Electronic Supplementary Material (ESI) for RSC Advances

Waste Reduction in Amide Synthesis by a Continuous Method Based on Recycling of the Reaction Mixture

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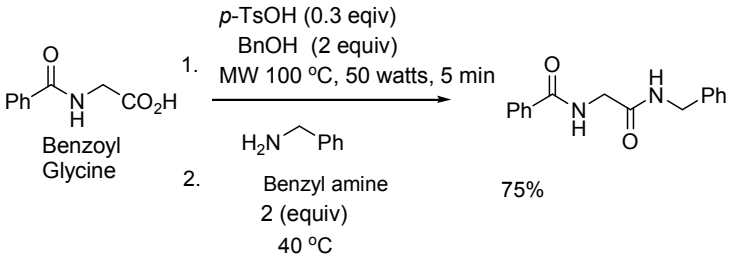
Supporting Information

E-factor calculation

1) Batch method



A. Without recovery and reuse of the reagents

Input		Output	
		Product	1.157g
Benzoyl glycine	1g	Benzoyl glycine	0.340g
Benzyl alcohol	1.2g	Benzyl alcohol	1.206g
Benzyl amine	1.20g	Benzyl amine	0.597g
p-TsOH	0.313g	*p*-TsOH	0.313g
Ethyl acetate	22g	Organic solvent waste	7.1g

hexane	49g	(assuming 90% recovery)	
Silica gel	20 g	Silica gel	20g
Total		Total waste	29.6g

$$\text{E-factor} = \frac{\text{29.6g of waste}}{\text{1.157g of product}} = 25.6$$

B. With recovery (using column chromatography) and reuse of the reagents

Input		Recycled	Output	
			Product	1.157g
Benzoyl glycine	1g	0.200g	Benzoyl glycine	0.140g
Benzyl alcohol	1.2g	0.888g	Benzyl alcohol	0.318g
Benzyl amine	1.20g	0.418g	Benzyl amine	0.179g
p-TsOH	0.313g	0.244g	*p*-TsOH	0.068g
Ethyl acetate	88g			
hexane	54g			
Acetic acid	1g			
methanol	8g		Organic solvent waste (assuming 90% recovery)	15g
Silica gel	20g		Silica gel	20g

Total	120.83g		Total waste	35.7g

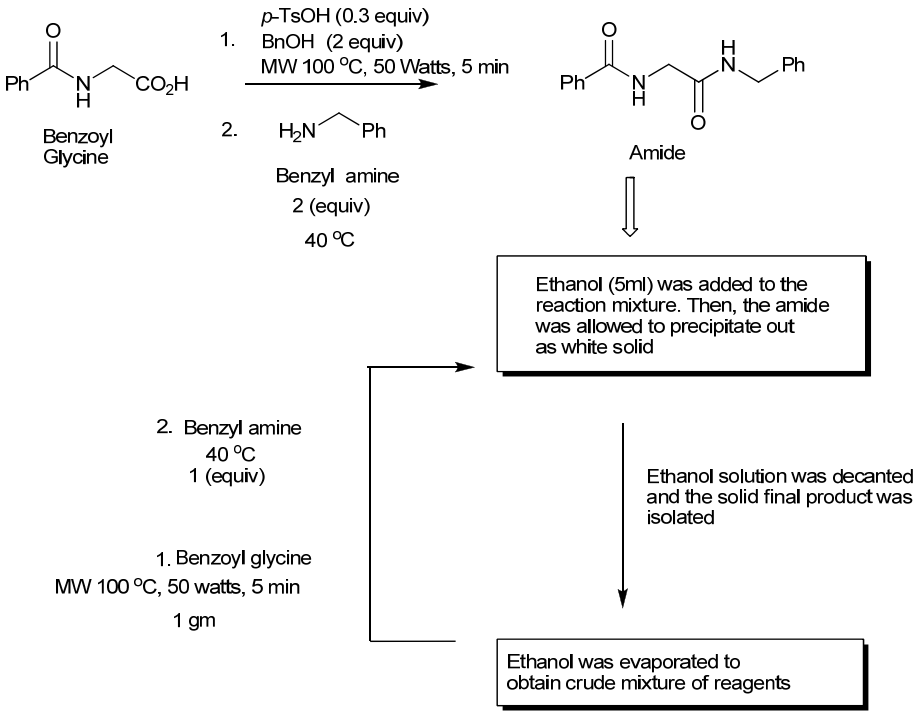
$$\text{E-factor} = \frac{\text{35.7g of waste}}{\text{1.157g of product}} = 30.8$$

C. With recovery (using product precipitation protocol) and reuse of the reagents

Input		Recycled	Output	
			Product	1.179g
Benzoyl glycine	1g	0.2g		
Benzyl alcohol	1.2g	1.2g		
Benzyl amine	1.2g	0.72g		
p-TsOH	0.313g	0.313g		
Ethanol	4g		Organic solvent waste (assuming 90% recovery)	0.4g
Total	7.713g		Total waste	0.4 g

$$\text{E-factor} = \frac{\text{0.4g of waste}}{\text{1.179g of product}} = 0.3$$

2) Continuous method

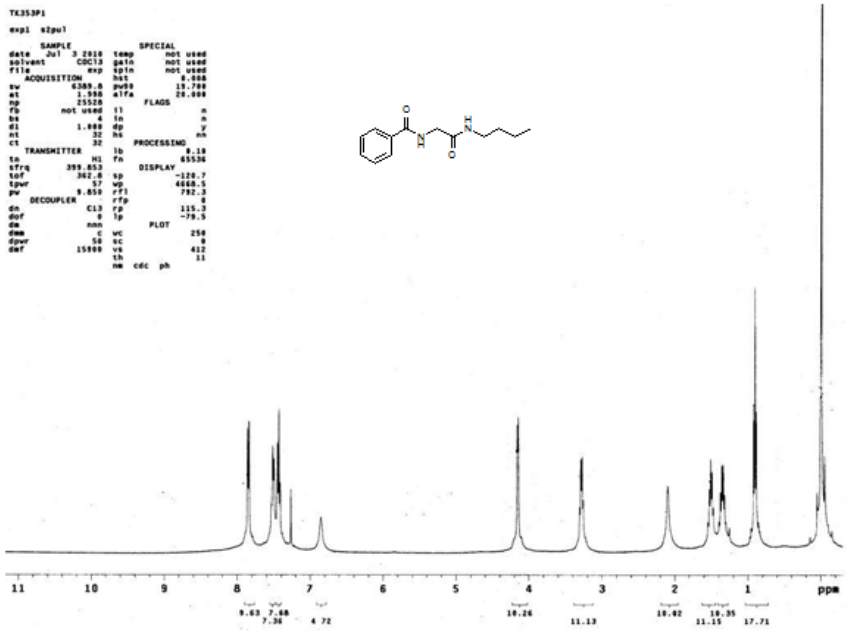


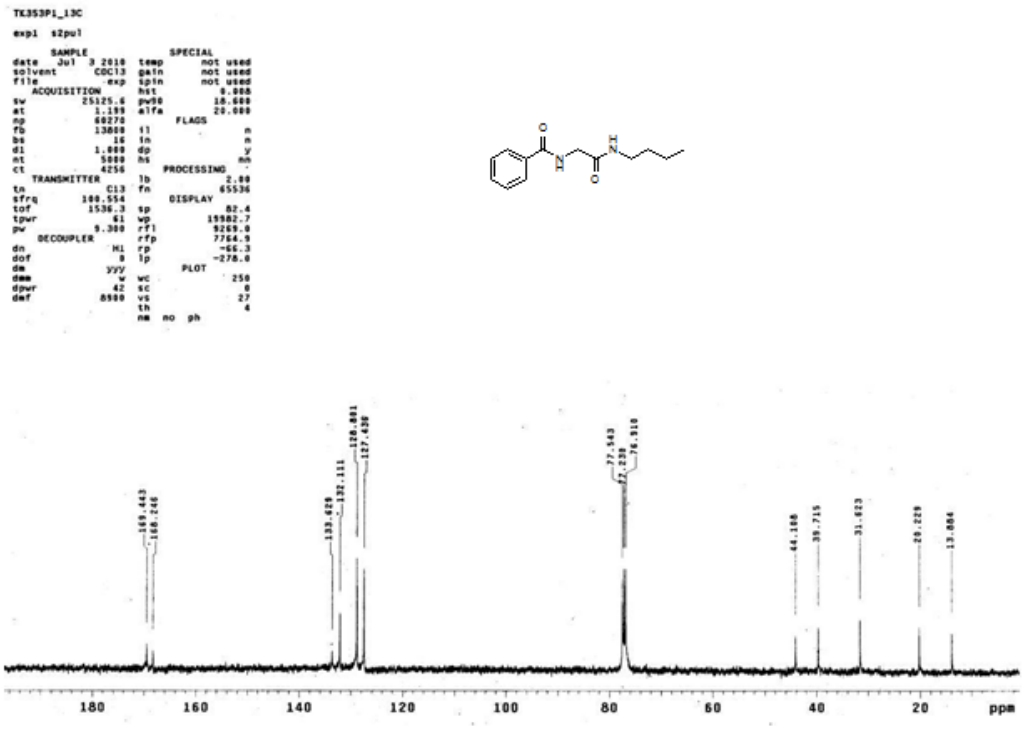
Input		Output	
		Product	5.7g
Benzoyl glycine	6g		
Benzyl amine	4.183g	Benzyl amine	0.6g
Benzyl alcohol	1.20g	Benzyl alcohol	1.2 g
p-TsOH	0.313g	*p*-TsOH	0.313g
HCL (aq.)	15 g	Aqueous waste	15g
Ethanol	24 g	Organic solvent waste (assuming 90% recovery)	5g
Ethyl acetate	27g		

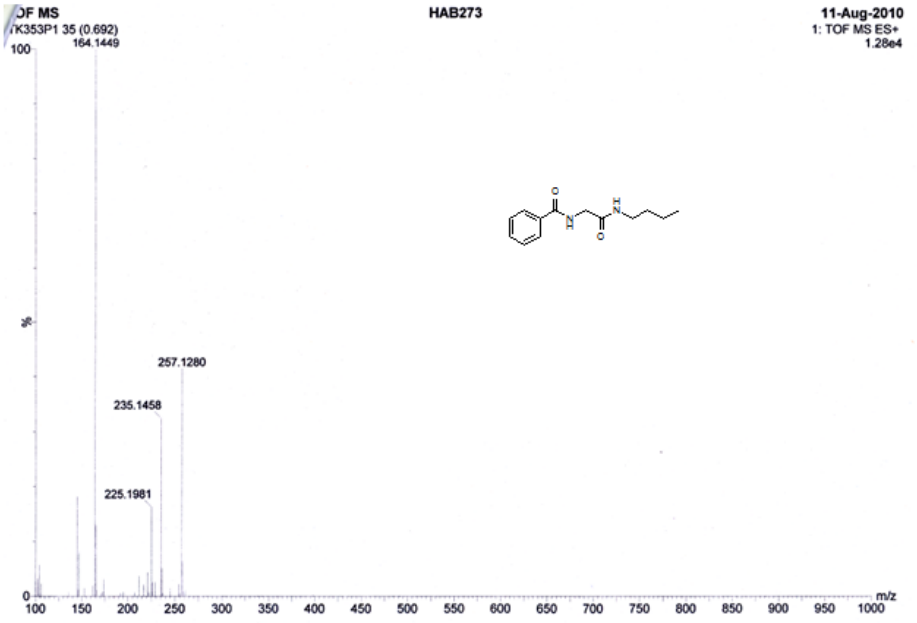
Total	77.696	Total waste	22.113 g

$$\text{E- Factor} = \frac{22.113 \text{ g of waste}}{5.70 \text{ g of product}} = 3.87$$

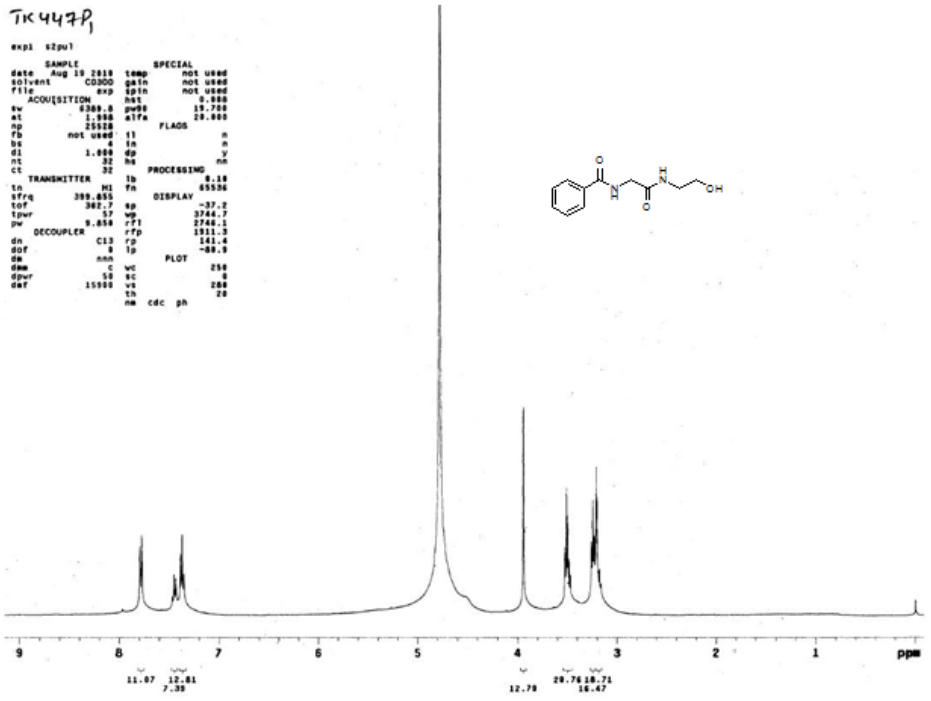
^{1}H NMR, 13C NMR and HRMS of Compound **1**

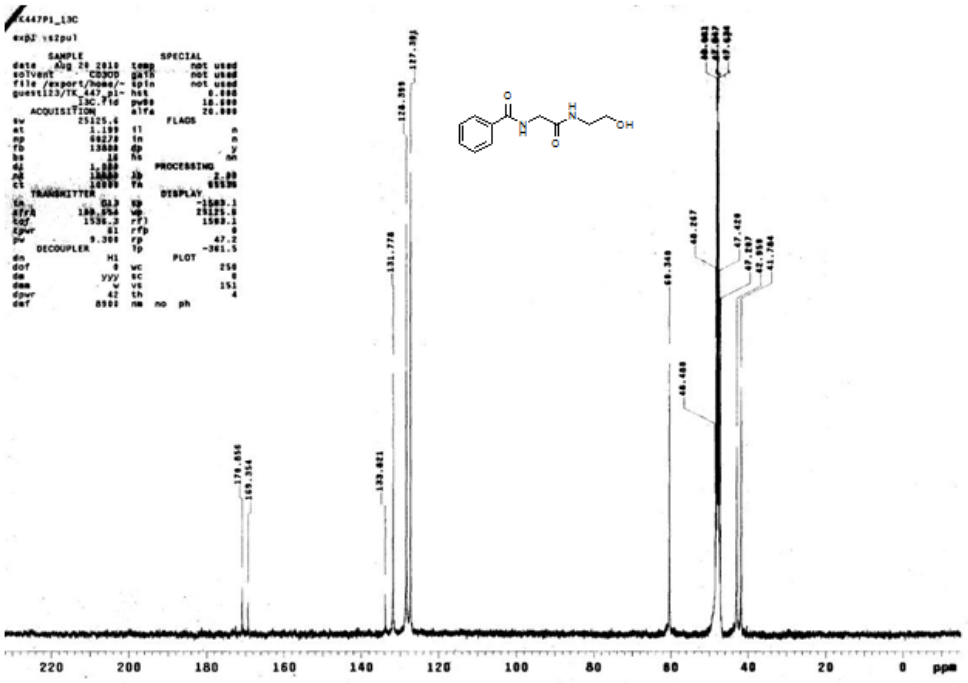


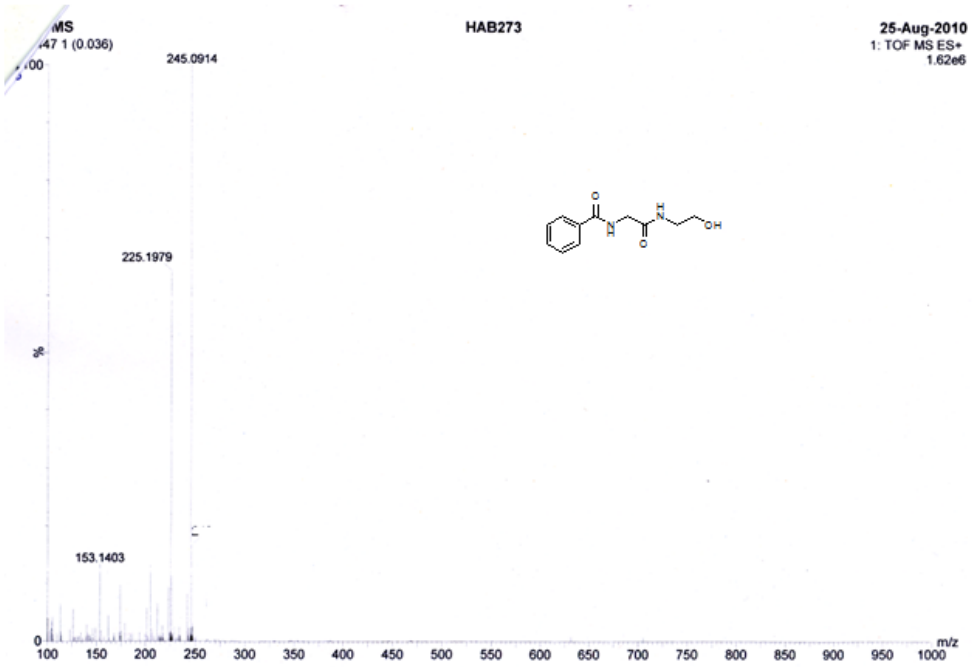




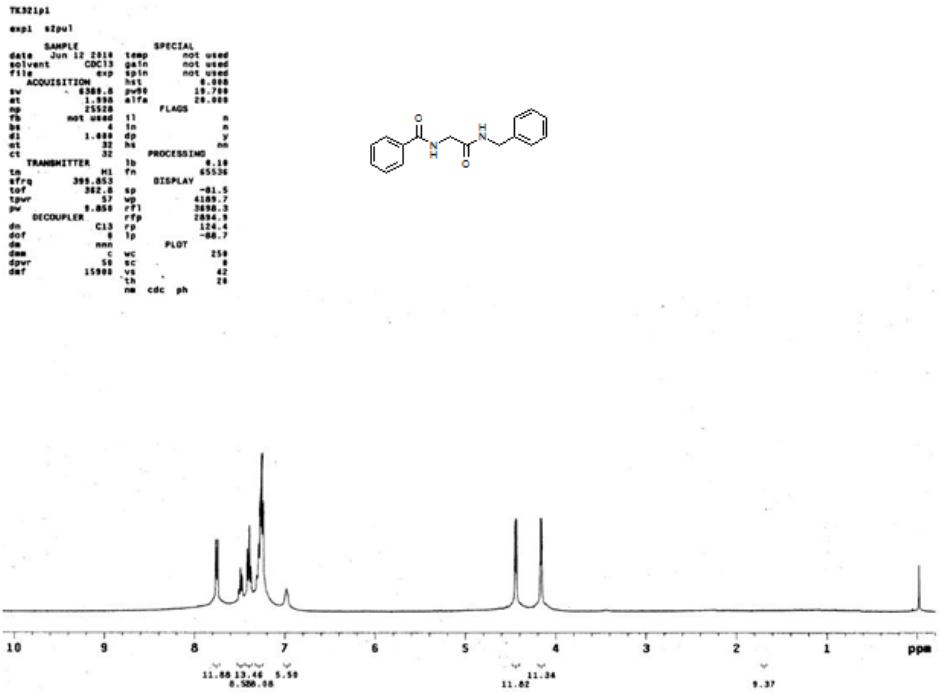
^{1}H NMR , ^{13}C NMR and HRMS of Compound **2**

