Pyrazole/pyrimidine derivatives endowed with azobenzenes as dual EGFR^{T790M} and VEGFR-2 inhibitors: Anticancer, docking, synthesis, design and ADMET assessments

Kurls E. Anwer[1], Mohamed A. Abdelgawad[2,*], Felemban Athary Abdulhaleem M[3], Nour E. A. Abd El-Sattar[1,4], Ahmed El-morsy[5,6], Tamer Nasr[7,8], Mohammed Elmowafy[9], Khaled El-Adl[10,11,*] and Naglaa M. Ahmed[12]

[1] Department of Chemistry - Faculty of Science - Ain Shams University – Abbassia – Cairo - Egypt

[2] Department of Pharmaceutical Chemistry, College of Pharmacy, Jouf University, Sakaka, 72388, Saudi Arabia

[3] Department of Biology – College of Sciences - Umm Al-Qura University – Makkah 21955 - Saudi Arabia

[4] Basic & Medical Sciences Department - Faculty of Dentistry - Alryada University for Science & Technology - Egypt

[5] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy (Boys), Al-Azhar University, Nasr City 11884, Cairo, Egypt

[6] Pharmaceutical Chemistry Department, College of Pharmacy, The Islamic University, Najaf, Iraq

[7] Medicinal Chemistry Department - Faculty of Pharmacy - Egypt-Japan University of Science and Technology (E-JUST) - P.O. 21934 – Alexandria - Egypt

[8] Department of Pharmaceutical Chemistry - Faculty of Pharmacy - Capital University (Formerly Helwan University) - Ain-Helwan - Cairo 11795 - Egypt

[9] Department of Pharmaceutics, College of Pharmacy, Jouf University, Sakaka 72388, Saudi Arabia

[10] Pharmaceutical Chemistry Department - Faculty of Pharmacy - Heliopolis University for Sustainable Development - Cairo, Egypt

[11] Pharmaceutical Medicinal Chemistry and Drug Design Department - Faculty of Pharmacy (Boys) - Al-Azhar University - Nasr City 11884 – Cairo – Egypt

[12] Pharmaceutical Organic Chemistry Department - Faculty of Pharmacy - Capital University (Formerly Helwan University) - Ain-Helwan - Cairo11795 - Egypt

*Corresponding Authors:

Mohamed A. Abdelgawad, mhmdgwd@ju.edu.sa

Khaled El-Adl, eladlkhaled74@azhar.edu.eg; khaled.eladl@hu.edu.eg; eladlkhaled74@yahoo.com

a. **Validation of the accuracy of Docking for VEGFR-2 inhibitors**

As cited in literature if the RMSD (root mean square deviation) of the best docked conformation is ≤ 2.0 Å from the bound ligand in the experimental crystal, the used scoring function is successful. Therefore, the docked results were compared to the crystal structure of the bound ligand–protein complex. The obtained success rates were highly excellent as cited in Table 1. The sorafenib ligand was docked in VEGFR-2 receptor (pdb code: 4ASD). The RMSD of the docked sorafenib was 0.36 Å as it seems exactly superimposed on the co-crystallized native bound one (**Figure 1s**). These results indicated the high accuracy of the docking simulation in comparison with the biological methods.

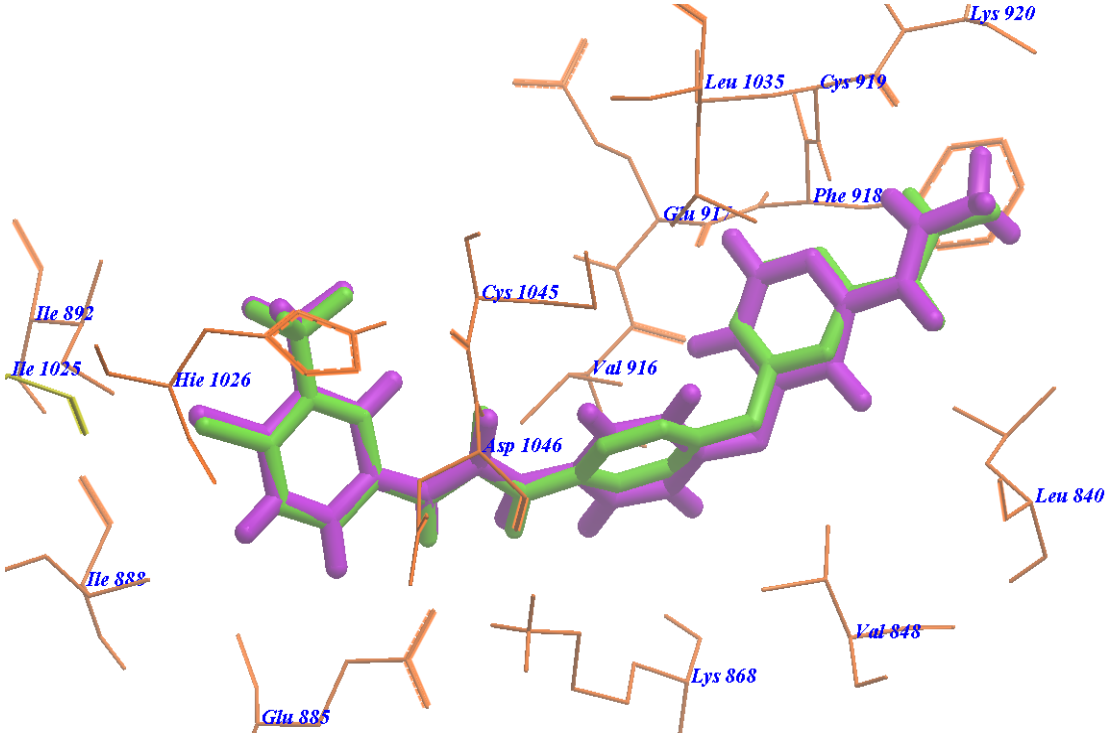


Figure 1s: Superimposition of sorafenib on the co-crystallized native bound one with 4ASD.

b. Validation of the accuracy of Docking for EGFR inhibitors

The Erlotinib ligand was docked in EGFR^{T790M} receptor (pdb code: 3W2O). The RMSD of the docked Erlotinib was 0.93 Å as it seems exactly superimposed on the co-crystallized native bound one (**Figure 2s**). These results indicated the high accuracy of the docking simulation in comparison with the biological methods.

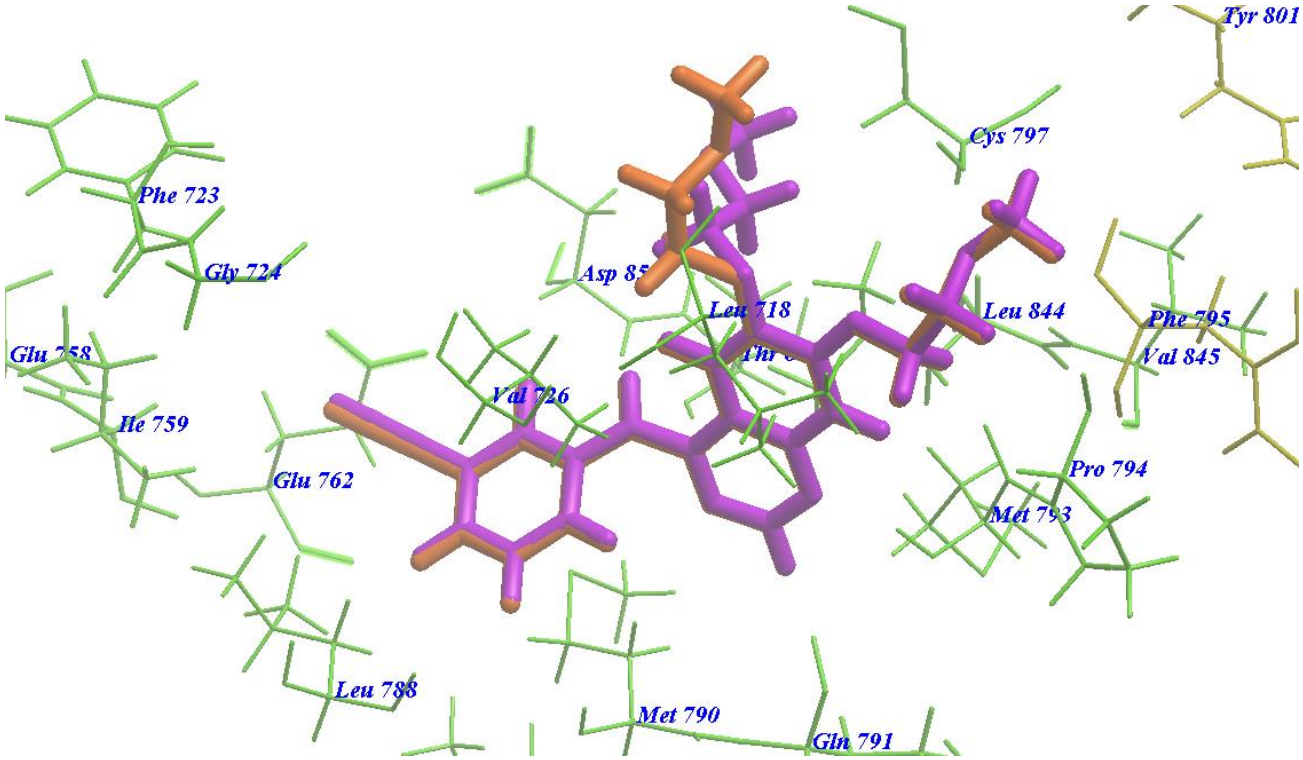


Figure 2s: Superimposition of Erlotinib on the co-crystallized native bound one with 3W2O.

All synthesized derivatives were subjected to molecular docking and the highest binding compounds were provided in the figures

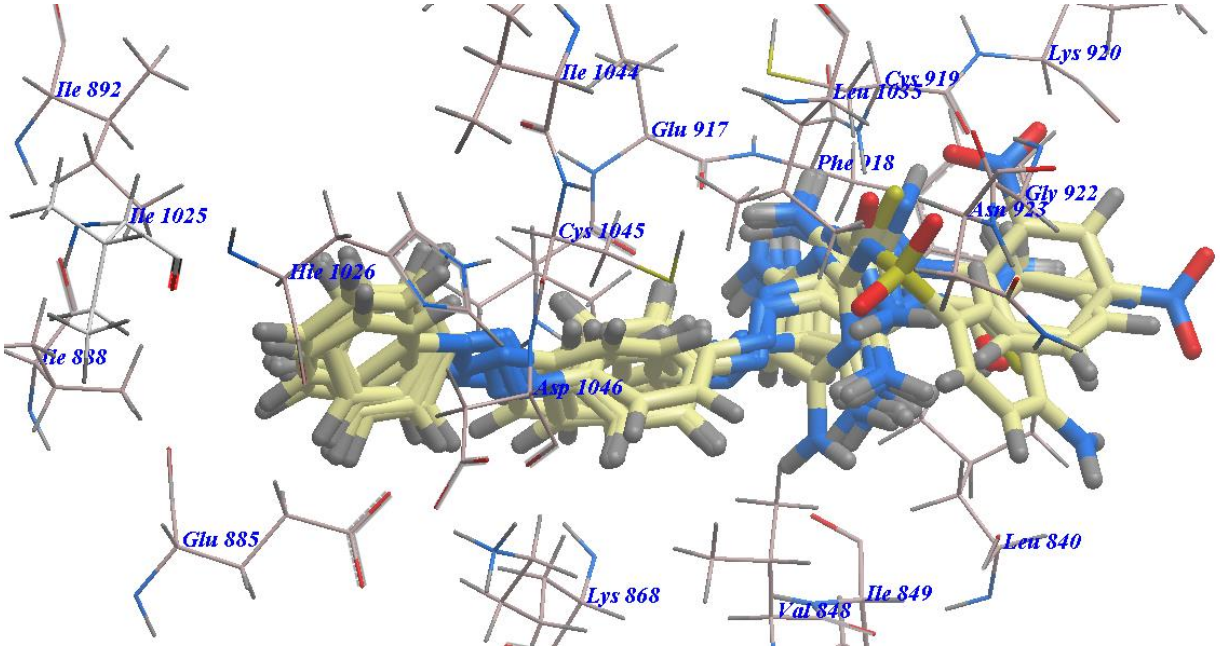
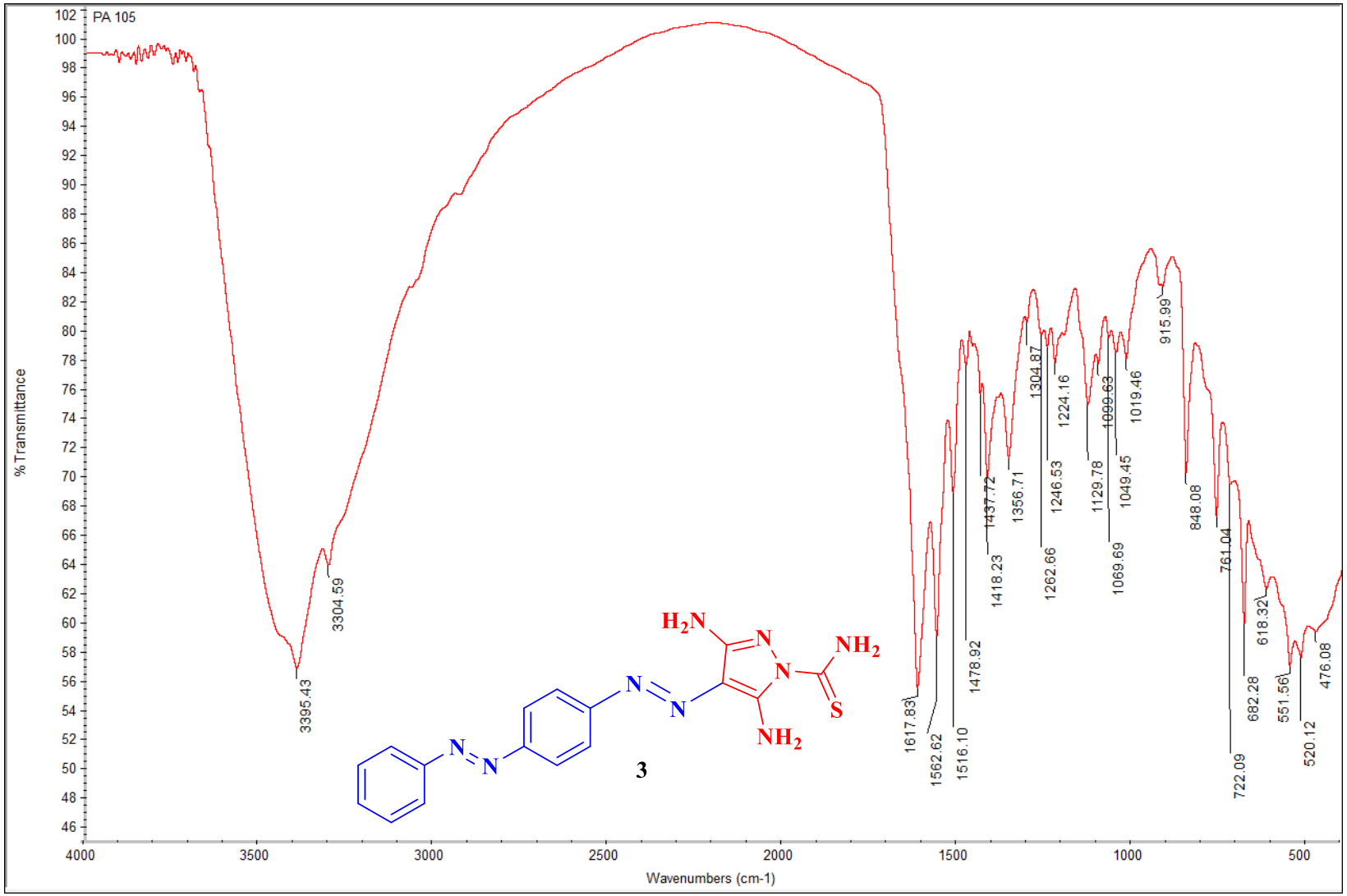
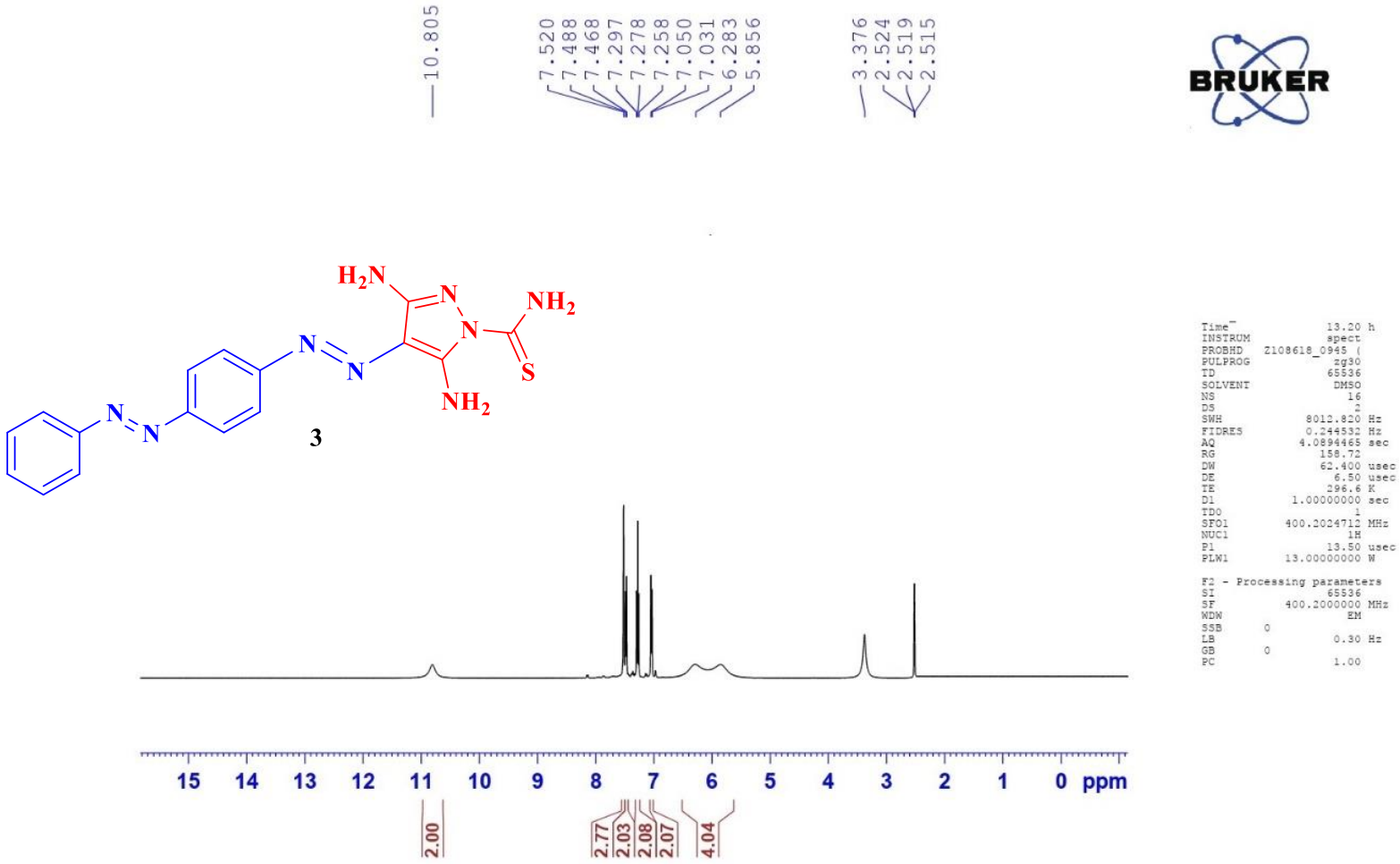


