

# Evaluation of the Local Anesthetic Activity, Acute Toxicity and Structure-Toxicity Relationship in Series of Synthesized 1-Aryltetrahydroisoquinoline Alkaloid Derivatives in Vivo and in Silico

Azizbek A. Azamatov <sup>1</sup>, Sherzod N. Zhurakulov <sup>1,2</sup>, Valentina I. Vinogradova <sup>1</sup>,  
Firuza Tursunkhodzhaeva <sup>1</sup>, Roaa M. Khinkar <sup>3</sup>, Rania T. Malatani <sup>3</sup>, Mohammed M. Aldurdunji <sup>4</sup>,  
Antonio Tiezzi <sup>5</sup> and Nilufar Z. Mamadalieva <sup>1,\*</sup>

<sup>1</sup> Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent 100170, Mirzo Ulugbek str. 77, Uzbekistan

<sup>2</sup> National University of Uzbekistan named after Mirzo Ulugbek, Tashkent 100174, University str. 4, Uzbekistan

<sup>3</sup> Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21589, Saudi Arabia

<sup>4</sup> Department of Clinical Pharmacy, College of Pharmacy, Umm Al-Qura University, P.O. Box 13578 Makkah 21955, Saudi Arabia

<sup>5</sup> Department for the Innovation in Biological, Agro-food and Forestal Systems, Tuscia University, 01100 Viterbo, Italy

\* Correspondence: nmamadalieva@yahoo.com

## Supplementary data

**Figure S1.** <sup>1</sup>H NMR spectrum of compound **3a**.

**Figure S2.** <sup>13</sup>C NMR spectrum of compound **3a**.

**Figure S3.** IR spectrum of compound **3a**.

**Figure S4.** <sup>1</sup>H NMR spectrum of compound **3b**.

**Figure S5.** <sup>13</sup>C NMR spectrum of compound **3b**.

**Figure S6.** IR spectrum of compound **3b**.

**Figure S7.** <sup>1</sup>H NMR spectrum of compound **3c**.

**Figure S8.** <sup>13</sup>C NMR spectrum of compound **3c**.

**Figure S9.** <sup>1</sup>H NMR spectrum of compound **3d**.

**Figure S10.** <sup>13</sup>C NMR spectrum of compound **3d**.

**Figure S11.** HSQC spectrum of compound **3d**.

**Figure S12.** HMBC spectrum of compound **3d**.

**Figure S13.** COSY spectrum of compound **3d**.

**Figure S14.** IR spectrum of compound **3d**.

**Figure S15.** +ESI-mass- spectrum *m/z* 330 (M+H)<sup>+</sup> of compound **3d**.

**Figure S16.** +ESI-mass- spectrum of compound **3d**.

**Figure S17.** <sup>1</sup>H NMR spectrum of compound **3e**.

**Figure S18.** <sup>13</sup>C NMR spectrum of compound **3e**.

**Figure S19.** <sup>1</sup>H NMR spectrum of compound **3f**.

**Figure S20.** <sup>13</sup>C NMR spectrum of compound **3f**.

**Figure S21.** IR spectrum of compound **3f**.

**Figure S22.** <sup>1</sup>H NMR spectrum of compound **3g**.

**Figure S23.** <sup>13</sup>C NMR spectrum of compound **3g**.

**Figure S24.** IR spectrum of compound **3g**.

**Figure S25.** <sup>1</sup>H NMR spectrum of compound **3h**.

**Figure S26.** <sup>13</sup>C NMR spectrum of compound **3h**.

**Figure S27.** +ESI-mass- spectrum *m/z* 394 (M+H)<sup>+</sup> from the isotope bromine 79, of compound **3h**.

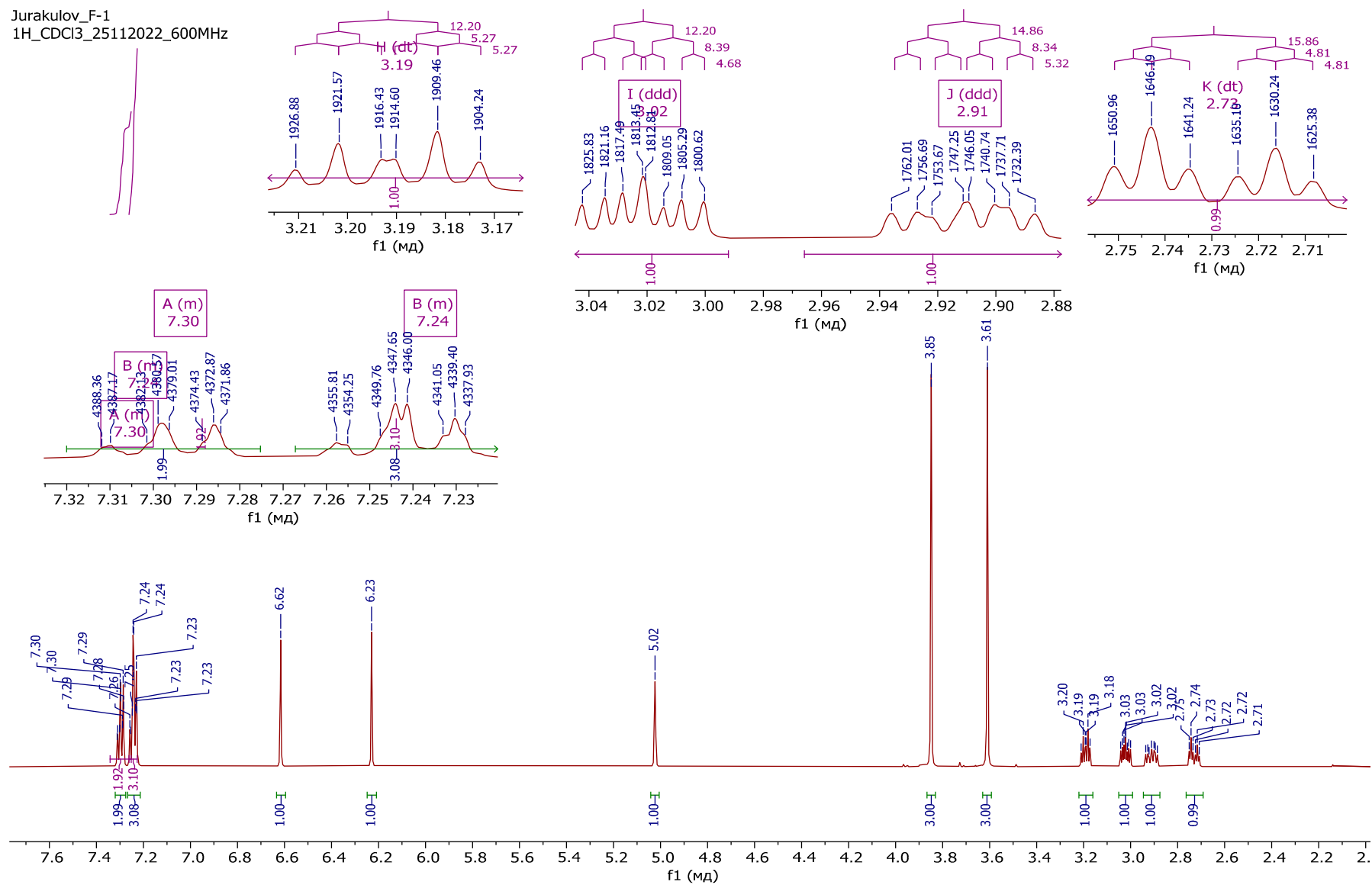
**Figure S28.** +ESI-mass- spectrum *m/z* 396 (M+H)<sup>+</sup> from the isotope bromine 81, of compound **3h**.

**Figure S29.** <sup>1</sup>H NMR spectrum of compound **3i**.

**Figure S30.** <sup>13</sup>C NMR spectrum of compound **3i**.

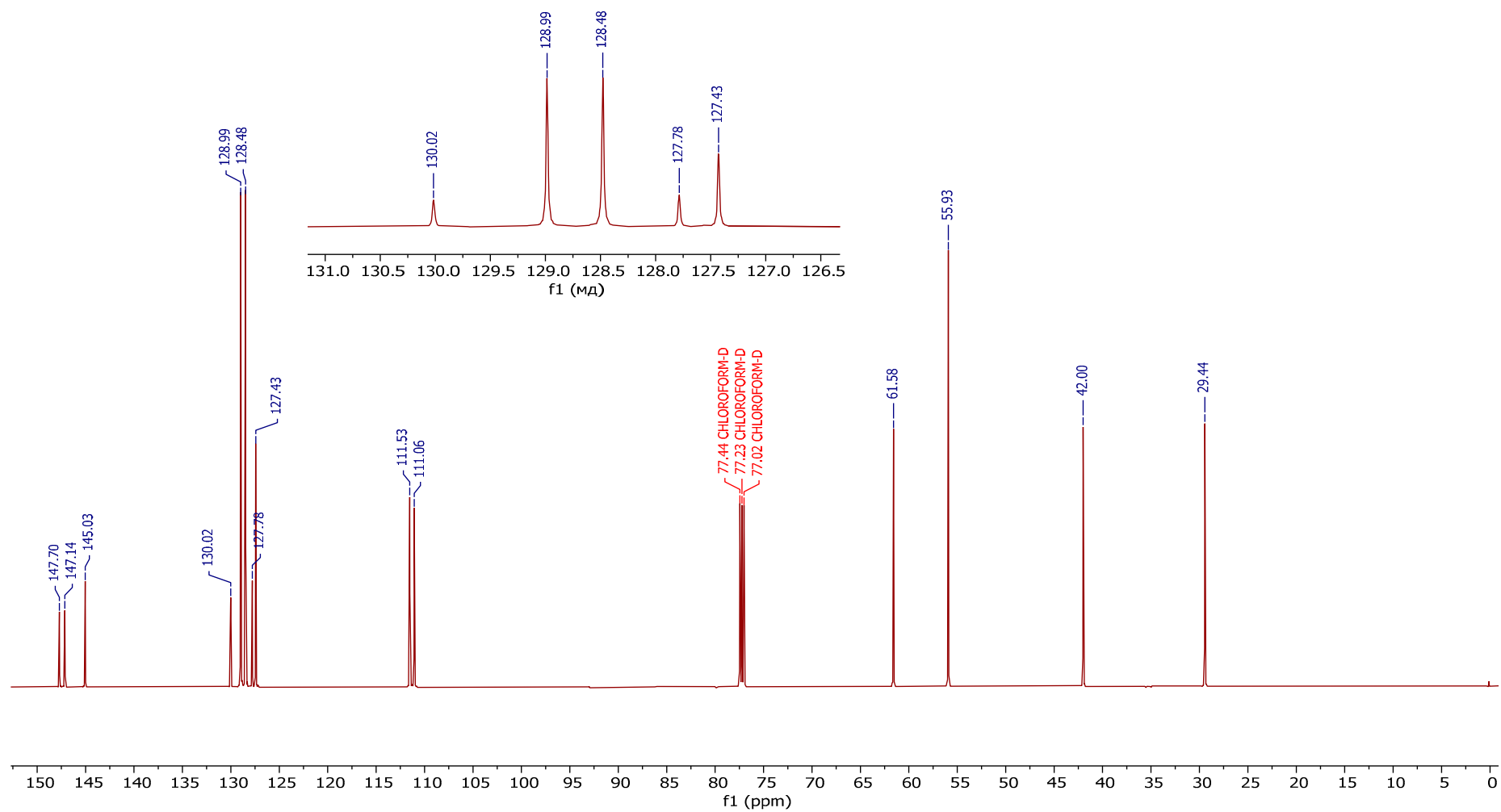
**Figure S31.** Diff-NOE spectrum of compound **3i**.  
**Figure S32.** COSY spectrum of compound **3i**.  
**Figure S33.** Dept spectrum of compound **3i**.  
**Figure S34.** Diff-decpl spectrum of compound **3i**.  
**Figure S35.** IR spectrum of compound **3i**.  
**Figure S36.**  $^1\text{H}$  NMR spectrum of compound **3j**.  
**Figure S37.**  $^{13}\text{C}$  NMR spectrum of compound **3j**.  
**Figure S38.** IR spectrum of compound **3j**.  
**Figure S39.**  $^1\text{H}$  NMR spectrum of compound **3k**.  
**Figure S40.**  $^1\text{H}$  NMR spectrum of compound **3l**.  
**Figure S41.**  $^{13}\text{C}$  NMR spectrum of compound **3l**.  
**Figure S41.**  $^{13}\text{C}$  NMR spectrum of compound **3l**.  
**Figure S43.** IR spectrum of compound **3m**.  
**Figure S44.**  $^1\text{H}$  NMR spectrum of compound **3n**.  
**Figure S45.** IR spectrum of compound **3n**.  
**Figure S46.**  $^1\text{H}$  NMR spectrum of compound **3o**.  
**Figure S47.**  $^{13}\text{C}$  NMR spectrum of compound **3o**.  
**Figure S48.**  $^1\text{H}$  NMR spectrum of compound **3p**.  
**Figure S49.** IR spectrum of compound **3n**.  
**Figure S50.**  $^1\text{H}$  NMR spectrum of compound **3q**.  
**Figure S51.** IR spectrum of compound **3q**.  
**Figure S52.**  $^1\text{H}$  NMR spectrum of compound **3r**.  
**Figure S53.**  $^1\text{H}$  NMR spectrum of compound **4a**.  
**Figure S54.**  $^{13}\text{C}$  NMR spectrum of compound **4a**.  
**Figure S55.** IR spectrum of compound **4a**.  
**Figure S56.**  $^1\text{H}$  NMR spectrum of compound **4b**.  
**Figure S57.**  $^{13}\text{C}$  NMR spectrum of compound **4b**.

Jurakulov\_F-1  
1H\_CDCI3\_25112022\_600MHz



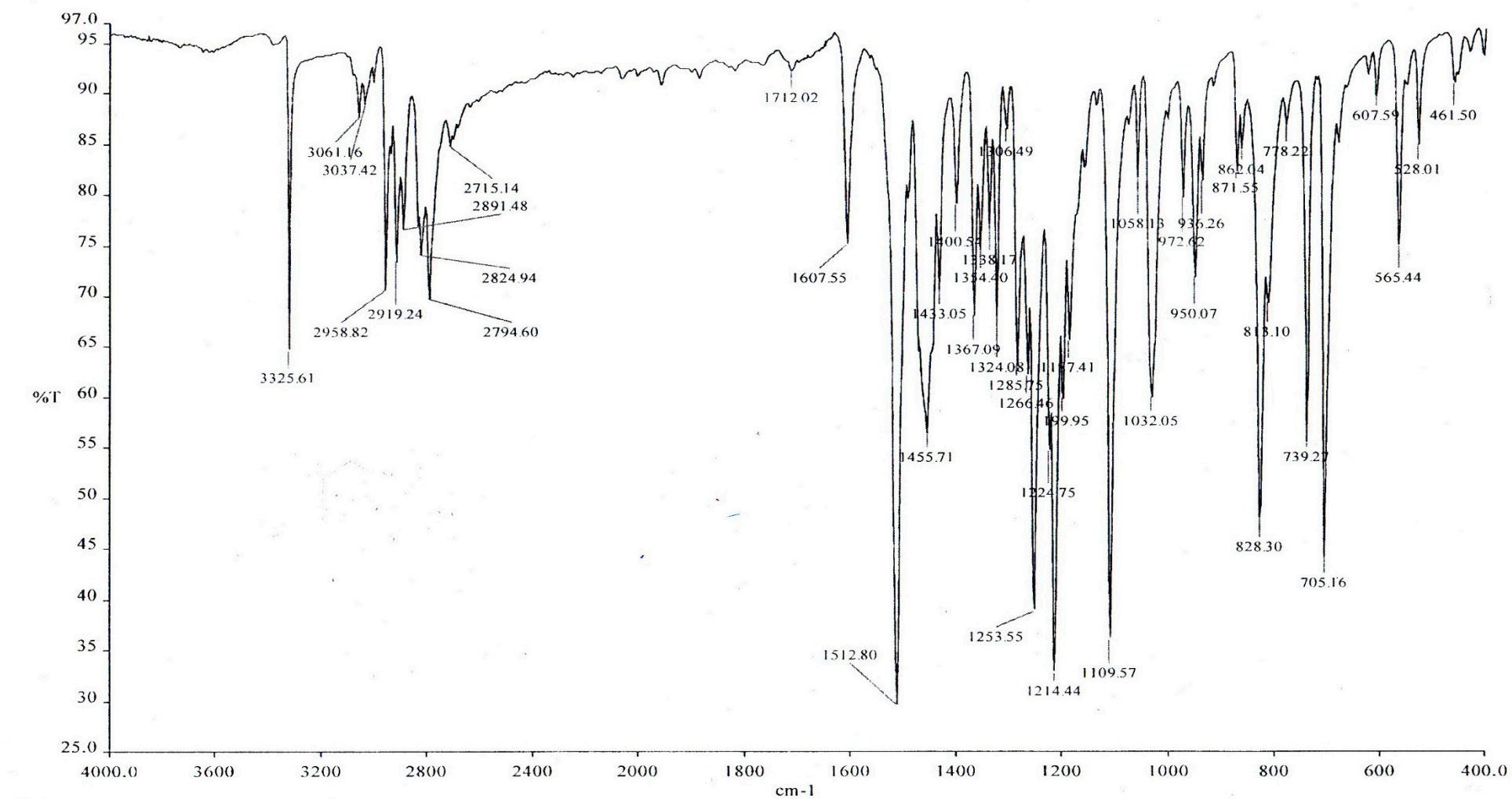
**Figure S1.**  $^1\text{H}$  NMR spectrum of compound **3a**.

Jurakulov\_F-1  
13C\_CDCl3\_25112022\_600MHz



**Figure S2.**  $^{13}\text{C}$  NMR spectrum of compound **3a**.





F-1

**Figure S3.** IR spectrum of compound **3a**.

Jurakulov\_F-2\_1H  
NMR, Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-2

Solvent: CDCl<sub>3</sub>  
Reference: HMDSO (0 ppm)  
Expernt: s2pul 1H  
Temp-re: 22 C  
Date: 04.01.20

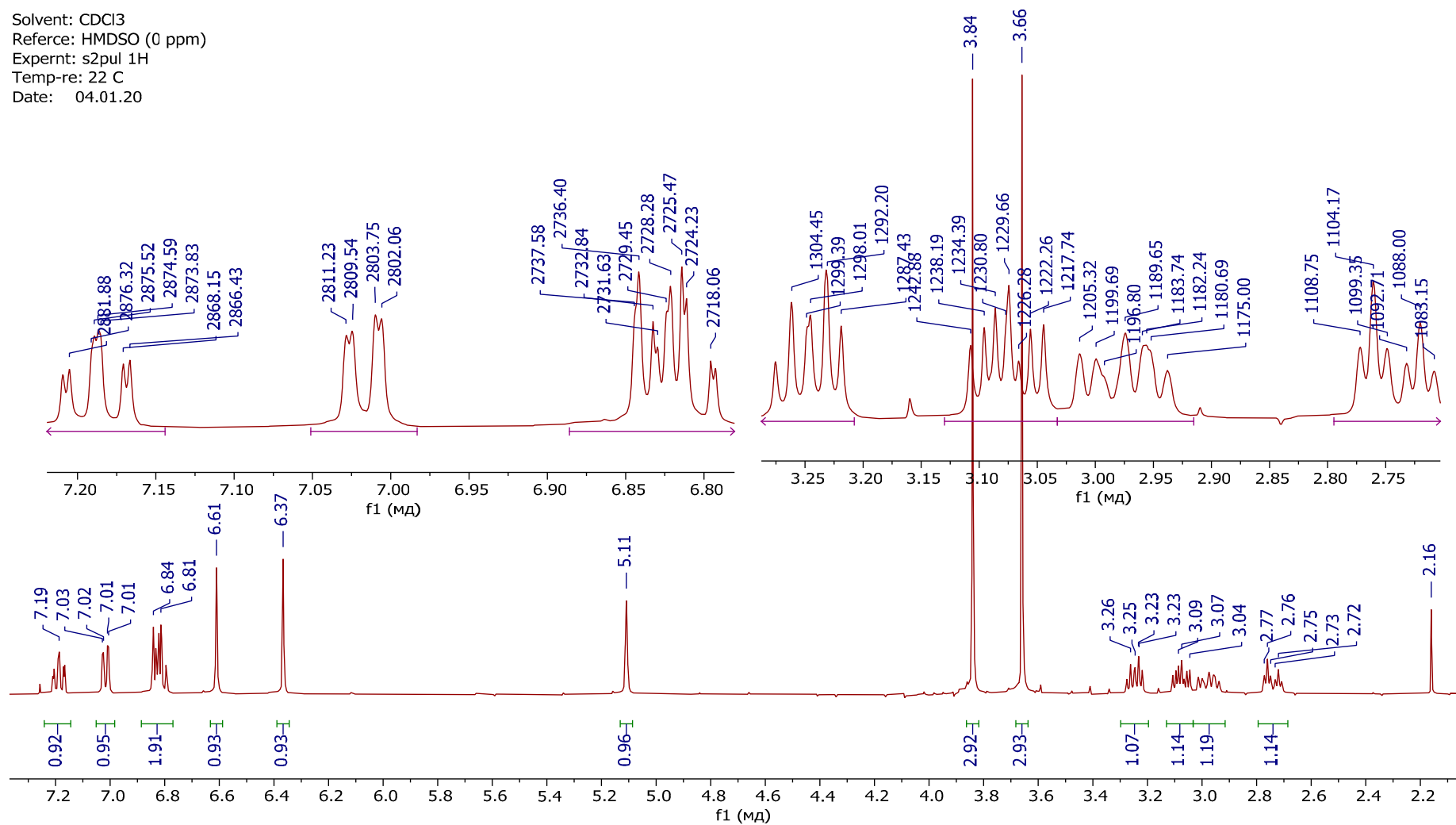


Figure S4. <sup>1</sup>H NMR spectrum of compound 3b.

Jurakulov\_F-2\_13C  
NMR Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-2

Solvent: CDCl<sub>3</sub>  
Refernt: CDCl<sub>3</sub> (77.16 ppm)  
Expermt: 13C  
Date: 04.01.20

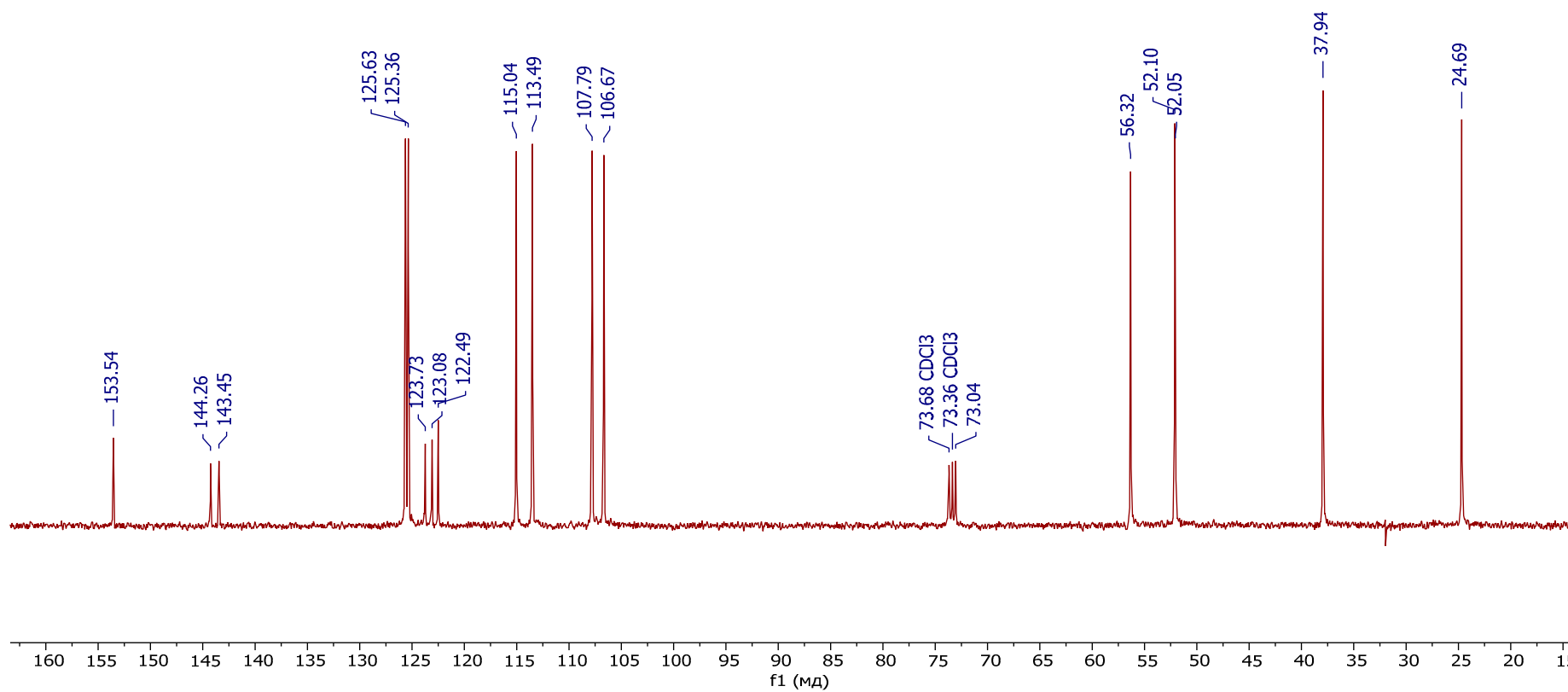


Figure S5. <sup>13</sup>C NMR spectrum of compound **3b**.

