

Design, synthesis, X-ray crystal structures, anticancer, DNA binding and molecular modelling studies of pyrazole–pyrazoline hybrid derivatives

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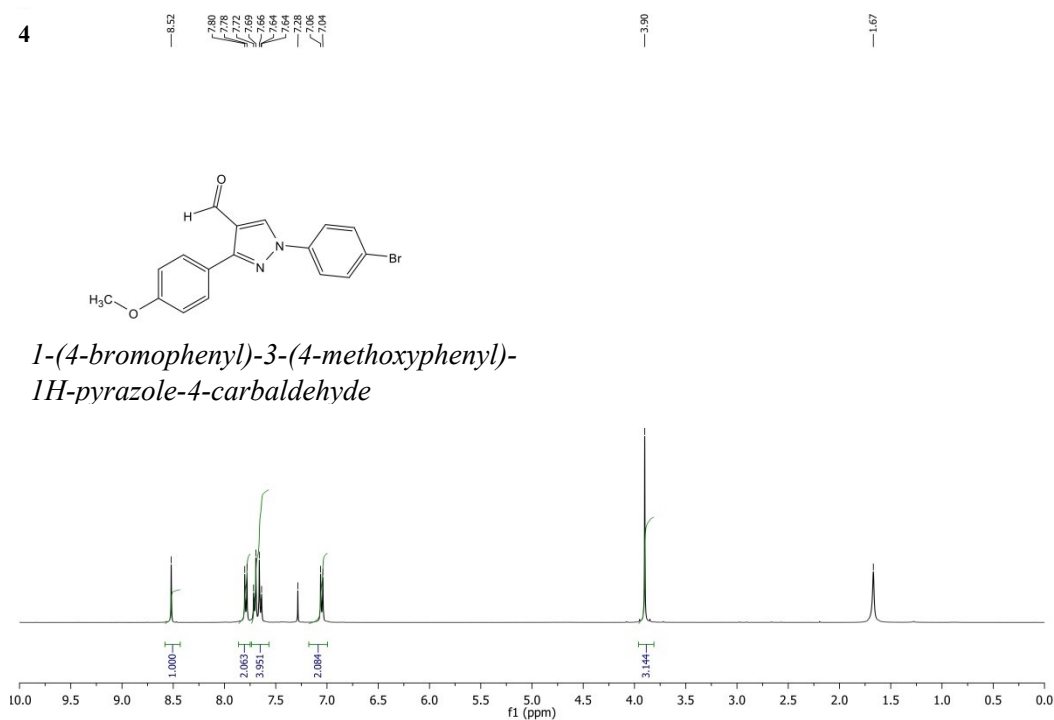
*Author for correspondence:

rahisuddin@jmi.ac.in (+919871460479)

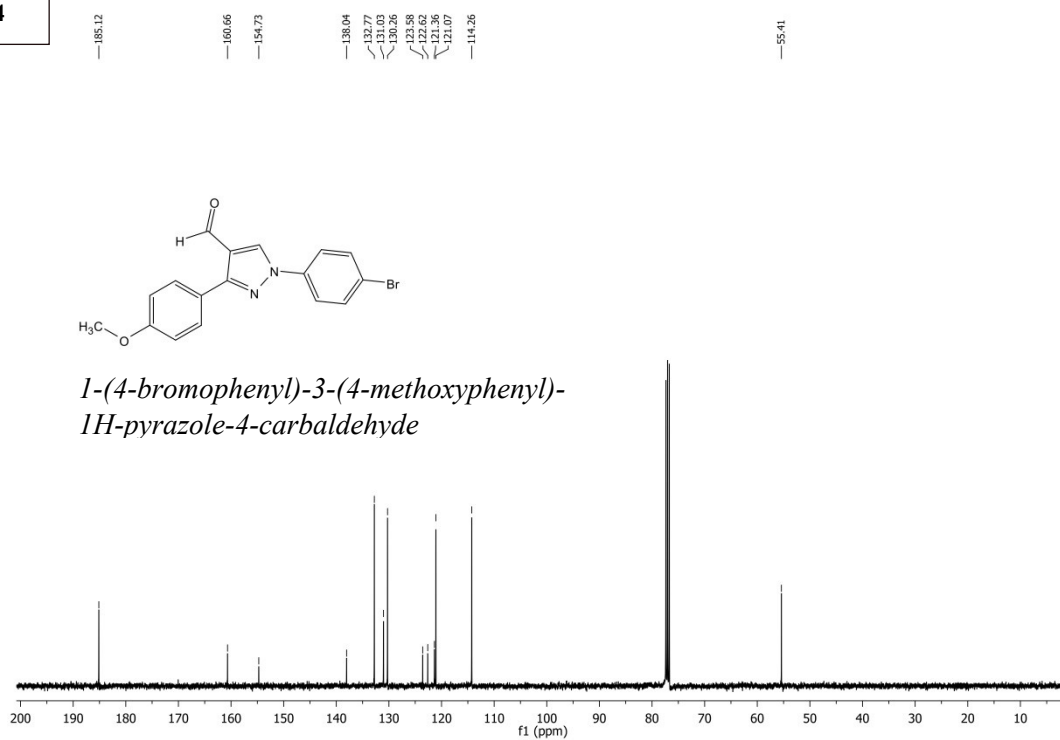
Materials and methods

All the reagents are commercially available were used as received without further purification. Substituted acetophenones (Spectrochem), formic acid (Fisher scientific), hydrazine hydrate (S.D. Fine Chemicals), and catalyst Pd(PPh₃)₄ Alfa Aesar. Melting points have been determined using open capillary tube and are uncorrected. Reaction progress was routinely monitored by TLC (thin layer chromatography) on silica gel (precoated 60 F₂₅₄Al

sheets, Merck). IR spectra of neat compounds were rerecorded on Agilent Technologies and expressed in wavenumber (cm^{-1}). ^1H and ^{13}C -NMR spectra were recorded using CDCl_3 as solvent on a Bruker 300 MHz spectrometer. Chemical shifts (δ) are given in ppm and tetramethylsilane (TMS) used as reference. To investigate the DNA-drug interaction, IVIUM potentiostat was used with a three-electrode system that was obtained from Metrohm, Dropsens (DS 220BT). Circular dichroism experiments were carried out using the Jasco J-815 spectrometer using a rectangular quartz cell of 1 cm path length. Fluorescence spectra were recorded at room temperature using an Agilent spectrophotometer. Electronic spectra of the compounds were obtained on a Labman UV–Visible spectrophotometer. The mass spectral analysis of all the heterocyclic derivatives was done by LC MS/MS Waters.

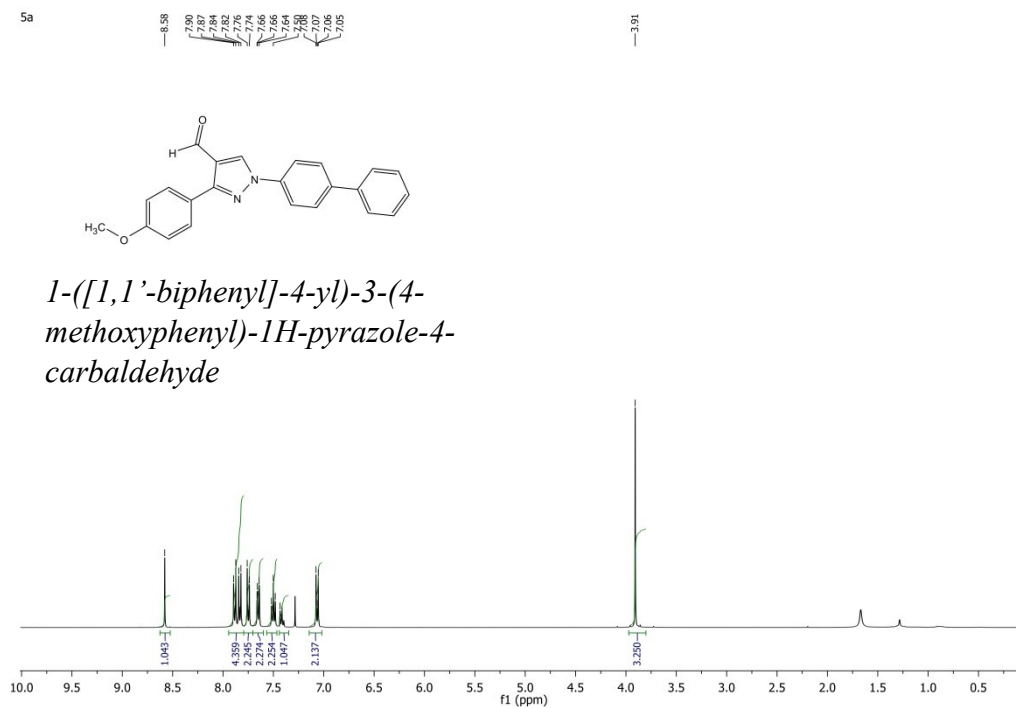


4



^{13}C -NMR spectra at 100 MHz in CDCl_3 of compound 4

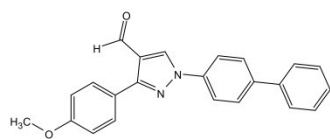
5a



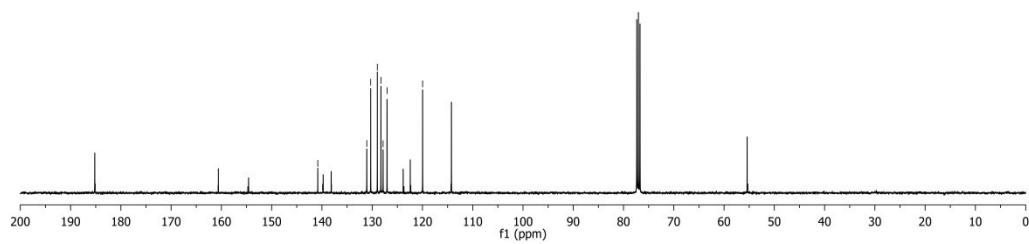
^1H -NMR spectra at 400 MHz in CDCl_3 of compound 5a

5a

—185.09
 —166.67
 —154.75
 —140.82
 —139.87
 —138.09
 —131.07
 —130.30
 —128.98
 —128.82
 —127.84
 —127.04
 —123.67
 —119.34
 —55.26

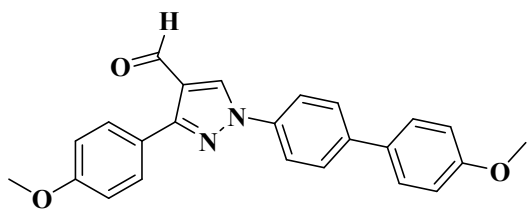
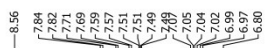


1-([1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde

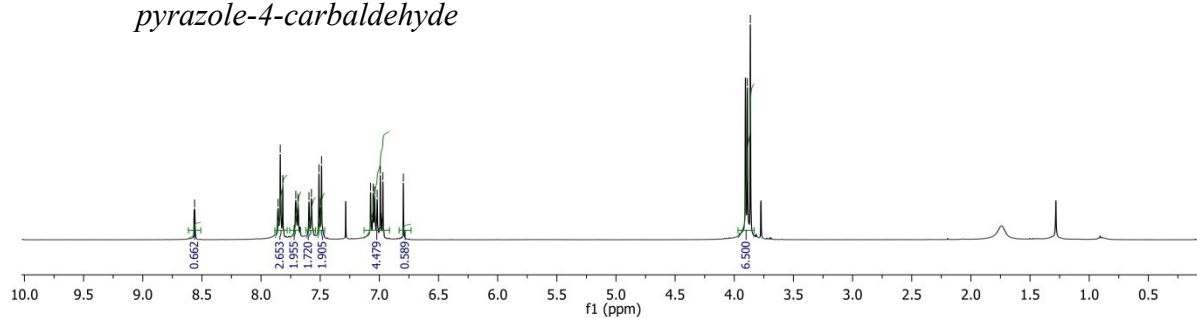


^{13}C -NMR spectra at 100 MHz in CDCl_3 of compound 5a

5b

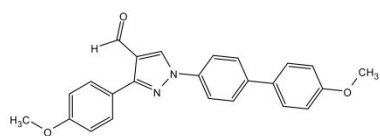
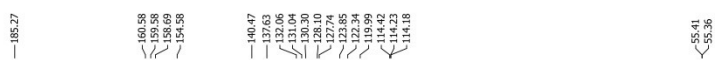


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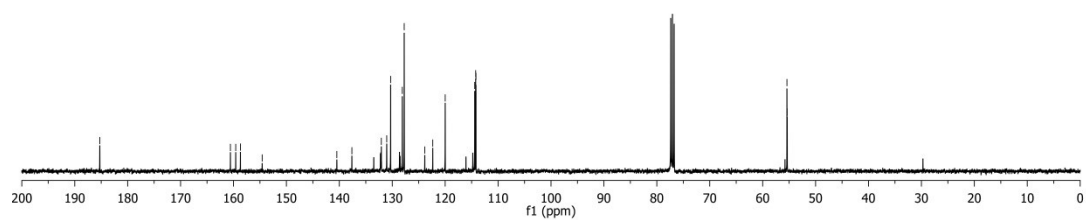


¹H-NMR spectra at 400 MHz in CDCl₃ of compound 5b

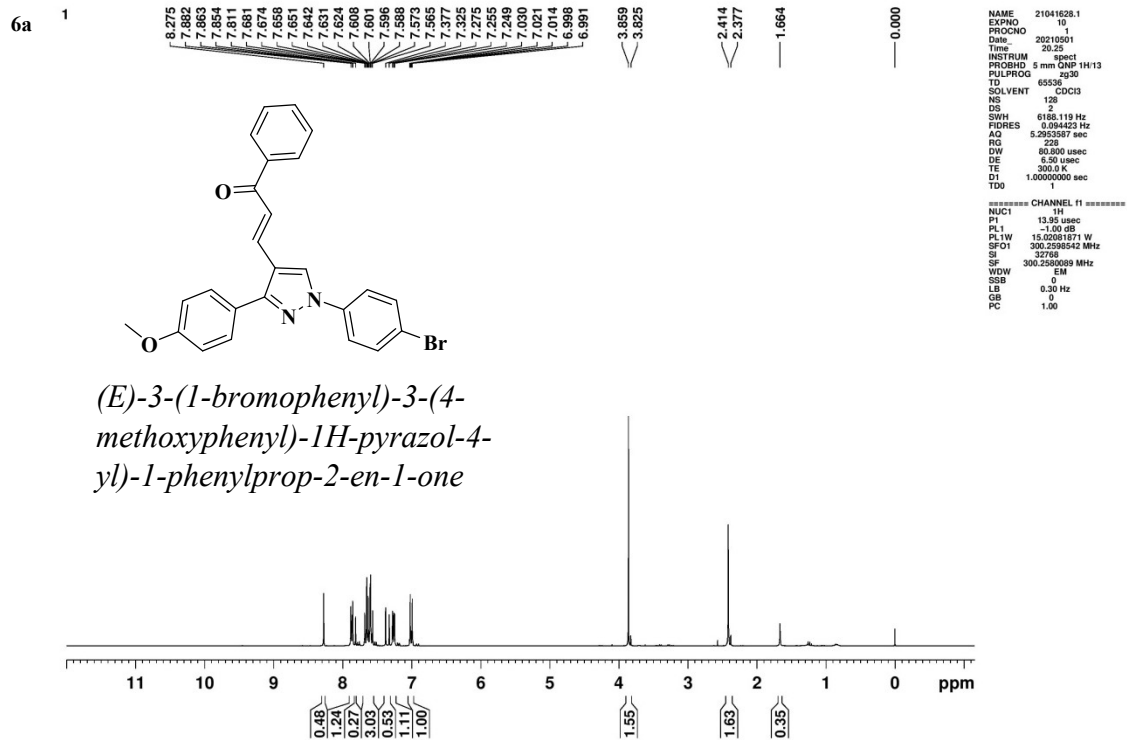
5b



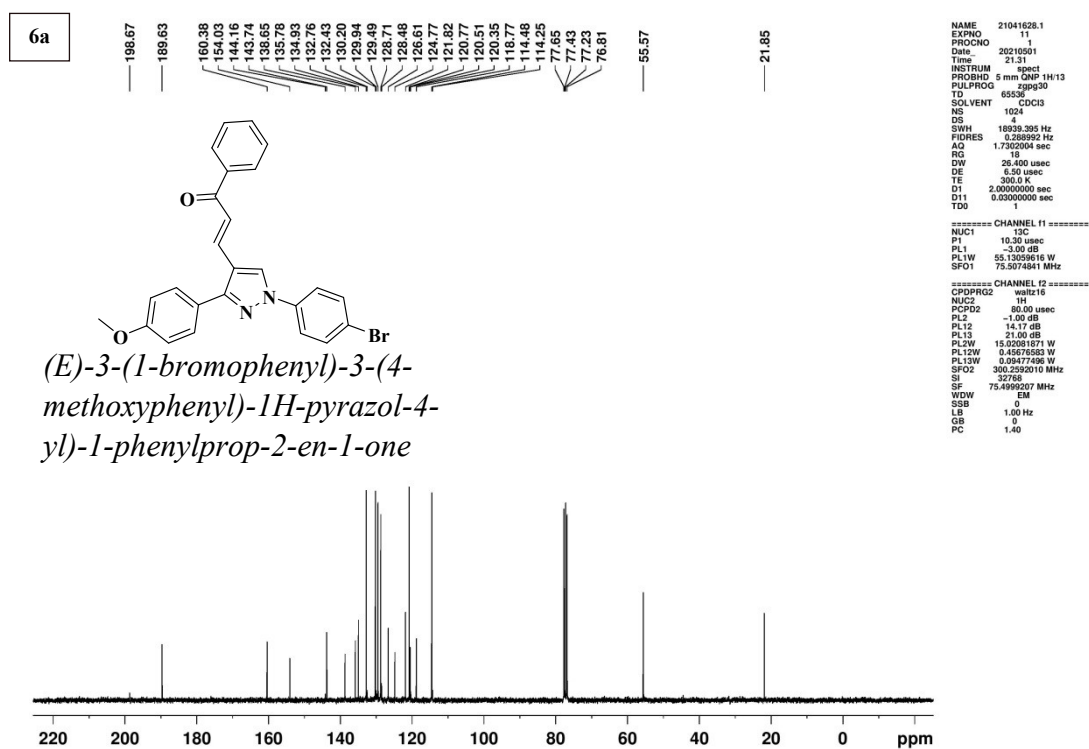
1-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde



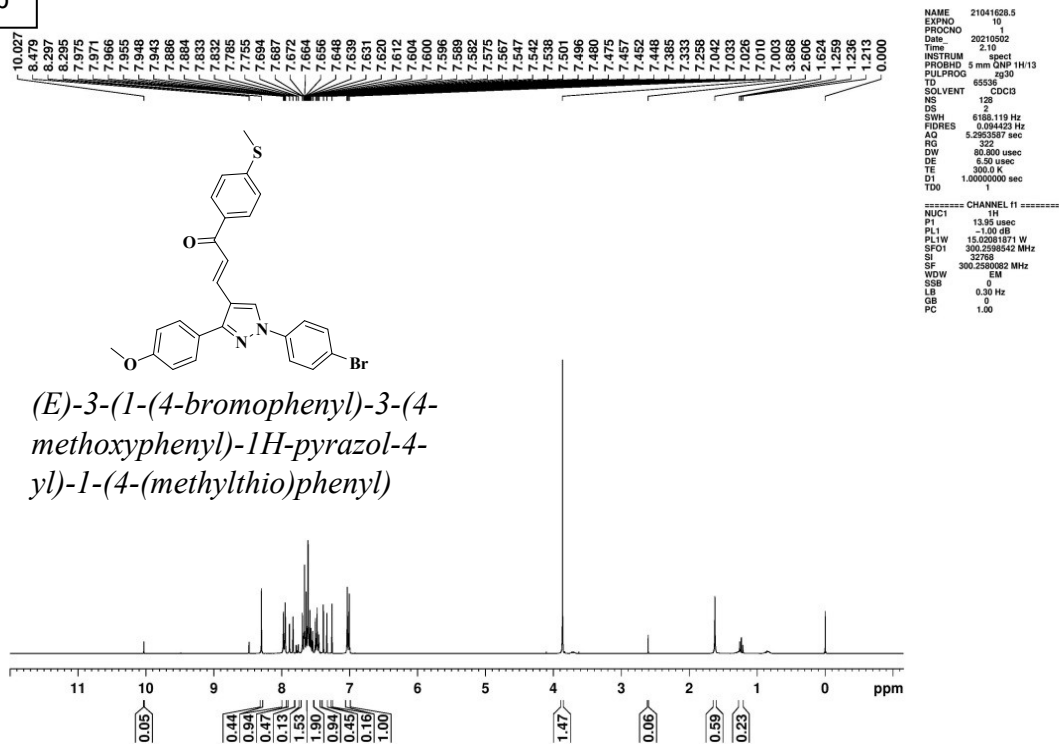
¹³C-NMR spectra at 100 MHz in CDCl₃ of compound 5b



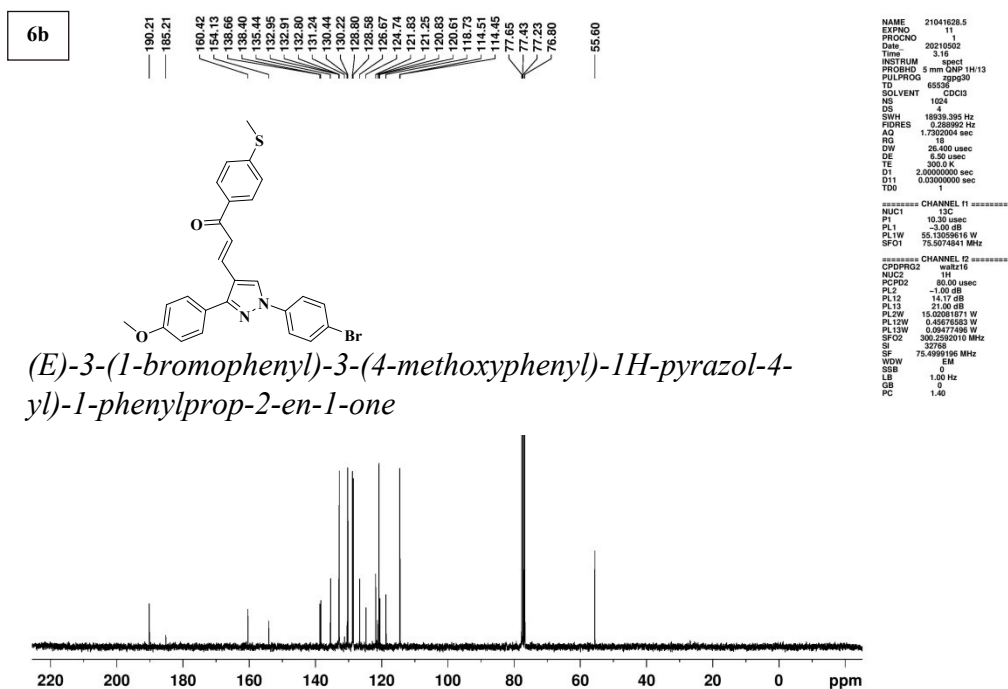
¹H-NMR spectra at 400 MHz in CDCl₃ of compound **6a**

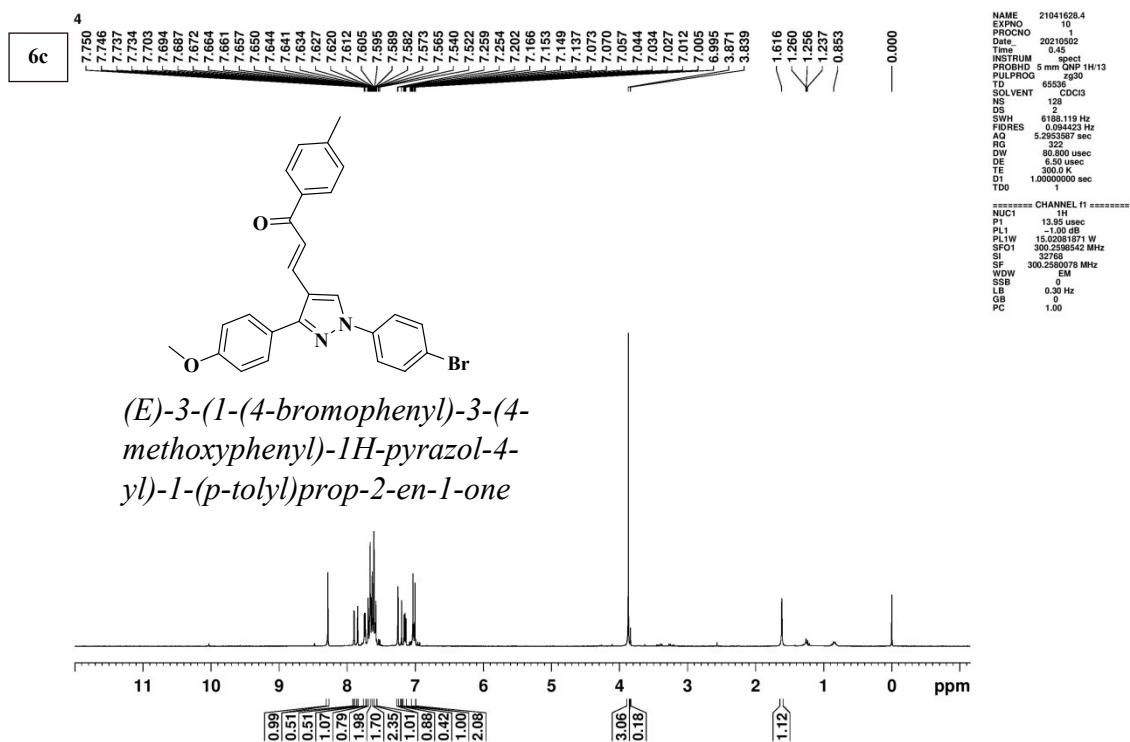


6b

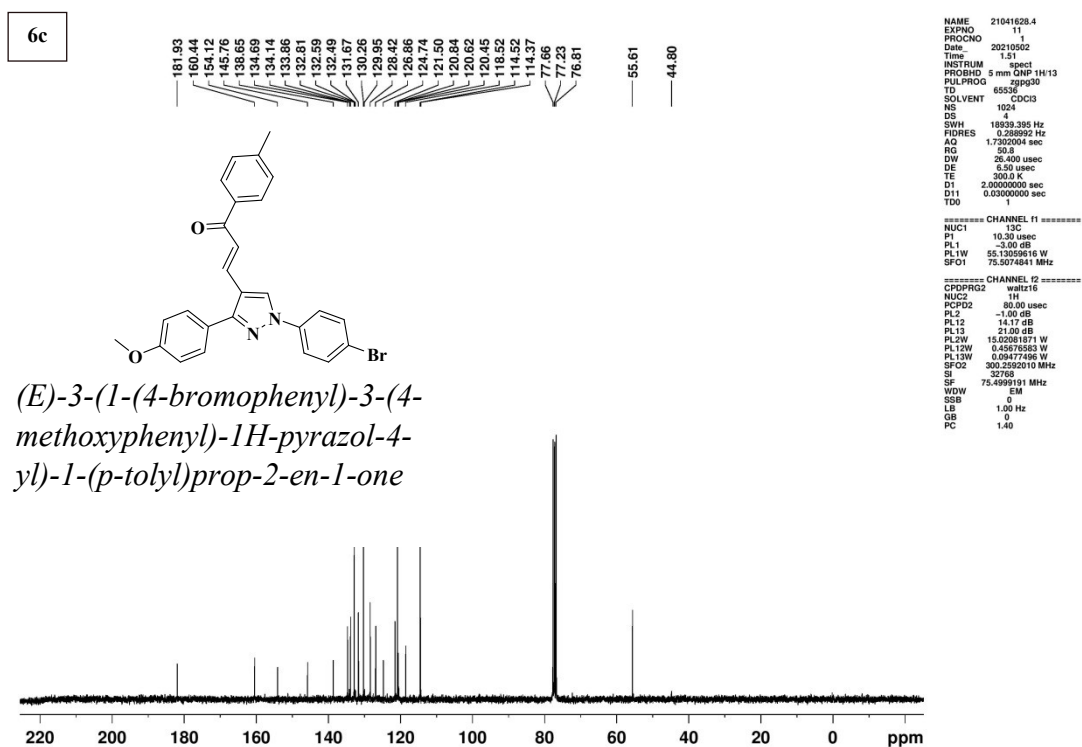


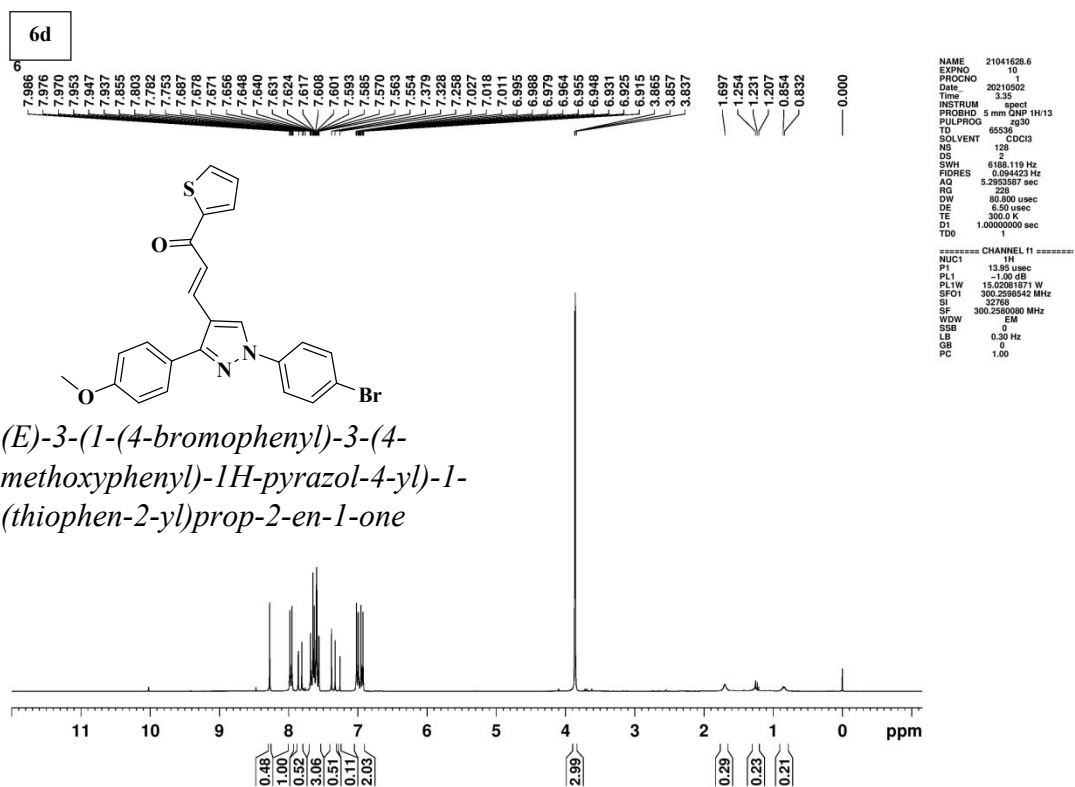
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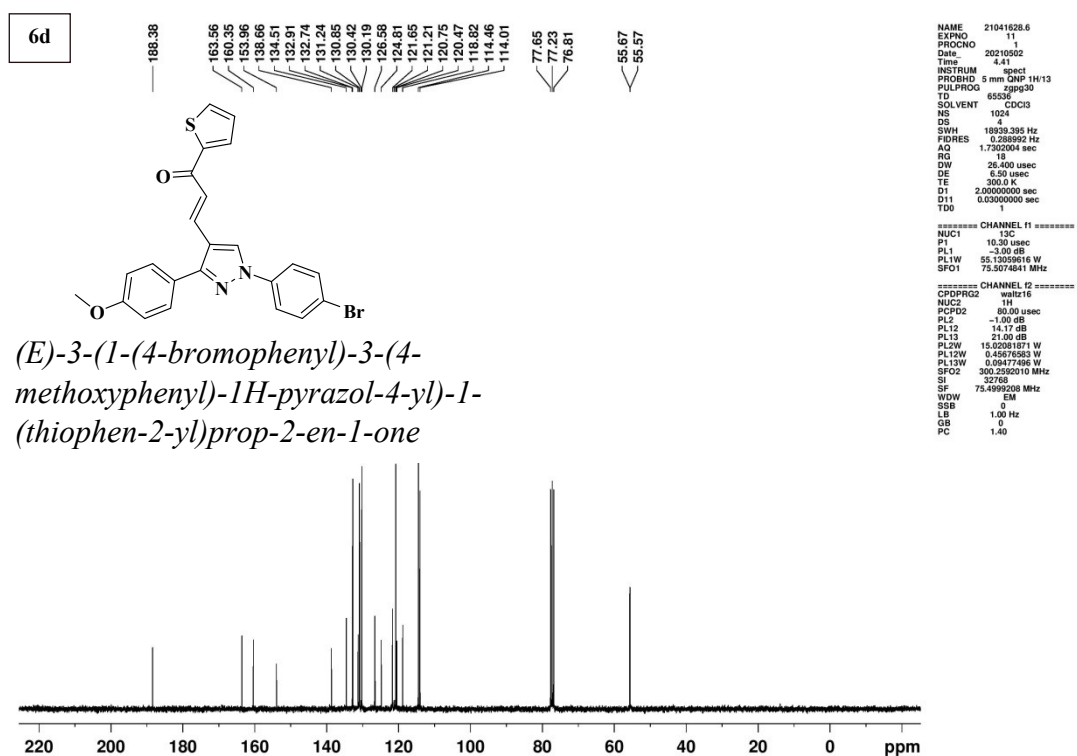


