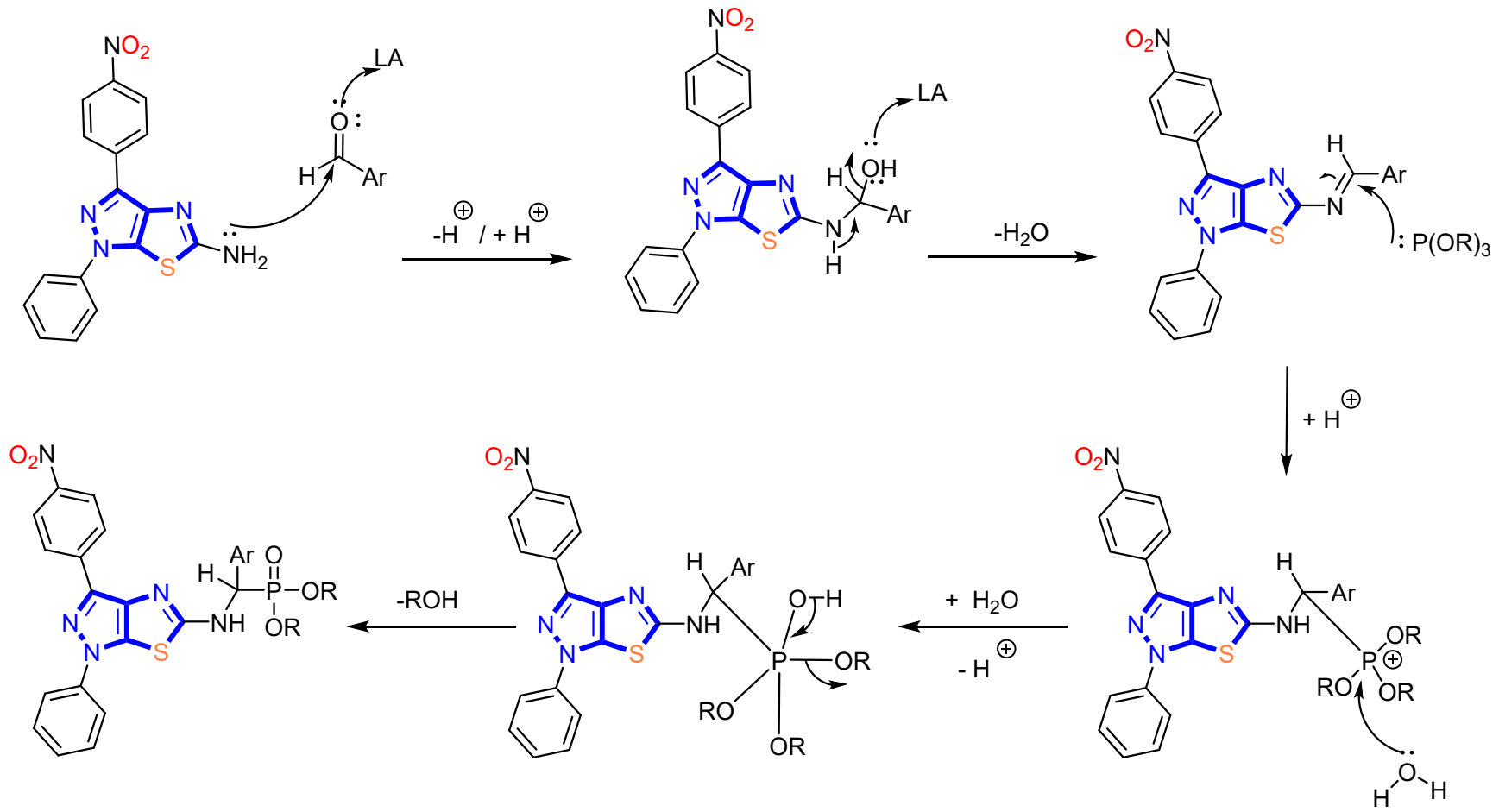
Electronic Supplementary Material (ESI) for RSC Advances.
This journal is © The Royal Society of Chemistry 2023

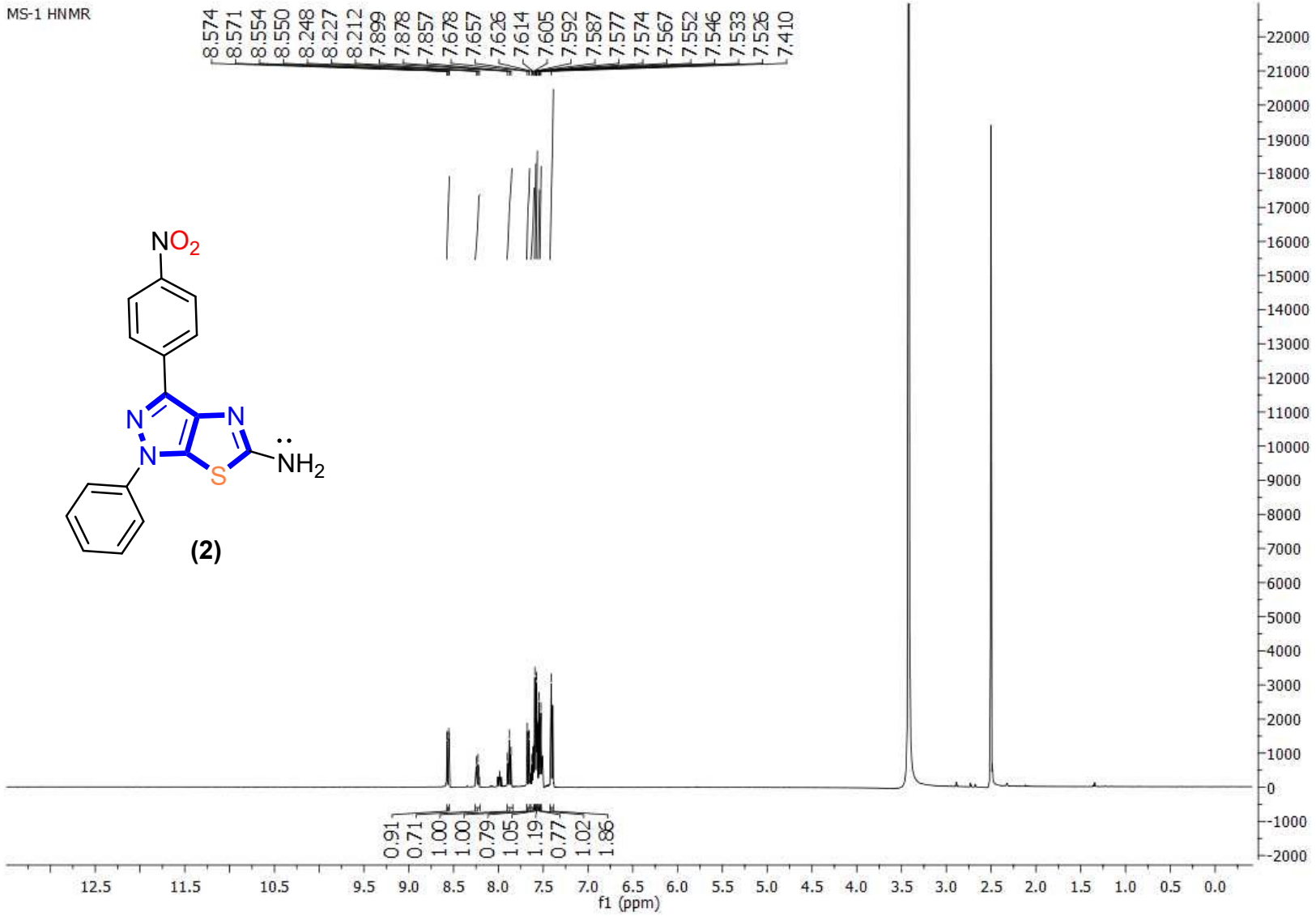
One-pot synthesis of pyrazolo[4,3-*d*]thiazole derivatives containing α-aminophosphonate as potential Mur A inhibitors against MDR pathogens with radiosterilization and molecular modeling simulation