Figure 3s: Superimposition of all docked compounds in the active site of VEGFR-2

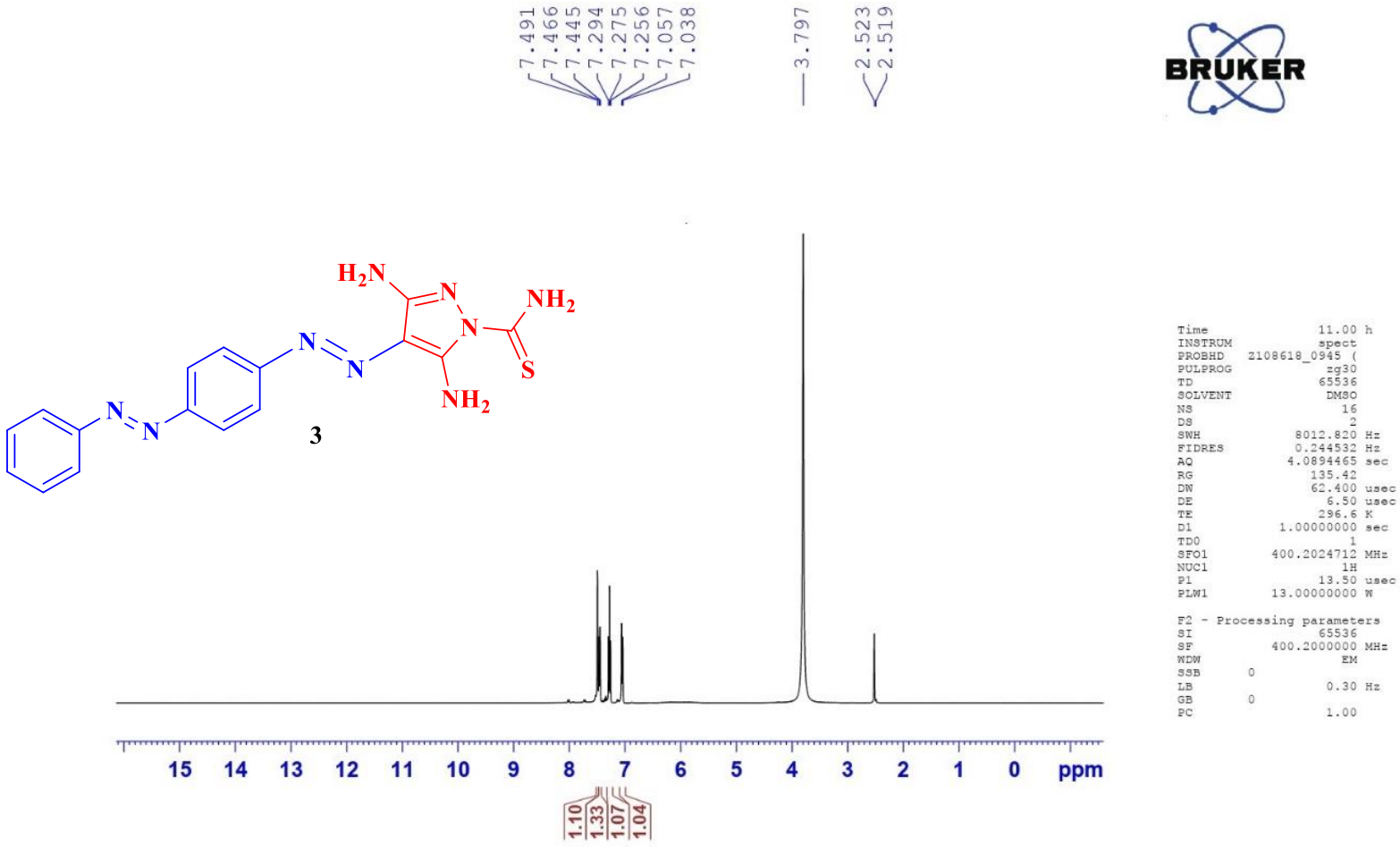
IR of compound 3



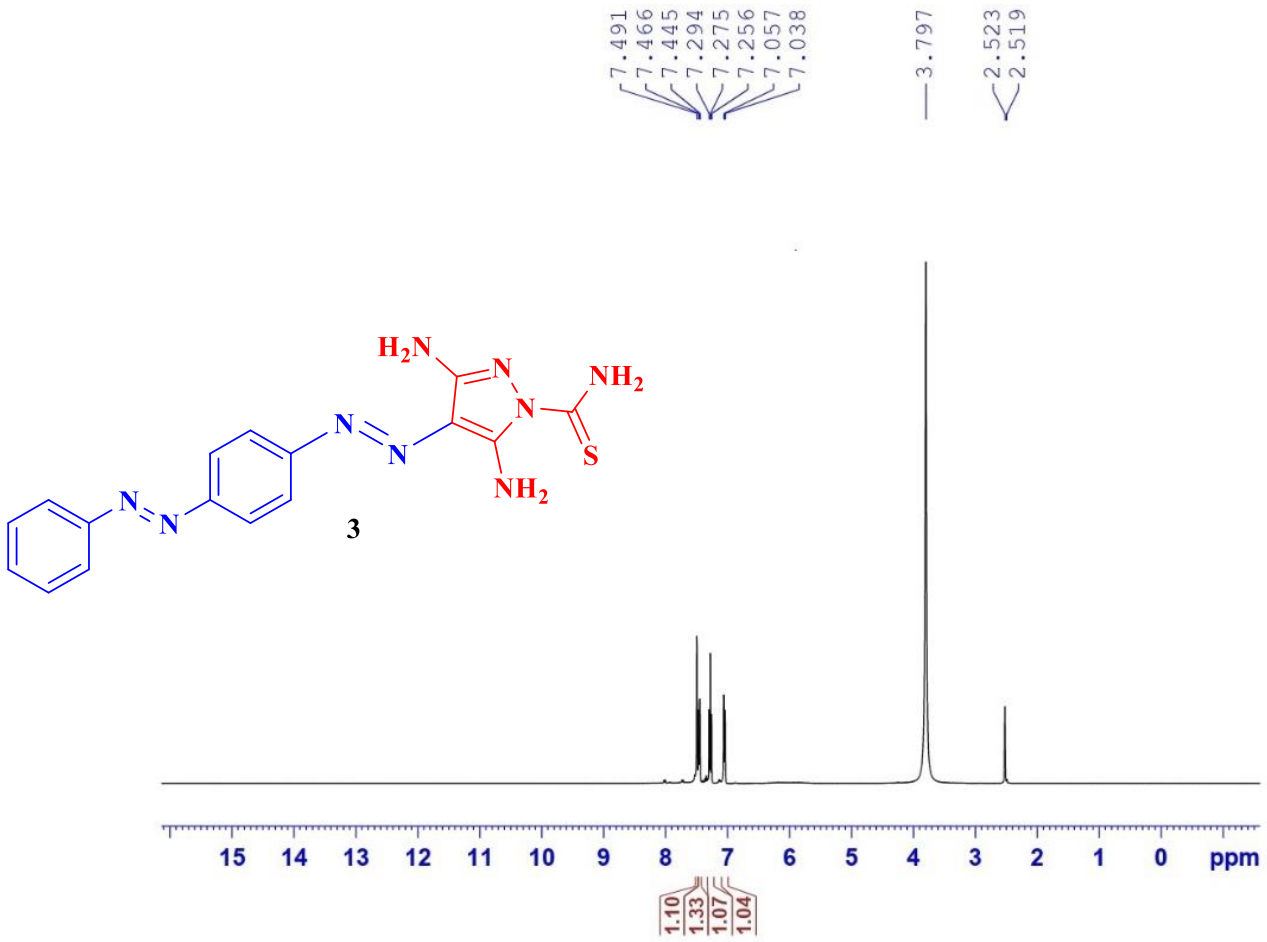
1HNMR of compound 3



D2O Of compound 3



13CNMR of compound 3

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TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH               8012.820 Hz
FIDRES               0.244532 Hz
AQ                4.0894465 sec
RG                   135.42
DW                   62.400 usec
DE                    6.50 usec
TE                   296.6 K
D1             1.00000000 sec
TD0                     1
SFO1           400.2024712 MHz
NUC1                   1H
P1                   13.50 usec
PLW1           13.00000000 W

F2 - Processing parameters
SI                  65536
SF             400.2000000 MHz
WDW                    EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
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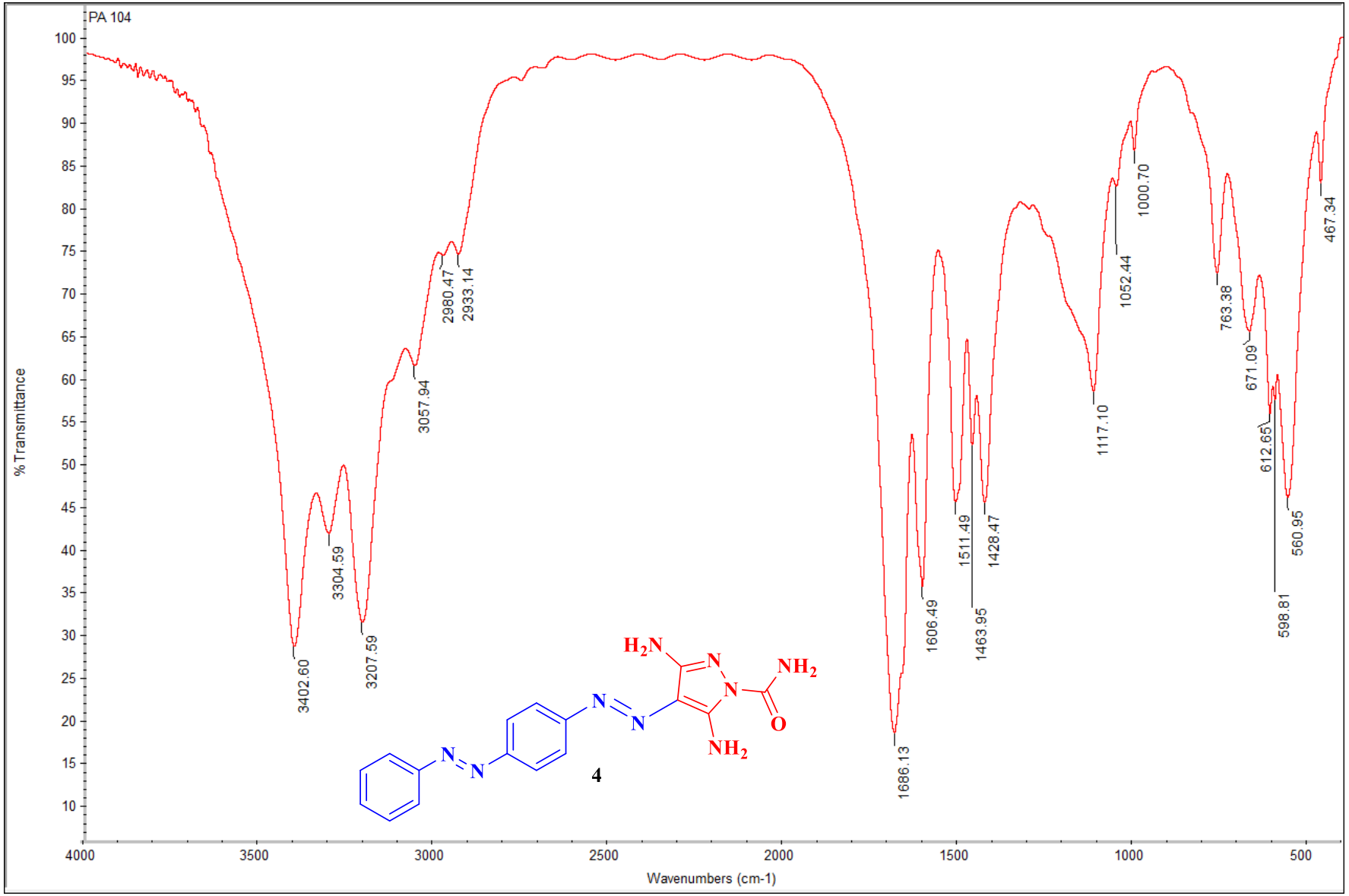
IR of compound 4



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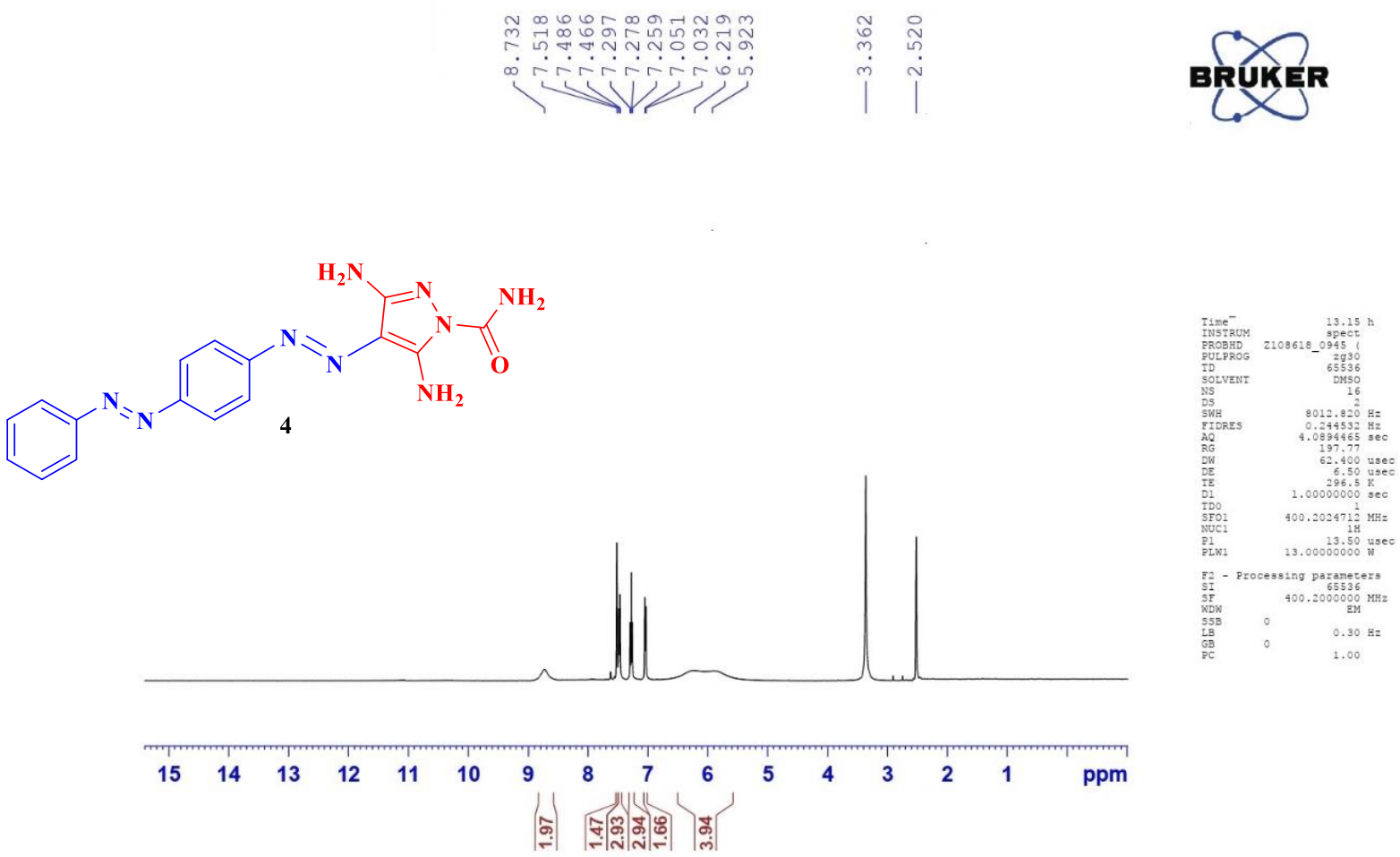
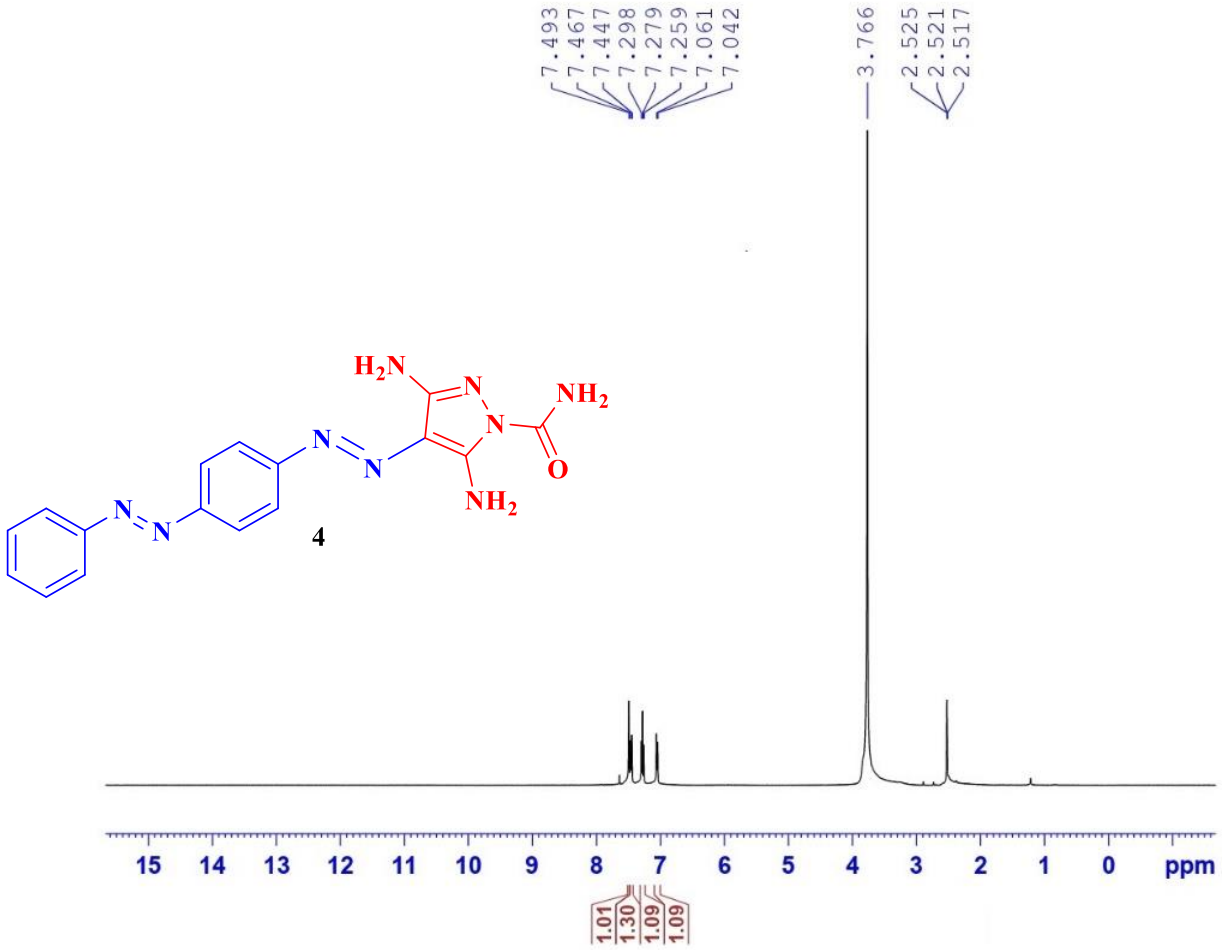


D2O Of compound 4

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TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
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FIDRES               0.244532 Hz
AQ                4.0894465 sec
RG                   176.72
DW                   62.400 usec
DE                    6.50 usec
TE                   296.6 K
D1                1.00000000 sec
TD0                     1
SFO1            400.2024712 MHz
NUC1                   1H
P1                   13.50 usec
PLW1           13.00000000 W

F2 - Processing parameters
SI                  65536
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WDW                    EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
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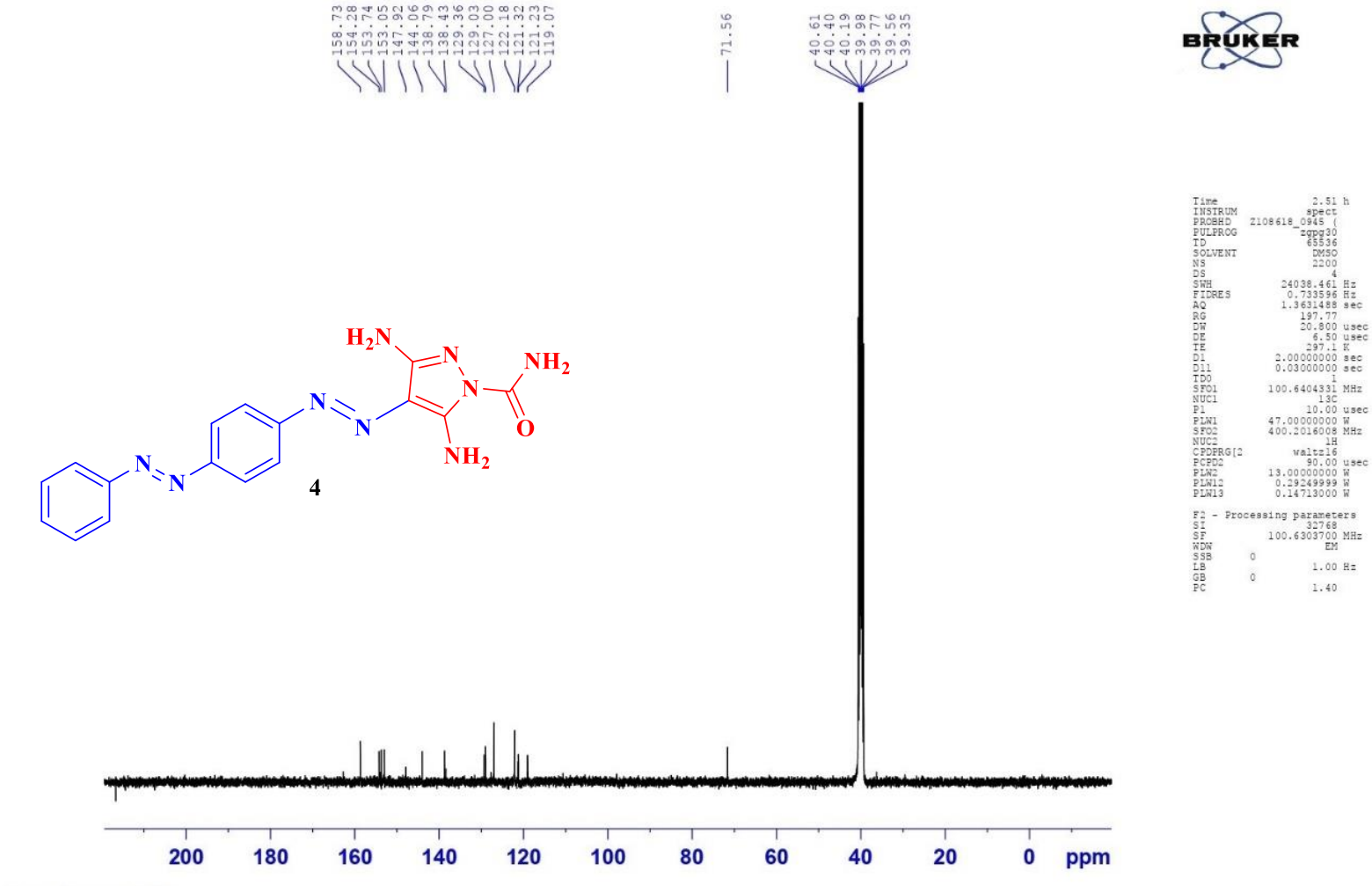
13CNMR of compound 4

