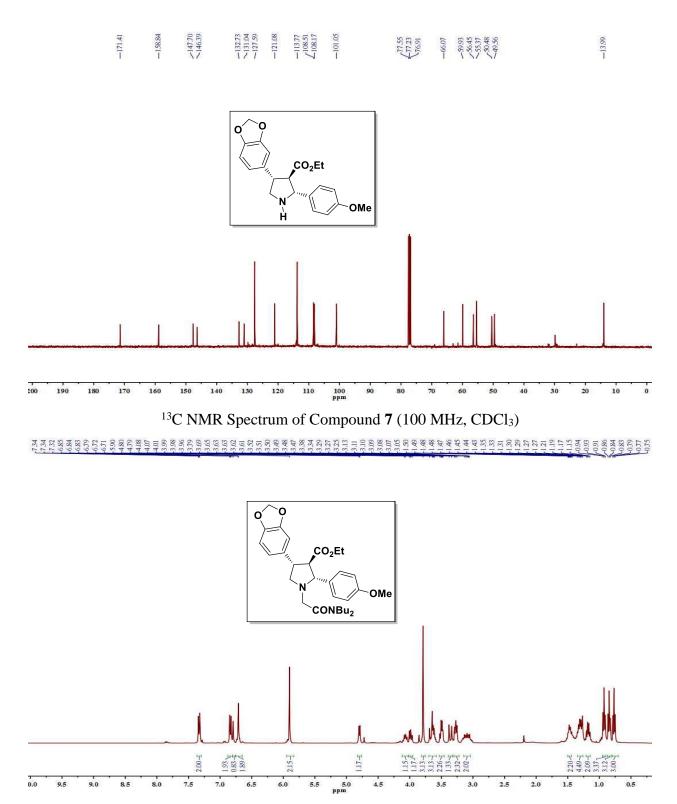
<sup>13</sup>C NMR Spectrum of Compound **20** (Major Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)



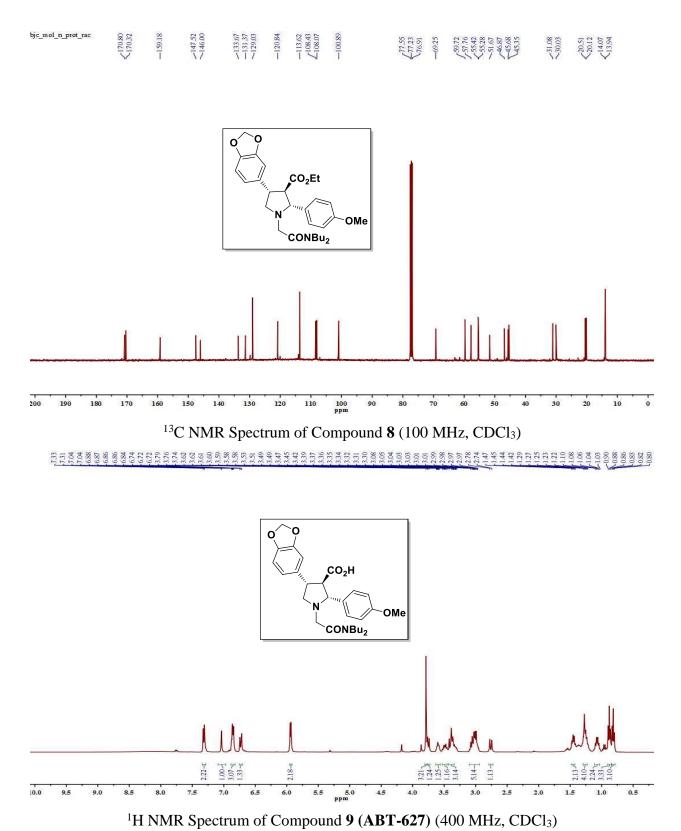
 $^{13}$ C NMR Spectrum of Compound **20** (Minor Diastereoisomer) (100 MHz, CDCl<sub>3</sub>)

