

Fragment-based design of α -cyanoacrylates and α -cyanoacrylamides targeting Dengue and Zika NS2B/NS3 proteases

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SUPPLEMENTARY MATERIAL

Figure 1S. FASTA sequence for NS3 protease from DENV-3 (PDB:2) used as template.

```
>2FOM_1|Chain A|polyprotein|Dengue virus 2 (11060)
GSHMLEADLELERAADVRWEEQAEISGSSPILSITISEDGSMSEIKNEEEE
QTLGGGGSGGGG
>2FOM_2|Chain B|polyprotein|Dengue virus 2 (11060)
AGVLWDVPSPPVVGKAELEDGAYRIKQKGILGYSQIGAGVYKEGTFHTMW
HVTRGAVLMHKGKRIEPSWADVKKDLISYGGGWKLEGEWKEGEEVQVLAL
EPGKNPRAVQTKPGLFKTNTGTIGAVSLDFSPGTSGPSPIVDKKGKVVGLY
GNGVVTRSGAYVSAIANTEKSIEDNPEIEDDIFRK
```

Figure 2S. Results from the alignment performed by using the Basic Local Alignment Search Tool (BLAST, <https://blast.ncbi.nlm.nih.gov/Blast.cgi>).

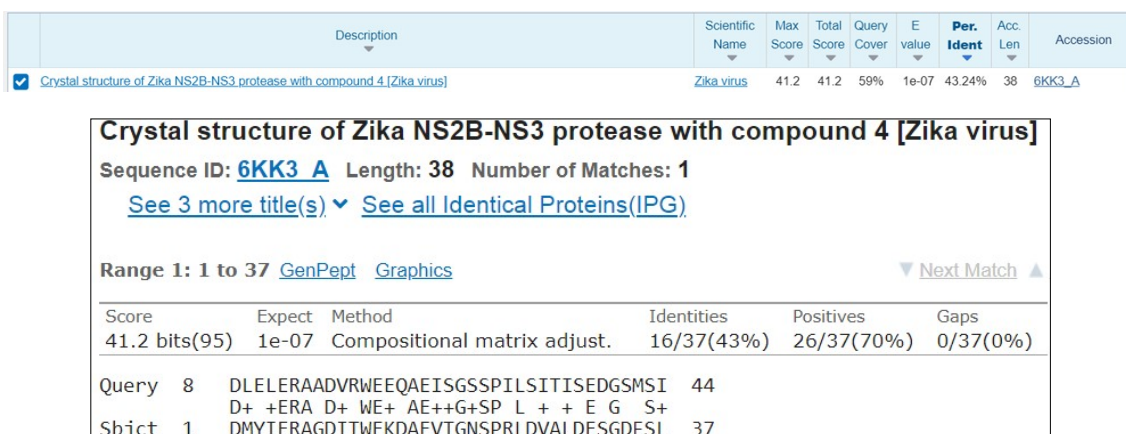


Figure 3S. Ramachandran plots for 2M9P NS2B/NS3-LQM467 after 200 ns dynamics simulations.

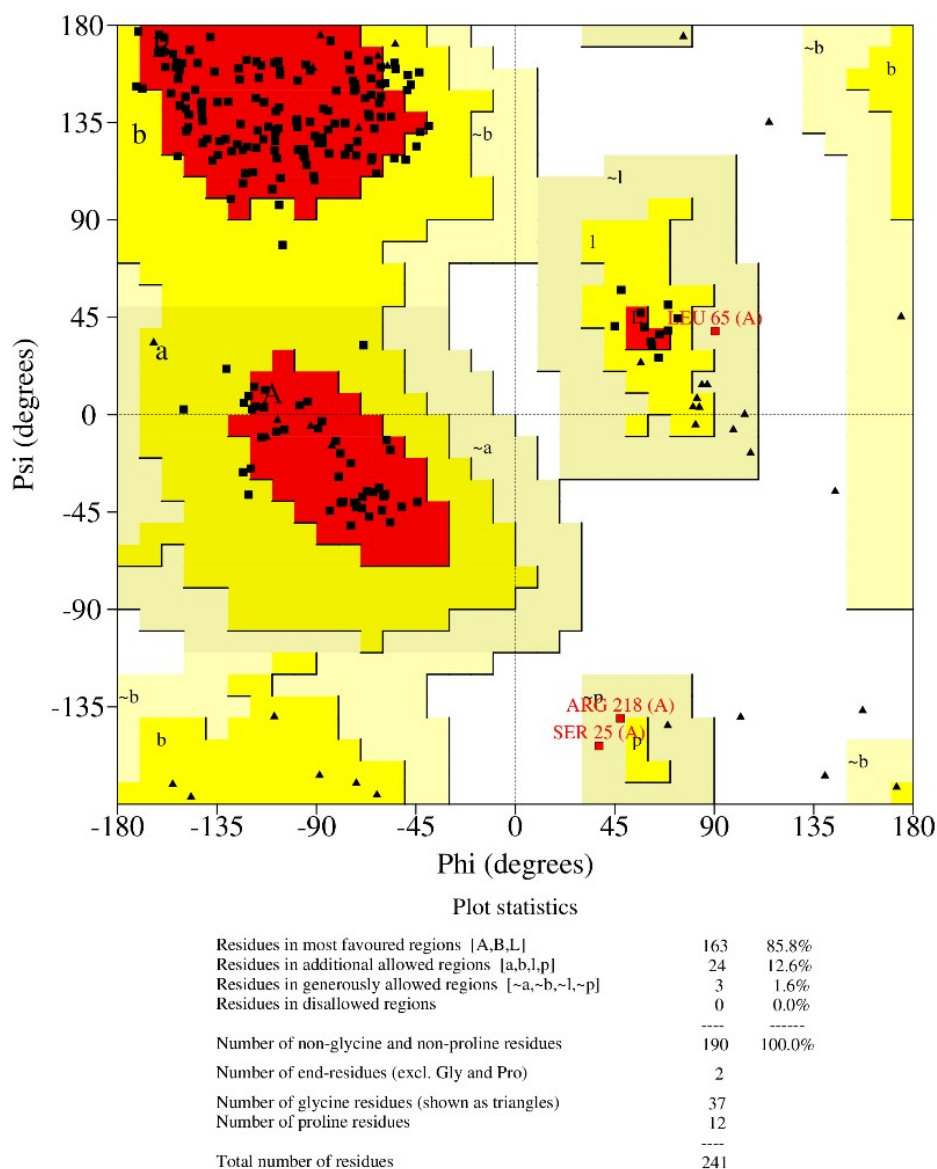
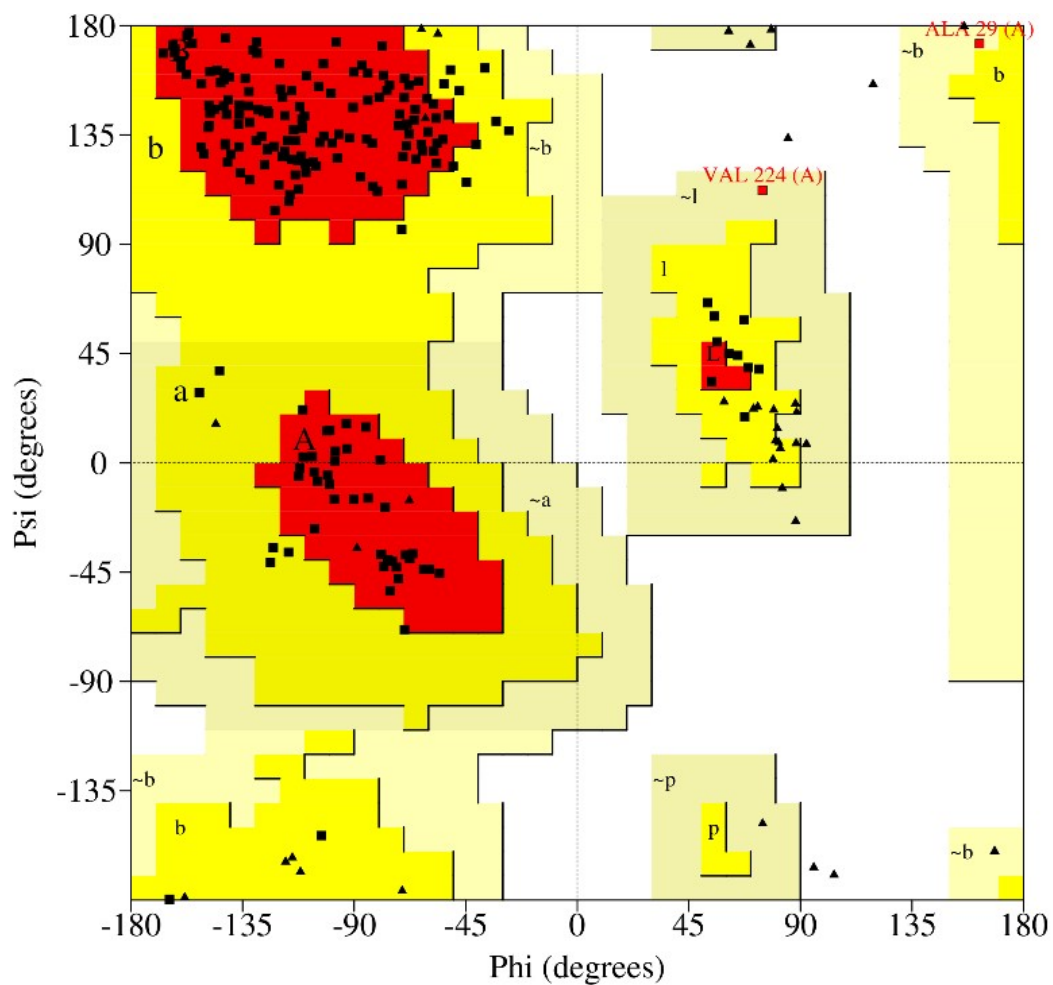


Figure 4S. Ramachandran plots for 2M9P NS2B/NS3-LQM471 after 200 ns dynamics simulations.



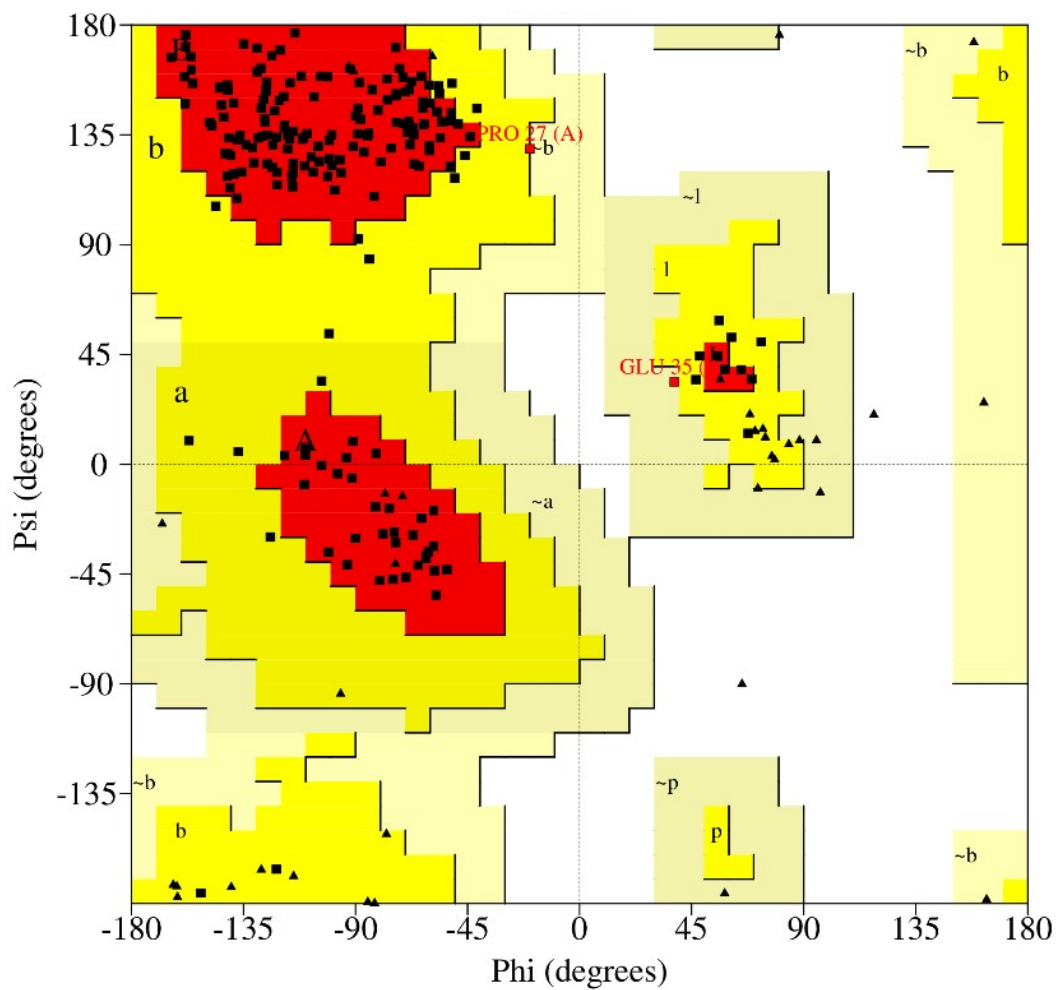
Plot statistics

Residues in most favoured regions [A,B,L]	167	87.9%
Residues in additional allowed regions [a,b,l,p]	21	11.1%
Residues in generously allowed regions [-a,-b,-l,-p]	2	1.1%
Residues in disallowed regions	0	0.0%

Number of non-glycine and non-proline residues	190	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	37	
Number of proline residues	12	

Total number of residues	241	

Figure 5S. Ramachandran plots for 2M9P NS2B/NS3-LQM472 after 200 ns dynamics simulations.



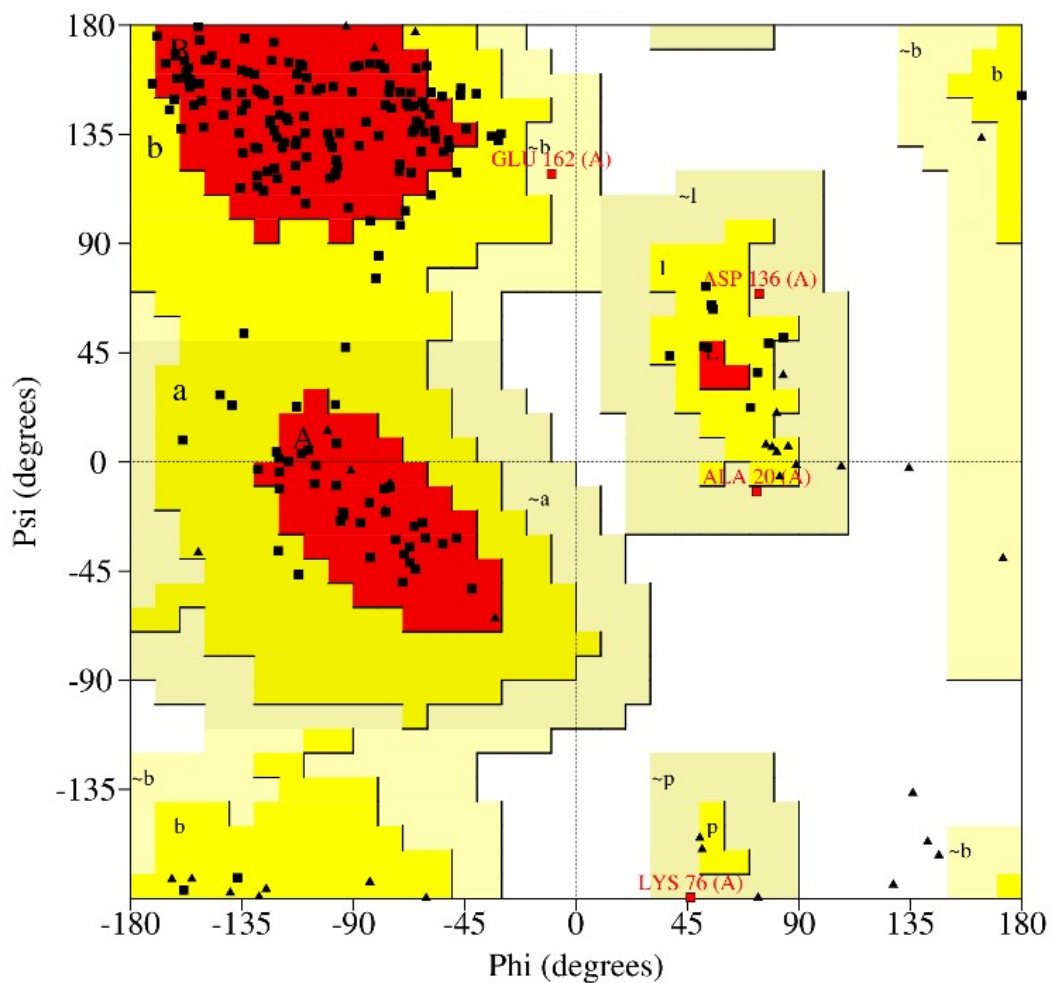
Plot statistics

Residues in most favoured regions [A,B,L]	169	88.9%
Residues in additional allowed regions [a,b,l,p]	20	10.5%
Residues in generously allowed regions [~a,~b,~l,~p]	1	0.5%
Residues in disallowed regions	0	0.0%

Number of non-glycine and non-proline residues	190	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	37	
Number of proline residues	12	

Total number of residues	241	

Figure 6S. Ramachandran plots for 2M9P NS2B/NS3-LQM474 after 200 ns dynamics simulations.



Plot statistics

Residues in most favoured regions [A,B,L]	152	80.0%
Residues in additional allowed regions [a,b,l,p]	34	17.9%
Residues in generously allowed regions [-a,-b,-l,-p]	4	2.1%
Residues in disallowed regions	0	0.0%

Number of non-glycine and non-proline residues	190	100.0%
Number of end-residues (excl. Gly and Pro)	2	
Number of glycine residues (shown as triangles)	37	
Number of proline residues	12	

Total number of residues	241	

Figure 7S. Solvent-Accessible Surface Area (SASA) plot for LQM467, 471, 472, and 474 in complex with 2M9P NS2B/NS3 protease during 200 ns dynamics simulations.

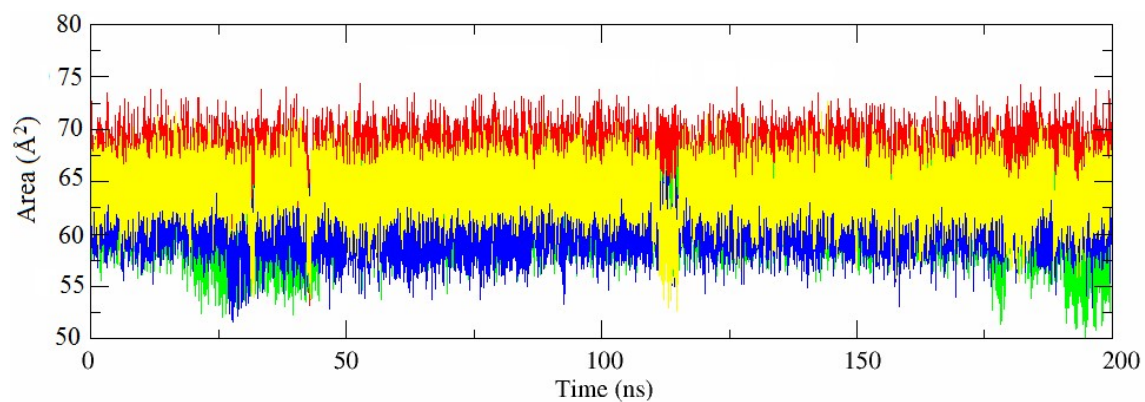


Figure 8S. Radius of Gyration (R_g) plot for LQM467, 471, 472, and 474 in complex with 2M9P NS2B/NS3 protease during 200 ns dynamics simulations.

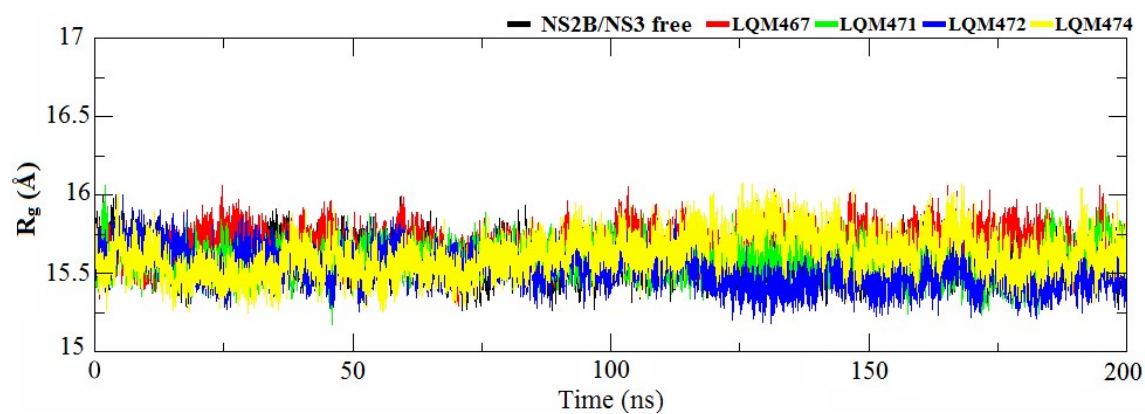
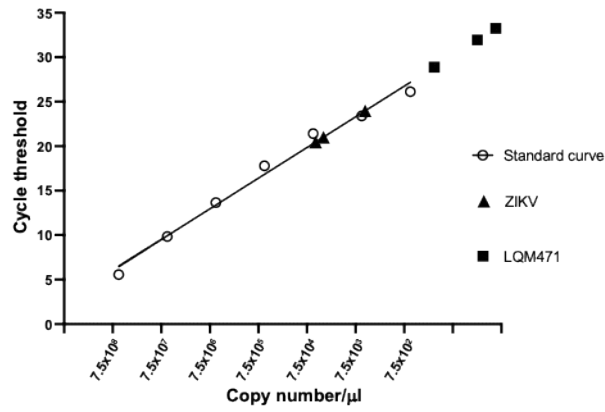
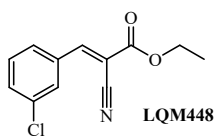


Figure 9S. The qPCR quantification curve of ZIKV viral RNA.

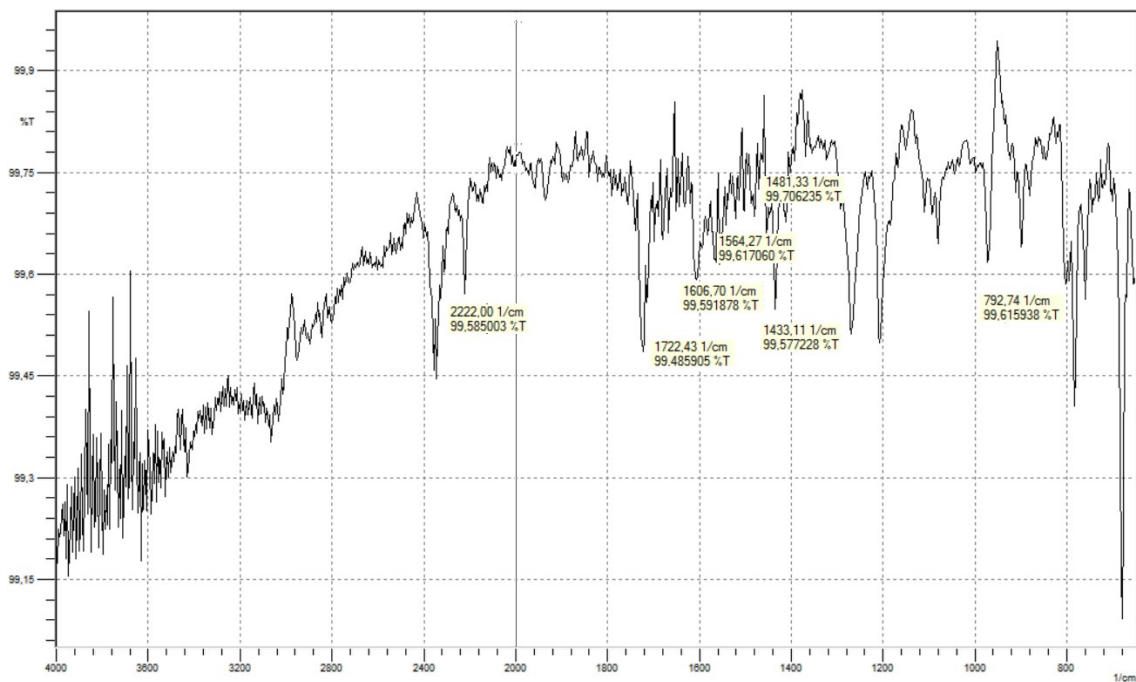
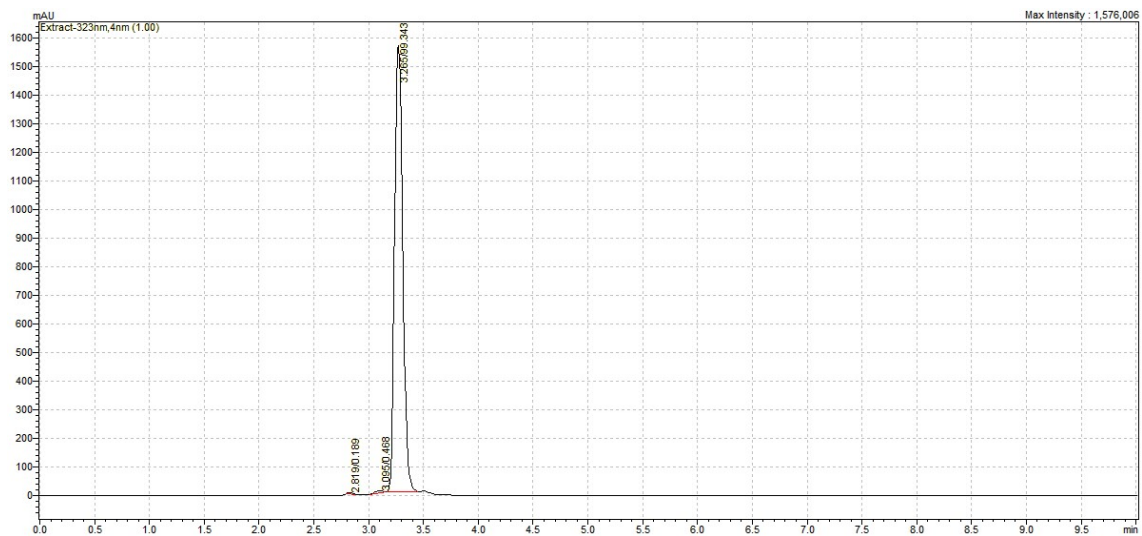


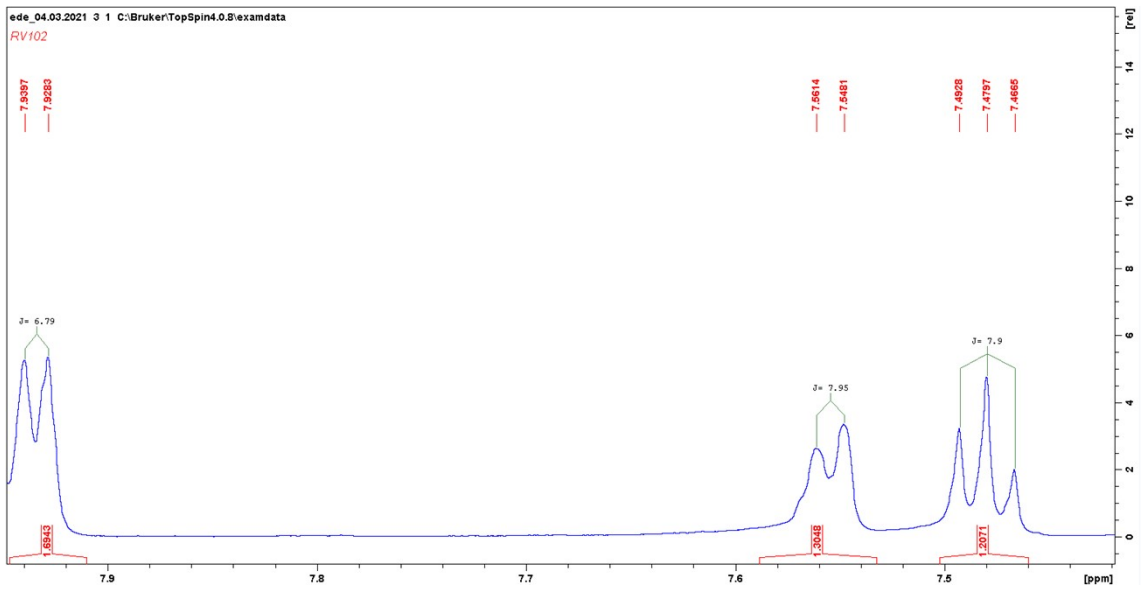
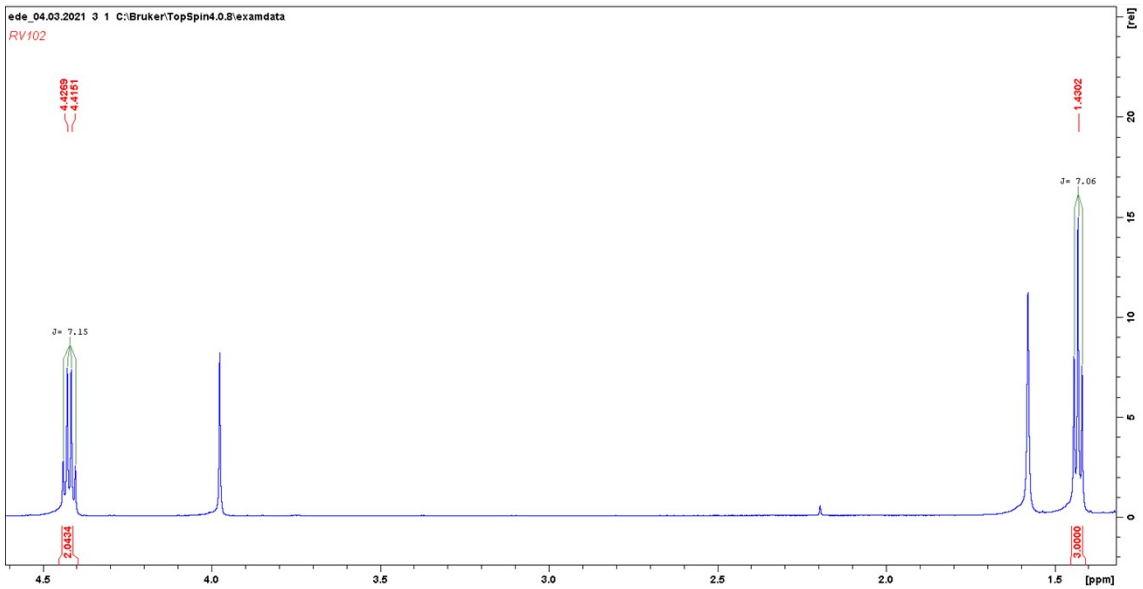
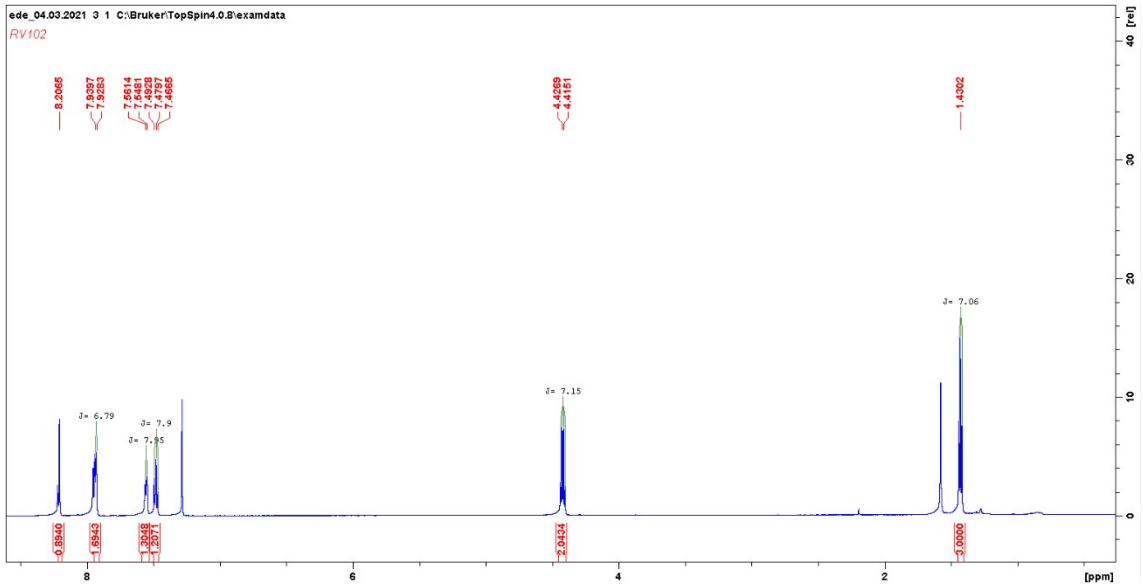
Standard curve of SYBR green-based qPCR amplification with linear regression analysis of seven serial dilutions ranging from 7.5×10^2 to 7.5×10^8 copies per microliter using a ZIKV genome fragment. The resulting quantification of ZIKV (untreated cells) and LQM471 samples were interpolated using the measured Ct (cycle threshold) and copy number estimated in the qPCR reaction ($n = 3$ biological replicates). LQM471 treated samples were detected with a Ct below the lowest point of the standard curve ($< 7.5 \times 10^2$ copies/ μL), while the ZIKV untreated samples presented a mean value of 3.9×10^4 copies/ μL in the qPCR reaction. The efficiency of the qPCR standard curve presented a slope of -3.4 and a coefficient of correlation of 0.987% .

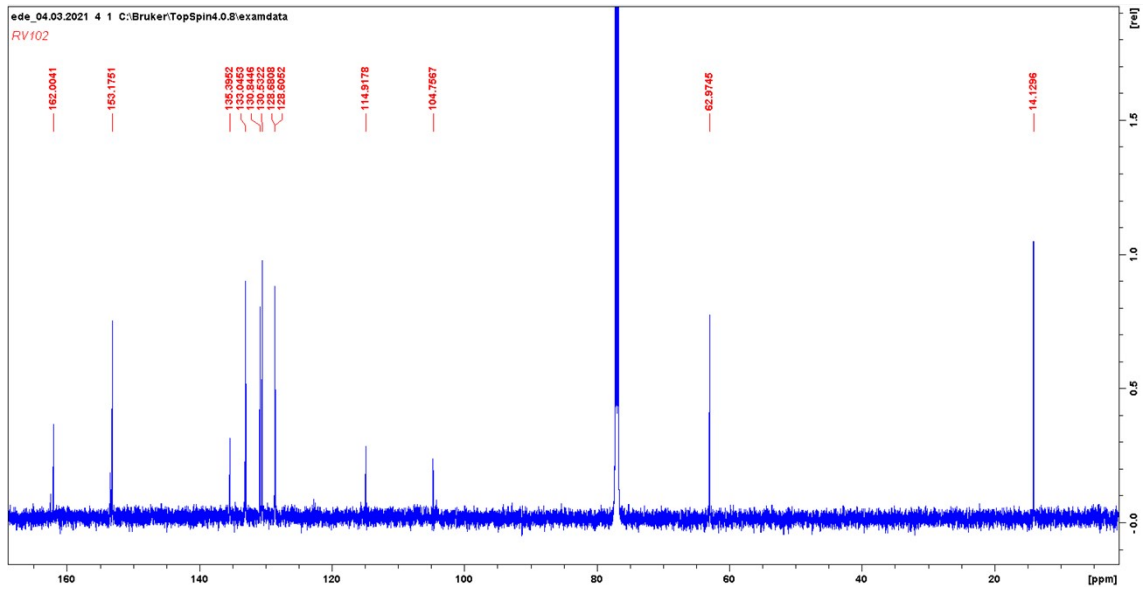
CHEMICAL CHARACTERIZATION



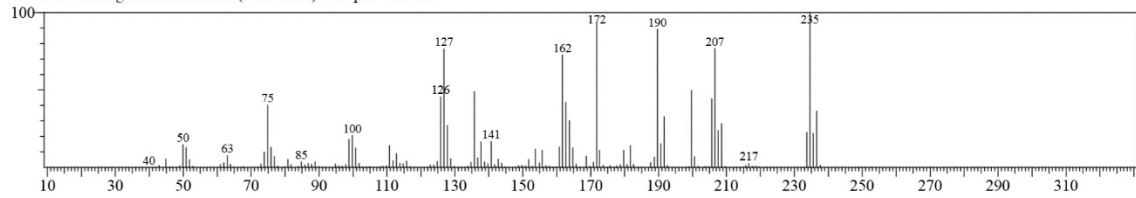
Ethyl (*E*)-3-(3-chlorophenyl)-2-cyanoacrylate
Chemical Formula: $C_{12}H_{10}ClNO_2$
Exact Mass: 235.67 g/mol

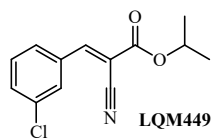




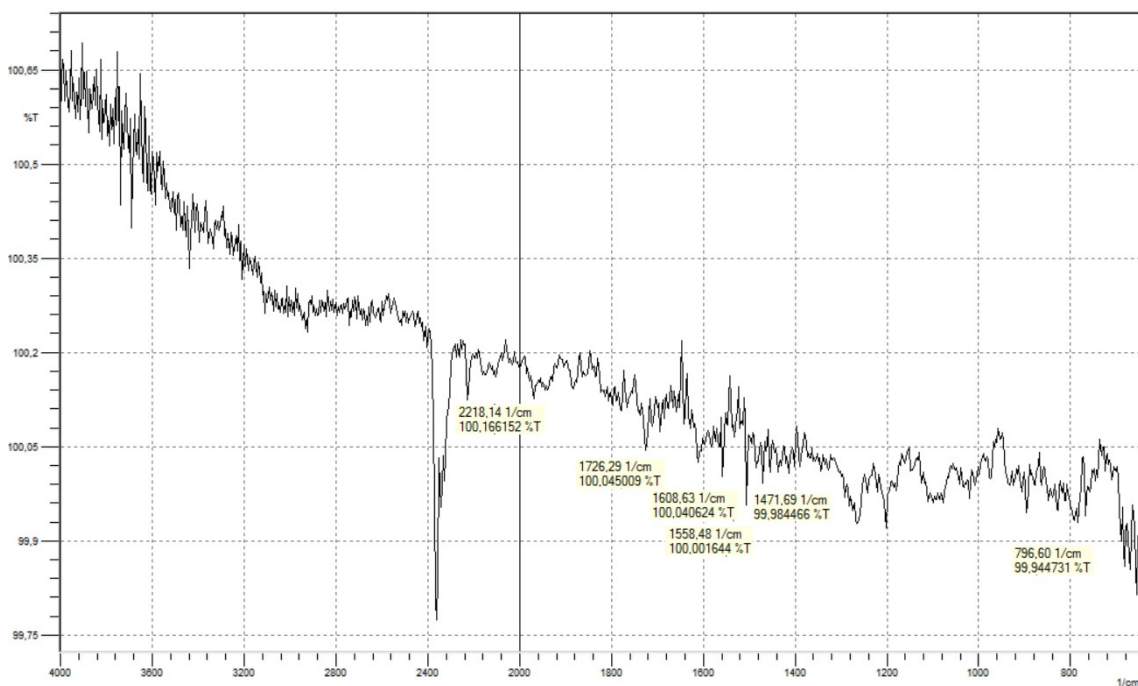
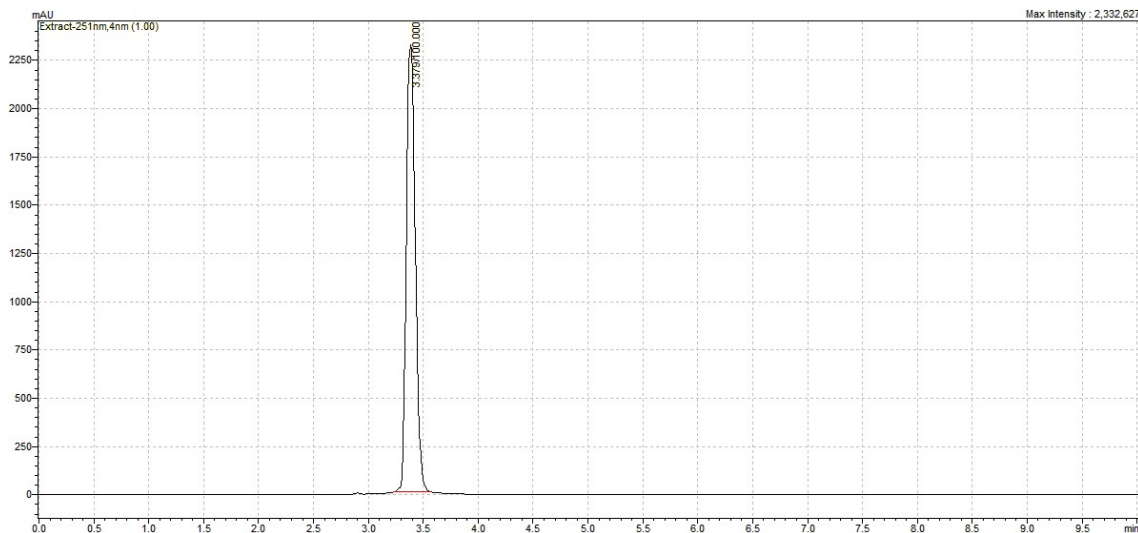


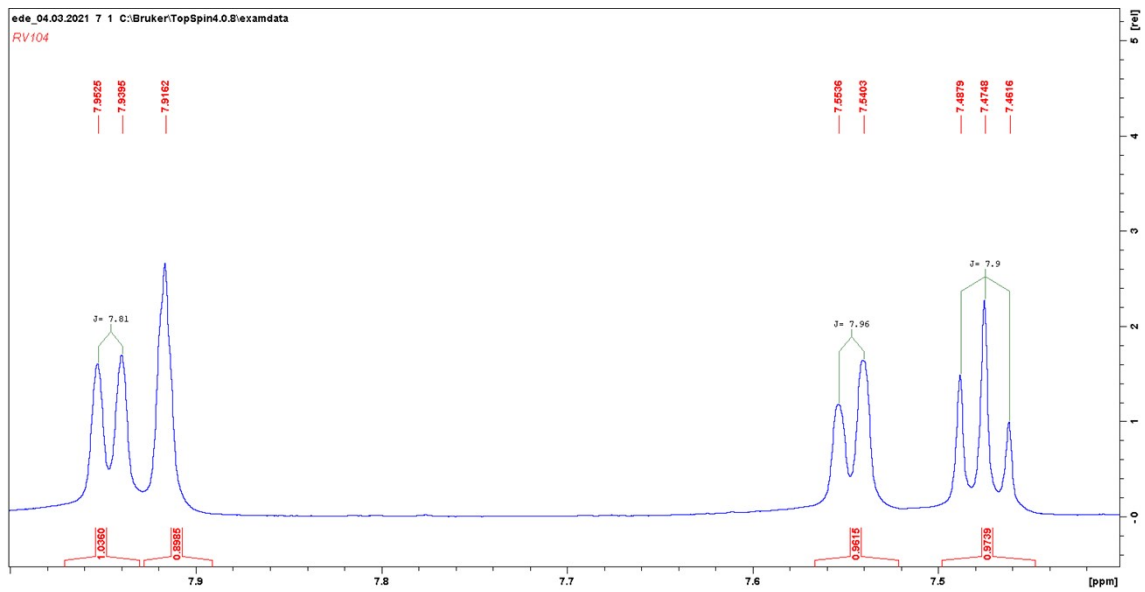
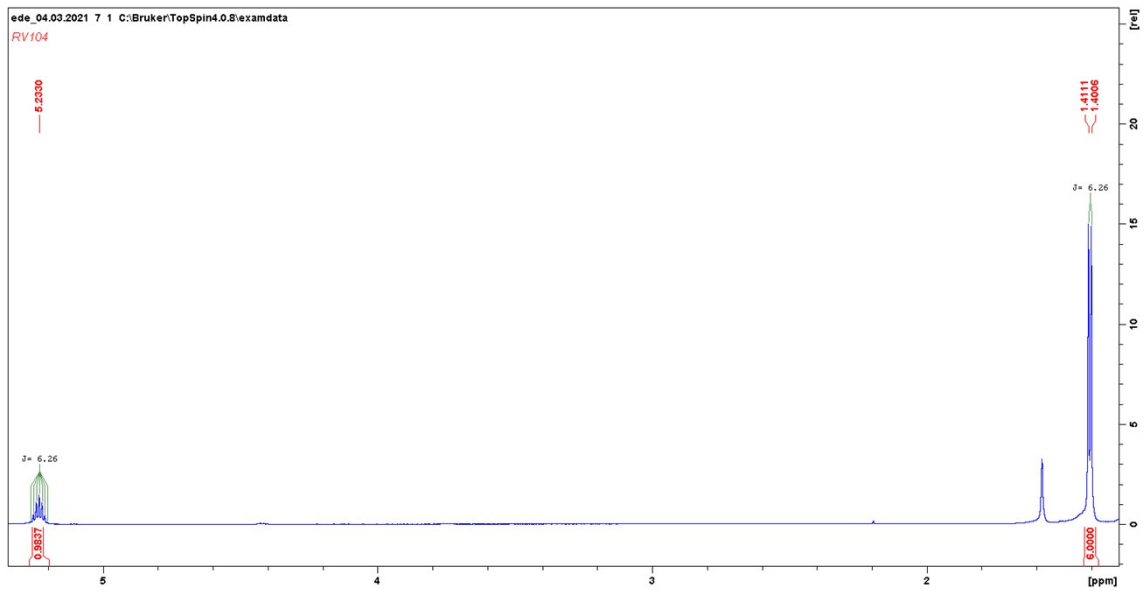
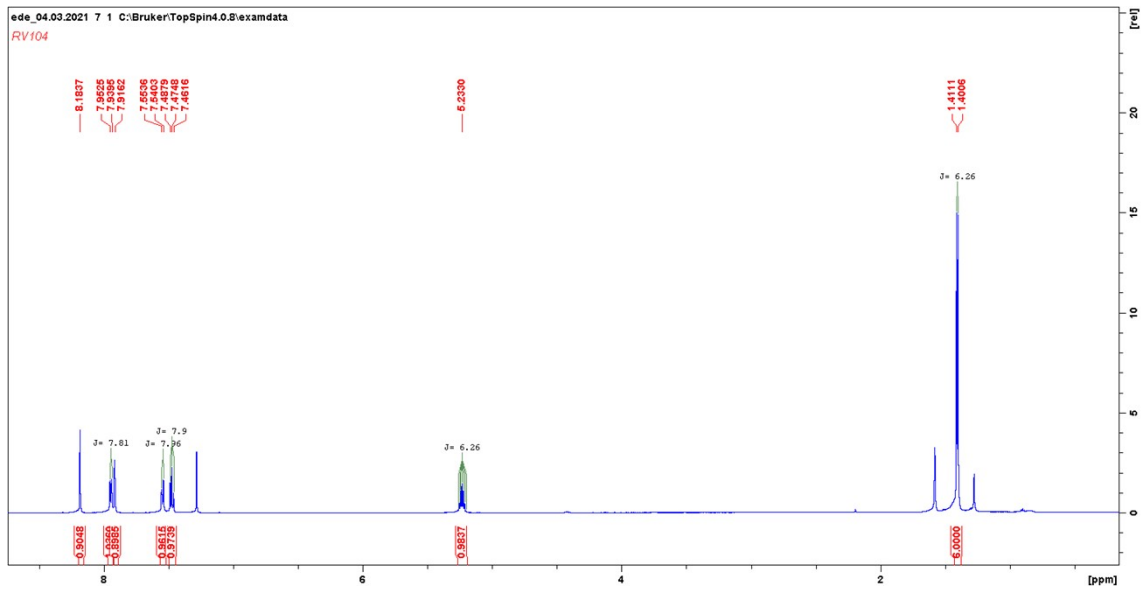
Spectrum1 #Data# RV102.qgd R.Time:13.925(Scan#:1072)
MassPeaks:169
RawMode:Averaged 13.517-14.017(1023-1083) BasePeak:234.60(10000)
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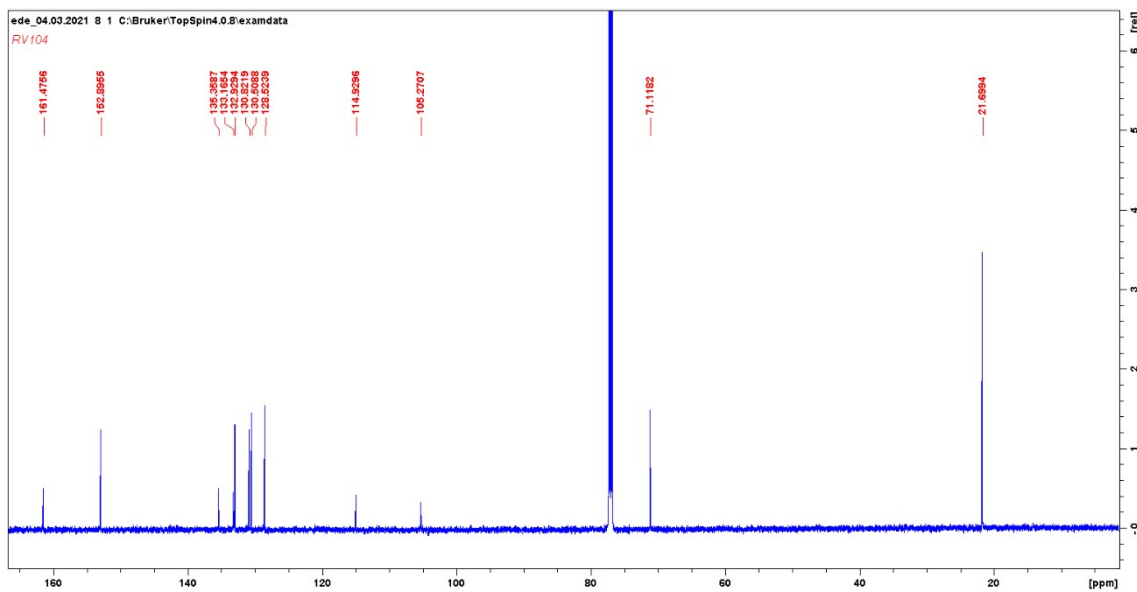




