Synthesis and Biological Evaluation of Thiazolyl-ethylidene hydrazino-thiazole Derivatives: A Novel Heterocyclic System

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3. Experimental section

Elemental analyses were measured by using a German made Elementarvario LIII CHNS analyzer. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Melting points were measured on an Electrothermal IA 9000 series digital melting point apparatus. NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer operating at 400 MHz (^{1}H-NMR) and run in deuterated dimethylsulphoxide (DMSO-*d6*). Chemical shifts were related to that of the solvent. ^{13}C-NMR was recorded on a BRUKER spectrometer at 100 MHz. IR spectra were recorded in potassium bromide discs on Pye-Unicam SP 3300 and Shimadzu FTIR 8101 PC infrared spectrophotometers.

3.2. Biological evaluation

3.2.1. Antimicrobial activity Assay

All microbial strains were provided from culture collection of the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. The antimicrobial activity was investigated on a dozen of newly synthesized compounds in order to increase the selectivity of these derivatives towards test microorganisms using well diffusion method [44]. Briefly, 100 μL of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 10^8 cells/ml for bacteria or 10^5 cells/mL for fungi. One hundred μL of each sample (at 1 mg/mL) was added to each well (10 mm diameter holes cut in the agar gel). The plates were incubated for 24-48 h at 37 °C (for bacteria and yeast) and for 48 h at 28 °C (for filamentous fungi). After incubation, the microorganism's growth was observed. Ampicillin and gentamycin were used as standard antibacterial drugs while amphotricin B was used as standard antifungal drug. The resulting inhibition zone diameters were measured in millimeters and used as criterion for the antimicrobial activity. If an organism is placed on the agar it will not grow in the area around the well if it is susceptible to the chemical. This area of no growth around the disc is known as a Zone of inhibition. The size of the clear zone is proportional to the inhibitory action of the compound under investigation. Solvent controls (DMSO) were included in every experiment as negative controls. DMSO was used for dissolving the tested compounds and showed no inhibition zones, confirming that it has no influence on growth of the tested microorganisms.

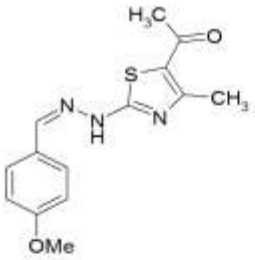
3.2.2. MIC Determination:

The active compounds were further investigated to determine their antimicrobial activity expressed in terms of minimum inhibitory concentration (MIC) using the modified agar well diffusion method that mentioned above. Concentrations between 0.1-1000 μg/mL of each active compound were tested and compared with standard drugs**.** The MIC was then determined as the lowest concentration inhibiting growth of the organism after 24-48 hours [47].

3.2.3. Cytotoxicity assay:

The tested human carcinoma cell lines; MDA-MB-231 cells (human breast carcinoma), HepG-2 cells (human Hepatocellular carcinoma) and HCT-116 cells (human colon carcinoma) were obtained from the American Type Culture Collection (ATCC, Rockville, MD). The cells were grown on RPMI-1640 medium supplemented with 10% inactivated fetal calf serum and 50μg/mL gentamycin (Lonza, Belgium). The cells were maintained at 37ºC in a humidified atmosphere with 5% CO_2 and were subcultured two to three times a week during the period of experiment.

For antitumor assays, the tumor cell lines were suspended in medium at cell density of $5x10^4$ cells/well in Corning® 96-well tissue culture plates and then incubated for 24 hours. The tested compounds were then added into 96-well plates (six replicates) to achieve eight concentrations for each compound. Six vehicle controls with media or 0.5 % DMSO were run for each 96 well plate as a control. After incubating for 24 h, the numbers of viable cells were determined by the MTT assay [48]. Briefly, the media was removed from the 96-well plate and replaced with 100 μl of fresh culture RPMI 1640 medium without phenol red then 10 μL of the 12 mM MTT stock solution {5 mg of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide purchased from Sigma-Aldrich (St. Louis, MO) in 1 mL of Phosphate buffered saline} to each well including the untreated controls. The 96 well plates were then incubated at 37°C and 5% CO_2 for 4 hours. An 85 μl aliquot of the media was removed from the wells, and 50 μl of DMSO was added to each well and mixed thoroughly with the pipette and incubated at 37 °C for 10 min. Then, the optical density was measured at 590 nm with the microplate reader (SunRise, TECAN, Inc, USA) to determine the number of viable cells and the percentage of viability was calculated as [(ODt/ODc)]x100% where ODt is the mean optical density of wells treated with the tested sample and ODc is the mean optical density of untreated cells. The relation between surviving cells and drug concentration is plotted to get the survival curve of each tumor cell line after treatment with the specified compound. The 50% inhibitory concentration (IC_{50}), the concentration required to cause toxic effects in 50% of intact cells, was estimated from graphic plots of the dose response curve for each conc. using GraphPad Prism software (San Diego, CA. USA)[49].



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DI Analysis
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Modified	: 01/01/2007 08:11:28 ص

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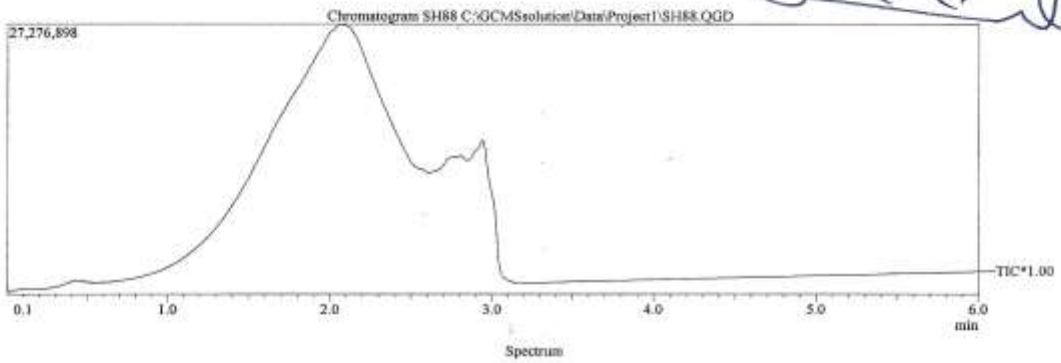

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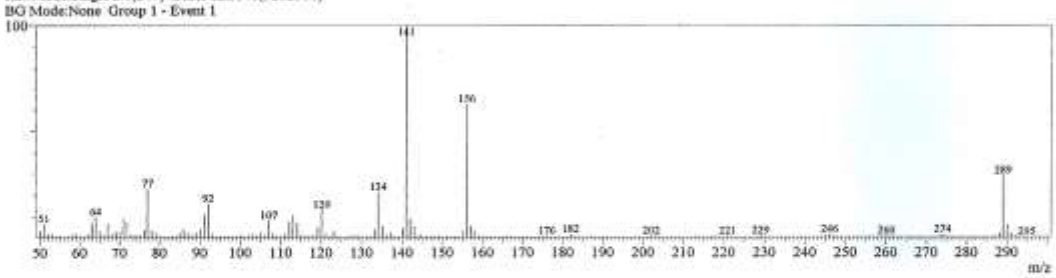

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1	50.05	165713	3.14	4	53.05	95380	1.81	7	56.05	13389	0.25
2	51.05	326223	6.18	5	54.05	28536	0.54	8	57.05	35505	0.67
3	52.05	76720	1.45	6	55.05	38755	0.73	9	58.00	73591	1.39