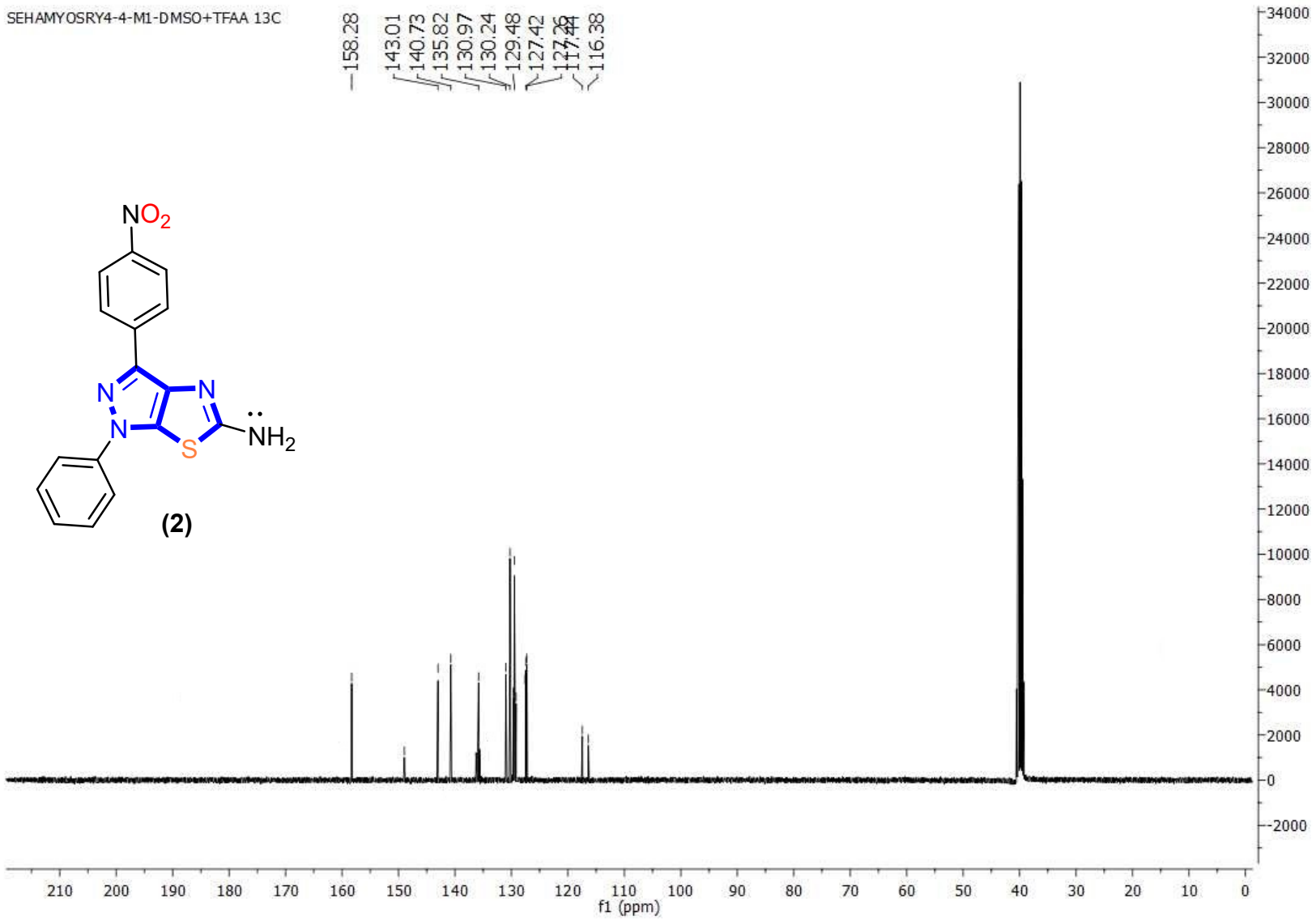
Ahmed Ragab [a,*], Seham A. Ibrahim [b,*], Dina S. Aboul-Magd [c,*], Mohamed H. Baren [b,]

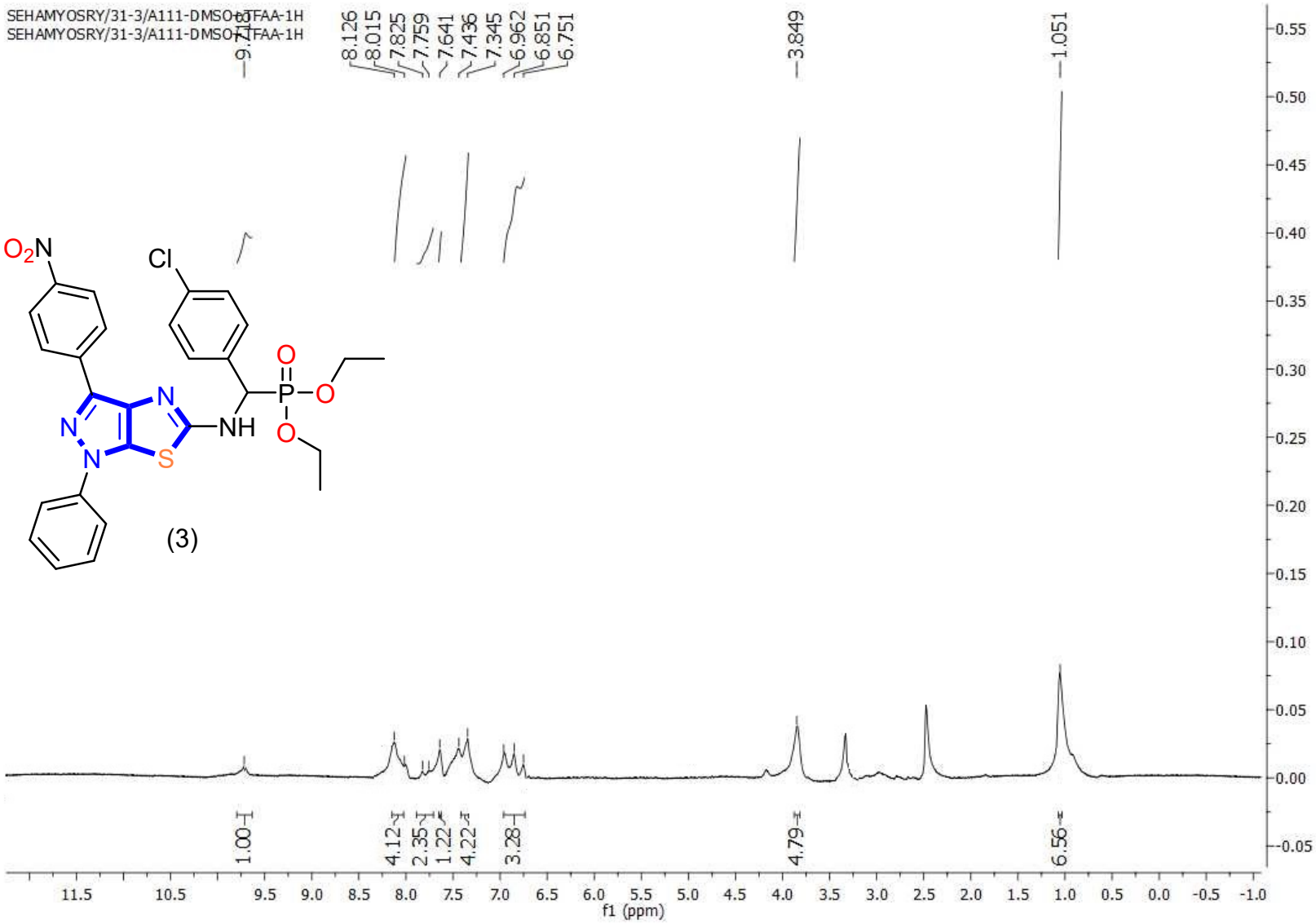
[a] Chemistry Department, Faculty of Science (Boys), Al-Azhar University, Nasr City, Cairo 11884, Egypt
[b] Chemistry Department, Faculty of Science, Tanta University, Tanta 31527, Egypt
[c] Drug Radiation Research Department, National Center for Radiation Research and Technology (NCRRT), Egyptian Atomic Energy Authority, Egypt