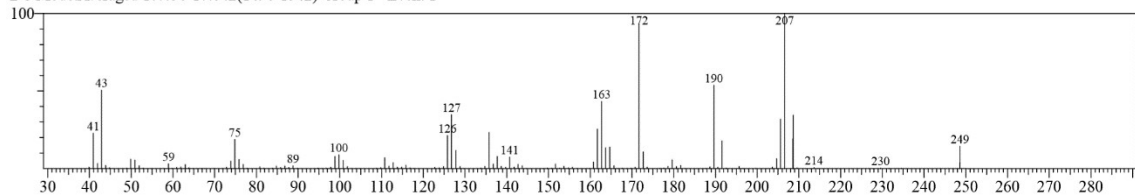
Isopropyl (*E*)-3-(3-chlorophenyl)-2-cyanoacrylate
 Chemical Formula: C₁₃H₁₂ClNO₂
 Exact Mass: 249.69 g/mol

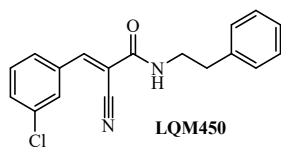




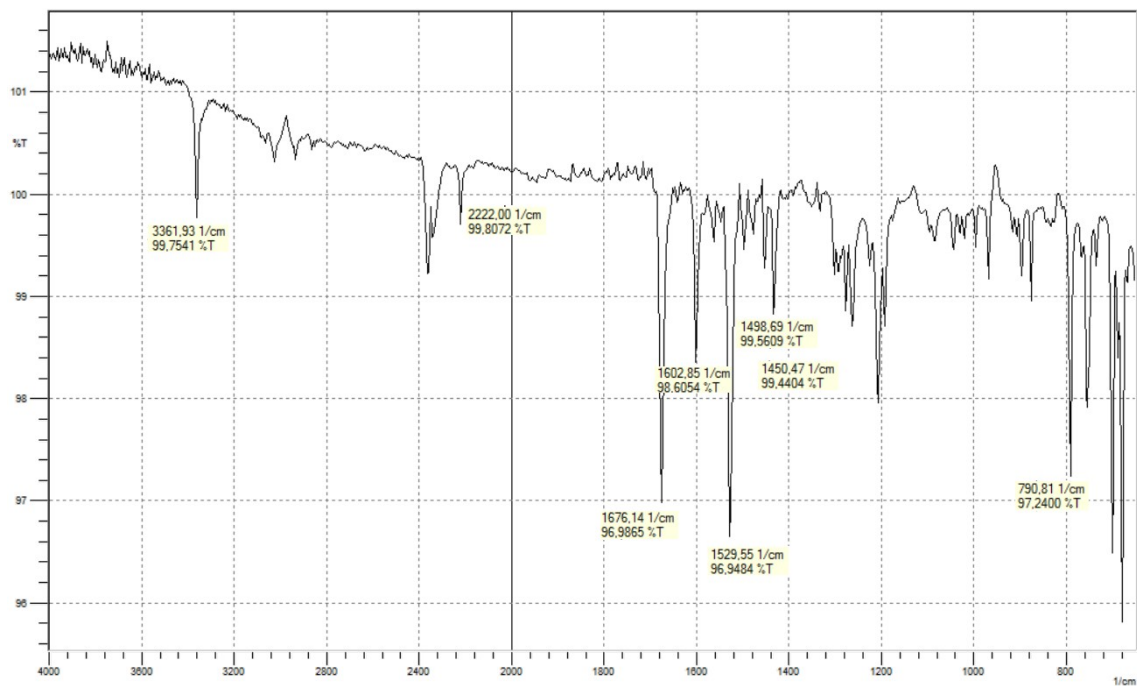
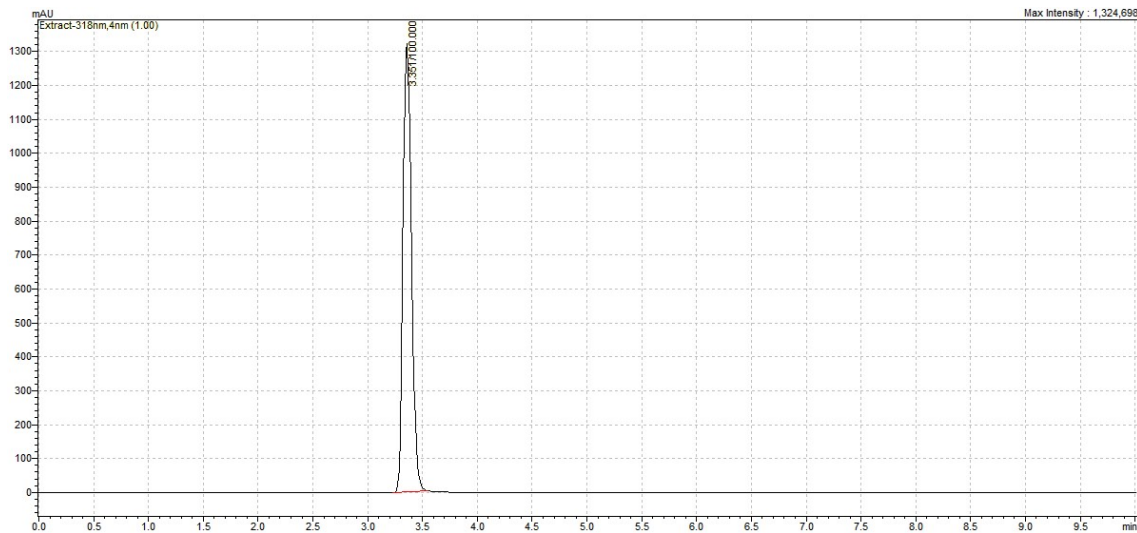


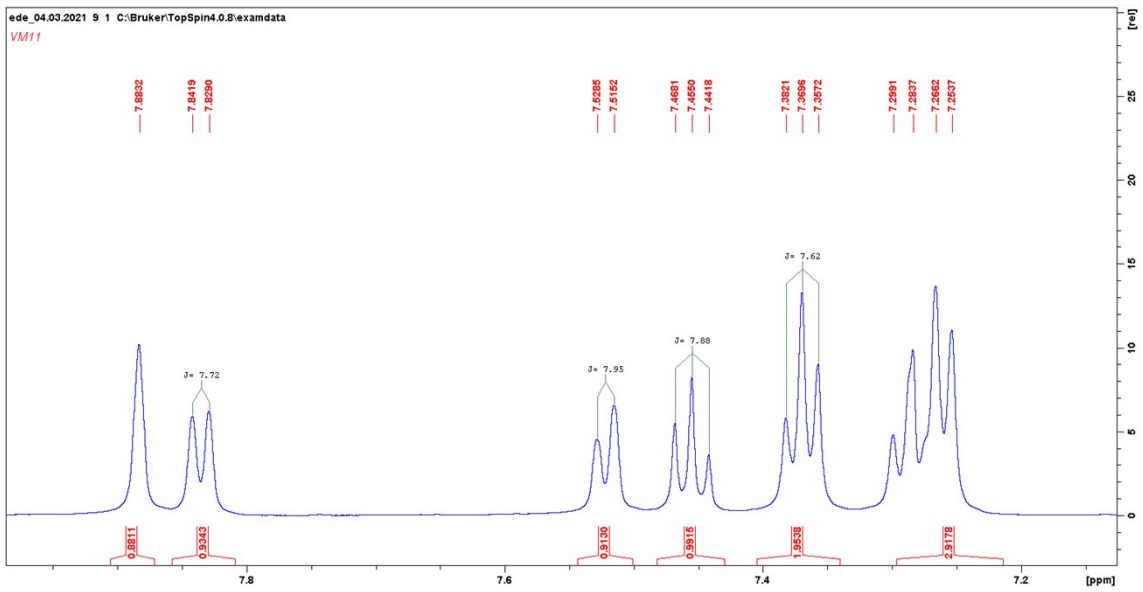
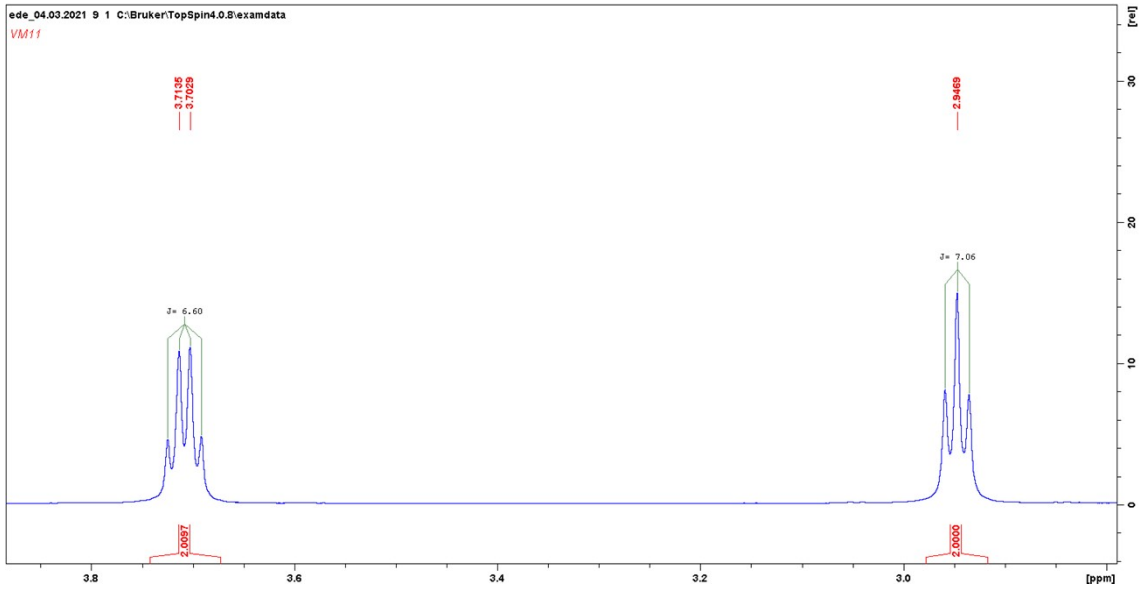
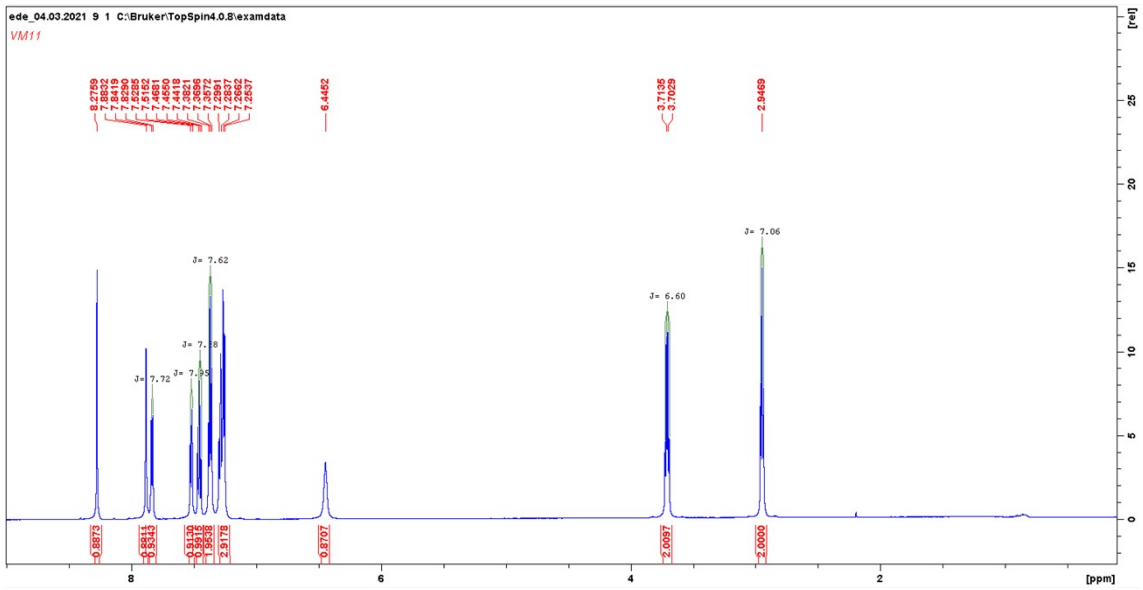
Spectrum1 #Data# RV104.qgd R.Time:14.133(Scan#:1097)
MassPeaks:203
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BG Mode:Averaged 17.458-17.842(1496-1542) Group 1 - Event 1

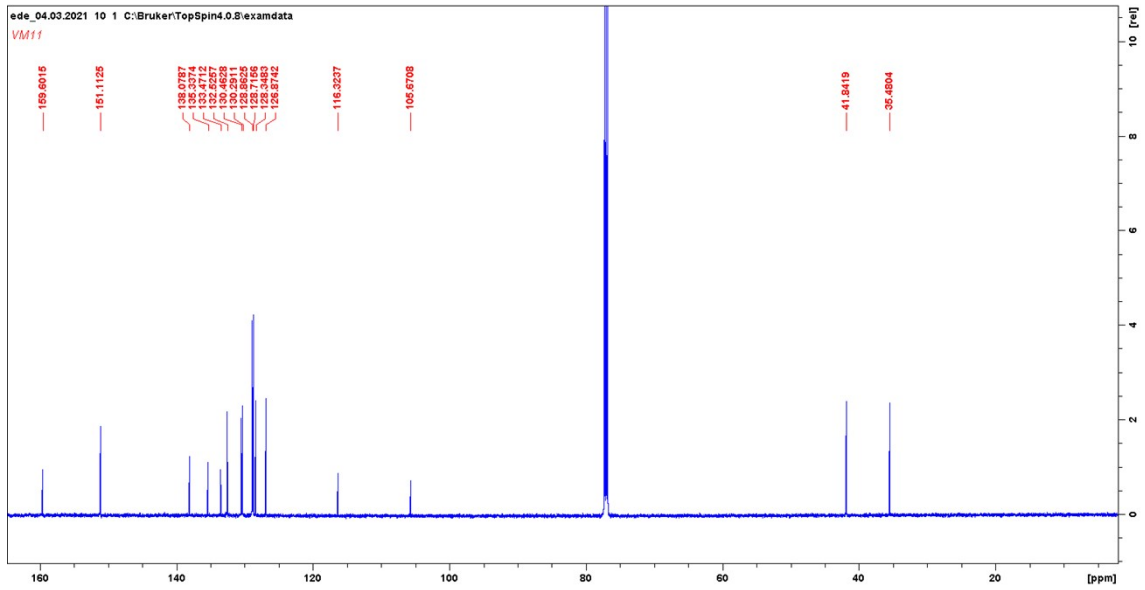




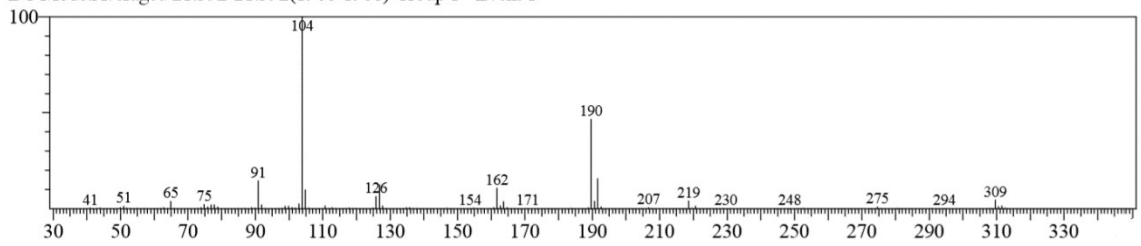
(*E*)-3-(3-Chlorophenyl)-2-cyano-*N*-phenethylacrylamide
Chemical Formula: C₁₈H₁₅ClN₂O
Exact Mass: 310.78 g/mol

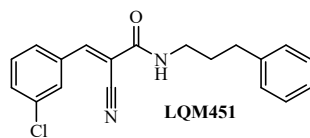




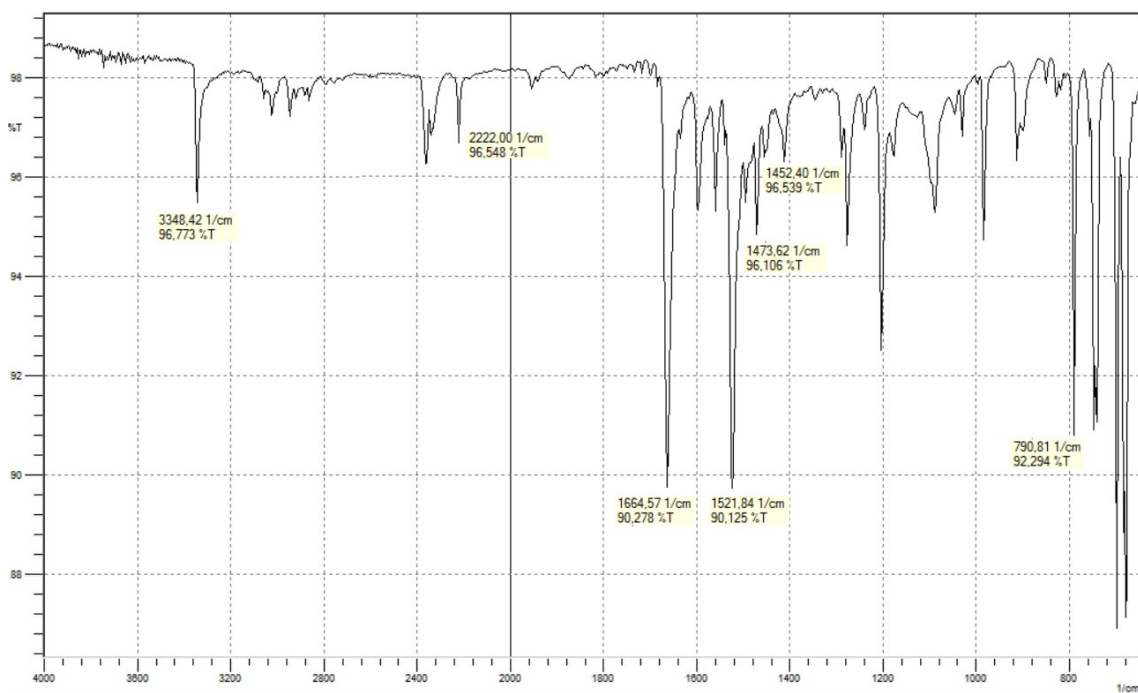
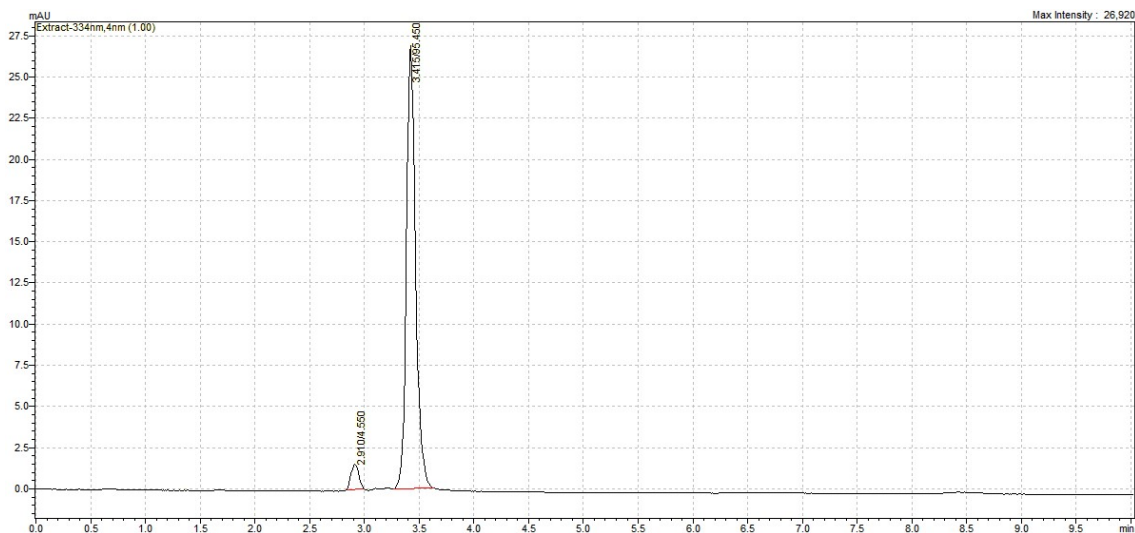


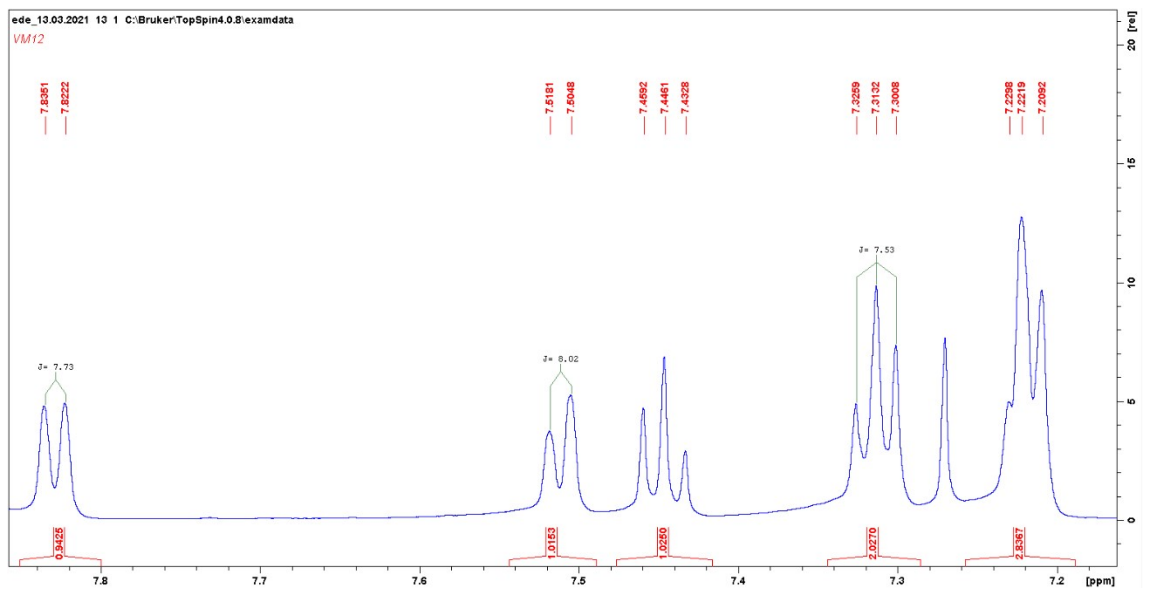
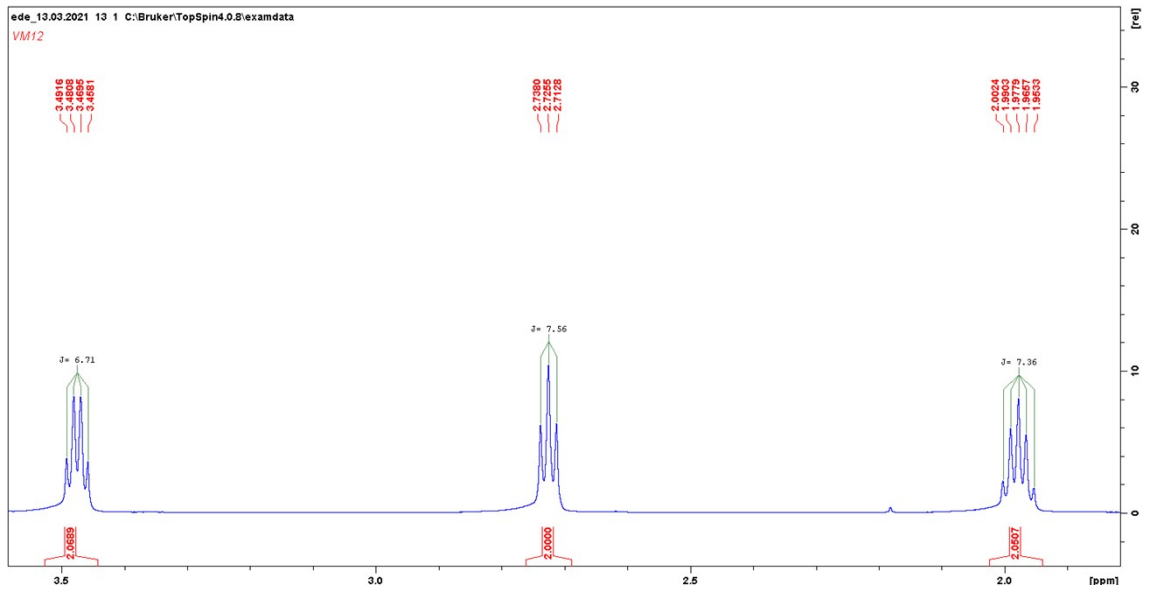
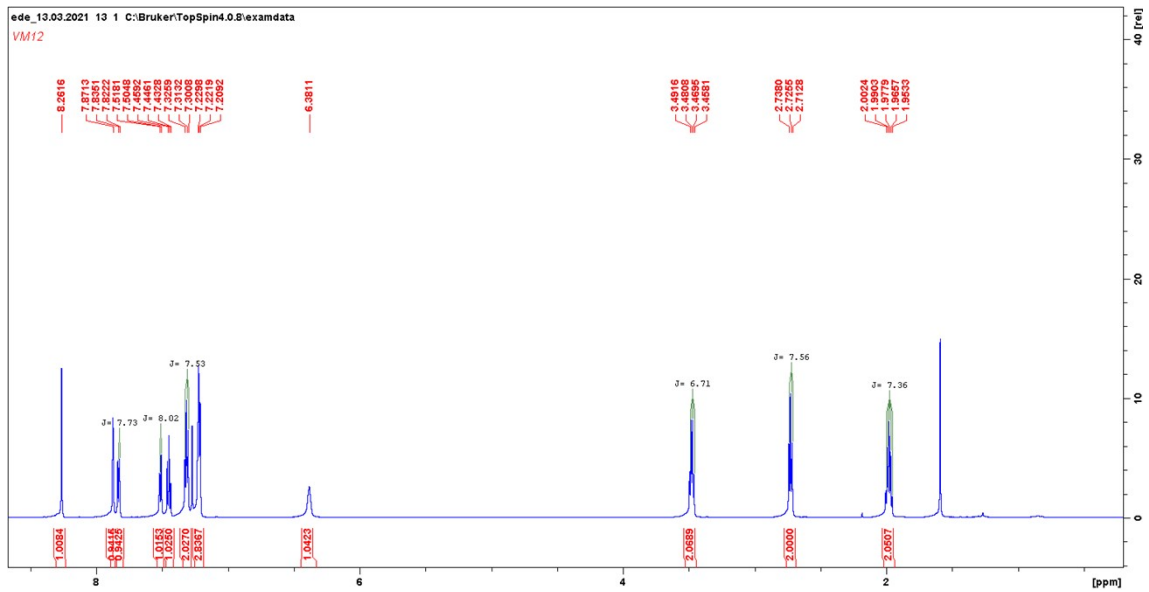
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BG Mode:Averaged 21.392-21.392(1968-1968) Group 1 - Event 1

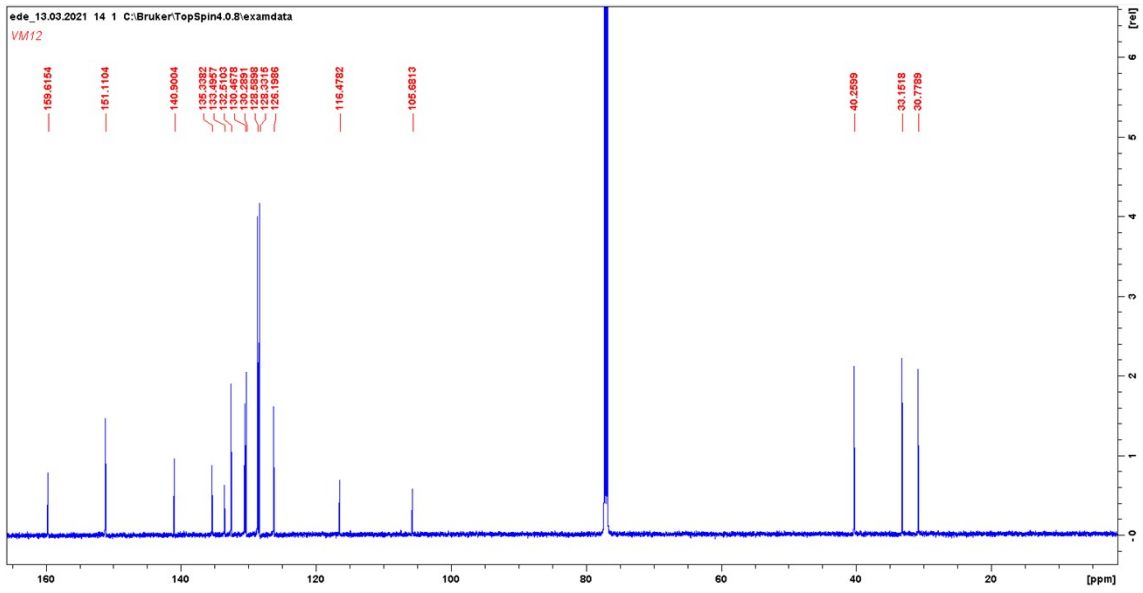




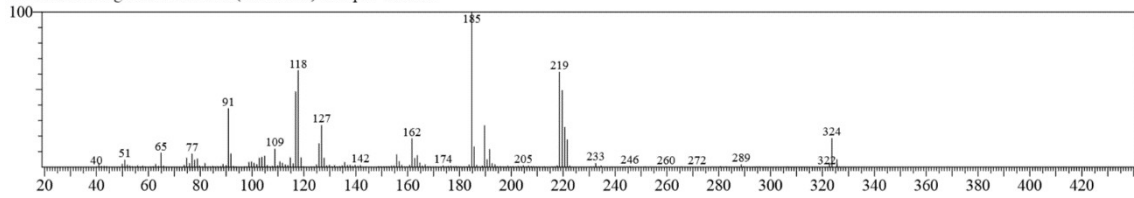
LQM451
(E)-3-(3-Chlorophenyl)-2-cyano-*N*-(3-phenylpropyl)acrylamide
 Chemical Formula: C₁₉H₁₇ClN₂O
 Exact Mass: 324.81 g/mol

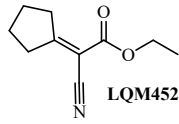




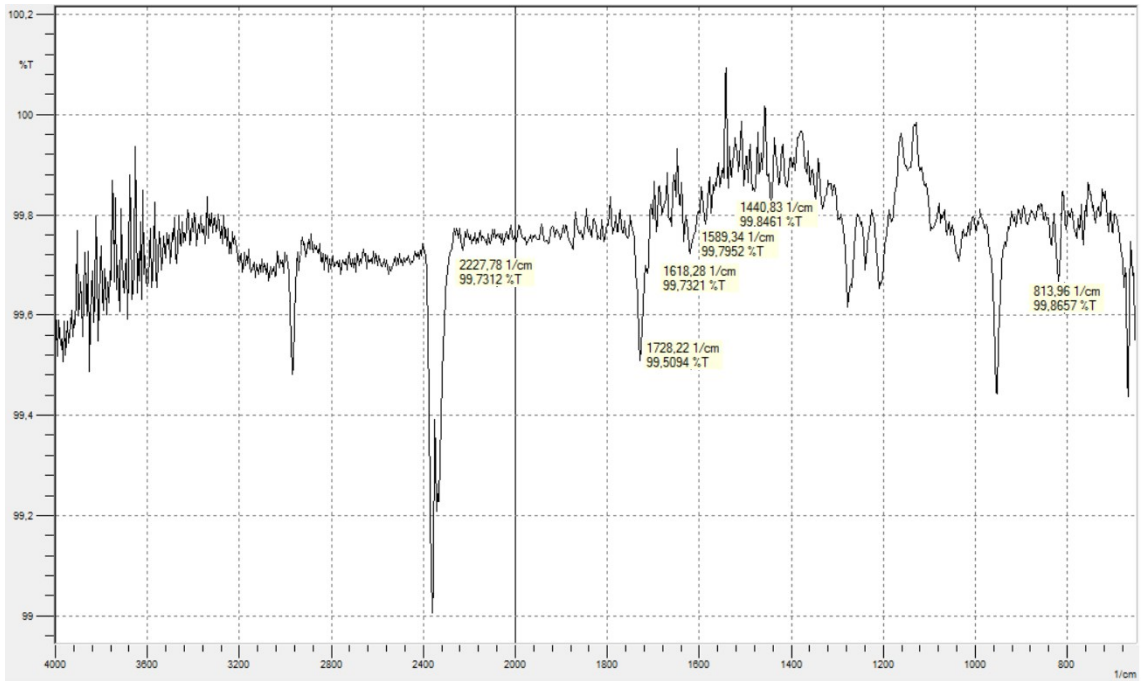
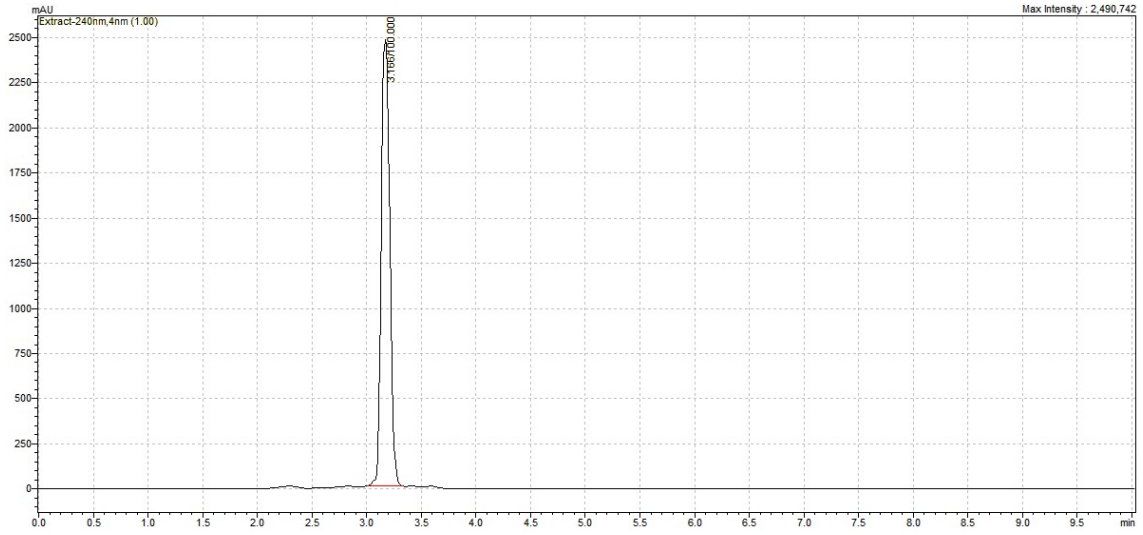


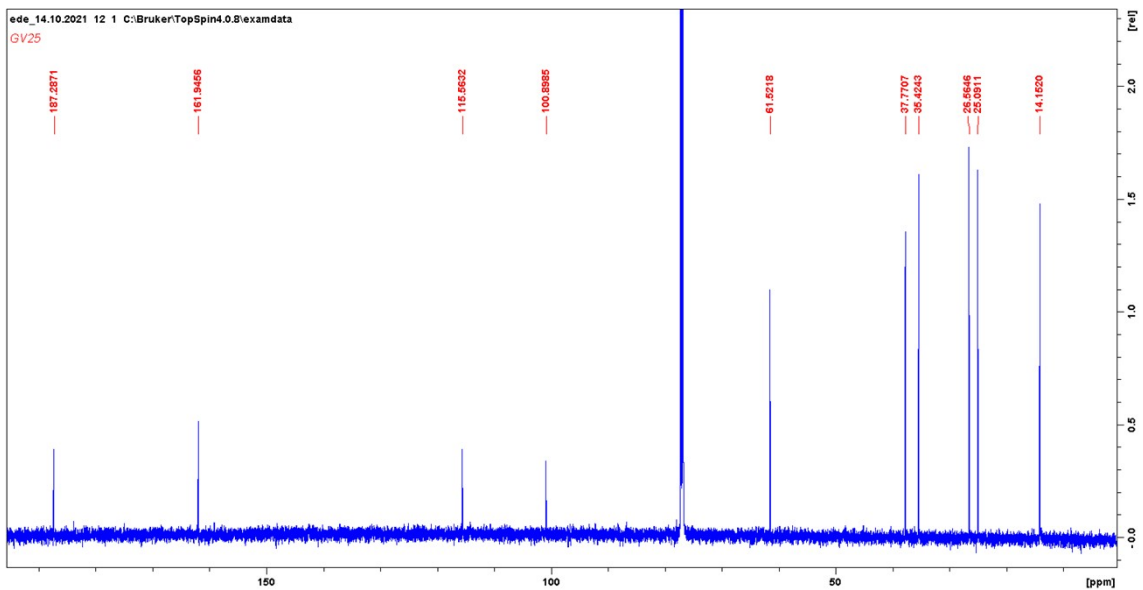
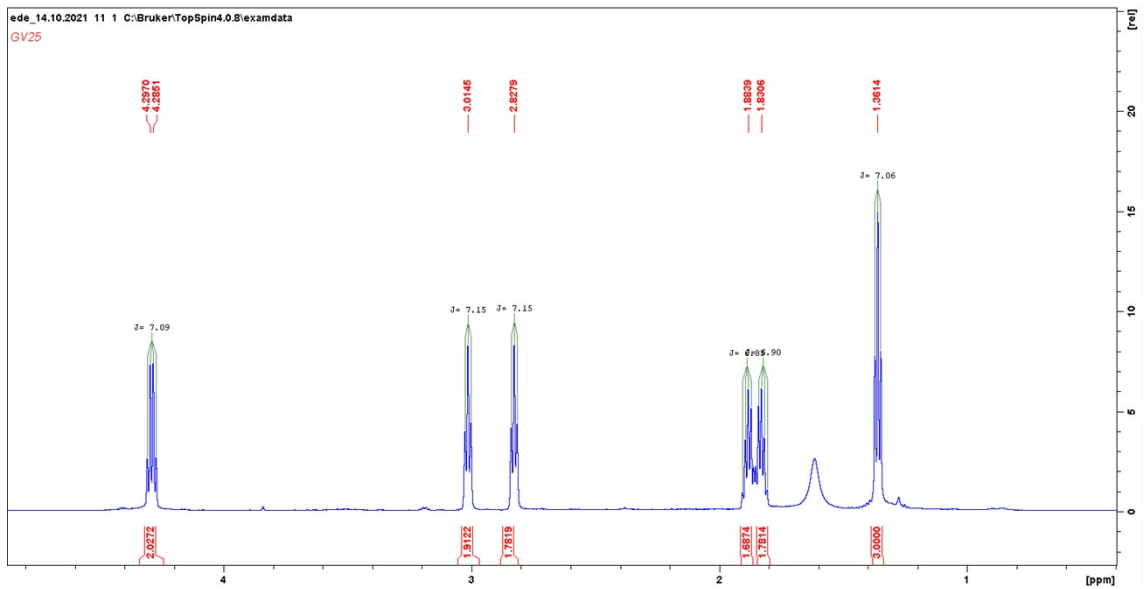
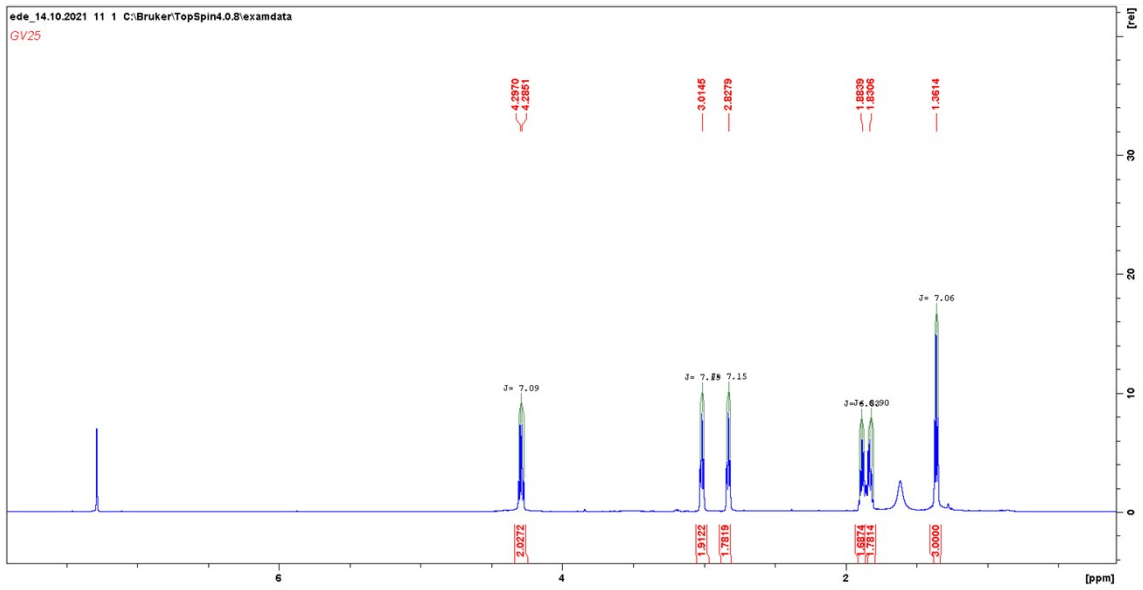
Spectrum1 #Data# VM12.qgd R.Time:23.008(Scan#:2162)
MassPeaks:264
RawMode:Averaged 22.092-23.433(2052-2213) BasePeak:184.75(10000)
BG Mode:Averaged 25.100-25.508(2413-2462) Group 1 - Event 1





Ethyl 2-cyano-2-cyclopentylideneacetate
Chemical Formula: C₁₀H₁₃NO₂
Exact Mass: 179.22 g/mol



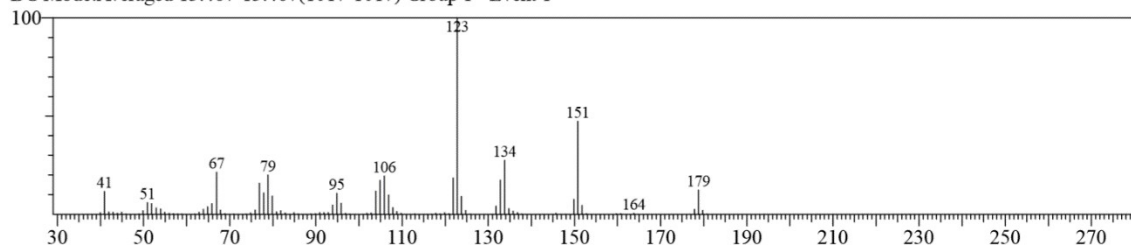


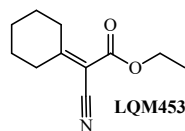
Spectrum1 #Data# GV25.qgd R.Time:9.075(Scan#:490)