Figure S1. Mass Spectra of compound 6

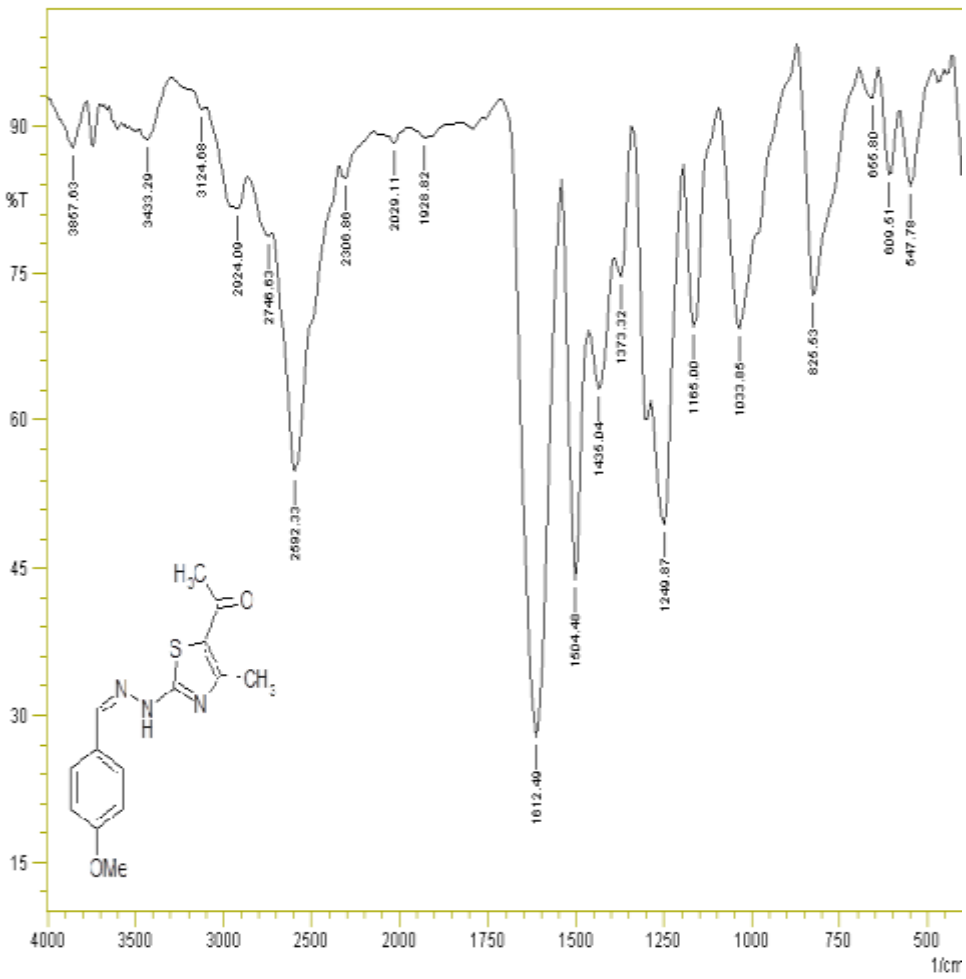


Figure S2. IR Spectra of compound 6

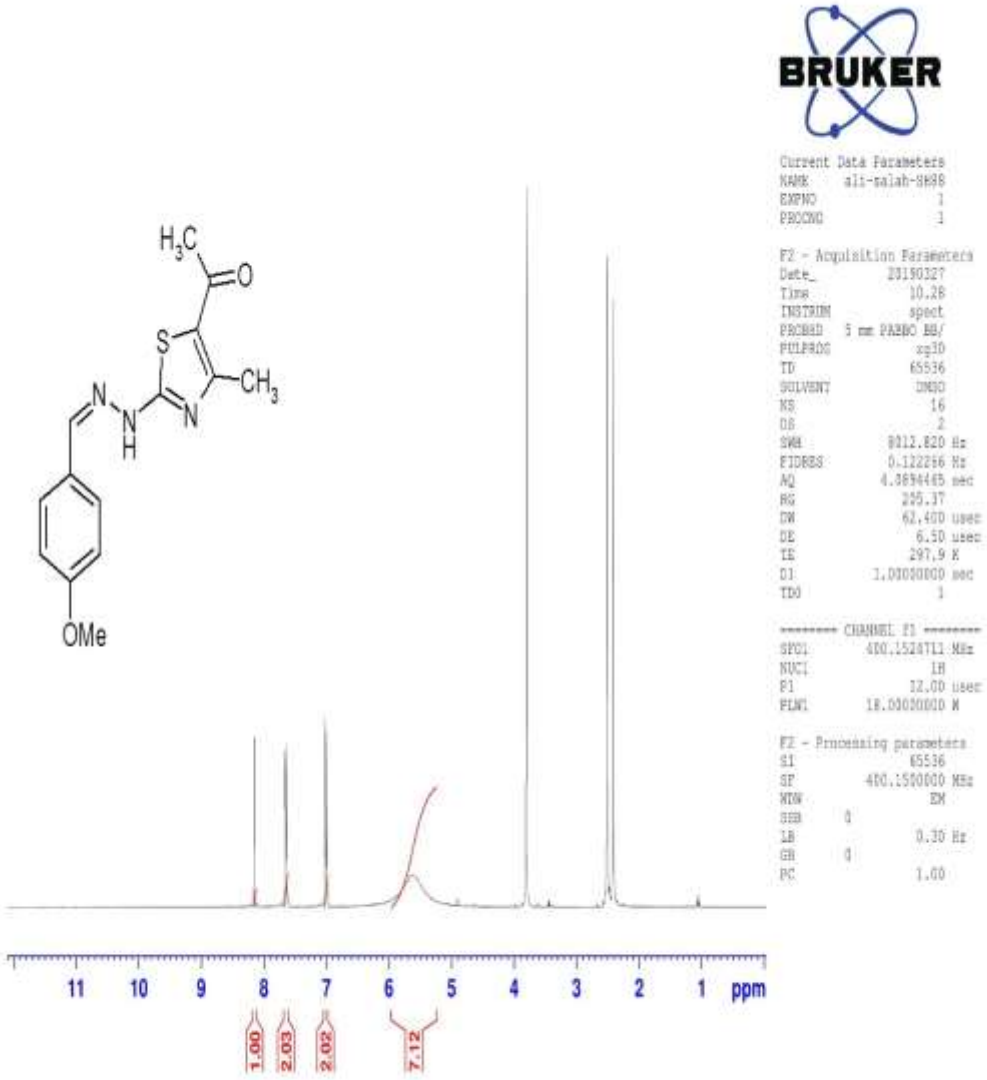


Figure S3. [1]HNMR Spectra of compound 6

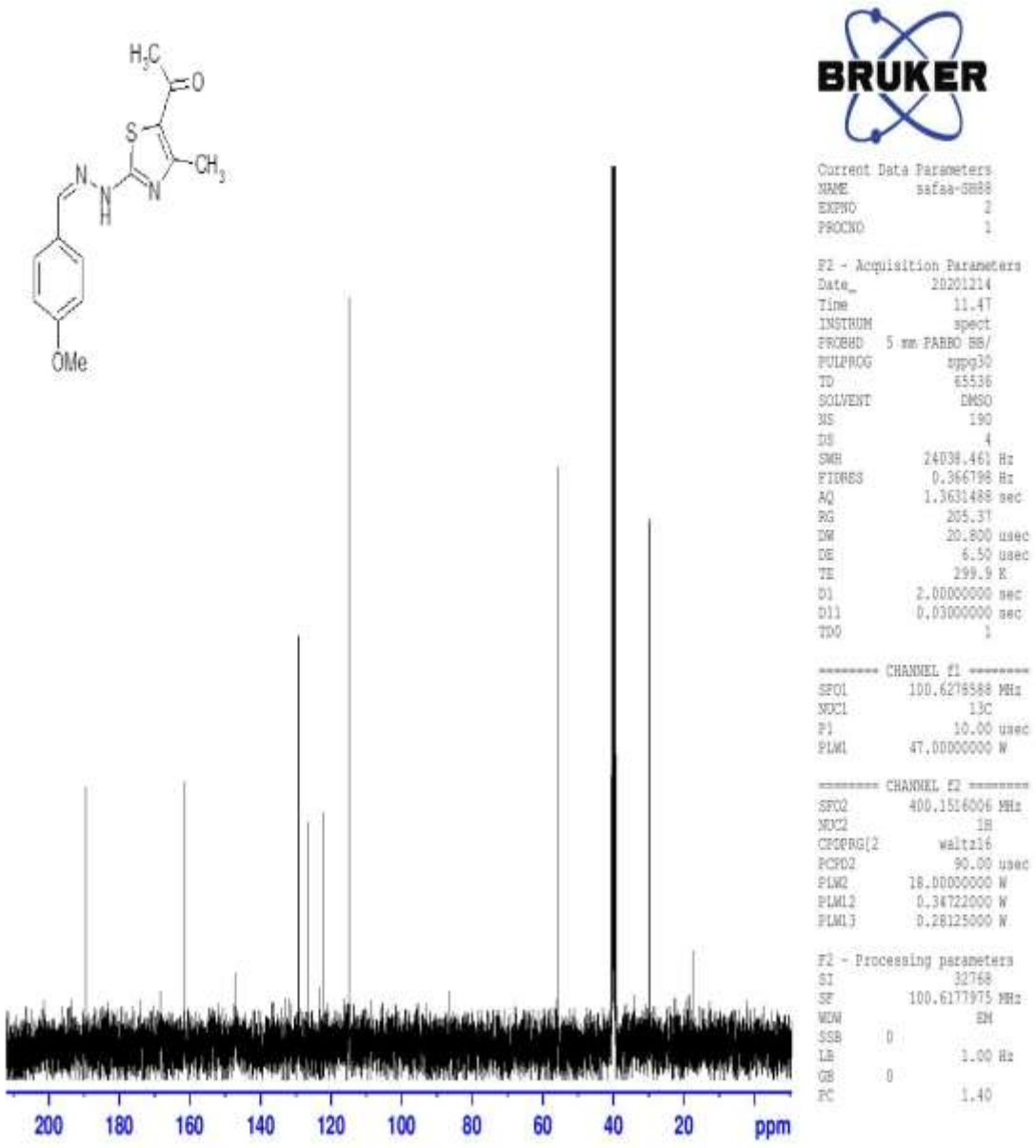


Figure S4. ^{13}C Spectra of compound 6

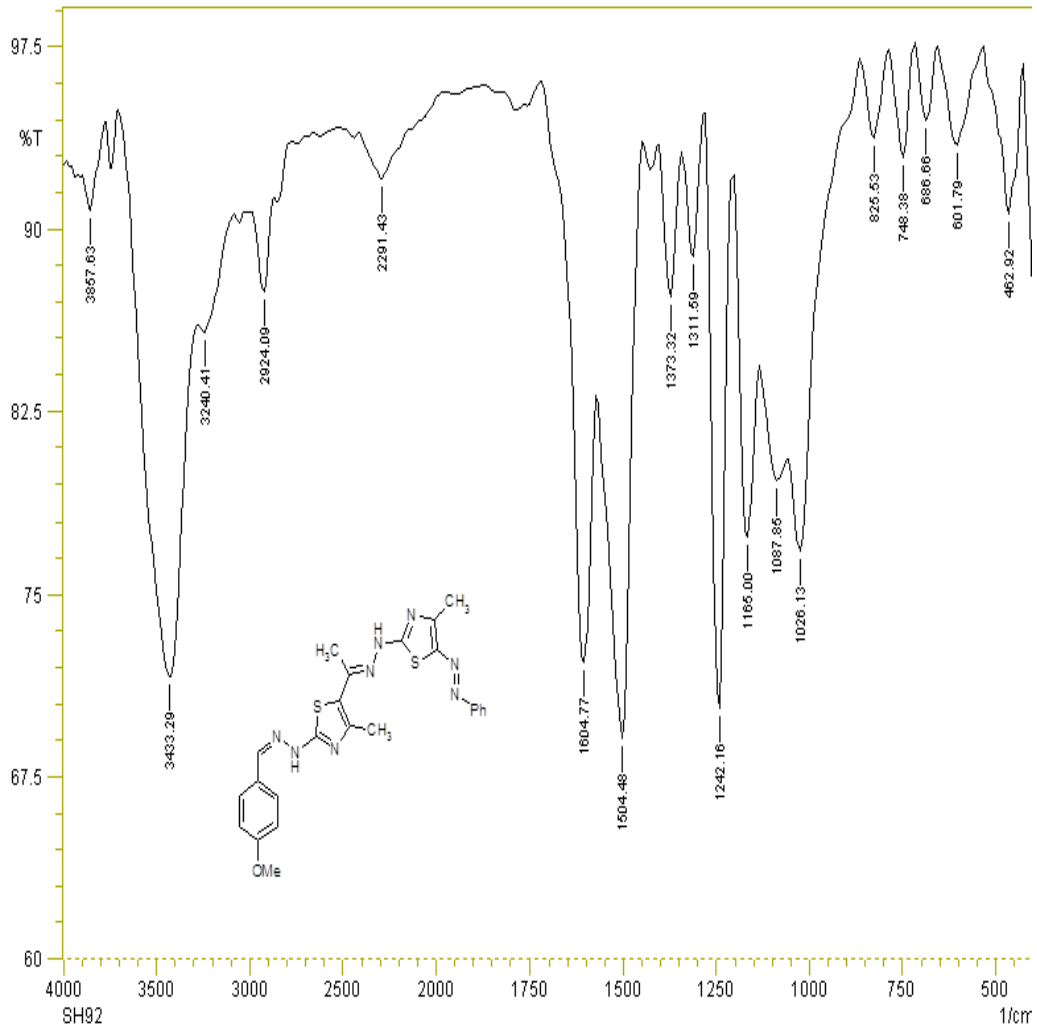


Figure S5. IR Spectra of compound 10a

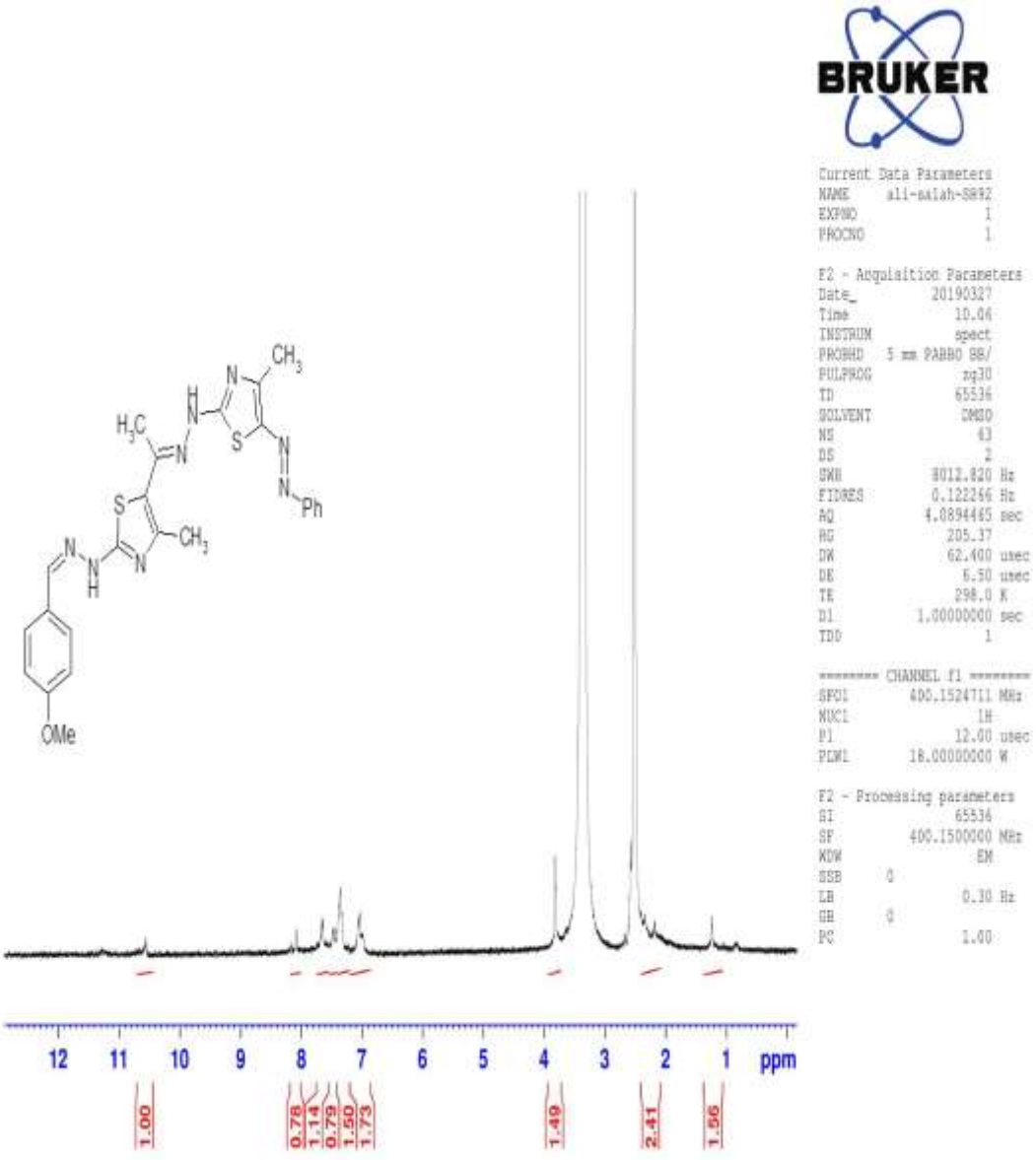


Figure S6. ^{1}HNMR Spectra of compound 10a

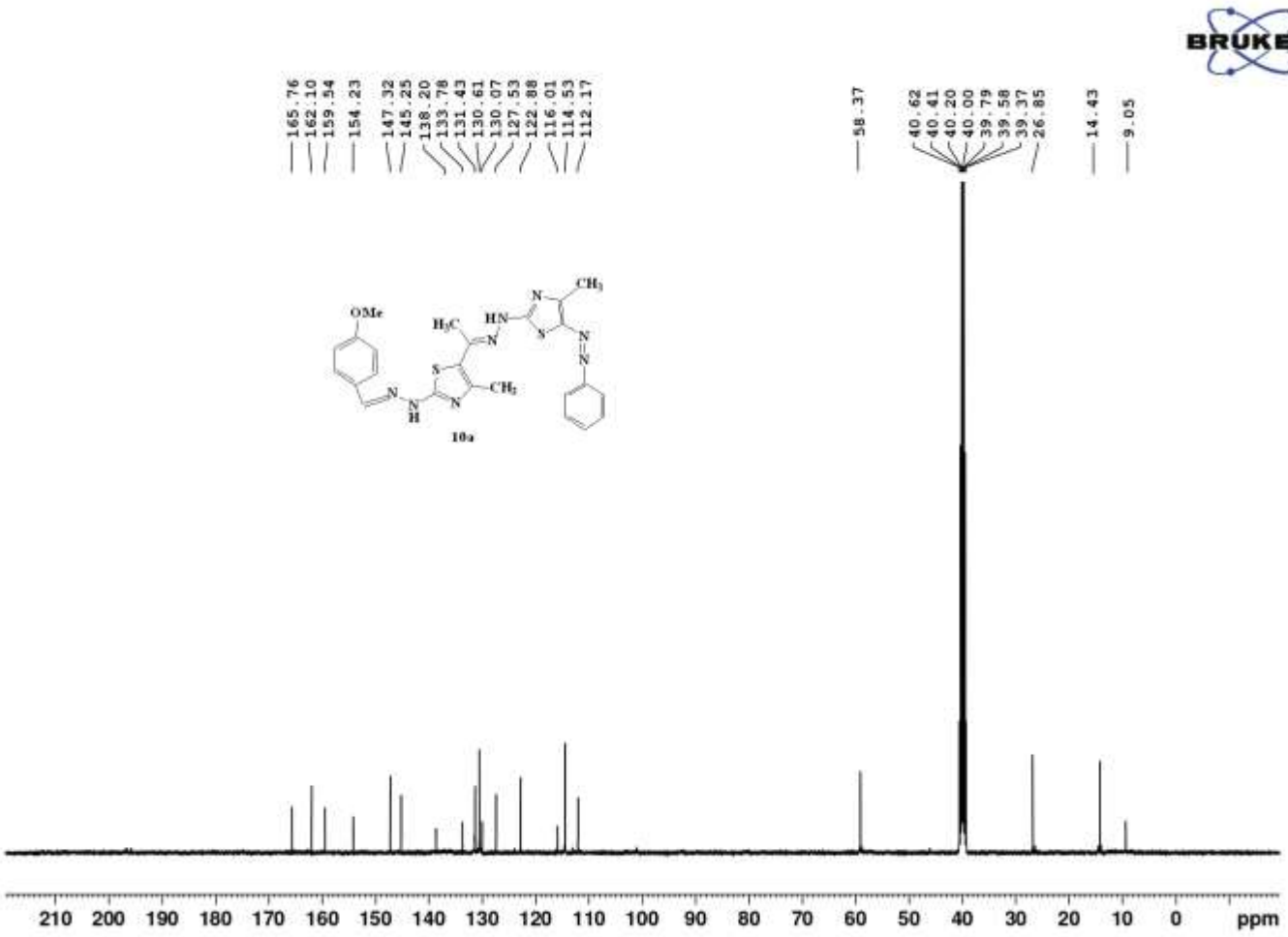
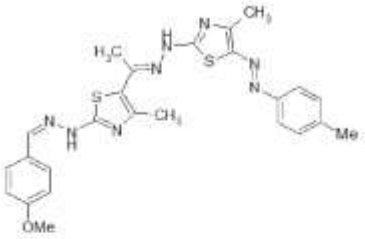


Figure S7. ^{13}CNMR Spectra of compound 10a



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Modified	: 01/01/2007 08:28:49 ص

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Event Time	:0.50sec
Scan Speed	:1250
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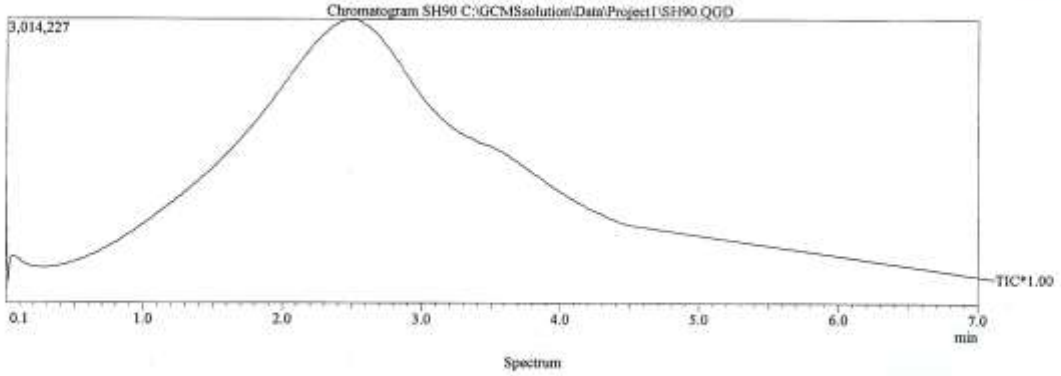

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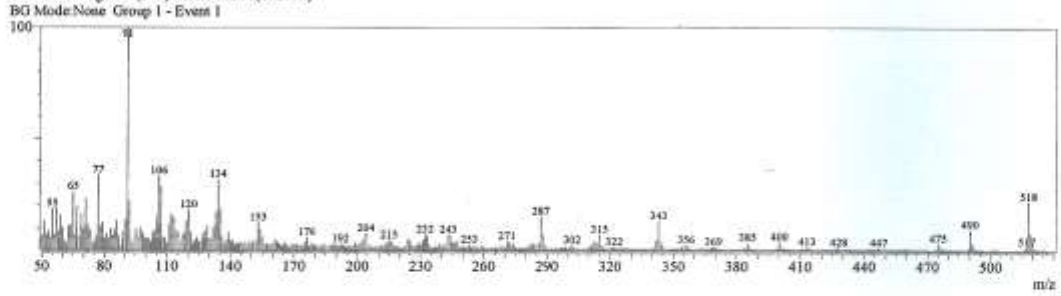

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2	51.05	24047	13.14	5	54.05	10326	5.64	8	57.05	34920	19.08
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Figure S8. Mass Spectra of compound 10b

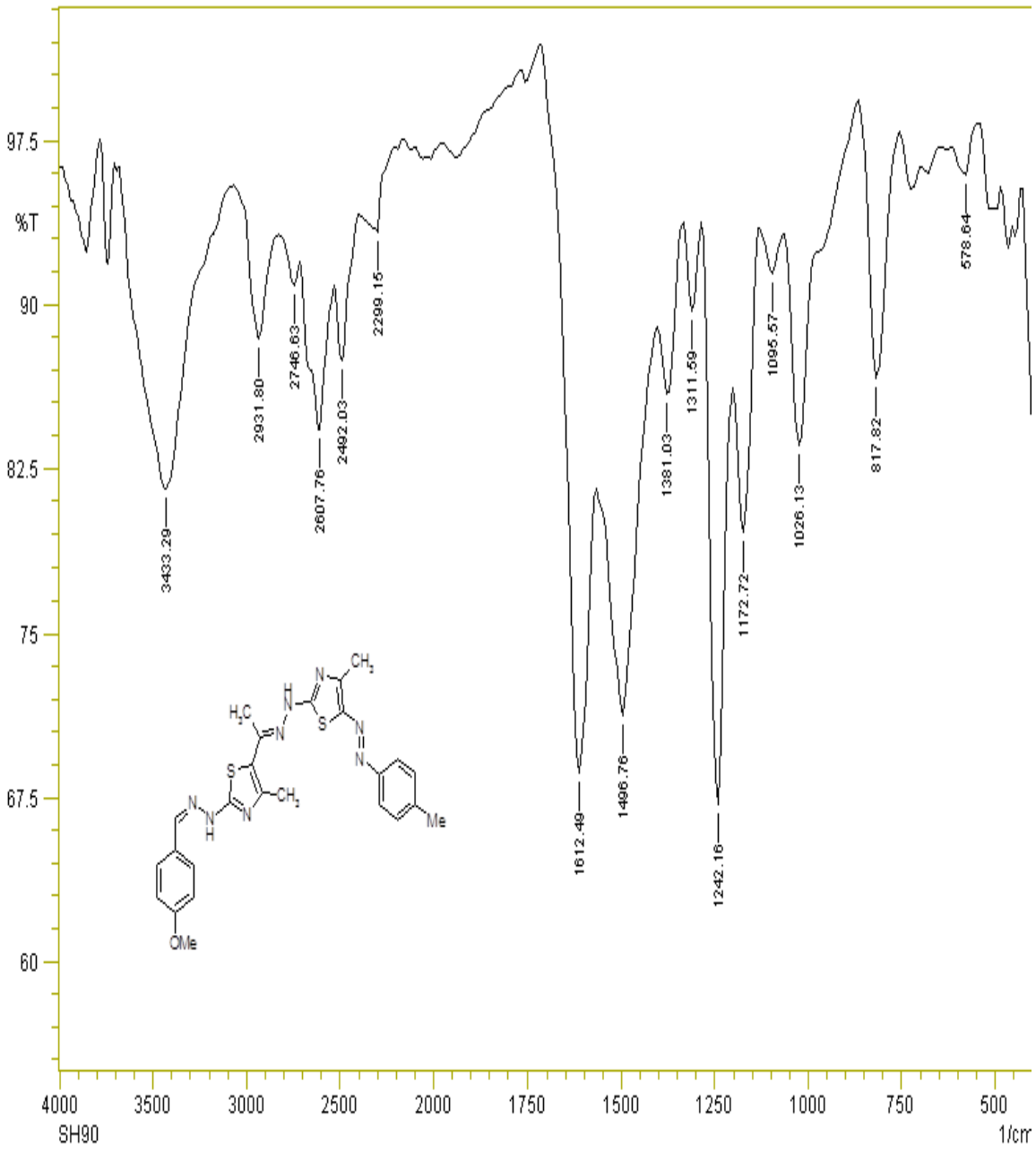


Figure S9. IR Spectra of compound 10b

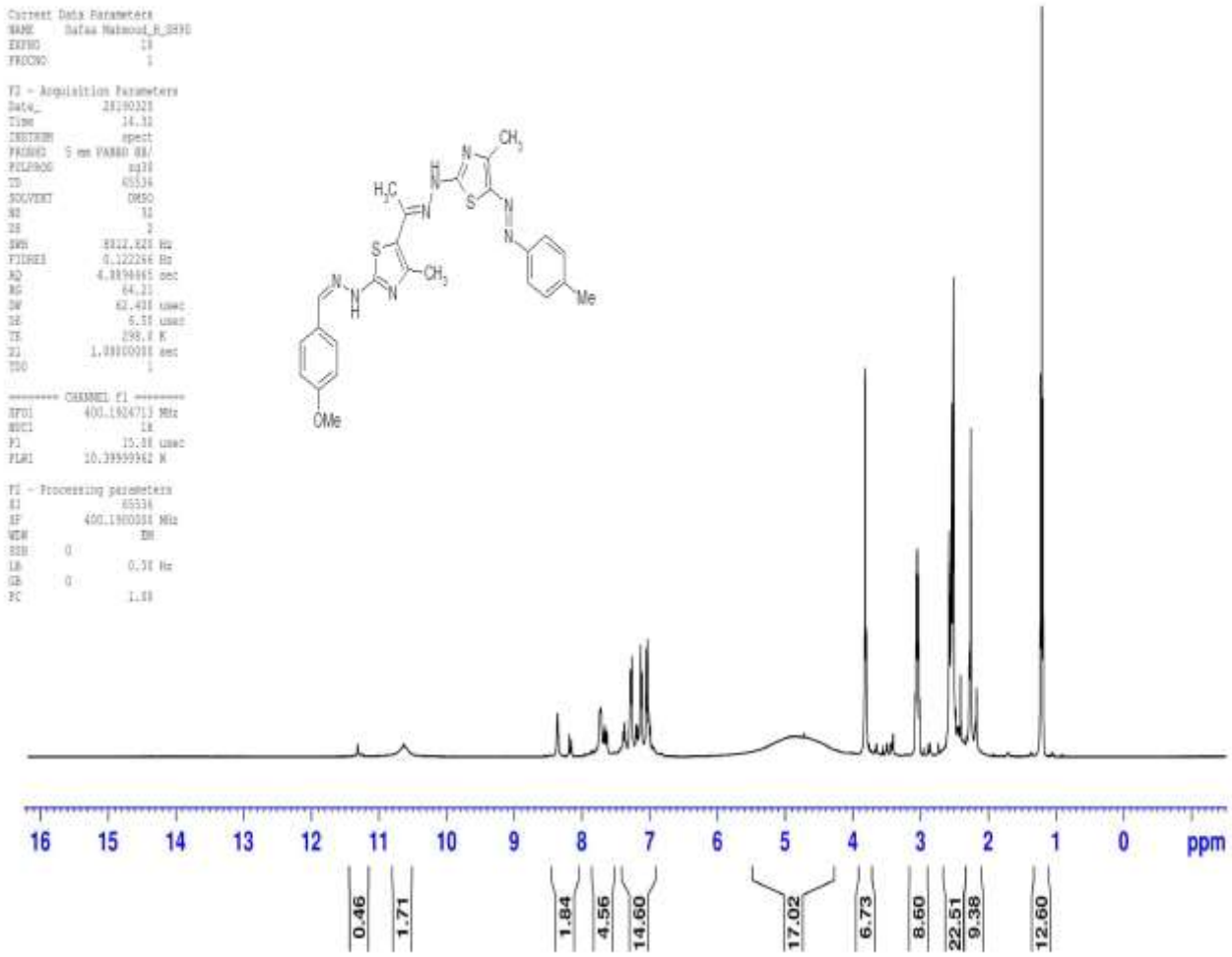
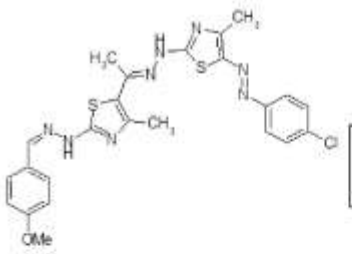