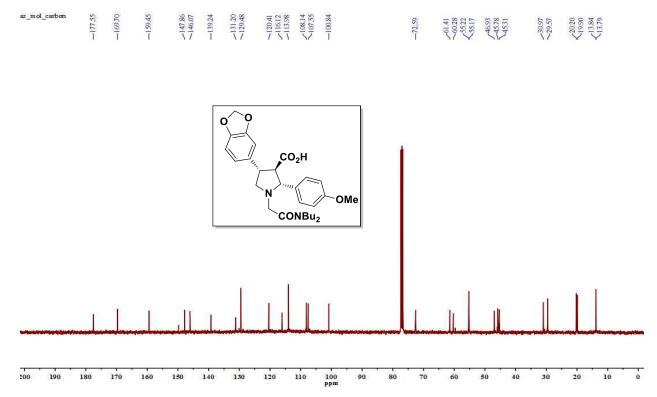


<sup>1</sup>H NMR Spectrum of Compound 7 (400 MHz, CDCl<sub>3</sub>)



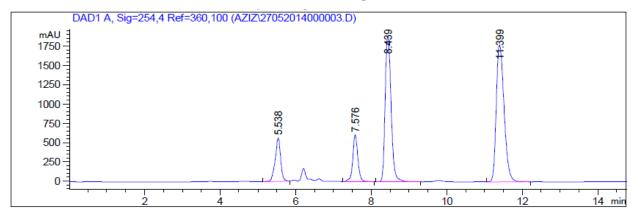
<sup>1</sup>H NMR Spectrum of Compound 8 (400 MHz, CDCl<sub>3</sub>)



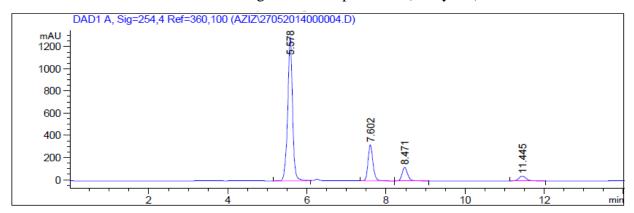


<sup>13</sup>C NMR Spectrum of Compound 9 (ABT-627) (100 MHz, CDCl<sub>3</sub>)

# **HPLC Chromatogram**



HPLC Chromatogram of Compound 2a (catalyst F)



Area Percent Report

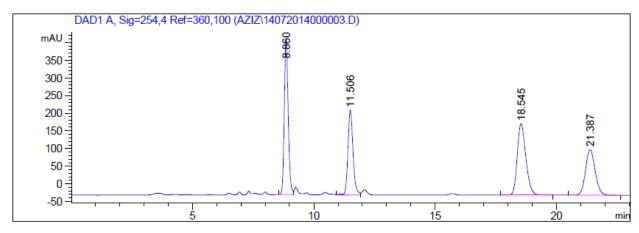
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Use Multiplier & Dilution Factor with ISTDs

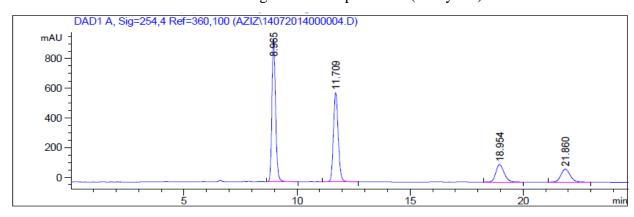
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Peak	${\tt RetTime}$	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	5.578	BV	0.1271	1.09664e4	1291.38562	70.6129
2	7.602	VB	0.1330	2814.12988	325.04605	18.1203
3	8.471	BB	0.1469	1189.12573	122.90531	7.6568
4	11.445	ВВ	0.1992	560.62067	43.25634	3.6099

HPLC Chromatogram of Compound 2a (catalyst H)



HPLC Chromatogram of Compound 2b (catalyst F)



