Engineering N-(2-pyridyl)aminoethyl alcohols as potential precursors of thermolabile protecting groups

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Contents:

(1) General remarks:

All reagents (analytical grade) were obtained from commercial suppliers and used without further purification. Hexane and dichloromethane were freshly distilled from CaH_2 and P_2O_5, respectively. All other solvents and liquid reagents were dried through storage over activated 3Å (MeOH, MeCN) molecular sieves. ^{1}H, ^{13}C-NMR. The NMR spectra were recorded at 298 K on a Bruker Advance DRX 400 spectrometer operating at frequencies 400.13201 MHz (^{1}H) and 100.62281 MHz (^{13}C).

Liquid secondary ion mass spectrum (low and high resolution) was obtained on an AMD 604 two sector mass spectrometer of reverse B/E geometry, made by AMD Intectra (Germany). A CsI gun supplied the primary ion beam (12 keV, Cs+). The secondary ion beam was accelerated to 8 kV. The compound was dissolved in 3-nitrobenzyl alcohol (Aldrich)

Table 1. NMR analysis of five compounds

Hydrogen at	**1**	**2**	**3**	**4**	**5**
C3	6.54 dd J=4.95, 7.03 Hz	6.44 dd J=7.09	6.47 dt Jt=7.23 Hz	X	6.49 m
C4	7.43 2xdd J= 2.01, 7.03 Hz	7.33 dd J=1.99, 7.09 Hz	7.24 t Jt=7.23 Hz	8.27 d J=4.77Hz	7.35 dd J= 1.96 Hz, 7.03 Hz
C5	6.58 dt J=1.38, 8.67 Hz	6.48 d J= 8.5 Hz	6.45 d Jd=8.6 Hz	6.56 t Jt=4.77 Hz	6.47 m
C6	8.06 dd J = 1.38, 4.86 Hz	7.94 dd J= 1.25, 5.05Hz	7.97 dd Jd=1.16, 4.95 Hz	8.27 d J=4.77Hz	7.96 dd J=1.85, 4.94 Hz
C8	3.59 m 4H	3.52 t J= 6.01 Hz	4.76 q Jq=4.4,	4.7 q J=3.8 Hz, J= 7.6 Hz	4.19 t Jt= 5.7 Hz
C7		3.31 q J= 5.87, 6.01 Hz	9a 3.52 ddd Jd= 4.4, 6.5, 13.20 Hz 9b 3.28 t, d Jt= 4.93 Hz, Jd=13.05 Hz	3.54 ddd Jt=4.72 Hz Jd=7.6 Hz	3.51 q Jq=5.56 Hz

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O1	4.79 m	4.76 m	5.68 m	5.5 d J= 4.06 Hz	
N2		6.42 m	6.52 m1H	6.96 t J= 4.76 Hz	6.67 t J= 5.64 Hz
aromatic	7.30 m 2H 7.21 m 3H		7.35 m 5H	7.30 m 5H	

The X-ray data, collected at the DESY synchrotron, were of good quality and crystal structures were solved for all the reported compounds[1] (Table 4)

Table 2. X-ray experimental details of **1** to **5**.

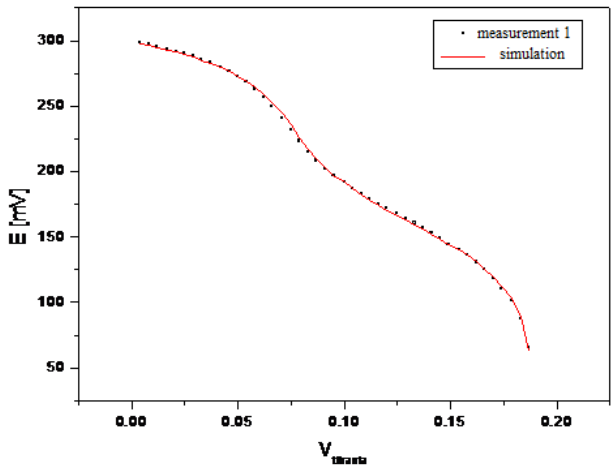
	1	**2**	**3**	**4**	**5**
formula	$C_{14}H_{16}N_2O$	$C_7H_{10}N_2O$	$C_{13}H_{14}N_2O$	$C_{12}H_{13}N_3O$	$C_{15}H_{18}N_4O_3$
fw	228.29	138.17	214.26	215.25	302.33
crystal system	monoclinic	orthorhombic	orthorhombic	monoclinic	monoclinic
space group	$P2_1/n$	$Pca2_1$	$P2_12_12_1$	$P2_1/c$	C2/c
a, Å	10.756(2)	8.841(2)	6.048(1)	5.605(1)	32.33(7)
b, Å	5.926(1)	9.053(2)	7.315(2)	20.972(4)	5.791(1)
c, Å	18.840(4)	8.630(2)	24.334(5)	9.500(2)	16.392(3)
β, deg	99.58(3)			108.1(3)	104.42(3)
V, $Å^3$	1184.1(4)	690.7(2)	1076.6(4)	1061.4(4)	2973.7(10)
wavelength, Å	0.81620	0.8125	0.81620	0.81620	0.80800
Z	4	4	4	4	8
Resolution range (Å)	*20.0-0.76 (0.77-0.76)	10-0.75 (0.76-0.75)	20.0-0.75 (0.76-0.75)	20.0-0.75 (0.76-0.75)	10.0-0.75 (0.76-0.75)
D_c, g/cm^3	1.281	1.329	1.322	1.347	1.351
μ, cm^{-1}	0.082	0.092	0.085	0.089	0.097
R_{merge} †	0.050 (0.135)	0.032 (0.039)	0.037 (0.095)	0.028 (0.057)	0.045 (0.086)
R_1 (obs. data)	0.0449	0.0435	0.0496	0.0473	0.0451
wR_2 (obs. data)	0.1207	0.1213	0.1389	0.1328	0.1283
independ refs	2806	906	1566	2574	3622
refs I > 2σ(I)	2732	885	1524	2522	3471

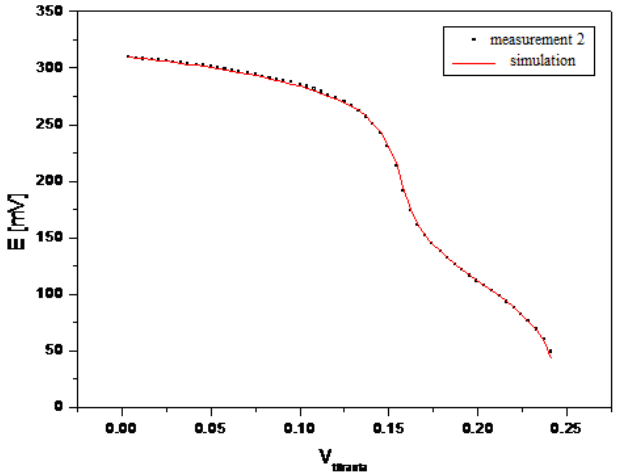
* Values in parenthesis are for the last resolution shell.

† $R_{merge} = \Sigma_{hkl} \Sigma_i |I_i (hkl) - \langle I(hkl)\rangle| / \Sigma_{hkl} \Sigma_i I_i (hkl)$, where $I_i (hkl)$ and $\langle I(hkl)\rangle$ are the observed individual and mean intensities of a reflection with the indices *hkl*, respectively, Σ_i is the sum over *i* measurements of a reflection with the indices *hkl*, and Σ_{hkl} is the sum over all reflections.

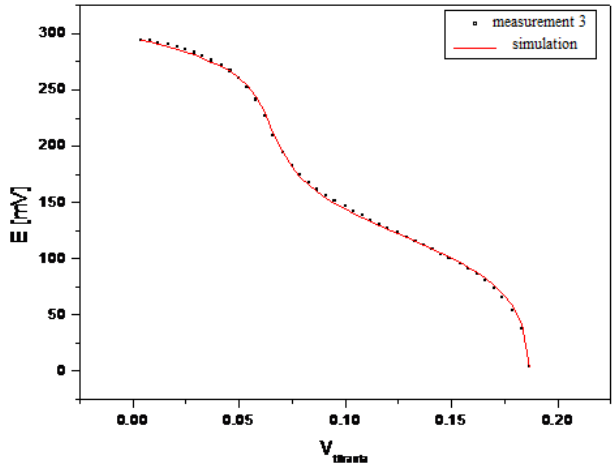
[1] Sheldrick GM. *Acta Cryst.*, A**64**, 112-122, 2008

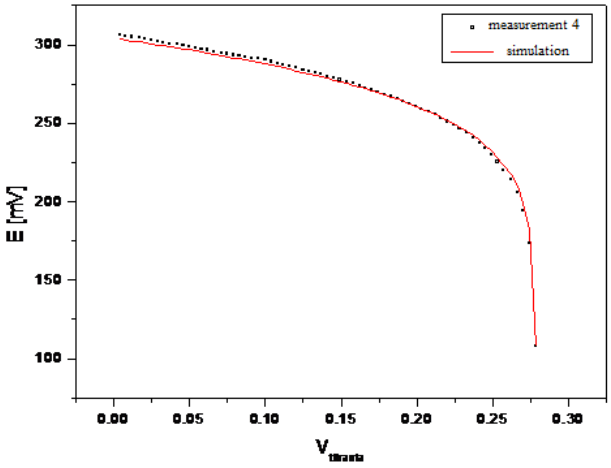
Potentiometric measurements carried out in acetonitrile/water (70%:30%)





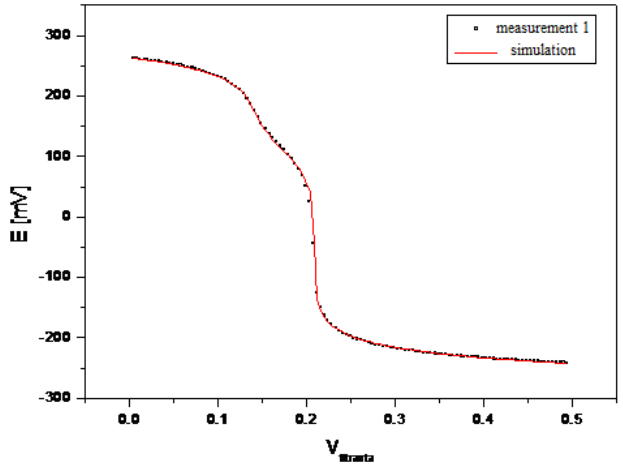
The solution was titrated contained: 2,0 ml of **1** c = $1{,}49 \cdot 10^{-3}$ M and acid HCl c = $2{,}81 \cdot 10^{-3}$ M Titrant: NaOH c = $2{,}87 \cdot 10^{-2}$ M	The solution was titrated contained: 2,0 ml of **2** c = $8{,}68 \cdot 10^{-4}$ M and methanesulfonic acid c = $2{,}66 \cdot 10^{-3}$ M Titrant: NaOH c = $2{,}13 \cdot 10^{-2}$ M
pKa = 5,39 ± 0,02	**pKa = 6,28 ± 0,02**

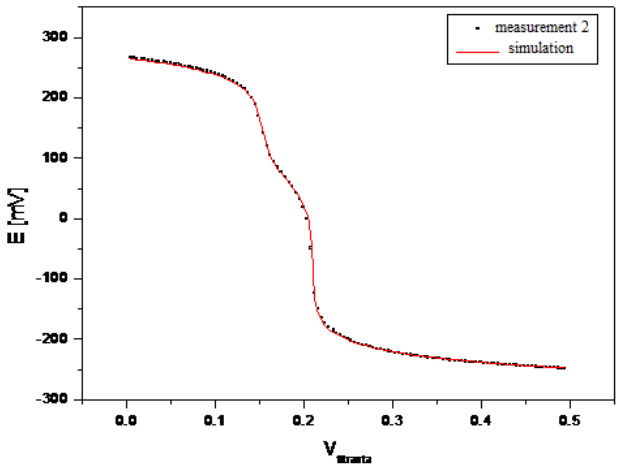




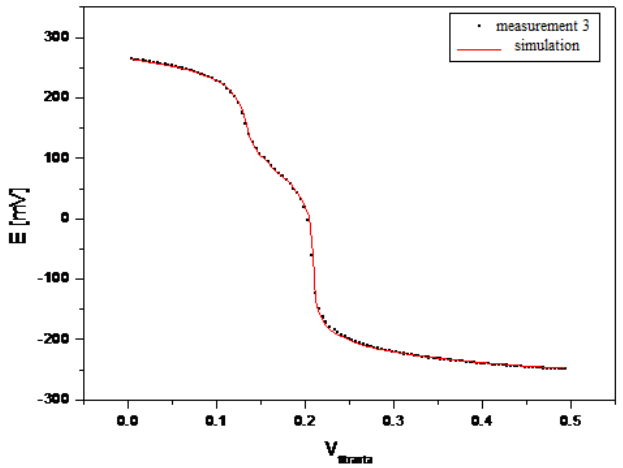
The solution was titrated contained: 2,0 ml : **2** o c = $1{,}68 \cdot 10^{-3}$ M and methanesulfonic acid c = $2{,}81 \cdot 10^{-3}$ M Titrant: NaOH c = $2{,}76 \cdot 10^{-2}$ M	The solution was titrated contained: 2,0 ml : **4** o c = $1{,}35 \cdot 10^{-3}$ M and methanesulfonic acid c = $2{,}71 \cdot 10^{-3}$ M Titrant: NaOH c = $1{,}34 \cdot 10^{-2}$ M
pKa = 6,08 ± 0,02	**pKa = 3,26 ± 0,06**

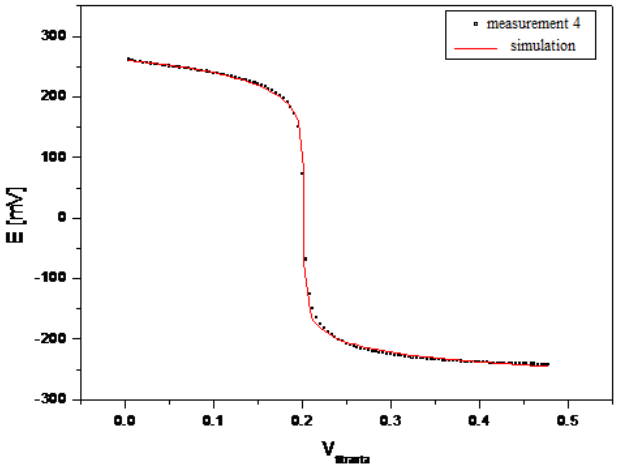
Potentiometric measurements carried out in methanol/water (50%:50%)



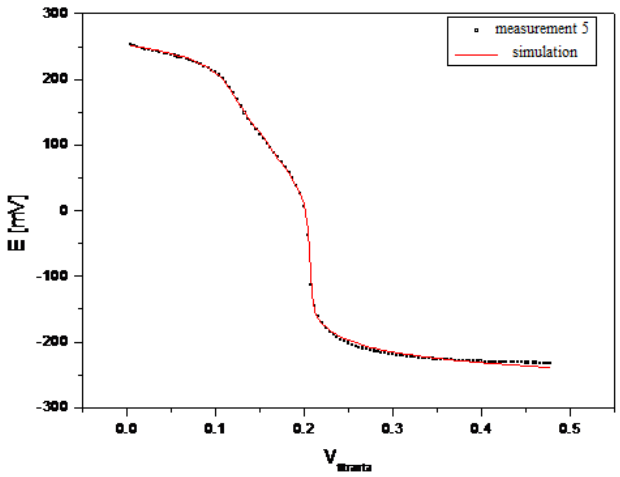


The solution was titrated contained: 2.0 ml of **1** c = $1.12 \cdot 10^{-3}$ M and 0.5 ml HCl = $1.25 \cdot 10^{-2}$ M Titrant: NaOH o c = $3.04 \cdot 10^{-2}$ M	The solution was titrated contained: 2.0 ml of **2** c = $9.34 \cdot 10^{-4}$ M and 0.5 ml HCl c = $1.25 \cdot 10^{-2}$ M Titrant: Roztwór NaOH o c = $3.04 \cdot 10^{-2}$ M
pKa = 5,44 ± 0,02	**pKa = 6,24 ± 0,02**