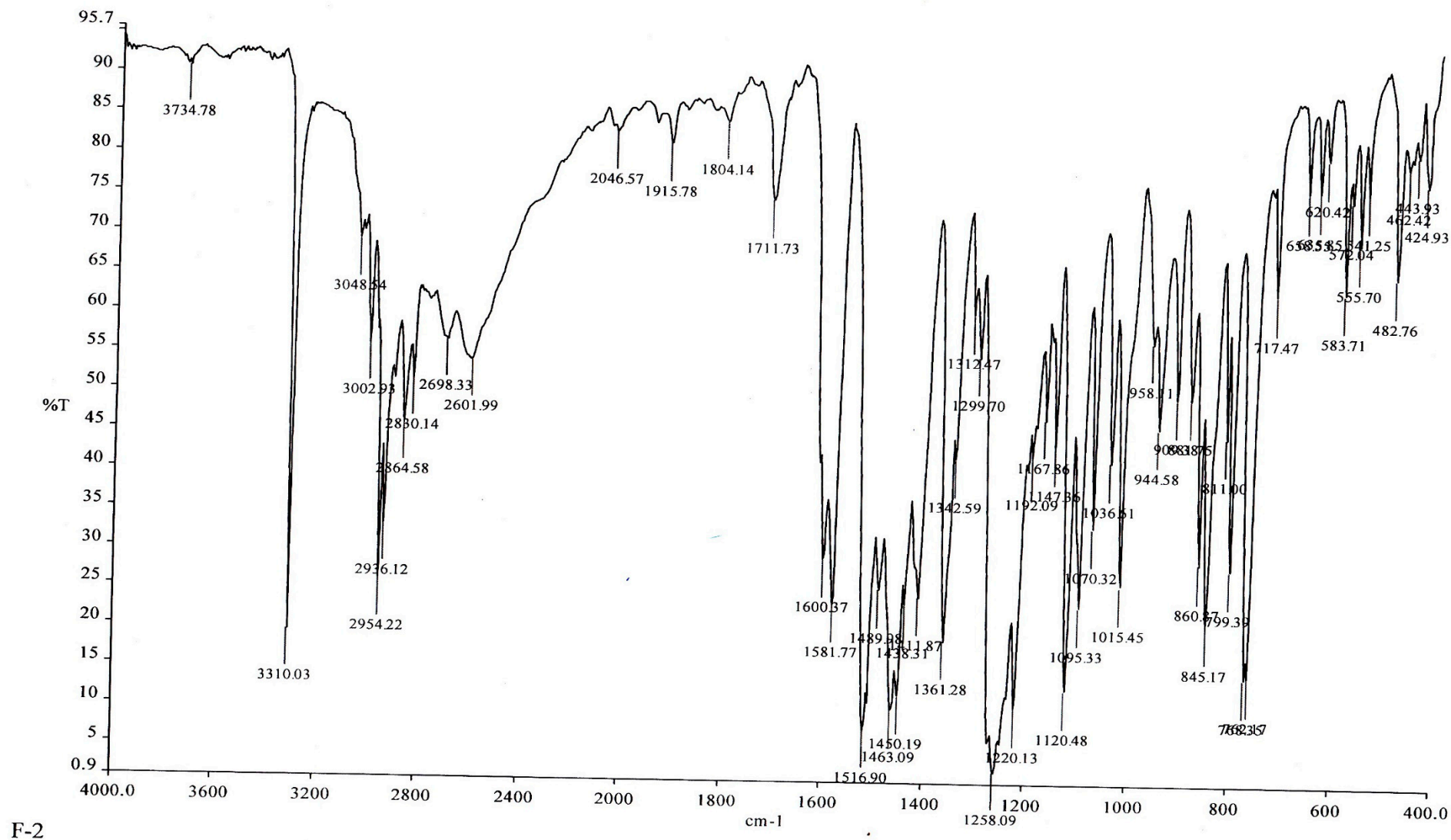
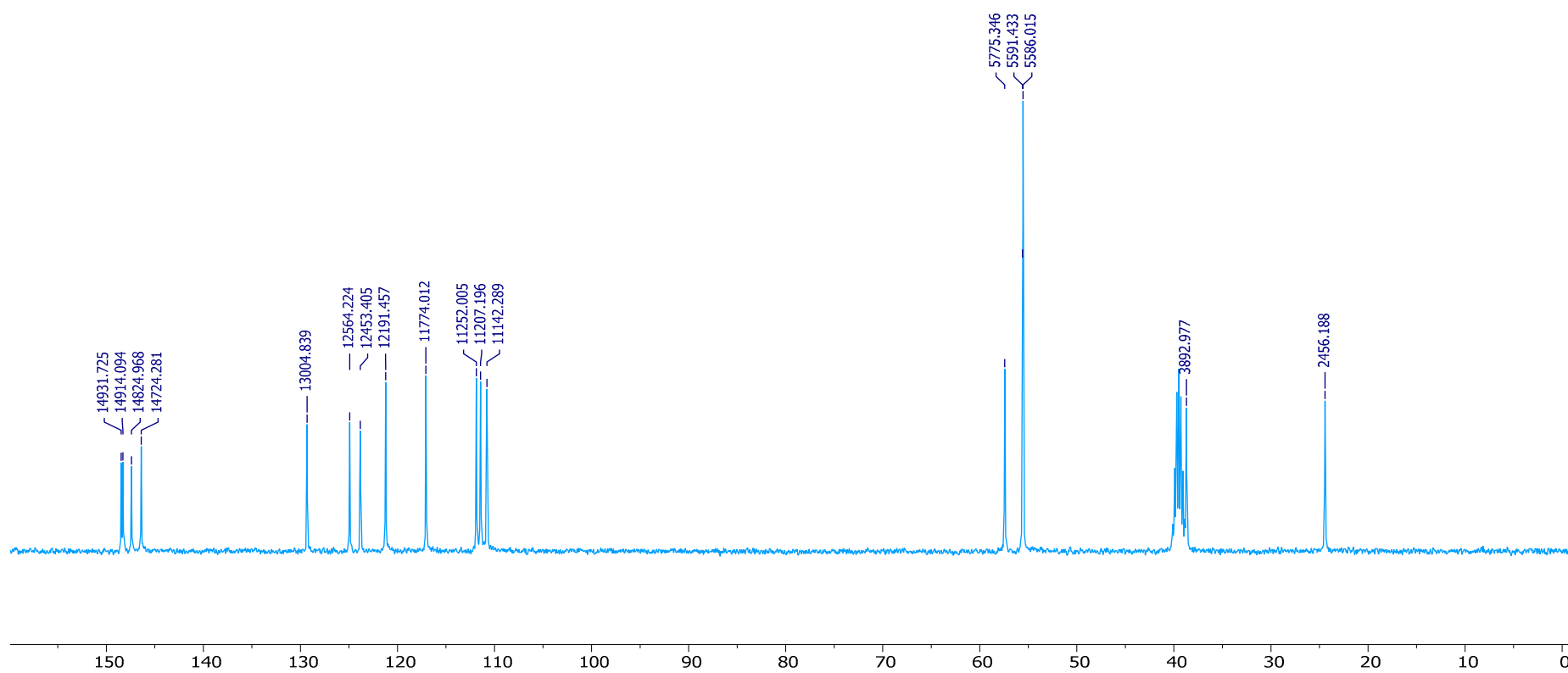


Figure S6. IR spectrum of compound **3b**.



F-5 DMSO-d6 Juraqulov Sh.N. 400 plus (Varian)



**Figure S8.** <sup>13</sup>C NMR spectrum of compound **3c**.

Jurakulov\_F-7\_1H  
NMR, Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-7

Solvent: CDCl<sub>3</sub>  
Reference: TMS (0 ppm)  
Expernt: s2pul 1H  
Temp-re: 22 C  
Date: 27.11.19

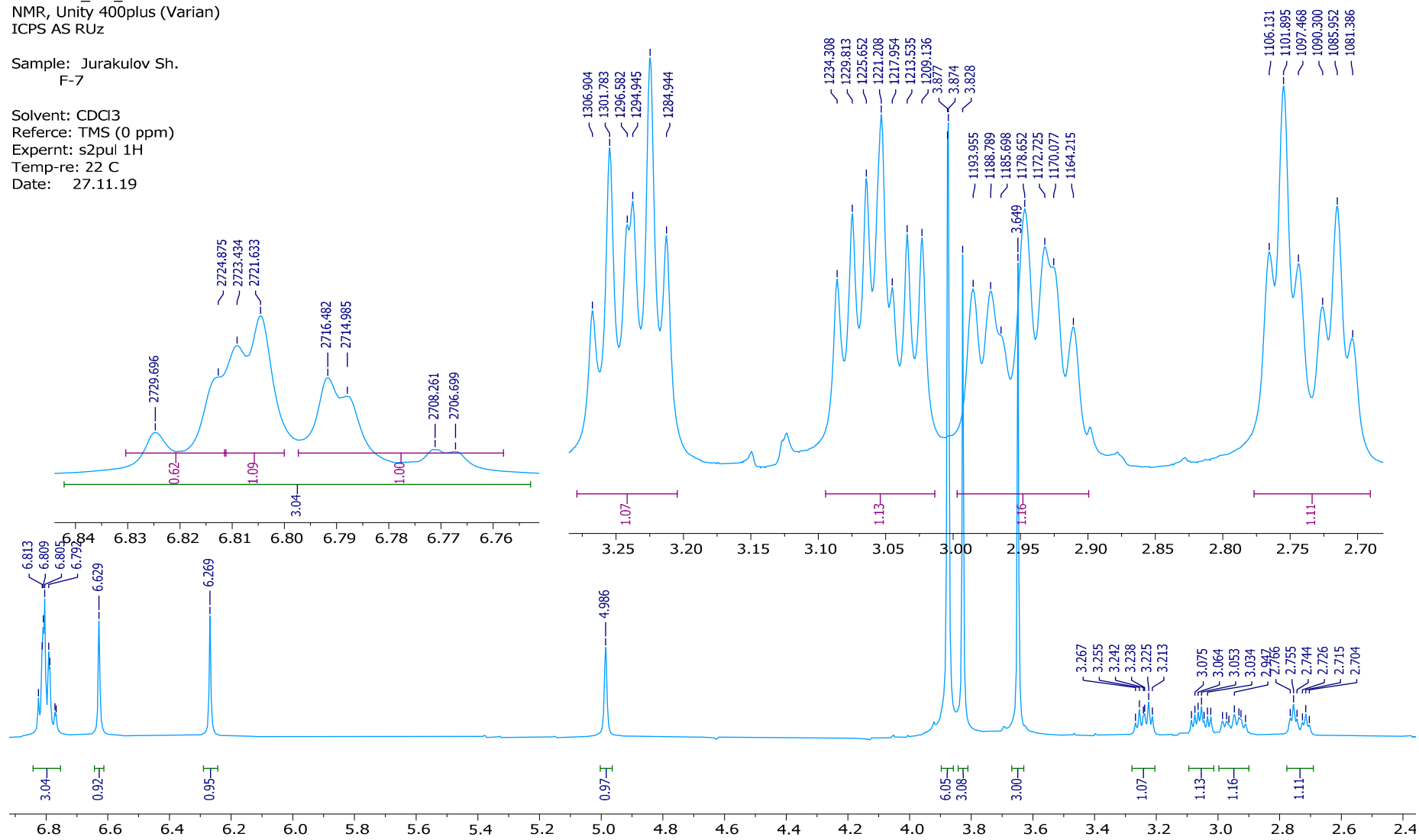
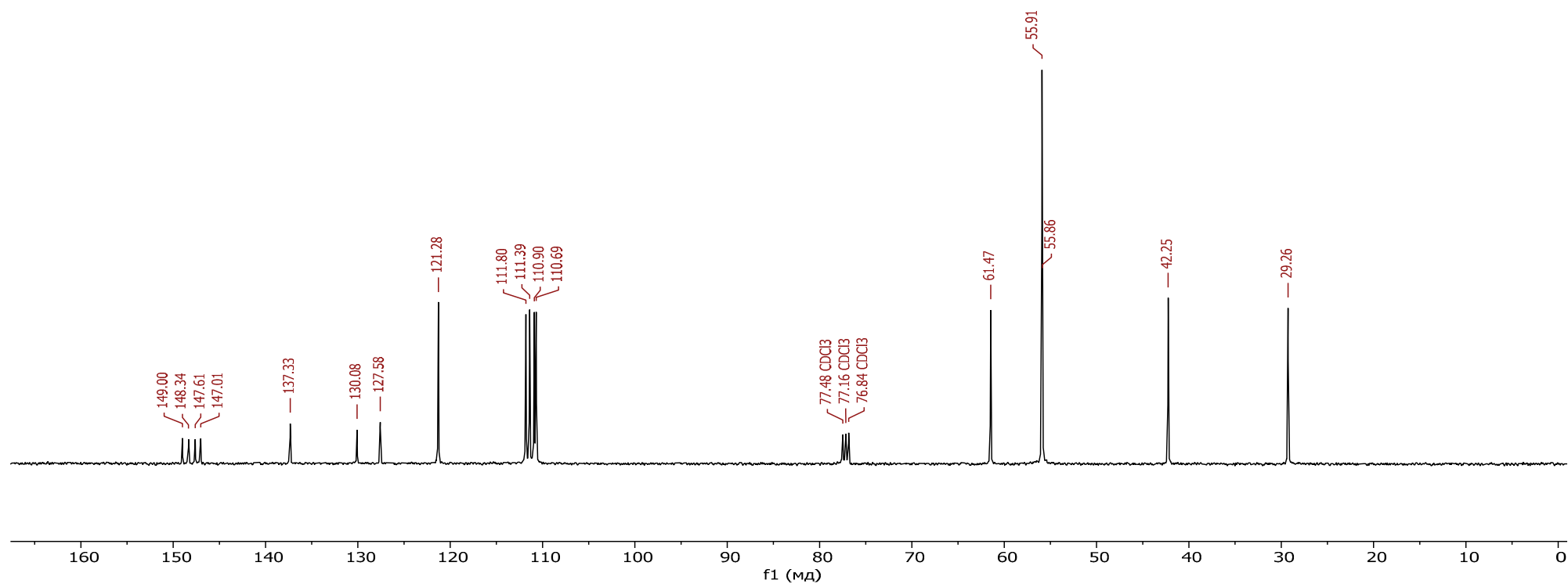


Figure S9. <sup>1</sup>H NMR spectrum of compound **3d**.

Jurakulov\_F-7\_13C  
NMR Unity 400plus (Varian)  
ICPS AS RUz

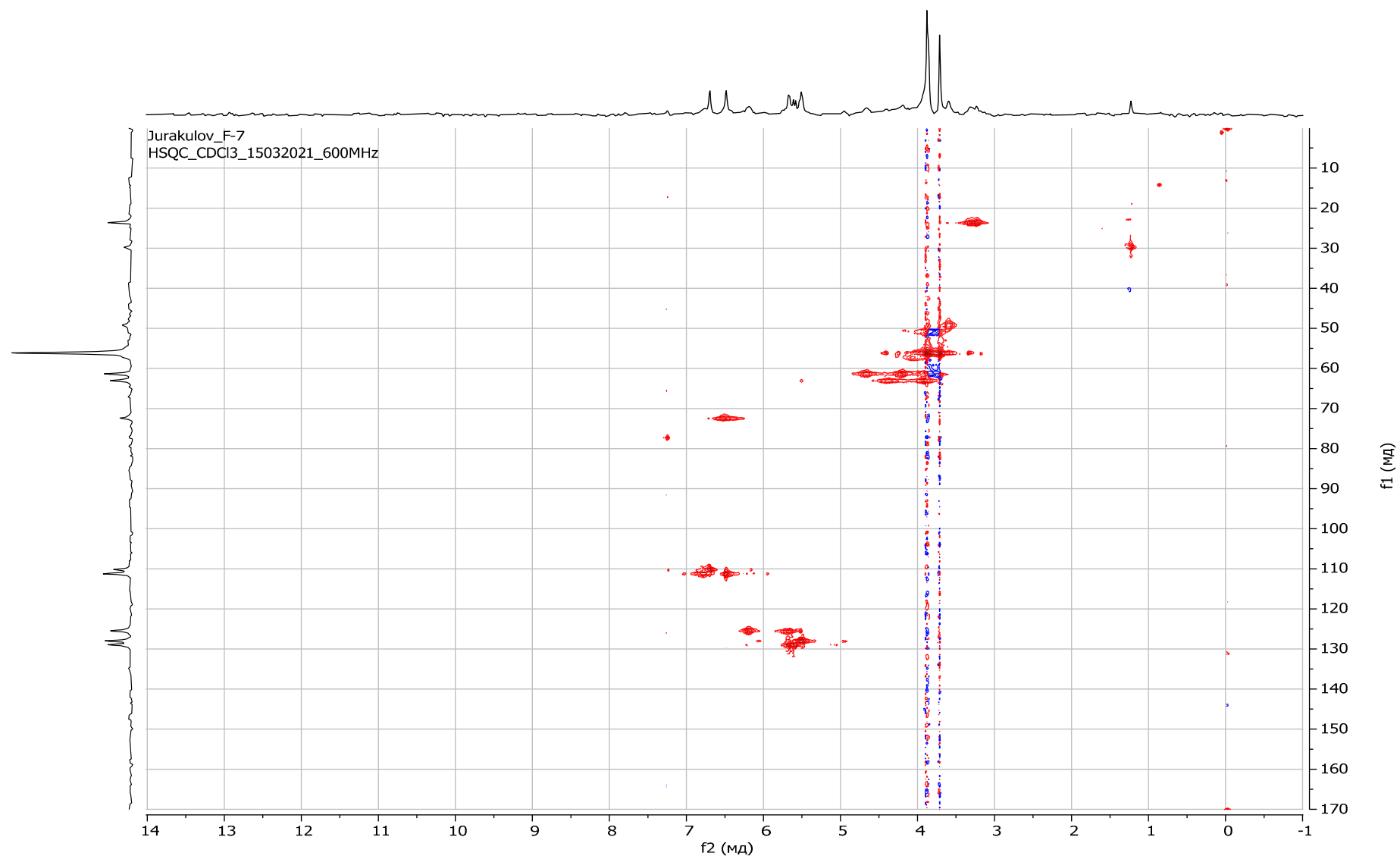
Sample: Jurakulov Sh.  
F-7

Solvent: CDCl<sub>3</sub>  
Refernt: CDCl<sub>3</sub> (77.16 ppm)  
Expermt: s2pul 13C  
Date: 27.11.19