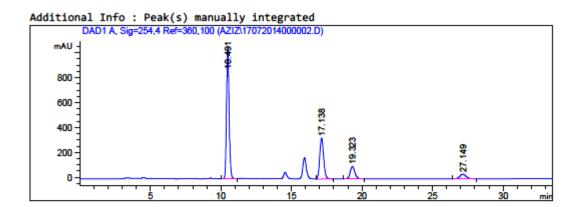
Area Percent Report

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Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
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1	8.965	VB	0.1748	1.09495e4	961.63416	43.3251
2	11.709	BB	0.2257	8857.30371	601.97253	35.0467
3	18.954	BB	0.3936	2993.21436	118.13834	11.8436
4	21.860	BB	0.4395	2472.86450	87.56722	9.7847

HPLC Chromatogram of Compound 2b (catalyst H)



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#### Area Percent Report

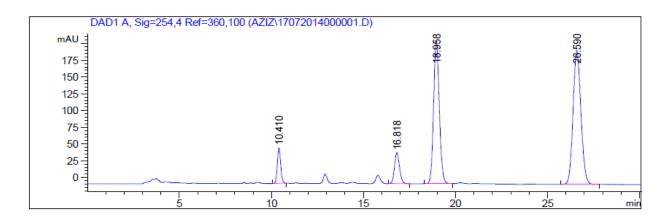
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
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1	10.491	BB	0.1978	1.34707e4	1049.05823	58.4579
2	17.138	BB	0.2966	6259.89355	328.07233	27.1657
3	19.323	BB	0.3443	2210.84521	99.09370	9.5943
4	27.149	BB	0.4696	1101.96289	35.95162	4.7821

HPLC Chromatogram of Compound 2c (catalyst F)



### Area Percent Report

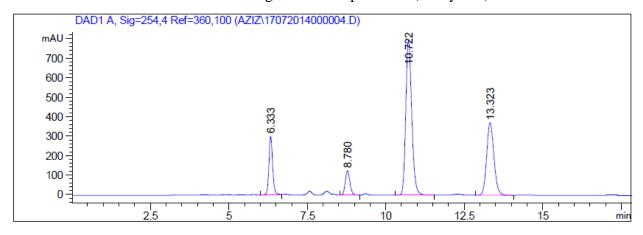
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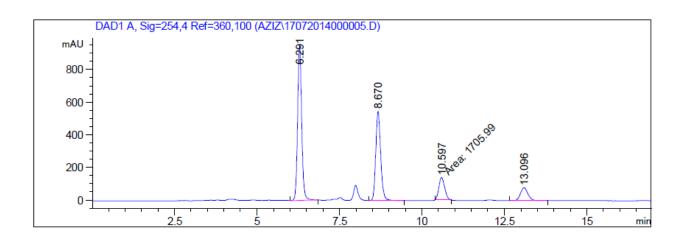
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Peak	RetTime	Type	Width	Area	Height	Area
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1	10.410	ВВ	0.1957	672.51135	53.13678	5.5600
2	16.818	BB	0.2886	870.13617	46.01580	7.1938
3	18.958	BB	0.3341	4607.40625	213.23586	38.0915
4	26.590	BB	0.4594	5945.58057	199.64818	49.1548

HPLC Chromatogram of Compound 2c (catalyst H)



HPLC Chromatogram of Compound 2d (catalyst F)