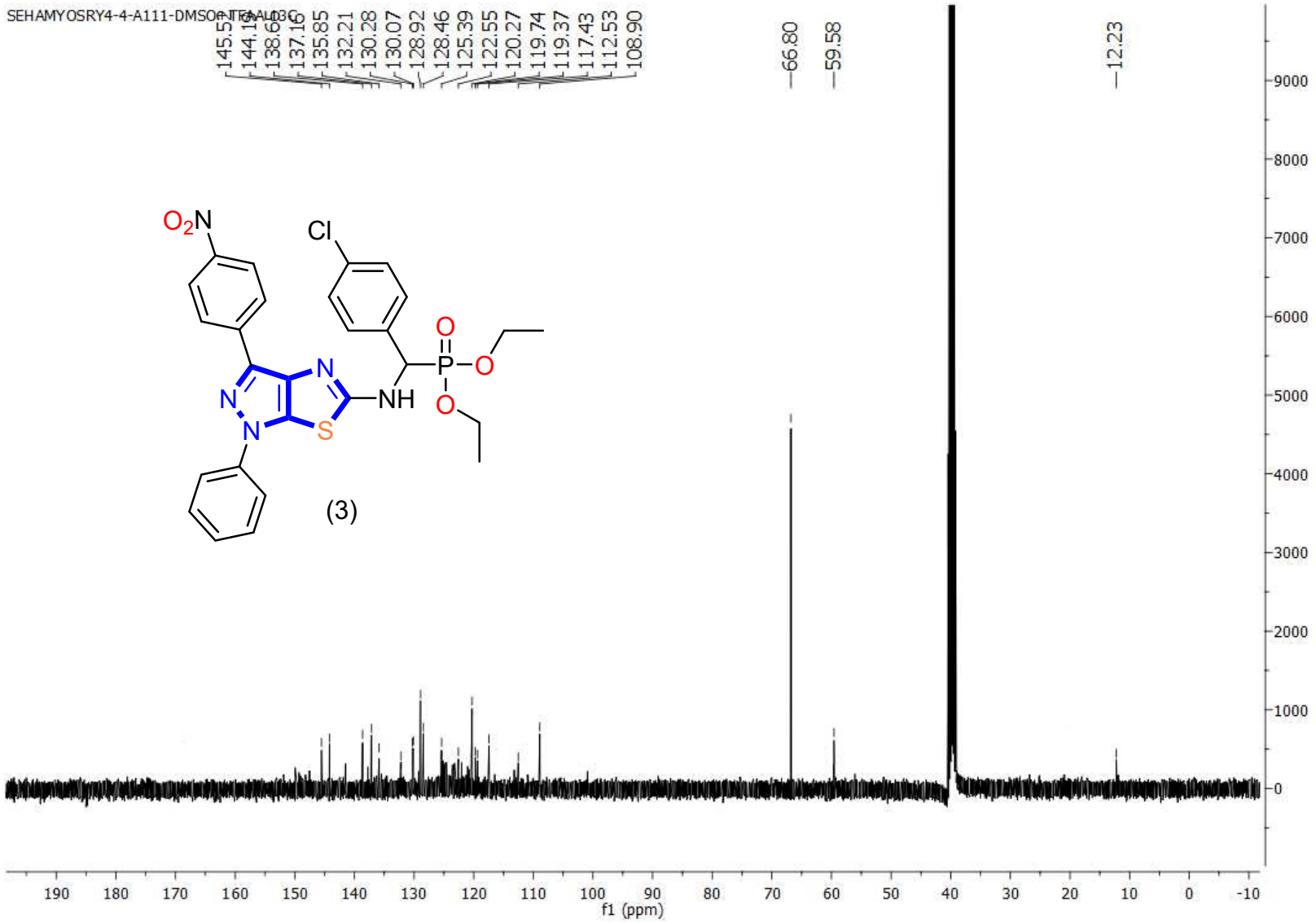


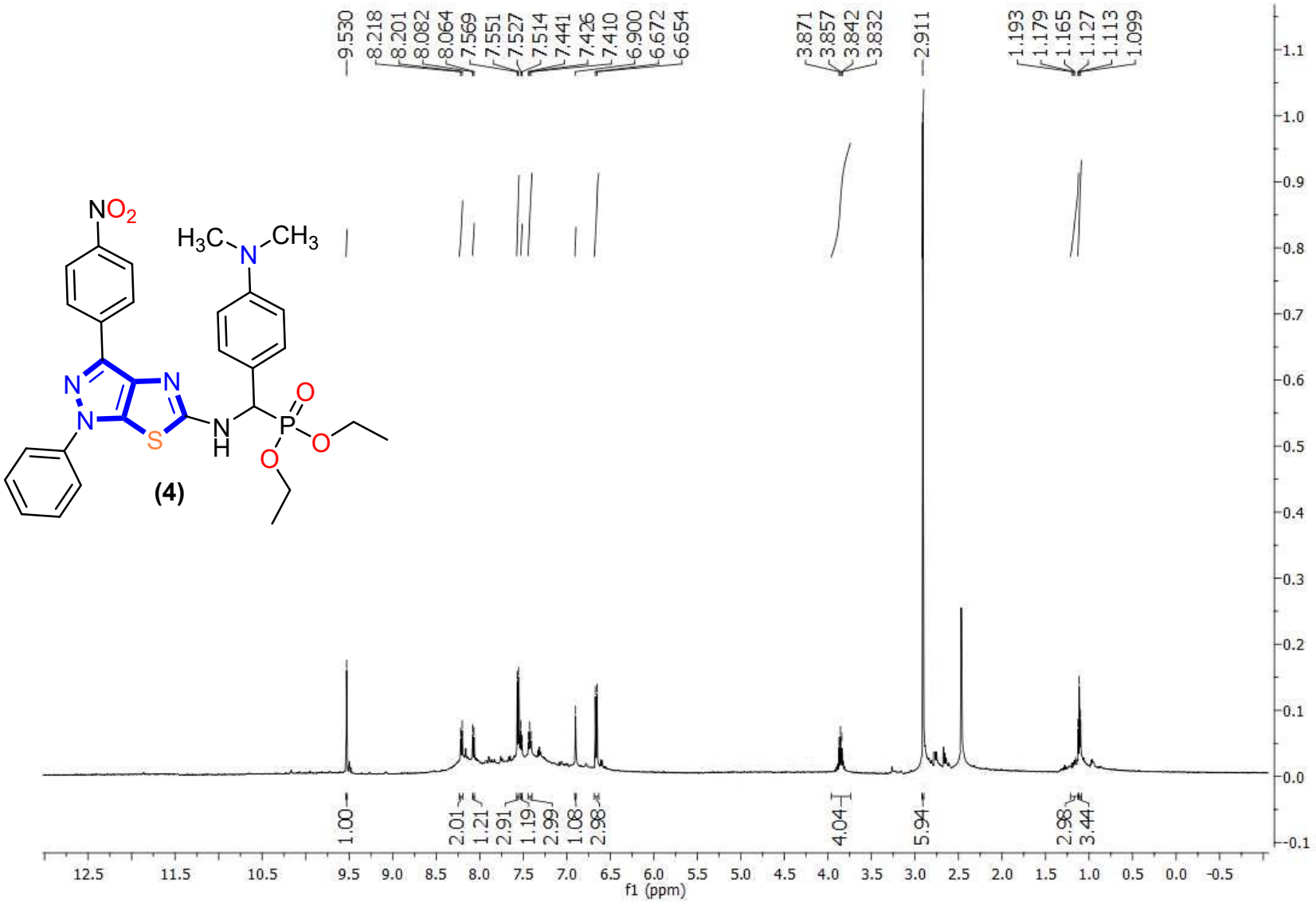
Scheme S1: Mechanismatic pathway for synthesizing α-aminophosphonates using LiClO4 as a catalyst