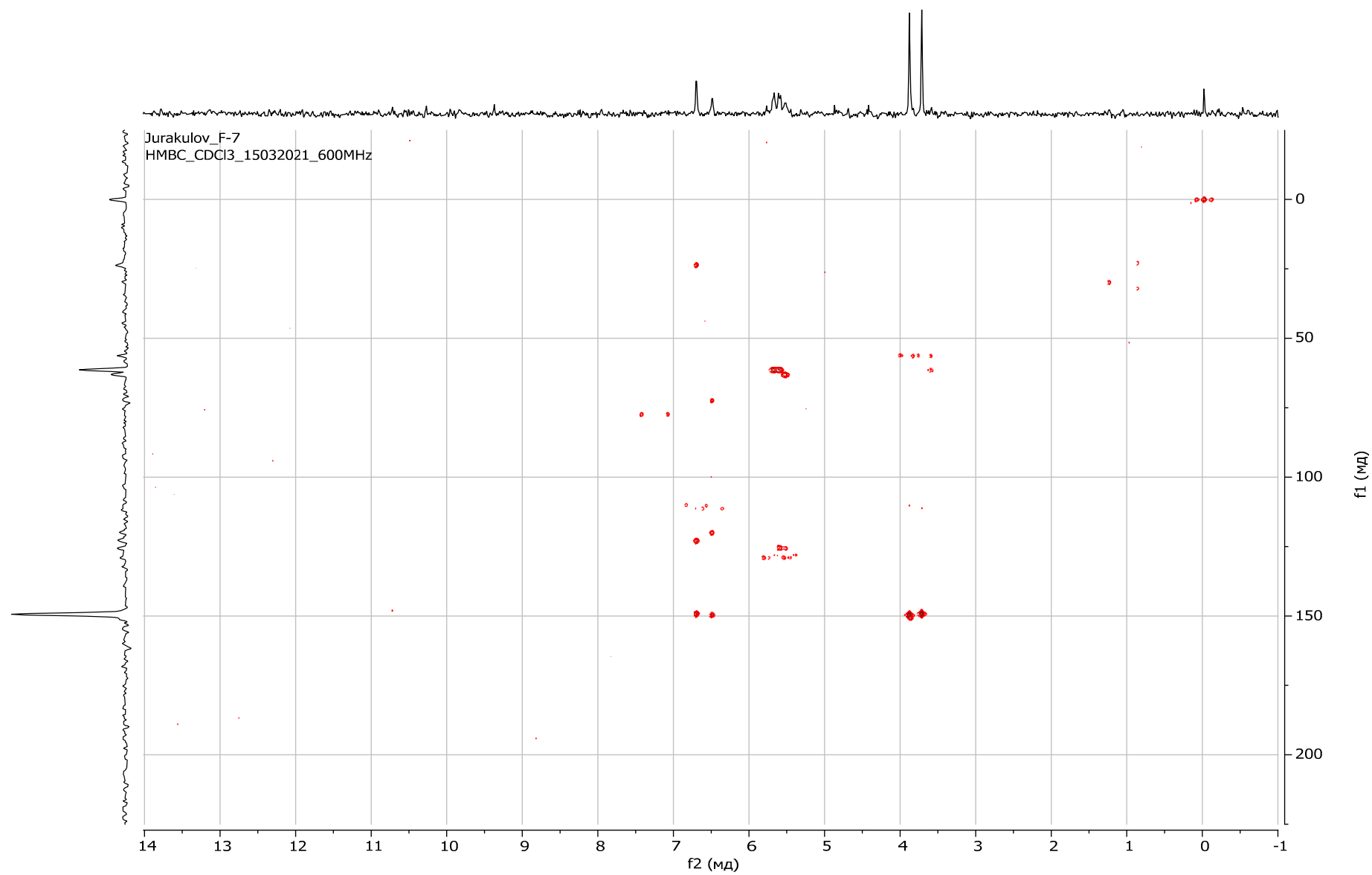


**Figure S10.** <sup>13</sup>C NMR spectrum of compound 3d.

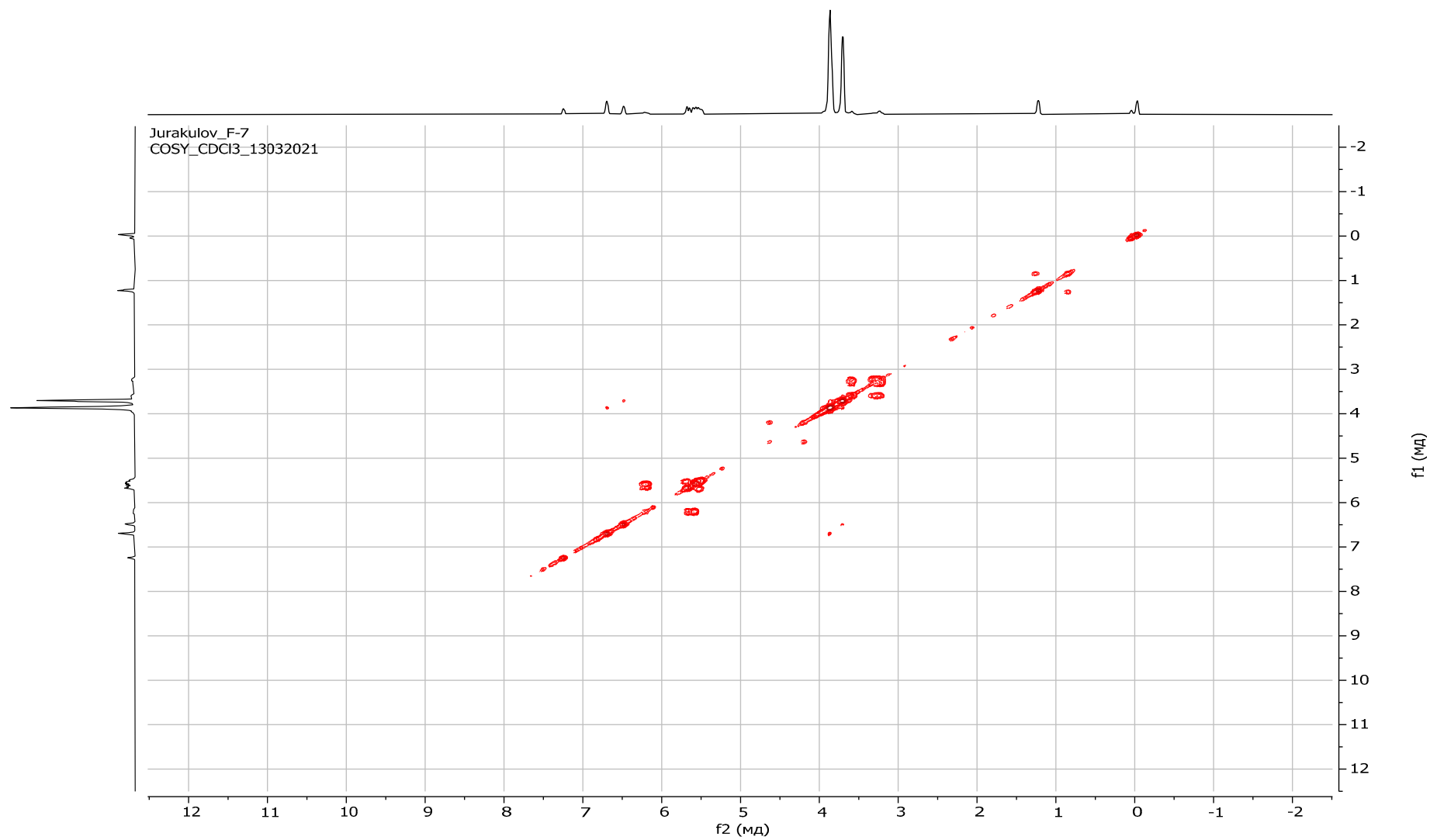




**Figure S11.** HSQC spectrum of compound **3d**.



**Figure S12.** HMBC spectrum of compound **3d**.



**Figure S13.** COSY spectrum of compound **3d**.

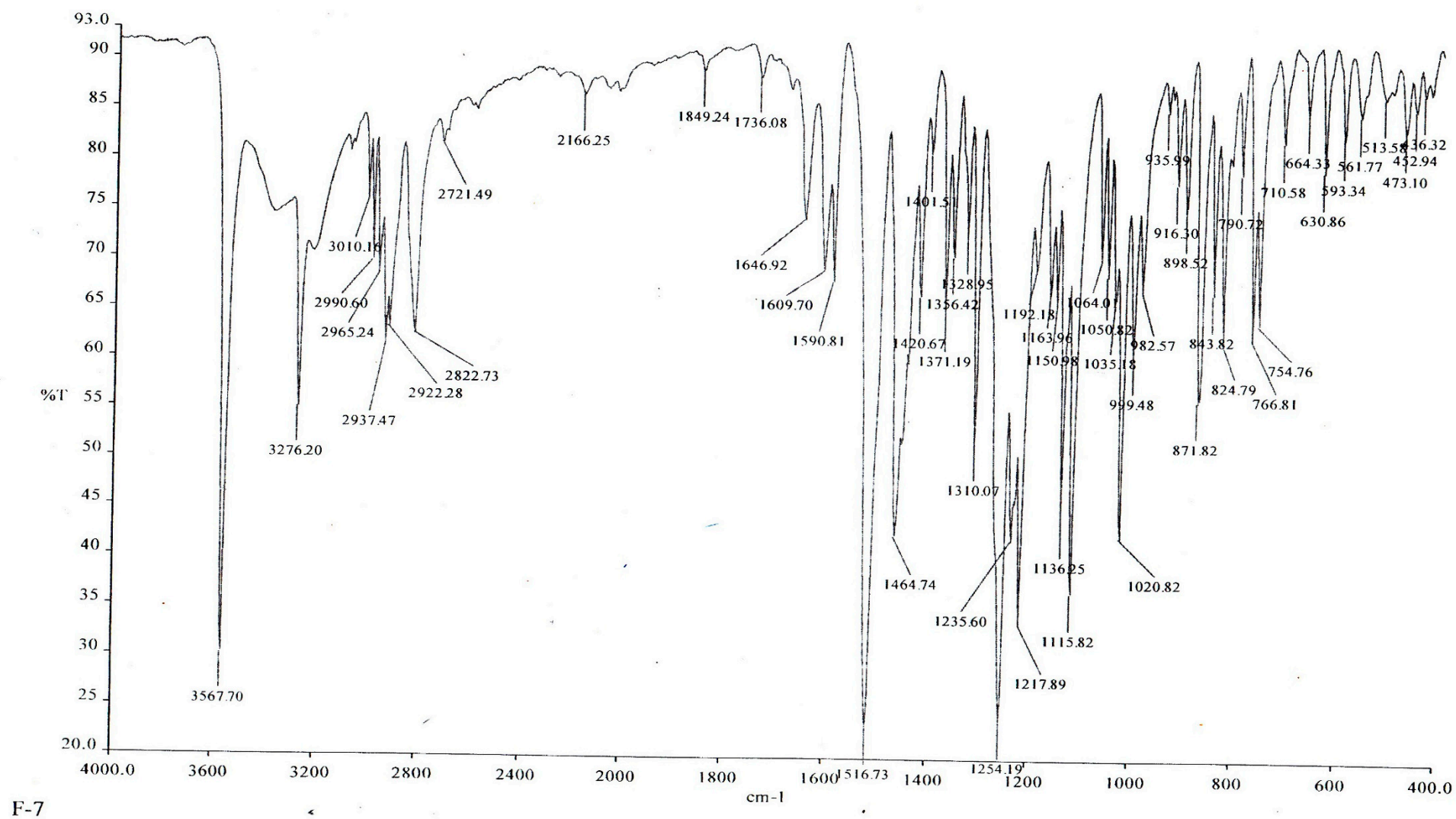
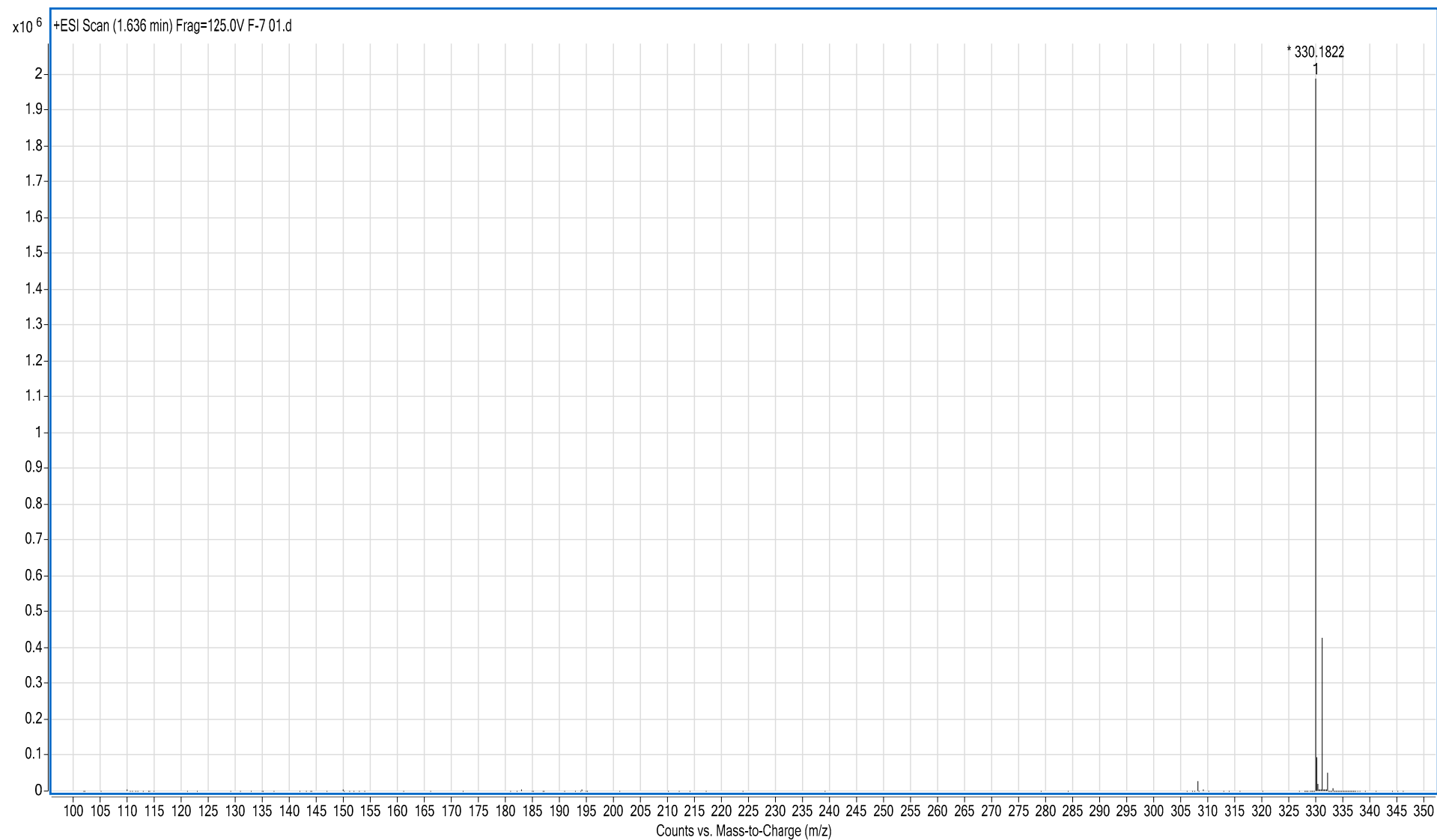
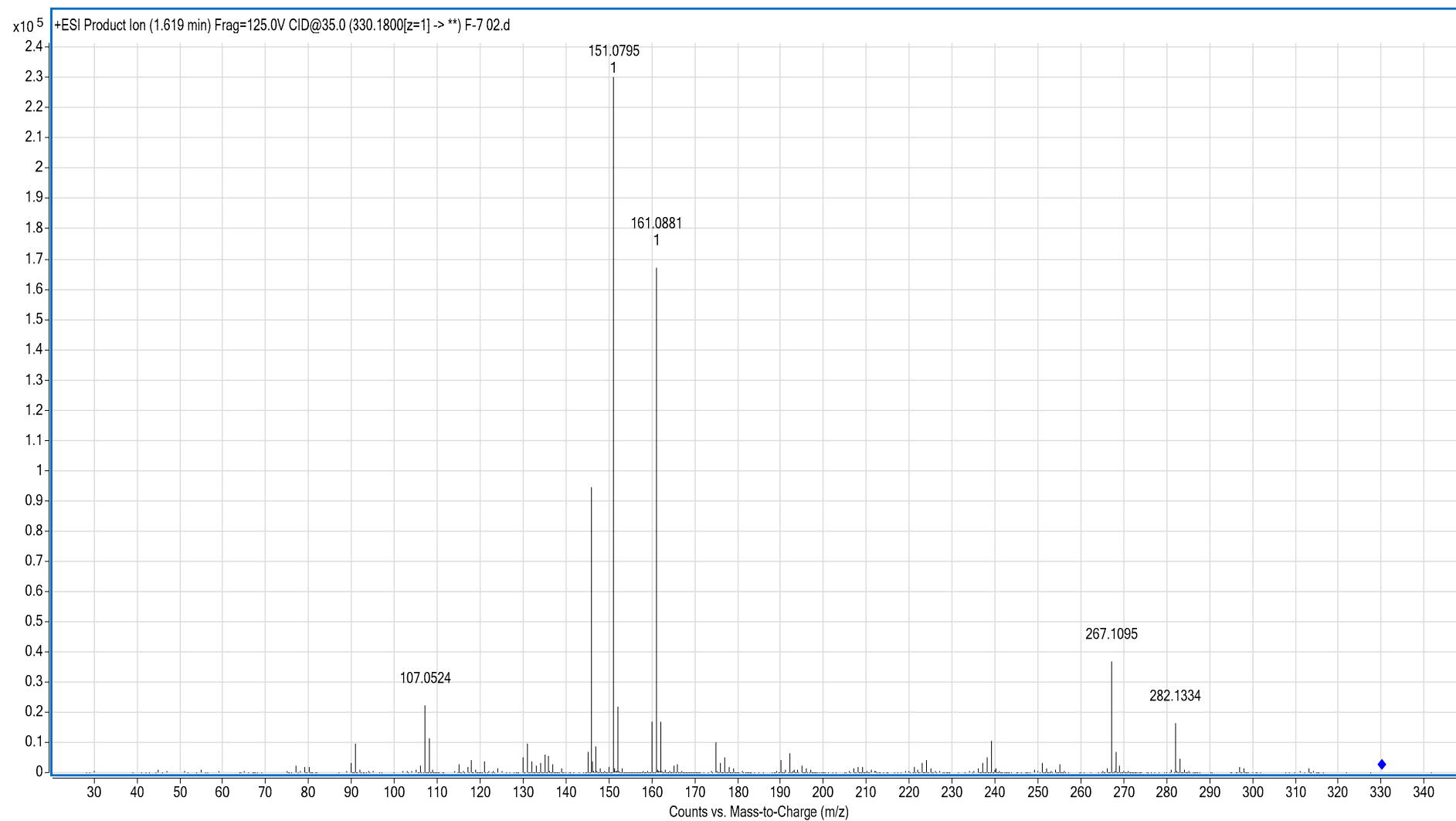


Figure S14. IR spectrum of compound 3d.



**Figure S15.** +ESI- mass- spectrum of compound **3d** ( $m/z$  330  $[M+H]^+$ ).



**Figure S16.** +ESI-mass- spectrum of compound **3d**.

Juraqulov Sh.N\_F-17\_single\_pulse-1-1600 Mr

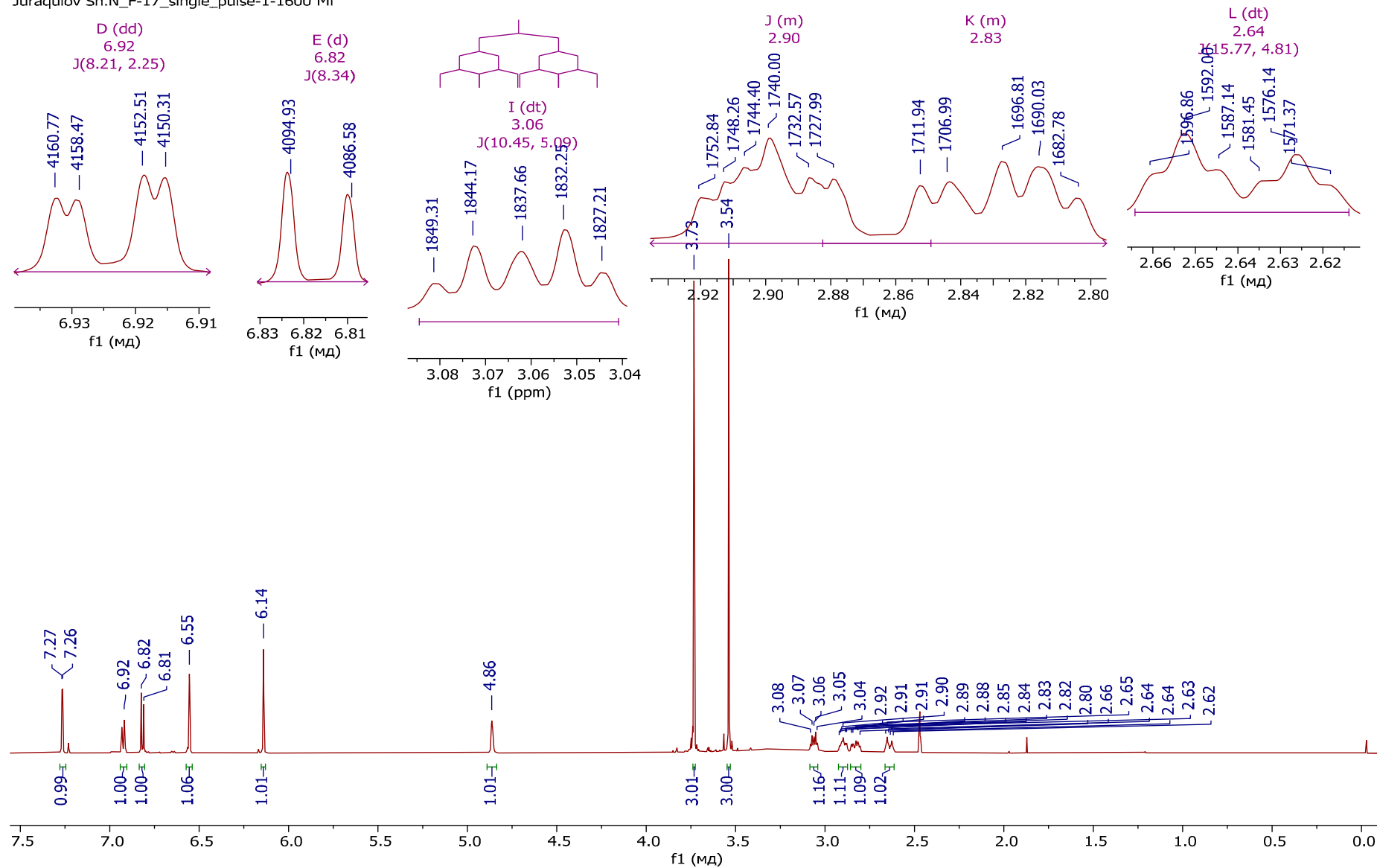
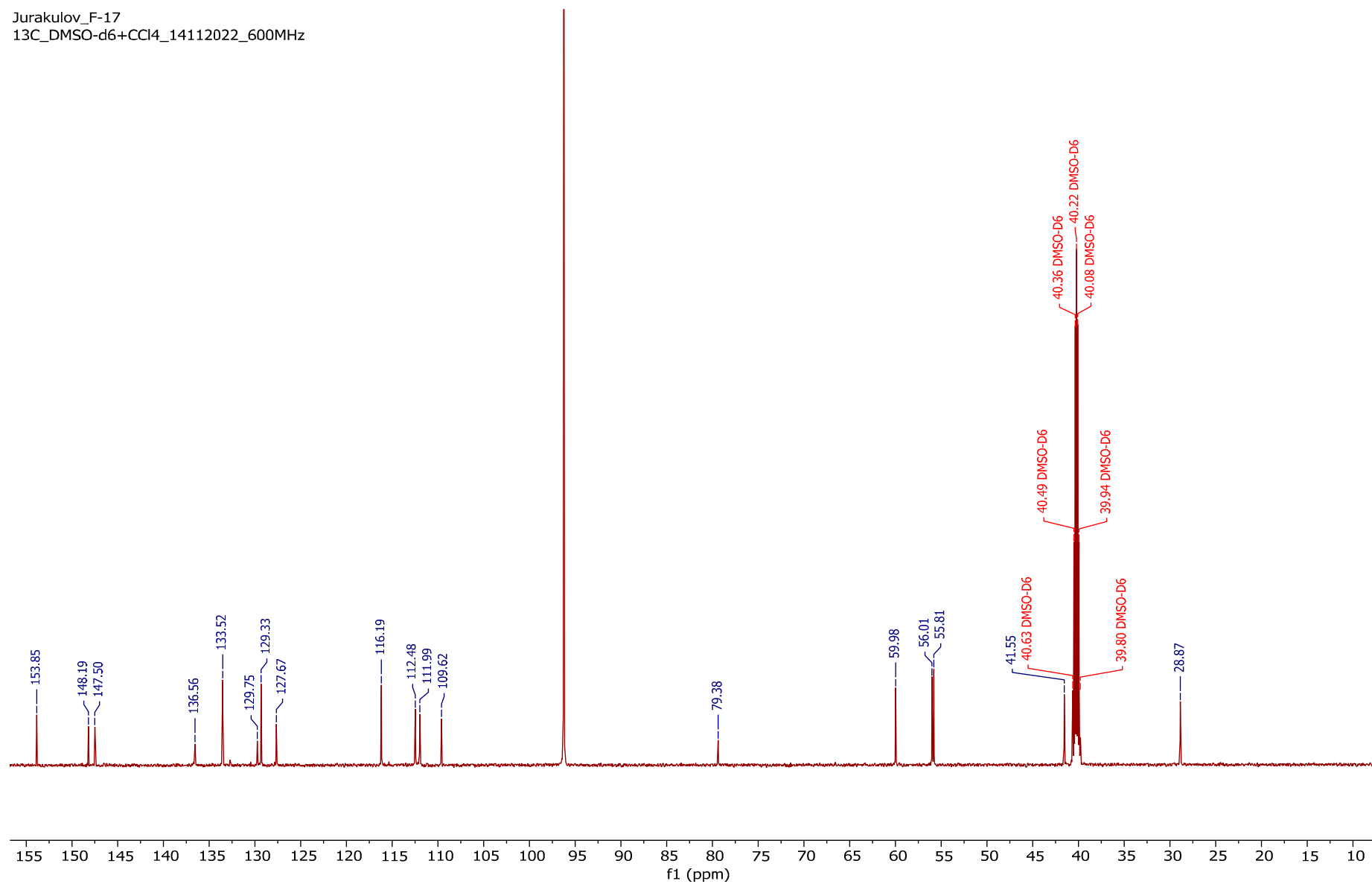


Figure S17.  $^1\text{H}$  NMR spectrum of compound **3e**.

Jurakulov\_F-17  
13C\_DMSO-d6+CCl4\_14112022\_600MHz



**Figure S18.** <sup>13</sup>C NMR spectrum of compound 3e



Juraquv\_F-10  
1H\_CDCl3\_24052021\_400 MHz

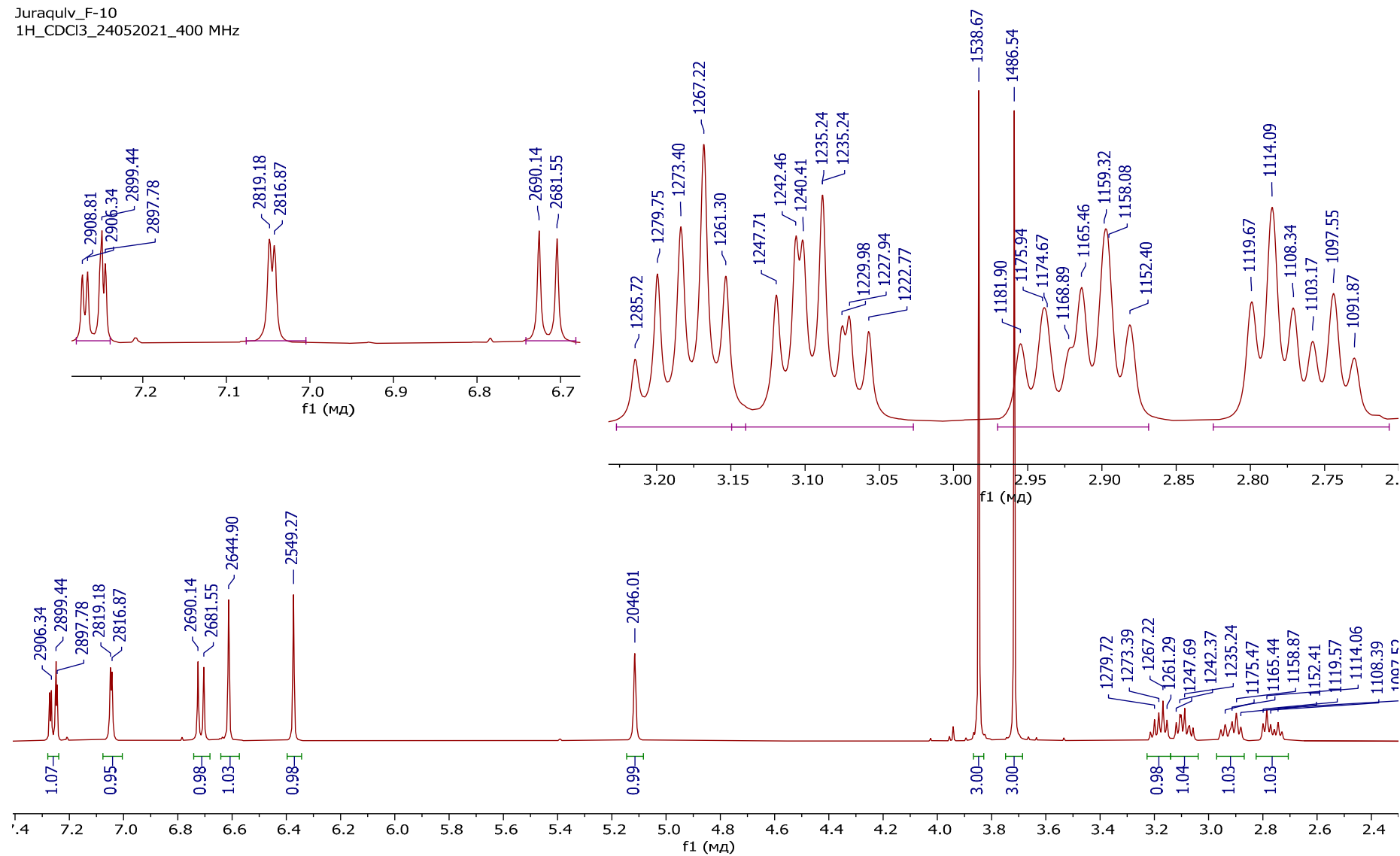
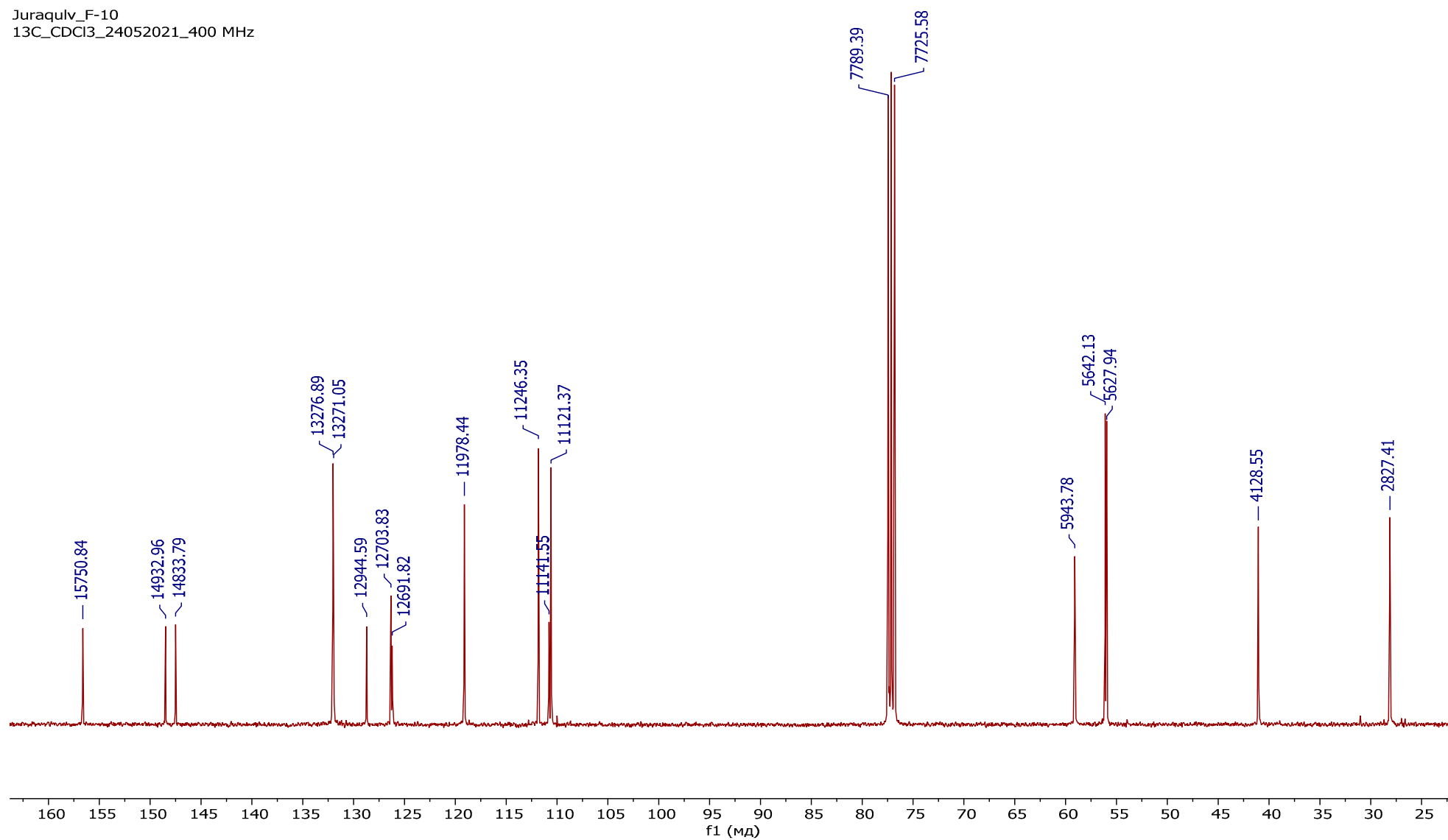
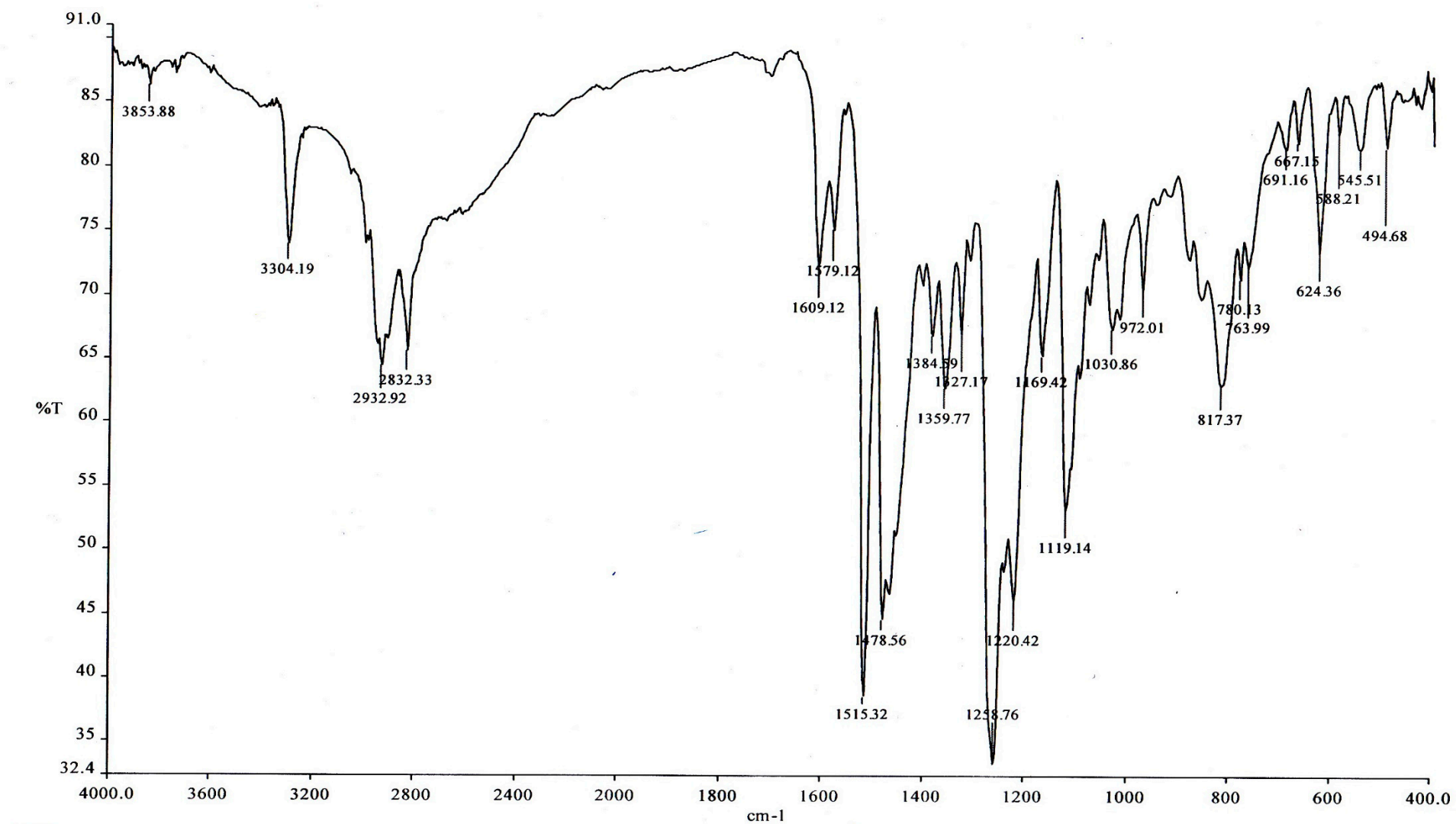


Figure S19.  $^1\text{H}$  NMR spectrum of compound **3f**.

Juraquv\_F-10  
13C\_CDCl3\_24052021\_400 MHz



**Figure S20.** <sup>13</sup>C NMR spectrum of compound **3f**.



F-10

Figure S21. IR spectrum of compound 3f.