Figure S10. ^{1}HNMR Spectra of compound 10b



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Analyzed	: 01/01/2007 08:32:36 ص
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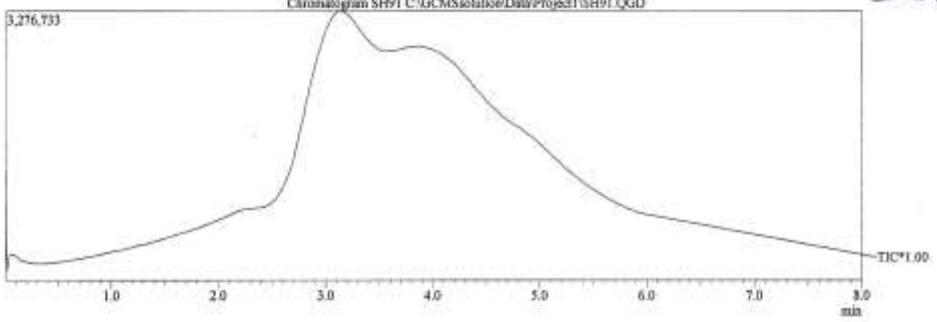
Chromatogram SH91 C:\GCMSsolution\Data\Project1\SH91.QGD



Spectrum

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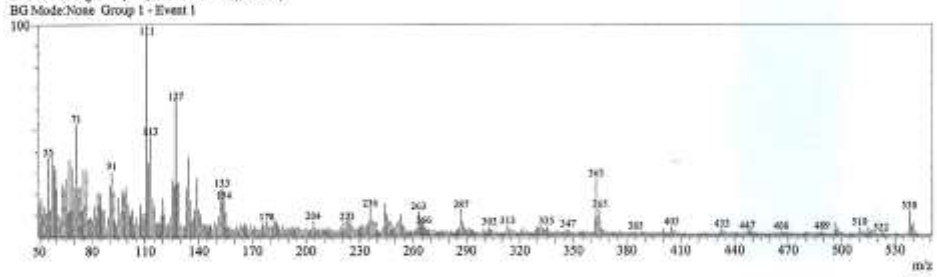

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2	51.05	18262	17.98	5	54.05	11145	10.97	8	57.05	39906	39.28
3	52.05	10457	10.29	6	55.05	37597	37.01	9	58.05	33877	33.35

Figure S11. Mass Spectra of compound 10c

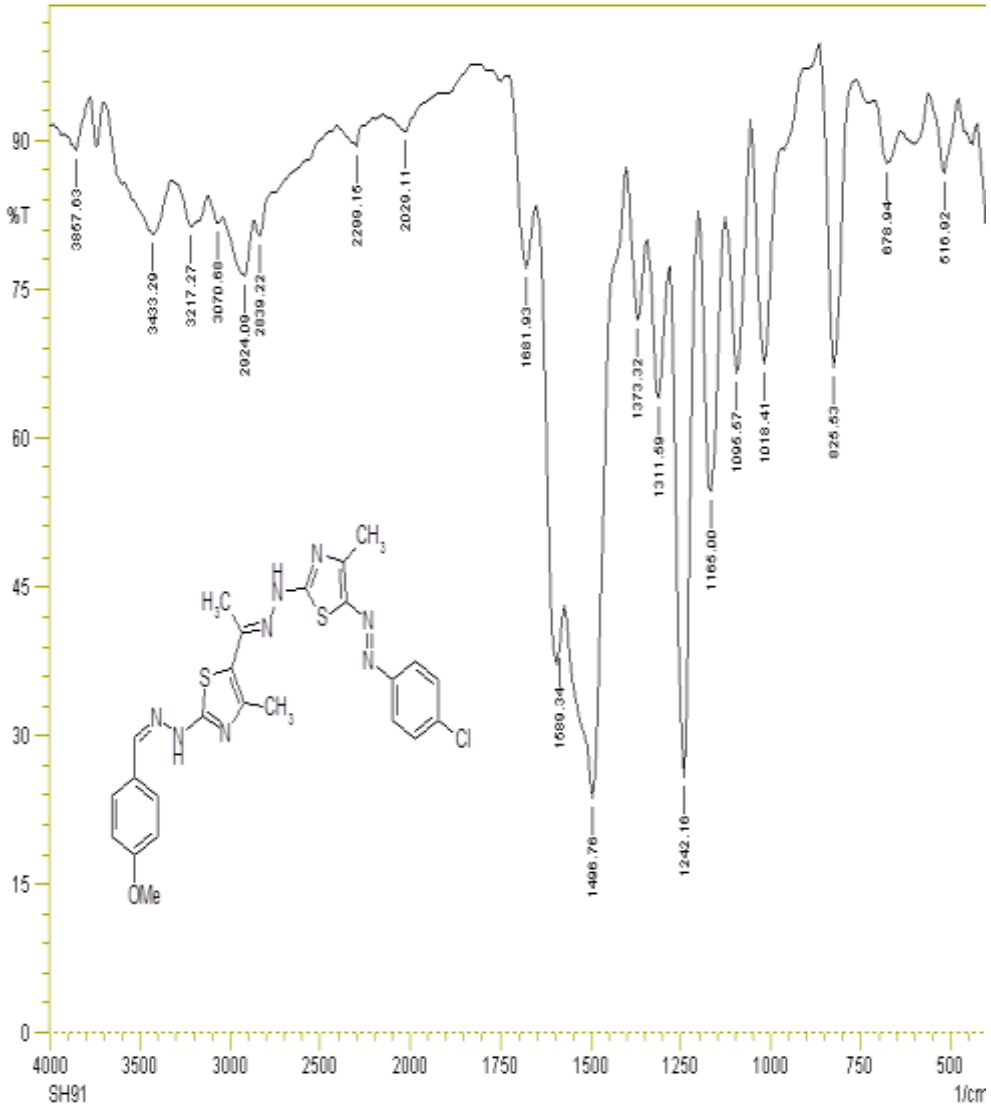


Figure S12. IR Spectra of compound 10c

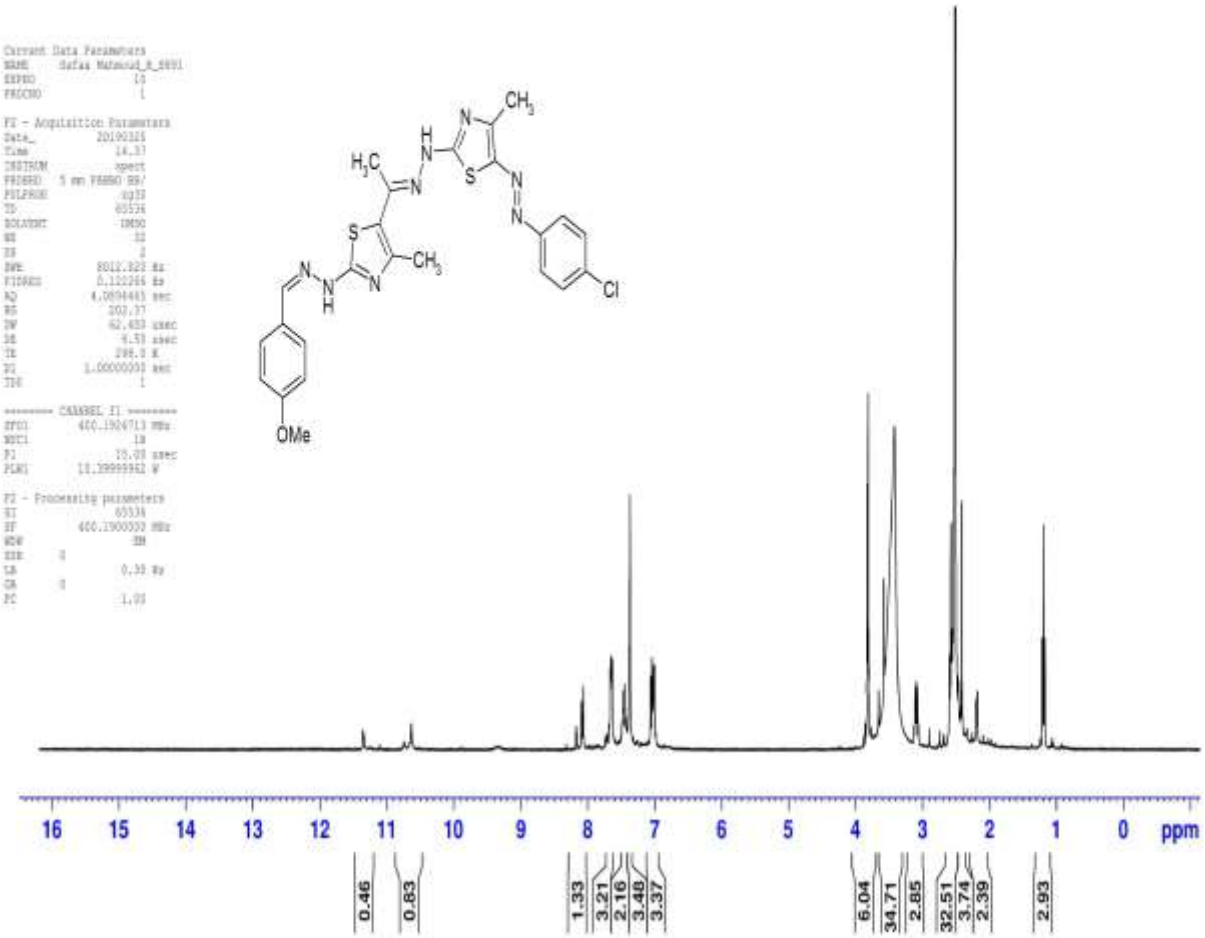


Figure S13. ^{1}HNMR Spectra of compound 10c

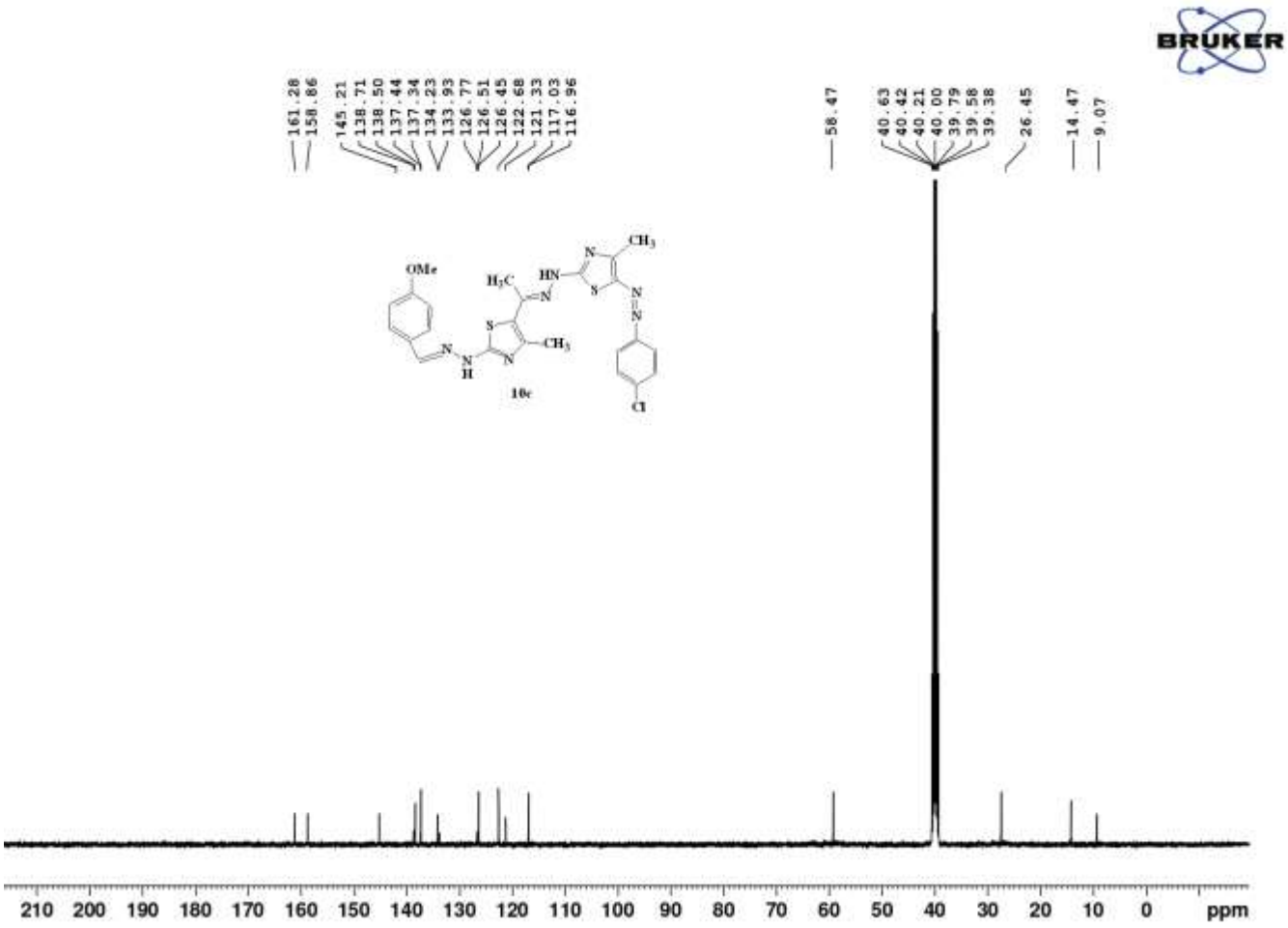
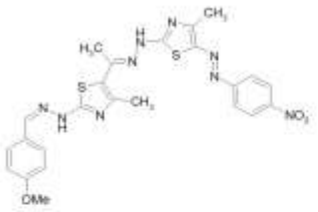


Figure S14. ^{13}CNMR Spectra of compound 10c



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Sample Information

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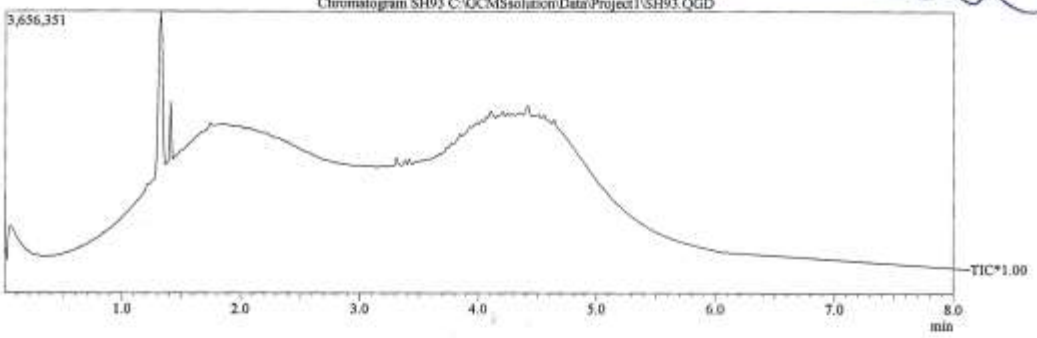

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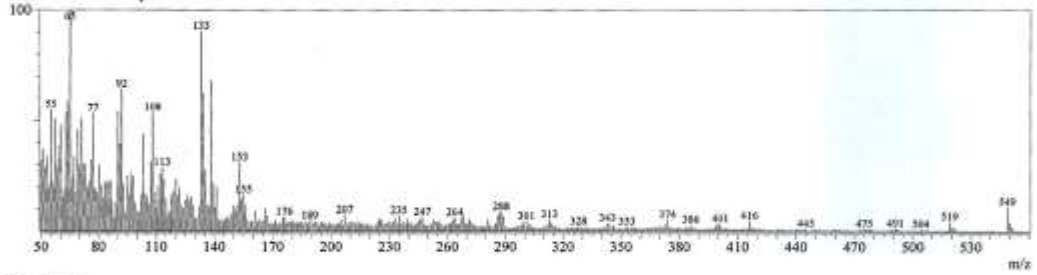