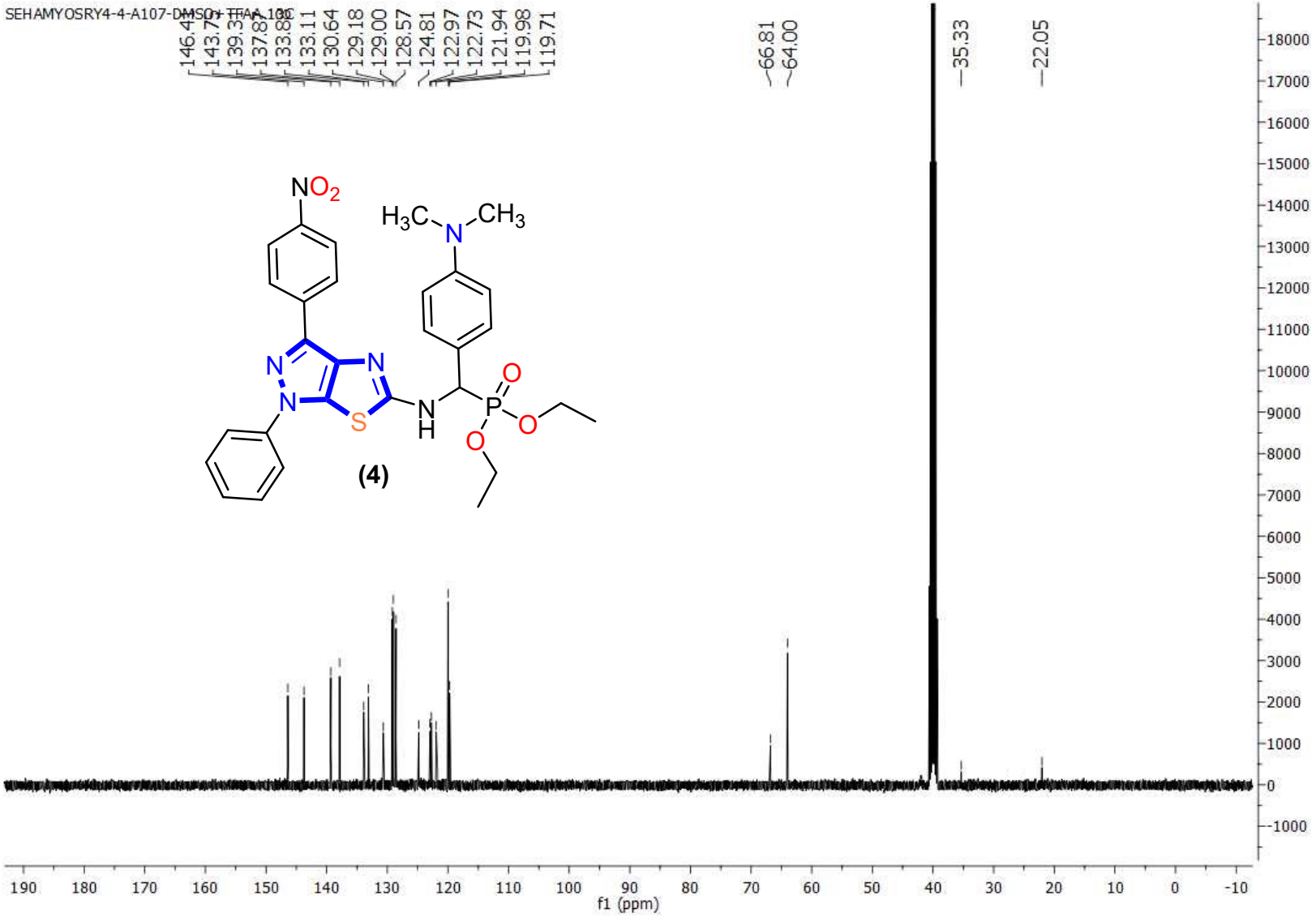

MS-1 HNMR
8.574
8.571
8.554
8.550
8.248
8.227
8.212
7.899
7.878
7.857
7.678
7.657
7.626
7.614
7.605
7.592
7.587
7.577
7.574
7.567
7.552
7.546
7.533
7.526
7.410
NO2
N
N
N
S
NH2
(2)
0.91
0.71
1.00
1.00
0.79
1.05
1.19
0.77
1.02
1.86
f1 (ppm)

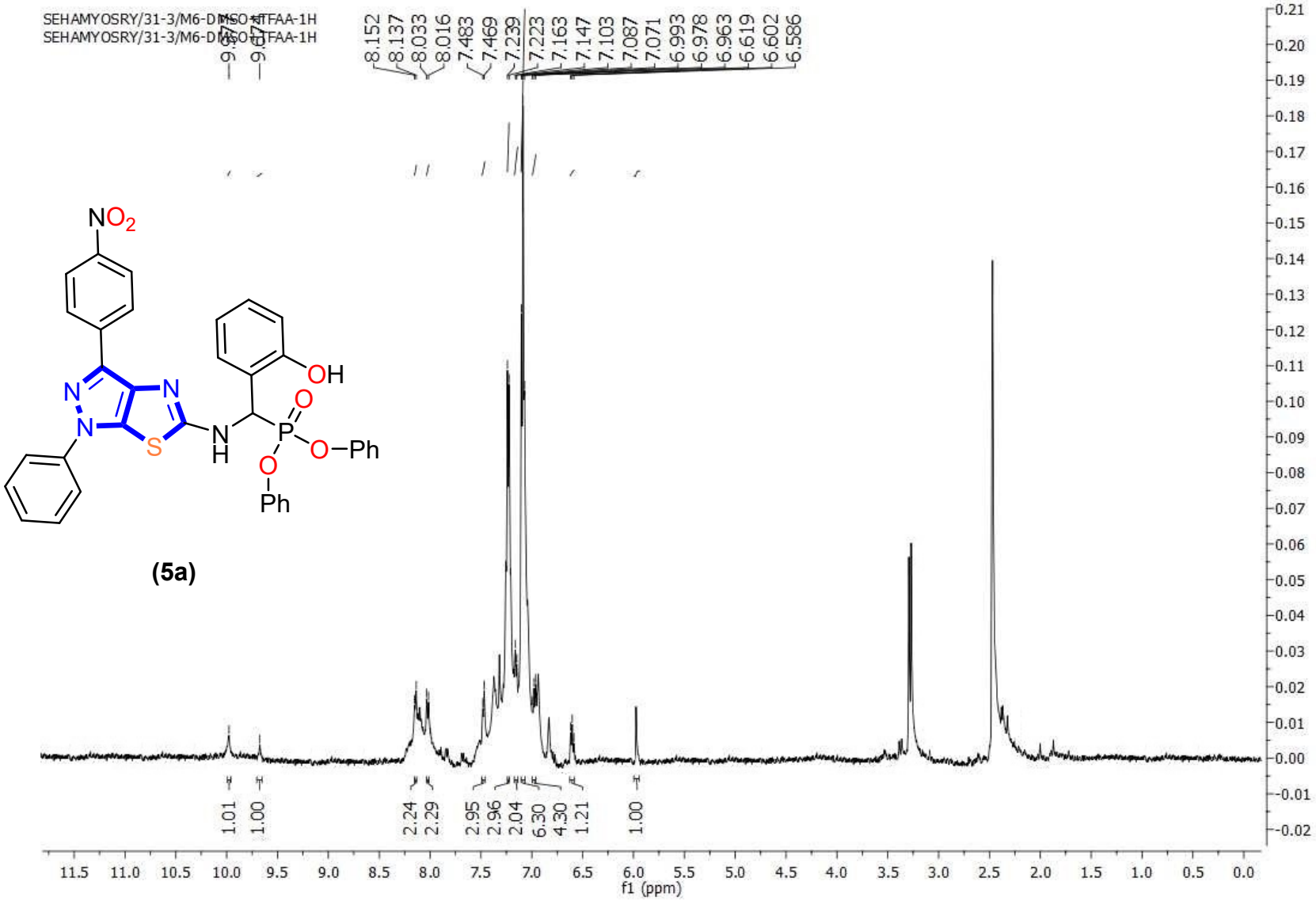

SEHAMYOSRY4-4-M1-DMSO+TFAA 13C
158.28
143.01
140.73
135.82
130.97
130.24
129.48
127.42
116.38
NO2
N
N
N
S
NH2
(2)
f1 (ppm)


SEHAMYOSRY/31-3/A111-DMSO+TFAA-1H
SEHAMYOSRY/31-3/A111-DMSO+TFAA-1H
9.771
8.126
8.015
7.825
7.759
7.641
7.436
7.345
6.962
6.851
6.751
3.849
1.051
O2N
Cl
O
P
O
O
N
N
N
NH
S
(3)
1.00
4.12
2.35
1.22
4.22
3.28
4.79
6.56
f1 (ppm)