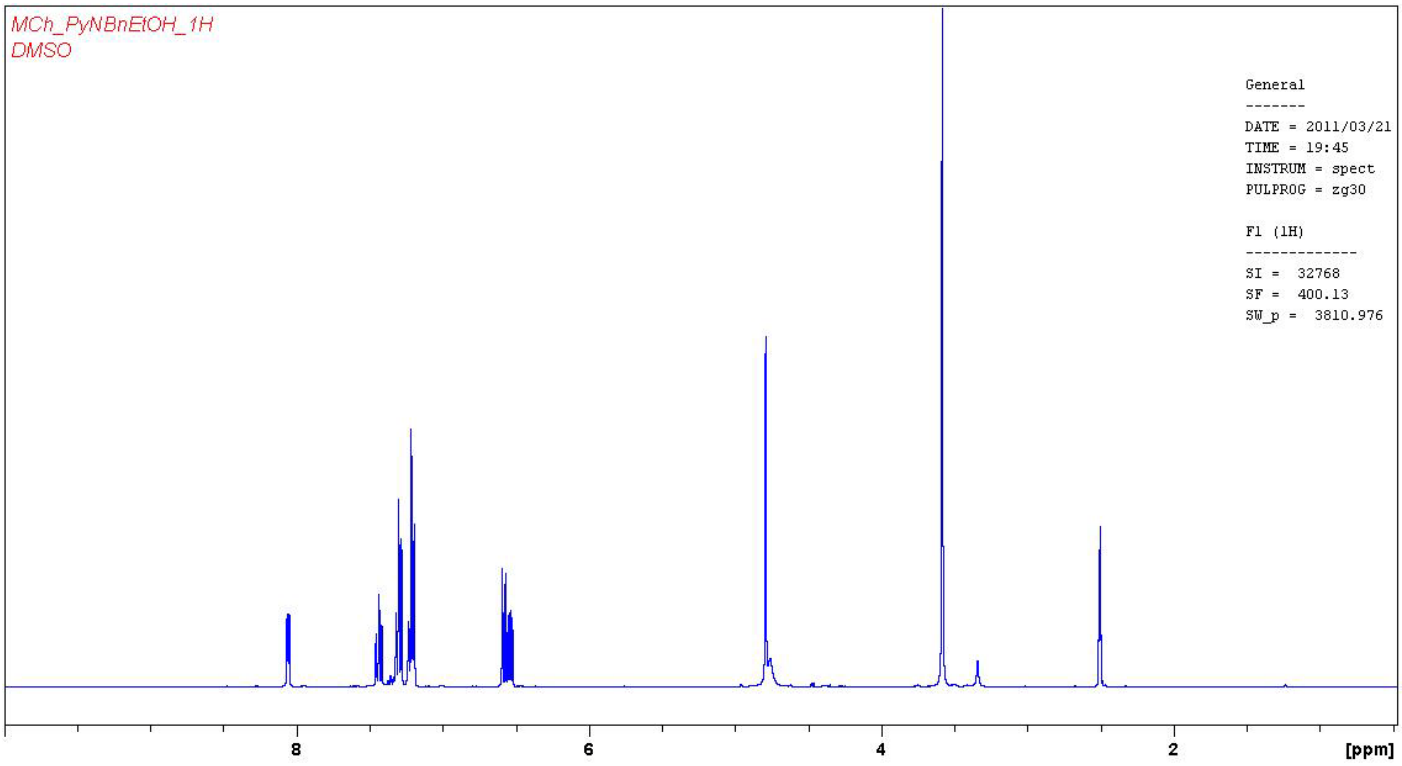
The solution was titrated contained: 2.0 ml of **3** c = $1.16 \cdot 10^{-3}$ M and 0.5 ml HCl c = $1.25 \cdot 10^{-2}$ M Titrant: NaOH o c = $3.04 \cdot 10^{-2}$ M	The solution was titrated contained: 2.0 ml of **4** c = $5.57 \cdot 10^{-4}$ M and 0.5 ml HCl c = $1.25 \cdot 10^{-2}$ M Titrant: NaOH c = $3.04 \cdot 10^{-2}$ M
pKa = 6.07 ± 0.02	**pKa = 3,58 ± 0,11**



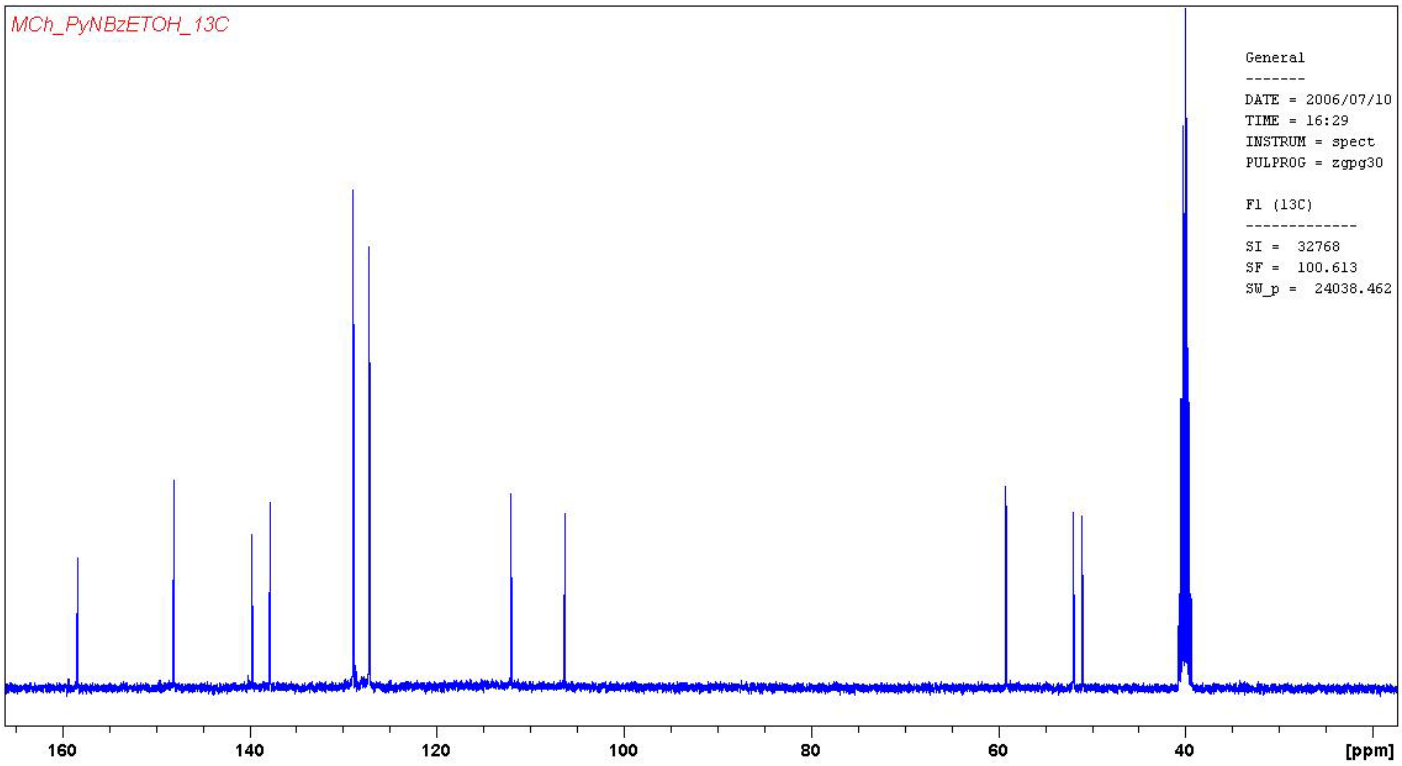
The solution was titrated contained: 2.0 ml of **5** c = $6.88 \cdot 10^{-4}$ M and 0.5 ml HCl c = $1.25 \cdot 10^{-2}$ M Titrant: NaOH c = $3.04 \cdot 10^{-2}$ M
pKa_1 = 4.97 ± 0,04 and pKa_2 = 6,42 ± 0.03

Compound **1**

^{1}H NMR



^{13}C NMR



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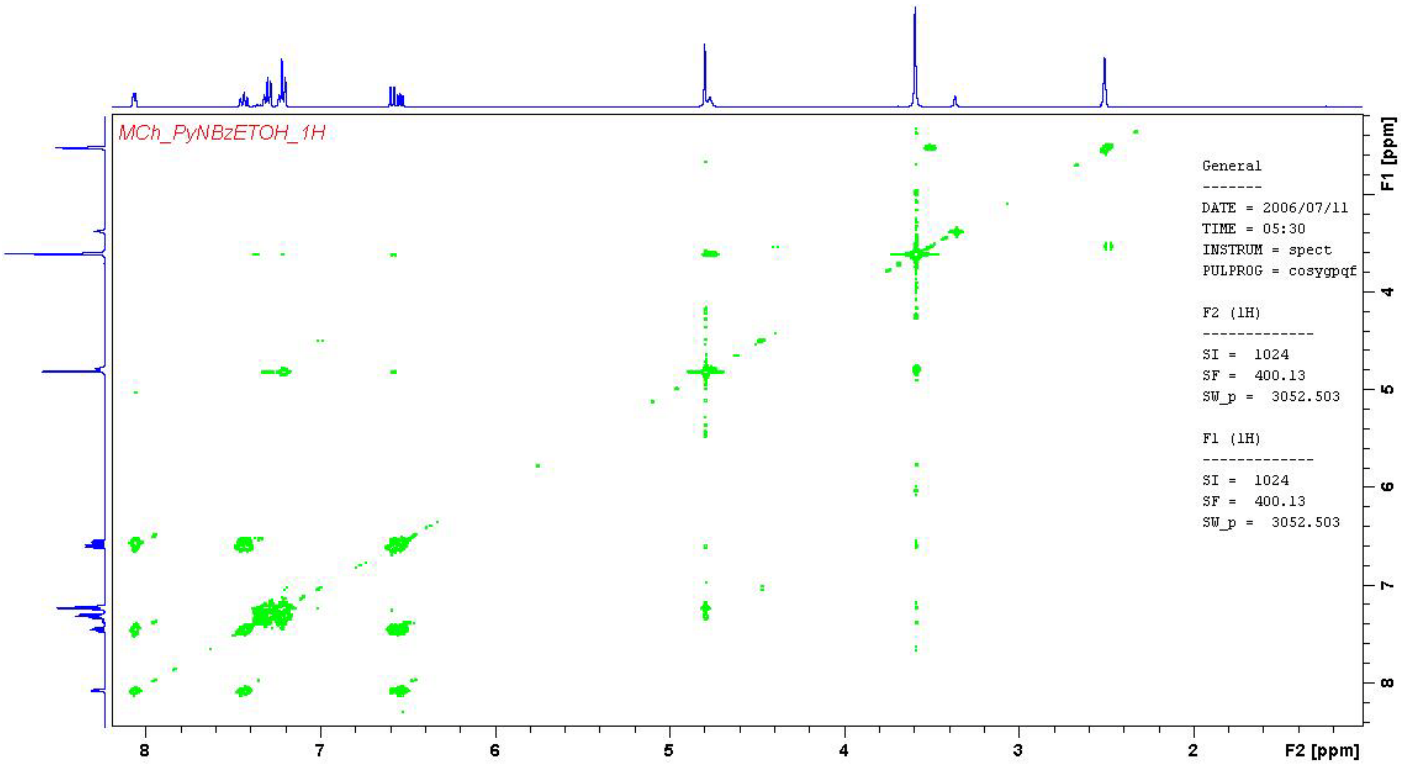

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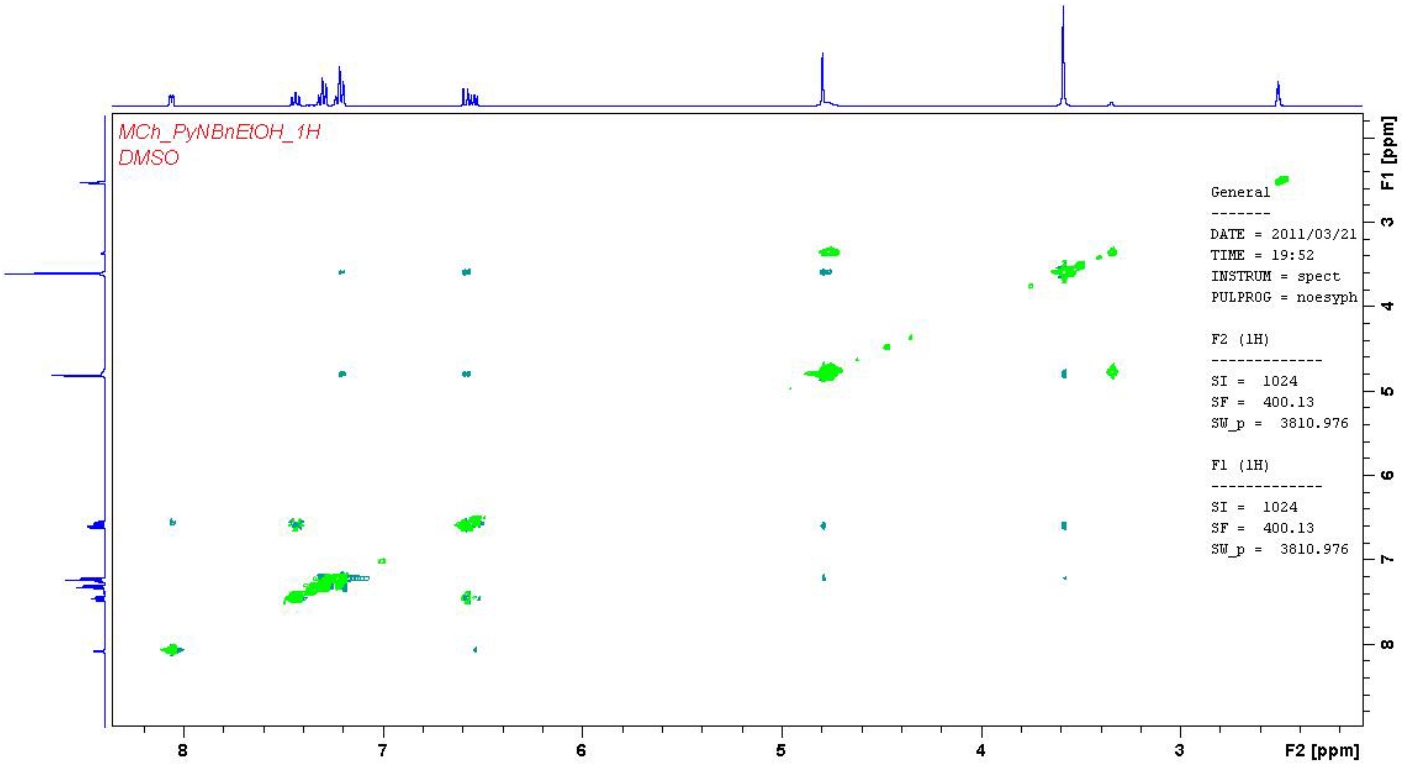

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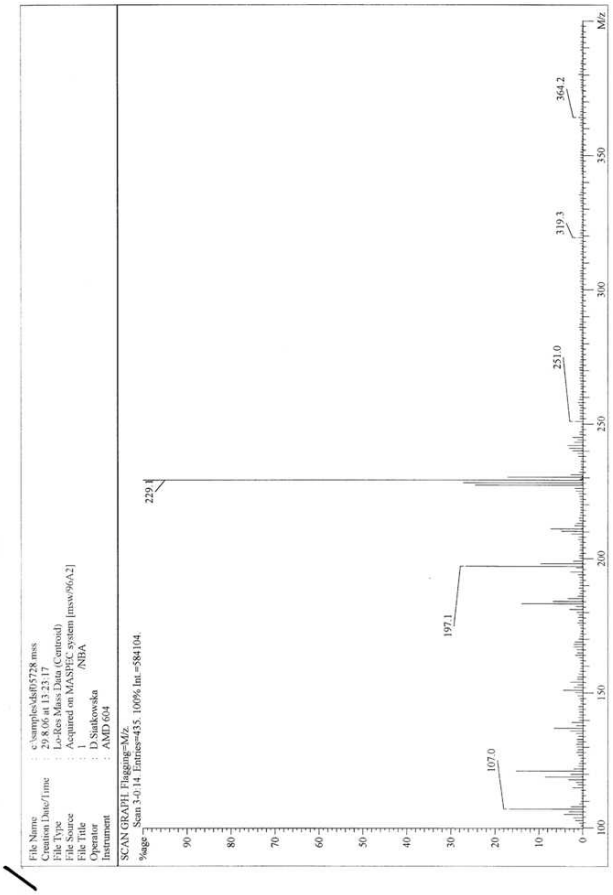

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Allowable error = minimum of 10.0 ppm, 5.0 mmu.