MassPeaks:120

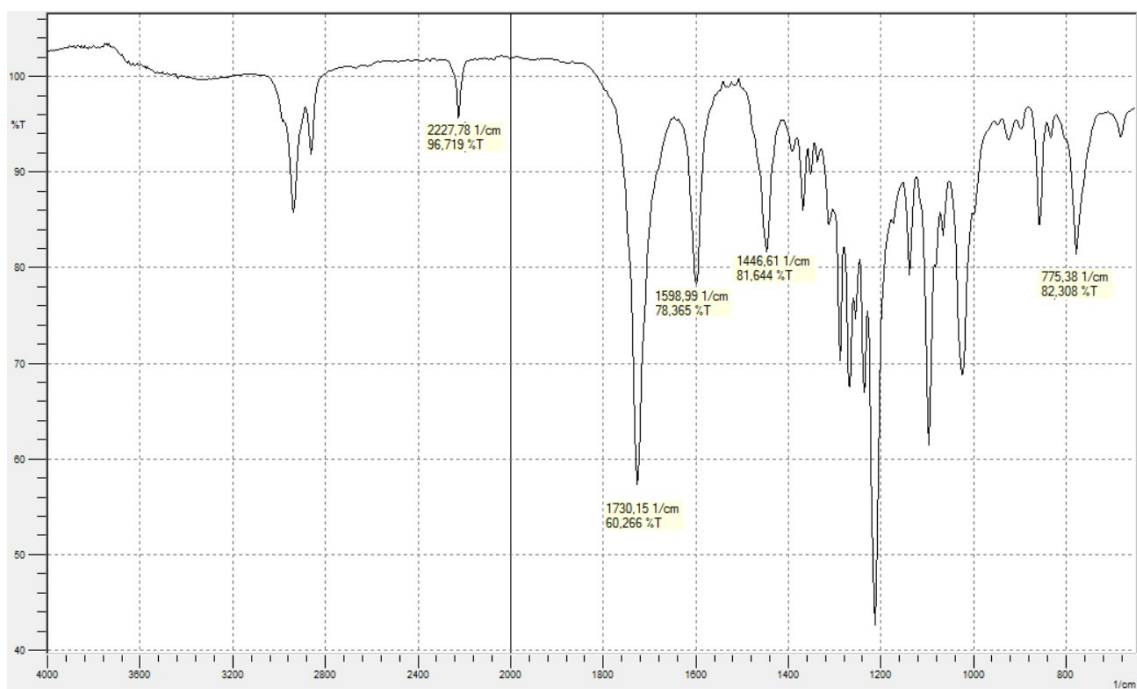
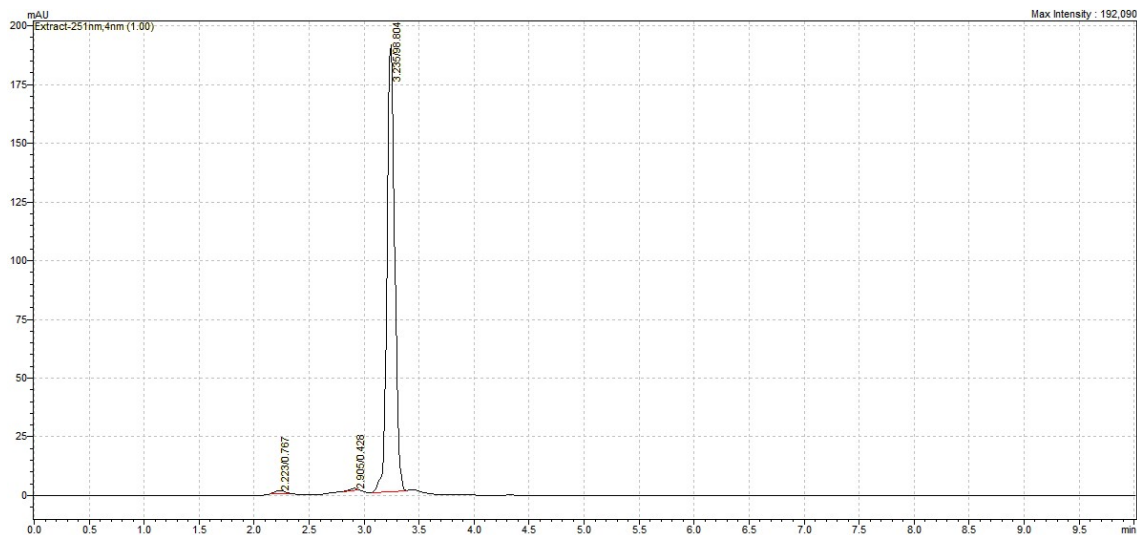
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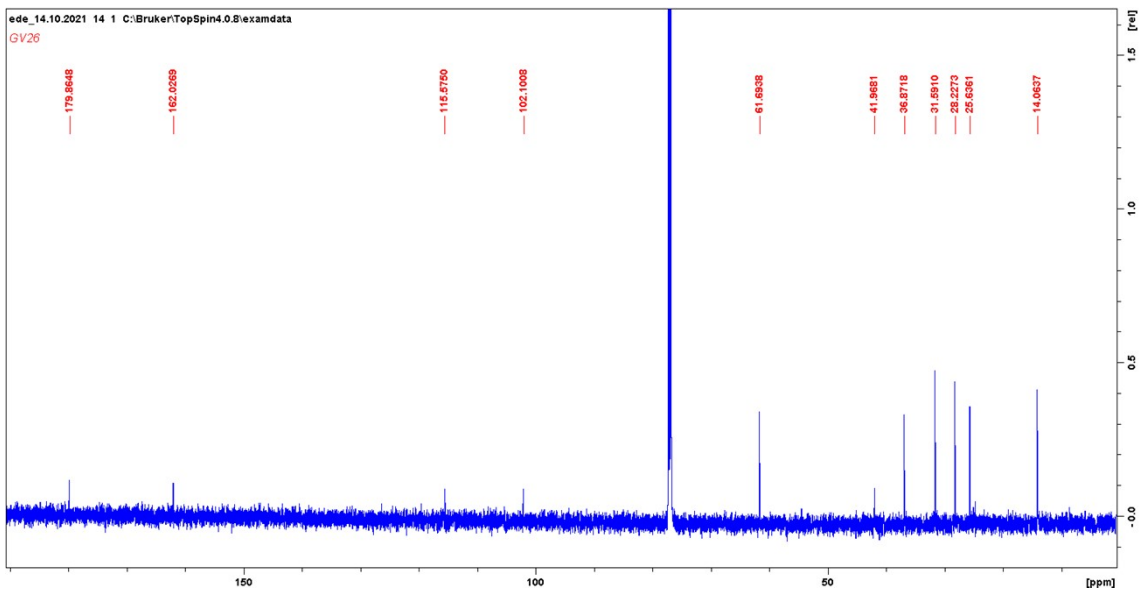
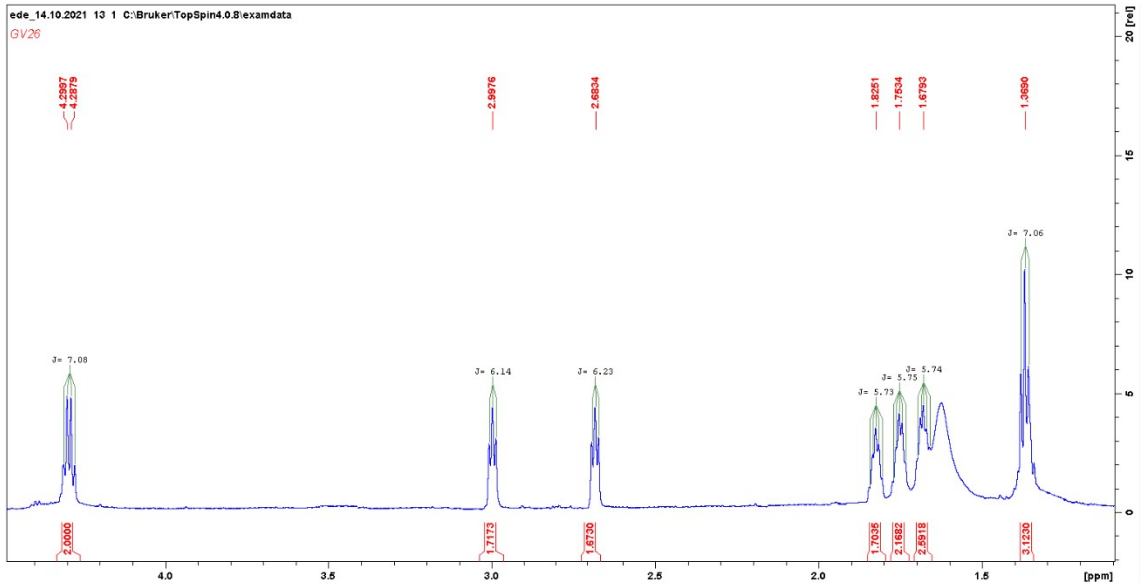
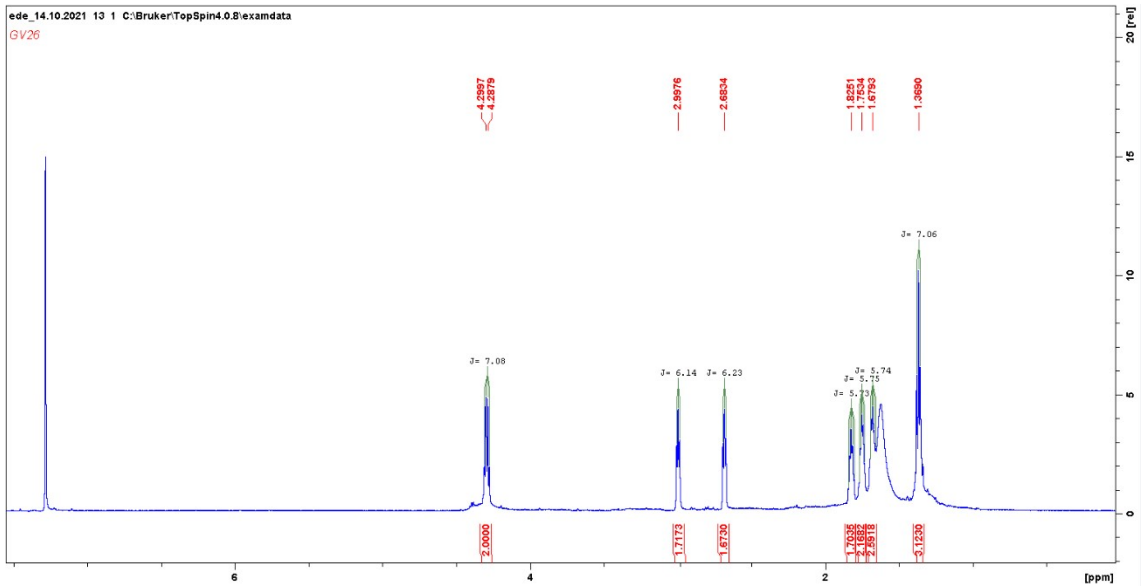
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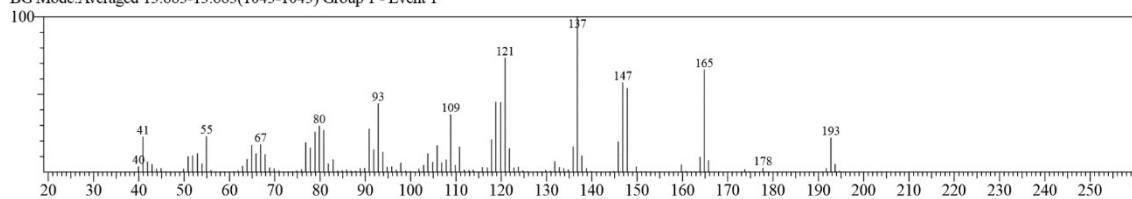


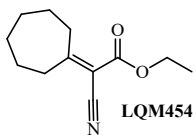
Ethyl 2-cyano-2-cyclohexylideneacetate
Chemical Formula: $C_{11}H_{15}NO_2$
Exact Mass: 193.25 g/mol



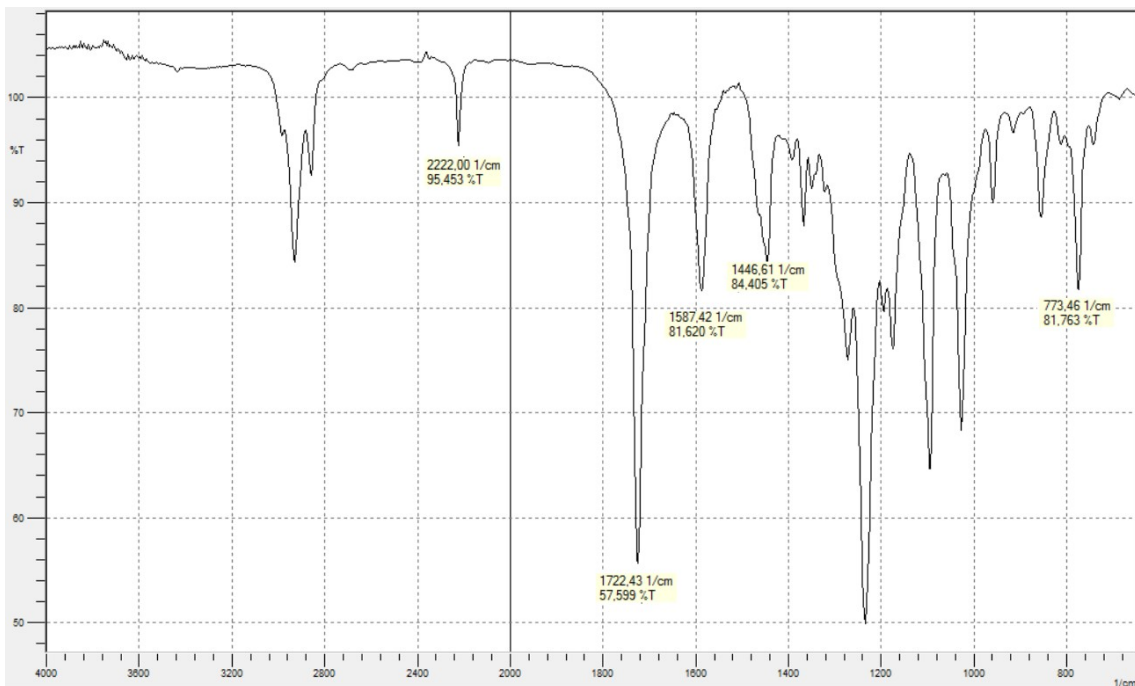
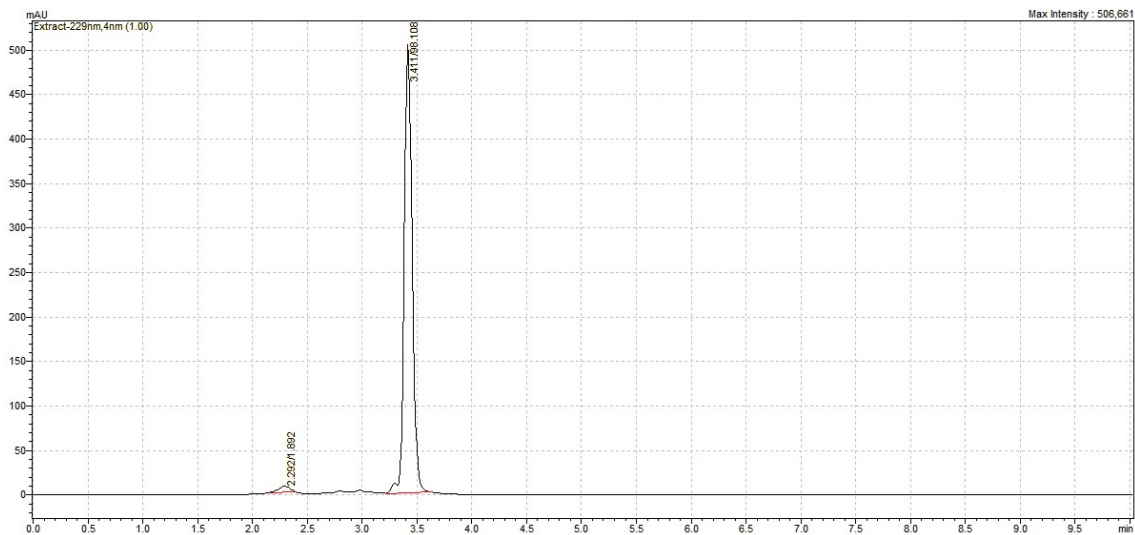


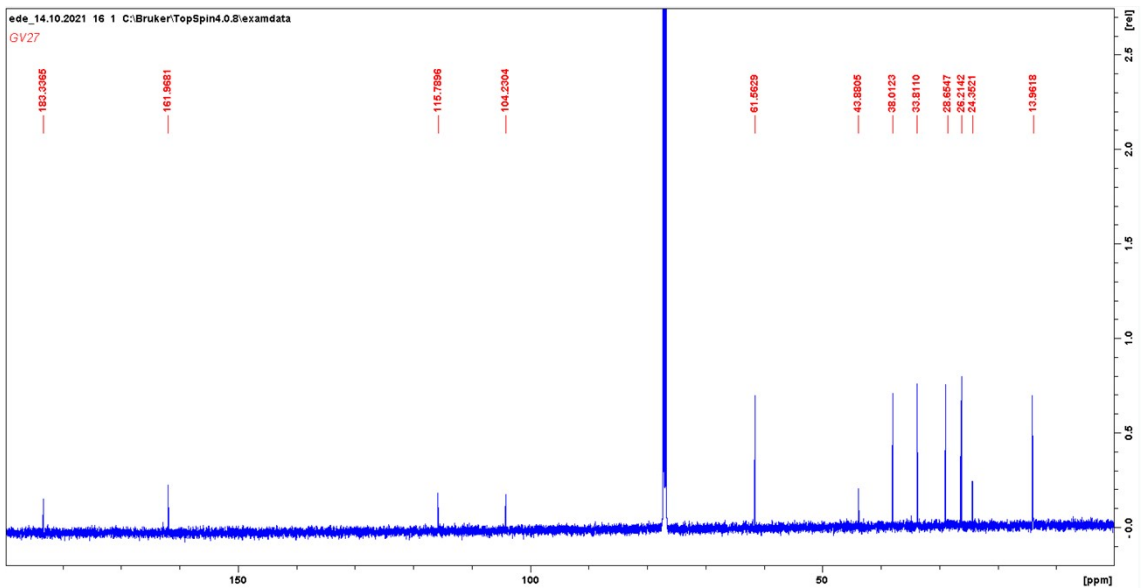
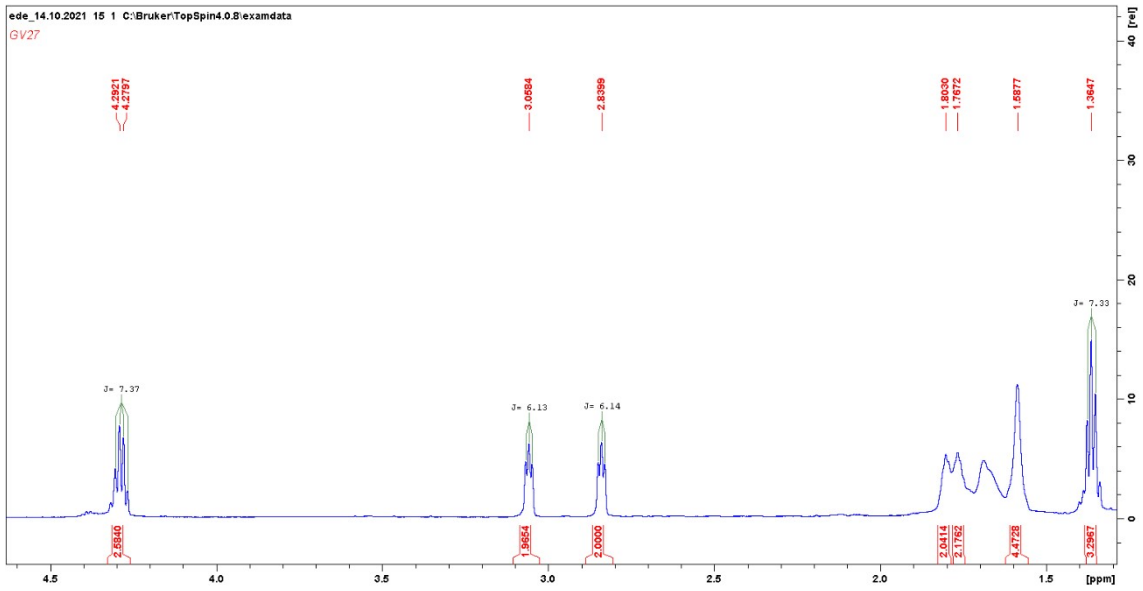
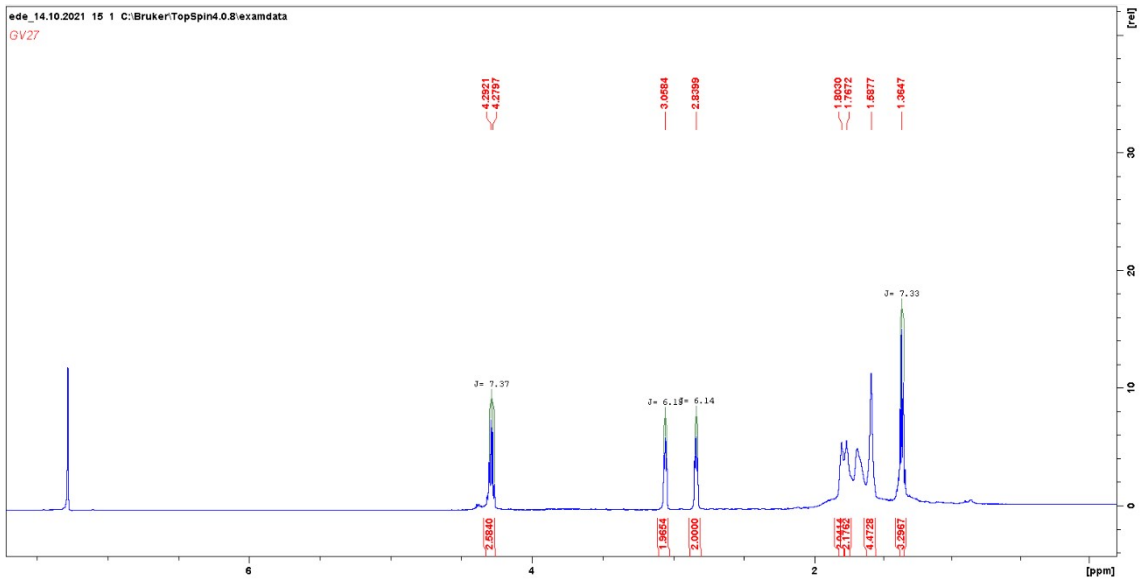
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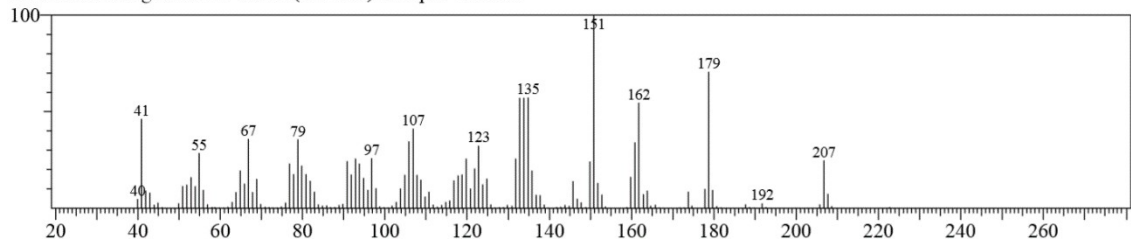


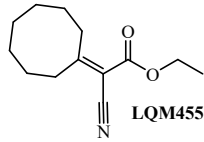
Ethyl 2-cyano-2-cycloheptylideneacetate
Chemical Formula: $C_{12}H_{17}NO_2$
Exact Mass: 207.27 g/mol



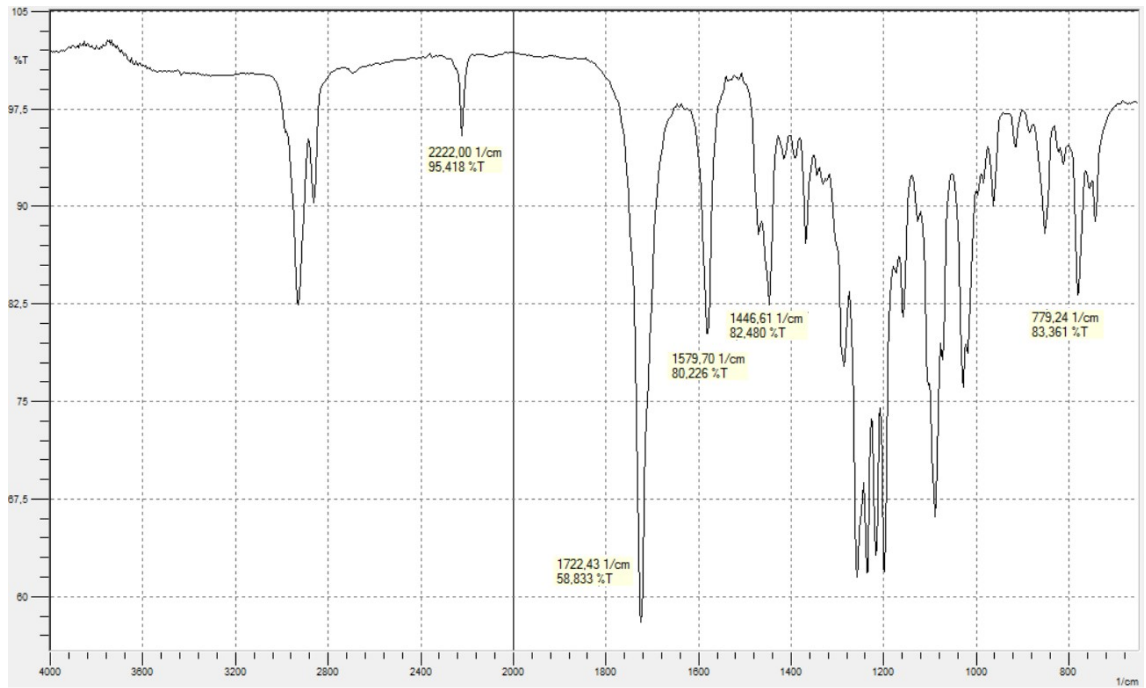
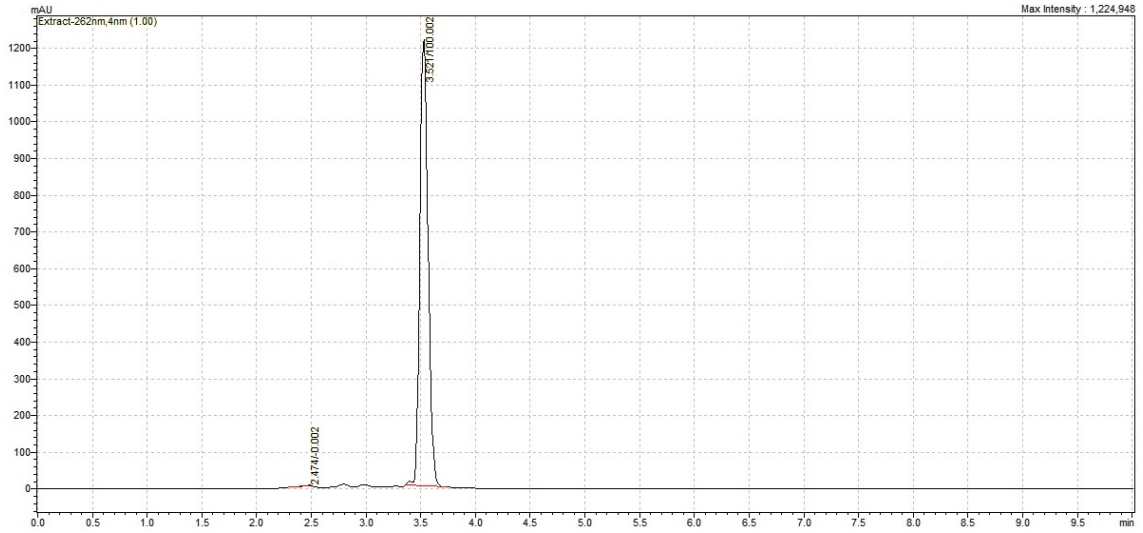


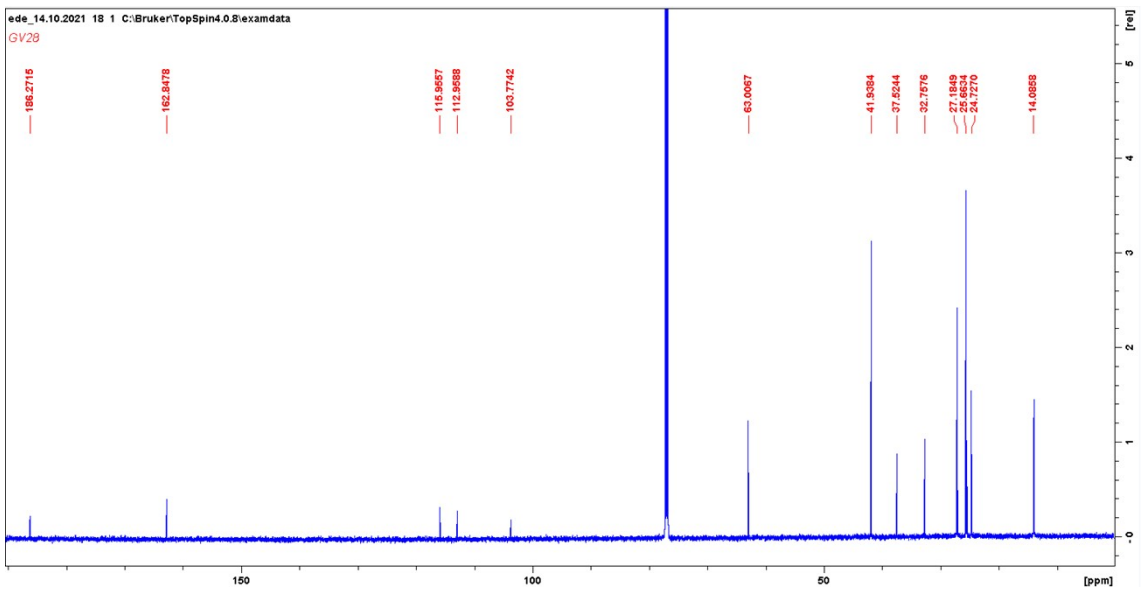
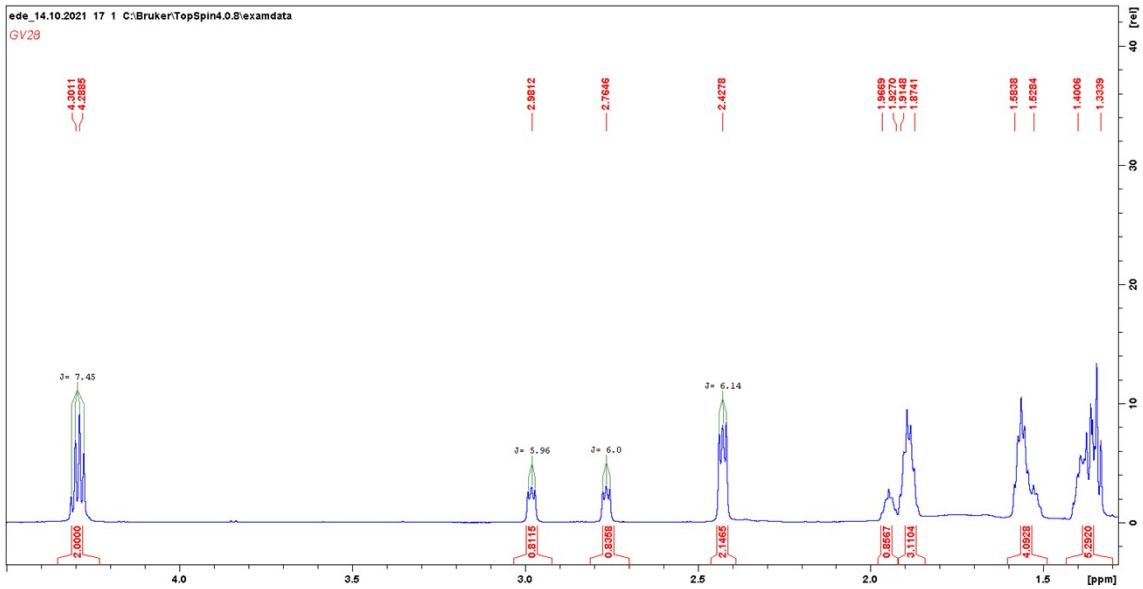
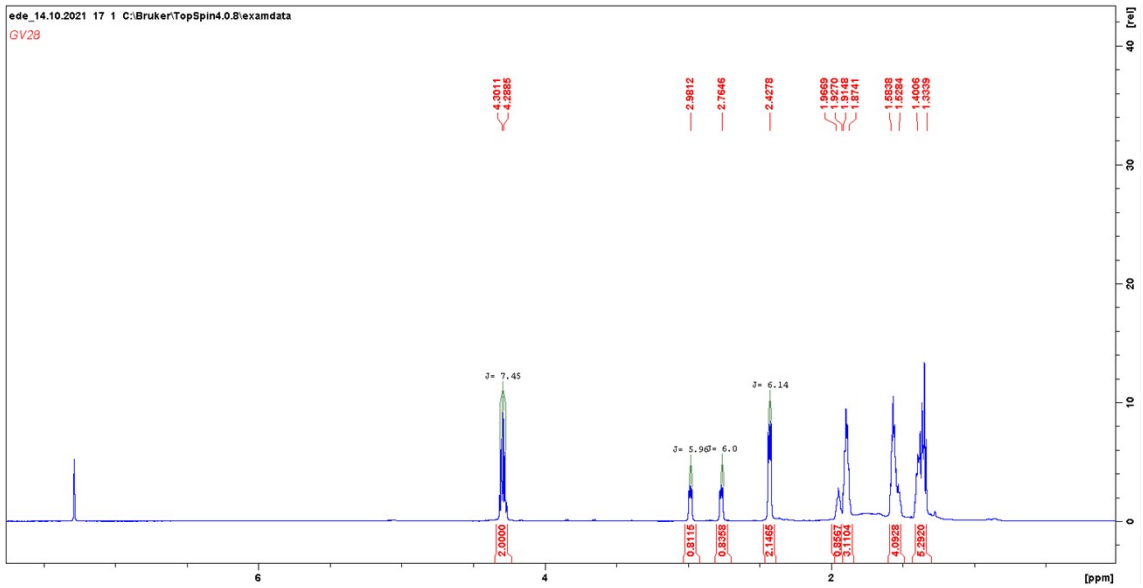
Spectrum1 #Data# GV27.qgd R.Time:11.975(Scan#:838)
MassPeaks:170
RawMode:Averaged 11.642-12.092(798-852) BasePeak:150.75(10000)
BG Mode:Averaged 12.242-12.242(870-870) Group 1 - Event 1



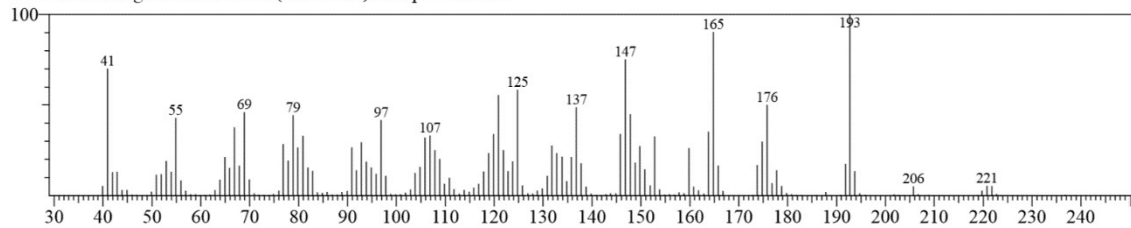


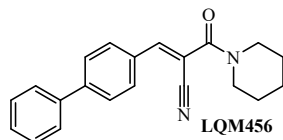
Ethyl 2-cyano-2-cyclooctylideneacetate
 Chemical Formula: $C_{13}H_{19}NO_2$
 Exact Mass: 221.30 g/mol



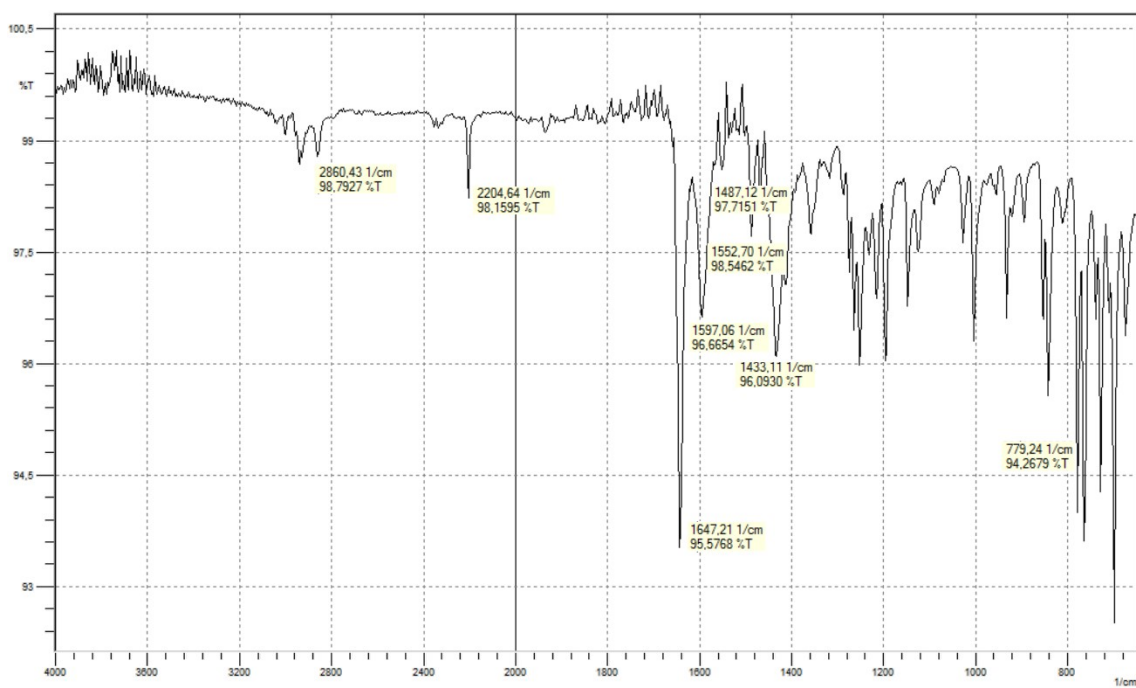
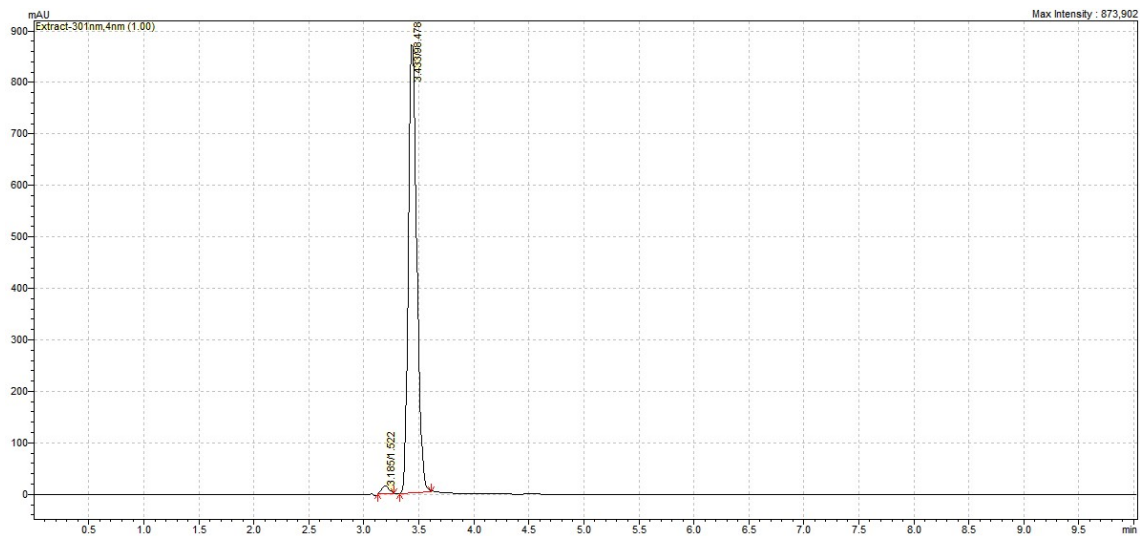


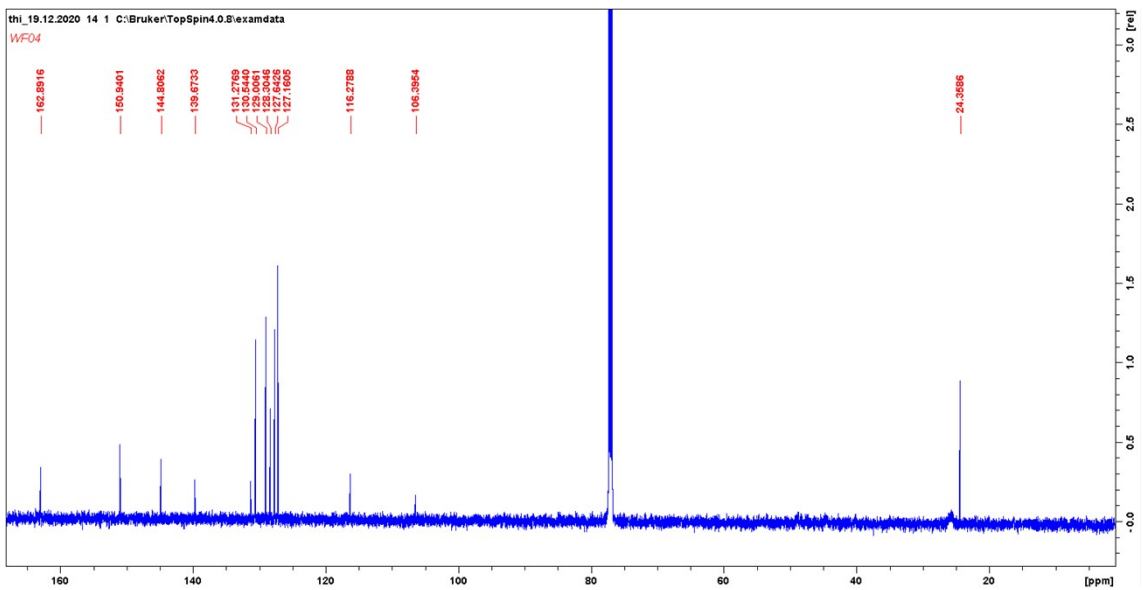
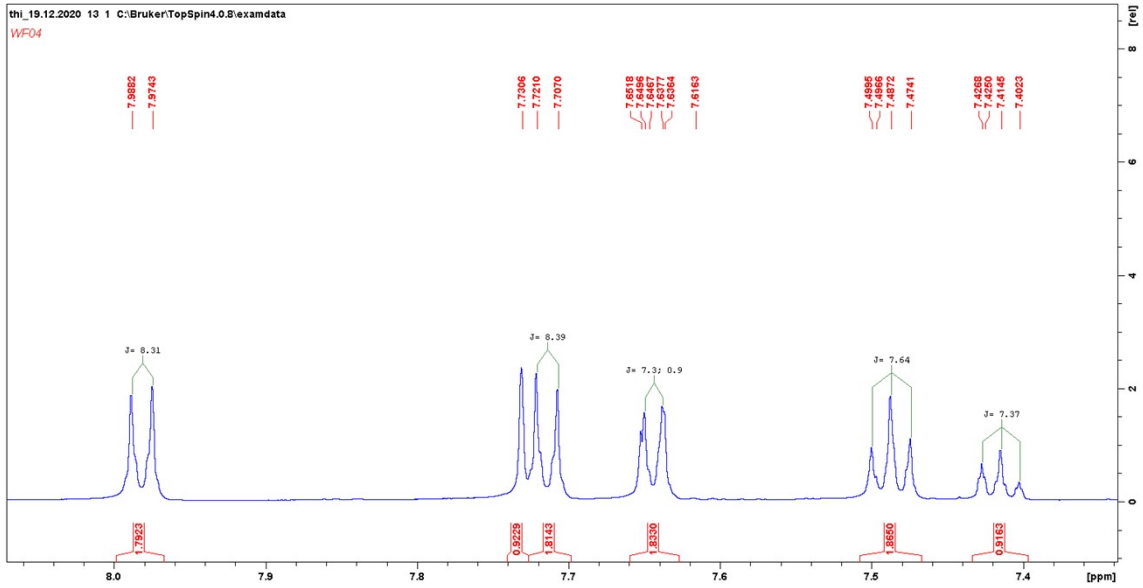
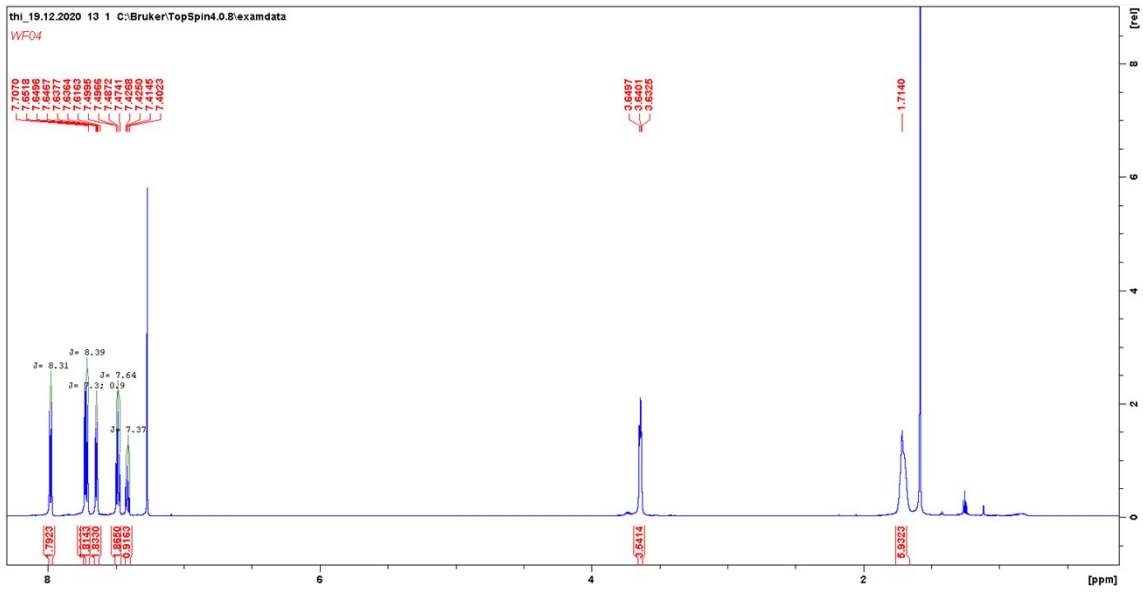
Spectrum1 #Data# GV28.qgd R.Time:12.933(Scan#:953)
MassPeaks:167
RawMode:Averaged 12.725-12.967(928-957) BasePeak:192.75(10000)
BG Mode:Averaged 14.950-14.950(1195-1195) Group 1 - Event 1



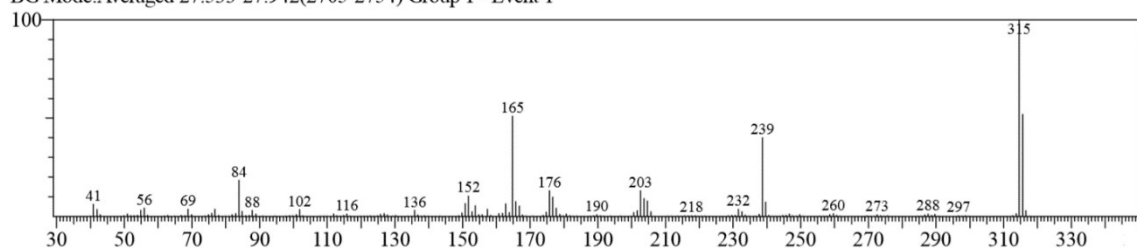


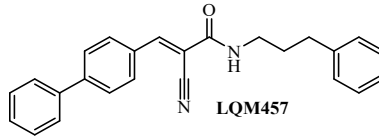
(*E*)-3-([1,1'-Biphenyl]-4-yl)-2-(piperidine-1-carbonyl)acrylonitrile
 Chemical Formula: C₂₁H₂₀N₂O
 Exact Mass: 316.40 g/mol



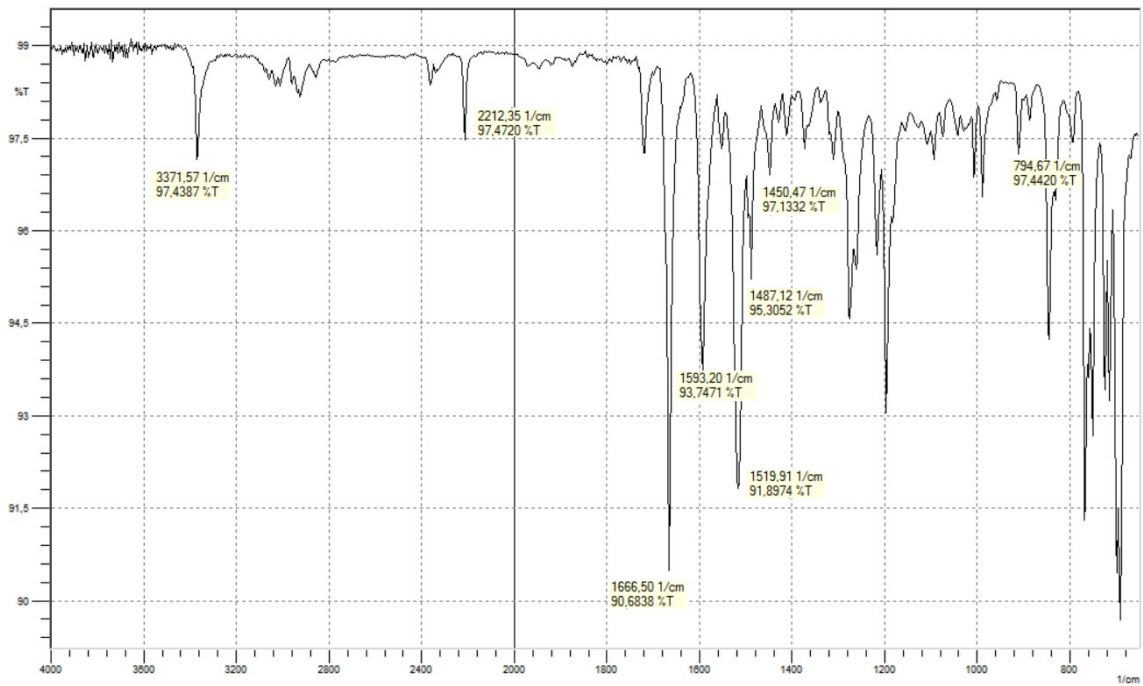
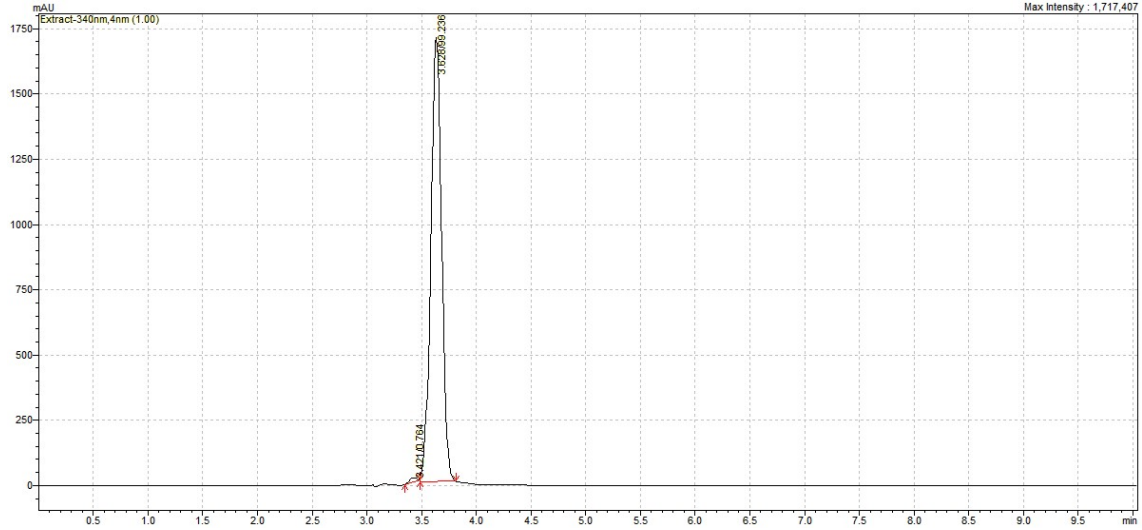