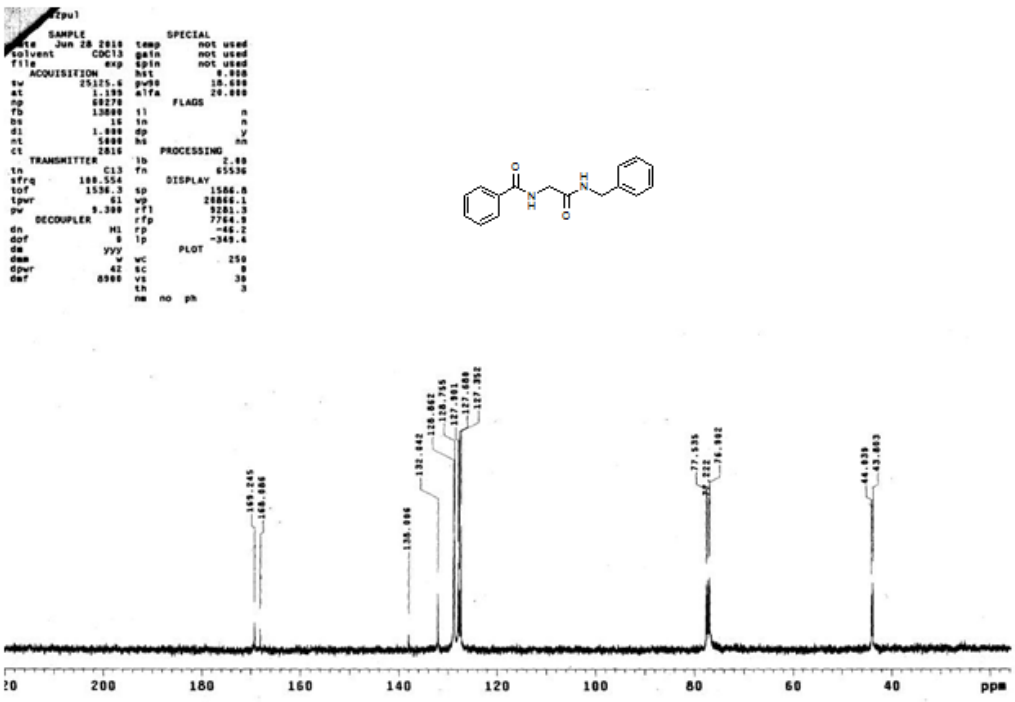


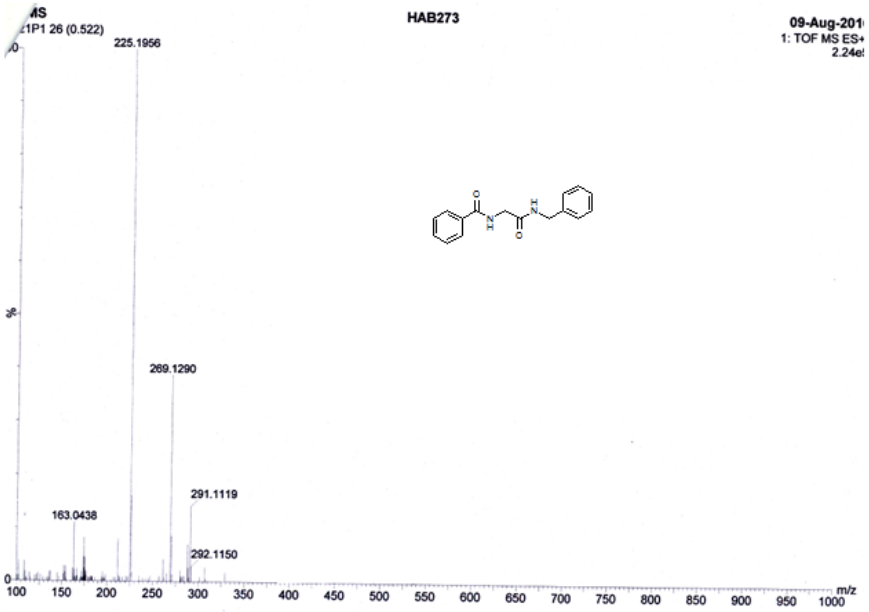




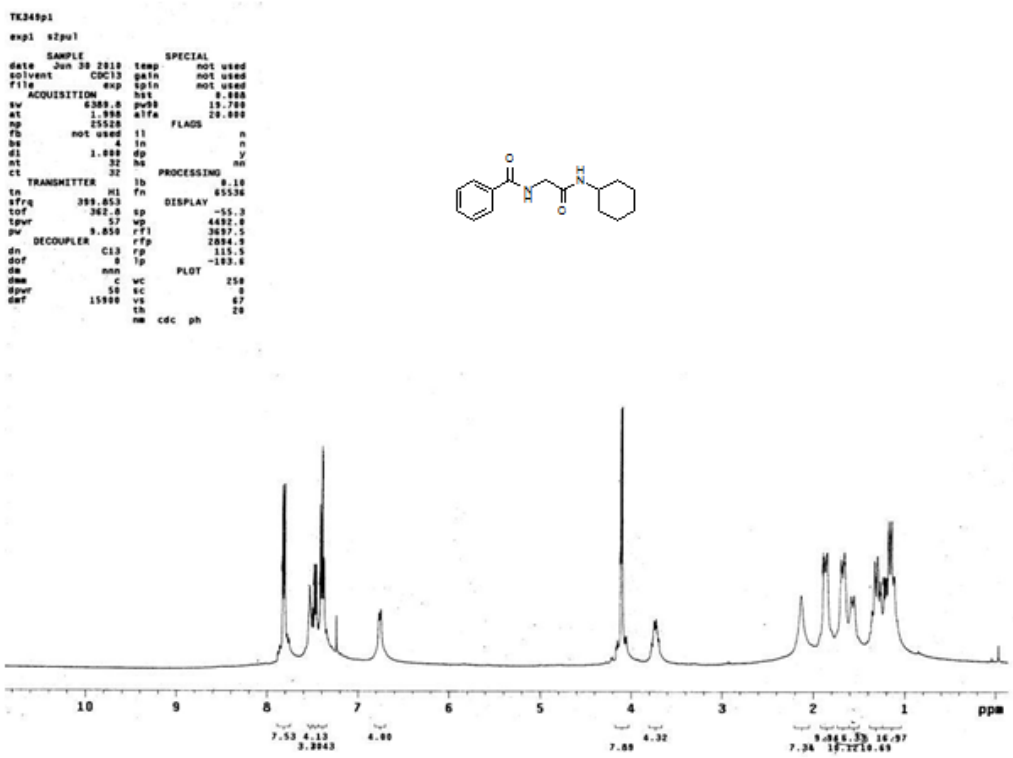
^{1}H NMR ,^{13}C NMR and HRMS of Compound **3**

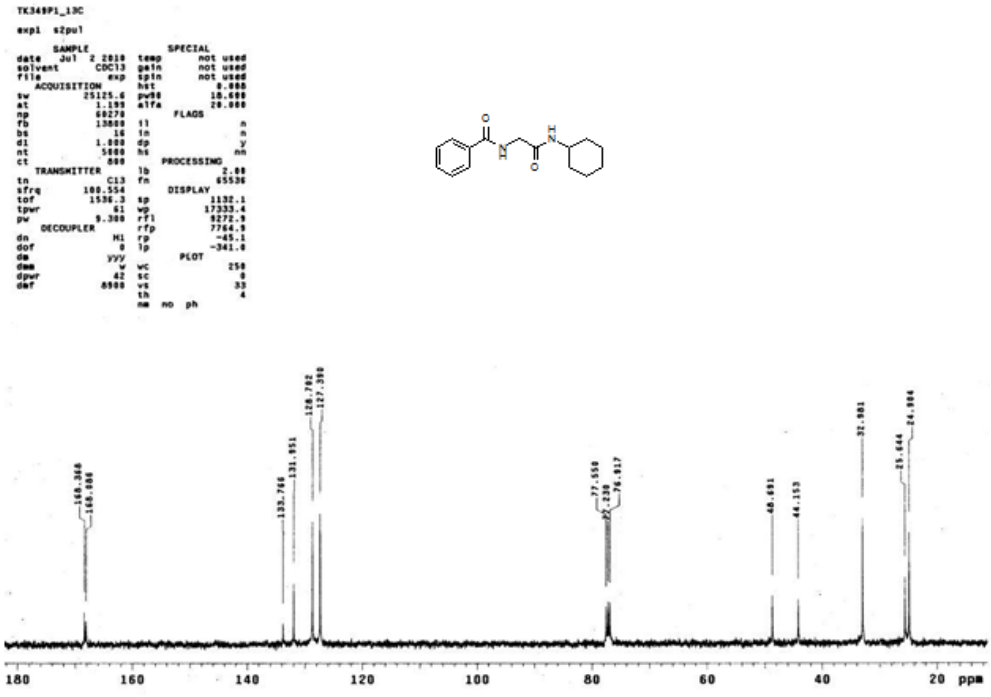


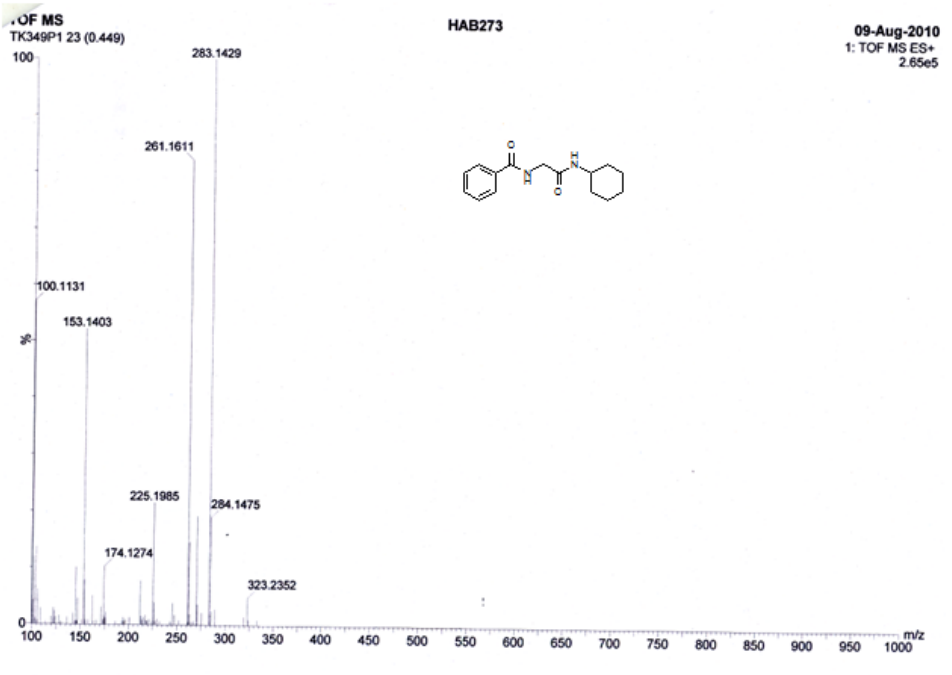




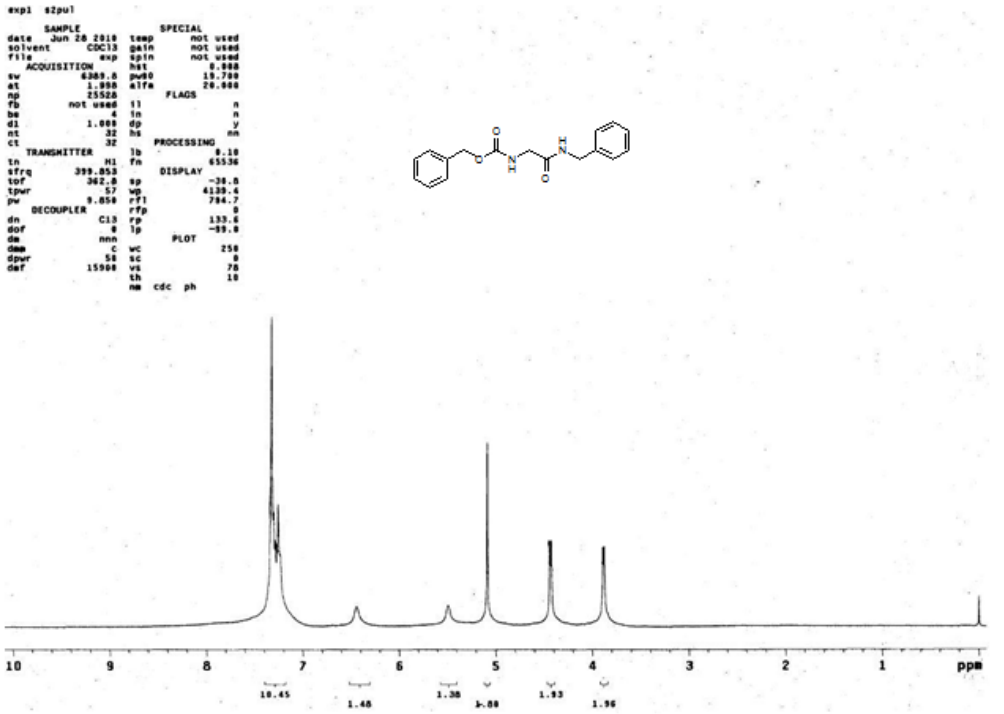
^{1}H NMR , ^{13}C NMR and HRMS of Compound **4**

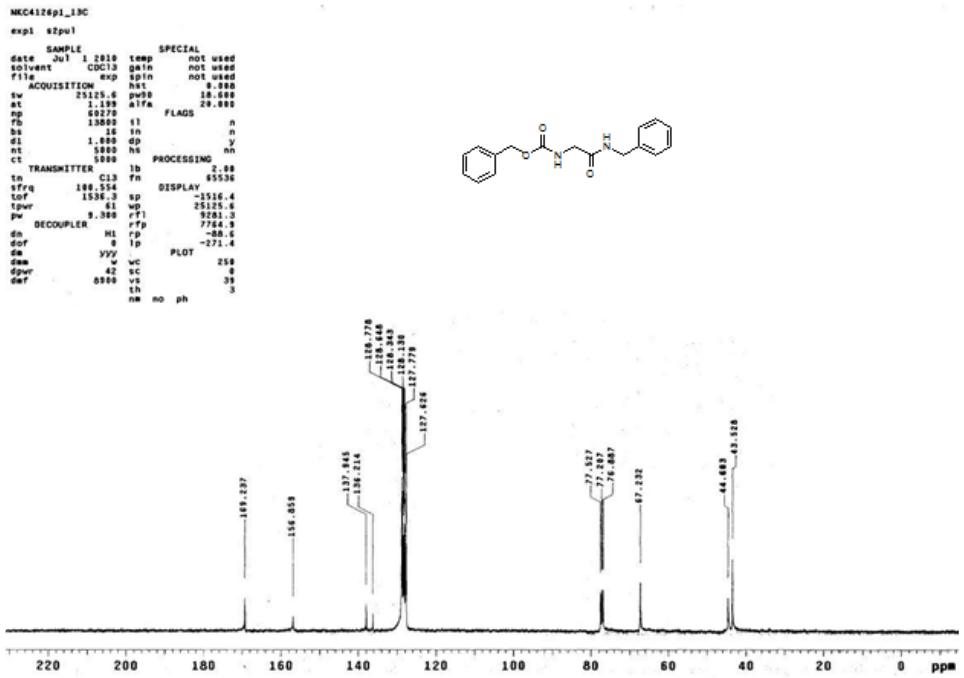


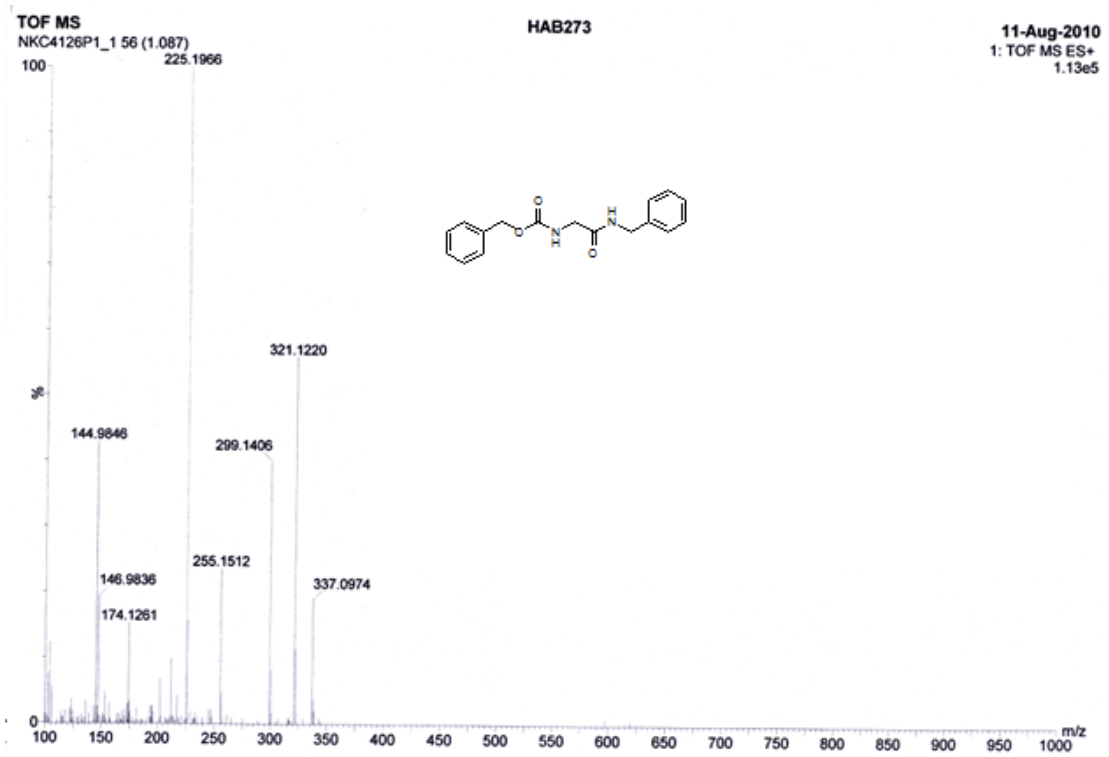




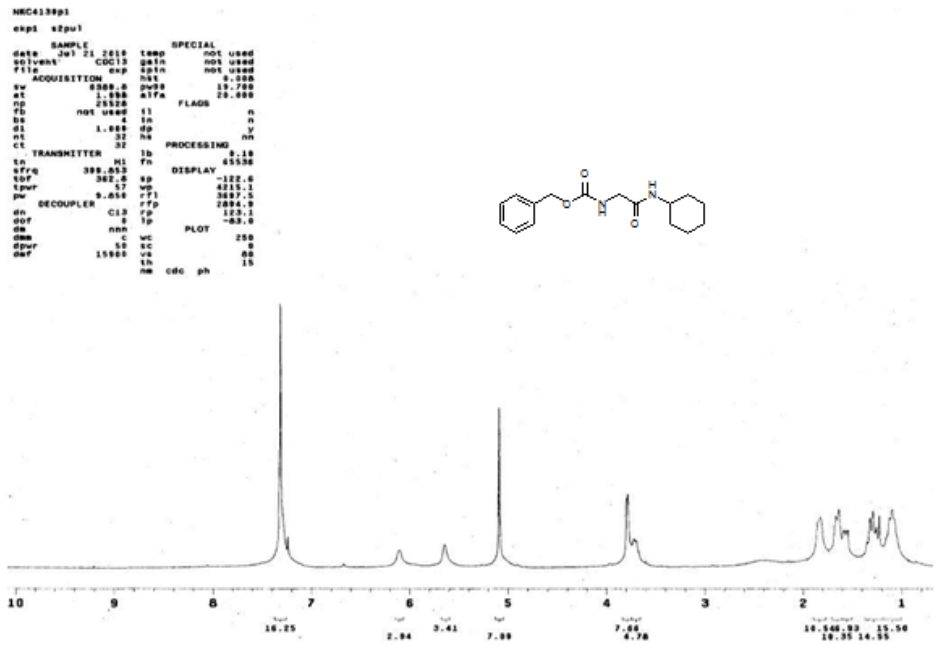
^{1}H NMR ,^{13}C NMR and HRMS of Compound **5**