Number of Peaks=13.
Base Peak=229.13382, 100% Int.=44635.

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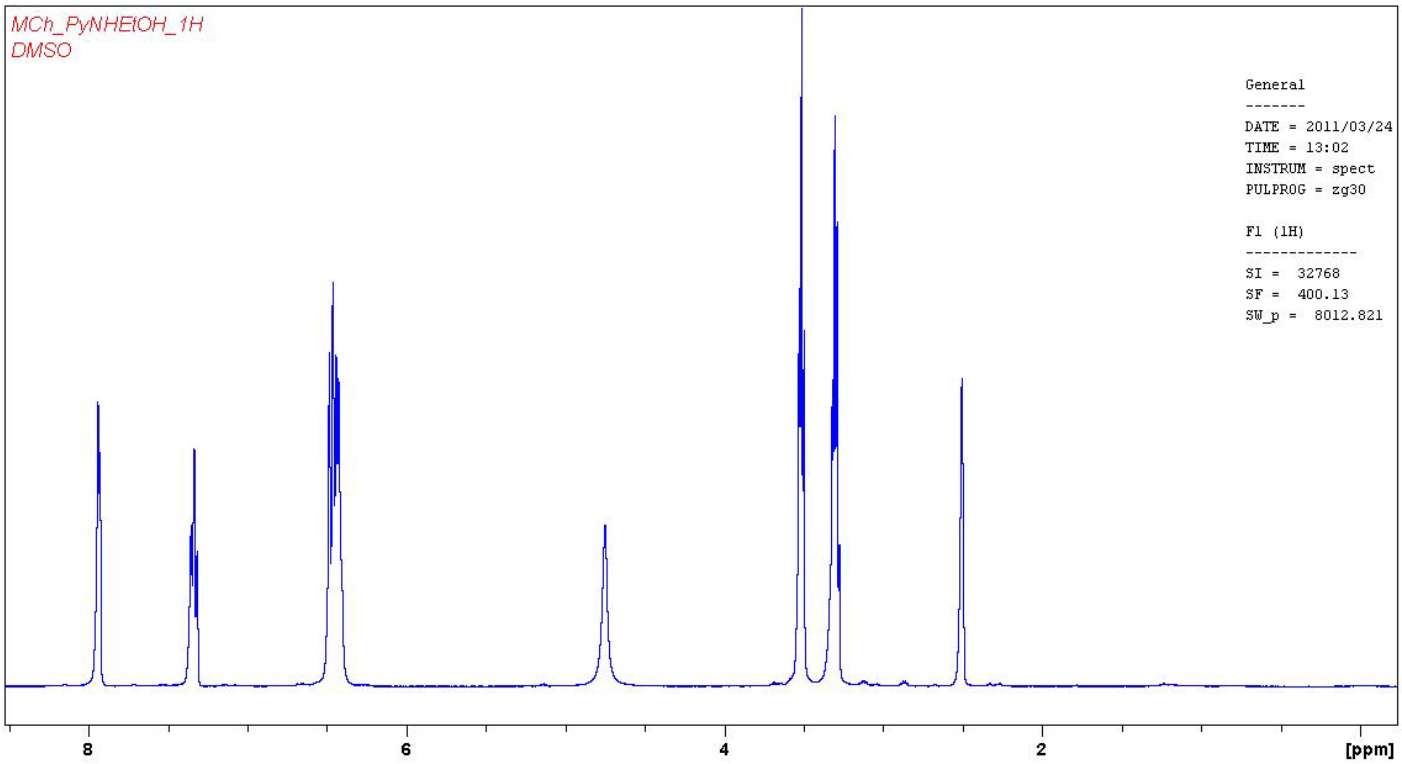
229.13382	100.00	229.13409	1.2	0.3	C14.H17.N2.O

***** End of Atomic Composition Report *****

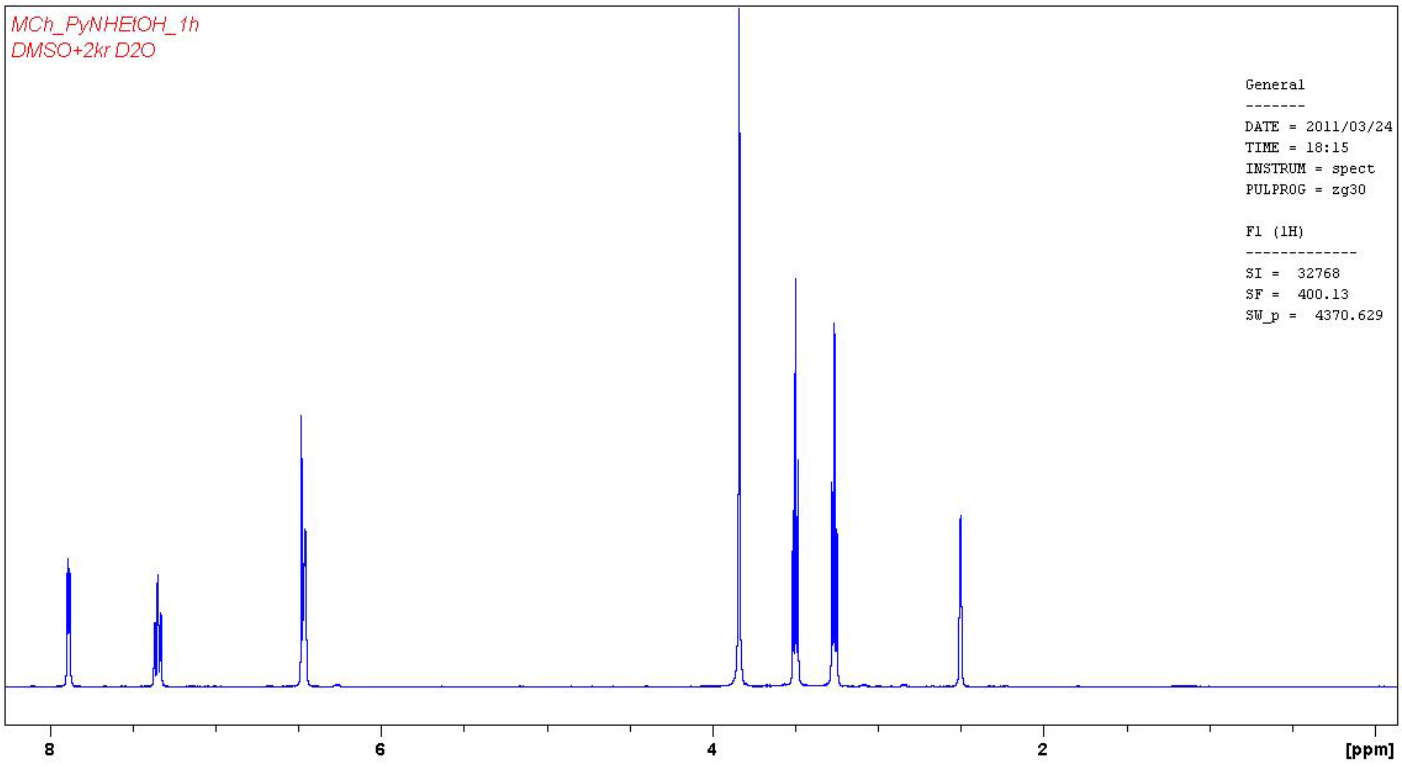
Page 1

Compound **2**

^{1}H NMR



^{1}H NMR+D_2O



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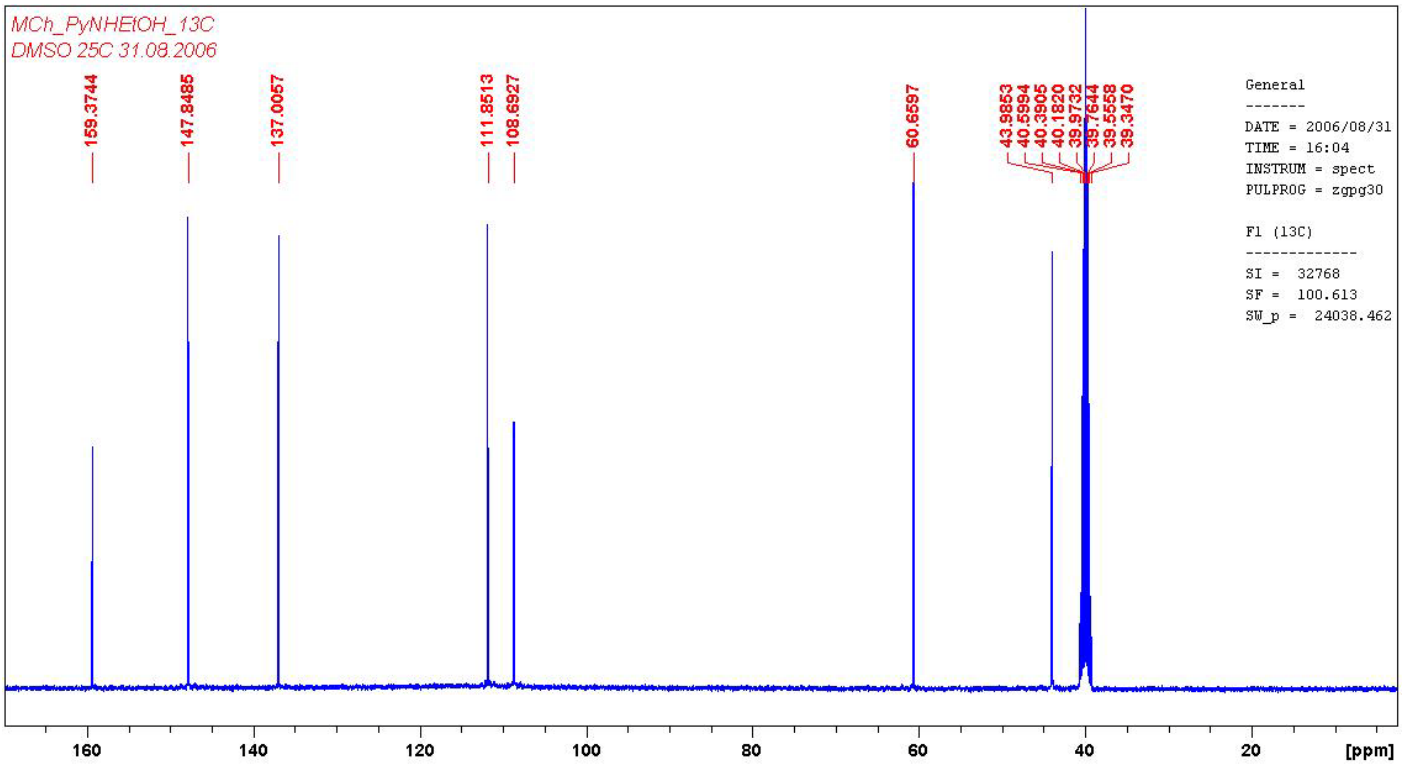

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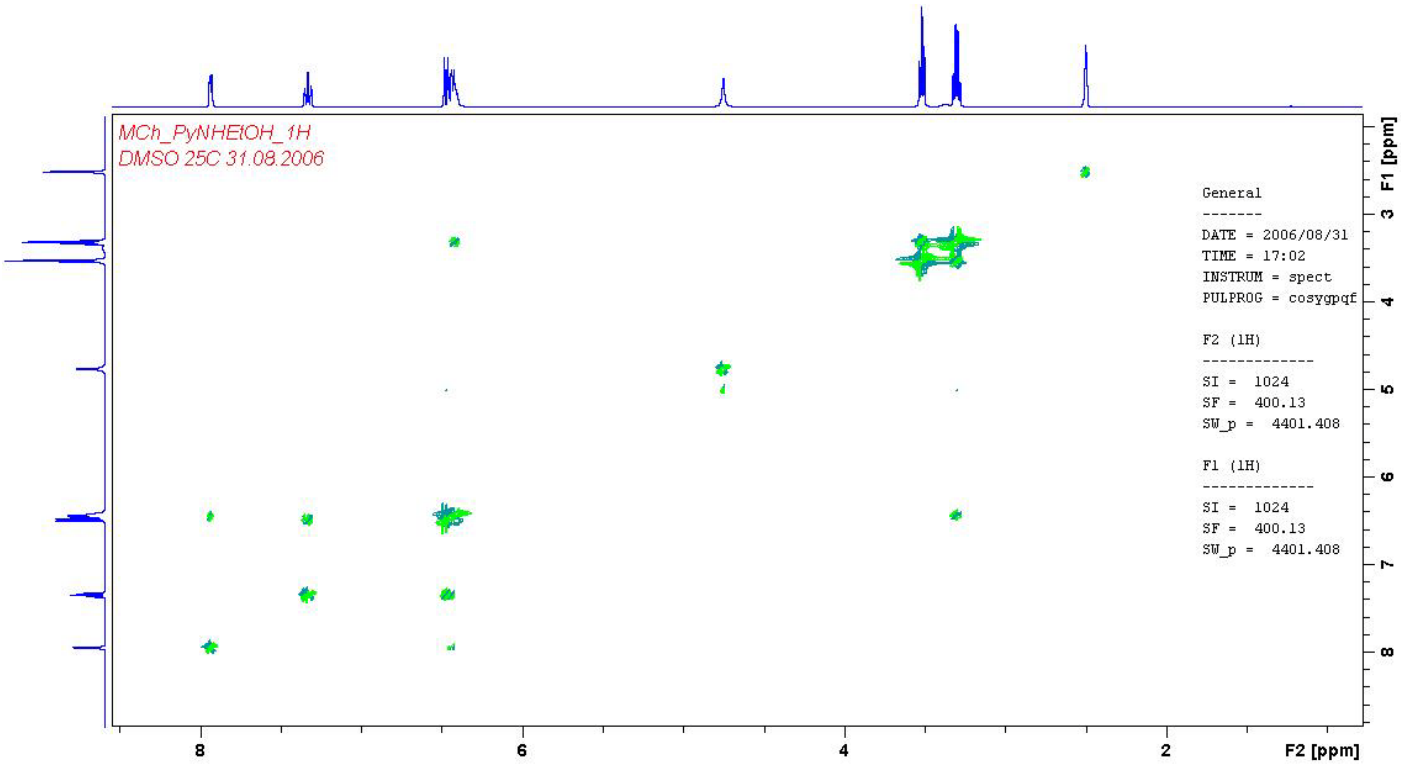