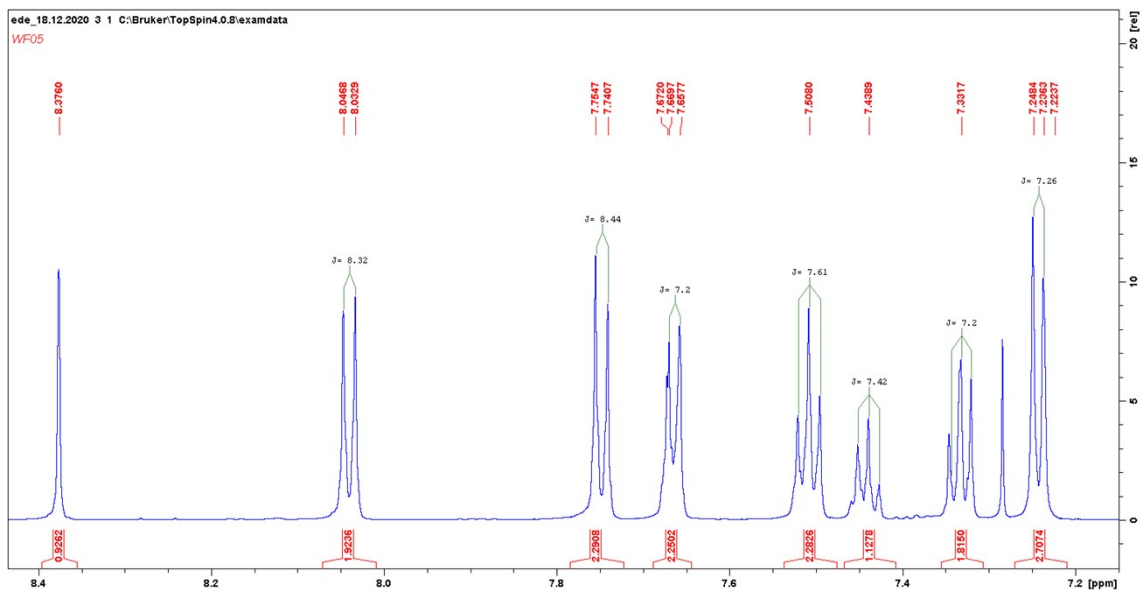
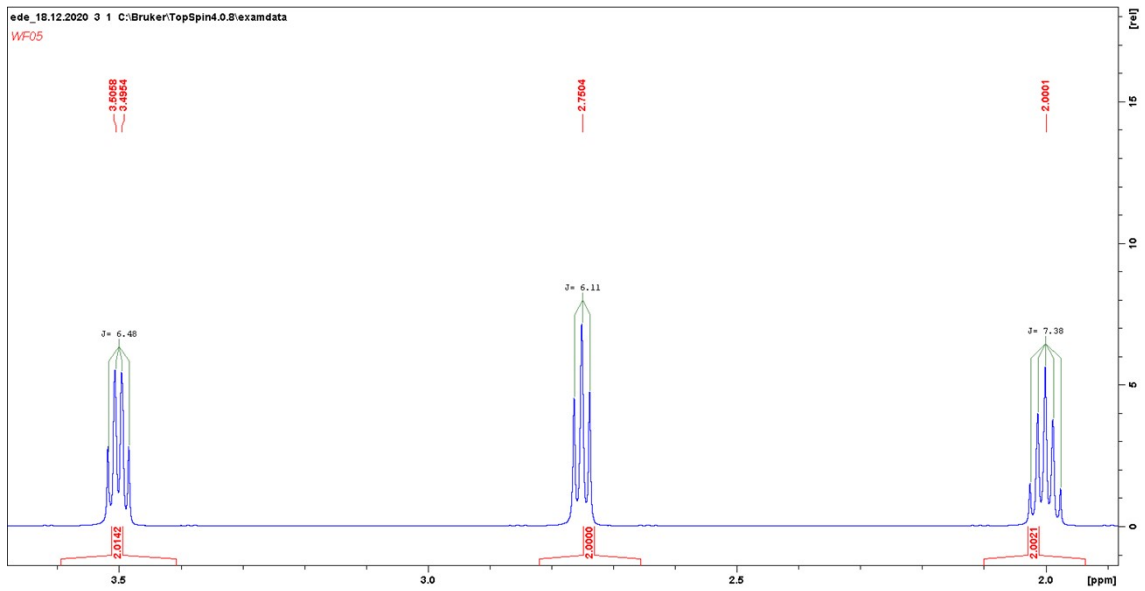
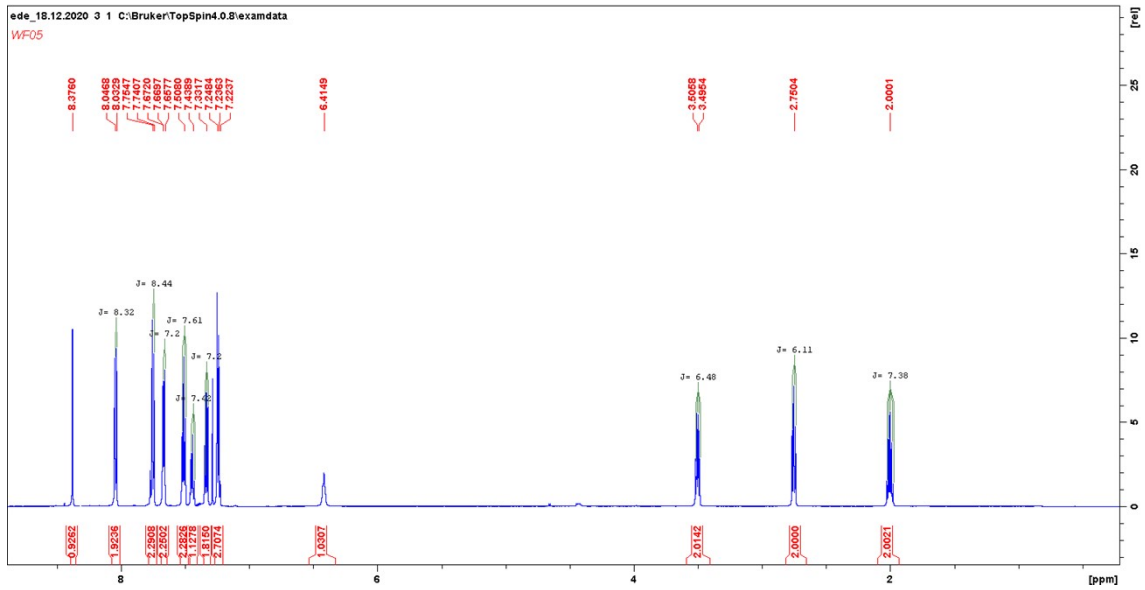
Spectrum1 #Data# WF04.qgd R.Time:25.300(Scan#:2437)
MassPeaks:254
RawMode:Averaged 24.733-25.508(2369-2462) BasePeak:314.60(10000)
BG Mode:Averaged 27.533-27.942(2705-2754) Group 1 - Event 1

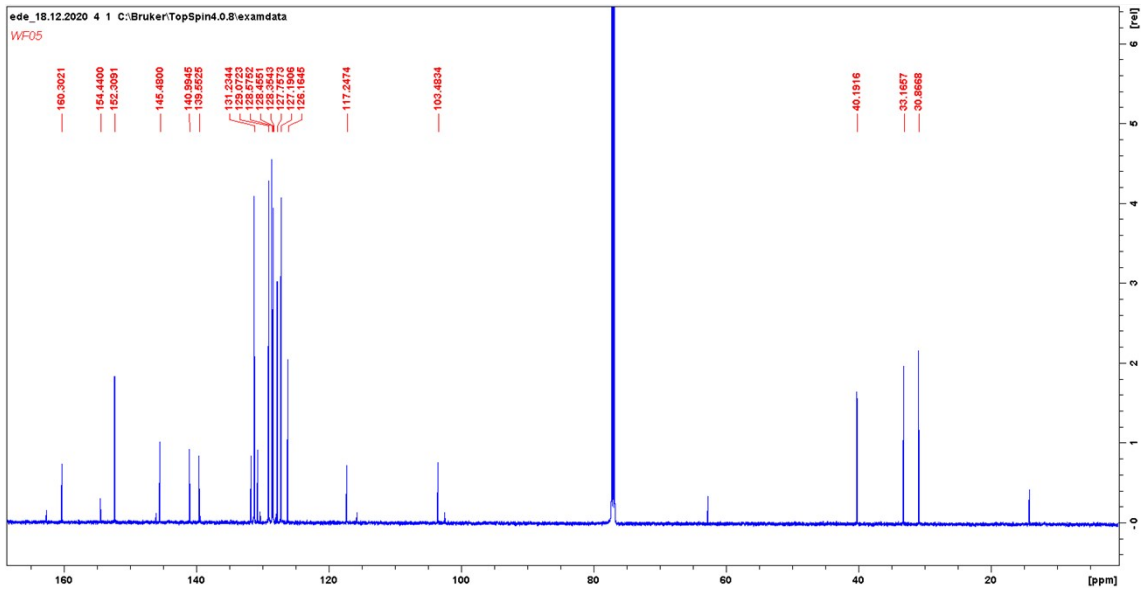




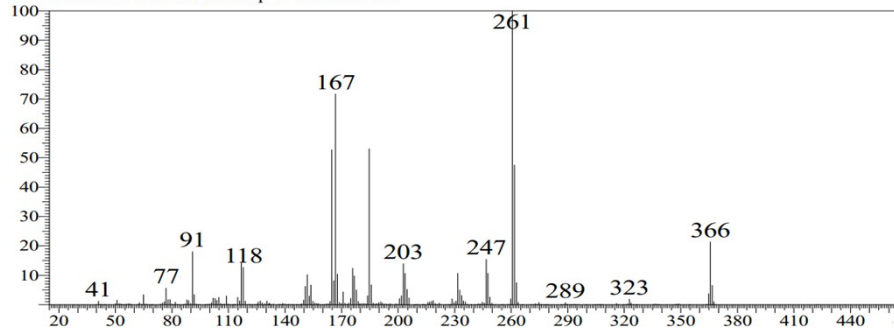
(E)-3-((1,1'-Biphenyl)-4-yl)-2-cyano-N-(3-phenylpropyl)acrylamide
 Chemical Formula: C₂₅H₂₂N₂O
 Exact Mass: 366.46 g/mol

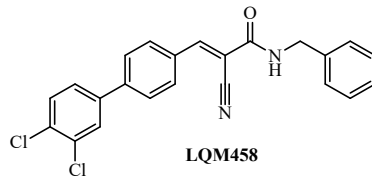




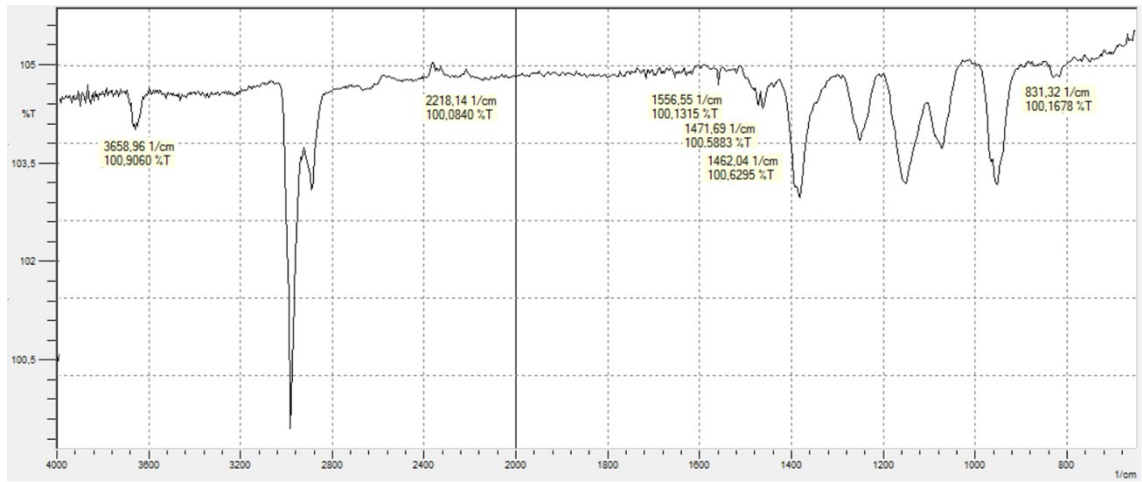
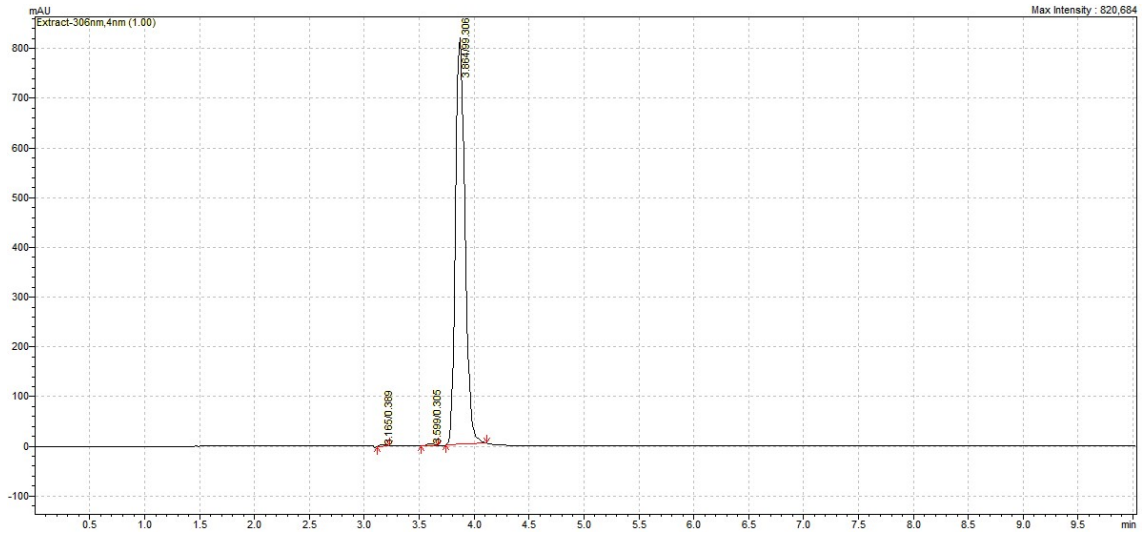


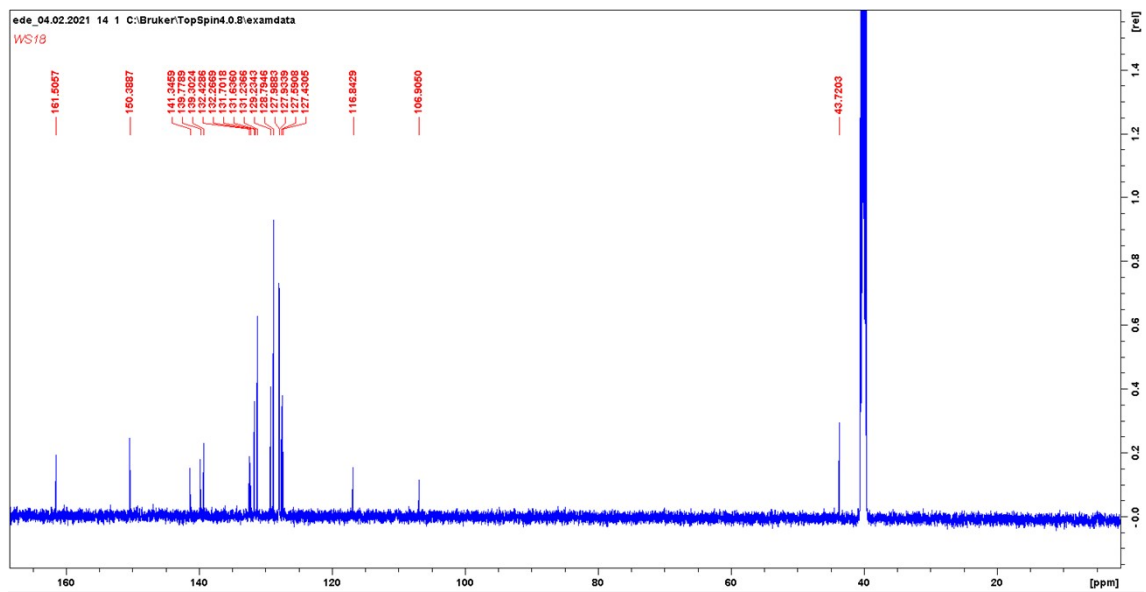
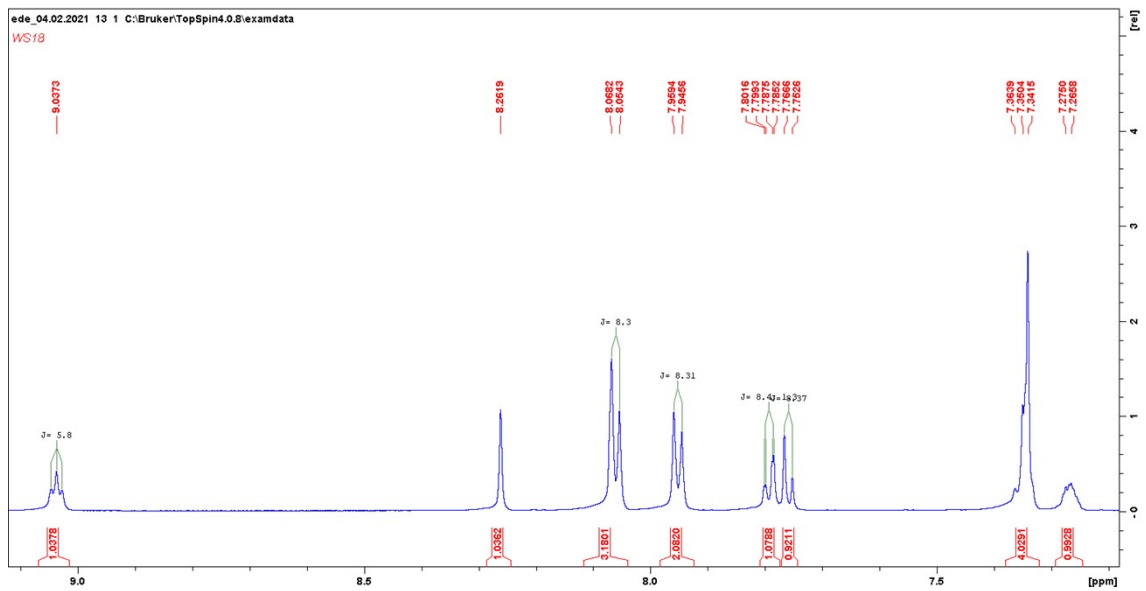
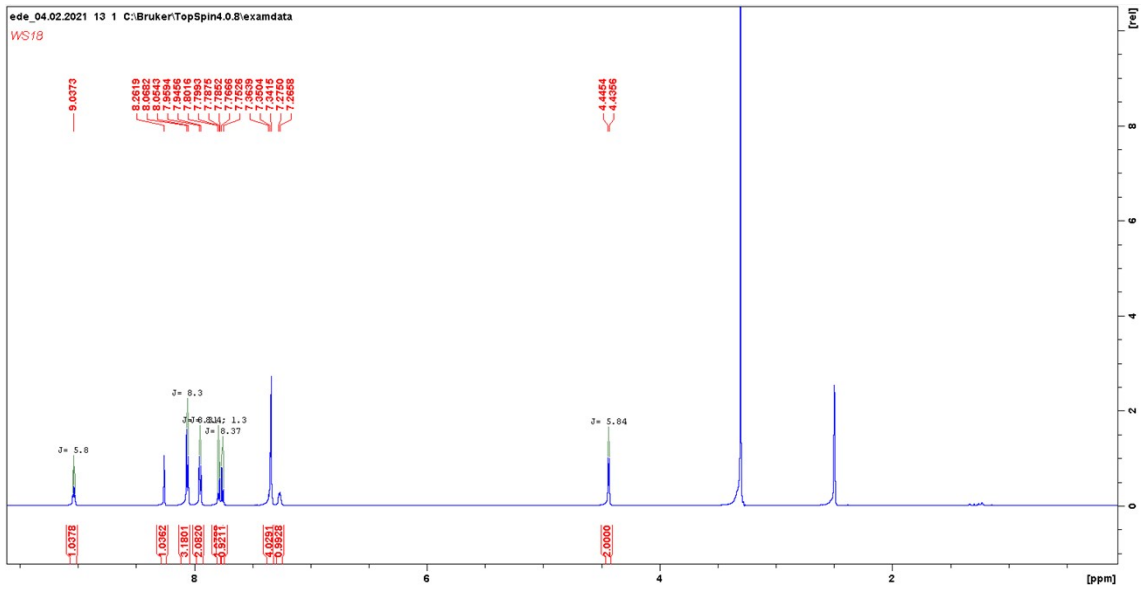
Line#: 1 R.Time:32.183(Scan#:3263)
MassPeaks:265
RawMode:Averaged 32.175-32.192(3262-3264) BasePeak:261(2795629)
BG Mode:Calc. from Peak Group 1 - Event 1 Scan



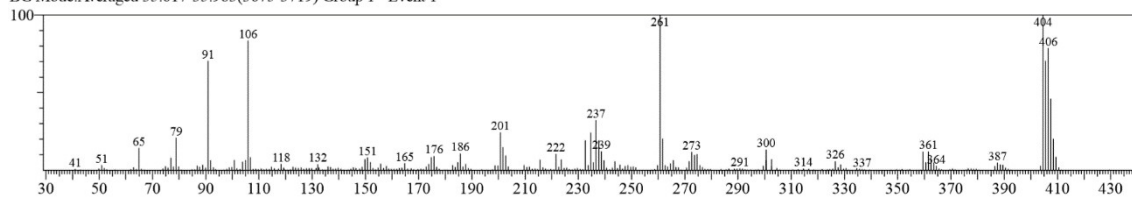


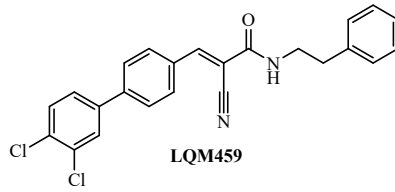
(E)-N-Benzyl-2-cyano-3-(3,4'-dichloro-[1,1'-biphenyl]-4-yl)acrylamide
 Chemical Formula: C₂₃H₁₆Cl₂N₂O
 Exact Mass: 406.06 g/mol



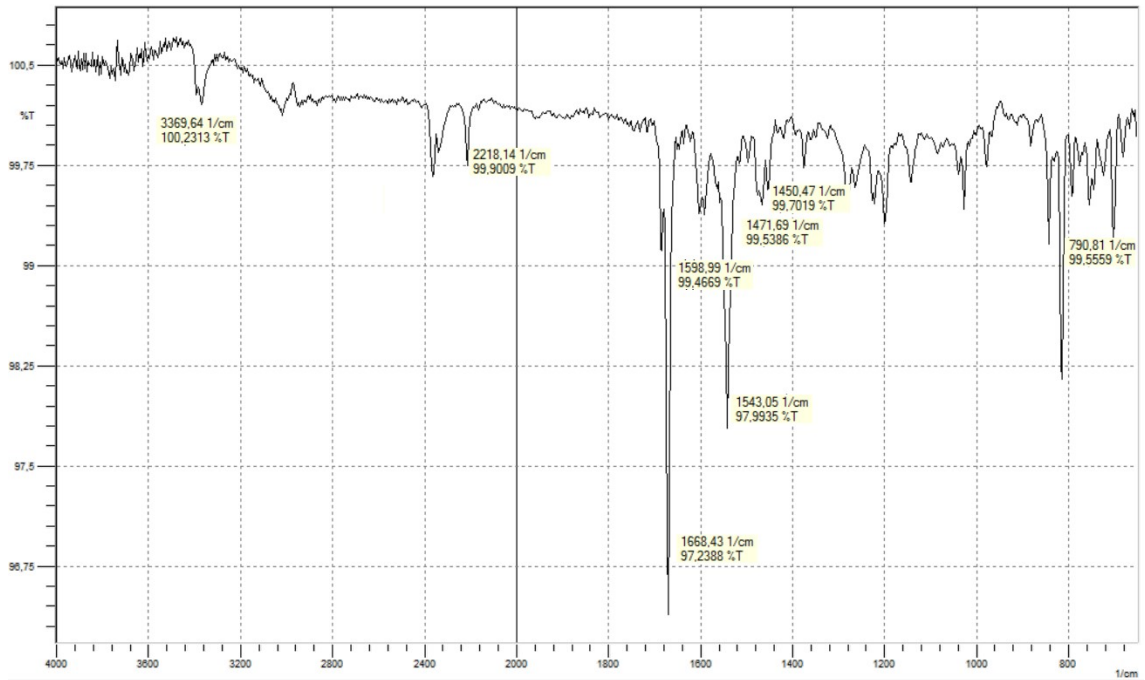
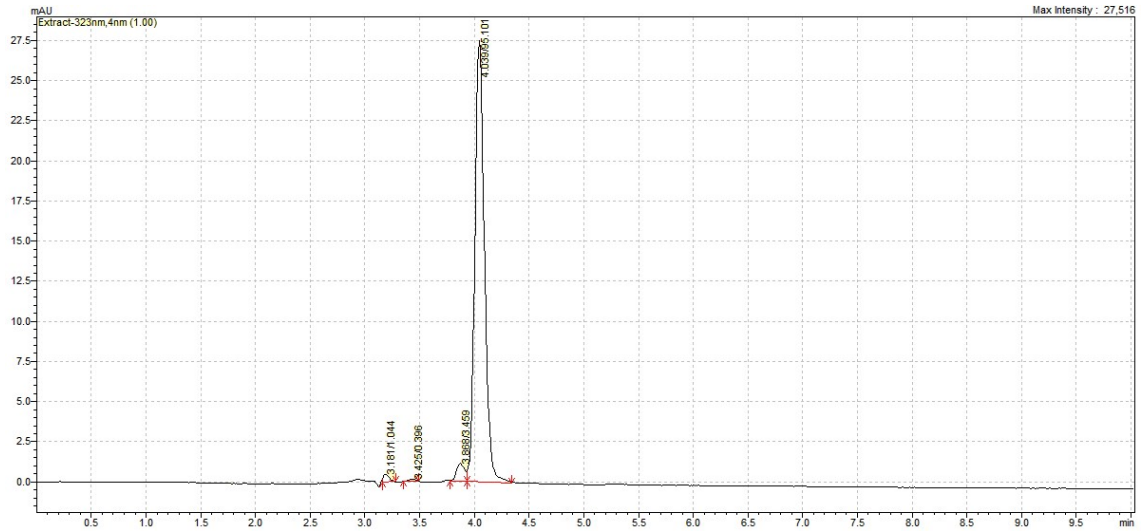


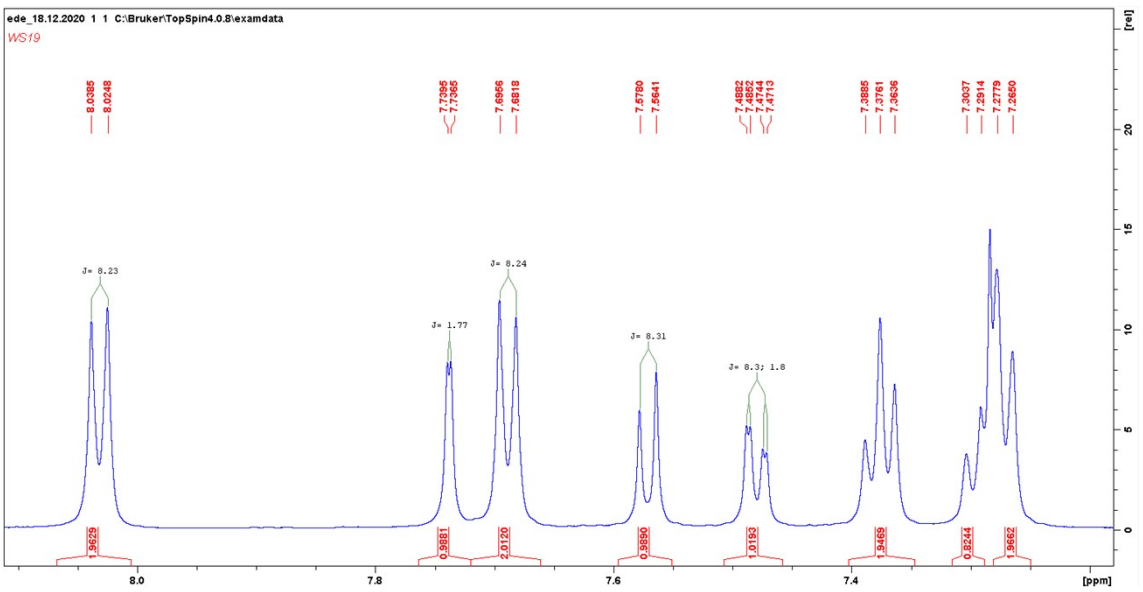
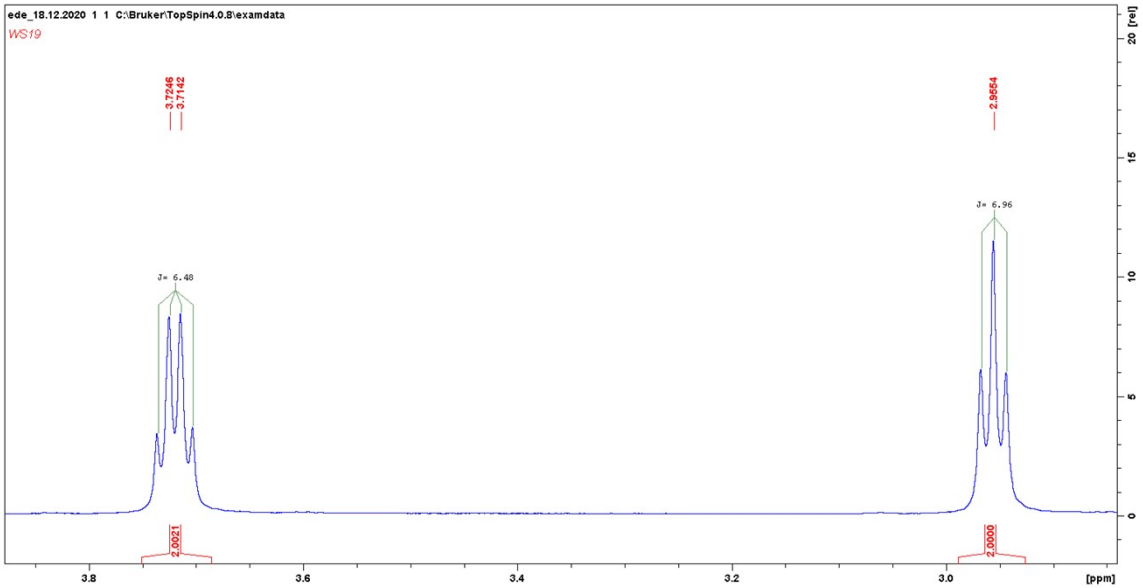
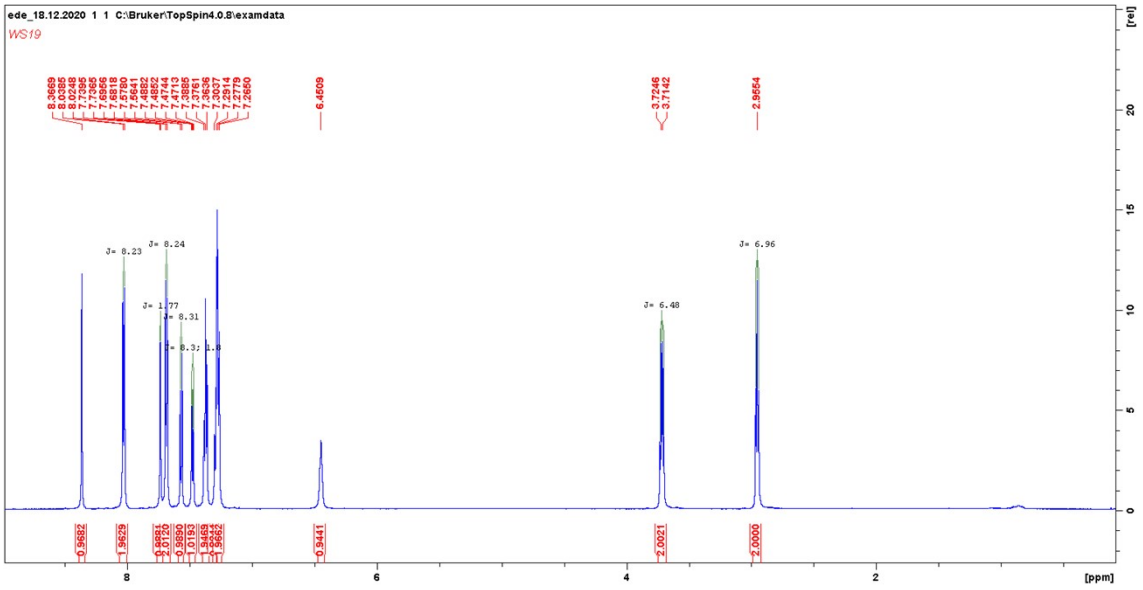
Spectrum1 #Data# WS 18.qgd R.Time:37.633(Scan#:3917)
MassPeaks:319
RawMode:Averaged 37.117-37.933(3855-3953) BasePeak:260.70(10000)
BG Mode:Averaged 35.617-35.983(3675-3719) Group 1 - Event 1

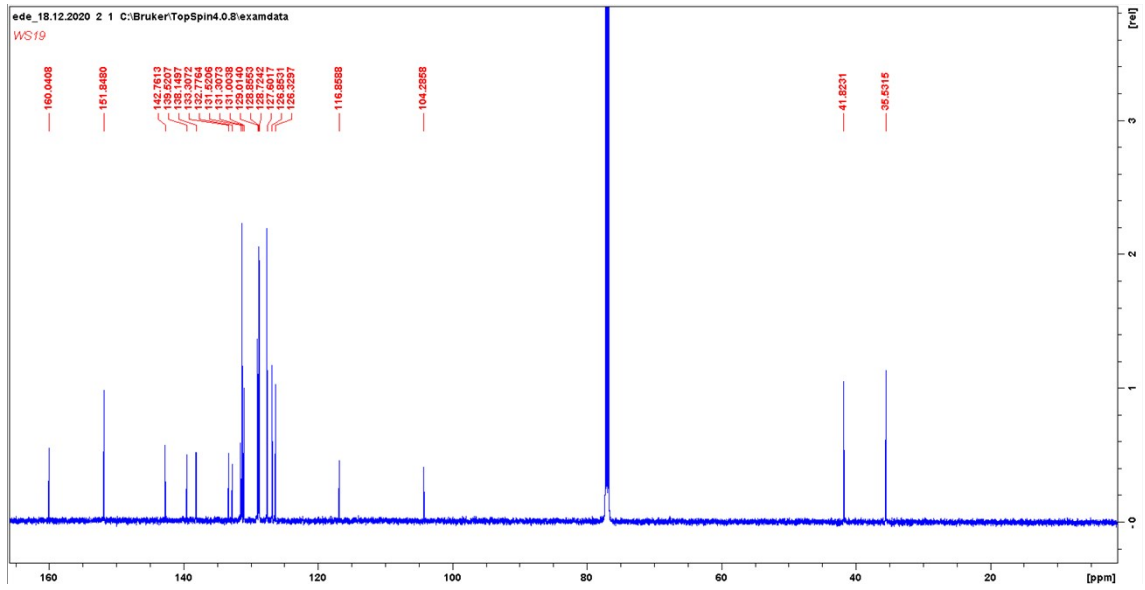




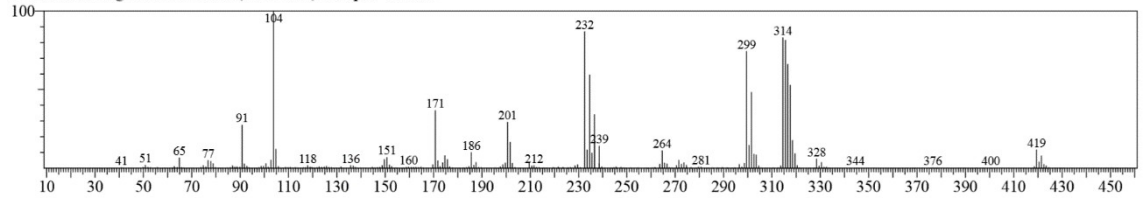
(E)-2-Cyano-3-(3',4'-dichloro-[1,1'-biphenyl]-4-yl)-N-phenethylacrylamide
 Chemical Formula: $C_{24}H_{18}Cl_2N_2O$
 Exact Mass: 421.32 g/mol

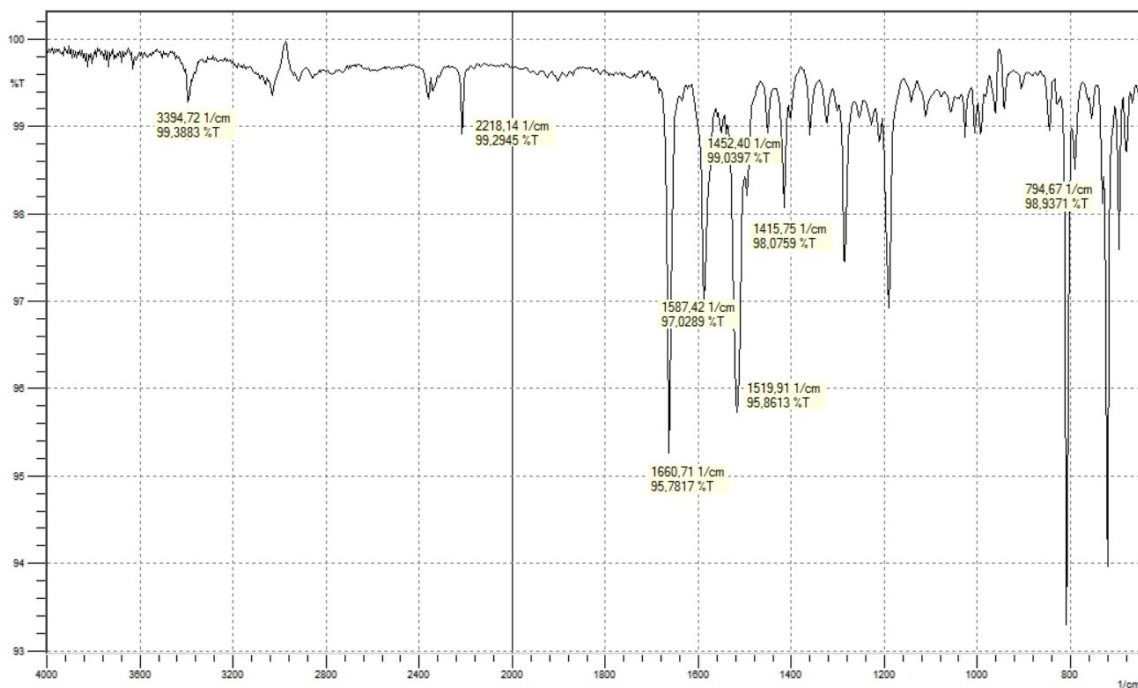
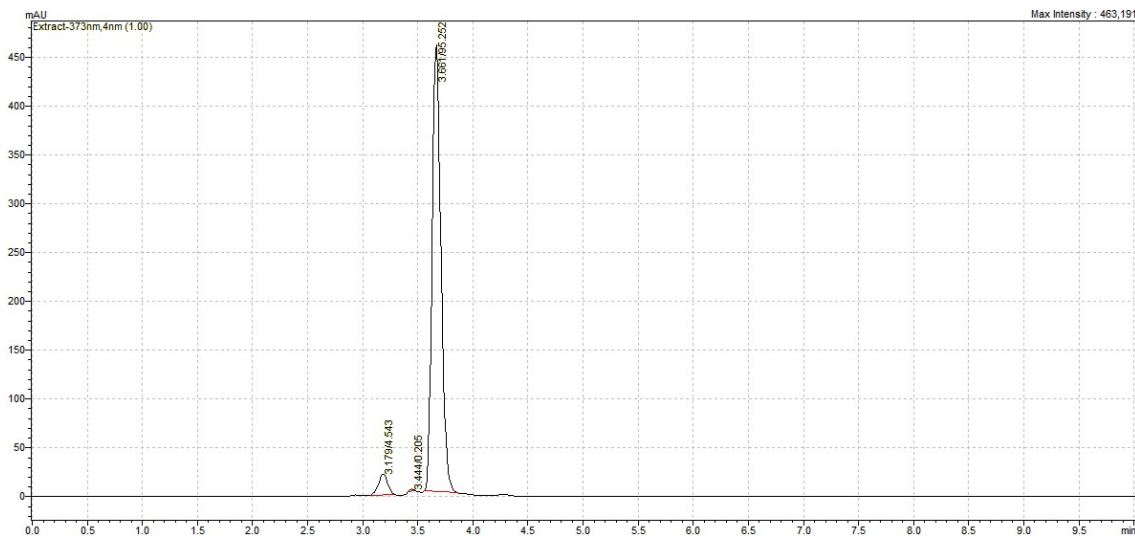
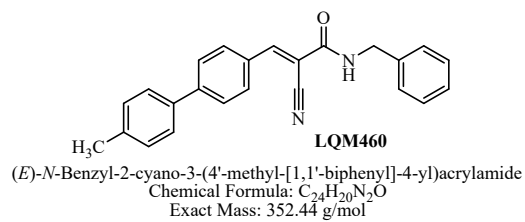


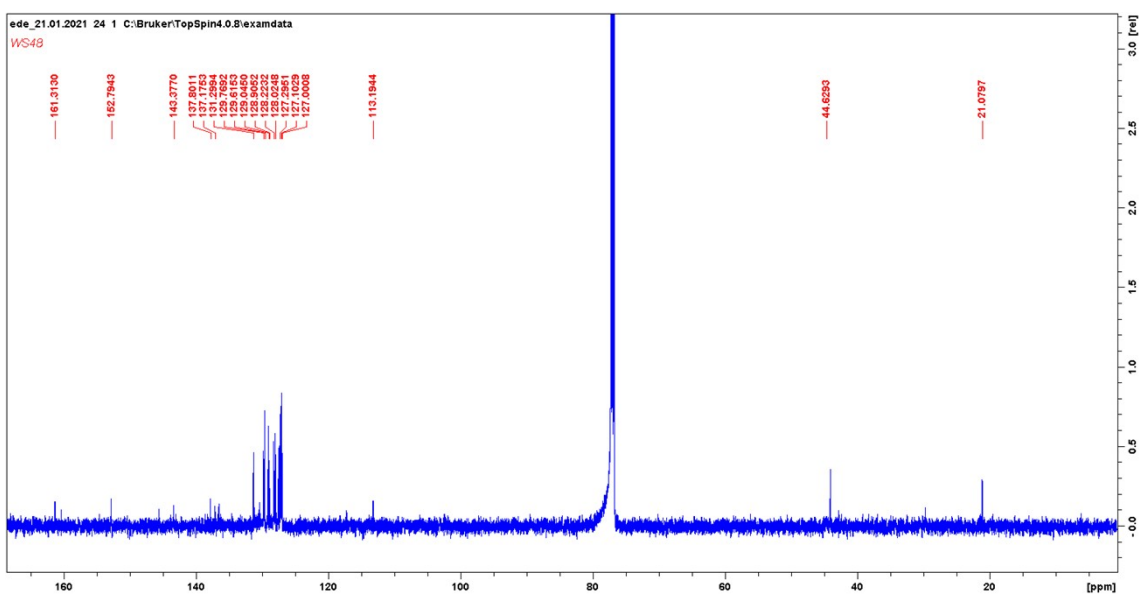
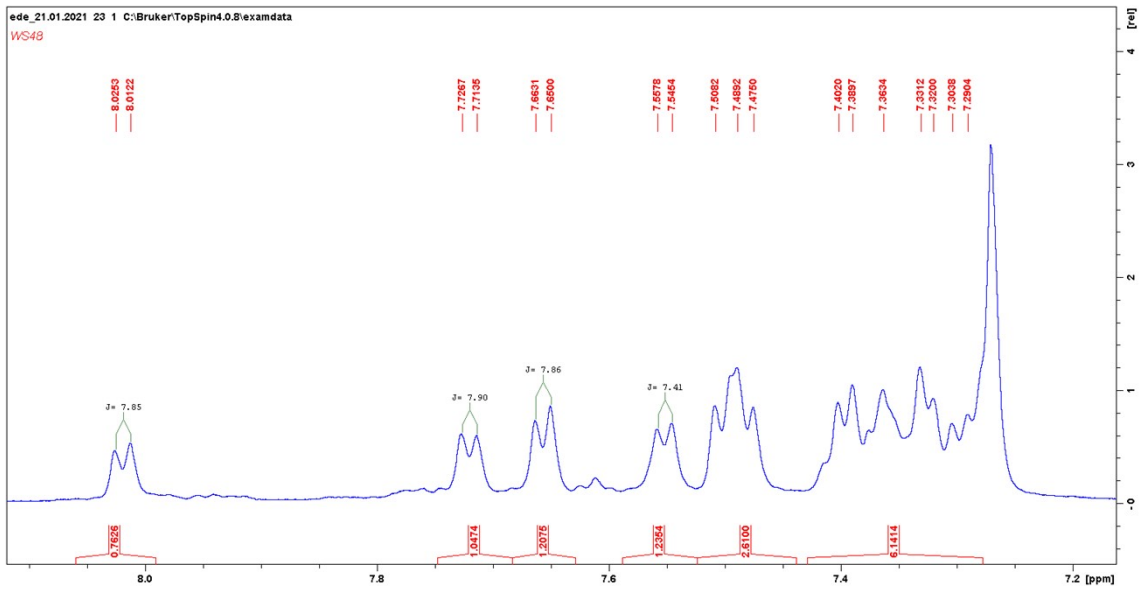
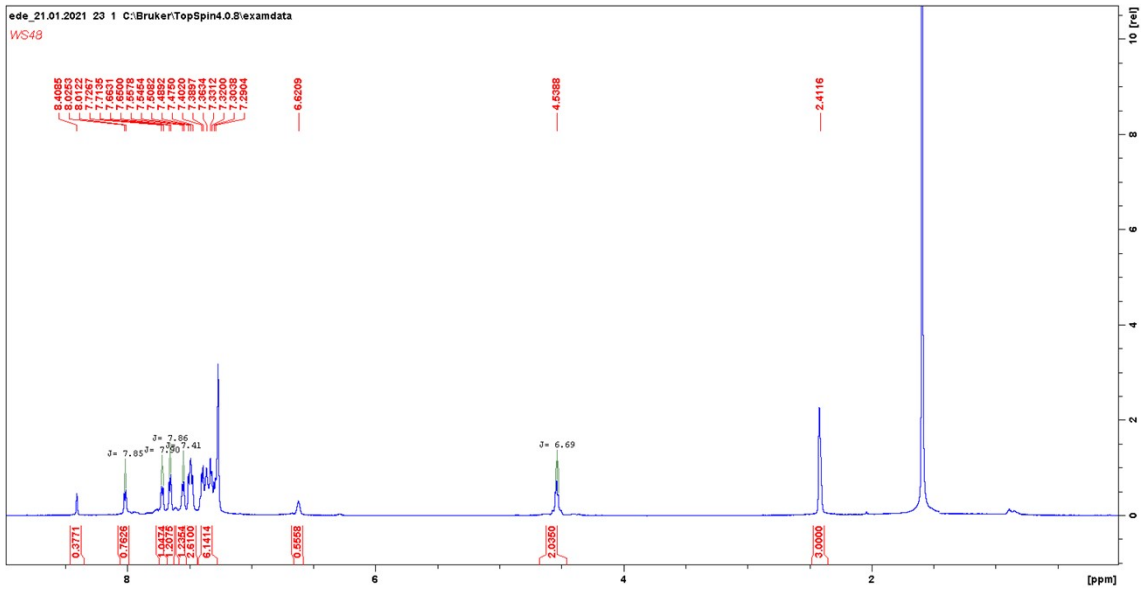