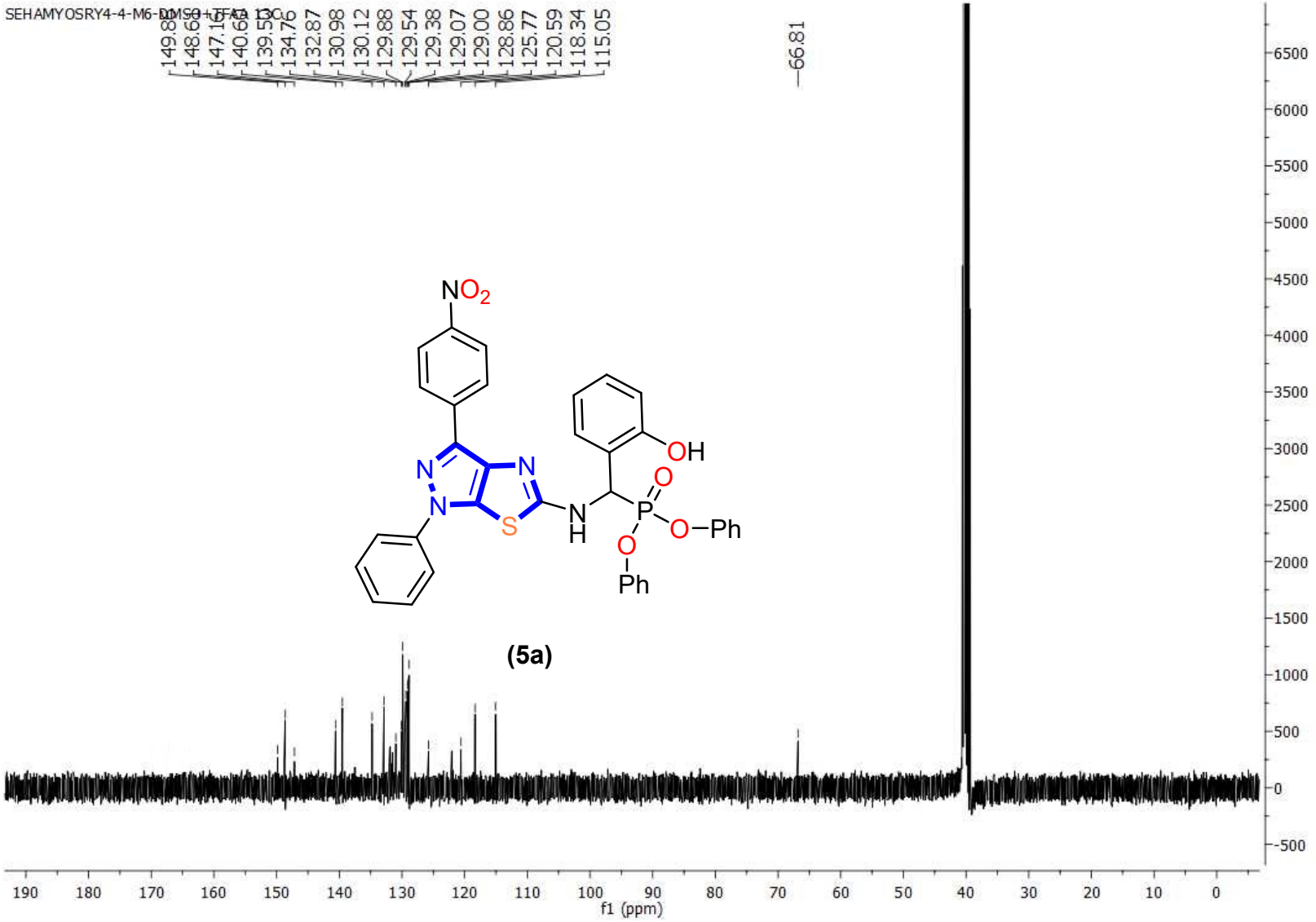

SEHAMYOSRY4-4-A111-DMSO+TFAAL03C
145.57
144.16
138.61
137.16
135.85
132.21
130.28
130.07
128.92
128.46
125.39
122.55
120.27
119.74
119.37
117.43
112.53
108.90
66.80
59.58
12.23
O2N
Cl
N
N
N
S
NH
O
P
O
O
(3)
f1 (ppm)

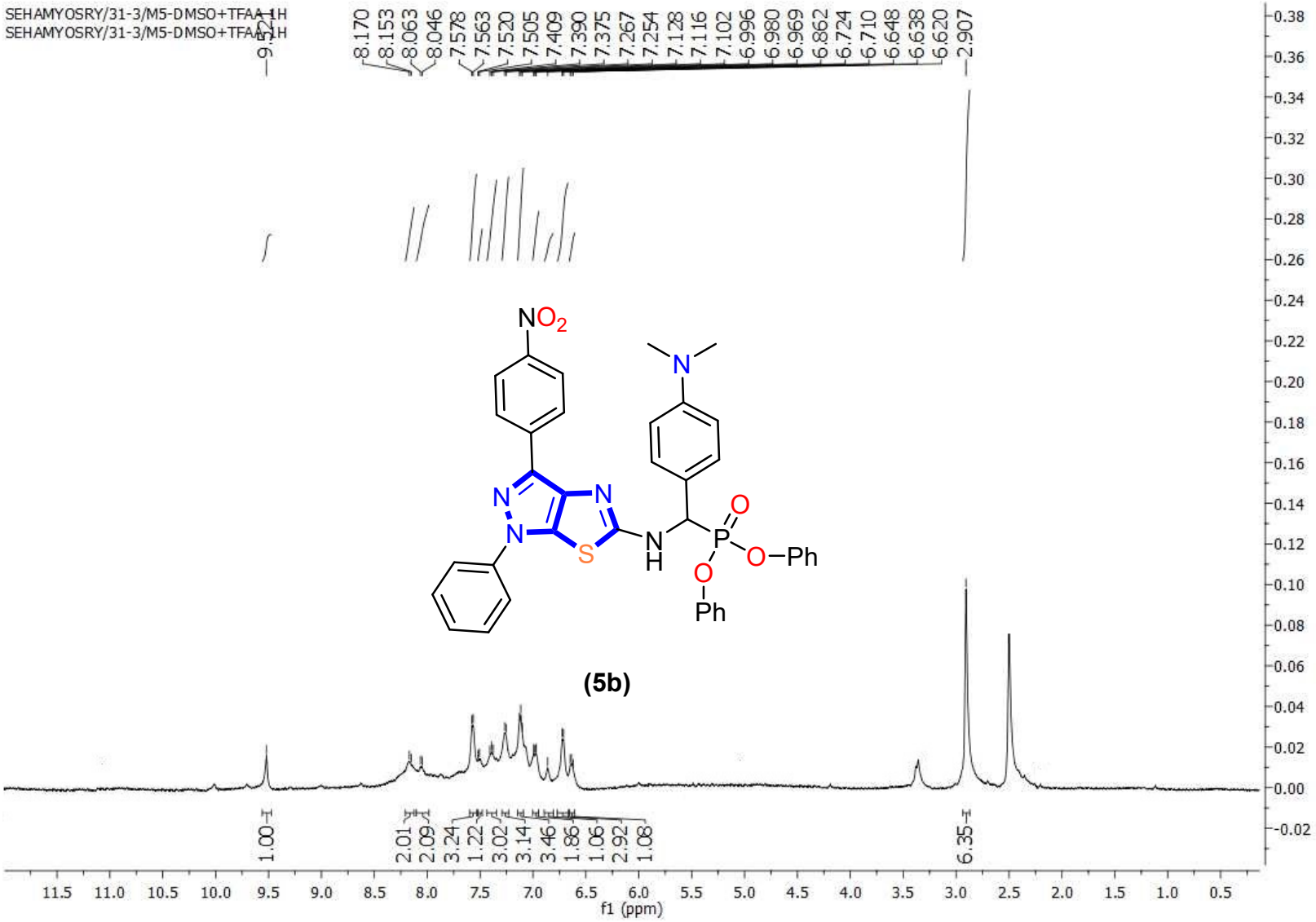

9.530
8.218
8.201
8.082
8.064
7.569
7.551
7.527
7.514
7.441
7.426
7.410
6.900
6.672
6.654
3.871
3.857
3.842
3.832
2.911
1.193
1.179
1.165
1.127
1.113
1.099
NO2
H3C
N
CH3
N
N
N
S
N
H
P
O
O
O
(4)
1.00
2.01
1.21
2.91
1.19
2.99
1.08
2.98
4.04
5.94
2.98
3.44
f1 (ppm)