¹H-NMR spectra at 300 MHz in CDCl₃ of compound 6c





¹H-NMR spectra at 300 MHz in CDCl₃ of compound 6d

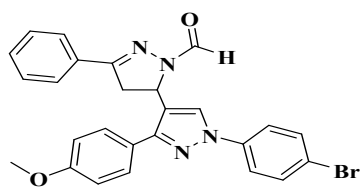


7a

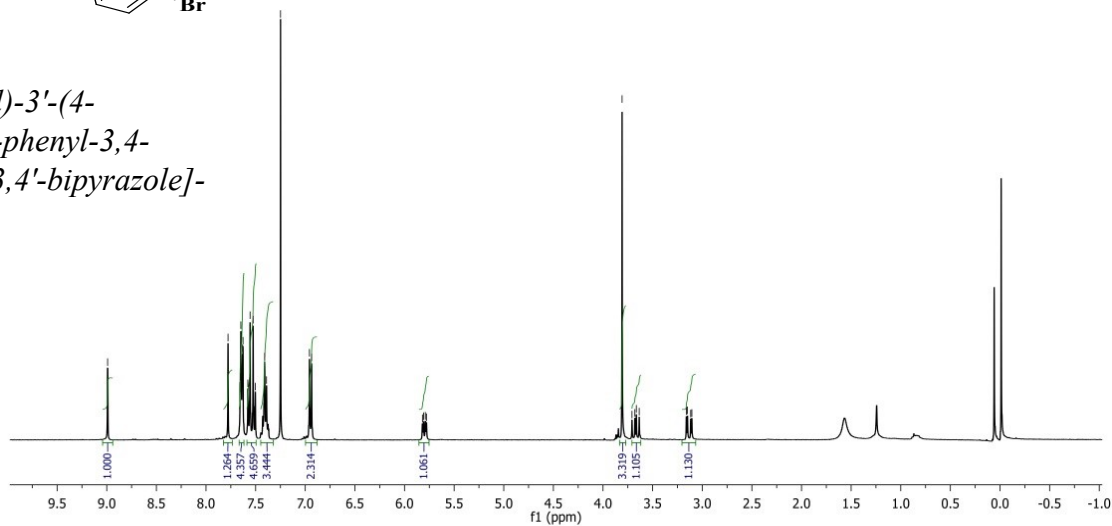
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5.82, 5.81, 5.81, 5.78

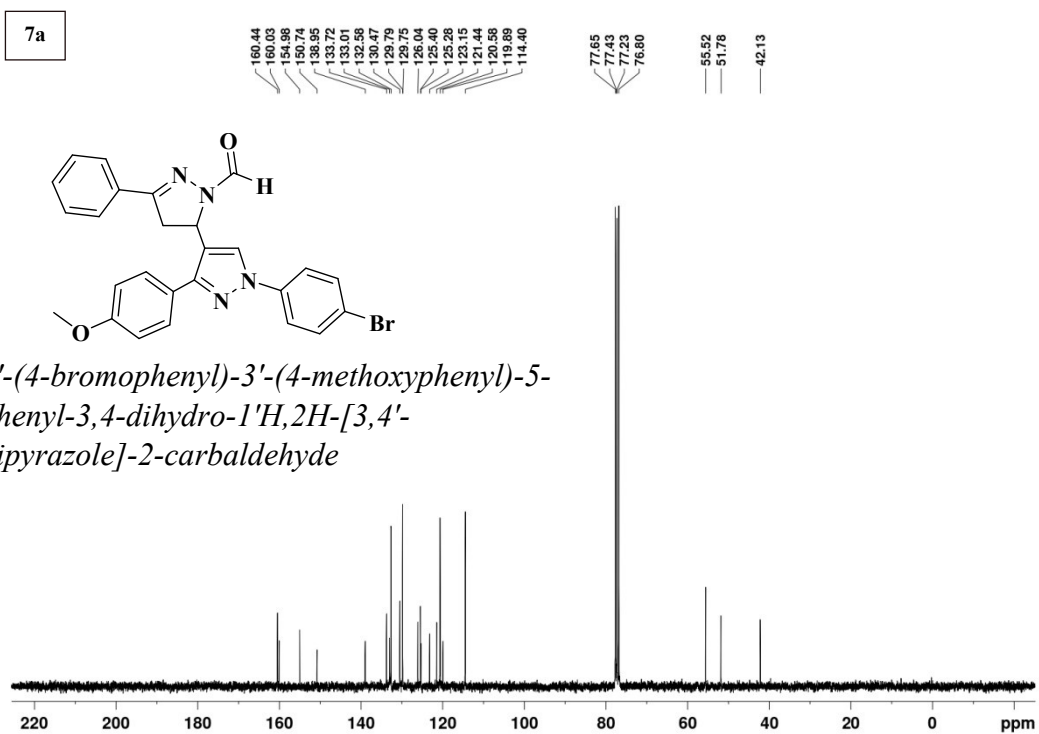
3.81, 3.71, 3.68, 3.66, 3.64, 3.15, 3.12, 3.10



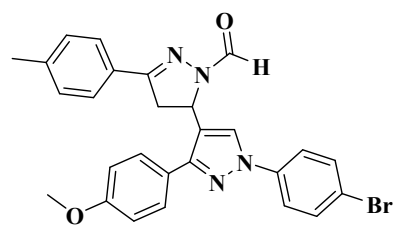
1'-(4-bromophenyl)-3'-(4-methoxyphenyl)-5-phenyl-3,4-dihydro-1'H,2H-[3,4'-bipyrazole]-2-carbaldehyde



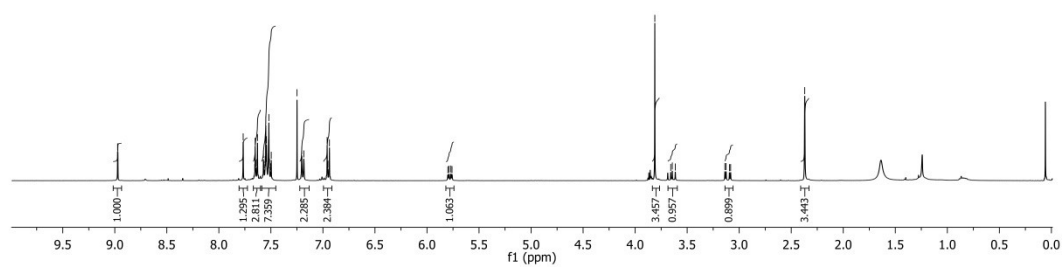
¹H-NMR spectra at 400 MHz in CDCl₃ of compound 7a



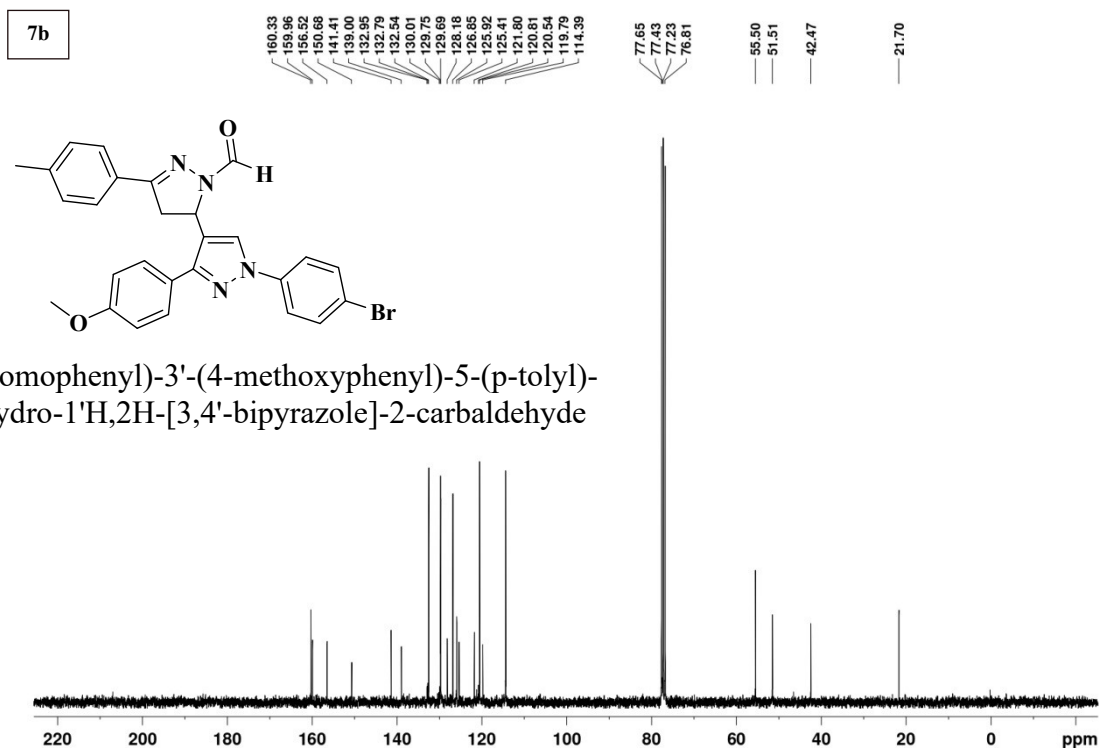
^{13}C -NMR spectra at 100 MHz in CDCl_3 of compound 7a

7b

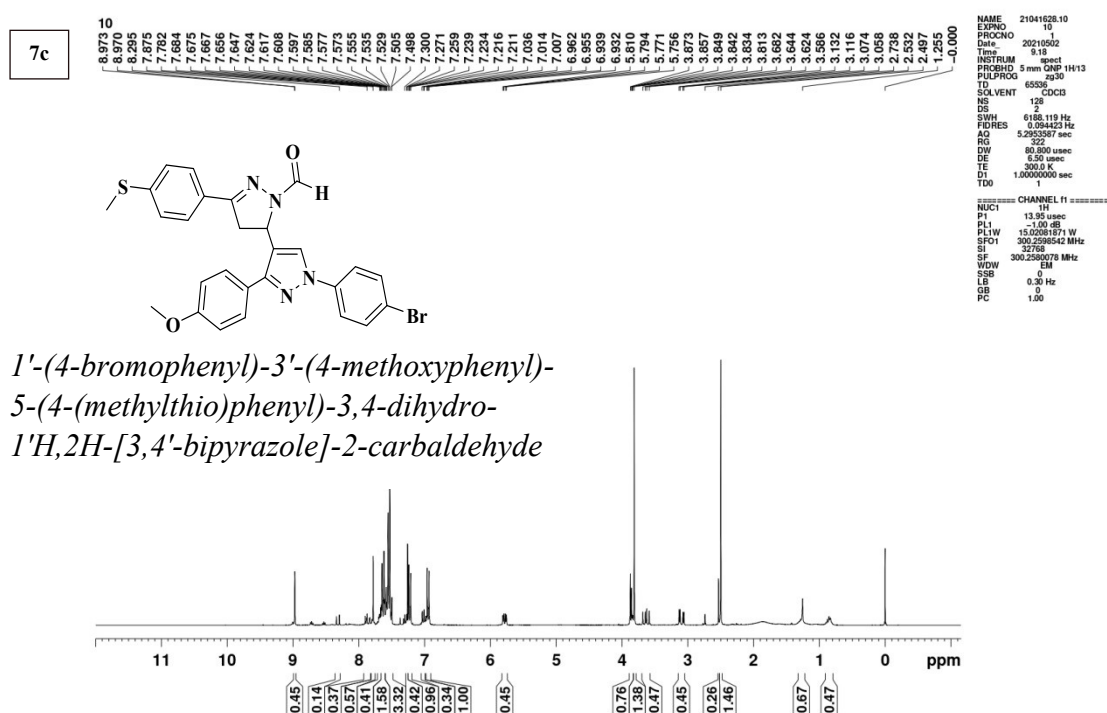
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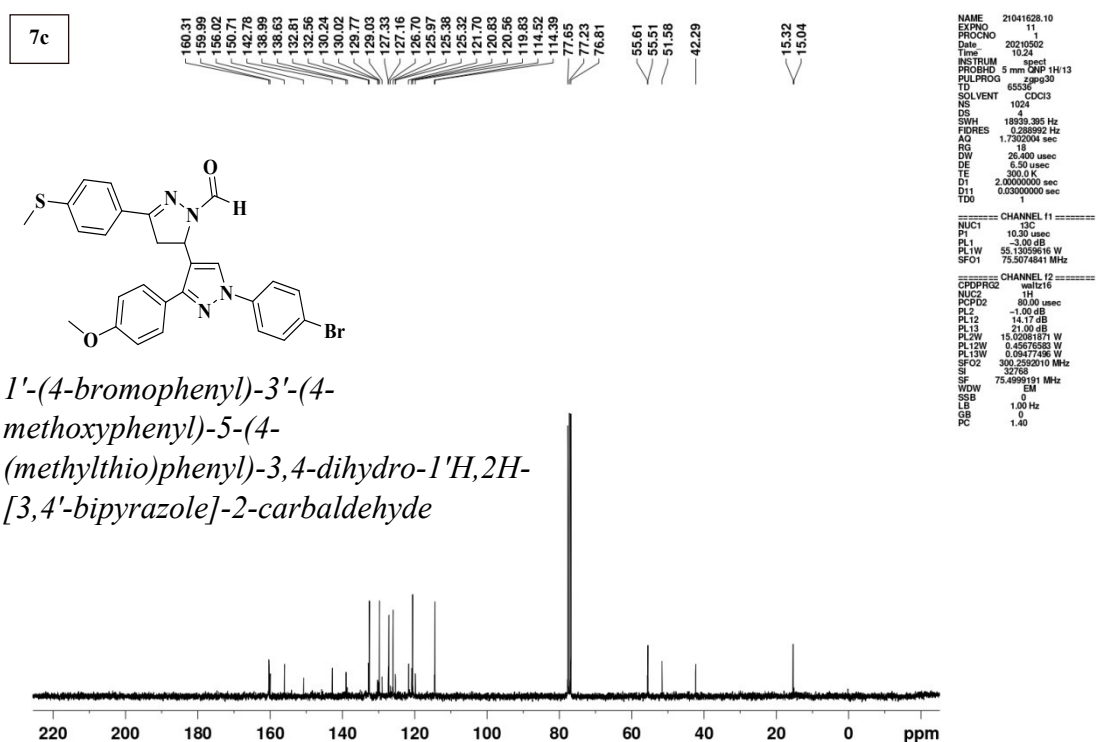
^1H -NMR spectra at 400 MHz in CDCl_3 of compound 7b



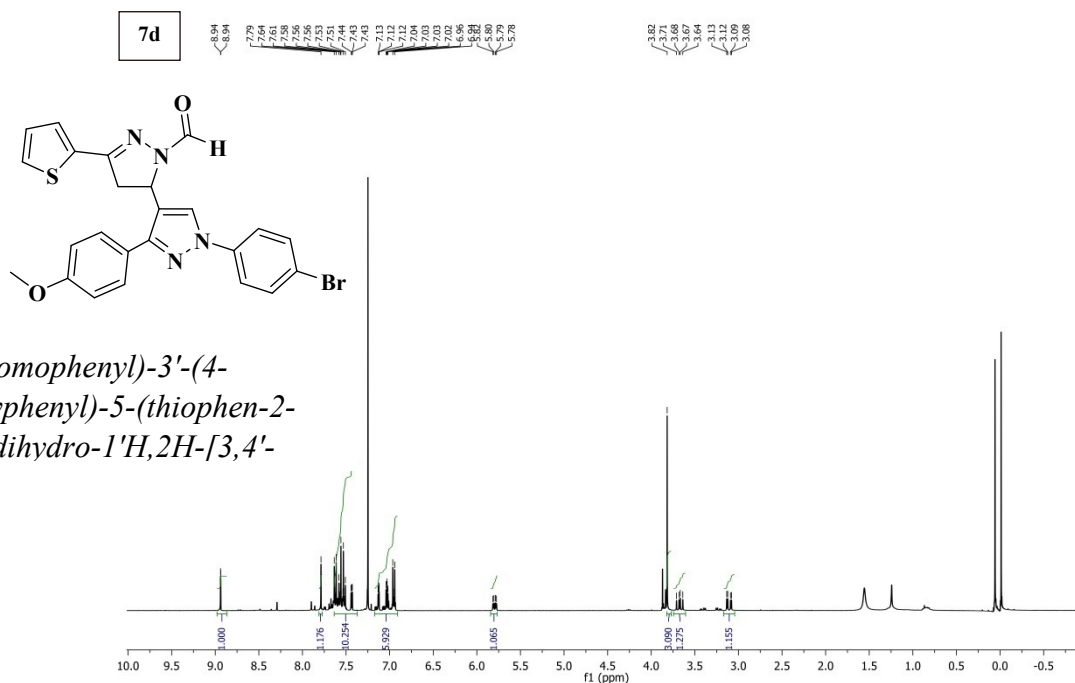
^{13}C -NMR spectra at 100 MHz in CDCl_3 of compound 7b



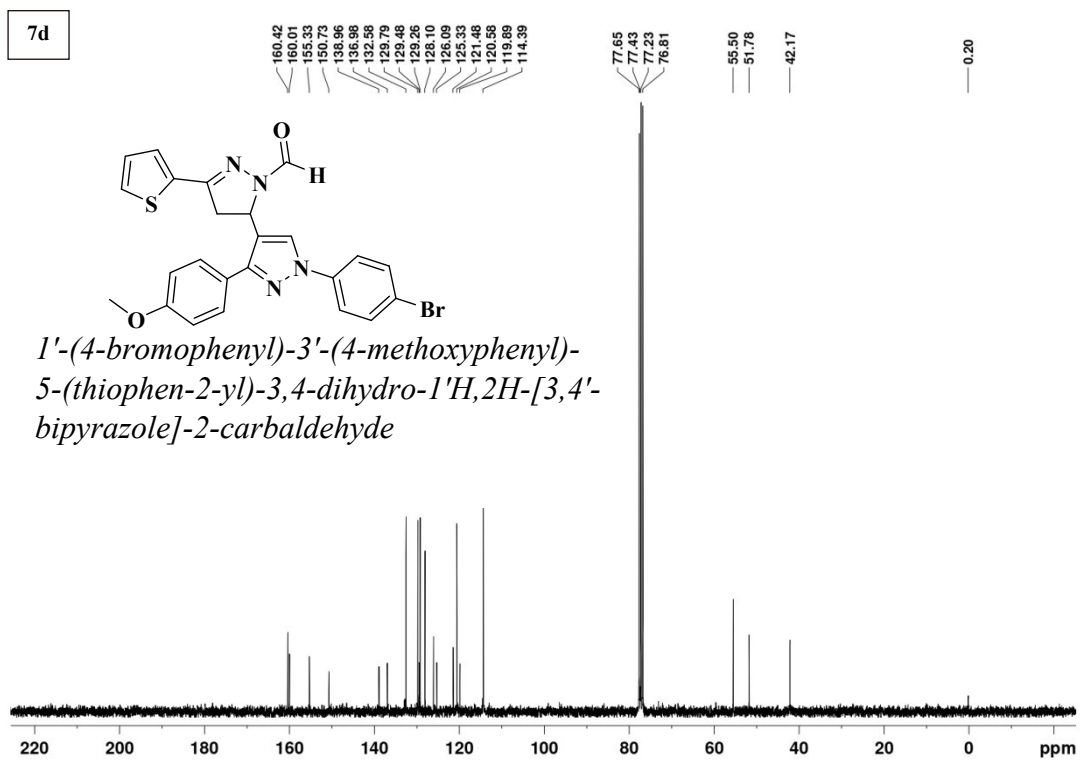
¹H-NMR spectra at 300 MHz in CDCl₃ of compound 7c



¹³C-NMR spectra at 75 MHz in CDCl₃ of compound 7c

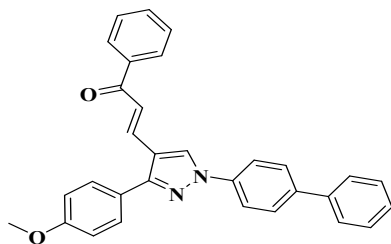
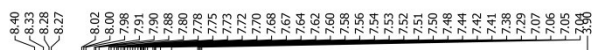


¹H-NMR spectra at 400 MHz in CDCl₃ of compound 7d

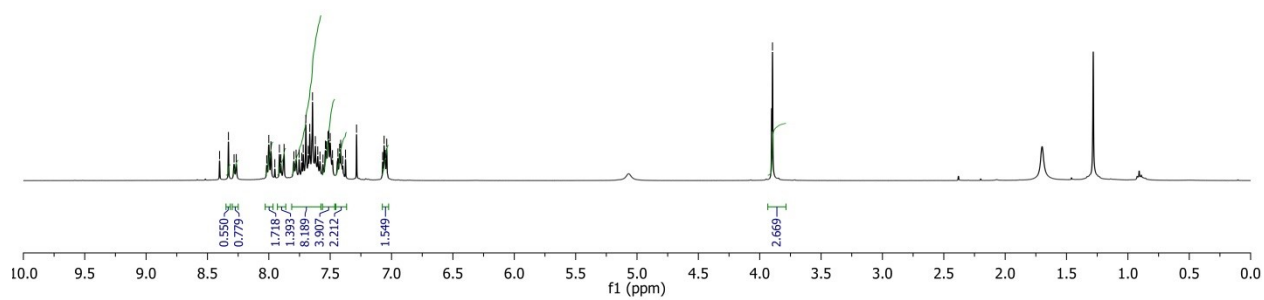


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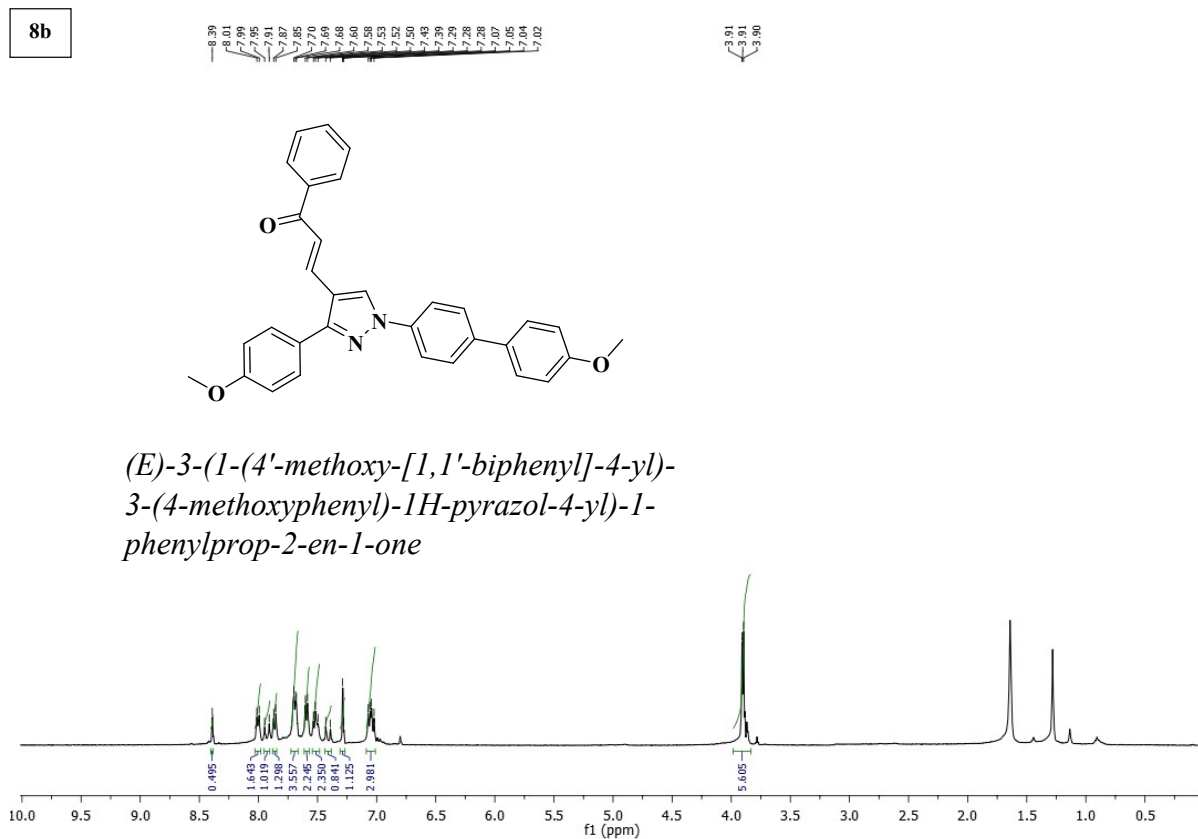
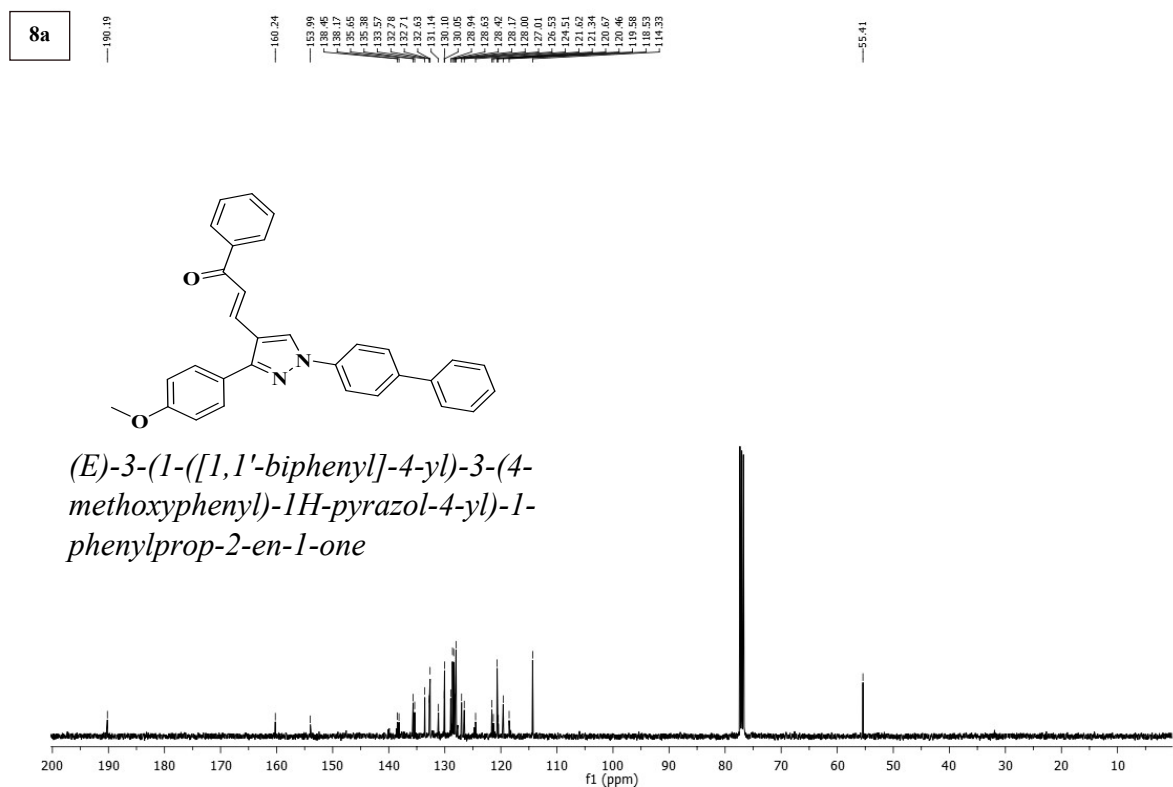
8a