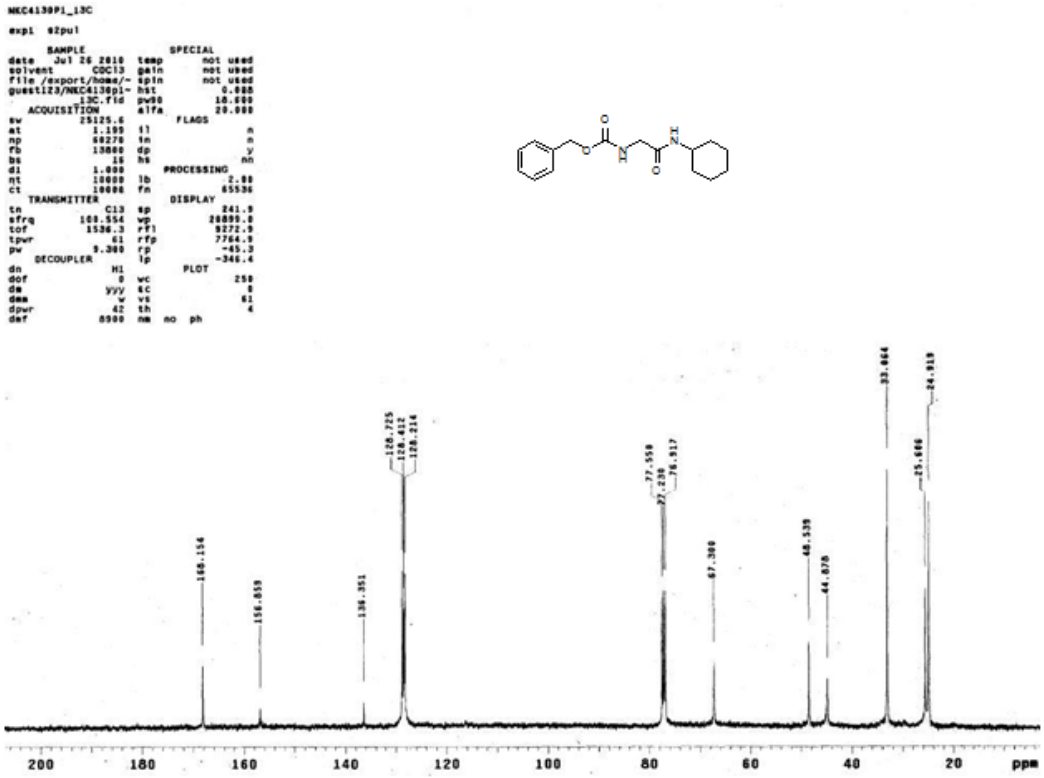


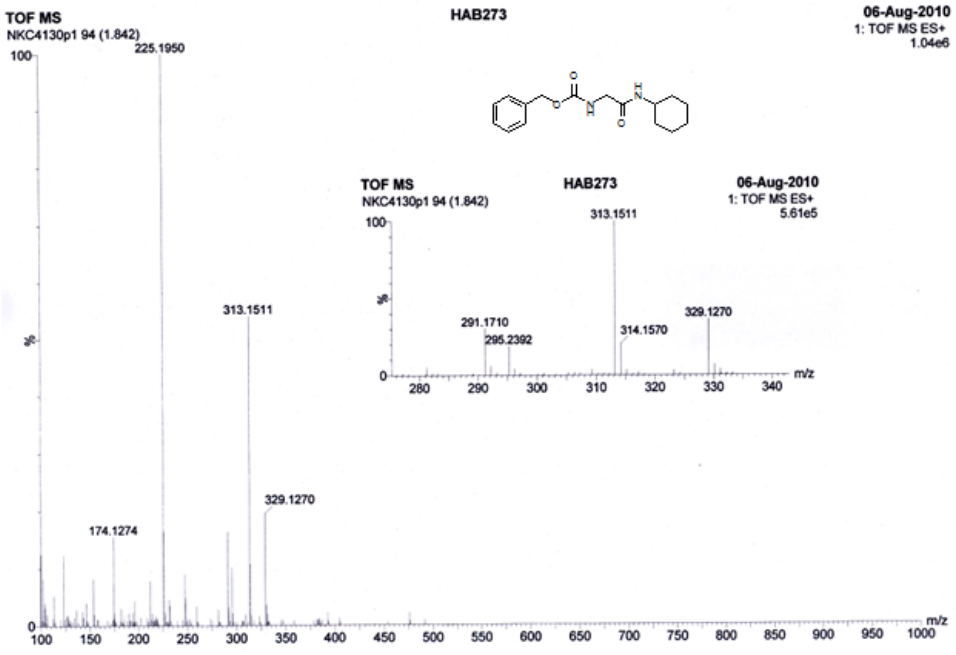




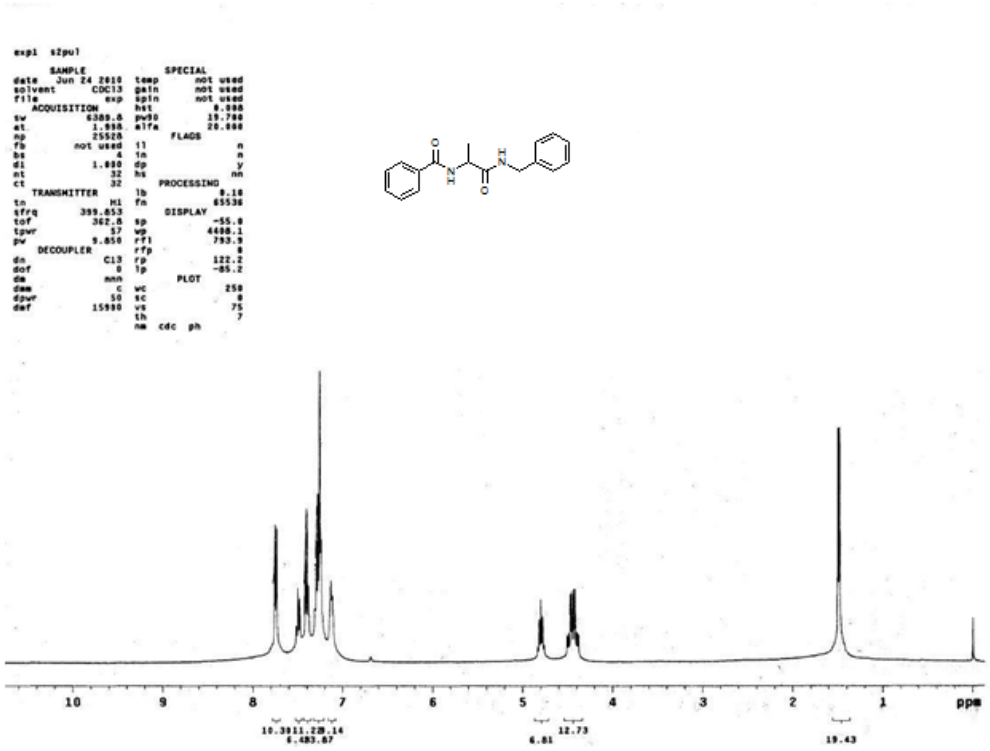
^{1}H NMR ,^{13}C NMR and HRMS of Compound **6**

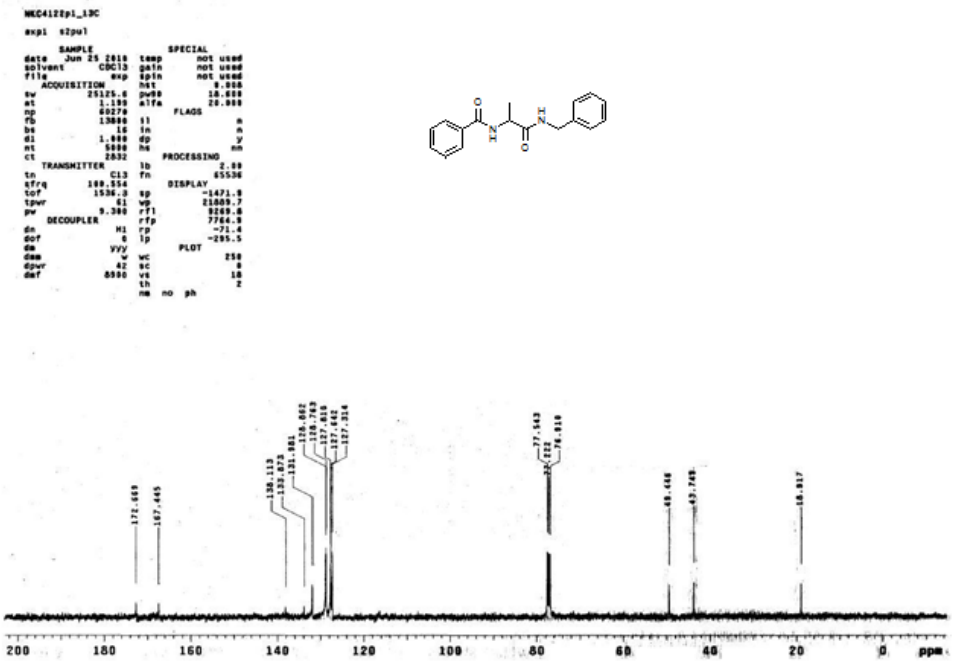


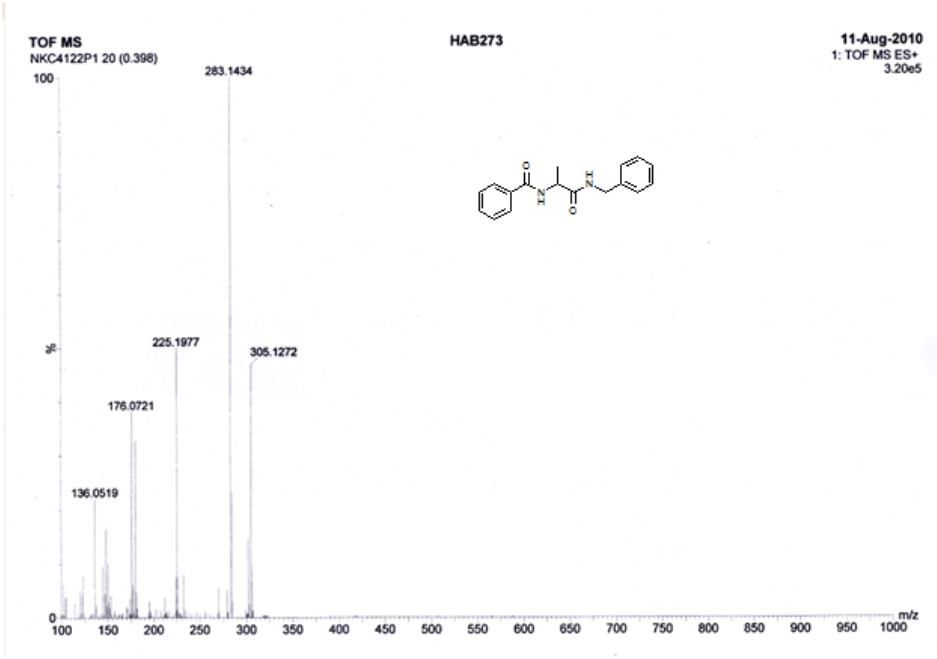




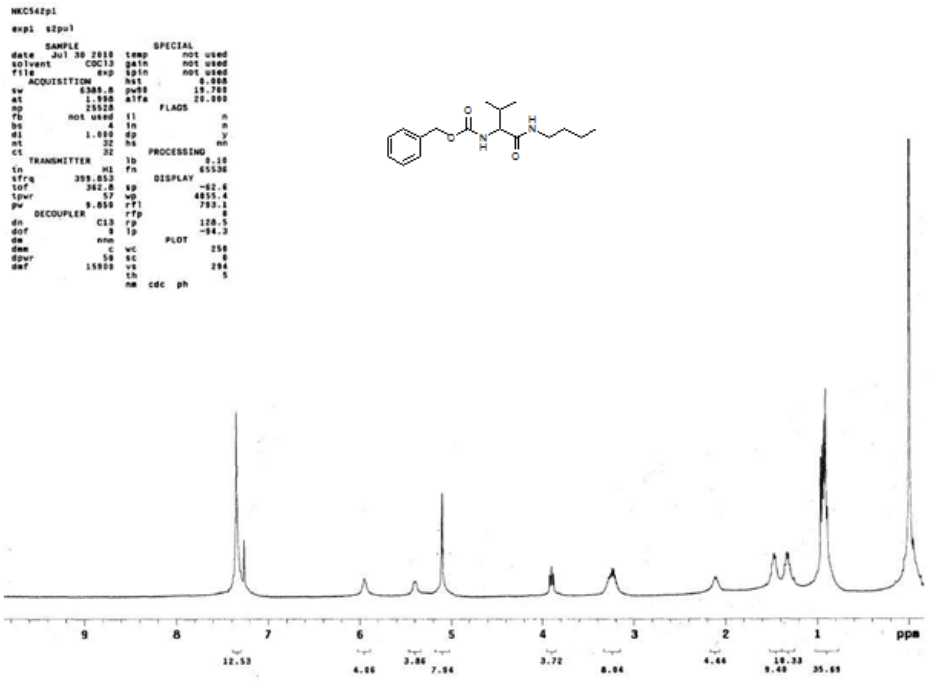
^{1}H NMR ,^{13}C NMR and HRMS of Compound **7**

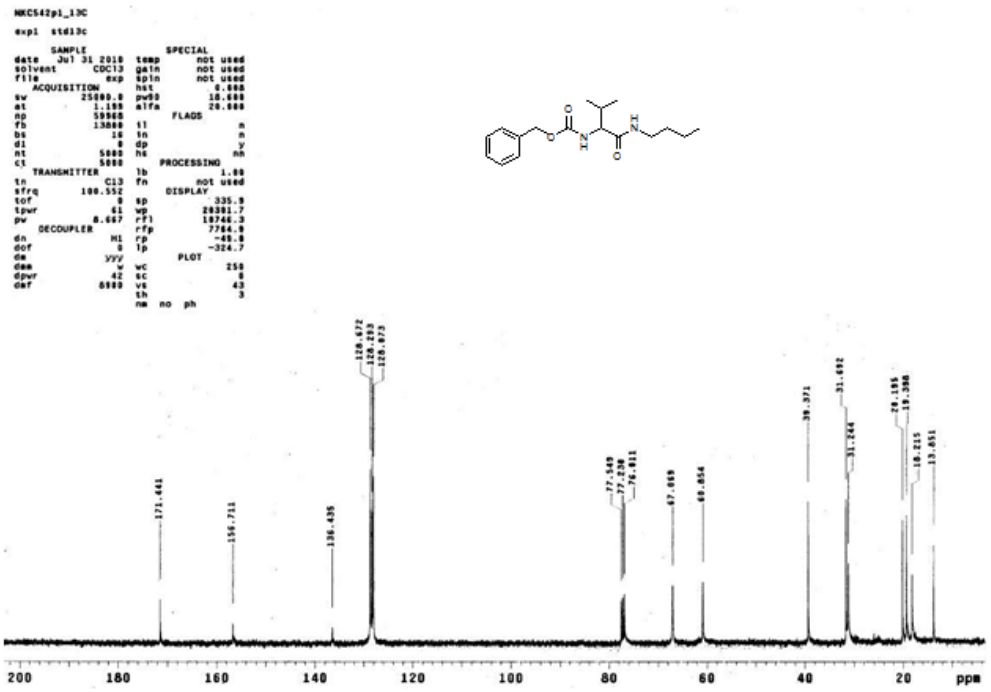


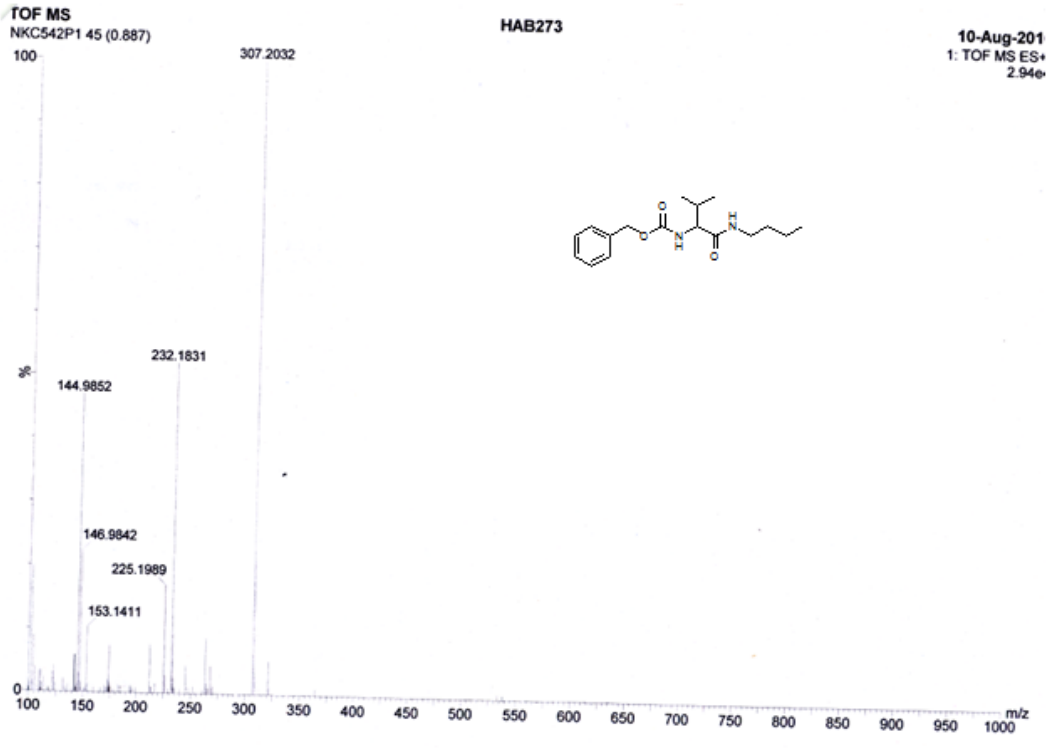




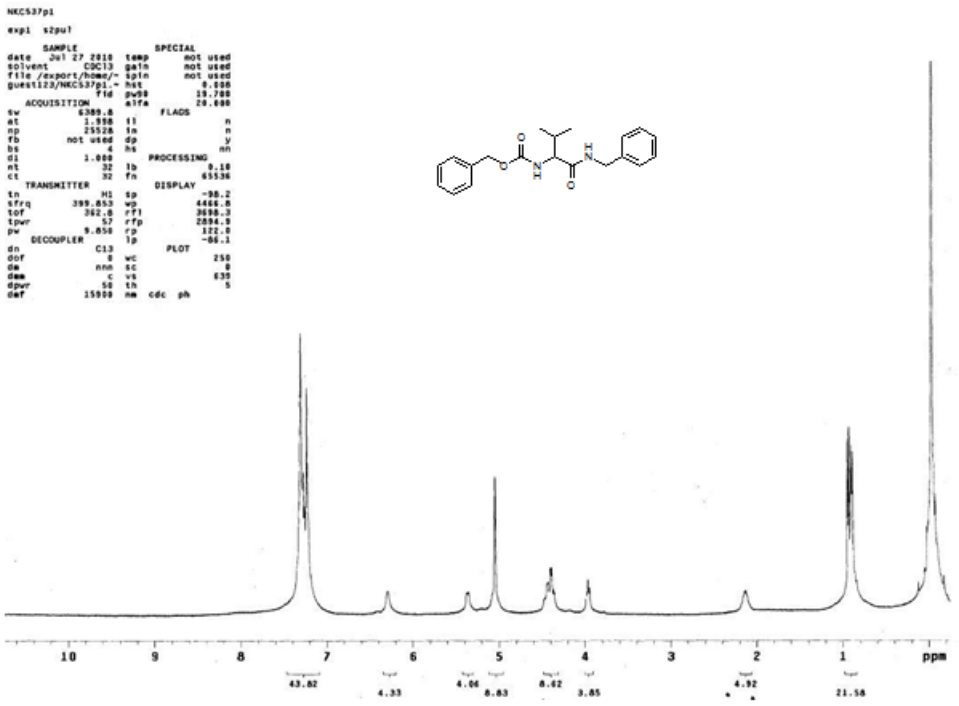
^{1}H NMR ,^{13}C NMR and HRMS of Compound **8**