## Area Percent Report

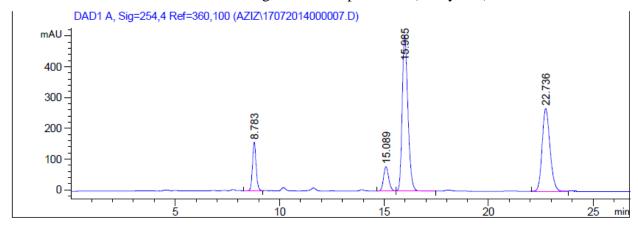
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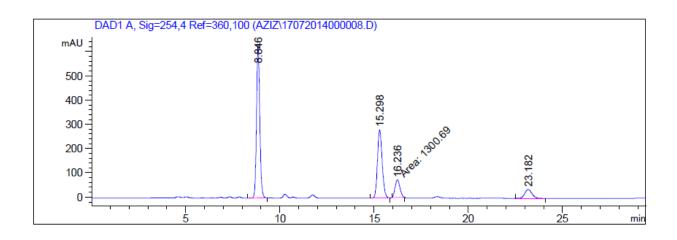
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
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1	6.291	ВВ	0.1291	8047.50488	947.17084	48.2571
2	8.670	BB	0.1593	5670.91504	545.29535	34.0058
3	10.597	MM	0.2056	1705.99304	138.32527	10.2300
4	13.096	BB	0.2446	1251.89551	79,12386	7.5070

HPLC Chromatogram of Compound 2d (catalyst H)



HPLC Chromatogram of Compound 2e (catalyst F)



## Area Percent Report

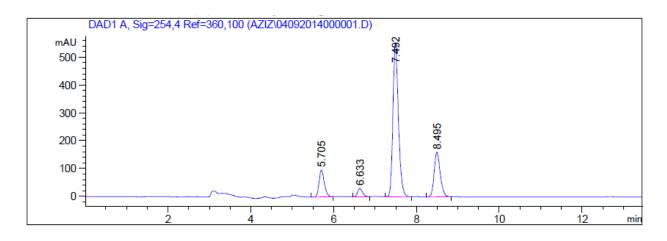
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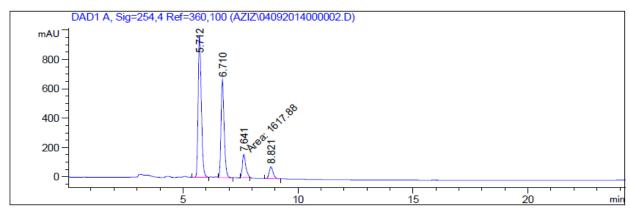
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Pea	ık	RetTime	Type	Width	Area	Height	Area
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	-						
	1	8.846	ВВ	0.1864	7602.93799	631.89838	51.3179
	2	15.298	BV	0.2703	4946.63770	282.51614	33.3886
	3	16.236	MM	0.2955	1300.69226	73.35119	8.7793
	4	23.182	BB	0.4060	965.09387	36.79242	6.5141

HPLC Chromatogram of Compound 2e (catalyst H)



HPLC Chromatogram of Compound 2f (catalyst F)



## Area Percent Report

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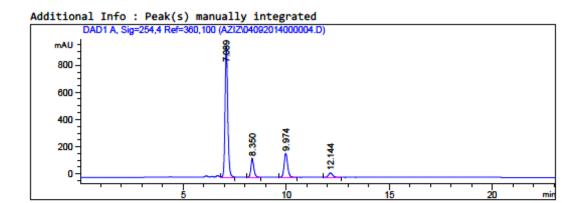
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Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	5.712	VB	0.1468	9366.77930	968.91626	51.2805
2	6.710	W	0.1442	6306.74854	667.74414	34.5277
3	7.641	MM	0.1731	1617.88049	155.77136	8.8574
1	8 821	RR	0 1707	974 35840	82 57642	5 33/13

HPLC Chromatogram of Compound 2f (catalyst H)



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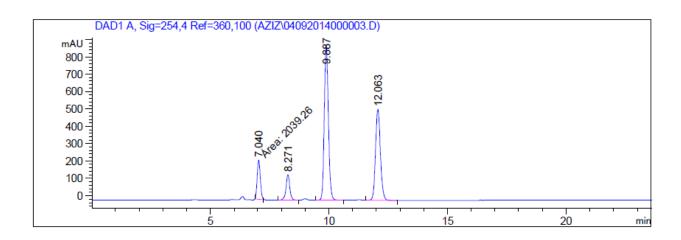
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Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.089	VB	0.1375	8706.03711	962.40027	68.7754
2	8.350	BV	0.1519	1422.05957	140.69531	11.2339
3	9.974	BB	0.1785	2078.02295	177.58360	16.4158
4	12.144	RR	0.2121	452,52609	32,56121	3.5748

