Insights Into Targeting the SARS-CoV-2: Design, Synthesis, *In Silico* Studies and Antiviral Evaluation of New Dimethylxanthine Derivatives

(Supplementary Materials)

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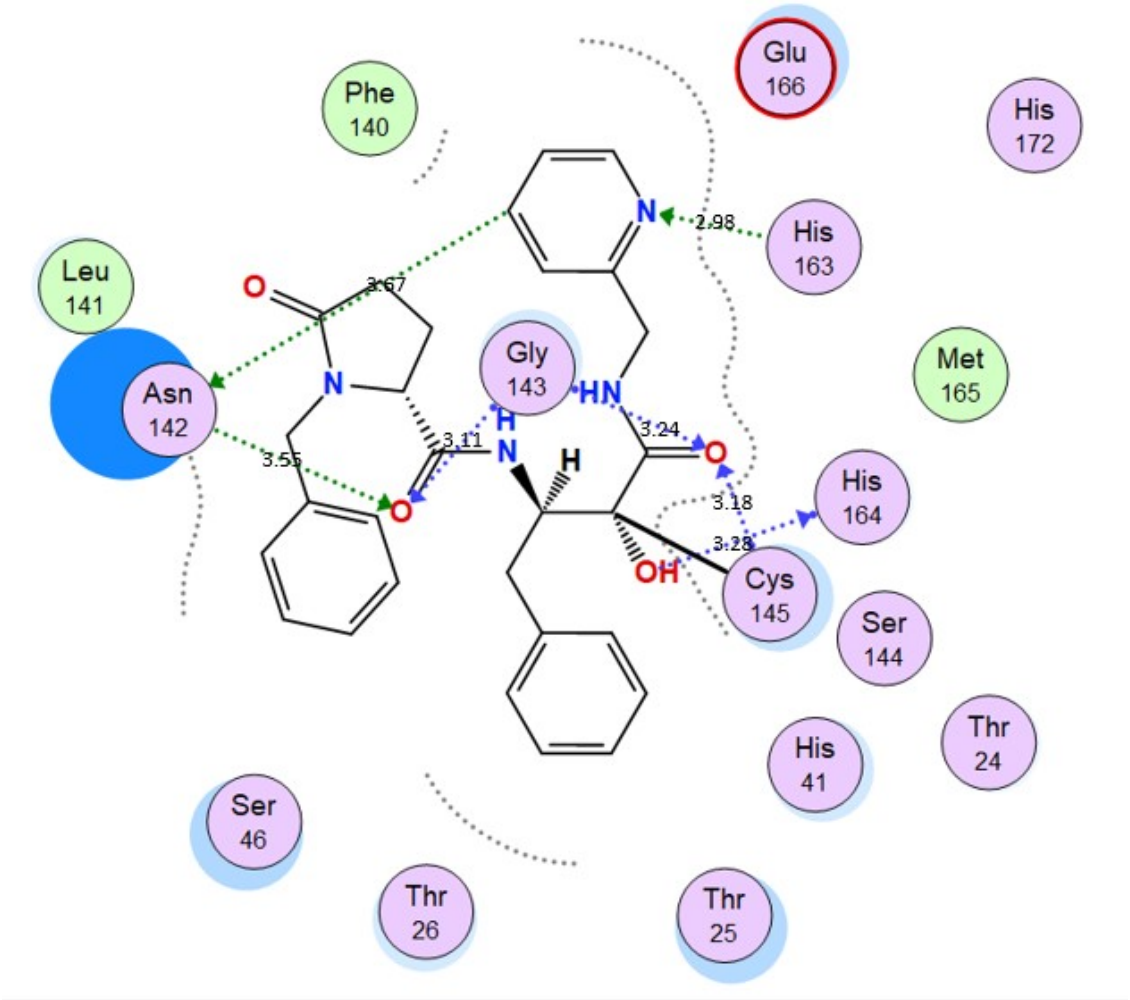
Content

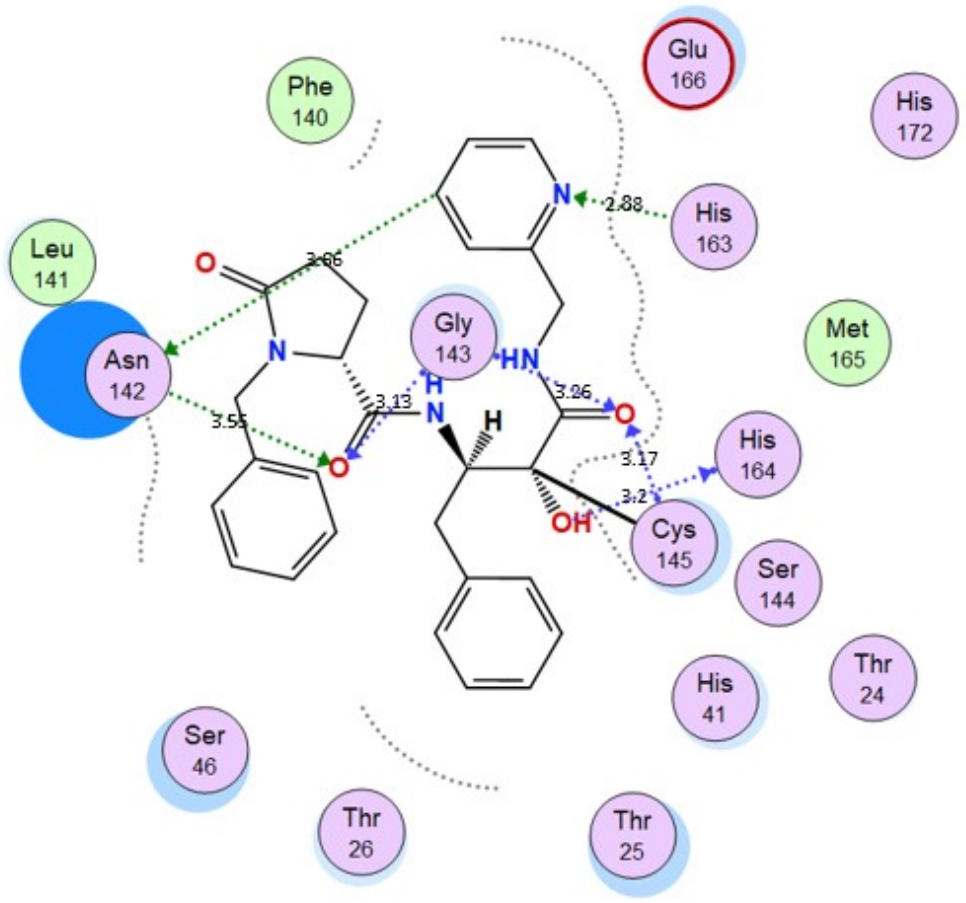
Supplementary Materials

1. Molecular Docking

Docking validation of the co-crystalized ligand, in the SARS-CoV-2 M_{pro} (PDB ID: 7AEH) active site



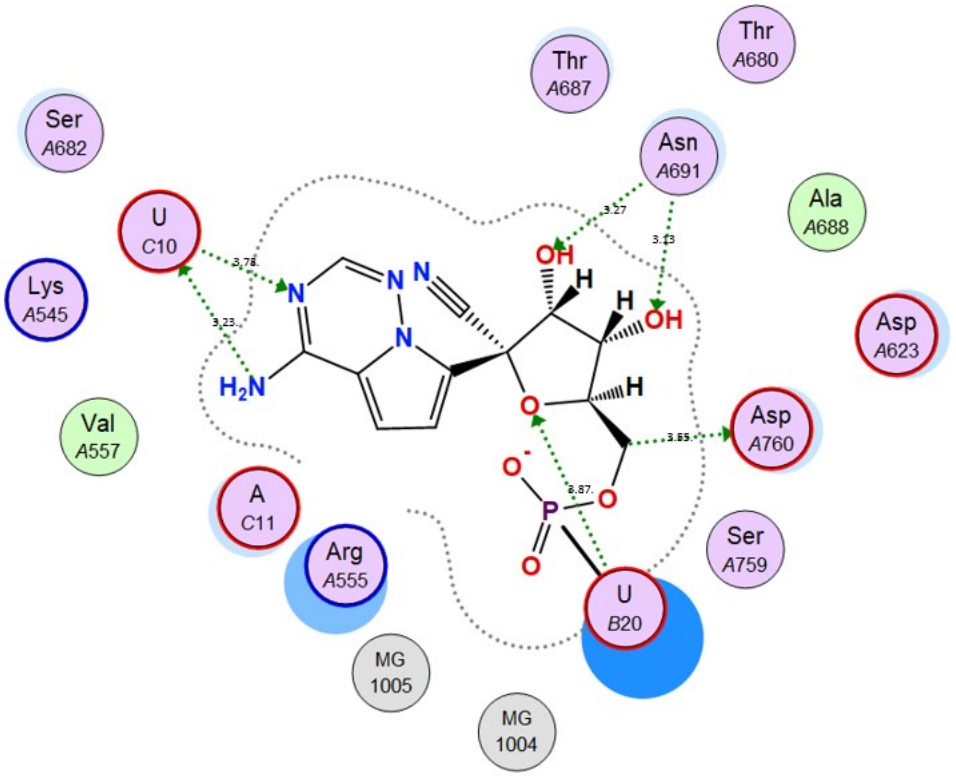
(A)



(B)

Figure 1S. (A) 2D interaction diagram showing ligand docking pose interactions with the key amino acids (hot spots) in the M_{pro} active site (Distance in Å). (B) 2D diagram of the docking pose in M_{pro} active site with RMSD of 0.75 Å.

Docking validation of the co-crystalized ligand, in the SARS-CoV-2 RdRp (PDB ID: 7BV2) active site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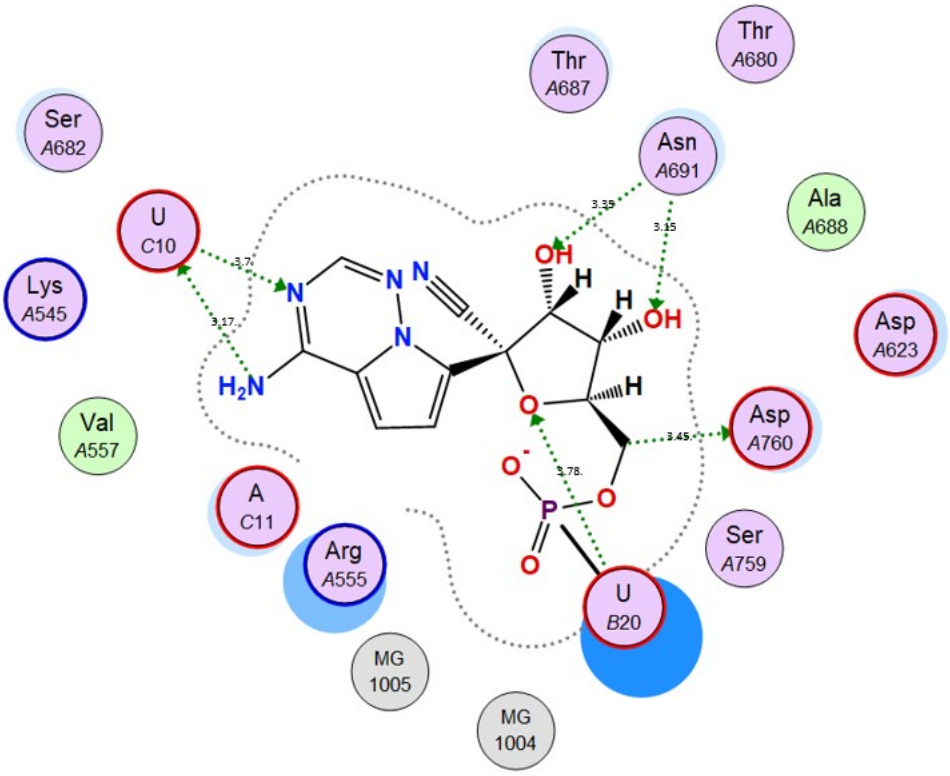
1005
MG
1004

(A)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Asp
A760
A
C11
Ser
A759
Arg
A555
U
B20
MG
1005
MG
1004

(B)

Figure 2S. (A) 2D interaction diagram showing ligand docking pose interactions with the key amino acids (hot spots) in the RdRp active site (Distance in Å). (B) 2D diagram of the docking pose in RdRp active site with RMSD of 0.56 Å.

Table 1S. Docking scores of the tested compounds in M_{pro} & RdRp.

Compound	M_{PRO} binding score (Kcal/mol)	RdRp binding score (Kcal/mol)
3	-15.23	-11.88
5	-15.90	-12.70
9a	-17.52	-13.72
9b	-16.50	-12.53
12a	-15.11	-11.96
12b	-16.01	-12.29
14	-14.90	-10.70
15a	-14.47	-10.98
15b	-16.43	-11.55
19	-16.57	-13.10