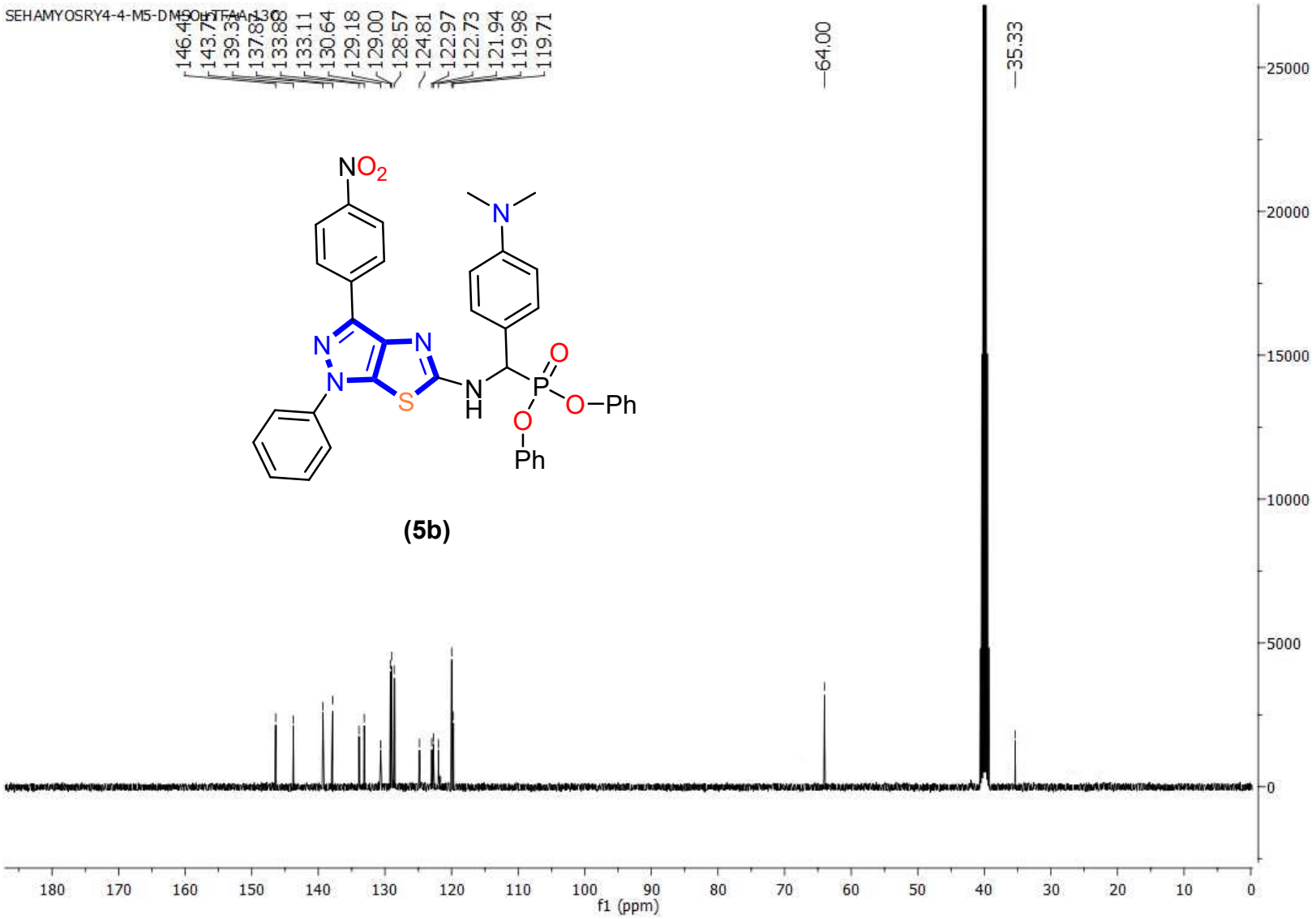

SEHAMYOSRY4-4-A107-DMSO+TFAA.10
146.43
143.71
139.31
137.87
133.88
133.11
130.64
129.18
129.00
128.57
124.81
122.97
122.73
121.94
119.98
119.71
66.81
64.00
35.33
22.05
NO2
H3C
N
CH3
N
N
N
S
N
H
P
O
O
O
(4)
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


SEHAMYOSRY/31-3/M6-DMSO+TFAA-1H
SEHAMYOSRY/31-3/M6-DMSO+TFAA-1H
9.877
9.674
8.152
8.137
8.033
8.016
7.483
7.469
7.239
7.223
7.163
7.147
7.103
7.087
7.071
6.993
6.978
6.963
6.619
6.602
6.586
NO2
N
N
N
S
N
H
OH
O
P
O
O
Ph
Ph
1.01
1.00
2.24
2.29
2.95
2.96
2.04
6.30
4.30
1.21
1.00
f1 (ppm)

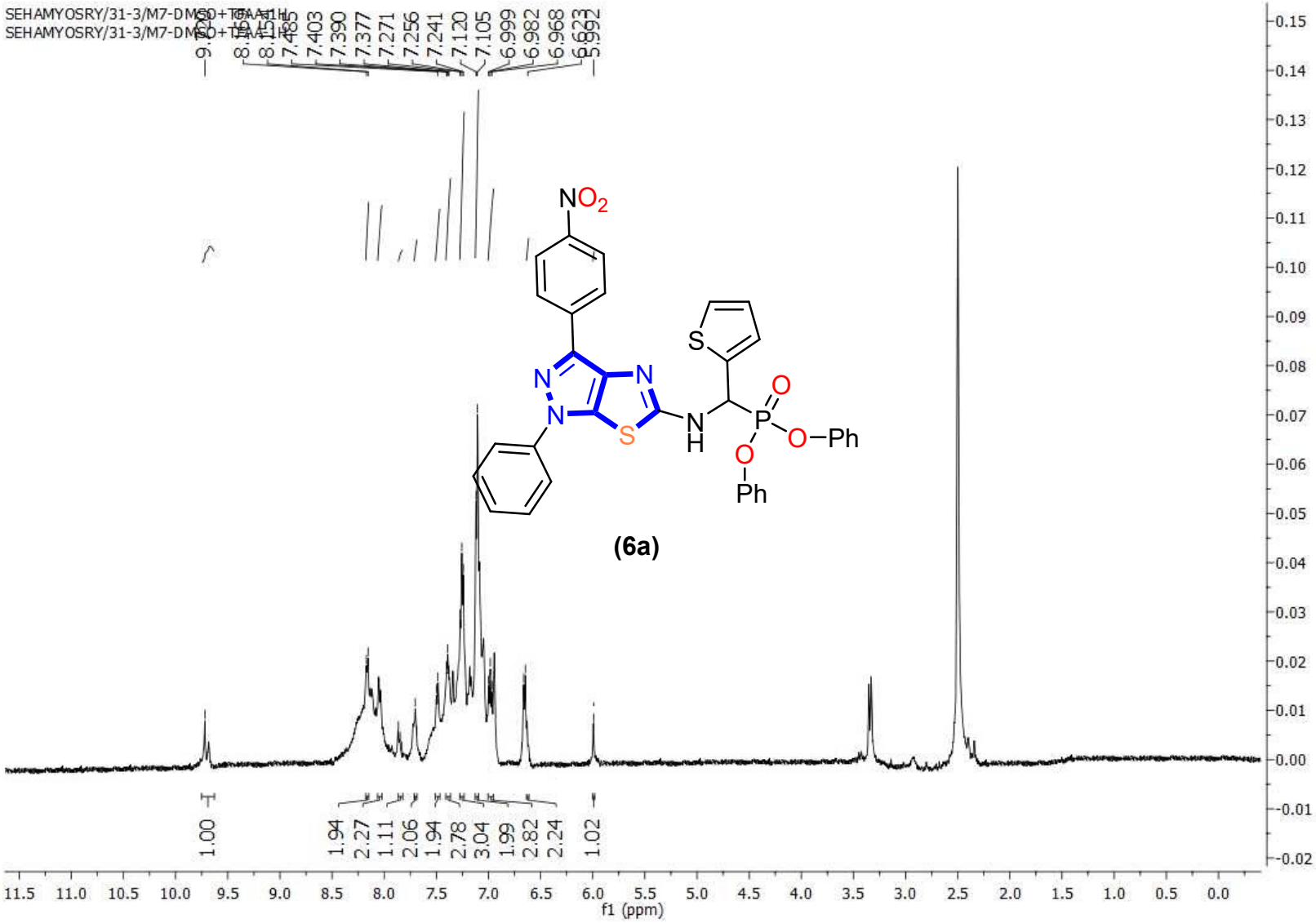
(5a)