HPLC Chromatogram of Compound 2g (catalyst F)



#### Area Percent Report

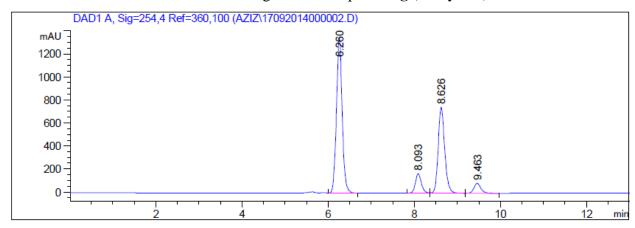
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

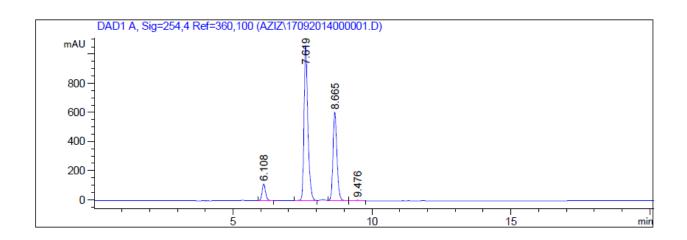
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.040	MM	0.1501	2039.25610	226.44124	9.3439
2	8.271	BB	0.1679	1634.19470	146.76547	7.4879
3	9.887	BB	0.1836	1.06843e4	892.76276	48.9553
4	12.063	BB	0.2184	7466.78711	523.46533	34.2129

HPLC Chromatogram of Compound 2g (catalyst H)



HPLC Chromatogram of Compound 2h (catalyst F)



## Area Percent Report

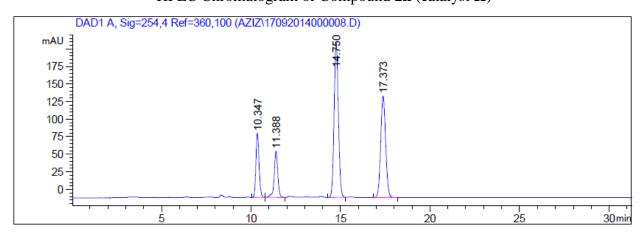
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

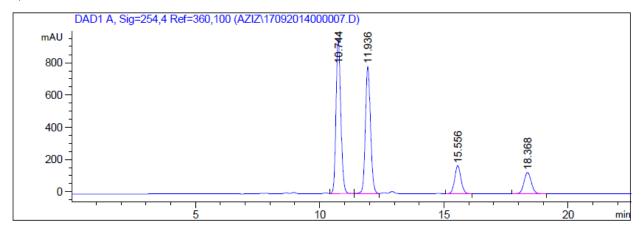
Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	6.108	BB	0.1309	990.18909	114.54664	5.7304
2	7.619	BV	0.1443	1.02623e4	1065.87573	59.3903
3	8.665	VB	0.1513	5996.02197	606.57910	34.7003
4	9.476	BB	0.1761	30.92213	2.65132	0.1790

HPLC Chromatogram of Compound 2h (catalyst H)



# HPLC Chromatogram of Compound 2i (catalyst

 $\mathbf{F}$ )



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## Area Percent Report

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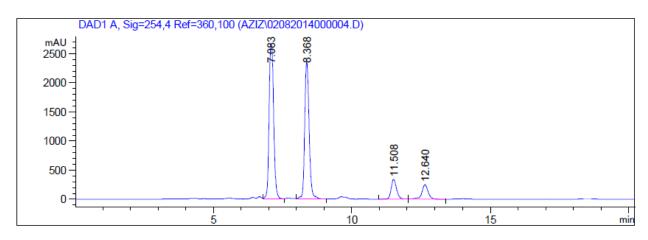
Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