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2	51.00	25494	36.57	5	54.05	14440	20.71	8	57.05	35226	50.53
3	52.00	20146	28.90	6	55.05	38075	54.61	9	58.05	19994	28.68

Figure S15. Mass Spectra of compound 10d

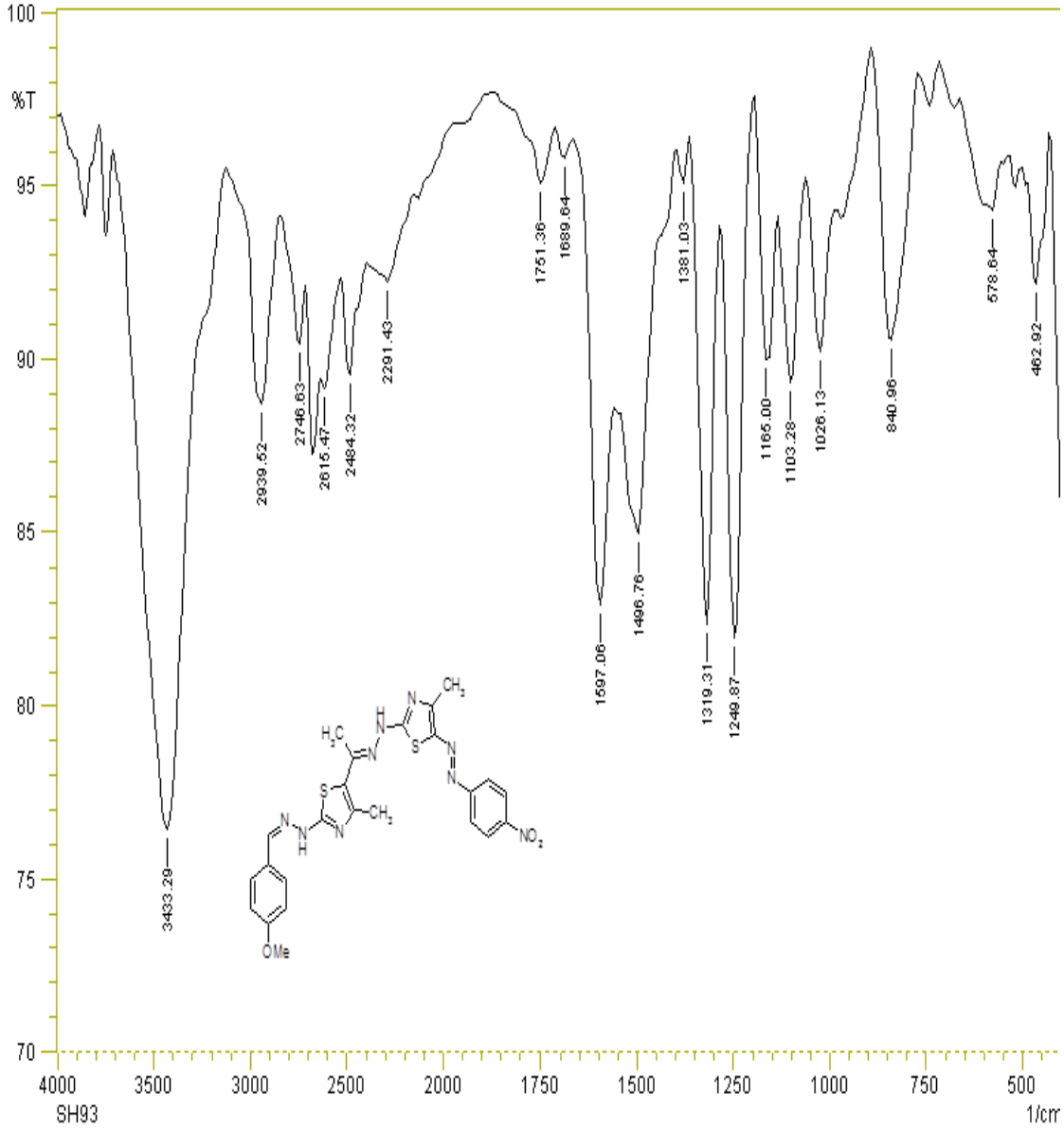


Figure S16. IR Spectra of compound 10d

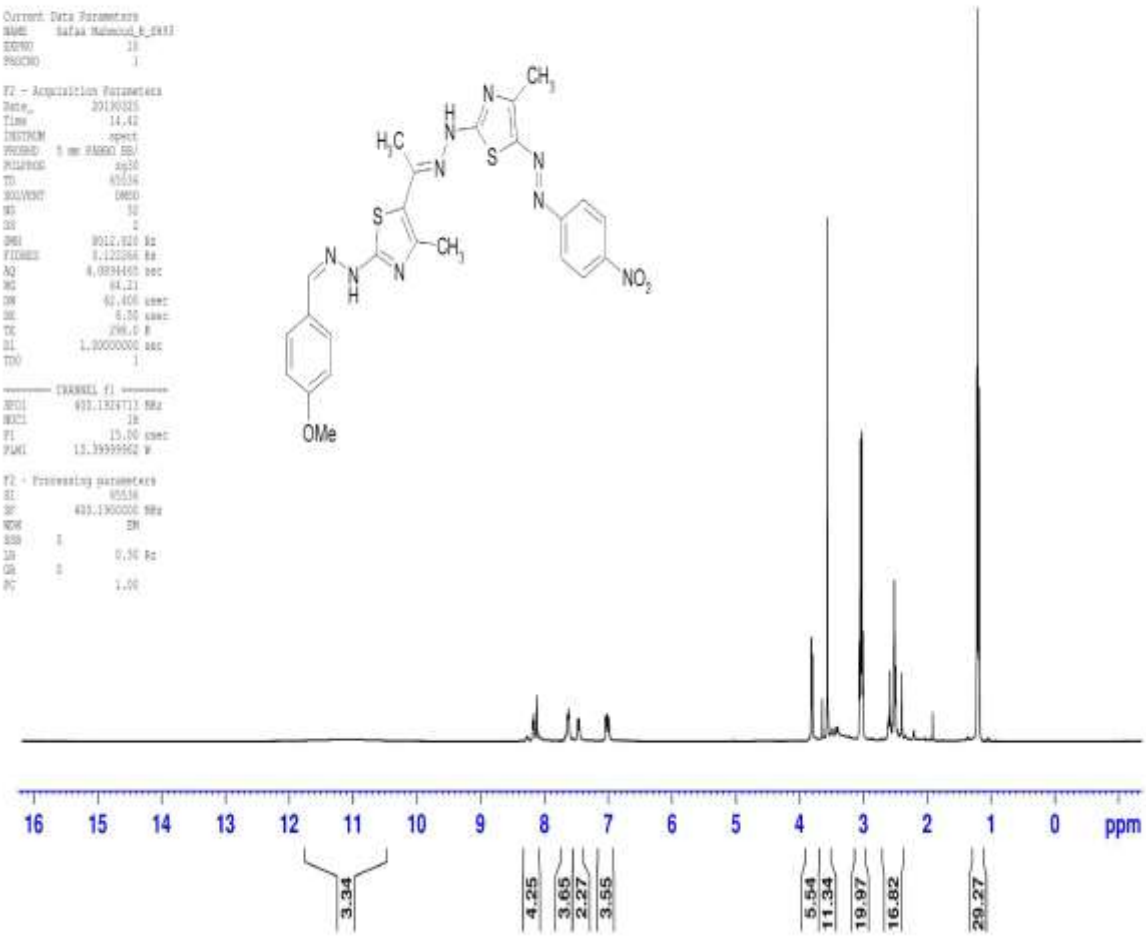
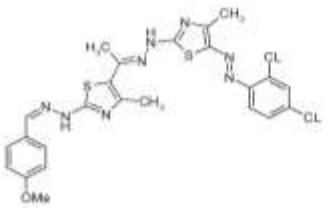


Figure S17. NMR Spectra of compound 10d



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Sample Information

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Analyzed	: 01/01/2007 09:33:45 ص
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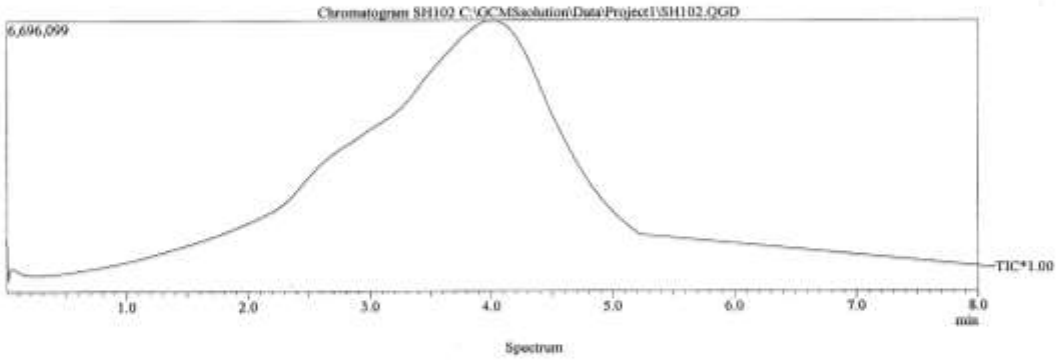
Org Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Report File	:
Tuning File	: C:\GCMSsolution\System\Tune1_default.qgt
$EndIf$Modified by	: Dr. Mai Younis
Modified	: 01/01/2007 09:39:02 ص

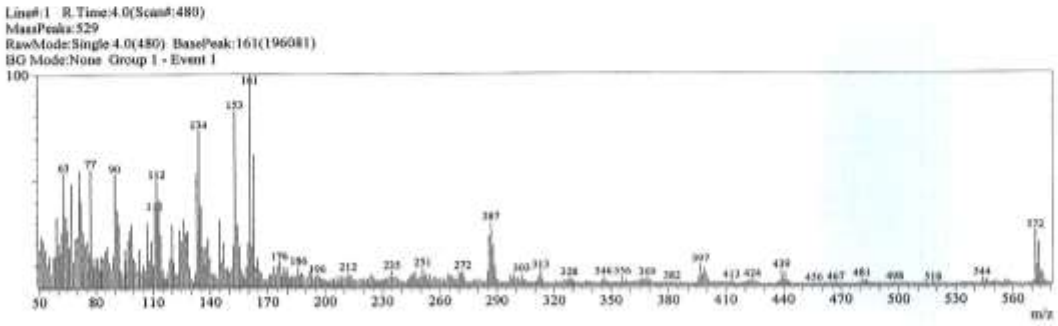
Method

------ Analytical Line 1 ------	
IonSourceTemp	:250.00 °C
[MS Table]	
--Group 1 - Event 1--	
Start Time	:0.00min
End Time	:10.00min
ACQ Mode	:Scan
Event Time	:0.50sec
Scan Speed	:1250
Start m/z	:50.00
End m/z	:600.00
Electron Voltage	: 70 eV
Ionization Mode	: EI

C:\GCMSsolution\Data\Project1\SH102.QGD



Spectrum



Mass Table
Line#:1 R.Time:4.0(Scan#:480)
MassPeaks:529
RawMode:Single 4.0(480) BasePeak:161(196081)
BG Mode:None Group 1 - Event 1

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
1	50.00	34062	17.37	4	53.05	34199	17.44	7	56.05	10551	5.38
2	51.05	45501	23.21	5	54.05	20894	10.66	8	57.05	26861	13.70
3	52.05	41835	21.34	6	55.05	28031	14.30	9	58.05	27539	14.04