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Time                  2.51 h
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PROBHD    Z108618_0945 (
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                     2200
DS                        4
SWH              24038.461 Hz
FIDRES            0.733598 Hz
AQ                1.3631488 sec
RG                   197.77
DW                  20.800 usec
DE                   6.50 usec
TE                  297.1 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                       1
SFO1           100.6404331 MHz
NUC1                    13C
P1                  10.00 usec
PLW1           47.00000000 W
SFO2           400.2016008 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2               90.00 usec
PLW2           13.00000000 W
PLW12           0.29249999 W
PLW13           0.14713000 W

F2 - Processing parameters
SI                    32768
SF           100.6303700 MHz
WDW                     EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
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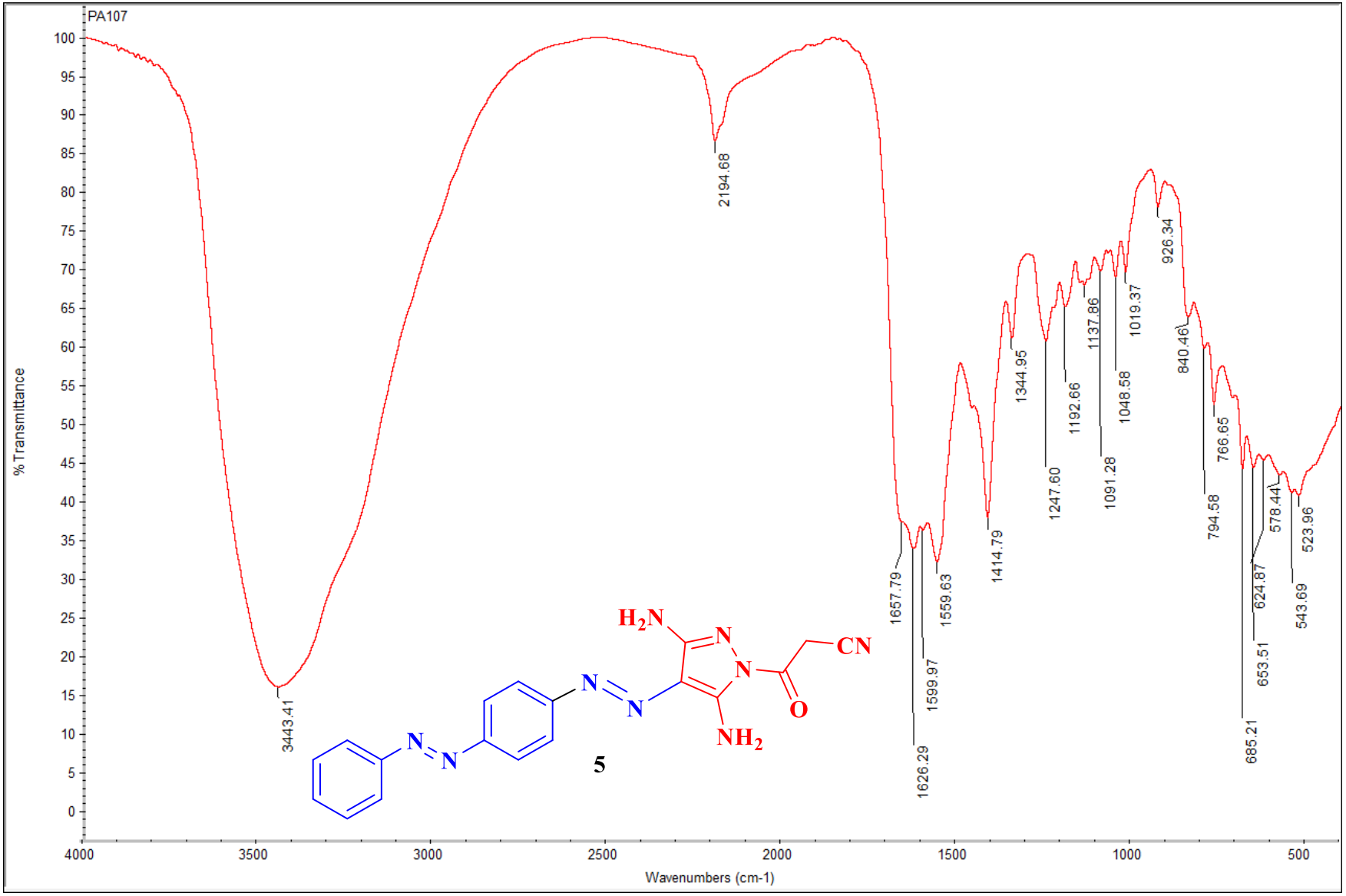
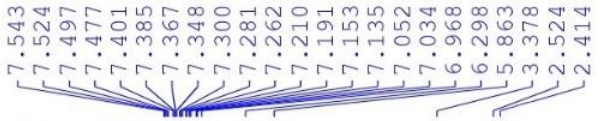
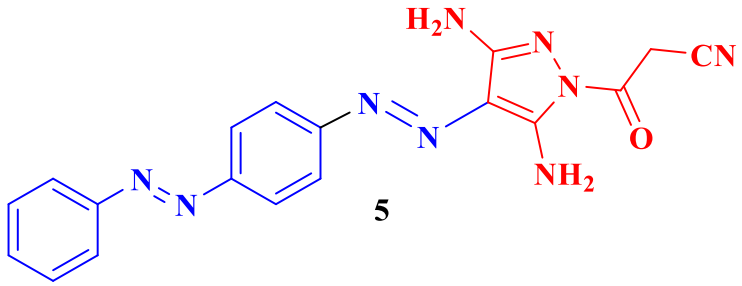
IR of compound 5



1HNMR of compound 5





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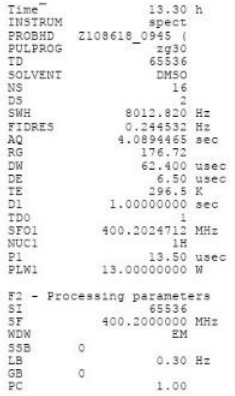
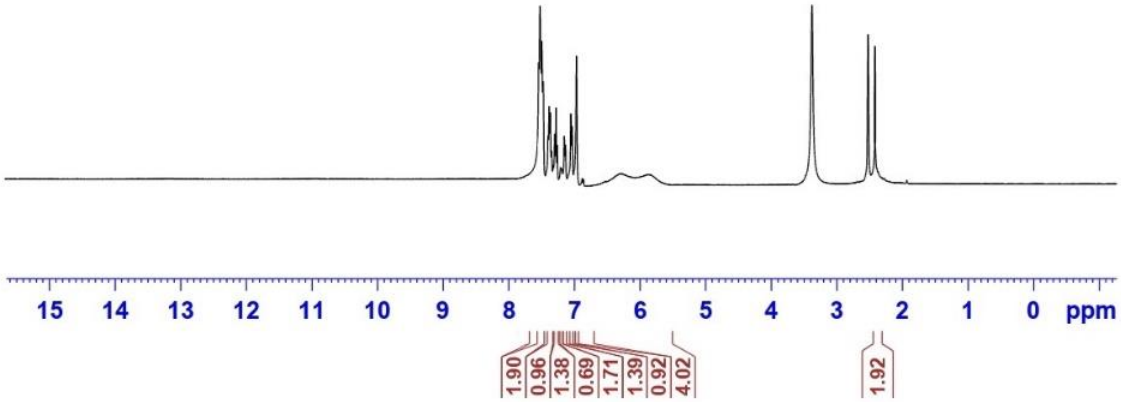
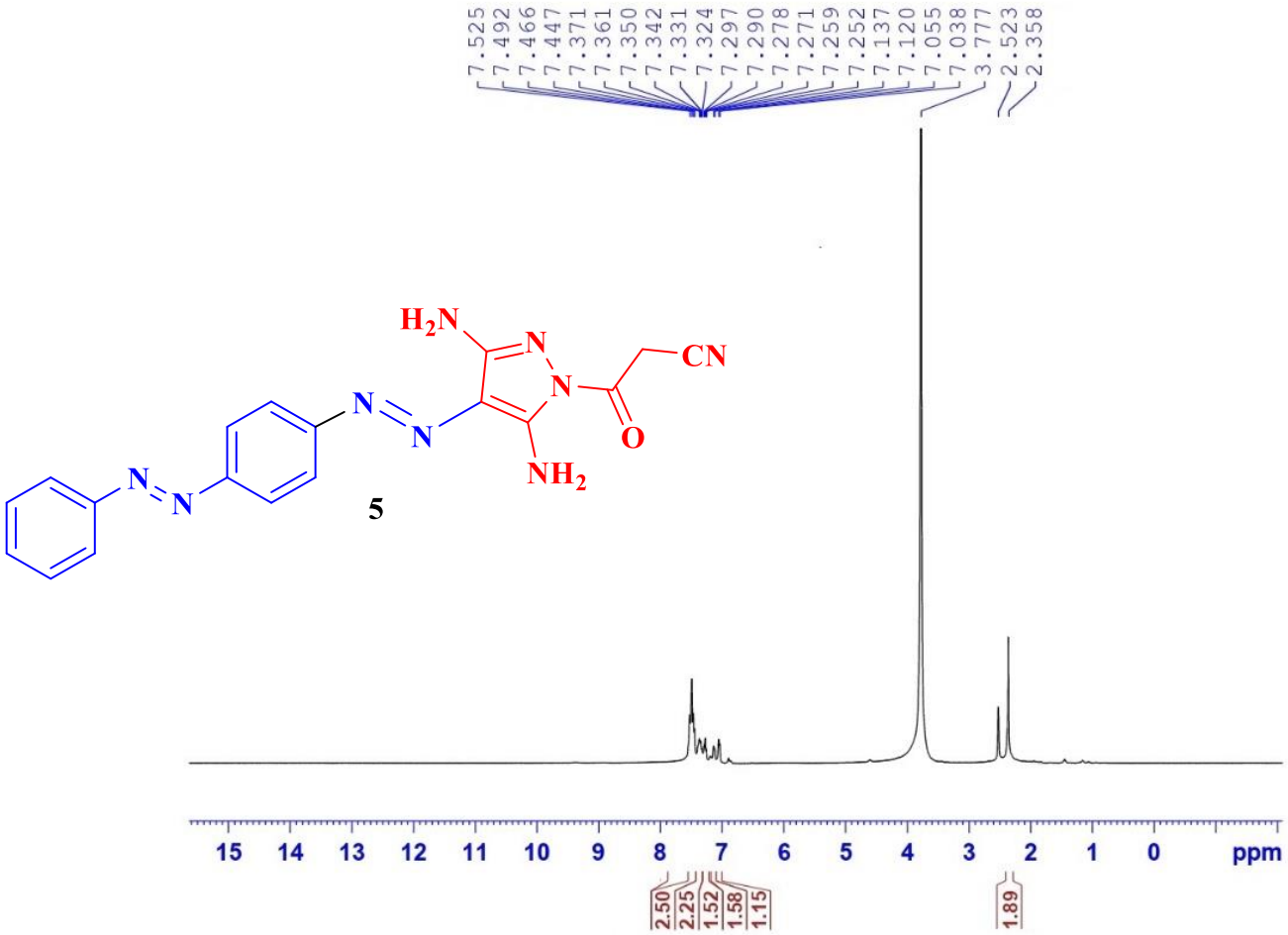




D2O Of compound 5



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PROBHD	Z108618_0945 (	
PULPROG	zg30	
TD	65536	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8012.820	Hz
FIDRES	0.244532	Hz
AQ	4.0894465	sec
RG	135.42	
DW	62.400	usec
DE	6.50	usec
TE	296.6	K
D1	1.00000000	sec
TD0	1	
SFO1	400.2024712	MHz
NUC1	1H	
P1	13.50	usec
PLW1	13.00000000	W
F2 - Processing parameters		
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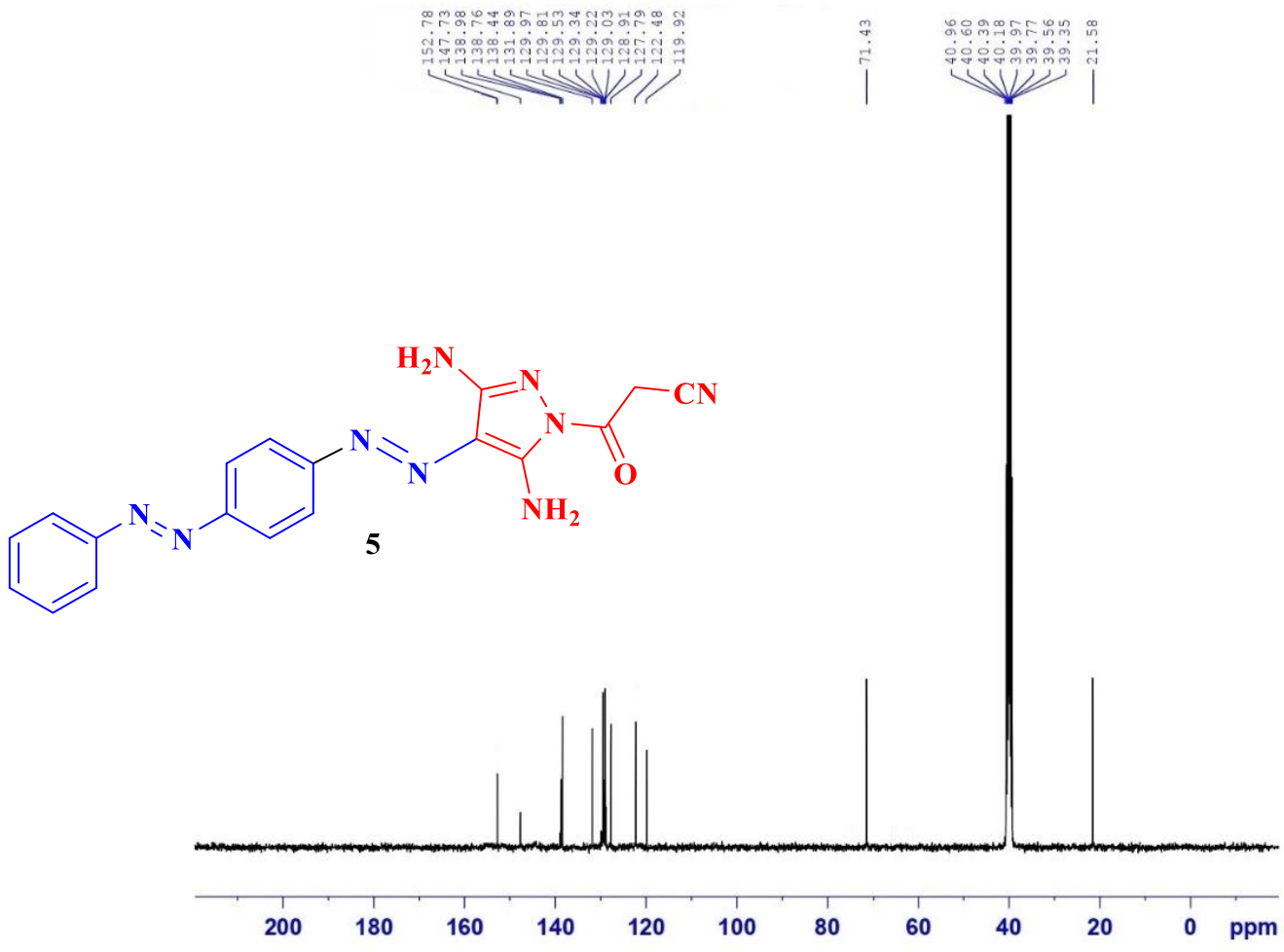
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

13CNMR of compound 5



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Time                  0.42 h
INSTRUM               spect
PROBHD    Z108618_0945 (
PULPROG               zgpg30
TD                    65536
SOLVENT               DMSO
NS                     2200
DS                        4
SWH               24038.461 Hz
FIDRES            0.733596 Hz
AQ                1.3631488 sec
RG                   197.77
DW                  20.800 usec
DE                   6.50 usec
TE                   297.3 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                       1
SFO1          100.6404331 MHz
NUC1                    13C
P1                   10.00 usec
PLW1          47.00000000 W
SFO2          400.2016008 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                90.00 usec
PLW2          13.00000000 W
PLW12          0.29249999 W
PLW13          0.14713000 W

F2 - Processing parameters
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WDW                     EM
SSB       0
LB                    1.00 Hz
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PC                    1.40
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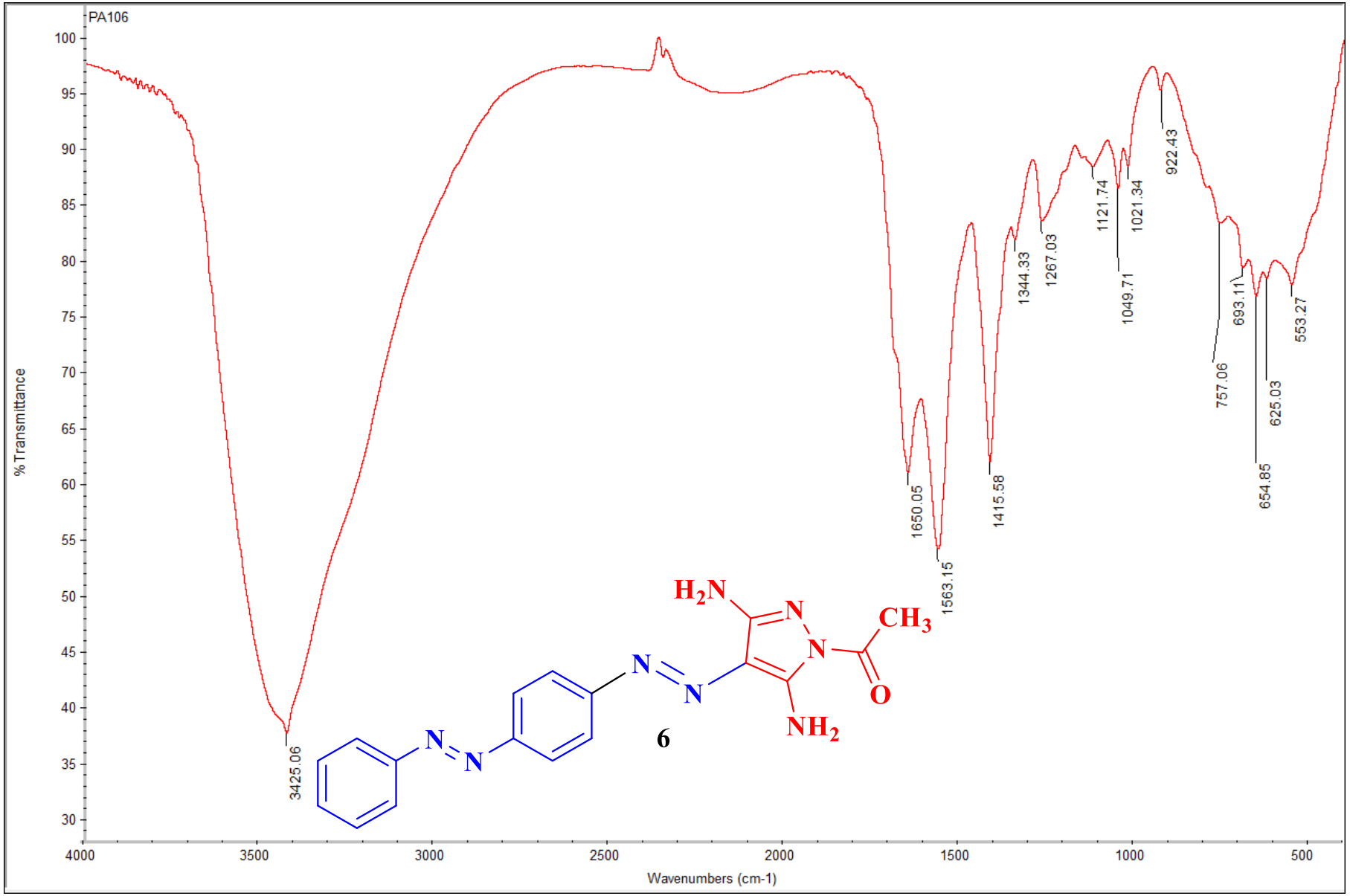
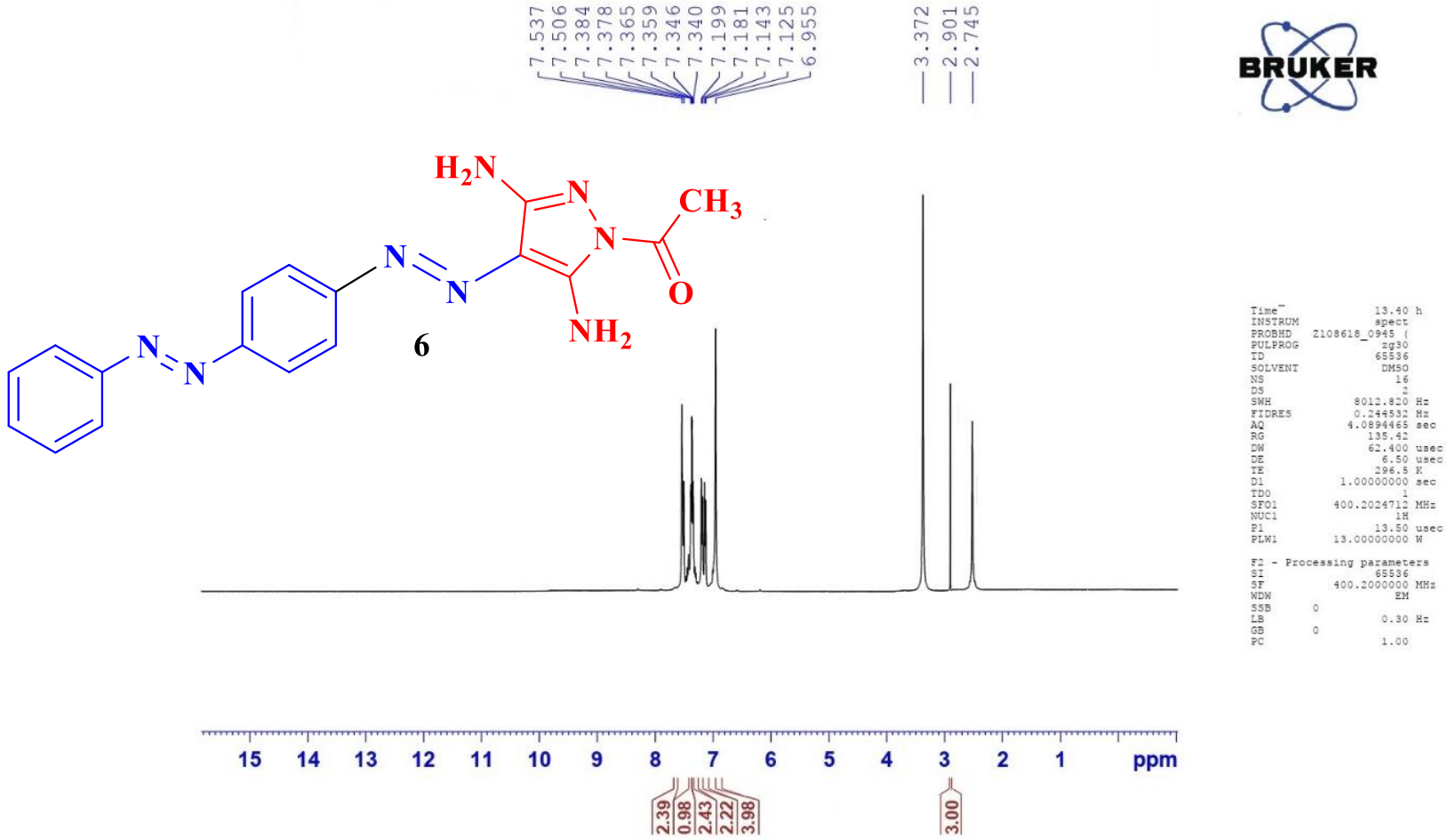
IR of compound 6