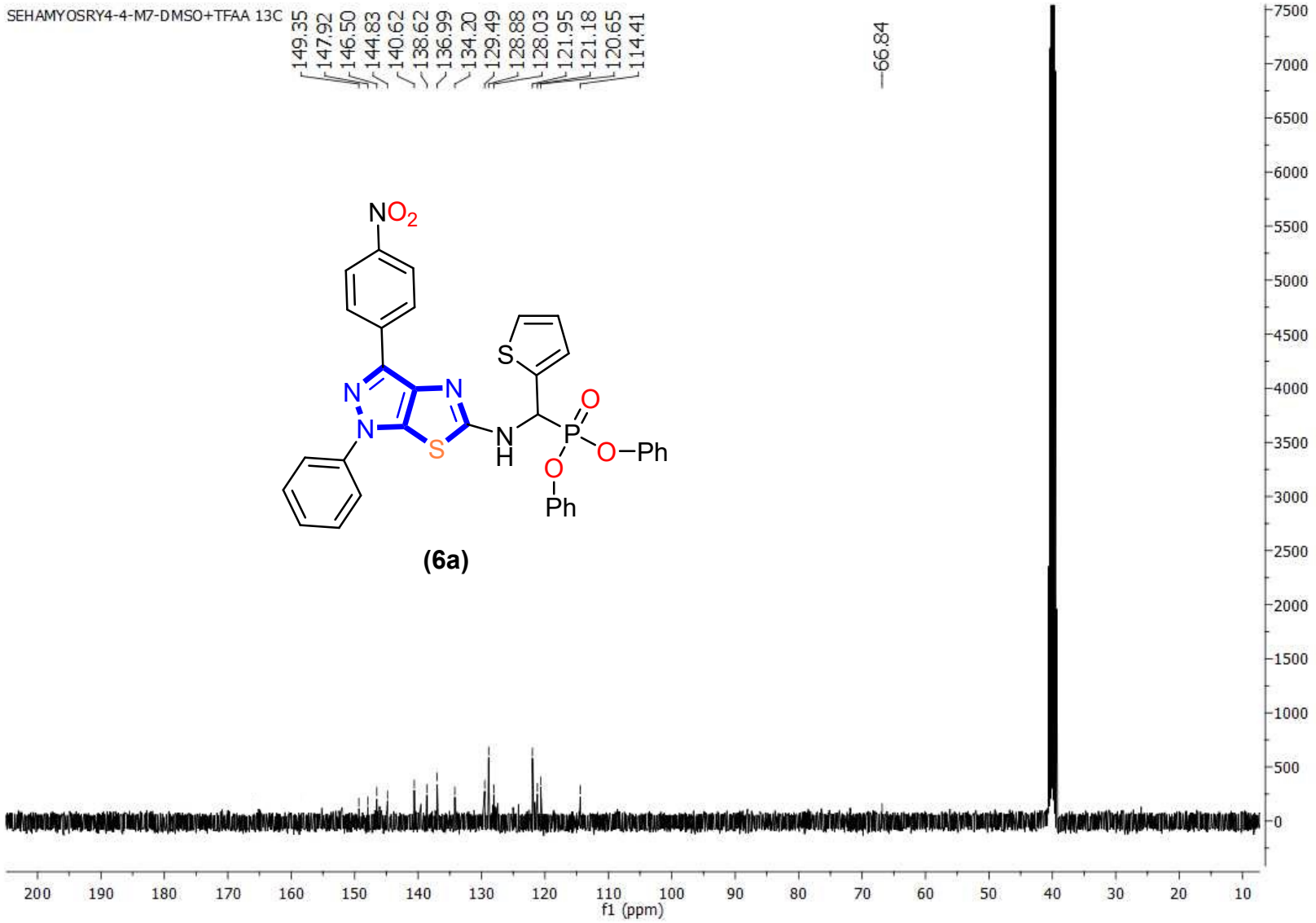

SEHAMYOSRY4-4-M6-DMSO+TFA 13C
149.88
148.69
147.16
140.68
139.53
134.76
132.87
130.98
130.12
129.88
129.54
129.38
129.07
129.00
128.86
125.77
120.59
118.34
115.05
66.81
NO2
OH
N
N
N
S
N
H
P
O
O
O–Ph
O
Ph
(5a)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

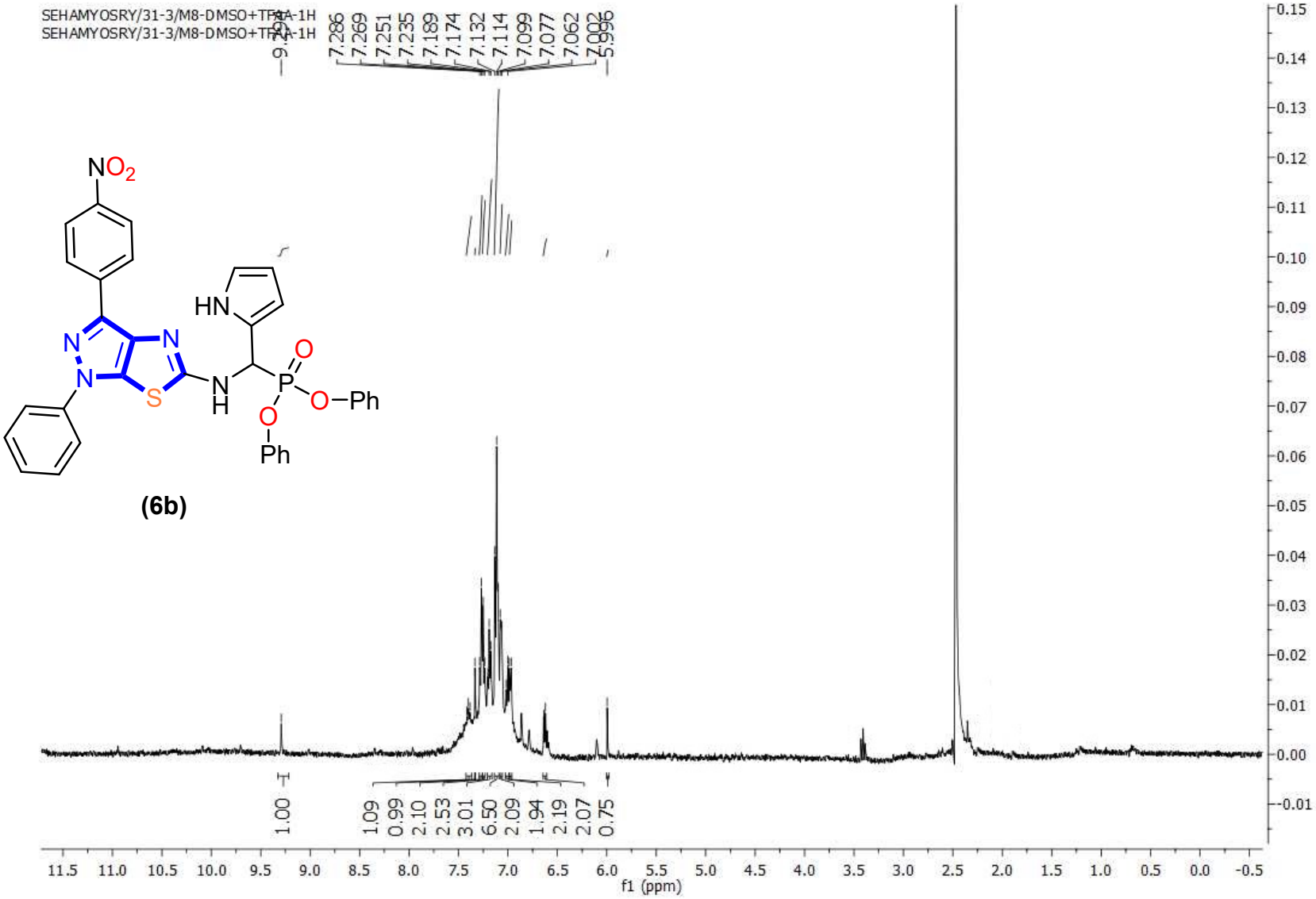

SEHAMYOSRY/31-3/M5-DMSO+TFAA-1H
SEHAMYOSRY/31-3/M5-DMSO+TFAA-1H
9.521
8.170
8.153
8.063
8.046
7.578
7.563
7.520
7.505
7.409
7.390
7.375
7.267
7.254
7.128
7.116
7.102
6.996
6.980
6.969
6.862
6.724
6.710
6.648
6.638
6.620
2.907
NO2
N
N
N
S
N
H
P
O
O
O–Ph
O
Ph
(5b)
1.00
2.01
2.09
3.24
1.22
3.02
3.14
3.46
1.86
1.06
2.92
1.08
6.35
f1 (ppm)