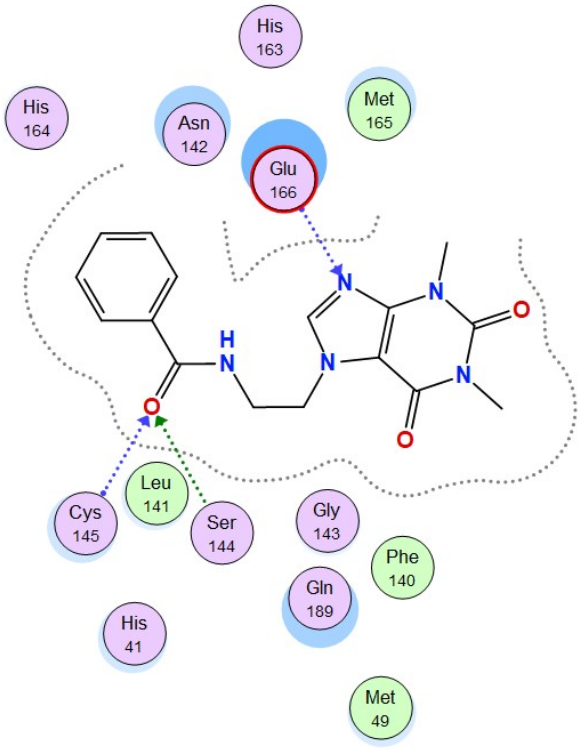


Figure 3S. 2D interaction of compound **3** in M_{pro} active site

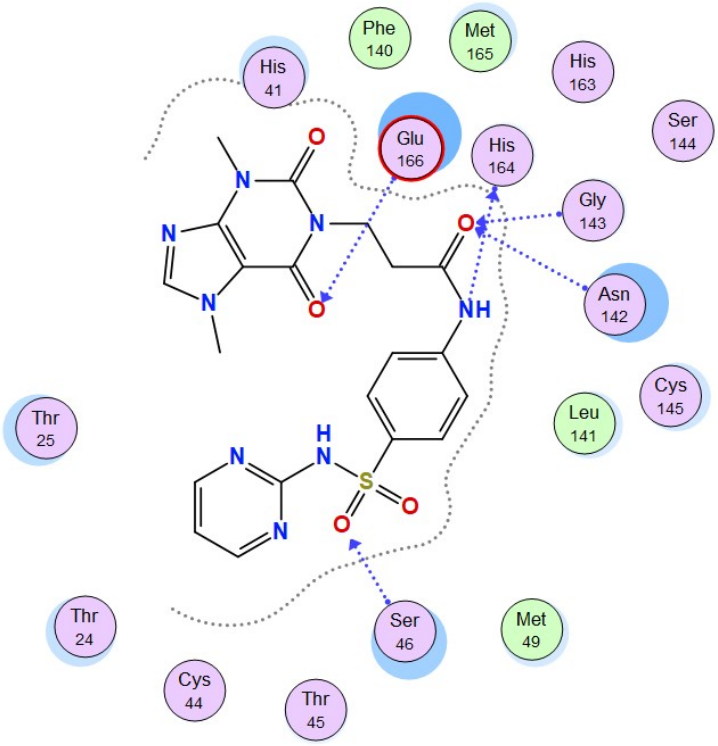


Figure 4S. 2D interaction of compound **9b** in M_{pro} active site

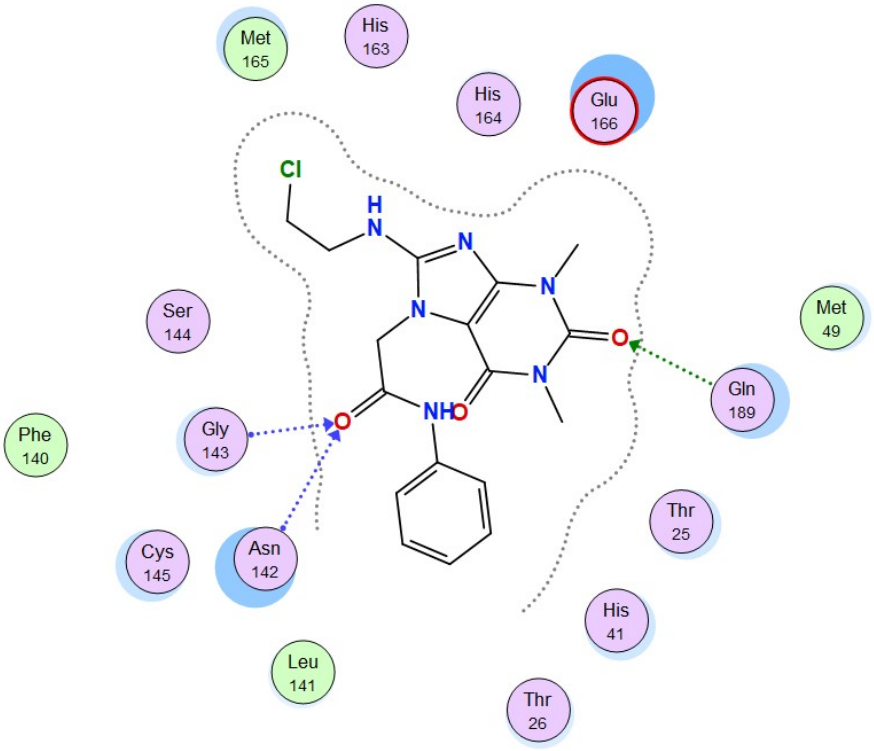


Figure 5S. 2D interaction of compound **12a** in M_{pro} active site

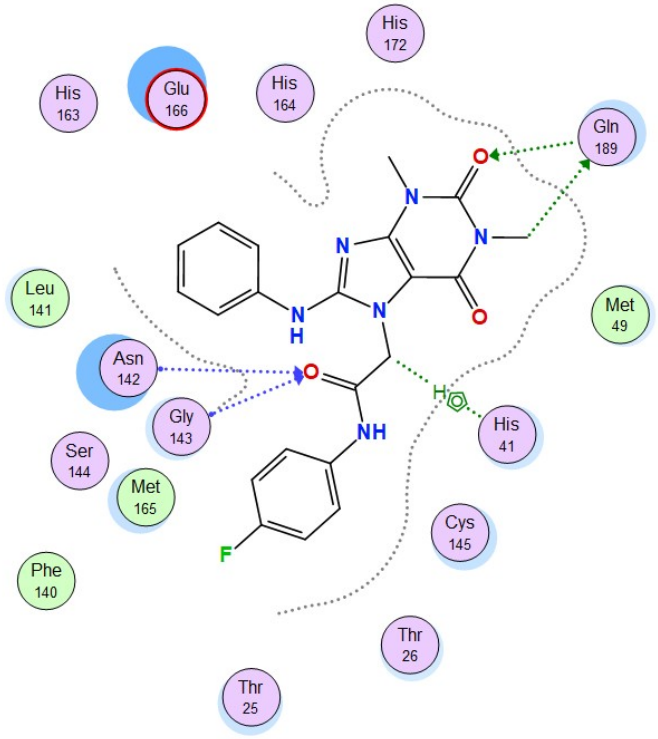


Figure 6S. 2D interaction of compound **12b** in M_{pro} active site

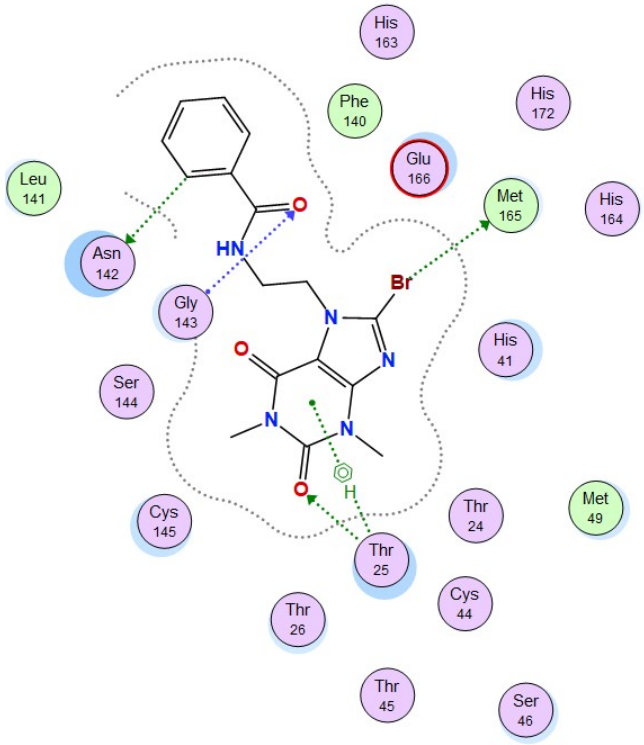


Figure 7S. 2D interaction of compound **14** in M_{pro} active site

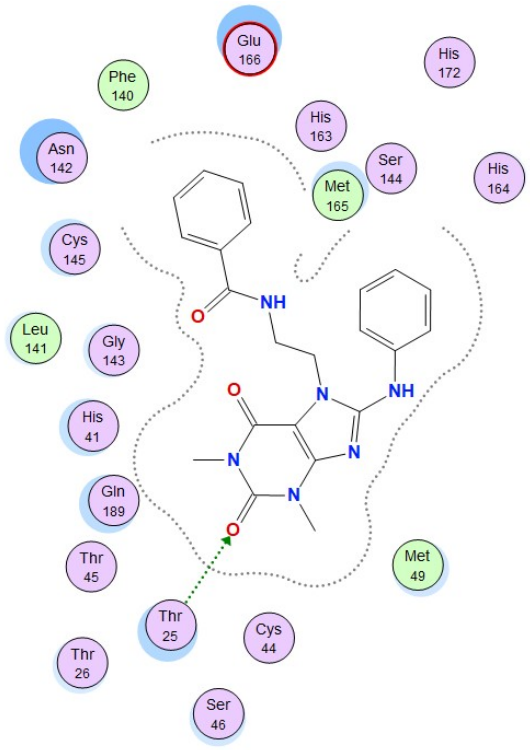


Figure 8S. 2D interaction of compound **15a** in M_{pro} active site

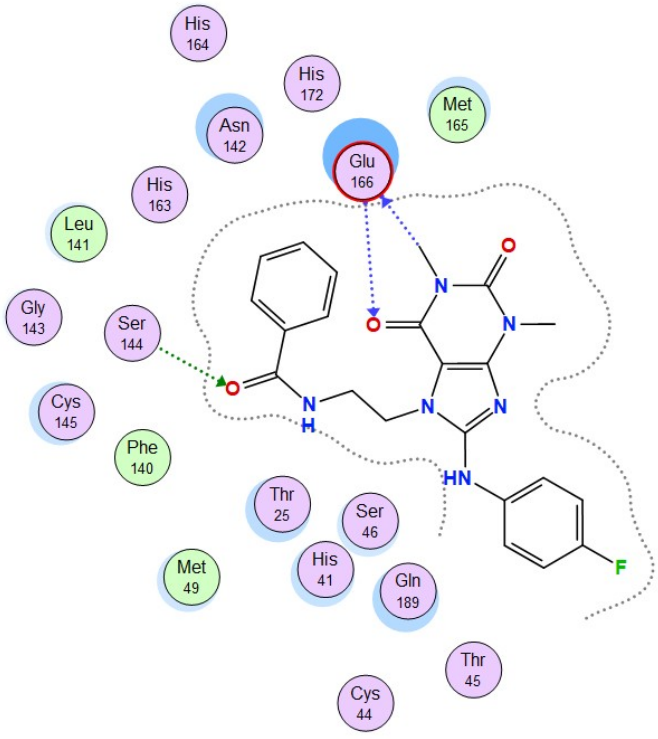


Figure 9S. 2D interaction of compound **15b** in M_{pro} active site

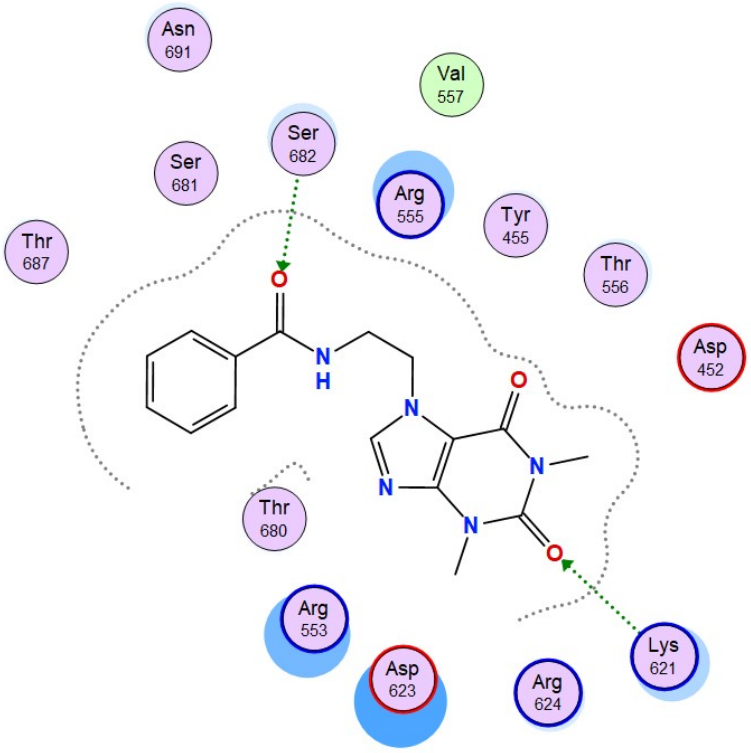


Figure 10S. 2D interaction of compound **3** in RdRp active site

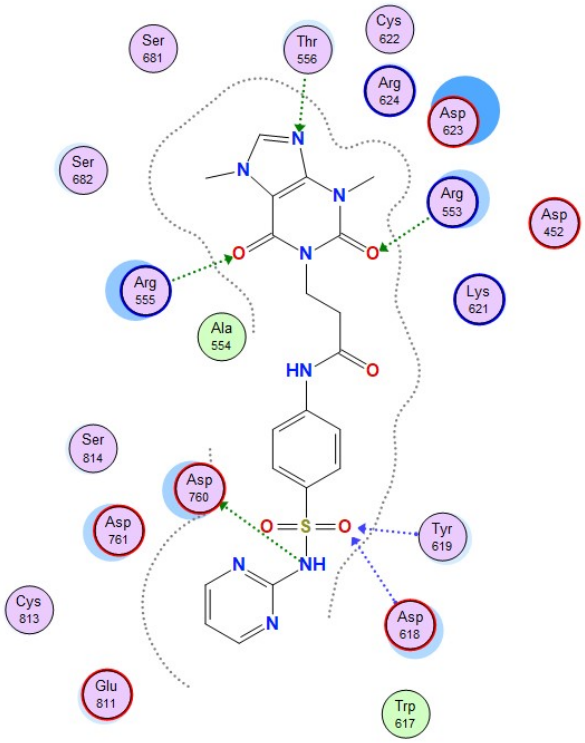


Figure 11S. 2D interaction of compound **9b** in RdRp active site

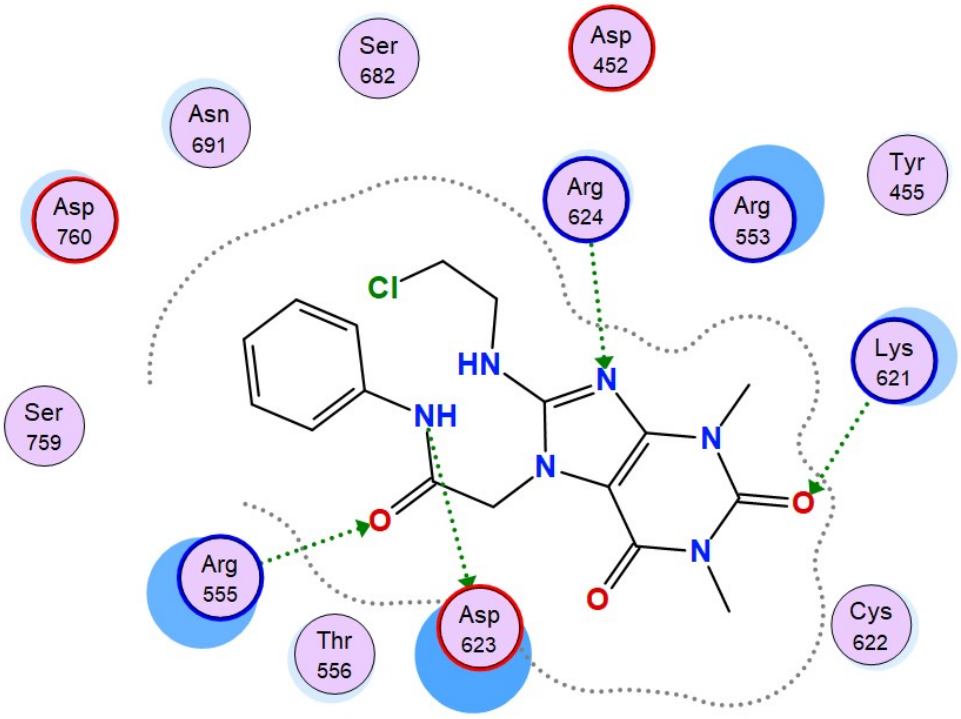


Figure 12S. 2D interaction of compound **12a** in RdRp active site

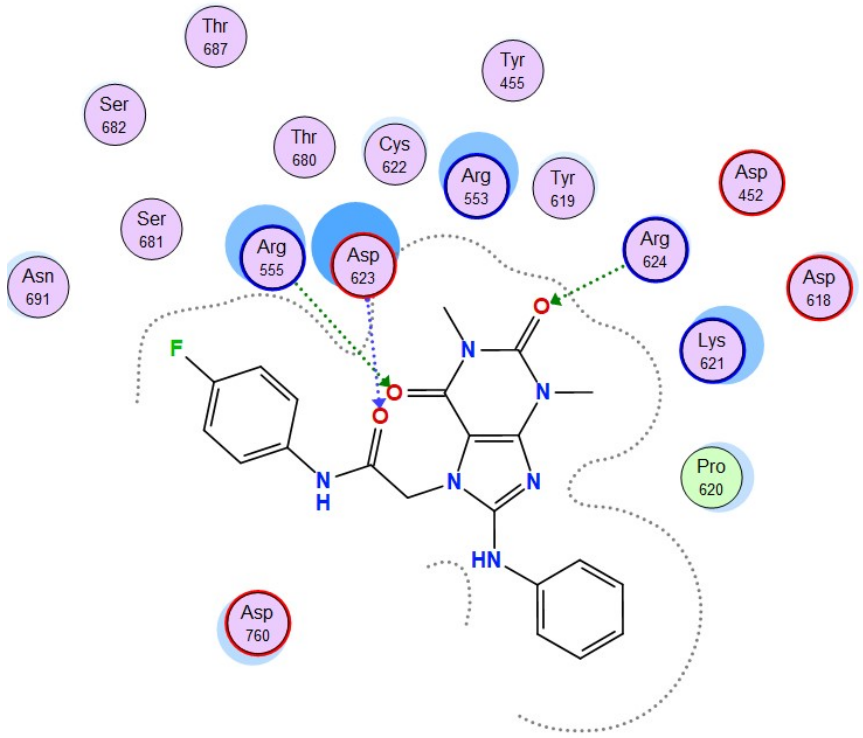


Figure 13S. 2D interaction of compound **12b** in RdRp active site

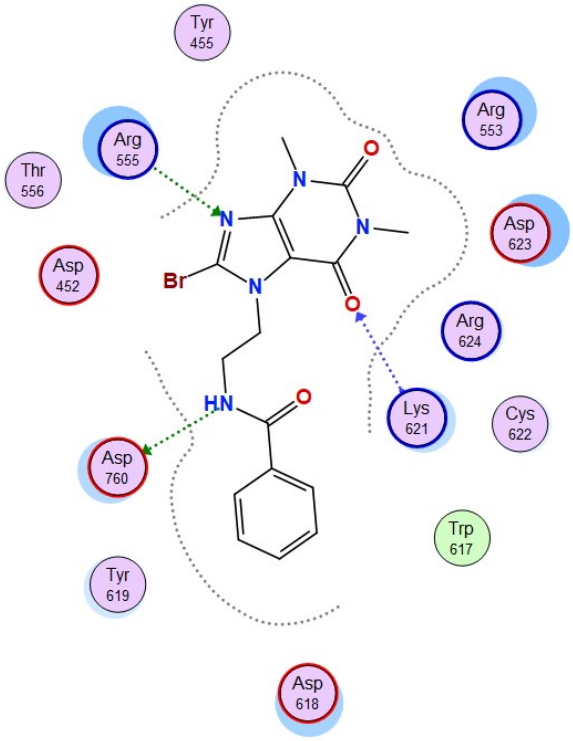


Figure 14S. 2D interaction of compound **14** in RdRp active site

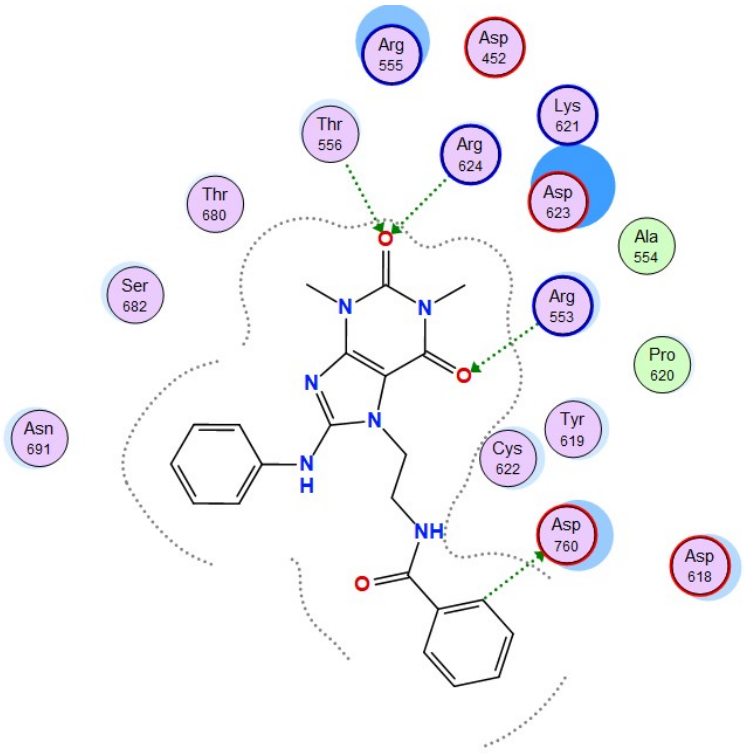


Figure 15S. 2D interaction of compound **15a** in RdRp active site

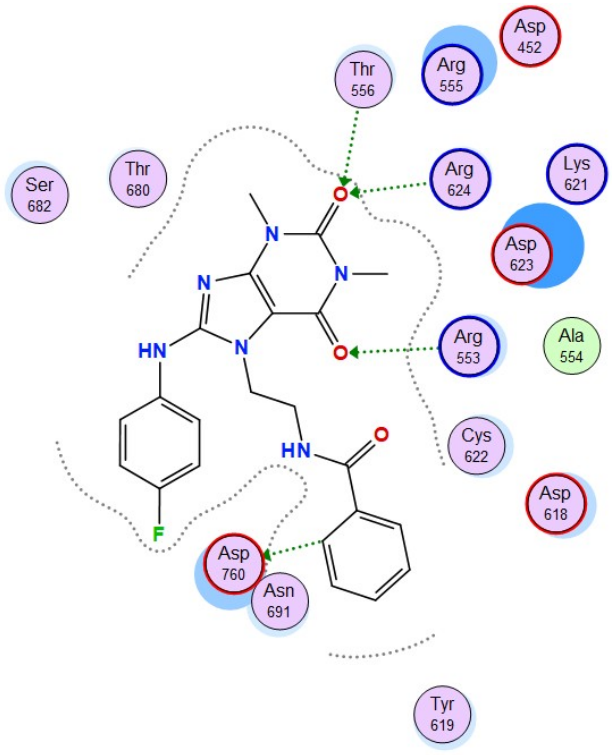


Figure 16S. 2D interaction of compound **15b** in RdRp active site

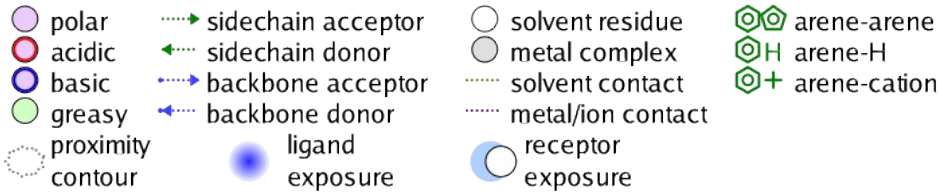


Figure 17S. A legend guide to binding interactions regarding all the performed docking studies.

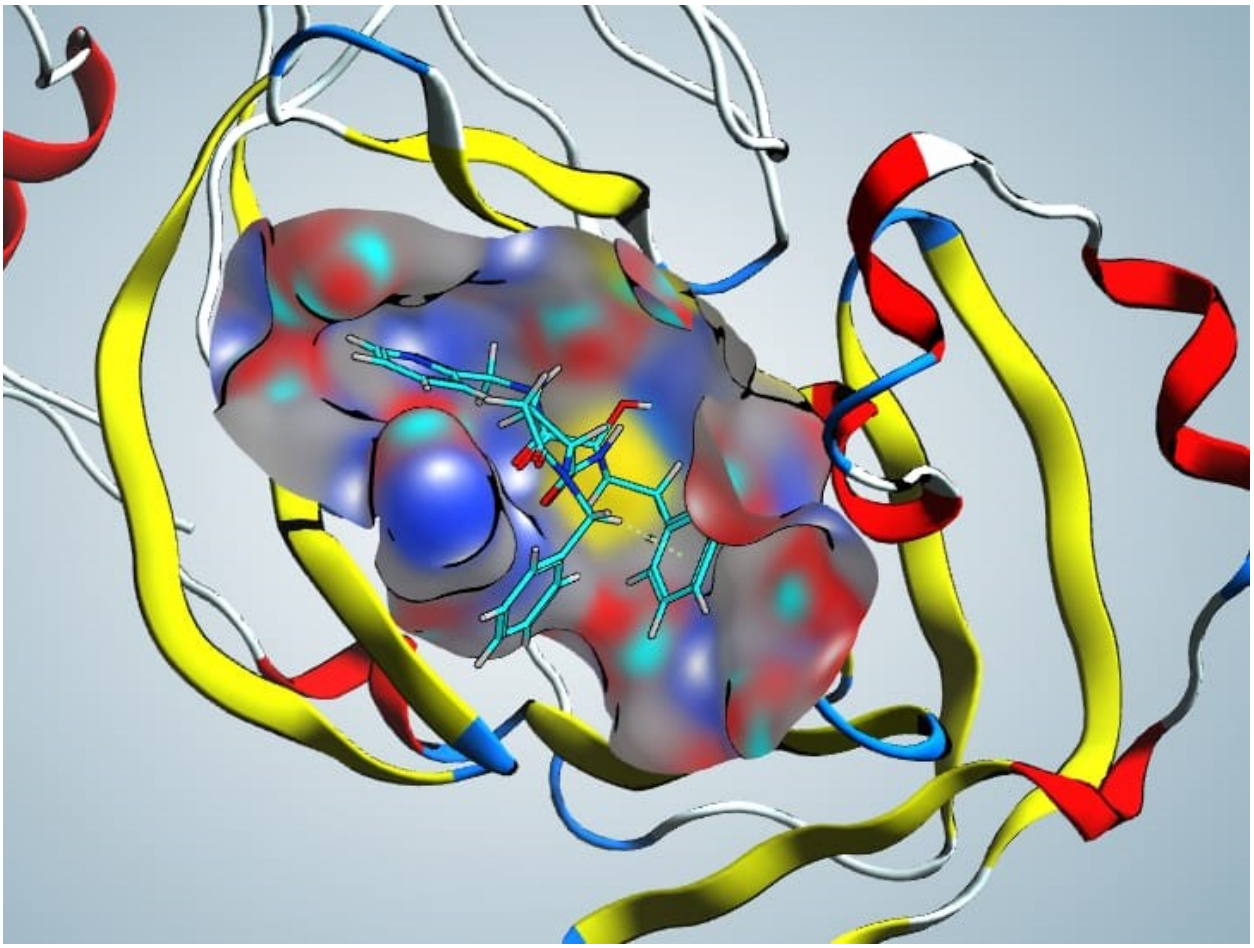


Figure 18S. 3D presentation of surface and map of SARS-CoV-2 M_{pro} active site (PDB ID: 7AEH) with compound **9a**.

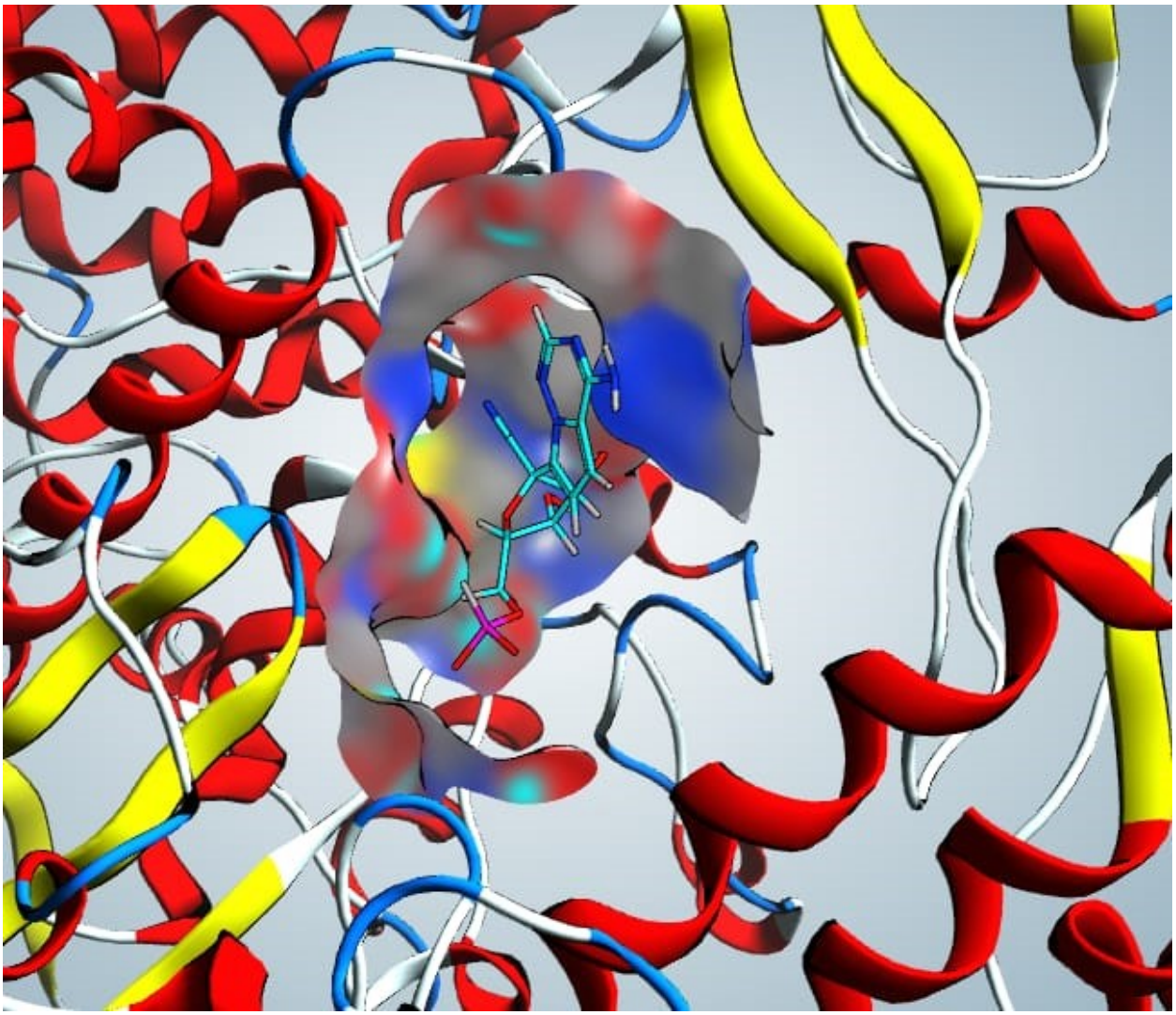
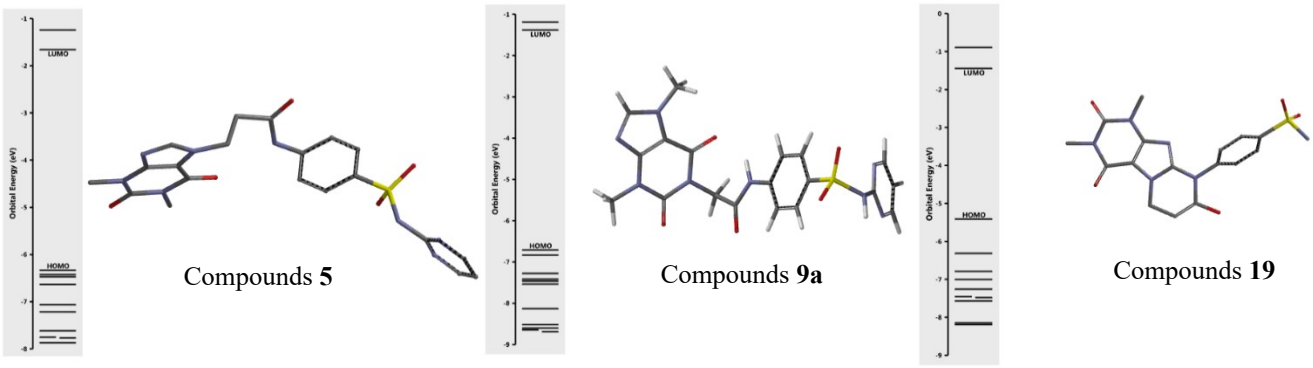


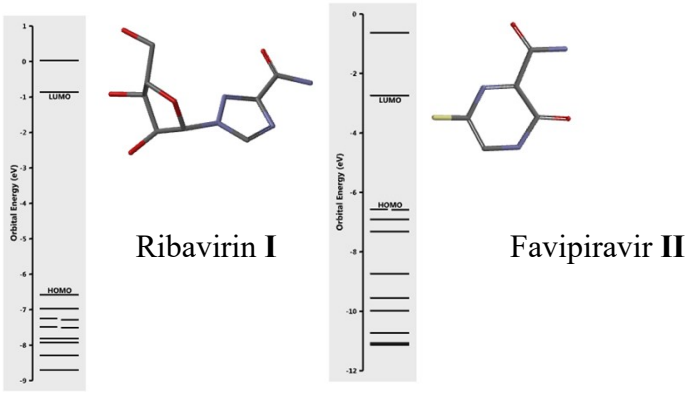
Figure 19S. 3D presentation of surface and map of SARS-CoV-2 RdRp active site (PDB ID: 7BV2) with compound **9a**.

2. Density functional theory (DFT) calculations

According to the performed docking studies, compounds **9a**, **19** and **5** were predicted to have interesting binding modes in the active site of SARS-CoV-2 M_{pro} and RdRp enzymes. Quantum chemical computations using the DFT/B3LYP approach with 6-311G++(d,p) basis set were utilized to get insights regarding the energy values of compounds **9a**, **19** and **5** (**Table 2S**) [1]. **Figure 20S-A** represents the optimized structures along with their HOMO and LUMO values. The DFT calculations revealed favorable energetic parameters for the three compounds, and particularly, compound **9a** was comparable with compounds **I** and **II** (**Figure 20S-B**).