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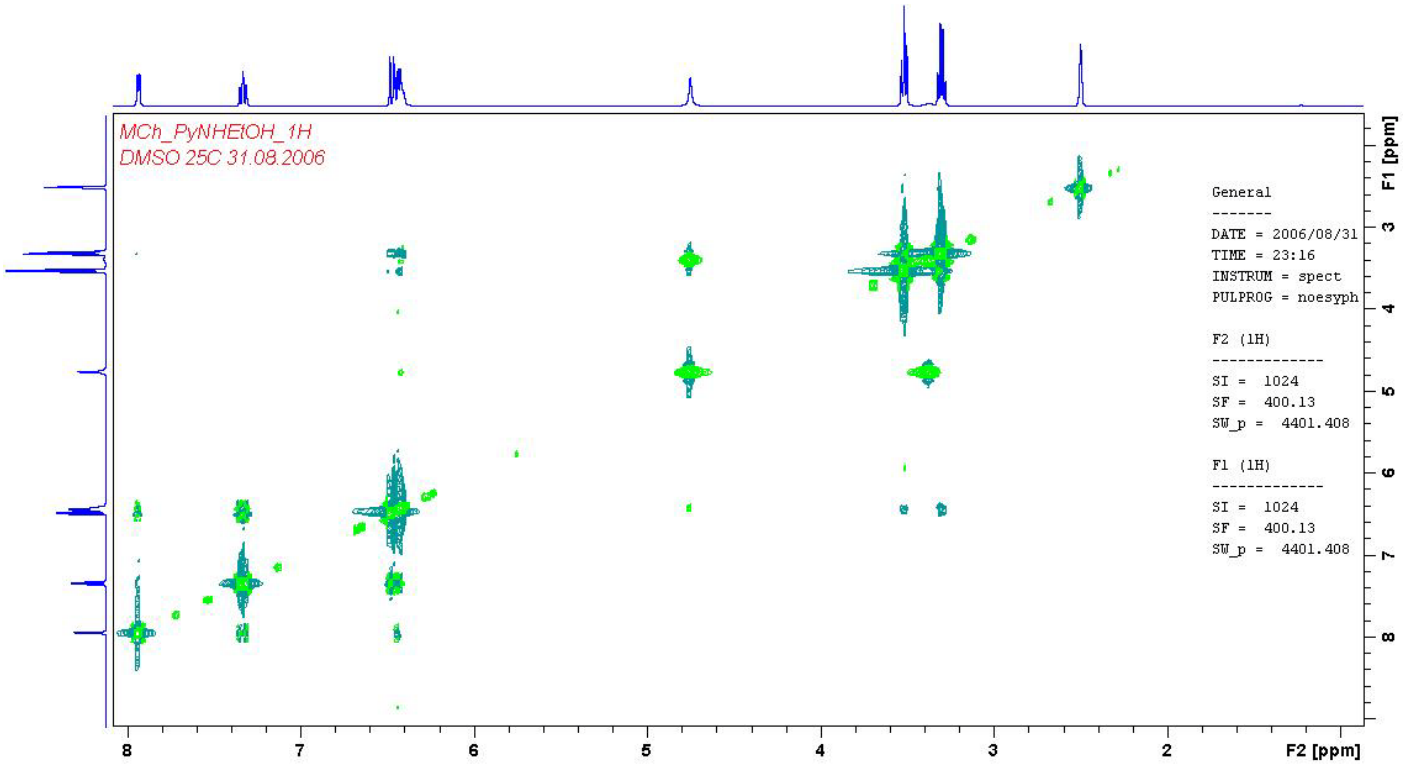
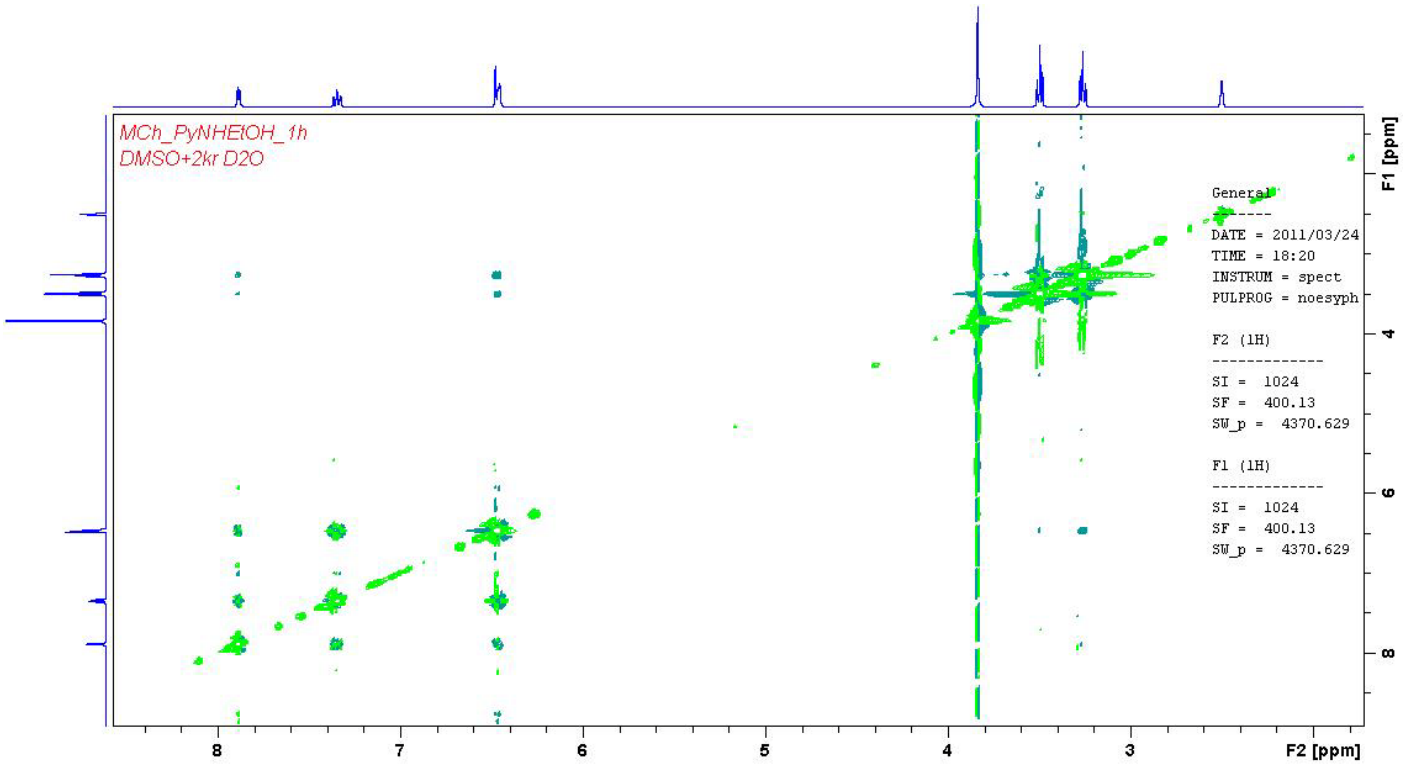


NOESY+ D_2O



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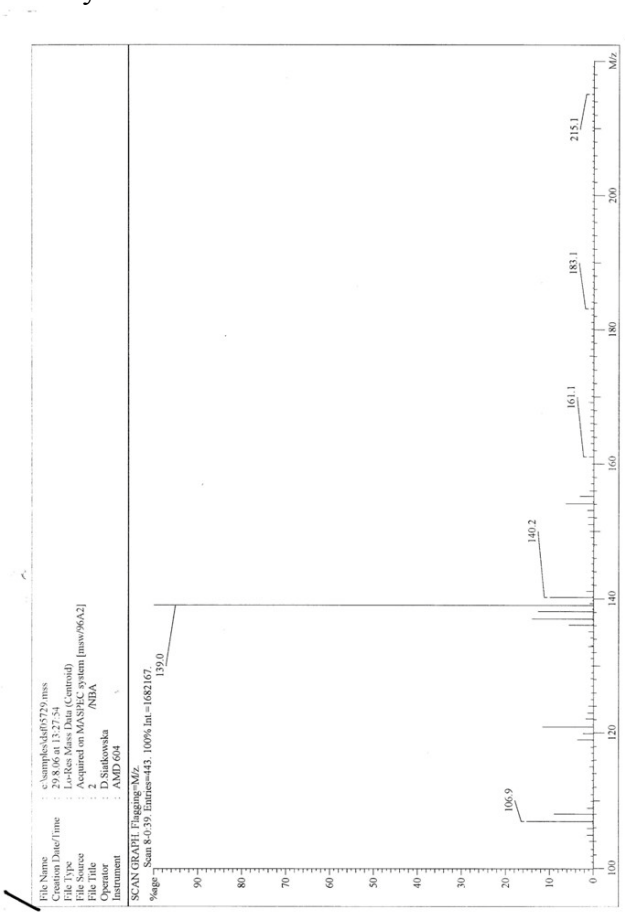

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O	0	1	2	Oxygen-16

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Base Peak=139.08638, 100% Int.=234253.

Mass	(%)	Calculated	ppm	mmu	Formula
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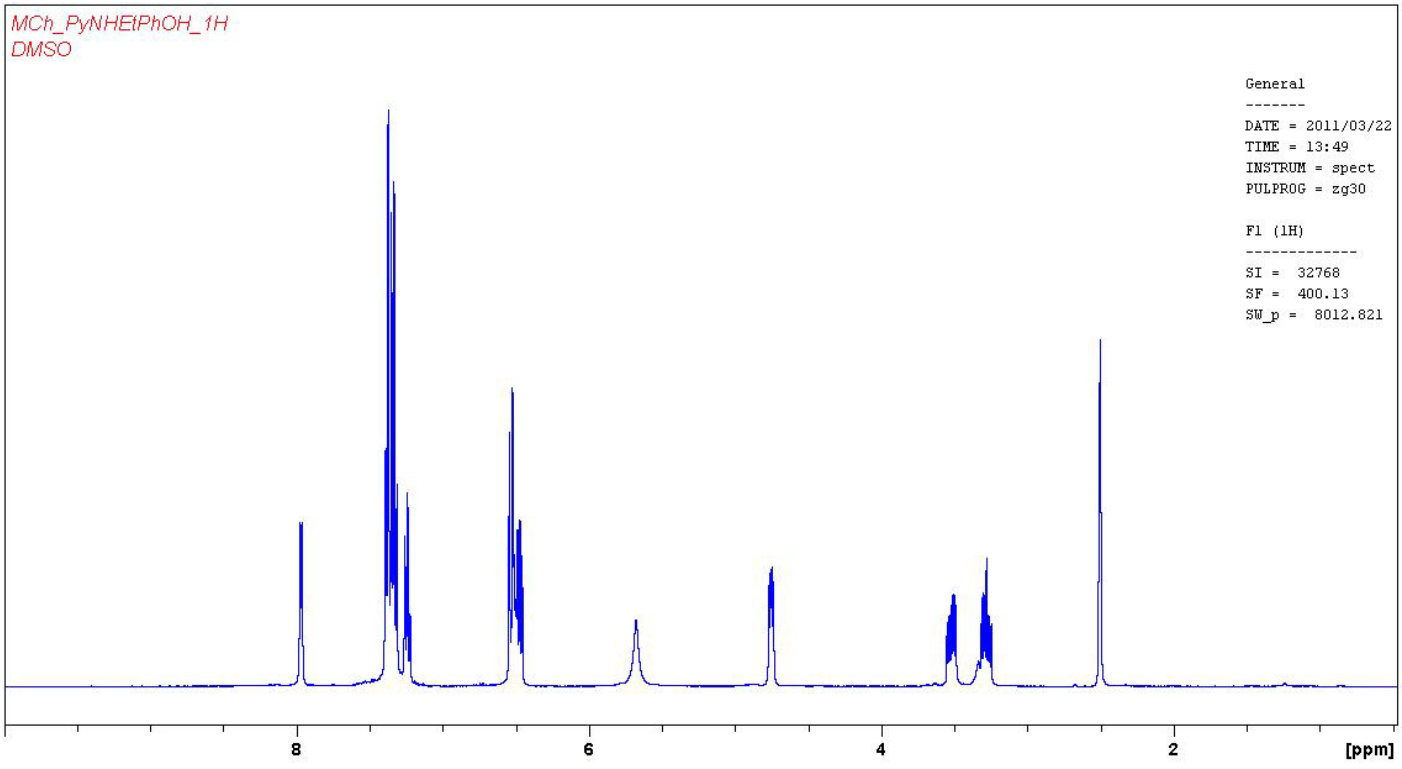
***** End of Atomic Composition Report *****