Figure S18. Mass Spectra of compound 10e

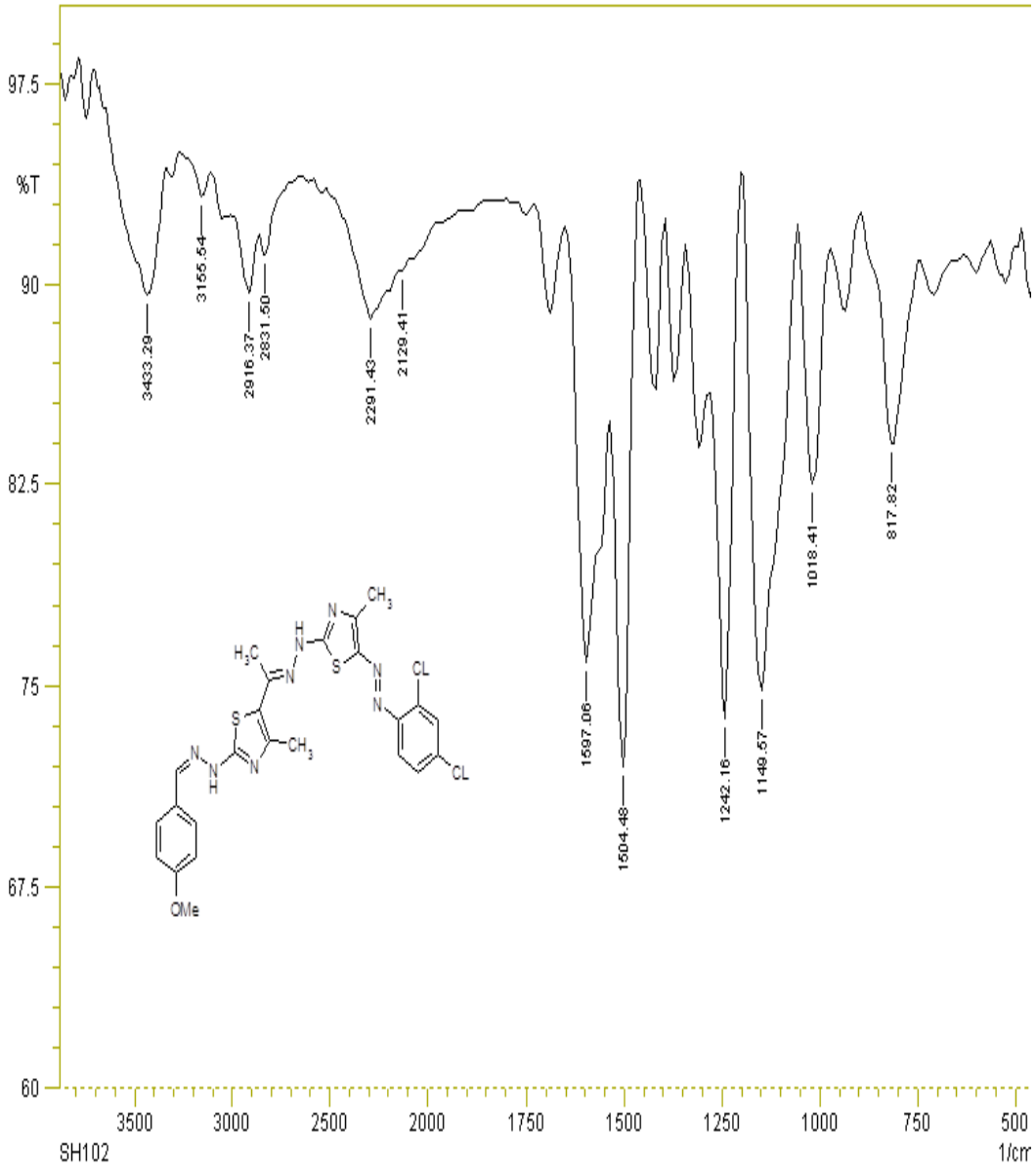


Figure S19. IR Spectra of compound 10e

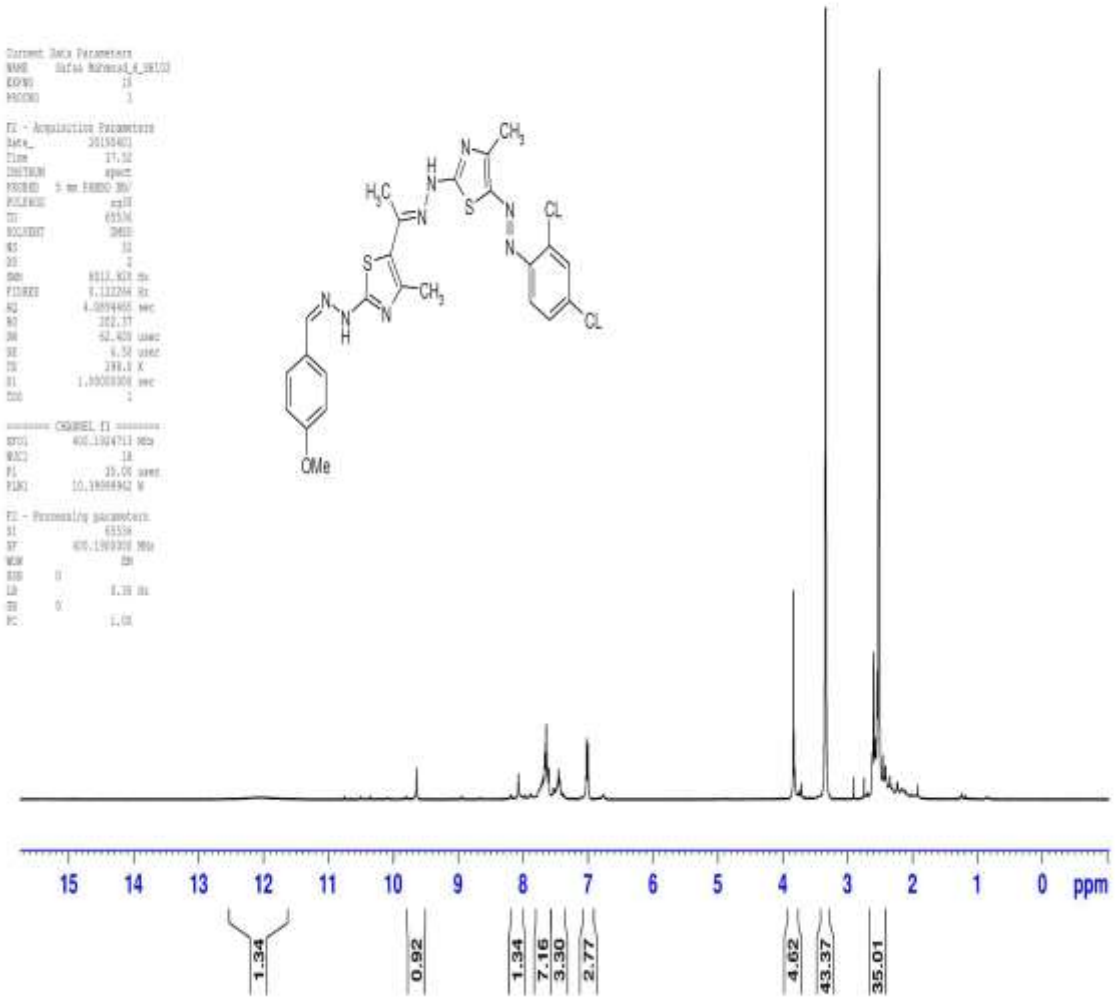


Figure S20. ^{1}HNMR Spectra of compound 10e

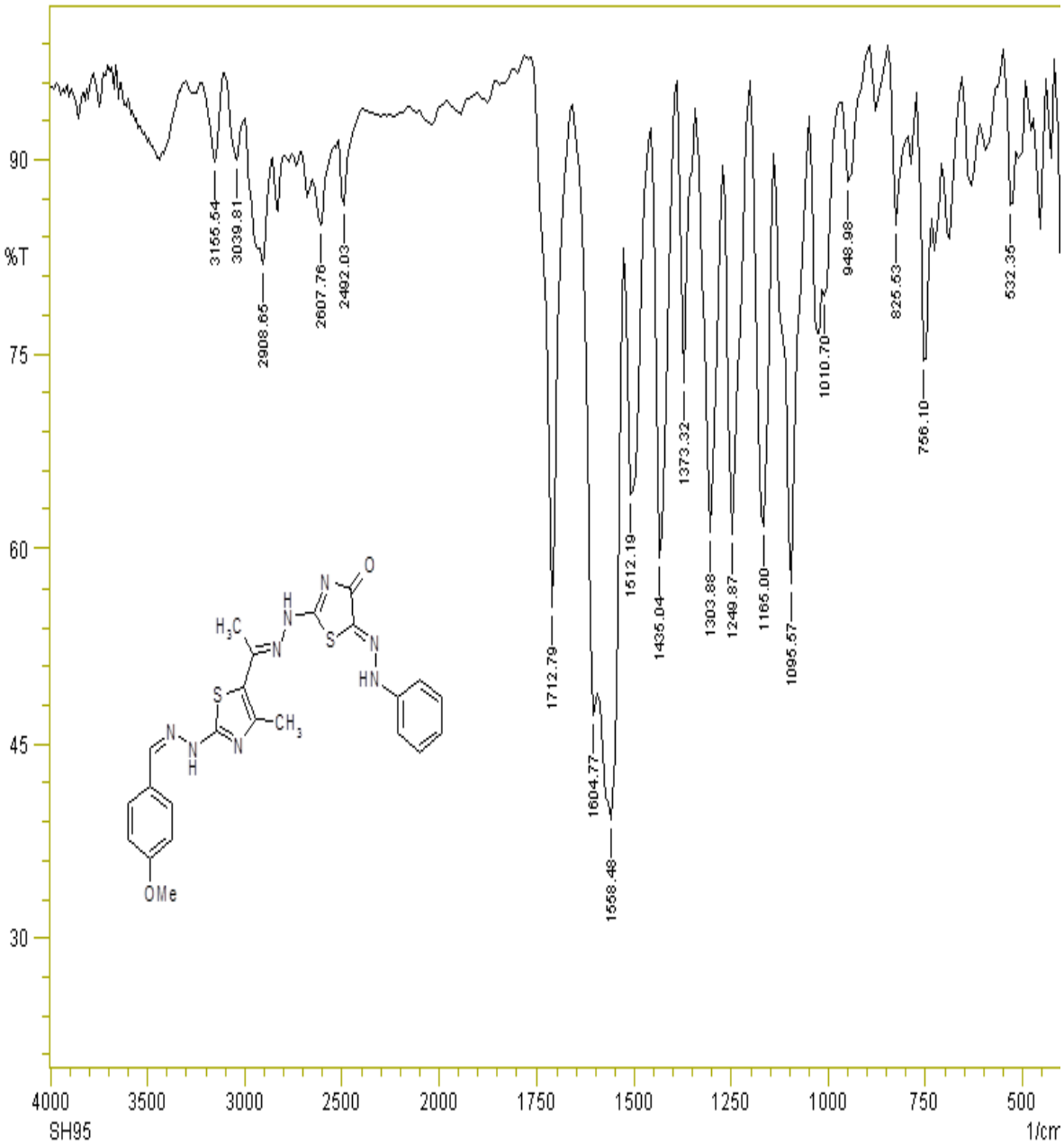


Figure S21. IR Spectra of compound 13a

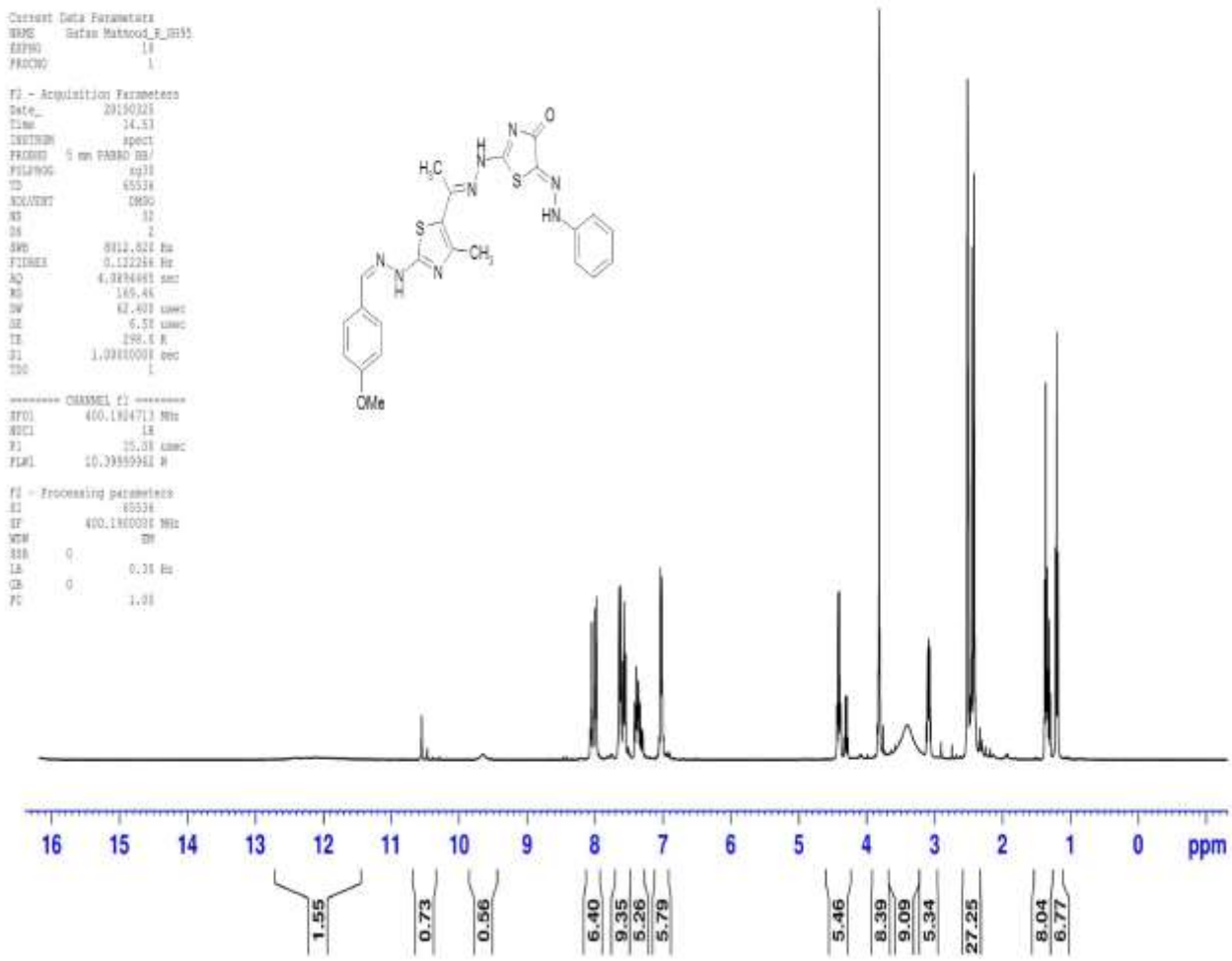


Figure S22. [1]HNMR Spectra of compound 13a

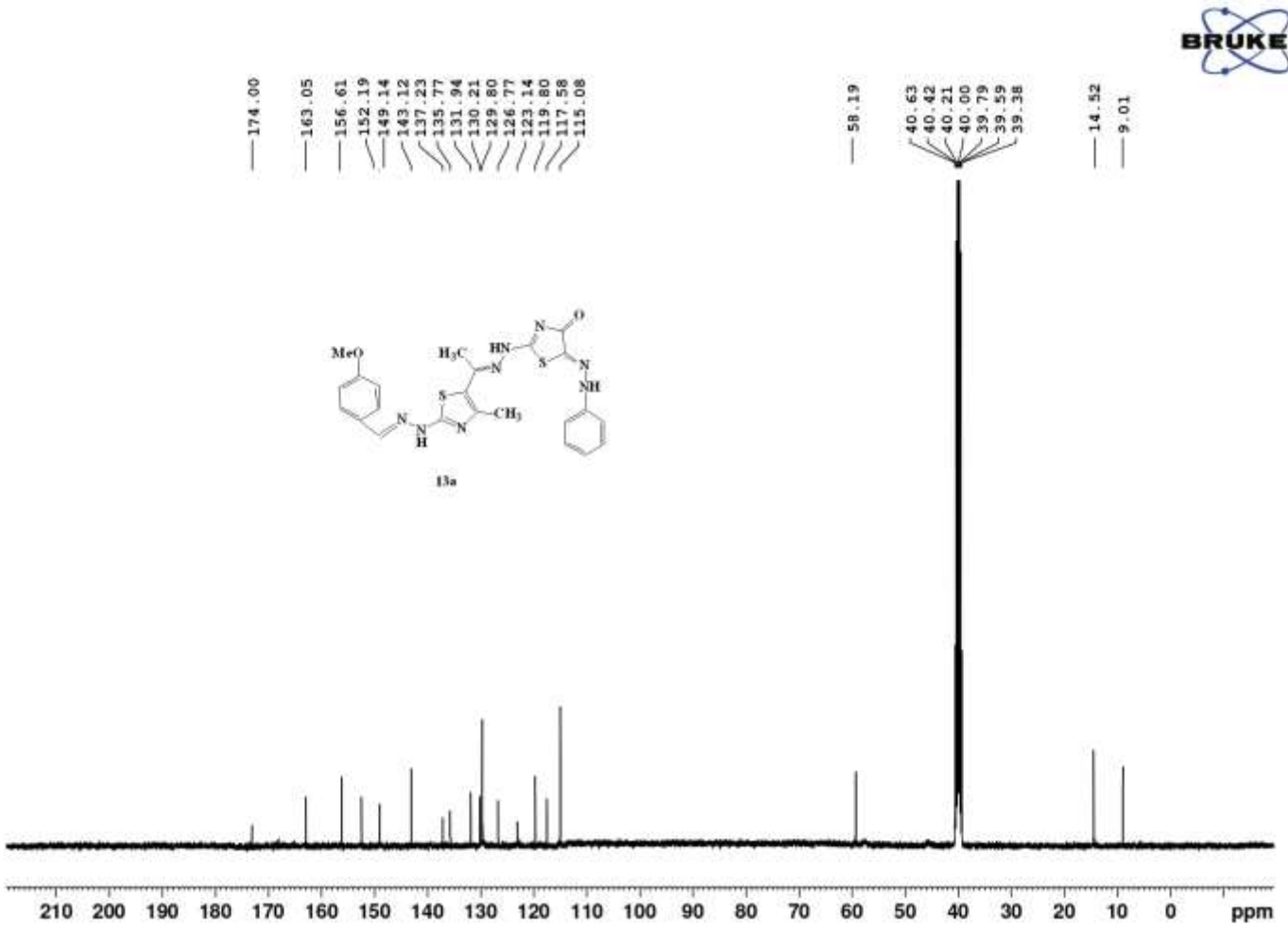


Figure S23. ^{13}CNMR Spectra of compound 13a

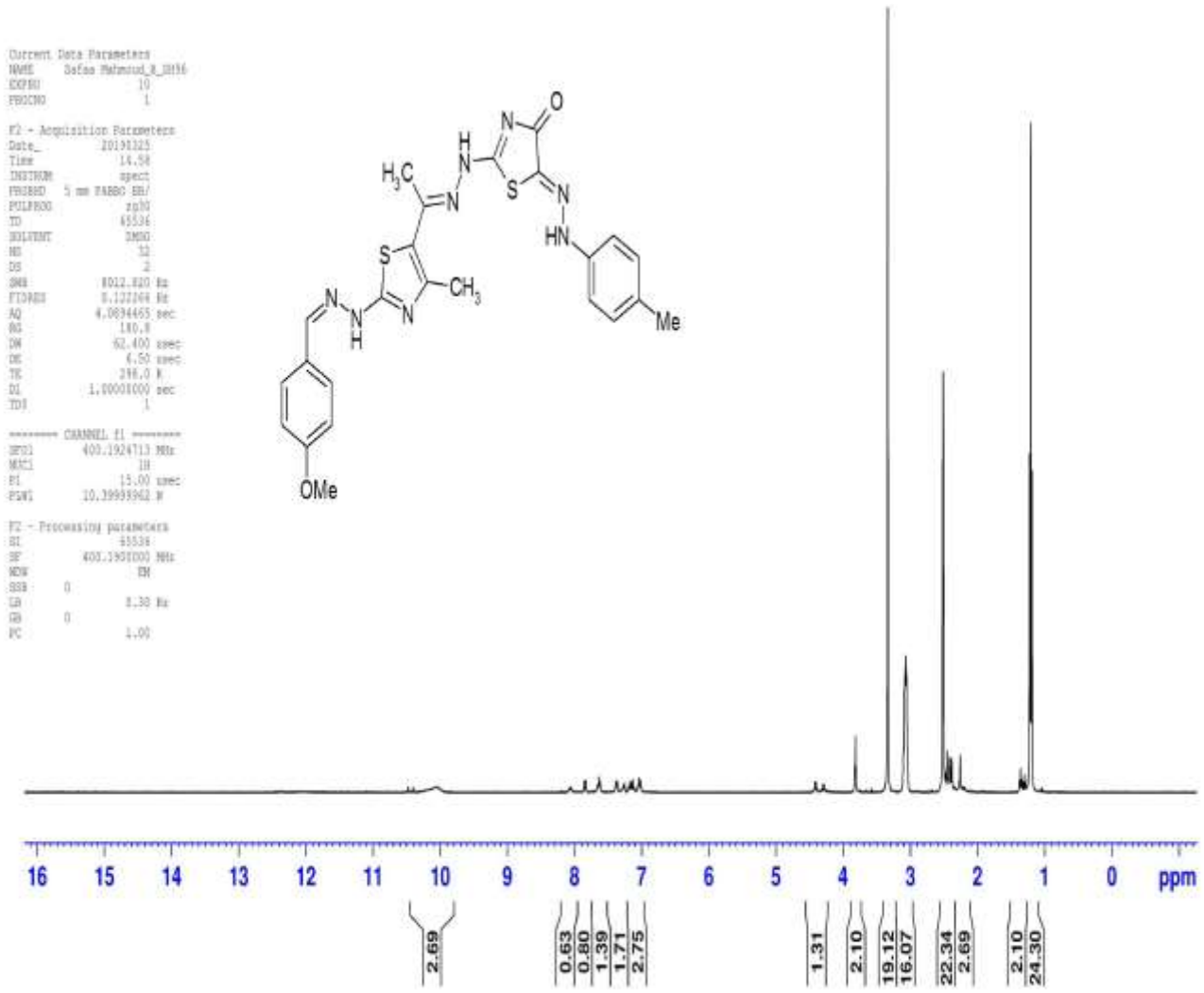
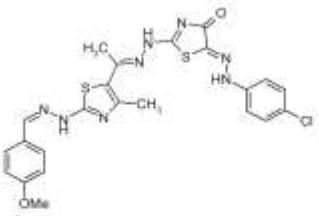


Figure S24. ^{1}HNMR Spectra of compound 13b



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DI Analysis
Shimadzu Qp-2010 Plus

Sample Information

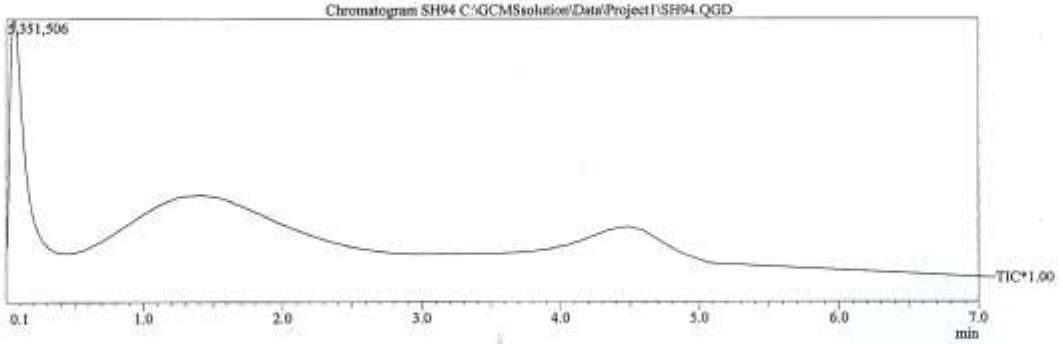
Analyzed by	: Dr. Mai Younis
Analyzed	: 01/01/2007 08:50:57 ص
Sample Name	: SH94
Sample ID	:
Customer Name	: Dr.Sobhy Goma - Science - Cairo
Data File	: C:\GCMSsolution\Data\Project1\SH94.QGD
Org Data File	: C:\GCMSsolution\Data\Project1\SH94.QGD
Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Org Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Report File	:
Tuning File	: C:\GCMSsolution\System\Tune1_default.qgt
$EndIf$Modified by	: Dr. Mai Younis
Modified	: 01/01/2007 08:56:05 ص

Method

====== Analytical Line 1 ======	
IonSourceTemp	:250.00 °C
[MS Table]	
--Group 1 - Event 1--	
Start Time	:0.00min
End Time	:10.00min
ACQ Mode	:Scan
Event Time	:0.50sec
Scan Speed	:1250
Start m/z	:50.00
End m/z	:600.00
Electron Voltage	: 70 eV
Ionization Mode	: EI