Jurakulov\_F-18\_1H  
NMR, Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-18

Solvent: CDCl<sub>3</sub>  
Reference: TMS (0 ppm)  
Expernt: s2pul 1H  
Temp-re: 22 C  
Date: 07.01.20

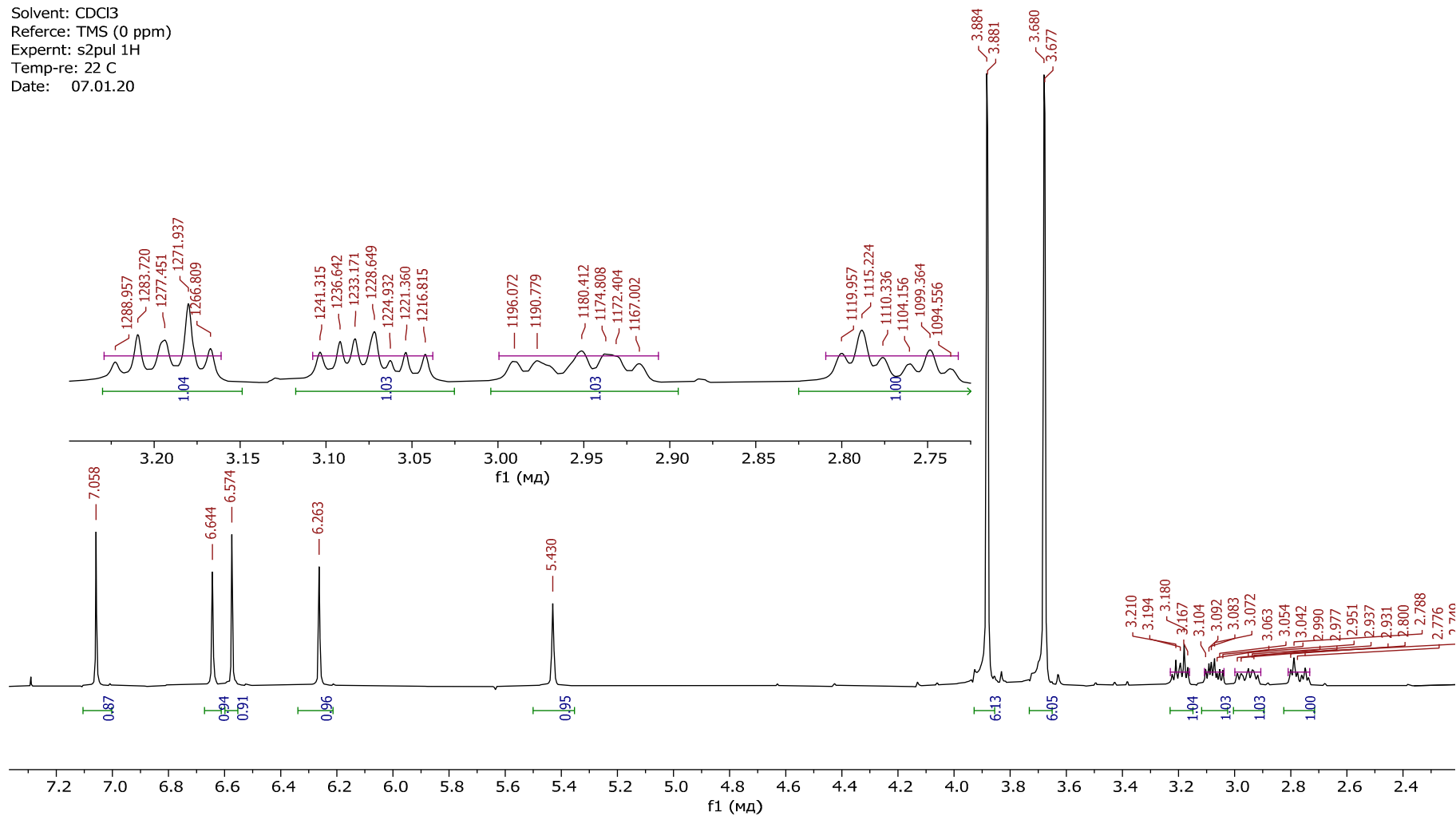
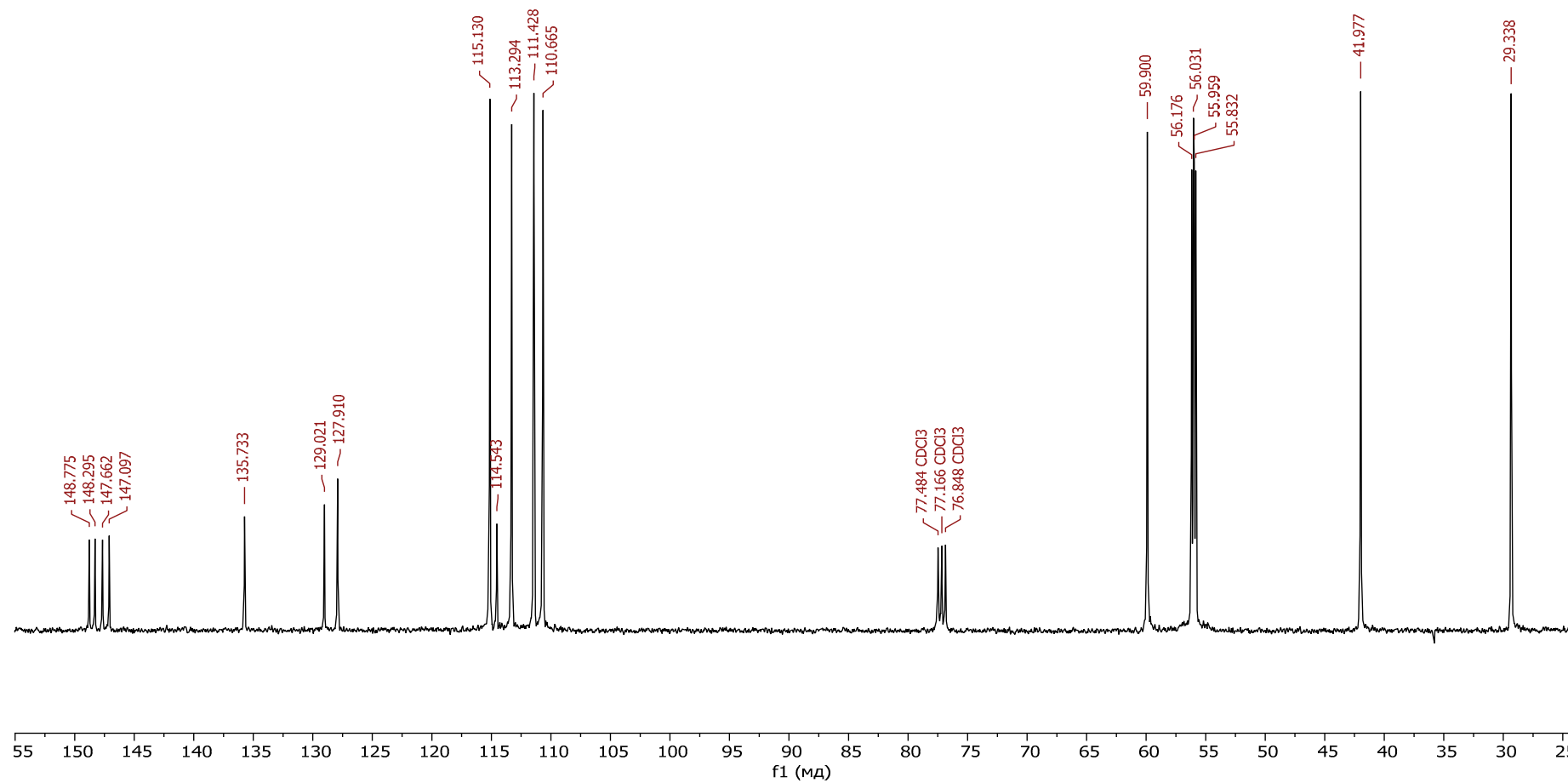


Figure S22. <sup>1</sup>H NMR spectrum of compound 3g.

Jurakulov\_F-18\_13C  
NMR Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-18

Solvent: CDCl<sub>3</sub>  
Refernt: CDCl<sub>3</sub> (77.16 ppm)  
Expermt: 13C  
Date: 07.01.20



**Figure S23.** <sup>13</sup>C NMR spectrum of compound **3g**.

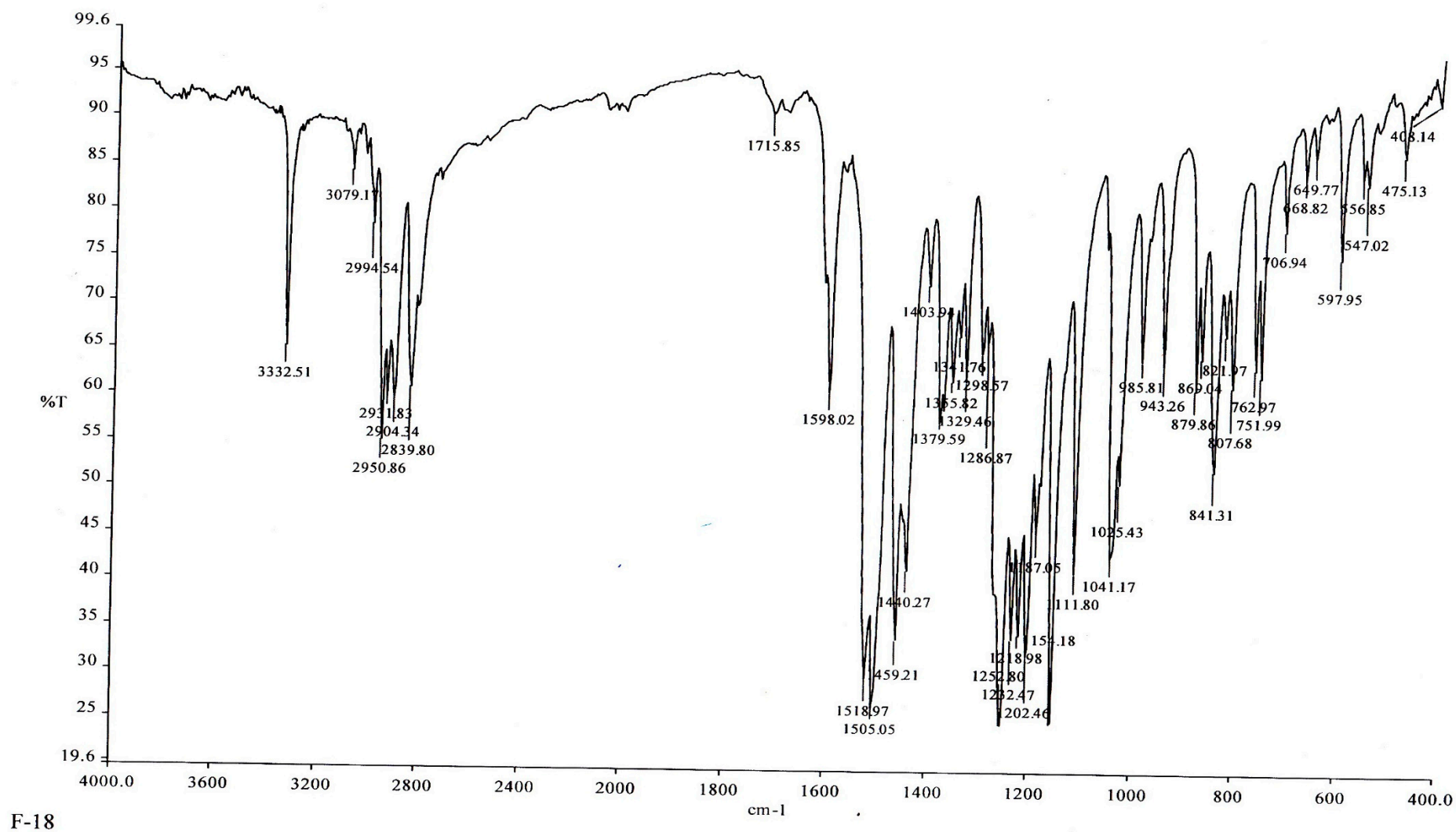


Figure S24. IR spectrum of compound **3g**.

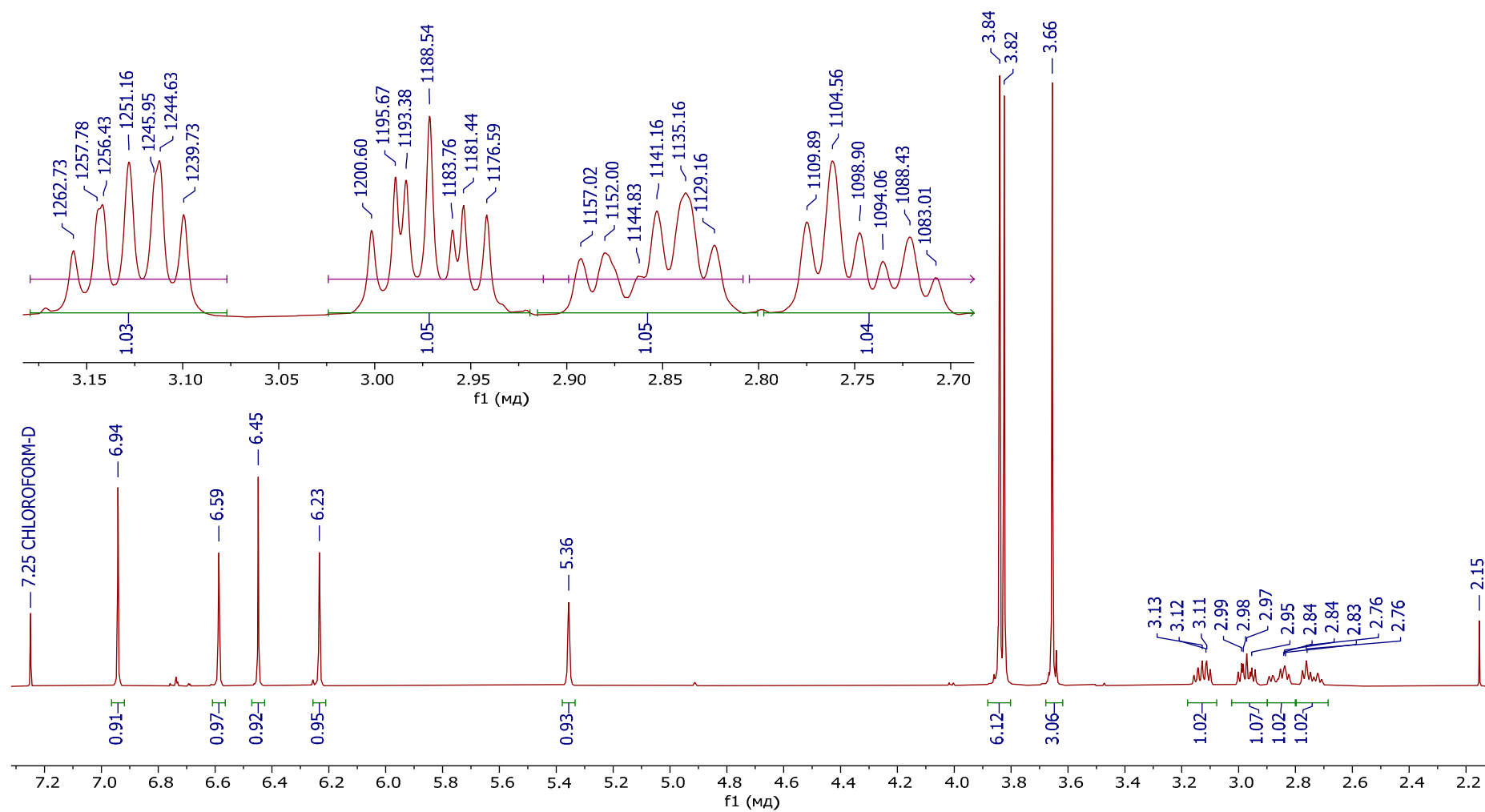
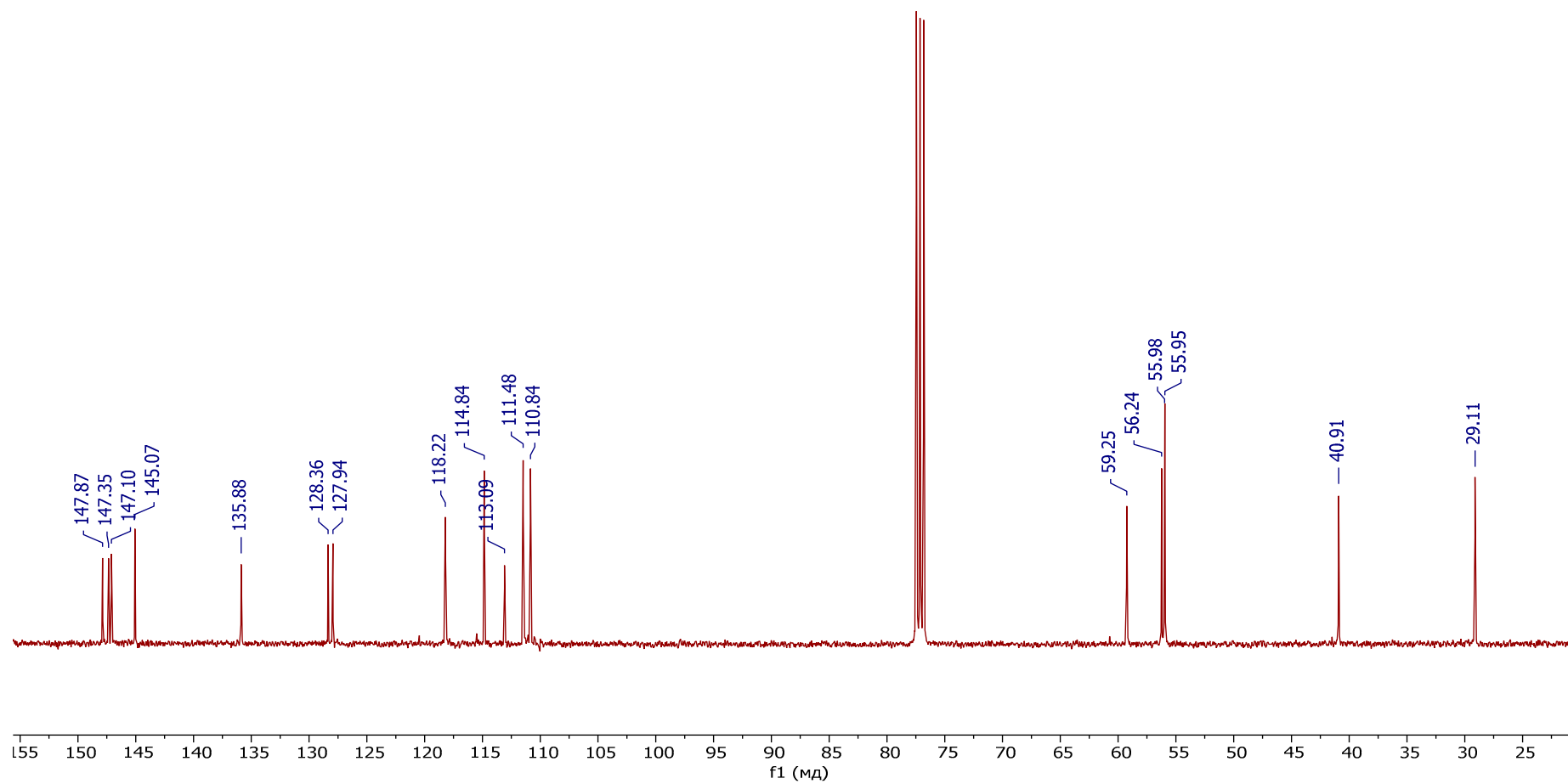
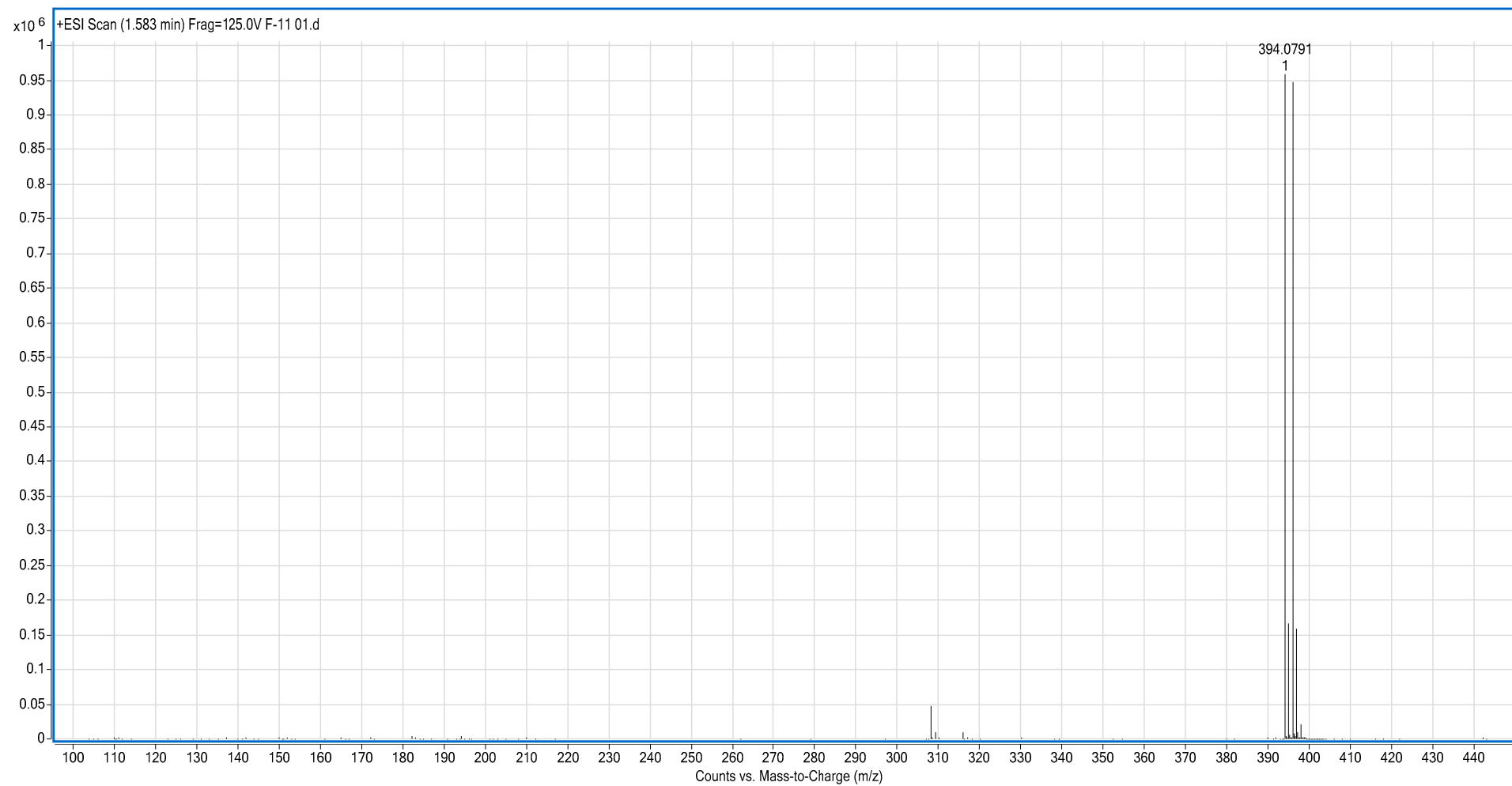


Figure S25. <sup>1</sup>H NMR spectrum of compound **3h**.