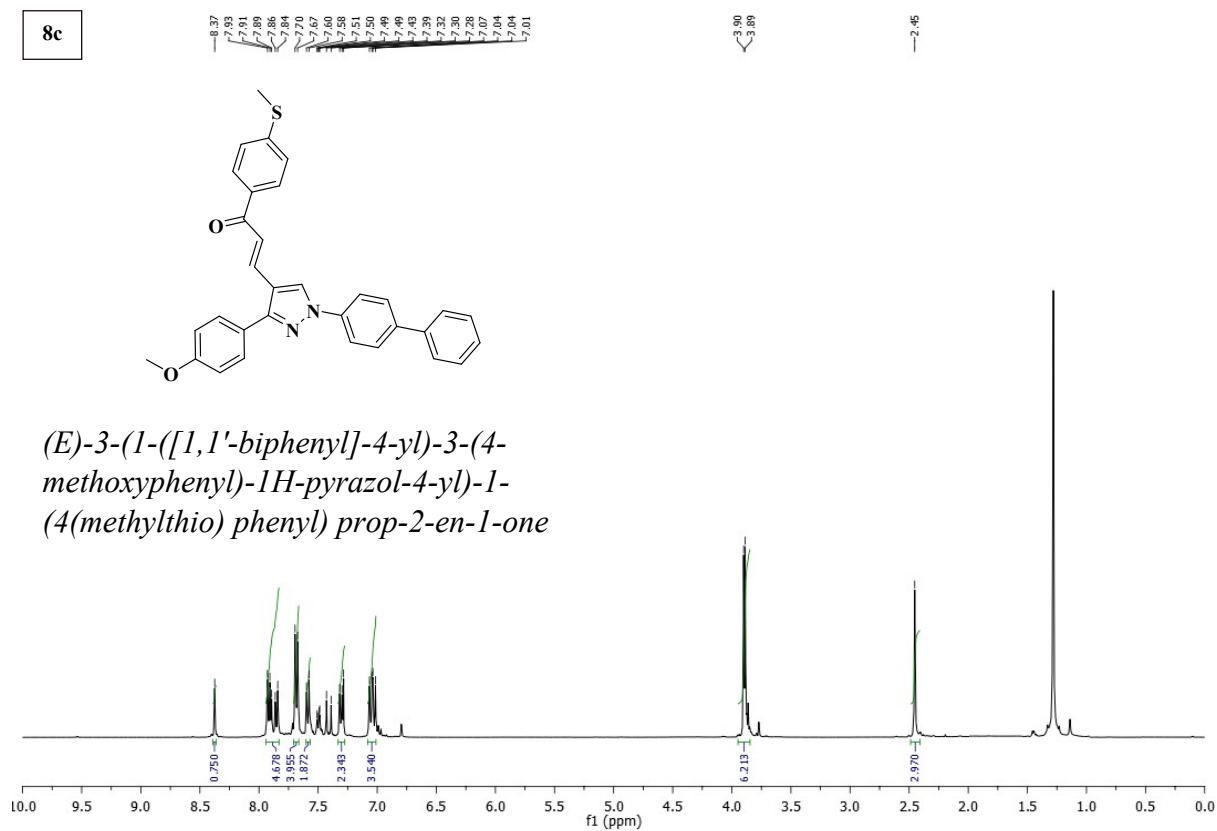
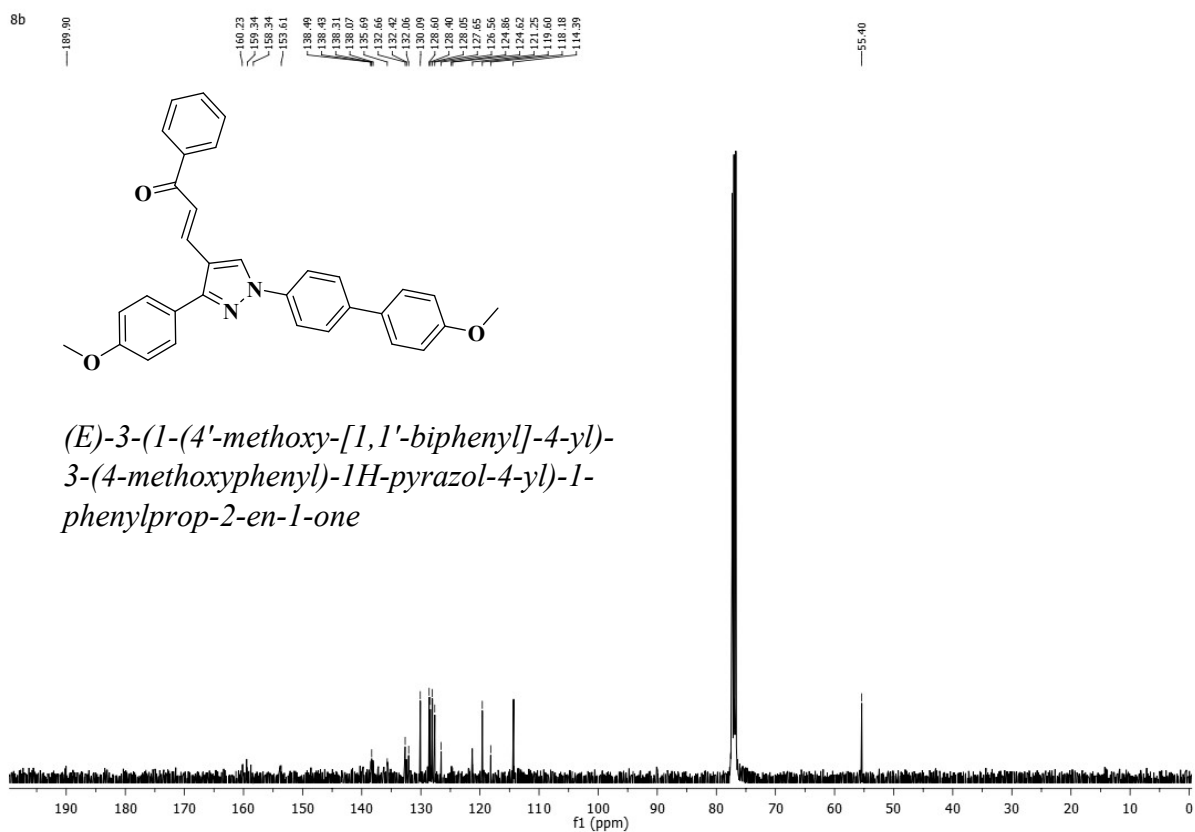


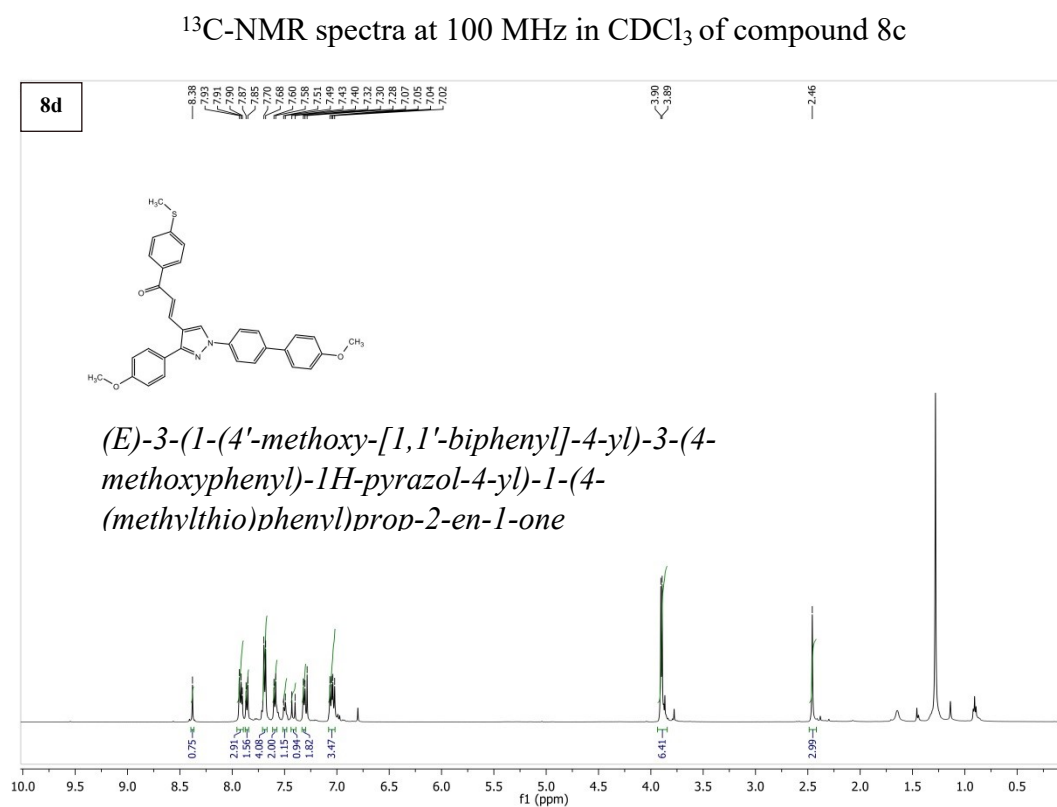
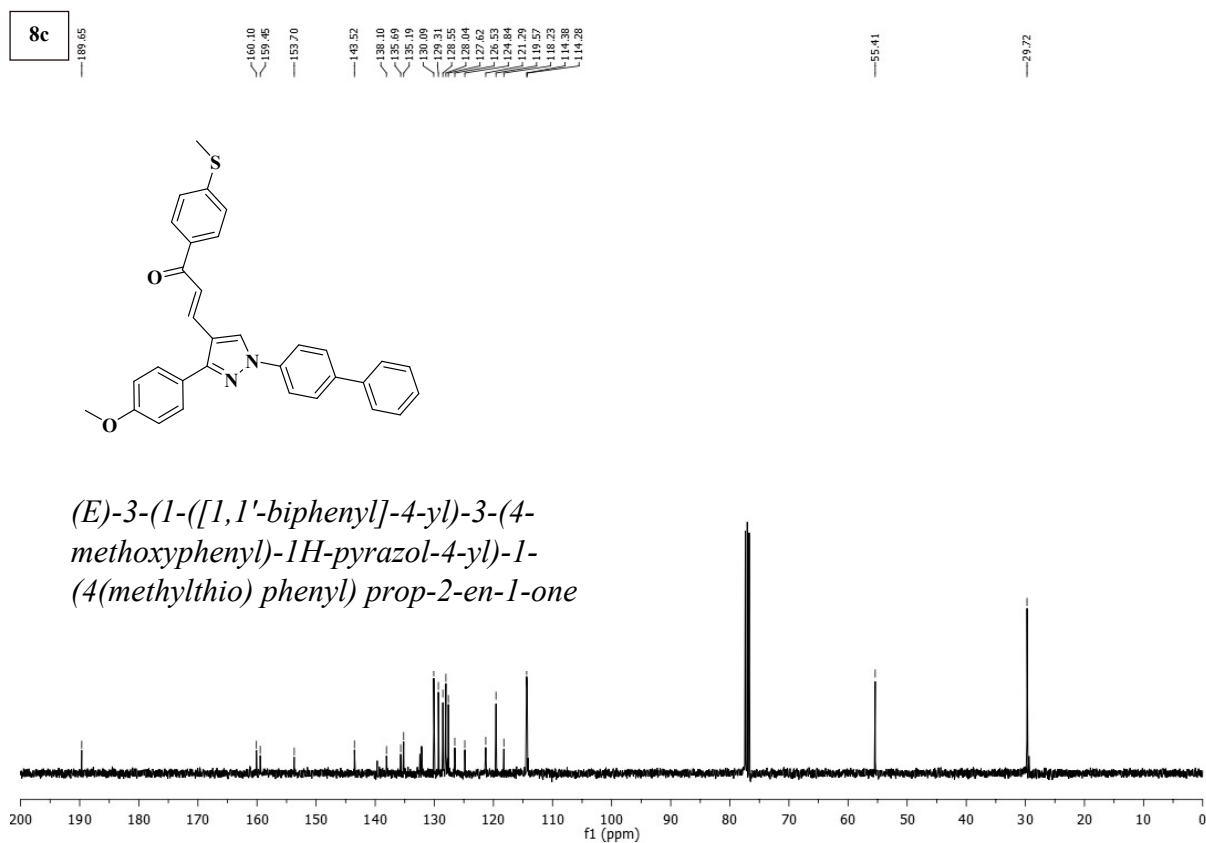
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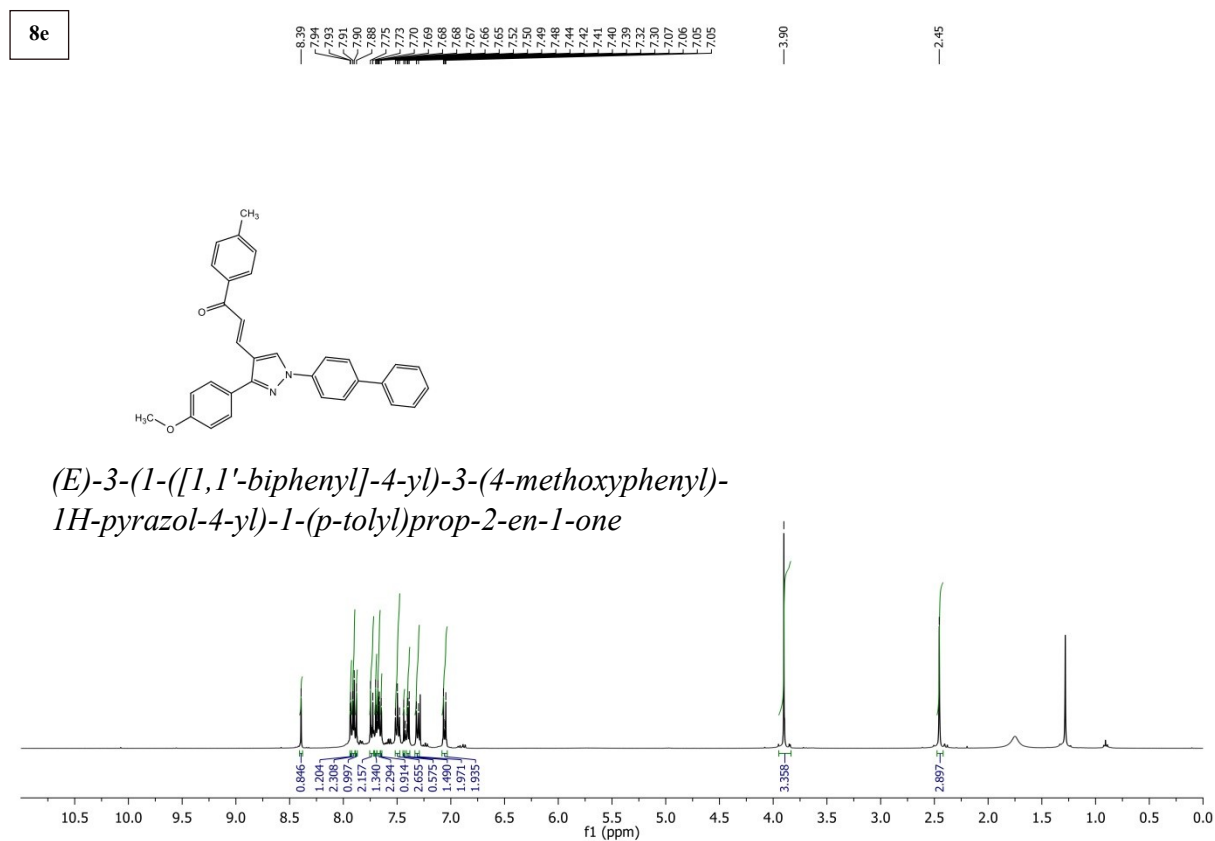
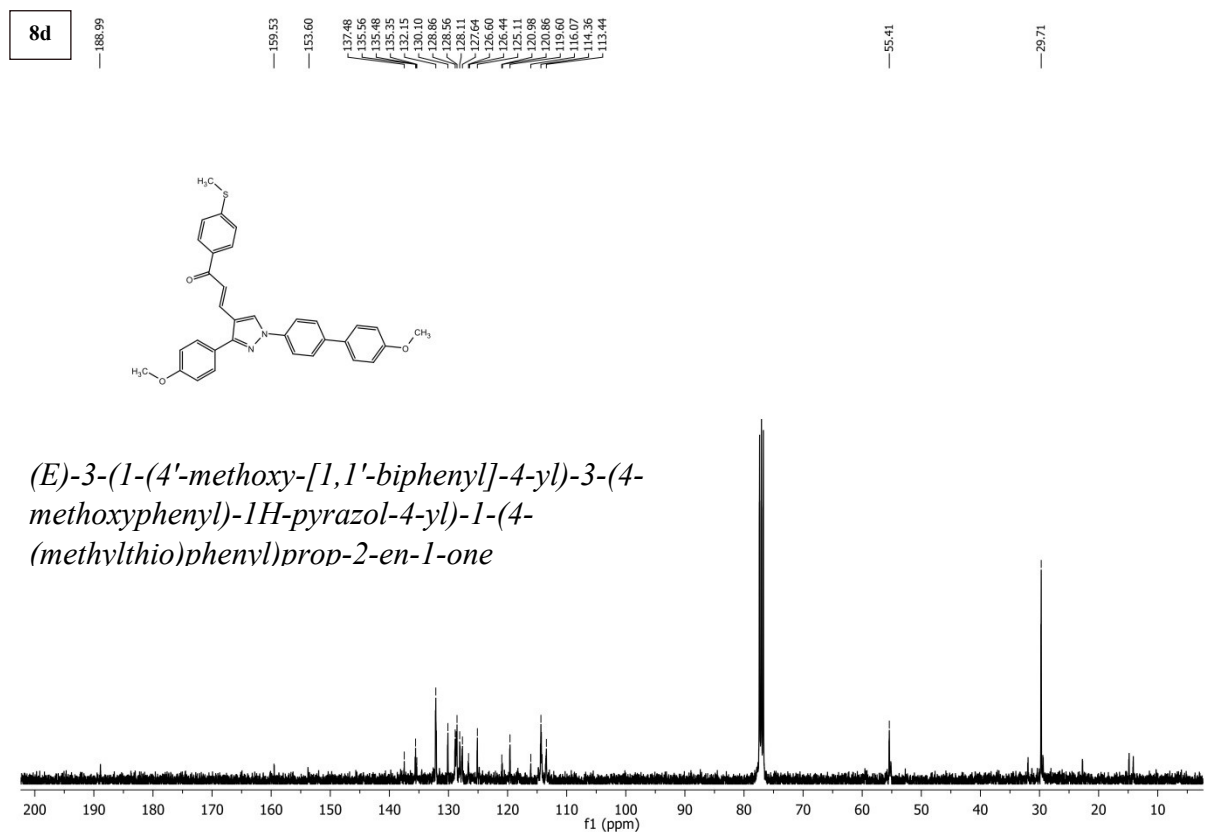


^1H -NMR spectra at 400 MHz in CDCl_3 of compound 8a

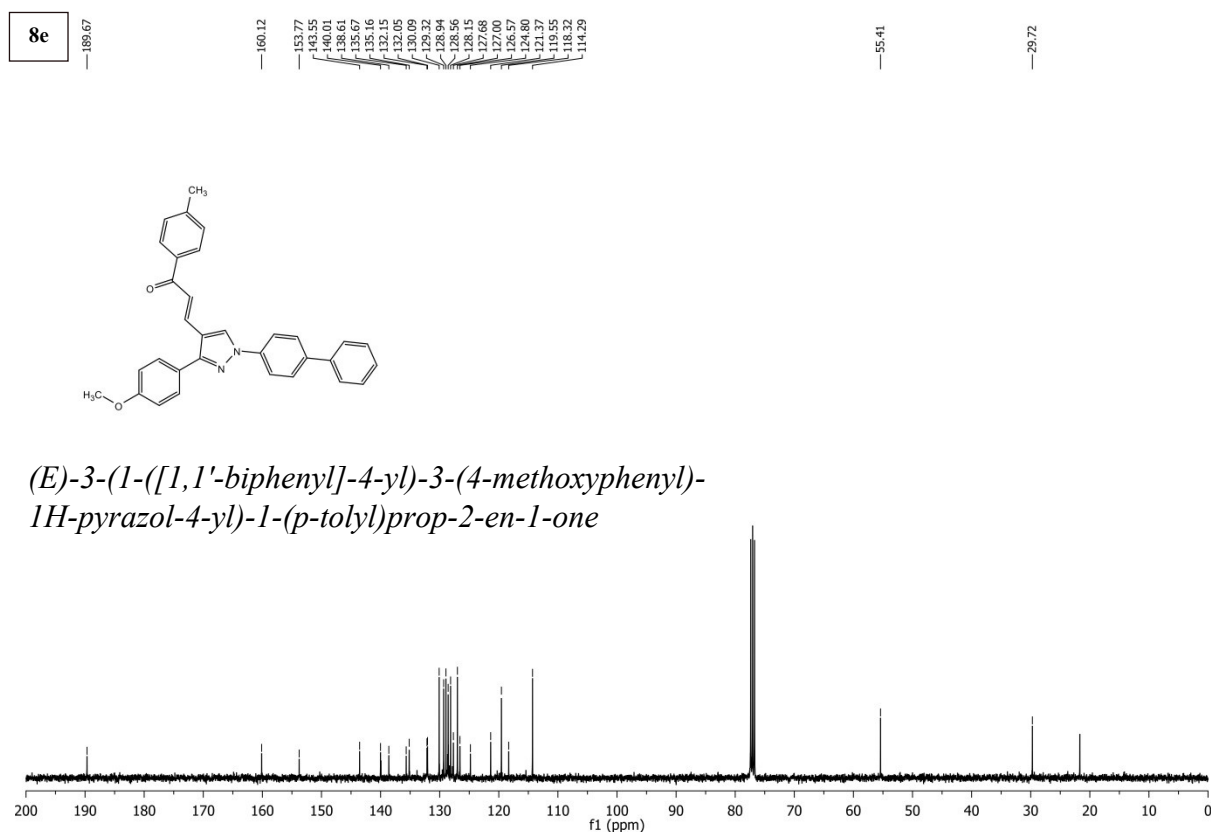




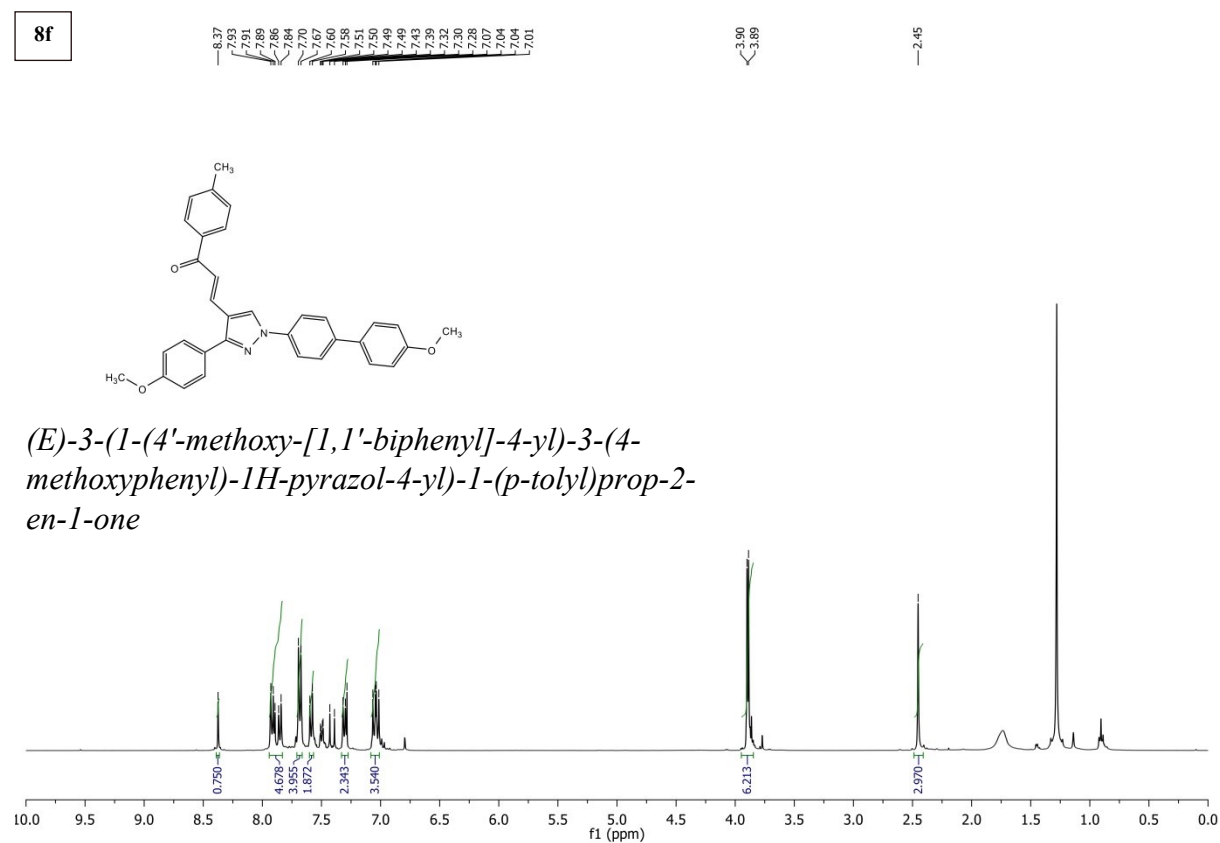




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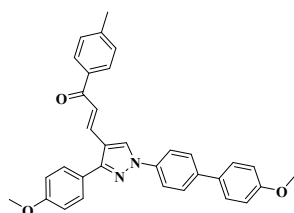


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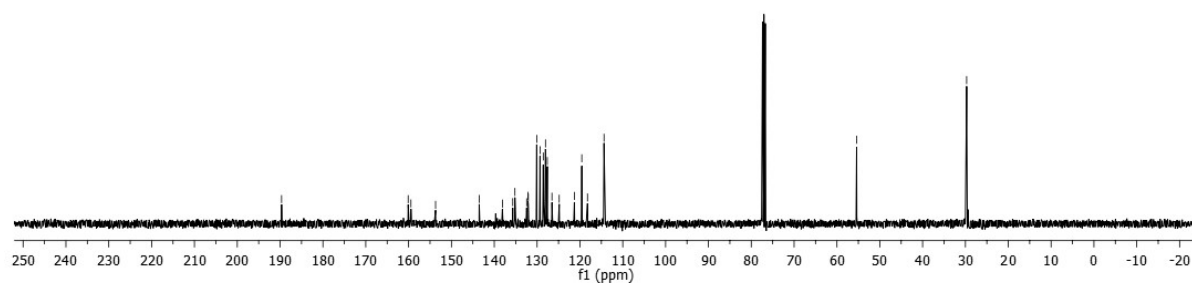


¹H-NMR spectra at 400 MHz in CDCl₃ of compound 8f

8f

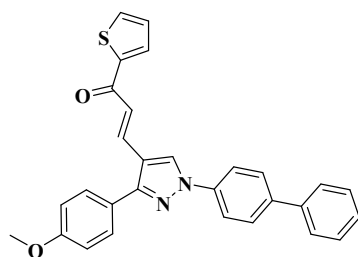


(E)-3-(1-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1-(p-tolyl)prop-2-en-1-one

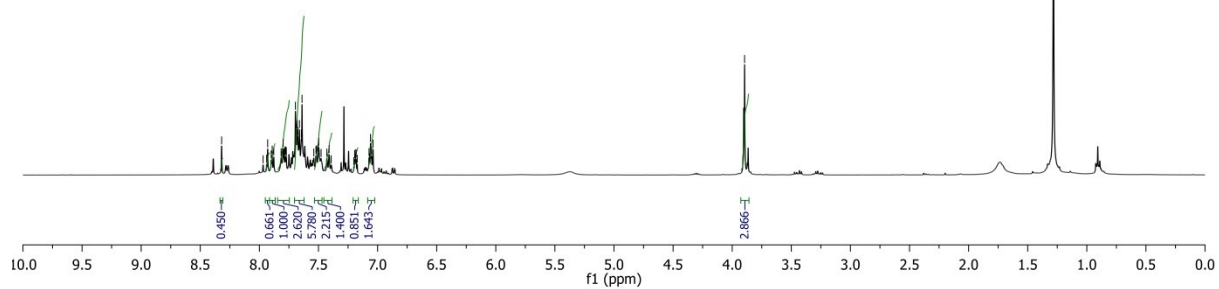


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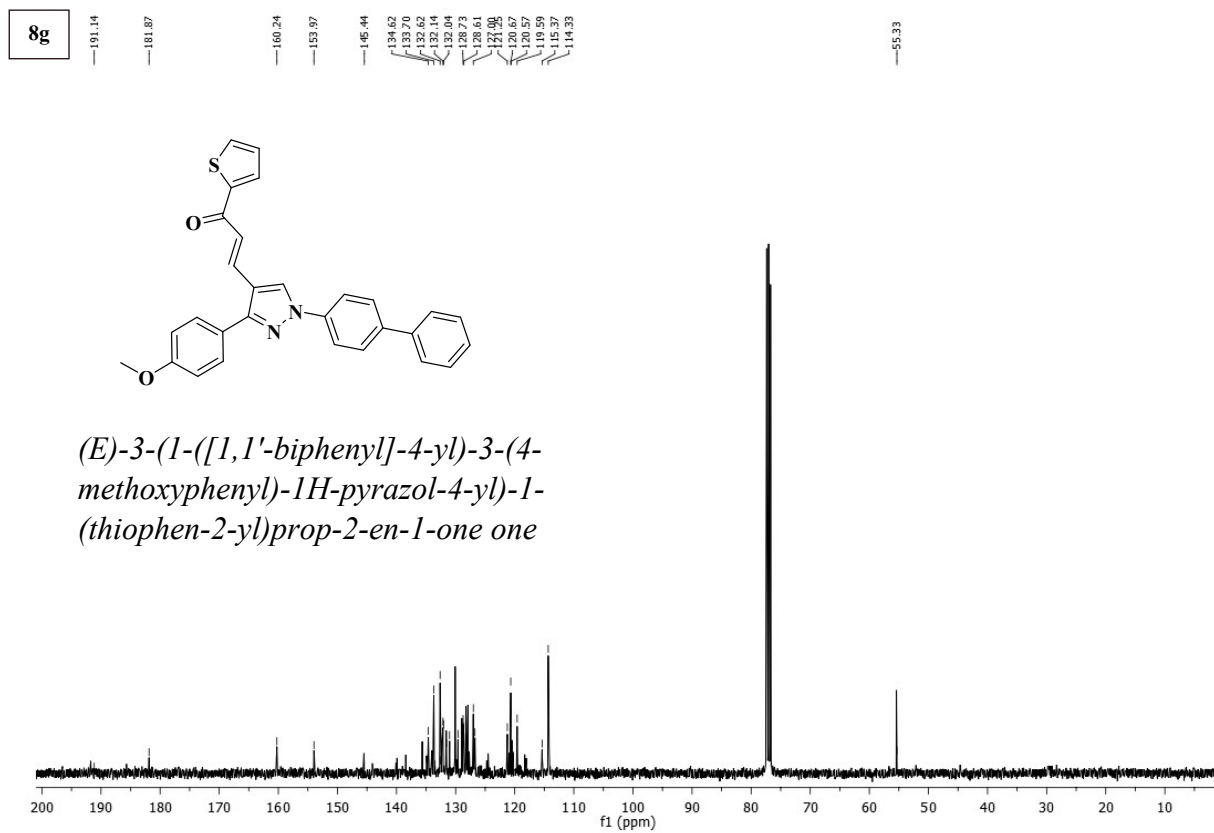
8g