(A)



(B)

Figure 20S. (**A**) DFT calculations for compounds **5, 9a** and **19**. (**B**) The most stable conformation of Ribavirin **I** and Favipiravir **II** according to DFT calculation [2, 3].

Table 2S. The molecular properties of compounds **5, 9a** and **19** after DFT calculations

Compound	Energy (a.u.)	Energy solvation (Kj/Mol)	E HOMO (eV)	E LUMO (eV)	Dipole Moment (Debye)	No. of conformers	% Of the most favorable conformer
5	-1985.50614	-143.63	-6.33	-1.66	8.11	1296	99.993
9a	-1946.20887	-125.68	-6.71	-1.38	9.11	216	99.989
19	-1721.30460	-112.69	-5.41	-1.45	8.50	24	99.601

The Spartan '14 program was used to perform the quantum chemistry calculations using the DFT method. Spartan '14 was used to display all of the data files. DFT at 6-311G++(d,p) basis set/B3LYP approach was utilized to optimize organic chemical structure of compound **5**, **9a** and **19** [1].

3. MM-PBSA calculations

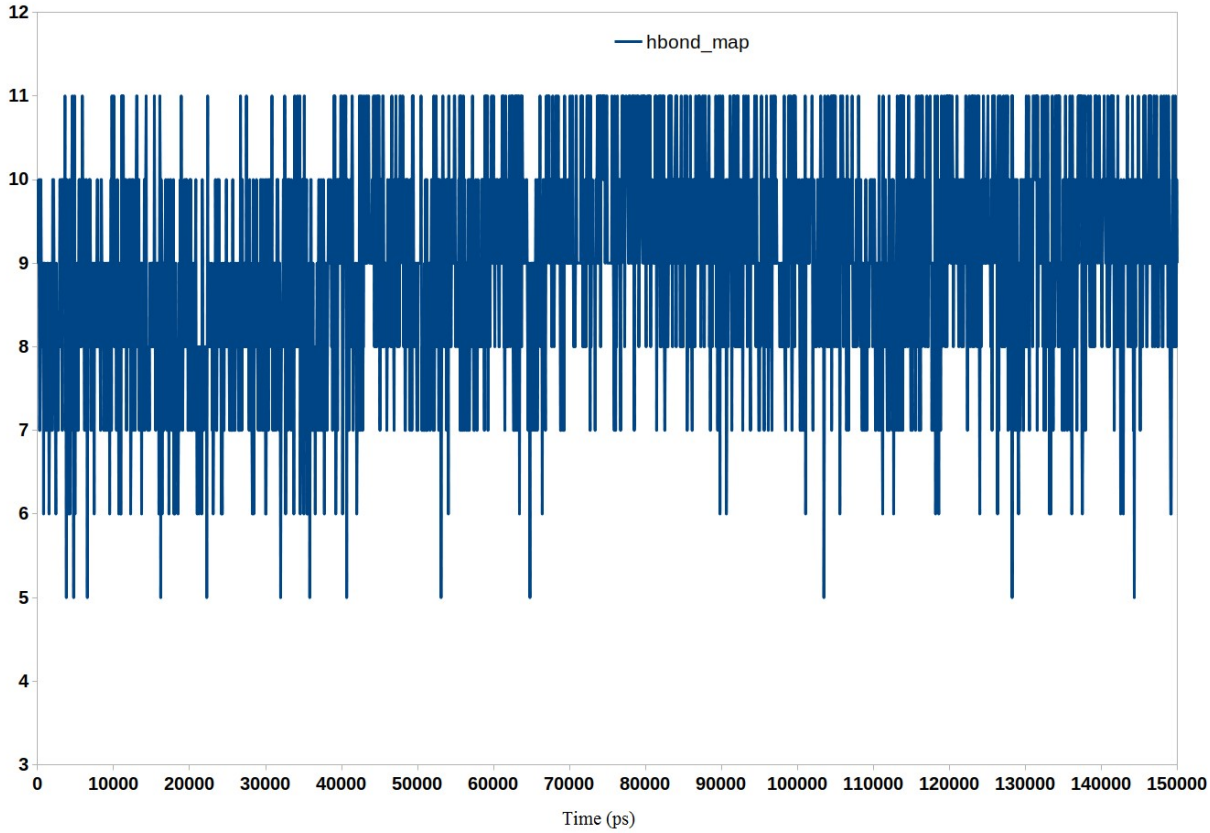
The total free energy of any of the three mentioned entities (complex, receptor and ligand) were calculated for all MD trajectories from its molecular mechanics potential energy plus the energy of the solvation, using the g_mmpbsa package. The following formula was used.

$$\Delta G_{(Binding)} = G_{(Complex)} - G_{(Receptor)} - G_{(Ligand)}$$

Where $G_{(Complex)}$ is the total free energy of the protein−ligand complex, $G_{(Receptor)}$ and $G_{(Ligand)}$ are the total free energies of the isolated protein and ligand in solvent, respectively. Individual energies along with the values of standard deviations were calculated and then summed together to yield the average total free energy of each component. Finally, to calculate the binding-free energy, the total free energy of the receptor and the ligand were subtracted from the total free energy of the complex [4].

4. Hydrogen bond analysis upon time evolution

For further insights into the binding process between compound **9a** and the active sites of M_{pro} and RdRp enzymes, hydrogen bond interactions during the MDS were analyzed using VMD 1.8.2 program [5]. As **Figure 21S-A** and **B** demonstrate, compound **9a** was able to form multiple hydrogen bond interactions with the M_{pro} and RdRp enzymes, respectively, throughout the entire MDS. Furthermore, the binding interactions between compound **9a** and both of M_{pro} or RdRp induced stable complexes as revealed from **Figure 22S-A** and **B**.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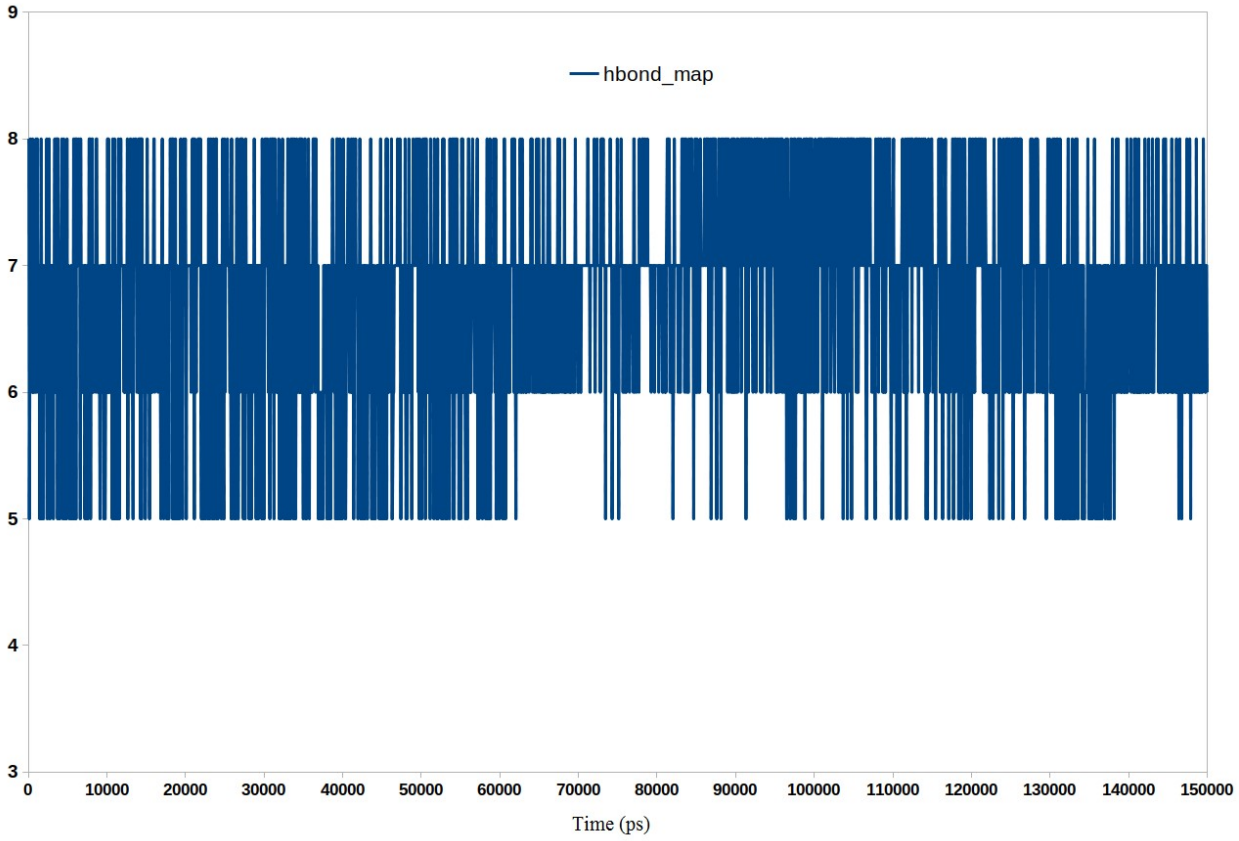
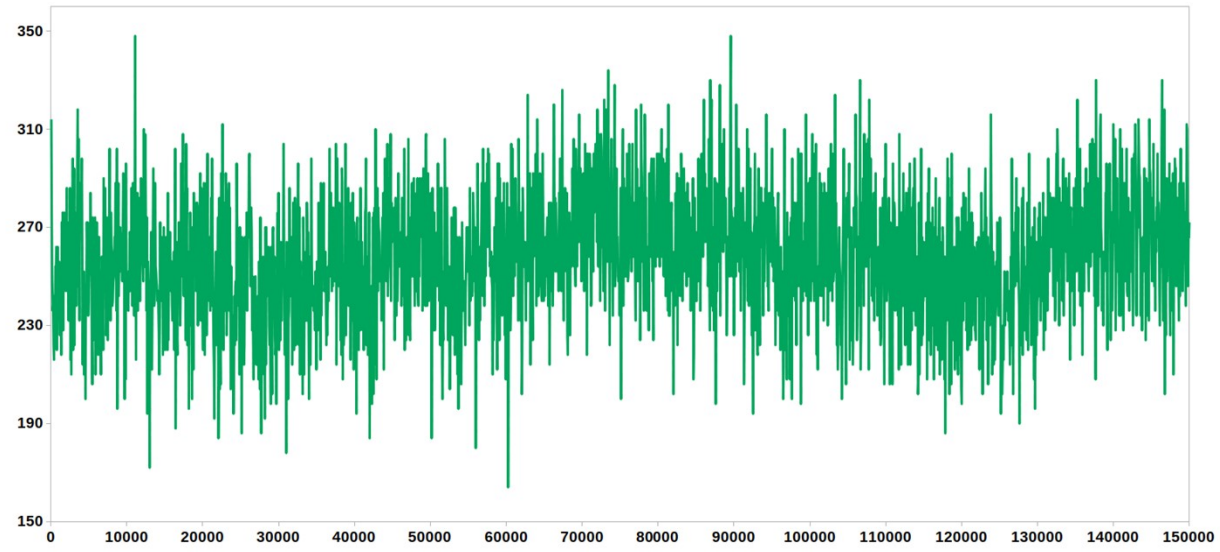
140000
150000
Time (ps)

(A)

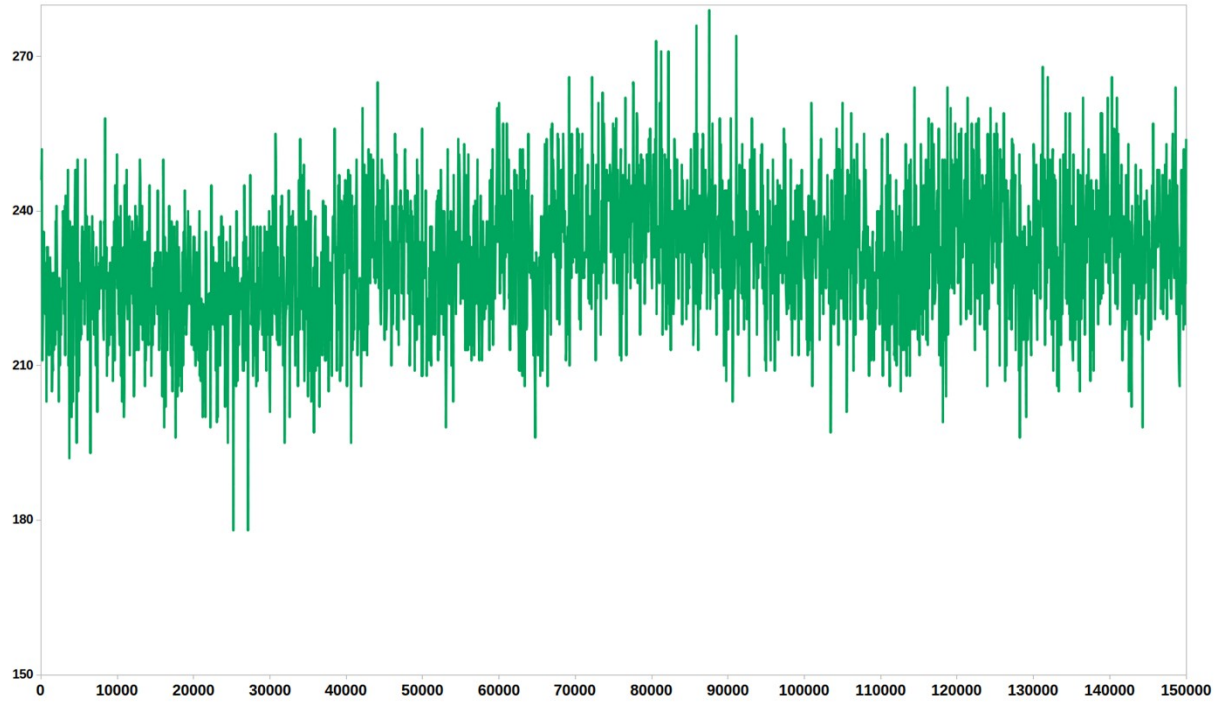


(B)

Figure 21S. The hydrogen bond contacts during the entire MDS; (A) compound **9a** with M_{pro}, (B) compound **9a** with RdRp.



(A)



(B)

Figure 22S. The hydrogen bond contacts during the entire MDS; (A) M_{pro} enzyme (B) RdRp enzyme.

