Design, Synthesis and Biological Evaluation of Novel 1,3-Diarylpyrazoles as Cyclooxygenase Inhibitors, Antiplatelet, and Anticancer Agents

Nazan Inceler^a, Yesim Ozkan ^b, Nilüfer Nermin Turan^c, Deniz Cansen Kahraman^d, Rengul Cetin-Atalay^d, Sultan Nacak Baytas^{a*}

^a Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Gazi University, 06330, Ankara, Turkey

^b Department of Biochemistry, Faculty of Pharmacy, Gazi University, 06330, Ankara, Turkey

^c Department of Pharmacology, Faculty of Pharmacy, Gazi University, 06330, Ankara, Turkey

^d Cancer Systems Biology Laboratory, Graduate School of Informatics, METU, 06800, Ankara, Turkey

Correspondence: Prof. Sultan Nacak Baytas

Division of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Gazi University, 06330 Etiler, Ankara-TURKEY;

E-mail: baytas@gazi.edu.tr; Fax: +90 (312) 223 5018

Figures

Page

Figure S1. Spectral data of Compound 2a	5
Figure S2. Spectral data of Compound 2b	5
Figure S3. Spectral data of Compound 7	6
Figure S4. Spectral data of Compound 3a	6
Figure S5. Spectral data of Compound 3b	7
Figure S6. Spectral data of Compound 8	8
Figure S7. Spectral data of Compound 4a	9
Figure S8. Spectral data of Compound 4b	9
Figure S9. Spectral data of Compound 9	11
Figure S10. Spectral data of Compound 5a	11
Figure S11. Spectral data of Compound 5b	13
Figure S12. Spectral data of Compound 5c	14
Figure S13. Spectral data of Compound 5d	16
Figure S14. Spectral data of Compound 5e	17
Figure S15. Spectral data of Compound 5f	19
Figure S16. Spectral data of Compound 5g	20
Figure S17. Spectral data of Compound 5h	22
Figure S18. Spectral data of Compound 5i	23
Figure S19. Spectral data of Compound 5j	25
Figure S20. Spectral data of Compound 5k	26
Figure S21. Spectral data of Compound 51	28
Figure S22. Spectral data of Compound 5m	29
Figure S23. Spectral data of Compound 5n	31
Figure S24. Spectral data of Compound 50	32
Figure S25. Spectral data of Compound 5p	33
Figure S26. Spectral data of Compound 5r	35
Figure S27. Spectral data of Compound 5s	37
Figure S28. Spectral data of Compound 10a	38
Figure S29. Spectral data of Compound 10b	40
Figure S30. Spectral data of Compound 10c	42
Figure S31. Spectral data of Compound 10d	43
Figure S32. Spectral data of Compound 10e	45
Figure S33. Spectral data of Compound 10f	46
Figure S34. Spectral data of Compound 10g	48
Figure S35. Spectral data of Compound 10h	49
Figure S36. Spectral data of Compound 10i	51

General procedure for the preparation of 3/4-[(1*E*)-1-(2-phenylhidraziniliden)ethyl] pyridine derivatives (2a, 7)

A solution of acetylpyridine derivative (0.052 mol), phenyl hydrazine (6.27 g, 0.058 mol) and acetic acid (2 ml, 0.035 mol) in ethanol was stirred for 2 hat reflux, and then evaporated. The precipitated was filtered off and dried.

N-Phenyl-N'-(1-pyridine-3-il-ethyliden)hydrazine 2a

Yield %90, mp 138.8 – 140 °C [1]. IR (FTIR/FTNIR-ATR): 3169 cm⁻¹ (N-H), 2993 cm⁻¹ (aliphatic C-H). ¹H-NMR (CDCl₃) δ : 8.98 (1H, d, *J*=2.4 Hz), 8.53 (1H, dd, *J*=1.6 Hz, 4.8 Hz), 8.10 (1H, dt, *J*=2 Hz, 8 Hz), 7.47 (1H, s), 7.31-7.26 (3H, m), 7.18 (2H, d, *J*=7.2 Hz), 6.91 (1H, t, *J*=7.2 Hz), 2.26 (3H, s). HRMS C₁₃H₁₄N₃ [M+H]⁺ *Calc*. 212.1188, Found m/z 212.1187. Anal. *Calc*. (%) for C₁₃H₁₃N₃ Calc. % C: 73.91 H: 6.20 N: 19.89, Found % C: 74.27 H: 6.08 N: 19.60.

4-(1-(2-phenylhydrazono)ethyl)pyridine 7

Yield 85%, mp 147°C (Lit. Mp. [1, 2]: 148-149 °C). IR (FTIR/FTNIR-ATR): 3227 cm⁻¹ (N-H), 1941 cm⁻¹ (C=N). ¹H-NMR (CDCl₃) δ : 8.58-8.60 (2H, d, *J*=6.4 Hz), 7.65 (2H, d, *J*=6 Hz), 7.59 (1H, s), 7.29-7.33 (2H, t, *J*=7.6 Hz), 7.19-7.22 (2H, d, *J*=7.6 Hz), 6.92-6.95 (1H, m, *J*=6.8 Hz, *J*=7.6 Hz), 2.22 (3H, s). HRMS C₁₃H₁₄N₃ [M+H]⁺ Calc. 212.1188, Found m/z 212.1180. Anal. Calc. (%) for C₁₃H₁₃N₃. C: 73.91 H: 6.20 N: 19.89, Found C: 74.21 H: 6.22 N: 19.38.

General procedure for the preparation of 1-phenyl-3-(pyridine-3/4-yl)-1*H*-pyrazole-4-carbaldehyde derivatives (3a,8)

In a dry flask, phosphoroxy chloride ($POCI_3$) (0.124 mol) was added drop wise to an ice-cold stirred solution of hydrazon derivative (0.041 mol) in 80 ml DMF. The reaction mixture was allowed to attain room temperature, and then heated at 50 °C for 4 h. The resulting mixture was poured onto crushed ice, neutralized with dilute NaOH and left overnight. The yellow precipitate obtained was purified by crystallization in toluene.

1-Phenyl-3-(pyridine-3-yl)-1*H*-pyrazole-4-carbaldehyde 3a

Yield %85, mp 158.8–160 °C [1]. IR (FTIR/FTNIR-ATR): 1673 cm⁻¹ (C=O). ¹H-NMR (CDCl₃) δ : 10.06 (1H, s), 9.12 (1H, d, *J*=2.4 Hz), 8.70 (1H, dd, *J*_a=1.6 Hz, *J*_b=4.8 Hz), 8.58 (1H, s), 8.47 (1H, dt, *J*_a=2 Hz, *J*_b=8 Hz), 7.81 (2H, d, *J*=7.6 Hz), 7.56-7.52 (2H, m), 7.46-7.41 (2H, m). HRMS C₁₅H₁₂N₃O [M+H]⁺ *Calc.* 250.0980, Found m/z 250.0979.

Anal. *Calc*. (%) for C₁₅H₁₂N₃O Calc. % C: 72.28 H: 4.45 N: 16.86, Found % C: 72.06 H: 4.46 N: 16.77

1-Phenyl-3-(pyridine-4-yl)-1H-pyrazole-4-carbaldehyde 8

Yield 13.8 (92%), mp 147 – 149 °C [1]. IR (FTIR/FTNIR-ATR): 1669 cm⁻¹ (C=O). ¹H-NMR (DMSO-d₆) δ : 10.04 (1H, s), 9.43 (1H, s), 8.73 (2H, d, *J*=1.6 Hz), 8.02-7.97 (4H, m), 7.62-7.58 (2H, m), 7.48-7.44 (1H, m). HRMS C₁₅H₁₂N₃O [M+H]⁺ *Calc*. 250.0980, Found m/z 250.0980. Anal. *Calc*. (%) for C₁₅H₁₁N₃O C: 72.28 H: 4.45 N: 16.86, Found C: 72.20 H: 4.42 N: 17.07

General procedure for the preparation of (2*E*)-3-[1-Substituted phenyl-3-(pyridine-3/4-yl)-1*H*-pyrazole-4-yl]prop-2-enoic acid derivatives (4a, 9)

To a solution of 1-phenyl-3-(pyridin-3/4-yl)-1*H*-pyrazole-4-carbaldehyde (8.72 mmol) in pyridine (20 ml), malonic acid (0.035 mol), and piperidine (0.0131 mol) were added, and the reaction mixture was refluxed for 4 h. On cooling, the reaction mixture was poured onto a solution (100 ml) of crushed ice and concentrated HCI (50% by volume) mixture, then, pH was adjusted to 5. The resulting precipitated was filtered off, washed with acidified water and dried.

(2E)-3-[1-Phenyl-3-(pyridine-3-yl)-1H-pyrazole-4-yl)acrylic acid 4a

Yield %91, mp 240–242 °C [1]. IR (FTIR/FTNIR-ATR): 1668 cm⁻¹ (C=O). ¹H-NMR (DMSO-d₆) δ : 12.38 (1H, s), 9.27 (1H, s), 8.84 (1H, d, *J*=1.6 Hz), 8.69 (1H, dd, *J*=1.6 Hz, *J*=5.2 Hz), 8.05 (1H, dt, *J*=2 Hz, 7.6 Hz), 7.94 (2H, d, *J*=7.6 Hz), 7.61-7.55 (2H, m), 7.48 (1H, d, *J*=15.6 Hz), 7.41 (2H, m), 6.48-6.44 (1H, d, *J*=16 Hz). HRMS C₁₇H₁₄N₃O₂ [M+H]⁺ Calc. 292.1086, Found m/z 292.1095.

(2E)-3-[1-Phenyl-3-(pyridin-4-yl)-1H-pyrazol-4-yl]acrylic acid 9

Yield 78%, mp 287 – 288 °C [1]. IR (FTIR/FTNIR-ATR): 1681cm⁻¹ (C=O), 2440 cm⁻¹ (C=C). ¹H-NMR (DMSO-d₆) δ : 9.27 (1H, s), 8.75-8.73 (2H, d, *J*=6 Hz), 7.96-7.93 (2H, d, *J*=8.4 Hz), 7.67-7.65 (2H, d, *J*=6.4 Hz), 7.60-7.53 (3H, m), 7.43-7.40 (1H, t, *J*=7.6 Hz), 6.51-6.47 (1H, d, *J*=16 Hz). HRMS C₁₇H₁₄N₃O [M+H]⁺ *Calc*. 292.1086, Found m/z 292.1089. Anal. *Calc*. (%) for C₁₇H₁₃N₃O C: 70.09 H: 4.50 N: 14.42, Found C: 69.92 H: 4.65 N: 14.34