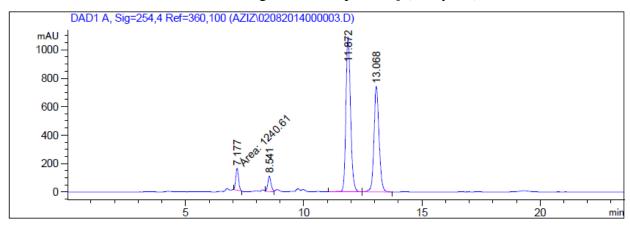
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	10.744	VB	0.2086	1.28922e4	960.40515	43.1507
2	11.936	BB	0.2205	1.12272e4	786.91205	37.5780
3	15.556	BB	0.2726	3071.67090	173.46368	10.2810
4	18.368	BB	0.3151	2686.03979	131.06013	8.9903

HPLC Chromatogram of Compound 2i (catalyst H)



HPLC Chromatogram of Compound 2j (catalyst F)



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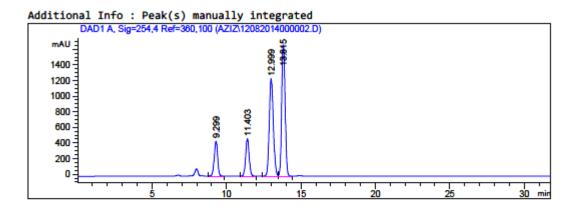
Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.177	MM	0.1351	1240.61340	153.01846	4.4066
2	8.541	W	0.1494	1048.92249	107.89597	3.7257
3	11.872	BB	0.2090	1.47802e4	1084.20447	52.4989
4	13.068	BB	0.2282	1.10836e4	742.25183	39.3687

HPLC Chromatogram of Compound 2j (catalyst H)



## Area Percent Report

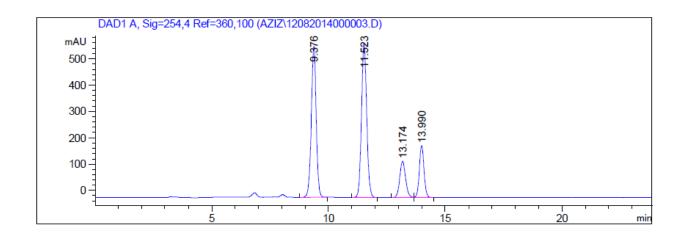
Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

ı	Peak	RetTime	Type	Width	Area	Height	Area
	#	[min]		[min]	[mAU*s]	[mAU]	%
,							
	1	9.299	BB	0.2478	7143.62842	448.66660	10.8272
	2	11.403	BB	0.2534	7899.78711	481.40689	11.9733
	3	12.999	BV	0.2952	2.38442e4	1246.58984	36.1394
	4	13.815	VB	0.2565	2.70909e4	1676,42993	41.0602

HPLC Chromatogram of Compound 2k (catalyst F)



## Area Percent Report

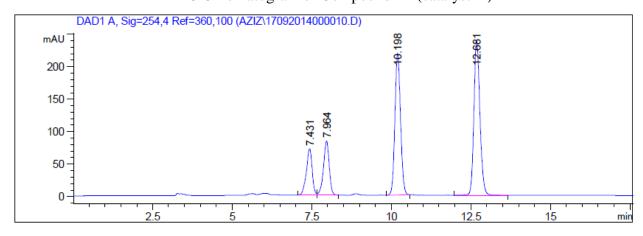
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