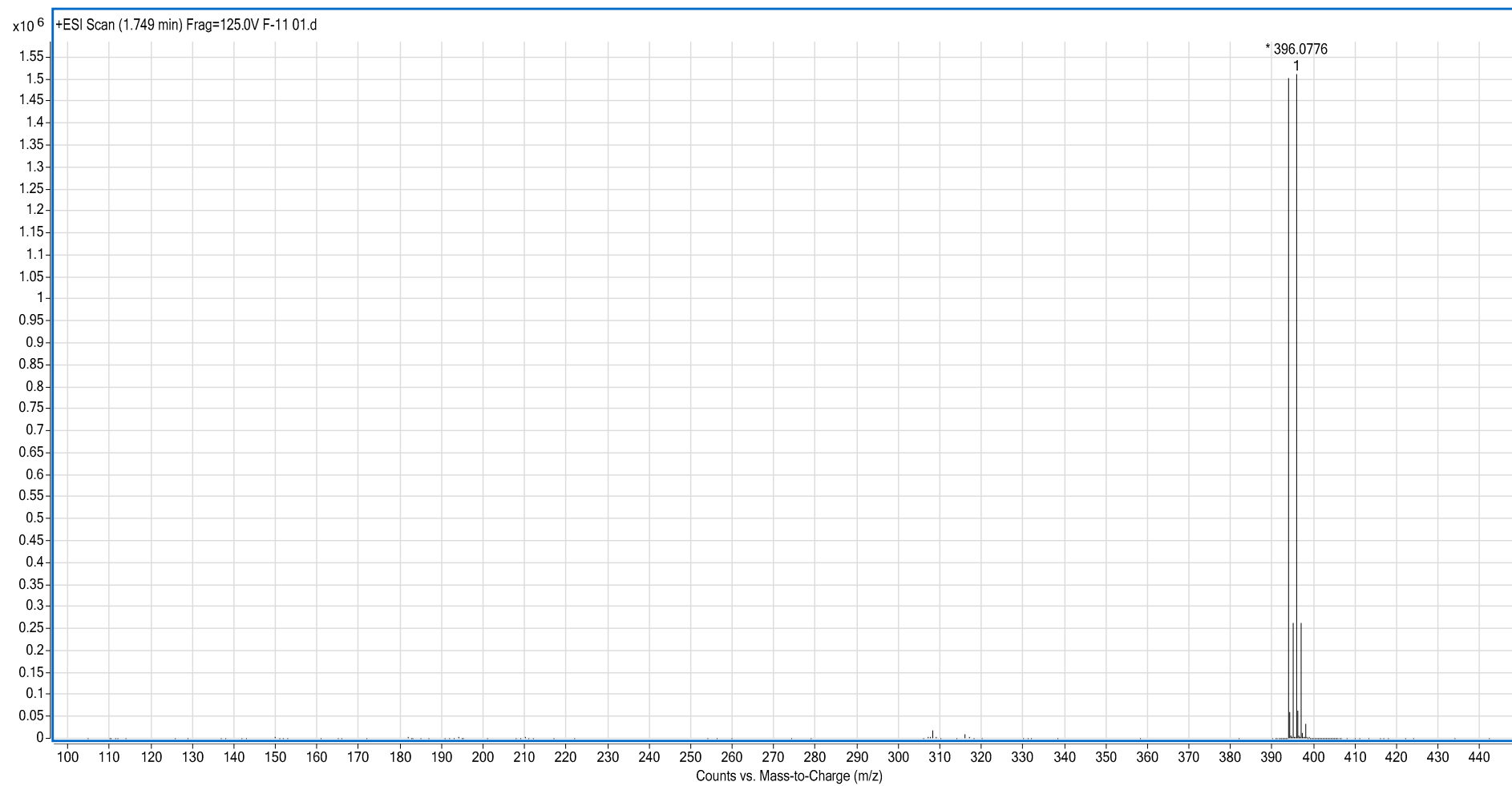


**Figure S26.** <sup>13</sup>C NMR spectrum of compound **3h**.

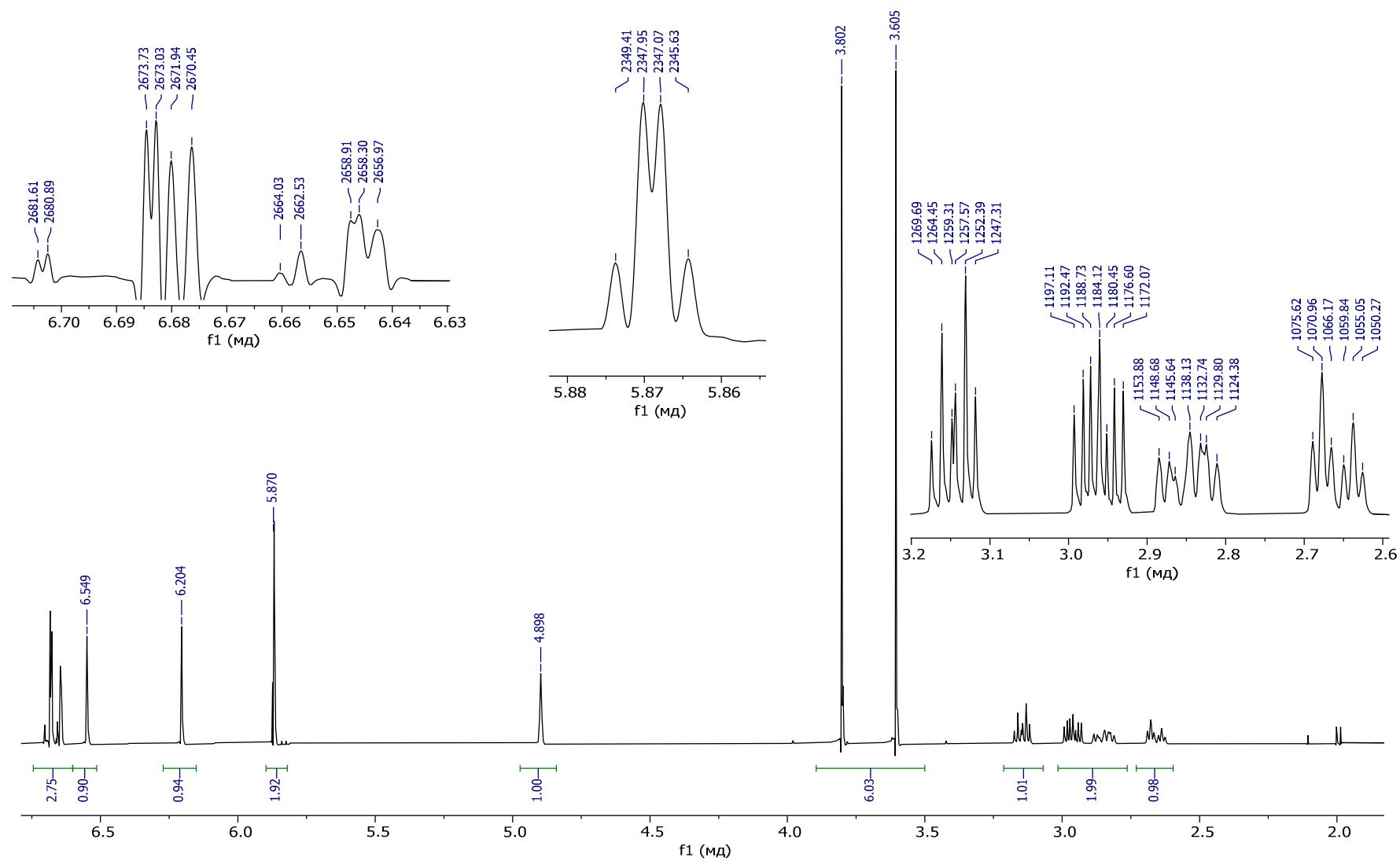




**Figure S27.** +ESI-mass- spectrum of compound **3h** ( $m/z$  394 ( $M+H$ )<sup>+</sup> from the isotope bromine 79).



**Figure S28.** +ESI-mass- spectrum of compound **3h** ( $m/z$  396 ( $M+H$ )<sup>+</sup> from the isotope bromine 81).

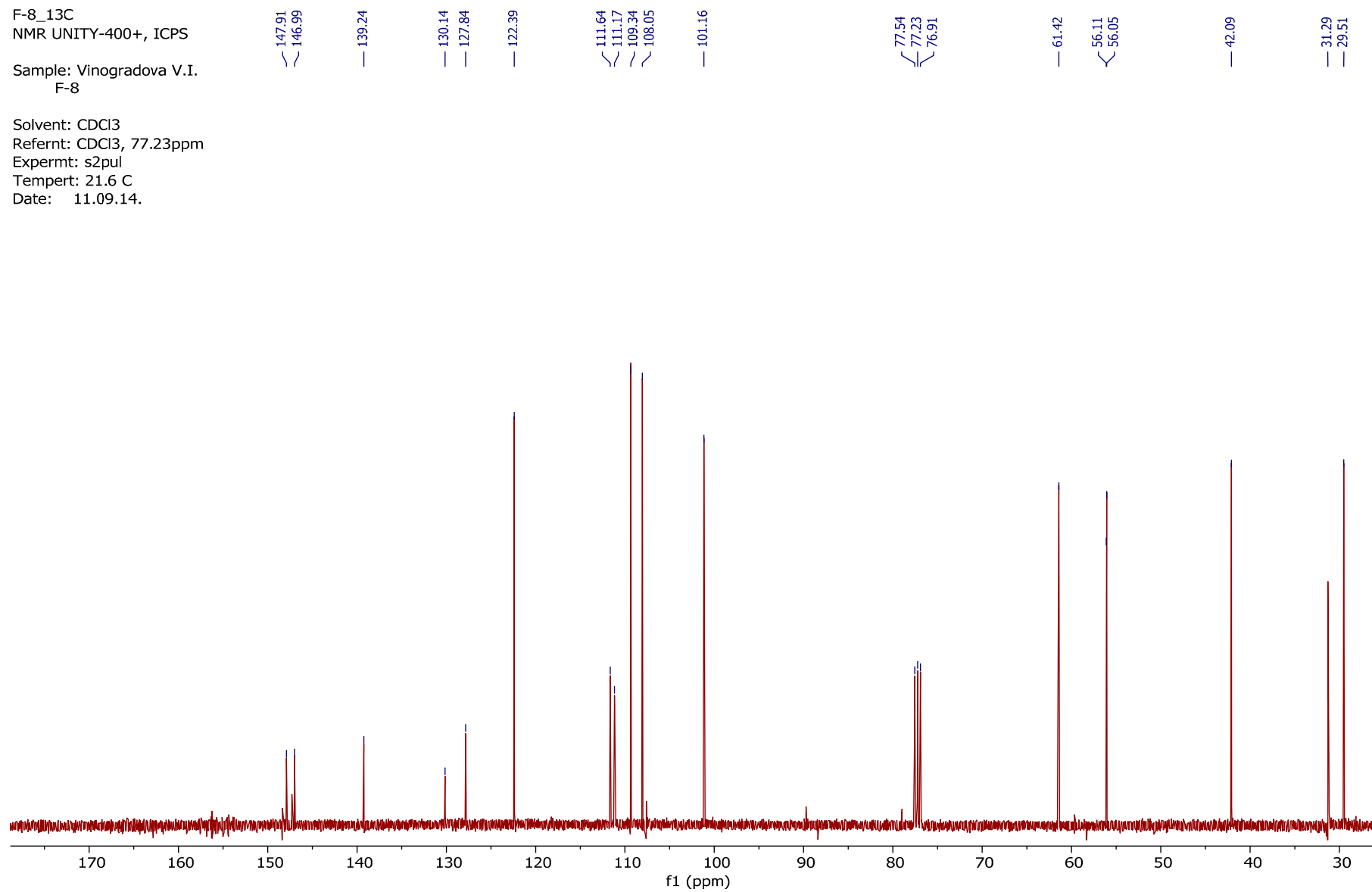


**Figure S29.** <sup>1</sup>H NMR spectrum of compound **3i**.

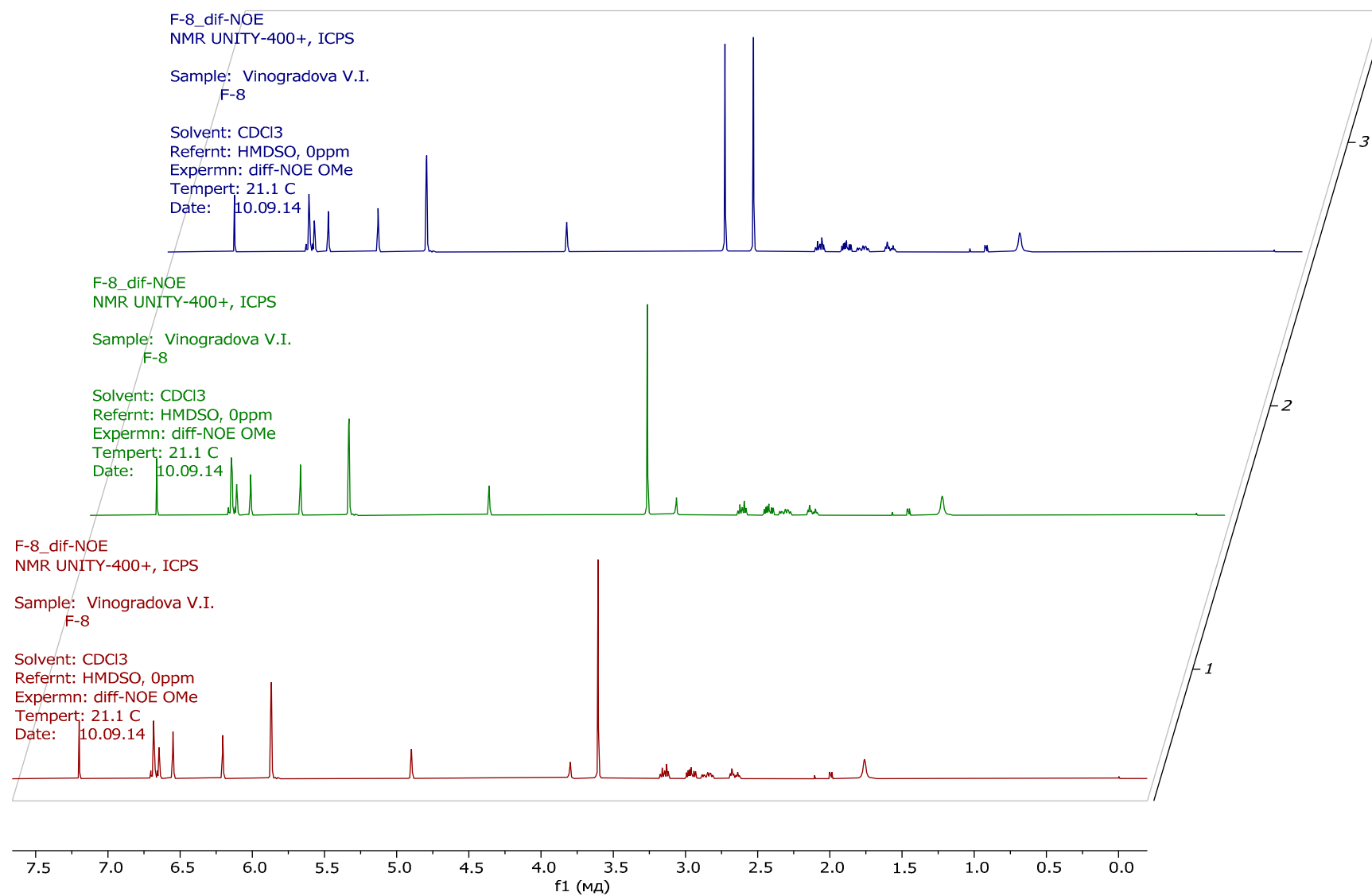
F-8\_13C  
NMR UNITY-400+, ICPS

Sample: Vinogradova V.I.  
F-8

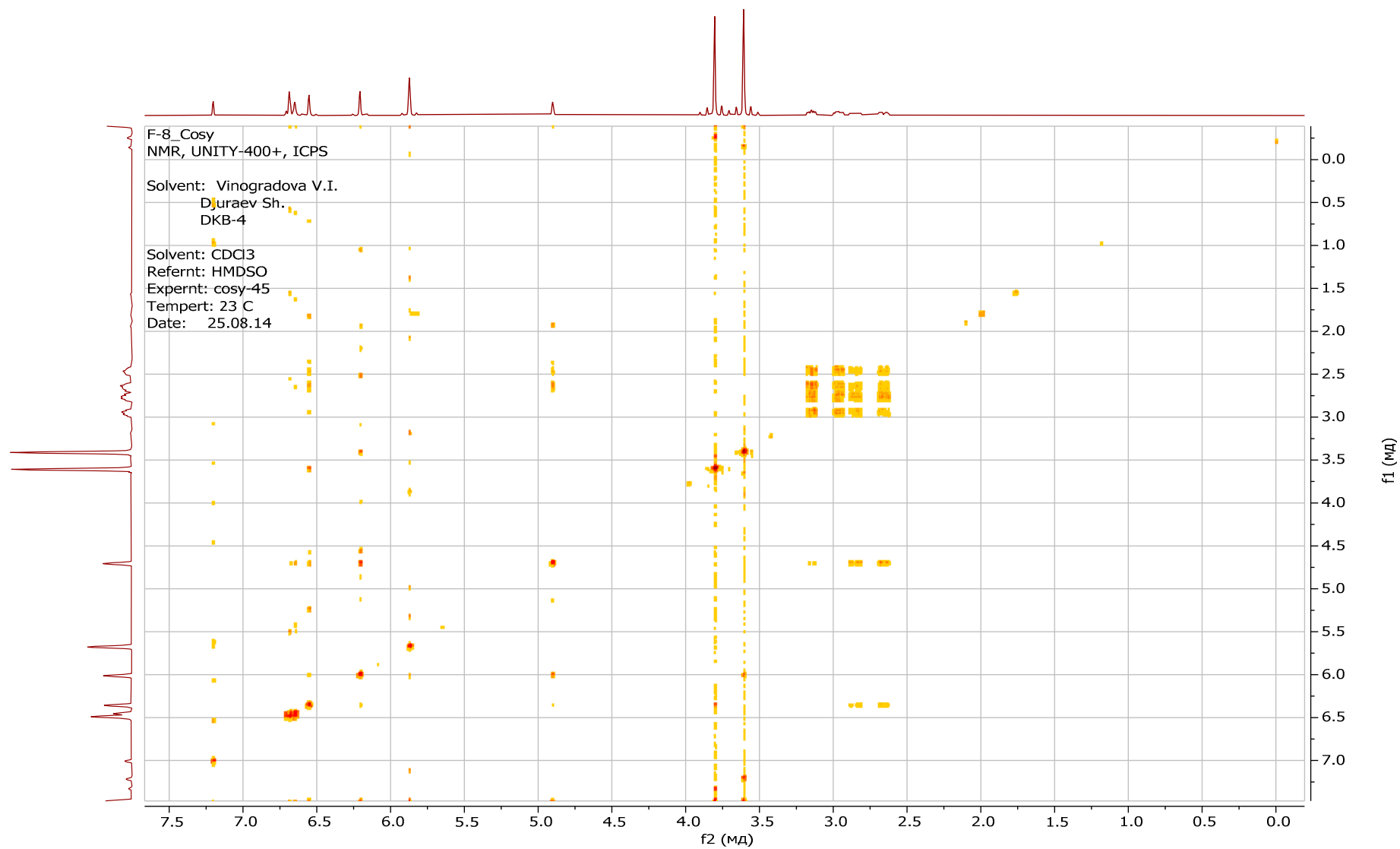
Solvent: CDCl<sub>3</sub>  
Refernt: CDCl<sub>3</sub>, 77.23ppm  
Expermt: s2pul  
Tempert: 21.6 C  
Date: 11.09.14.



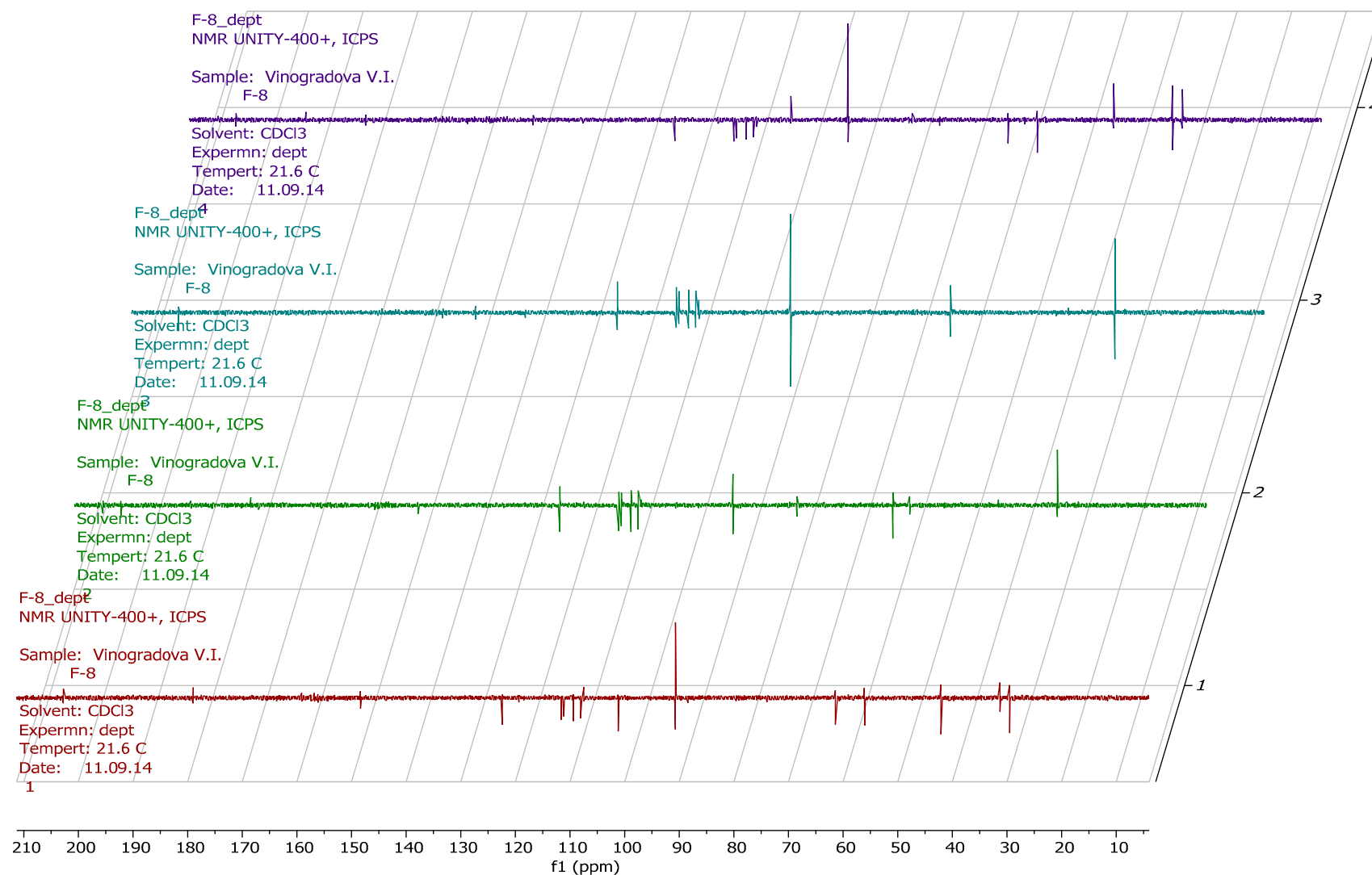
**Figure S30.** <sup>13</sup>C NMR spectrum of compound **3i**.



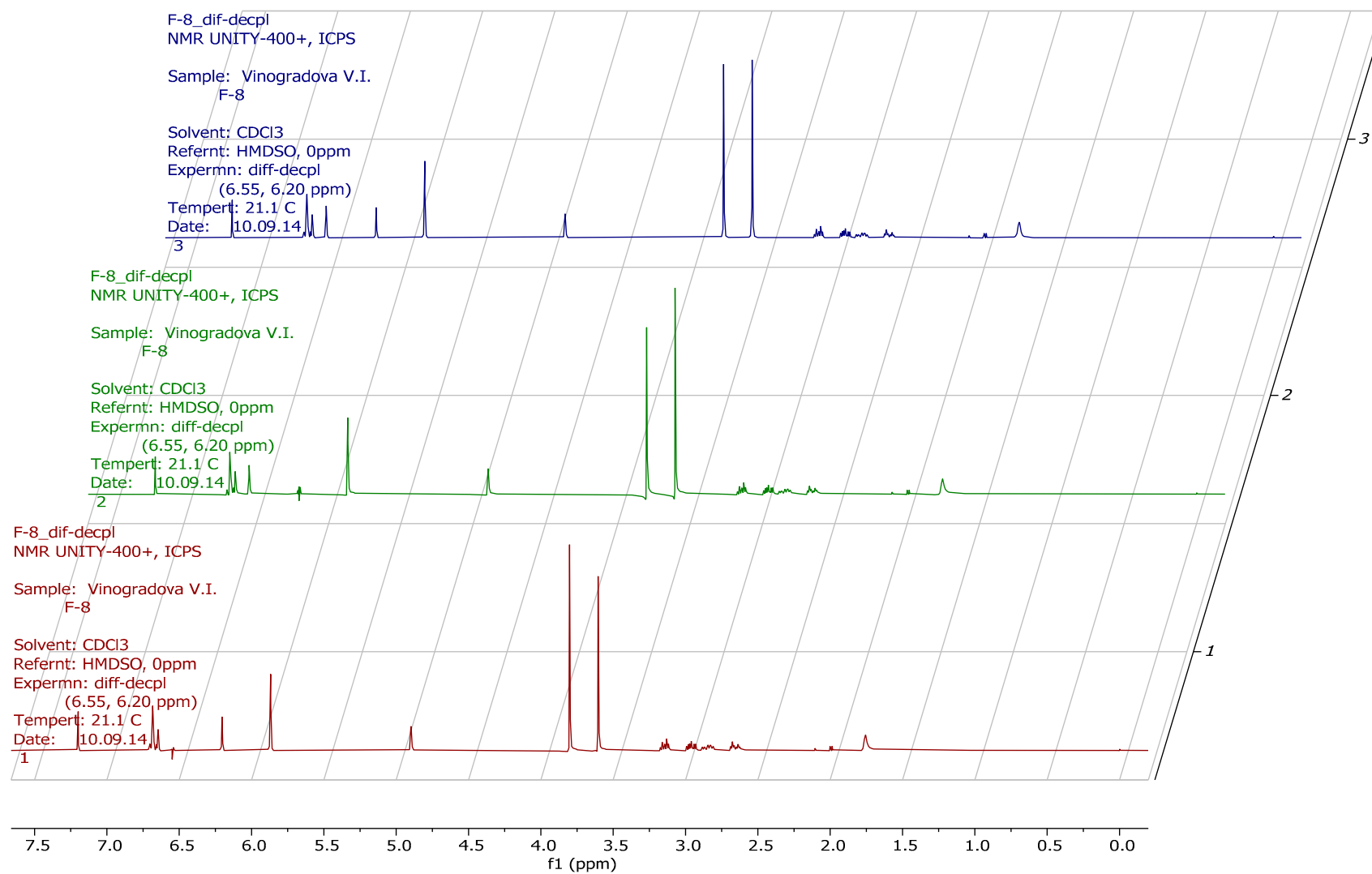
**Figure S31.** Diff-NOE spectrum of compound **3i**.



**Figure S32.** COSY spectrum of compound **3i**.



**Figure S33.** Dept spectrum of compound **3i**.



**Figure S34.** Diff-decpl spectrum of compound **3i**.



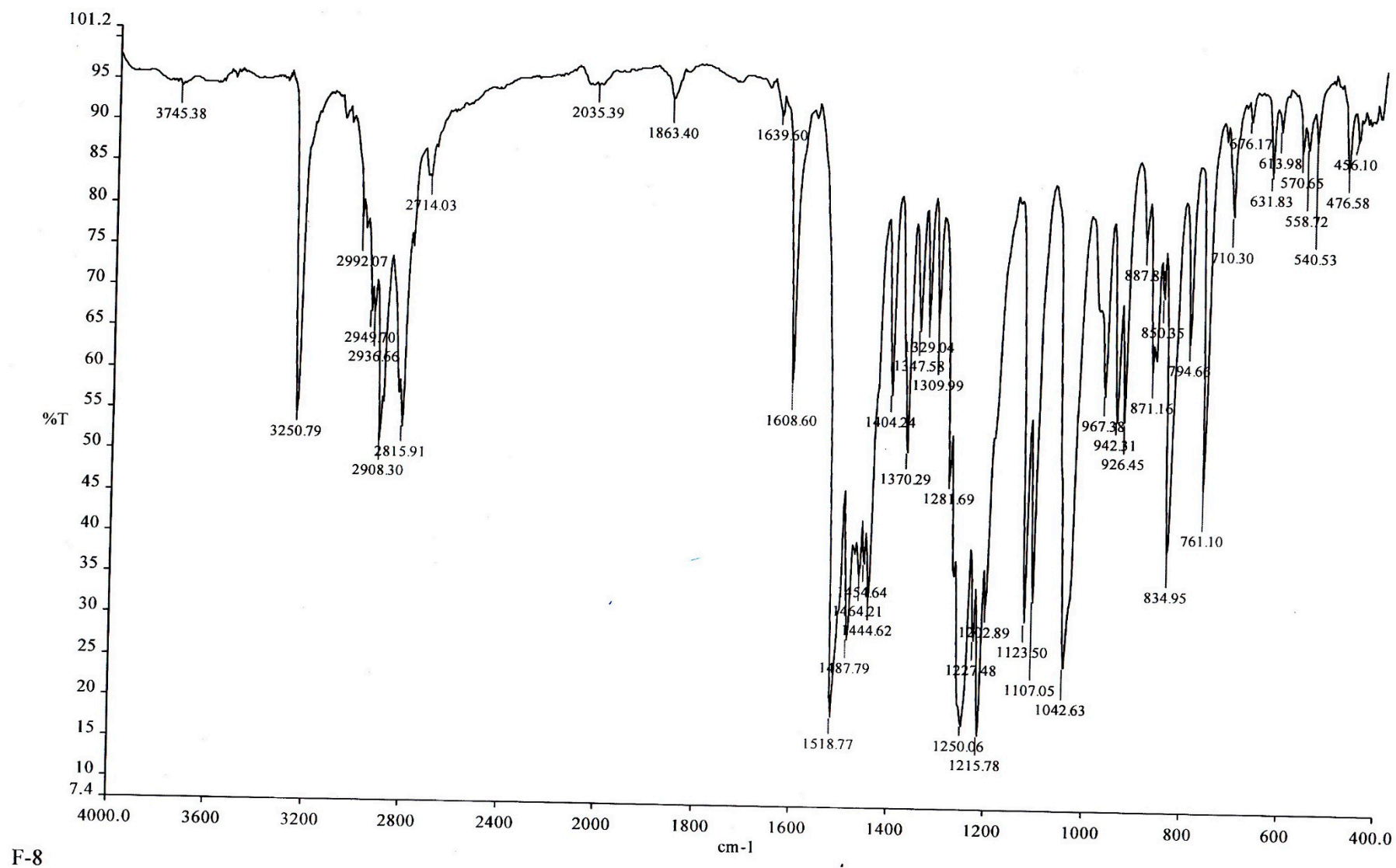


Figure S35. IR spectrum of compound 3i.