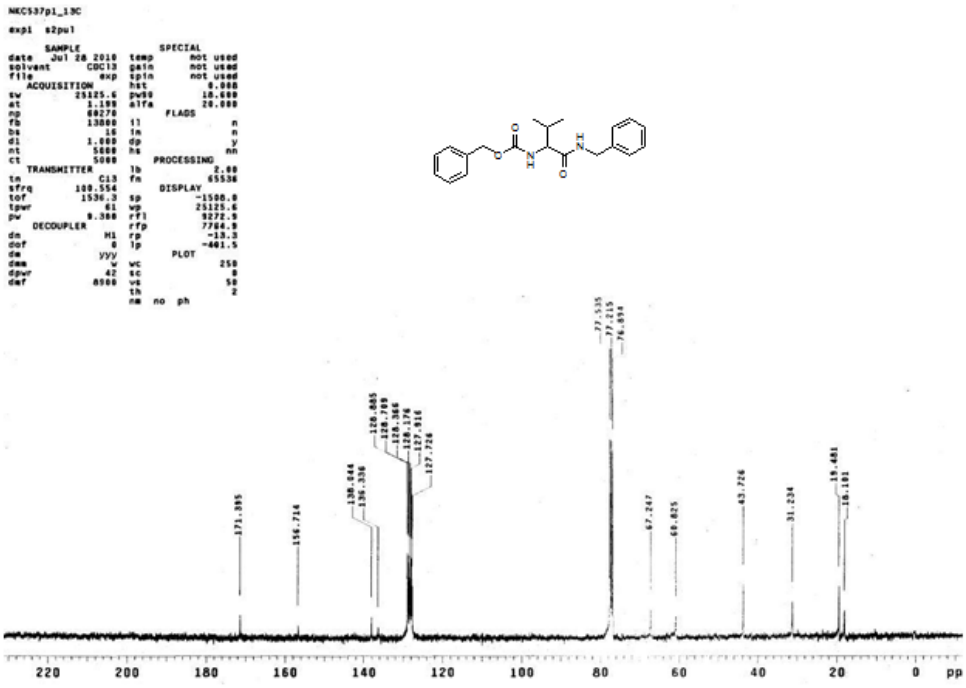


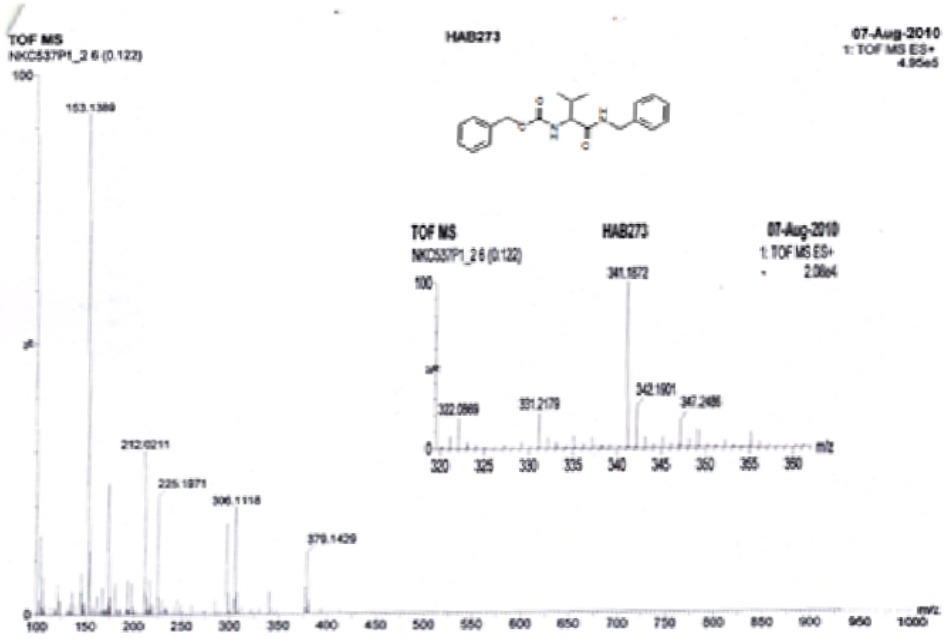




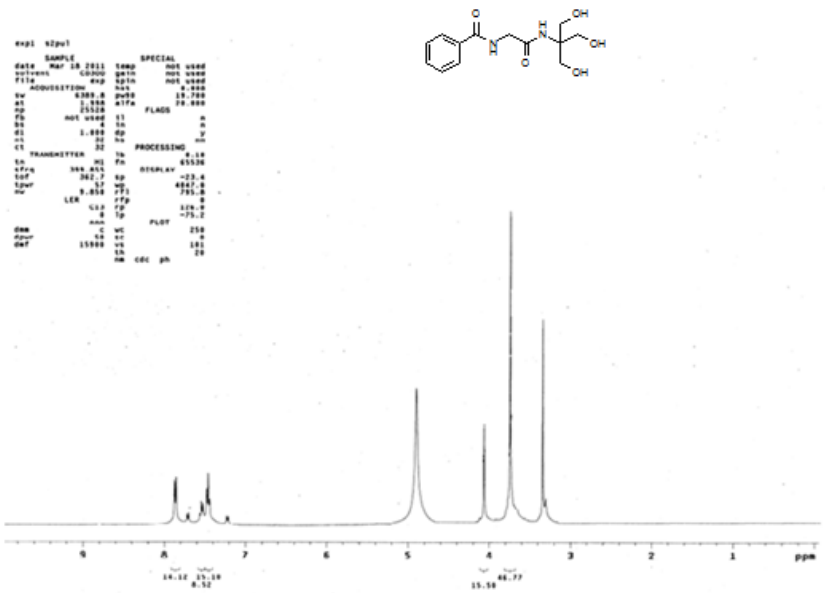
^{1}H NMR ,^{13}C NMR and HRMS of Compound **9**

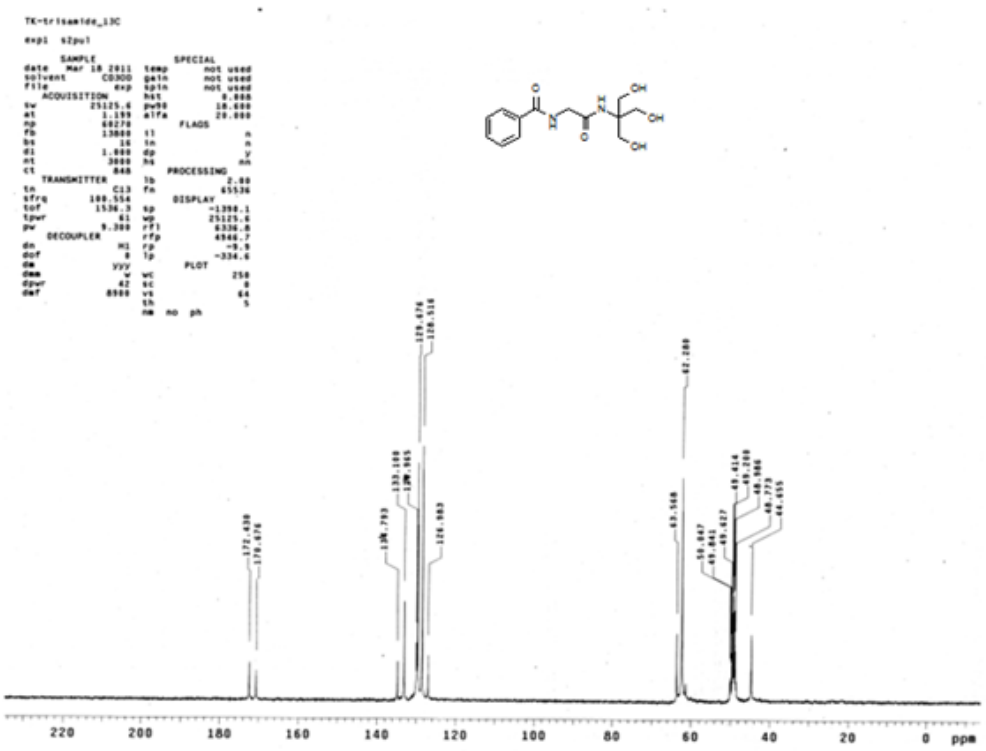






^{1}H NMR ,^{13}C NMR and HRMS of Compound **10**





Sample Name	TK-Bngly-tris	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
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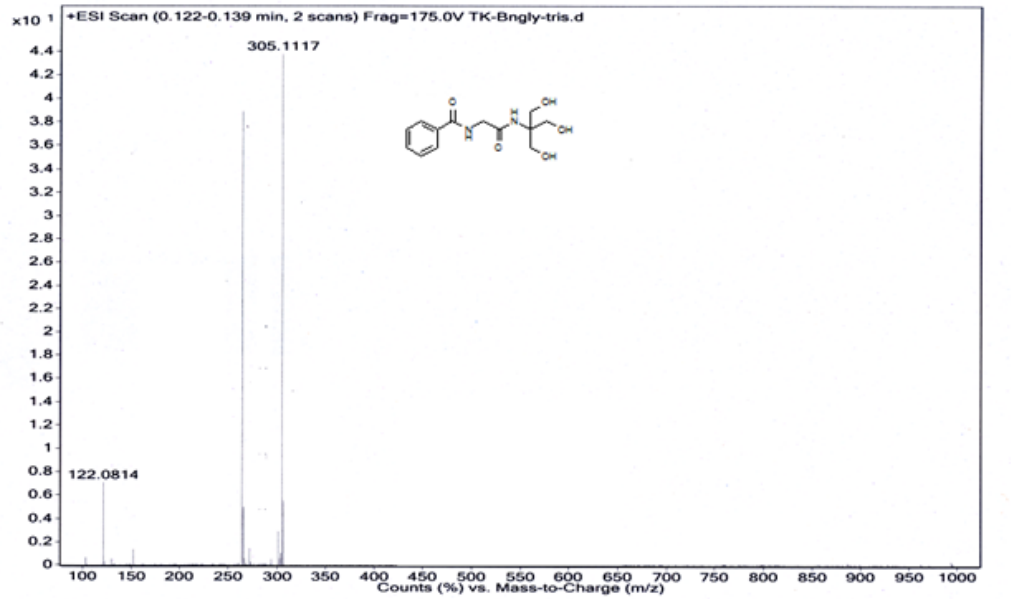
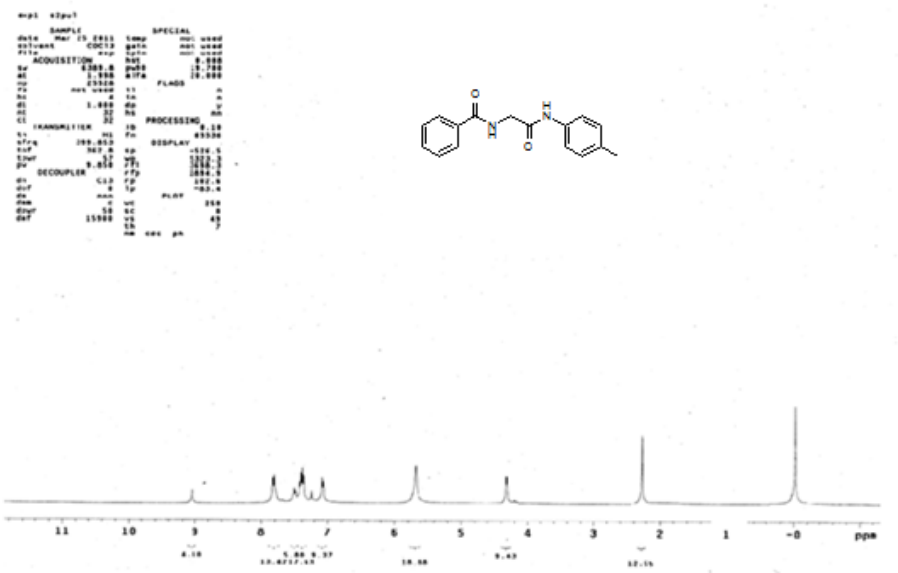
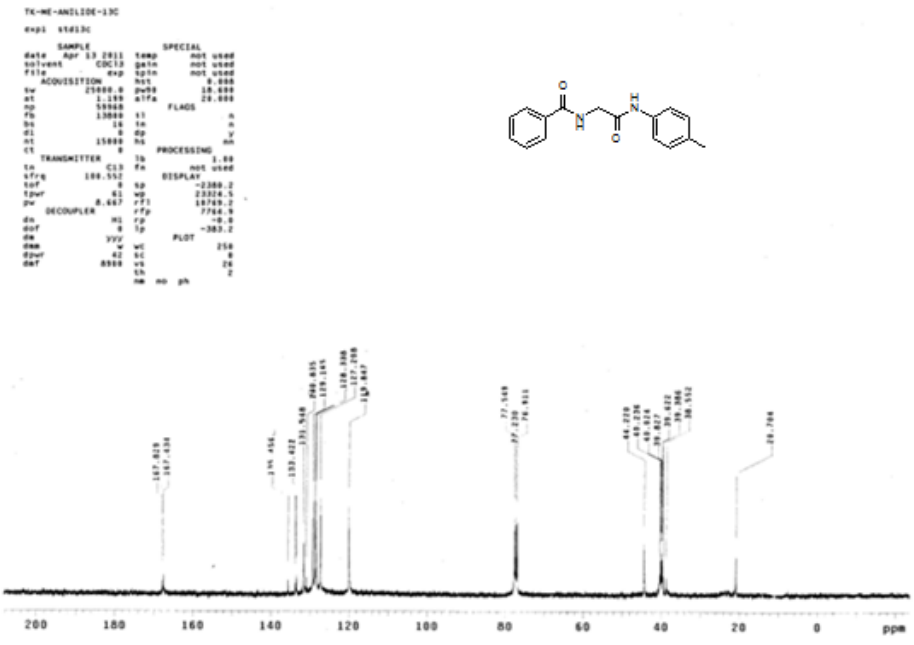


^{1}H NMR ,^{13}C NMR and HRMS of Compound **11**





Sample Name	TK-ME-ANILIDE	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
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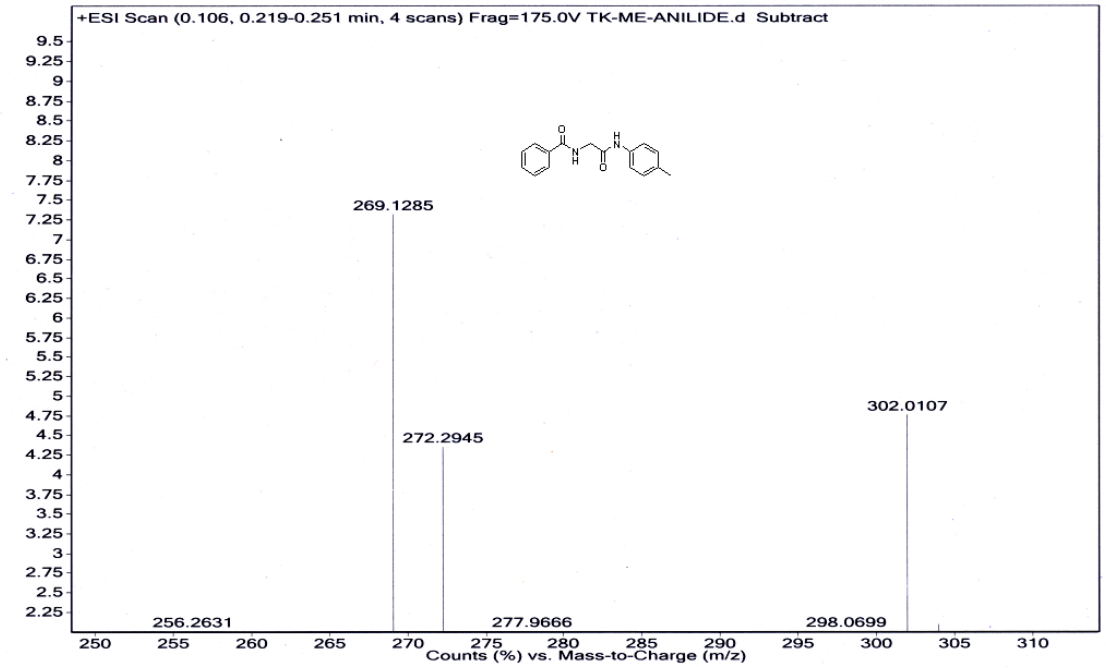
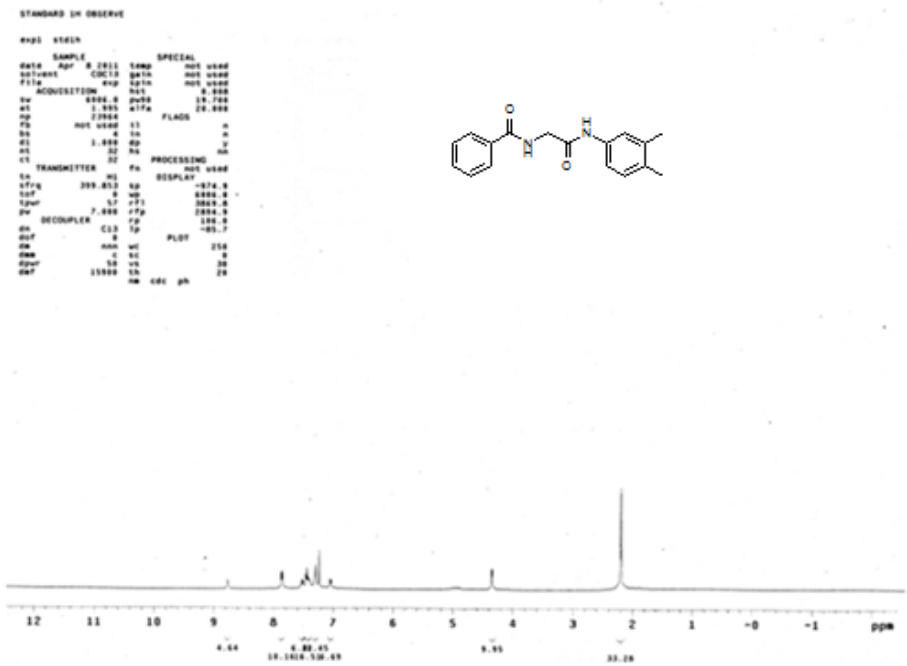
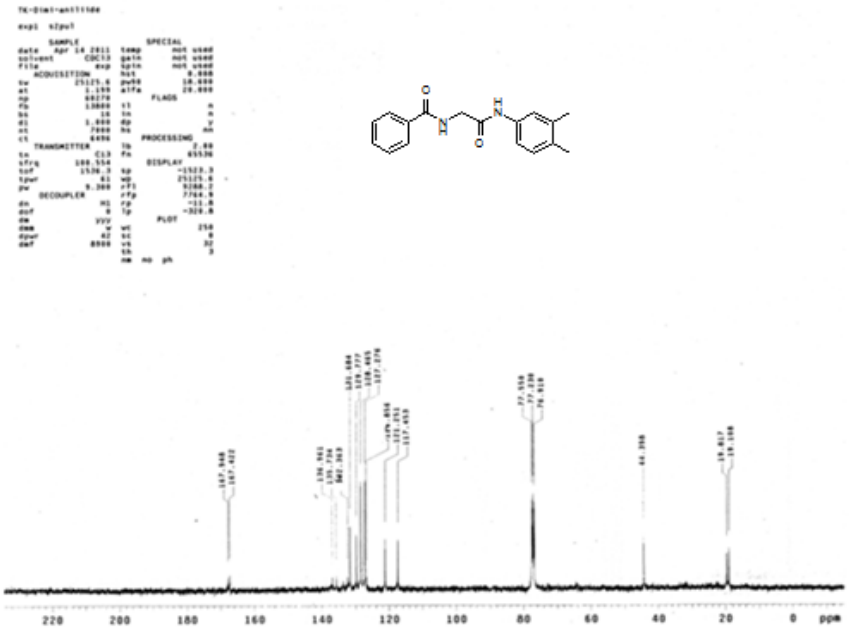