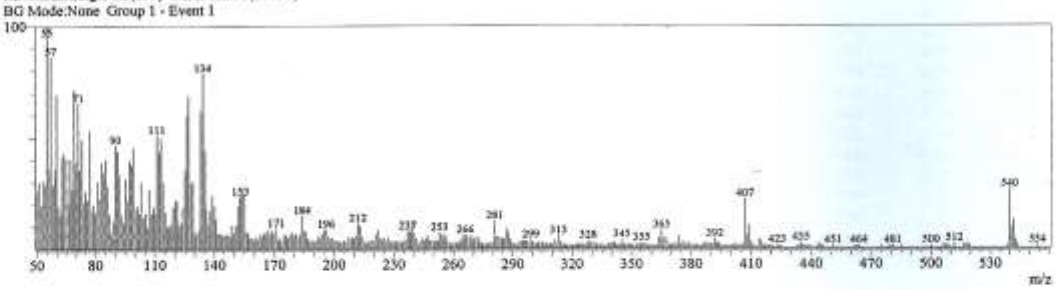
C:\GCMSsolution\Data\Project1\SH94.QGD

Chromatogram SH94 C:\GCMSsolution\Data\Project1\SH94.QGD



Spectrum

Line#:1 R.Time:4.5(Scan#:539)
MassPeaks:412
RawMode:Single 4.5(539) BasePeak:55(35636)
BG Mode:None Group 1 - Event 1



Mass Table
Line#:1 R.Time:4.5(Scan#:539)
MassPeaks:412
RawMode:Single 4.5(539) BasePeak:55(35636)
BG Mode:None Group 1 - Event 1

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
1	50.00	9441	26.49	4	53.05	10939	30.70	7	56.05	12758	35.80
2	51.05	10628	29.82	5	54.05	10270	28.82	8	57.05	30668	86.06
3	52.05	6961	19.53	6	55.05	35636	100.00	9	58.05	10337	29.01

Figure S25 Mass Spectra of compound 13c

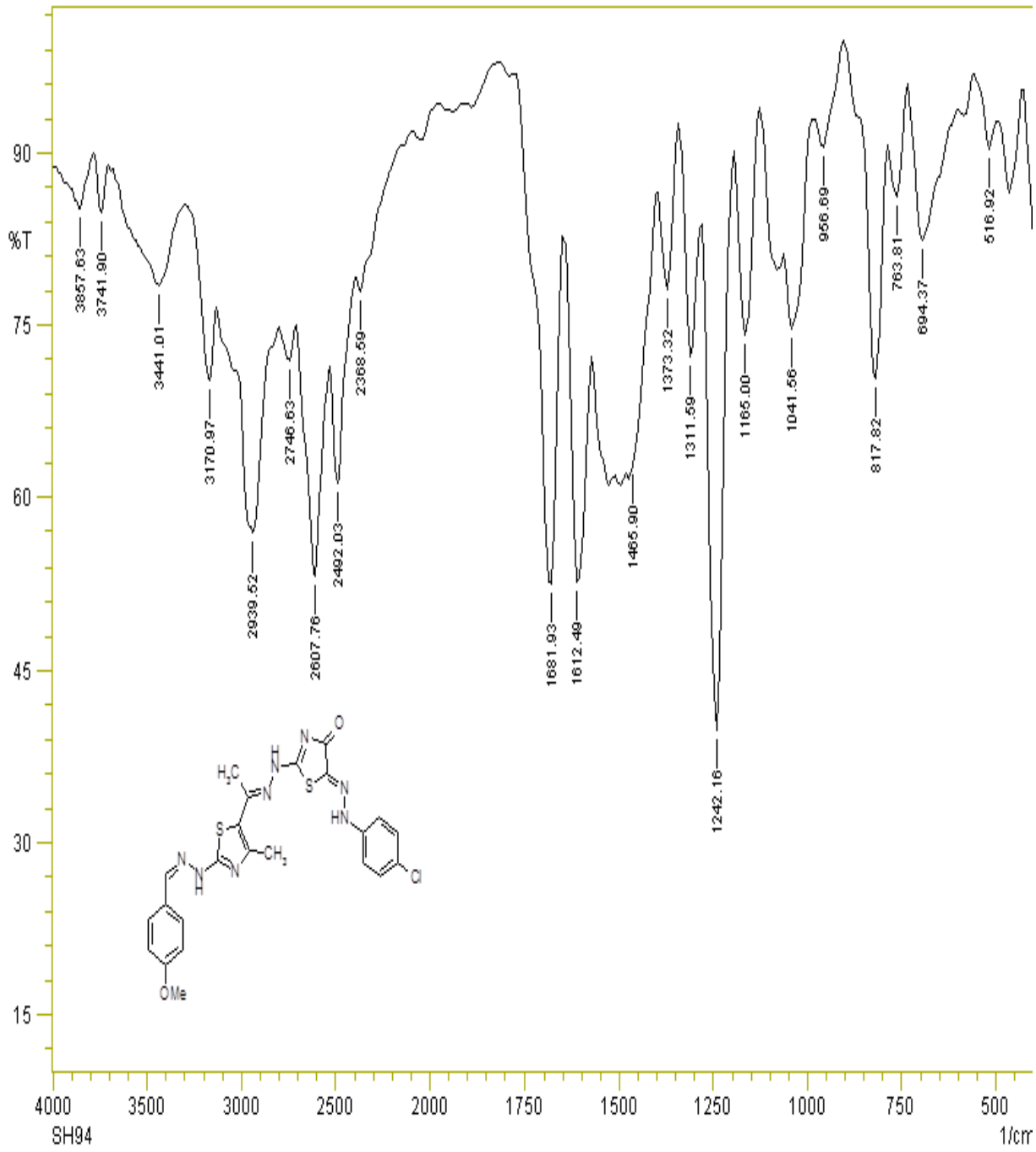
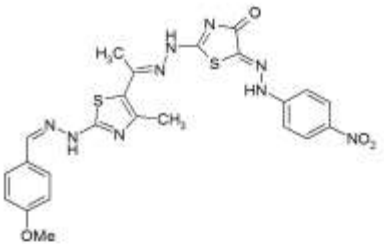


Figure S26. IR Spectra of compound 13c



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DI Analysis
Shimadzu Qp-2010 Plus

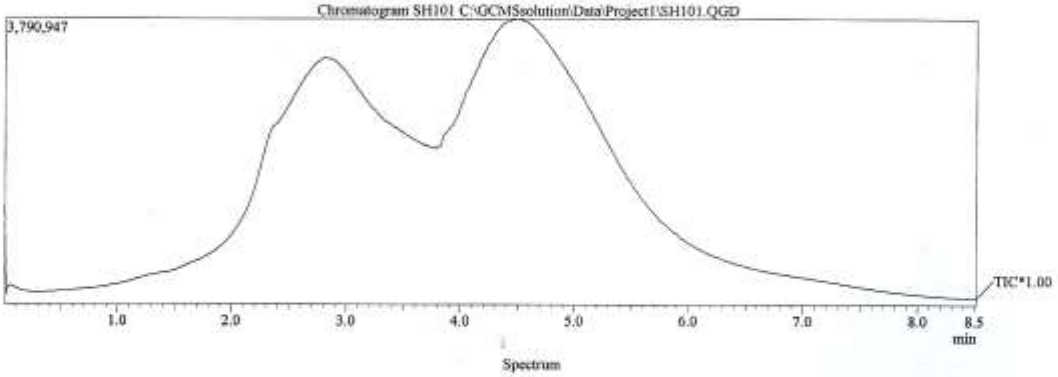
Sample Information

Analyzed by	: Dr. Mai Younis
Analyzed	: 01/01/2007 09:21:28 ص
Sample Name	: SH101
Sample ID	:
Customer Name	: Dr.Sobby Goma - Science - Cairo
Data File	: C:\GCMSsolution\Data\Project1\SH101.QGD
Org Data File	: C:\GCMSsolution\Data\Project1\SH101.QGD
Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Org Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Report File	:
Tuning File	: C:\GCMSsolution\System\Tune1_default.qgt
EndModified by	: Dr. Mai Younis
Modified	: 01/01/2007 09:30:02 ص

Method

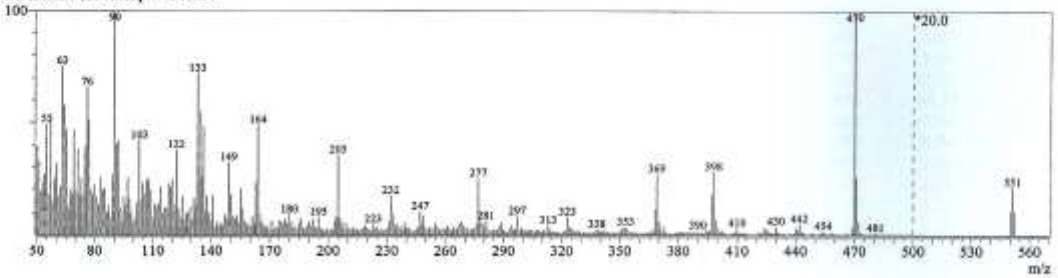
------ Analytical Line 1 ------	
IonSourceTemp	:250.00 °C
[MS Table]	
--Group 1 - Event 1--	
Start Time	:0.00min
End Time	:10.00min
ACQ Mode	:Scan
Event Time	:0.50sec
Scan Speed	:1250
Start m/z	:50.00
End m/z	:600.00
Electron Voltage	: 70 eV
Ionization Mode	: EI

C:\GCMSsolution\Data\Project1\SH101.QGD



Spectrum

Line#:1 R.Time:3.8(Scan#:456)
MassPeaks:401
RawMode:Single 3.8(456) BasePeak:90(60458)
BG Mode:None Group 1 - Event 1



Mass Table
Line#:1 R.Time:3.8(Scan#:456)
MassPeaks:401
RawMode:Single 3.8(456) BasePeak:90(60458)
BG Mode:None Group 1 - Event 1

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
1	50.00	23729	39.25	4	53.05	13846	22.90	7	56.10	10561	17.47
2	51.00	19703	32.59	5	54.00	16124	26.67	8	57.05	30814	50.97
3	52.05	11438	18.92	6	55.05	29574	48.92	9	58.05	8809	14.57

Figure S27. Mass Spectra of compound 13d

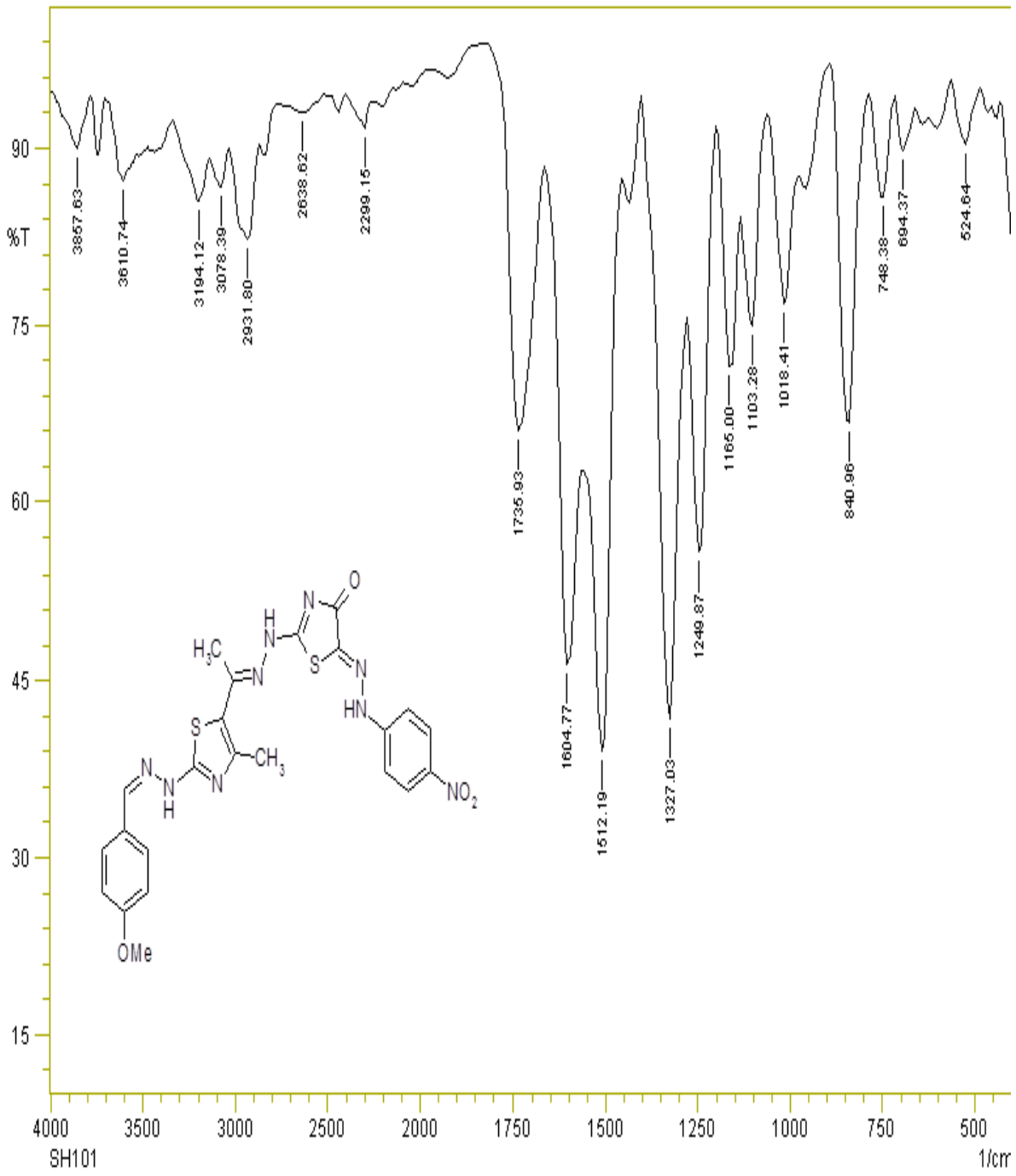


Figure S28. IR Spectra of compound 13d

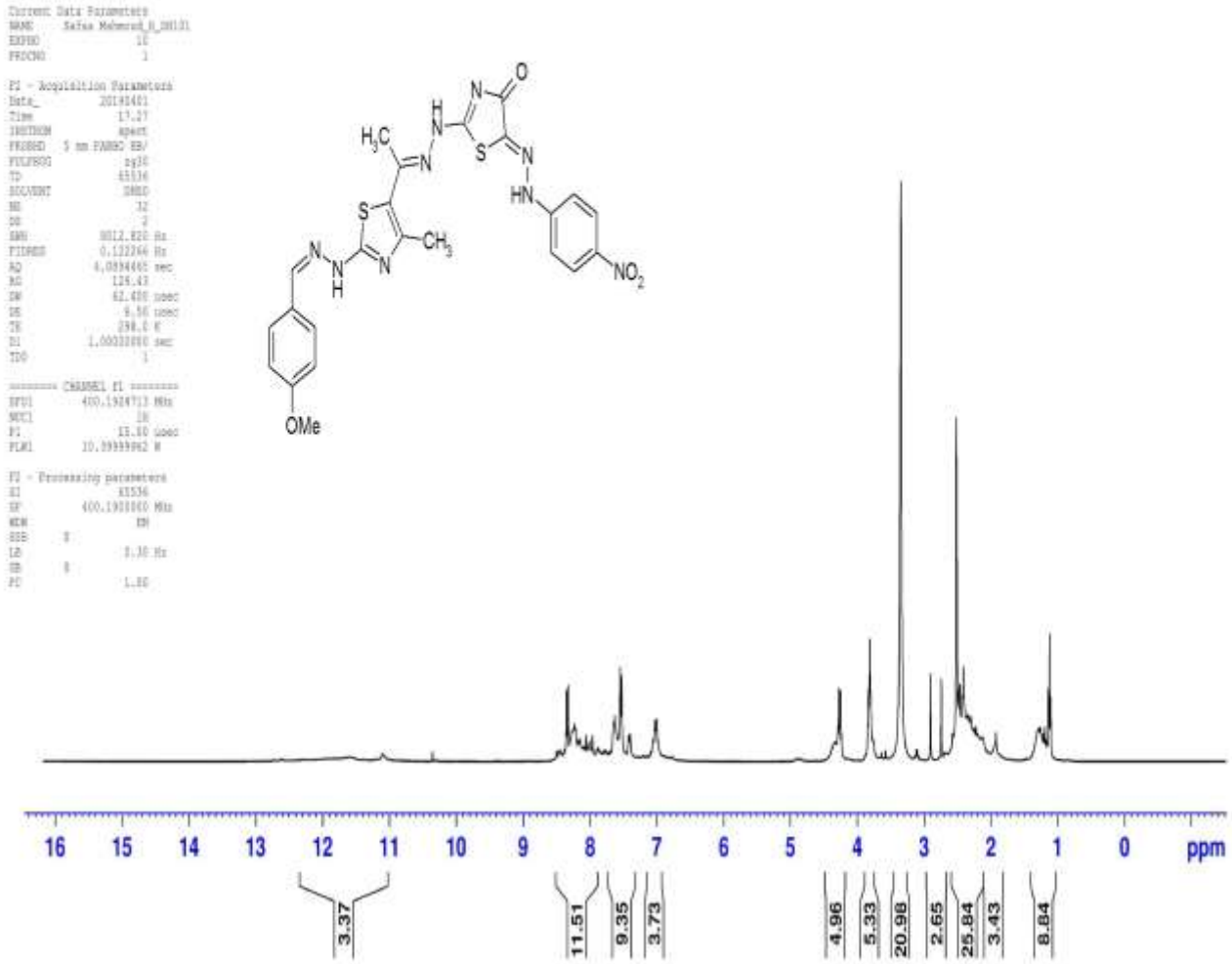
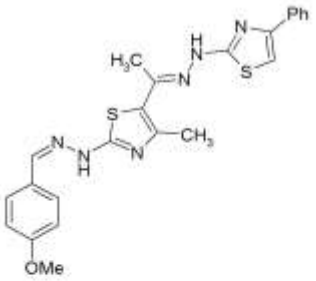


Figure S29. ^{1}HNMR Spectra of compound 13d



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DI Analysis
Shimadzu Qp-2010 Plus