(E)-3-(1-([1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one

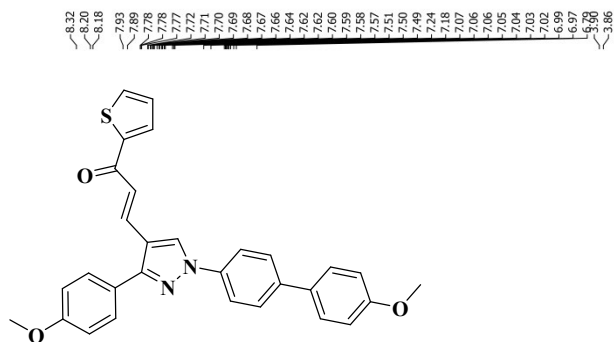


¹H-NMR spectra at 400 MHz in CDCl₃ of compound 8g

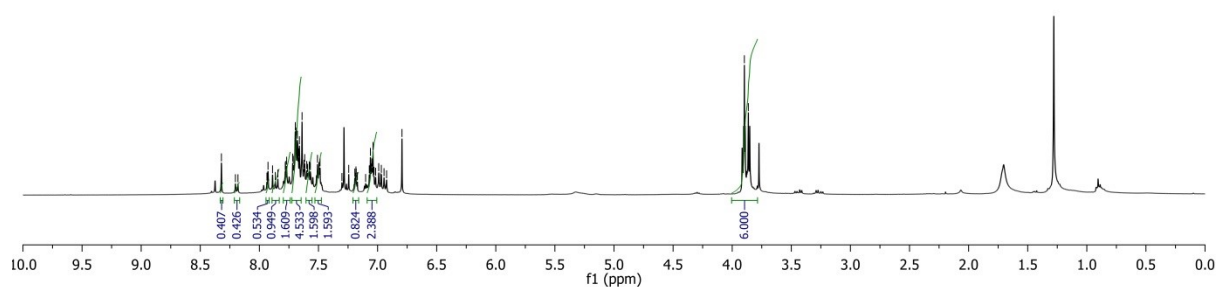


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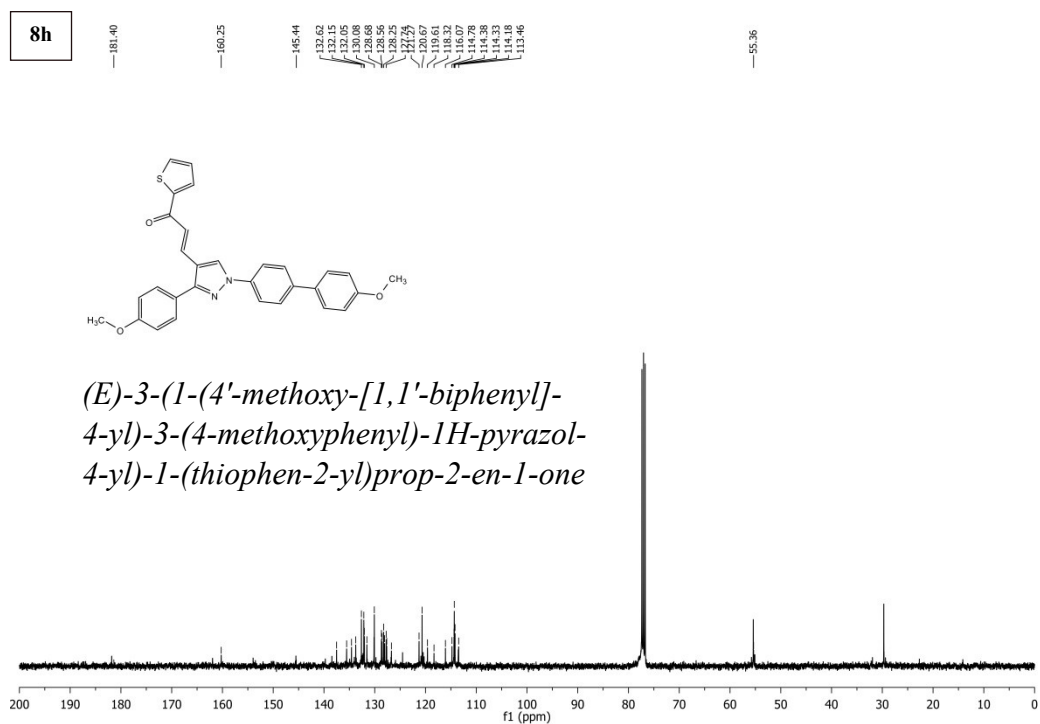
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(E)-3-(1-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one

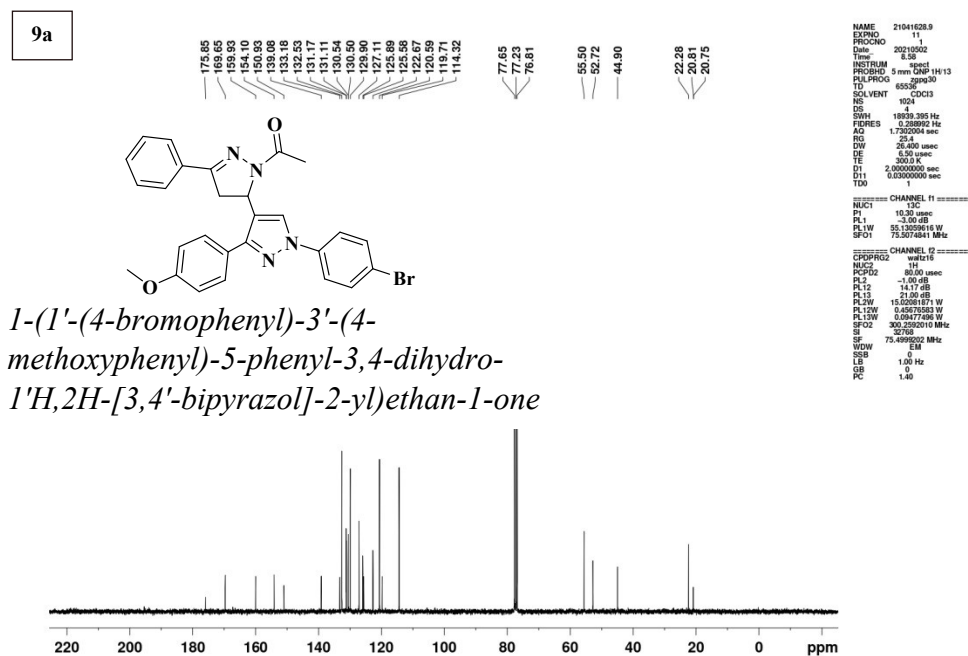
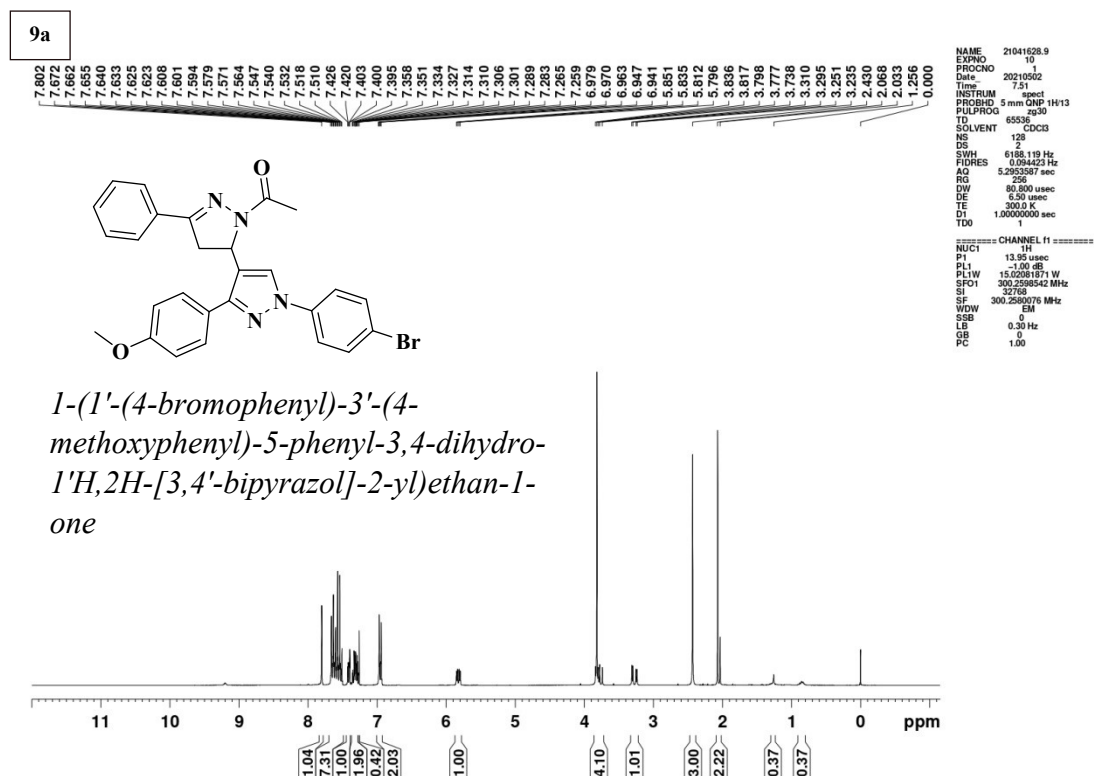


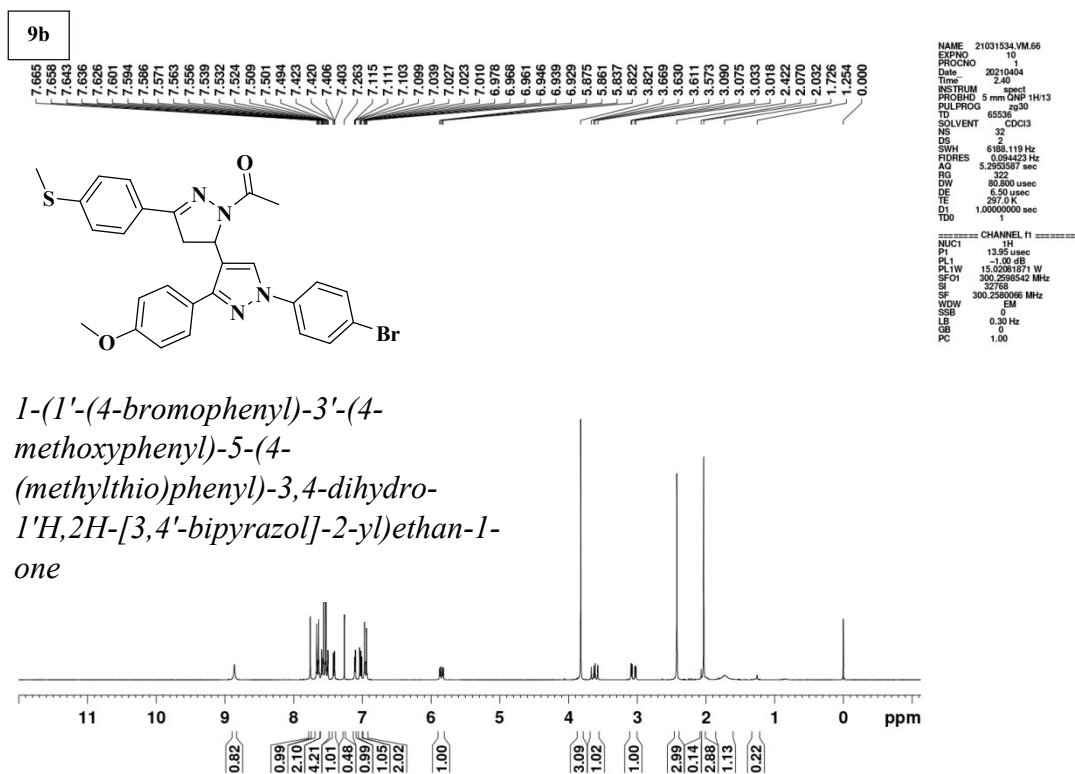
^1H -NMR spectra at 400 MHz in CDCl_3 of compound 8h



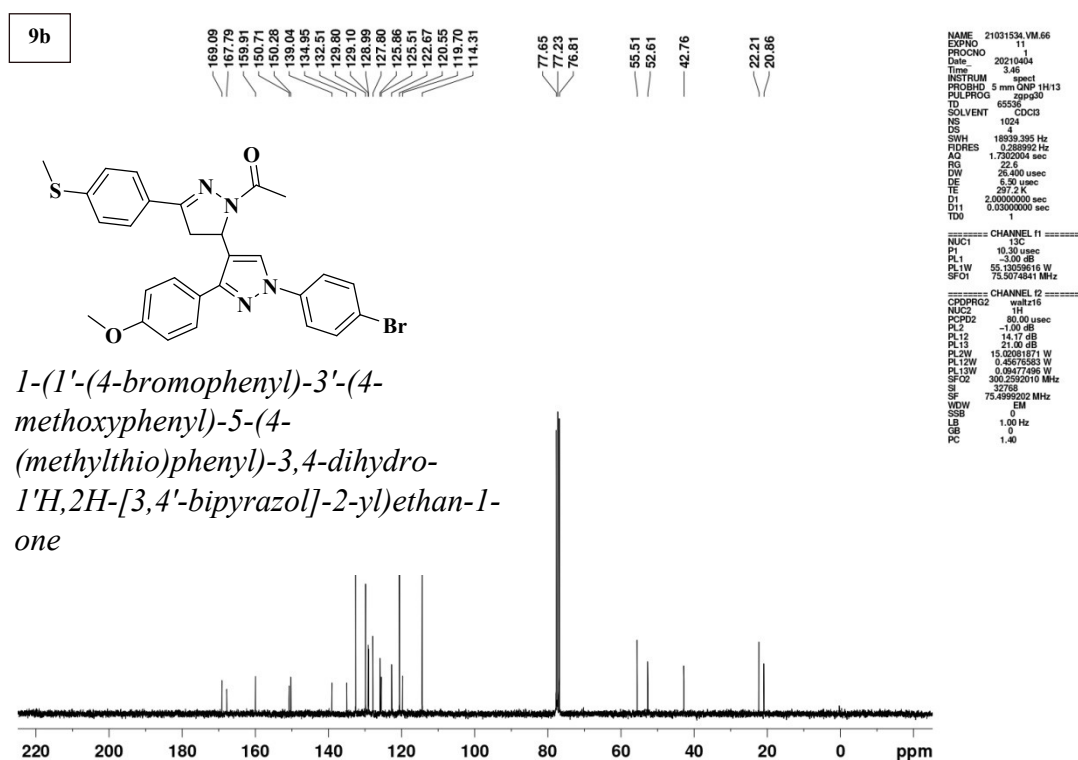
(E)-3-(1-(4'-methoxy-[1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one

^{13}C -NMR spectra at 100 MHz in CDCl_3 of compound 8h

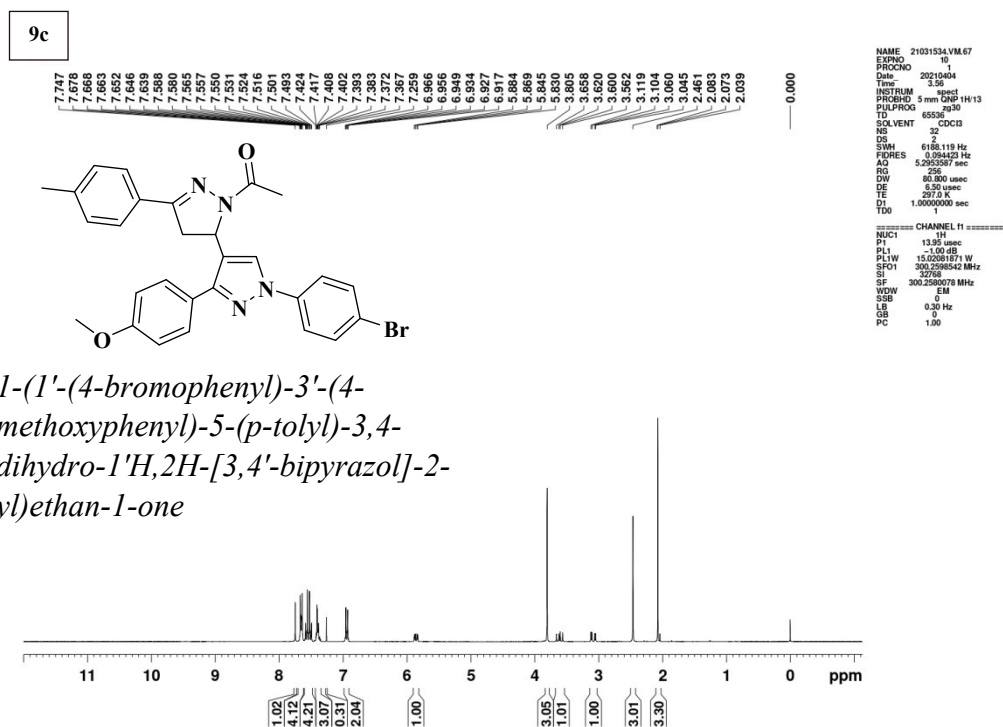




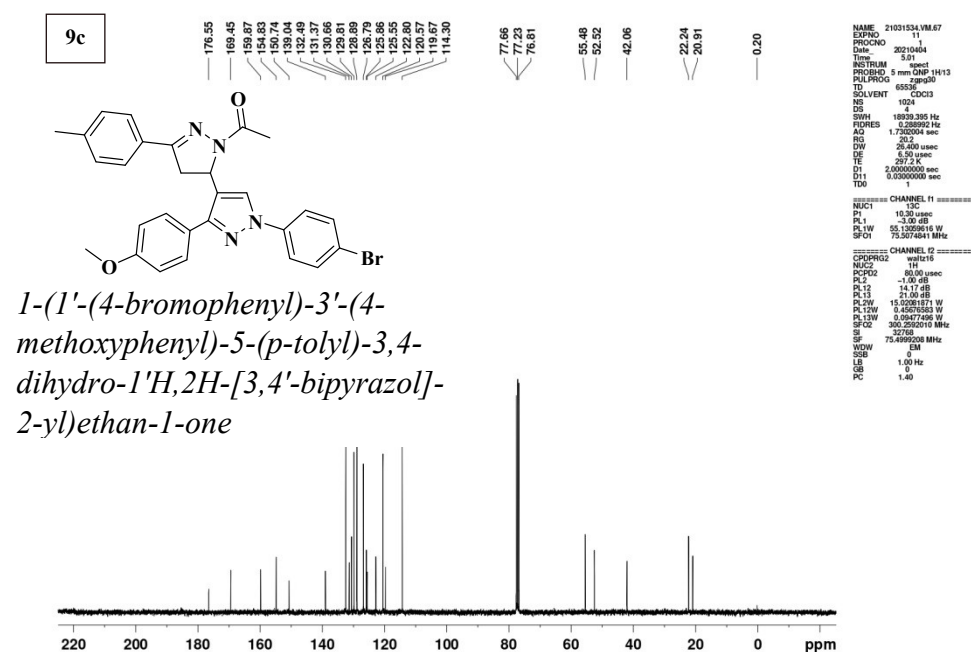
¹H-NMR spectra at 300 MHz in CDCl₃ of compound **9b**



¹³C-NMR spectra at 75 MHz in CDCl₃ of compound **9b**



¹H-NMR spectra at 300 MHz in CDCl₃ of compound **9c**



¹³C-NMR spectra at 75 MHz in CDCl₃ of compound **9c**

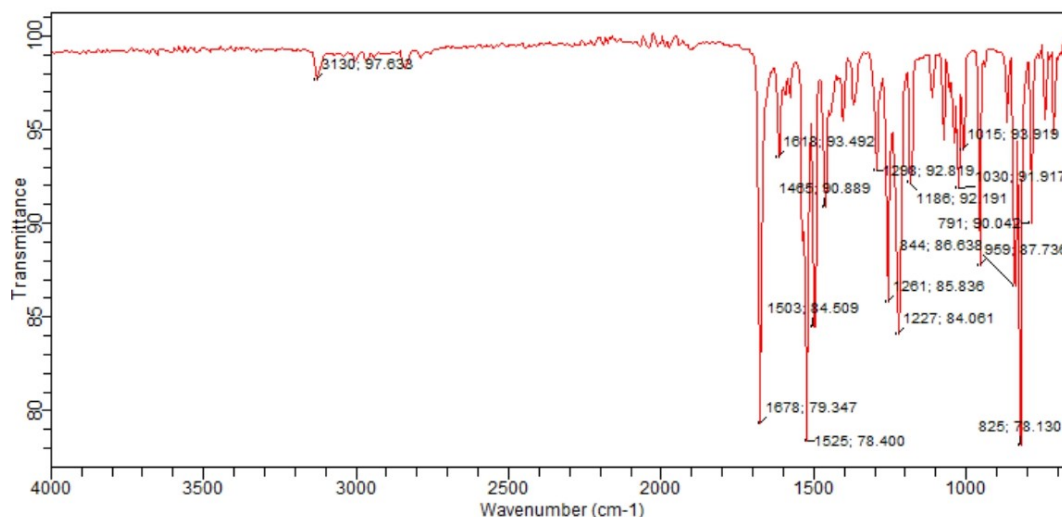
Figure S1. The ¹H and ¹³C NMR spectra of **4**, **5a**, **5b**, **6a-6d**, **7a-7d**, **8a-8h** and **9a-9c** synthesised compounds.



Agilent Technologies

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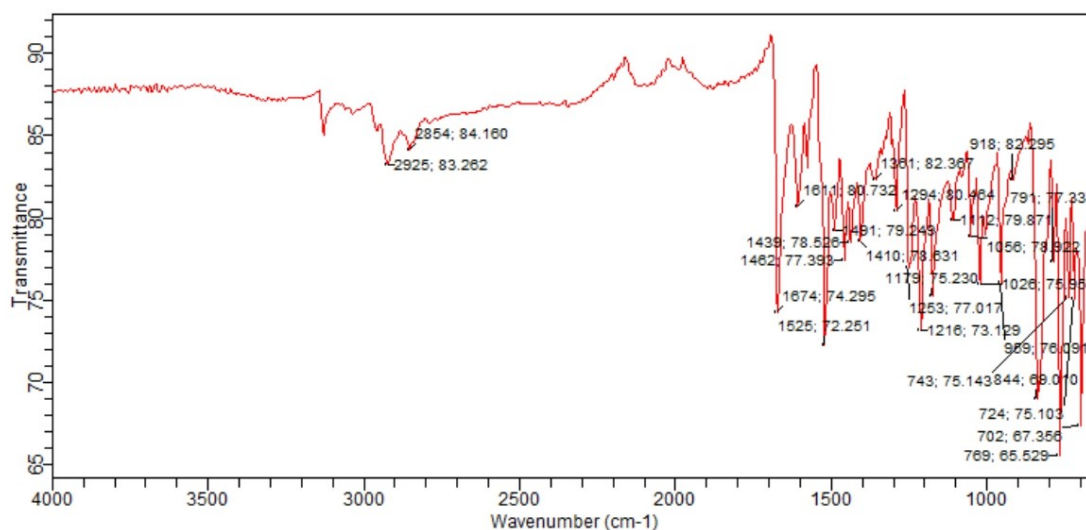
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Agilent Technologies

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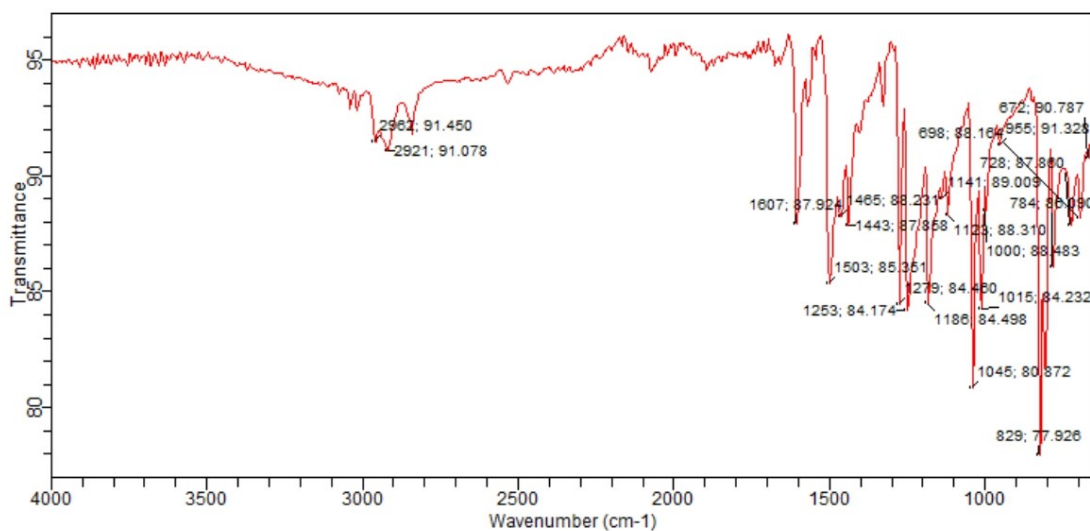
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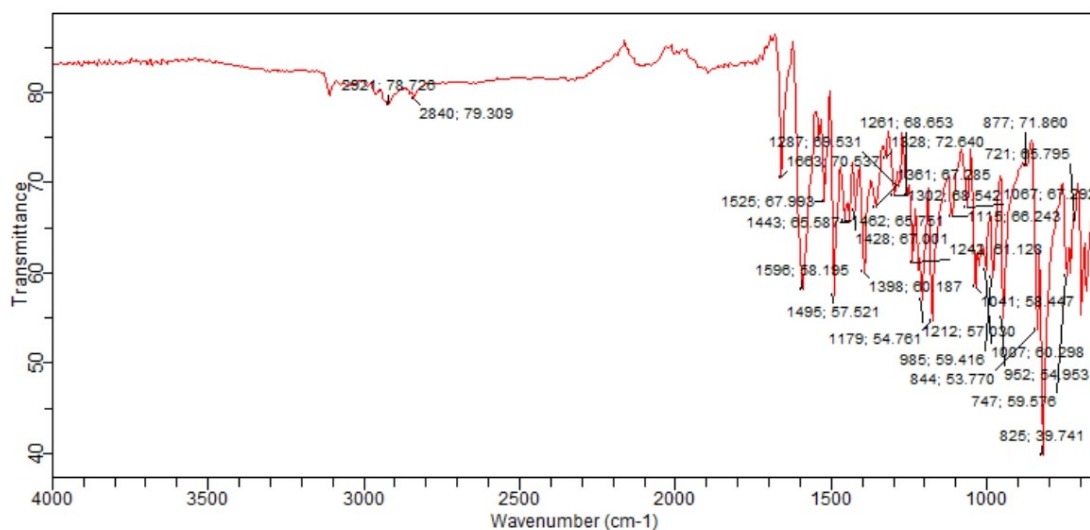
Agilent Technologies

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Agilent Technologies

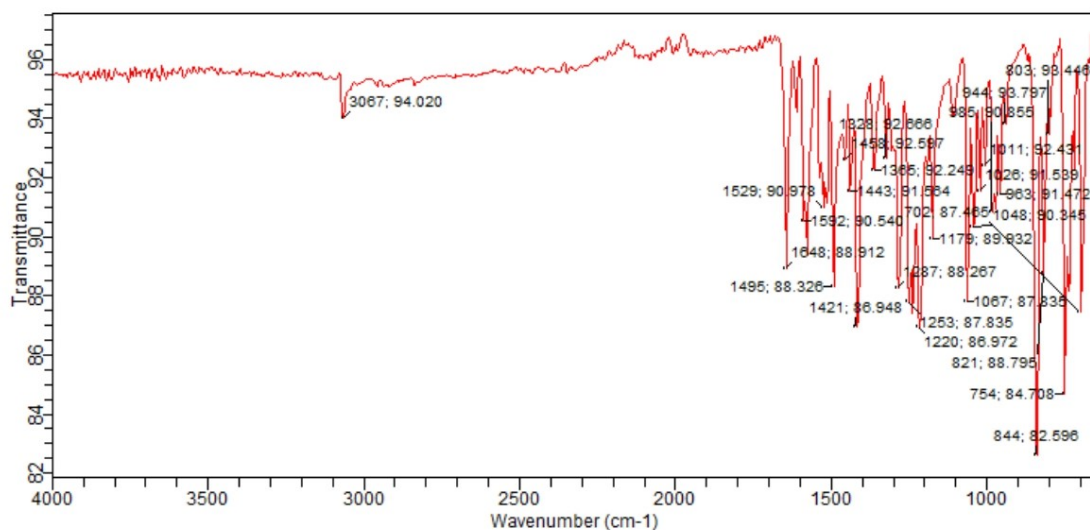
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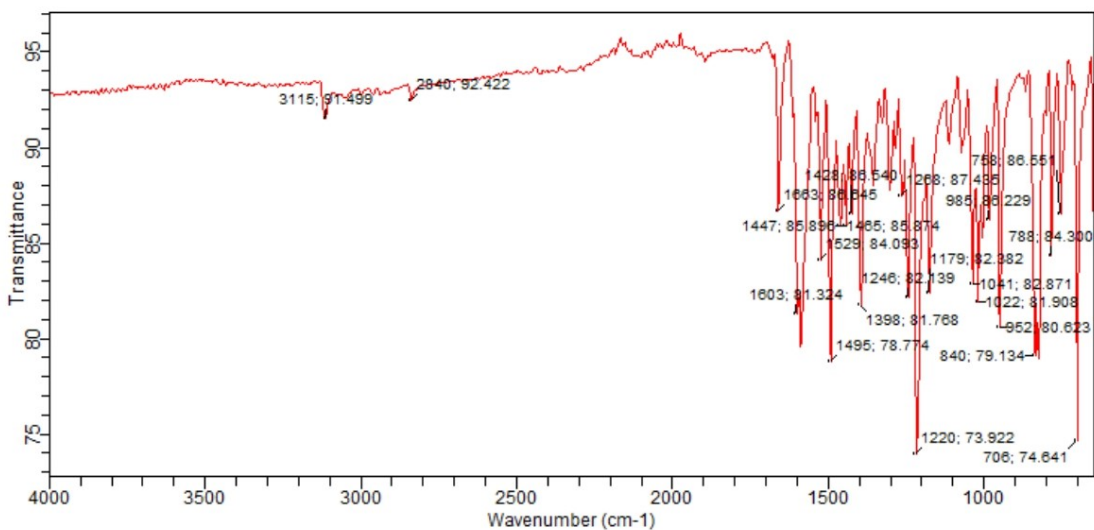
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File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM45_2022-08-30T16-58-17.a2r



Agilent Technologies

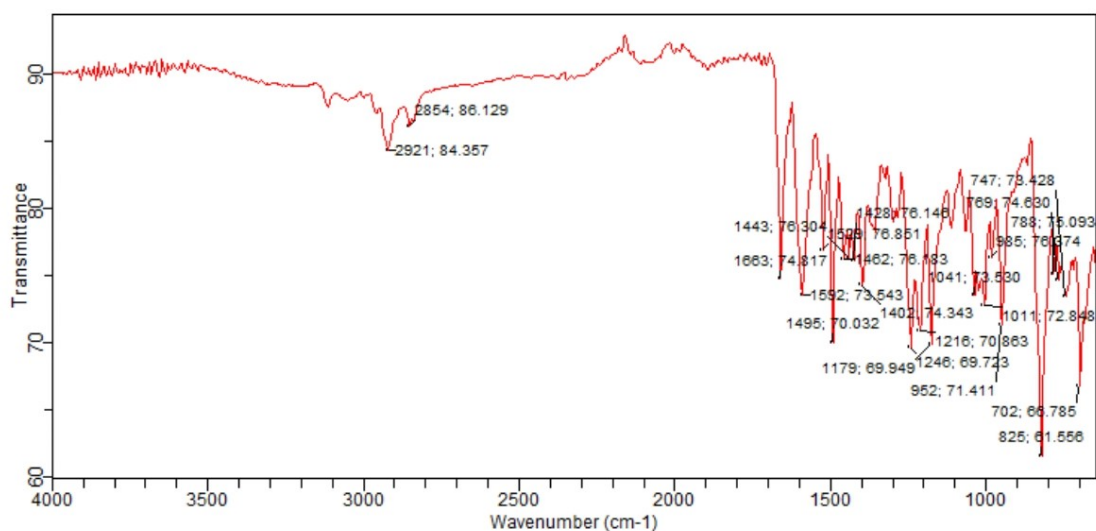
Sample ID: **6c** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 17:00:44
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM46_2022-08-30T17-01-22.a2r