^{1}H NMR , ^{13}C NMR and HRMS of Compound **12**





Sample Name	me-anilide 2	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
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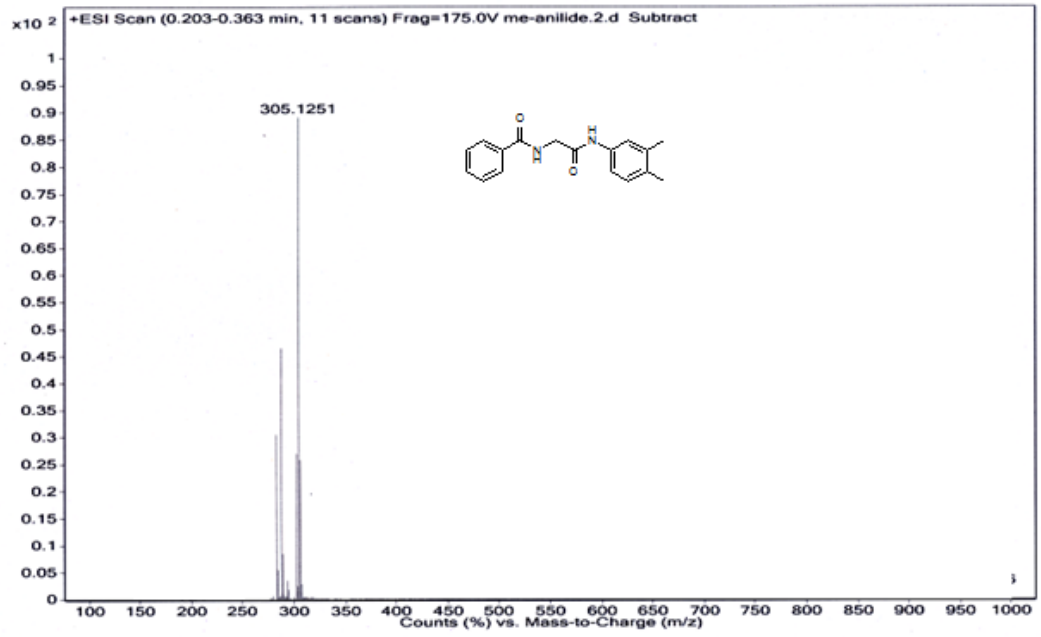
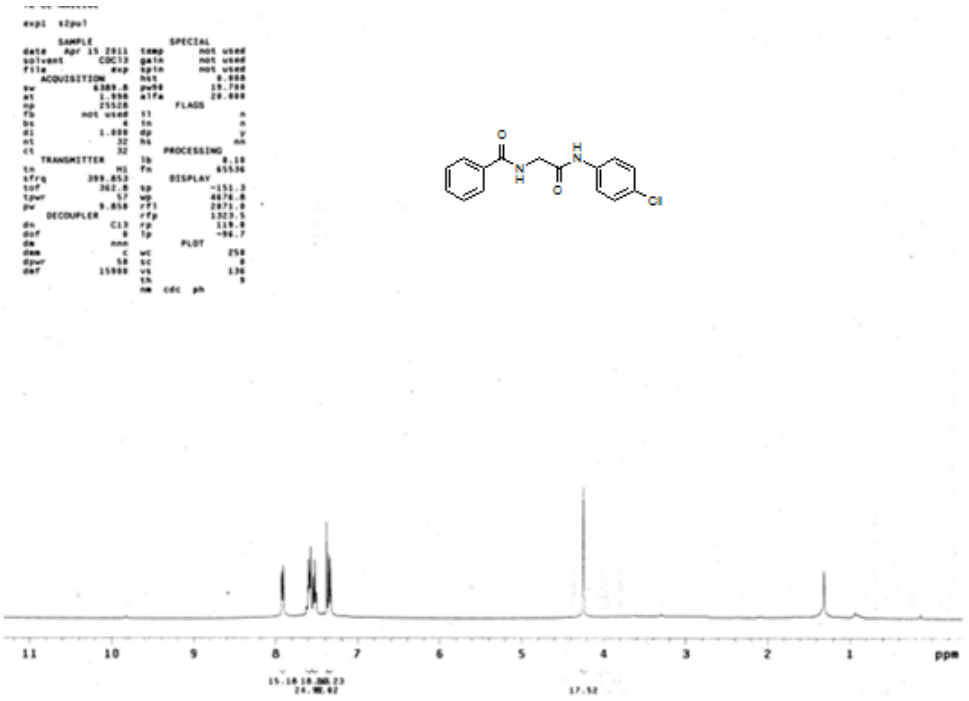
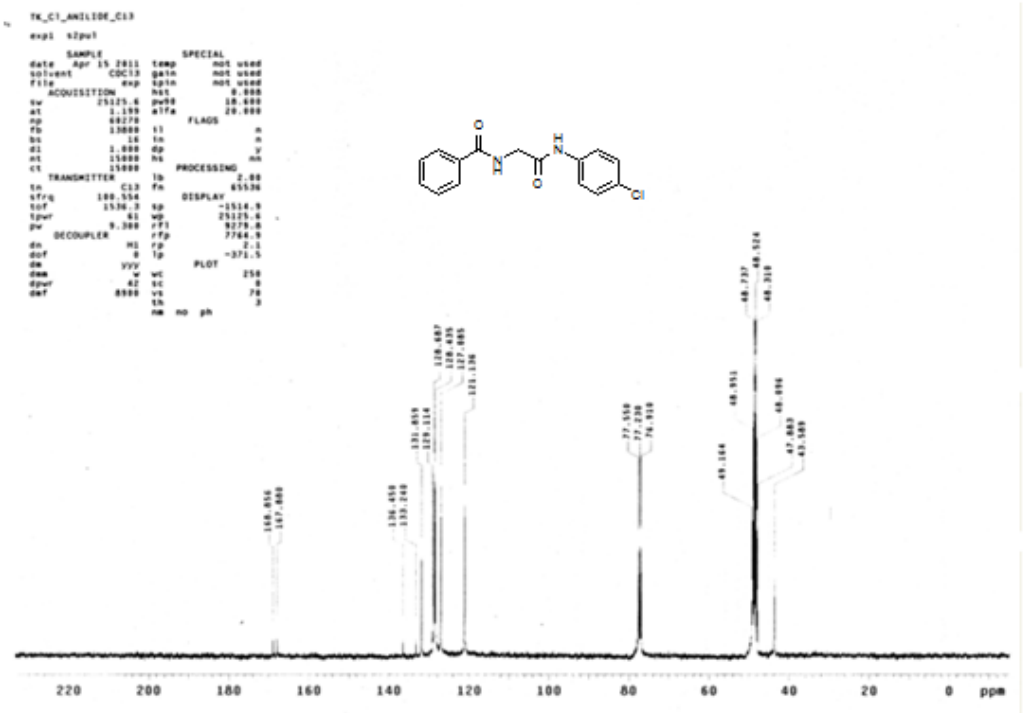


^{1}H NMR ,^{13}C NMR and HRMS of Compound **13**





Sample Name	cl-anilide 2	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
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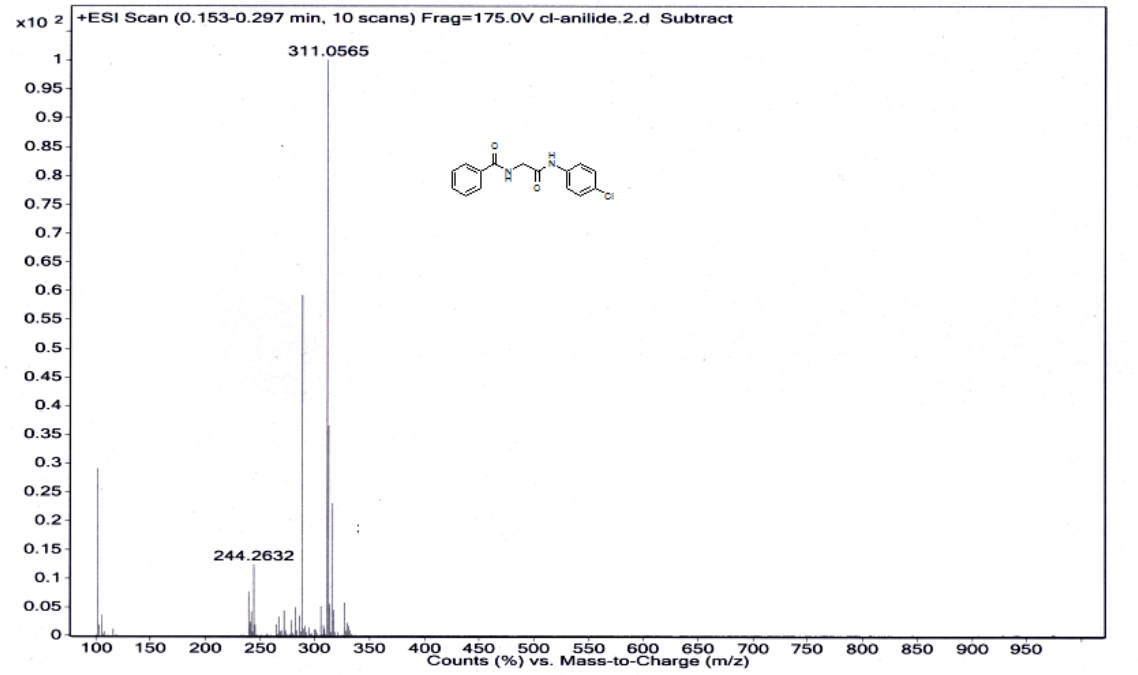
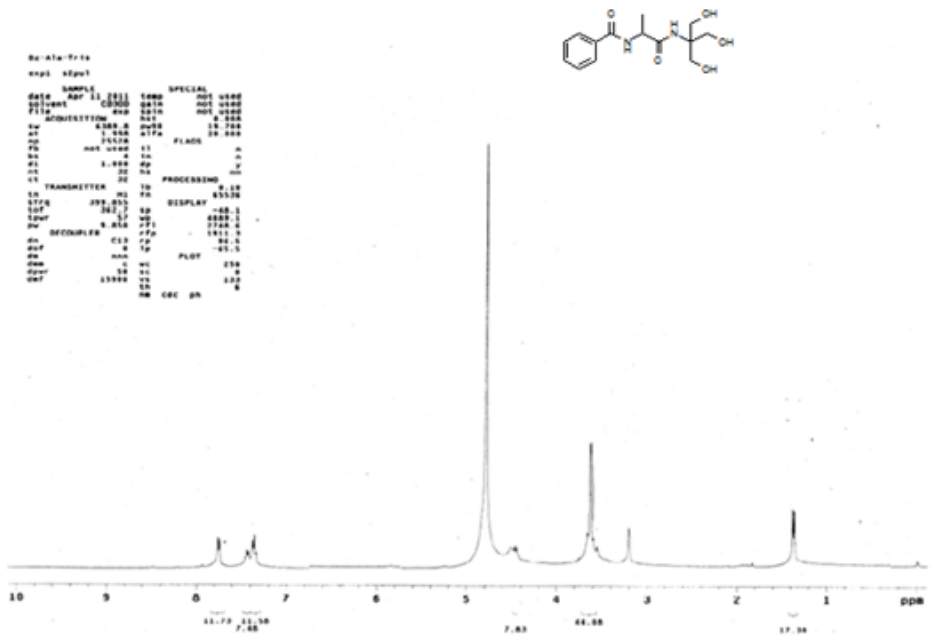
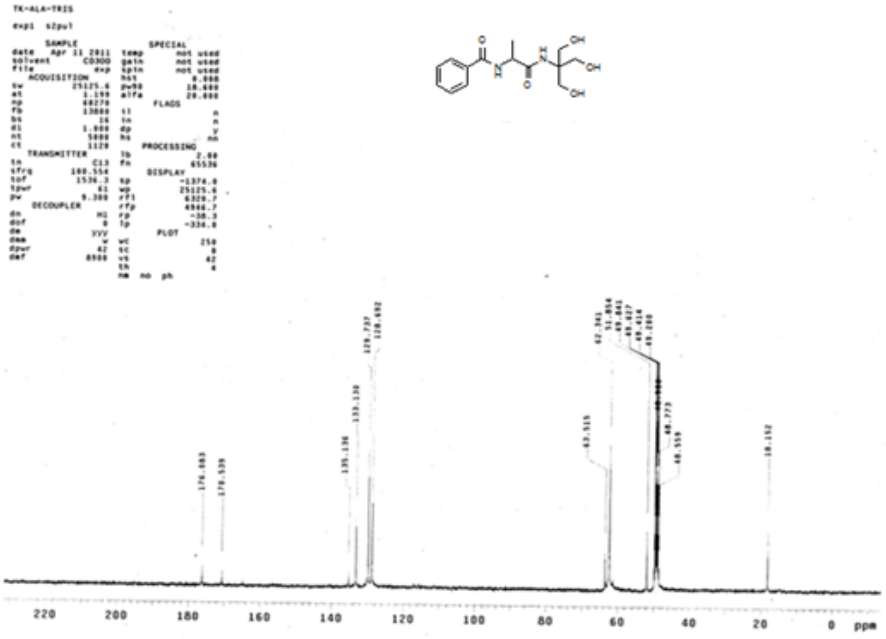


^{1}H NMR ,^{13}C NMR and HRMS of Compound **14**





Sample Name	TK-Bnala-tris	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
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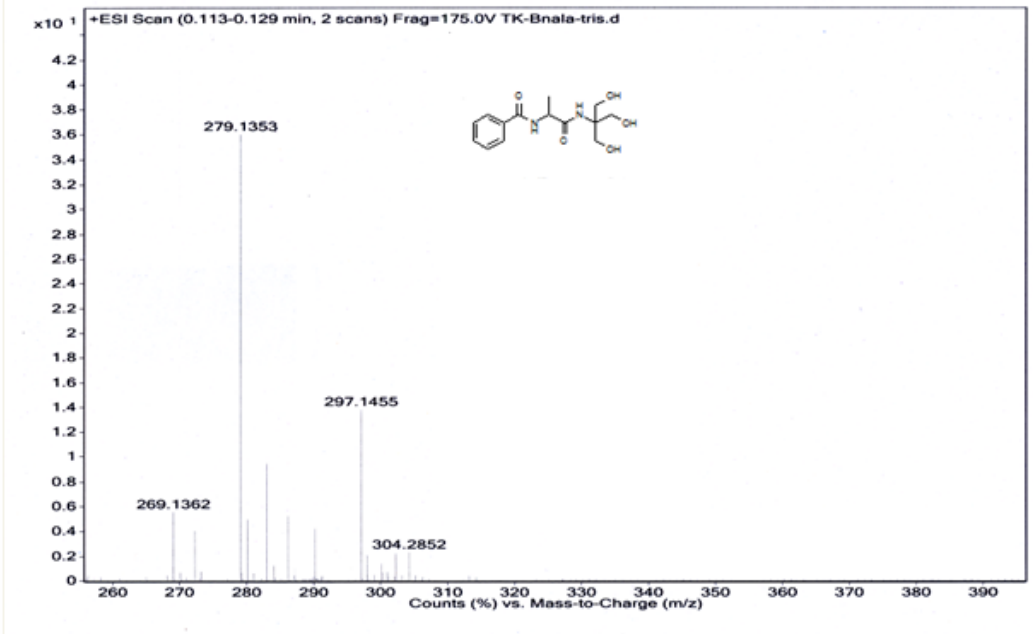
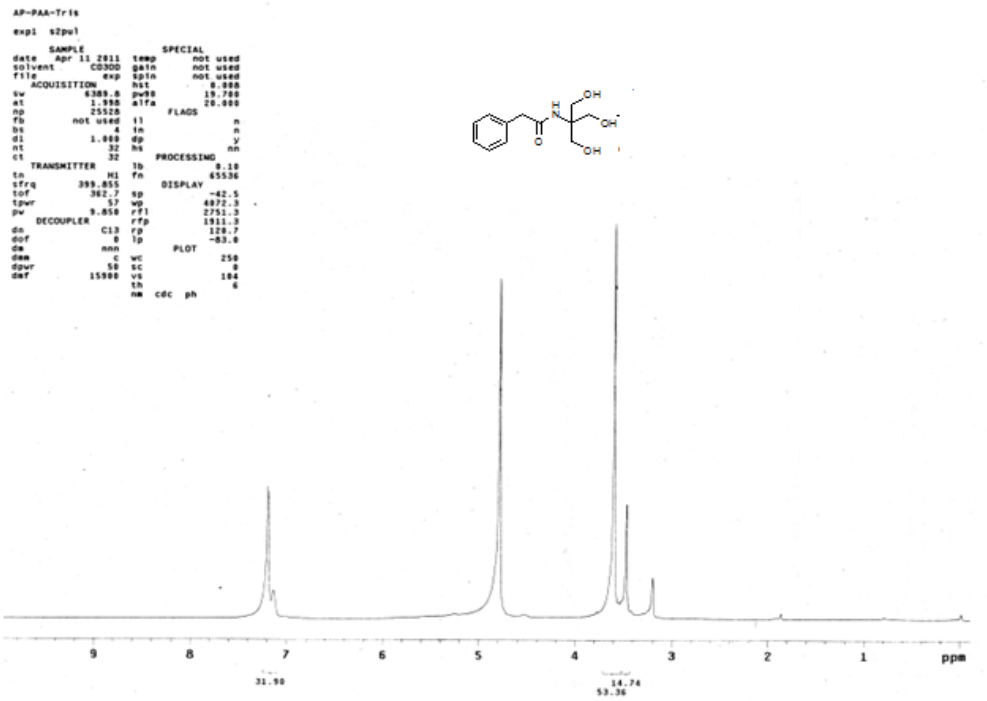
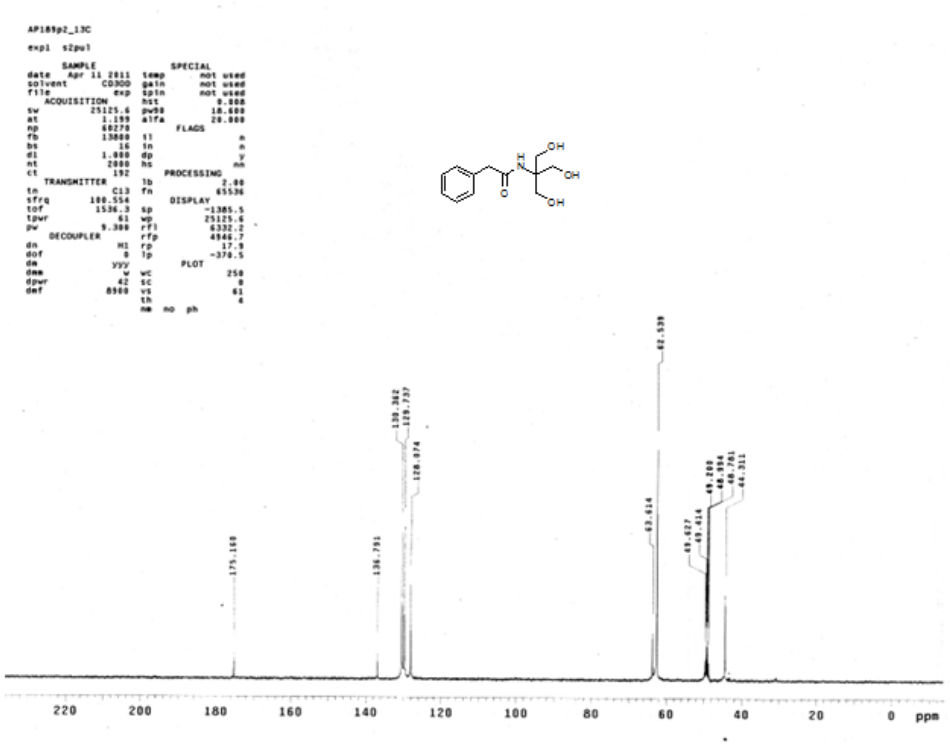
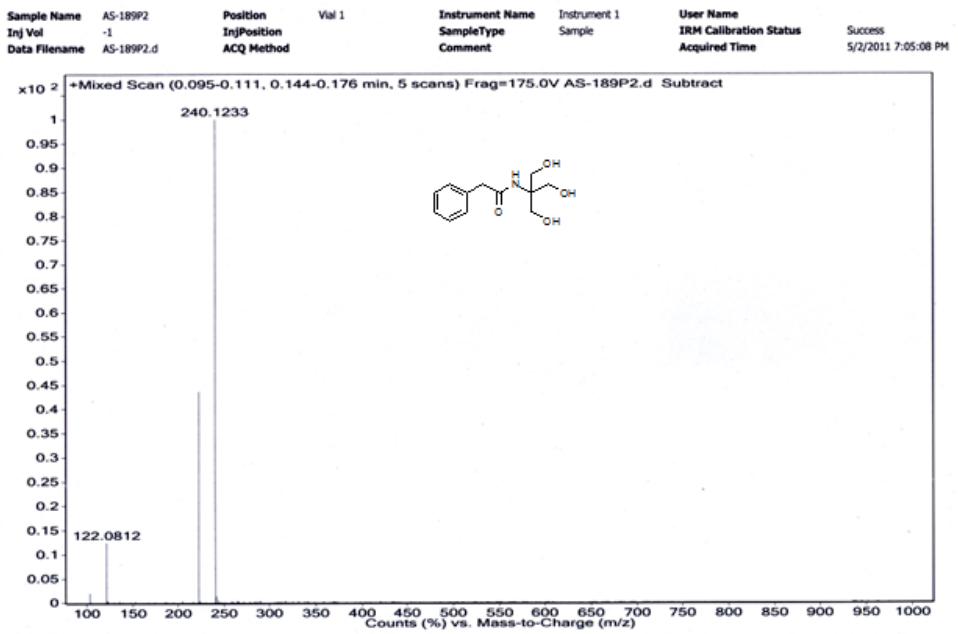