5. NCI-60 cell lines panel

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-787131 / 1 | **Conc:** 1.00E-5 Molar | **Test Date:** Sep 14, 2015
Experiment ID: 1509OS61 | **Report Date:** Oct 02, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	90.94
HL-60(TB)	93.81
K-562	106.97
MOLT-4	101.45
RPMI-8226	96.45
SR	111.30
Non-Small Cell Lung Cancer	
A549/ATCC	89.37
EKVX	109.89
HOP-62	83.88
HOP-92	92.07
NCI-H226	105.59
NCI-H23	93.54
NCI-H322M	110.95
NCI-H460	111.01
NCI-H522	95.34
Colon Cancer	
COLO 205	106.55
HCC-2998	99.18
HCT-116	98.82
HCT-15	108.91
HT29	97.83
KM12	99.11
SW-620	104.39
CNS Cancer	
SF-268	106.03
SF-295	113.73
SF-539	97.34
SNB-19	104.64
SNB-75	85.28
U251	98.43
Melanoma	
LOX IMVI	95.83
MALME-3M	106.62
M14	93.97
MDA-MB-435	113.27
SK-MEL-2	104.84
SK-MEL-28	112.07
SK-MEL-5	112.16
UACC-257	95.71
Ovarian Cancer	
IGROV1	111.09
OVCAR-3	115.96
OVCAR-4	114.56
OVCAR-5	102.20
OVCAR-8	104.22
NCI/ADR-RES	104.17
SK-OV-3	89.78
Renal Cancer	
786-0	100.18
A498	111.86
ACHN	103.27
CAKI-1	96.06
RXF 393	120.56
SN12C	100.12
TK-10	99.65
UO-31	86.29
Prostate Cancer	
PC-3	86.03
DU-145	112.00
Breast Cancer	
MCF7	98.06
MDA-MB-231/ATCC	103.18
HS 578T	99.29
BT-549	98.37
T-47D	95.55
MDA-MB-468	102.79
Mean	101.74
Delta	17.86
Range	36.68

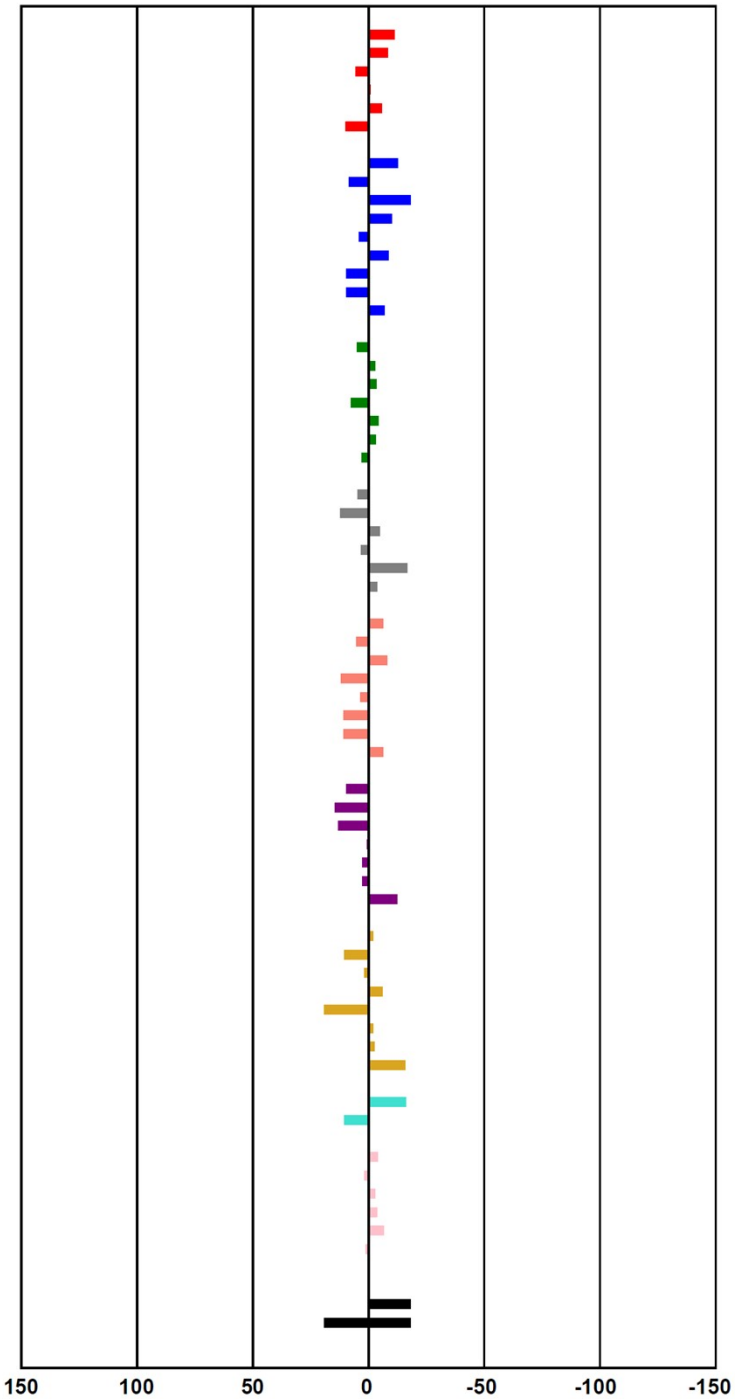


Figure. 23S. NCI-60 cell line panel of compound **5**

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-787132 / 1 | **Conc:** 1.00E-5 Molar | **Test Date:** Sep 14, 2015

Experiment ID: 1509OS61 | **Report Date:** Oct 02, 2015

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	98.47
HL-60(TB)	101.34
K-562	103.36
MOLT-4	100.25
RPMI-8226	101.35
SR	109.51
Non-Small Cell Lung Cancer	
A549/ATCC	92.85
EKVX	109.25
HOP-62	91.87
HOP-92	93.60
NCI-H226	104.71
NCI-H23	101.75
NCI-H322M	106.66
NCI-H460	106.61
NCI-H522	84.61
Colon Cancer	
COLO 205	106.19
HCC-2998	104.52
HCT-116	95.59
HCT-15	110.39
HT29	96.93
KM12	104.91
SW-620	102.37
CNS Cancer	
SF-268	108.33
SF-295	109.08
SF-539	98.93
SNB-19	102.20
SNB-75	88.81
U251	98.13
Melanoma	
LOX IMVI	97.80
MALME-3M	99.00
M14	94.21
MDA-MB-435	106.48
SK-MEL-2	104.14
SK-MEL-28	110.56
SK-MEL-5	109.16
UACC-257	95.47
Ovarian Cancer	
IGROV1	105.17
OVCAR-3	113.27
OVCAR-4	105.45
OVCAR-5	100.49
OVCAR-8	98.96
NCI/ADR-RES	111.00
SK-OV-3	91.38
Renal Cancer	
786-0	108.33
A498	92.99
ACHN	109.85
CAKI-1	93.09
RXF 393	118.10
SN12C	107.58
TK-10	108.11
UO-31	82.45
Prostate Cancer	
PC-3	84.37
DU-145	115.51
Breast Cancer	
MCF7	100.09
MDA-MB-231/ATCC	100.15
HS 578T	105.38
BT-549	102.10
T-47D	92.54
MDA-MB-468	104.79
Mean	101.70
Delta	19.25
Range	35.65

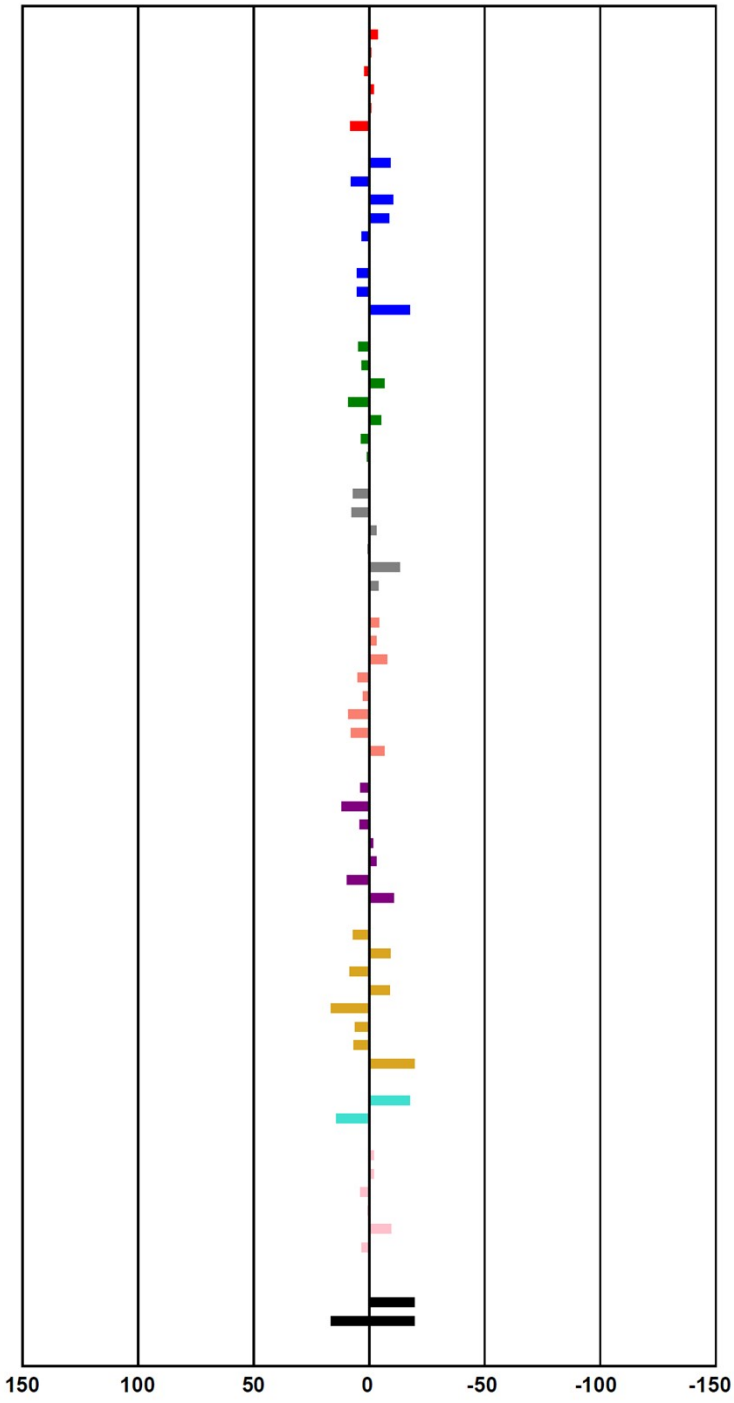


Figure. 24S. NCI-60 cell line panel of compound **9a**

6. Oral toxicity prediction of compounds 5, 9a and 19

Table 3S. *In silico* oral toxicity prediction for compounds **5, 9a** and **19**

Compound	LD_{50} (mg/kg)	Predicted Toxicity Class [a]	Average similarity (%)	Prediction accuracy (%)
5	300	3	60.56	68.07
9a	598	4	60.75	68.07
19	500	4	47.93	54.26
Remdesivir	1000	4	40.93	54.26
Favipiravir	1717	4	39.16	23.00

[a] Toxicity Class ranging from 1 to 6 according to the Global Harmony System (GHS) [6].

The ProTox web server was used to estimate rodent oral toxicity and indication of possible toxicity targets for compounds **5, 9a** and **19** as reported previously [6]. As seen in **Table 3S**, the evaluated LD_{50} was ranged from 300 to 598 mg/kg for the predicted compounds. The evaluated molecules were predicted to be in toxicity classes of 3 or 4, and have no toxic fragments. Furthermore, the submitted compounds were found to be not binding to toxic targets, only compound 19 was found to have a probable hepatotoxicity, figures S-S.

Molweight	484.49
Number of hydrogen bond acceptors	30
Number of hydrogen bond donors	2
Number of atoms	54
Number of bonds	57
Number of rotable bonds	8
Molecular refractivity	123.38
Topological Polar Surface Area	171.25
octanol/water partition coefficient(logP)	1.28

(A)

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.52
Toxicity end points	Carcinogenicity	carcino	Inactive	0.61
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.76
Toxicity end points	Cytotoxicity	cyto	Inactive	0.56
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.92
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.93
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.95
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.95
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.84
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.91
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99

(B)

Figure 25S. Physical characters (A) and Toxicity Model Report (B) for compound **5.**

Molweight	470.46
Number of hydrogen bond acceptors	28
Number of hydrogen bond donors	2
Number of atoms	51
Number of bonds	54
Number of rotable bonds	7
Molecular refractivity	118.58
Topological Polar Surface Area	171.25
octanol/water partition coefficient(logP)	0.89

(A)

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.56
Toxicity end points	Carcinogenicity	carcino	Inactive	0.60
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.74
Toxicity end points	Cytotoxicity	cyto	Inactive	0.56
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.92
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.94
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.95
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.95
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.88
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.91
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99

(B)

Figure 26S. Physical characteristics (A) and Toxicity Model Report (B) for compound **9a**

Molweight	404.4
Number of hydrogen bond acceptors	24
Number of hydrogen bond donors	2
Number of atoms	44
Number of bonds	47
Number of rotable bonds	2
Molecular refractivity	104.2
Topological Polar Surface Area	153.83
octanol/water partition coefficient(logP)	1.48

(A)

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Active	0.50
Toxicity end points	Carcinogenicity	carcino	Inactive	0.62
Toxicity end points	Immunotoxicity	immuno	Inactive	0.98
Toxicity end points	Mutagenicity	mutagen	Inactive	0.75
Toxicity end points	Cytotoxicity	cyto	Inactive	0.60
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	1.0
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.96
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.99
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.99
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.86
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.92
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99

(B)

Figure 27S. Physical characteristics (A) and Toxicity Model Report (B) for compound **19**

Molweight	602.58
Number of hydrogen bond acceptors	48
Number of hydrogen bond donors	4
Number of atoms	77
Number of bonds	80
Number of rotable bonds	14
Molecular refractivity	150.43
Topological Polar Surface Area	213.36
octanol/water partition coefficient(logP)	3.28

(A)

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.56
Toxicity end points	Carcinogenicity	carcino	Inactive	0.55
Toxicity end points	Immunotoxicity	immuno	Inactive	0.90
Toxicity end points	Mutagenicity	mutagen	Inactive	0.62
Toxicity end points	Cytotoxicity	cyto	Inactive	0.55
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.86
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.93
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.90
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.89
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.95
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.93
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.93
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.77
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.81
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.86

(B)

Figure 28S. Physical characteristics (A) and Toxicity Model Report (B) for **Remdesivir**

Molweight	157.1
Number of hydrogen bond acceptors	8
Number of hydrogen bond donors	2
Number of atoms	15
Number of bonds	15
Number of rotable bonds	1
Molecular refractivity	32.91
Topological Polar Surface Area	88.84
octanol/water partition coefficient(logP)	-0.29

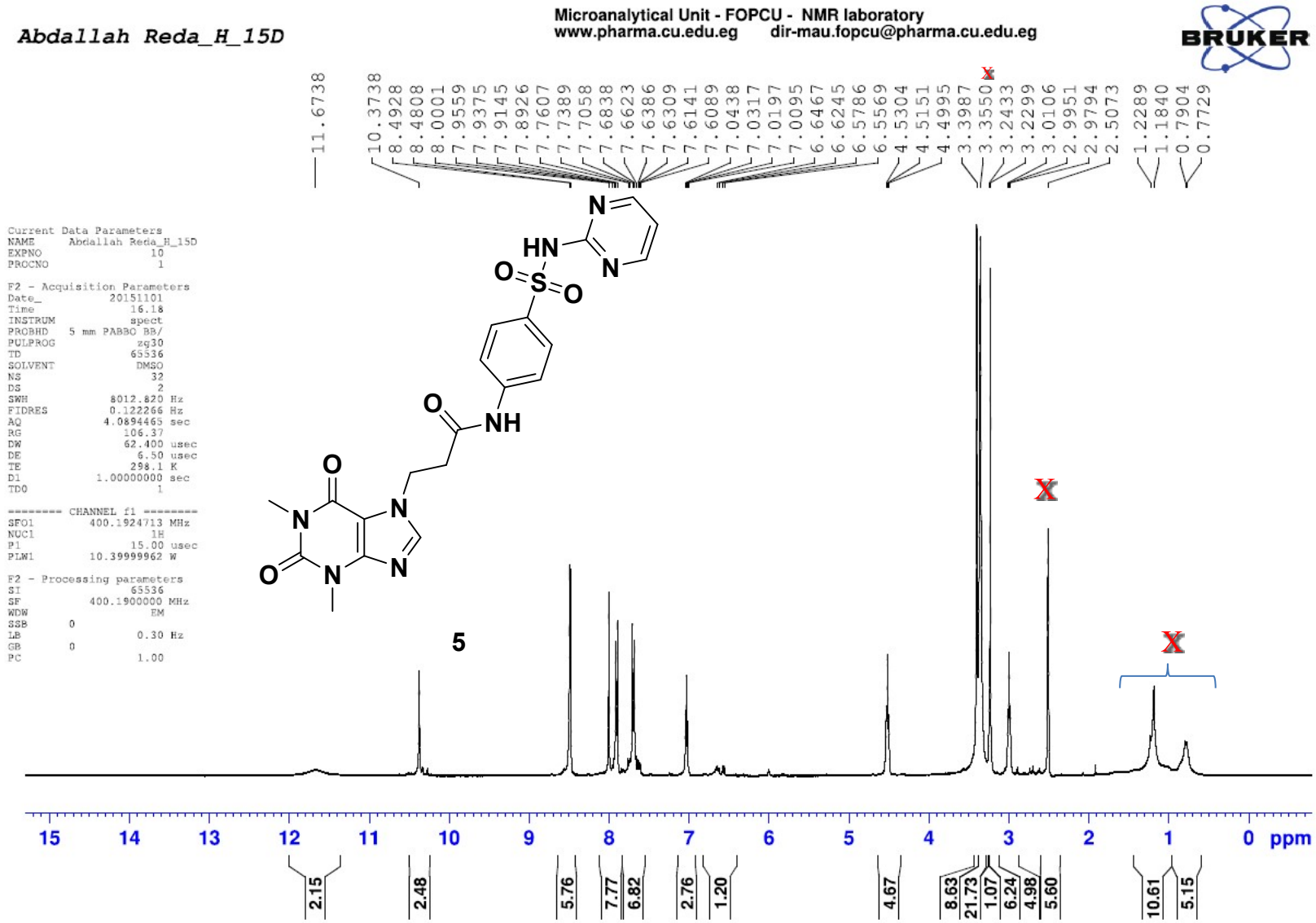
(A)