Figure S1. Spectral data of Compound 2a

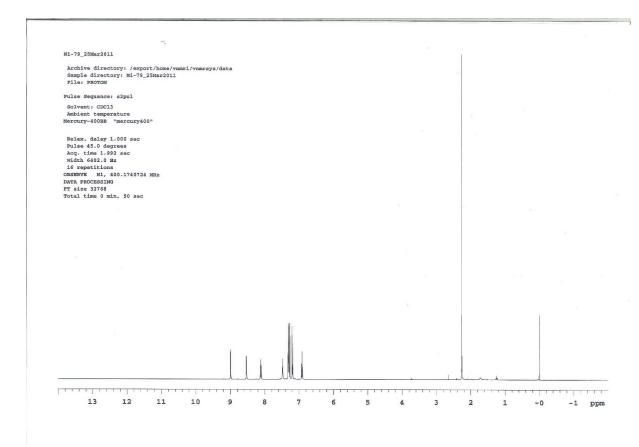


Figure S2. Spectral data of Compound 2b

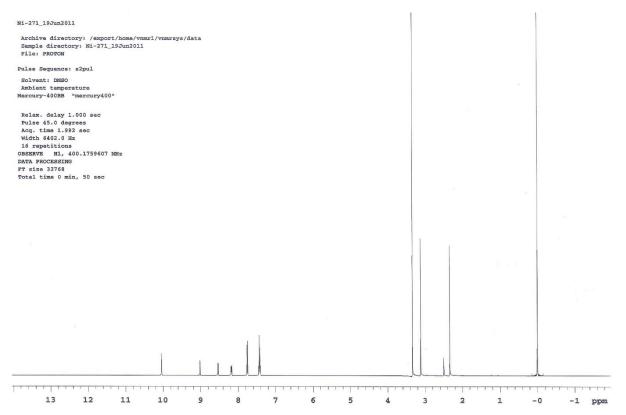


Figure S3. Spectral data of Compound 7

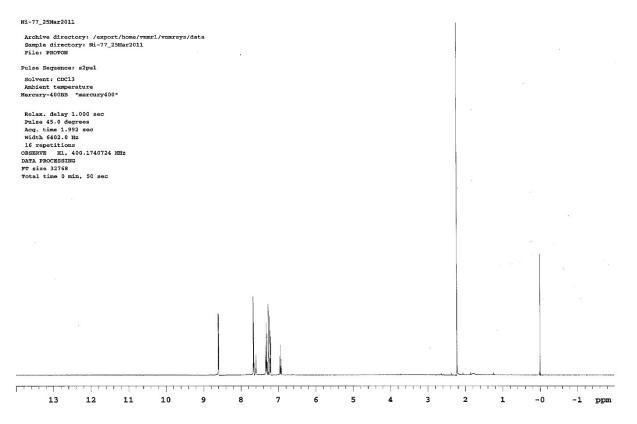


Figure S4. Spectral data of Compound 3a

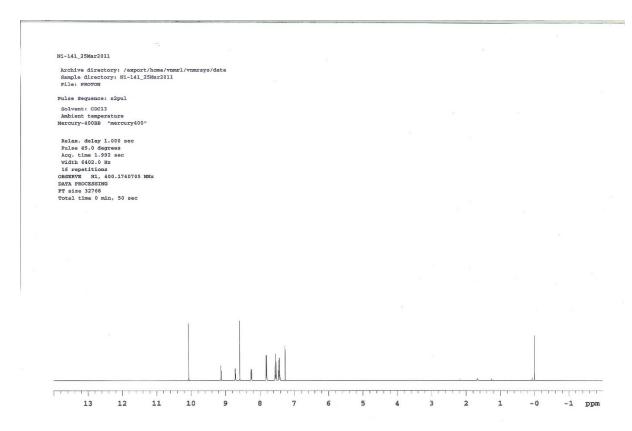
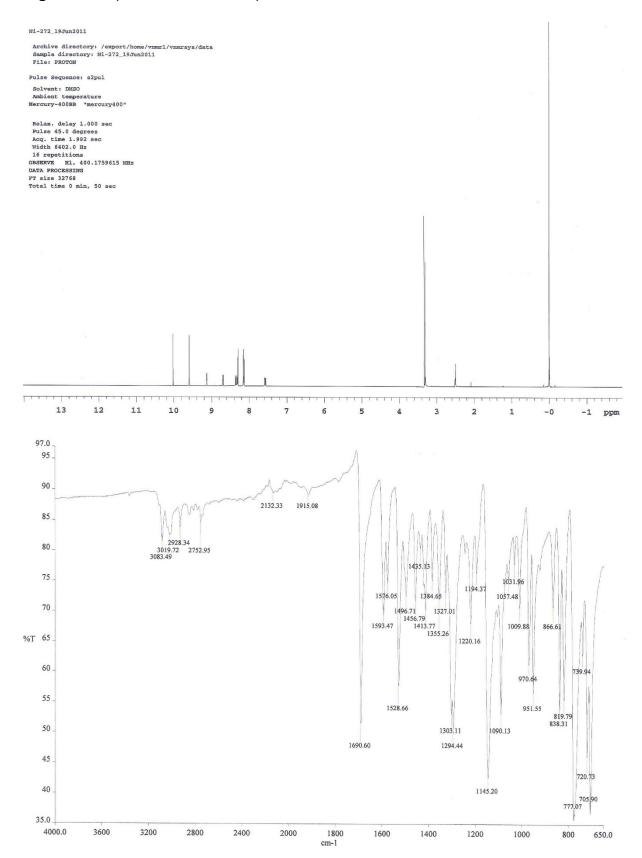


Figure S5. Spectral data of Compound 3b



Page 1 of 1

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 125 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-40 H: 1-40 N: 1-8 O: 1-5 S: 1-1 NI-272-2 71 (2.763) Cm (69:71) 1: TOF MS ES+

1: TOF MS ES	+								1.05e+004
100	199.9881	328.0748							
-	227.983	8							
%-	271.1	879							
171.99	37	329.07		496.1104 50					0015570
130.5326		39	1.2841	490.1104 59	6.2695 653	3.1312 677.7448	834.7868	921.6285	964.5576 m/z
100	200	300	400	500	600	700	800	900	1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (N	orm) Formula		
328.0748	328.0756	-0.8	-2.4	11.5	238.7	0.0	C16 H14	N3 03	S

Figure S6. Spectral data of Compound 8

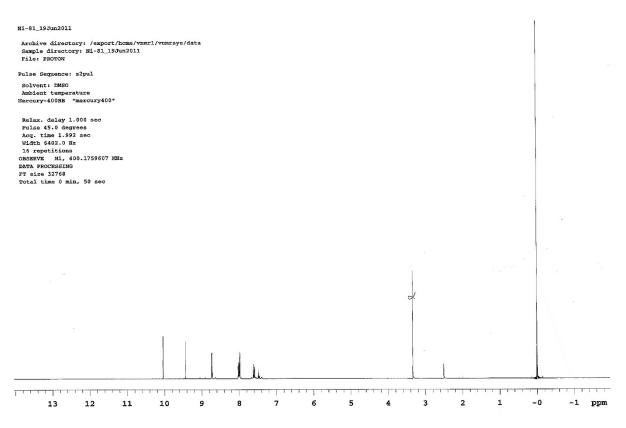
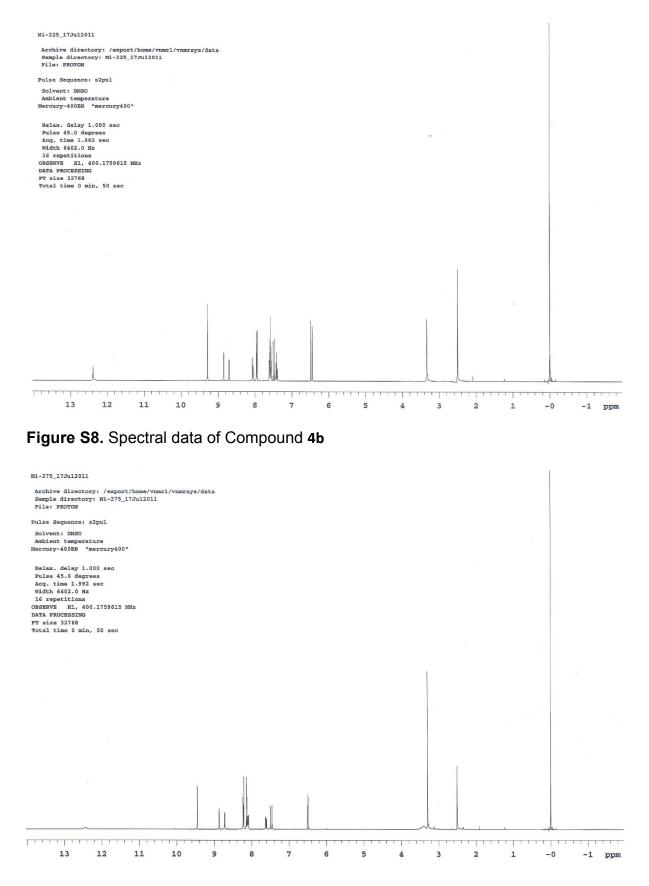
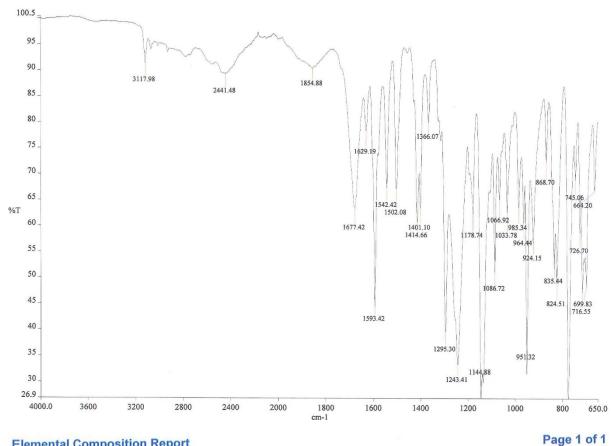


Figure S7. Spectral data of Compound 4a





Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 158 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-40 H: 1-40 N: 1-8 O: 1-6 S: 1-1 NI-275 57 (2.233) Cm (57:60) 1: TOF MS ES+

1: TOF MS ES	3+										ç	9.33e+004
100		370	.0852									
0-171.993	199.9885 227.98 200	335 290.0956 300	371.0876 372.0857 400	483.1692 509.18 500	600 627.1505	670.1912	775.2214	1111	988 900 988 900 9	.3452		.8041 m/z 1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
370.0852	370.0862	-1.0	-2.7	12.5	257.3	0.0		C18	H16	NЗ	04	S

Figure S9. Spectral data of Compound 9

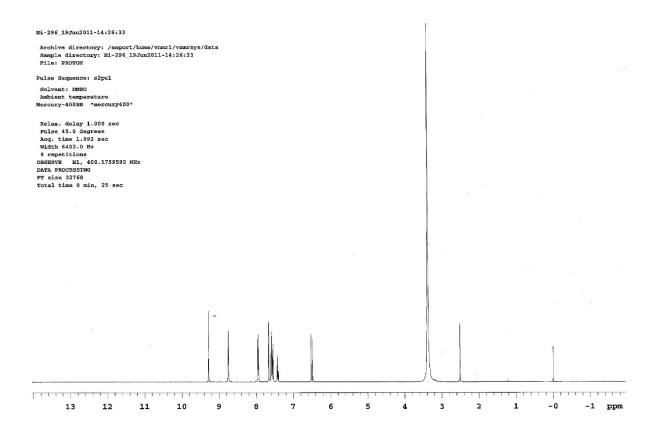
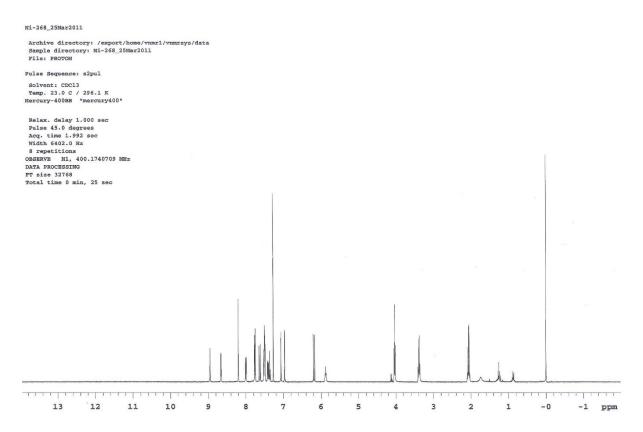
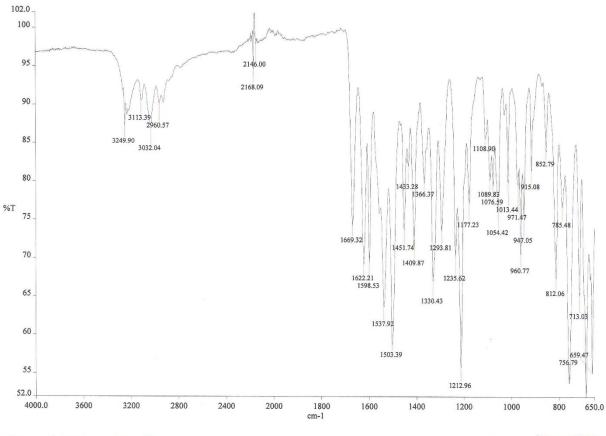