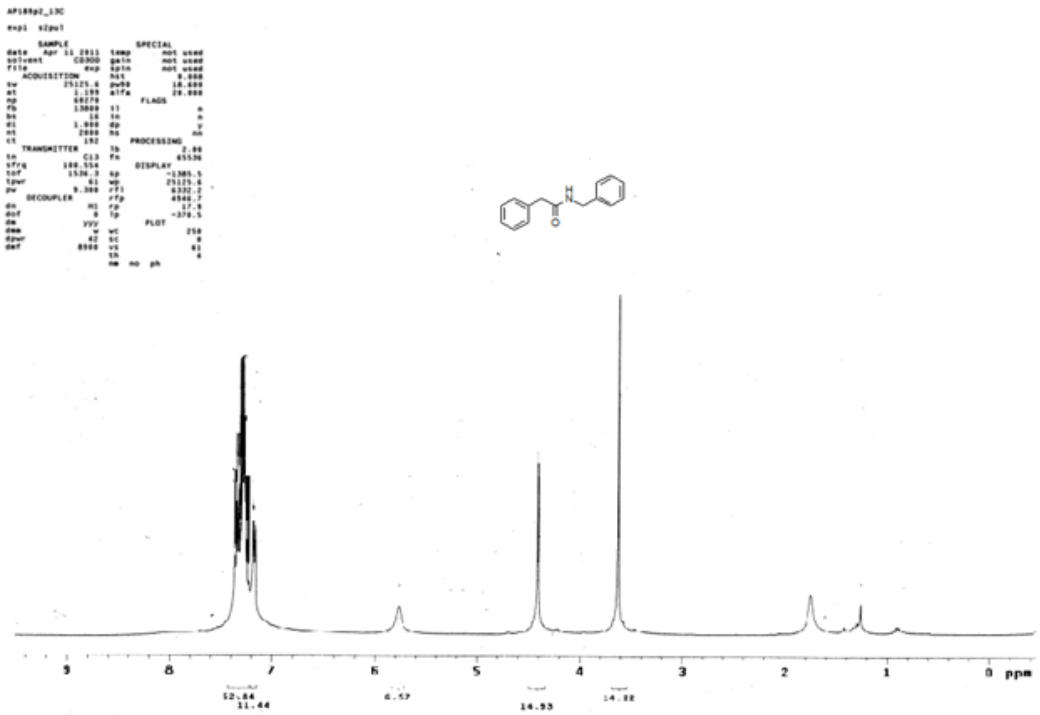
^{1}H NMR ,^{13}C NMR and HRMS of Compound **15**

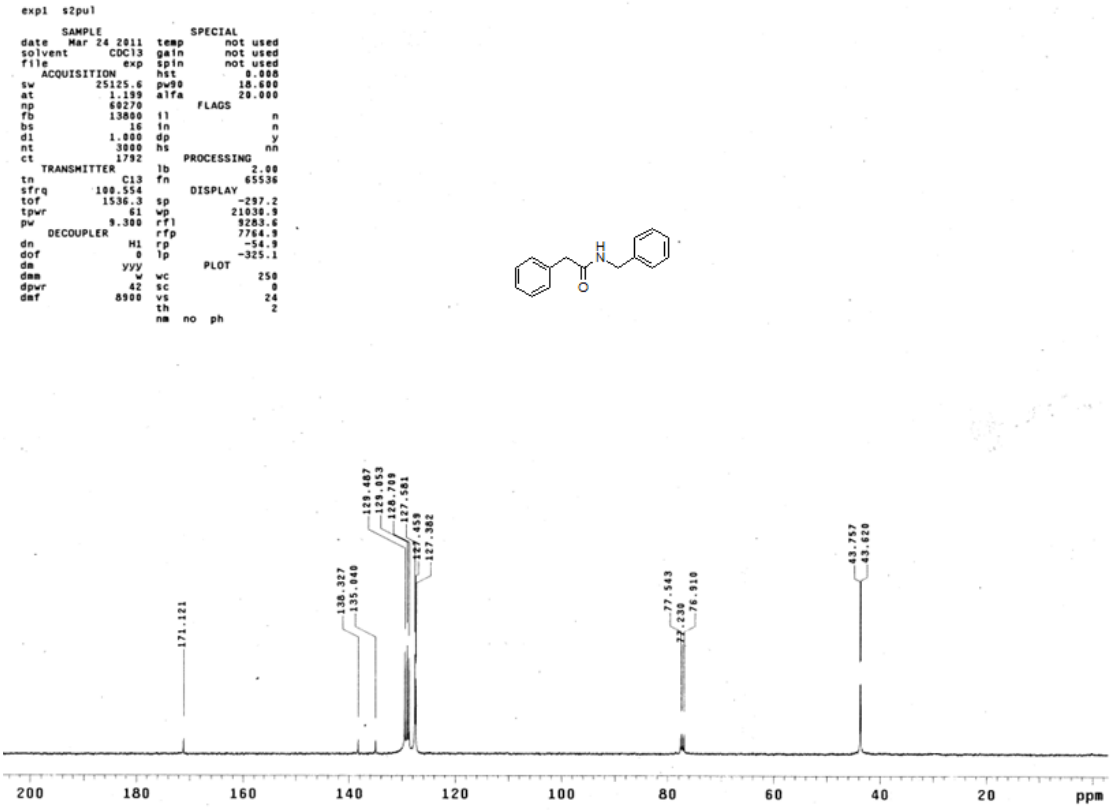




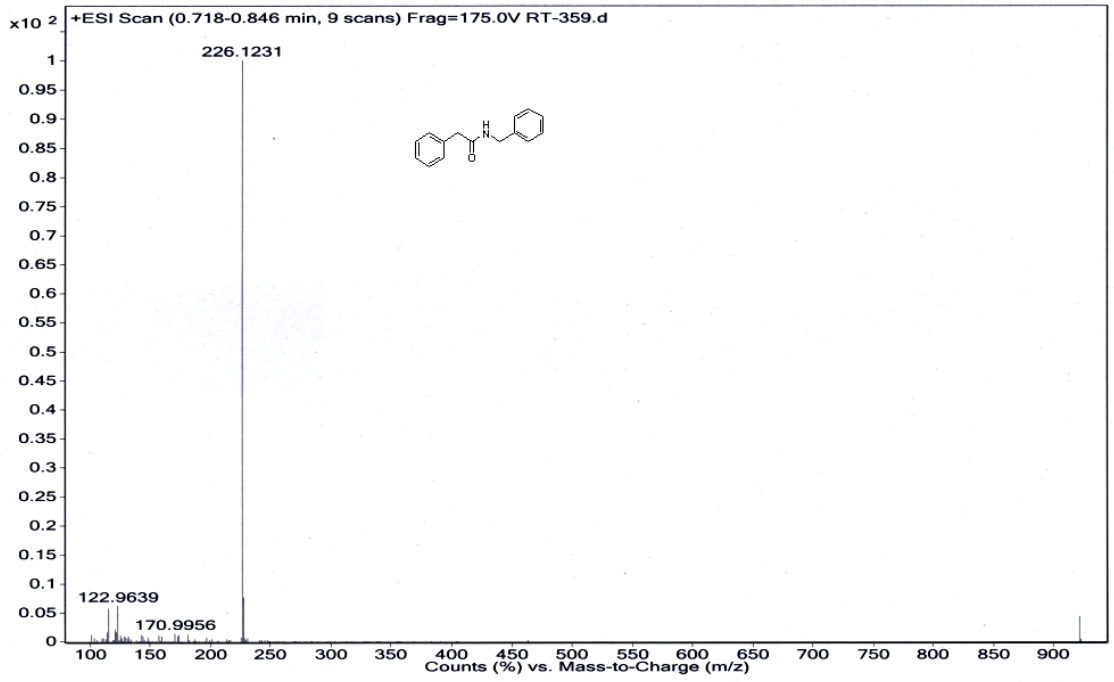


^{1}H NMR , ^{13}C NMR and HRMS of Compound **16**

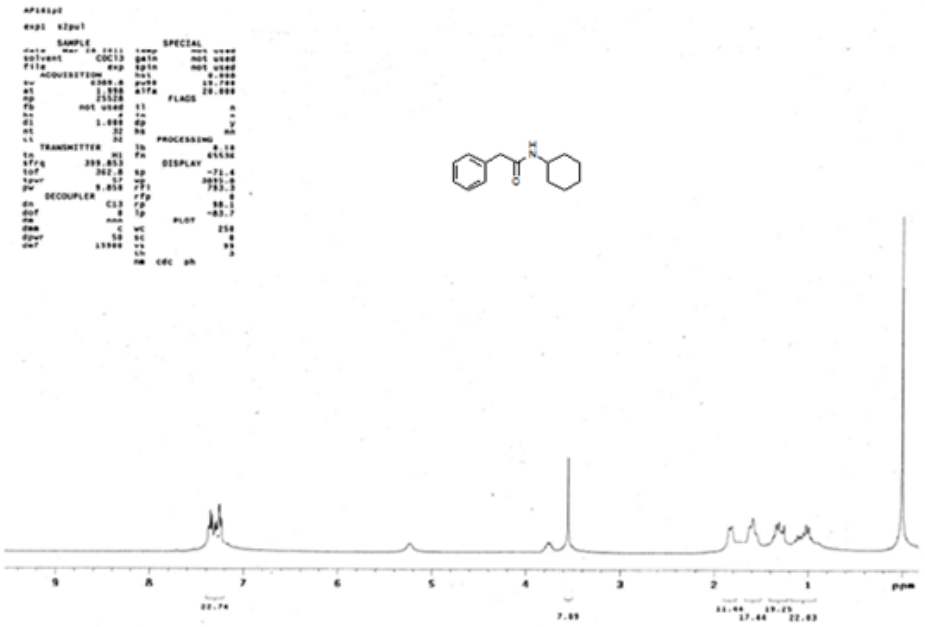


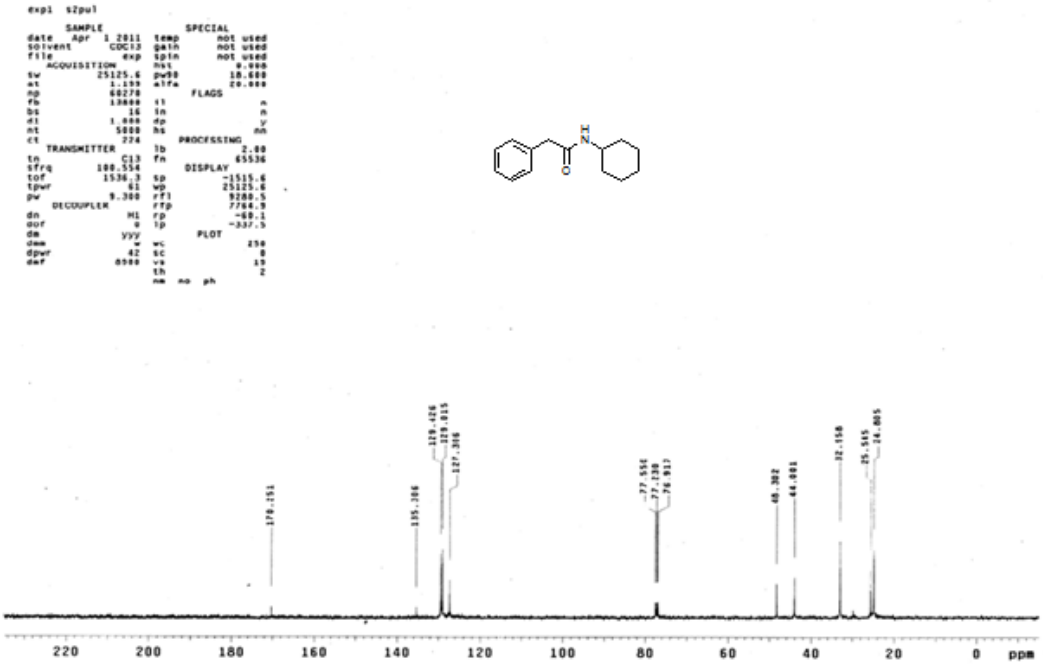


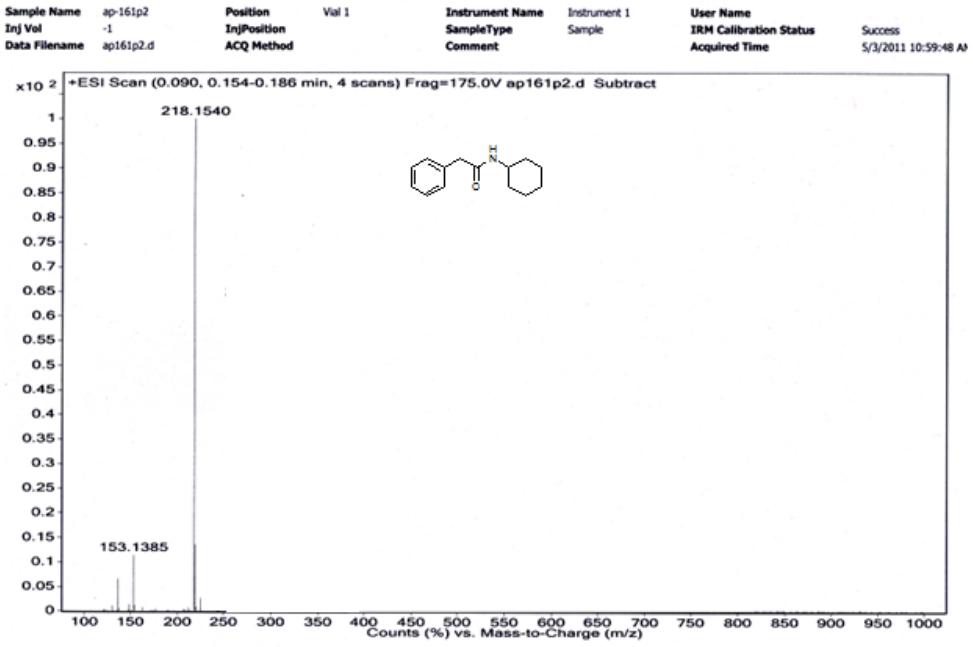
Sample Name	RT-359	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	RT-359.d	**ACQ Method**		**Comment**		**Acquired Time**	8/5/2011 12:22:05 PM



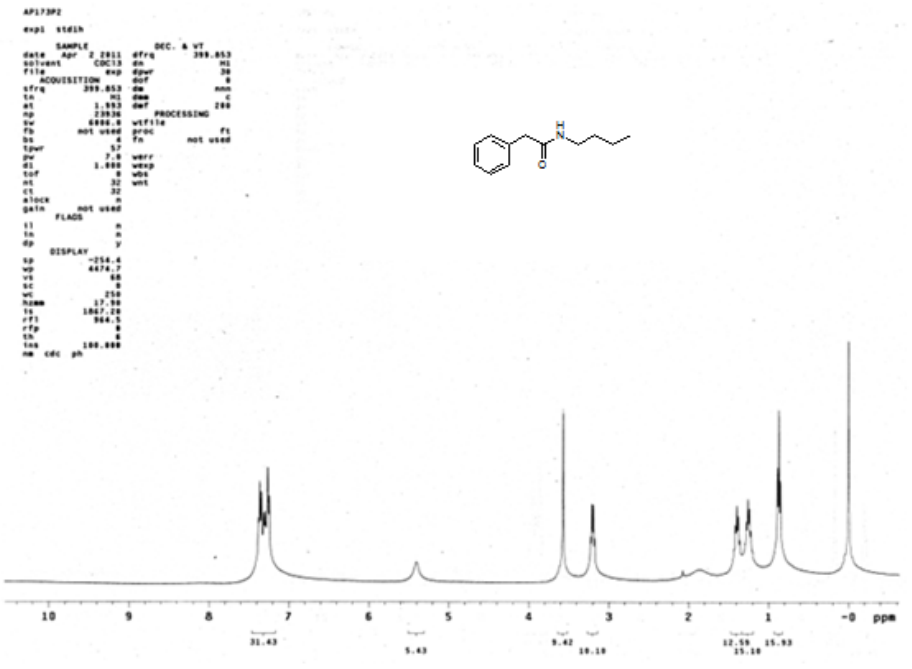
^{1}H NMR ,^{13}C NMR and HRMS of Compound **17**



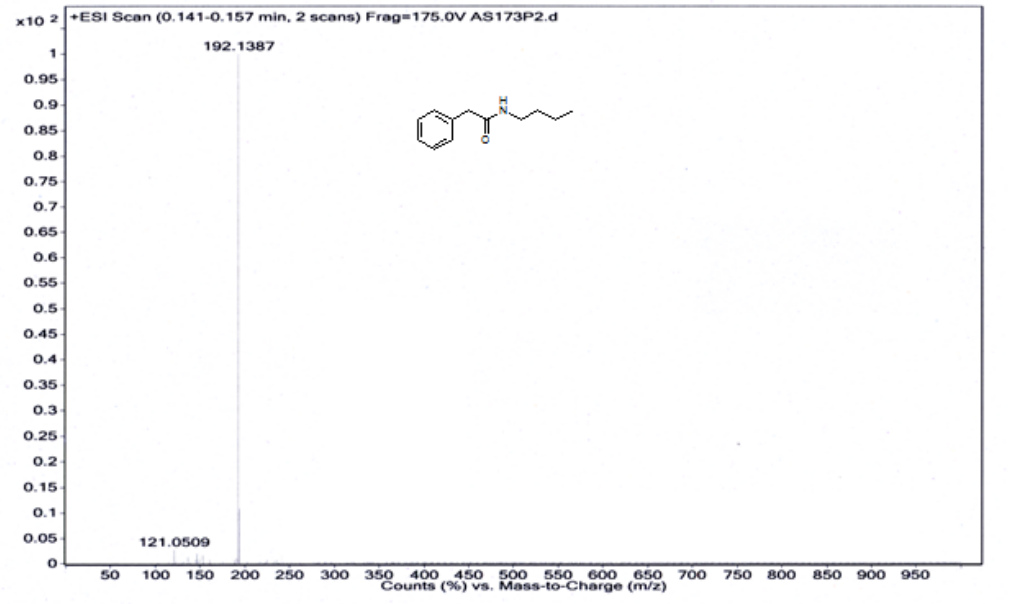




^{1}H NMR ,^{13}C NMR and HRMS of Compound **18**



Sample Name	AS173P2	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	AS173P2.d	**ACQ Method**		**Comment**		**Acquired Time**	5/2/2011 7:56:28 PM