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.66
Toxicity end points	Carcinogenicity	carcino	Active	0.53
Toxicity end points	Immunotoxicity	immuno	Inactive	0.99
Toxicity end points	Mutagenicity	mutagen	Inactive	0.76
Toxicity end points	Cytotoxicity	cyto	Inactive	0.84
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.82
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.95
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.96
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.96
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.89
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.50
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.58

(B)

Figure 29S. Physical characteristics (A) and Toxicity Model Report (B) for **Favipiravir**

7. Spectral data



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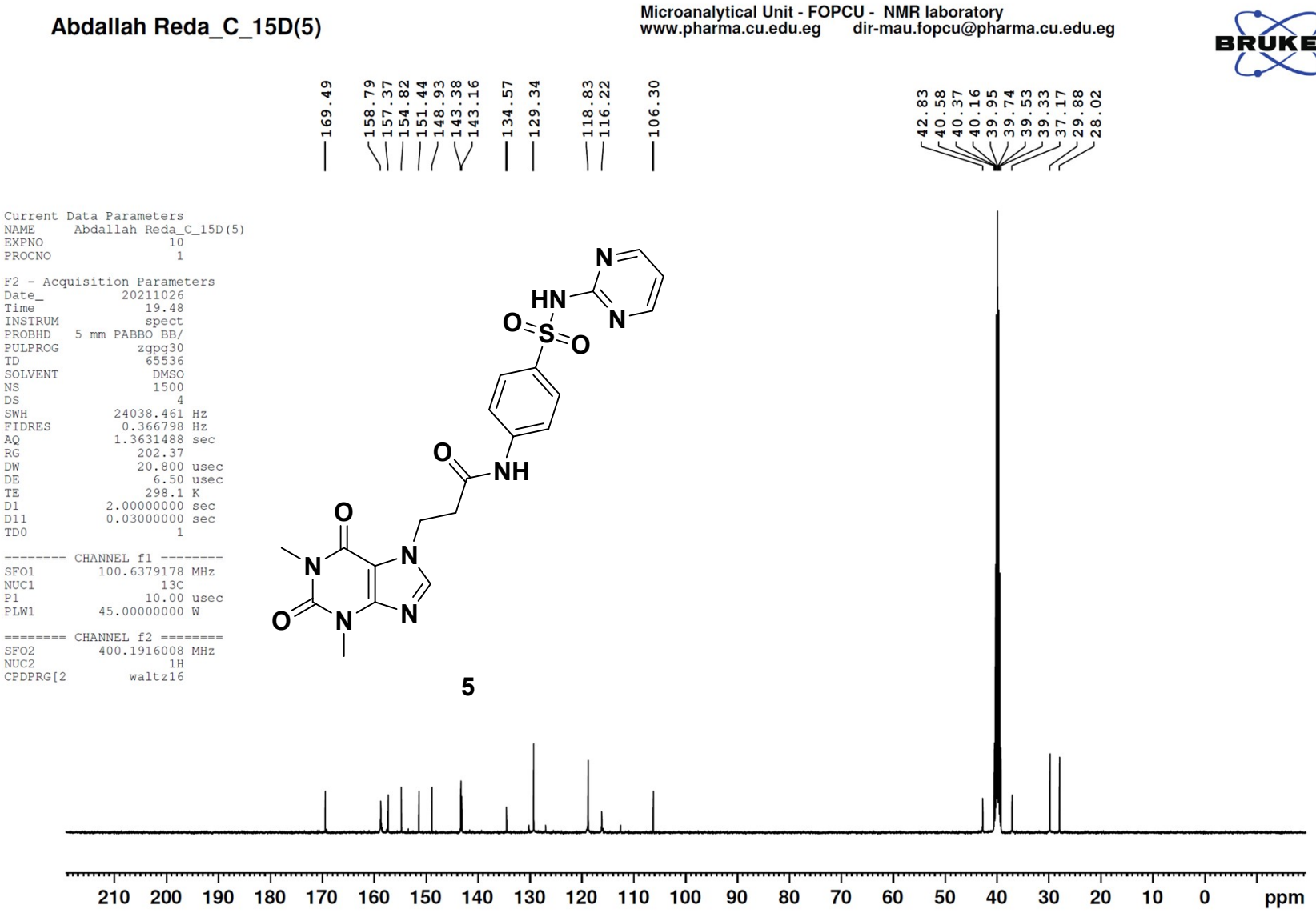
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Microanalytical Unit - FOPCU - NMR laboratory
www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg
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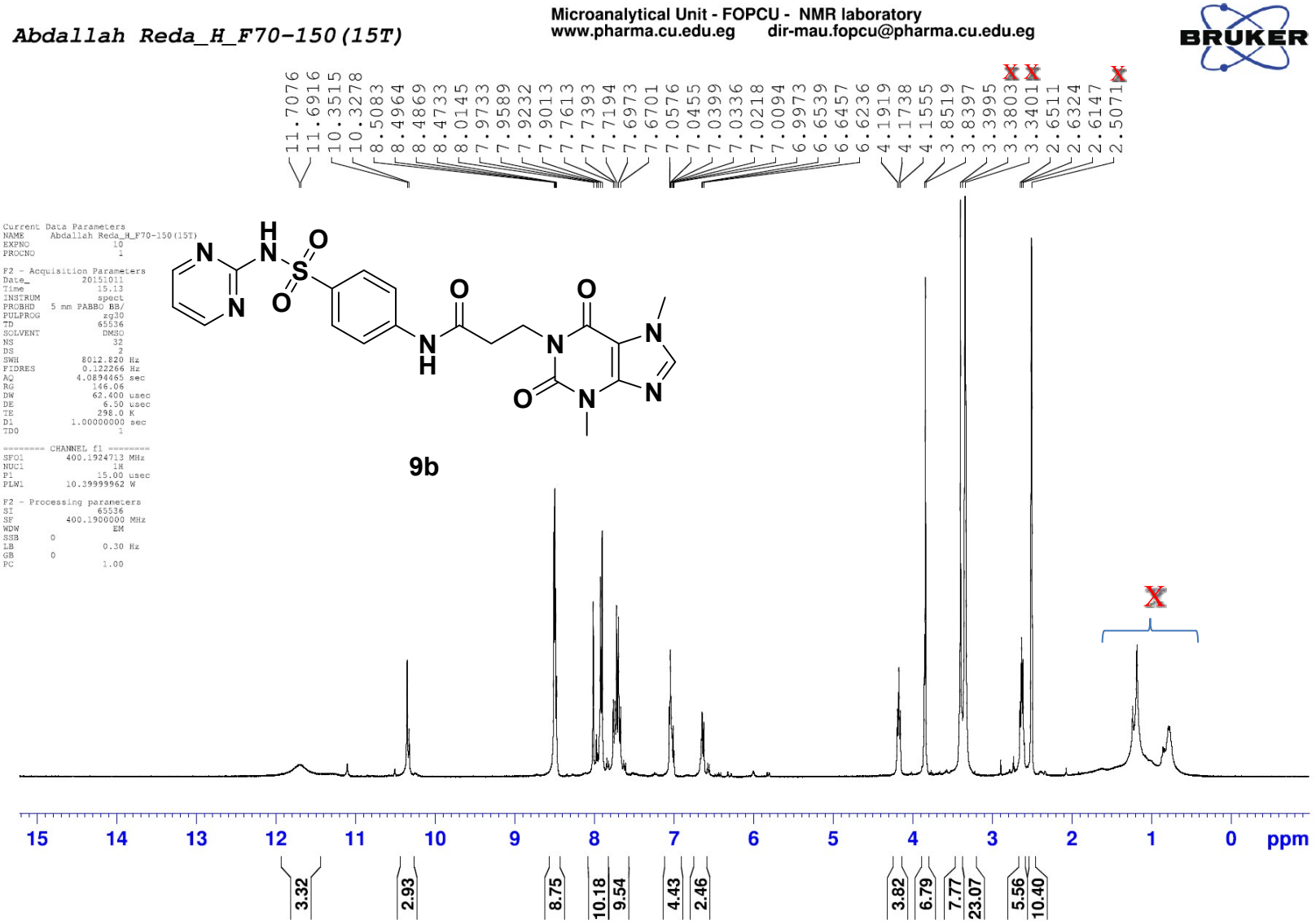