Figure S10. Spectral data of Compound 5a





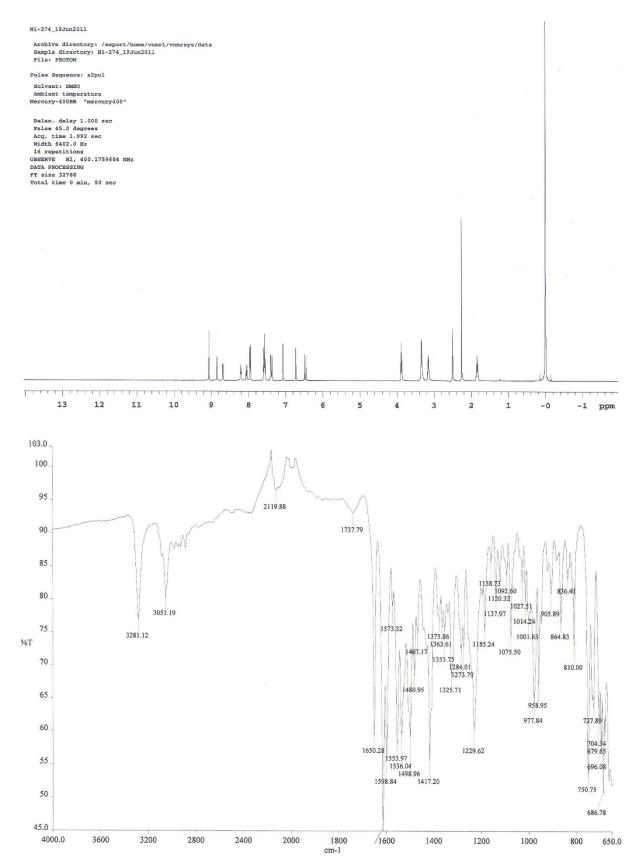
Page 1 of 1

2.94e+004

Tolera	ent predictic	PPM / DBE: min =				
100 for Eleme C: 1-3 NI_268		N: 1-8 O: 1-5	ithin limits (up to 50 close:	st results for each mass)	
100	200.	0971	399.1915			
%-	199.9876	200.5998	400.1938			

0	271.1875	2824 413.207	1 516.2706	544.1125613.48	⁰⁴ 710.7549 797	7.3740 859.29	96 899.30	32 974.0341 m/z
100 200	300	400	500	600	a start start starts	800	900	1000
Minimum: Maximum:	5.0	5.0	-1.5 50.0					
Mass Calc.	Mass mDa	PPM	DBE	i-FIT	i-FIT (Norm) Formula	i -	
399.1915 399.1 399.1		-1.3 -4.5	10.5	141.2 141.0	0.8 0.6	C22 H2 C23 H2		05 0

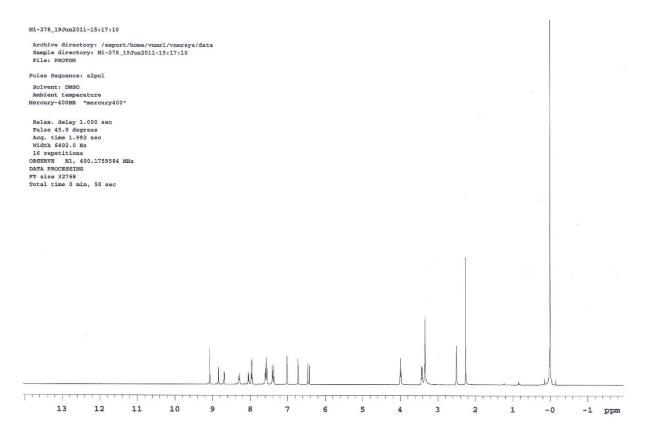
Figure S11. Spectral data of Compound 5b

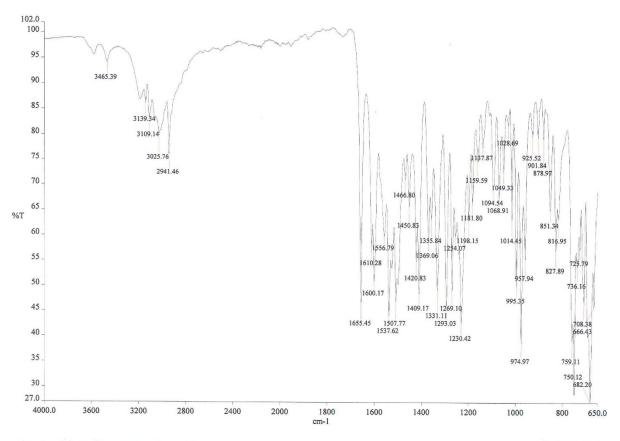


Page 1 of 1

Single Mass Ana Tolerance = 5.0 PF Element prediction: Number of isotope	M / DI			0					
Monoisotopic Mass, I 26 formula(e) evalua Elements Used: C: 1-40 H: 1-40 NI-274 50 (1.949) Cm (ted with 1 N: 1-8	tron lons results within O: 1-1	i limits (up to 5	0 closest r	esults for eac	h mass)			
1: TOF MS ES+	49.52)								5.75e+005
100 - 207.1	032								0.700.000
			413.2074						
%-	207.6088		414.2122						
199.9000	208.1105	331.1572	415.2142	530.1398	3_558.1356658	.1011 726.0785	825.4093	925.3362	993.3232
100 200		300	400	500	600	700	800	900	1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass Calc.	Mass	mDa	PPM	DBE	i-FIT	i-FIT (N	orm) Formu	La	
413.2074 413.2	2090	-1.6	-3.9	15.5	492.5	0.0	C24 I	H25 N6 O	

Figure S12. Spectral data of Compound 5c





Page 1 of 1

2.64e+004

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 75 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-27 H: 1-33 N: 1-6 O: 1-5 NI-278X 52 (2.012) Cm (52:55) 1: TOF MS ES+

200.0978 399.1918 100-1 199.9873 % 227.9830 400.1945 171.9929 271.1873 317.1387 461.2292 531.2717 563.2602 899.3074929.4607 648.3521 797.3785 m/z 0 1000 900 500 800 100 200 300 400 600 700 -1.5 Minimum: 5.0 5.0 50.0 Maximum: i-FIT (Norm) Formula Mass Calc. Mass mDa PPM DBE i-FIT -0.2 10.5 180.2 1.0 C22 H27 N2 05 399.1918 399.1920 -0.5 399.1933 -1.5 -3.8 15.5 179.6 0.4 C23 H23 N6 0

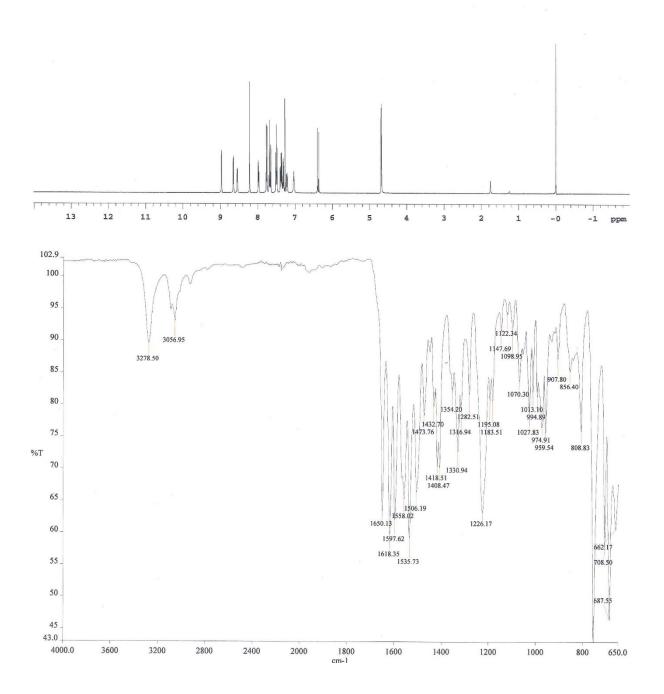
Figure S13. Spectral data of Compound 5d

Ni-266_25Mar2011

Archive directory: /export/home/vnmr1/vnmrsys/data Sample directory: Ni-266_25Mar2011 File: PROTON

Pulse Sequence: s2pul Solvent: CDC13 Temp. 23.0 C / 296.1 K Mercury-400BB "mercury400"

Relax. delay 1.000 sec Pulse 45.0 degrees Acq. tims 1.992 sec Width 6402.0 Hz 16 repetitions OBSENVE H1, 400.1740709 MHz DATA PROCESSING FT size 32768 Total time 0 min, 50 sec



Page 1 of 1

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 21 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-30 H: 1-30 N: 1-8 O: 1-1 NI266 53 (2.078) Cm (51:60) 1: TOF MS ES+

2.52e+005

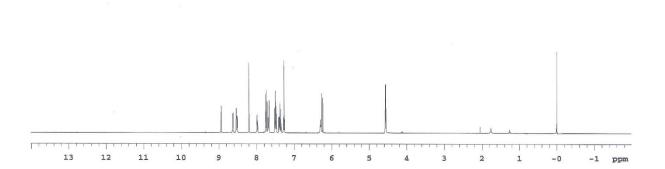
	191.5822								2.52e+005
100	101.0022								.1
		382	2.1656						
%-									
182.9	192.0863 266. 851	0919 _271.1882	383.1678 384.1687	499.2434_52	7.0885 647.2	763 003	3.3201 785.3028 787.3066	005 0540	
100	200	300	400	500	600	700	800	900	1000 m/z
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (1	Norm) Formu	ıla	
382.1656	382.1668	-1.2	-3.1	16.5	449.7	0.0	C23	H20 N5	0

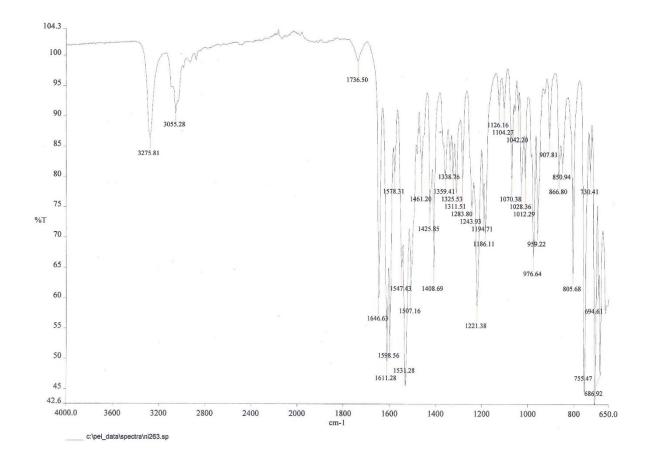
Figure S14. Spectral data of Compound 5e

Ni-263_25Mar2011 Archive directory: /export/home/vnmr1/vnmrsys/data Sample directory: Ni-263_25Mar2011 File: PROTON Pulse Sequence: s2pul

Solvent: CDC13 Ambient temperature Mercury-400BB "mercury400"

Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.992 sec Width 6402.0 Hz 32 repetitions OSSERVE HI, 400.1740701 MHH DATA PROCESSING FT size 32768 Total time 1 min, 40 sec





Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 188 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-40 H: 1-40 N: 1-8 O: 1-7 NI263 49 (1.916) Cm (48:50) 1: TOF MS ES+