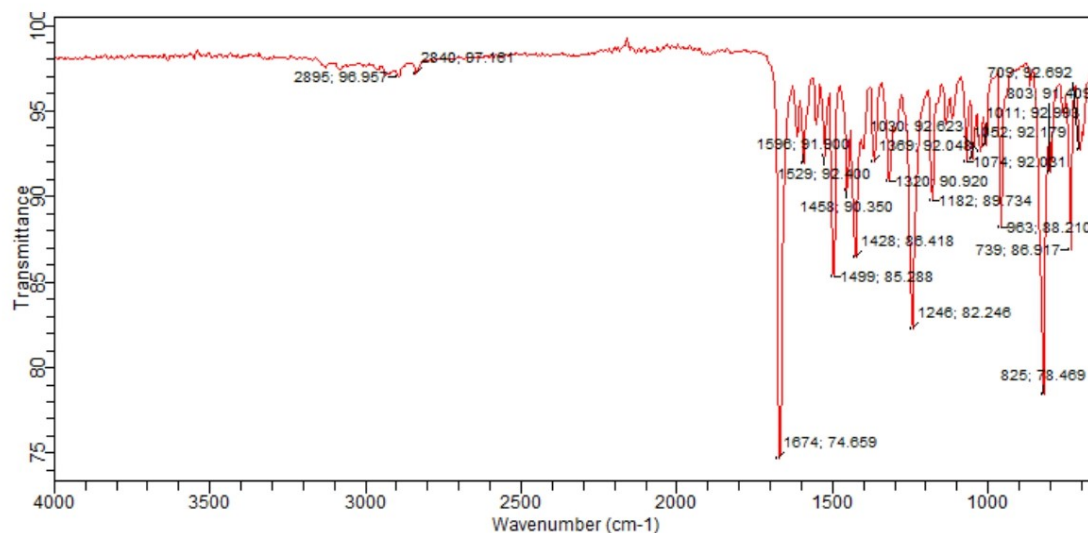
Agilent Technologies

Sample ID: **6d** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 17:06:47
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM50_2022-08-30T17-07-40.a2r



Agilent Technologies

Sample ID: **7a** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 17:08:25
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM55_2022-08-30T17-08-59.a2r

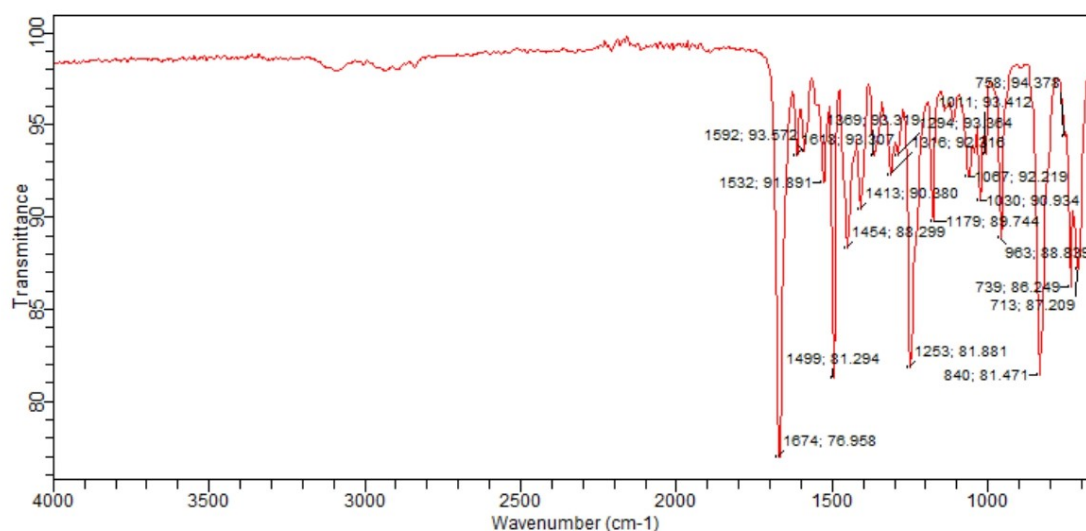




Agilent Technologies

Sample ID: 7b
Sample Scans: 64
Background Scans: 16
Resolution: 8 cm⁻¹
System Status: Good
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM56_2022-08-30T17-10-33.a2r

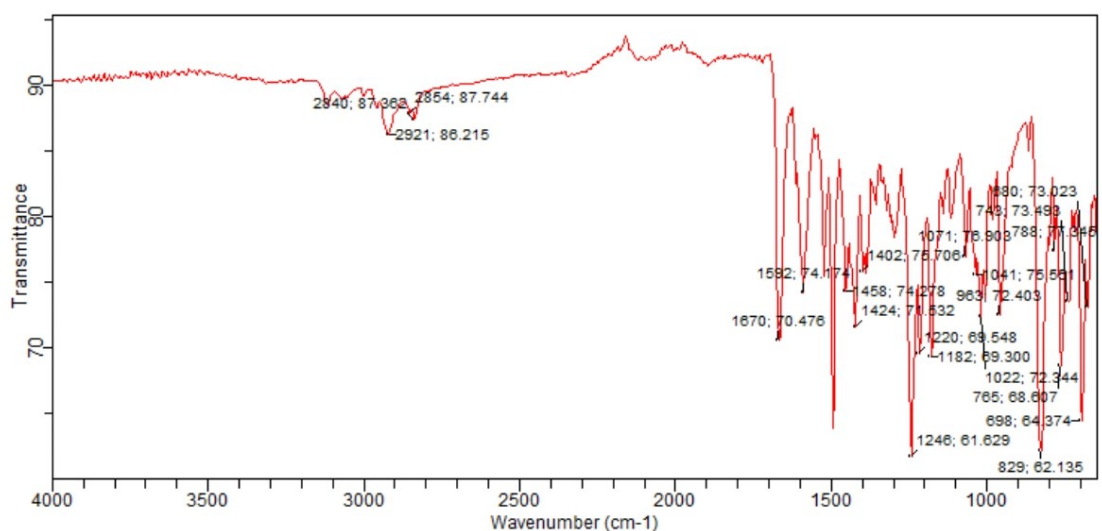
Method Name: jamia
User: abid
Date/Time: 30-08-2022 17:09:55
Range: 4000.00 - 650.00
Apodization: Happ-Genzel



Agilent Technologies

Sample ID: 7c
Sample Scans: 64
Background Scans: 16
Resolution: 8 cm⁻¹
System Status: Good
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM52_2022-08-30T17-02-56.a2r

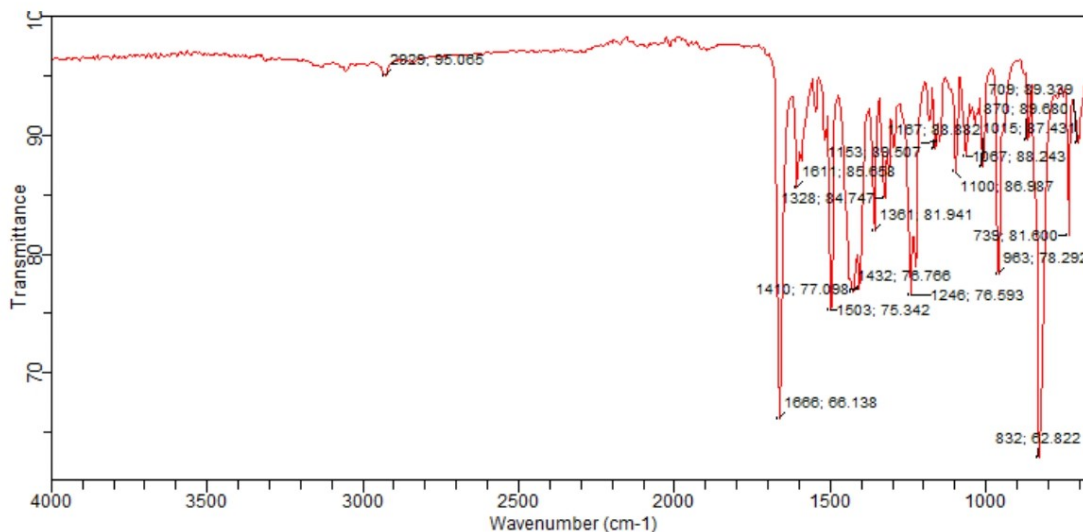
Method Name: jamia
User: abid
Date/Time: 30-08-2022 17:02:22
Range: 4000.00 - 650.00
Apodization: Happ-Genzel





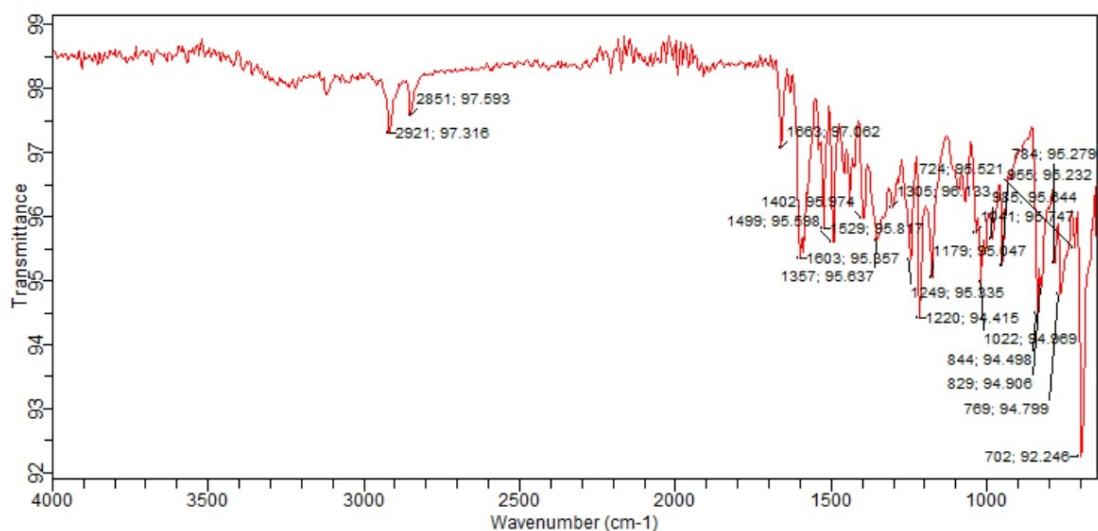
Agilent Technologies

Sample ID: **7d** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 17:12:41
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\12_2022-08-30T17-13-23.a2r



Agilent Technologies

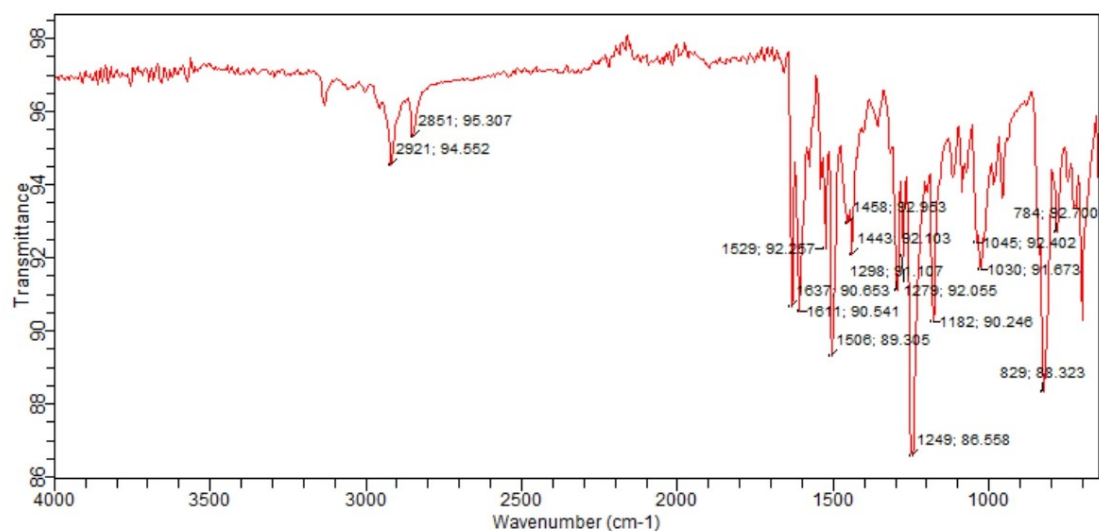
Sample ID: **8a** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 16:36:11
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC16_2022-08-30T16-37-27.a2r





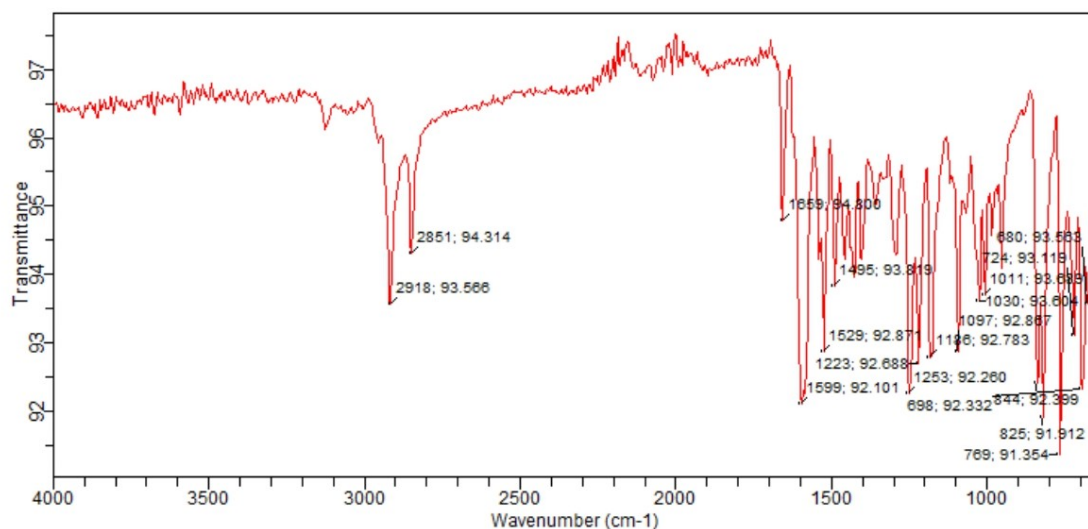
Agilent Technologies

Sample ID: **8b** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 16:49:29
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC17_2022-08-30T16-50-07.a2r



Agilent Technologies

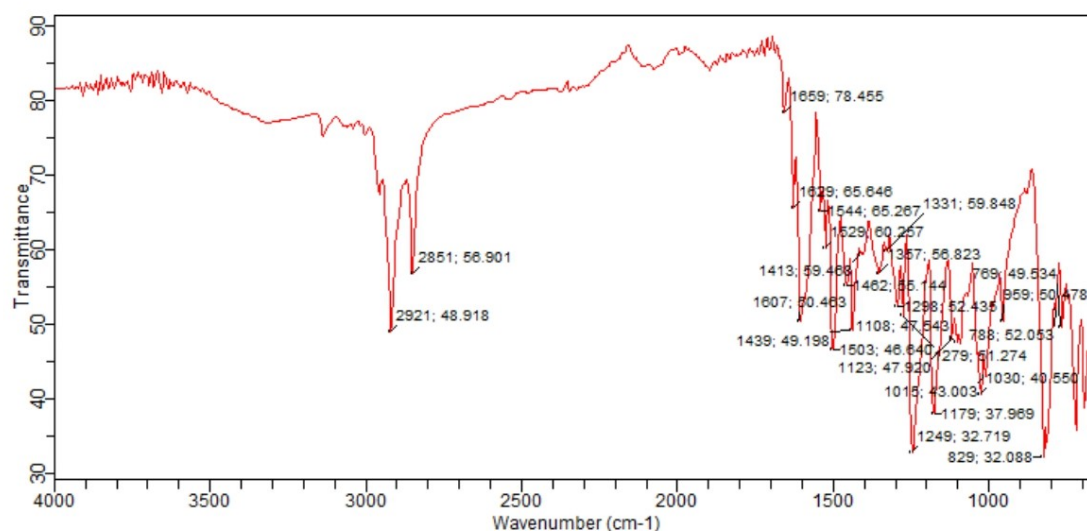
Sample ID: **8c** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 16:39:46
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC19_2022-08-30T16-40-44.a2r





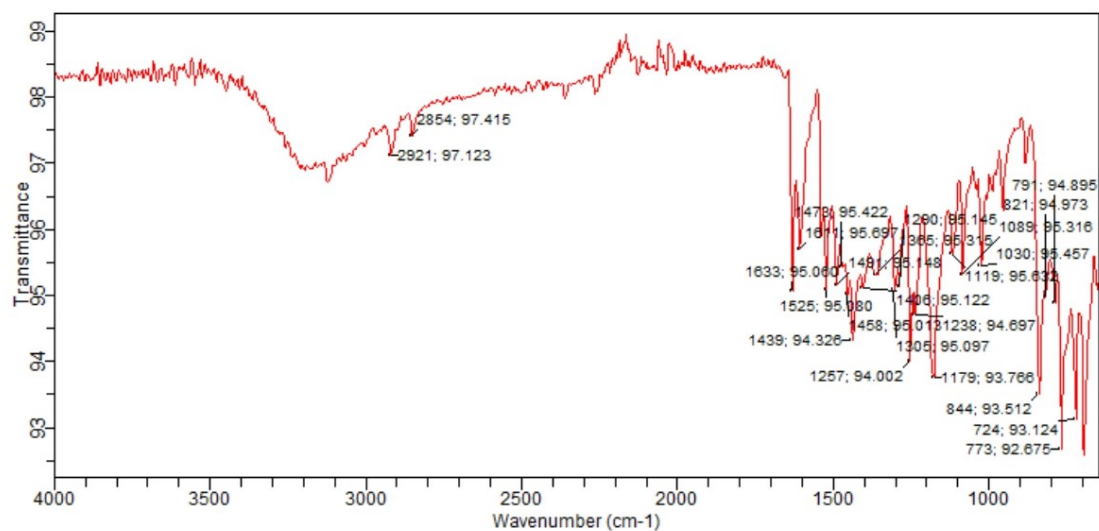
Agilent Technologies

Sample ID: **8d** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 16:45:56
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC20_2022-08-30T16-46-35.a2r



Agilent Technologies

Sample ID: **8e** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 16:44:19
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC22_2022-08-30T16-44-59.a2r

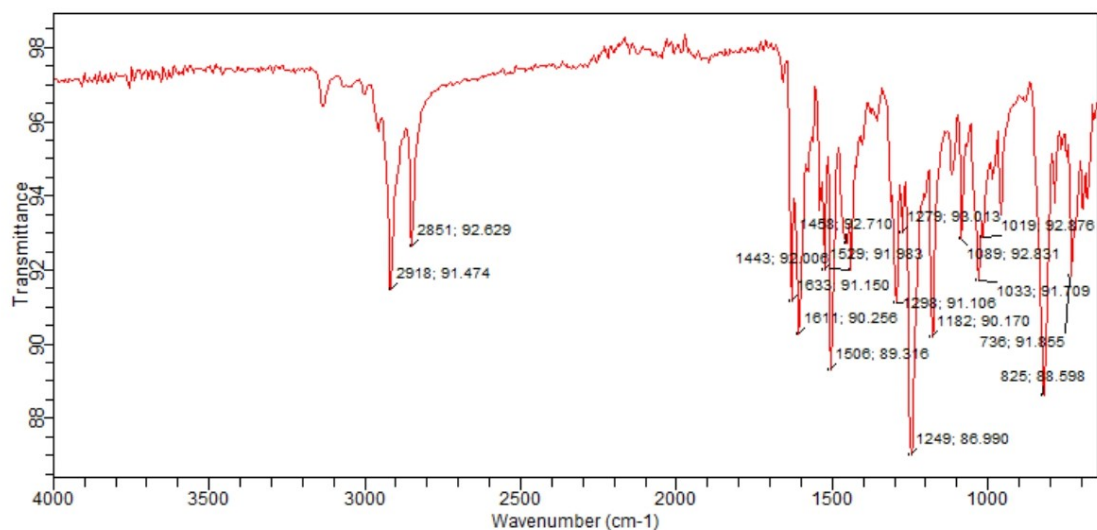




Agilent Technologies

Sample ID: 8f
Sample Scans: 64
Background Scans: 16
Resolution: 8 cm⁻¹
System Status: Good
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC23_2022-08-30T16-48-32.a2r

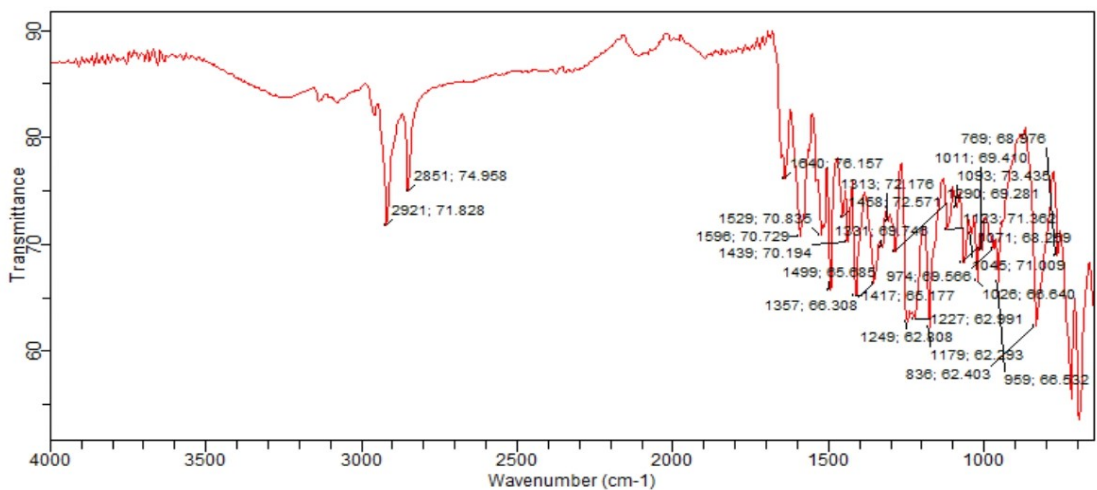
Method Name: jamia
User: abid
Date/Time: 30-08-2022 16:47:49
Range: 4000.00 - 650.00
Apodization: Happ-Genzel



Agilent Technologies

Sample ID: 8g
Sample Scans: 64
Background Scans: 16
Resolution: 8 cm⁻¹
System Status: Good
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC24_2022-08-30T16-42-49.a2r

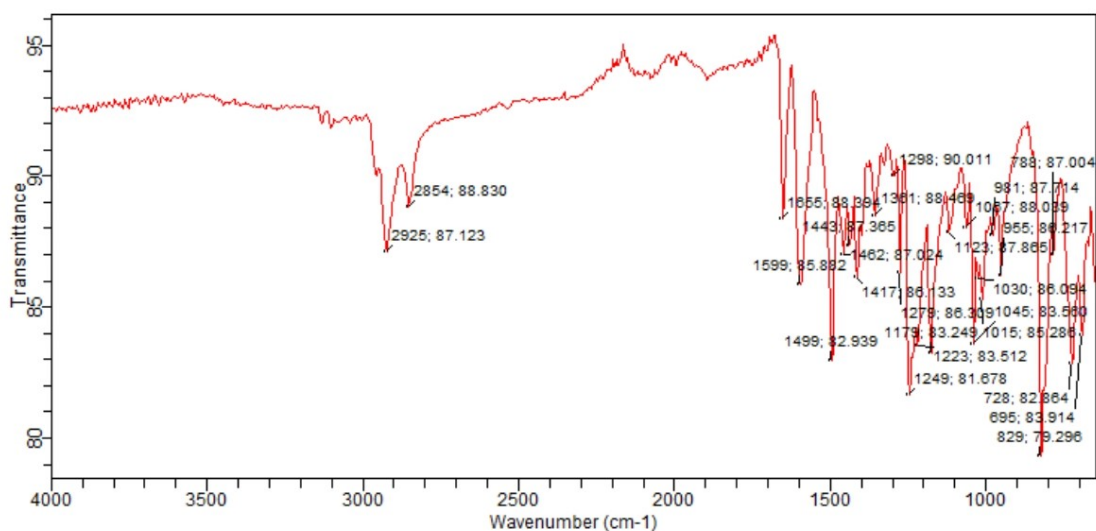
Method Name: jamia
User: abid
Date/Time: 30-08-2022 16:42:12
Range: 4000.00 - 650.00
Apodization: Happ-Genzel





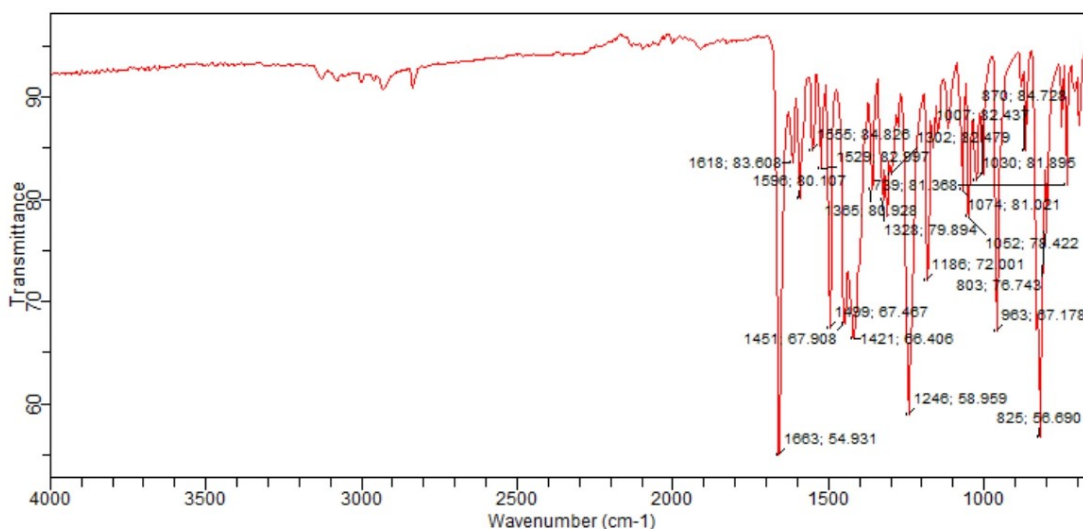
Agilent Technologies

Sample ID: **8h** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 16:51:03
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\SC25_2022-08-30T16-51-44.a2r



Agilent Technologies

Sample ID: **9a** Method Name: jamia
Sample Scans: 64 User: abid
Background Scans: 16 Date/Time: 30-08-2022 17:11:20
Resolution: 8 cm⁻¹ Range: 4000.00 - 650.00
System Status: Good Apodization: Happ-Genzel
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM64_2022-08-30T17-11-57.a2r

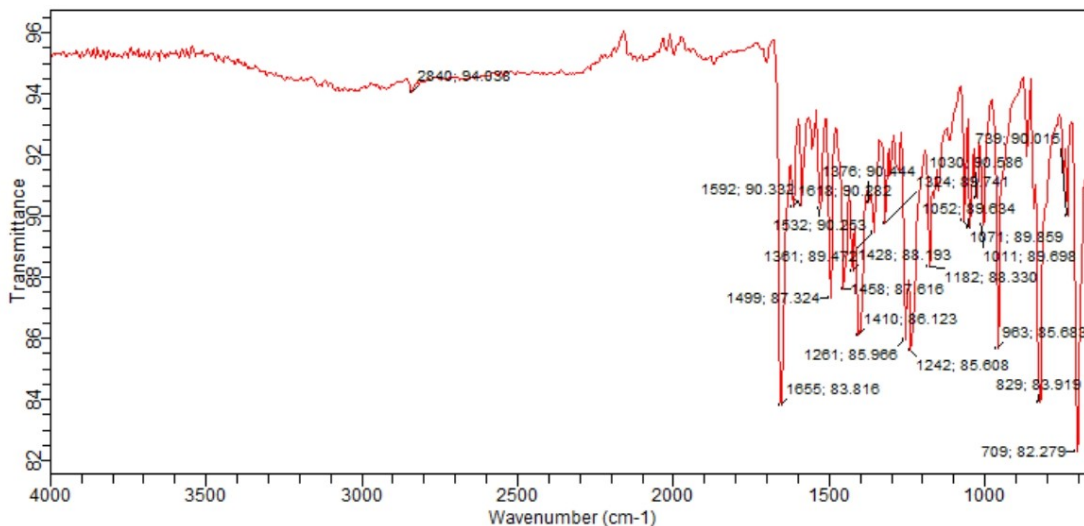




Agilent Technologies

Sample ID: **9b**
Sample Scans: 64
Background Scans: 16
Resolution: 8 cm⁻¹
System Status: Good
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM66_2022-08-30T17-05-58.a2r

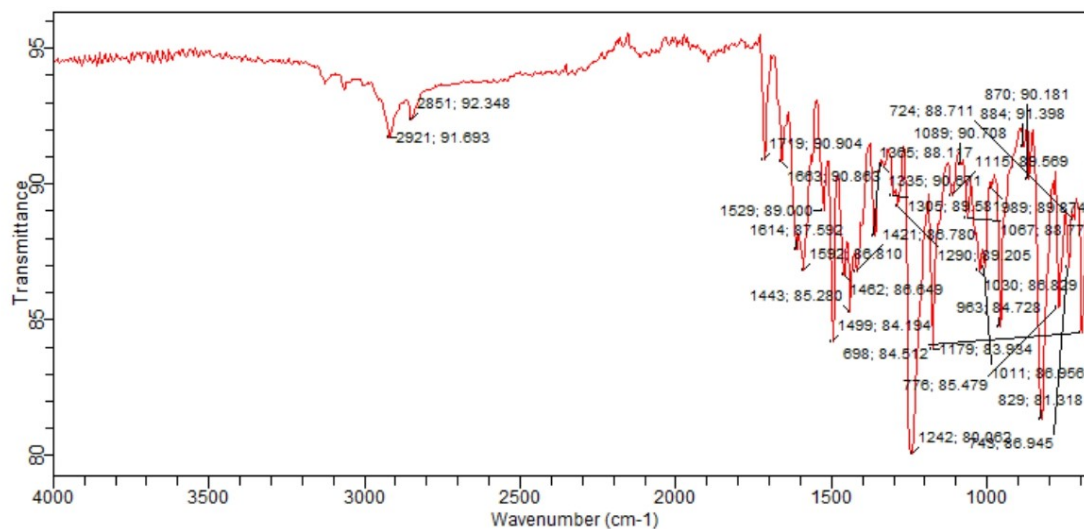
Method Name: jamia
User: abid
Date/Time: 30-08-2022 17:05:21
Range: 4000.00 - 650.00
Apodization: Happ-Genzel



Agilent Technologies

Sample ID: **9c**
Sample Scans: 64
Background Scans: 16
Resolution: 8 cm⁻¹
System Status: Good
File Location: C:\Program Files\Agilent\MicroLab PC\Results\Masood\VM67_2022-08-30T16-59-55.a2r

Method Name: jamia
User: abid
Date/Time: 30-08-2022 16:59:18
Range: 4000.00 - 650.00
Apodization: Happ-Genzel





Agilent Technologies

Sample ID:	9d	Method Name:	jamia
Sample Scans:	64	User:	abid
Background Scans:	16	Date/Time:	30-08-2022 17:14:14
Resolution:	8 cm ⁻¹	Range:	4000.00 - 650.00
System Status:	Good	Apodization:	Happ-Genzel
File Location:	C:\Program Files\Agilent\MicroLab PC\Results\Masood\3_2022-08-30T17-14-52.a2r		