Jurakulov\_F-9\_1H  
NMR, Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-9

Solvent: CDCl<sub>3</sub>  
Reference: TMS (0 ppm)  
Expernt: s2pul 1H  
Temp-re: 22 C  
Date: 06.01.20

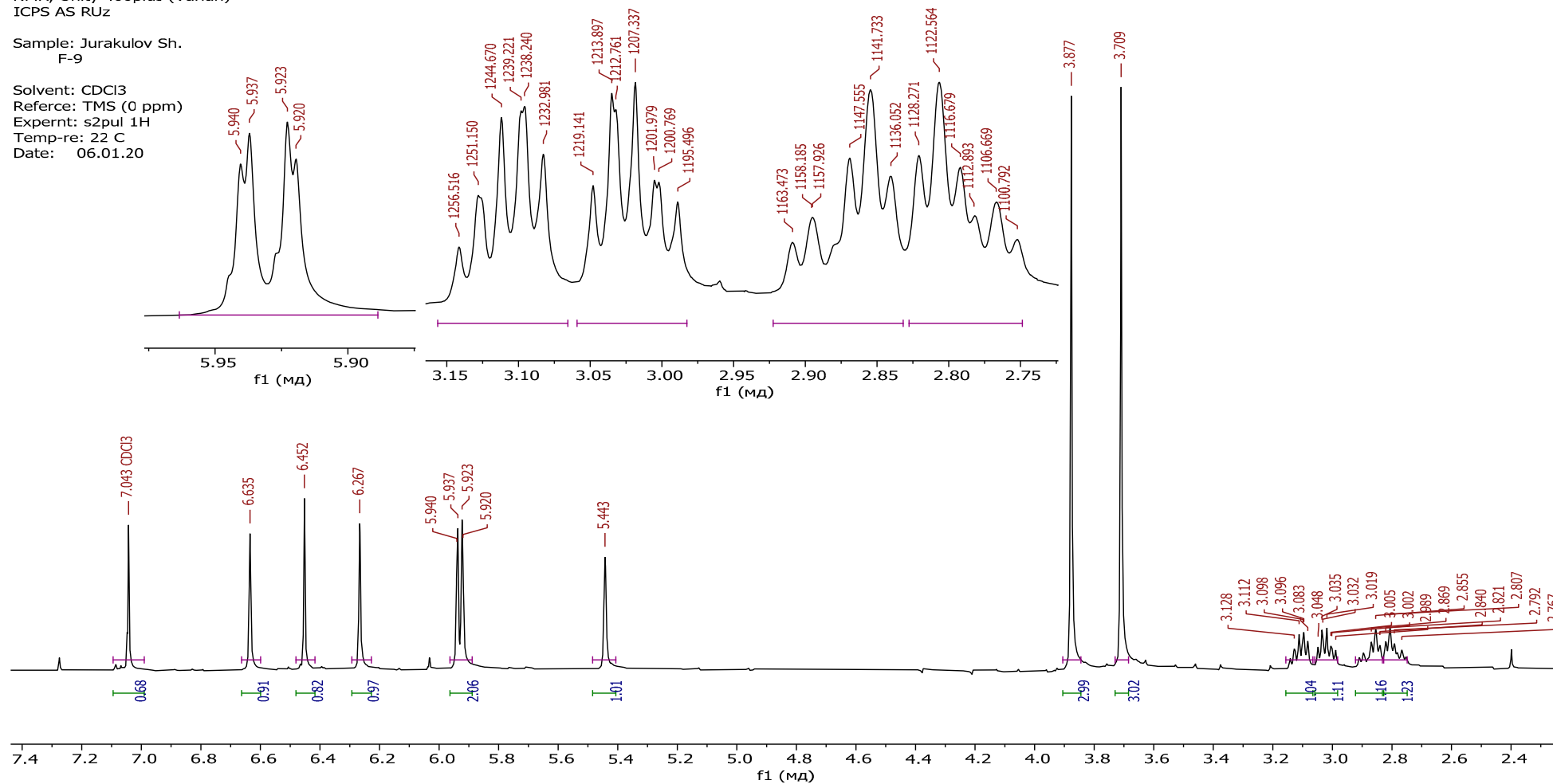


Figure S36. <sup>1</sup>H NMR spectrum of compound **3j**.

Jurakulov\_F-9\_13C  
NMR Unity 400plus (Varian)  
ICPS AS RUz

Sample: Jurakulov Sh.  
F-9

Solvent: CDCl<sub>3</sub>  
Refernt: CDCl<sub>3</sub> (77.16 ppm)  
Expermt: 13C  
Date: 06.01.20

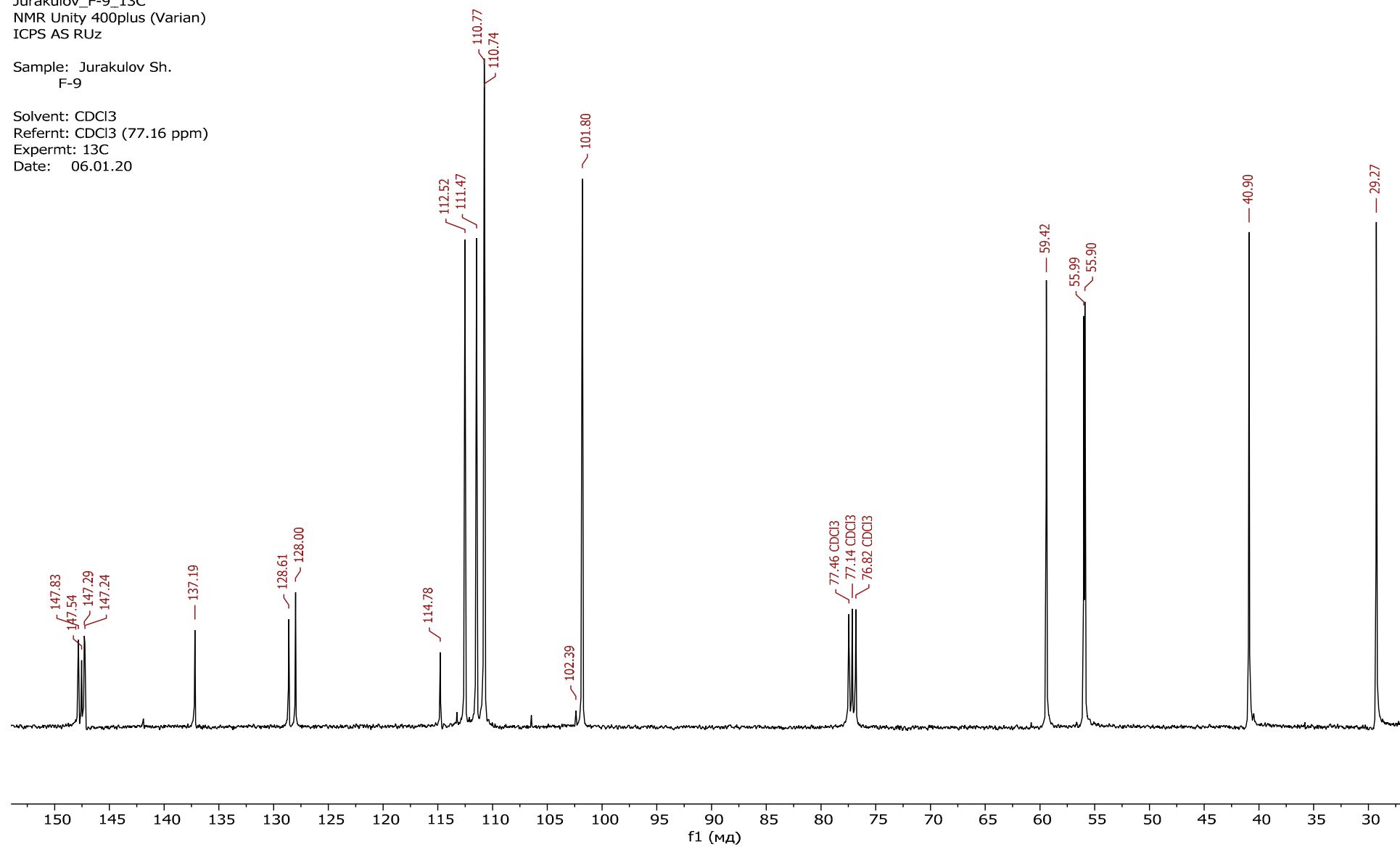


Figure S37. <sup>13</sup>C NMR spectrum of compound **3j**.

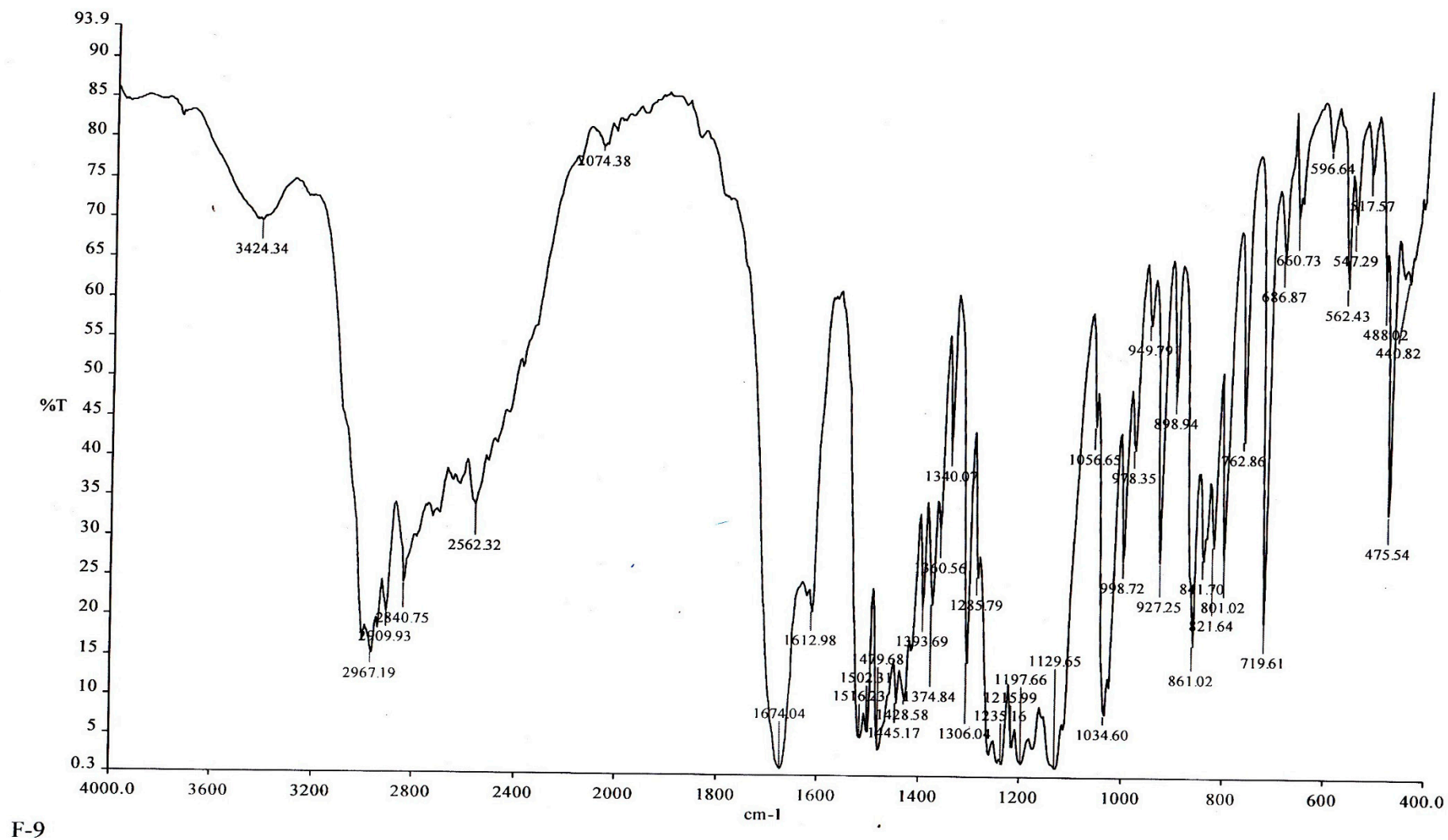


Figure S38. IR spectrum of compound 3j.

XJIPC Varian MR-400 2012\_37  
Vinogradova B.I.\_F\_14\_2\_H1 CDCl3

Sample Name:  
Vinogradova\_B\_I\_F\_14\_2\_H1  
Data Collected on:  
wormhole-vnmrs400  
Archive directory:  
/home/nmr400/vnmrsys/data/2012  
Sample directory:  
Vinogradova\_B\_I\_F\_14\_2\_H1\_20120419\_01  
FidFile: PROTON\_01

Pulse Sequence: PROTON (s2pul)  
Solvent: cdcl3  
Data collected on: Apr 19 2012

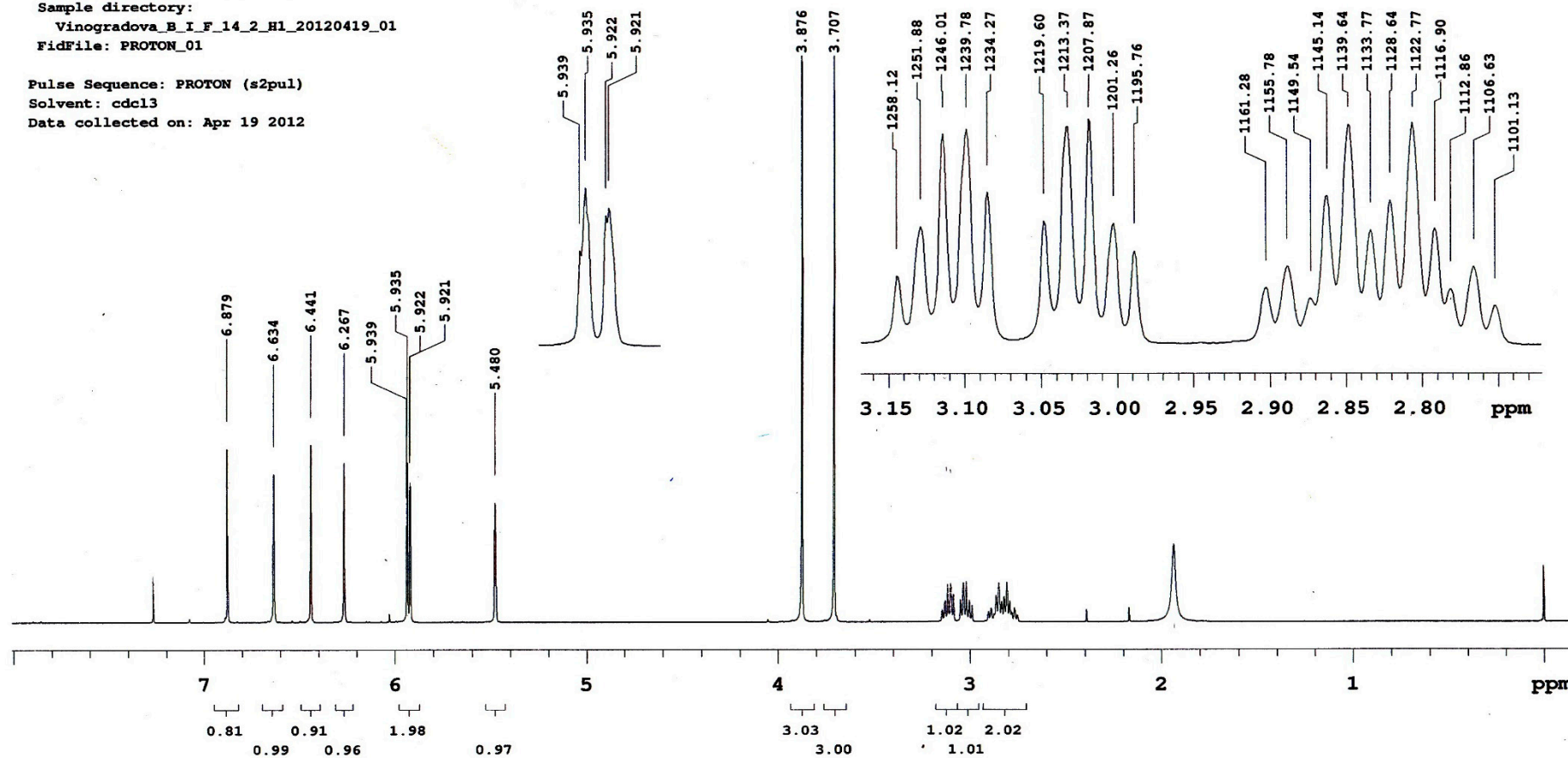
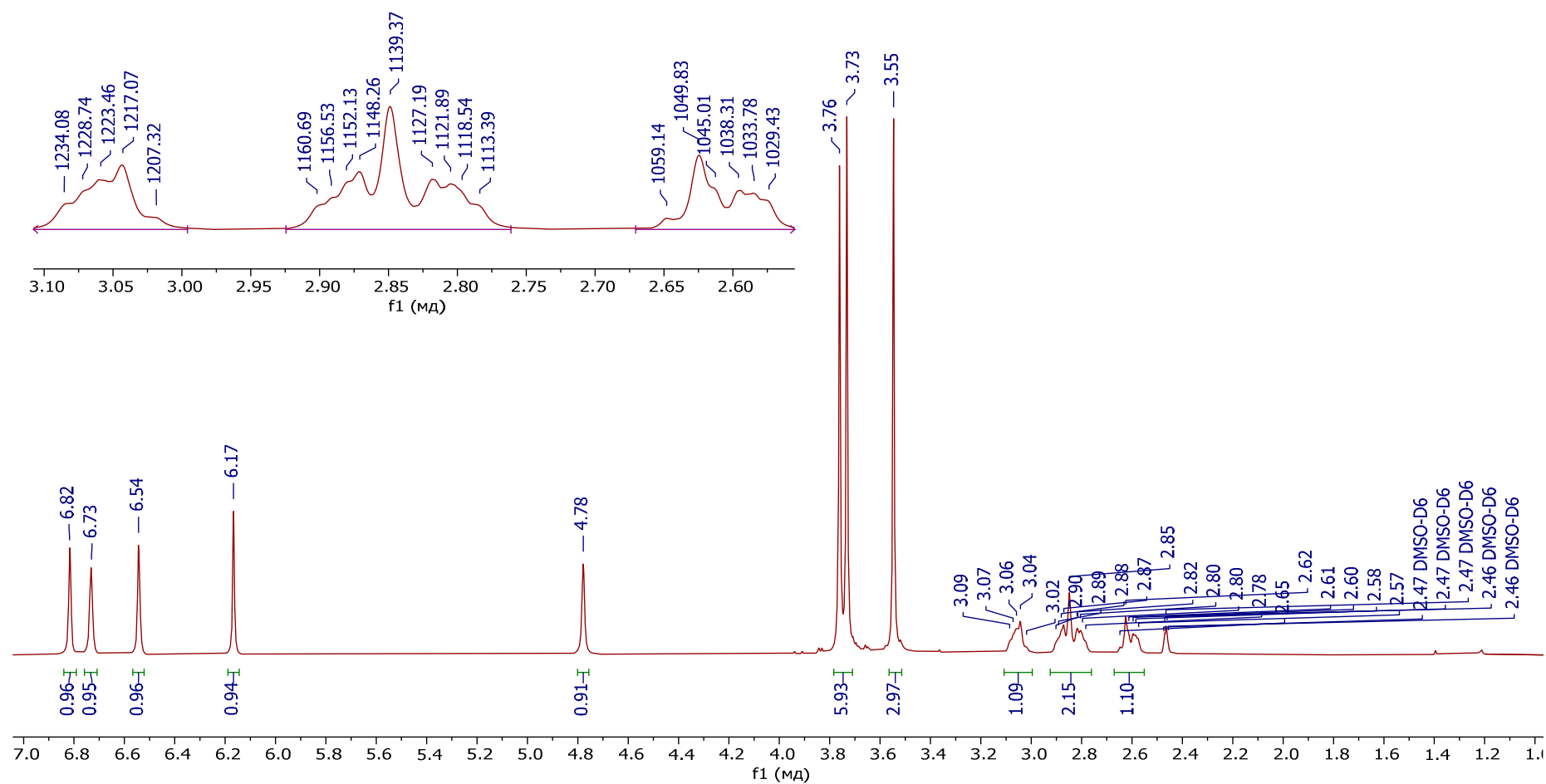
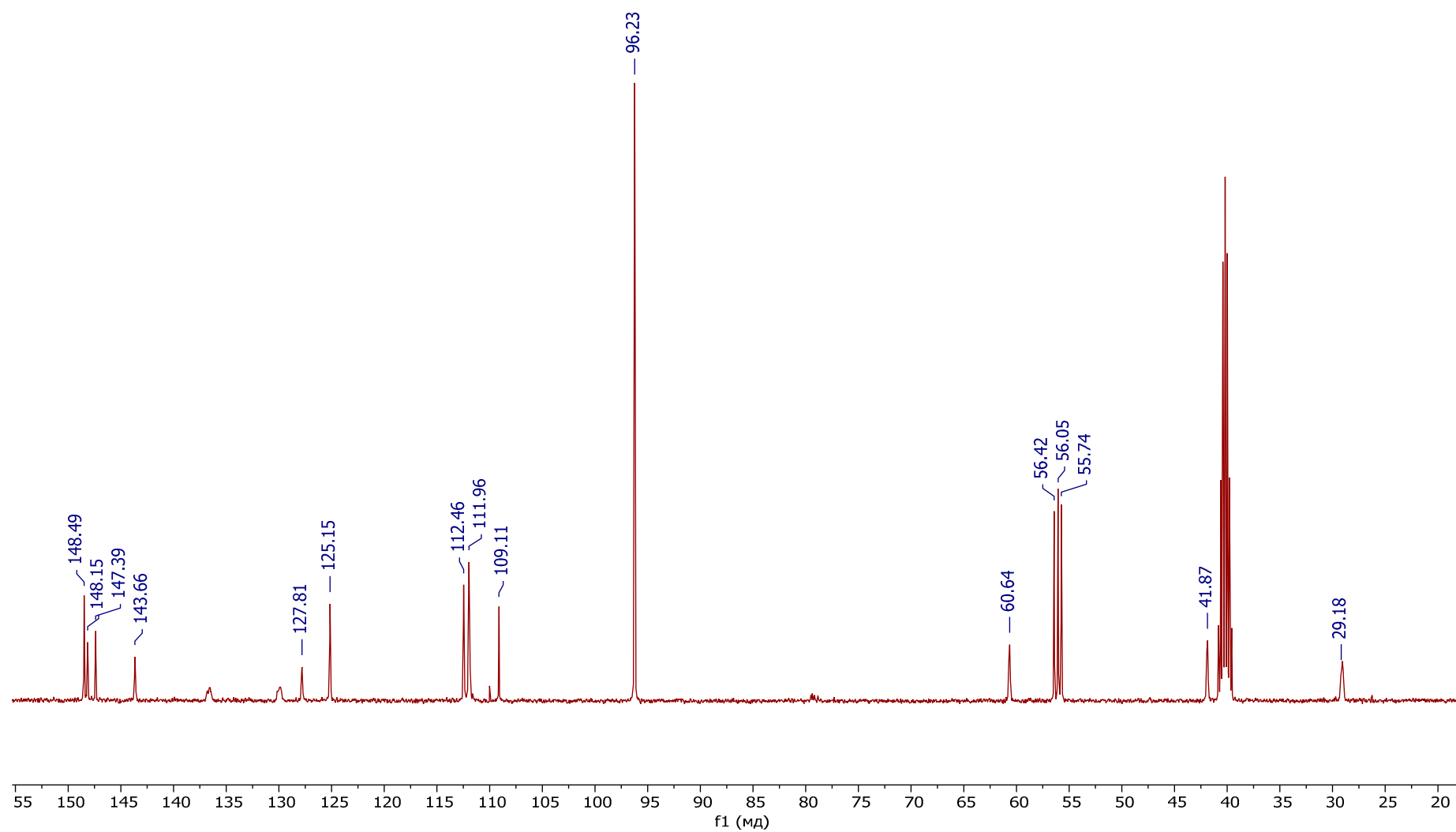


Figure S39. <sup>1</sup>H NMR spectrum of compound 3k.



**Figure S40.**  $^1\text{H}$  NMR spectrum of compound **3l**.



**Figure S41.**  $^{13}\text{C}$  NMR spectrum of compound **3l**.

NMR UNITY 400plus (Varian)  
ICPS AS RUZ

Sample : Vinogradova V.I.  
Jurakulov Sh.N.  
F-27

Solvent: CDCl<sub>3</sub>  
Refernc: HMDSO 0 ppm  
Expermt: s2pu1  
Date: 6.06.13

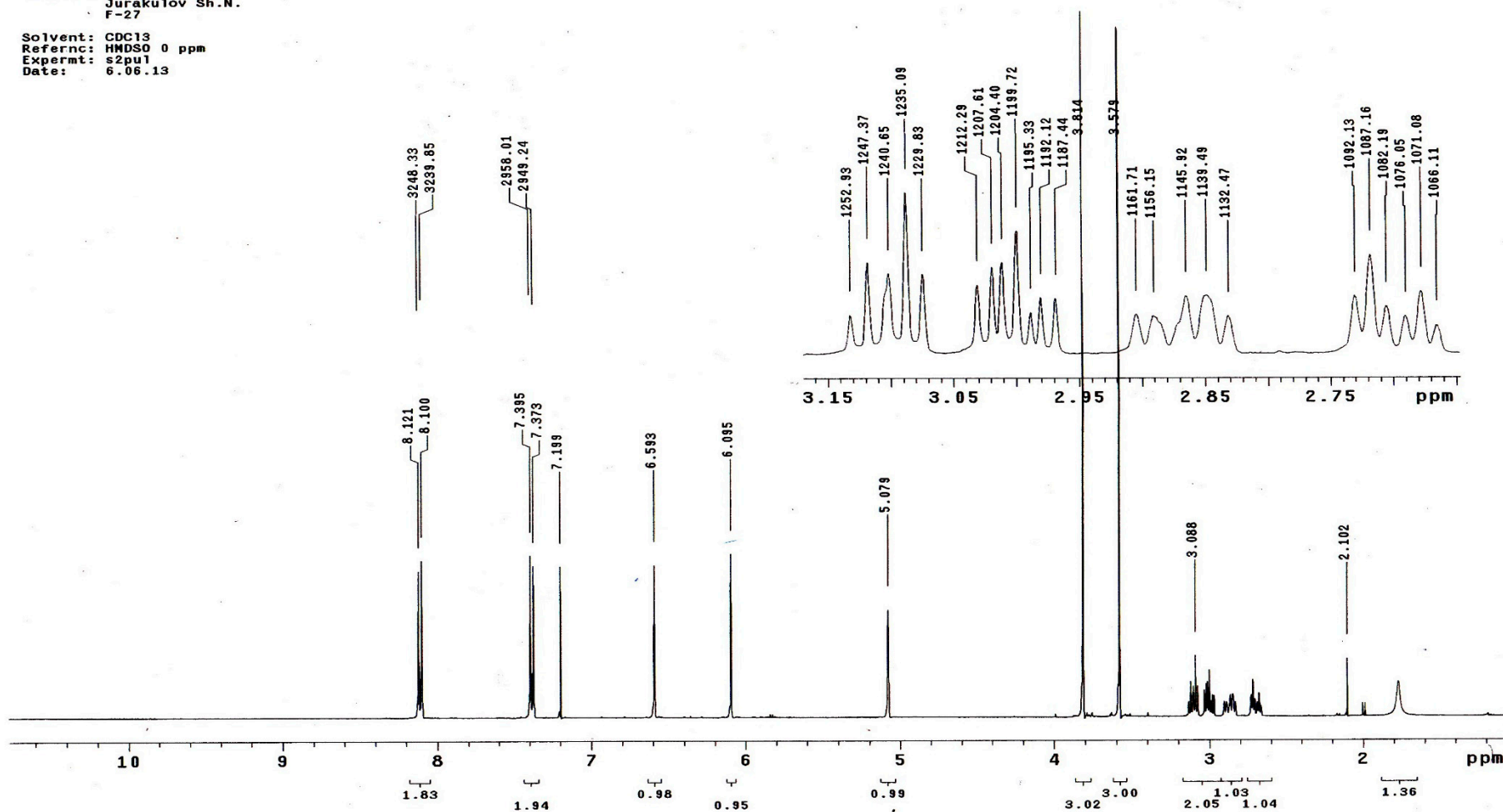
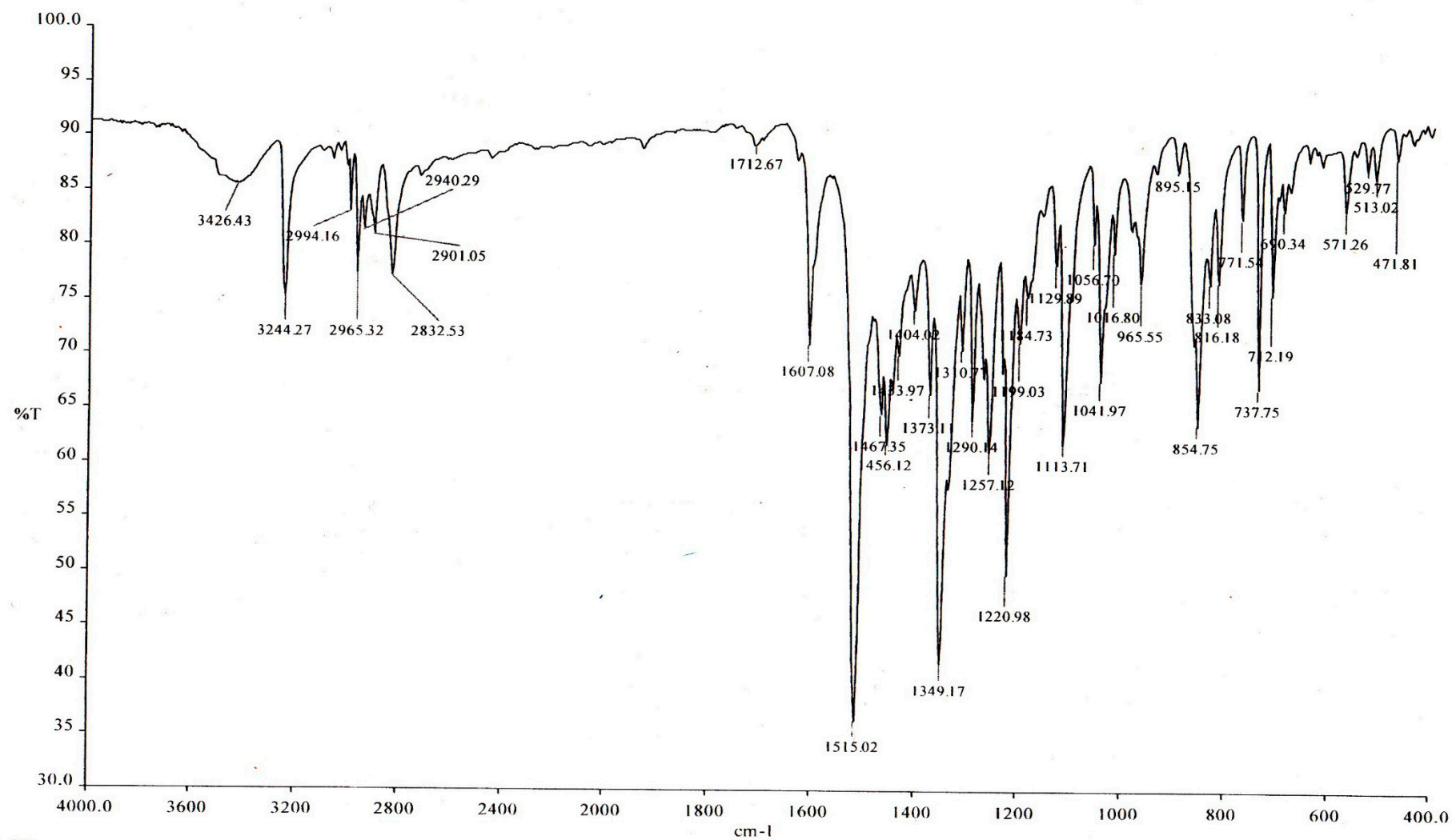


Figure S42. <sup>1</sup>H NMR spectrum of compound **3m**.