3.17e+005 191.5832 100 4 382.1678 % 192.0883 763.3268 383.1711 764.3297 212.0994 384.1748 291.1259 762.1213 786.3096 863.2494 958.2286 182.9854 499.0936 527.0897 652.3543 0m/z 100 300 400 500 600 700 800 900 1000 200 -1.5 50.0 Minimum: 5.0 5.0 Maximum: Mass Calc. Mass mDa PPM DBE i-FIT i-FIT (Norm) Formula 382.1668 436.6 C23 H20 N5 O 382.1678 1.0 2.6 16.5 0.0

Page 1 of 1

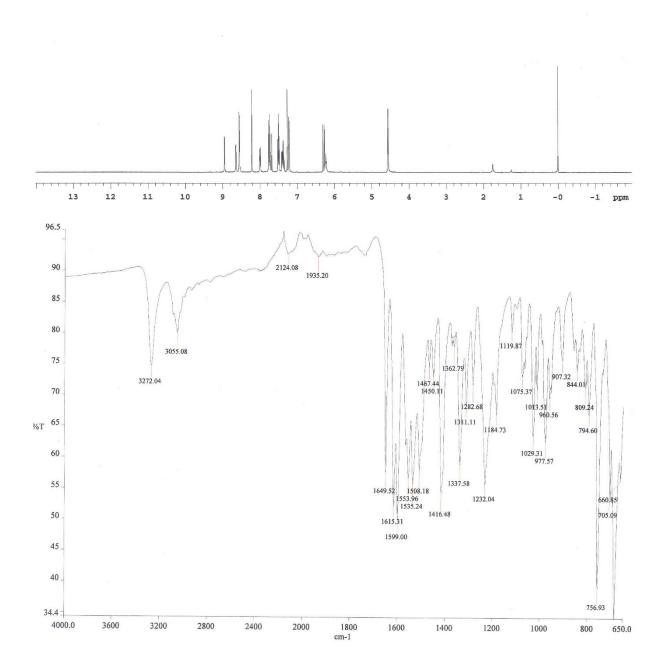
Figure S15. Spectral data of Compound 5f

Ni-267_25Mar2011

Archive directory: /export/home/vnmr1/vnmrsys/data Sample directory: Ni-267_25Mar2011 File: PROTON

Pulse Sequence: s2pul Solvent: CDC13 Temp. 23.0 C / 296.1 K Mercury-400BB "mercury400"

Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.992 sec Width 6402.0 Hz 8 repetitions OSEENVE HI, 400.1740701 HHH DATA PROCESSING FT size 32768 Total time 0 min, 25 sec



Page 1 of 1

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 21 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-30 H: 1-30 N: 1-8 O: 1-1 NI267 51 (1.981) Cm (51:54) 1: TOF MS ES+

100	191.	5853								7.85e+004
										1
%			38	2.1676						
0	182.9856	192.0868 212.0993 212.6022		383.1698 414.1549	499.243852	1.2245	763.3 672.2827694.2659	266 785.3047	865.2607 931	
100	. epecer	200	300	400	500	600	700	800	900	1000 m/z
Minimum Maximum			5.0	5.0	-1.5 50.0					
Mass	Ca	lc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (No	rm) Formu	la	
382.167	76 38:	2.1668	0.8	2.1	16.5	151.5	0.0	C23	H20 N5 O	

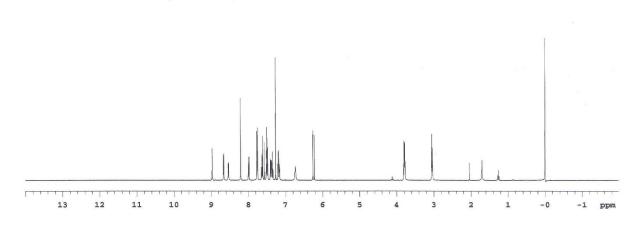
Figure S16. Spectral data of Compound 5g

Ni-269_25Mar2011

Archive directory: /export/home/vnmr1/vnmrsys/data Sample directory: Ni-269_25Mar2011 File: PROTON Pulse Sequence: s2pul

Solvent: CDC13 Temp. 23.0 C / 295.1 K Mercury-400BB "mercury400"

Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.992 sec Width 6402.0 Hz 8 repetitions OBSERVE H1, 400.1740709 MHz DATA PROCESSING FT size 32768 Total time 0 min, 25 sec



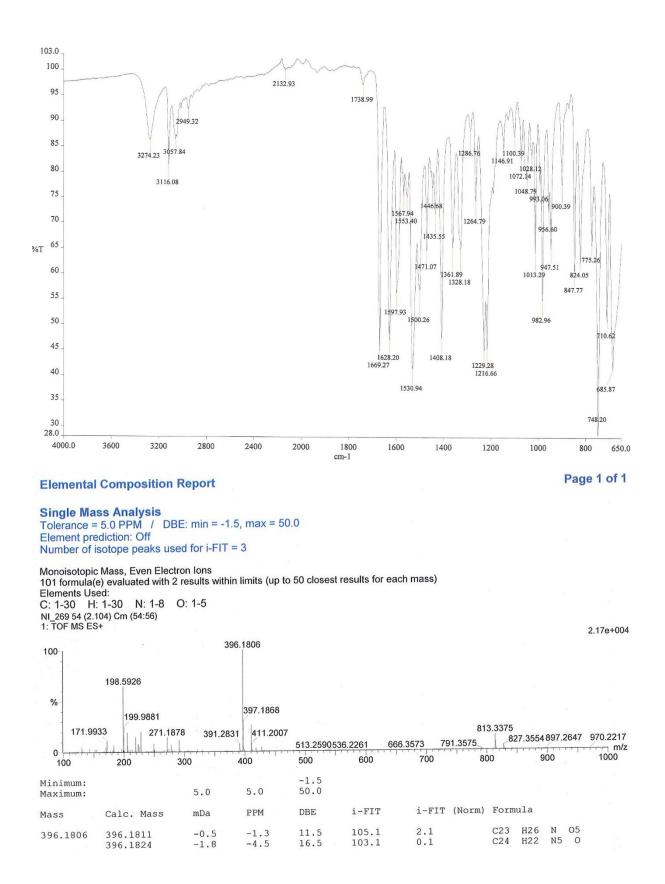
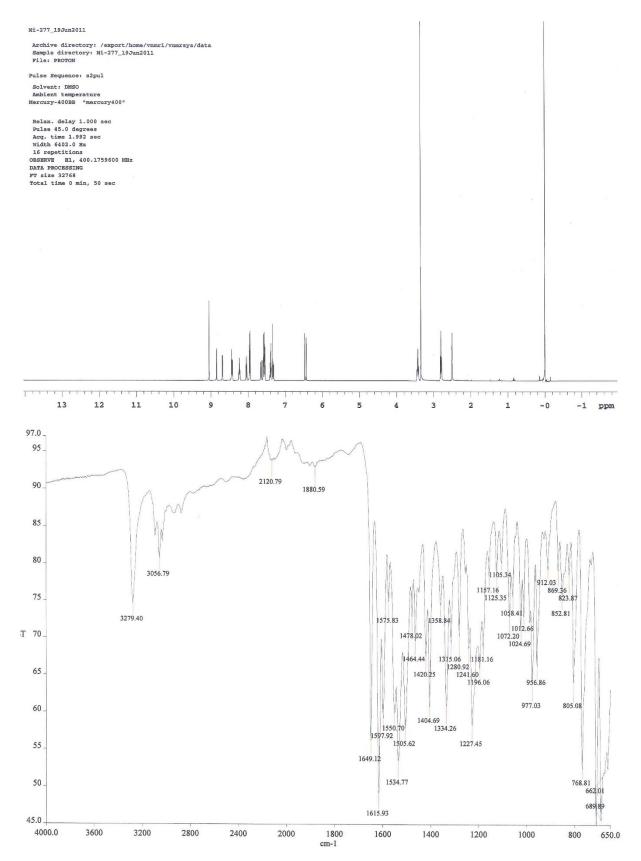


Figure S17. Spectral data of Compound 5h



Page 1 of 1

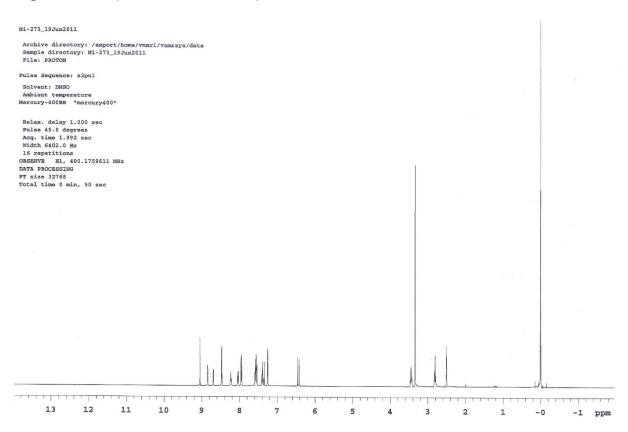
2 900+005

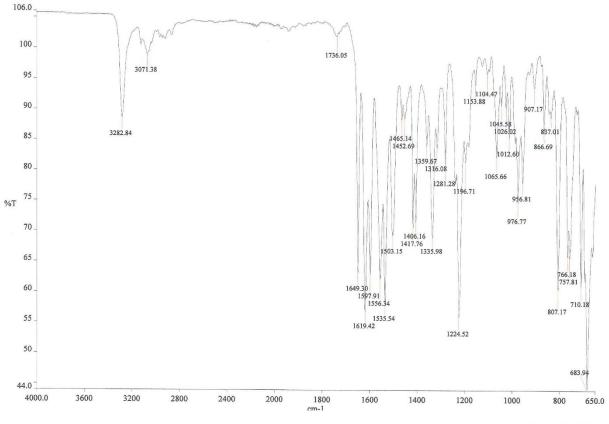
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 134 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-40 H: 1-40 N: 1-8 O: 1-5 NI-277 49 (1.917) Cm (49:52) 1: TOF MS ES+

	100 5007									3.80e+005
100	198.5907									
-		3	96.1811							
0	- Arton -	271.1899	397.1867 418.164	554	.2295	tere free	1.3599	3.3416		2 959.2719
100	200	300	400	500	600	700	80	0	900	1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Formula		
396.1811	396.1811 396.1824	0.0 -1.3	0.0 -3.3	11.5 16.5	405.9 405.1	1.2		C23 H2 C24 H2		

Figure S18. Spectral data of Compound 5i





Page 1 of 1

1.22e+004

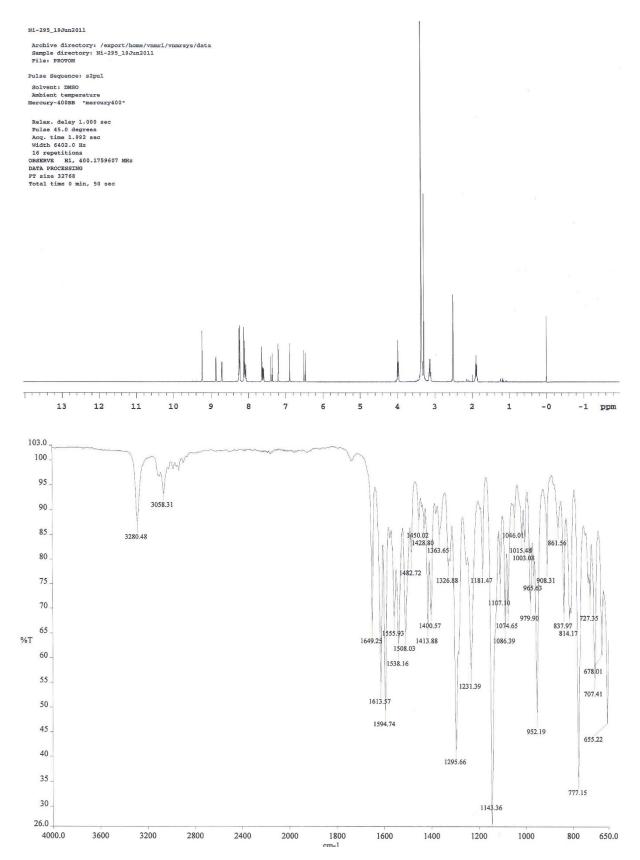
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 27 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-40 H: 1-40 N: 1-8 O: 1-1 NI-273 72 (2.794) Cm (71:73) 1: TOF MS ES+