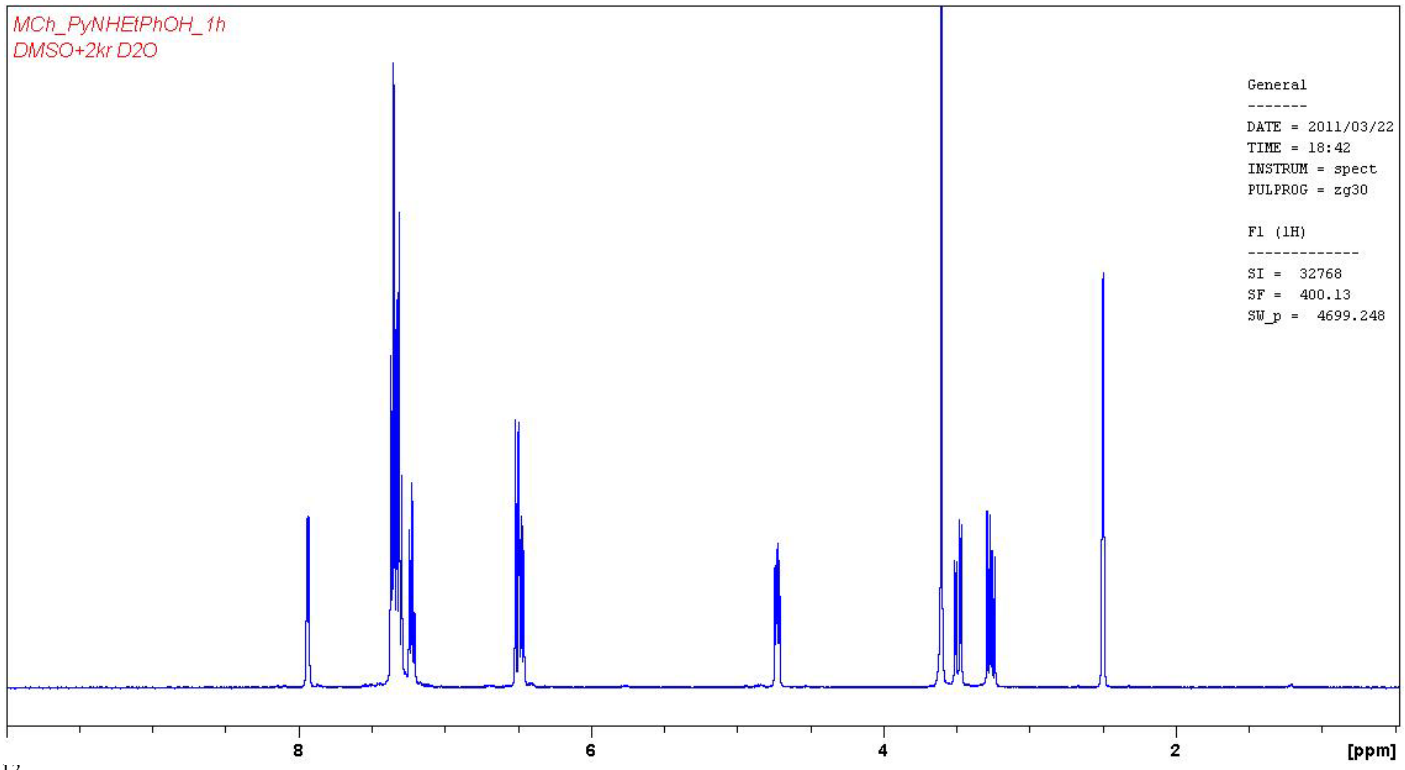
Page 1

Compound **3**

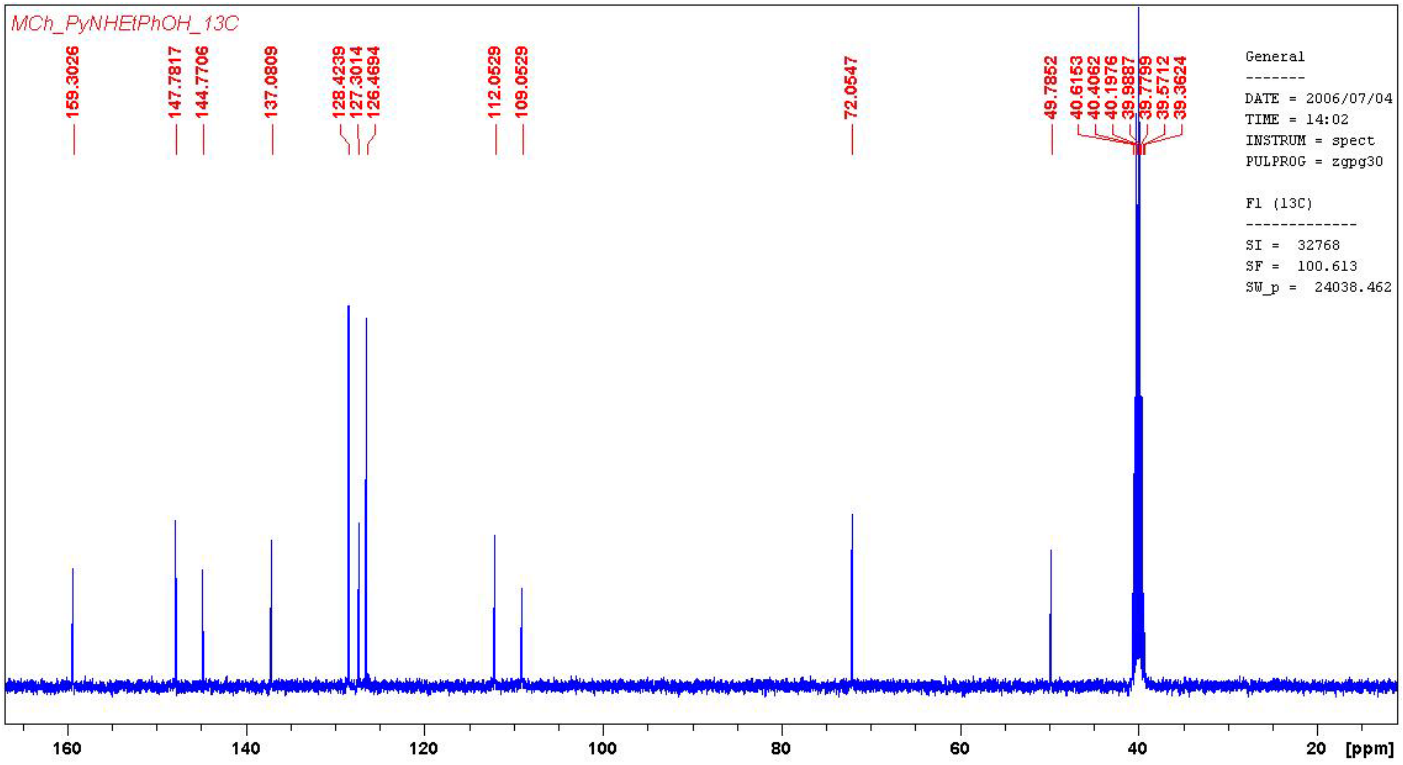
^{1}H NMR



^{1}H NMR+D_2O



^{13}C NMR



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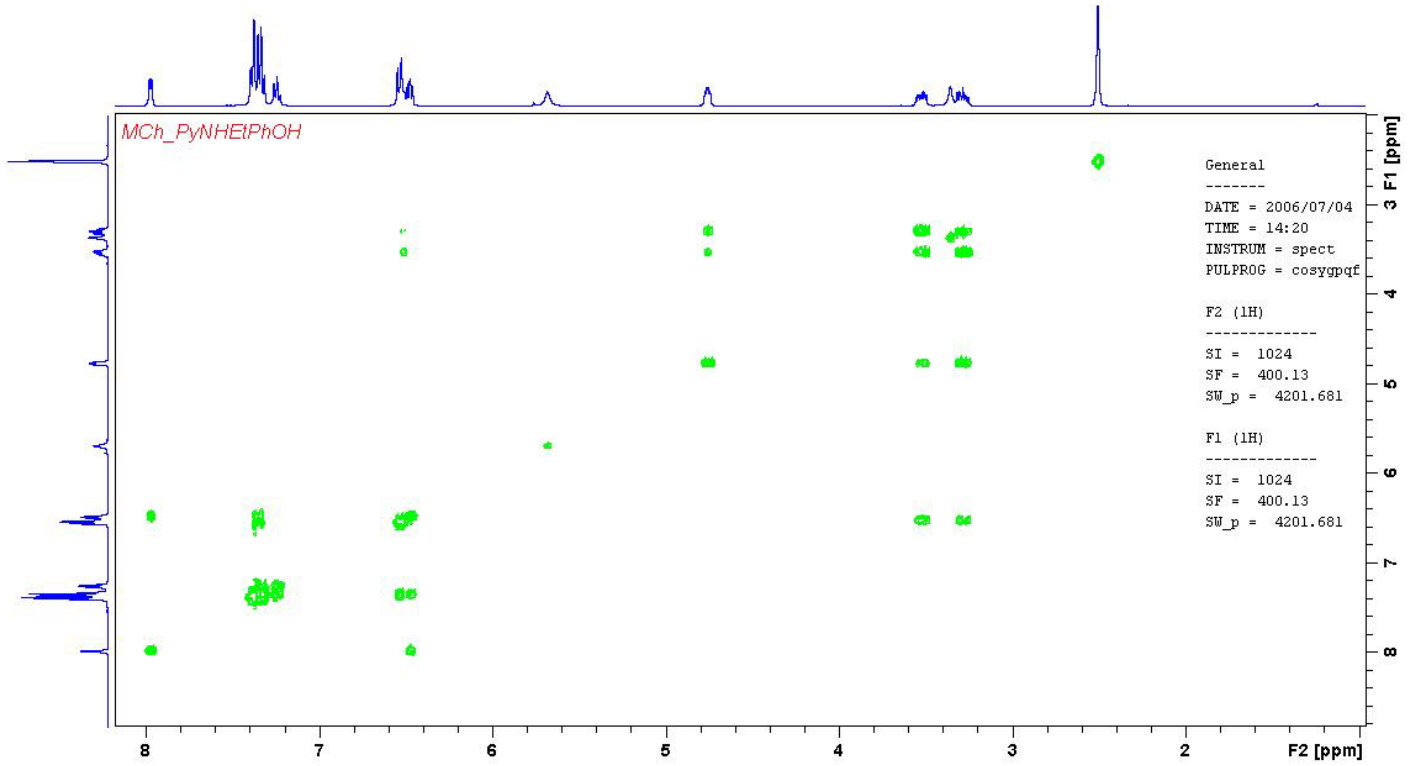

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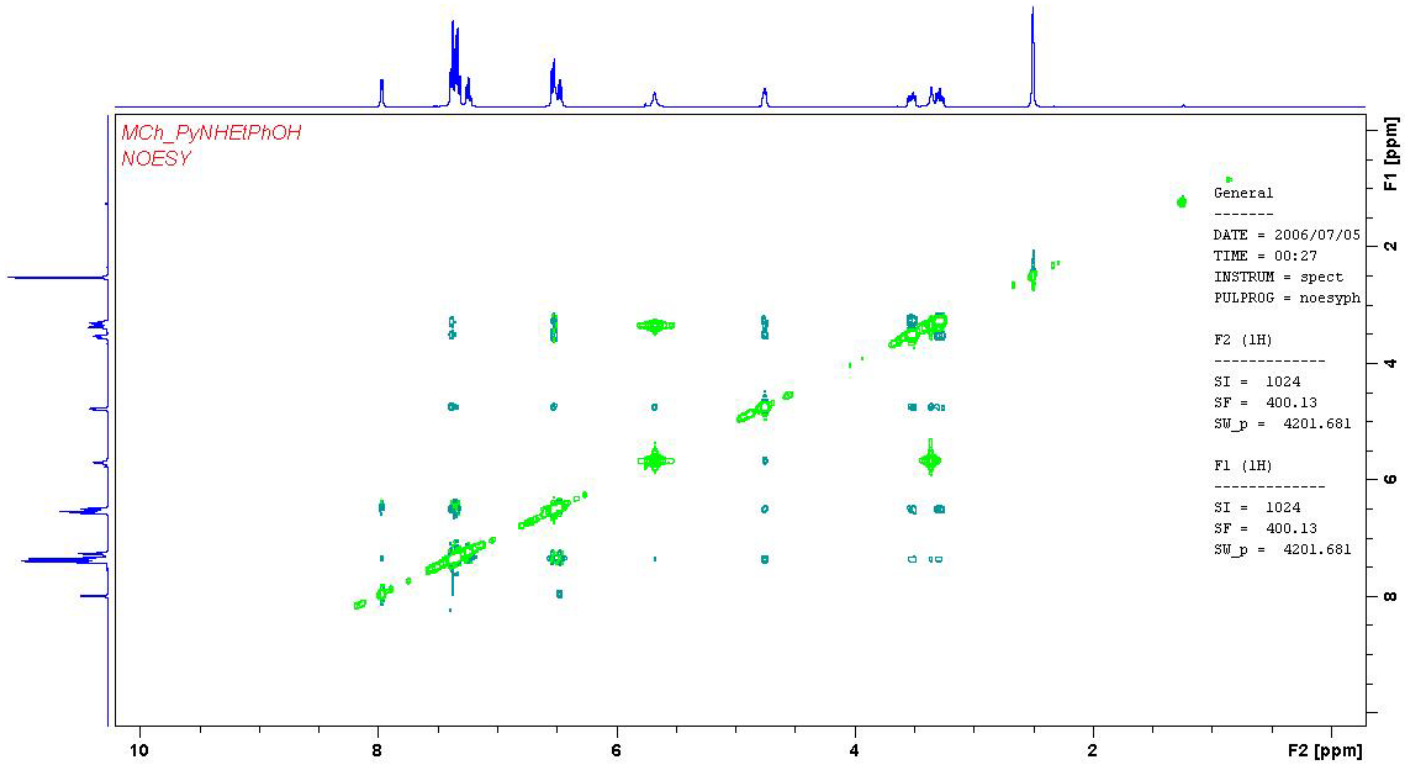
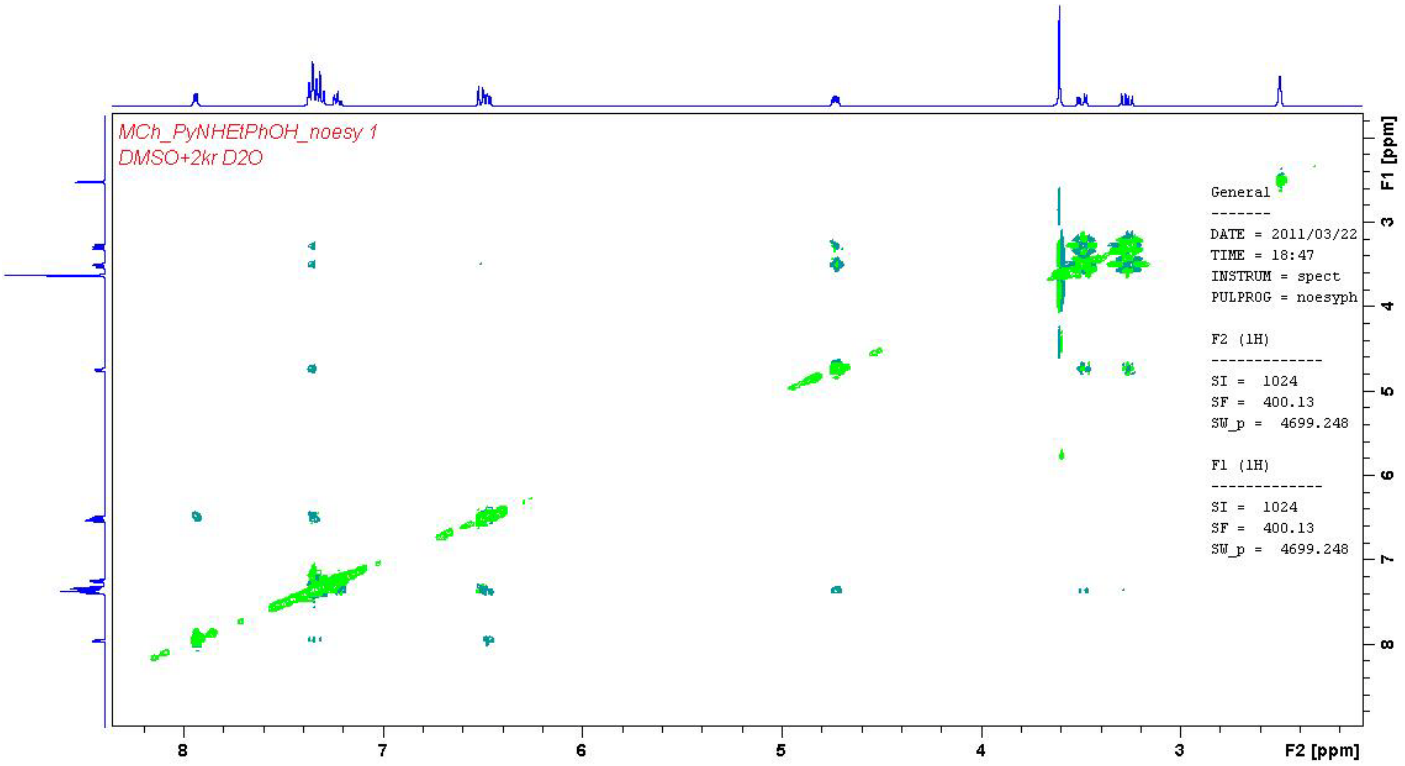