1HNMR of compound 6



BRUKER

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TD	65536	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8012.820	Hz
FIDRES	0.244532	Hz
AQ	4.0894465	sec
RG	135.42	
DW	62.400	usec
DE	6.50	usec
TE	296.5	K
D1	1.00000000	sec
TD0	1	
SFO1	400.2024712	MHz
NUC1	1H	
P1	13.50	usec
PLW1	13.00000000	W
F2 - Processing parameters		
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WDW	EM	
SSB	0	
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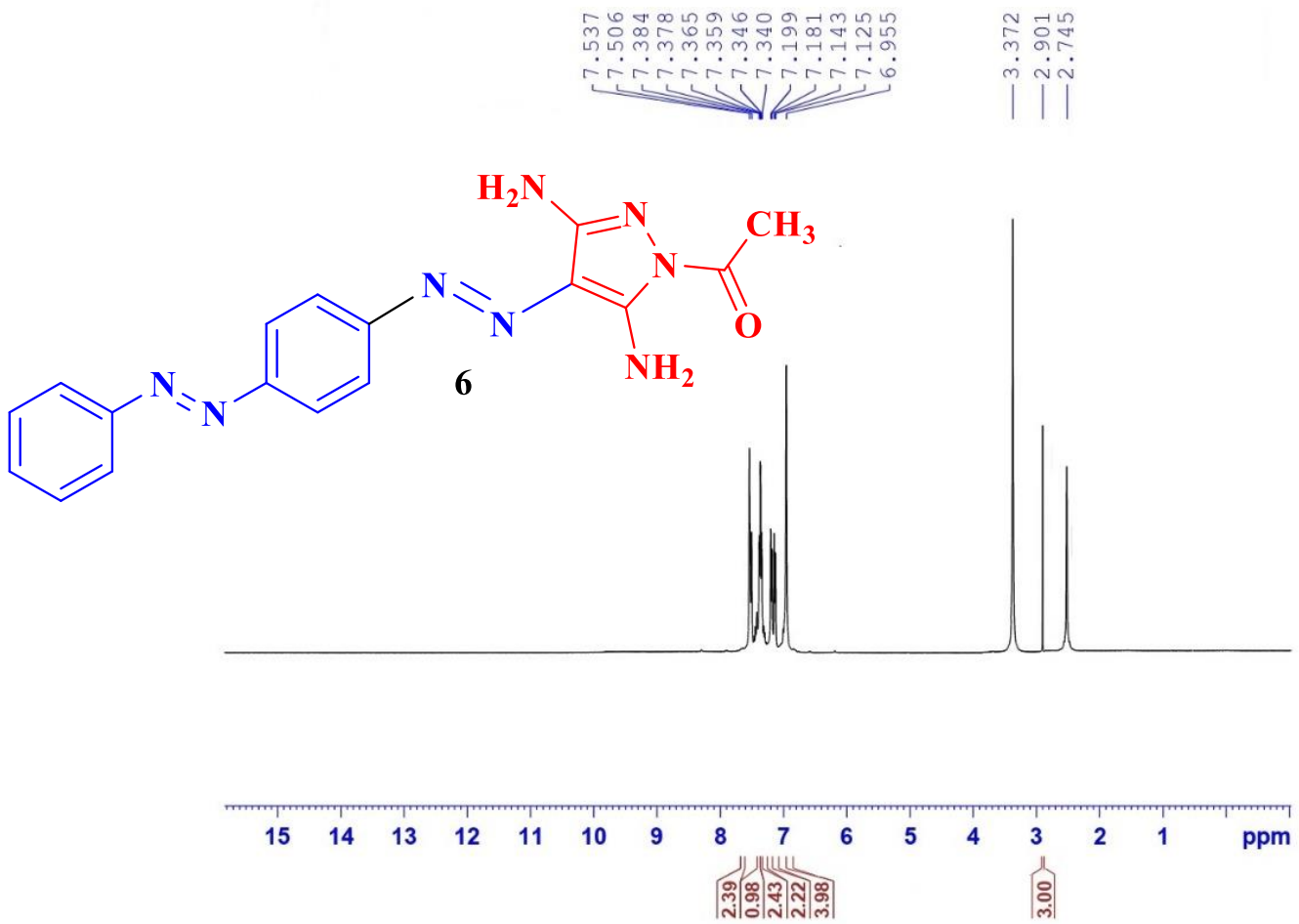
D2O Of compound 6



BRUKER

Time	13.40 h
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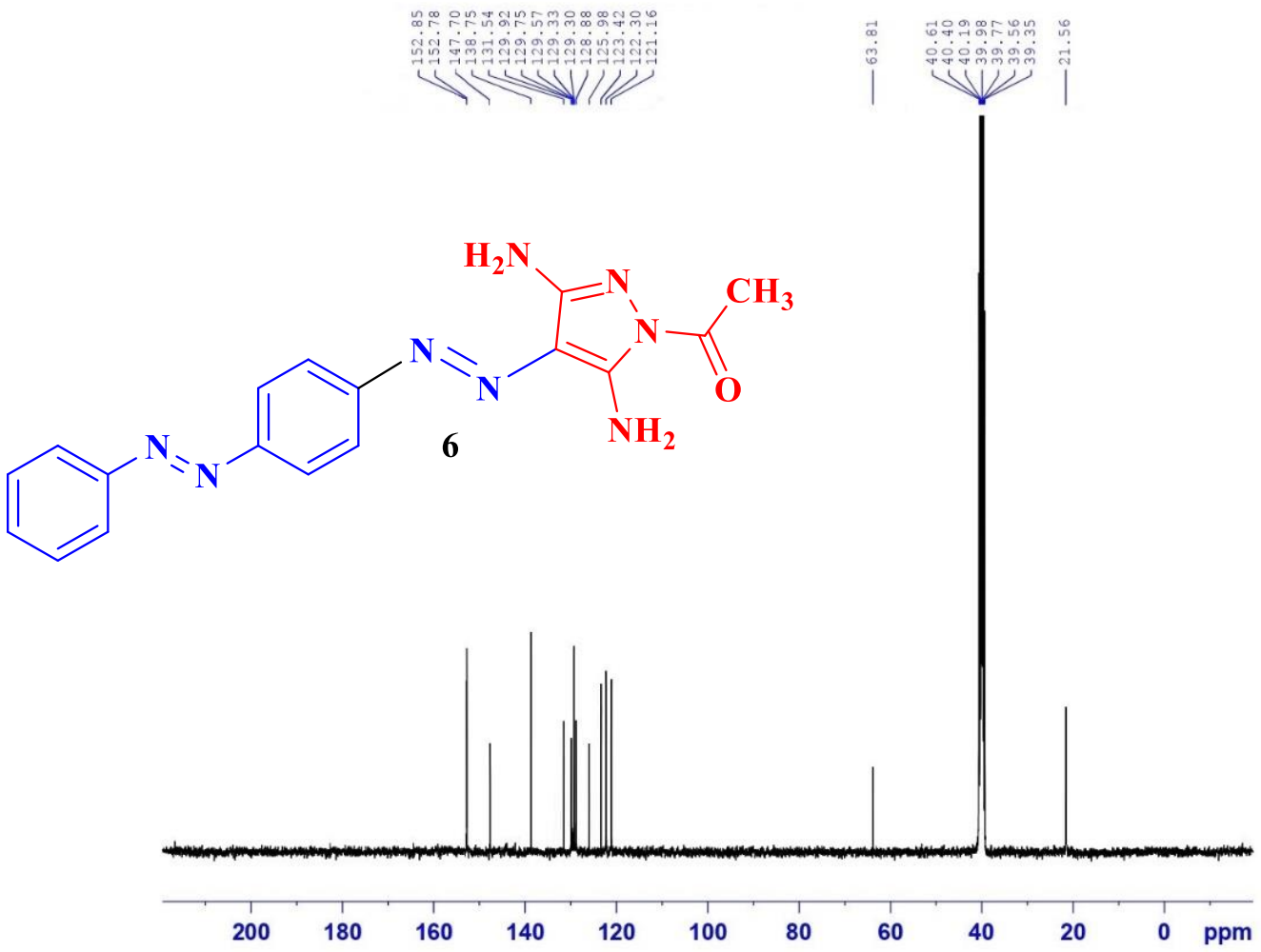
PROBHD	Z108618_0945 (
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.244532 Hz
AQ	4.0894465 sec
RG	135.42
DW	62.400 usec
DE	6.50 usec
TE	296.5 K
D1	1.00000000 sec
TD0	1
SFO1	400.2024712 MHz
NUC1	1H
P1	13.50 usec
PLW1	13.00000000 W

F2 - Processing parameters

SI	65536
SF	400.2000000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

13CNMR of compound 6



BRUKER

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SOLVENT	DMSO
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FIDRES	0.733596 Hz
AQ	1.3631488 sec
RG	197.77
DW	20.800 usec
DE	6.50 usec
TE	297.1 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
SFO1	100.6404331 MHz
NUC1	13C
P1	10.00 usec
PLW1	47.00000000 W
SFO2	400.2016008 MHz
NUC2	1H
CPDPRG[2	waltz16
PCPD2	90.00 usec
PLW2	13.00000000 W
PLW12	0.29249999 W
PLW13	0.14713000 W

F2 - Processing parameters

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WDW	EM
SSB	0
LB	1.00 Hz
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PC	1.40

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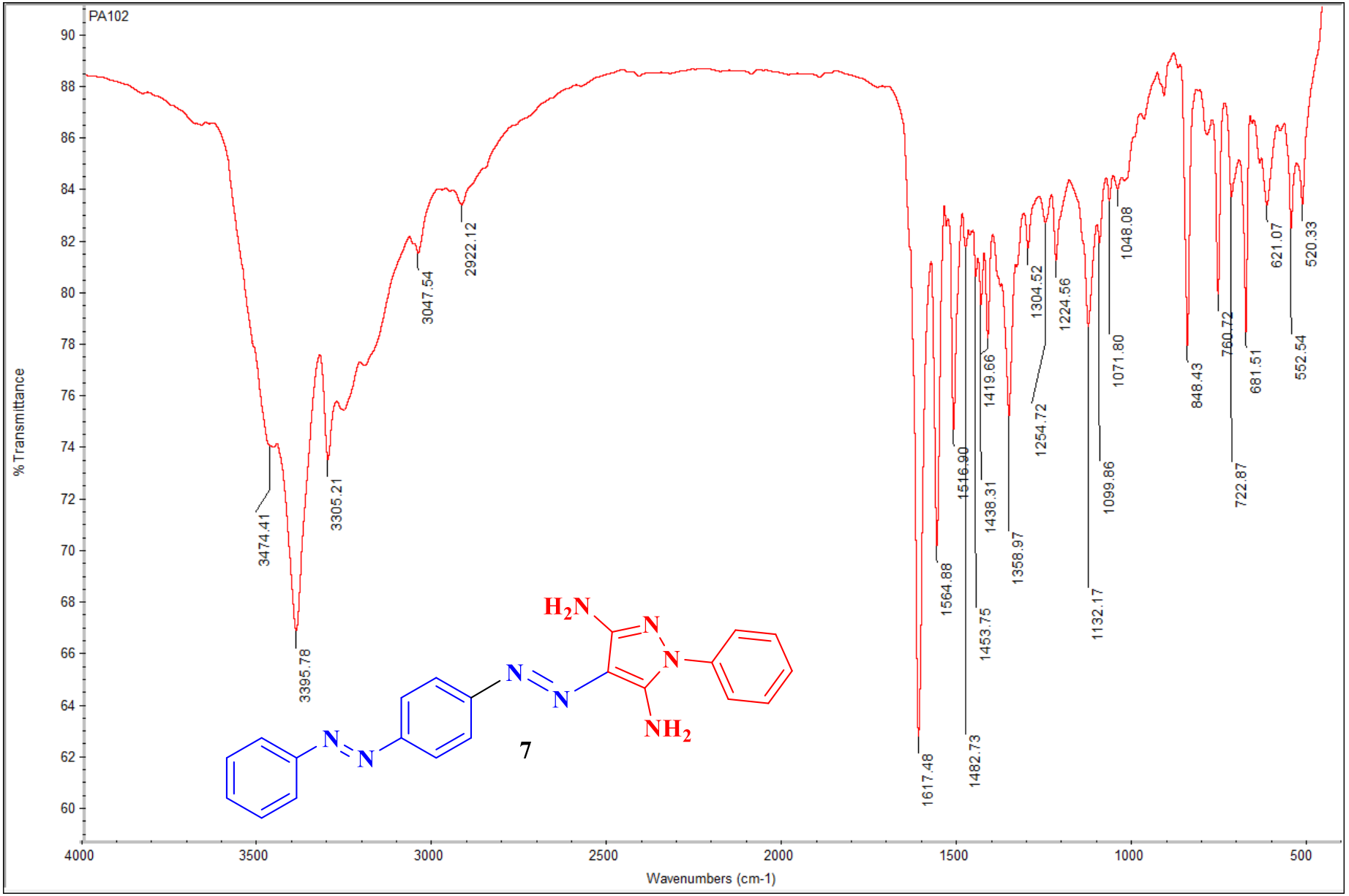
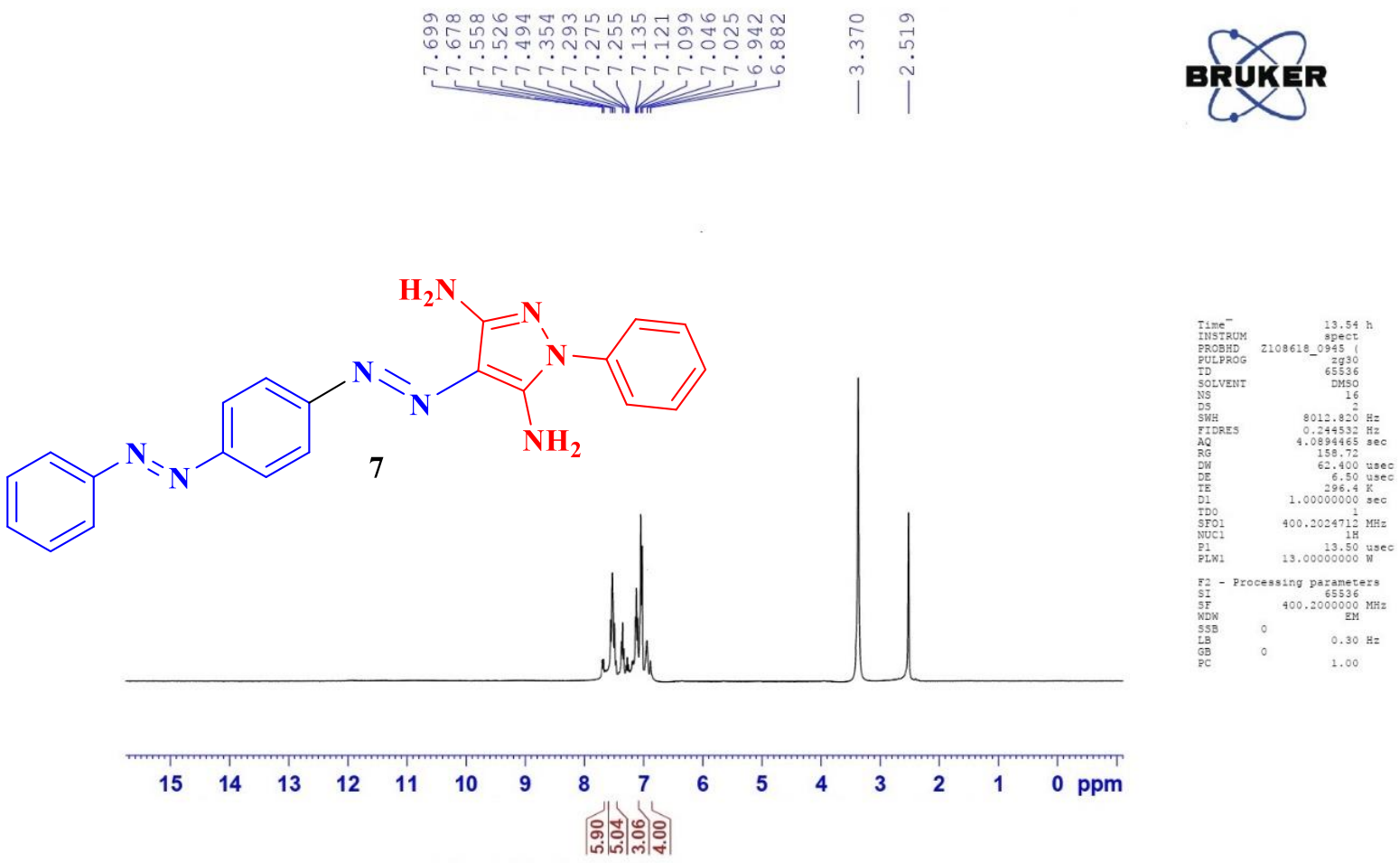
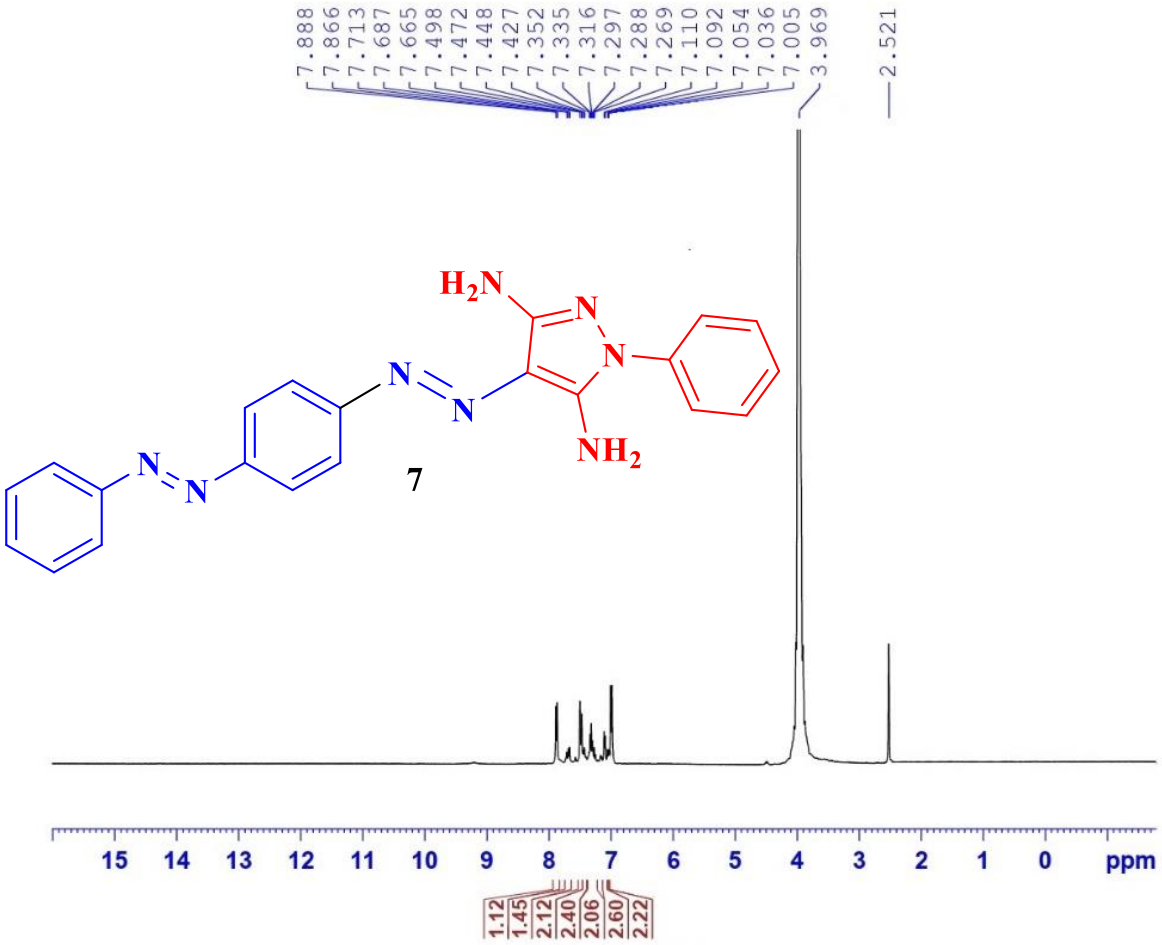