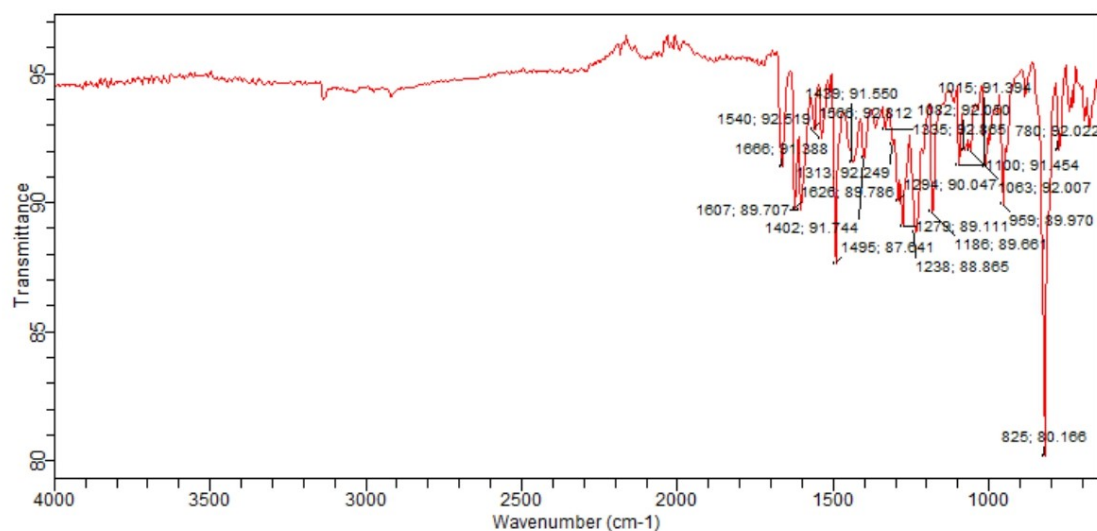


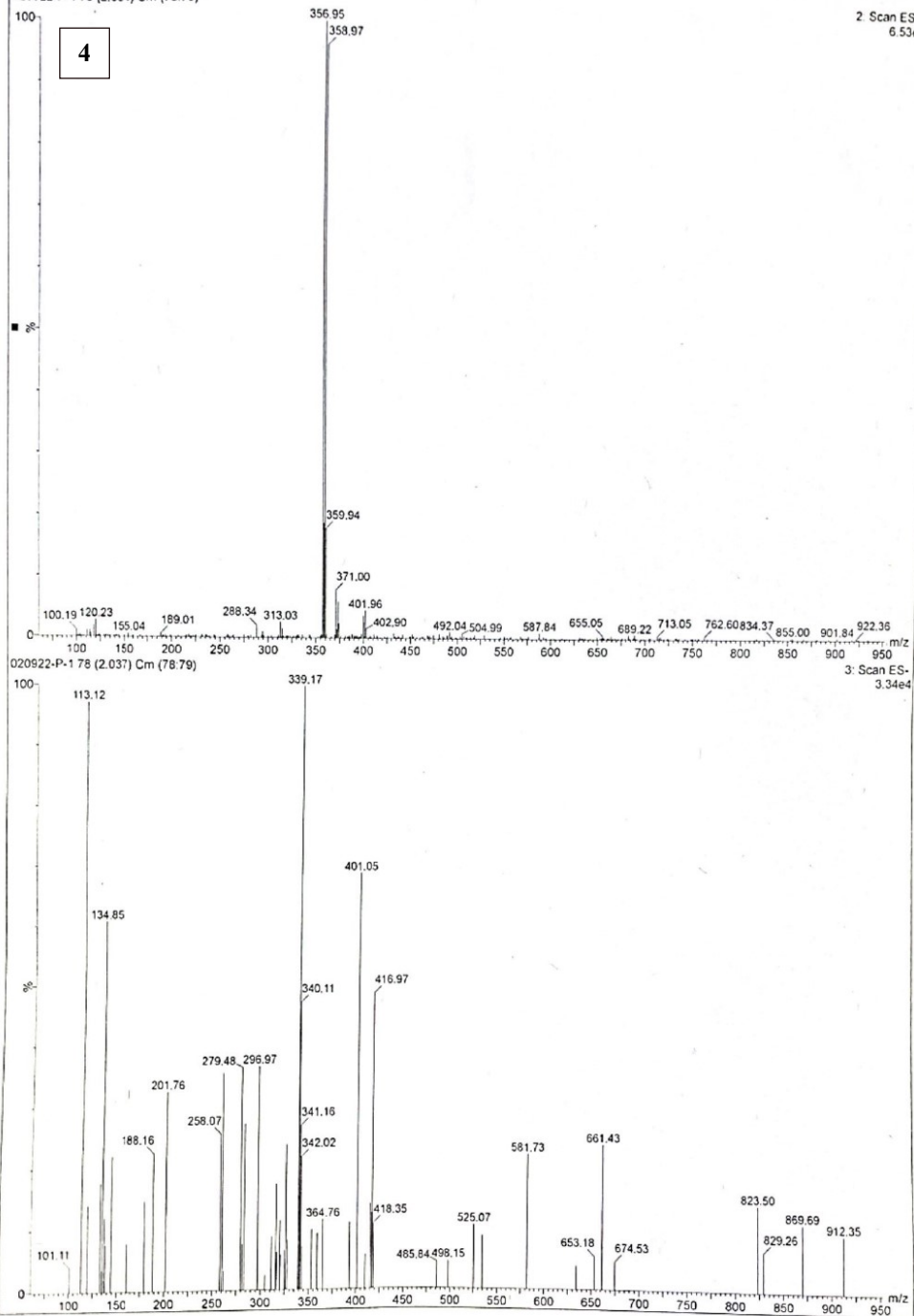
Figure S2. The FT-IR spectra of **4**, **5a**, **5b**, **6a-6d**, **7a-7d**, **8a-8h** and **9a-9d** synthesised compounds.

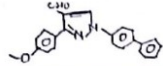
356

Sample Name : P-1
Test Name : NEW-JBL-3-MIN-elsd
Date & Time : 02-Sep-2022,20:45:03
020922-P-1 79 (2.054) Cm (78.79)

Instrument ID # LCM-0001
INTERNAL

2 Scan ES+
6.53e6

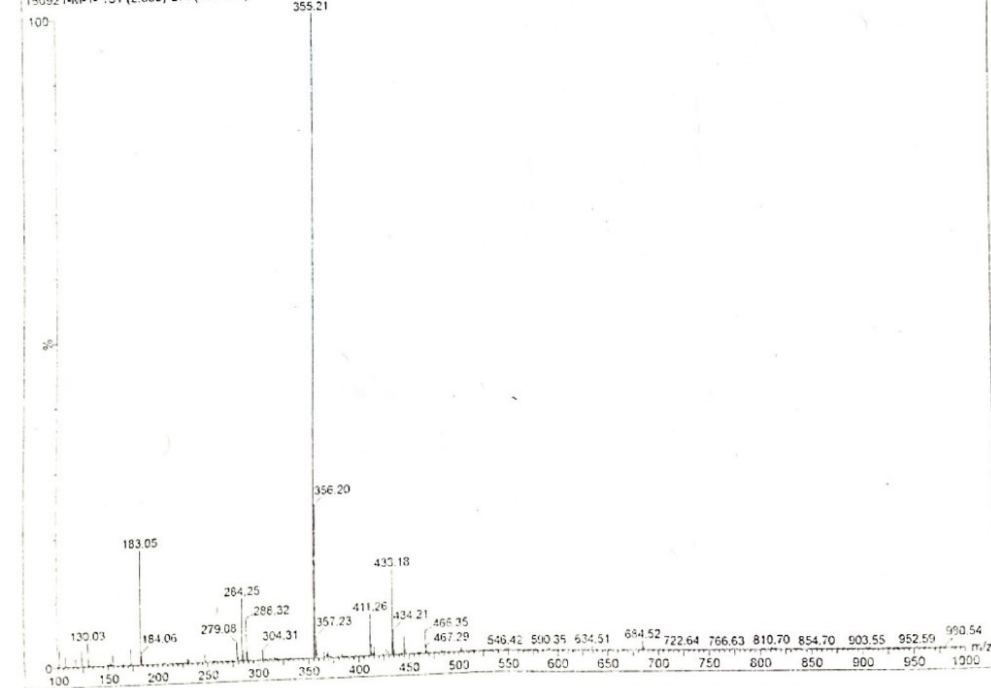
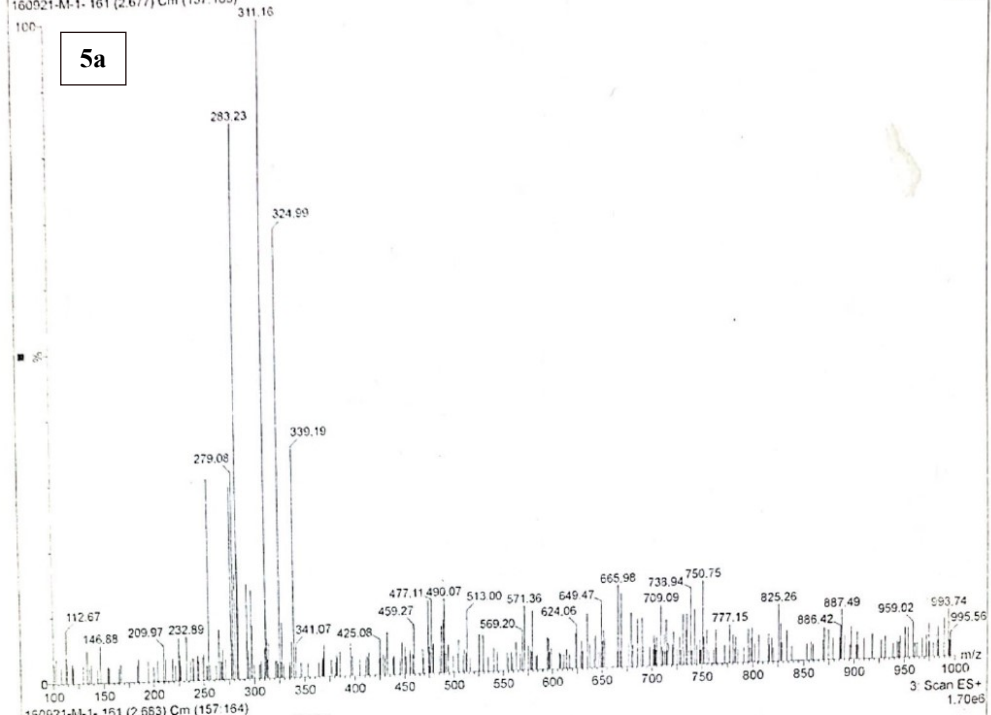


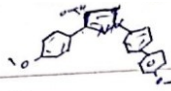


Instrument ID # QDA 01
Internal

Sample Name : M-1
Test Name : NEW-4-MIN-AA-1
Date & Time : 16-Sep-2021, 15:01:16
150921-M-1- 161 (2.677) Cm (157.163)

2 Scan ES-
6.94e3



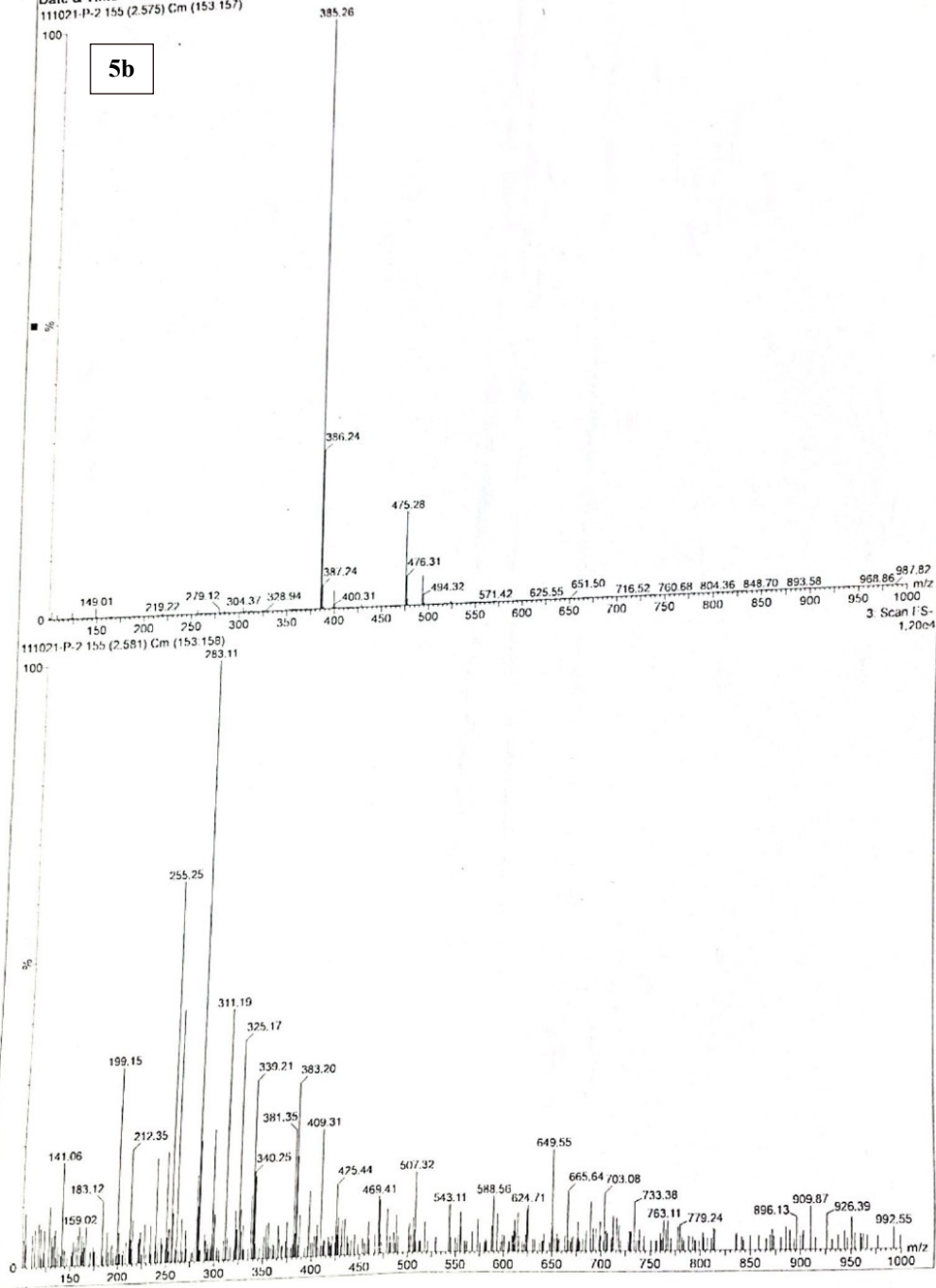


INSTRUMENT ID # UPLC-MS-08
Internal

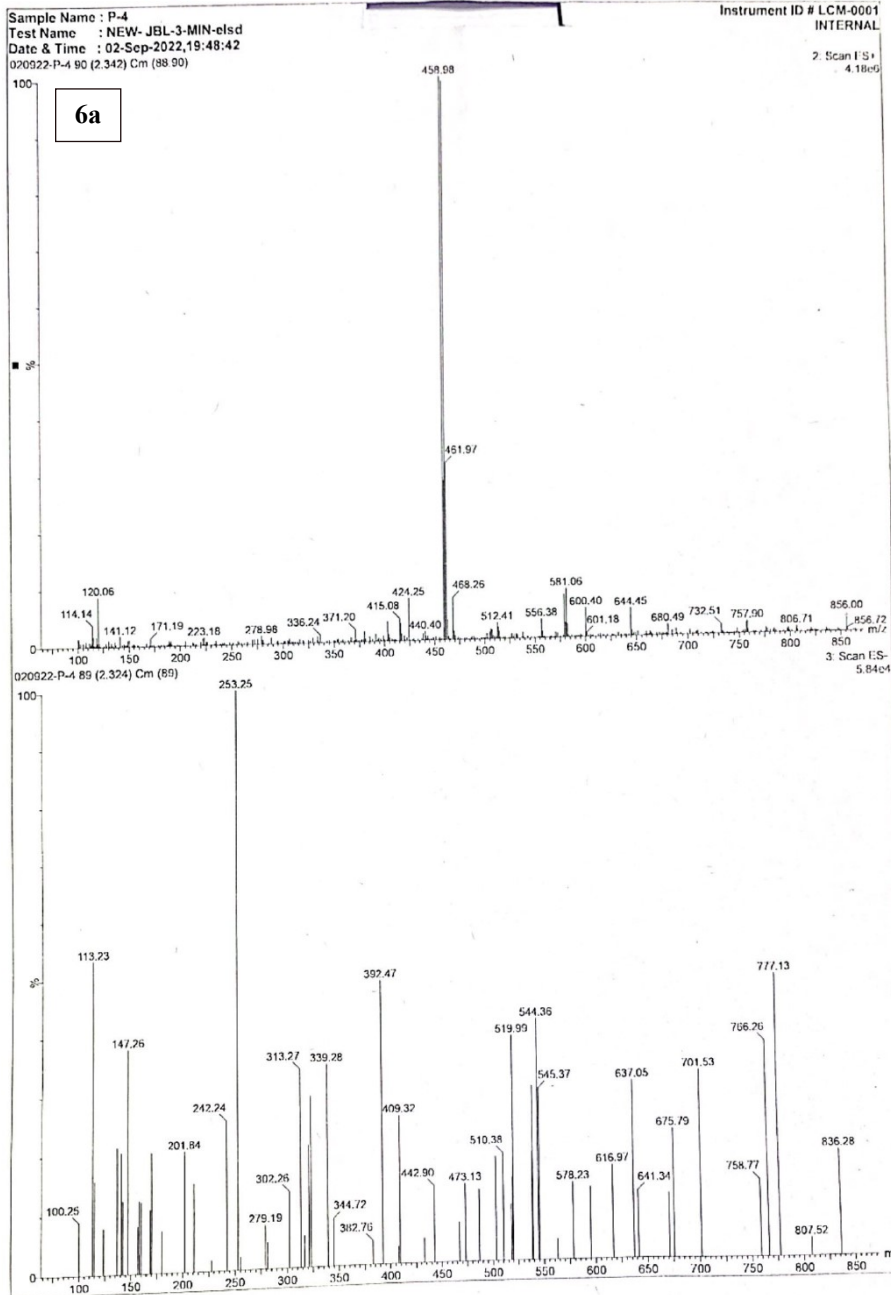
Sample Name : P-2
TEST NAME : NEW-4-MIN-AA
Date & Time : 11-Oct-2021 16:21:15
111021-P-2 155 (2.575) Cm (153.157)

2. Scan 1 S+
1.19e7

5b



450

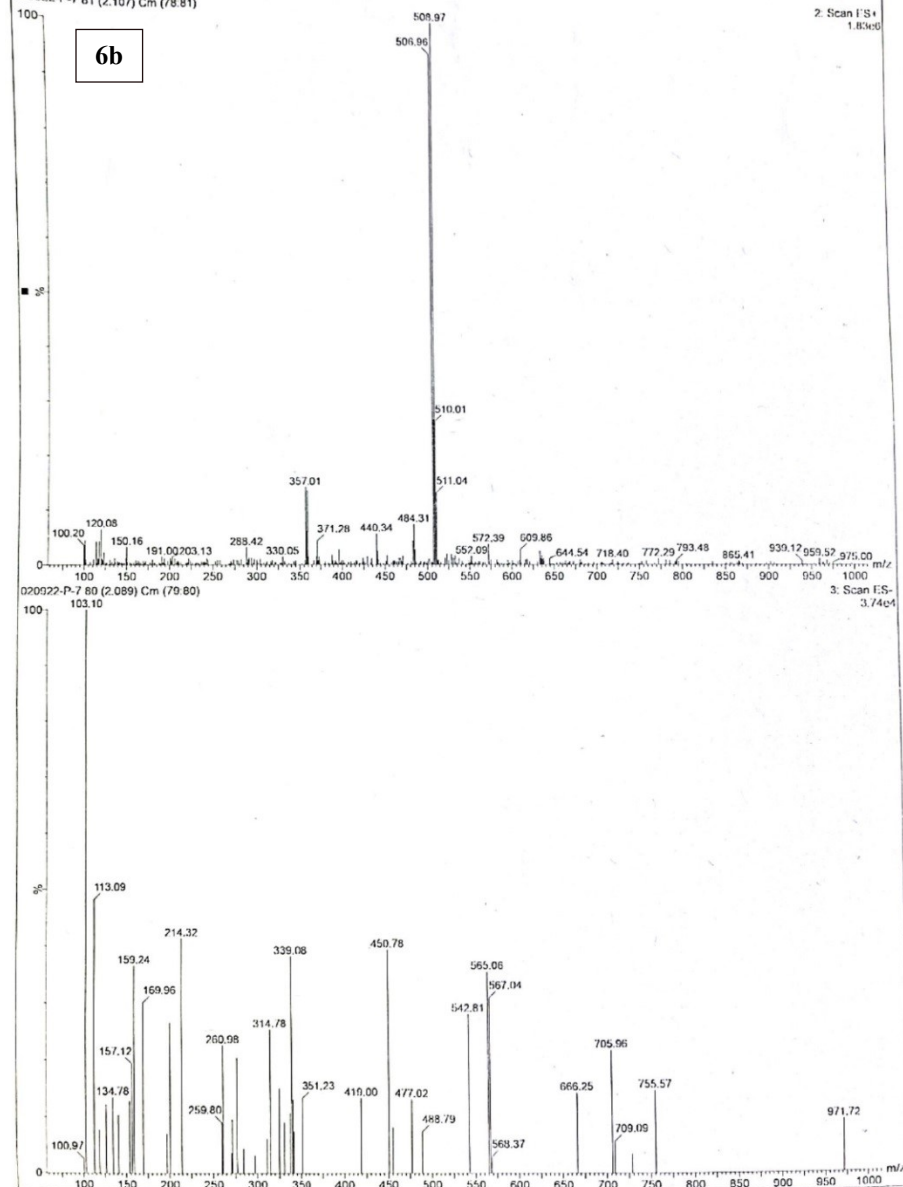


508

Sample Name : P-7
Test Name : NEW-JBL-3-MIN-elad
Date & Time : 02-Sep-2022,19:52:45
020922-P-7 81 (2.107) Cm (78.81)

Instrument ID # LCM-0001
INTERNAL

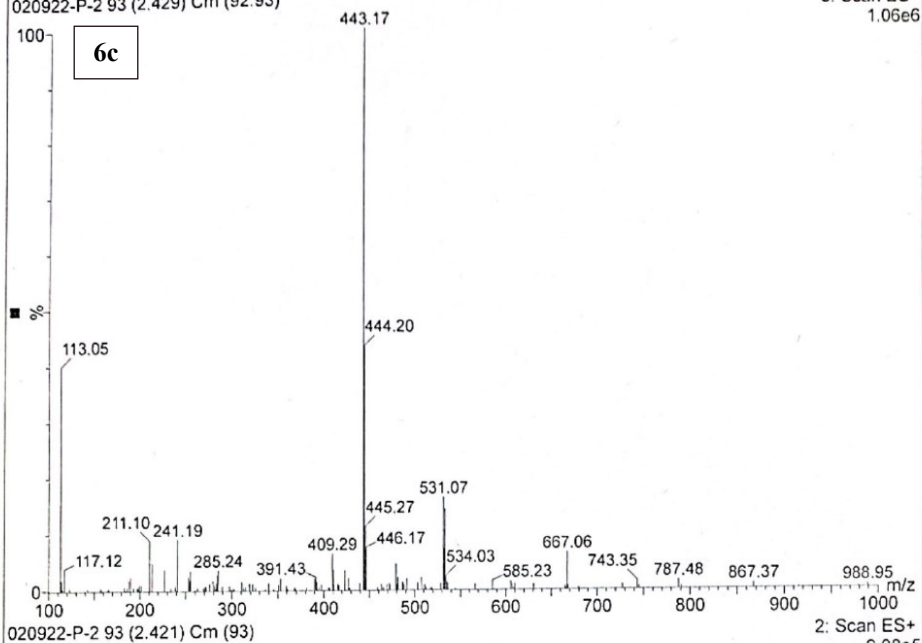
2: Scan 1'S+
1.83e0



Sample Name : P-2
Test Name : NEW-JBL-3-MIN-AA
Date & Time : 02-Sep-2022 20:15
020922-P-2 93 (2.429) Cm (92:93)

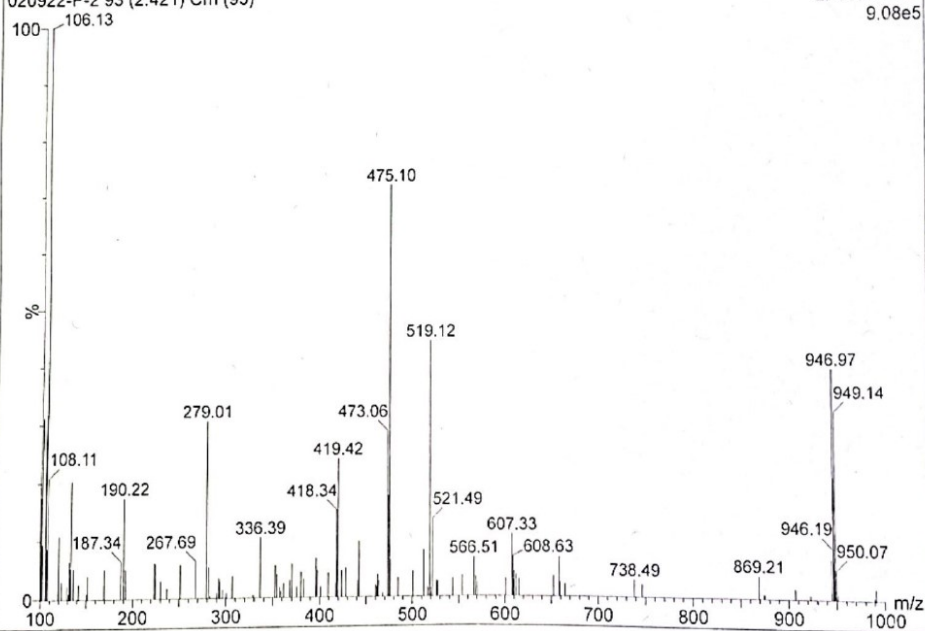
Instrument ID # LCM-0002

3: Scan ES-
1.06e6



2: Scan ES+
9.08e5

472

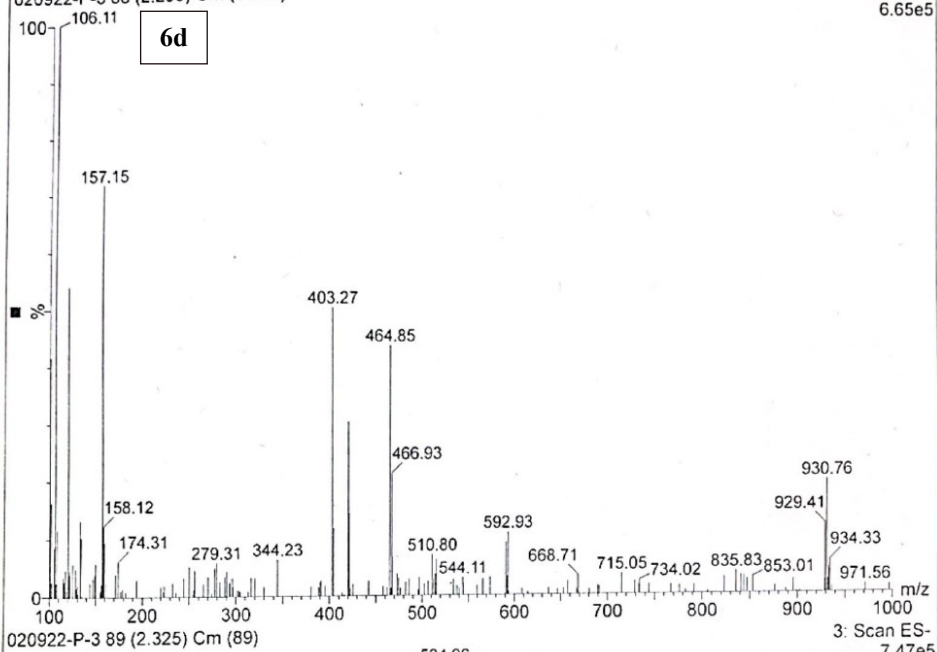


466

Sample Name : P-3
Test Name : NEW-JBL-3-MIN-AA
Date & Time : 02-Sep-2022 20:24:03
020922-P-3 88 (2.290) Cm (88:89)

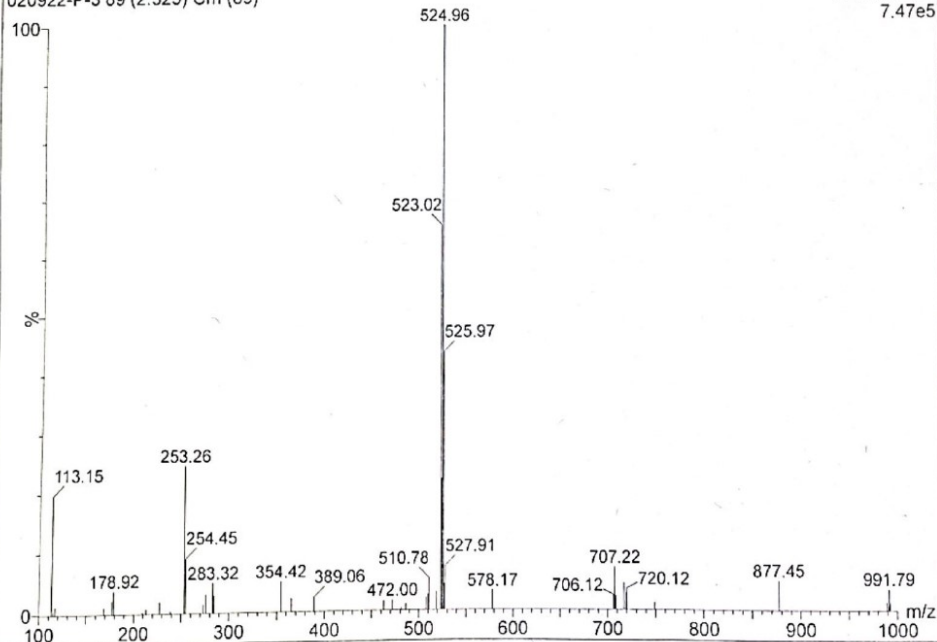
Instrument ID # LCM-0002

2: Scan ES+
6.65e5



020922-P-3 89 (2.325) Cm (89)