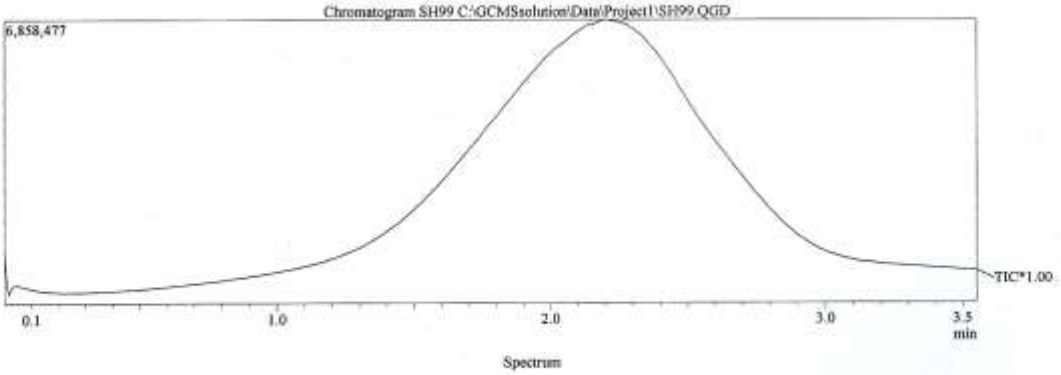
Sample Information

Analyzed by	: Dr. Mai Younis
Analyzed	: 01/01/2007 09:06:14 ص
Sample Name	: SH99
Sample ID	:
Customer Name	: Dr.Sobby Goma - Science - Cairo
Data File	: C:\GCMSsolution\Data\Project1\SH99.QGD
Org Data File	: C:\GCMSsolution\Data\Project1\SH99.QGD
Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Org Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Report File	:
Tuning File	: C:\GCMSsolution\System\Tune1_default.qgt
SEndIfSModified by	: Dr. Mai Younis
Modified	: 01/01/2007 09:09:51 ص

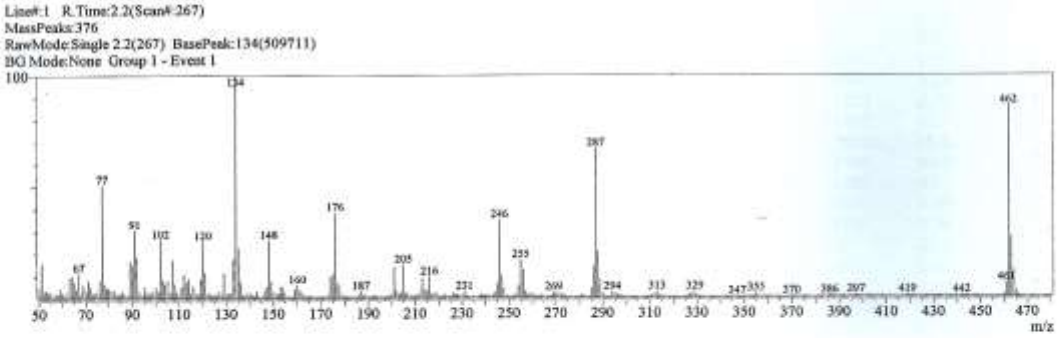
Method

------- Analytical Line 1 -------	
IonSourceTemp	:250.00 °C
[MS Table]	
--Group 1 - Event 1--	
Start Time	:0.00min
End Time	:10.00min
ACQ Mode	:Scan
Event Time	:0.50sec
Scan Speed	:1250
Start m/z	:50.00
End m/z	:600.00
Electron Voltage	: 70 eV
Ionization Mode	: EI

C:\GCMSsolution\Data\Project1\SH99.QGD



Spectrum



Mass Table
Line#:1 R.Time:2.2(Scan#:267)
MassPeaks:376
RawMode:Single 2.2(267) BasePeak:134(509711)
BG Mode:None Group 1 - Event 1

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
1	50.00	23529	4.62	4	53.05	17845	3.50	7	56.05	4171	0.82
2	51.00	78679	15.44	5	54.05	11917	2.34	8	57.05	10513	2.06
3	52.05	15268	3.00	6	55.05	13808	2.71	9	58.00	9826	1.93