1HNMR of compound 7



D2O Of compound 7



BRUKER

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TD	65536	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8012.820	Hz
FIDRES	0.244532	Hz
AQ	4.0894465	sec
RG	60.97	
DW	62.400	usec
DE	6.50	usec
TE	296.6	K
D1	1.00000000	sec
TD0	1	
SFO1	400.2024712	MHz
NUC1	1H	
P1	13.50	usec
PLW1	13.00000000	W

F2 - Processing parameters

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WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
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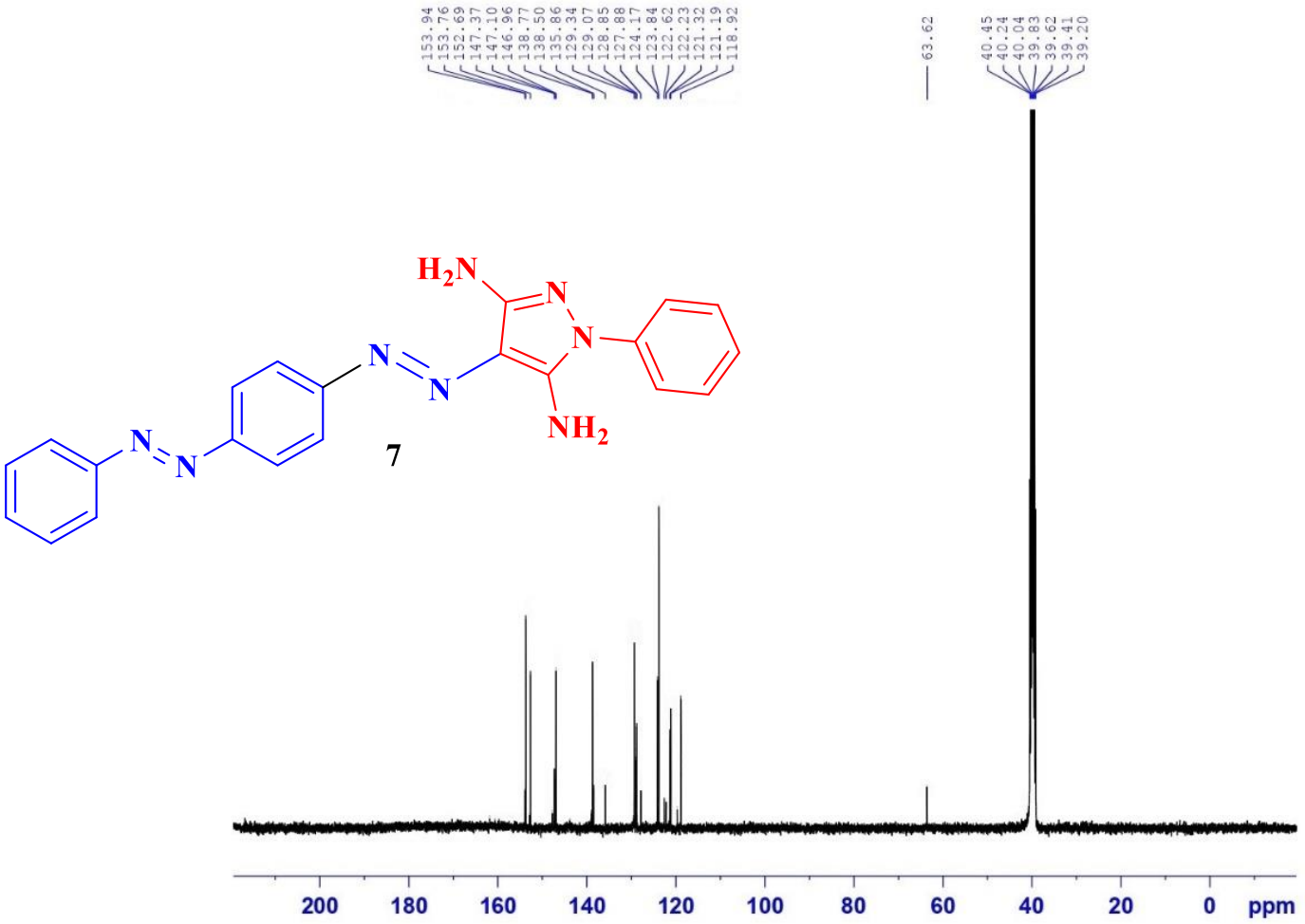
13CNMR of compound 7



BRUKER

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TD                    65536
SOLVENT                DMSO
NS                      2200
DS                         4
SWH               24038.461 Hz
FIDRES             0.733596 Hz
AQ                 1.3631488 sec
RG                    197.77
DW                   20.800 usec
DE                    6.50 usec
TE                   297.4 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1
SFO1             100.6404331 MHz
NUC1                     13C
P1                   10.00 usec
PLW1             47.00000000 W
SFO2             400.2016008 MHz
NUC2                     1H
CPDPRG[2              waltz16
PCPD2                90.00 usec
PLW2             13.00000000 W
PLW12             0.29249999 W
PLW13             0.14713000 W

F2 - Processing parameters
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SF               100.6303700 MHz
WDW                         EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
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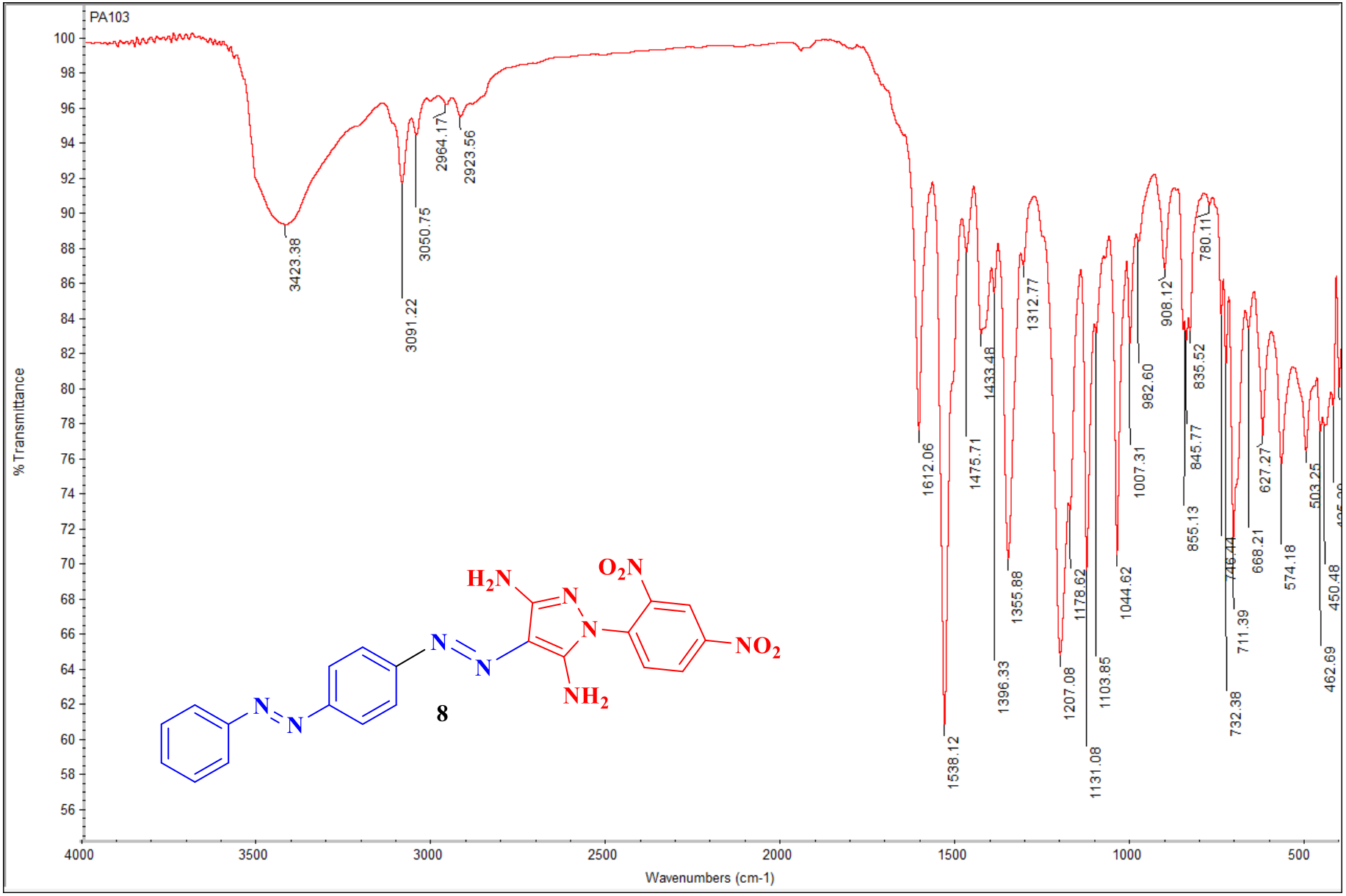
IR of compound 8



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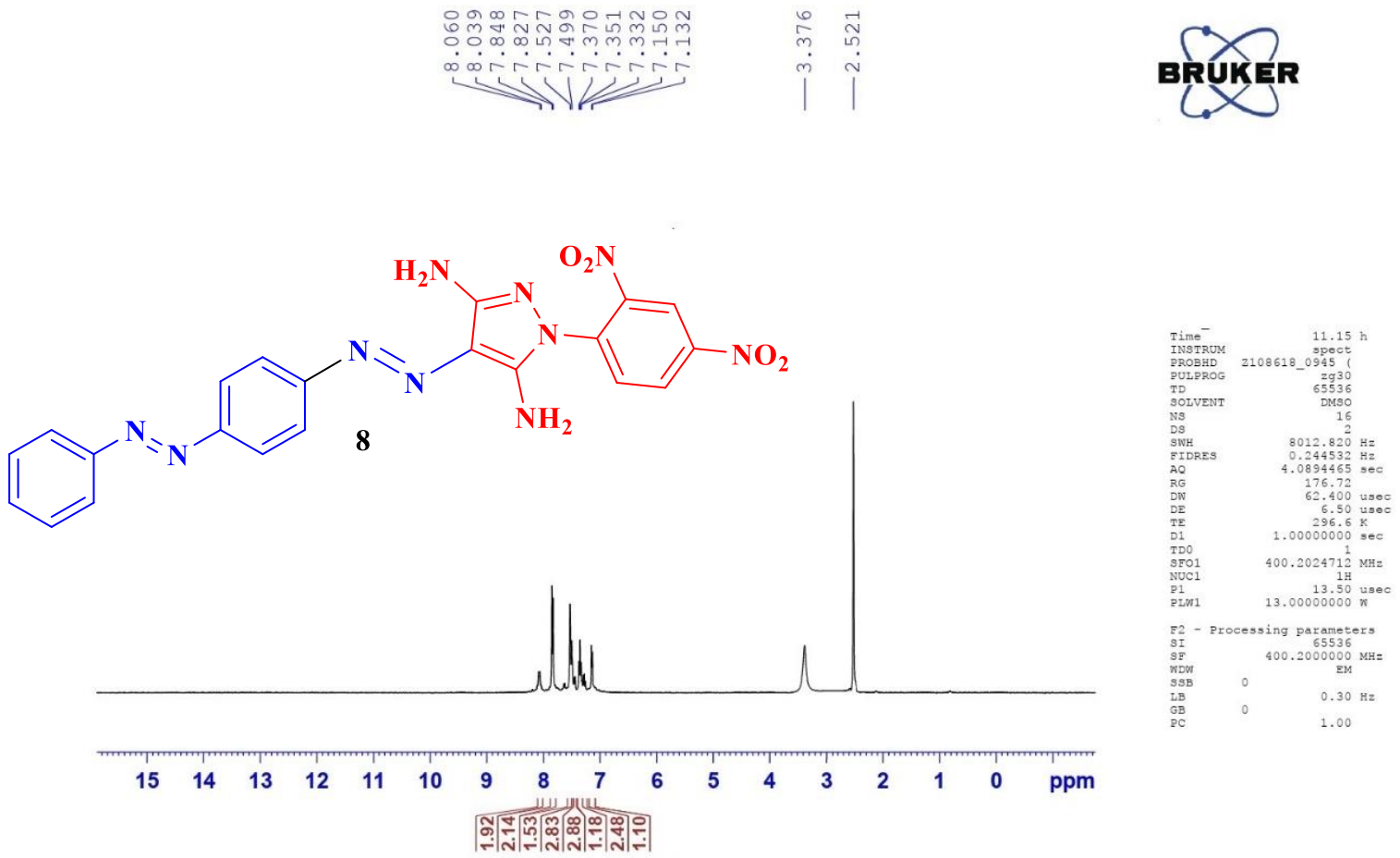
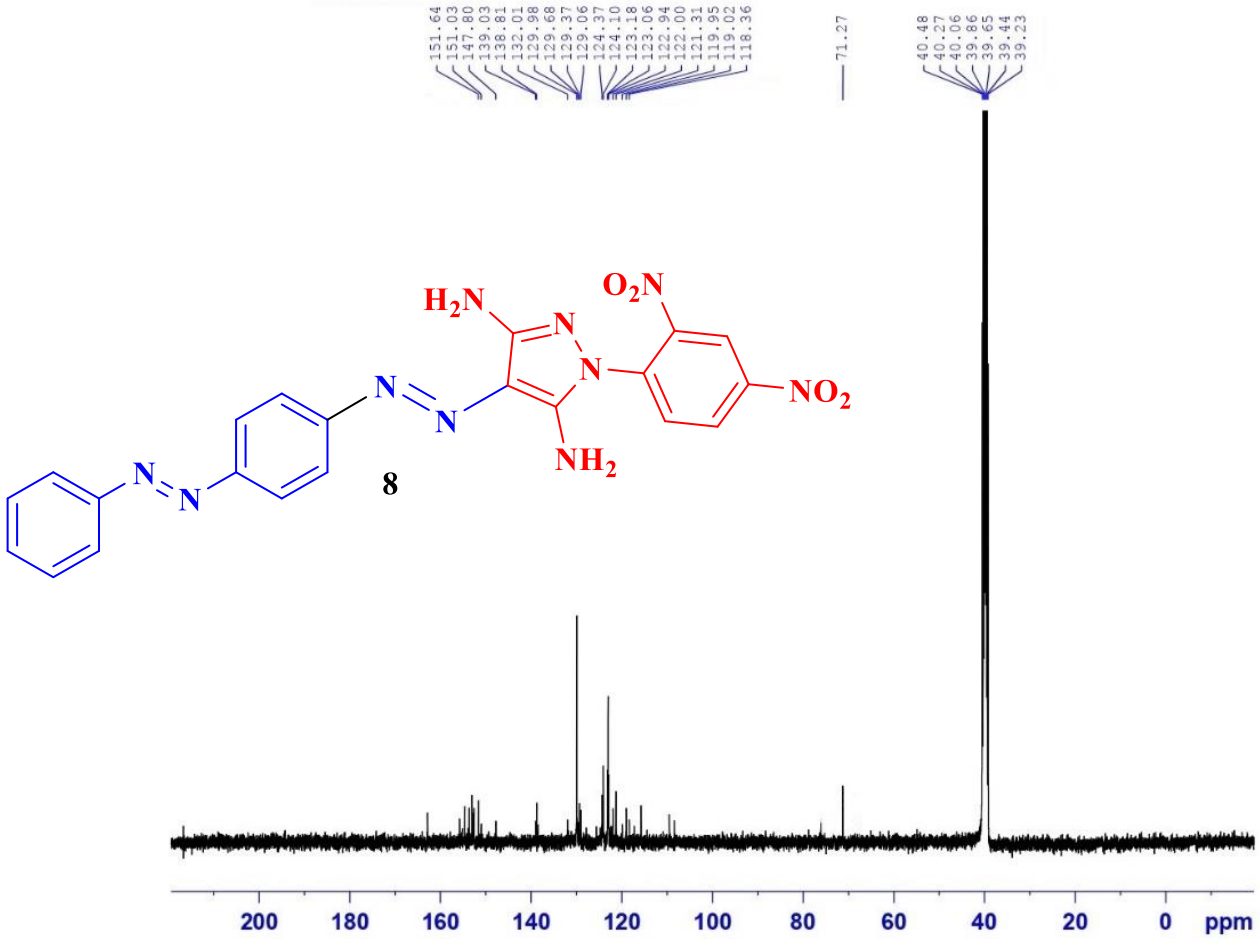


13CNMR of compound 8



BRUKER

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TD                   65536
SOLVENT              DMSO
NS                    2200
DS                       4
SWH              24038.461 Hz
FIDRES           0.733596 Hz
AQ               1.3631488 sec
RG                   197.77
DW                 20.800 usec
DE                  6.50 usec
TE                  297.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           100.6404331 MHz
NUC1                    13C
P1                 10.00 usec
PLW1           47.00000000 W
SFO2           400.2016008 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2              90.00 usec
PLW2           13.00000000 W
PLW12           0.29249999 W
PLW13           0.14713000 W