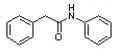


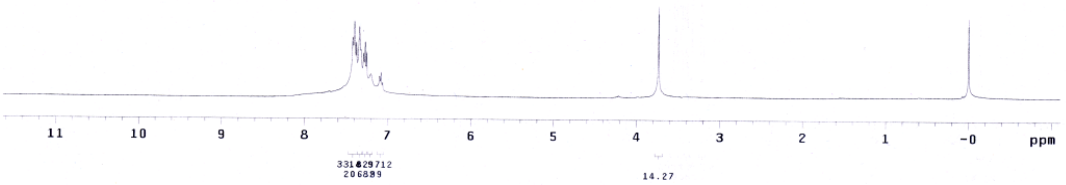
^{1}H NMR , ^{13}C NMR and HRMS of Compound **19**

AP179P2

expl s2pul

SAMPLE		SPECIAL	
date	Apr 7 2011	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	6389.8	pw90	19.700
at	1.998	alfa	20.000
np	25528	FLAGS	
fb	not used	il	n
bs	4	in	n
d1	1.000	dp	y
nt	32	hs	nn
ct	32	PROCESSING	
TRANSMITTER		lb	0.10
tn	H1	fn	65536
sfrq	399.853	DISPLAY	
tof	362.8	sp	-444.2
tpwr	57	wp	5096.7
pw	9.850	rfl	796.8
DECOUPLER		rfp	0
dn	C13	rp	83.4
dof	0	lp	-46.5
dm	nnn	PLOT	
dmm	c	wc	250
dpwr	50	sc	0
dmf	15900	vs	22
		th	4
		nm	cdc ph

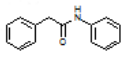


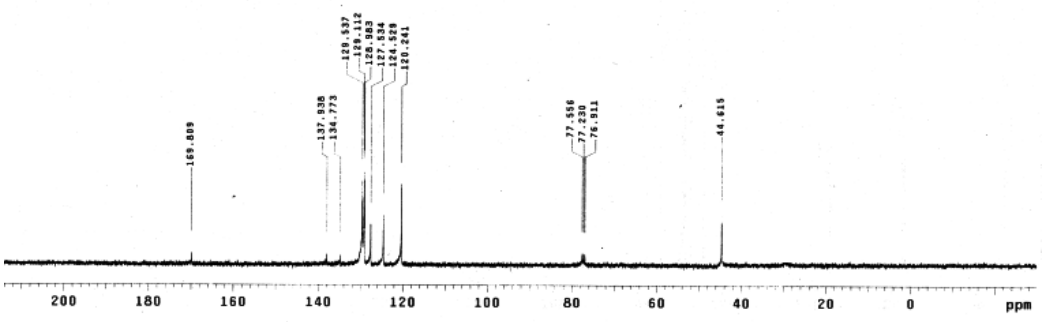


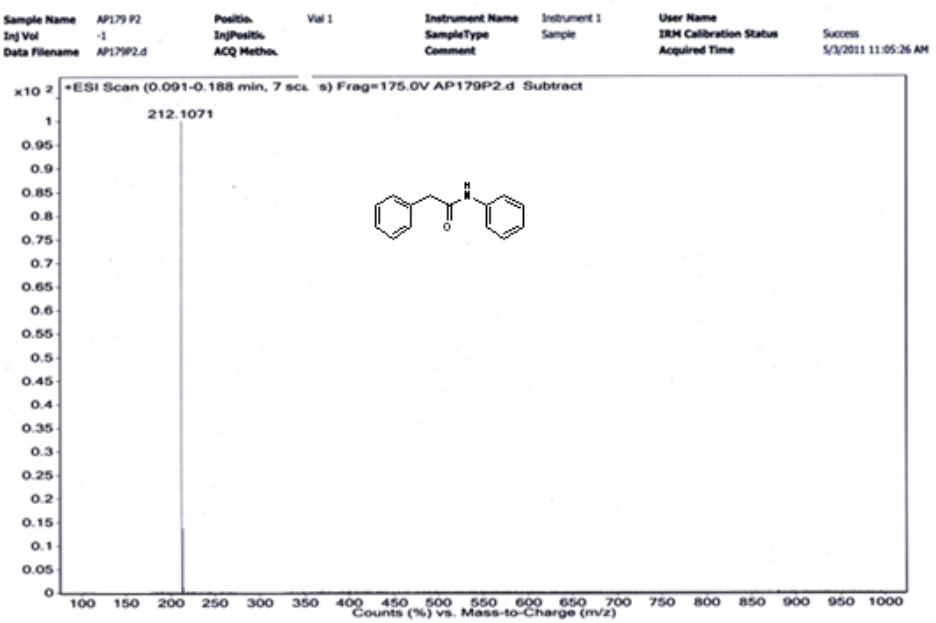
AP-ANILIDE (AP 179)

expl std13c

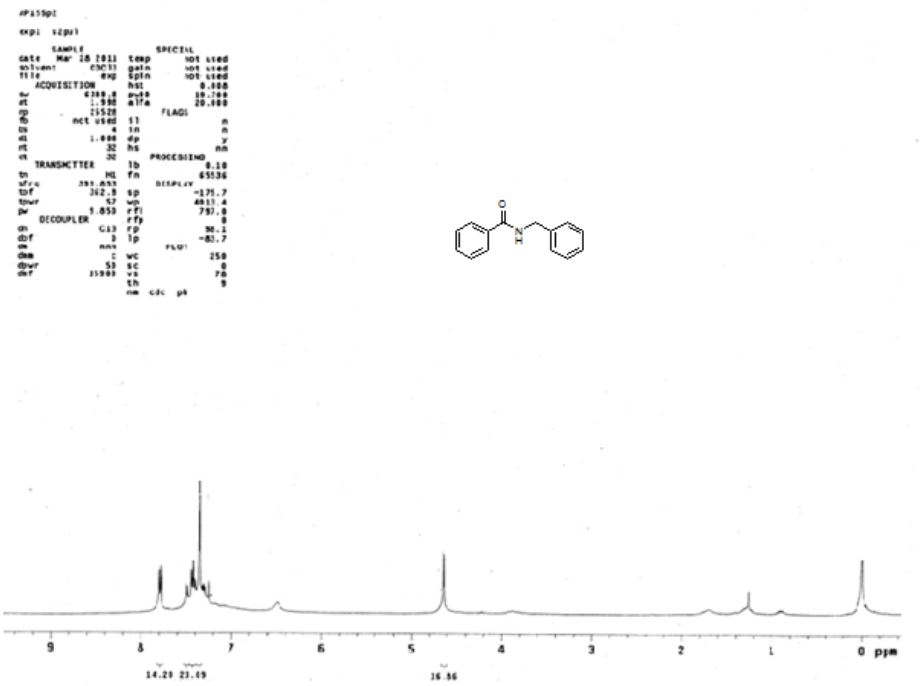
SAMPLE		SPECIAL	
date	Apr 13 2011	temp	not used
solvent	CDCl3	gain	not used
file	exp	spin	not used
ACQUISITION		hst	0.008
sw	25000.0	pw90	10.600
at	1.199	alfa	20.000
np	59968	FLAGS	
fb	13800	il	n
bs	16	in	n
d1	0	dp	y
nt	2000	hs	nn
ct	0	PROCESSING	
TRANSMITTER		lb	1.00
tn	C13	fn	not used
sfrq	100.552	DISPLAY	
tof	0	sp	-2993.6
tpwr	61	wp	25000.0
pw	8.667	rfl	10758.5
DECOUPLER		rfp	7764.9
dn	H1	rp	-86.6
dof	0	lp	-270.0
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	42	sc	0
dmf	6900	vs	22
		th	2
		nm	no ph

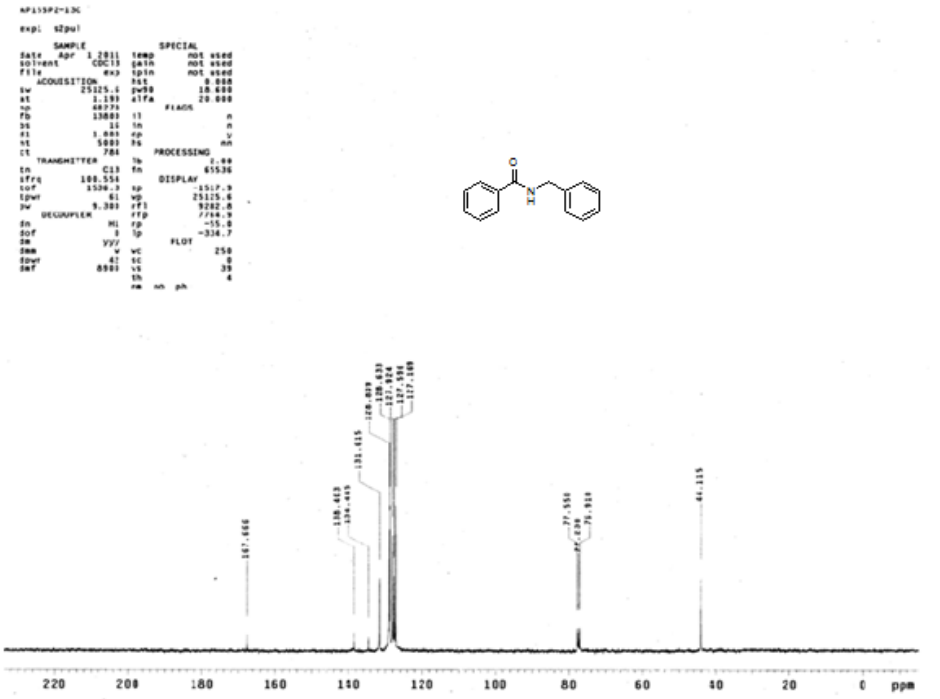




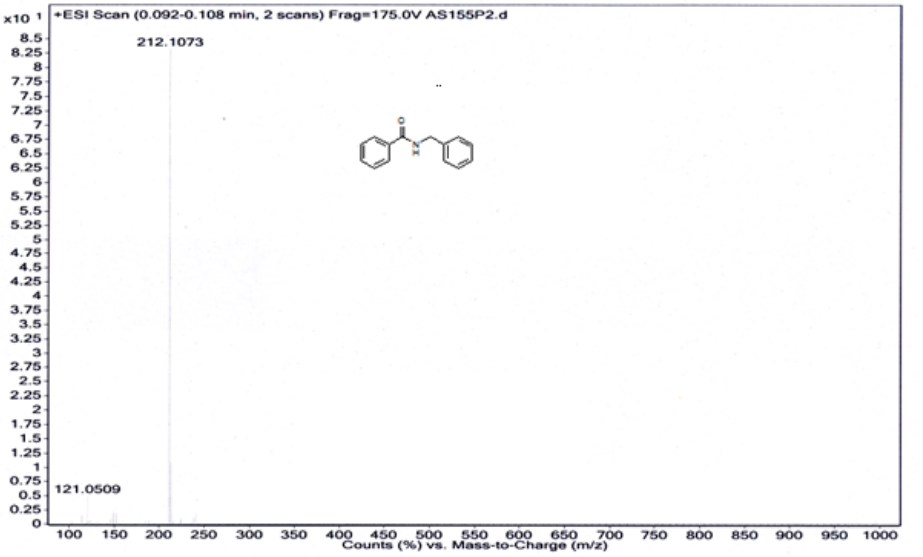


^{1}H NMR ,^{13}C NMR and HRMS of Compound **20**

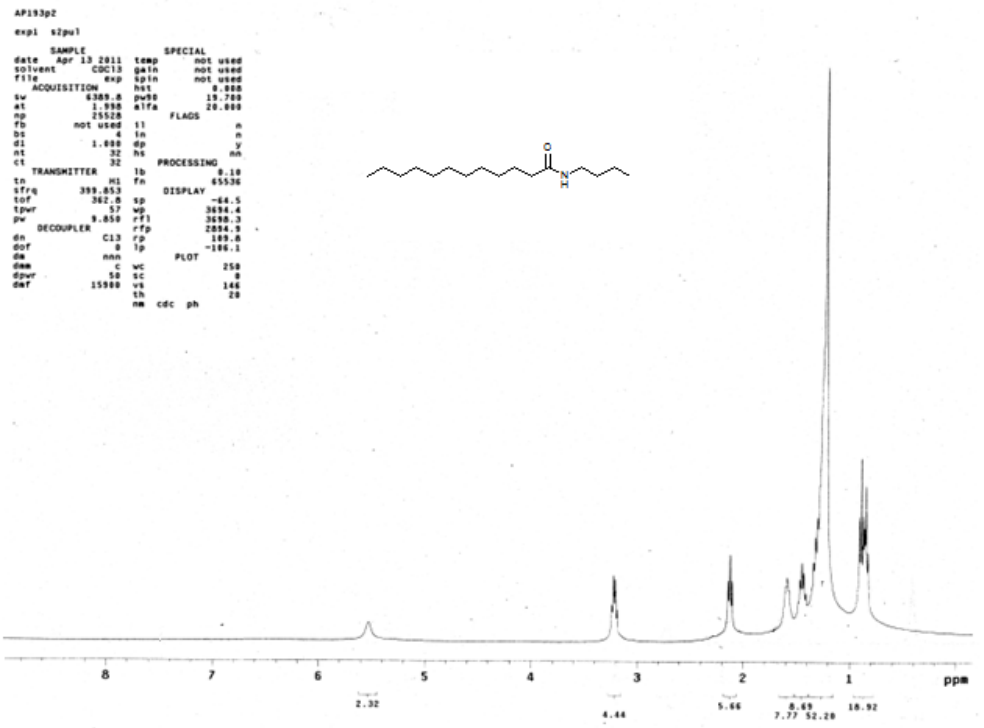


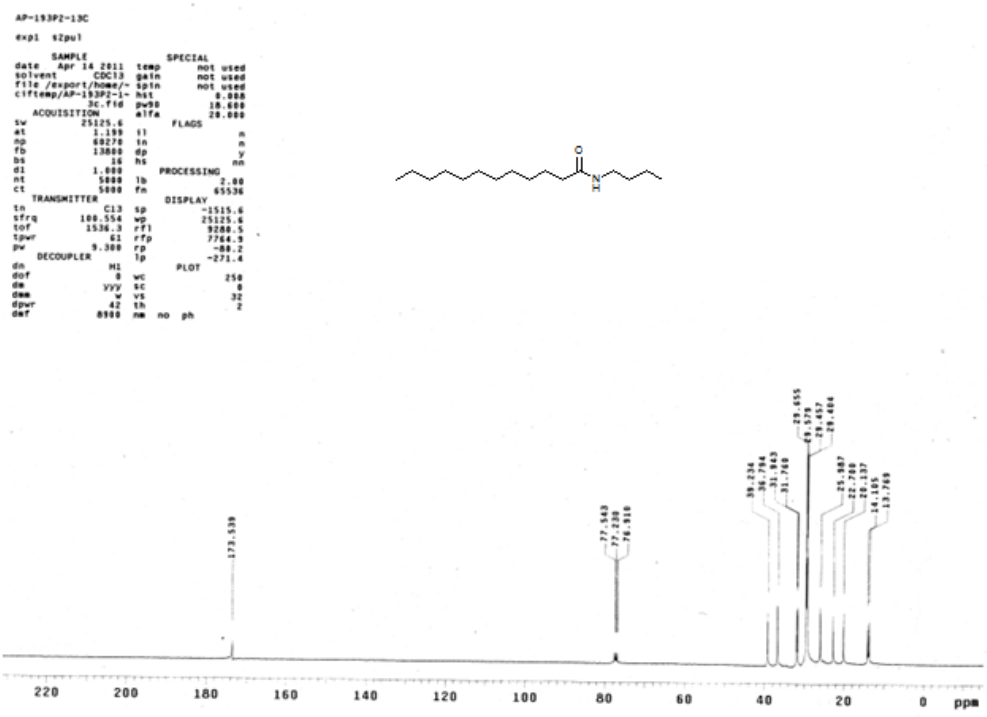


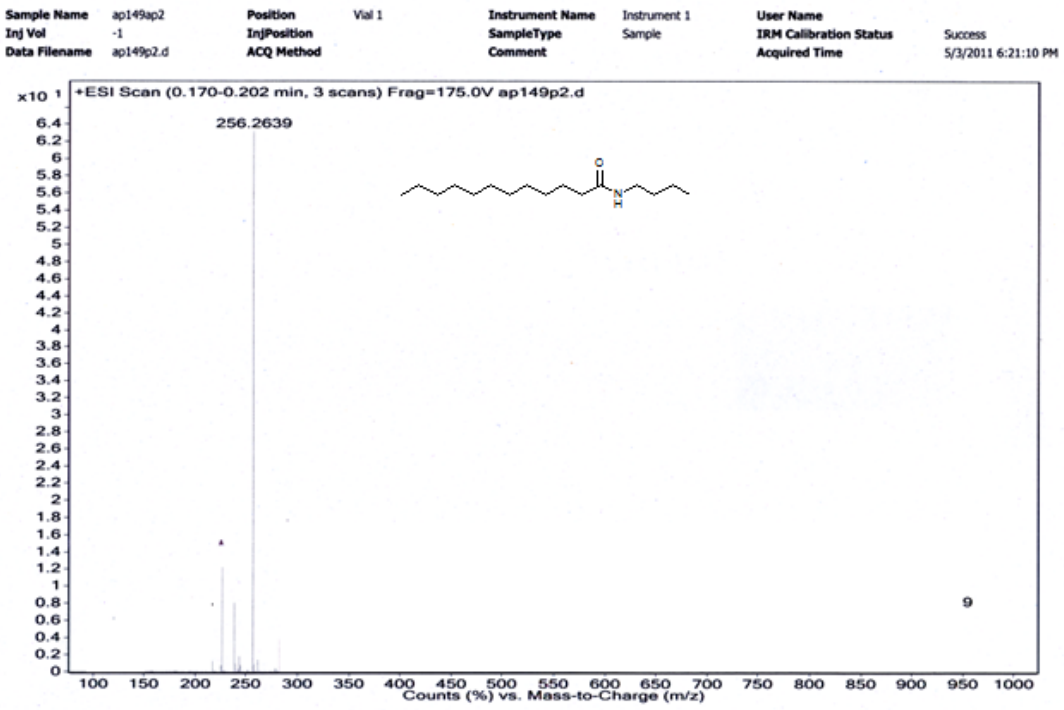
Sample Name	AS155P2	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	AS155P2.d	**ACQ Method**		**Comment**		**Acquired Time**	5/2/2011 4:37:20 PM