100	199.9882								
-	227.982	29							
%-									
171.9	929 271.1	3	396.1806						
169.97	B1	391.284	41 397.1844	463.2430 53	5.2556 627.4688	3689.6807	734.9449		964.4969 m/z
0-1 100	200	300	400	500	600	700	800	900	1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm) Form	nula	
396.1806	396.1824	-1.8	-4.5	16.5	115.8	0.0	C24	H22 N5	0

Figure S19. Spectral data of Compound 5j



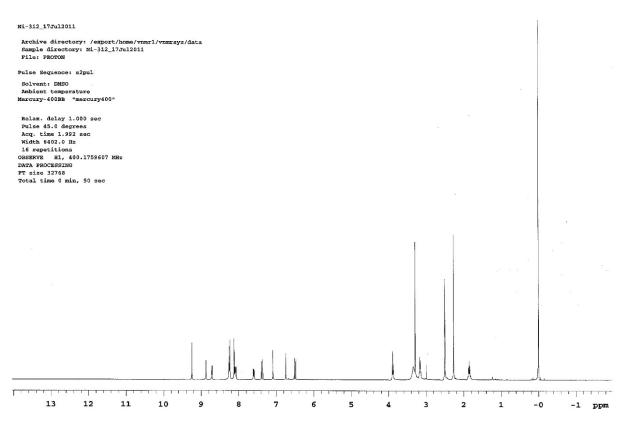
Page 1 of 1

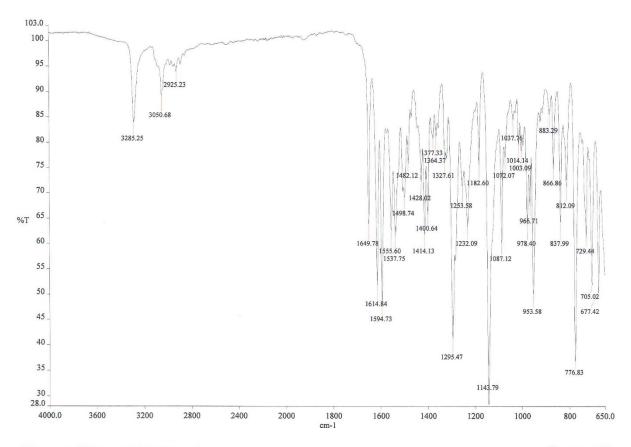
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 399 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-50 H: 1-50 N: 1-8 O: 1-6 S: 1-2 NI-295-2 41 (1.605) 1: TOF MS ES+

1. 101 110 1	0.										1	.05e+005
100			47	7.1704								
%-	(59.5996	409.1331	478.1736 499.151	5 567.1435 629	0.1182 697.1	036 765.0	854	9	53.338	975. 34	3218
100	200	300	400	500	600	700	80	00	ç	000		1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
477.1704	477.1702 477.1709	0.2 -0.5	0.4 -1.0	6.5 15.5	240.9 230.3	10.6 0.0		C16 C24	H29 H25	N8 N6	05 03	S2 S

Figure S20. Spectral data of Compound 5k





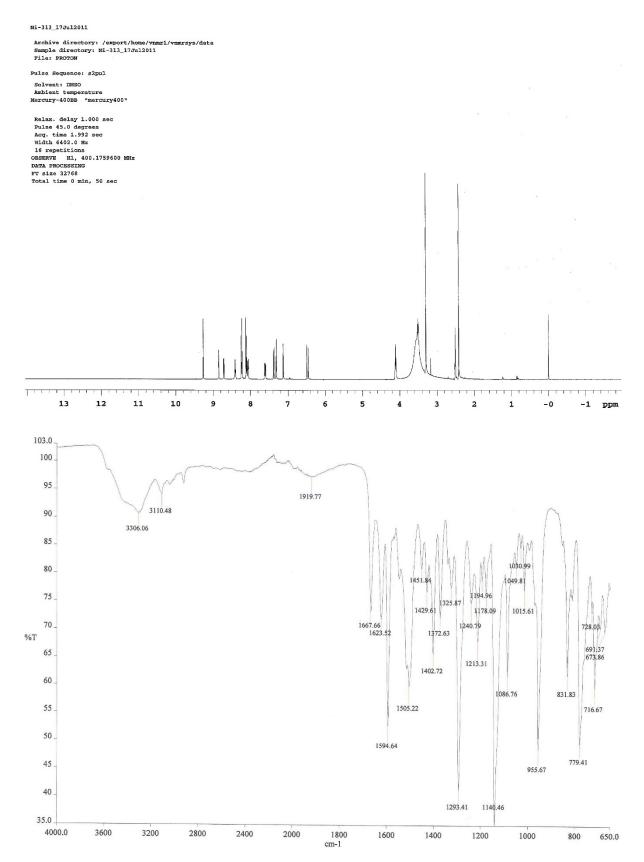
Page 1 of 1

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 180 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-29 H: 1-50 N: 1-9 O: 1-3 S: 1-2 NI-312 47 (1.821) Cm (47:49) 1: TOF MS ES+

1: TOP MS ES	5+									ŧ	5.92e+004
100			4	91.1847							
%- - - - - - - - - - - - - - - - - - -	208.0412 7.0142 2 200 2	96.9726 356 	5.9109 424.89 	492.1878 493.1842 500	553.1102_618 600	2886 704.7985 700	786.7567		371 9:	22.734	4 1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norn	n) Form	nula			
491.1847	491.1865 491.1827	-1.8 2.0	-3.7 4.1	15.5 14.5	185.9 188.8	0.1 2.9	C25 C28	H27 H31	N6 N2	03 02	S S2

Figure S21. Spectral data of Compound 5I

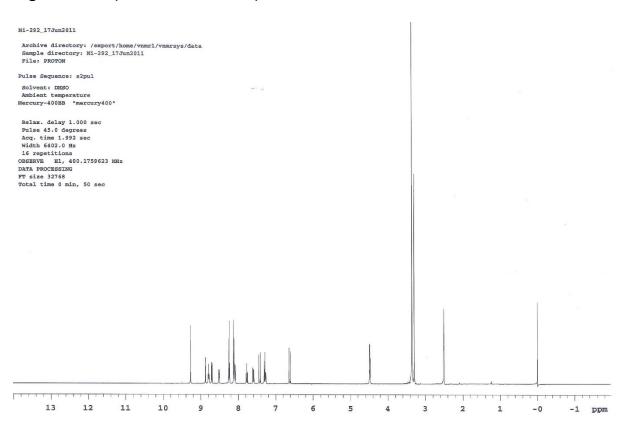


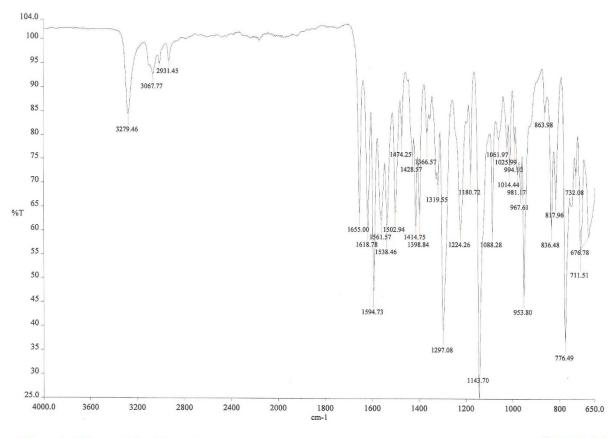
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 196 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-29 H: 1-50 N: 1-9 O: 1-3 S: 1-2 NI-313 44 (1.696) Cm (44:46) 1: TOF MS ES+

1: TOF MS ES	S+								1.75e+005
100			477	7.1708					
%-	239.0897			478.1743					
0 1 1	44 208.0423 239.5	912 296.9729	424.8990	479.1711	608.2671_6	36.8117_704.8009	786.7573 8	354.7394 9	53.3411 m/z
100	200	300	400	500	600	700	800	900	1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (No)	m) Formu	la	
477.1708	477.1709	-0.1	-0.2	15.5	329.5	0.0	C24	H25 N6	03 S

Figure S22. Spectral data of Compound 5m





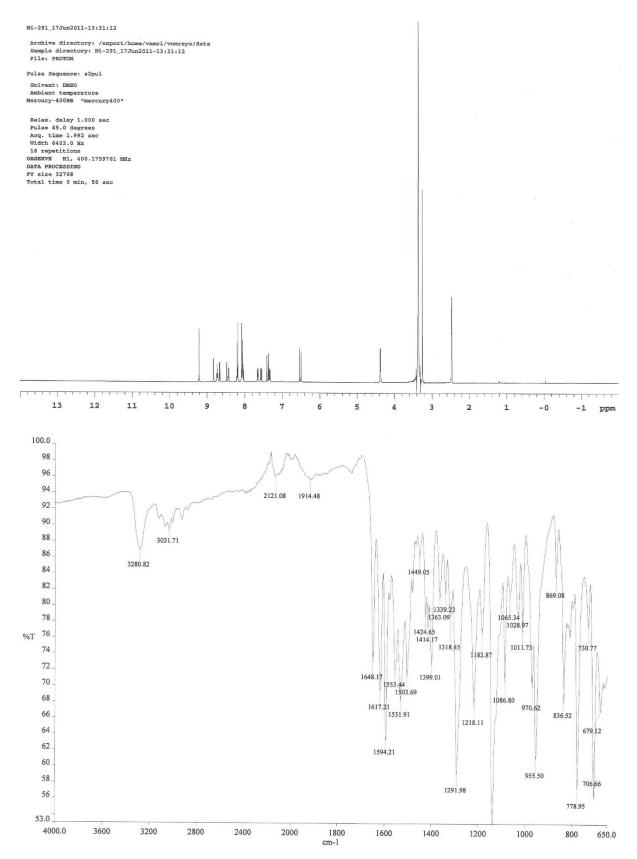
Page 1 of 1

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 395 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-50 H: 1-50 N: 1-8 O: 1-6 S: 1-2 NI-292 36 (1.382) 1: TOF MS ES+

											1	.01e+005
100			460.1	447						941	.2703	
- - %	230.5739			482.1251							942.:	2709
0-1		51.5893 356.91		1.9.1.1.1.1.1.1	8550.1176612.0	TTTTTT			919.2	1171	Ir.	4.2725 m/z
100 Minimum: Maximum:	200	300 5.0	400 5.0	500 -1.5 50.0	600	700	80	0	5	00		1000
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
460.1447	460.1443 460.1437	0.4 1.0	0.9 2.2	16.5 7.5	235.6 241.0	0.0 5.3		C24 C16	H22 H26	N5 N7	03 05	S S2