NOESY+D_2O



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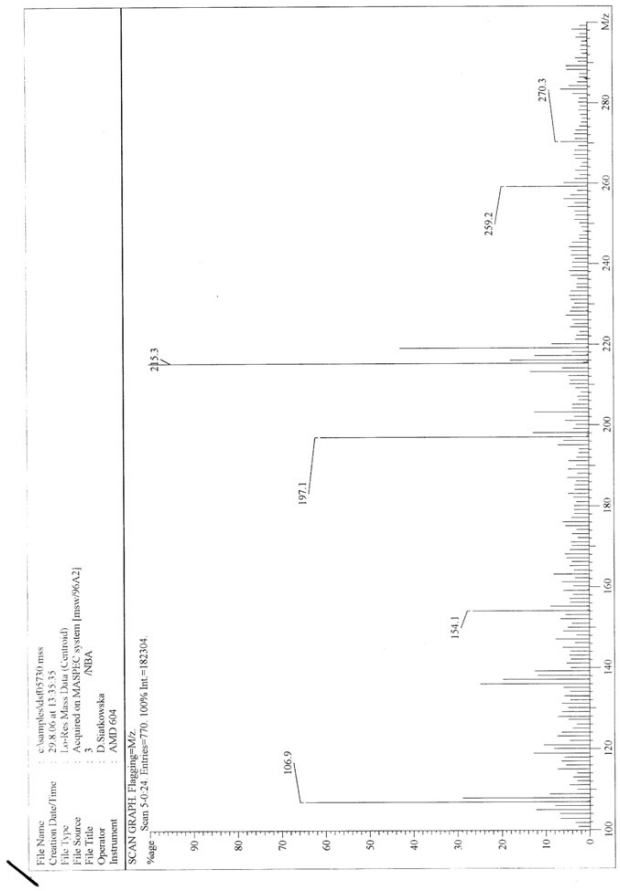

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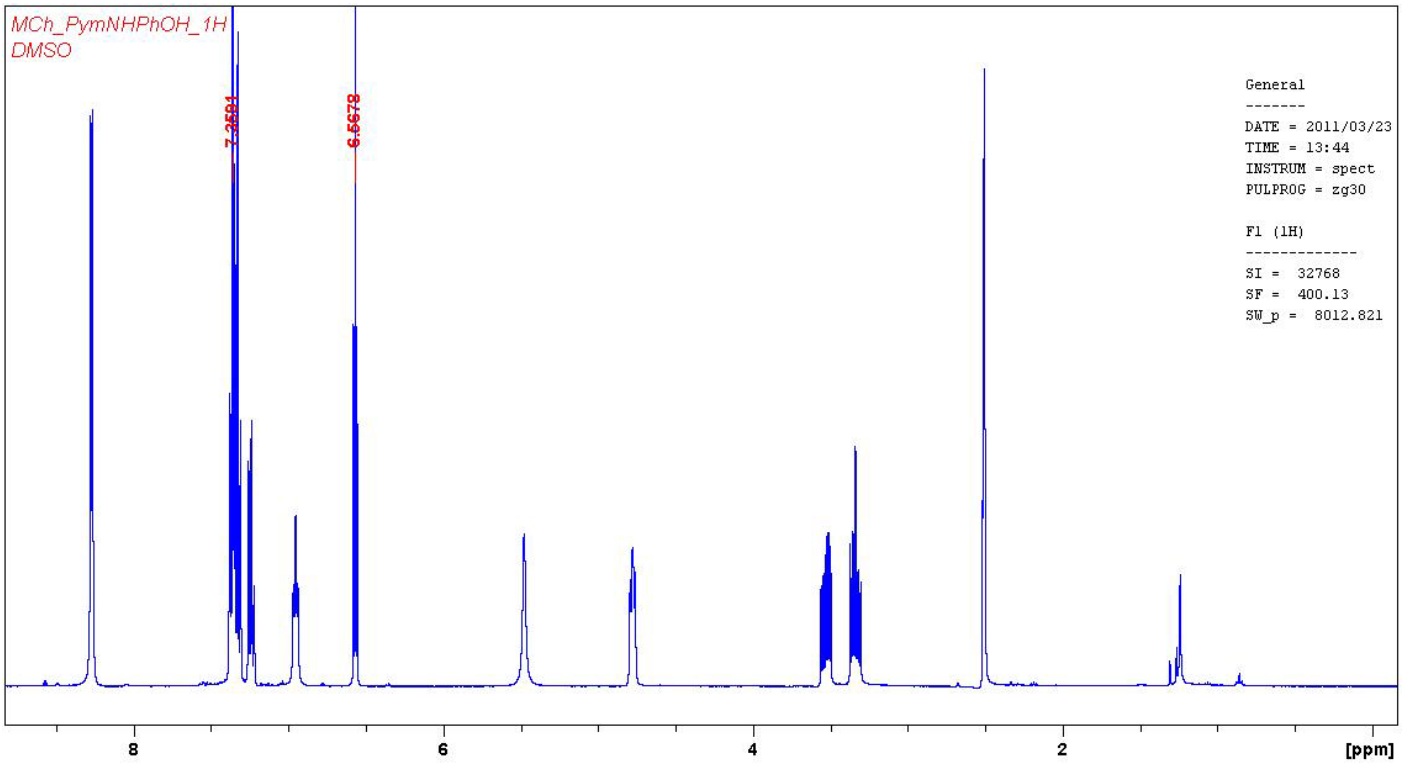
Page 1

Compound **4**

^{1}H NMR



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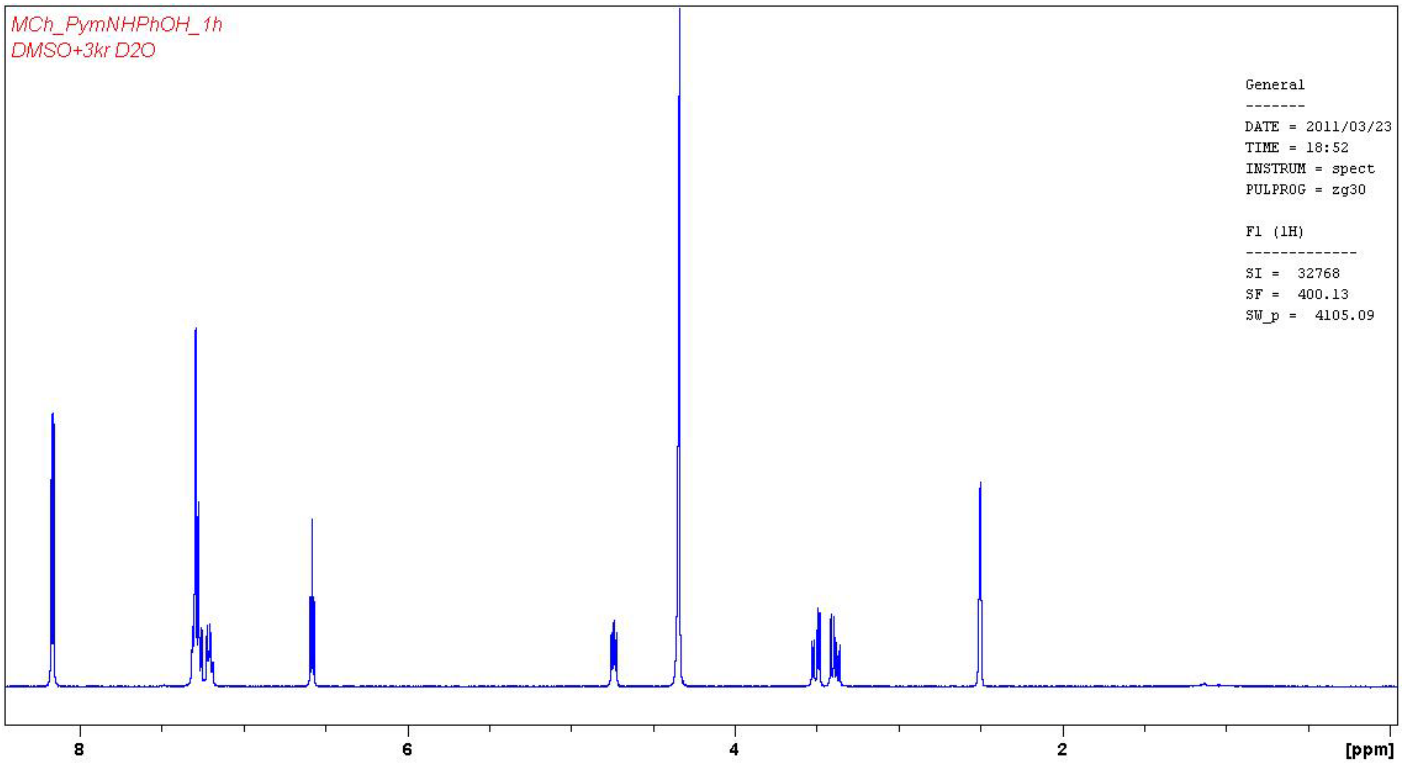
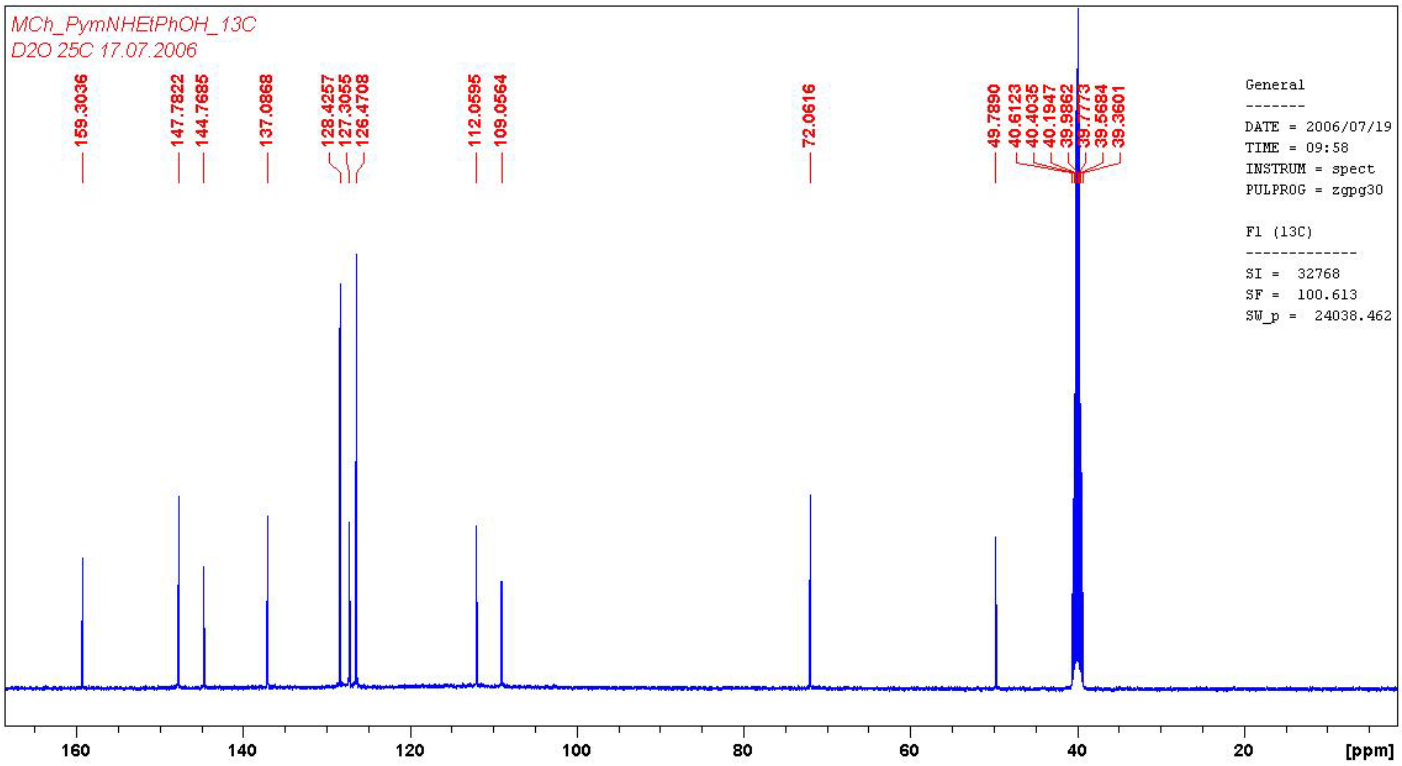