F-27

**Figure S43.** IR spectrum of compound **3m**.

NMR UNITY 400plus (Varian)  
ICPS AS RUZ

Sample : Vinogradova V.I.  
Jurakulov Sh.N.  
F-26

Solvent: DMSO  
Refernc: HMDSO 0 ppm  
Expermt: s2pul  
Date: 31.05.13

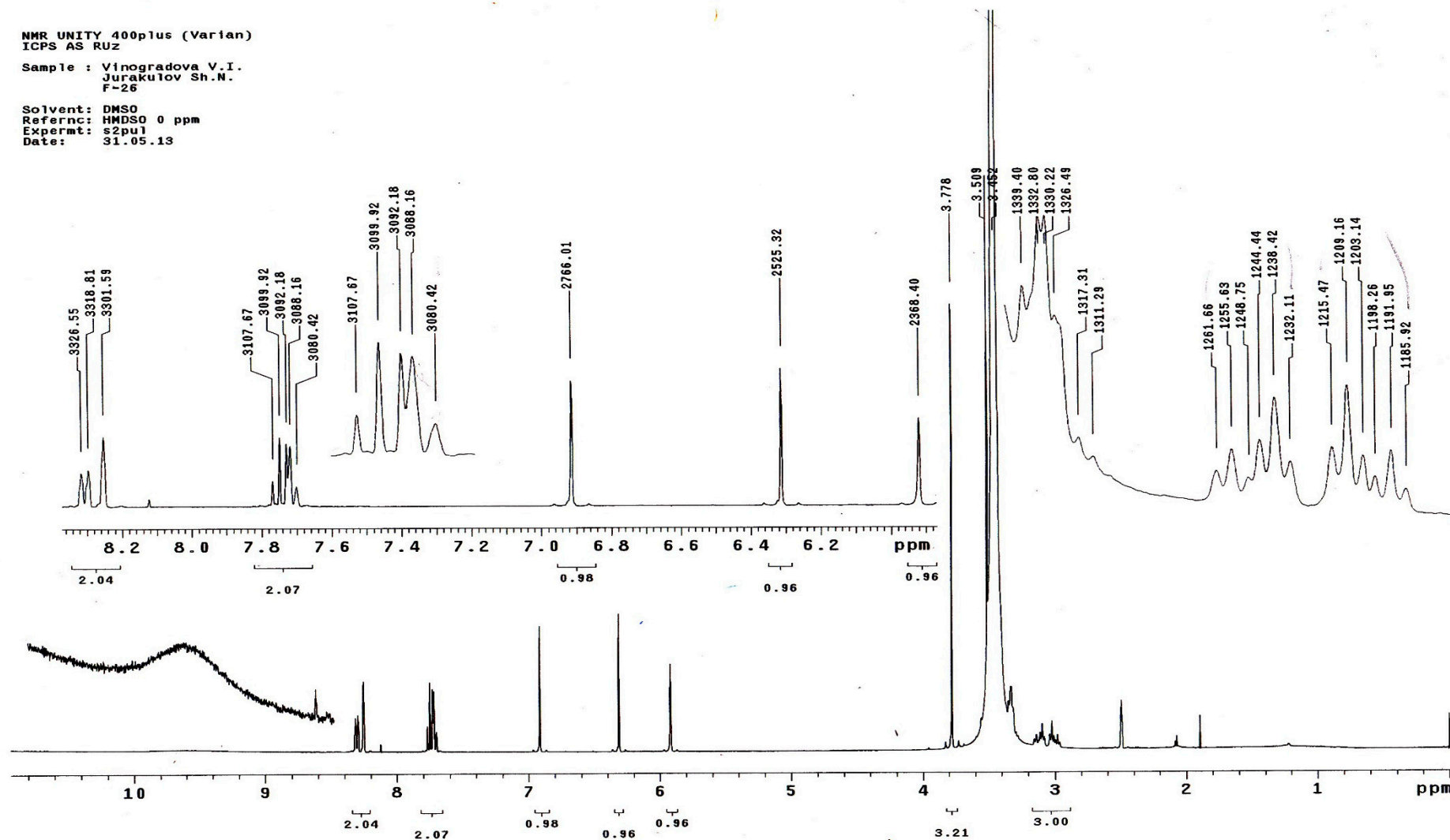
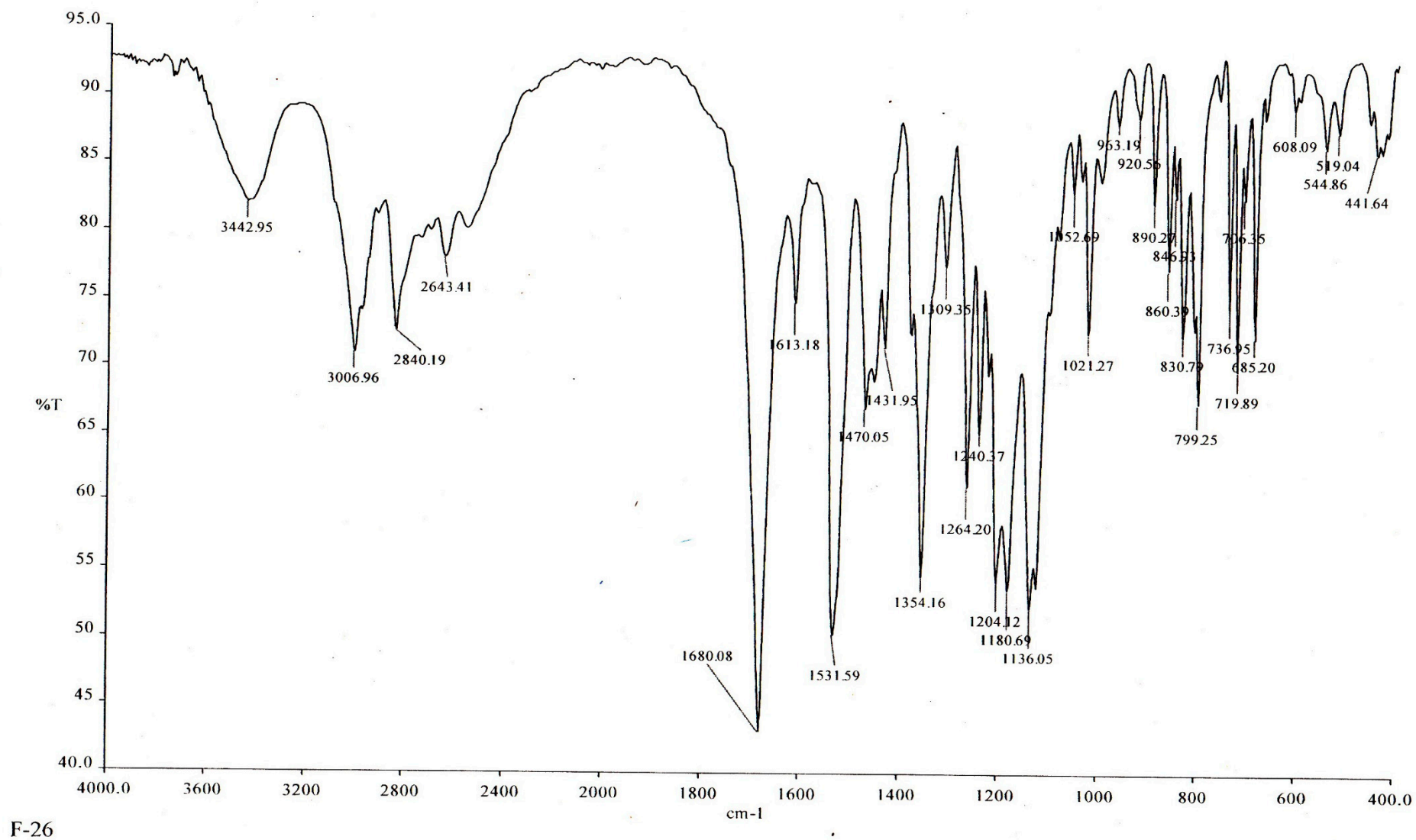


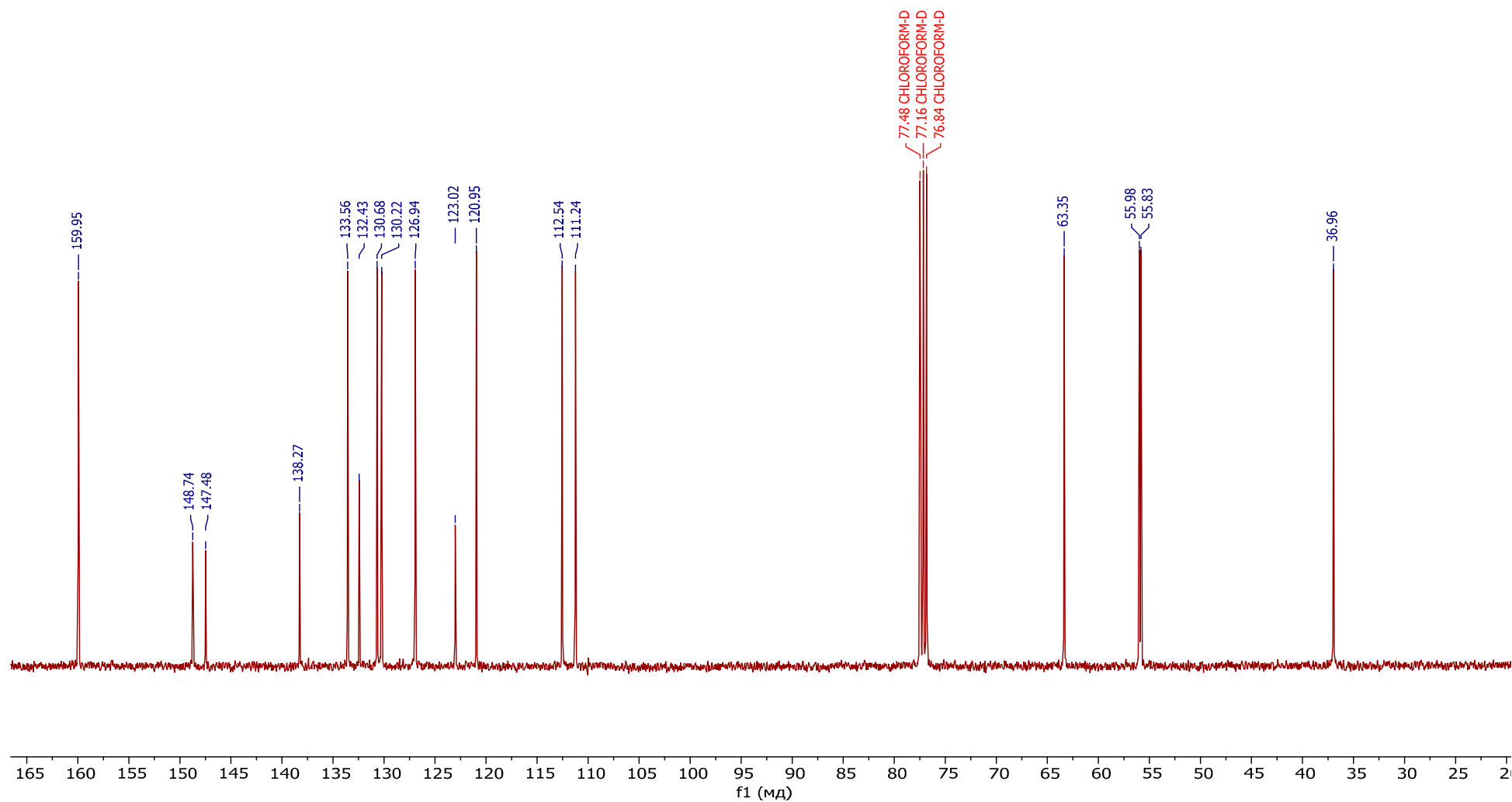
Figure S44.  $^1\text{H}$  NMR spectrum of compound **3n**.



**Figure S45.** IR spectrum of compound **3n**.

**Figure S46.**  $^1\text{H}$  NMR spectrum of compound **30**.

Juraqulov\_F-25  
13C\_CDCI3\_23062021\_400 MHz

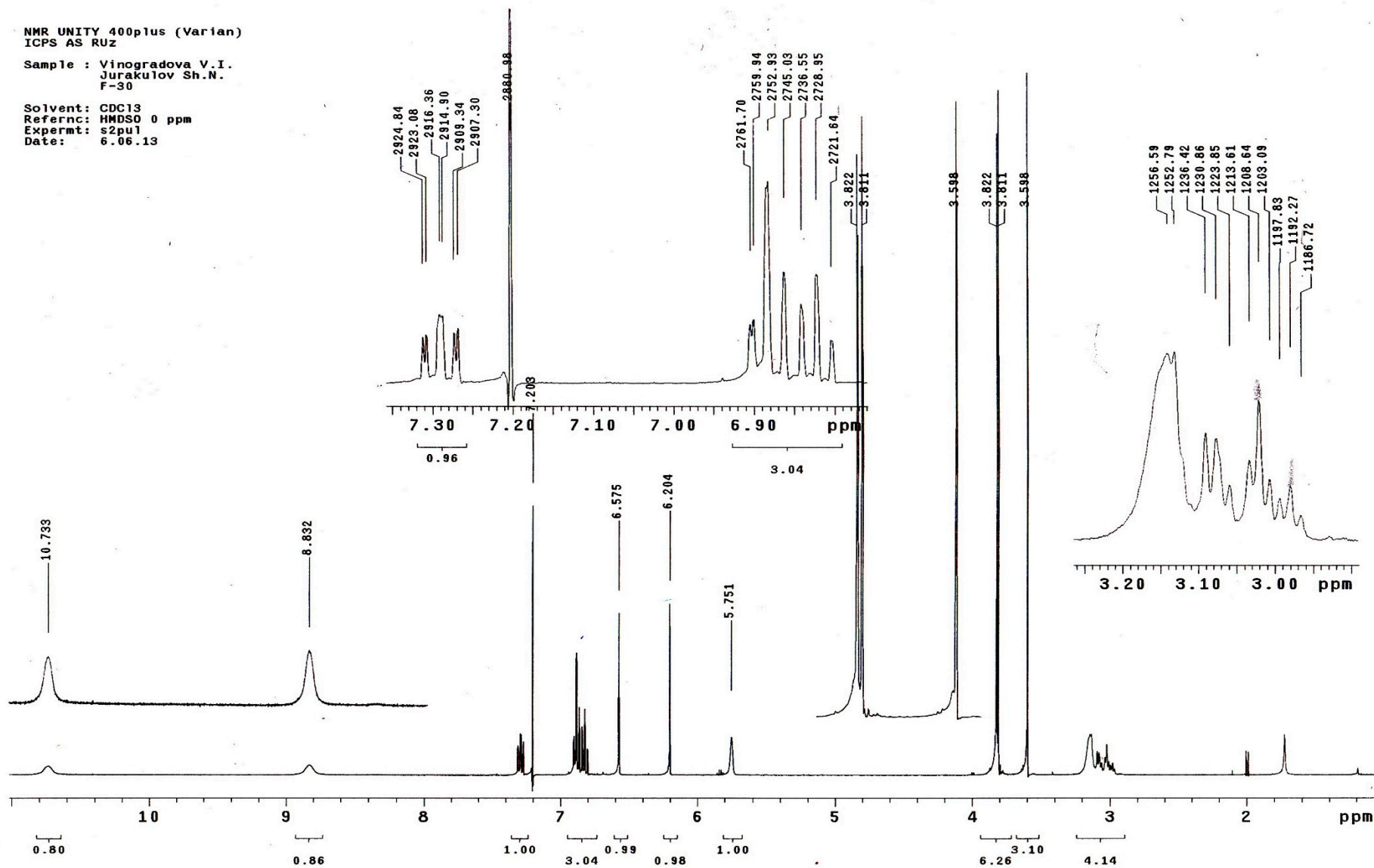


**Figure S47.** <sup>13</sup>C NMR spectrum of compound **3o**.

NMR UNITY 400plus (Varian)  
ICPS AS RUZ

Sample : Vinogradova V.I.  
Jurakulov Sh.N.  
F-30

Solvent: CDC13  
Refernc: HMDSO 0 ppm  
Expermt: s2pu1  
Date: 6.06.13



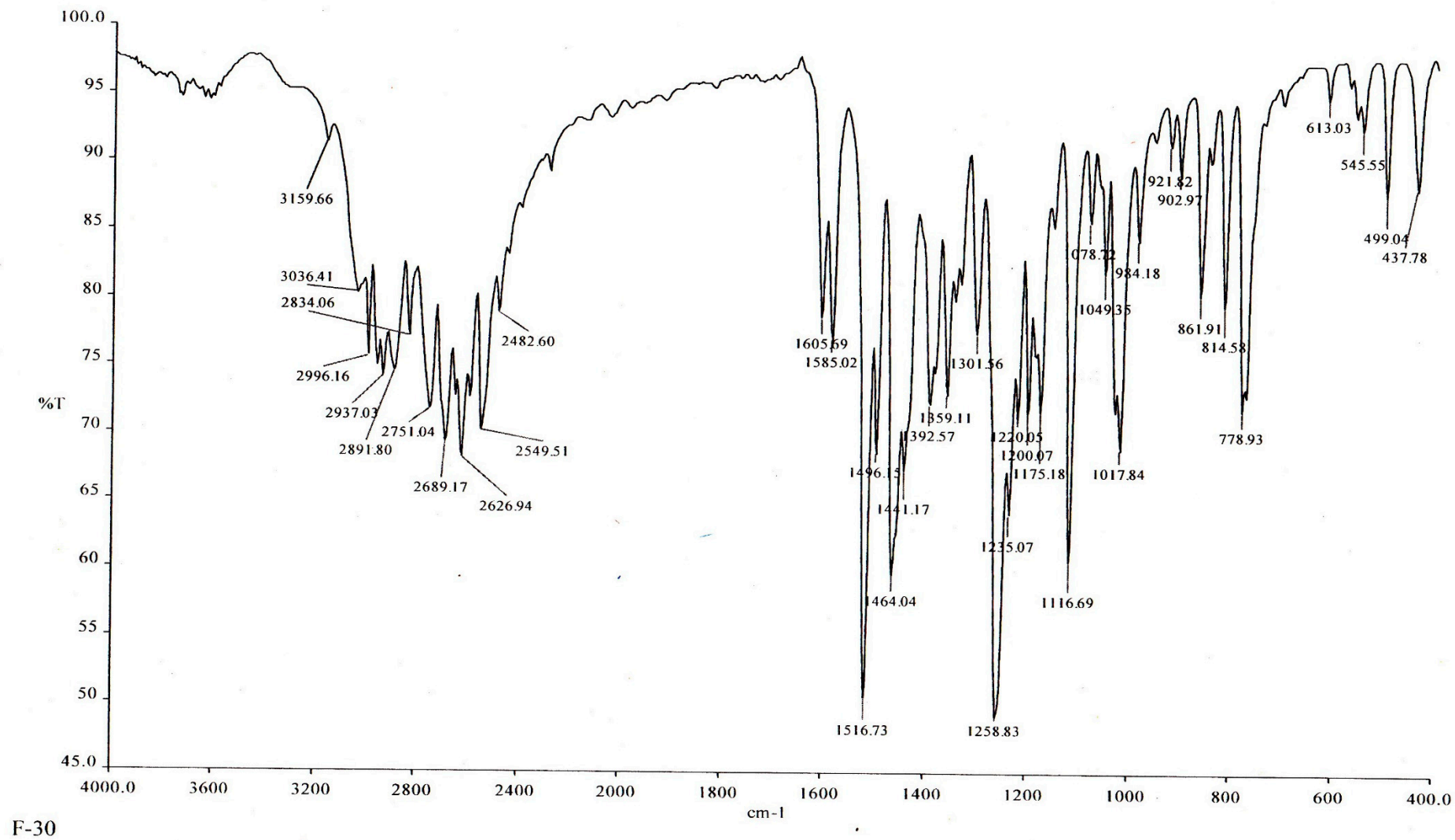
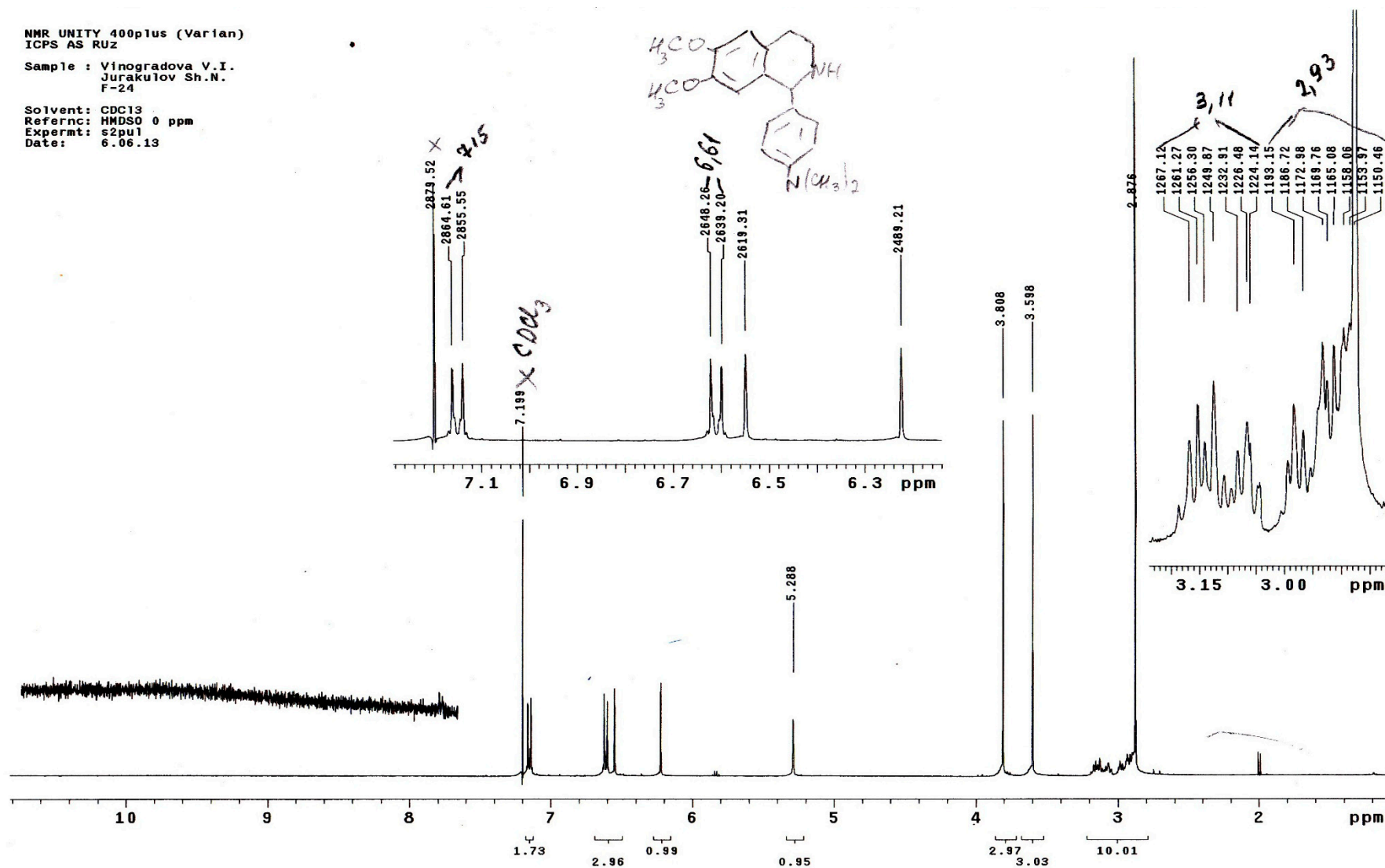


Figure S49. IR spectrum of compound 3n.