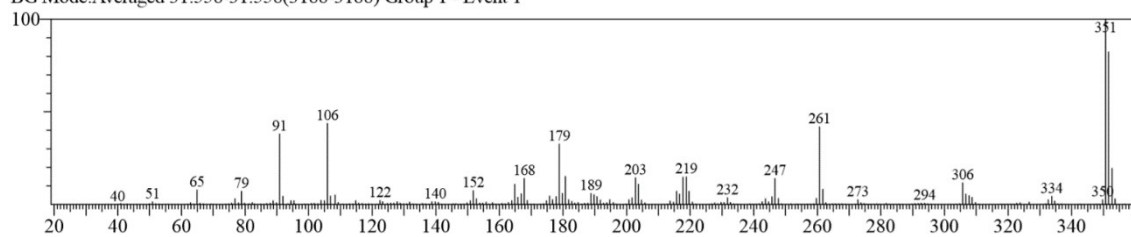
Spectrum1 #Data# WS19.qgd R.Time:41.442(Scan#:4374)
MassPeaks:259
RawMode:Averaged 40.242-41.625(4230-4396) BasePeak:103.85(10000)
BG Mode:Averaged 39.308-39.308(4118-4118) Group 1 - Event 1

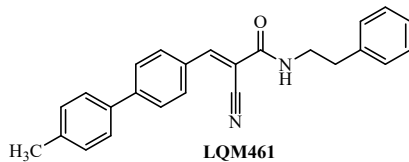




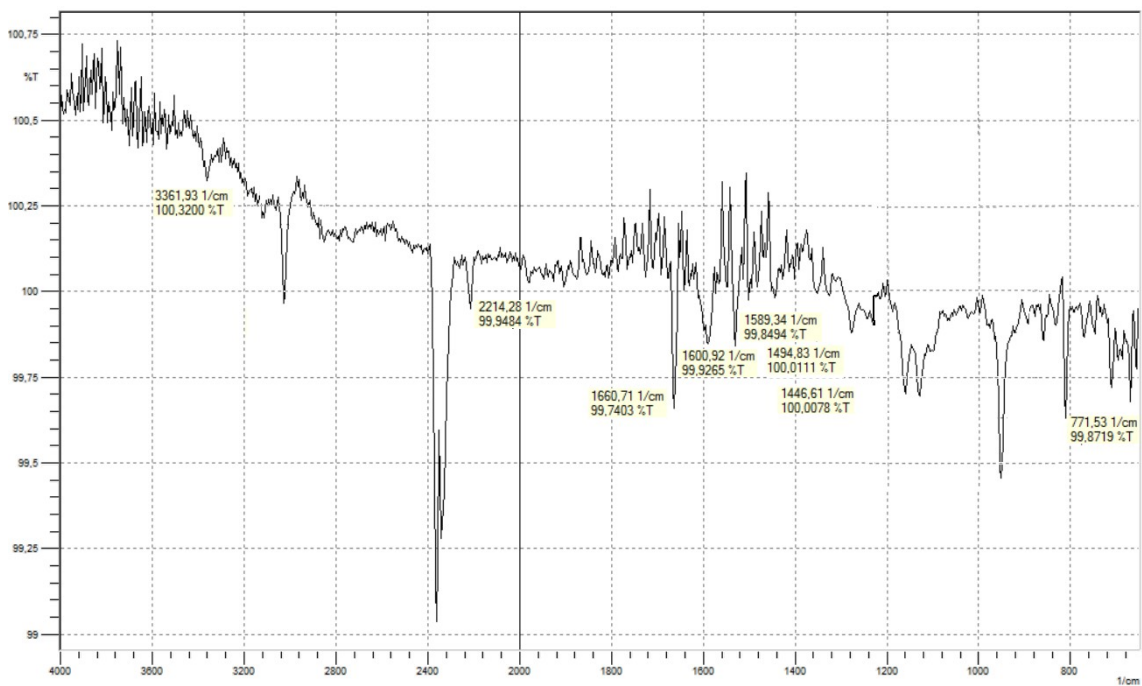
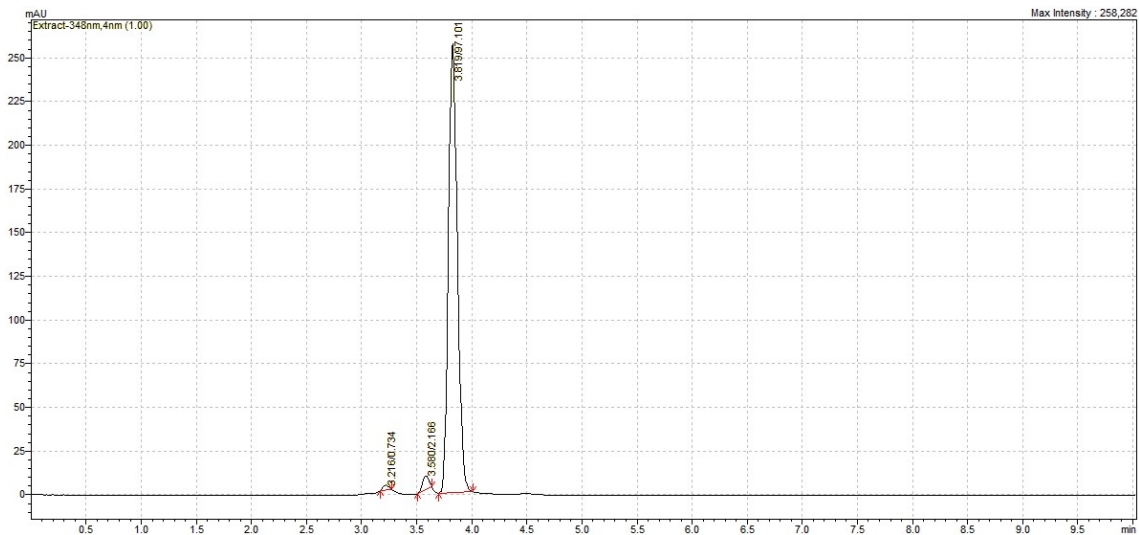


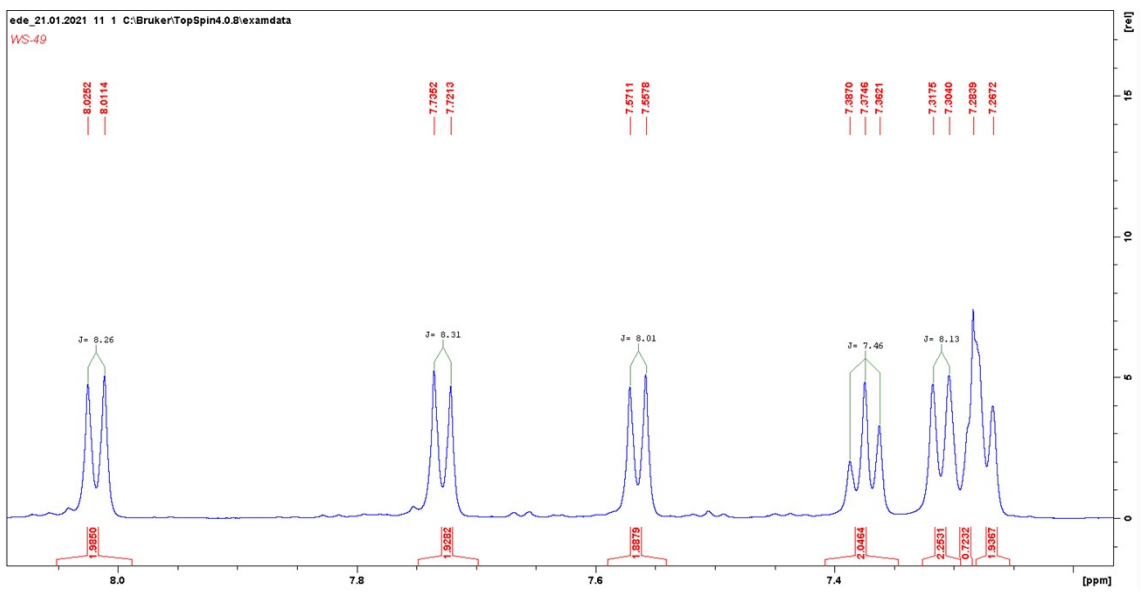
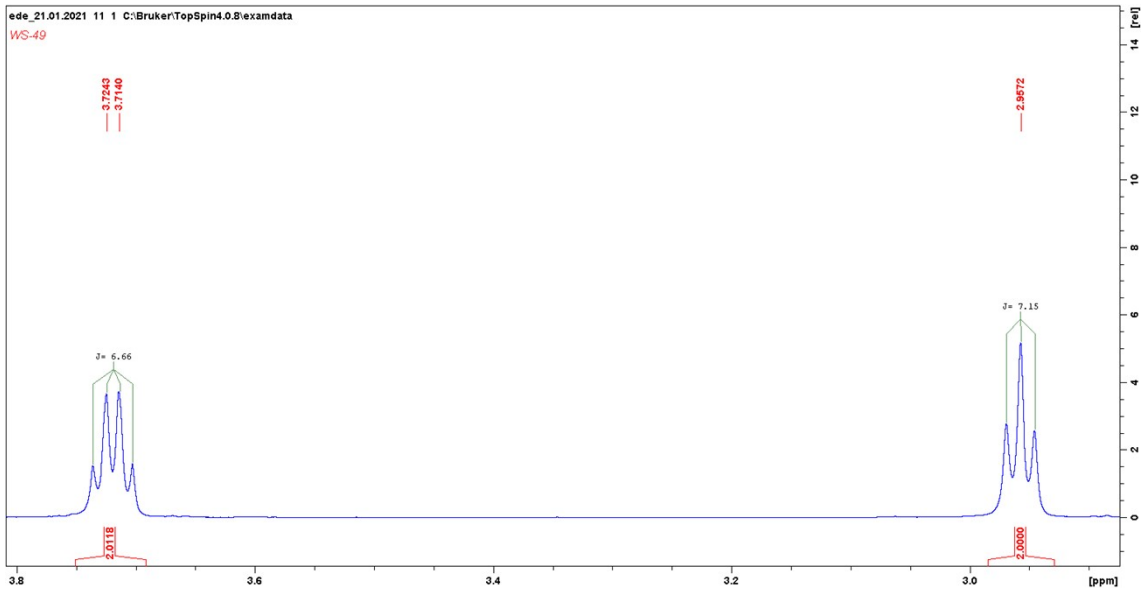
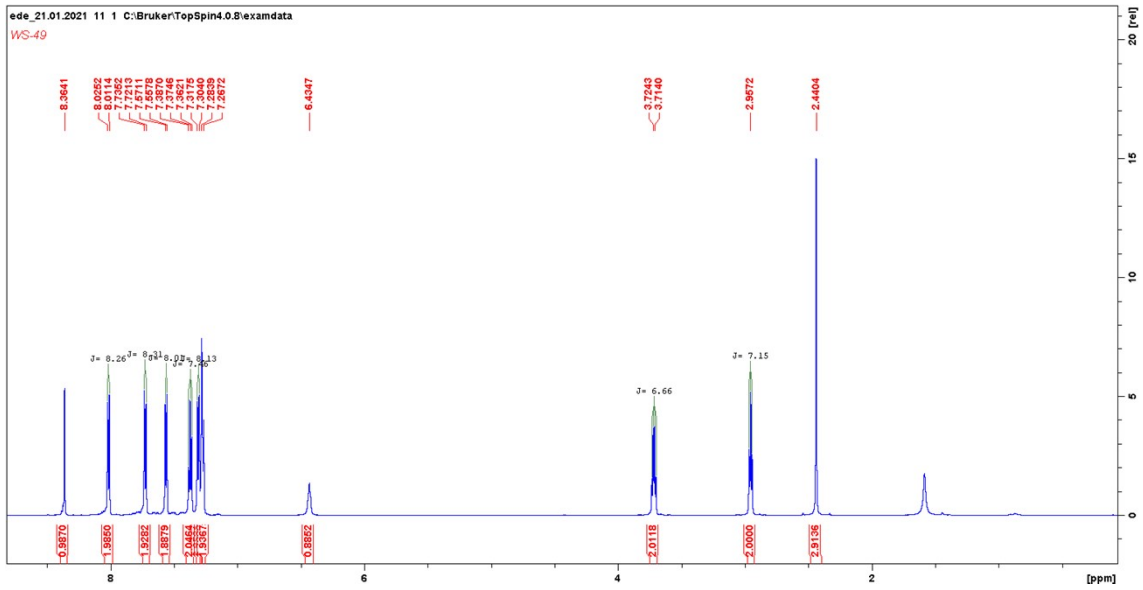
Spectrum1 #Data# WS48 1,029.qgd R.Time:29.458(Scan#:2936)
MassPeaks:280
RawMode:Averaged 29.158-30.258(2900-3032) BasePeak:350.65(10000)
BG Mode:Averaged 31.558-31.558(3188-3188) Group 1 - Event 1

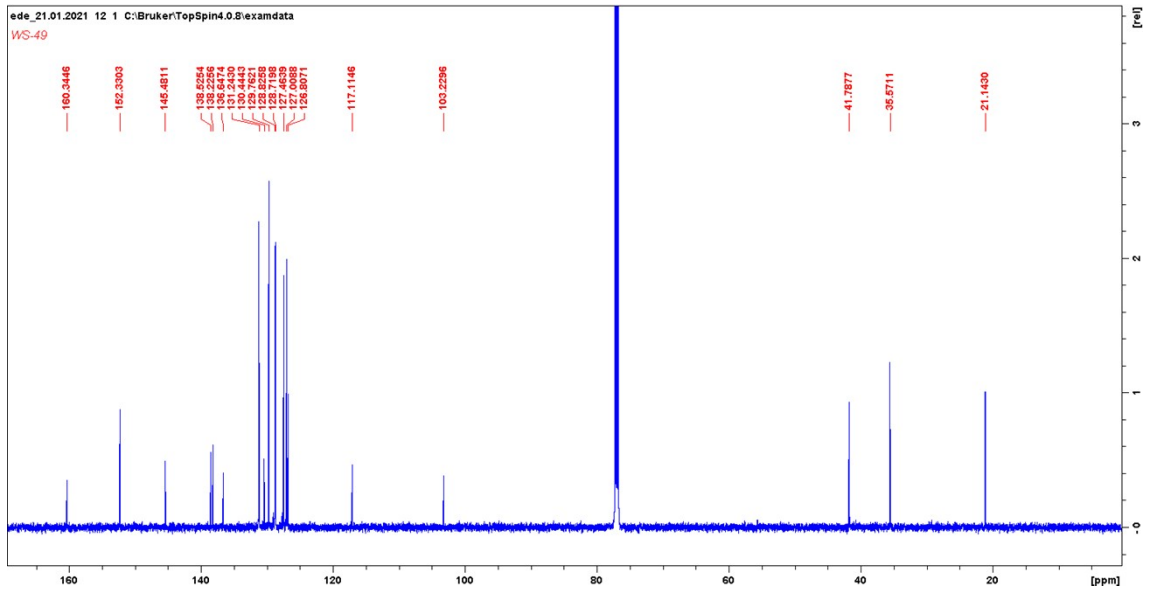




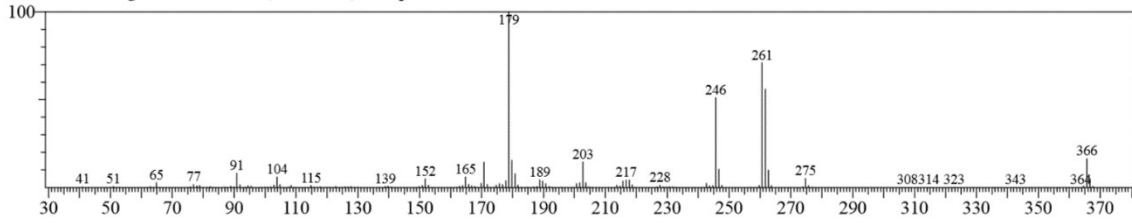
(E)-2-Cyano-3-(4'-methyl-[1,1'-biphenyl]-4-yl)-N-phenethylacrylamide
 Chemical Formula: C₂₅H₂₇N₂O
 Exact Mass: 366.46 g/mol

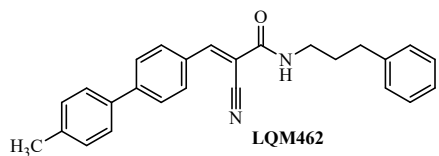




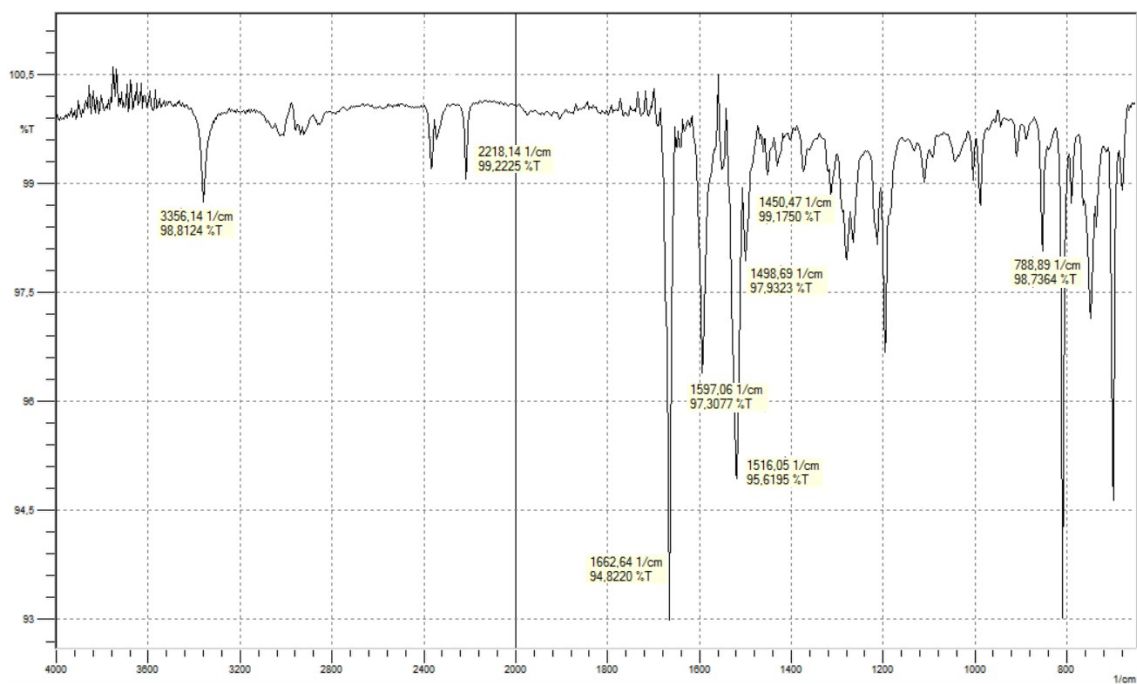
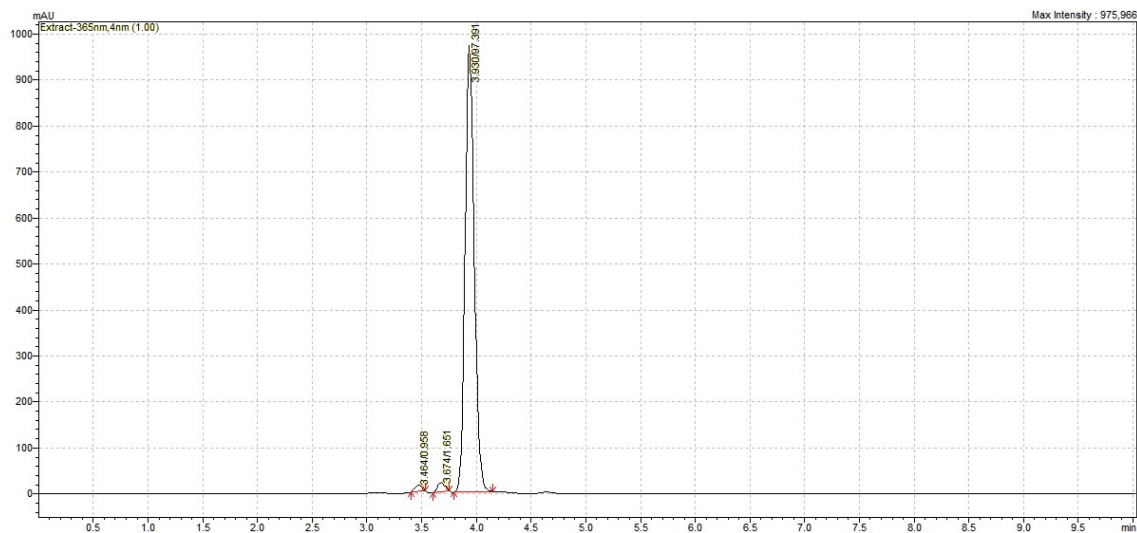


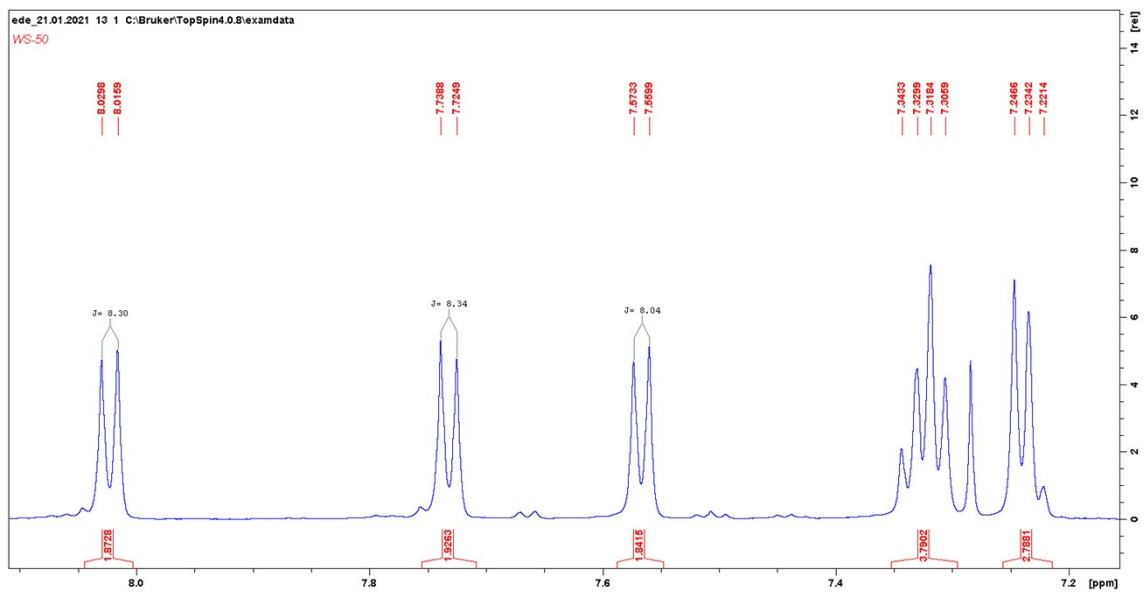
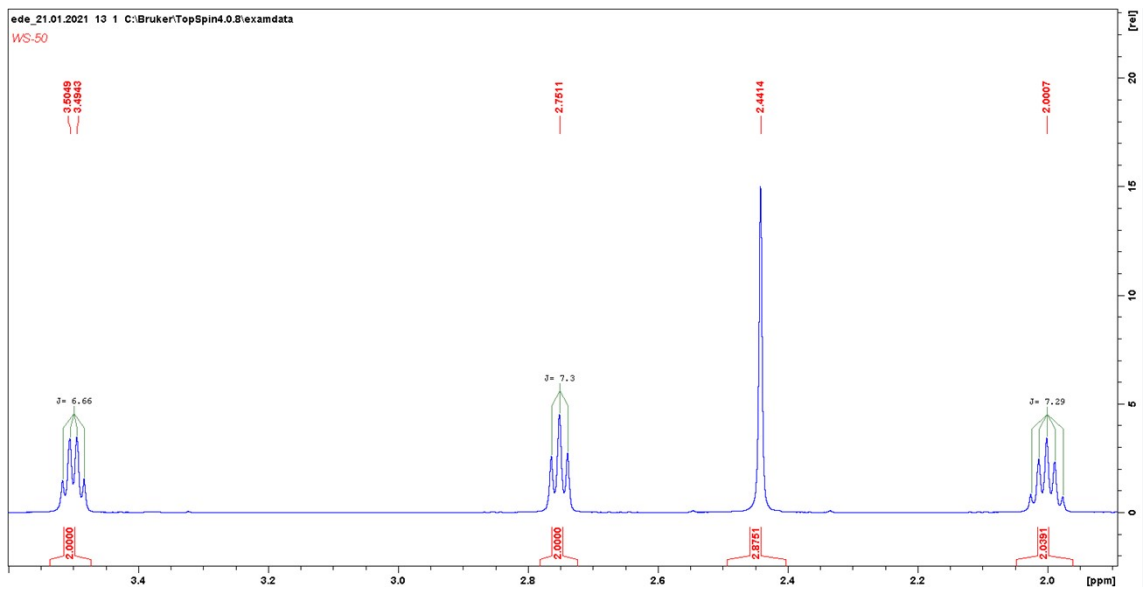
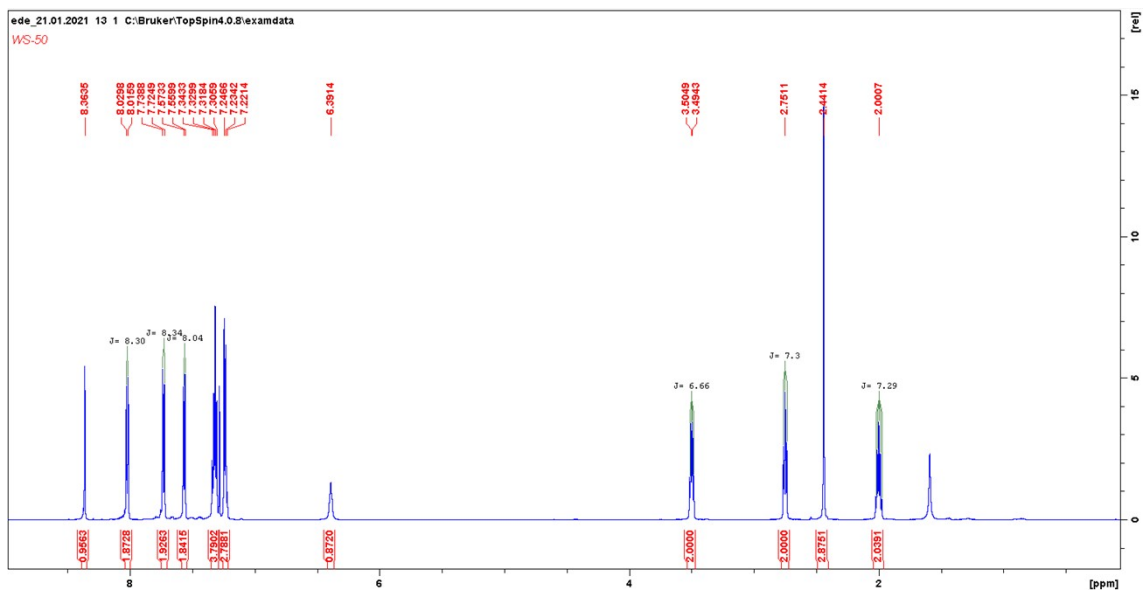
Spectrum1 #Data# WS49.qgd R.Time:31.317(Scan#:3159)
MassPeaks:215
RawMode:Averaged 30.925-31.783(3112-3215) BasePeak:178.80(10000)
BG Mode:Averaged 30.058-30.058(3008-3008) Group 1 - Event 1

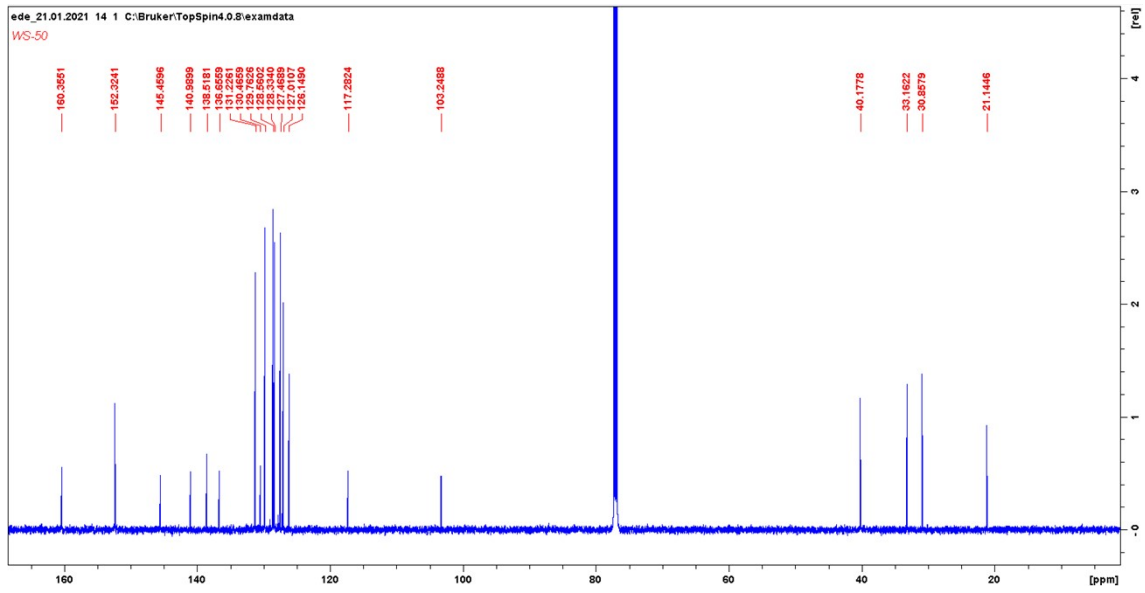




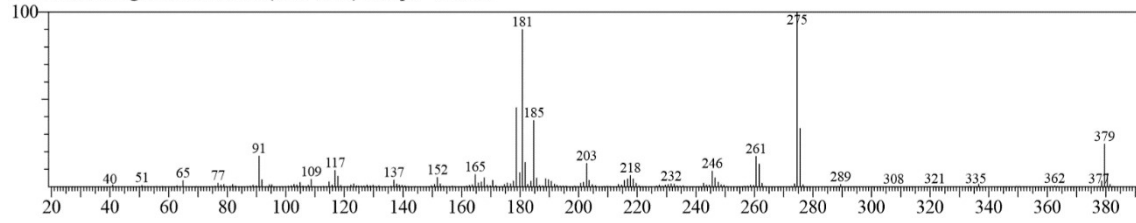
(E)-2-Cyano-3-(4'-methyl-[1,1'-biphenyl]-4-yl)-N-(3-phenylpropyl)acrylamide
 Chemical Formula: C₂₆H₂₄N₂O
 Exact Mass: 380.49 g/mol

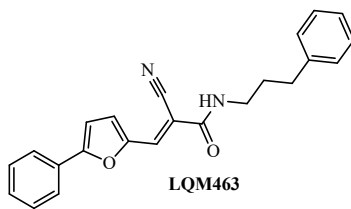




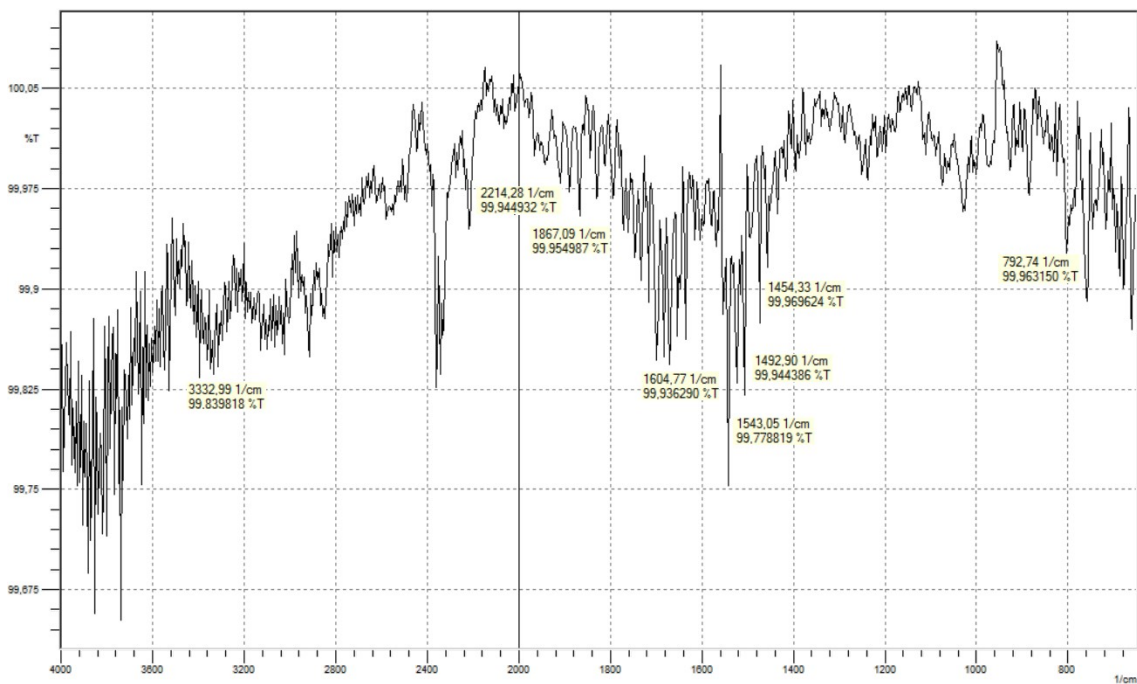
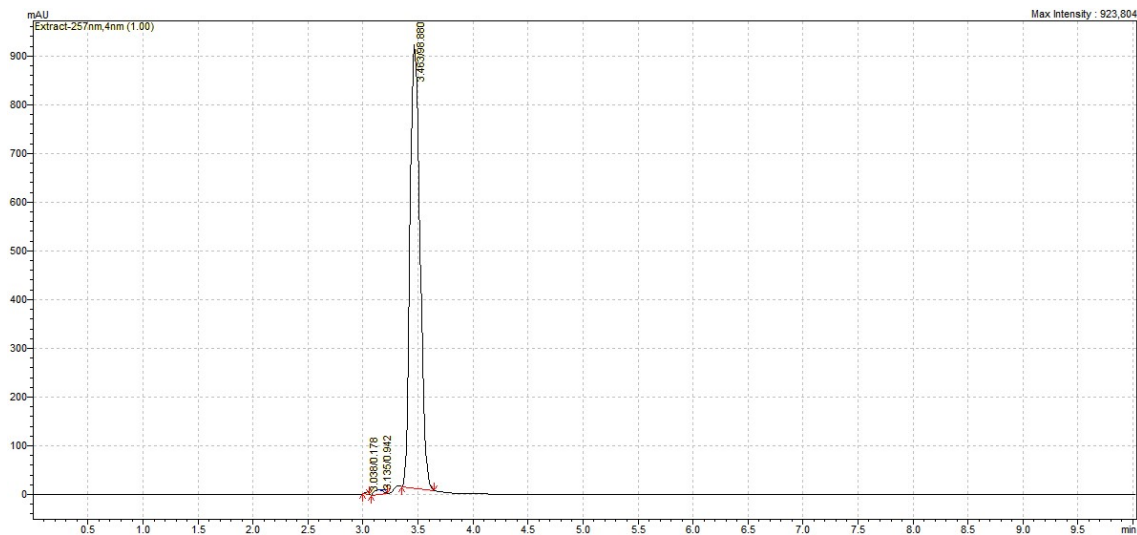


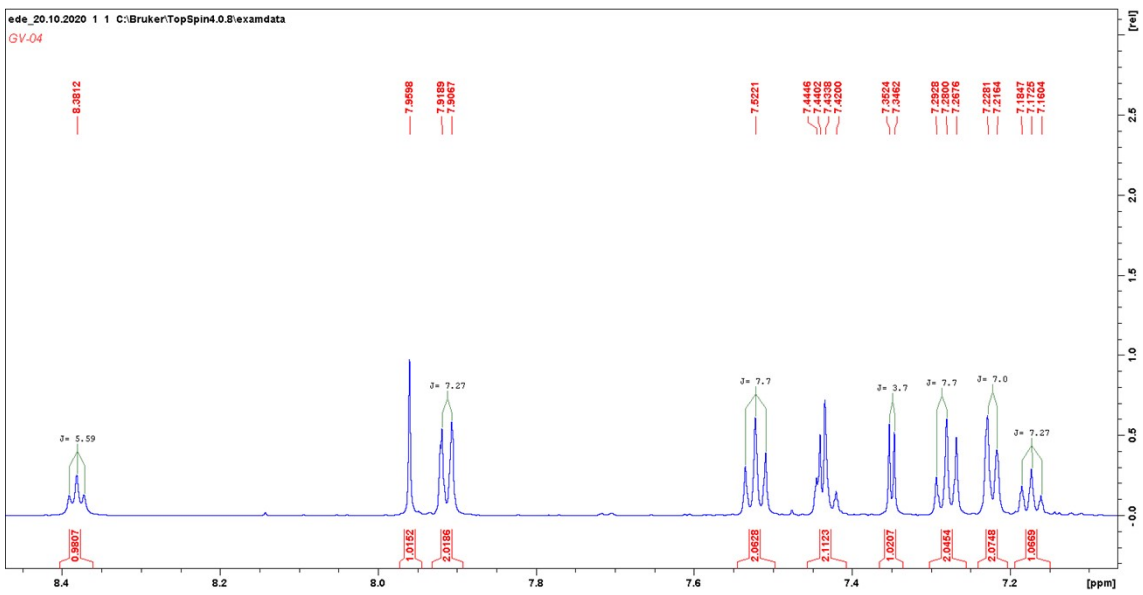
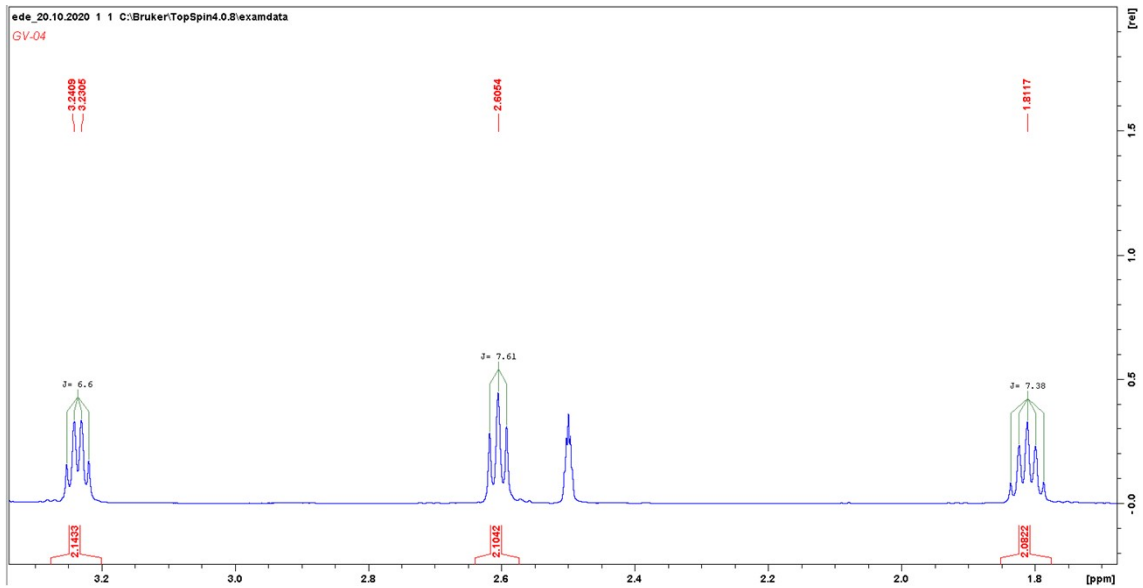
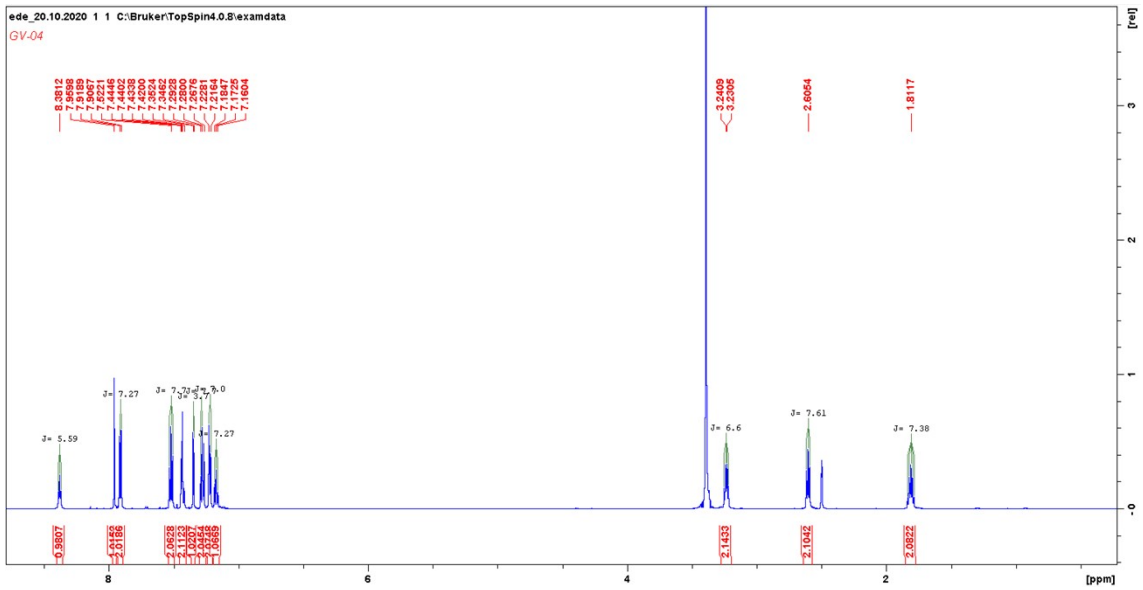
Spectrum1 #Data# WS50.qgd R.Time:35.875(Scan#:3706)
MassPeaks:290
RawMode:Averaged 34.058-36.325(3488-3760) BasePeak:274.60(10000)
BG Mode:Averaged 37.633-37.633(3917-3917) Group 1 - Event 1

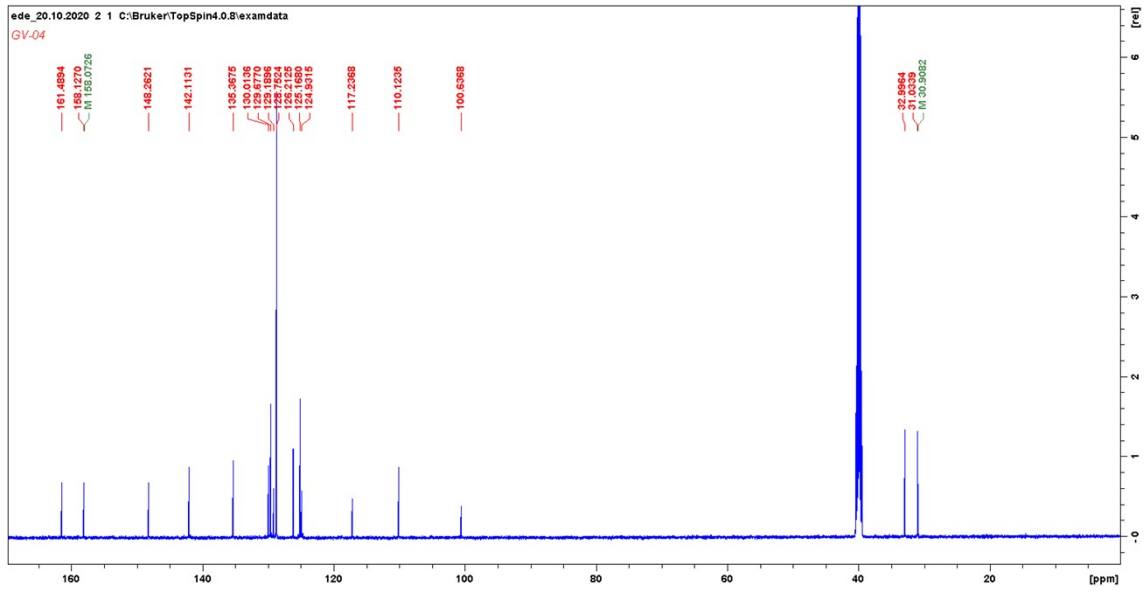




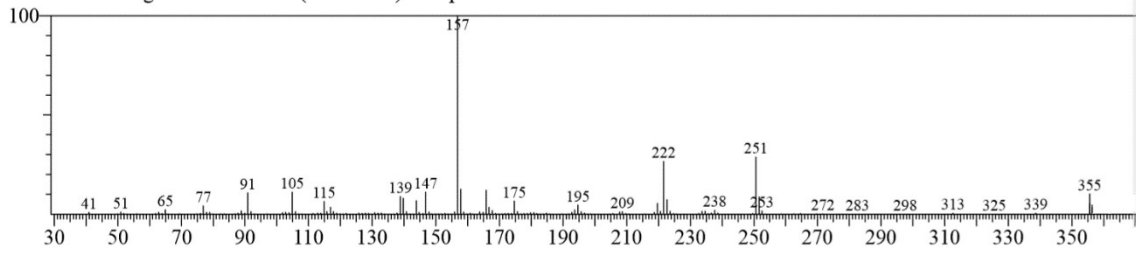
(E)-2-Cyano-3-(5-phenylfuran-2-yl)-N-(3-phenylpropyl)acrylamide
 Chemical Formula: C₂₃H₂₀N₂O₂
 Exact Mass: 356.43 g/mol

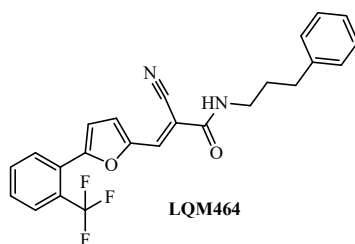




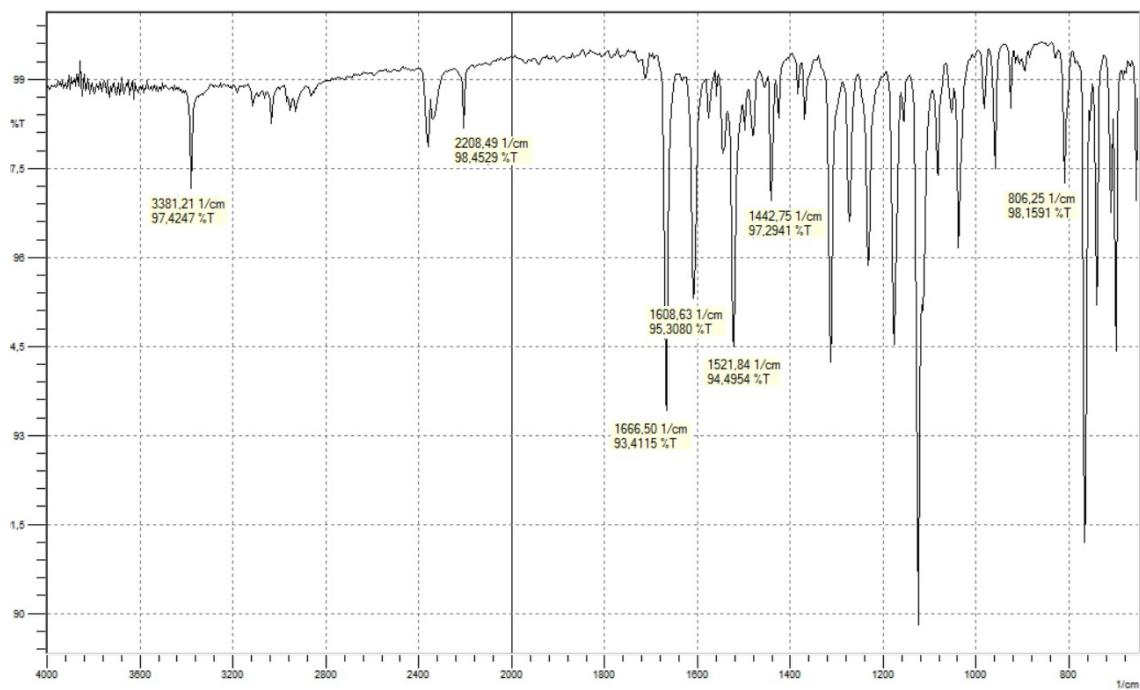
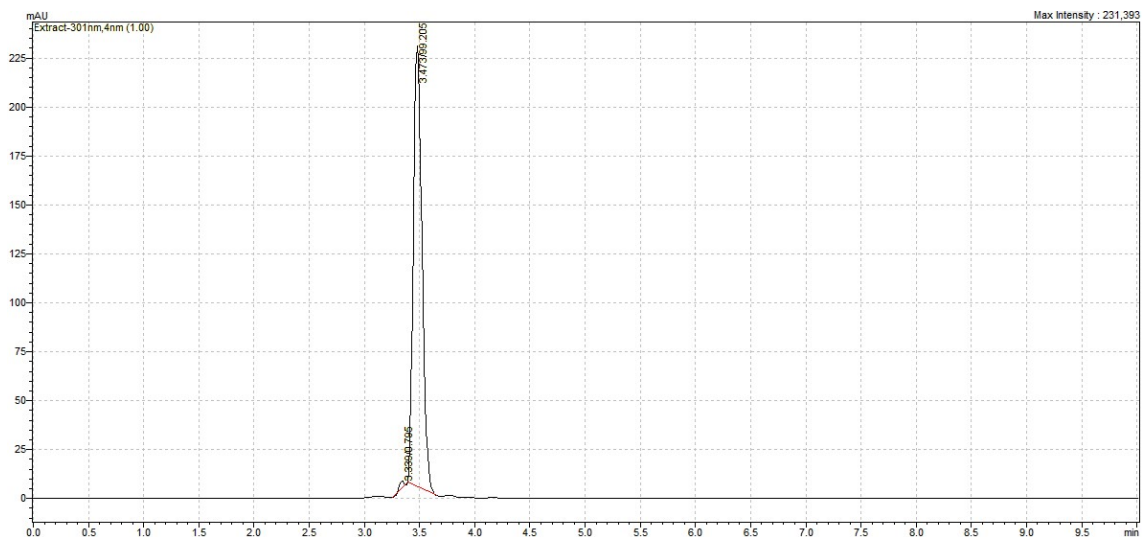