Figure S23. Spectral data of Compound 5n



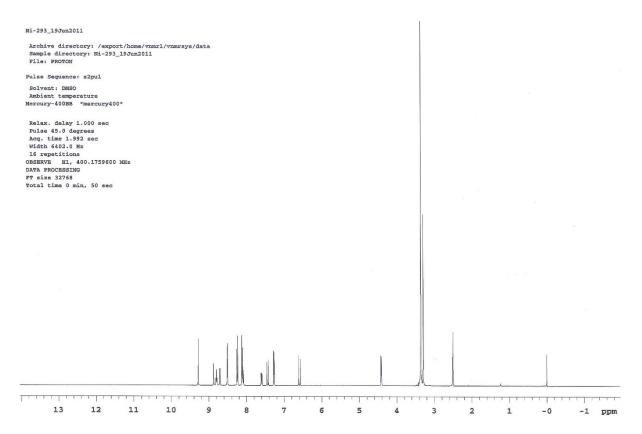
Page 1 of 1

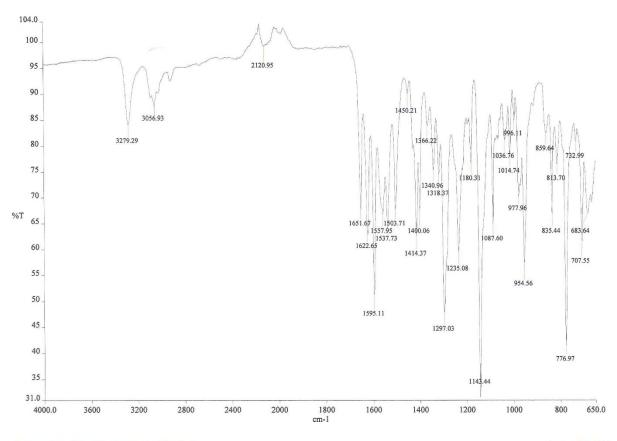
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 331 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-25 H: 1-25 N: 1-8 O: 1-6 S: 1-2 Ni: 0-1 NI-291 24 (0.912) Cm (21:26) 1: TOF MS ES+

1. TOT WOLD											2	.67e+005
100			460.14	47								
-	230.5746											
%	231.0764		46	61.1480 62.1476 .522.0	669 601.0975 65	94.0773	772.0565		919.28	66941	.2684	
0 - 	200	+ receptor a	00	500	600	700	80	0	9	00		1000 m/z
Minimum: Maximum:		5.0	5.0	-1.5 50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
460.1447	460.1443	0.4	0.9	16.5	485.1	0.0		C24	H22	N5	03	S

Figure S24. Spectral data of Compound 50





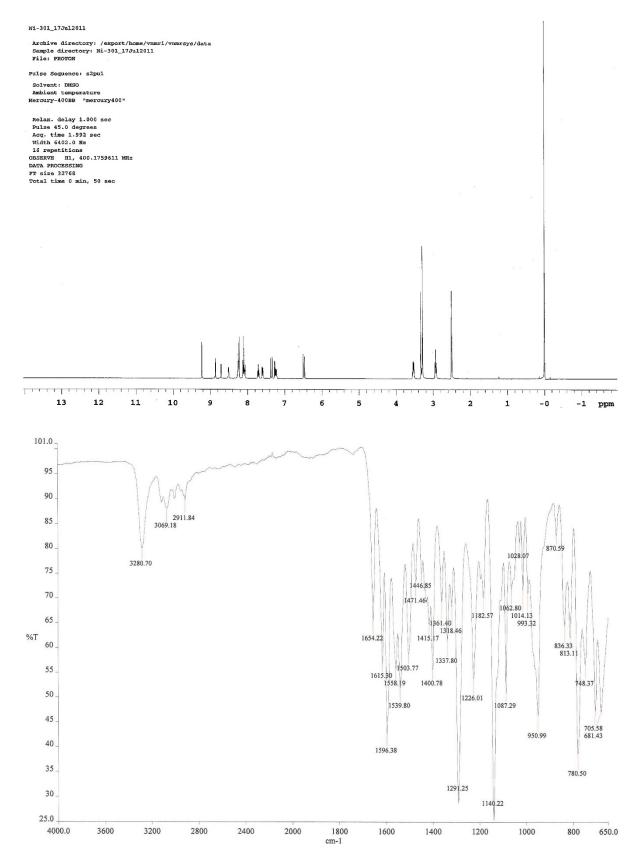
Page 1 of 1

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 395 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-50 H: 1-50 N: 1-8 O: 1-6 S: 1-2 NI-293-2 42 (1.635) Cm (42:44) 1: TOF MS ES+

1: TOF MS ES	S+									4	1.34e+004
100			460.1	440							
%-	230.5743	884	4	461.1454							
0 143.05 0 100	208.0400 598 200			462.1449 _{523.}	1525 618.10386 600	580.0739 748.0 700	0618810.0346 800		93 ⁹⁴¹ 900	.2663	
Minimum: Maximum:		5.0	5.0	-1.5 50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm) For	mula			
460.1440	460.1443 460.1437	-0.3 0.3	-0.7 0.7	16.5 7.5	118.9 129.1	0.0 10.3	C24 C16	H22 H26	N5 N7	03 05	S S2

Figure S25. Spectral data of Compound 5p



Page 1 of 1

2 400+004

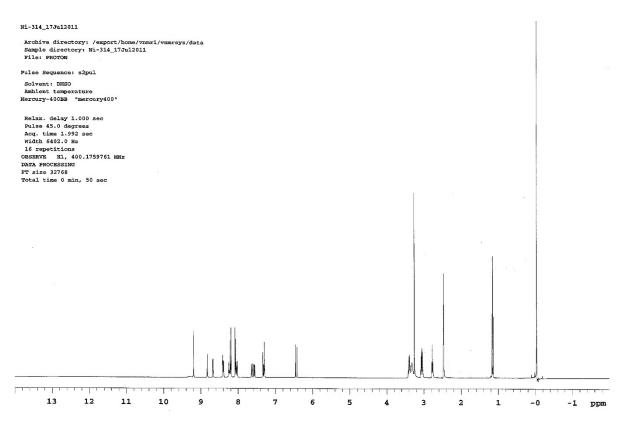
Single Mass Analysis

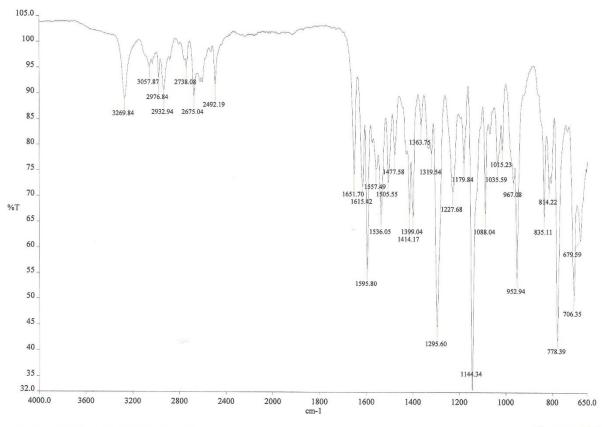
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 58 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-25 H: 1-33 N: 1-6 O: 1-4 S: 1-2 NI-301 48 (1.851) Cm (48:52) 1: TOF MS ES+

100 -	208.0400								Ζ.	40e+004
			474	4.1592						
% 143.05		20.0700 2	06 4929	496.1411						
-		96.9709 3 356.909	96.1828 97	497.1442	614.82686	636.8170_704	.8055_772.7892	834.7515 9	16.71949	/
0 	200	300	400	500	600	700	800	900		m/z 1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm) Form	nula		
474.1592	474.1600	-0.8	-1.7	16.5	202.8	0.0	C25	H24 N5	03	S

Figure S26. Spectral data of Compound 5r





Page 1 of 1

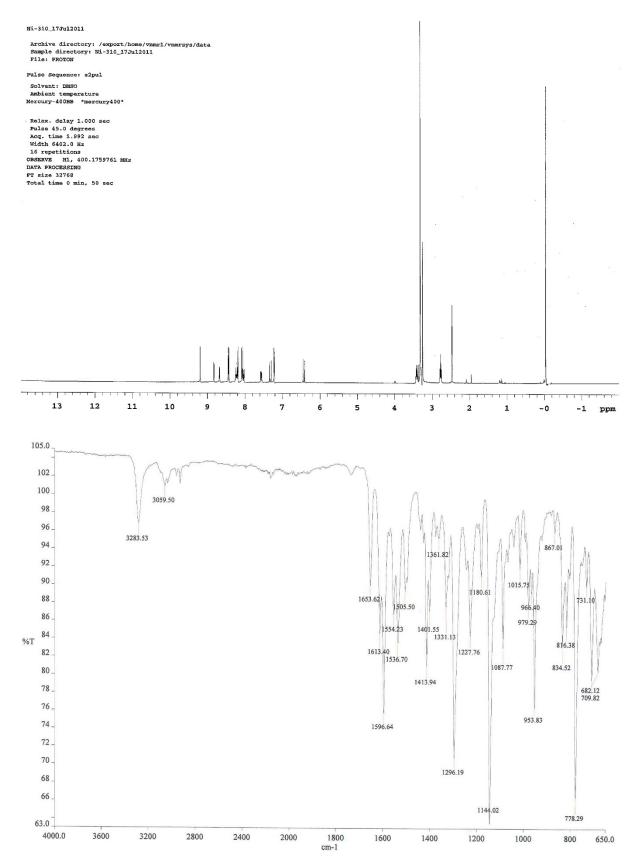
2.86e+004

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 200 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-29 H: 1-50 N: 1-9 O: 1-3 S: 1-2 NI-314 45 (1.758) Cm (45:48) 1: TOF MS ES+

100 	208.0414 237.58 7.0140	132	474.	1578 496.1417								
0-1	238.08 14. mil 4. july 4. july 200	296.9722	⁸ 424.8967 	497.1426 498.1386 	627.2383 600	704.7982 700	111111	717	846.759 9	92 9	22.72	51 •••• m/z 1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
474.1578	474.1561 474.1600	1.7 -2.2	3.6 -4.6	15.5 16.5	208.7 205.3	3.4 0.0		C28 C25	H28 H24	N N5	02 03	S2 S

Figure S27. Spectral data of Compound 5s



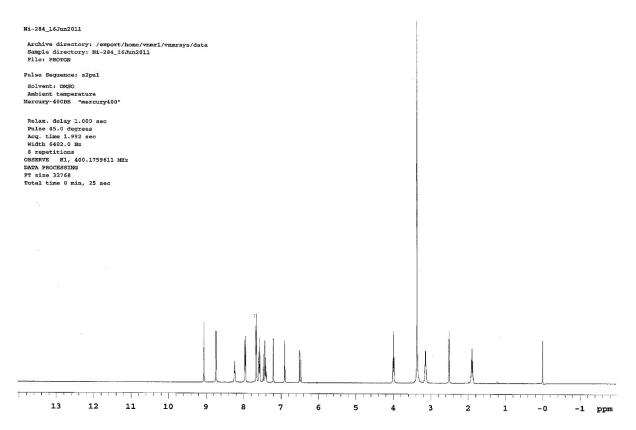
Page 1 of 1

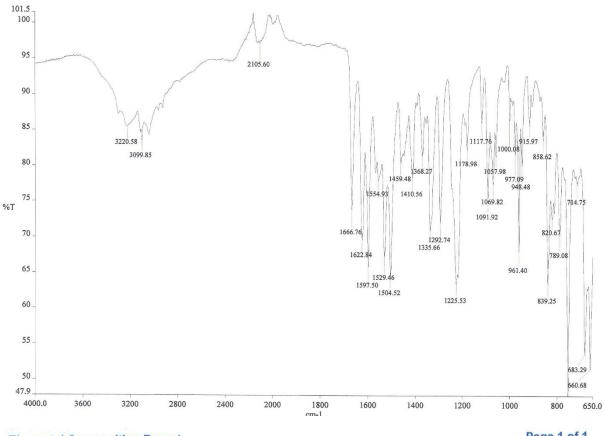
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 134 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-30 H: 1-25 N: 1-6 O: 1-6 S: 1-2 NI-310 44 (1.692) 1: TOF MS ES+

1: TOF MS ES	3+								3.24e+004
100-			474	.1590					
%- 143.05	237.5823 08.0397 238.08 997 25	29 8.5946 _{356.91}	04 424.8985	496.1402 497.144 537.16	5	32.1176.694.0963	66.7605	906.6911	969.3005 m/z
100	200	300	400	500	600	700	800	900	1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (No	rm) Formu	ıla	
474.1590	474.1600	-1.0	-2.1	16.5	111.5	0.0	C25	H24 N5	03 S