Figure S30. Mass Spectra of compound 16

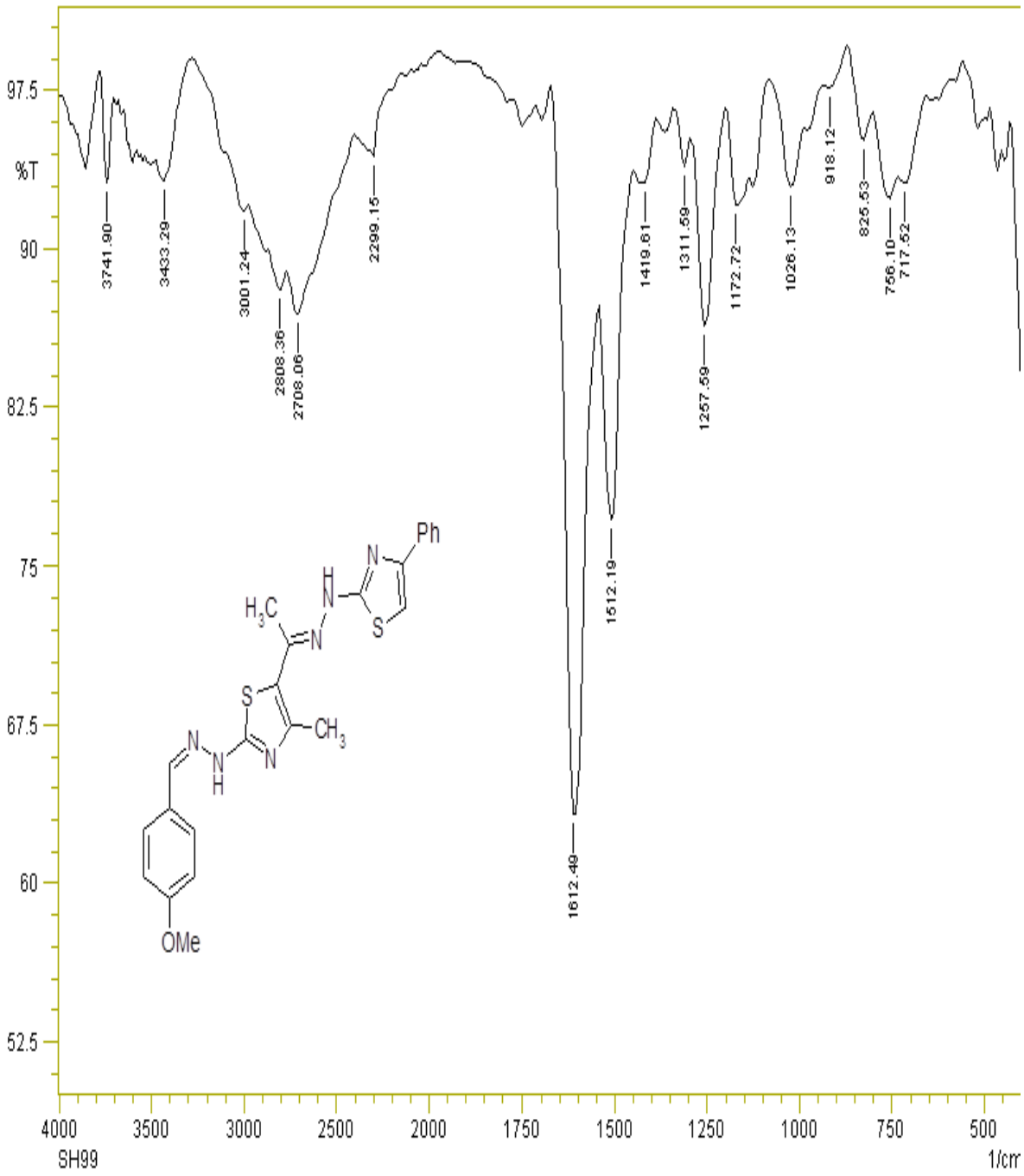


Figure S31. IR Spectra of compound 16

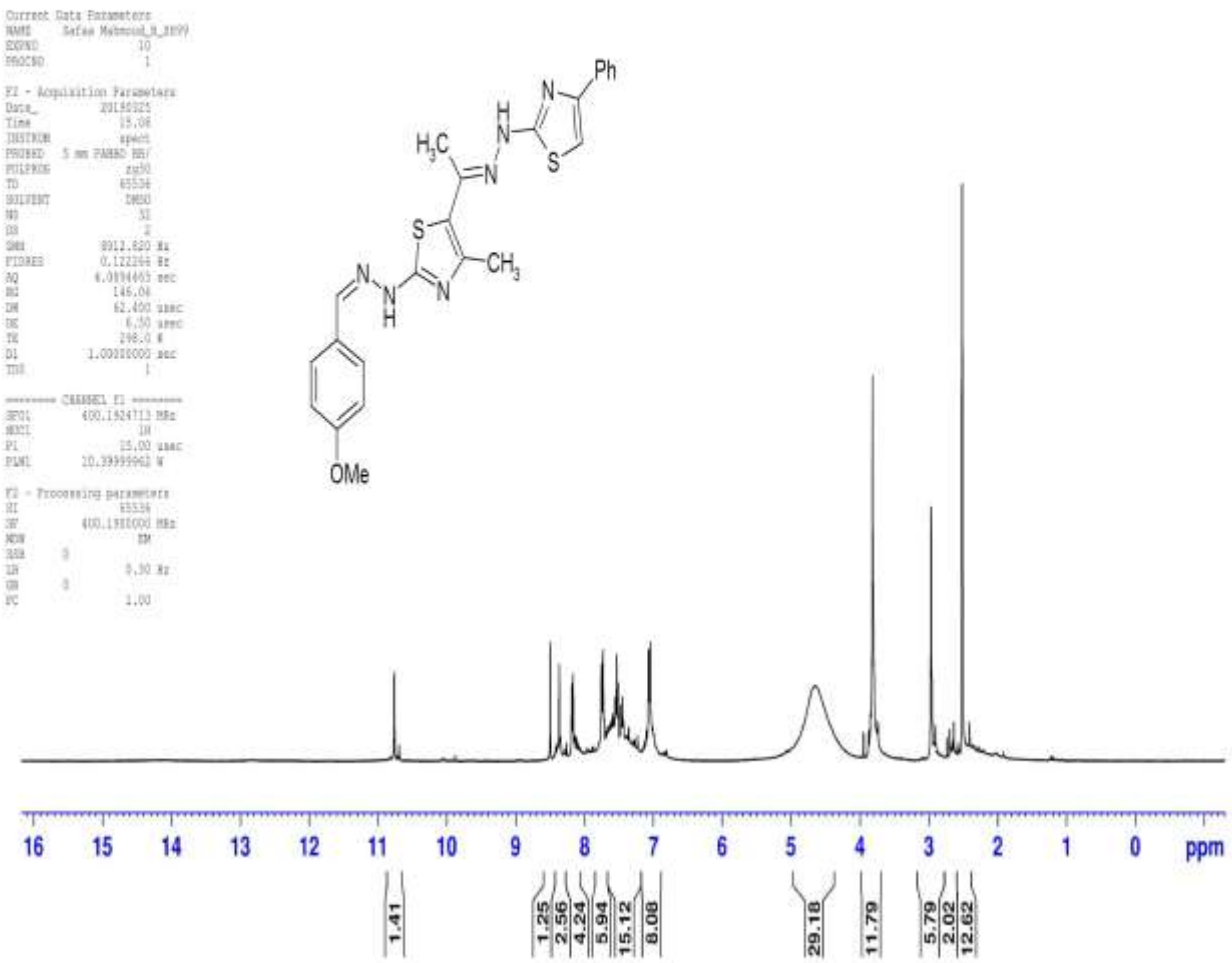


Figure S32. [1]HNMR Spectra of compound 16

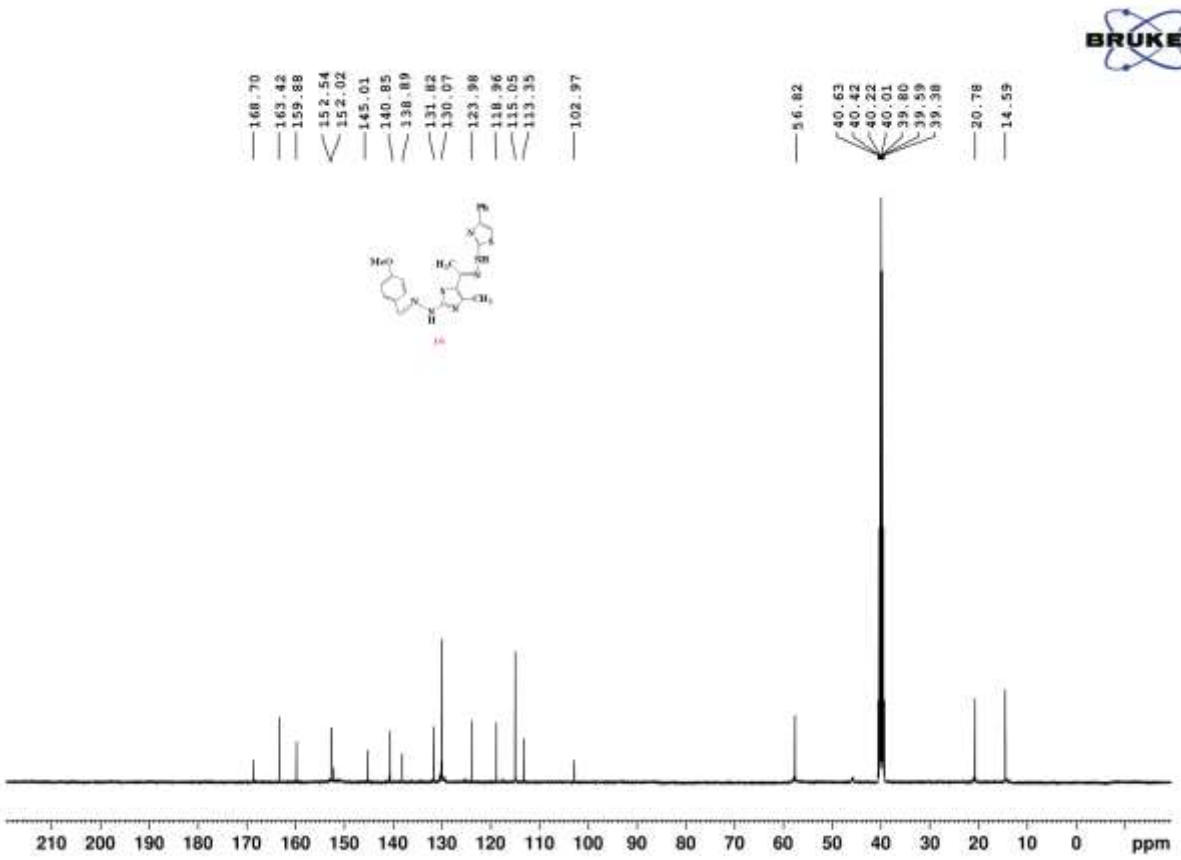


Figure S33. ^{13}CNMR Spectra of compound 16

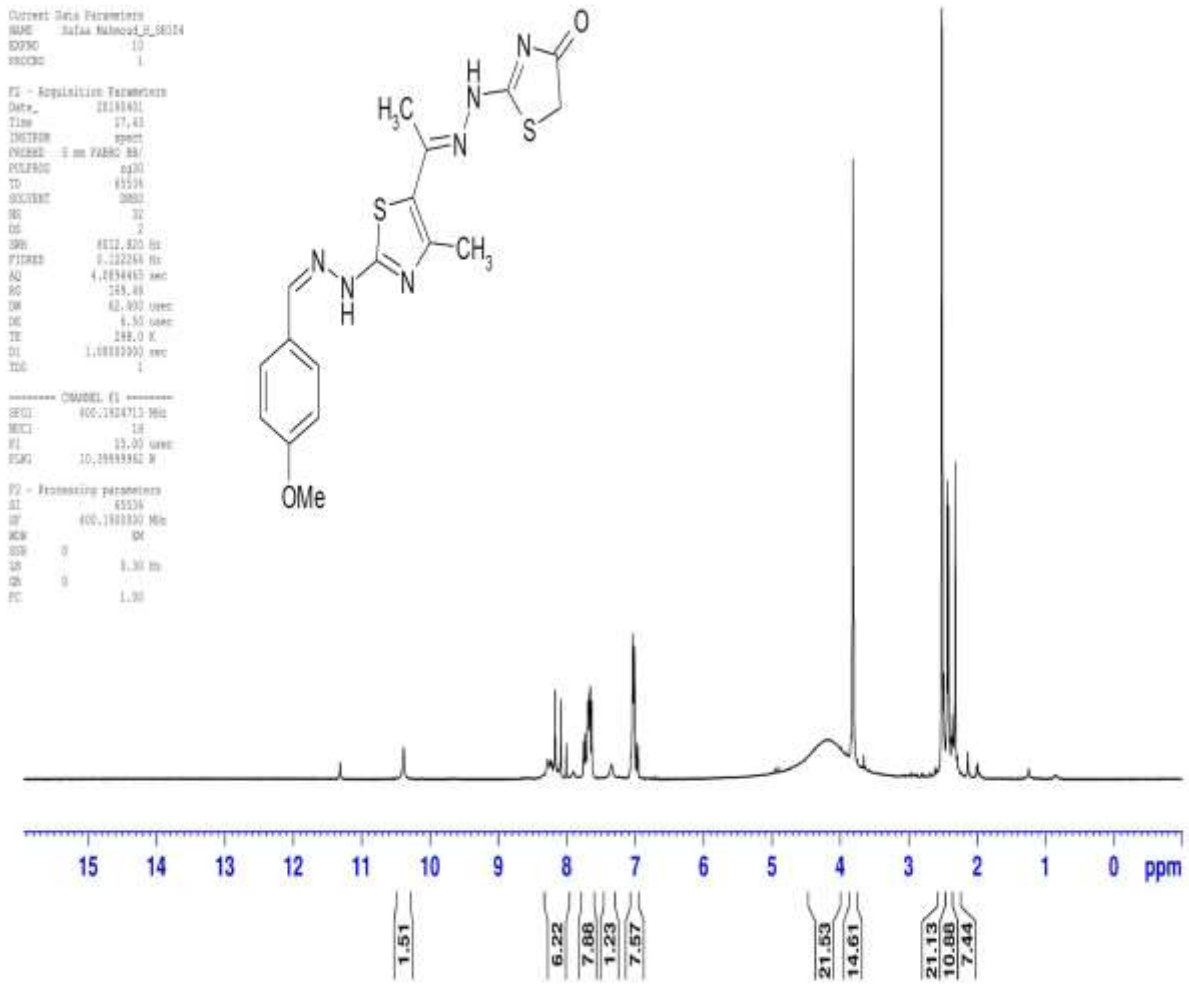


Figure S34. [1]HNMR Spectra of compound 18

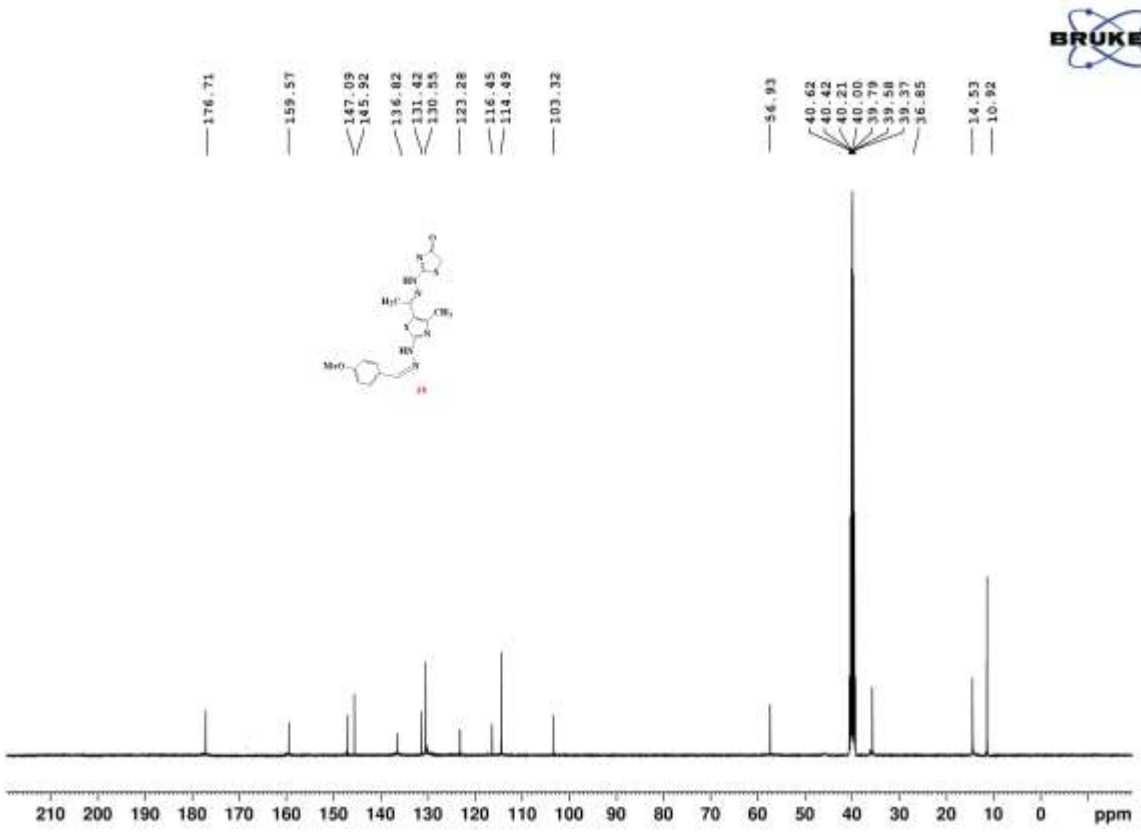
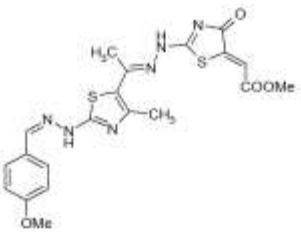


Figure S35. ^{13}CNMR Spectra of compound 18



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Micro Analytical Center

DI Analysis
Shimadzu Qp-2010 Plus

Sample Information

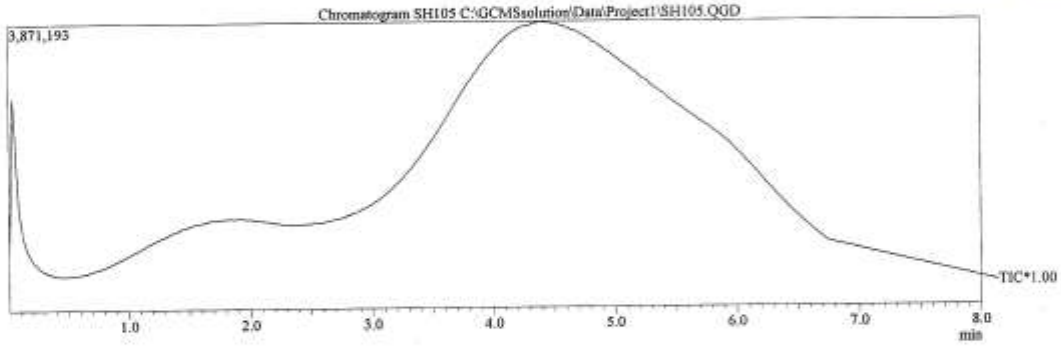
Analyzed by	: Dr. Mai Younis
Analyzed	: 01/01/2007 09:41:15 ص
Sample Name	: SH105
Sample ID	:
Customer Name	: Dr.Sobhy Goma - Science - Cairo
Data File	: C:\GCMSsolution\Data\Project1\SH105.QGD
Org Data File	: C:\GCMSsolution\Data\Project1\SH105.QGD
Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Org Method File	: C:\GCMSsolution\Data\Project1\High Temperature Op
Report File	:
Tuning File	: C:\GCMSsolution\System\Tune1_default.qgt
$EndIf$Modified by	: Dr. Mai Younis
Modified	: 01/01/2007 09:48:04 ص

Method

——— Analytical Line 1 ———	
IonSourceTemp	:250.00 °C
[MS Table]	
--Group 1 - Event 1--	
Start Time	:0.00min
End Time	:10.00min
ACQ Mode	:Scan
Event Time	:0.50sec
Scan Speed	:1250
Start m/z	:50.00
End m/z	:600.00
Electron Voltage	: 70 eV
Ionization Mode	: EI

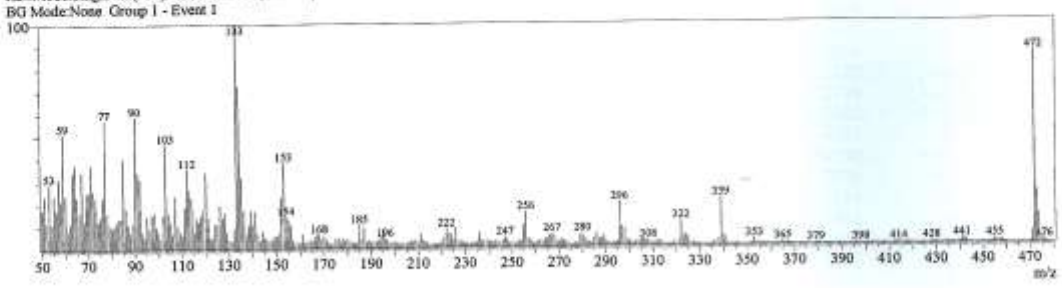
C:\GCMSsolution\Data\Project1\SH105.QGD

Chromatogram SH105 C:\GCMSsolution\Data\Project1\SH105.QGD



Spectrum

Line#:1 R.Time:4.6(Scan#:553)
MassPeaks:401
RawMode:Single 4.6(553) BasePeak:133(140068)
BG Mode:None Group 1 - Event 1



Mass Table
Line#:1 R.Time:4.6(Scan#:553)
MassPeaks:401
RawMode:Single 4.6(553) BasePeak:133(140068)
BG Mode:None Group 1 - Event 1

#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.	#	m/z	Abs. In	Rel. Int.
1	50.05	24167	17.25	4	53.05	40257	28.74	7	56.05	23846	17.02
2	51.05	32810	23.42	5	54.05	15261	10.90	8	57.05	43515	31.07
3	52.05	16005	11.43	6	55.05	33204	23.71	9	58.05	29811	21.28

Figure S36. Mass Spectra of compound 20

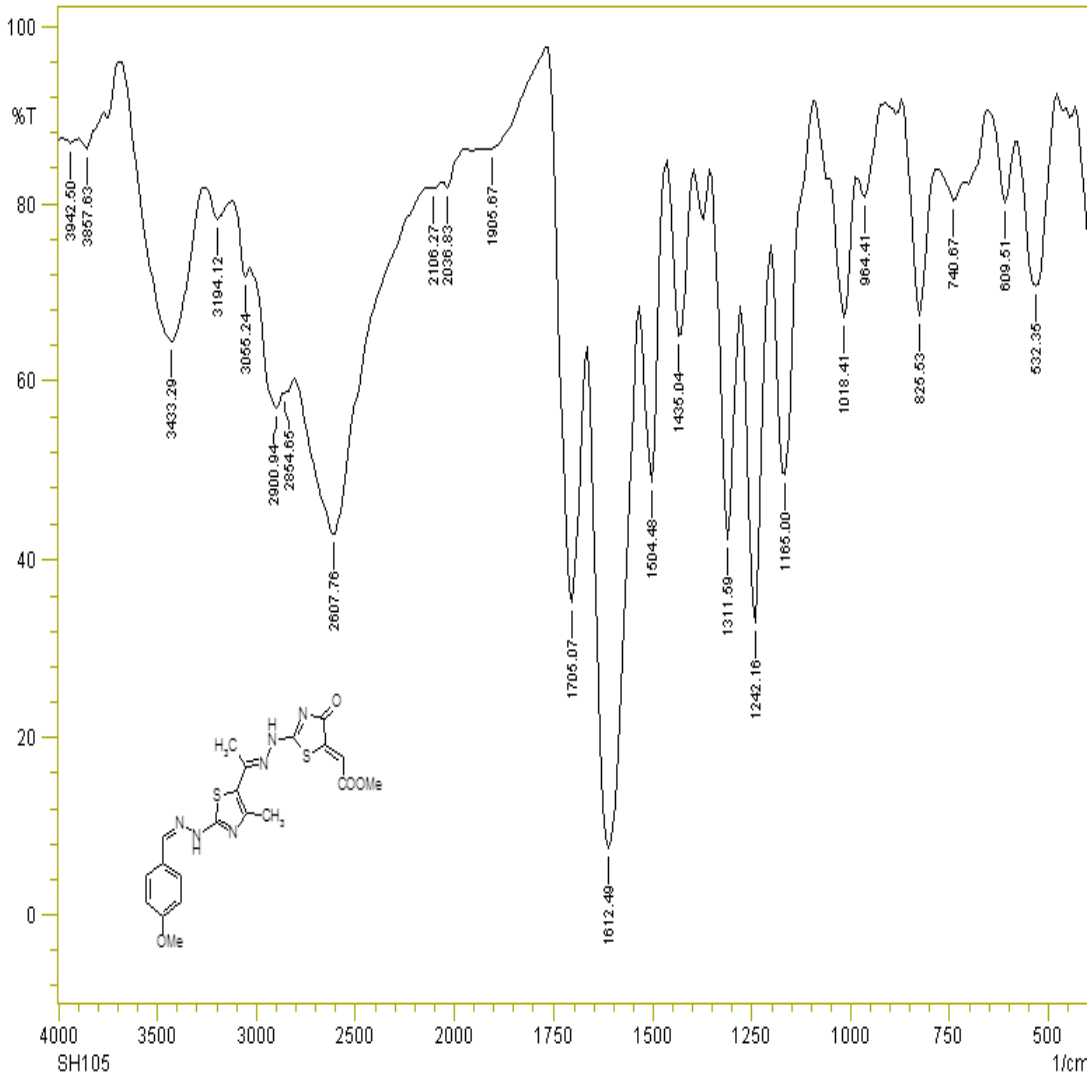


Figure S37. IR Spectra of compound 20

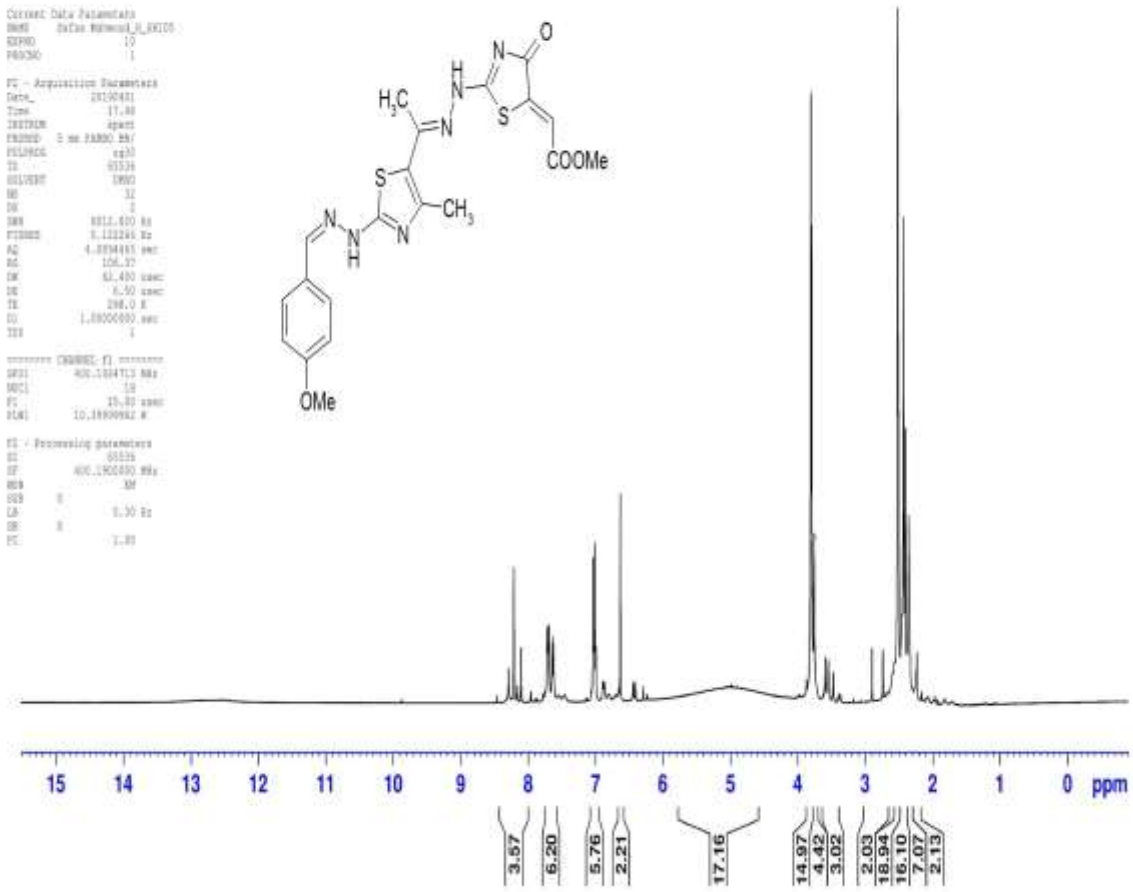


Figure S38. ^{1}HNMR Spectra of compound 20

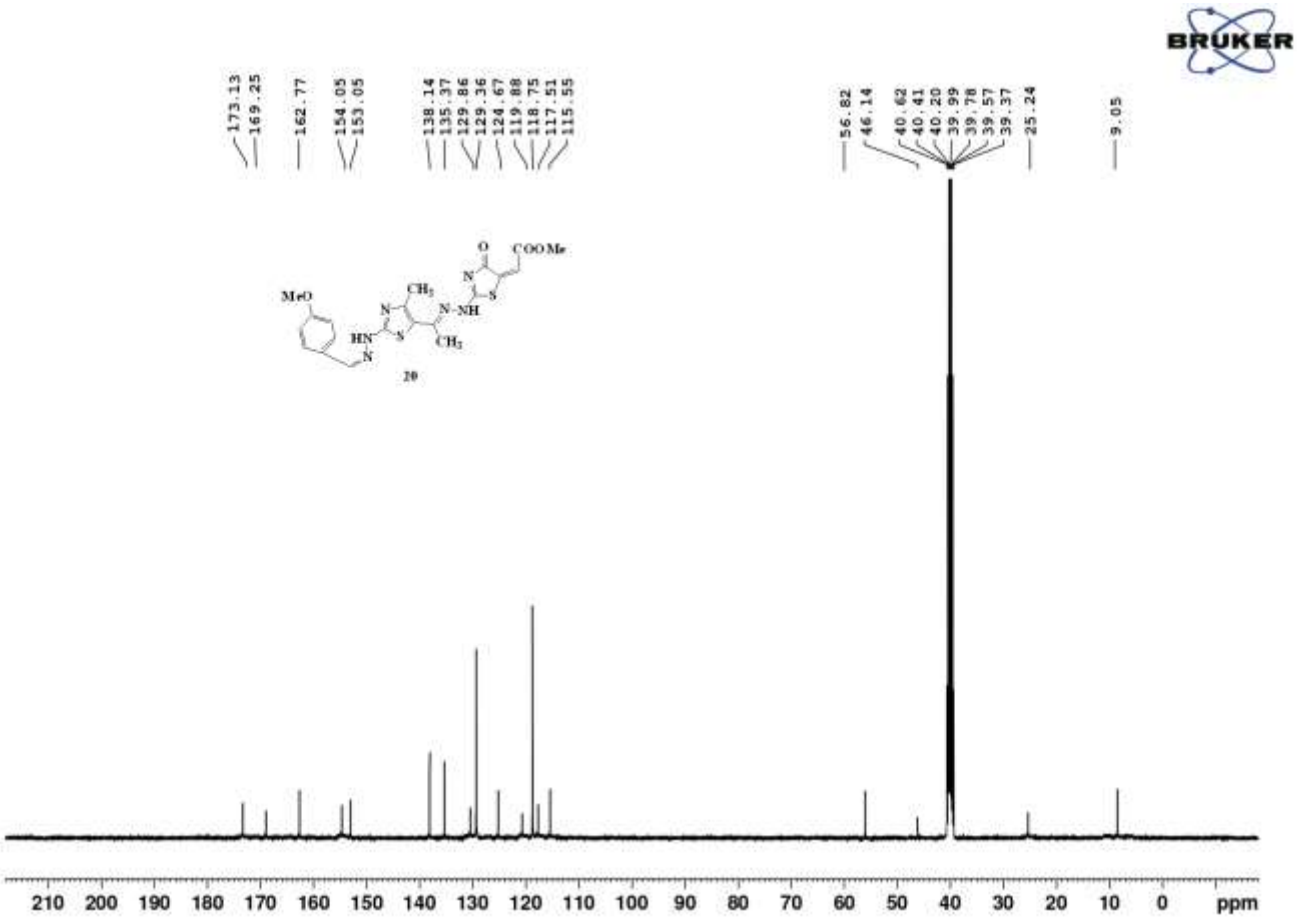


Figure S39. ^{13}CNMR Spectra of compound 20