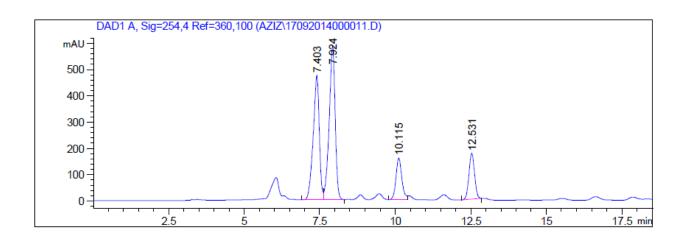
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area	
#	[min]		[min]	[mAU*s]	[mAU]	%	
							l
1	9.376	BB	0.2219	8352.37012	573.53320	36.9568	
2	11.523	BB	0.2392	9100.32422	585.91217	40.2662	
3	13.174	BV	0.2702	2409.10352	137.66310	10.6596	
4	13.990	VB	0.2142	2738.58252	196.99352	12.1174	

HPLC Chromatogram of Compound 2k (catalyst H)



HPLC Chromatogram of Compound 21 (catalyst F)



# Area Percent Report

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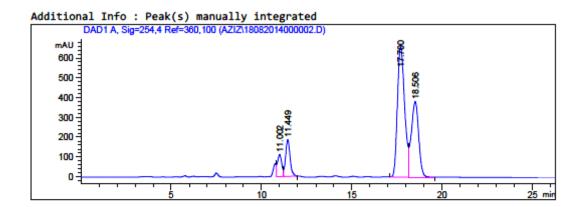
Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	7.403	BV	0.2054	6618.39844	472.66504	34.7281
2	7.924	W	0.2044	8061.20215	586.24323	42.2988
3	10.115	BV	0.2057	2140.74805	158.39182	11.2330
4	12.531	BB	0.1996	2237.39502	174.47870	11.7401

HPLC Chromatogram of Compound 21 (catalyst H)



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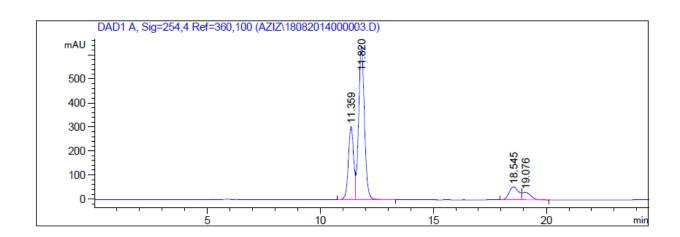
Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	11.002	w	0.2452	1834.40442	111.91914	5.3660
2	11.449	VB	0.2627	3203.34888	186.21306	9.3705
3	17.700	BV	0.4291	1.83078e4	660.98444	53.5543
4	18.506	VB	0.4303	1.08399e4	382.93246	31.7091

HPLC Chromatogram of Compound 2m (catalyst F)



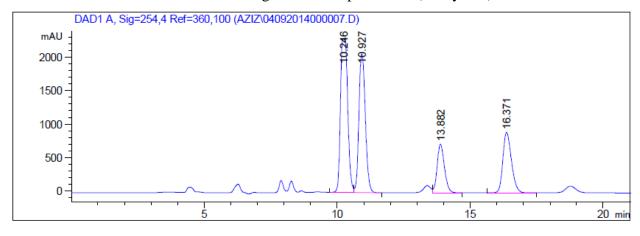
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

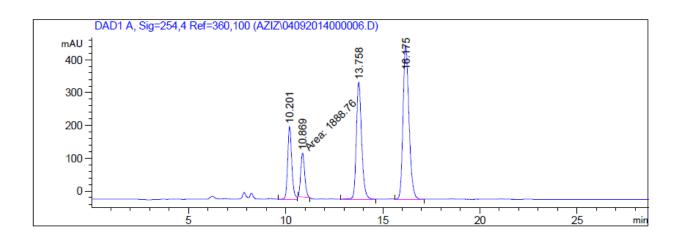
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	11.359	BV	0.2499	4980.87061	306.00101	26.4605
2	11.820	VB	0.2747	1.14358e4	639.37091	60.7519
3	18.545	BV	0.4485	1596.30933	53.75303	8.4803
4	19.076	VB	0.3913	810.80170	30.97958	4.3073