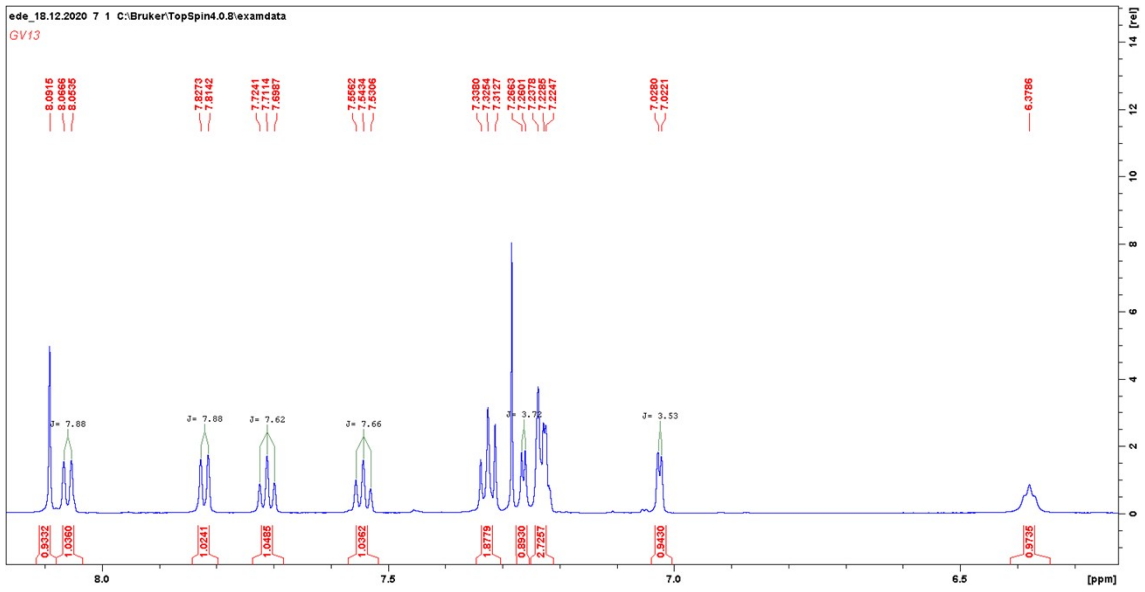
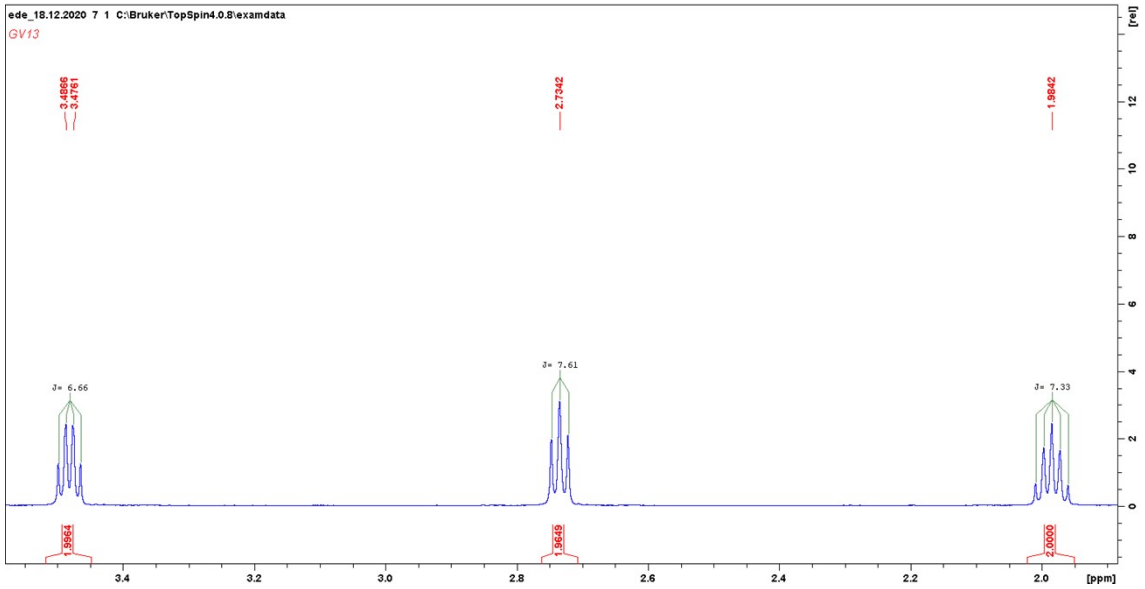
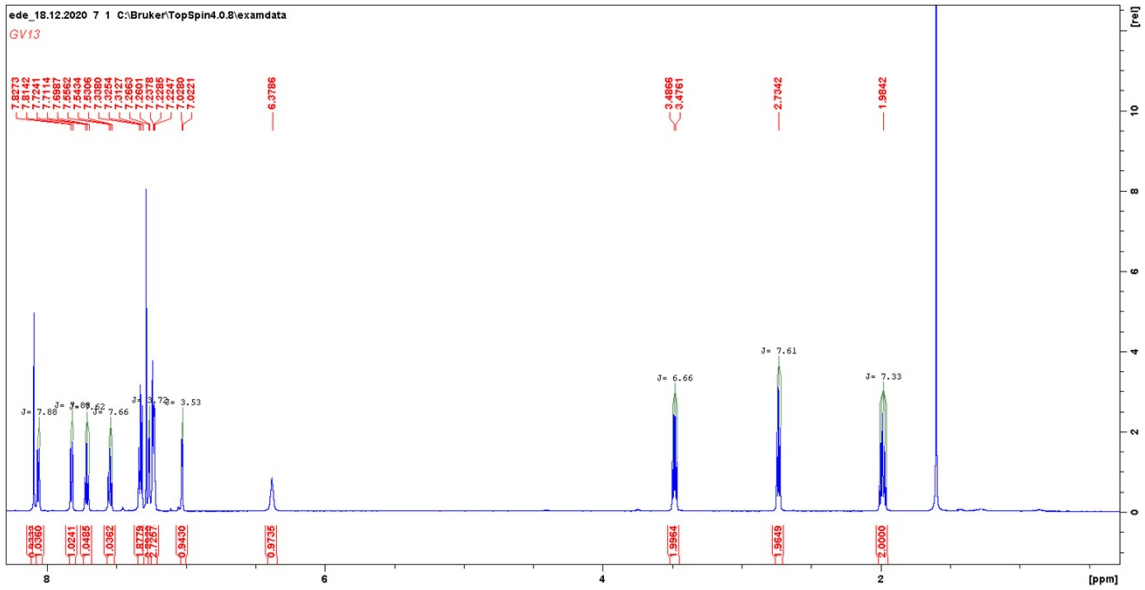
Spectrum1 #Data# GV04.qgd R.Time:28.892(Scan#:2868)
 MassPeaks:279
 RawMode:Averaged 28.275-29.342(2794-2922) BasePeak:156.80(10000)
 BG Mode:Averaged 30.958-30.958(3116-3116) Group 1 - Event 1

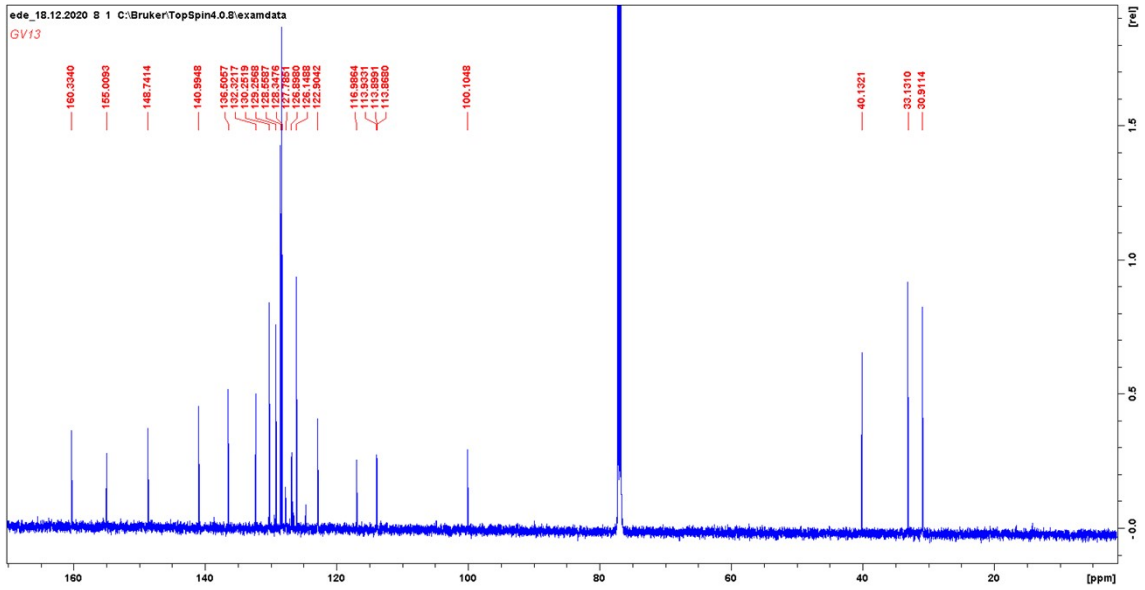




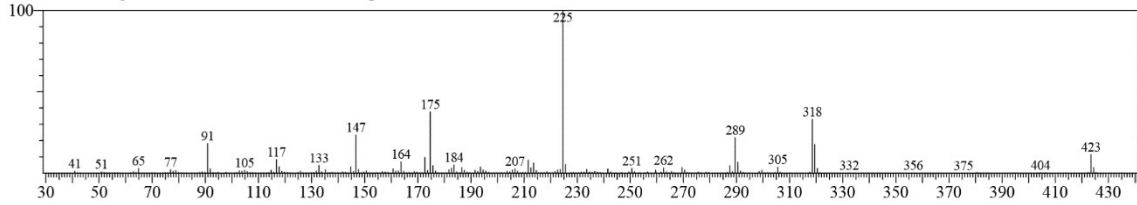
(E)-2-Cyano-N-(3-phenylpropyl)-3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)acrylamide
 Chemical Formula: C₂₄H₁₉F₃N₂O₂
 Exact Mass: 424.42 g/mol

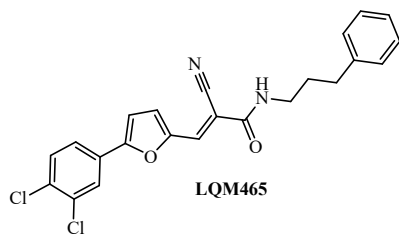




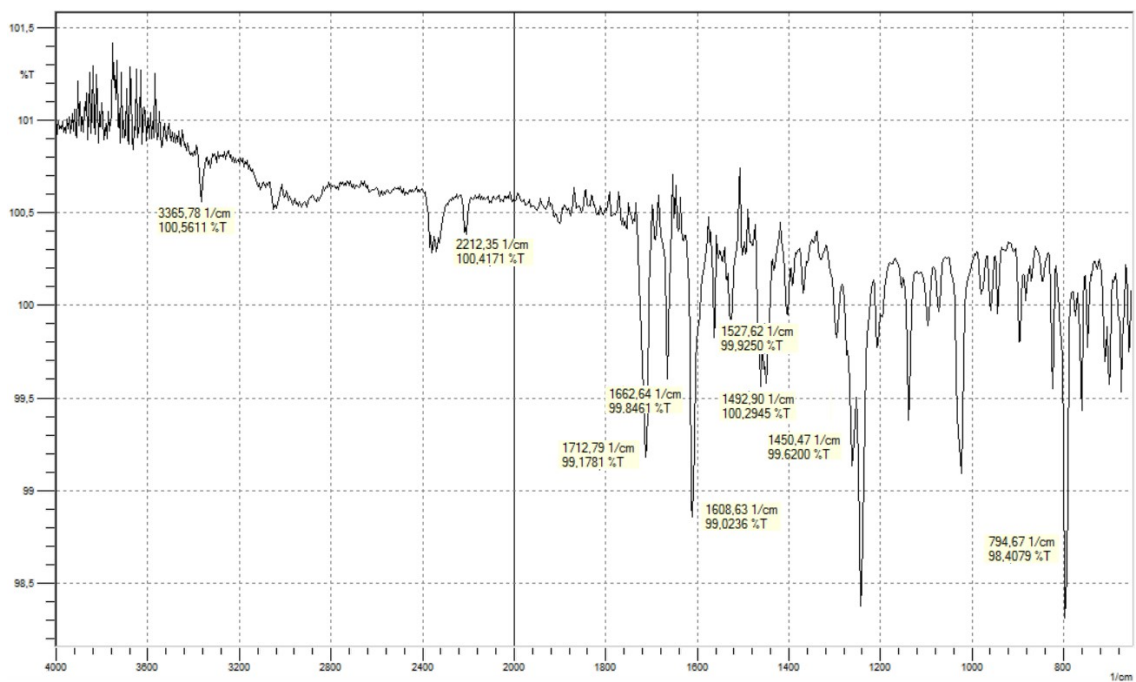
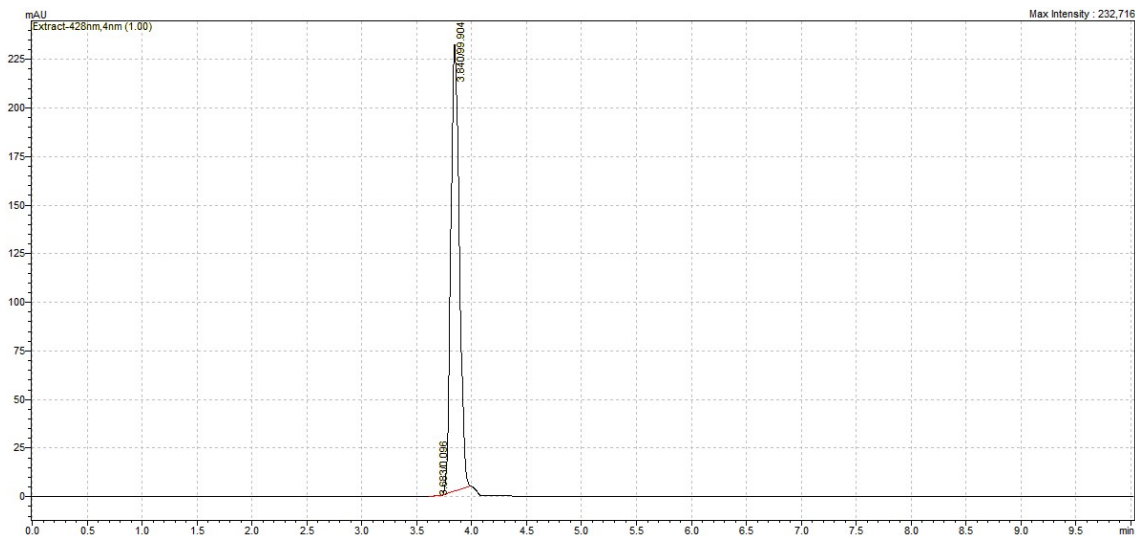


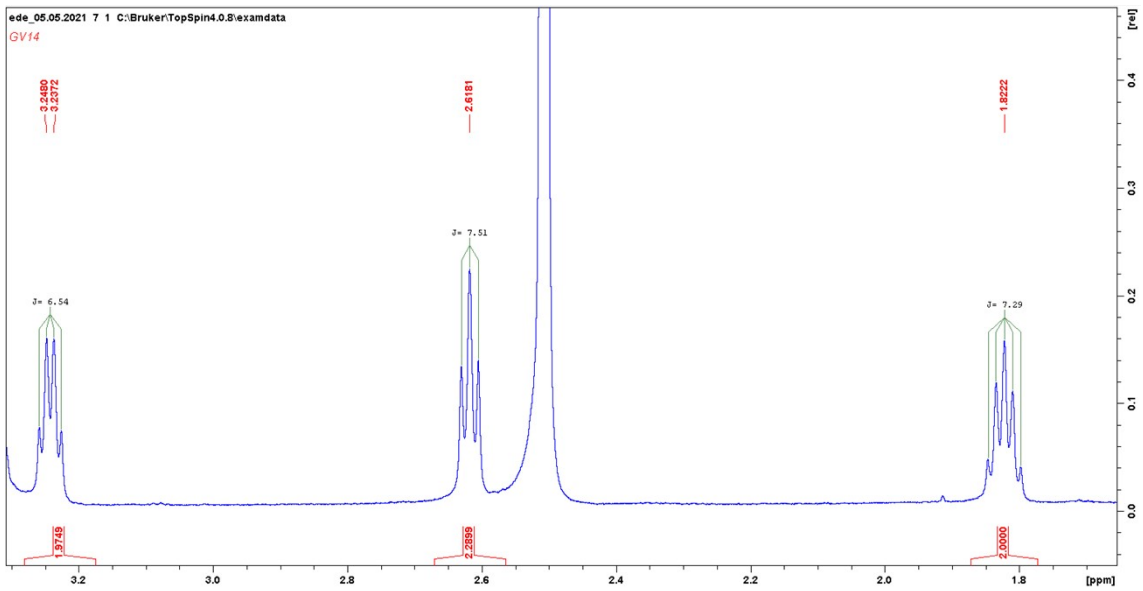
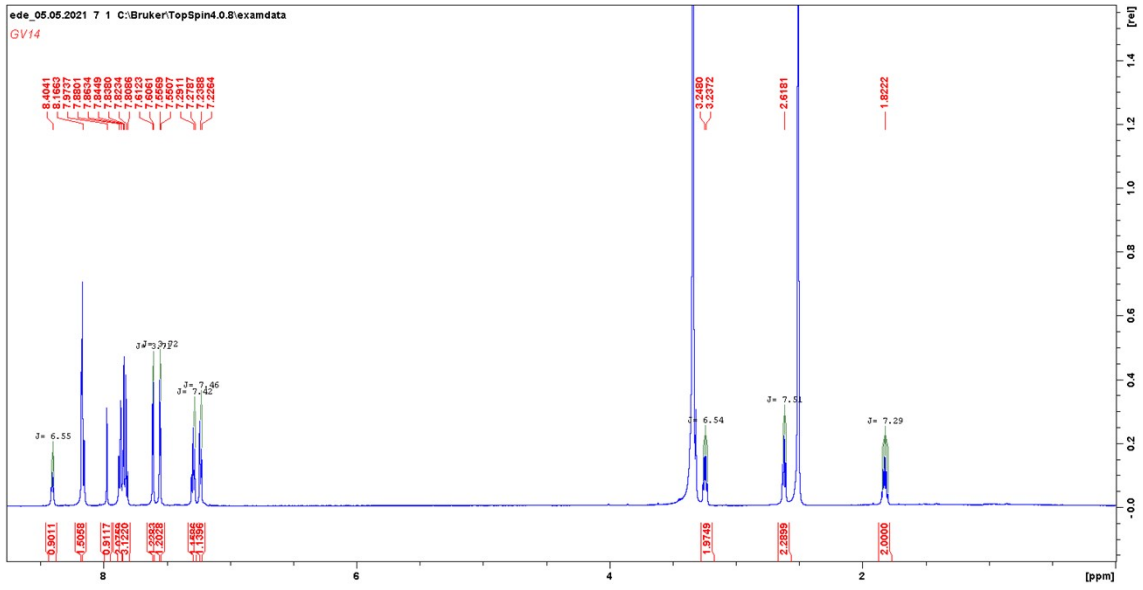
Spectrum1 #Data# GV13.qgd R.Time:26.317(Scan#:2559)
MassPeaks:348
RawMode:Averaged 25.725-26.967(2488-2637) BasePeak:224.60(10000)
BG Mode:Averaged 28.617-28.617(2835-2835) Group 1 - Event 1

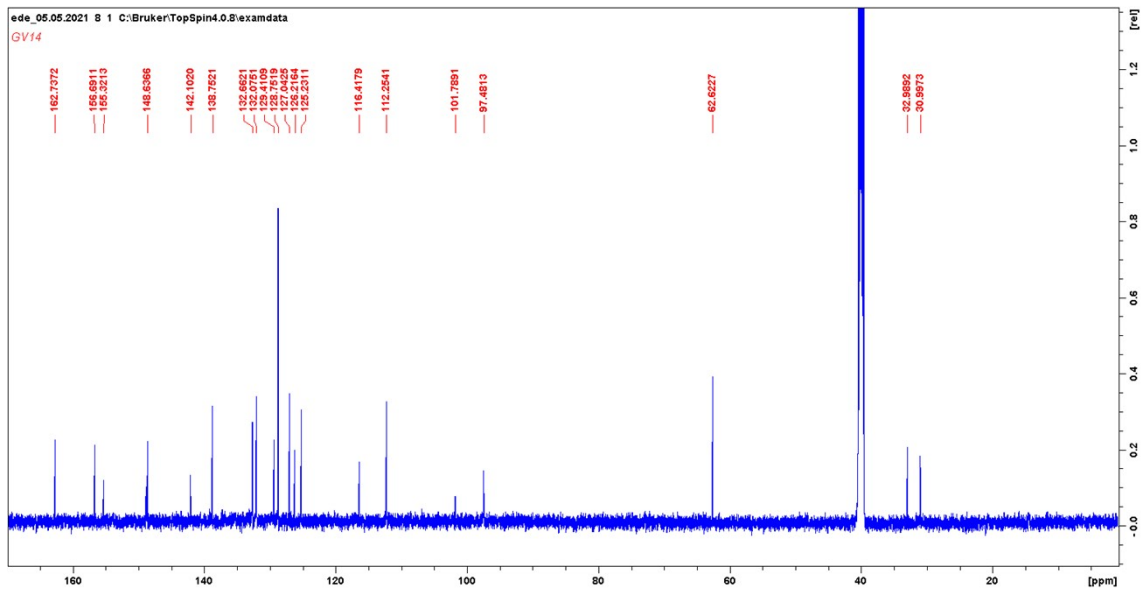
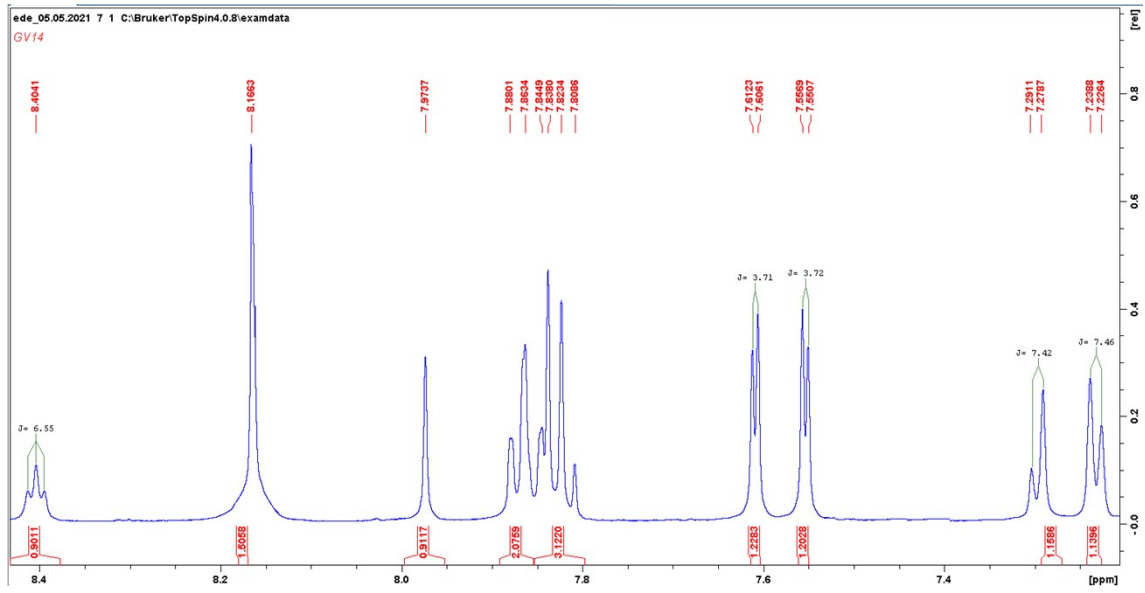




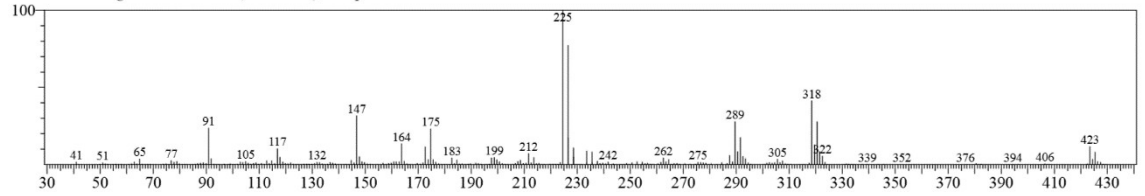
(E)-2-Cyano-3-(5-(3,4-dichlorophenyl)furan-2-yl)-N-(3-phenylpropyl)acrylamide
 Chemical Formula: $C_{23}H_{18}Cl_2N_2O_2$
 Exact Mass: 425.31 g/mol

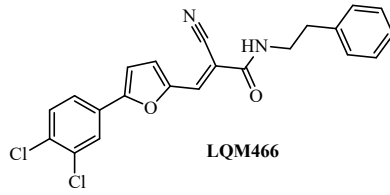






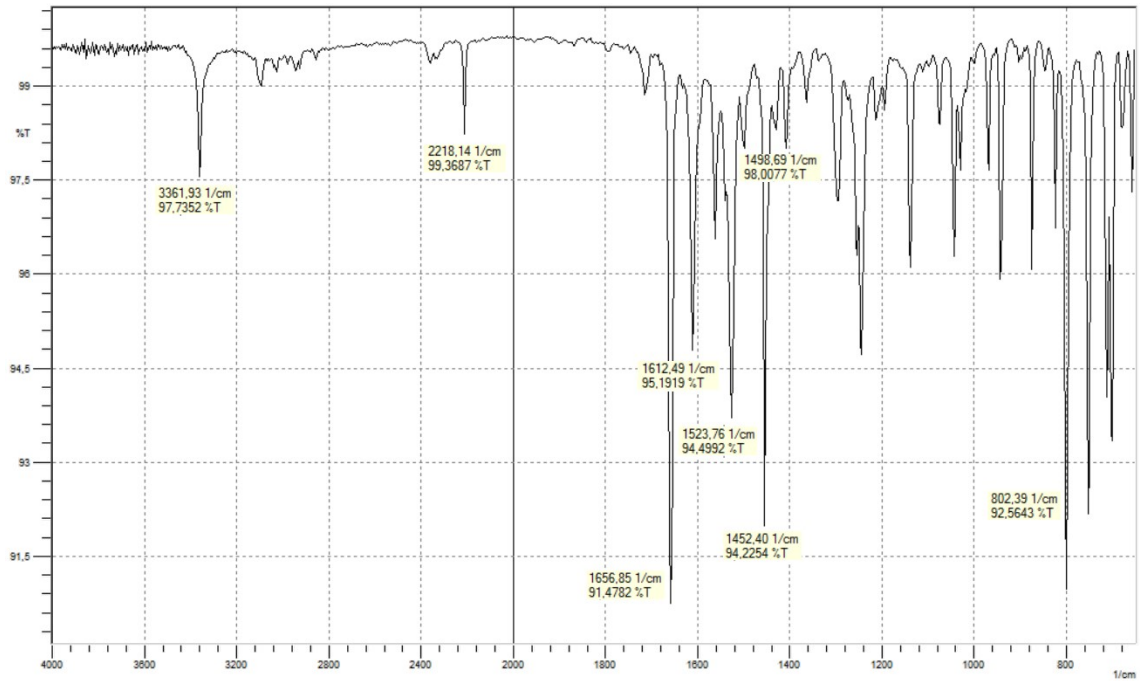
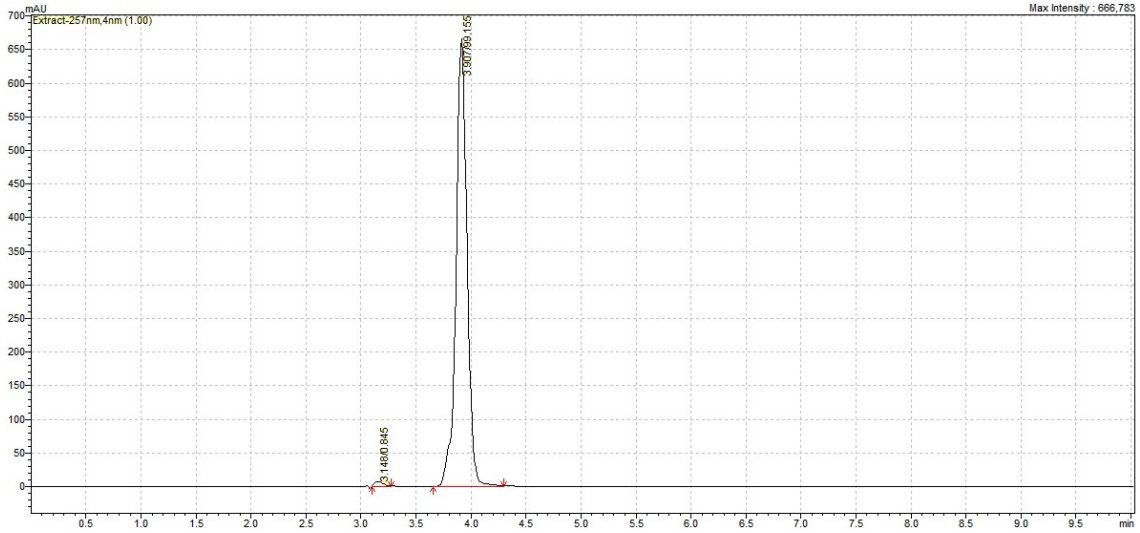
Spectrum1 #Data# GV 14.qgd R.Time:39.750(Scan#:4171)
MassPeaks:316
RawMode:Averaged 38.667-40.317(4041-4239) BasePeak:224.60(10000)
BG Mode:Averaged 36.875-37.183(3826-3863) Group 1 - Event 1

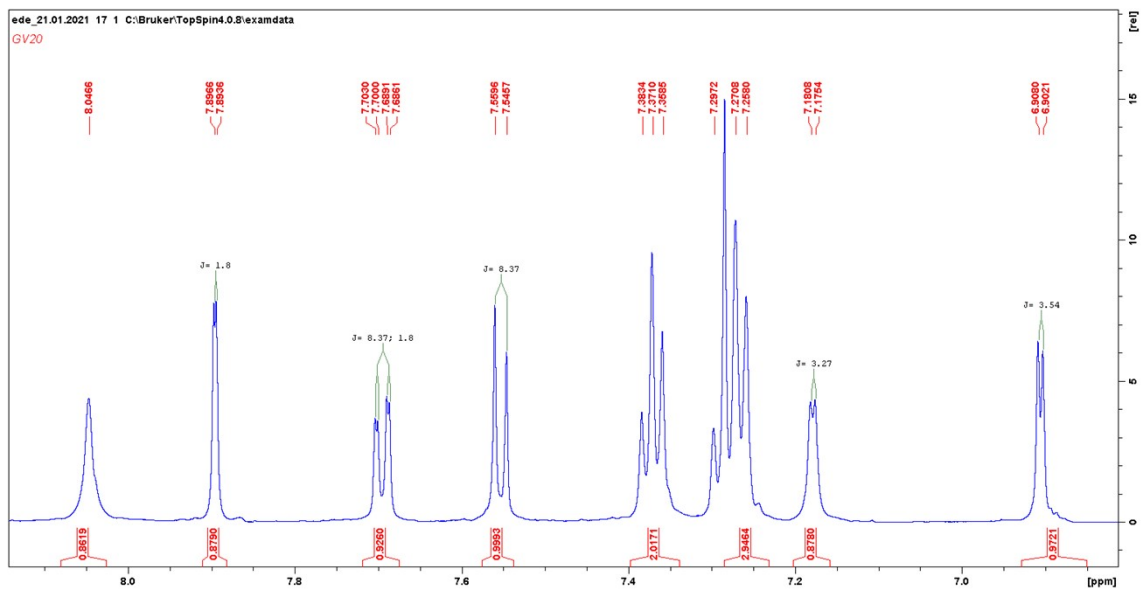
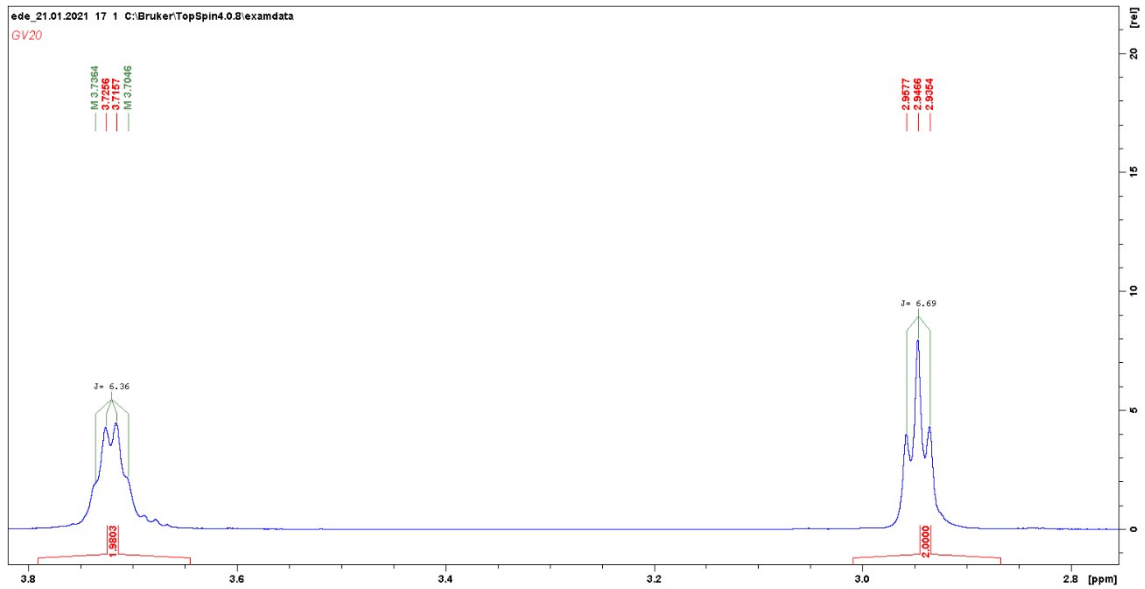
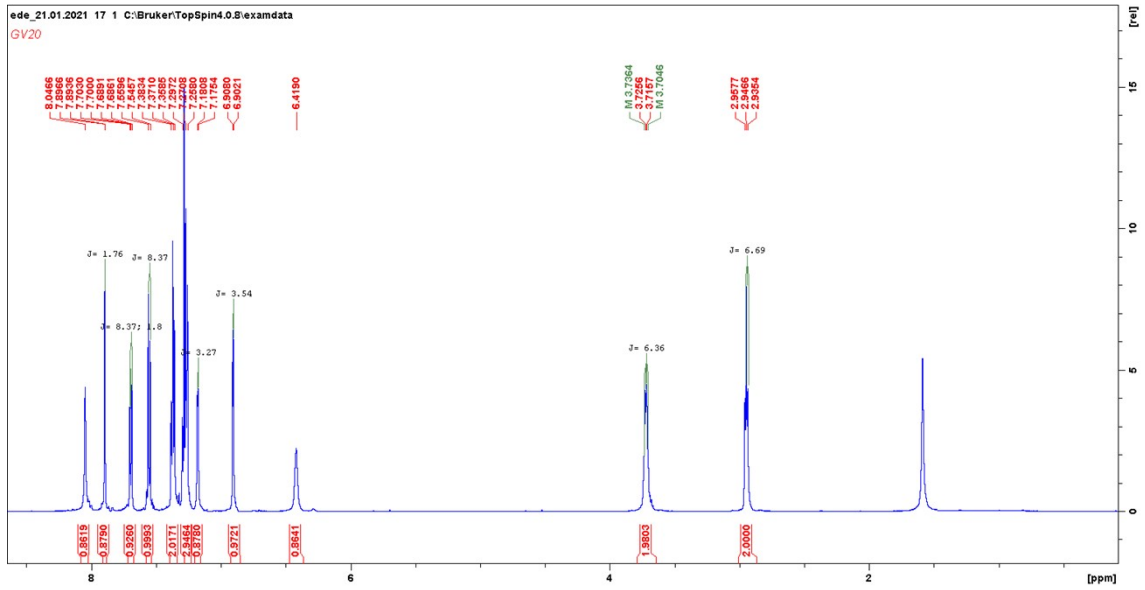


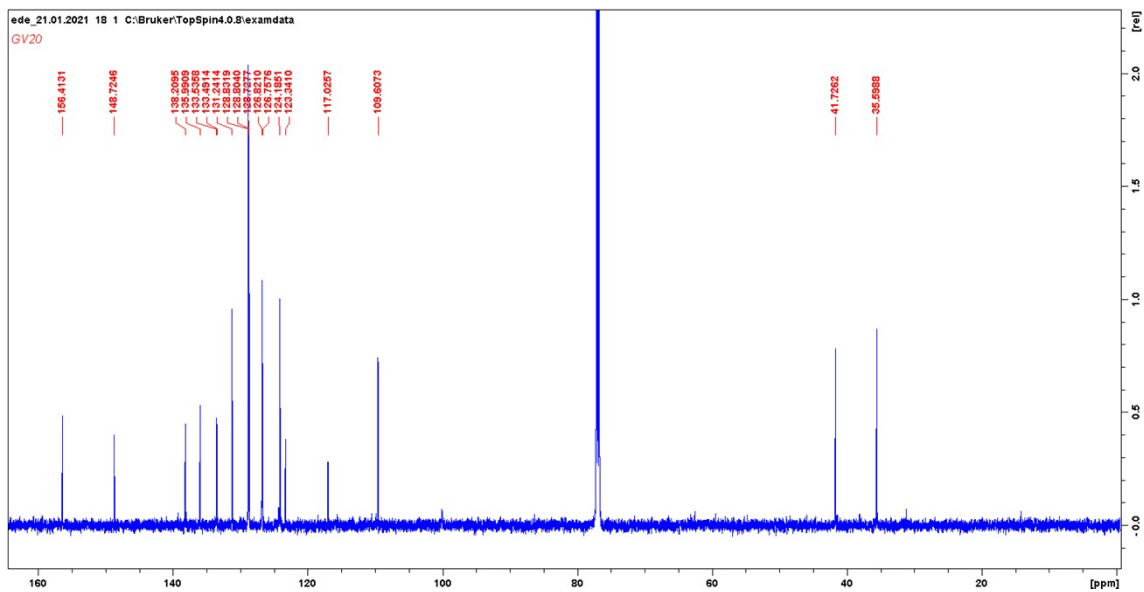


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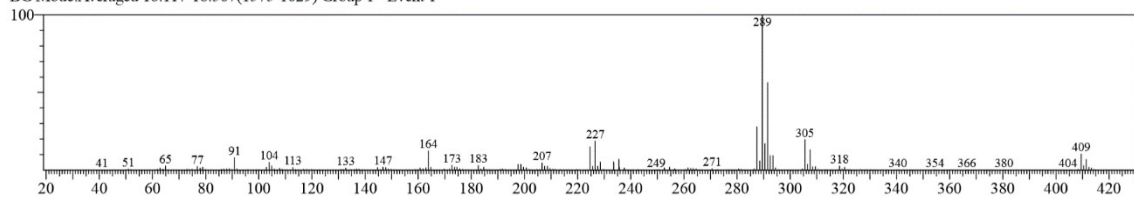
(*E*)-2-Cyano-3-(5-(3,4-dichlorophenyl)furan-2-yl)-*N*-phenethylacrylamide
 Chemical Formula: C₂₂H₁₆Cl₂N₂O₂
 Exact Mass: 411.28 g/mol

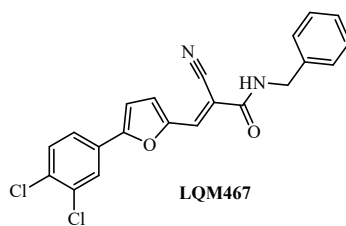




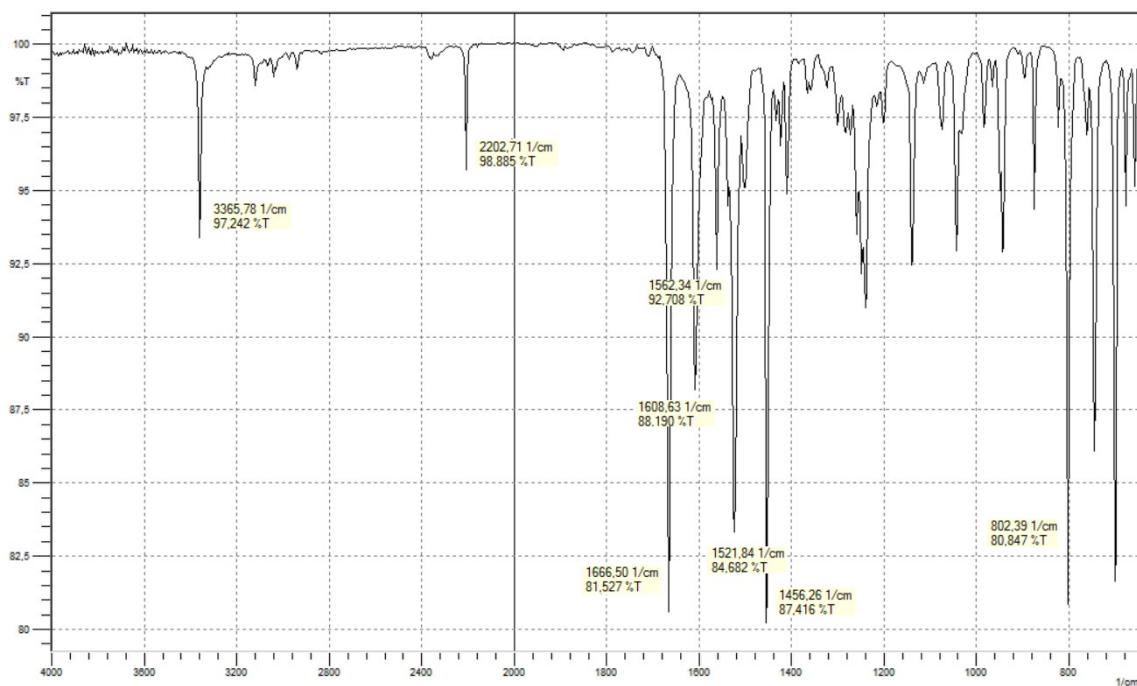
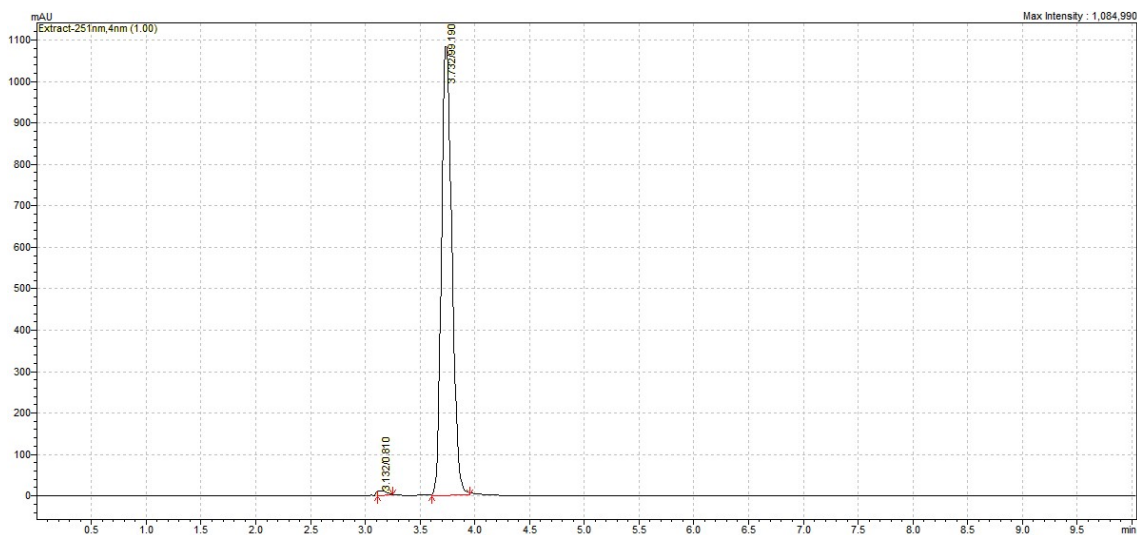