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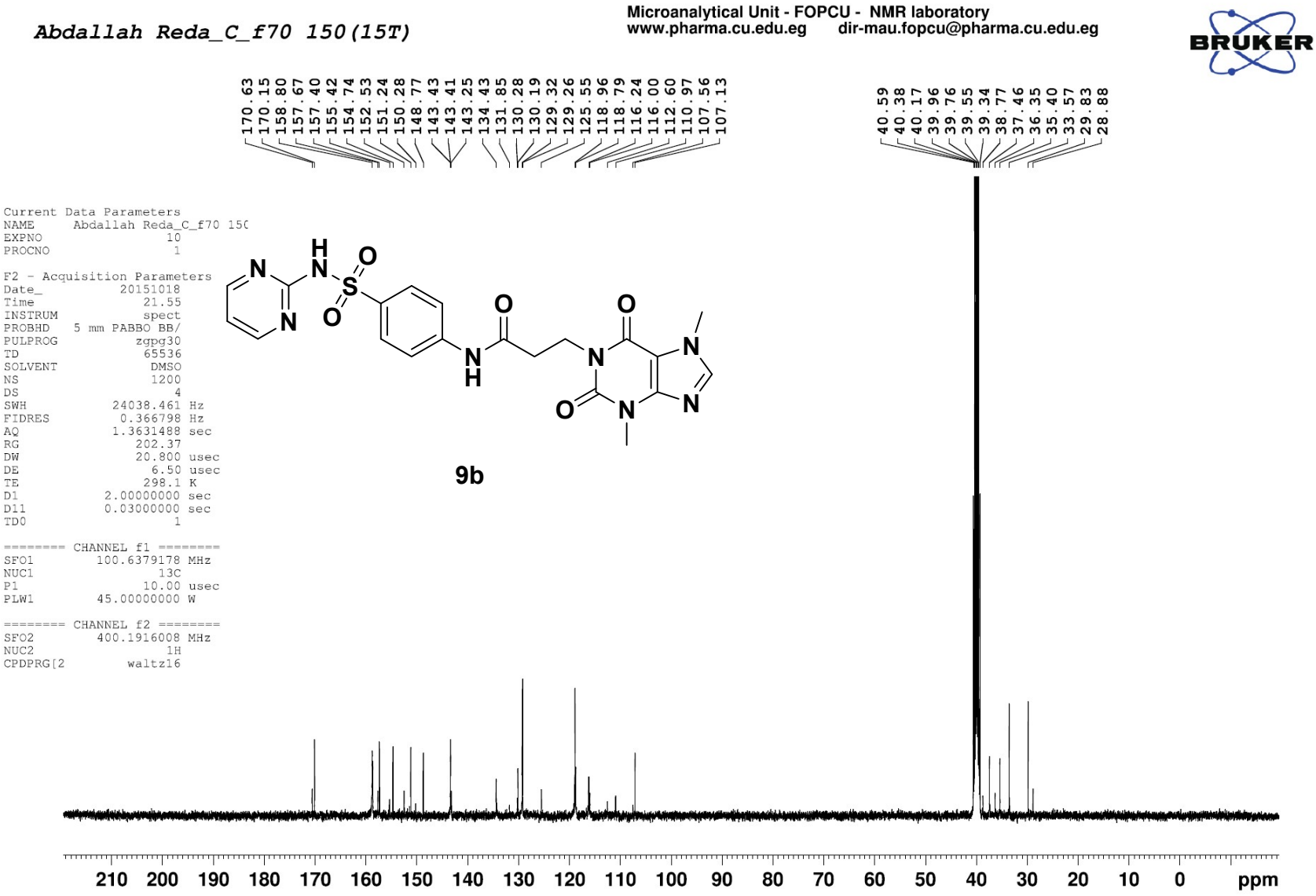
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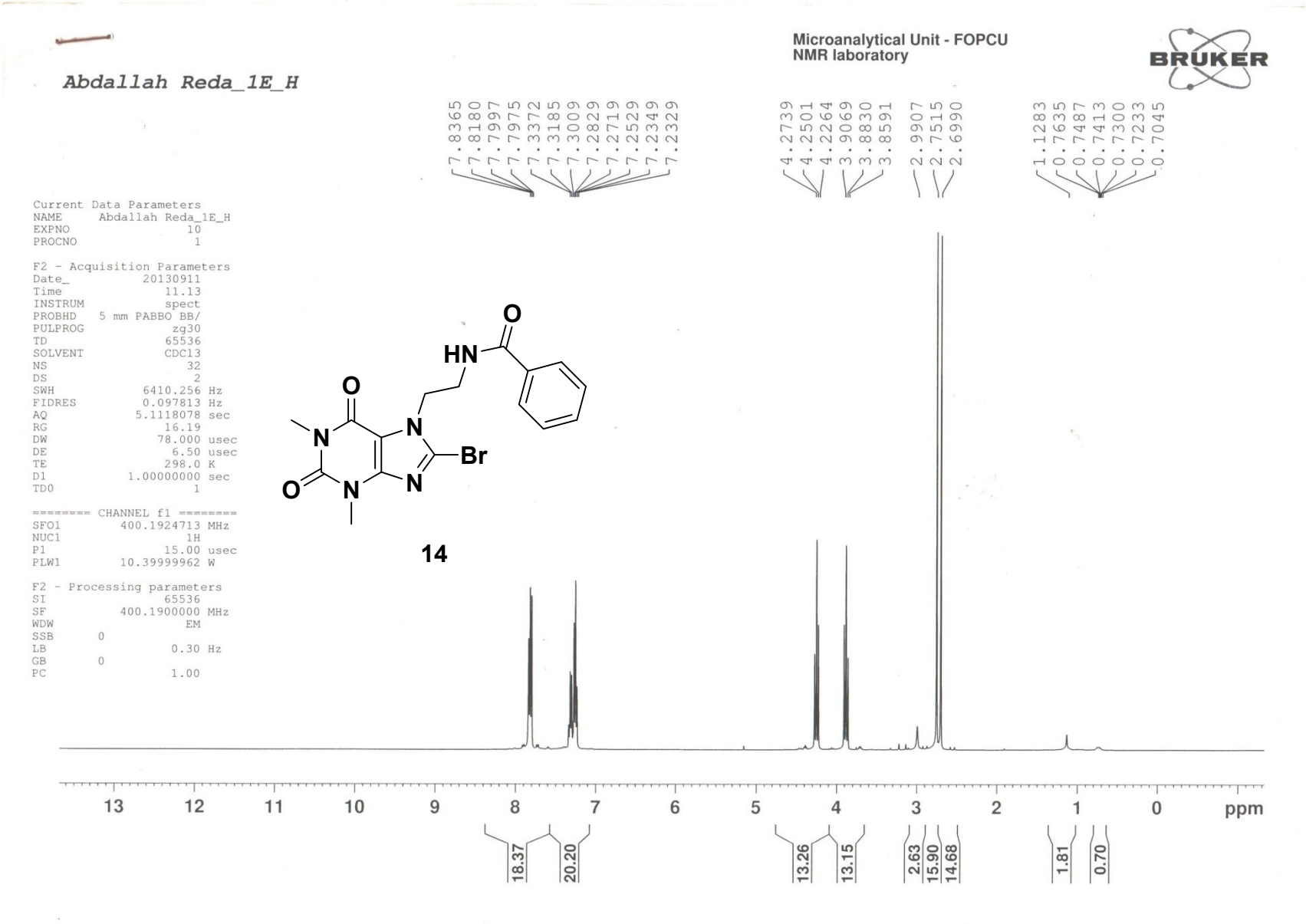
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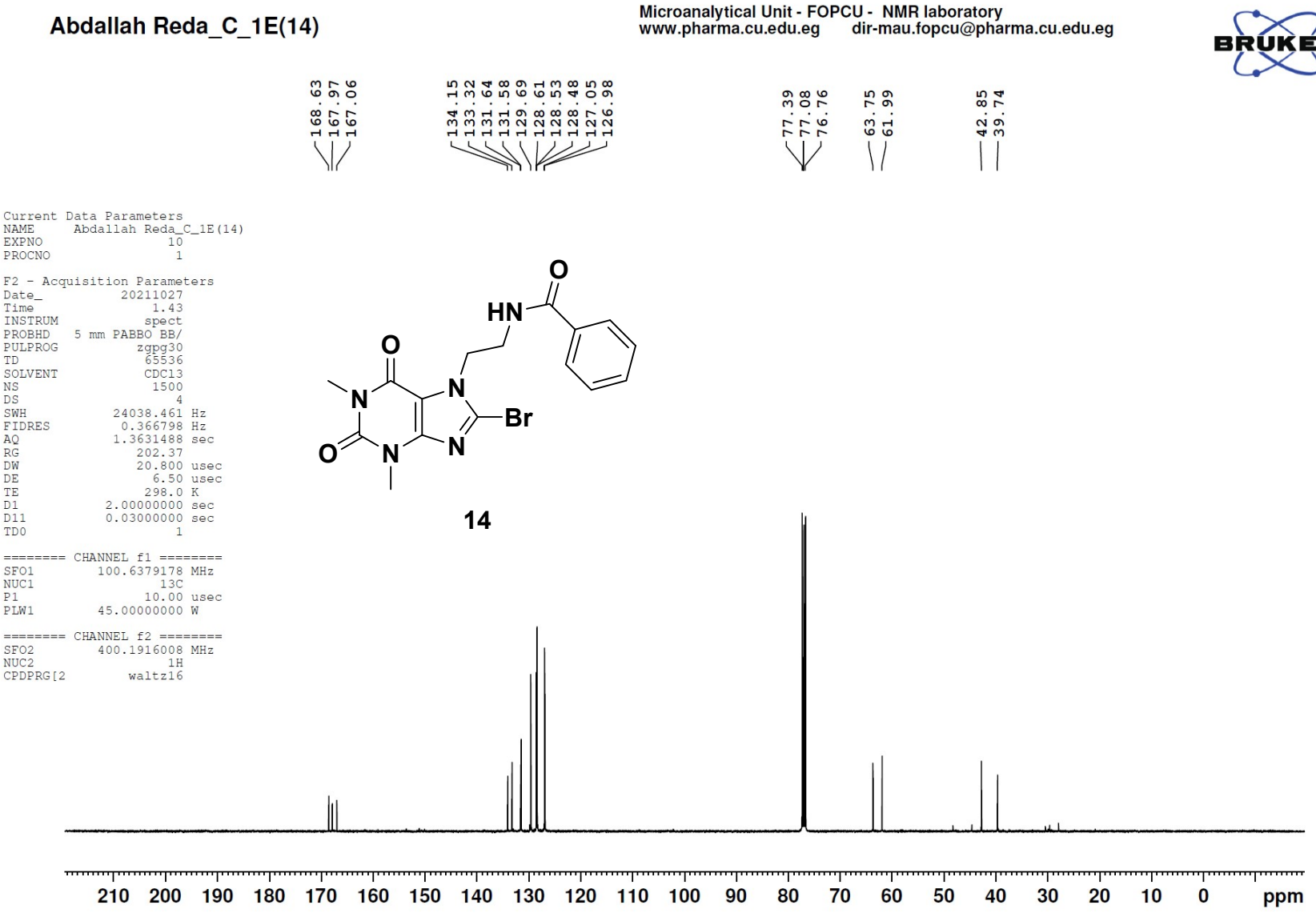
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www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg
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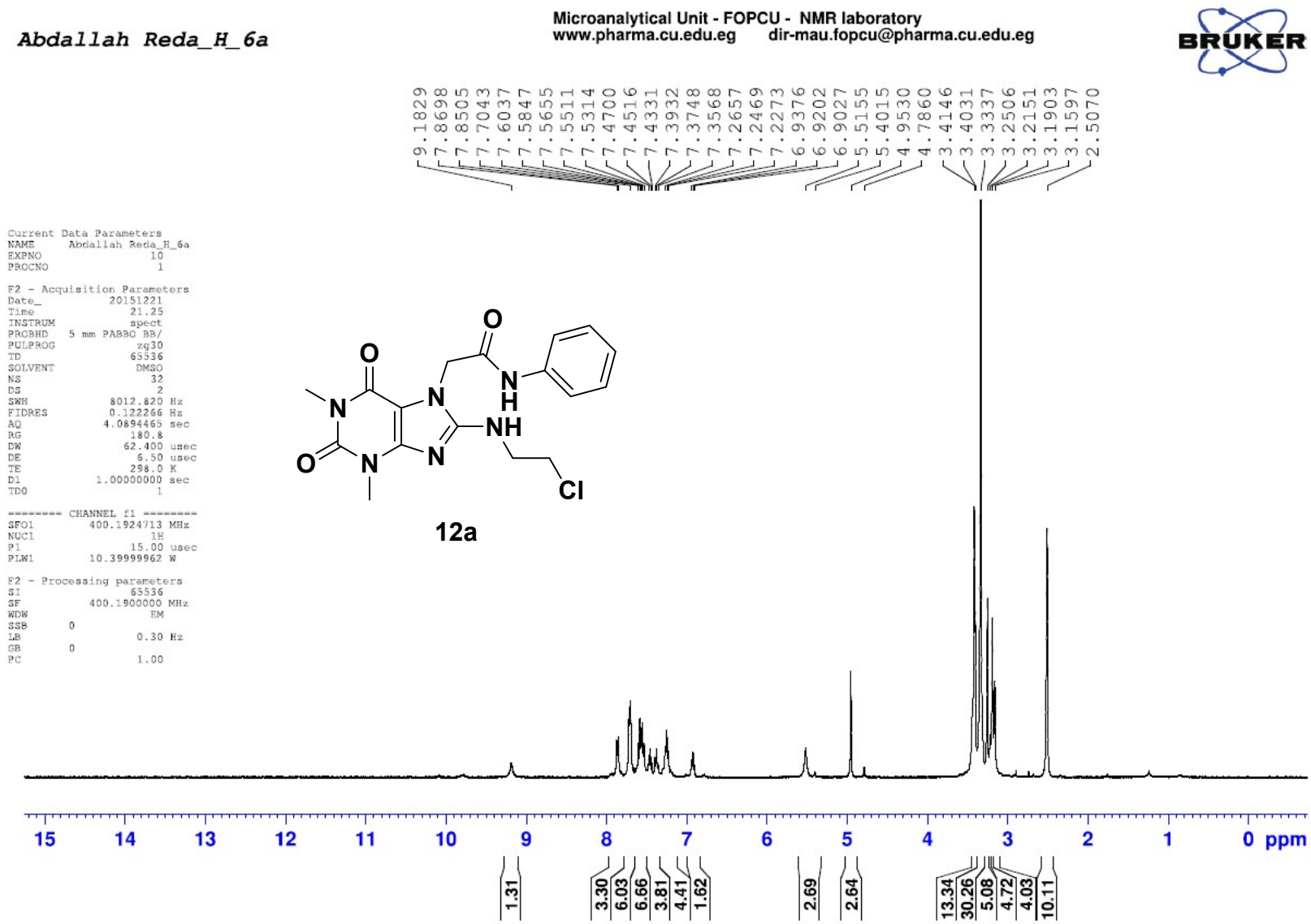
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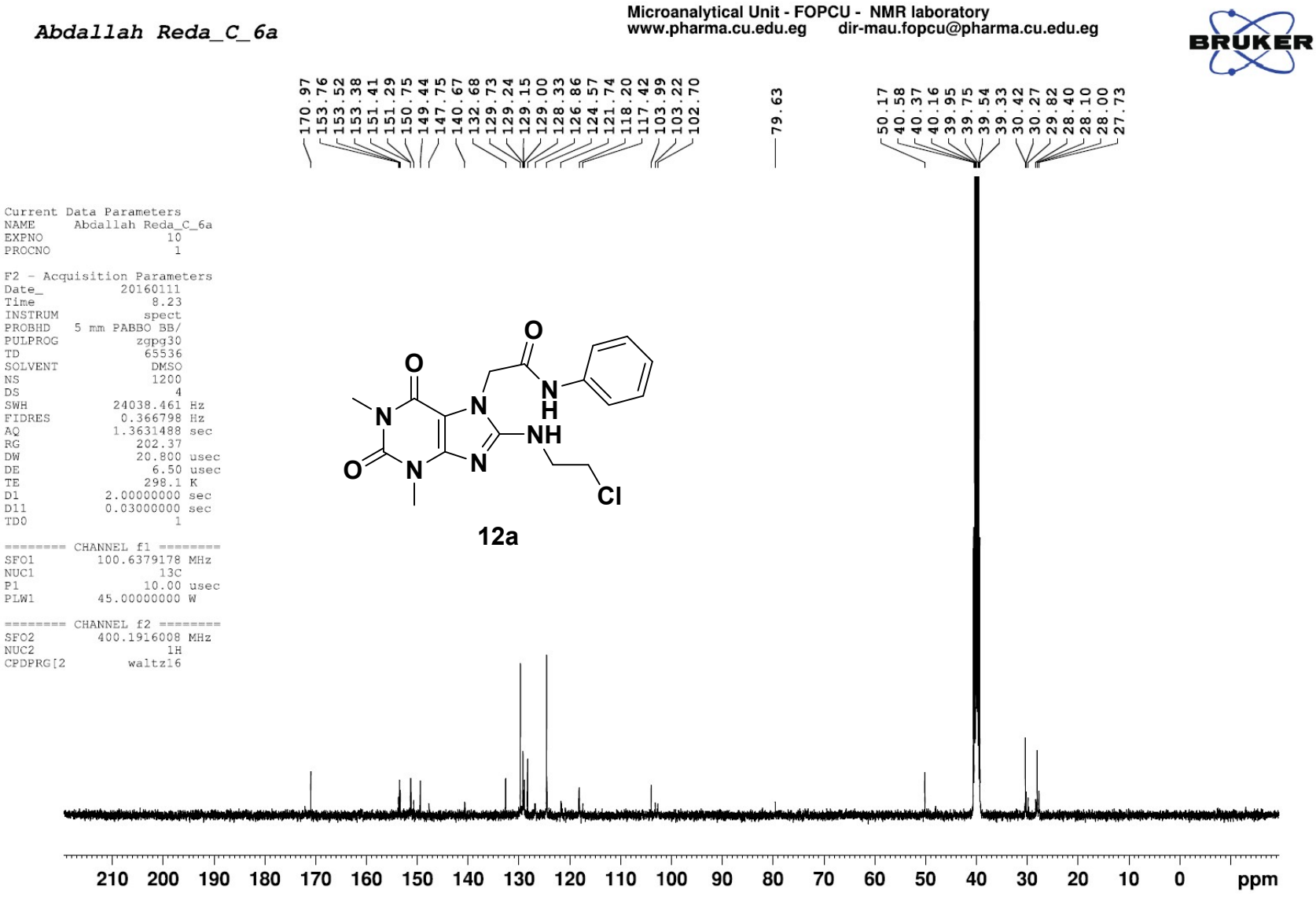
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Microanalytical Unit - FOPCU - NMR laboratory
www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg
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NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W
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NUC2 1H
CPDPRG[2 waltz16
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H
NH
Cl
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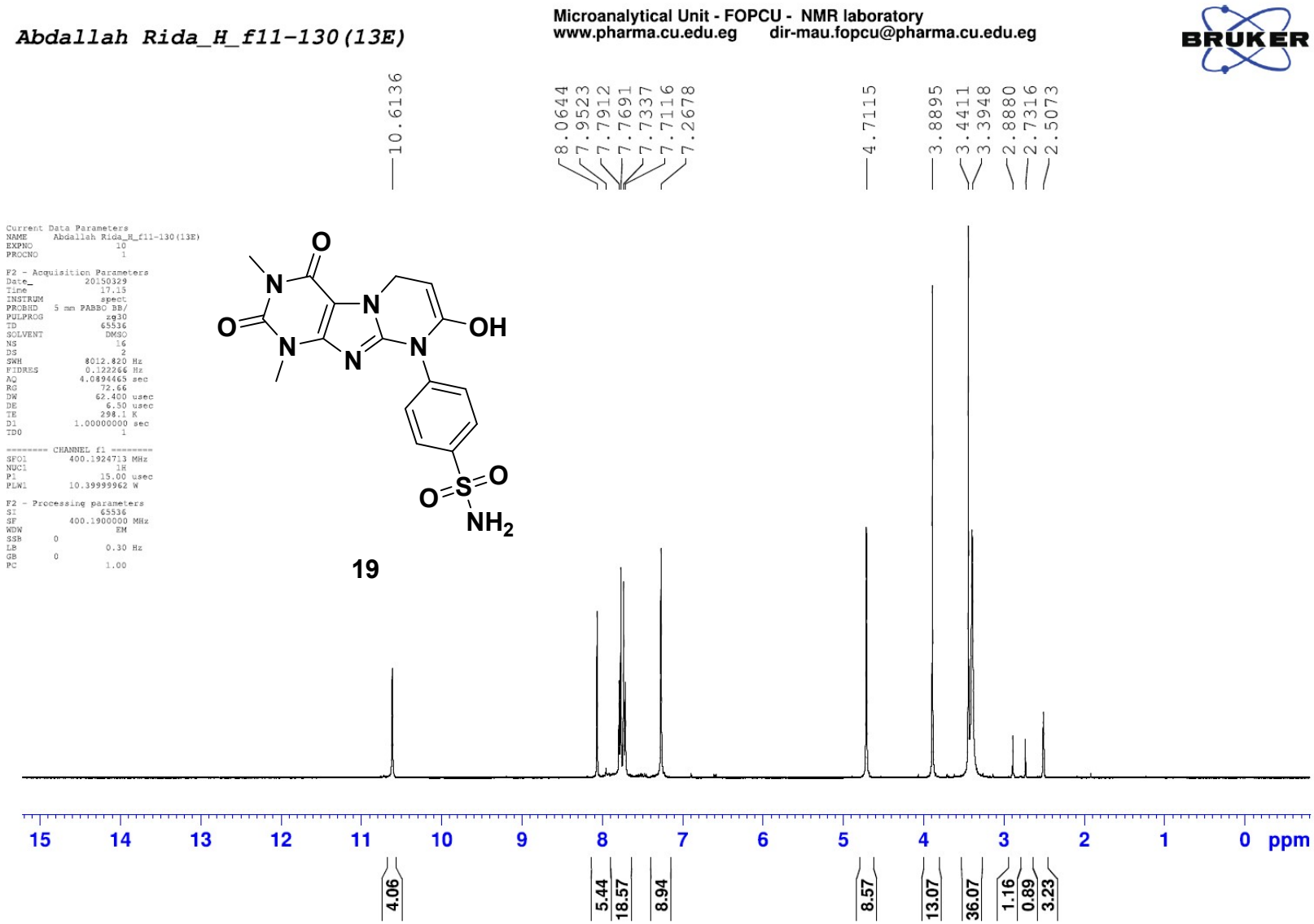
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7.7337
7.7116
7.2678
4.7115
3.8895
3.4411
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NUC1 1H
P1 15.00 usec
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SF 400.1900000 MHz
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PC 1.00
19
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
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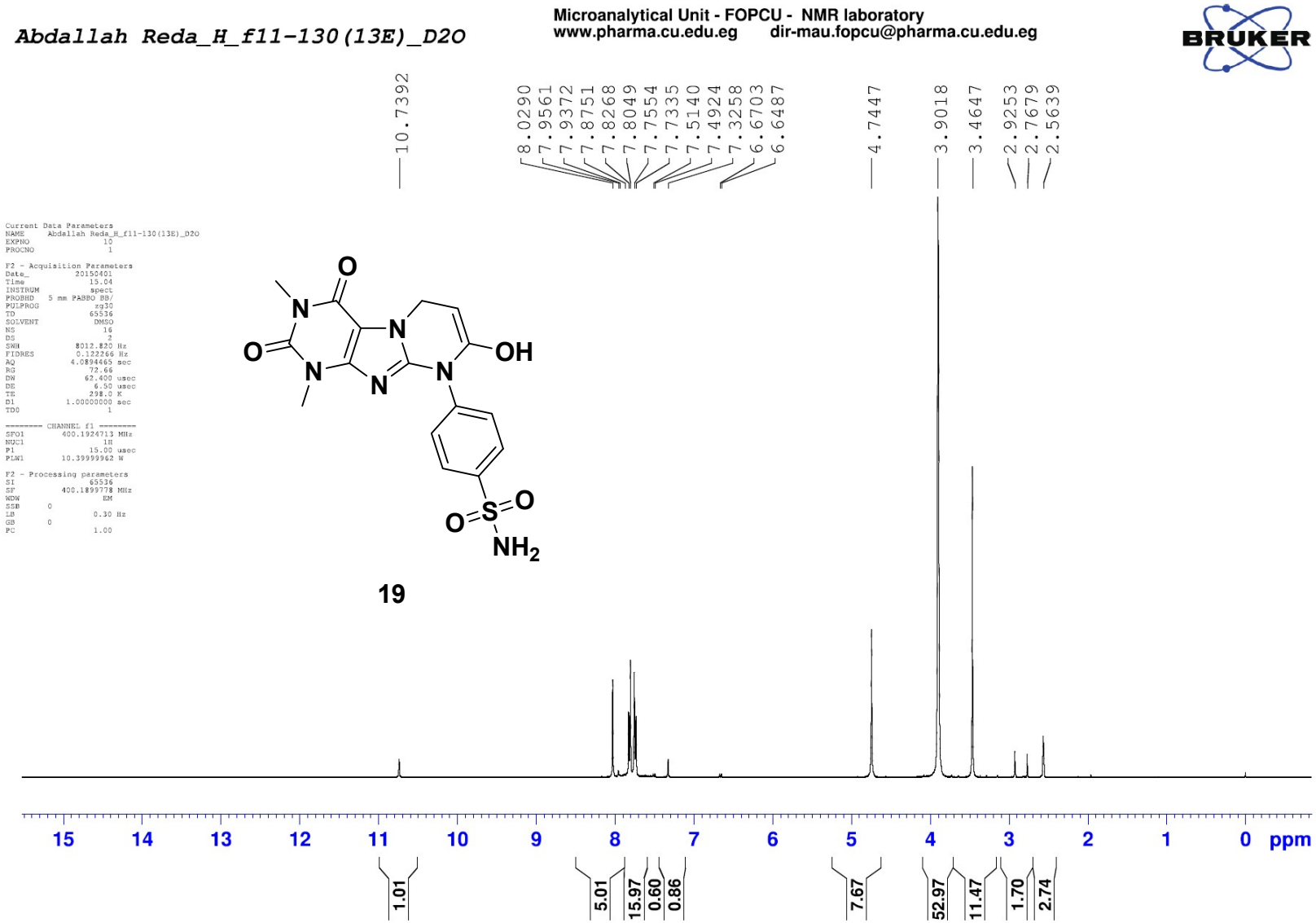
5.44
18.57
8.94
8.57
13.07
36.07
1.16
0.89
3.23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Microanalytical Unit - FOPCU - NMR laboratory
www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg
BRUKER
10.7392
8.0290
7.9561
7.9372
7.8751
7.8268
7.8049
7.7554
7.7335
7.5140
7.4924
7.3258
6.6703
6.6487
4.7447
3.9018
3.4647
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2.5639
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SOLVENT DMSO
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DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 72.66