HPLC Chromatogram of Compound 2m (catalyst H)



HPLC Chromatogram of Compound 2n (catalyst F)



## Area Percent Report

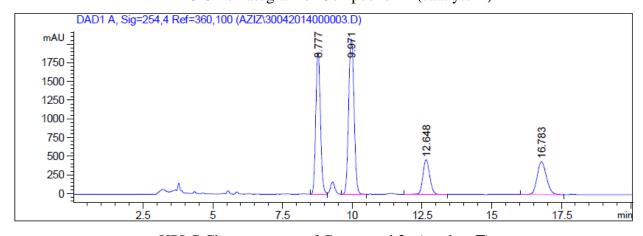
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

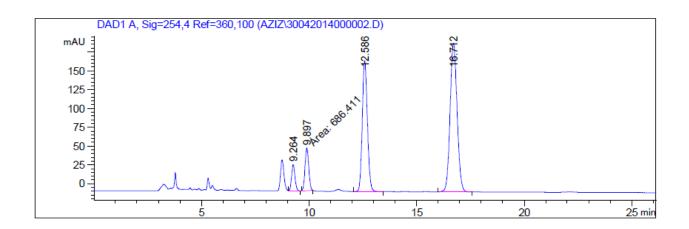
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Ρ	eak	RetTime	Type	Width	Area	Height	Area	
	#	[min]		[min]	[mAU*s]	[mAU]	%	
-								
	1	10.201	BV	0.2242	3219.21802	220.70094	14.7473	
	2	10.869	MM	0.2365	1888.75598	133.11102	8.6524	
	3	13.758	BB	0.2909	6735.30957	355.76675	30.8546	
	4	16.175	BB	0.3287	9985.94043	468.39224	45.7457	

HPLC Chromatogram of Compound 2n (catalyst H)



HPLC Chromatogram of Compound 20 (catalyst F)



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#### Area Percent Report

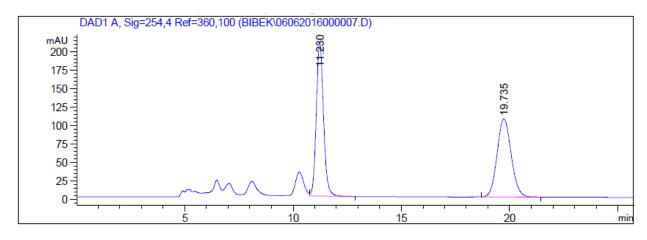
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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

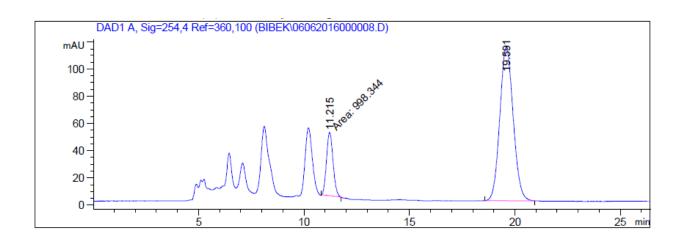
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area	
#	[min]		[min]	[mAU*s]	[mAU]	%	
1	9.264	W	0.1726	394.29639	35.22050	4.6862	
2	9.897	MM	0.2011	686.41125	56.90174	8.1580	
3	12.586	BB	0.2570	2870.93481	173.50891	34.1209	
4	16.712	BB	0.3542	4462.36670	197.05769	53.0350	

HPLC Chromatogram of Compound 20 (catalyst H)



HPLC Chromatogram of Compound (±) ABT-627



# Area Percent Report

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Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	11.215	MM	0.3573	998.34399	46.56297	16.6861
2	19.591	BB	0.6724	4984.74121	113.06143	83.3139

HPLC Chromatogram of Compound ABT-627