3: Scan ES-
7.47e5



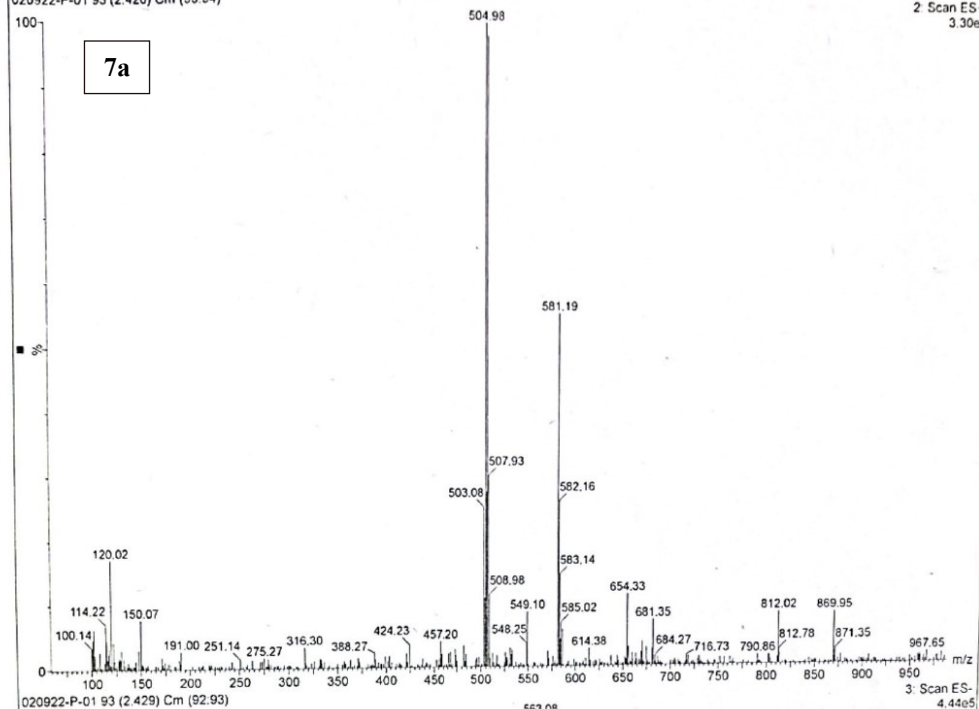
502

Sample Name : P-01
Test Name : NEW- JBL-3-MIN-elsd
Date & Time : 02-Sep-2022,20:48:58
020922-P-01 93 (2.420) Cm (93.94)

Instrument ID # LCM-000
INTERNA

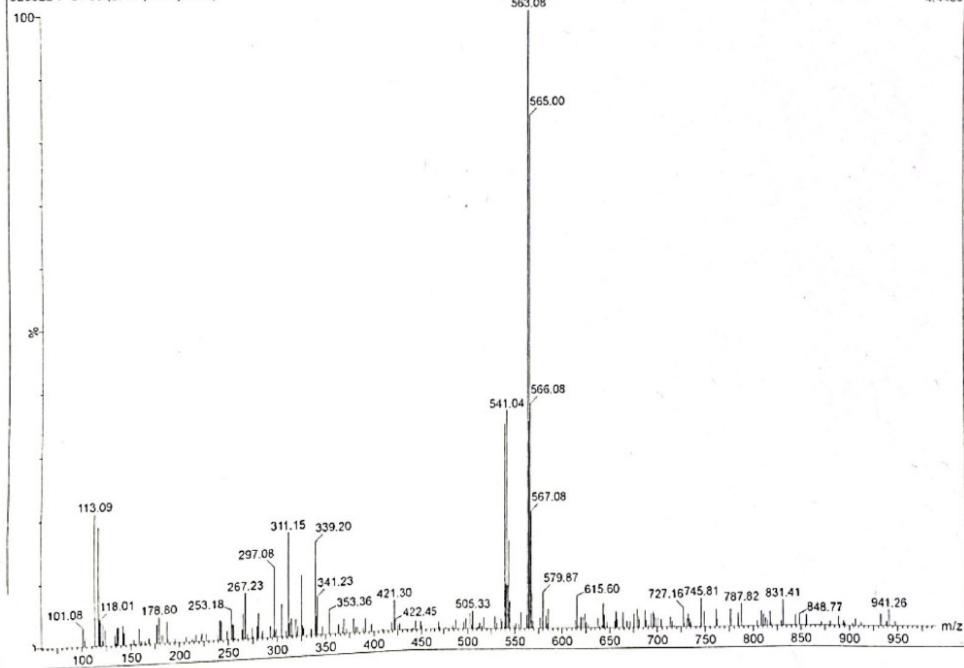
2 Scan ES+
3.30e1

7a

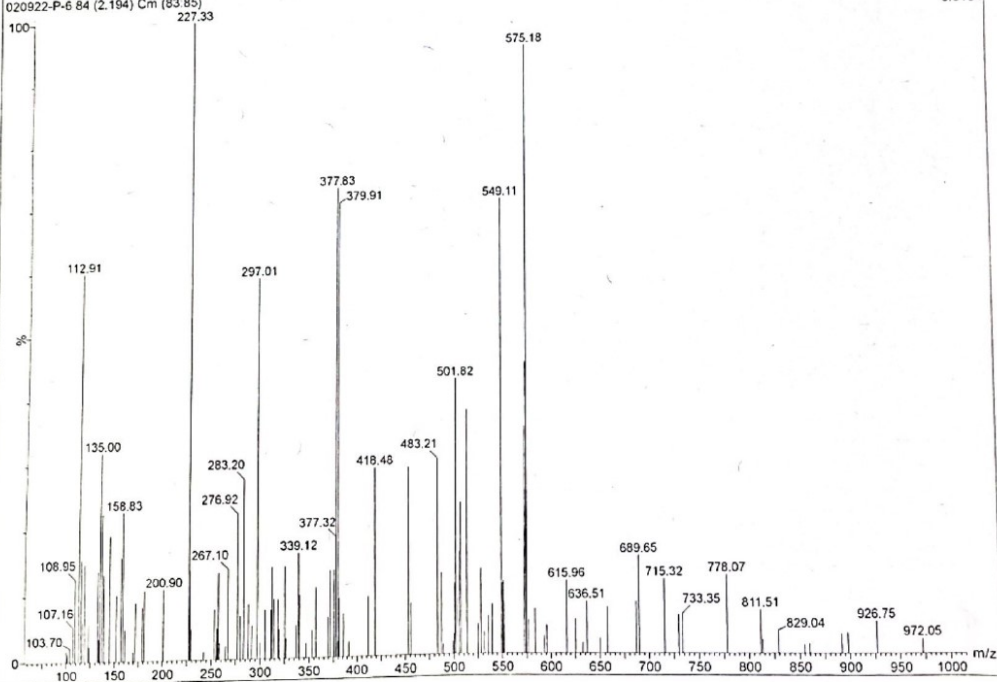
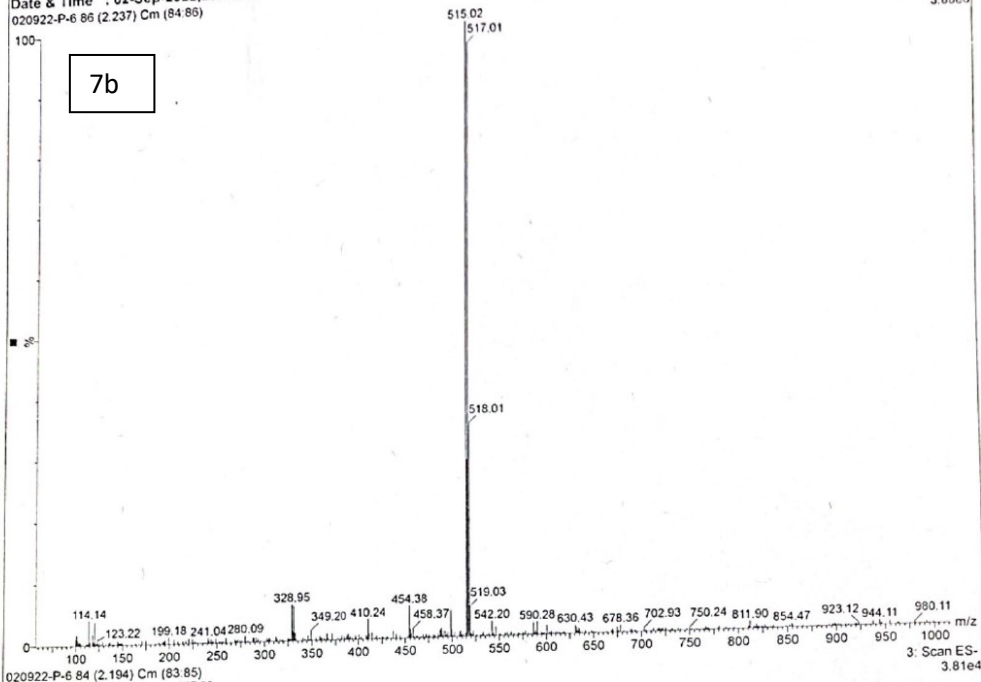


020922-P-01 93 (2.429) Cm (92.93)

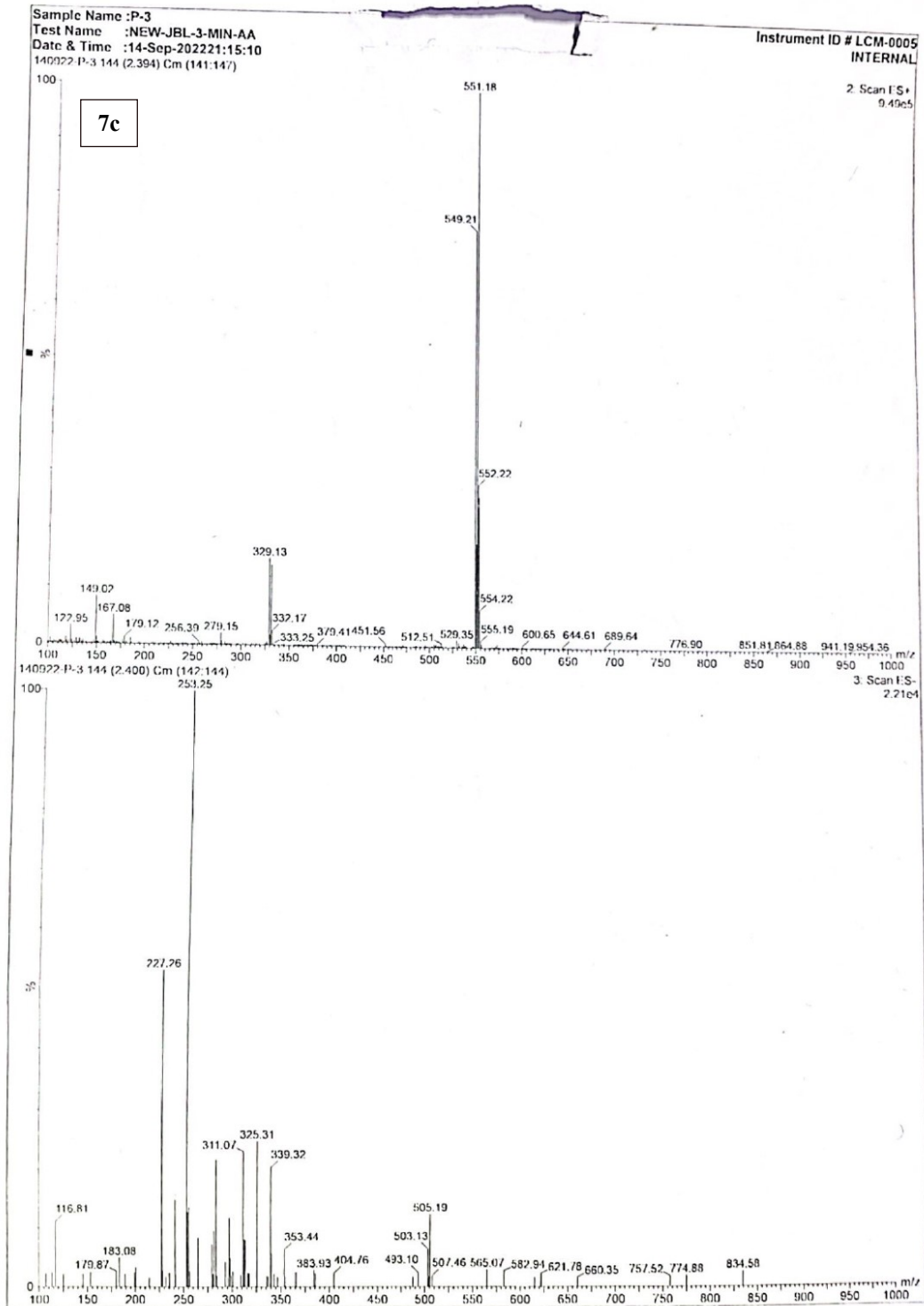
3 Scan ES-
4.44e5



514

Instrument ID # LCM-0001
INTERNALSample Name : P-6
Test Name : NEW-JBL-3-MIN-elsd
Date & Time : 02-Sep-2022,20:40:59
020922-P-6 86 (2.237) Cm (84.86)2. Scan ES+
3.88e6

548-12

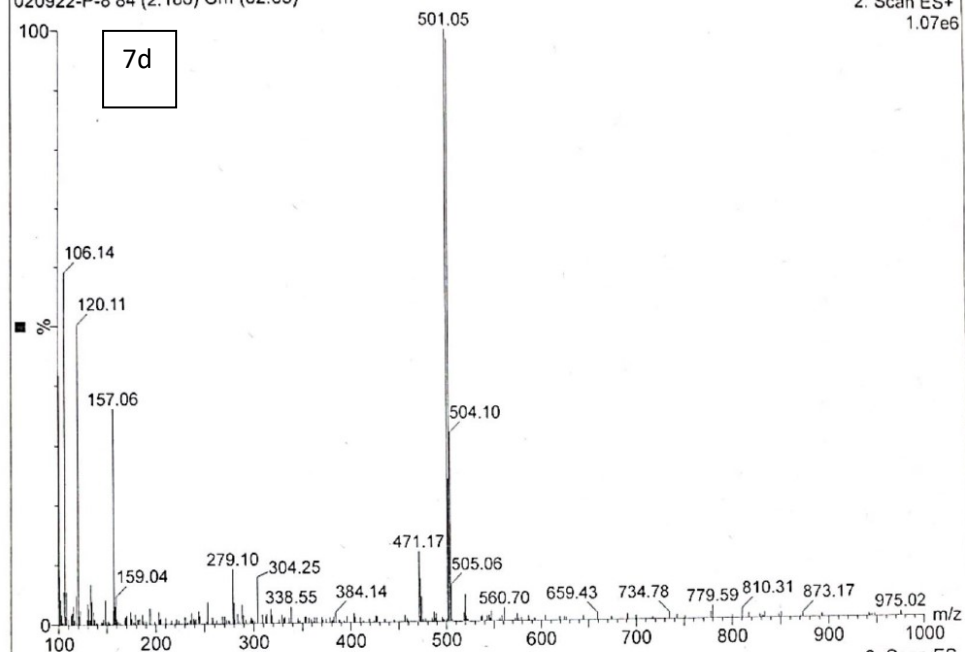


500

Sample Name : P-8
Test Name : NEW-JBL-3-MIN-AA
Date & Time : 02-Sep-2022 20:27:50
020922-P-8 84 (2.186) Cm (82:85)

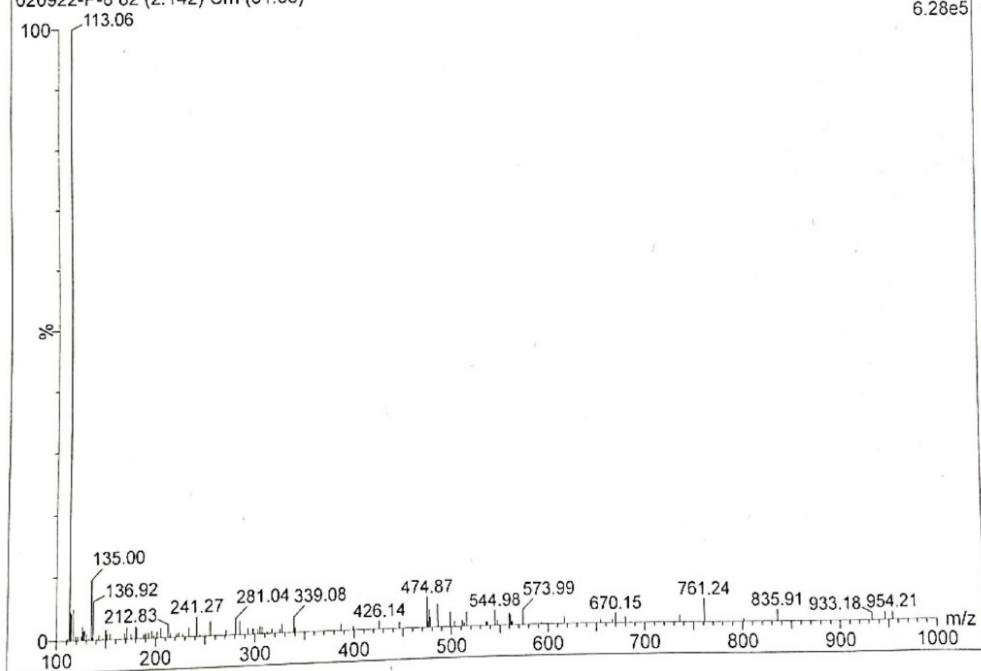
Instrument ID # LCM-0002

2: Scan ES+
1.07e6



020922-P-8 82 (2.142) Cm (81:83)

3: Scan ES-
6.28e5

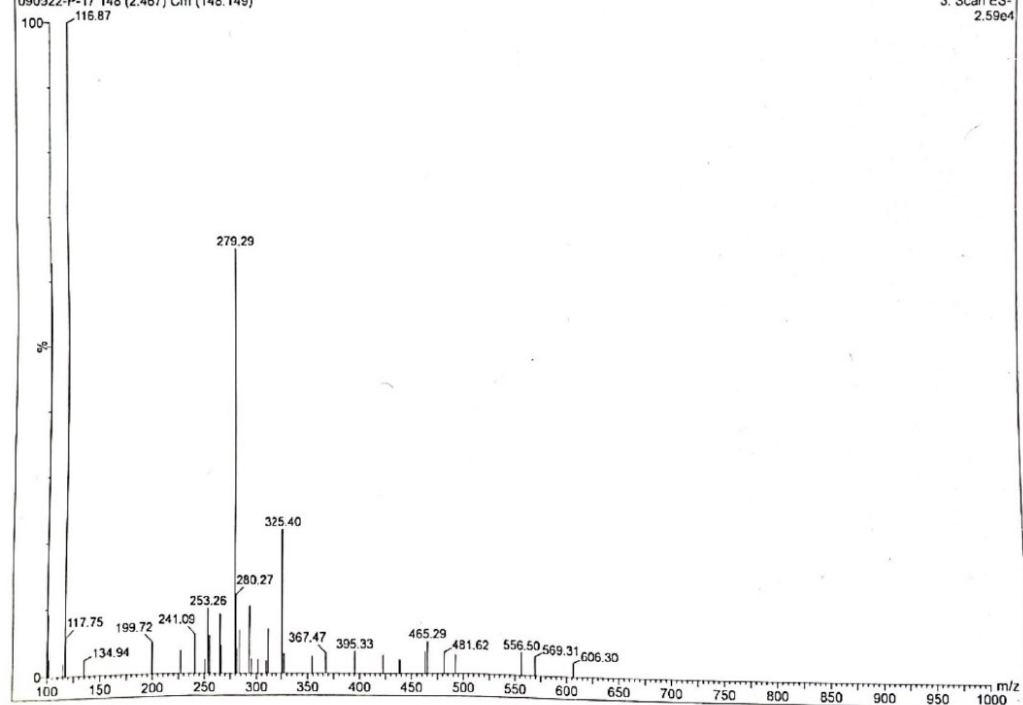
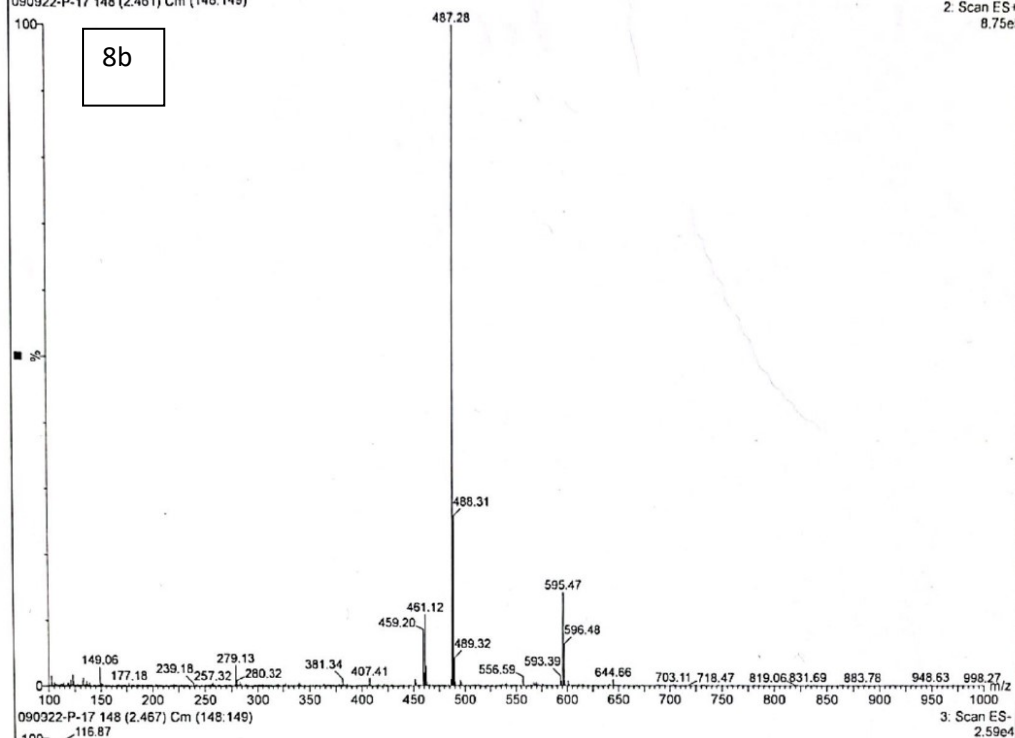


8a

Sample Name :P-17
Test Name :NEW-JBL-3-MIN-AA
Date & Time :09-Sep-2022 0:38:51
090922-P-17 148 (2.461) Cm (146:149)

Instrument ID # LCM-0005
INTERNAL

2: Scan ES+
8.75e5



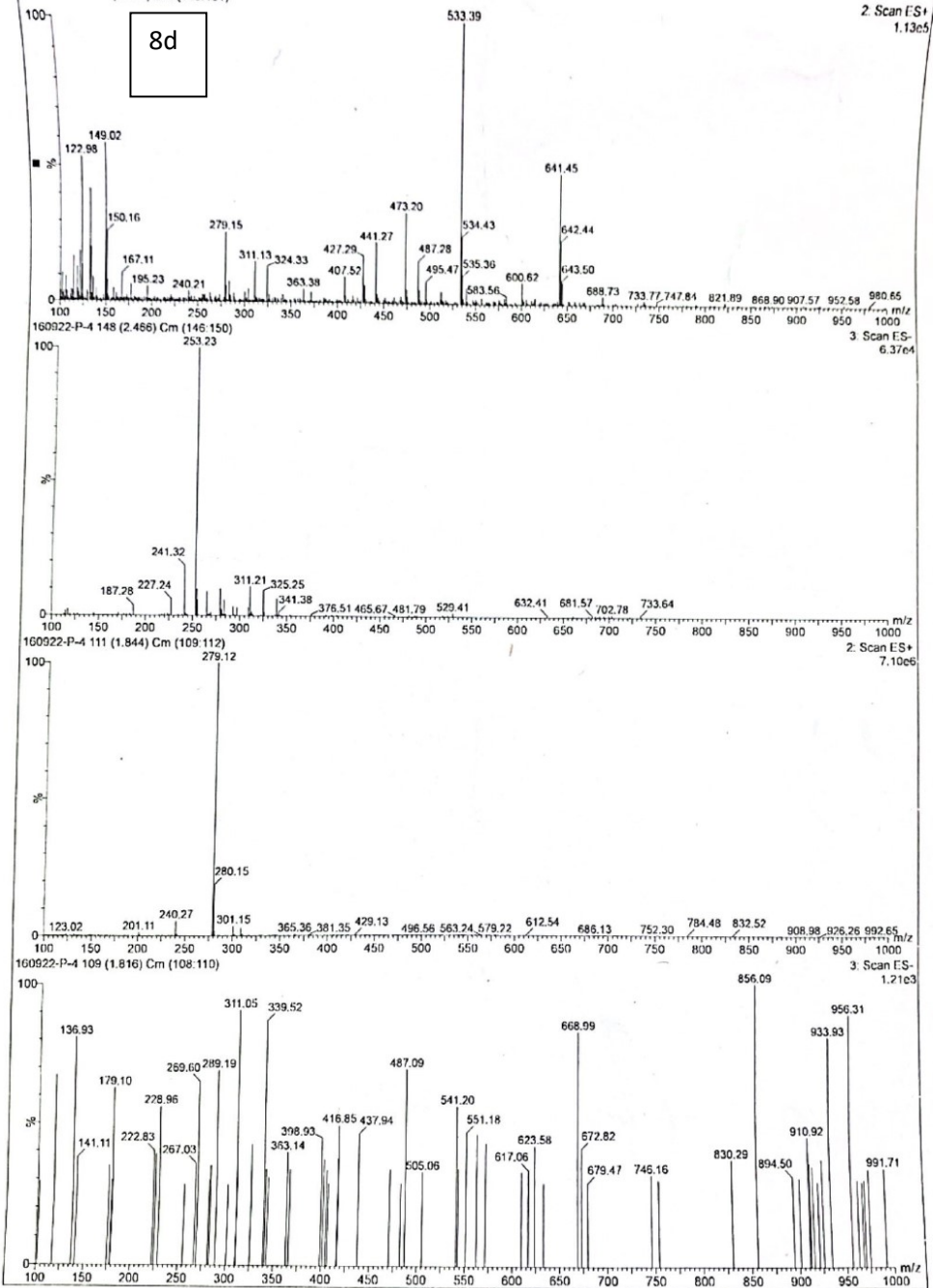


8c

532

Sample Name :P-4
Test Name :NEW-JBL-3-MIN-AA
Date & Time :16-Sep-2022 19:22:30
160922-P-4 149 (2.477) Cm (146.151)

Instrument ID # LCM-0005
INTERNAL

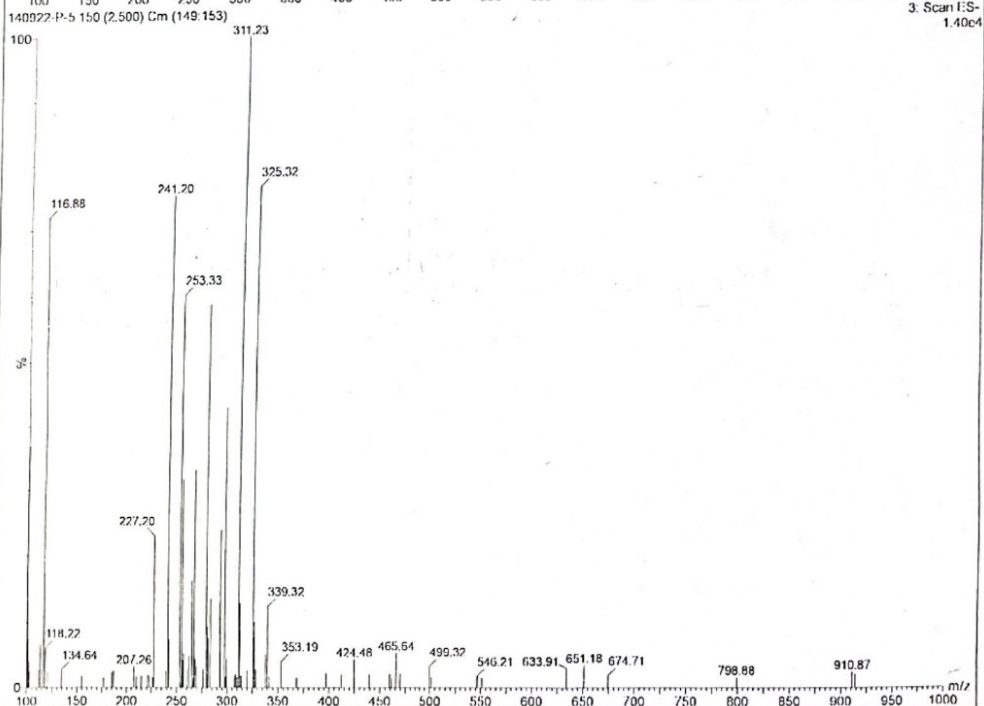
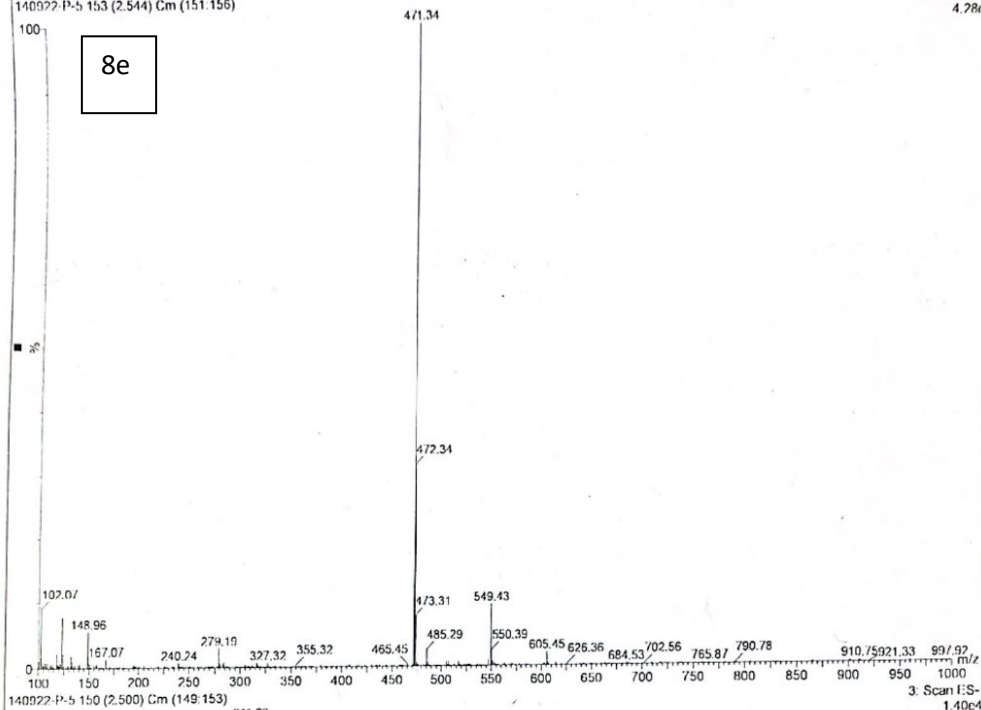


470-20

Sample Name : P-5
Test Name : NEW-JBL-3-MIN-AA
Date & Time : 14-Sep-2022 11:20
140922-P-5 153 (2.544) Cm (151.156)