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
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NUC1 1H
P1 15.00 usec
PLW1 10.39999962 W
F2 - Processing parameters
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
N
N
O
N
N
N
OH
O
S
O
NH2
19
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
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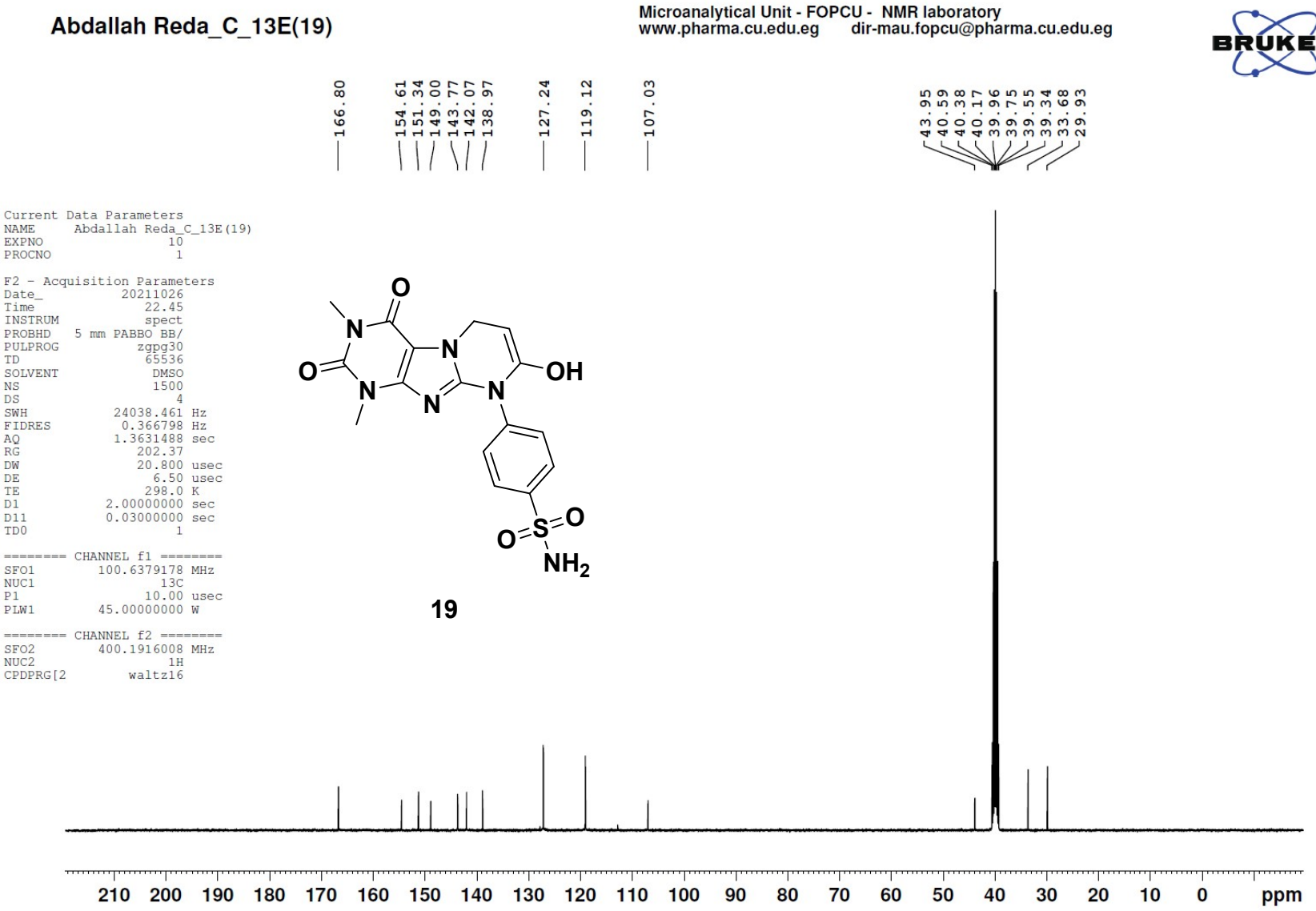
1.70
2.74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Microanalytical Unit - FOPCU - NMR laboratory
www.pharma.cu.edu.eg dir-mau.fopcu@pharma.cu.edu.eg
BRUKER
166.80
154.61
151.34
149.00
143.77
142.07
138.97
127.24
119.12
107.03
43.95
40.59
40.38
40.17
39.96
39.75
39.55
39.34
33.68
29.93
Current Data Parameters
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EXPNO 10
PROCNO 1
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DS 4
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RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
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D11 0.03000000 sec
TD0 1
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NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W
======== CHANNEL f2 ========
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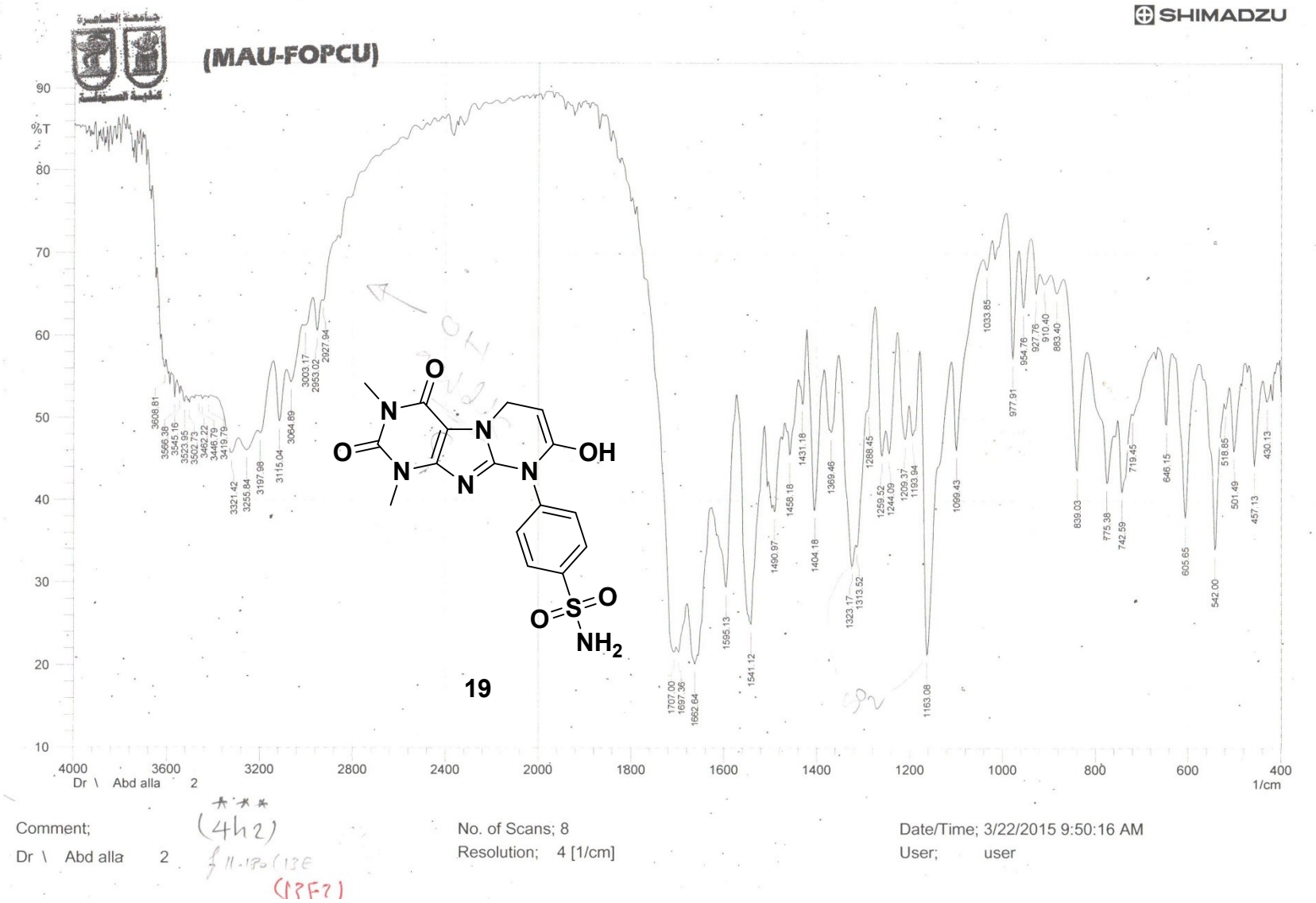
NUC2 1H
CPDPRG[2 waltz16
O
N
N
O
N
N
N
OH
O
S
O
NH2
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SHIMADZU
(MAU-FOPCU)
%T
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3566.38
3545.16
3523.95
3502.73
3482.22
3446.79
3419.79
3321.42
3255.84
3197.98
3115.04
3064.89
3003.17
2953.02
2927.94
1707.00
1697.36
1662.64
1595.13
1541.12
1490.97
1458.18
1431.18
1404.18
1369.46
1323.17
1313.52
1288.45
1259.52
1244.09
1209.37
1193.94
1163.08
1099.43
1033.85
977.91
954.76
927.76
910.40
883.40
839.03
775.38
742.59
719.45
646.15
605.65
542.00
518.85
501.49
457.13
430.13
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
1/cm
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Dr \ Abd alla 2
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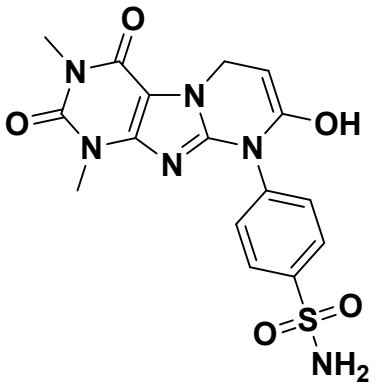
19