^{13}C NMR



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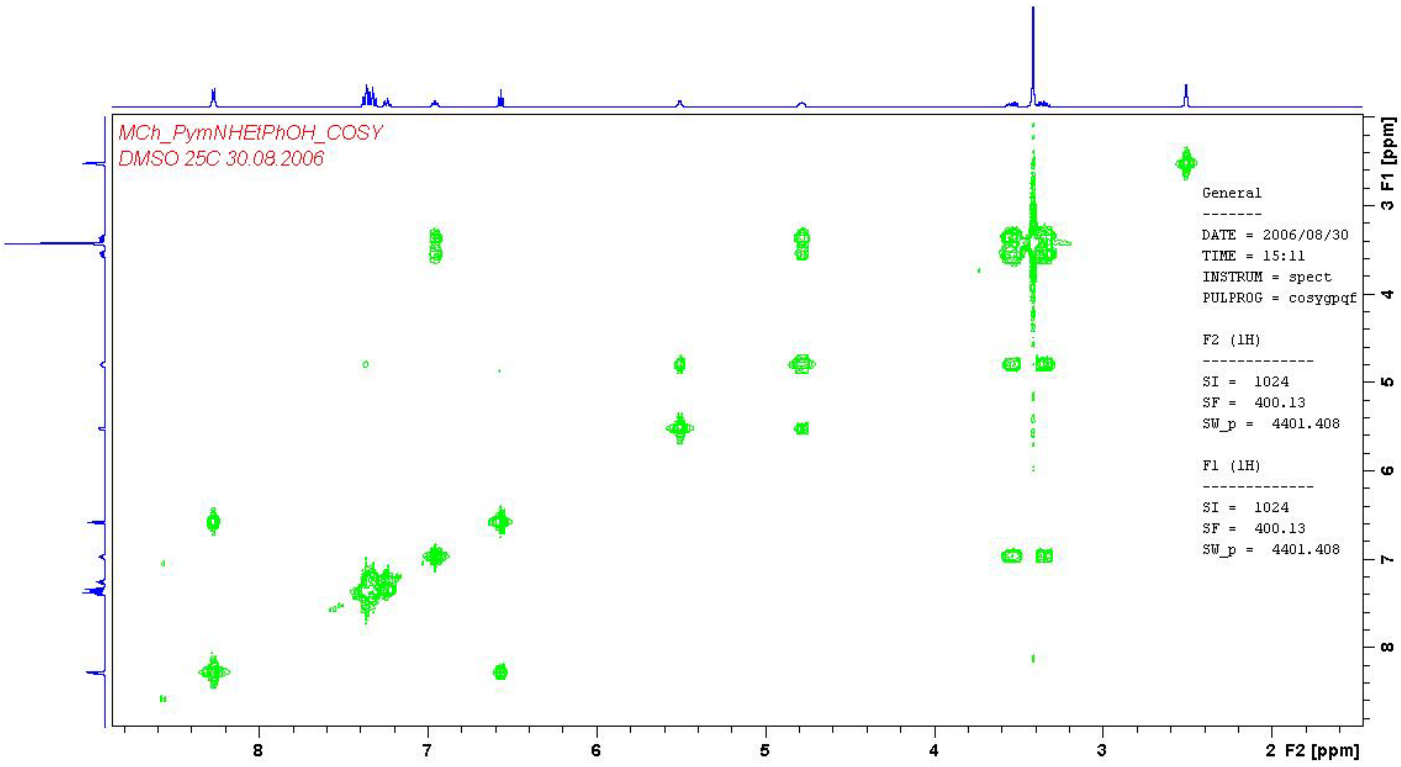
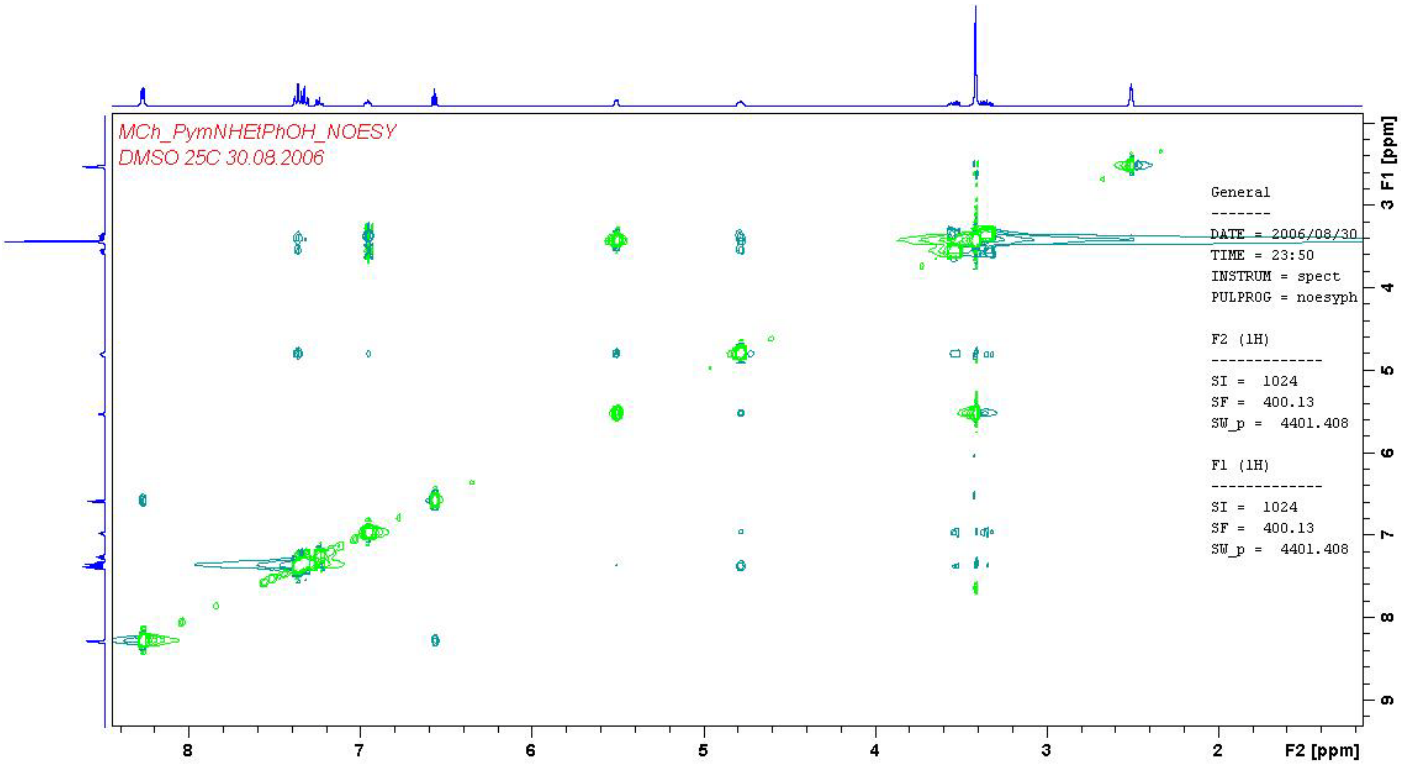
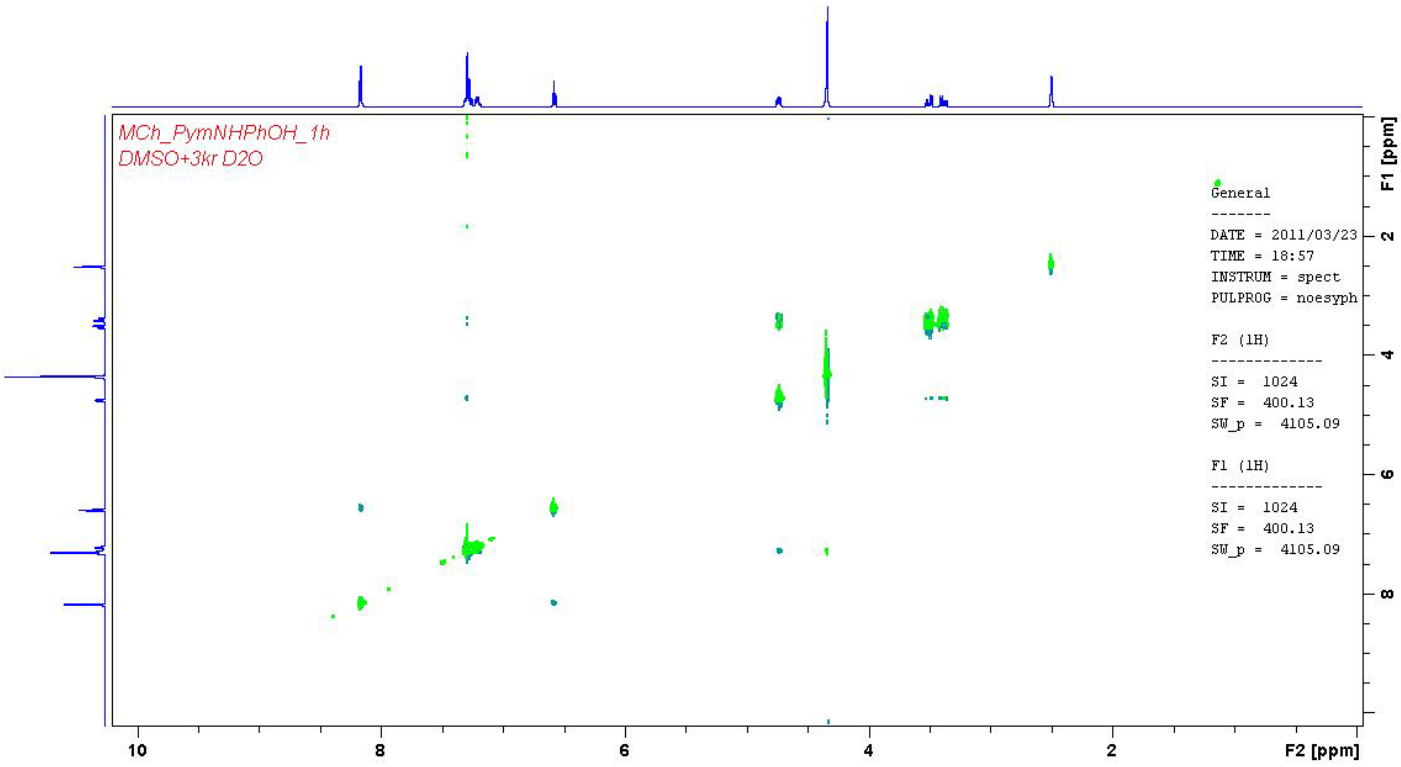


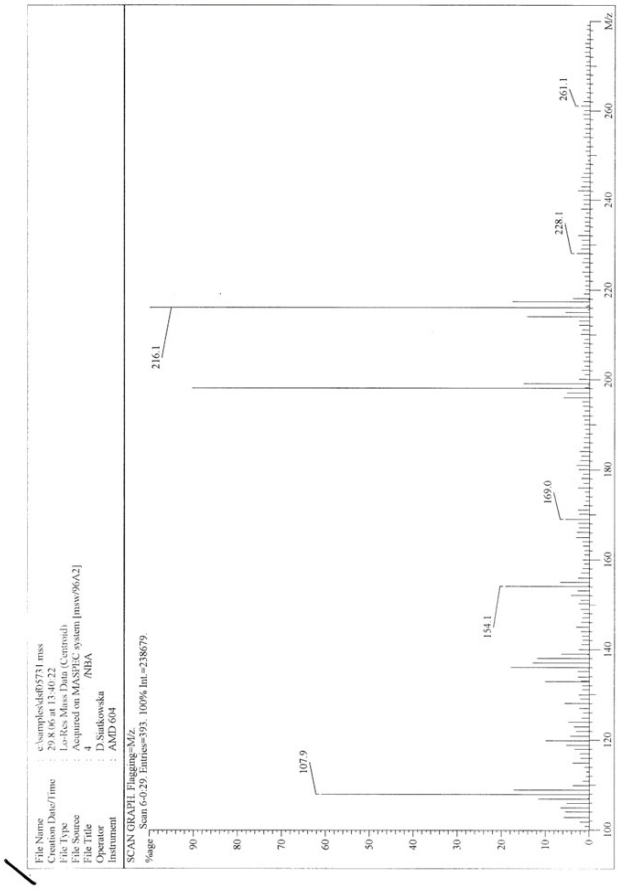
NOESY



NOESY+D_2O



MS analysis



ASD05500.TXT

ATOMIC COMPOSITION REPORT

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File Date/Time : 7.9.06 at 11:43:58
File Type : Hi-Res Mass Spectrum
File Source : Acquired on MASPEC system [msw/96A2] as c:\samples\dsv05741.mss
File Title : 4 /NBA
Source File : c:\samples\dsv05741.mss
Source Scan(s) : 2:16

Sort Field : M/z (ascending).

Scan Filter : none.

Selected isotopes:

Symbol	Min	Max	V'cy	Name
C	0	12	4	Carbon-12
H	4	14	1	Hydrogen-1
N	0	3	3	Nitrogen-14
O	0	1	2	Oxygen-16

Allowable error = minimum of 10.0 ppm, 5.0 mmu.

Number of Peaks=12.
Base Peak=198.09870, 100% Int.=15115.

Mass	(%)	Calculated	ppm	mmu	Formula
216.11295	56.90	216.11369	3.4	0.7	C12.H14.N3.O

***** End of Atomic Composition Report *****

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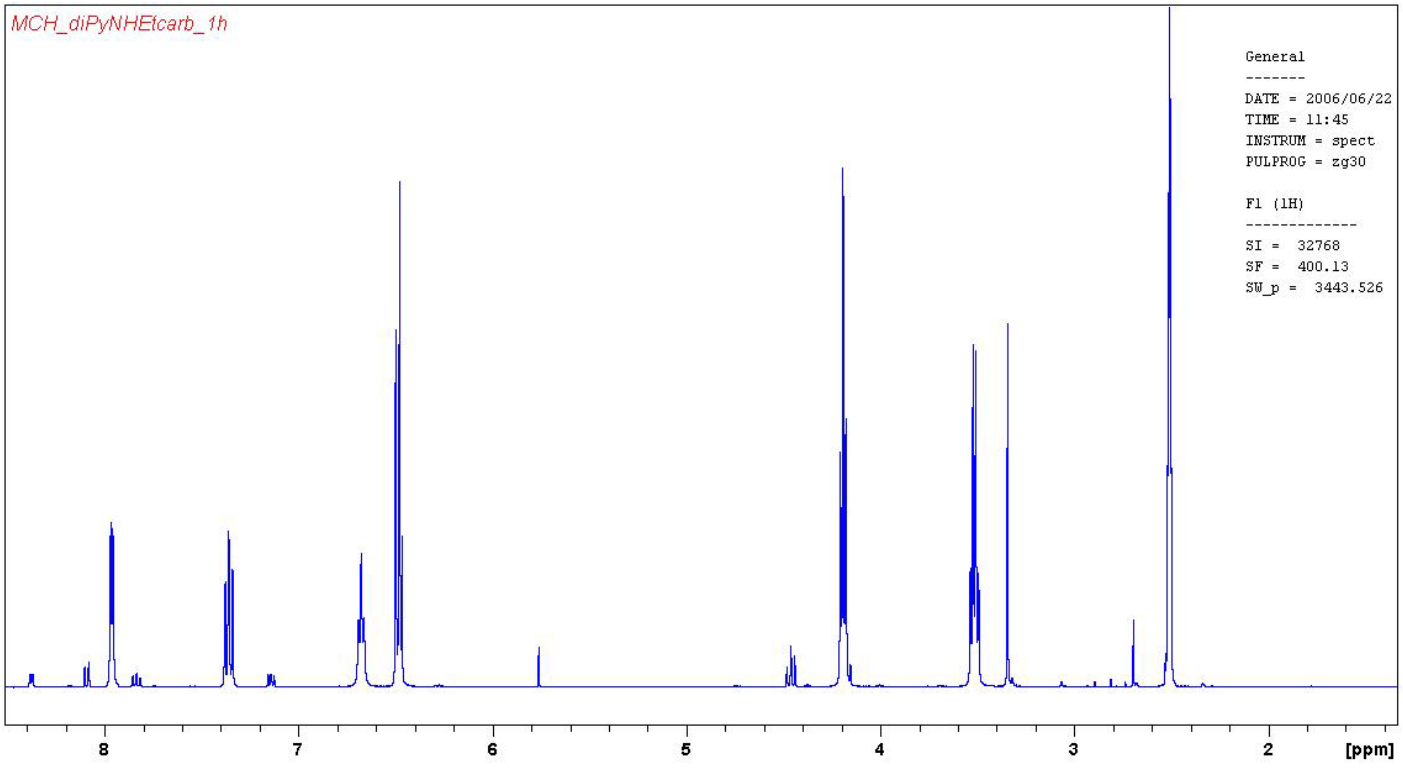
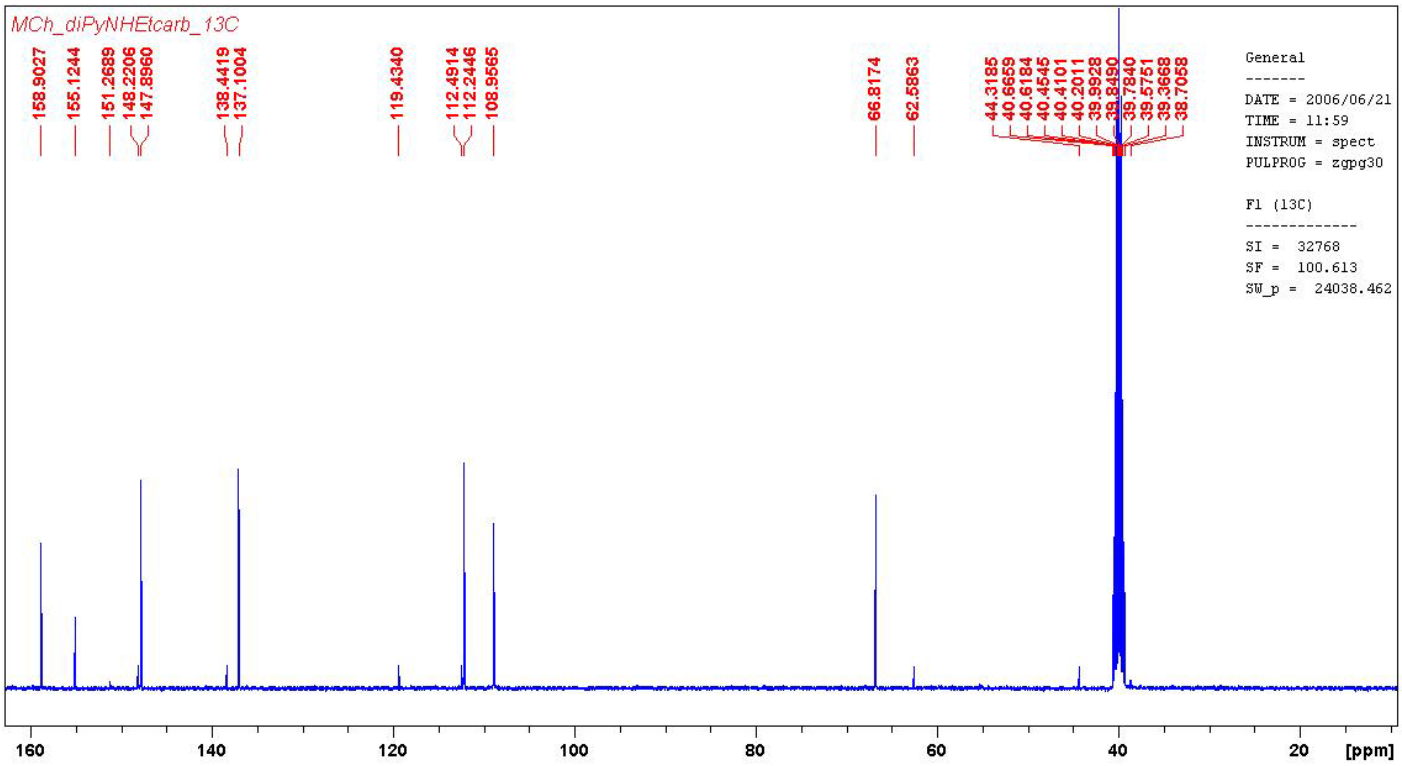
Compound **5**