Figure S28. Spectral data of Compound 10a





Page 1 of 1

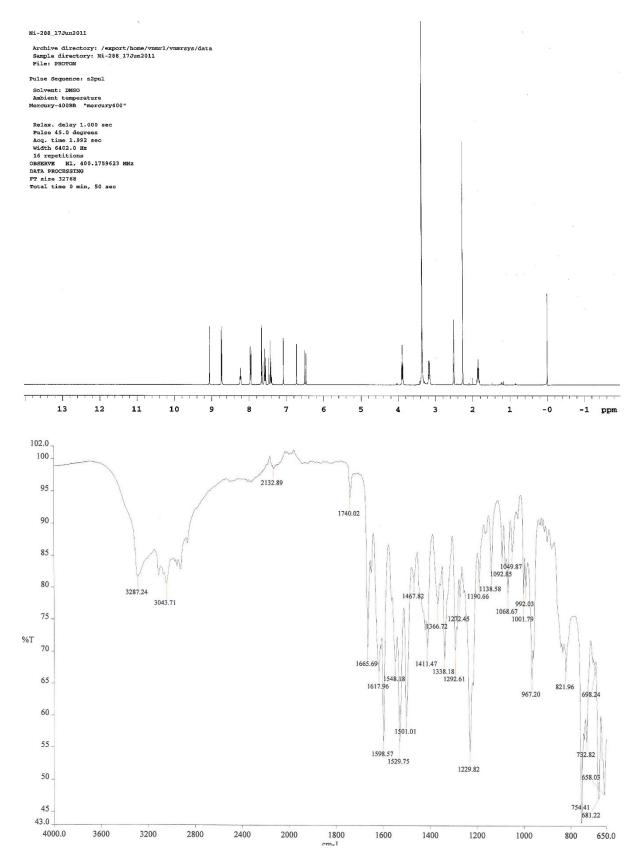
4.04e+005

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 75 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-27 H: 1-33 N: 1-6 O: 1-5 NI-284 42 (1.636) Cm (41:44) 1: TOF MS ES+

100		200.	0964											
%				3	99.1945									
			200.6012						797.3	3826				
- 1 - 1 -					400.1977					798.38	67			
	199	.9877	201.1025	331.1557	401.2010	516.1234	544.1190 6	61.0508	796.6210	799.39	930 g	014.314	2 942.3	3032 _{m/z}
0)	2	00	300	400	500	600	700	80	00		900		1000
Minim	111m •					-1.5								
Maxim				5.0	5.0	50.0								
Mass		Cal	c. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
399.1	945	399	.1933	1.2	3.0	15.5	497.9	0.0		C23	H23	NG	0	

Figure S29. Spectral data of Compound 10b



Page 1 of 1

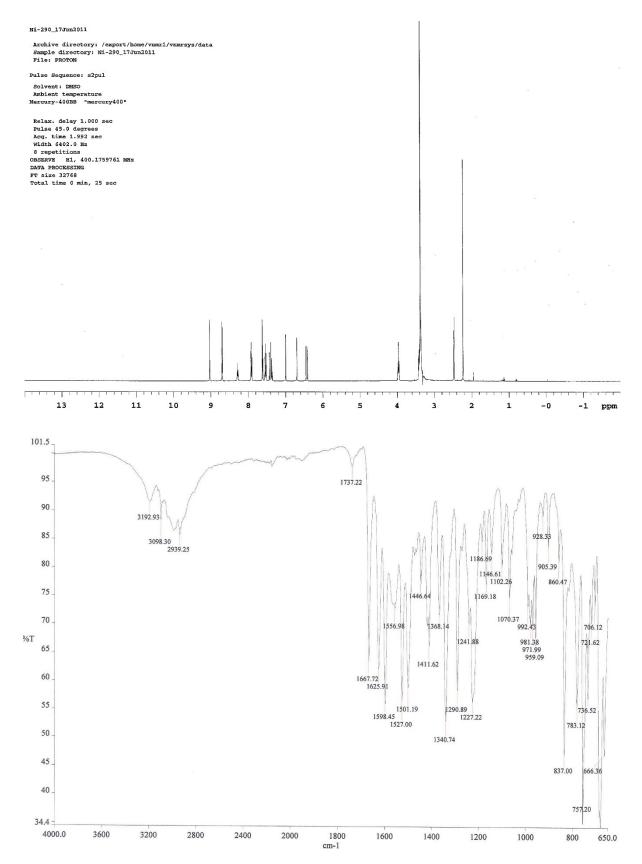
S	ing	le N	las	s A	nal	ysi	S	

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 180 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-25 H: 1-25 N: 1-8 O: 1-6 Ni: 0-1 NI288 44 (1.696) Cm (44:46) 1: TOF MS ES+

1.37e+005 207.1045 100 % 413.2079 207.6079 414.2121 825.4144 199.9880 208.1097 847.3962 925.3445 427.2250 530.2892552.2753 624.3184 676.0823 824.3984 331.1566 m/z 0-....... 111 900 800 1000 300 400 500 600 700 100 200 -1.5 50.0 Minimum: 5.0 Maximum: 5.0 i-FIT (Norm) Formula i-FIT Mass Calc. Mass mDa PPM DBE 0.0 C24 H25 N6 O -1.1 -2.7 15.5 283.8 413.2079 413.2090

Figure S30. Spectral data of Compound 10c



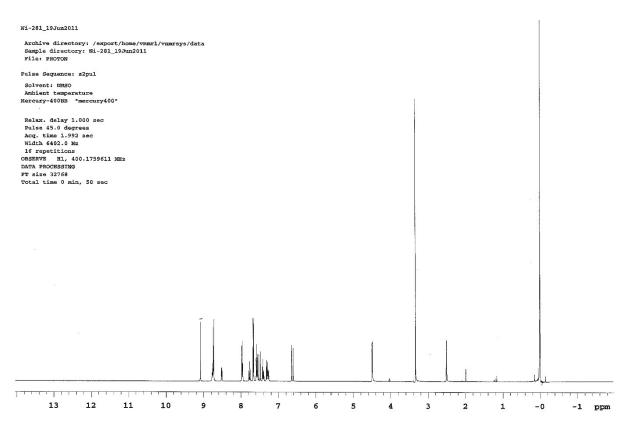
Page 1 of 1

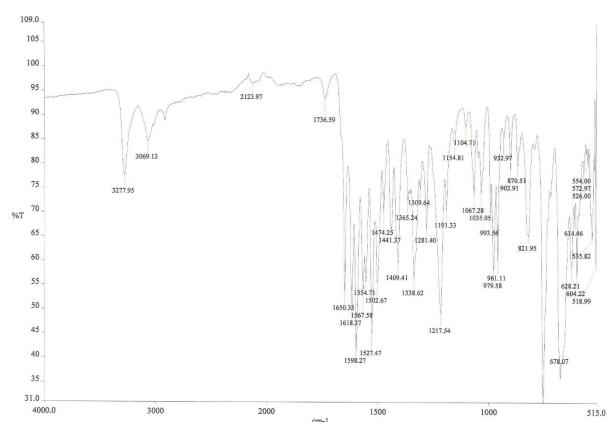
Single Mass Analysis	
Tolerance = 5.0 PPM /	DBE: $min = -1.5$, $max = 50.0$
Element prediction: Off	
Number of isotope peaks	used for $i-FIT = 3$

Monoisotopic Mass, Even Electron Ions 189 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-25 H: 1-25 N: 1-8 O: 1-6 Ni: 0-1 NI290 41 (1.602) Cm (41:44) 1: TOF MS ES+

1: TOF MS ES	3+							2.85e+00)5
100	200.0966								
		3	99.1944 						
%	200.6015		400.1984				797.3849 798.3877		
199	207.1074	317.1401	413.209	⁹ 516.2744	544.1190 661	.0493	796.9634 799.3918	897.3134 992.2876	7
0 100	200	300	400	500	600	700	800	900 1000	-
Minimum: Maximum:		5.0	5.0	-1.5 50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm) Formula		
399.1944	399.1933	1.1	2.8	15.5	445.6	0.0	C23 H2	3 N6 O	

Figure S31. Spectral data of Compound 10d





Page 1 of 1

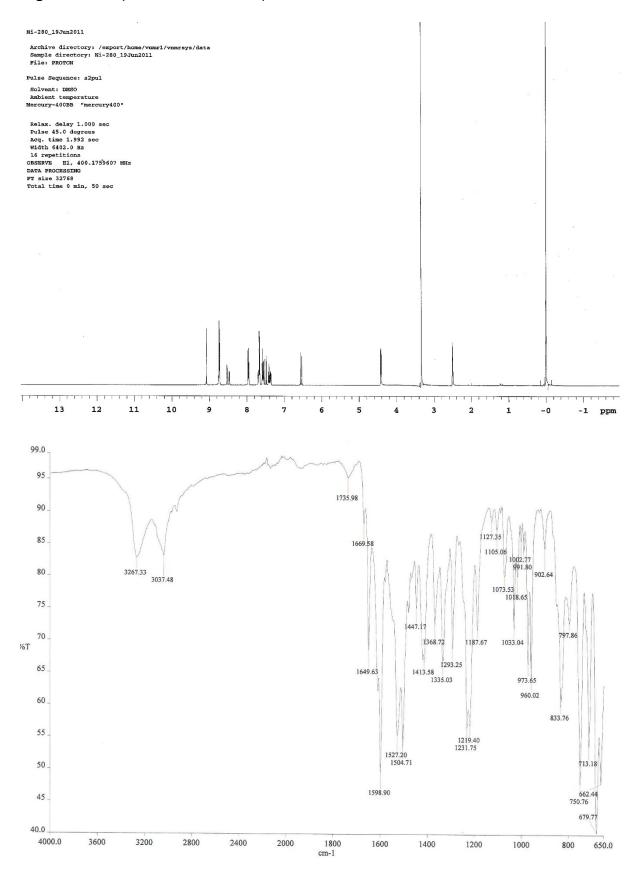
1.62e+005

Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 77 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-27 H: 1-33 N: 1-6 O: 1-5 NI-281 45 (1.762) Cm (43:45) 1: TOF MS ES+

100 1	91.5831											.0201000
		382	2.1650									
%-	192.0867		383.1700									
171.9935	212.1000	274.0975	384.1741	527.0940	644.0239		763.32697	785.309	³ 863.	2525	973.3	826 m/z
0 1 100	200	300	400	500	600	700	80	00	5	900		1000
Minimum: Maximum:		5.0	5.0	-1.5 50.0								
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Form	ula			
382.1650	382.1654	-0.4	-1.0	11.5	387.1	2.0		C22 C23	H24 H20	N N5	05 0	