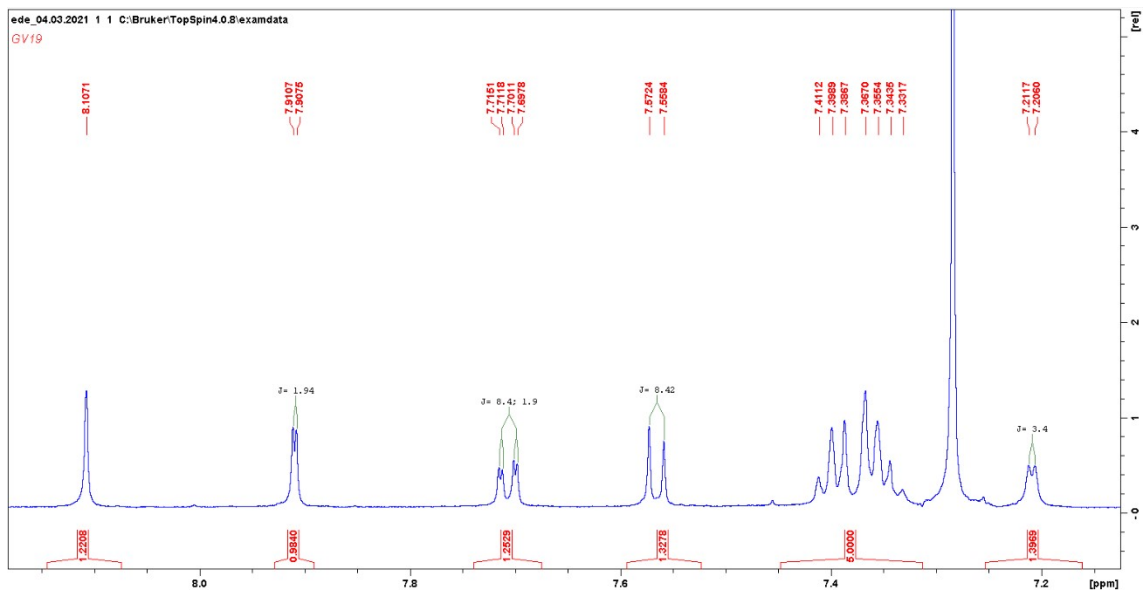
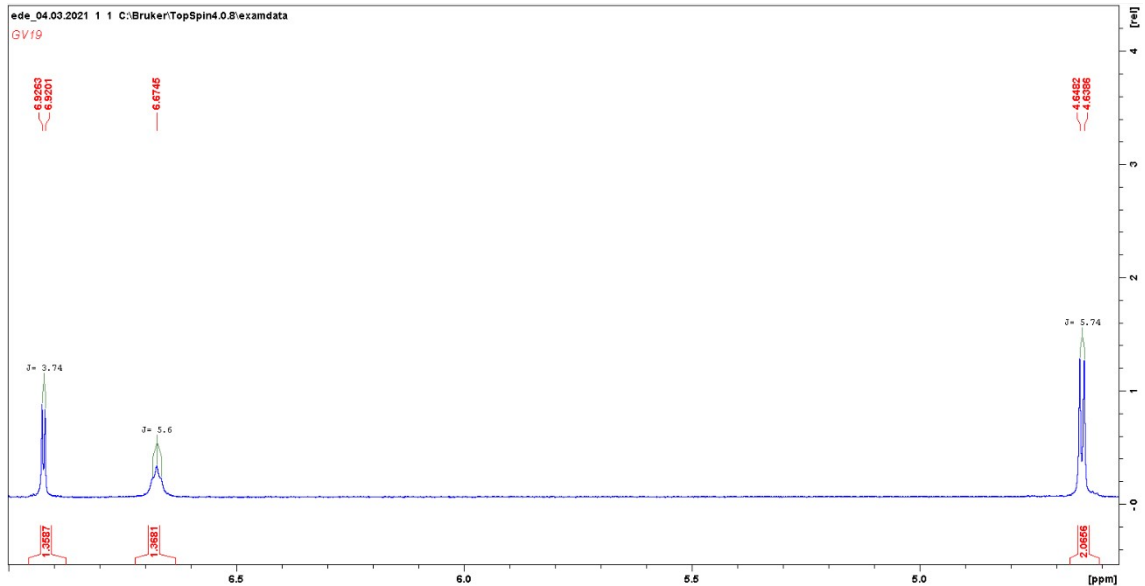
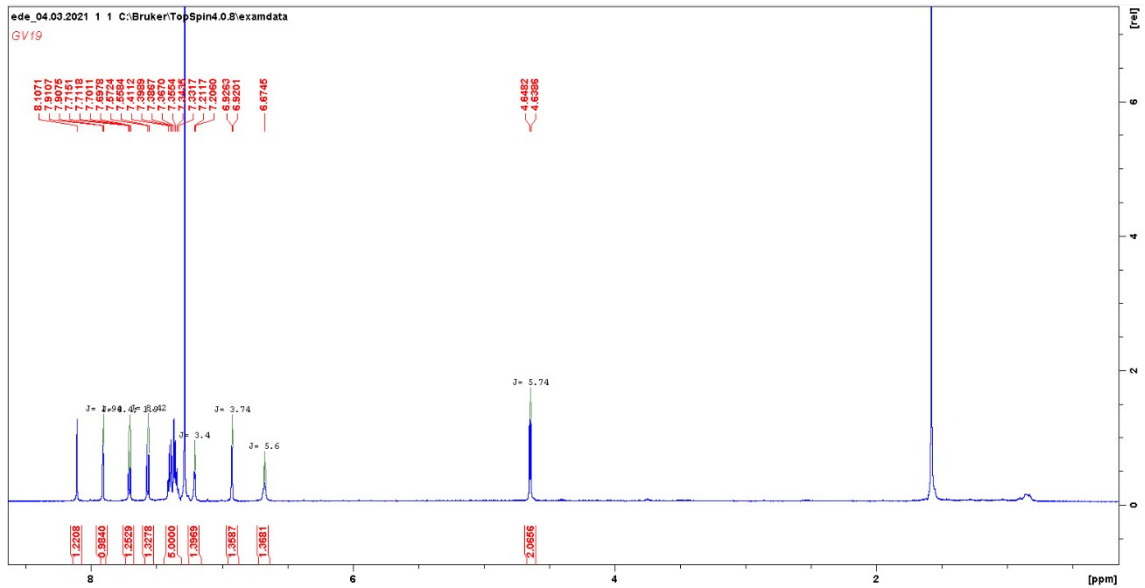
Spectrum1 #Data# GV 20 2.qgd R.Time:35.850(Scan#:3703)
MassPeaks:300
RawMode:Averaged 34.467-36.467(3537-3777) BasePeak:289.50(10000)
BG Mode:Averaged 18.117-18.567(1575-1629) Group 1 - Event 1

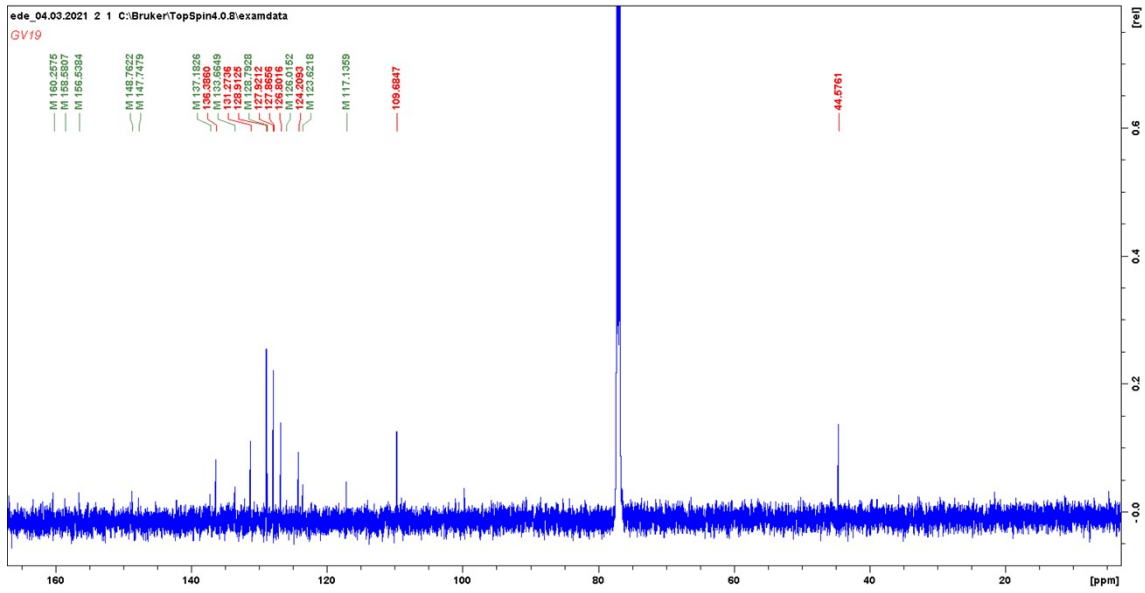




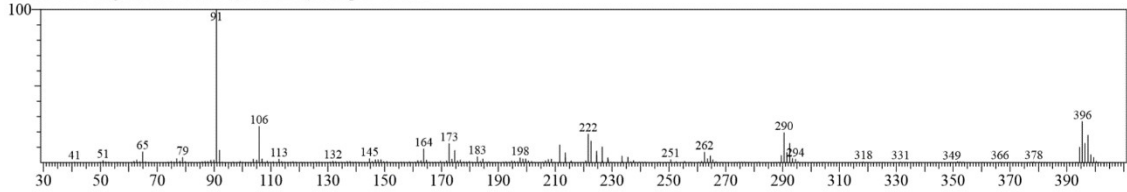
(E)-N-Benzyl-2-cyano-3-(5-(3,4-dichlorophenyl)furan-2-yl)acrylamide
 Chemical Formula: C₂₁H₁₄Cl₂N₂O₂
 Exact Mass: 397.26 g/mol

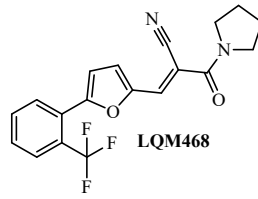




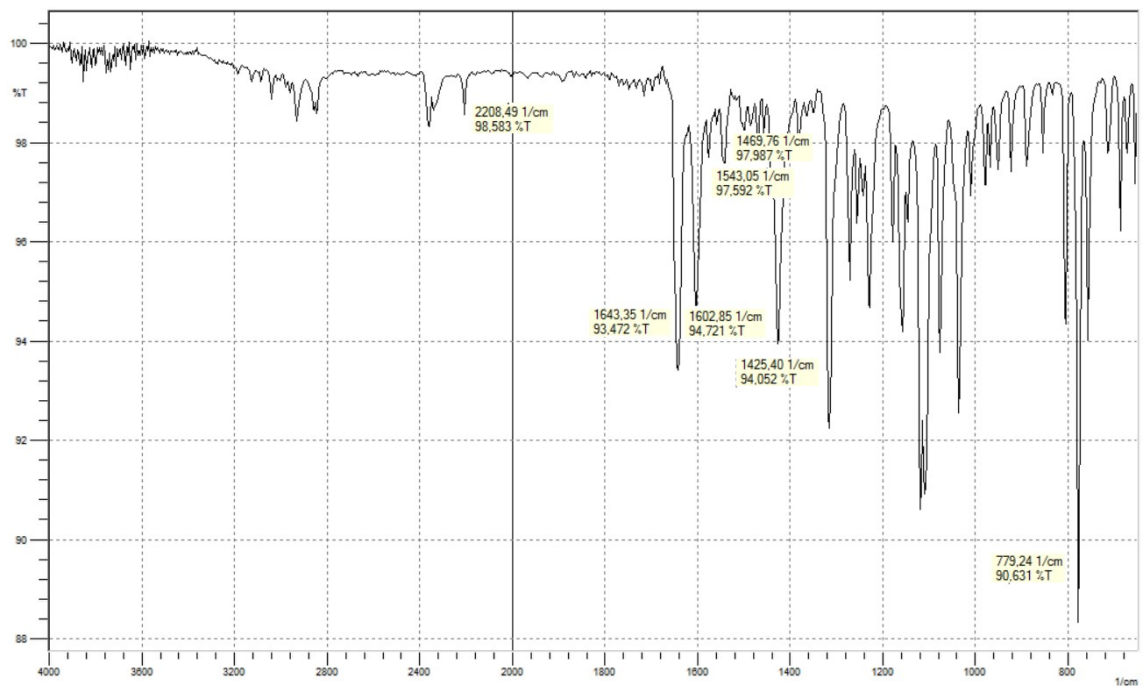
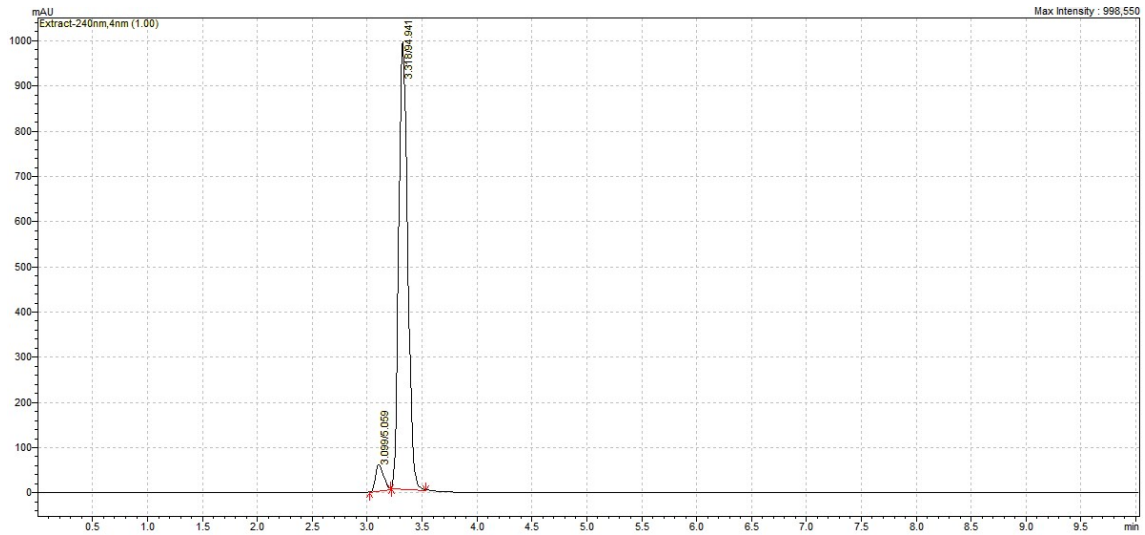


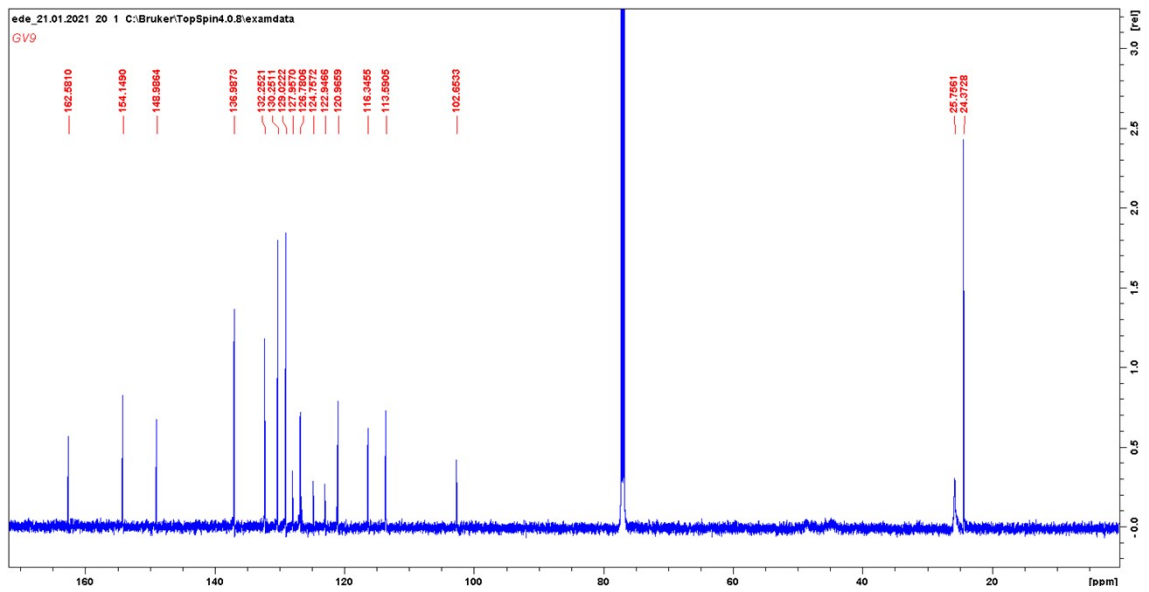
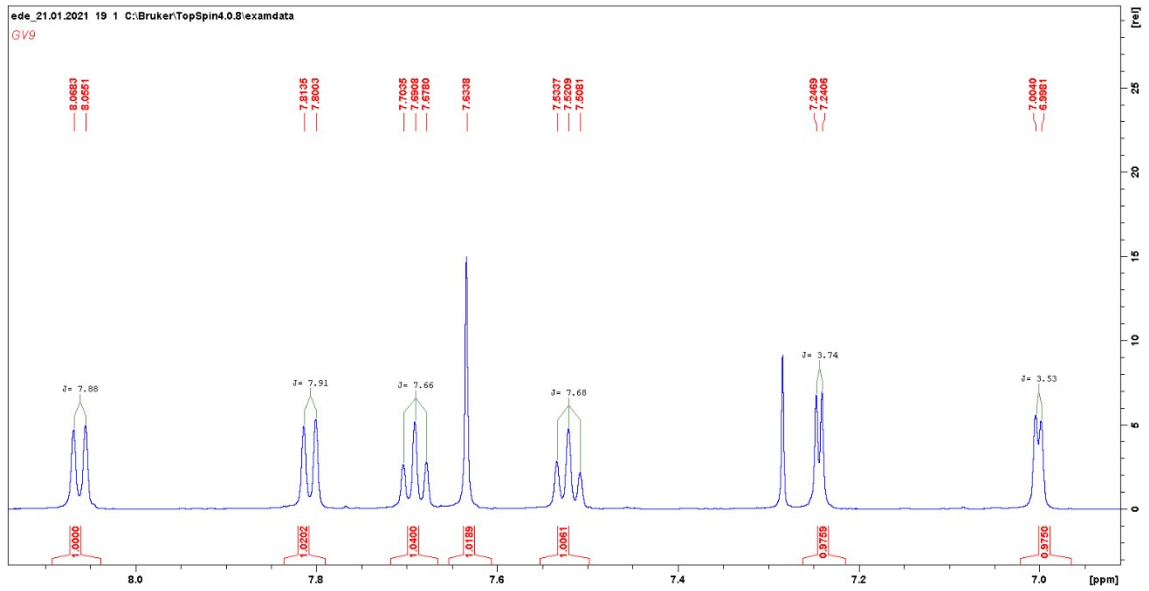
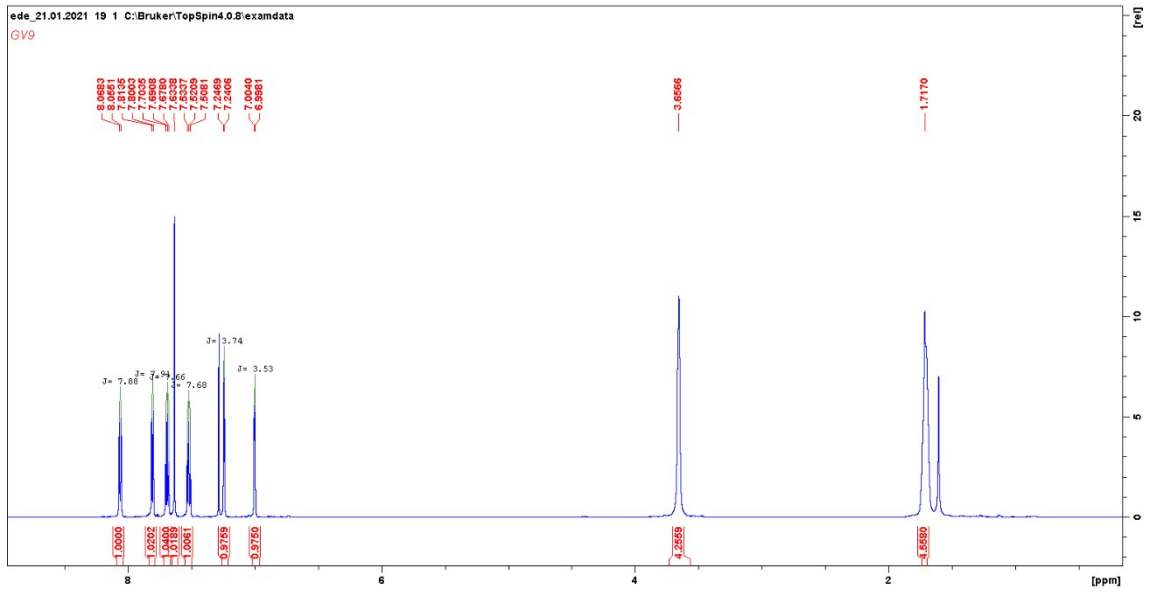
Spectrum1 #Data# GV19.qgd R.Time:33.517(Scan#:3423)
 MassPeaks:318
 RawMode:Averaged 32.608-33.867(3314-3465) BasePeak:90.85(10000)
 BG Mode:Averaged 32.000-32.000(3241-3241) Group 1 - Event 1



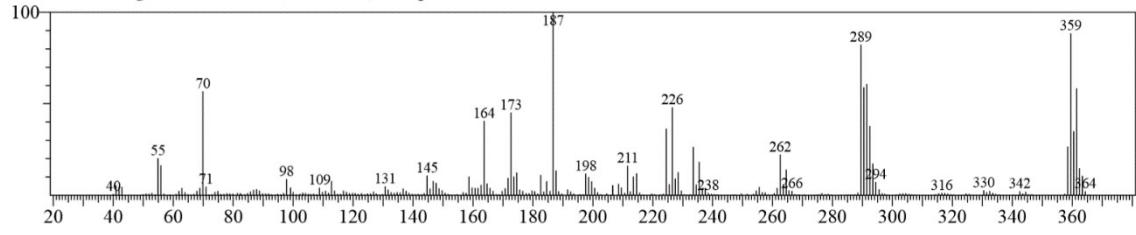


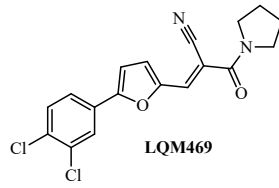
(*E*)-2-(Pyrrolidine-1-carbonyl)-3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)acrylonitrile
 Chemical Formula: C₁₉H₁₅F₃N₂O₂
 Exact Mass: 360.34 g/mol



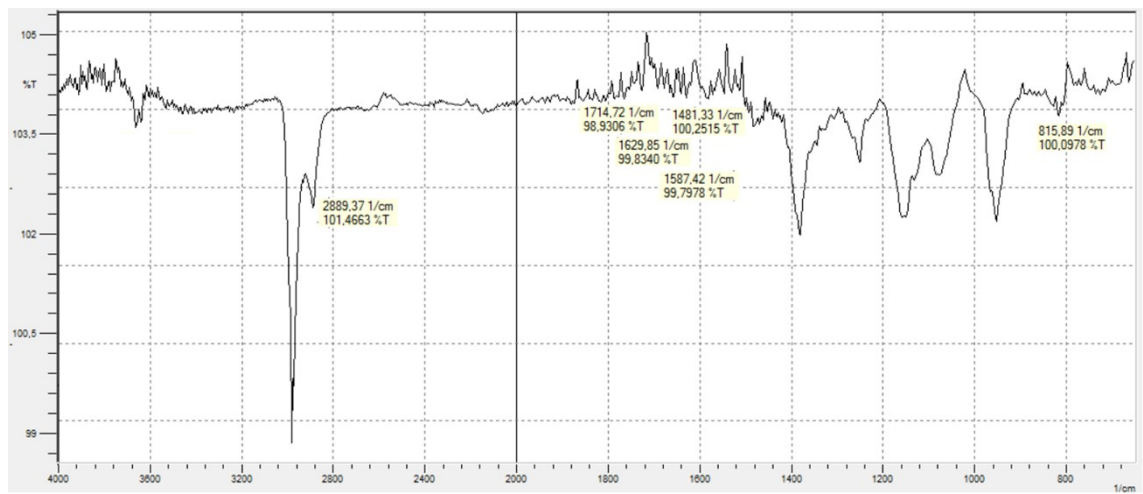
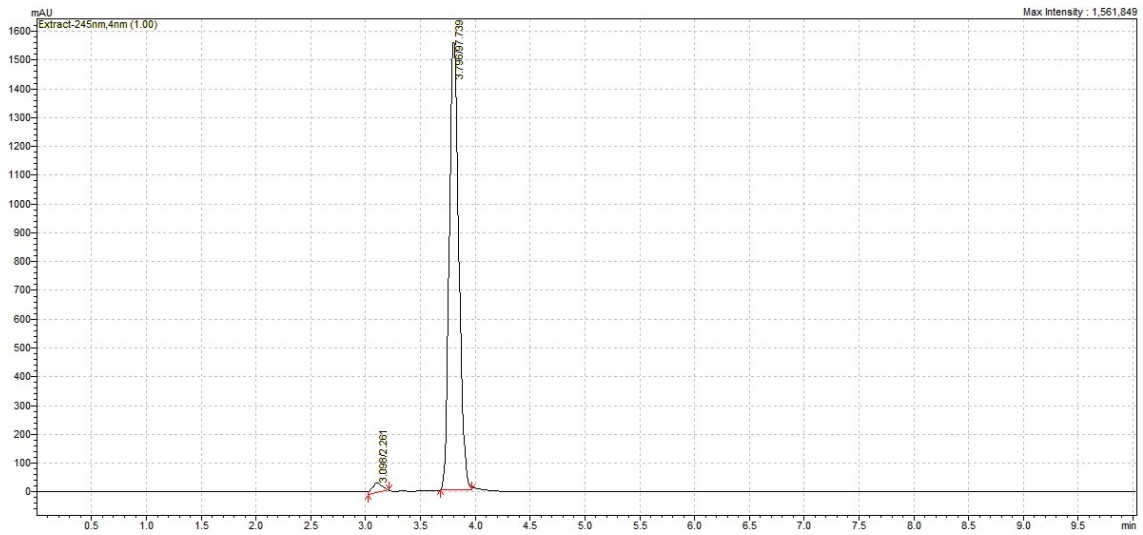


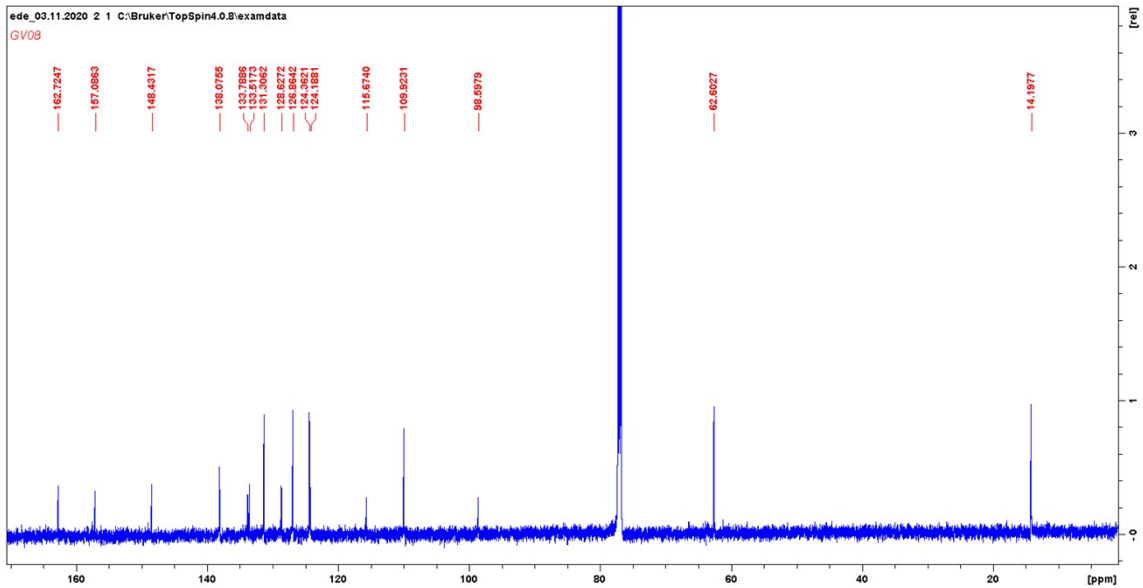
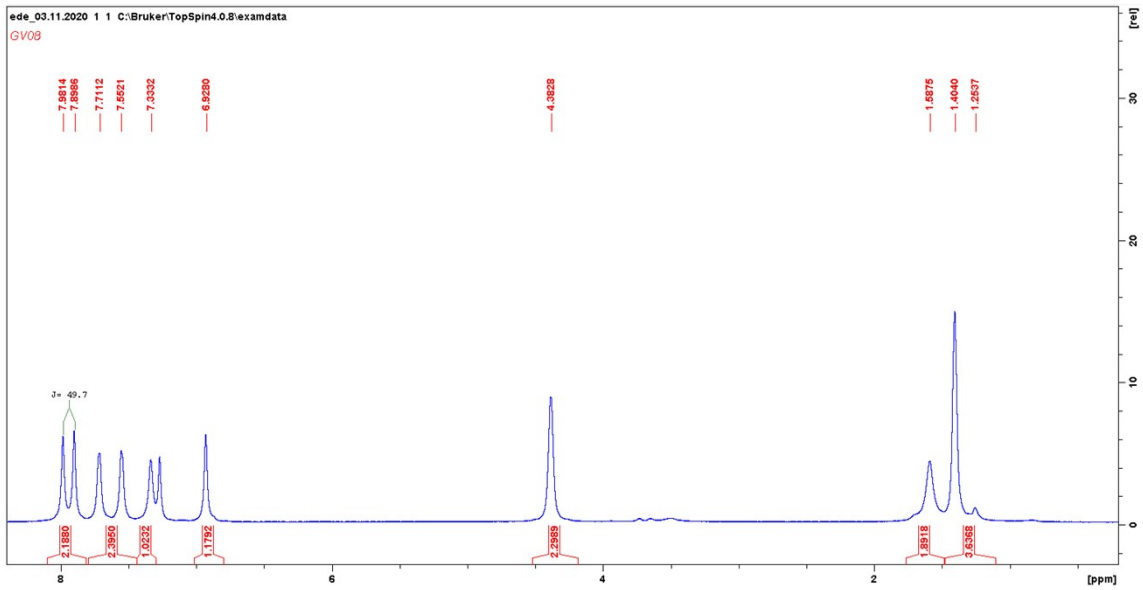
Spectrum1 #Data# GV10.qgd R.Time:27.833(Scan#:2741)
MassPeaks:295
RawMode:Averaged 27.308-28.442(2678-2814) BasePeak:186.70(10000)
BG Mode:Averaged 33.500-33.500(3421-3421) Group 1 - Event 1



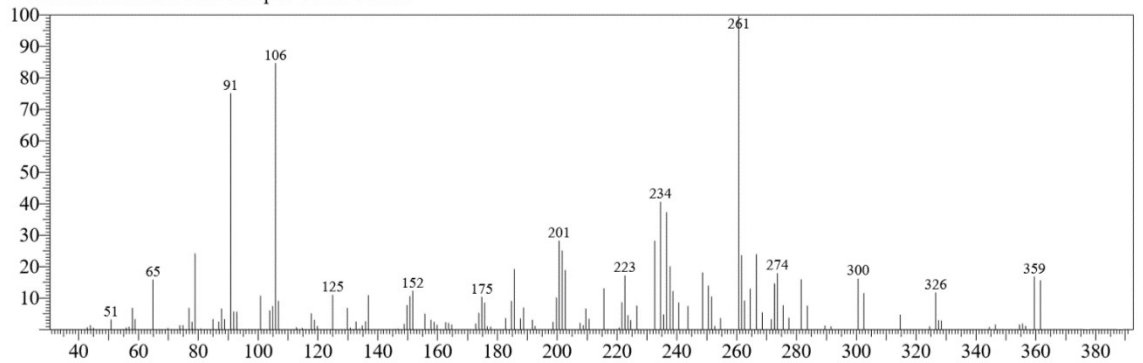


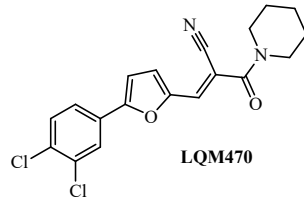
(E)-3-(5-(3,4-Dichlorophenyl)furan-2-yl)-2-(pyrrolidine-1-carbonyl)acrylonitrile
 Chemical Formula: C₁₈H₁₄Cl₂N₂O₂
 Exact Mass: 361.22 g/mol



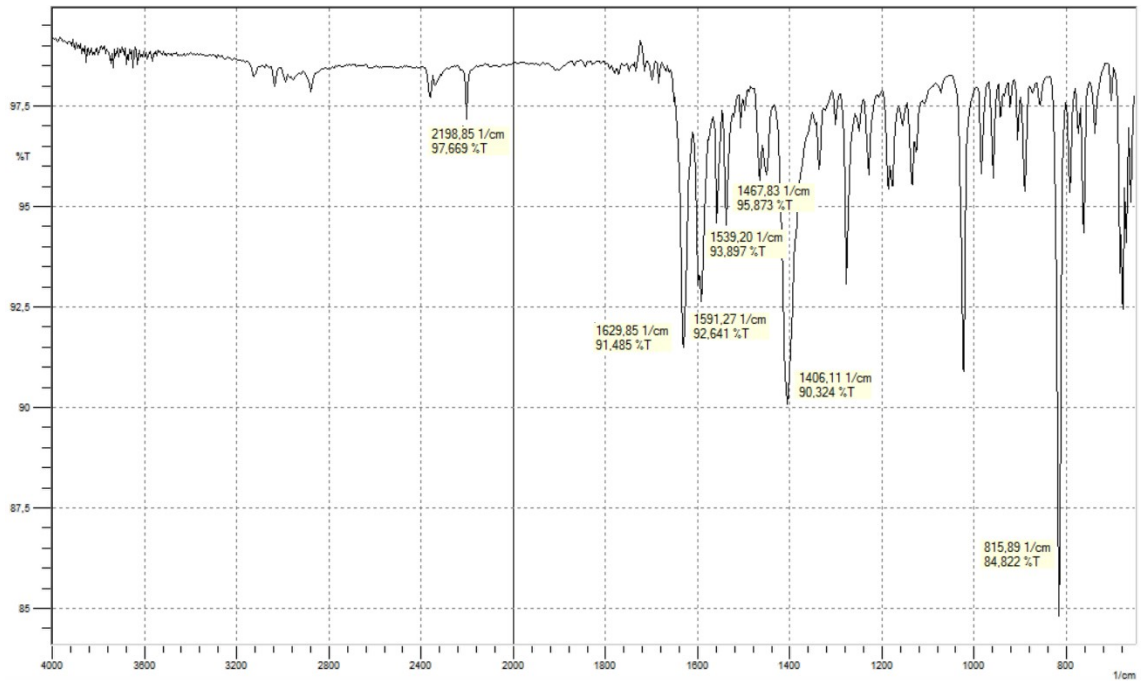
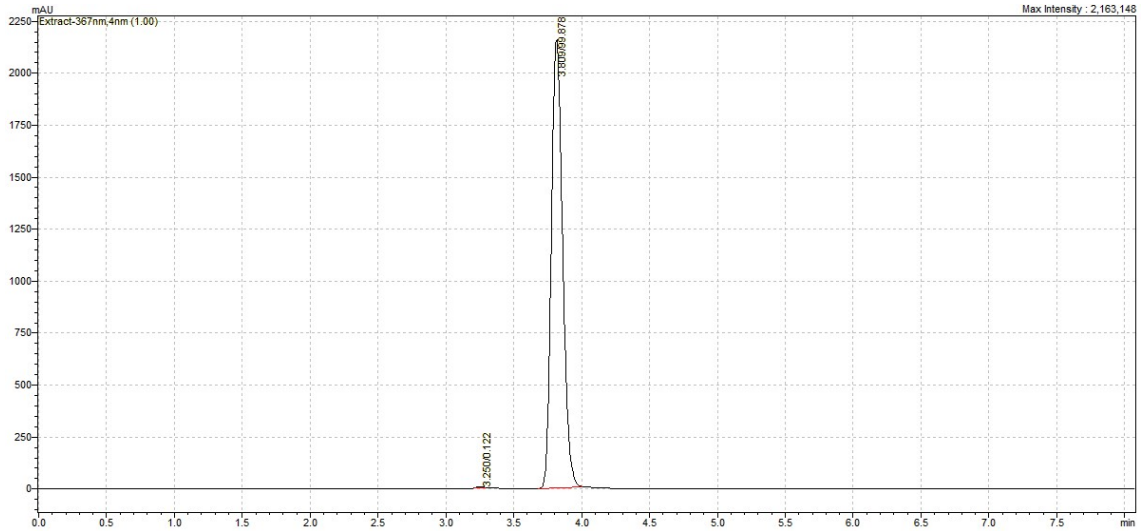


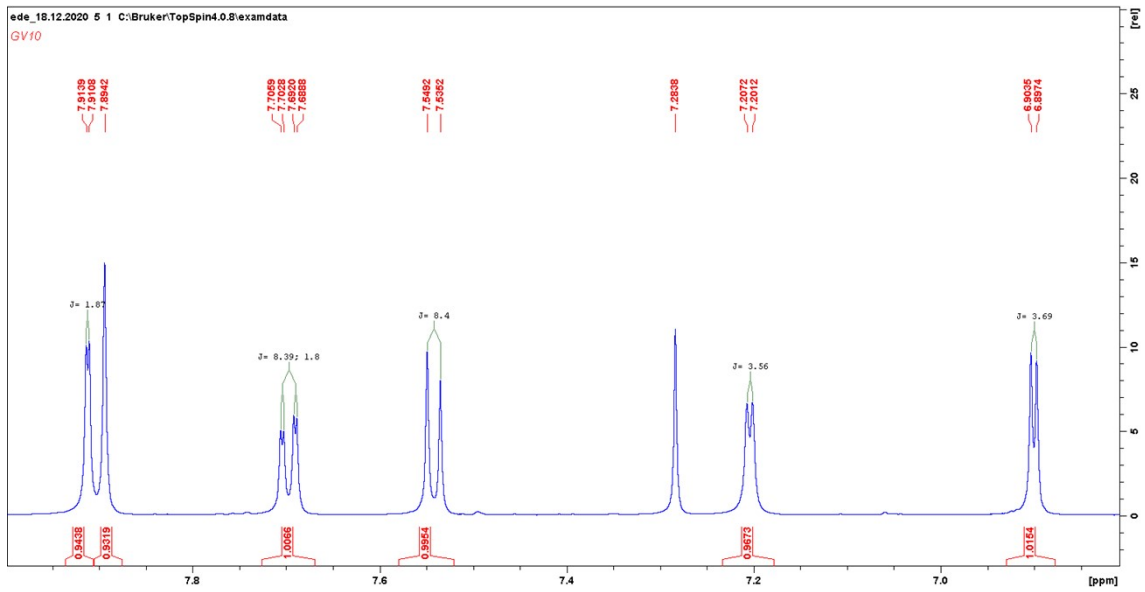
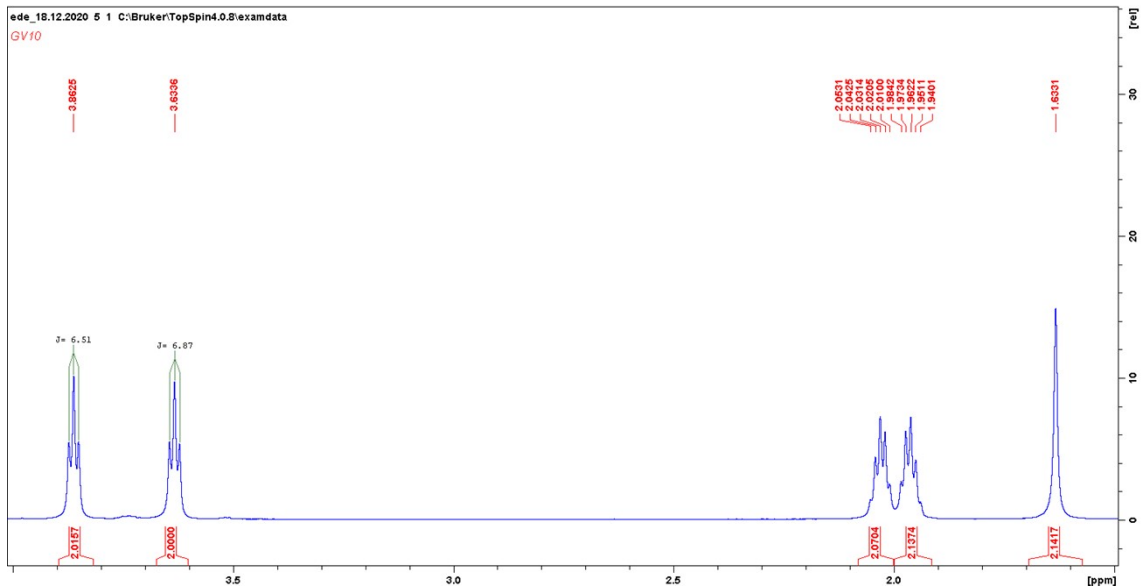
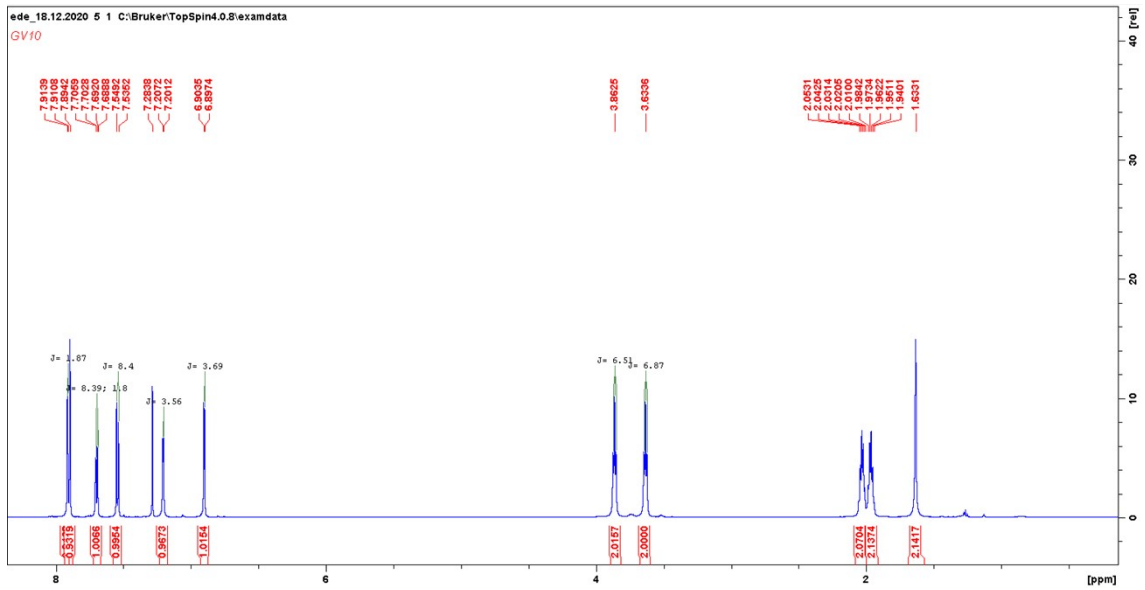
Line#:24 R.Time:37.300(Scan#:3877)
MassPeaks:144
RawMode:Averaged 37.292-37.308(3876-3878) BasePeak:261(10196)
BG Mode:Calc. from Peak Group 1 - Event 1 Scan

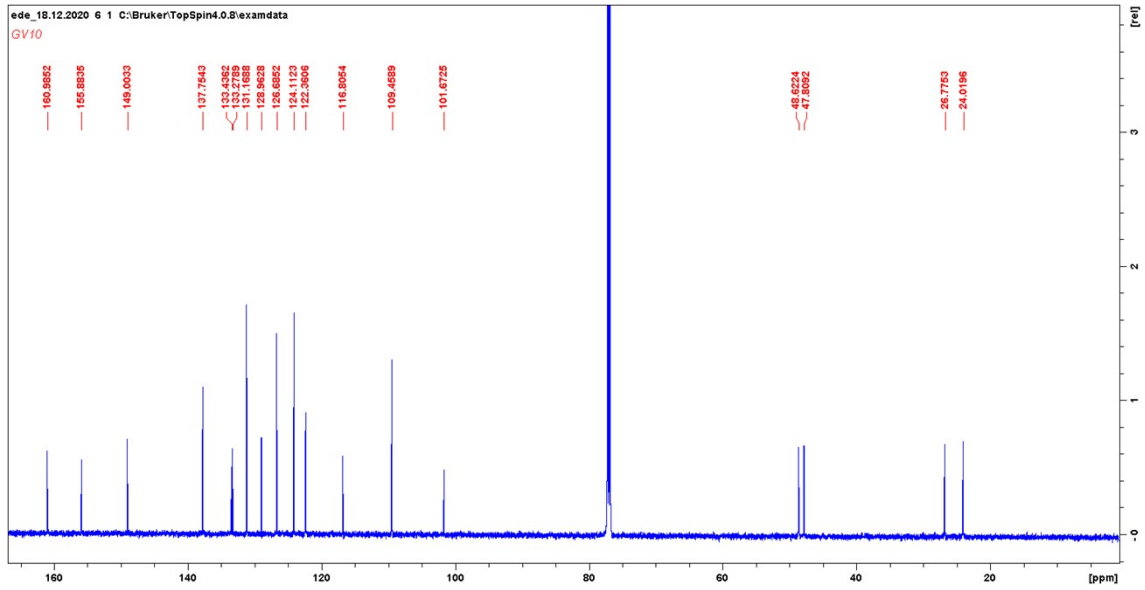




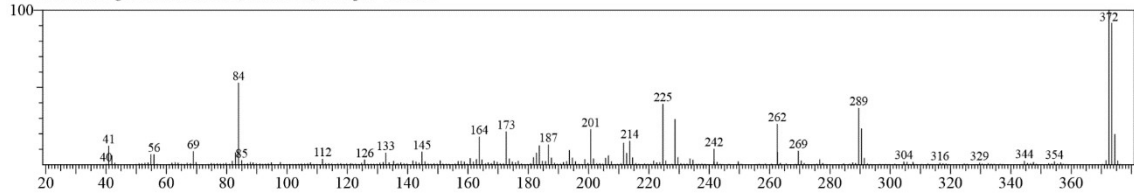
(E)-3-(5-(3,4-Dichlorophenyl)furan-2-yl)-2-(piperidine-1-carbonyl)acrylonitrile
 Chemical Formula: $C_{19}H_{16}Cl_2N_2O_2$
 Exact Mass: 375.25 g/mol

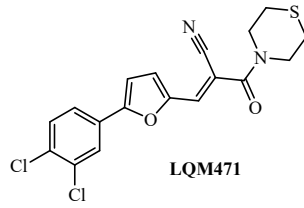




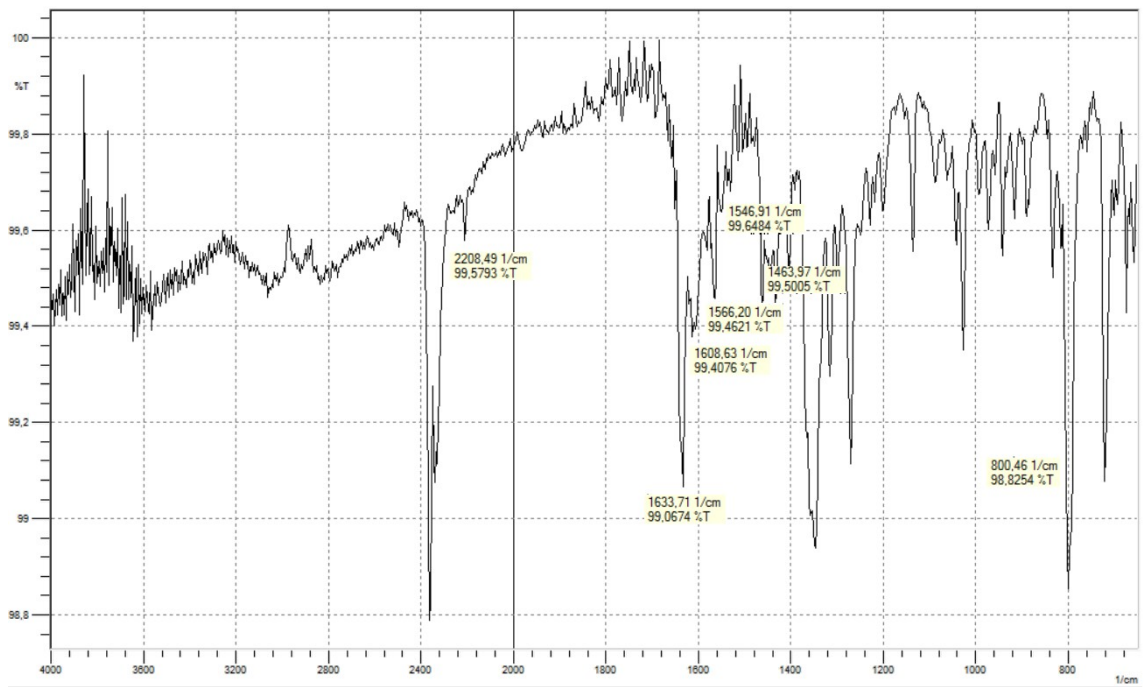
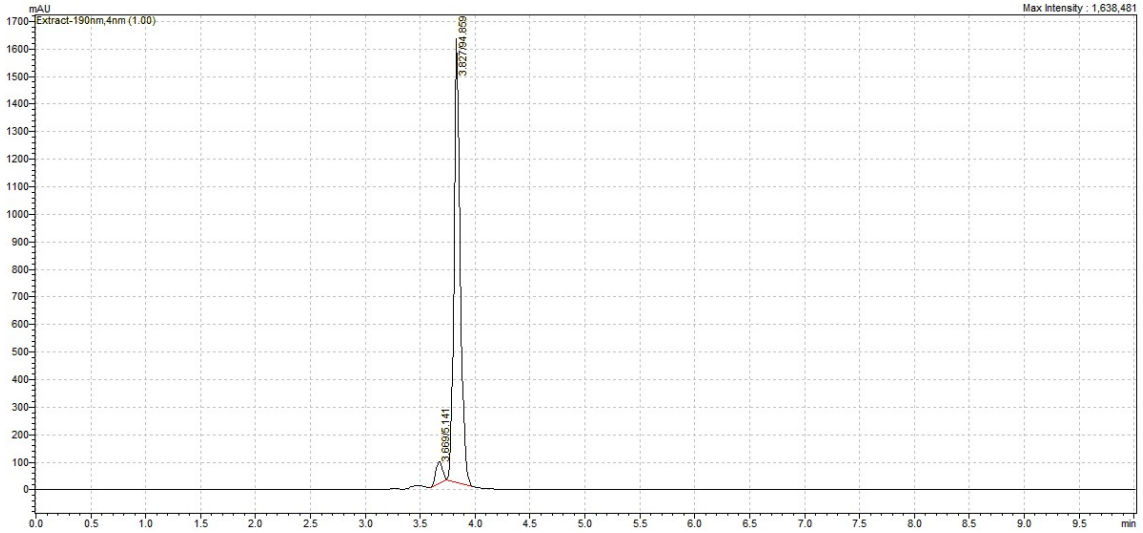