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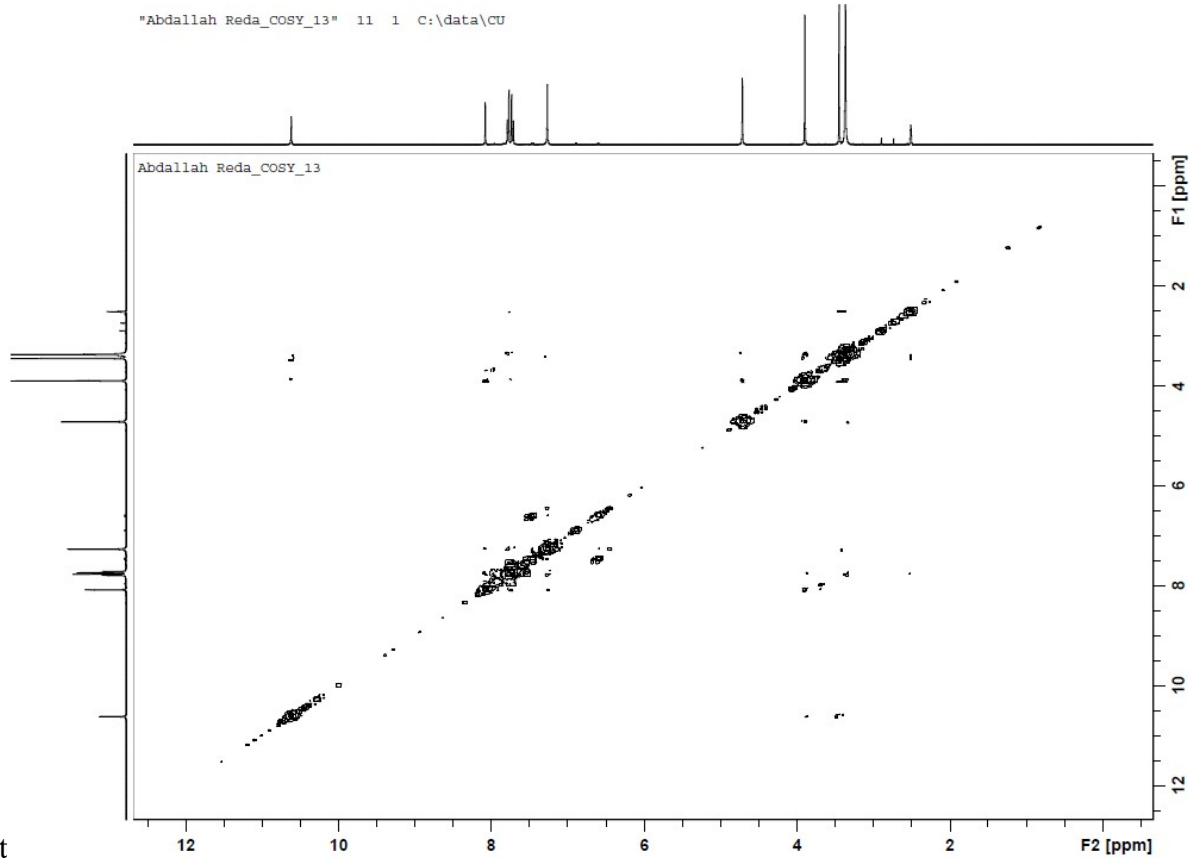

^{1}H-^{1}H COSY, 2D-NMR chart

References

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