Figure S32. Spectral data of Compound 10e



45

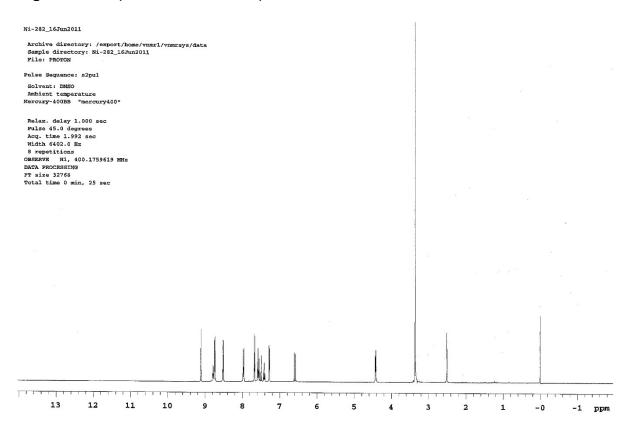
Page 1 of 1

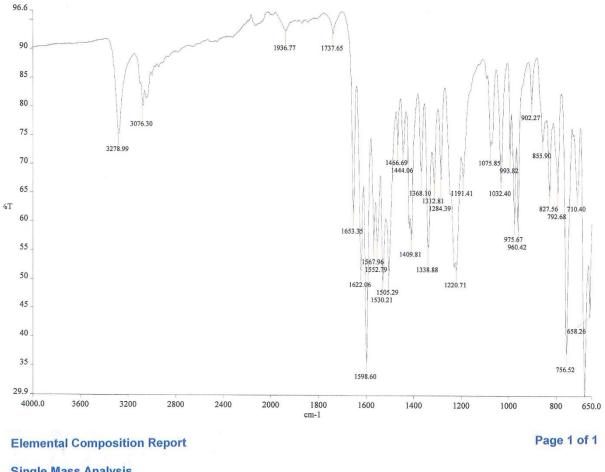
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron lons 77 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-27 H: 1-33 N: 1-6 O: 1-5 NI-280X 44 (1.697) Cm (44:46) 1: TOF MS ES+

1.10	OF MS ES+												1.49e+005
100	19	1.5832											
12	1.1.1	13	38	2.1654									
%	문제 관련 :	- 1. A.											
		192.0869		383.1692									
1.2.5													
	171.9931	212.0987	271.1886	384.1710	527.0902	577.0770 6	45.0369	763.32557	85.308	3 865.	2565	958.2	355 m/z
0- 10	171.9931	212.0987 200	271.1886	384.1710 400	527.0902 500	577.0770 6 600	45.0369 700	763.32557		TITT	2565	958.2	355 m/z 1000
10 Mini	 00 Lmum:	Affraire		Krante		*******		,				958.2	
10	Lmum: .mum:	Affraire	300	400	500 -1.5	*******		 80		ç		958.2	

Figure S33. Spectral data of Compound 10f





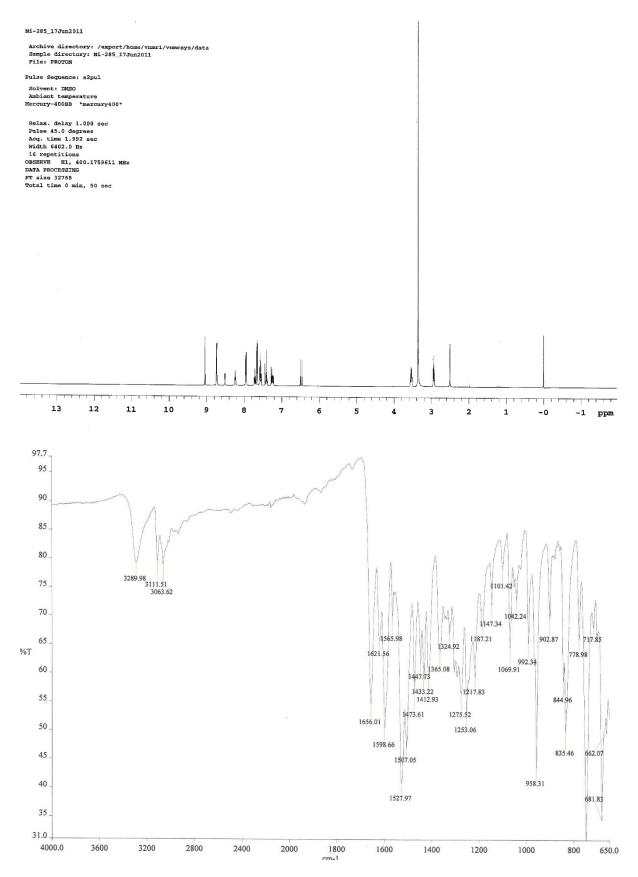
Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions 77 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-27 H: 1-33 N: 1-6 O: 1-5 NI-282 43 (1.665) Cm (43:45) 1: TOF MS ES+

191.5833 100 382.1663 % 192.0872 383.1704 212.0984 384.1734 763.3278785.3109 865.2553 908.2463 171.9935 499.0980 527.0922 644.0262 271.1896 0m/z 700 800 900 1000 500 600 300 400 100 200 -1.5 Minimum: 50.0 Maximum: 5.0 5.0 DBE i-FIT i-FIT (Norm) Formula Calc. Mass mDa PPM Mass 456.6 C23 H20 N5 O -1.3 2.4 16.5 0.7 382.1663 382.1668 -0.5 H24 N 05 0.7 C22 0.9 456.6 382.1654 11.5

1.84e+005

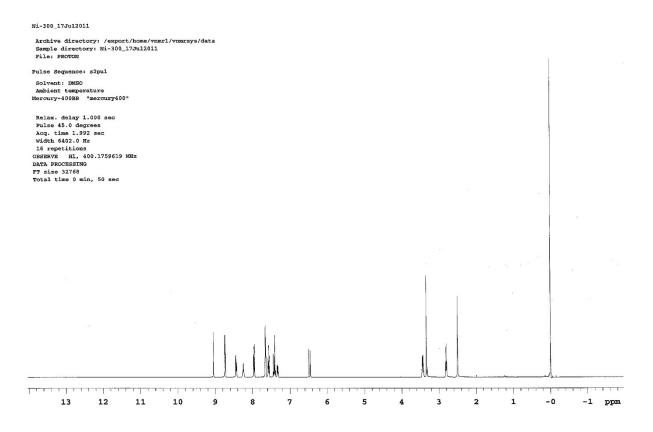
Figure S34. Spectral data of Compound 10g



Page 1 of 1

Single Mass Ana	lysis										
Tolerance = 5.0 PP	M / DBE: min = -1	1.5, max = 50.0	C								
Element prediction:											
Number of isotope	beaks used for i-FIT	= 3									
Number of lootope											
Monoisotopic Mass, E	ven Electron lons										
72 formula(e) evaluate	ed with 2 results within	n limits (up to 50) closest r	esults for eac	ch mass)						
Elements Used:											
T —	N: 1-6 O: 1-5										
NI-285 45 (1.765) Cm (4	(5:49)										
1: TOF MS ES+									8.0)5e+004	
198.592	21										
100											
-	3	396.1817									
	5										
%-											
19	9.0942	397.1855				813	3.3412				
171.9931	219.1068 291.1241			570 0055	050 0050	91.3574	815.348	82 897	2615959.	2632	
		410.1970	541.10	90 572.2055	658.0359		- Chine in	- 097.		m/z	
100 200	300	400	500	600	700	80	0	900	1	1000	
100 200	000	100									
Minimum:			-1.5								
Maximum:	5.0	5.0	50.0								
	Mass mDa	PPM	DBE	i-FIT	i-FIT	(Norm)	Formul	a			
Mass Calc.	Mass IIIDa	PPM		TIT		(
396.1817 396.1	811 0.6	1.5	11.5	266.1	1.7		A 400 A	126 N	05		
396.1		-1.8	16.5	264.6	0.2		C24 H	122 N5	0		

Figure S35. Spectral data of Compound 10h



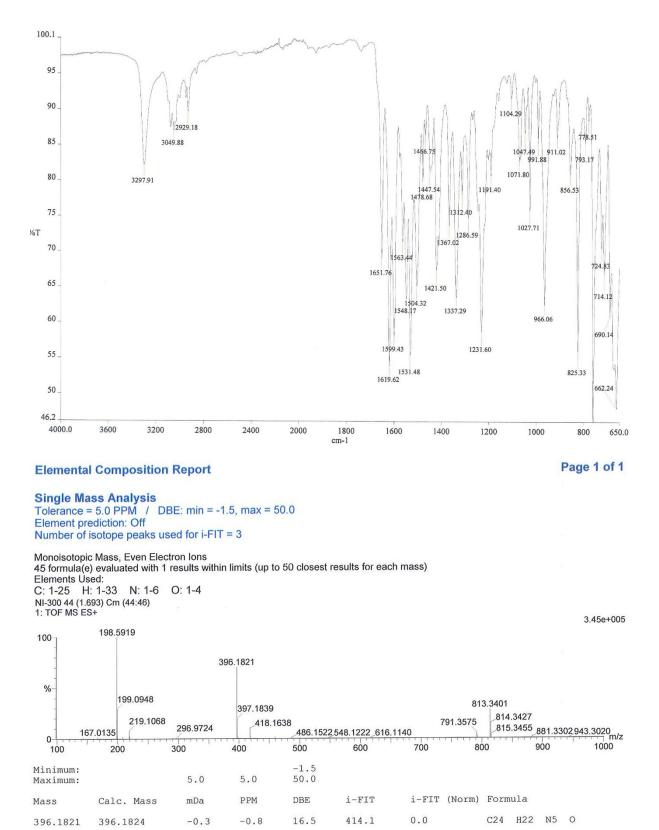
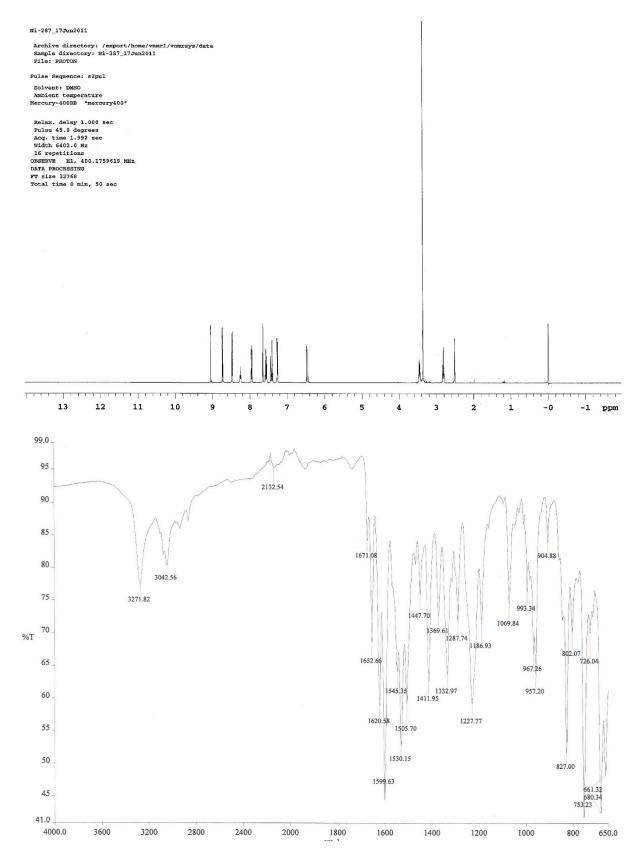


Figure S36. Spectral data of Compound 10i



Single Mass Analysis Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0 Element prediction: Off Number of isotope peaks used for i-FIT = 3 Monoisotopic Mass, Even Electron lons 177 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass) Elements Used: C: 1-25 H: 1-25 N: 1-8 O: 1-6 Ni: 0-1 NI287 42 (1.632) Cm (42:44) 1: TOF MS ES+ 2.12e+005 198.5917 100 396.1837 % 199.0960 397.1873 291.1252 410.1982 391,2864 791.3627813.3441 841.3775 908.2947 198.4532 513.1147_541.1119_605.1085 0 m/z 900 1000 100 200 300 400 500 600 700 800 -1.5 Minimum: 5.0 5.0 50.0 Maximum: i-FIT (Norm) Formula PPM DBE i-FTT mDa Mass Calc. Mass

References

396.1837

396.1824

1.3

3.3

 S.N.I. Baytas, N.; Yılmaz, A.; , Synthesis, cytotoxicity and molecular properties prediction of novel 1,3-diarylpyrazole derivatives, Med. Chem. Res., 22 (2013) 4893-4908
C.C. Chu, Teague, P. C., 4-Pyridylhydantoins, J. Org. Chem., 23 (1958) 1578.

16.5

432.5

0.0

C24 H22 N5 O

Page 1 of 1