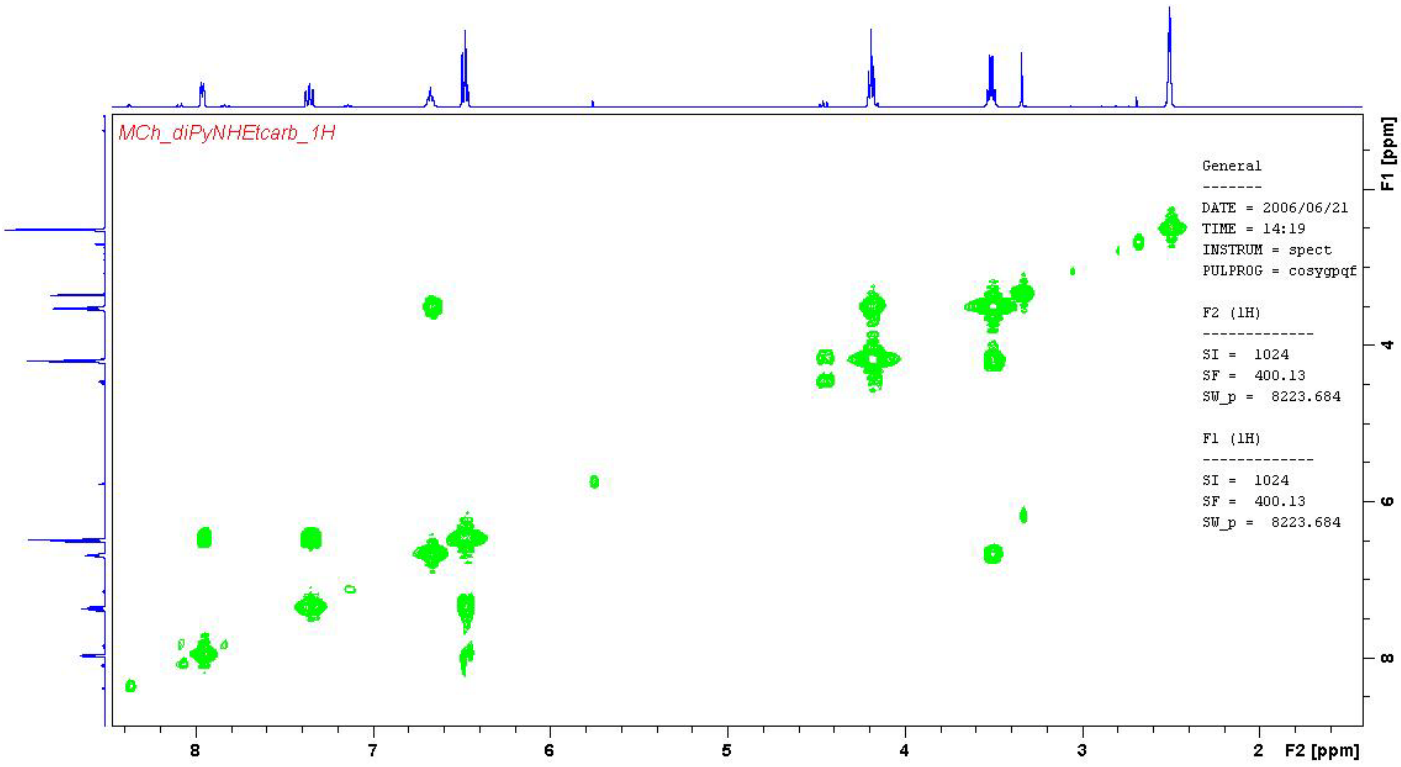
^{1}H NMR



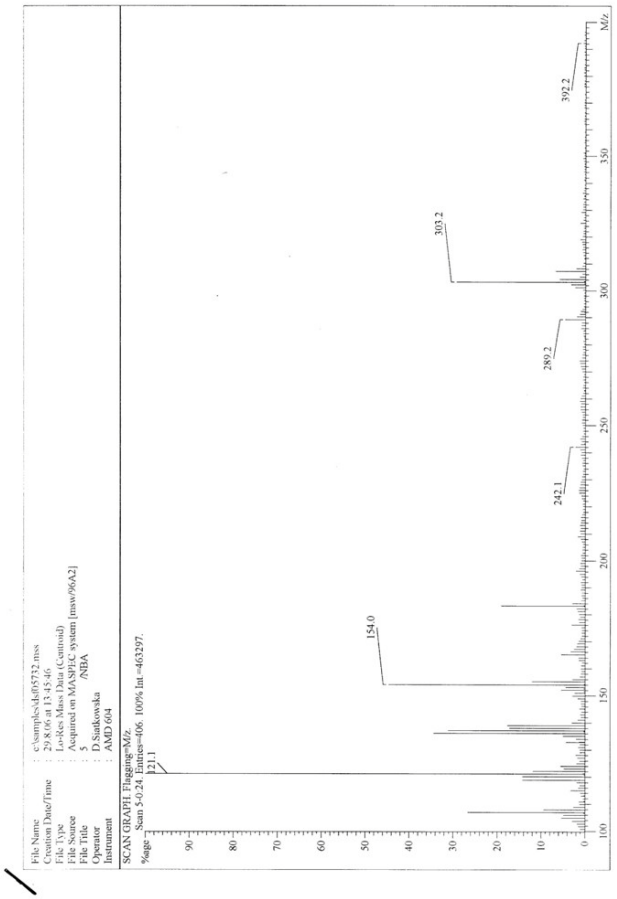
^{13}C NMR

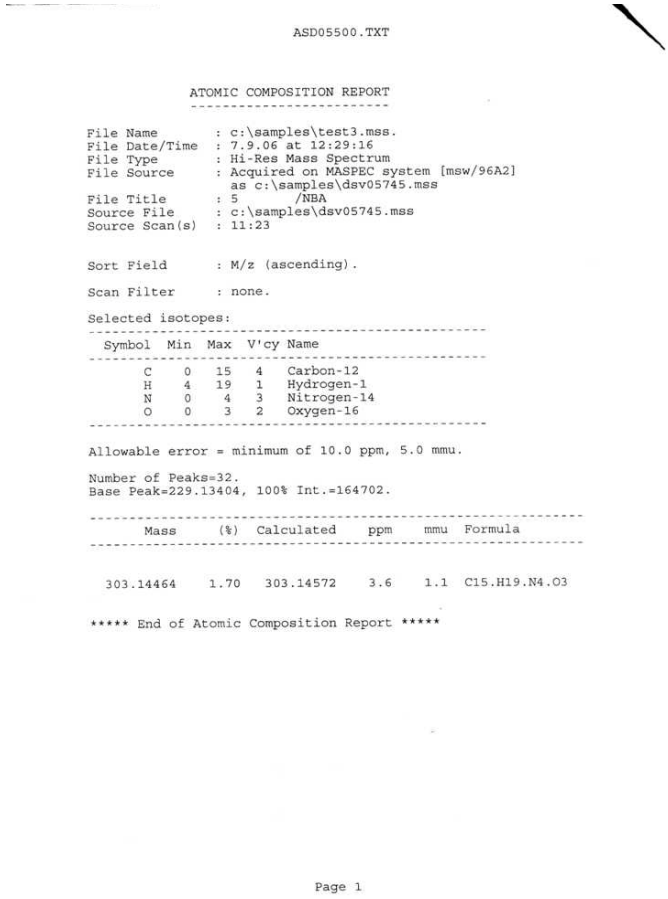


COSY



MS analysis





ASD05500.TXT

ATOMIC COMPOSITION REPORT

File Name : c:\samples\test3.mss.
File Date/Time : 7.9.06 at 12:29:16
File Type : Hi-Res Mass Spectrum
File Source : Acquired on MASPEC system [msw/96A2] as c:\samples\dsv05745.mss
File Title : 5 /NBA
Source File : c:\samples\dsv05745.mss
Source Scan(s) : 11:23

Sort Field : M/z (ascending).

Scan Filter : none.

Selected isotopes:

Symbol	Min	Max	V'cy	Name
C	0	15	4	Carbon-12
H	4	19	1	Hydrogen-1
N	0	4	3	Nitrogen-14
O	0	3	2	Oxygen-16

Allowable error = minimum of 10.0 ppm, 5.0 mmu.

Number of Peaks=32.
Base Peak=229.13404, 100% Int.=164702.

Mass	(%)	Calculated	ppm	mmu	Formula
303.14464	1.70	303.14572	3.6	1.1	C15.H19.N4.O3

***** End of Atomic Composition Report *****

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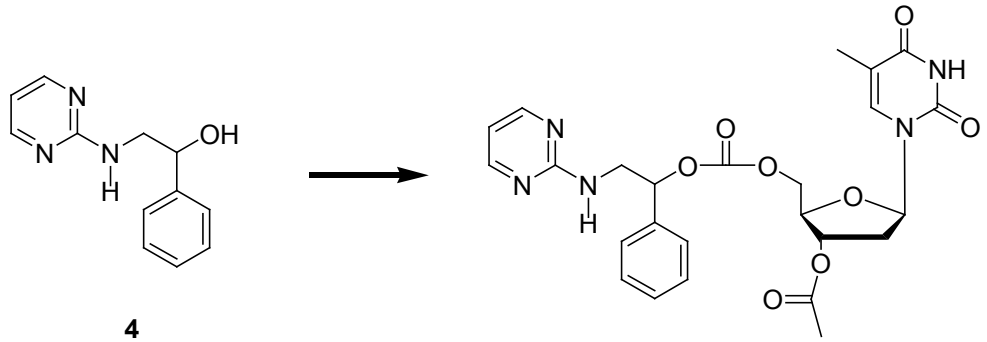
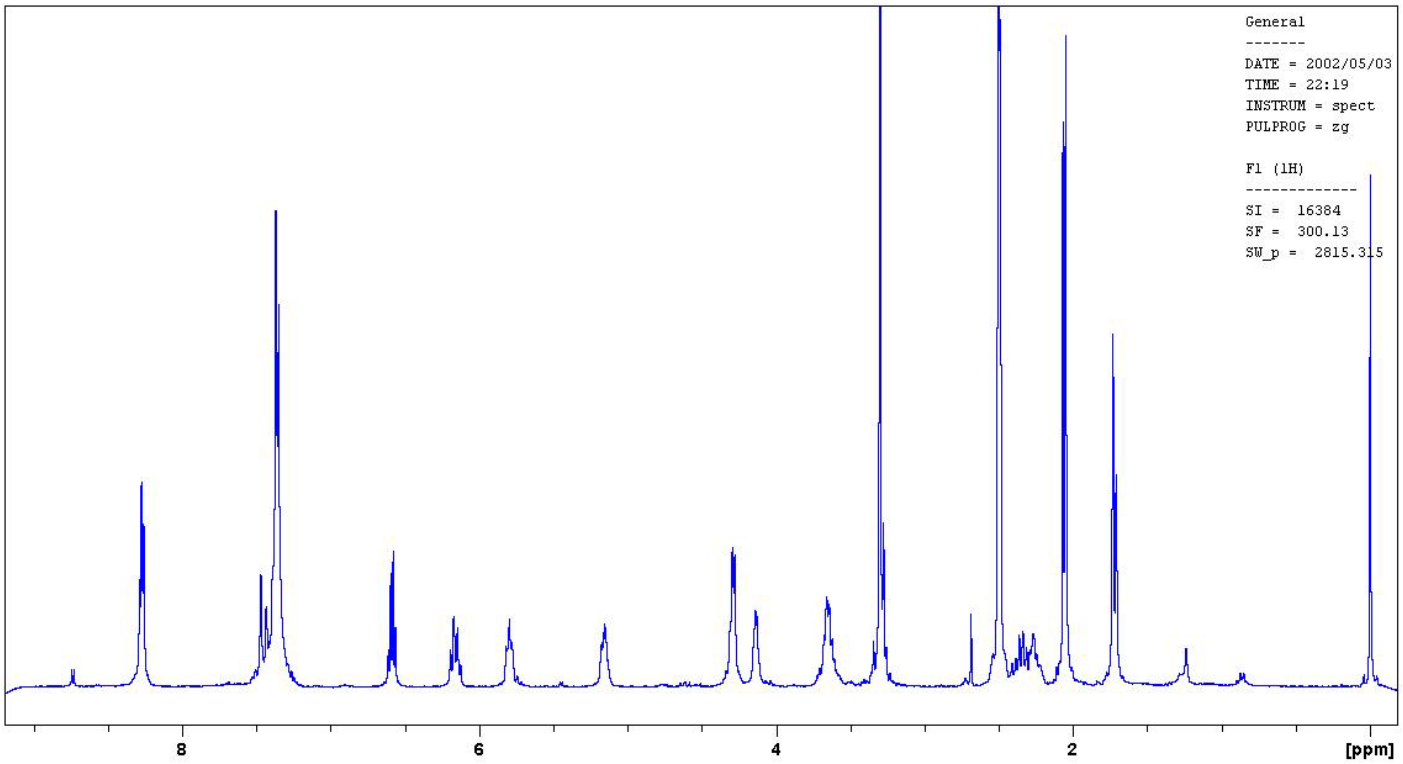
Analysis of termostability of compound 4

The compound **4** was converted into thermolabile 5'-carbonates in 3'acetyl thymidine (see scheme below)



4

^{1}H NMR spectrum of 5'-carbonates-3'-acetyl thymidine formed from **4**



HPLC analysis of termostability carbonates from **4** in 90 ºC