Instrument ID # LCM-0005
INTERNAL

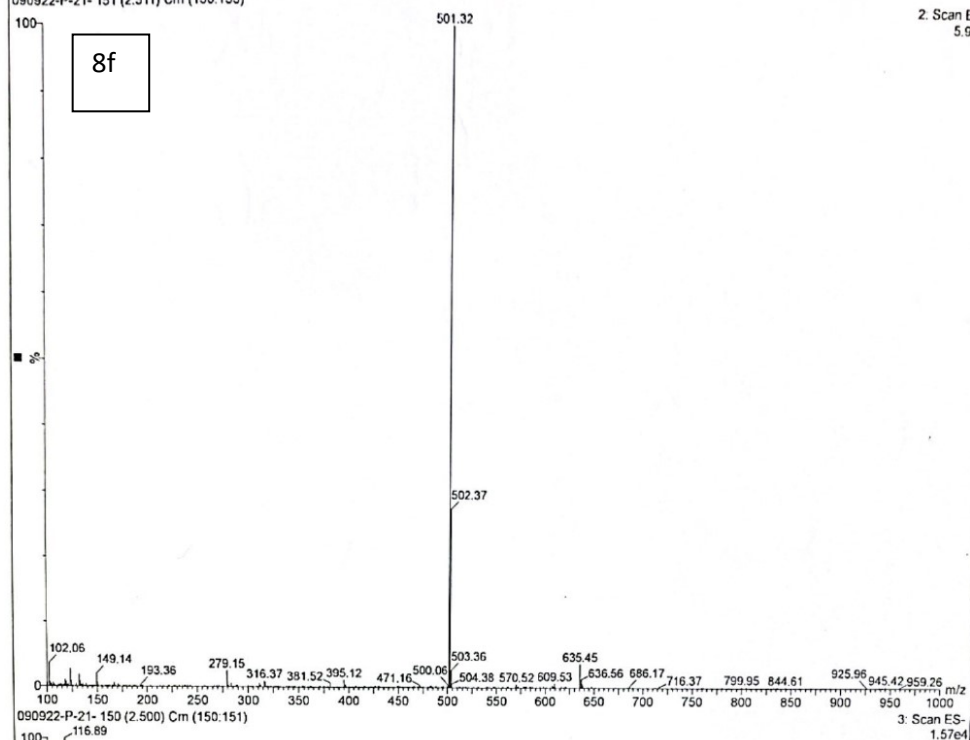
2. Scan 1: S+
4.28e5



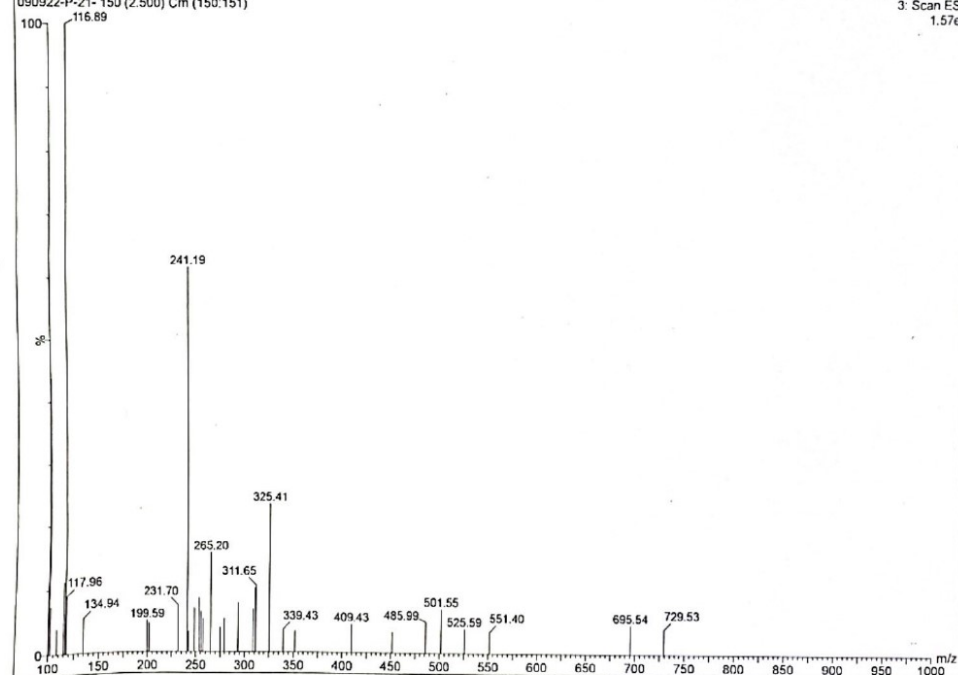
Sample Name :P-21
Test Name :NEW-JBL-3-MIN-AA
Date & Time :09-Sep-202220:50:27
090922-P-21- 151 (2.511) Cm (150.153)

Instrument ID # LCM-0005
INTERNAL

2. Scan ES+
5.92e5



3. Scan ES-
1.57e4



Sample Name :P-22

Instrument ID # LCM-0005

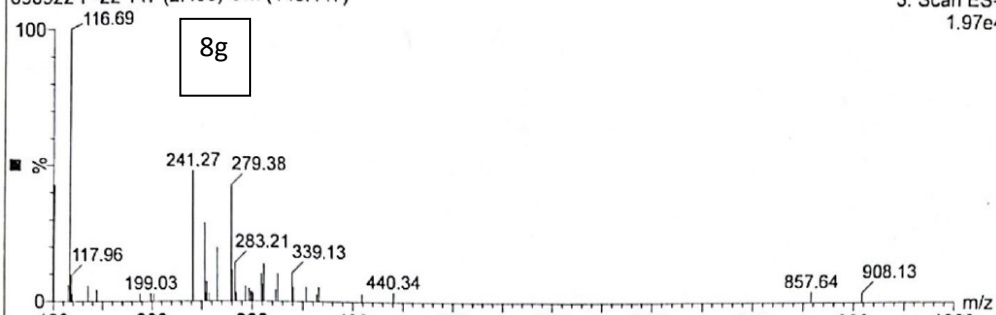
Test Name :NEW-JBL-3-MIN-AA

INTERNAL

Date & Time :09-Sep-202222:30:12

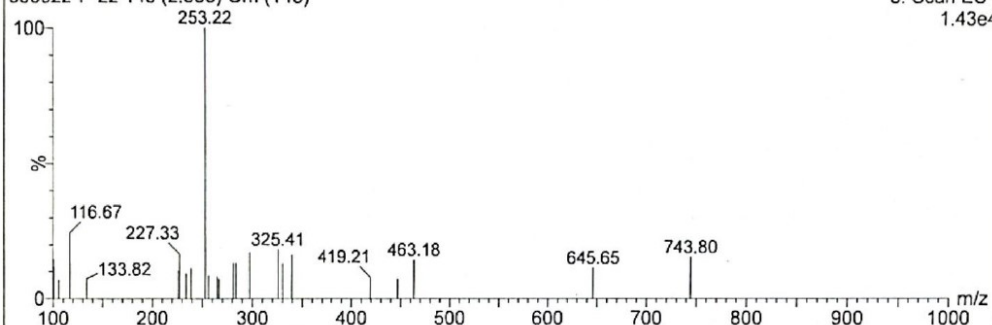
090922-P-22 147 (2.450) Cm (146:147)

3: Scan ES-
1.97e4



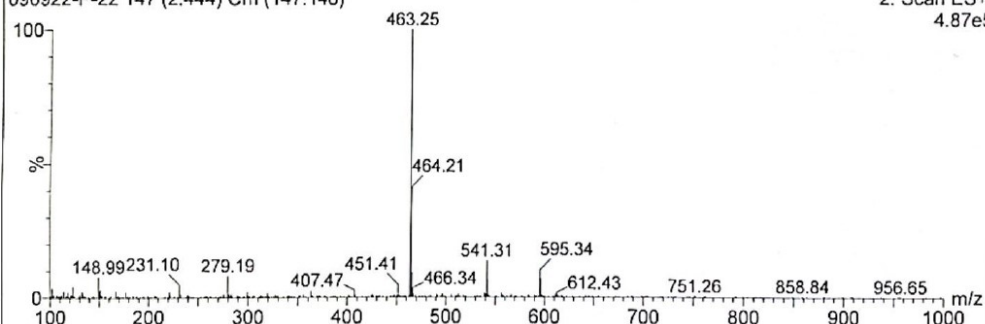
090922-P-22 143 (2.383) Cm (143)

3: Scan ES-
1.43e4



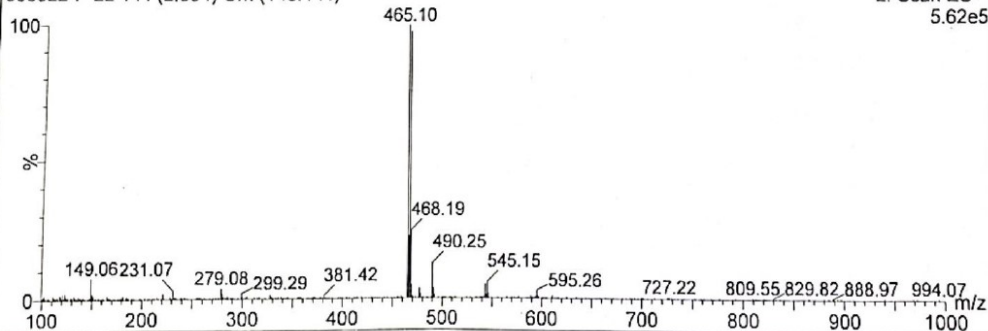
090922-P-22 147 (2.444) Cm (147:148)

2: Scan ES+
4.87e5



090922-P-22 144 (2.394) Cm (143:144)

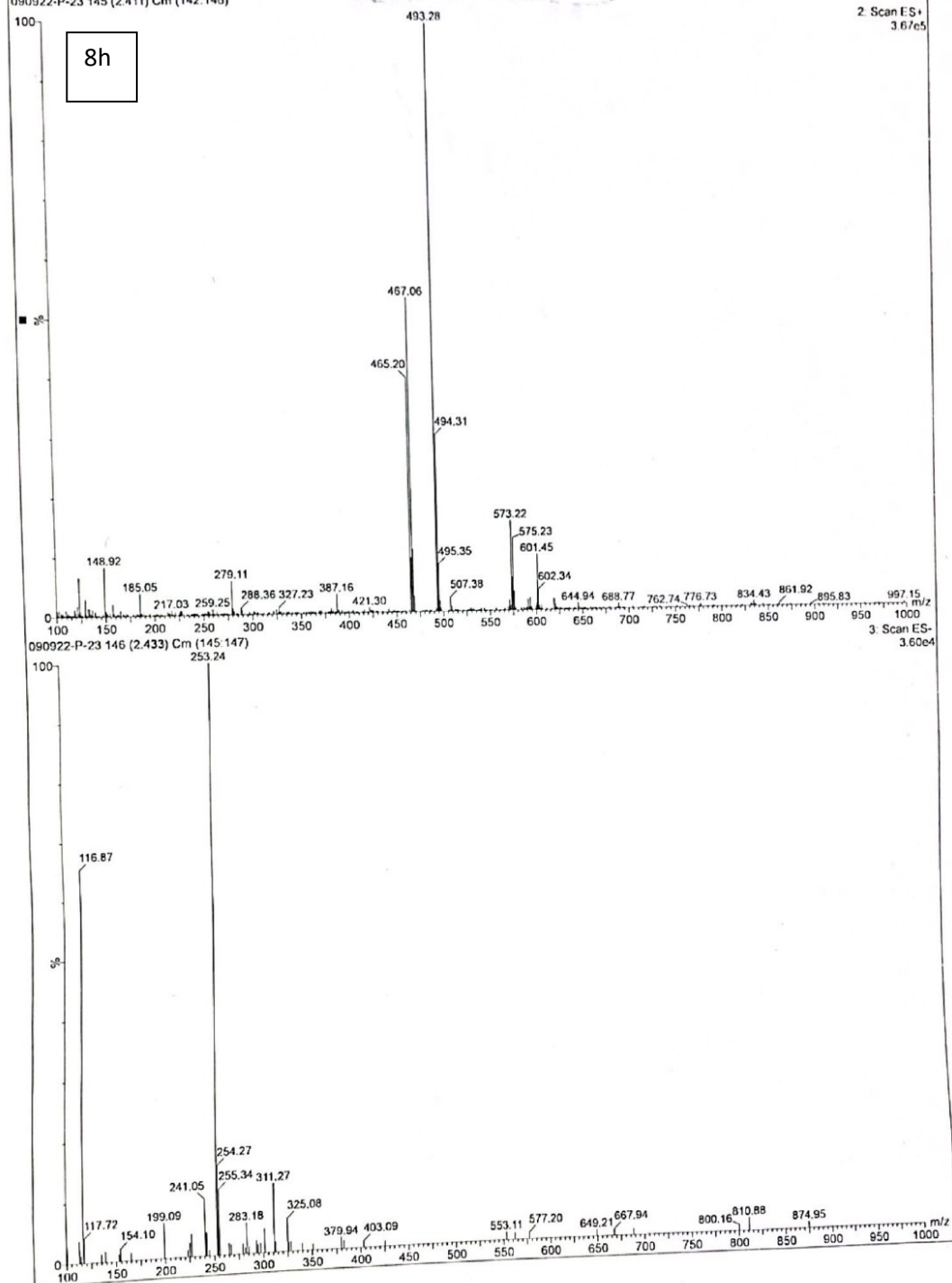
2: Scan ES+
5.62e5



Sample Name :P-23
Test Name :NEW-JBL-3-MIN-AA
Date & Time :09-Sep-2022 04:46:41
090922-P-23 145 (2.411) Cm (142.146)

Instrument ID # LCM-0005
INTERNAL

2. Scan ES+
3.67e5



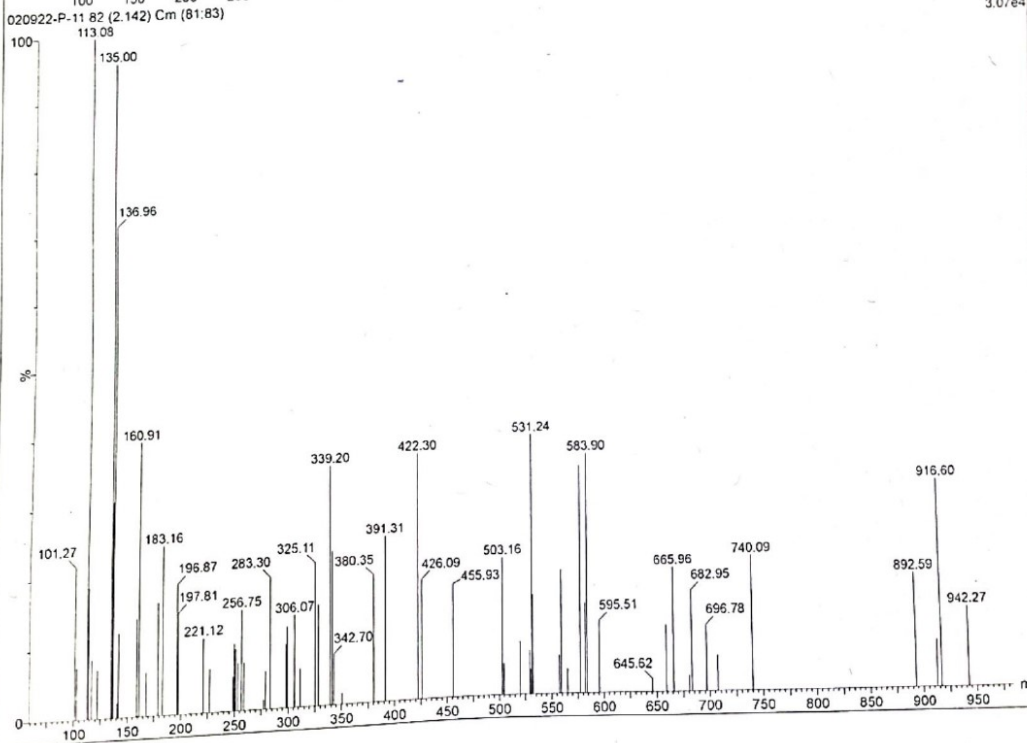
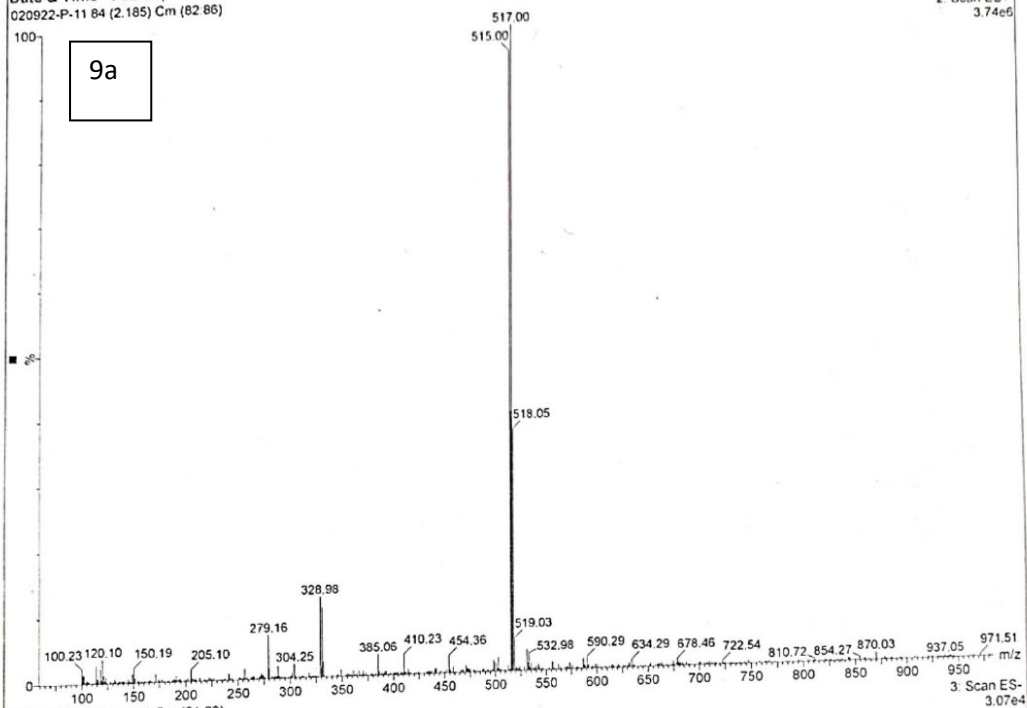
514

Sample Name : P-11
 Test Name : NEW- JBL-3-MIN-elstd
 Date & Time : 02-Sep-2022,20:52:56
 020922-P-11 84 (2.185) Cm (82.86)

Instrument ID # LCM-0001
 INTERNAL

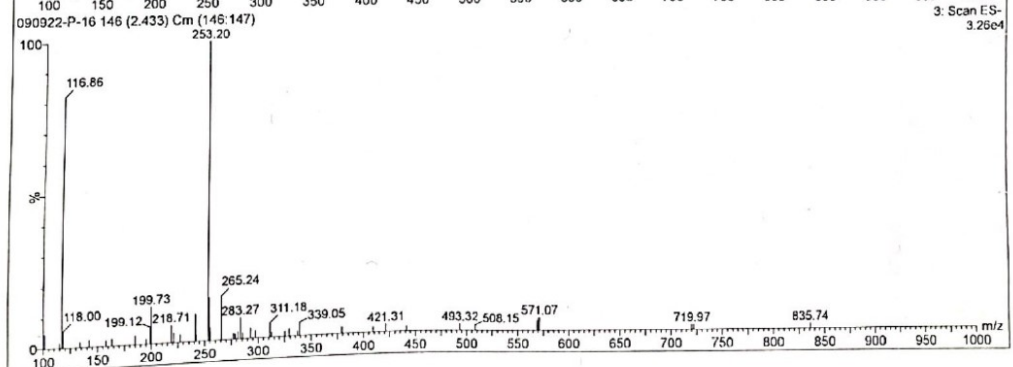
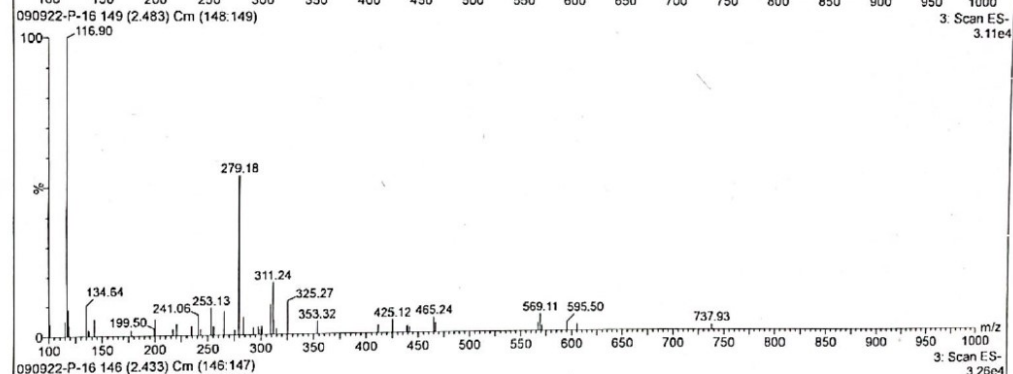
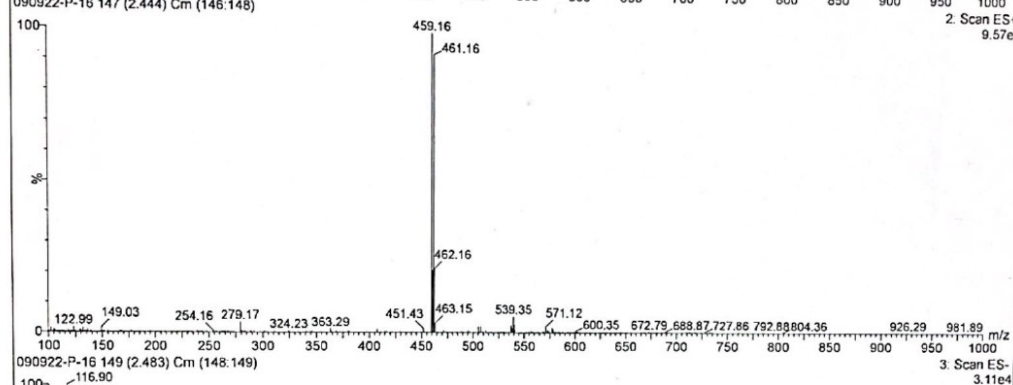
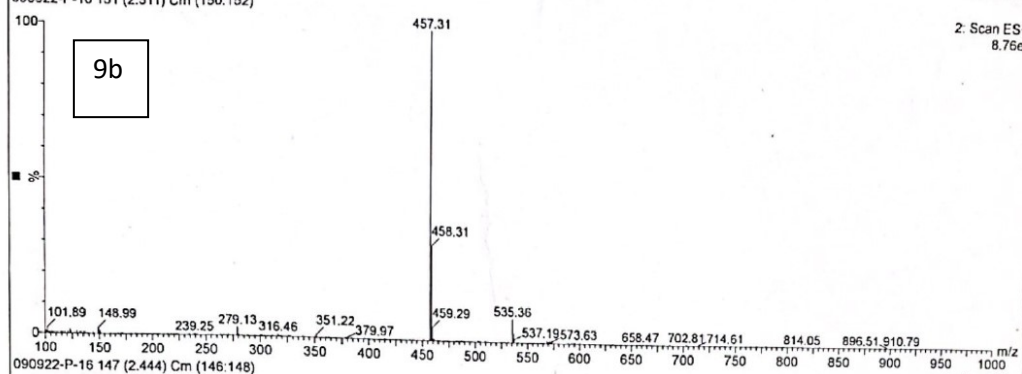
2. Scan ES+
 3.74e6

9a



Test Name :NEW-JBL-3-MIN-AA
Date & Time :09-Sep-202220:35:02
090922-P-16 151 (2.511) Cm (150:152)

Instrument ID # LCM-0005
INTERNAL

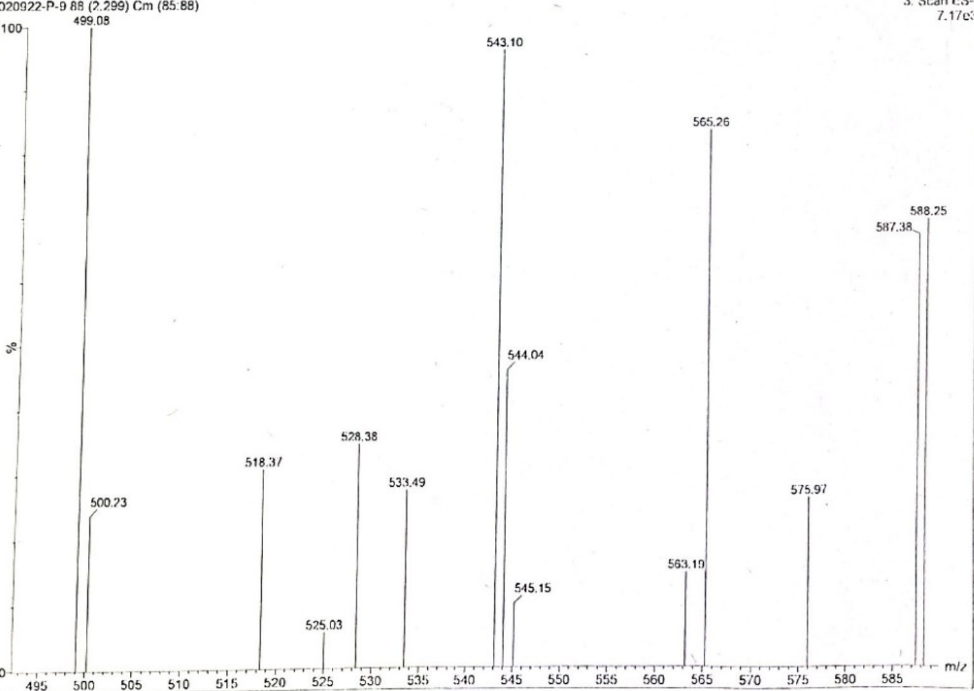
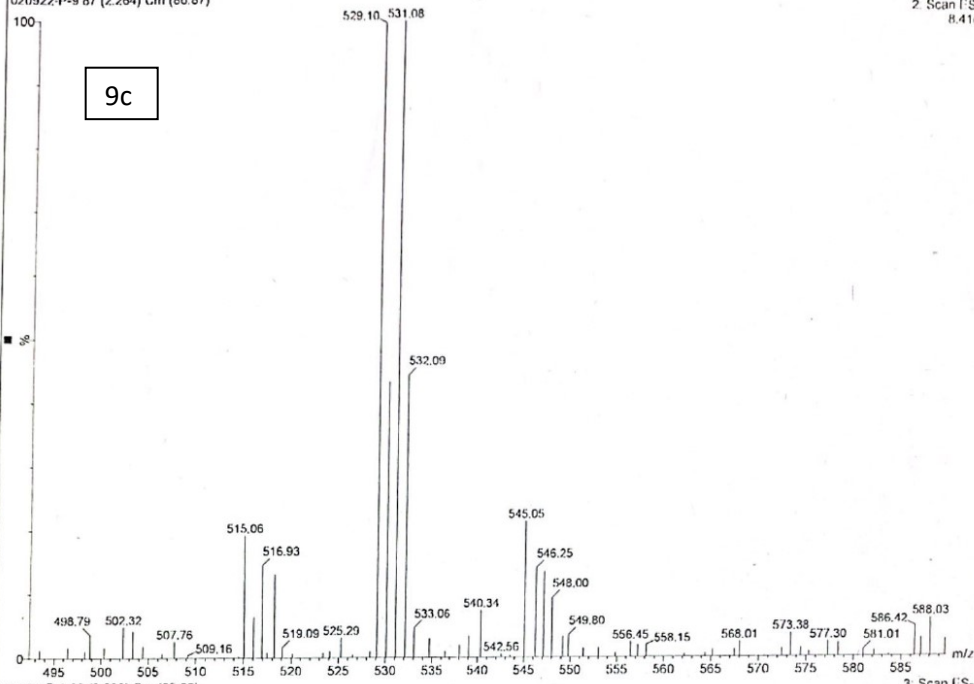


528

Sample Name : P-9
 Test Name : NEW-JBL-3-MIN-elsd
 Date & Time : 02-Sep-2022,19:44:43
 020922-P-9 87 (2.264) Cm (86.87)

Instrument ID # LCM-0001
 INTERNAL

2. Scan ES+
 8.41e5



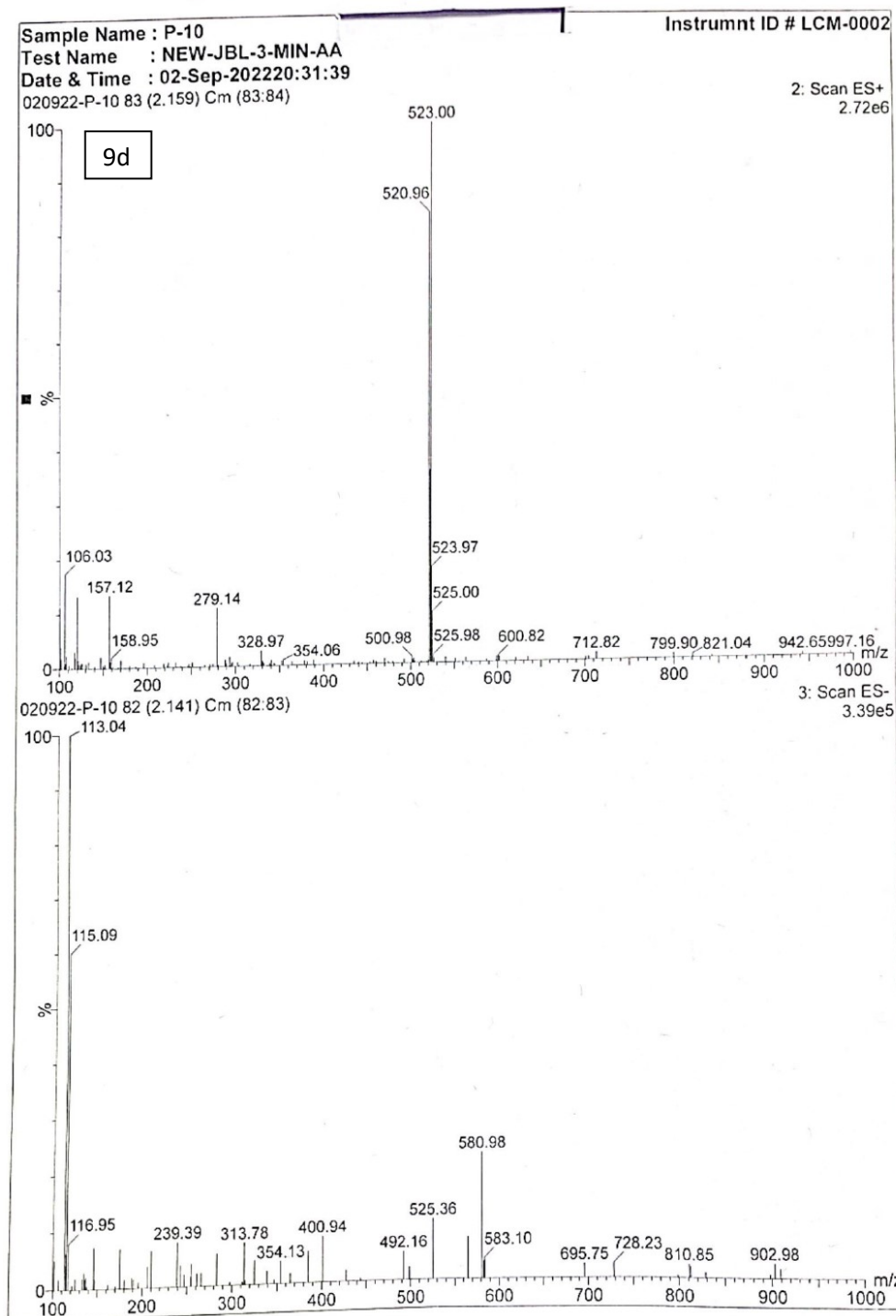


Figure S3. The mass spectra of **4**, **5a**, **5b**, **6a-6d**, **7a-7d**, **8a-8h** and **9a-9d** synthesised compounds.