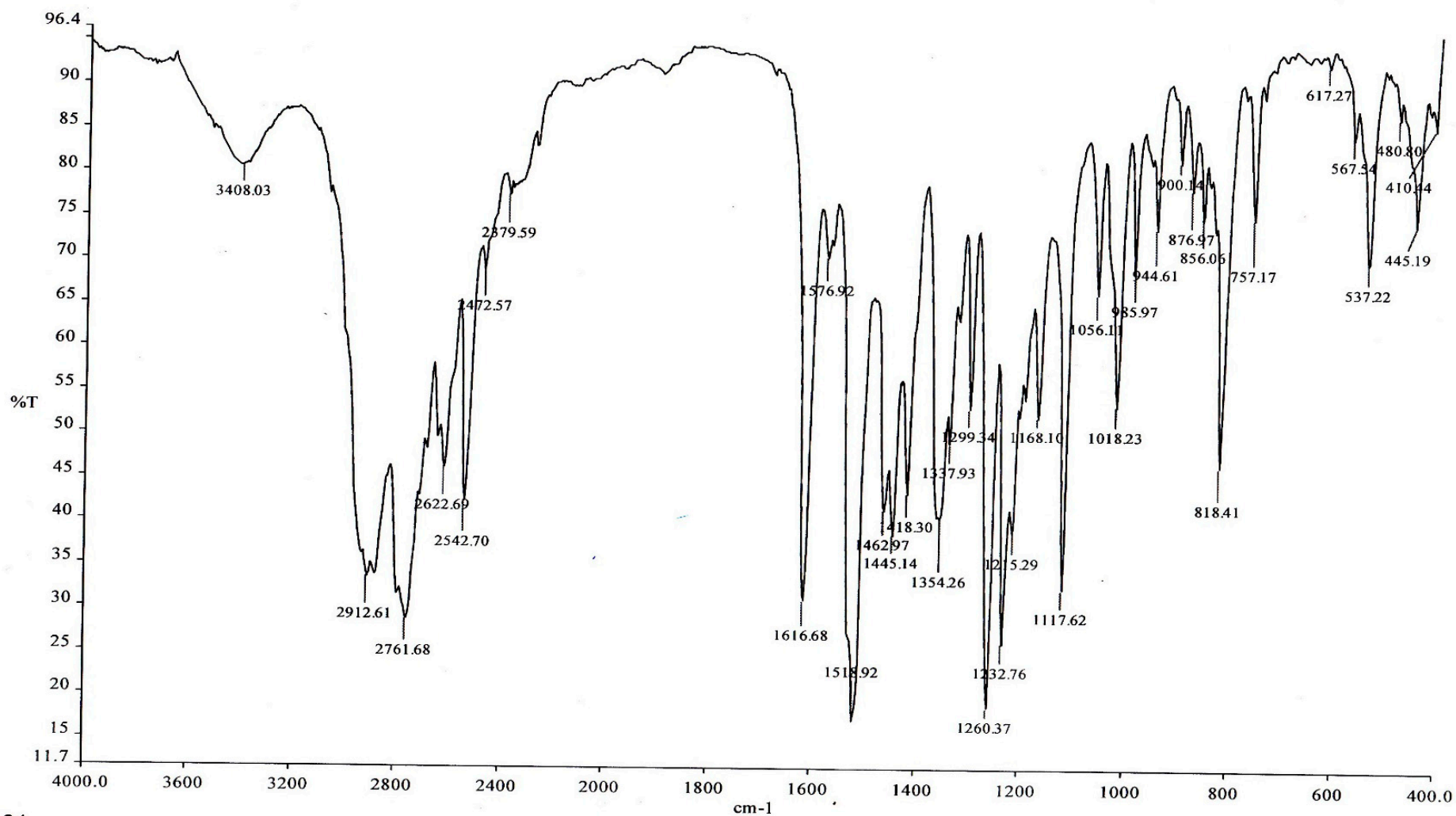


Solvent: CDCl3  
Referenc: HMDSO 0 ppm  
Expermt: s2pu1  
Date: 6.06.13



**Figure S50.**  $^1\text{H}$  NMR spectrum of compound **3q**.





F-24

Figure S51. IR spectrum of compound 3q.

Juraculov\_F-37\_C13  
NMR, UNITY-400plus(Varian)  
ICPS AS RUz

Sample: Juraculov Sh/N/Sh.N.  
F-37

Solvent: CDCl<sub>3</sub>  
Refernc: HMDSO  
Exper-t: 1H  
Date: 22.01.18

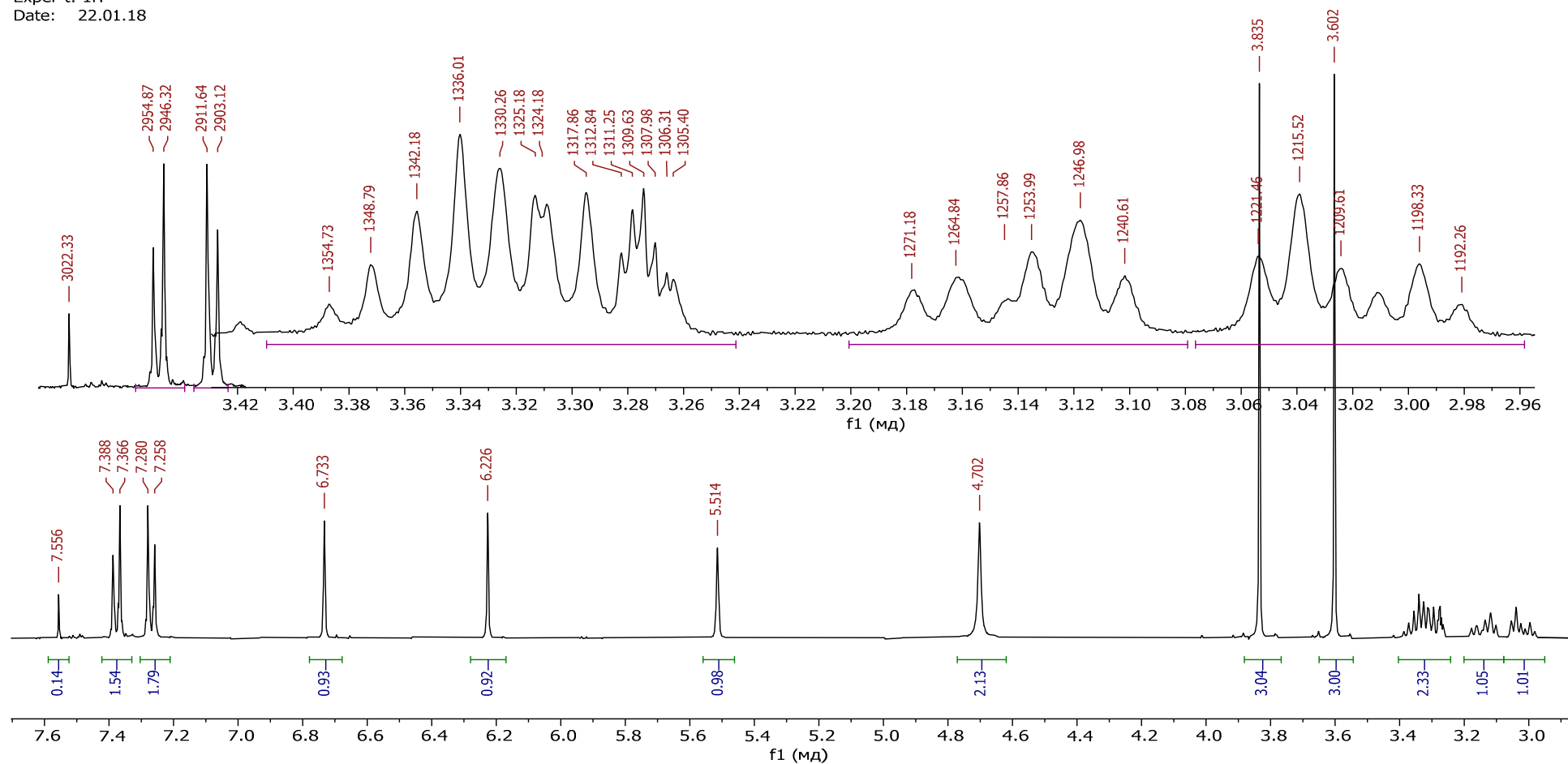


Figure S52. <sup>1</sup>H NMR spectrum of compound **3r**.

Jurakulov\_NH-2  
1H\_DMSO-d6+CCl4\_29092021\_400 MHz

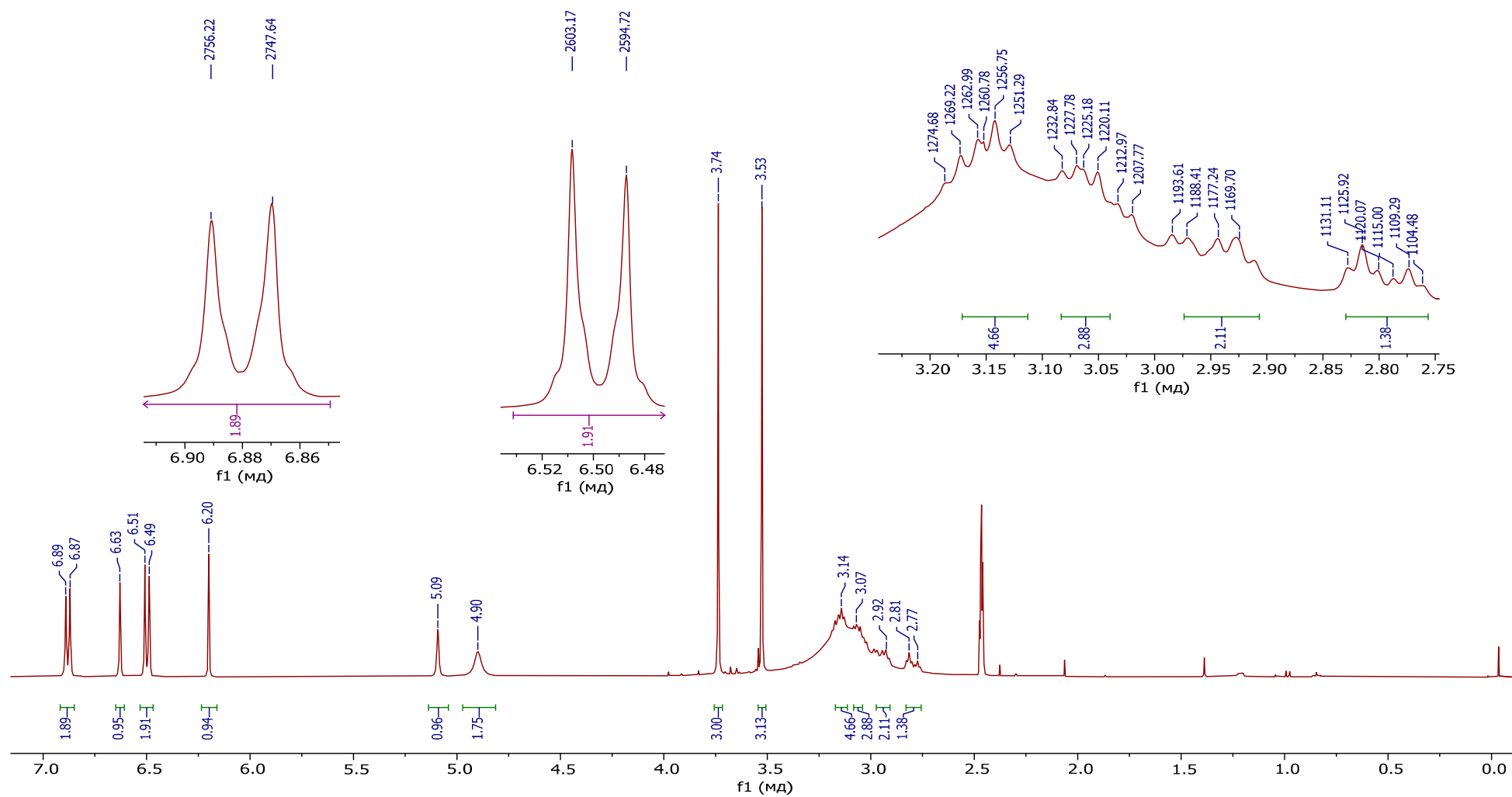
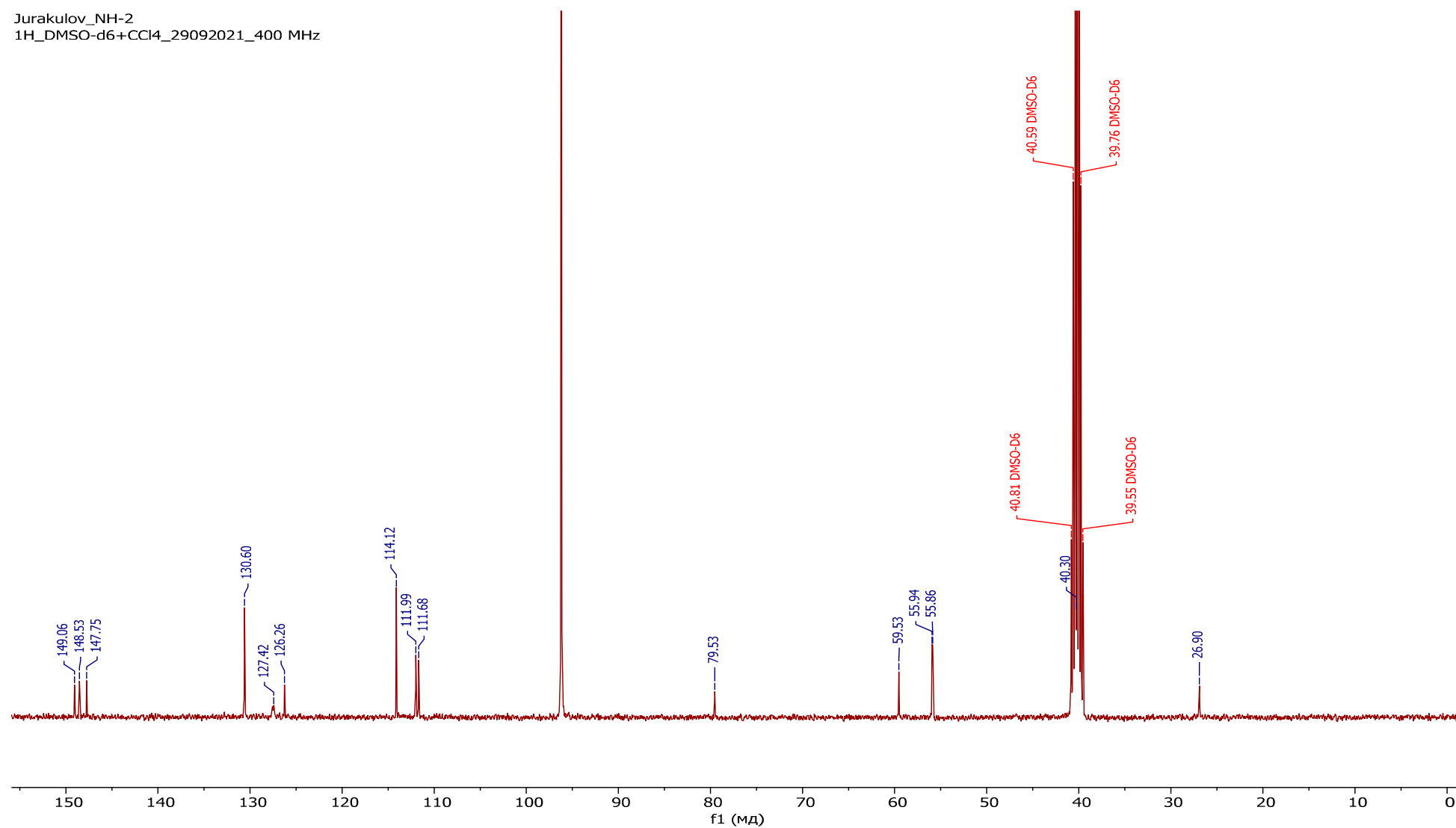


Figure S53. <sup>1</sup>H NMR spectrum of compound 4a.

Jurakulov\_NH-2  
1H\_DMSO-d6+CCl4\_29092021\_400 MHz



**Figure S54.** <sup>13</sup>C NMR spectrum of compound **4a**.

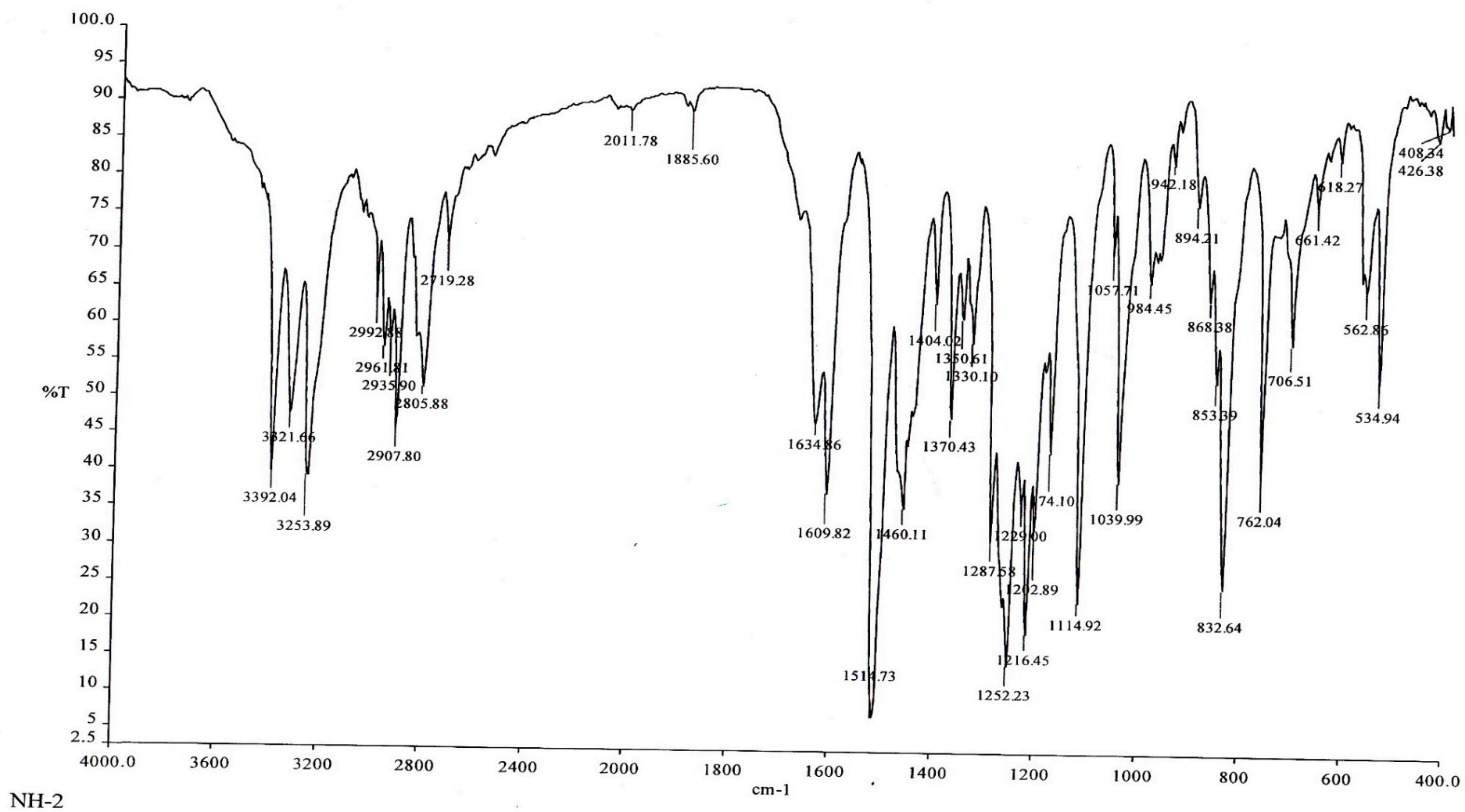
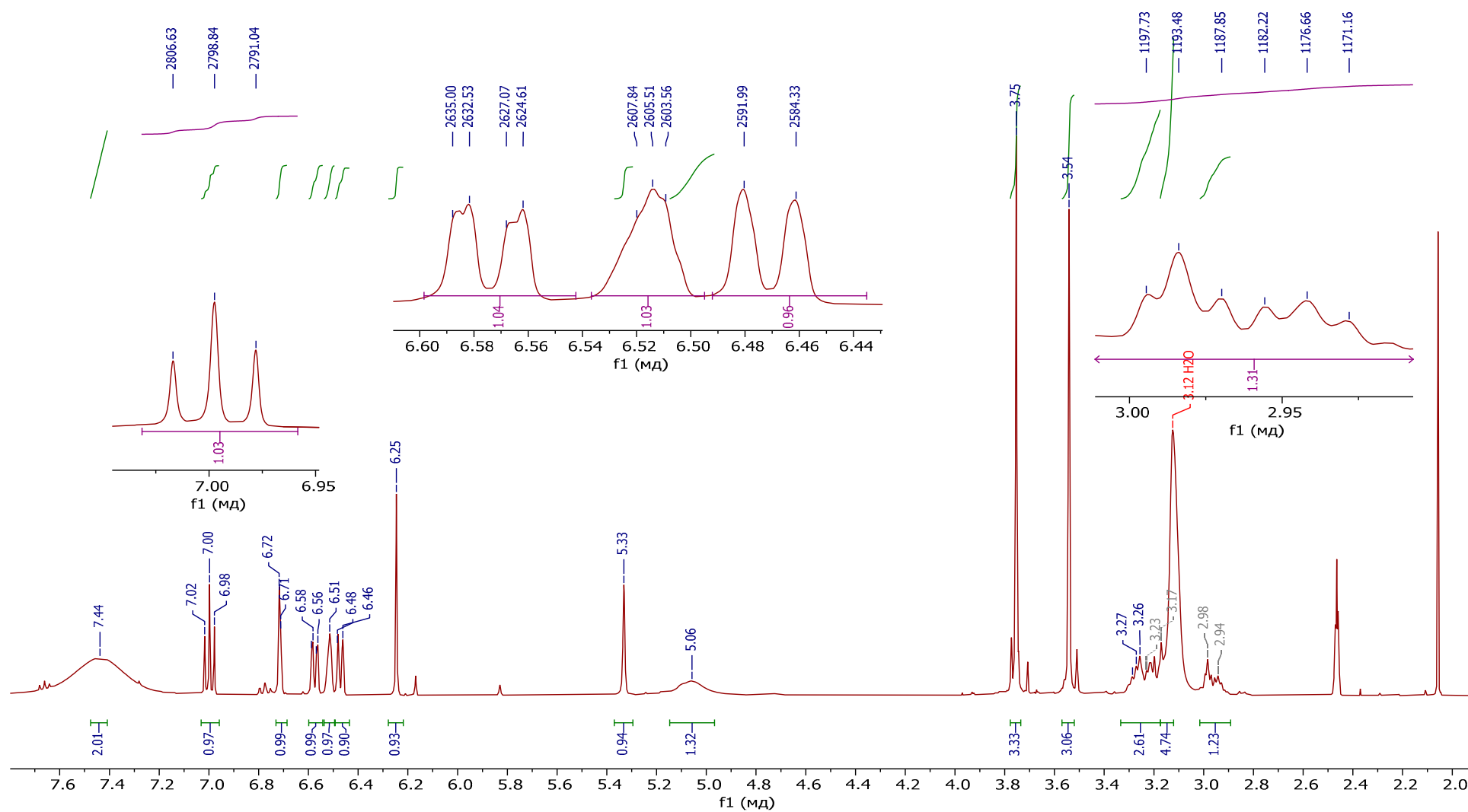


Figure S55. IR spectrum of compound 4a.



**Figure S56.**  $^1\text{H}$  NMR spectrum of compound **4b**.

Jurakulov\_NH-1  
1H\_DMSO-d6+CCl4\_29092021\_400 MHz

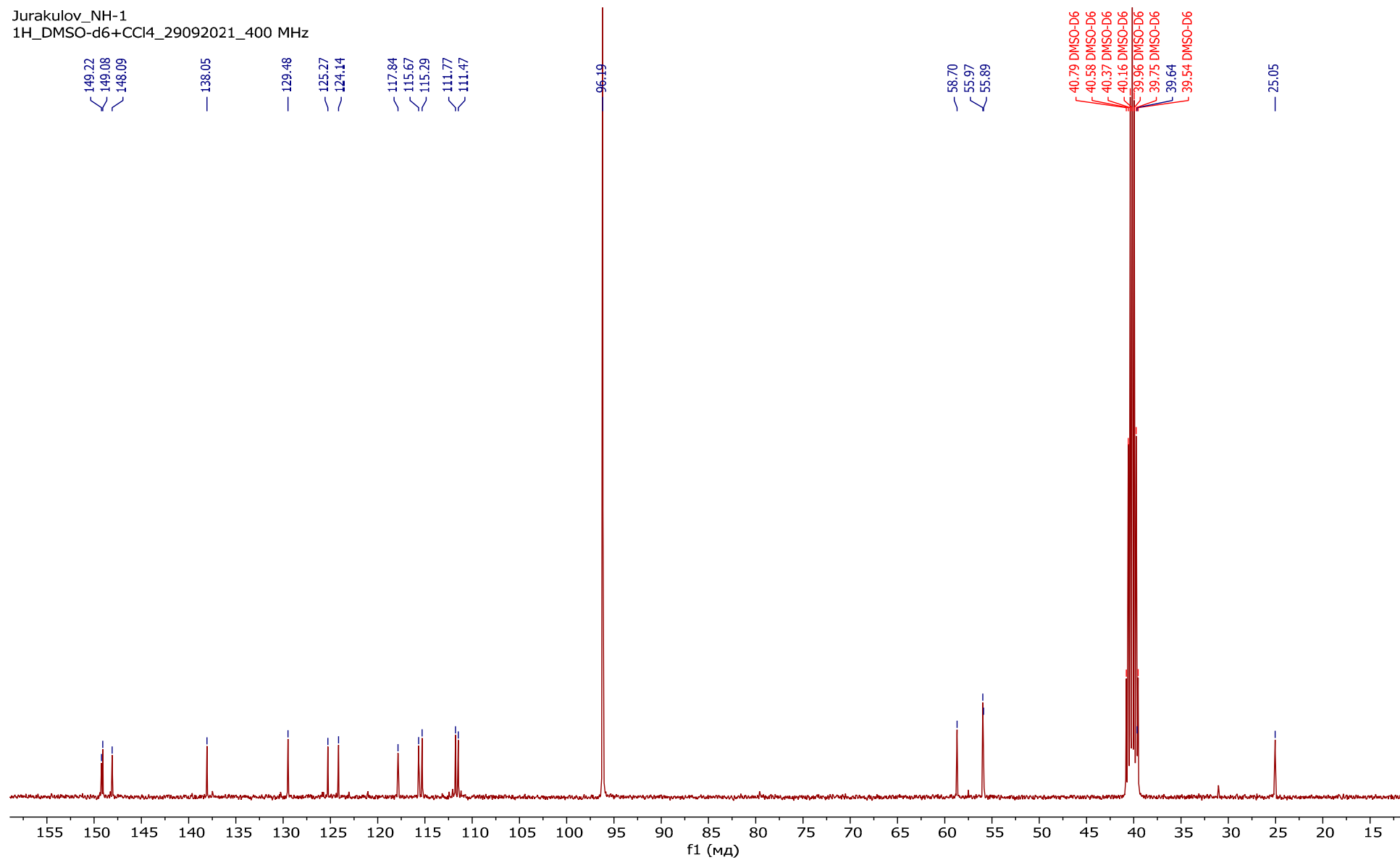


Figure S57.  $^{13}\text{C}$  NMR spectrum of compound **4b**.