F2 - Processing parameters
SI                   32768
SF             100.6303700 MHz
WDW                     EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 1.40
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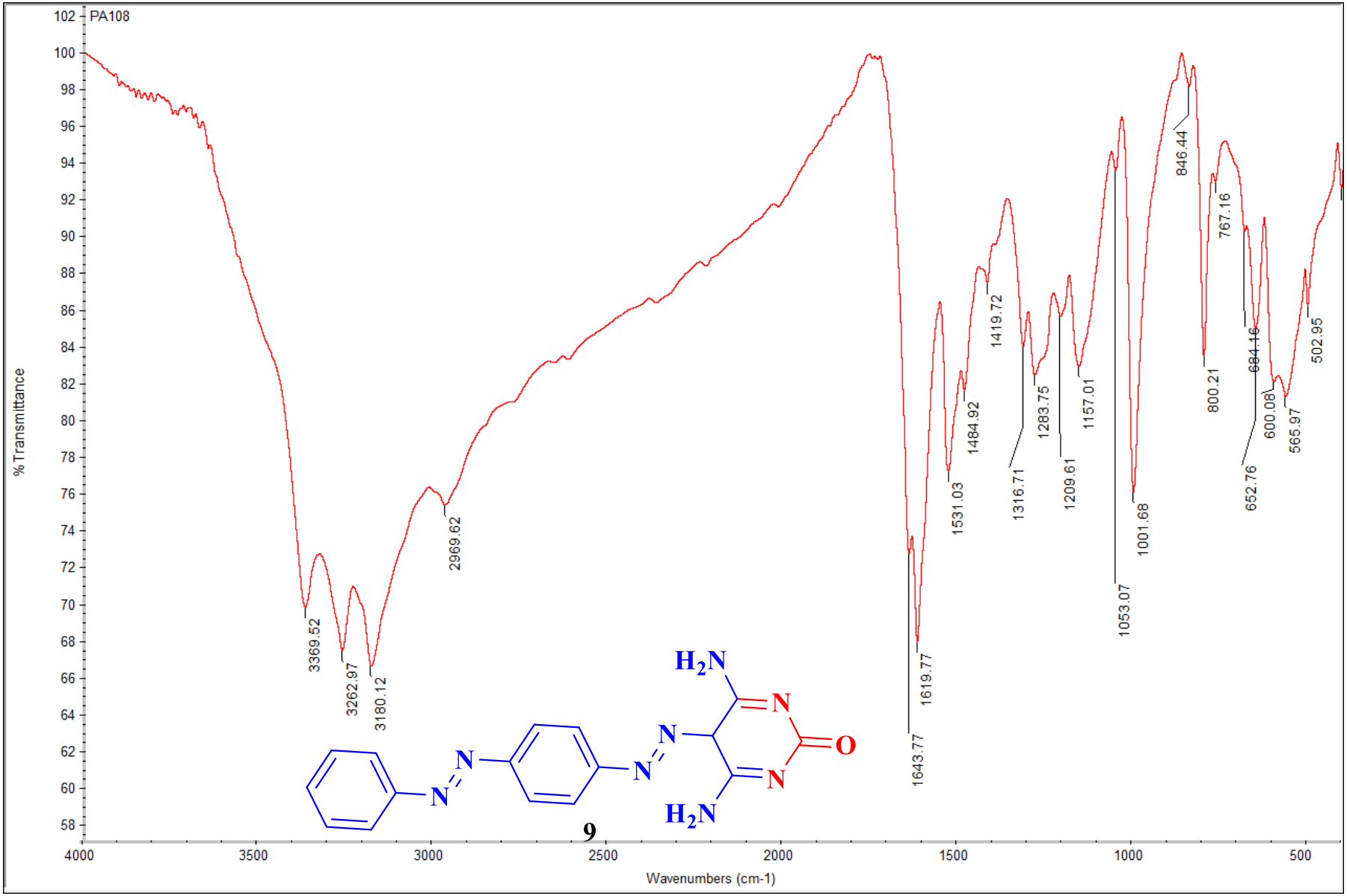
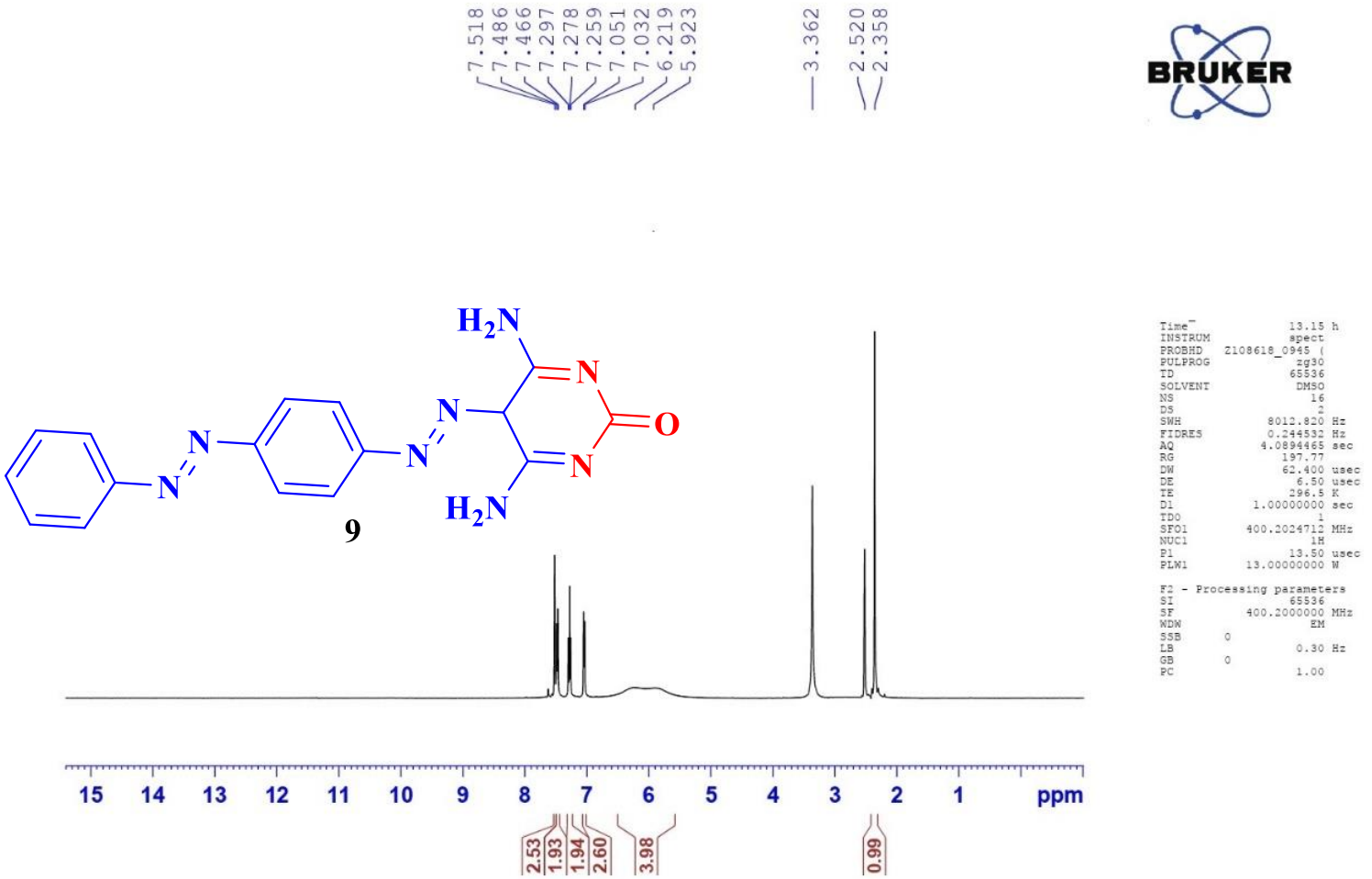
IR of compound 9



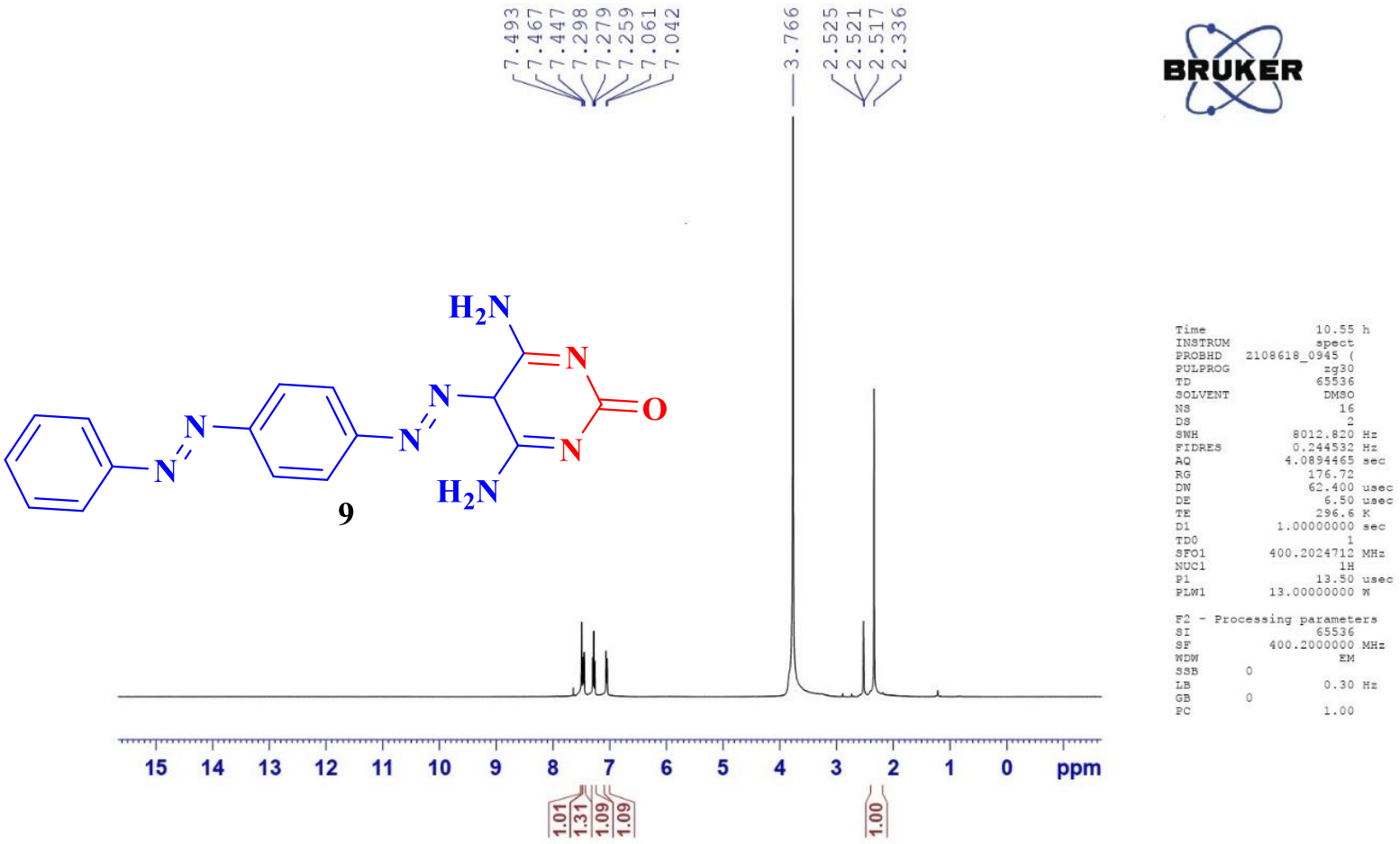
9

1HNMR of compound 9




```
Time                  13.15 h
INSTRUM                spect
PROBHD    Z108618_0945 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES                0.244532 Hz
AQ                 4.0894465 sec
RG                    197.77
DW                    62.400 usec
DE                     6.50 usec
TE                    296.5 K
D1                 1.00000000 sec
TD0                       1
SFO1              400.2024712 MHz
NUC1                      1H
P1                    13.50 usec
PLW1              13.00000000 W

F2 - Processing parameters
SI                    65536
SF                400.2000000 MHz
WDW                       EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

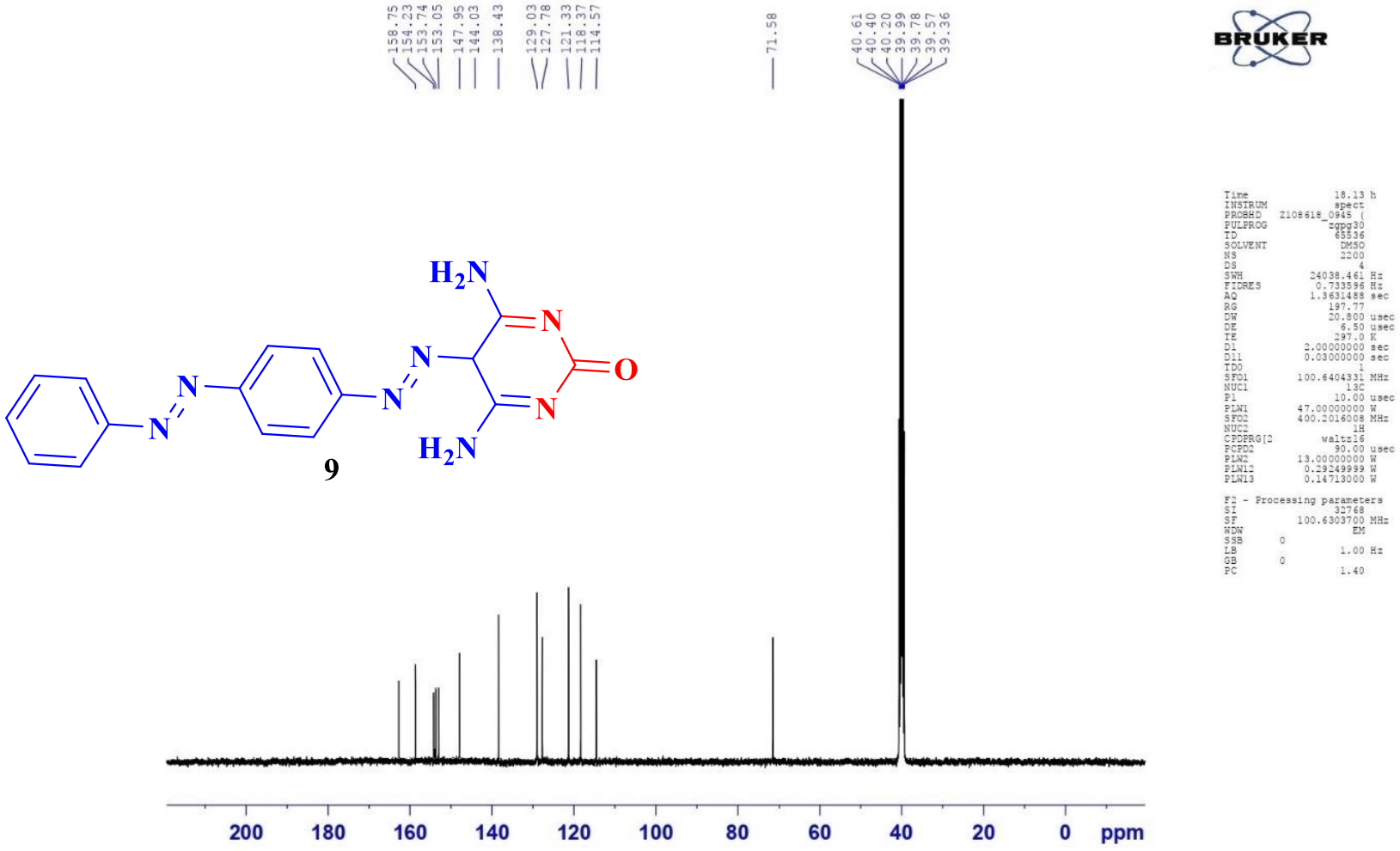
D2O Of compound 9



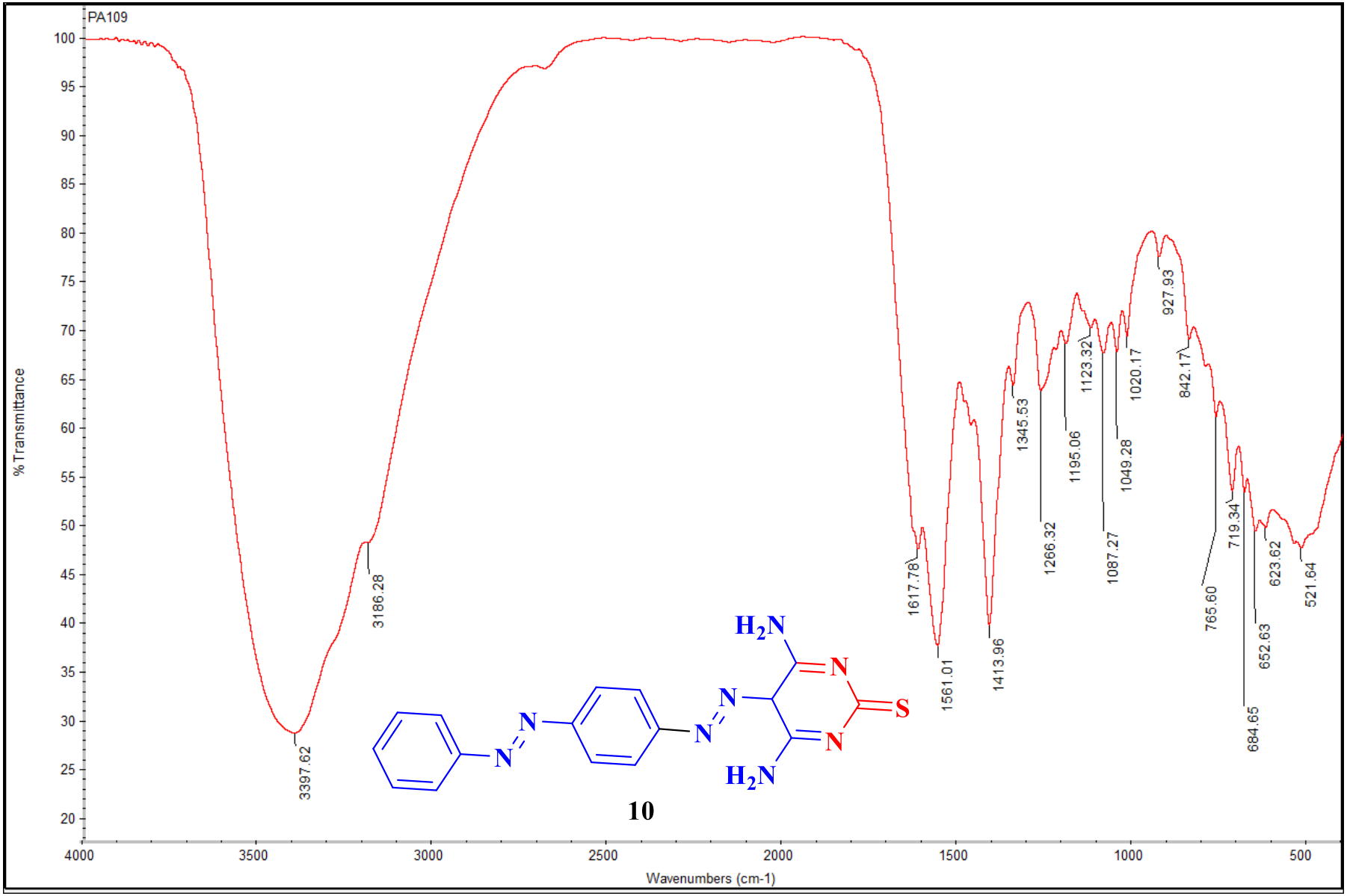
BRUKER

```
Time                 10.55 h
INSTRUM               spect
PROBHD    Z108618_0945 (
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               8012.820 Hz
FIDRES               0.244532 Hz
AQ                4.0894465 sec
RG                   176.72
DW                   62.400 usec
DE                    6.50 usec
TE                   296.6 K
D1             1.00000000 sec
TD0                      1
SFO1           400.2024712 MHz
NUC1                    1H
P1                   13.50 usec
PLW1          13.00000000 W

F2 - Processing parameters
SI                   65536
SF             400.2000000 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