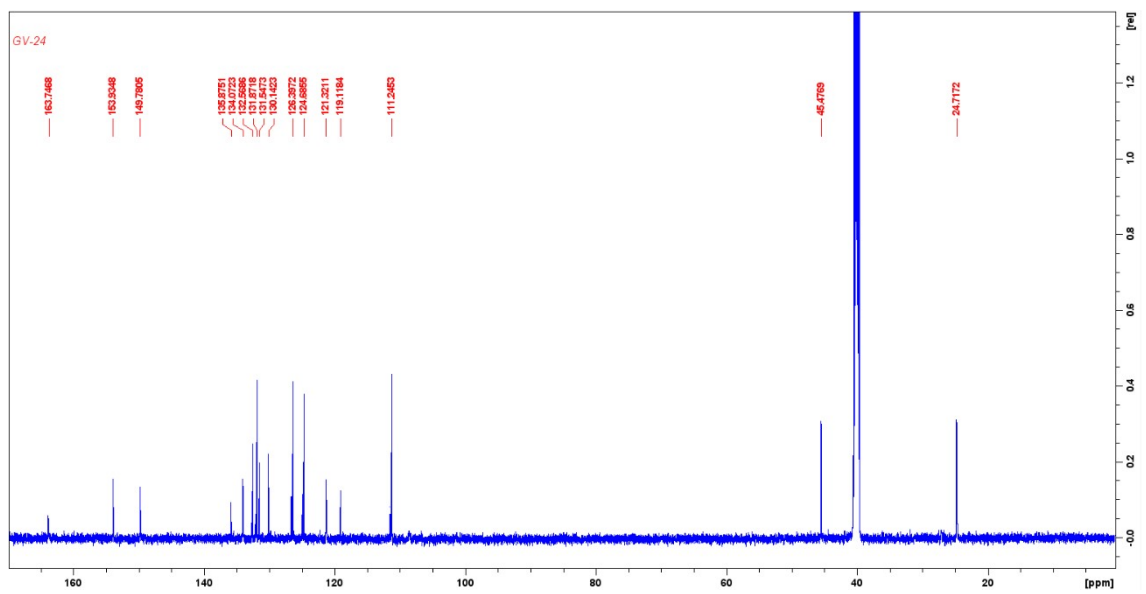
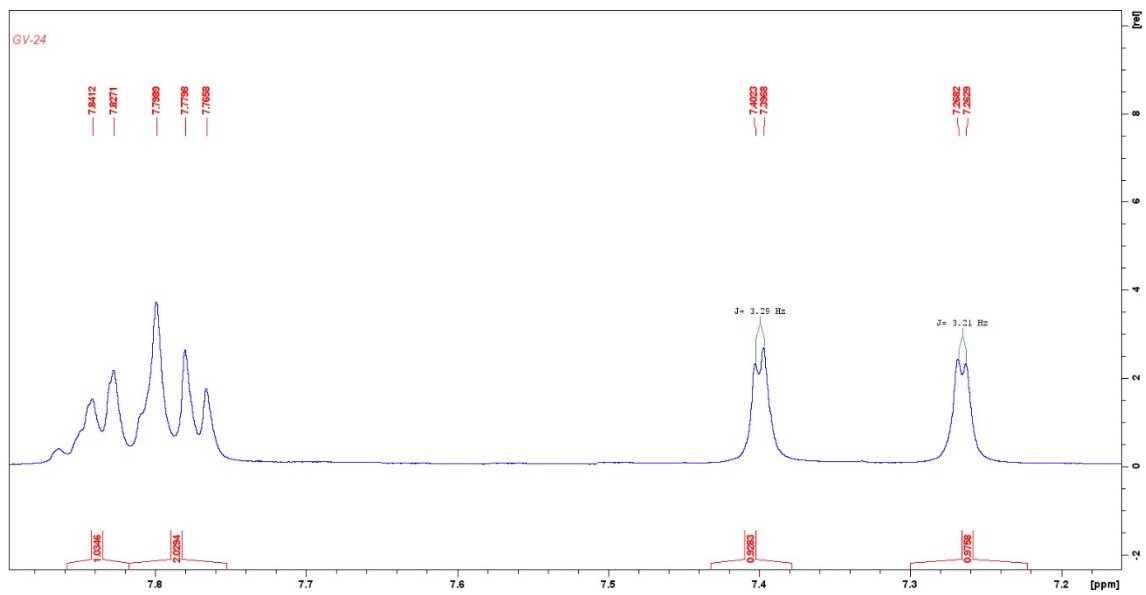
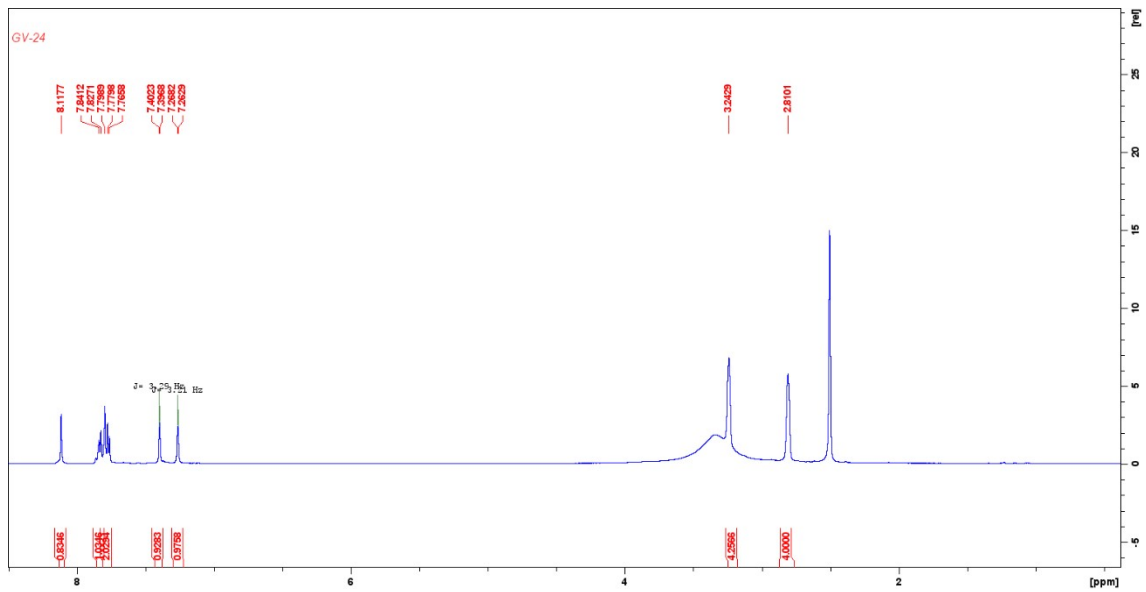
Spectrum1 #Data# GV09.qgd R.Time:22.042(Scan#:2046)
MassPeaks:297
RawMode:Averaged 21.883-22.150(2027-2059) BasePeak:372.50(10000)
BG Mode:Averaged 22.425-22.425(2092-2092) Group 1 - Event 1



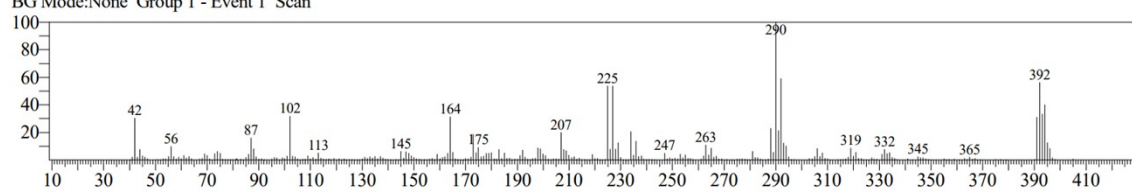


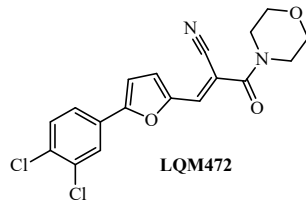
(E)-3-(5-(3,4-Dichlorophenyl)furan-2-yl)-2-(thiomorpholine-4-carbonyl)acrylonitrile
 Chemical Formula: C₁₈H₁₄Cl₂N₂O₂S
 Exact Mass: 393.28 g/mol



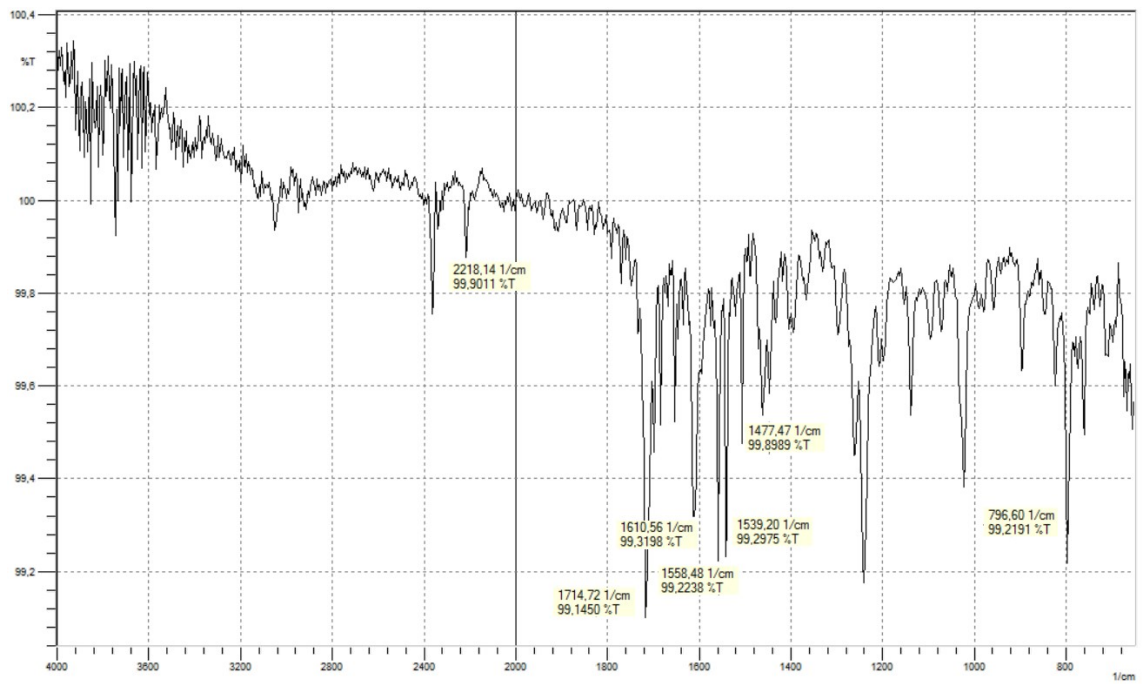
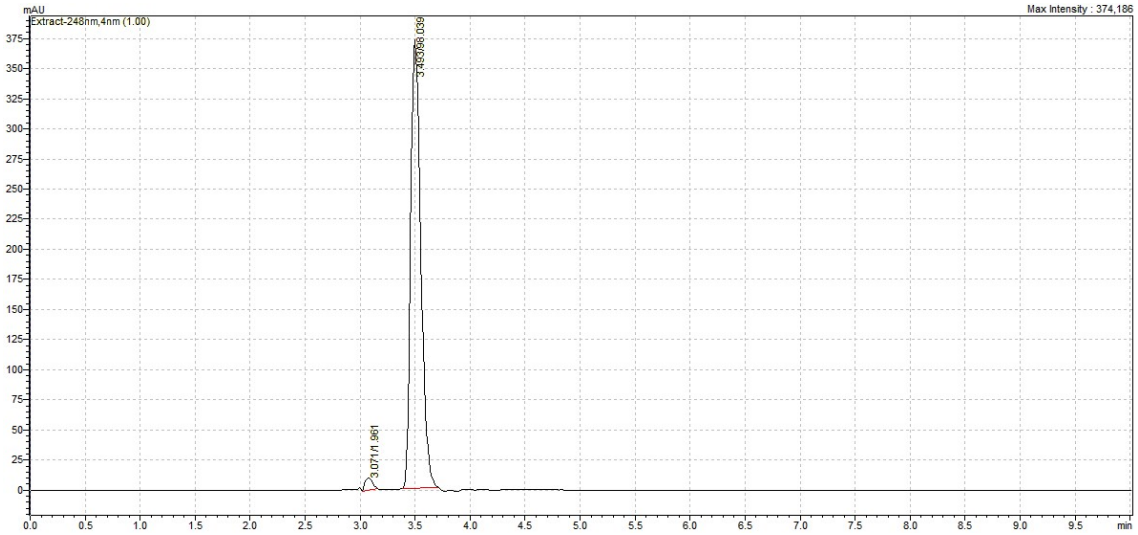


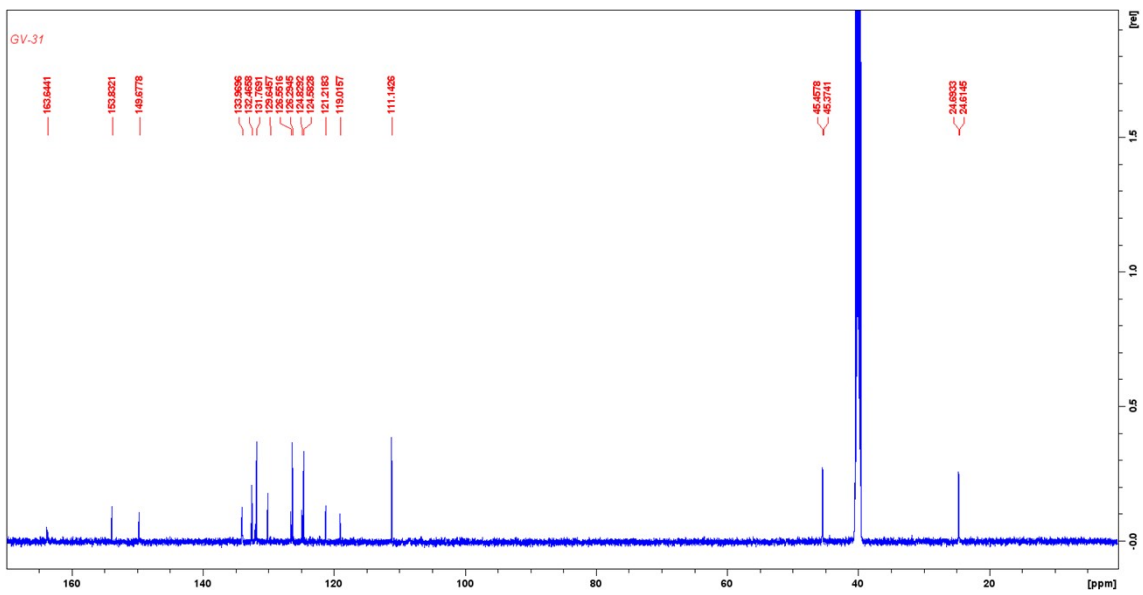
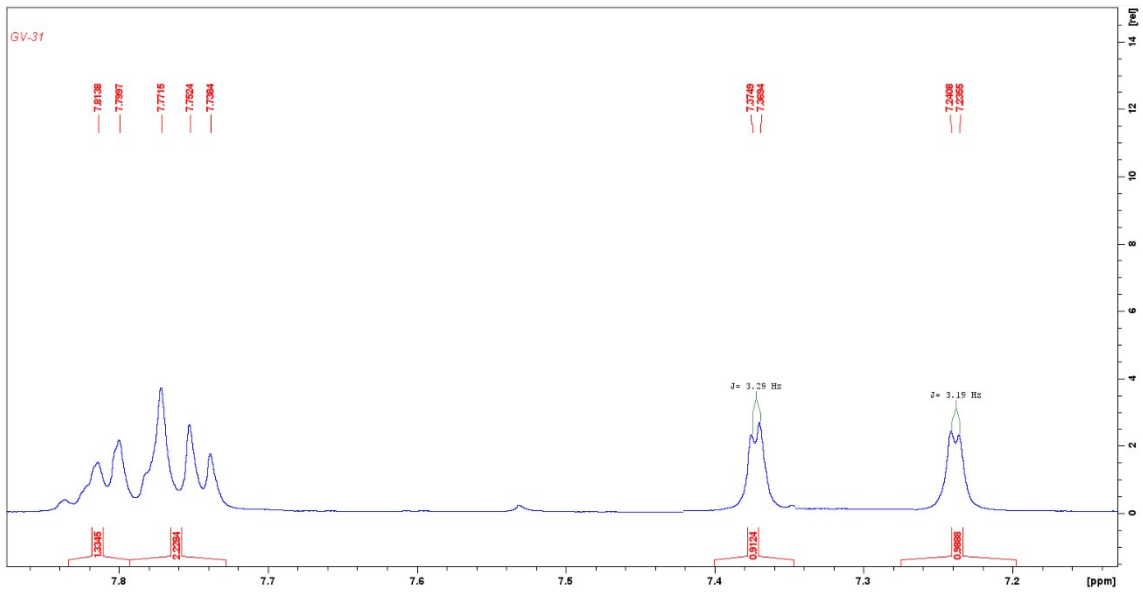
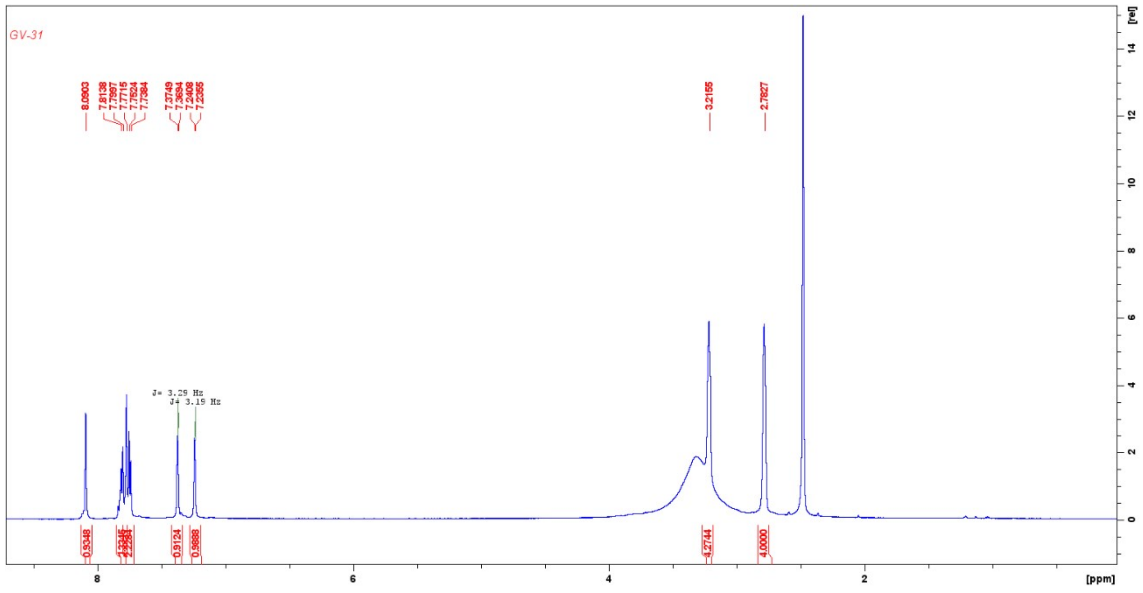
Line#:1 R.Time:32.908(Scan#:3350) MassPeaks:309
RawMode:Averaged 32.550-33.192(3307-3384) BasePeak:289.95(181529)
BG Mode:None Group 1 - Event 1 Scan



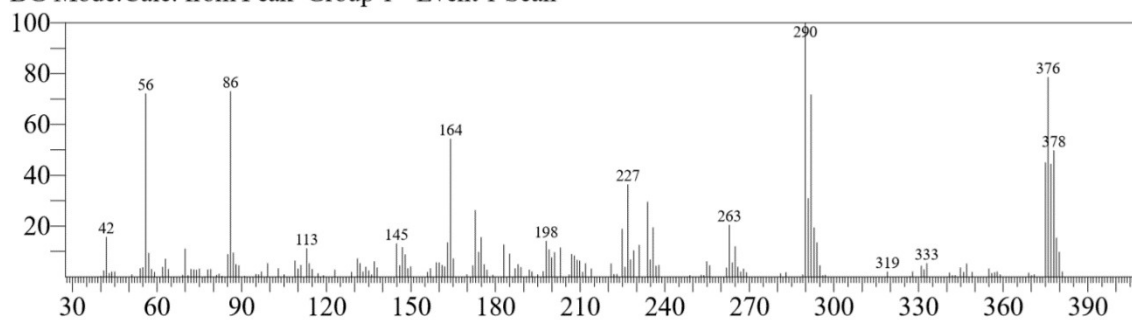


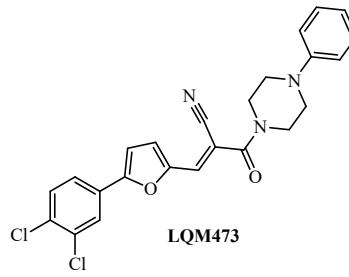
(E)-3-(5-(3,4-Dichlorophenyl)furan-2-yl)-2-(morpholine-4-carbonyl)acrylonitrile
 Chemical Formula: $C_{18}H_{14}Cl_2N_2O_3$
 Exact Mass: 377.22 g/mol



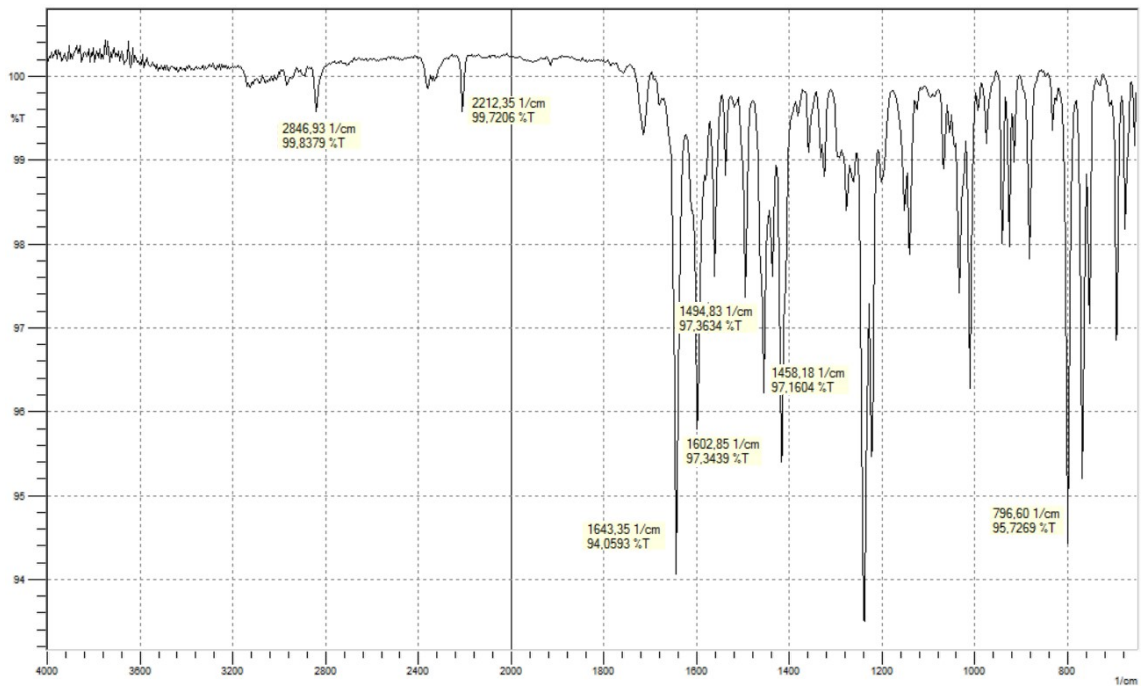
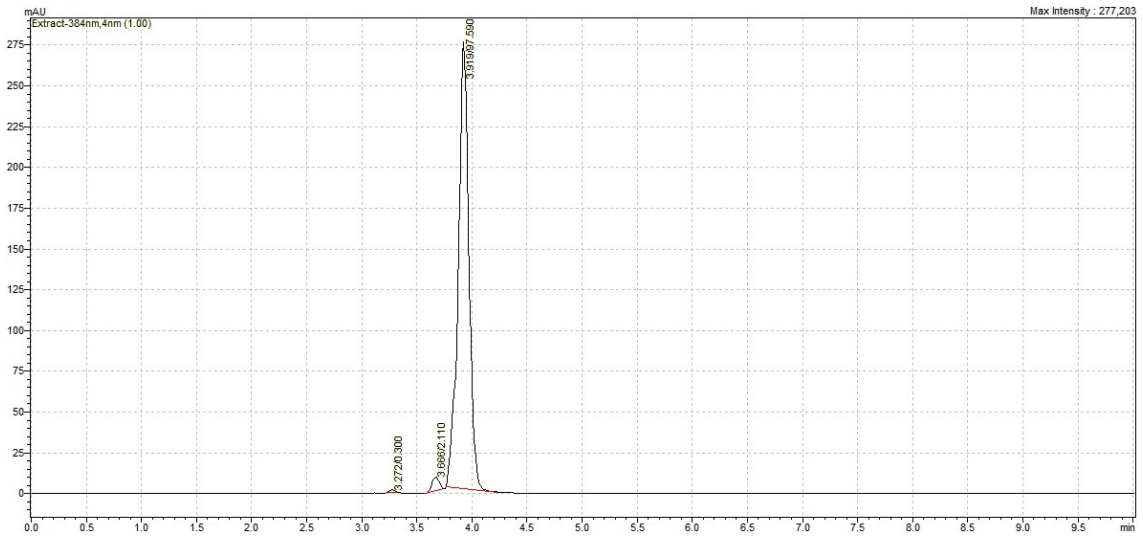


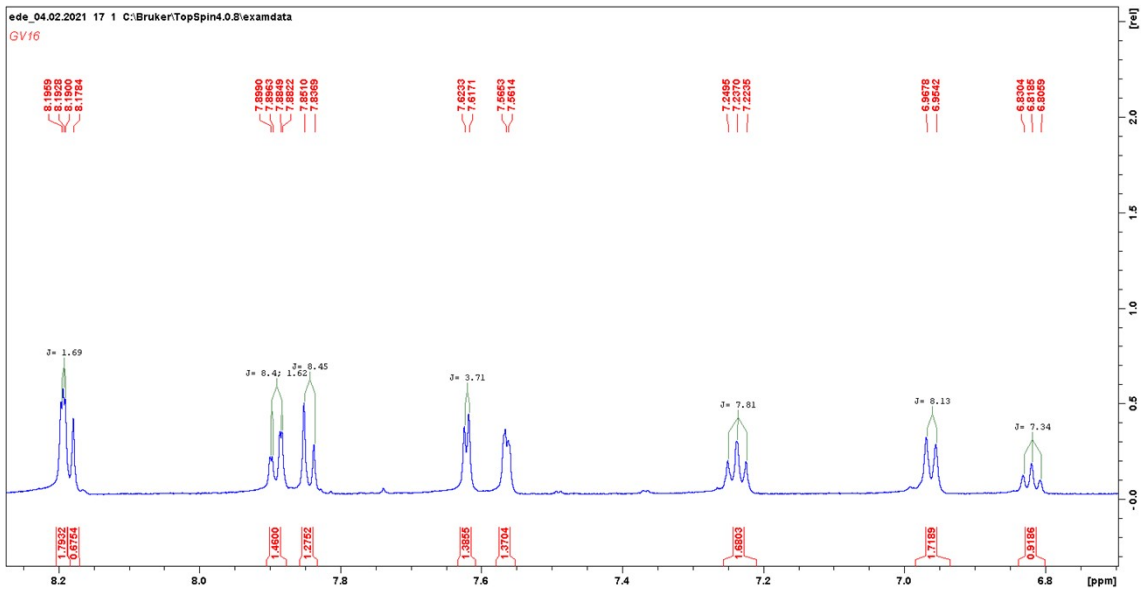
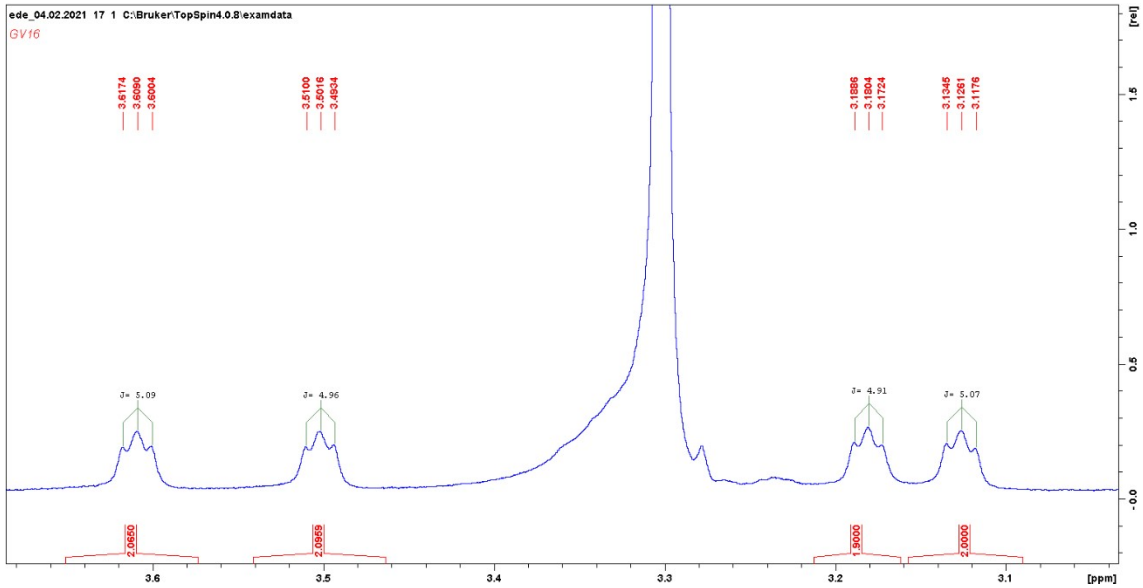
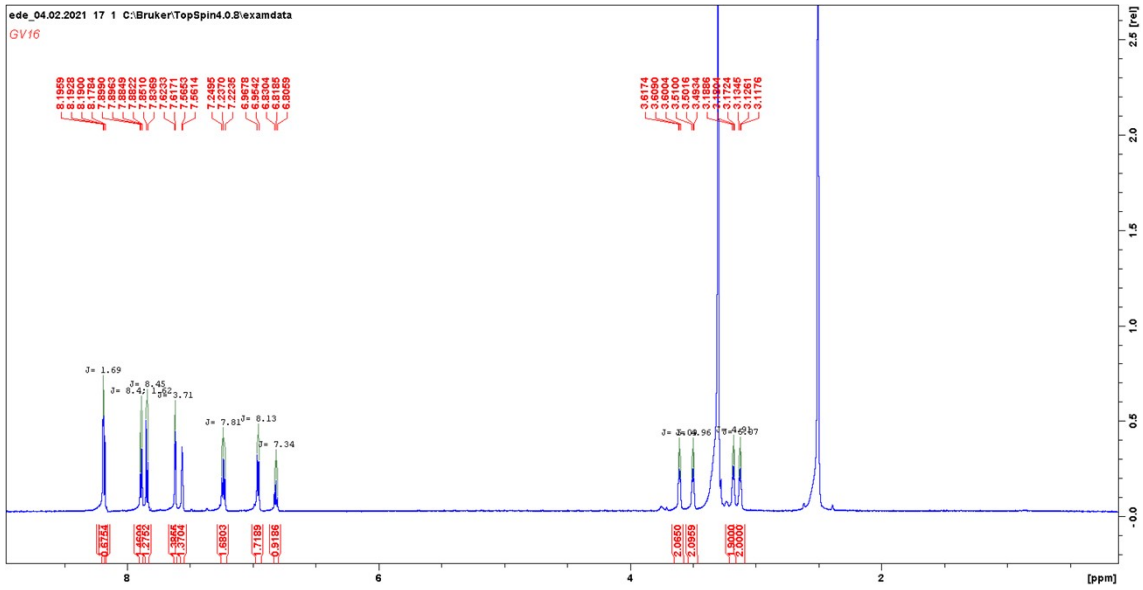
Line#:1 R.Time:27.600(Scan#:2713)
MassPeaks:178
RawMode:Averaged 27.592-27.608(2712-2714) BasePeak:290(36902)
BG Mode:Calc. from Peak Group 1 - Event 1 Scan

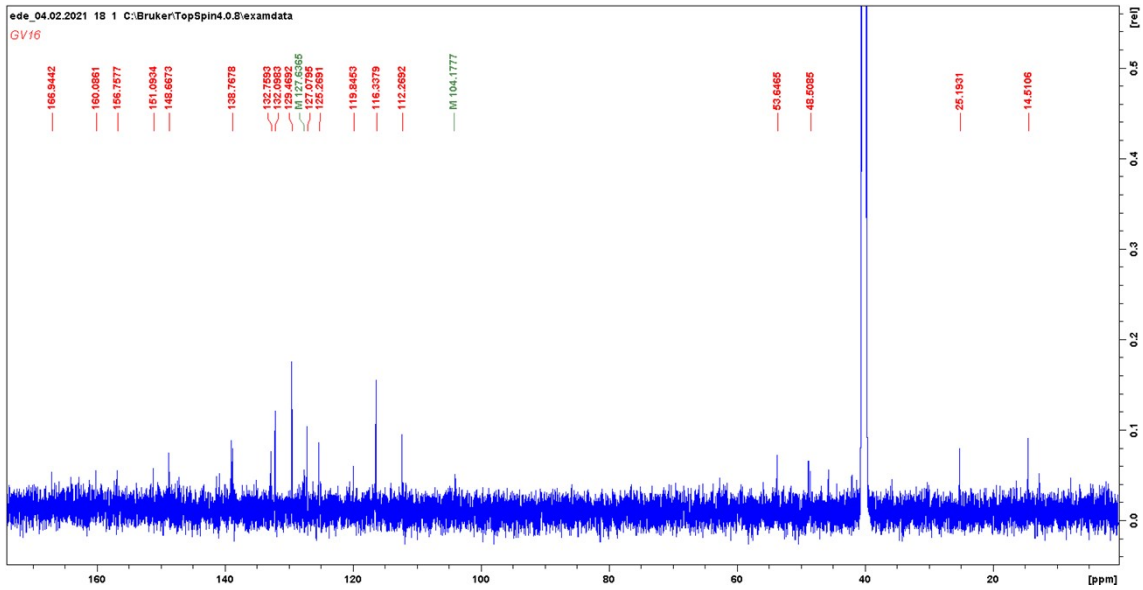




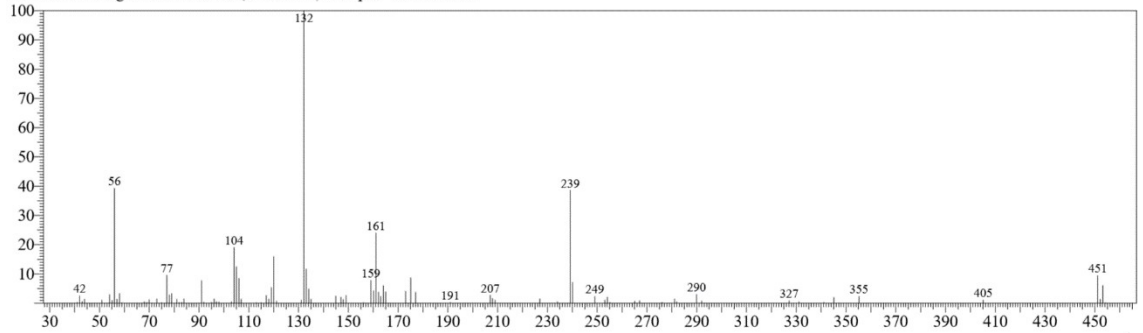
(E)-3-(5-(3,4-Dichlorophenyl)furan-2-yl)-2-(4-phenylpiperazine-1-carbonyl)acrylonitrile
 Chemical Formula: $C_{24}H_{19}Cl_2N_3O_2$
 Exact Mass: 452.34 g/mol

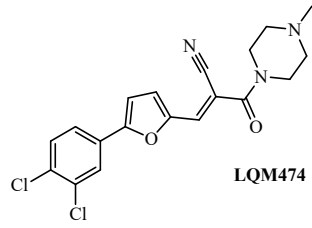




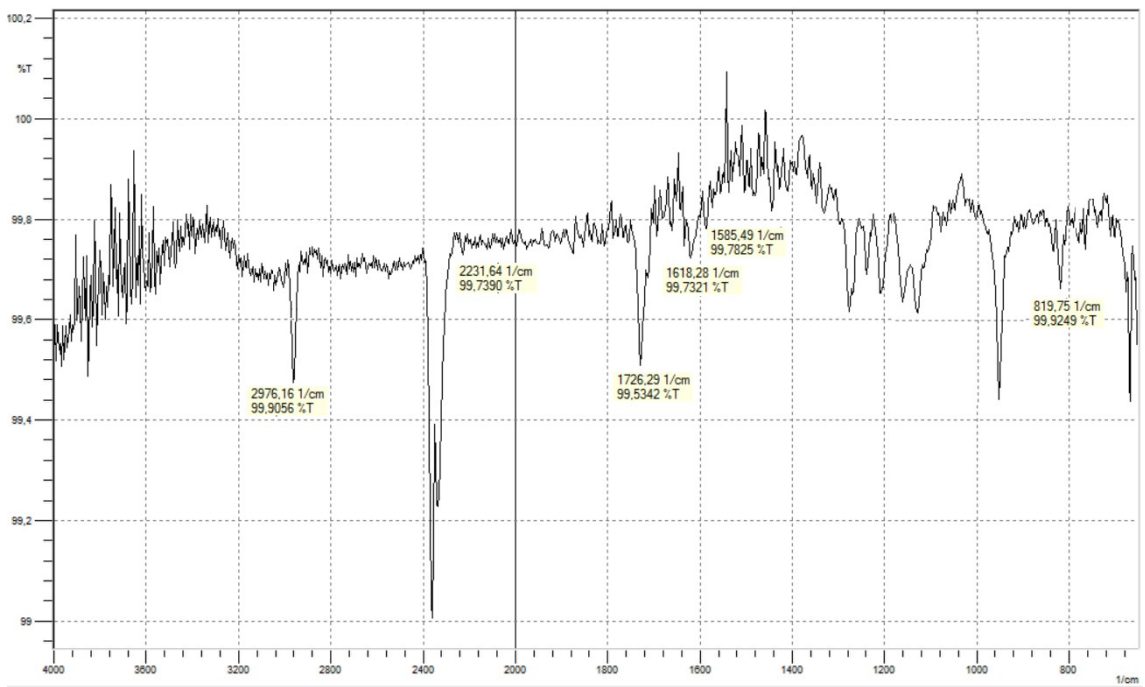
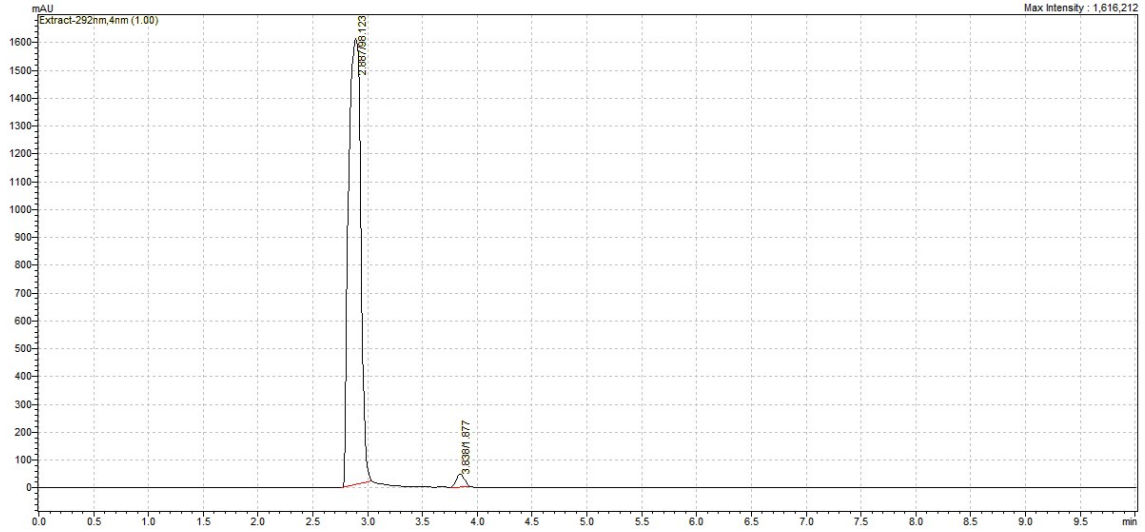


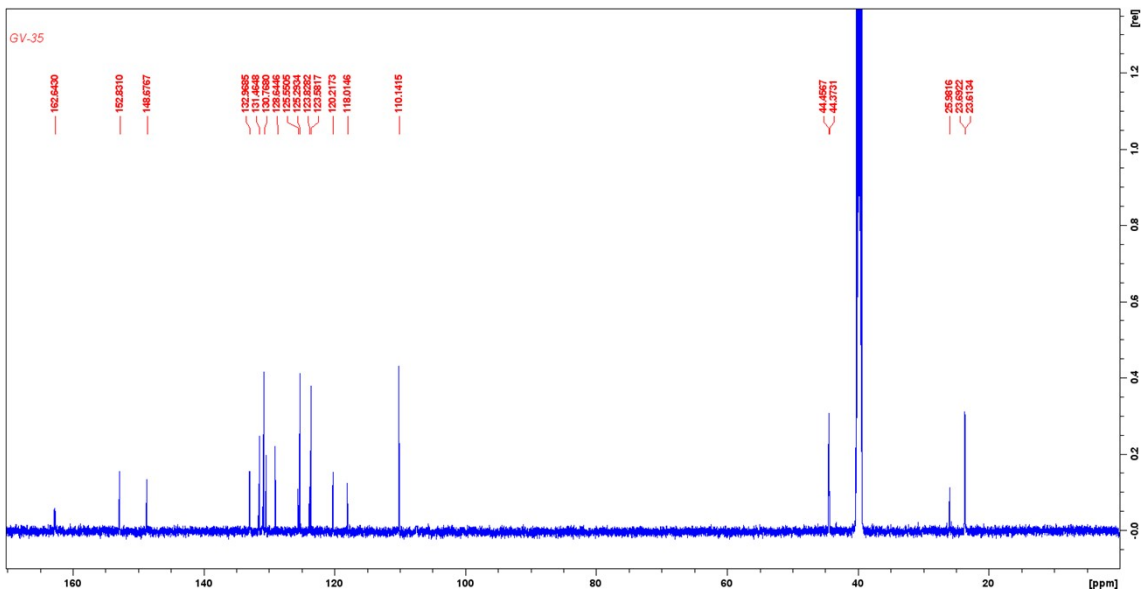
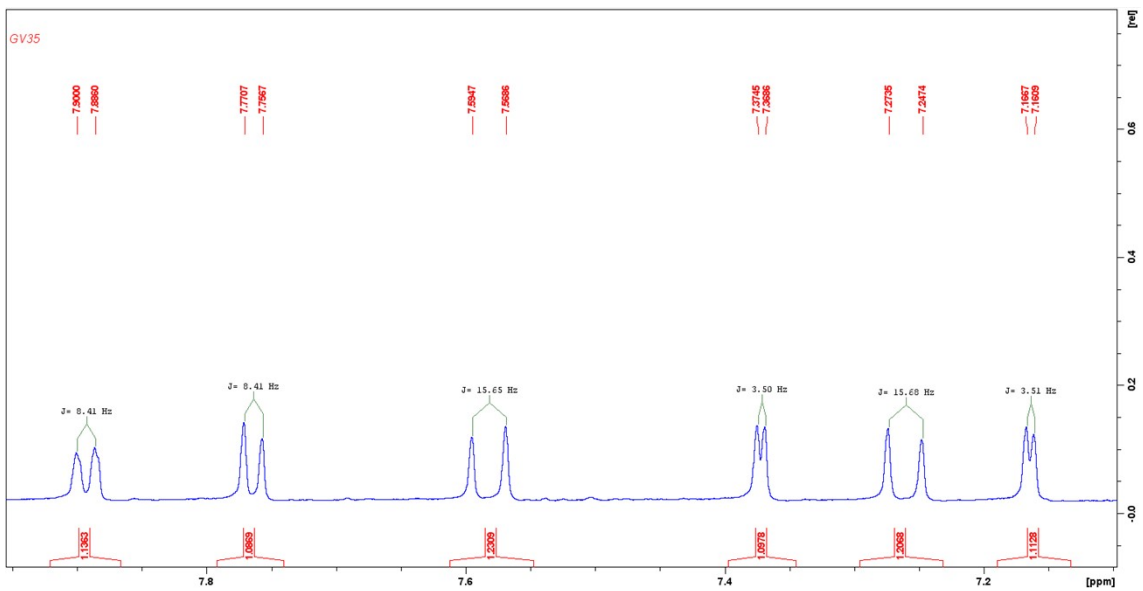
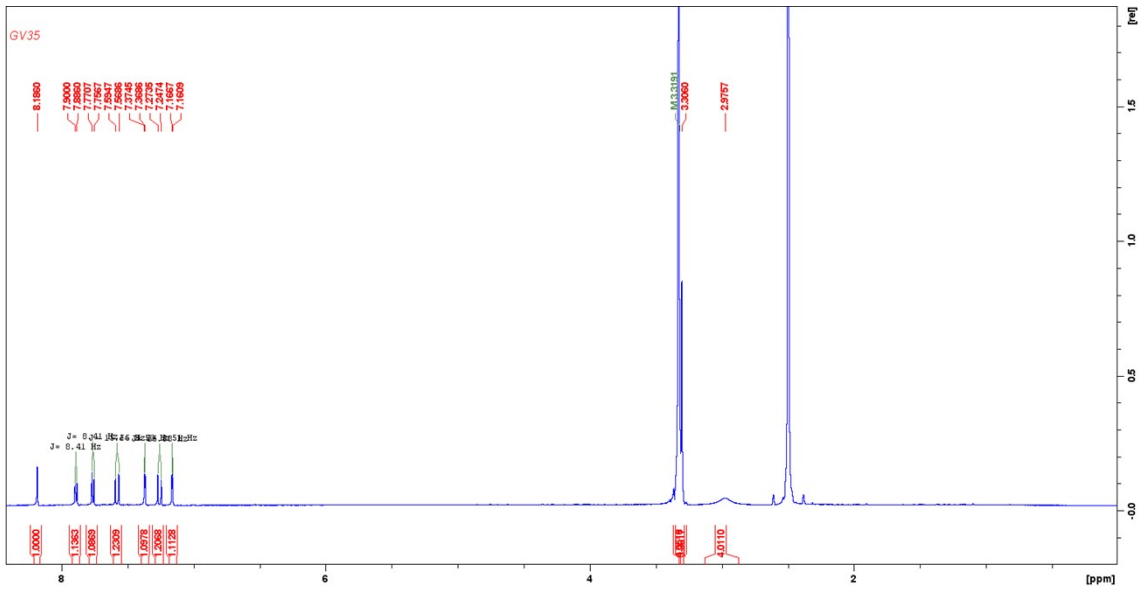
Line#:1 R.Time:23.875(Scan#:2266)
MassPeaks:97
RawMode:Averaged 23.650-24.025(2239-2284) BasePeak:132(29496)
BG Mode:Averaged 23.142-23.200(2178-2185) Group 1 - Event 1 Scan





(E)-3-(5-(3,4-dichlorophenyl)furan-2-yl)-2-(4-methylpiperazine-1-carbonyl)acrylonitrile
 Chemical Formula: C₁₉H₁₇Cl₂N₃O₂
 Exact Mass: 389.26 g/mol





Line#:1 R.Time:18.908(Scan#:1670)

MassPeaks:384

RawMode:Averaged 18.842-18.925(1662-1672) BasePeak:385(3345951)

BG Mode:Averaged 19.000-19.008(1681-1682) Group 1 - Event 1 Scan