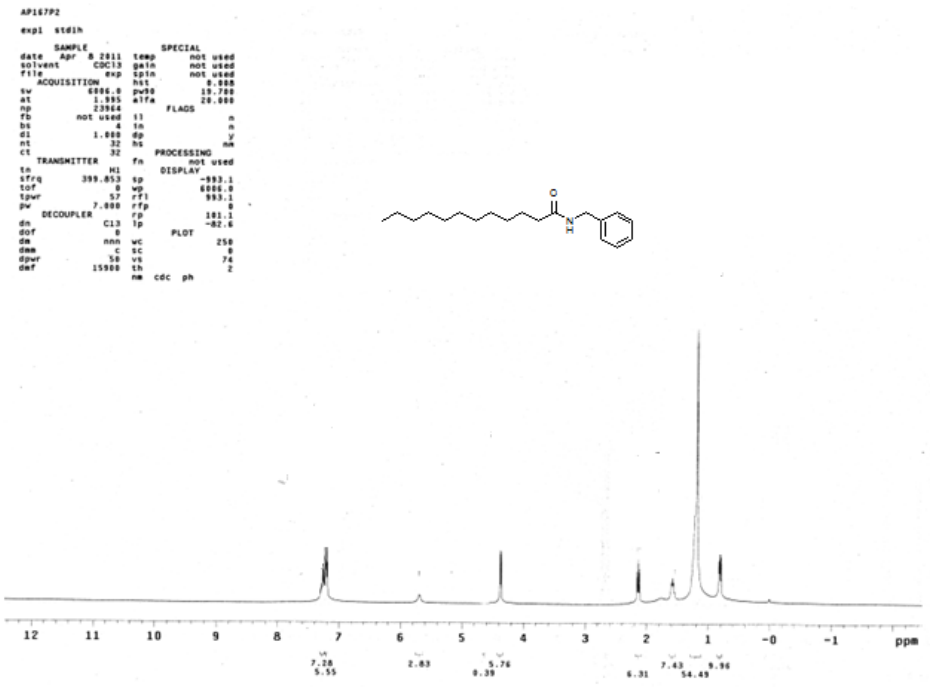
^{1}H NMR ,^{13}C NMR and HRMS of Compound **21**

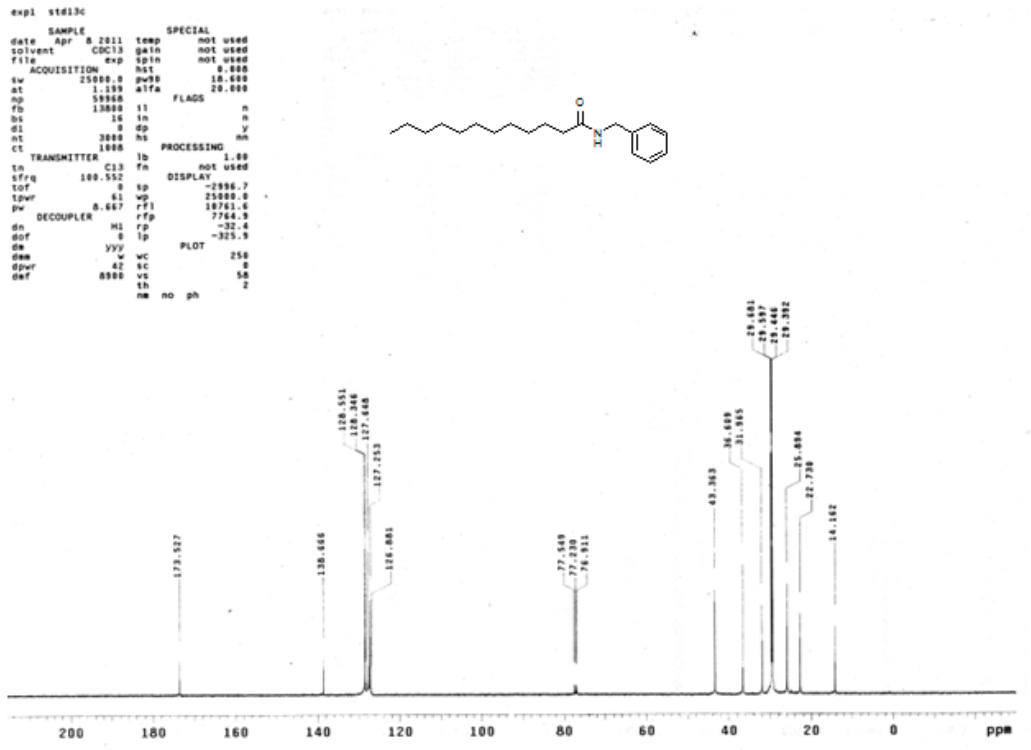




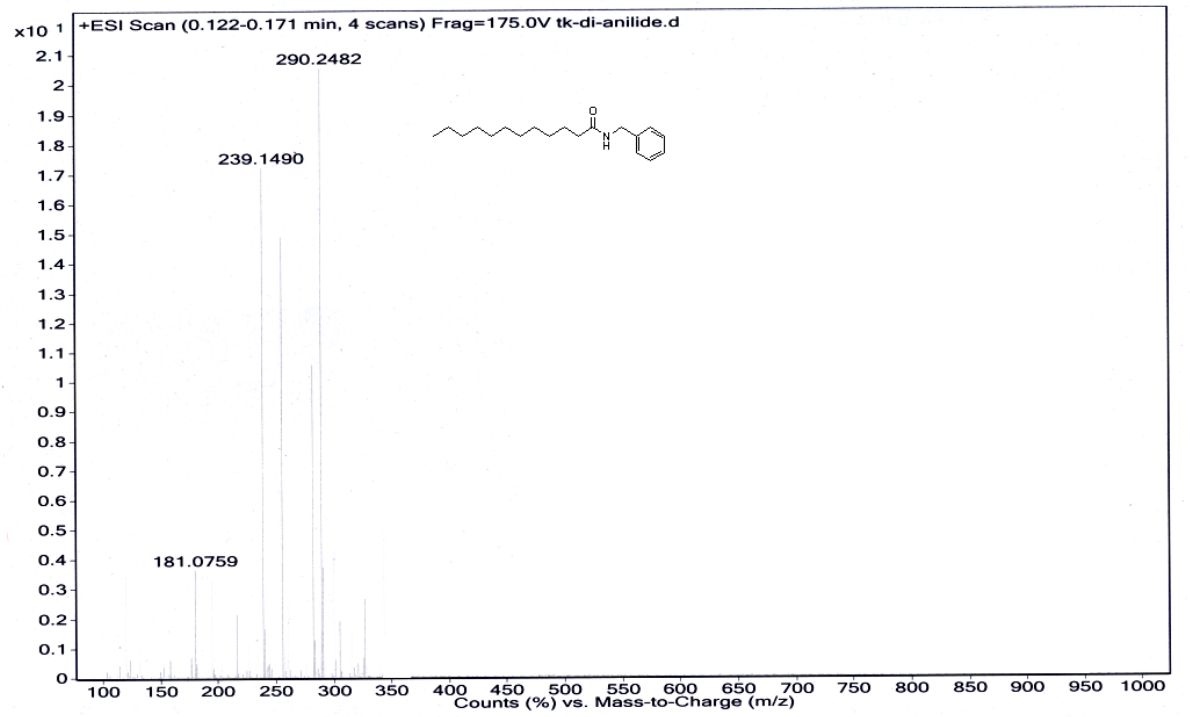


^{1}H NMR ,^{13}C NMR and HRMS of Compound **22**

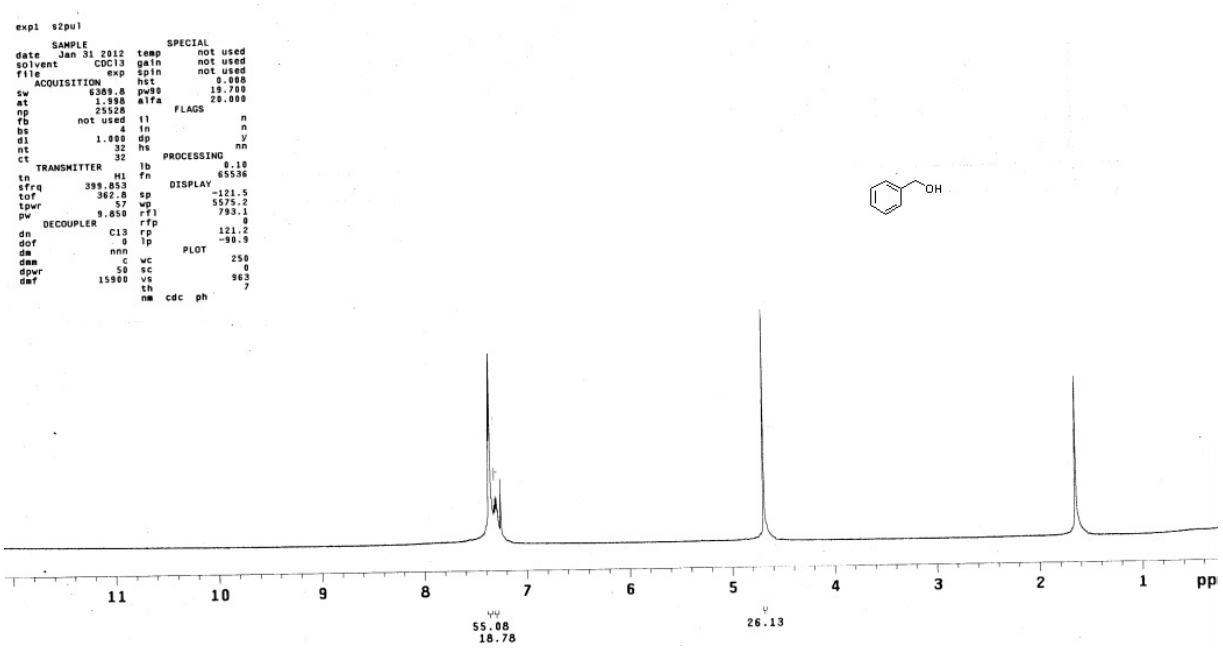


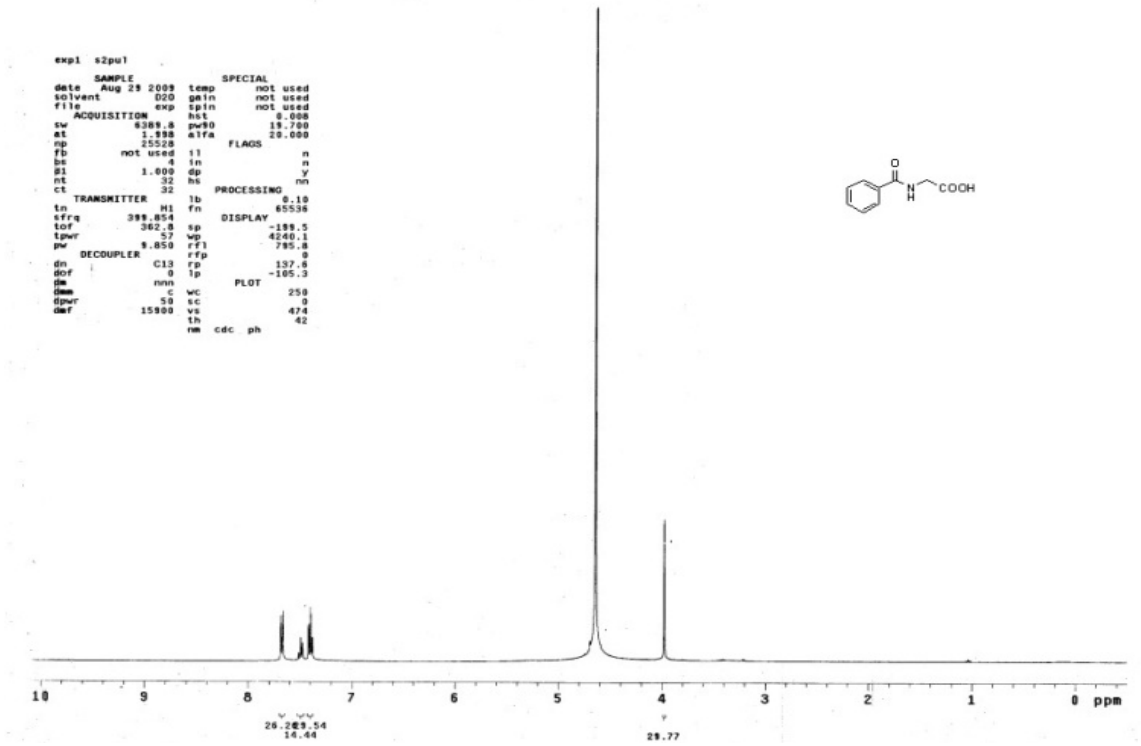


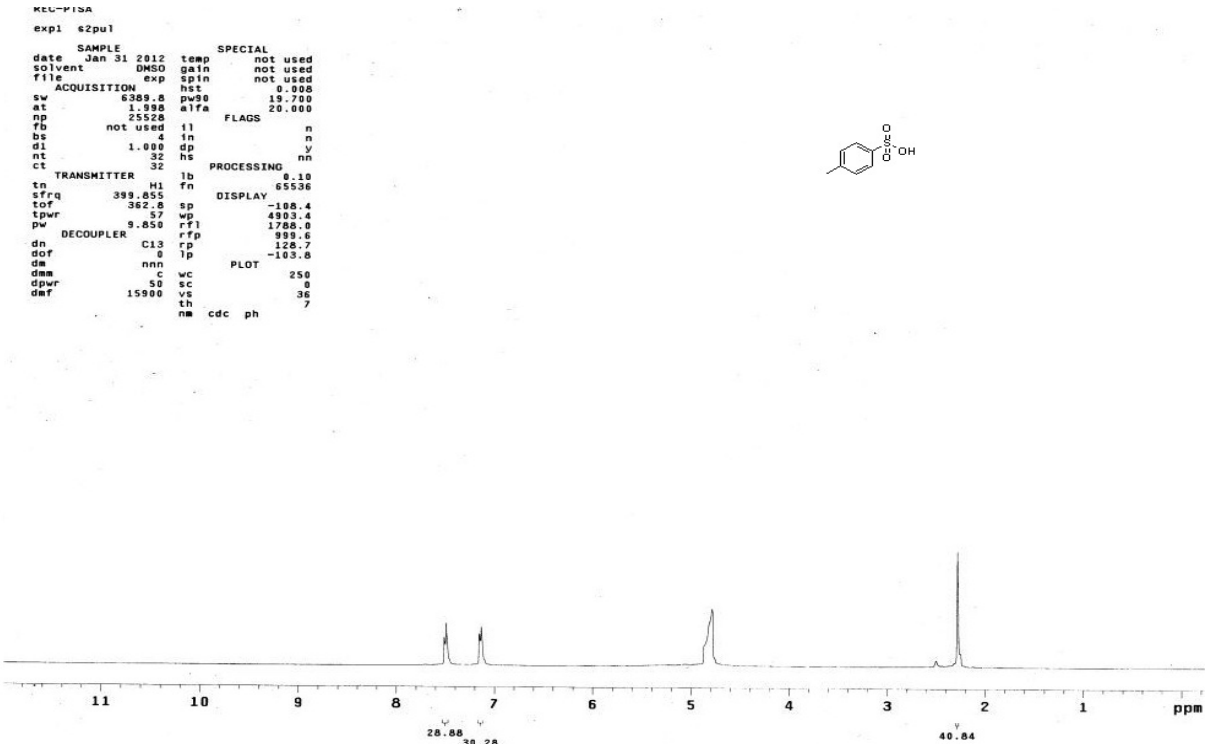
Sample Name	1	**Position**	Vial 1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	1	**ACQ Method**		**Comment**		**Acquired Time**	5/3/2011 6:26:06 PM

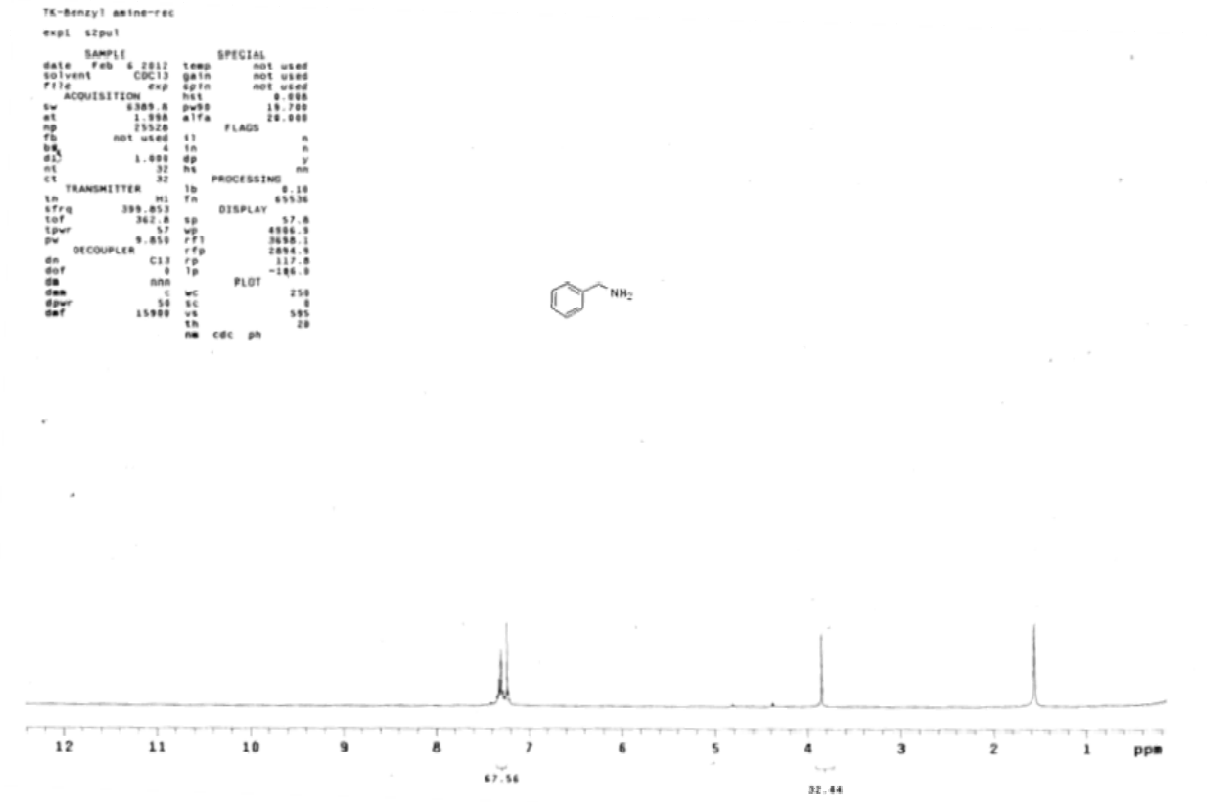


^{1}H NMR spectra of the recovered materials









Crystallographic data of N-2-benzyl amino-2-oxoethyl benzamide (3) CCDC # 837222

Compound reference	tk4
Chemical formula	$C_{16}H_{16}N_2O_2$
Formula Mass	268.31
Crystal system	Orthorhombic
a/Å	10.0436(5)
b/Å	14.5106(8)
c/Å	9.4623(5)
α/°	90.00
β/°	90.00
γ/°	90.00
Unit cell volume/Å^3	1379.02(13)
Temperature/K	296(2)
Space group	*Pca*21
No. of formula units per unit cell, *Z*	4
No. of reflections measured	17142
No. of independent reflections	3382
R_{int}	0.1407
Final R_1 values ($I > 2\sigma(I)$)	0.0521
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1182
Final R_1 values (all data)	0.1304
Final $wR(F^2)$ values (all data)	0.1419

Crystallographic data of N-Cyclohexyl-2-phenyl-acetamide (17) CCDC # 837072

Compound reference	1
Chemical formula	$C_{14}H_{19}NO$
Formula Mass	217.30
Crystal system	triclinic
a/Å	9.493(5)
b/Å	11.707(5)
c/Å	12.816(6)
α/°	79.59(3)
β/°	73.54(4)
γ/°	73.58(3)
Unit cell volume/Å^3	1302.5(11)
Temperature/K	296(2)
Space group	*P-1*
No. of formula units per unit cell, *Z*	4
No. of reflections measured	8043
No. of independent reflections	2452
R_{int}	0.0702
Final R_1 values ($I > 2\sigma(I)$)	0.0672
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1619
Final R_1 values (all data)	0.1314
Final $wR(F^2)$ values (all data)	0.2003