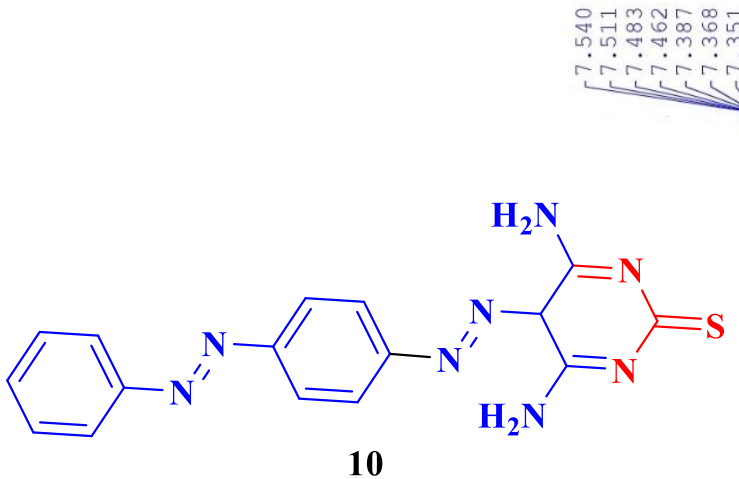
13CNMR of compound 9



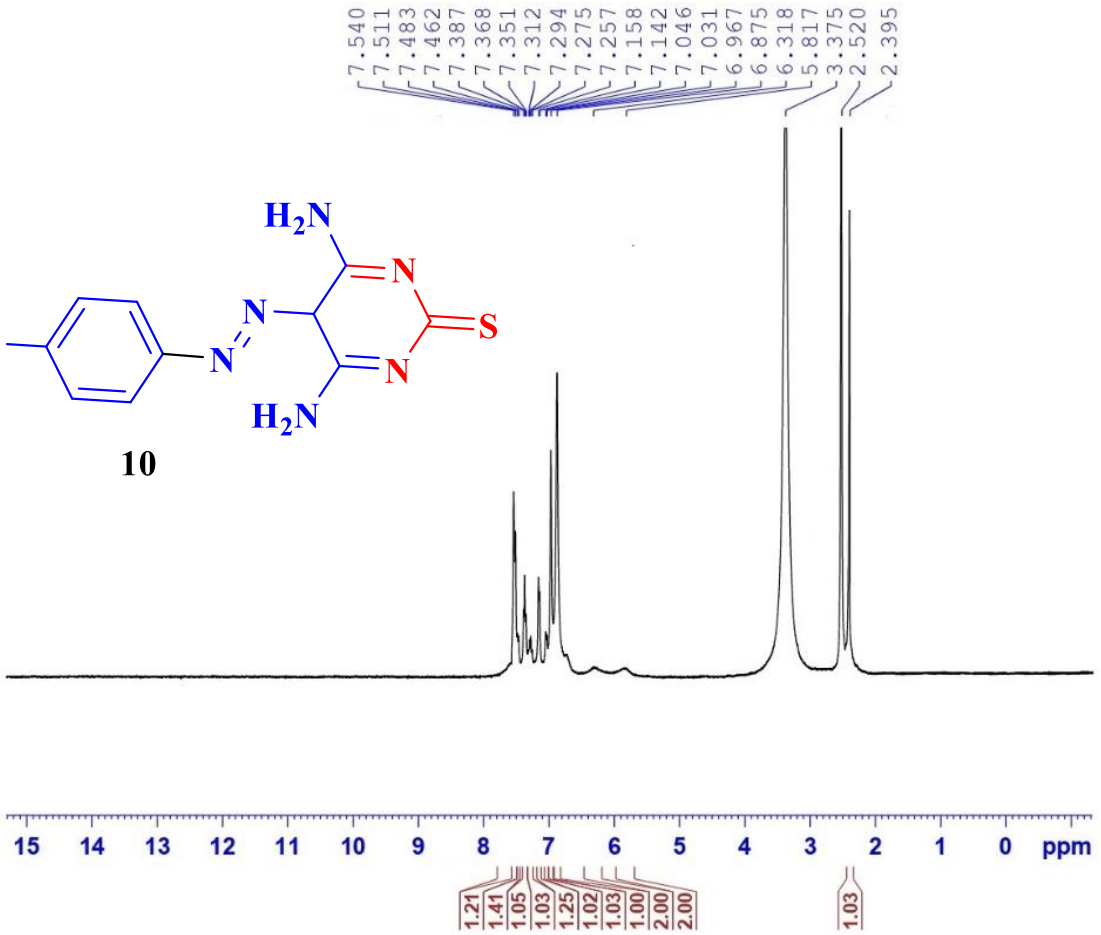
IR of compound 10



1HNMR of compound 10

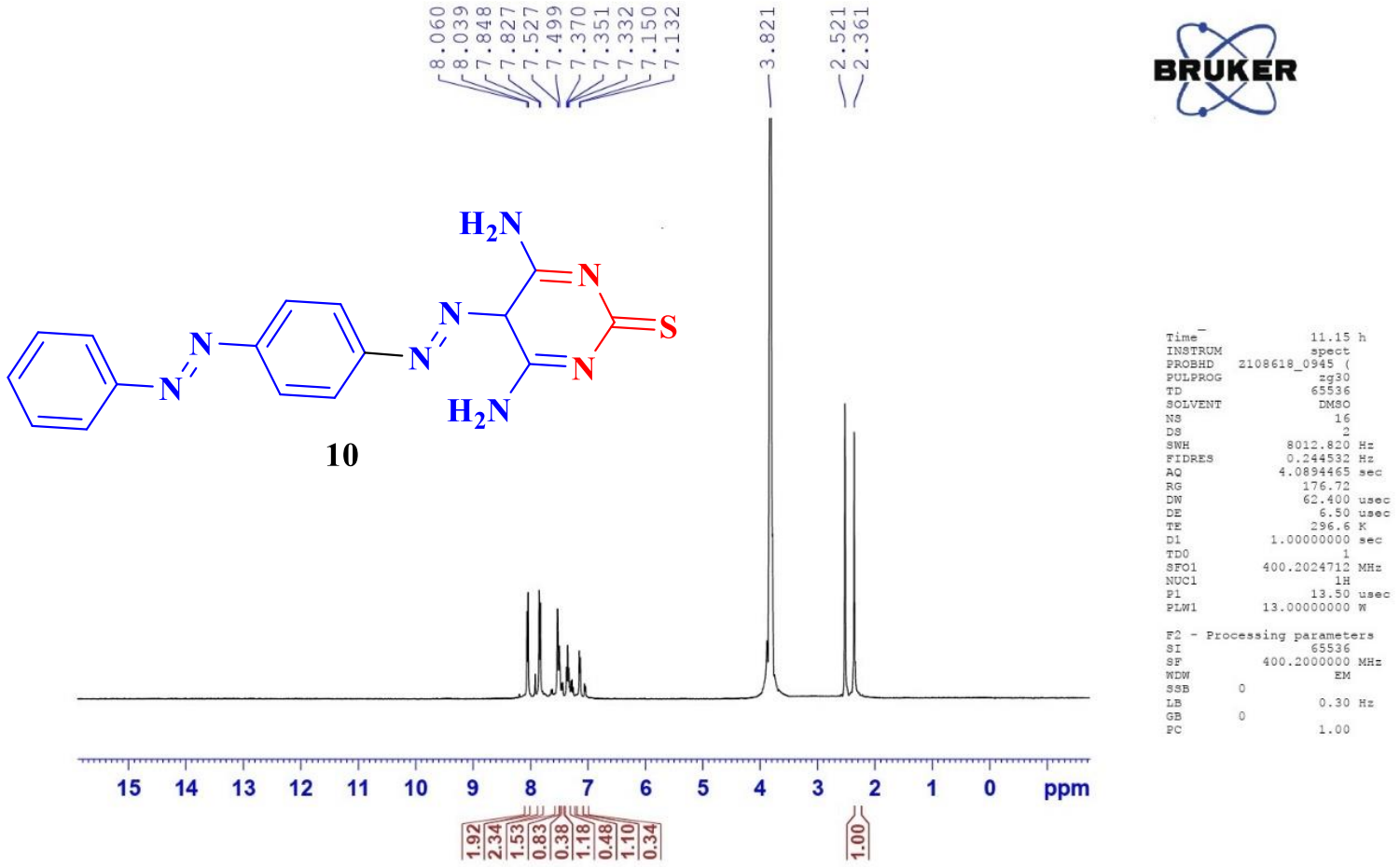


10




```
Time                 13.35 h
INSTRUM               spect
PROBHD    Z108618_0945 (
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8012.820 Hz
FIDRES                0.244532 Hz
AQ                 4.0894465 sec
RG                    197.77
DW                    62.400 usec
DE                     6.50 usec
TE                    296.4 K
D1                 1.00000000 sec
TD0                       1
SFO1              400.2024712 MHz
NUC1                      1H
P1                    13.50 usec
PLW1              13.00000000 W

F2 - Processing parameters
SI                    65536
SF                400.2000000 MHz
WDW                      EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

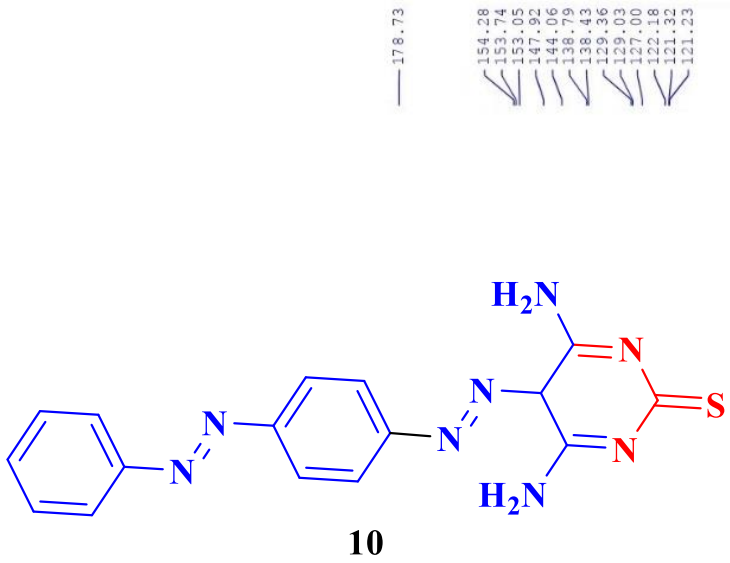
D2O Of compound 10



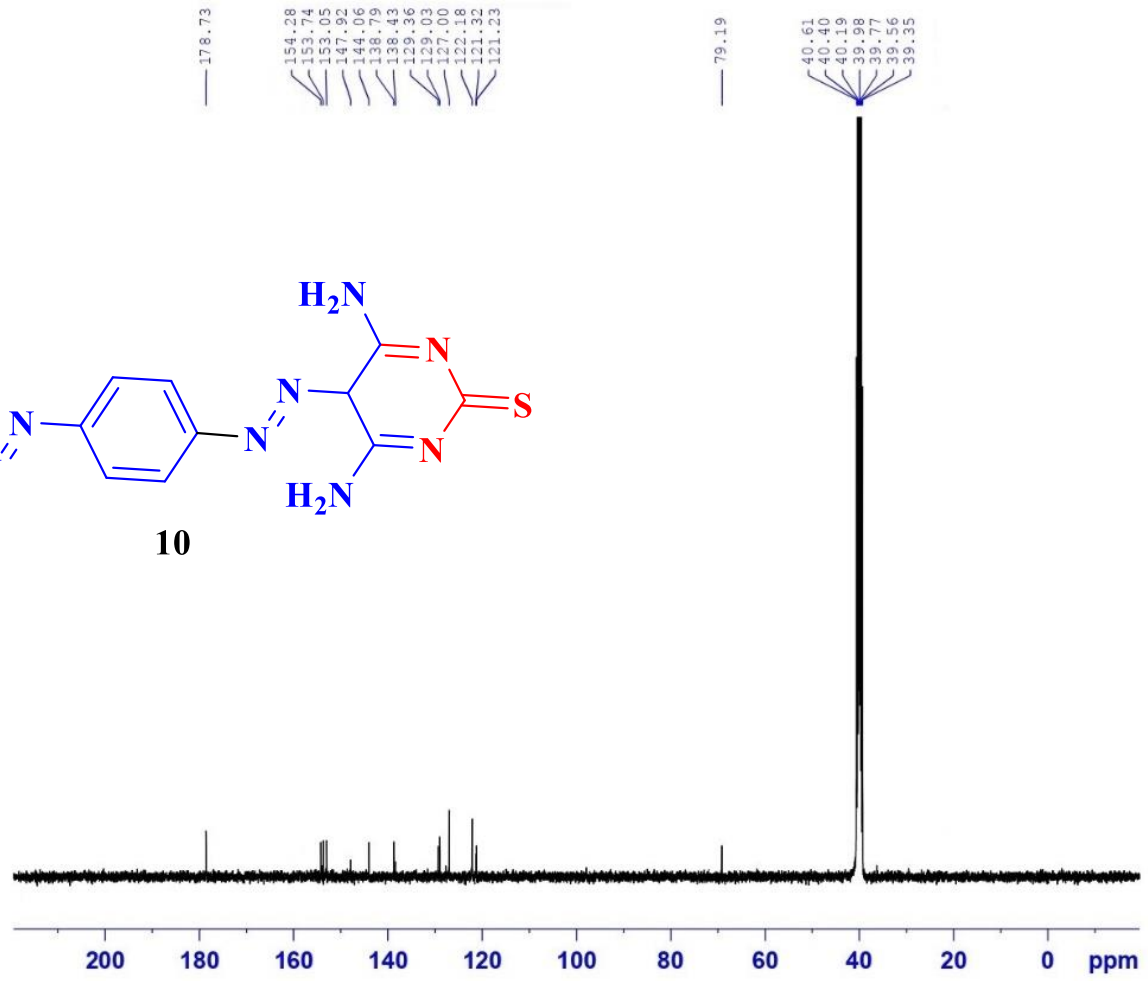
BRUKER

Time	11.15	h
INSTRUM	spect	
PROBHD	Z108618_0945 (	
PULPROG	zg30	
TD	65536	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8012.820	Hz
FIDRES	0.244532	Hz
AQ	4.0894465	sec
RG	176.72	
DW	62.400	usec
DE	6.50	usec
TE	296.6	K
D1	1.00000000	sec
TD0	1	
SFO1	400.2024712	MHz
NUC1	1H	
P1	13.50	usec
PLW1	13.00000000	W
F2 - Processing parameters		
SI	65536	
SF	400.2000000	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

13CNMR of compound 10



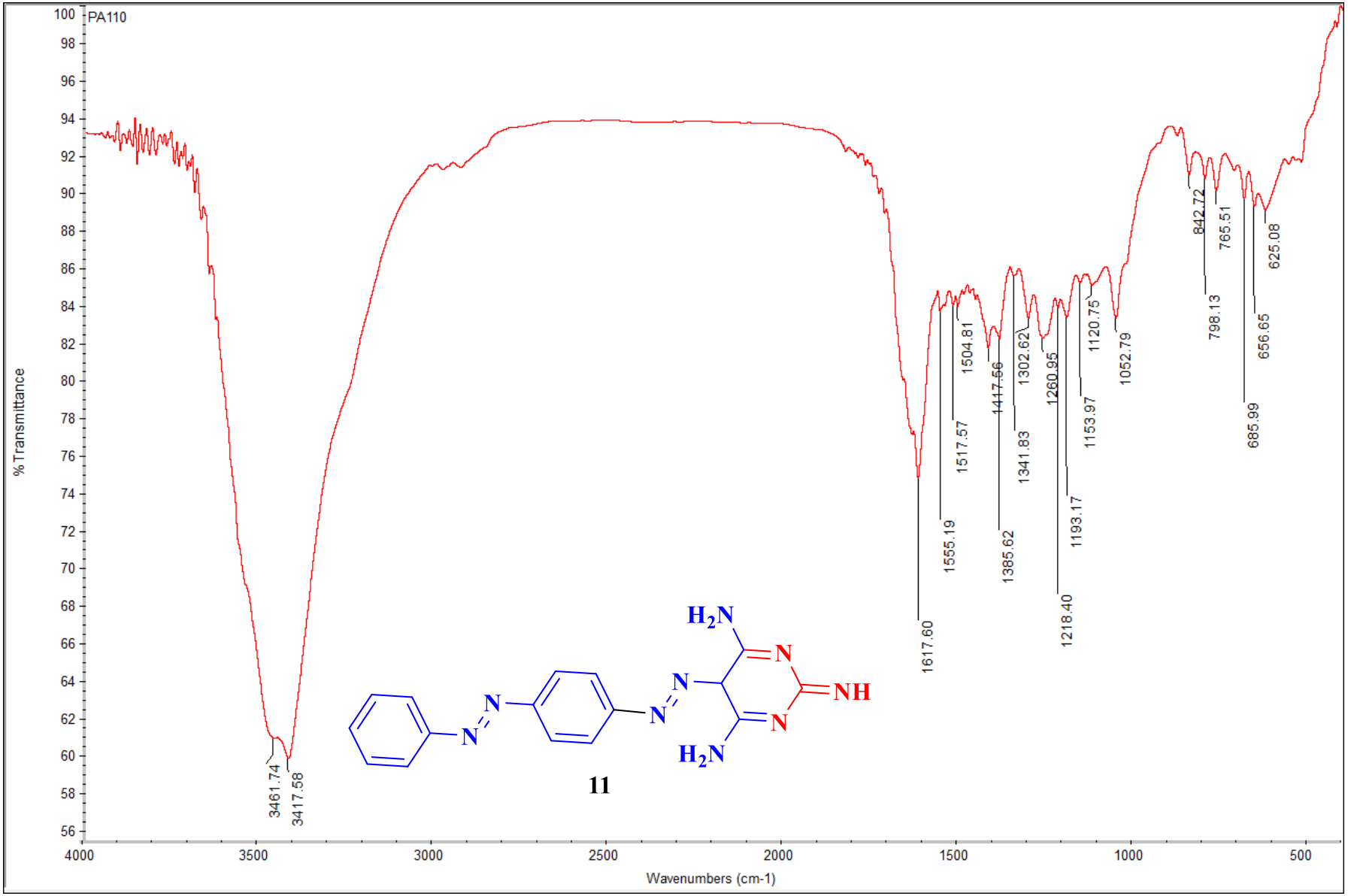
10



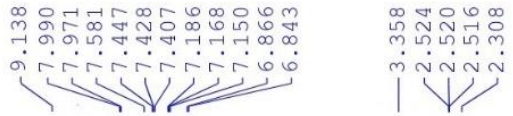
BRUKER

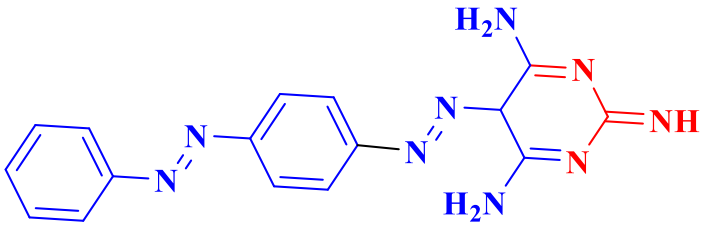
```
Time                  2.51 h
INSTRUM               spect
PROBHD    Z108618_0945 (
PULPROG               zgpg30
TD                     65536
SOLVENT                DMSO
NS                      2200
DS                         4
SWH               24038.461 Hz
FIDRES             0.733596 Hz
AQ                 1.3631488 sec
RG                    197.77
DW                   20.800 usec
DE                    6.50 usec
TE                    297.1 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1
SFO1             100.6404331 MHz
NUC1                     13C
P1                   10.00 usec
PLW1             47.00000000 W
SFO2             400.2016008 MHz
NUC2                     1H
CPDPRG[2              waltz16
PCPD2                90.00 usec
PLW2             13.00000000 W
PLW12             0.29249999 W
PLW13             0.14713000 W

F2 - Processing parameters
SI                       32768
SF               100.6303700 MHz
WDW                         EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

IR of compound 11

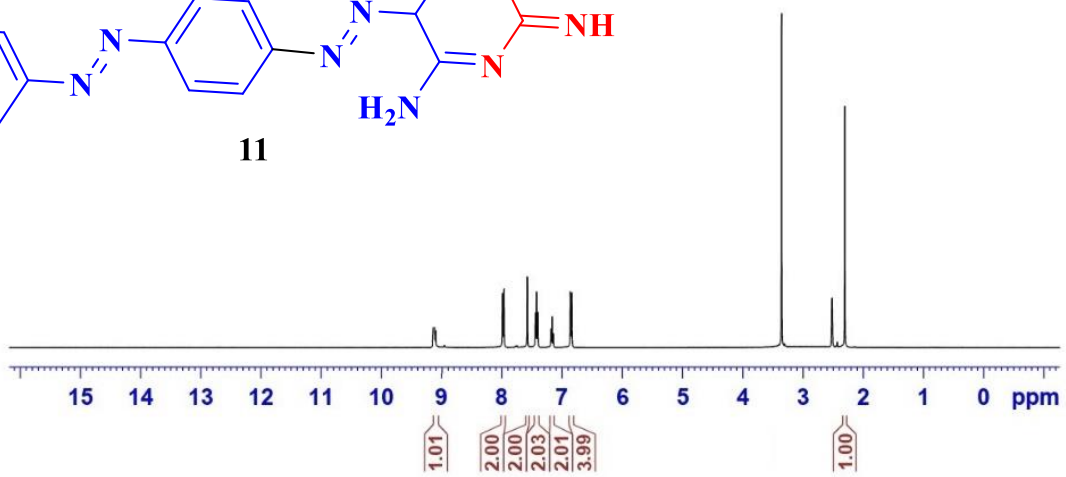


1HNMR of compound 11



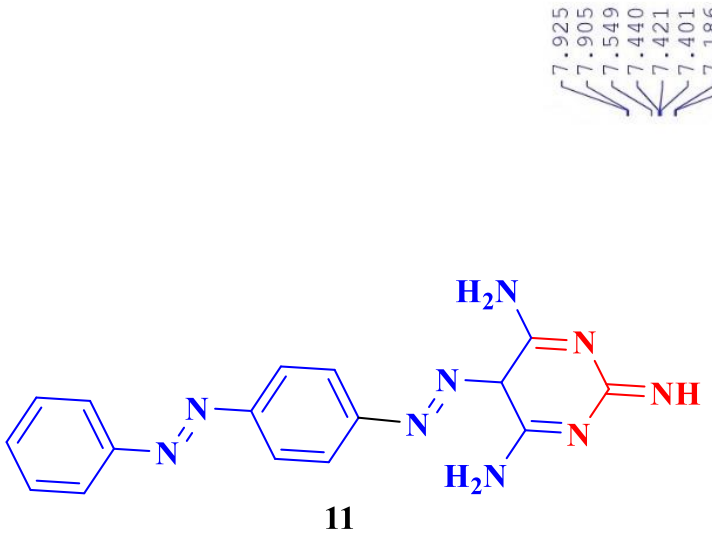


11

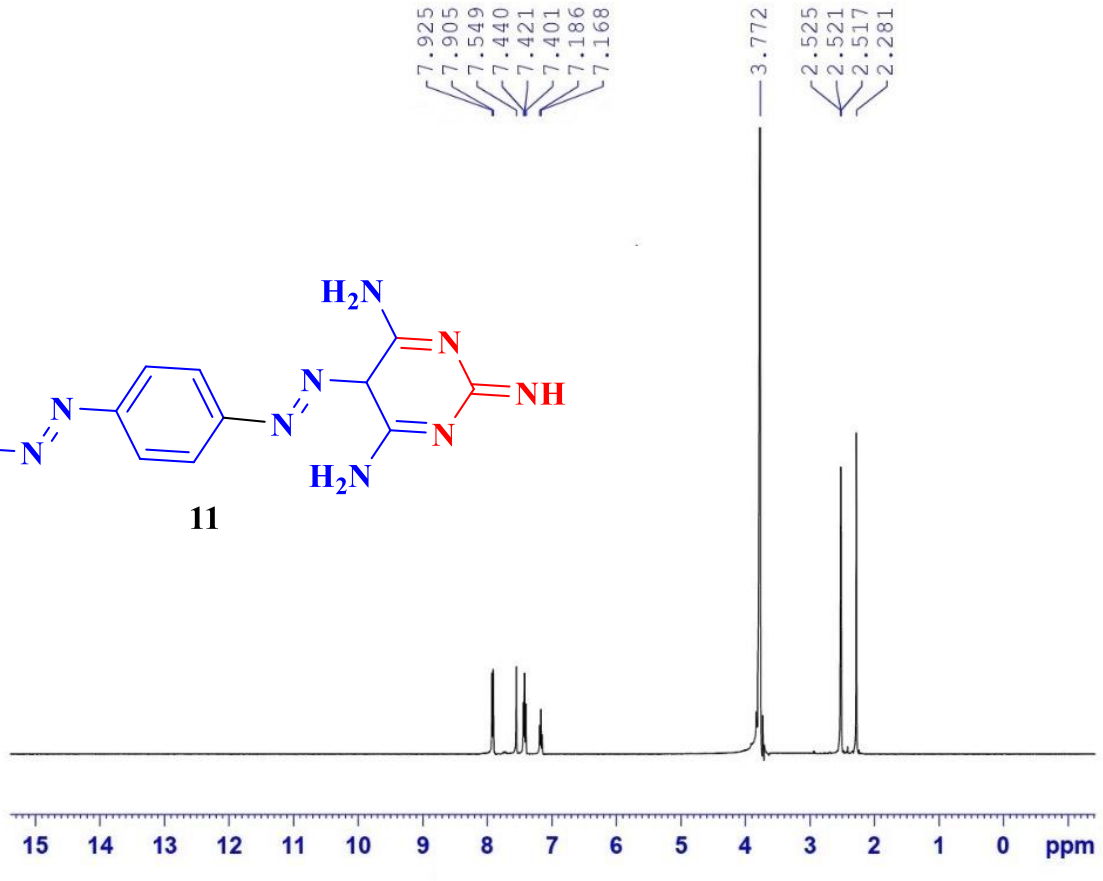



```
Time                12.32 h
INSTRUM              spect
PROBHD    Z108618_0945 (
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH              8012.820 Hz
FIDRES           0.244532 Hz
AQ               4.0894465 sec
RG                  176.72
DW                  62.400 usec
DE                   6.50 usec
TE                  0 K
D1               1.00000000 sec
TD0                     1
SFO1           400.2024712 MHz
NUC1                   1H
P1                  13.50 usec
PLW1           13.00000000 W

F2 - Processing parameters
SI                  65536
SF             400.2000000 MHz
WDW                    EM
SSB                 0
LB                   0.30 Hz
GB                  0
PC                   1.00
```

D2O Of compound 11



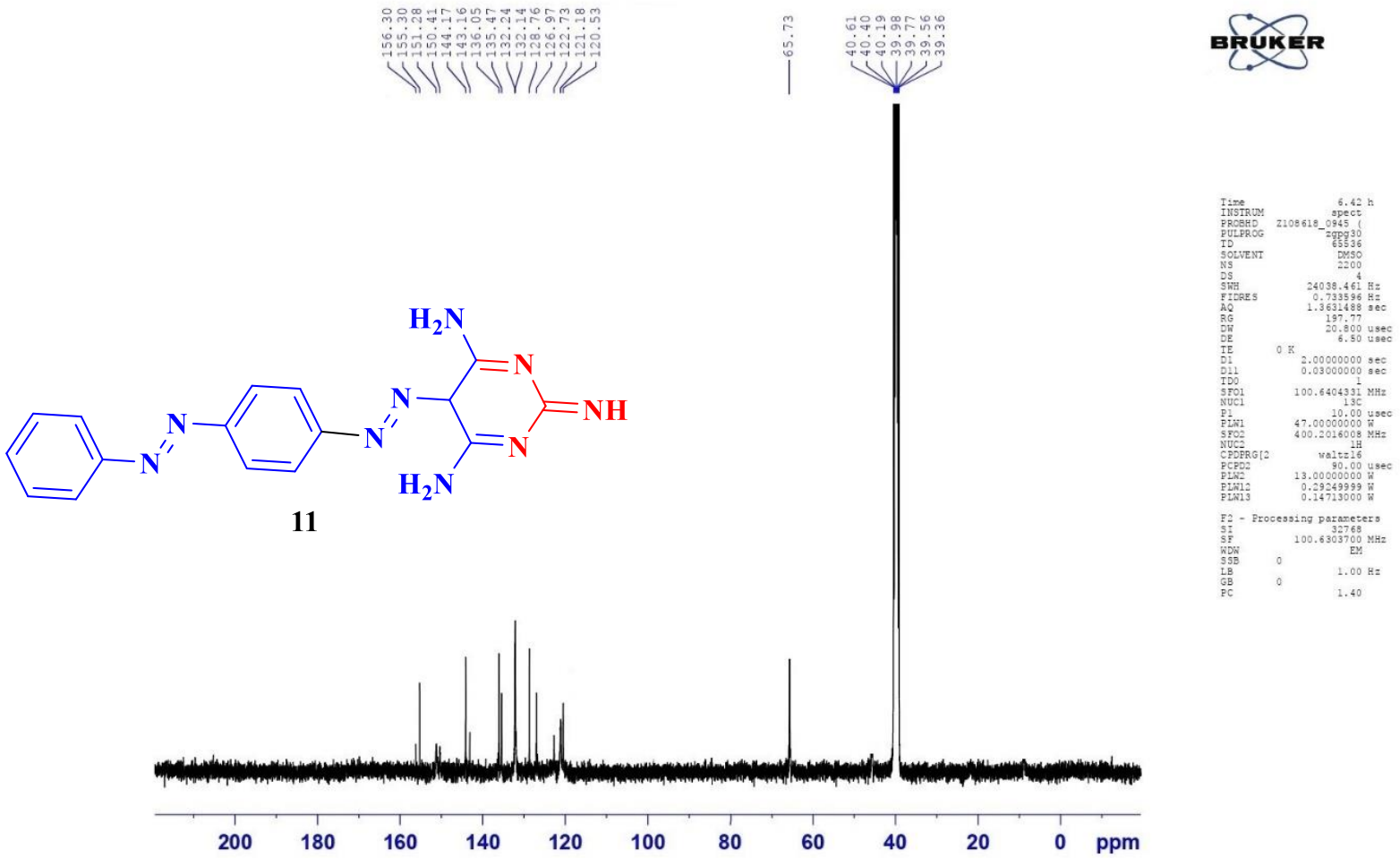
11



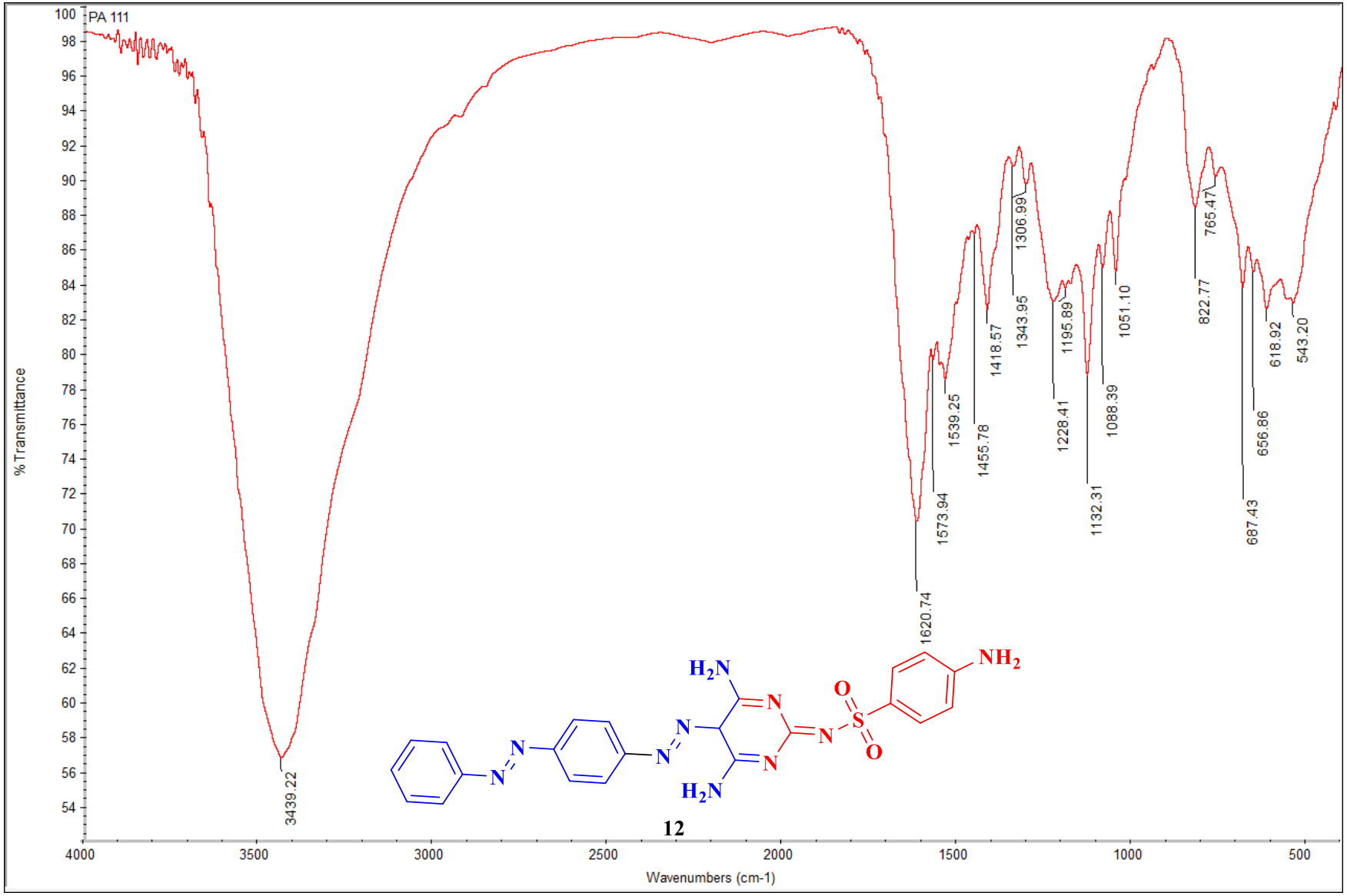
BRUKER

Time	12.10	h
INSTRUM	spect	
PROBHD	Z108618_0945 (	
PULPROG	zg30	
TD	65536	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8012.820	Hz
FIDRES	0.244532	Hz
AQ	4.0894465	sec
RG	197.77	
DW	62.400	usec
DE	6.50	usec
TE	296.5	K
D1	1.00000000	sec
TD0	1	
SFO1	400.2024712	MHz
NUC1	1H	
P1	13.50	usec
PLW1	13.00000000	W
F2 - Processing parameters		
SI	65536	
SF	400.2000000	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

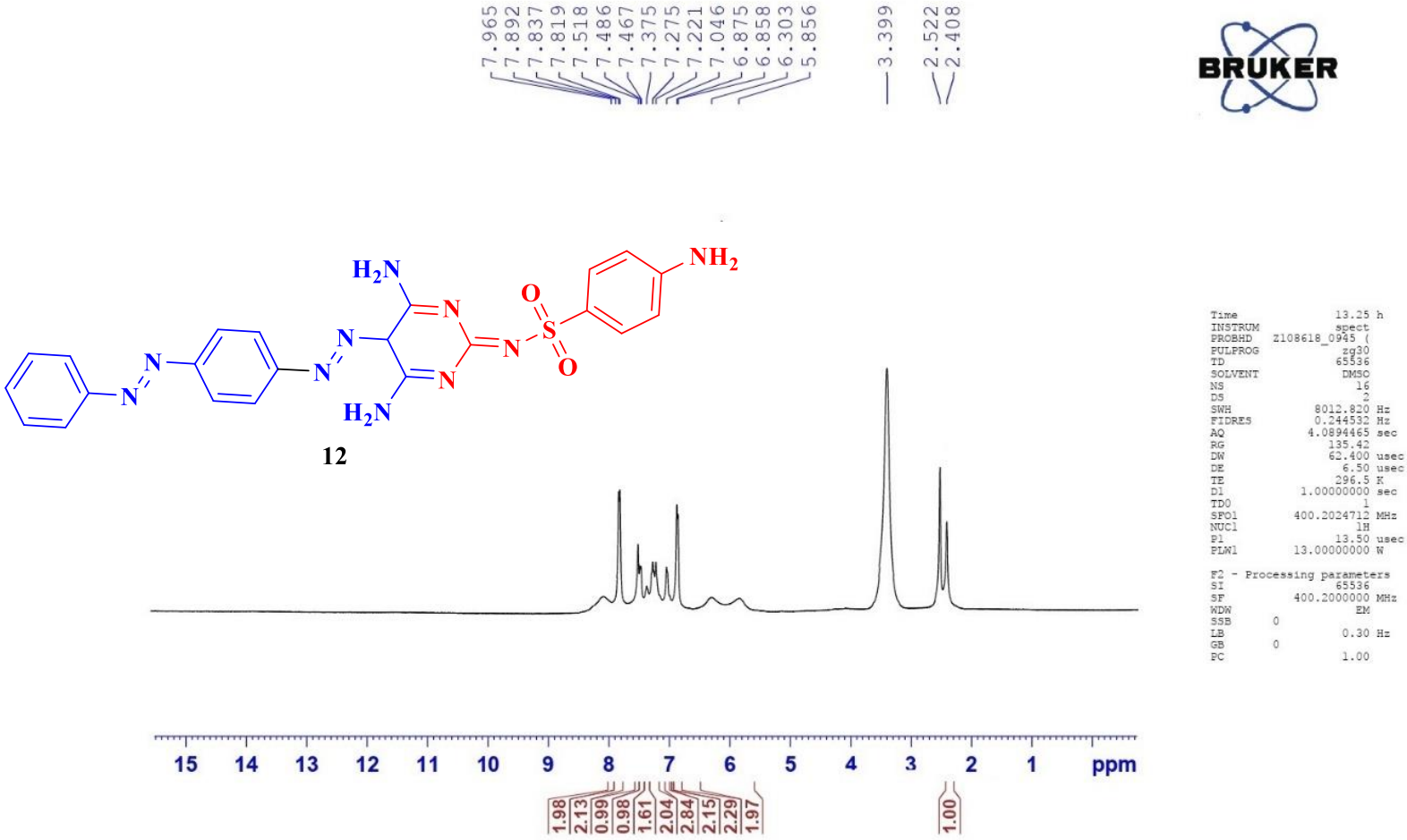
13CNMR of compound 11



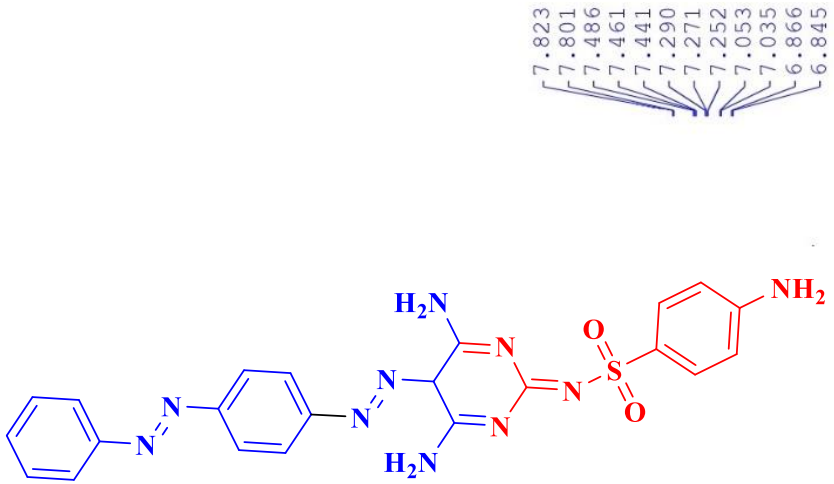
IR of compound 12



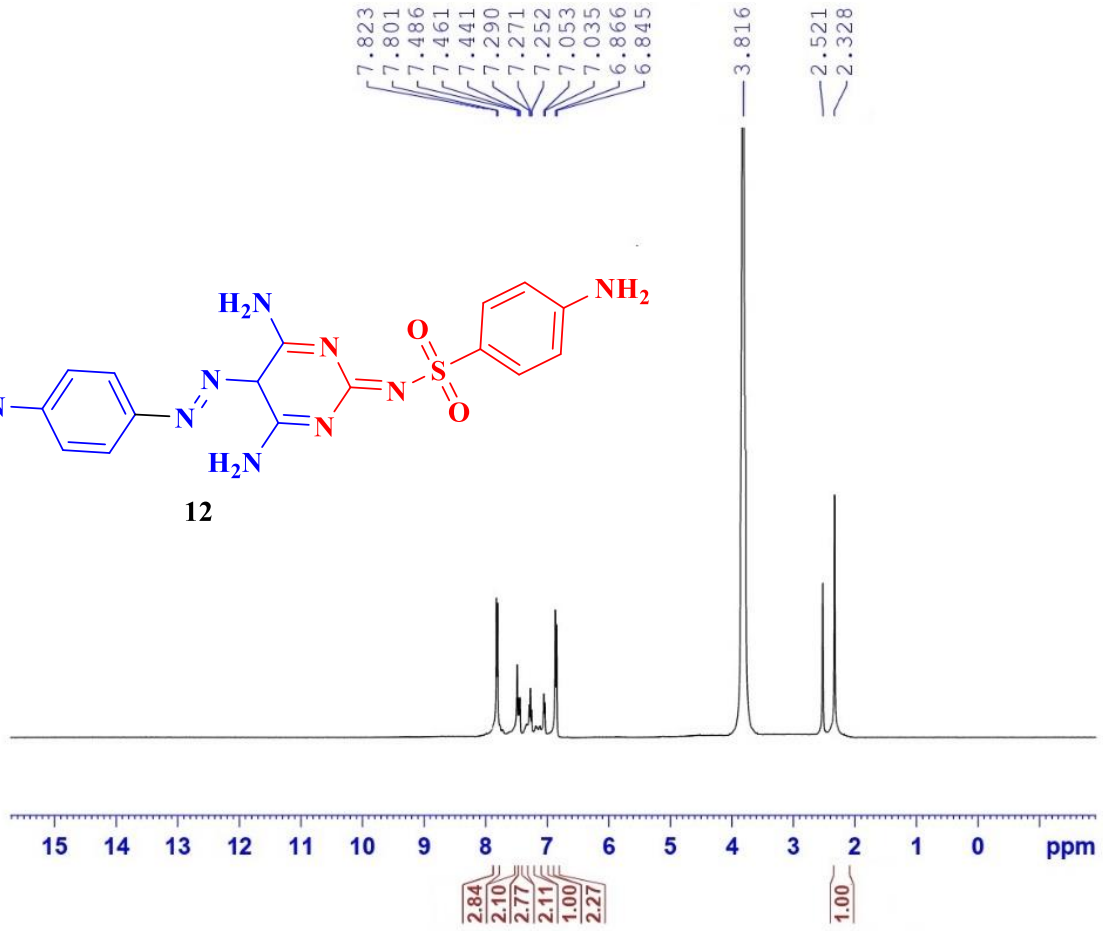
1HNMR of compound 12



D2O Of compound 12

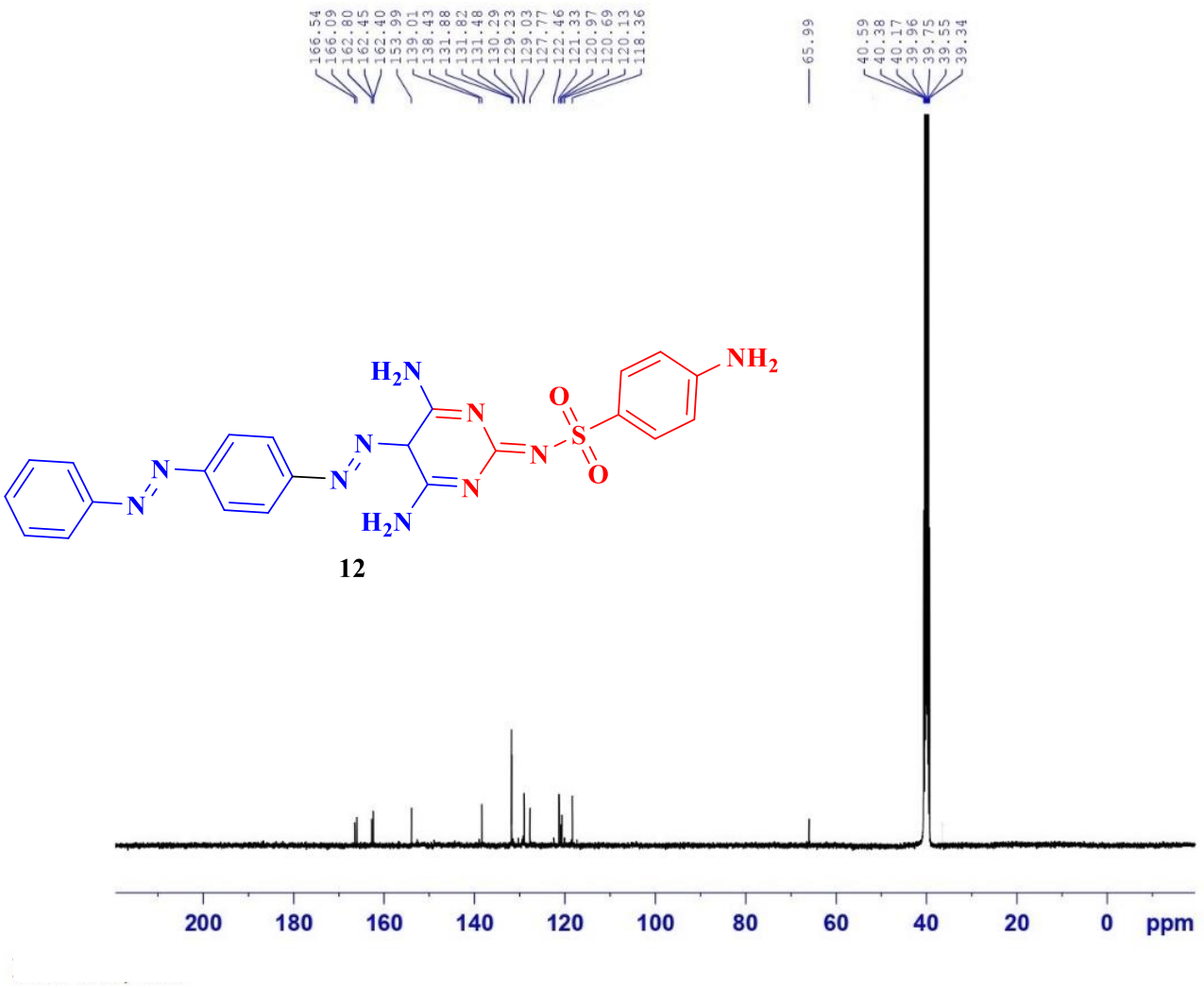


12




```
Time                  11.05 h
INSTRUM               spect
PROBHD    Z108618_0945 (
PULPROG               zg30
TD                    65536
SOLVENT               DMSO
NS                    16
DS                    2
SWH                   8012.820 Hz
FIDRES                0.244532 Hz
AQ                    4.0894465 sec
RG                    120.93
DW                    62.400 usec
DE                    6.50 usec
TE                    296.6 K
D1                    1.00000000 sec
TD0                   1
SFO1                  400.2024712 MHz
NUC1                  1H
P1                    13.50 usec
PLW1                  13.00000000 W

F2 - Processing parameters
SI                    65536
SF                    400.2000000 MHz
WDW                   EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
```

13CNMR of compound 12



12