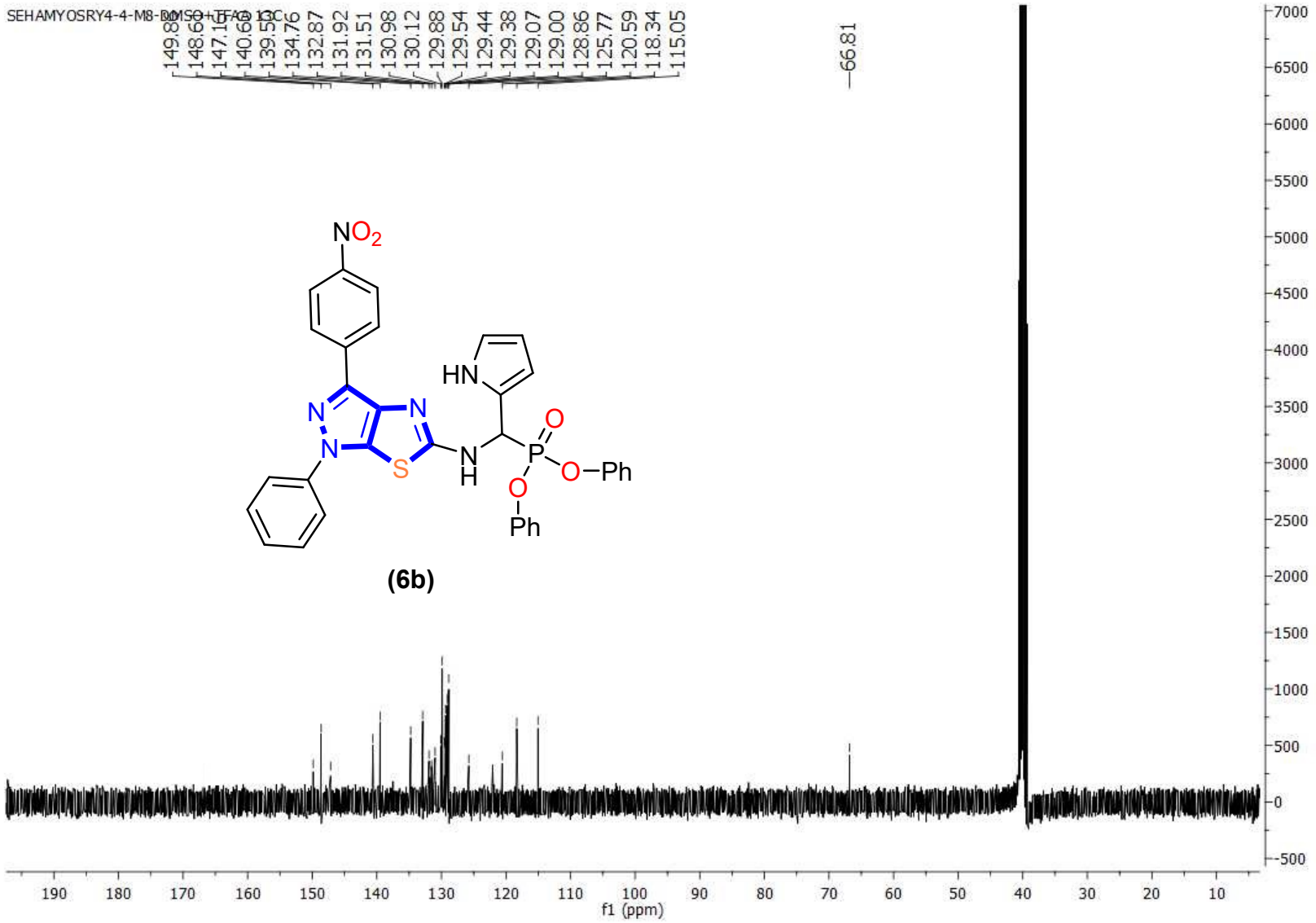

SEHAMYOSRY4-4-M5-DMSO+TFAA-130
146.45
143.75
139.32
137.82
133.88
133.11
130.64
129.18
129.00
128.57
124.81
122.97
122.73
121.94
119.98
119.71
64.00
35.33
NO2
N
N
N
S
N
H
P
O
O
O
Ph
Ph
25000
20000
15000
10000
5000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(5b)


SEHAMYOSRY/31-3/M7-DMSO+TFAA1H
SEHAMYOSRY/31-3/M7-DMSO+TFAA1H
NO2
S
N
N
N
S
N
H
P
O
O
O
Ph
Ph
(6a)
f1 (ppm)


SEHAMYOSRY4-4-M7-DMSO+TFAA 13C
149.35
147.92
146.50
144.83
140.62
138.62
136.99
134.20
129.49
128.88
128.03
121.95
121.18
120.65
114.41
66.84
NO2
S
N
N
N
S
N
H
O
P
O
O–Ph
O
Ph
(6a)
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


SEHAMYOSRY/31-3/M8-DMSO+TFA-1H
SEHAMYOSRY/31-3/M8-DMSO+TFA-1H
9.79
7.286
7.269
7.251
7.235
7.189
7.174
7.132
7.114
7.099
7.077
7.062
7.002
5.996
NO2
HN
N
N
N
S
NH
P
O
O
O
Ph
O
Ph
(6b)
1.00
1.09
0.99
2.10
2.53
3.01
6.50
2.09
1.94
2.19
2.07
0.75
f1 (ppm)


SEHAMYOSRY4-4-M8-DMSO+TFA 13C
149.80
148.60
147.16
140.65
139.53
134.76
132.87
131.92
131.51
130.98
130.12
129.88
129.54
129.44
129.38
129.07
129.00
128.86
125.77
120.59
118.34
115.05
66.81
NO2
HN
N
N
N
S
H
O
P
O–Ph
O
Ph
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

(6b)

BNL Cell Line:

5a	Raw data			Blank Corrected Data			Viability %				
Conc	1			2			3			Mean	STD
C	2.8672	2.8849	2.7978	2.82993	2.84763	2.76053	100	100	100	100	**0**
0.01	2.8808	2.9186	2.9121	2.84353	2.88133	2.87483	101.096	102.44	102.209	101.915	**0.58668839**
0.1	2.9428	2.9096	2.8283	2.90553	2.87233	2.79103	103.301	102.12	99.2297	101.55	**1.71008789**
1	2.8005	2.6718	2.6261	2.76323	2.63453	2.58883	98.2413	98.6656	96.0409	97.6493	**2.62514003**
10	2.6503	2.5339	2.6211	2.61303	2.49663	2.58383	95.3482	95.2098	96.3101	95.6227	**1.75800603**
100	2.4549	2.5035	2.4491	2.41763	2.46623	2.41183	92.8481	95.576	94.6419	94.3554	**0.86722831**
Blank	0.036	0.0393	0.0365	Blank Average		0.03727	Control average		2.8127		

5b	Raw data			Blank Corrected Data			Viability %				
Conc	1			2			3			Mean	STD
C	2.818	2.8789	2.8446	2.7818	2.8427	2.8084	100	100	100	100	**0**
0.01	2.8461	2.8631	2.8191	2.8099	2.8269	2.7829	99.9621	100.567	99.0015	99.8435	**0.64450797**
0.1	2.839	2.8729	2.7879	2.8028	2.8367	2.7517	99.7095	100.915	97.8916	99.5055	**1.24288625**
1	2.0507	2.0642	2.2176	2.0145	2.028	2.1814	93.6657	92.146	92.6032	92.805	**2.69289347**
10	2.2301	2.2926	2.3126	2.1939	2.2564	2.2764	86.89798	88.12142	87.83292	87.61744	**1.25005447**
100	2.2092	2.1974	2.2946	2.173	2.1612	2.2584	73.15447	73.73468	72.19257	73.02724	**1.54067969**
Blank	0.0375	0.0355	0.0356	Blank Average		0.0362	Control average		2.81097		

Dox	Raw data			Blank Corrected Data			Viability %				
Conc	1			2			3			Mean	STD
C	2.7691	2.7738	2.8972	2.7328	2.7375	2.8609	100	100	100	100	**0**
0.01	2.7839	2.765	2.8297	2.7476	2.7287	2.7934	98.9389	98.2584	100.588	99.2618	**0.97815396**
0.1	2.7736	2.7421	2.839	2.7373	2.7058	2.8027	98.568	97.4337	100.923	98.9749	**1.45326531**
1	2.6501	2.5414	2.561	2.6138	2.5051	2.5247	94.1209	90.2067	90.9125	91.7467	**1.70336502**
10	1.6712	1.8409	1.8259	1.6349	1.8046	1.7896	58.8715	64.9822	64.4421	62.7653	**2.76214621**
100	0.2462	0.2203	0.2332	0.2099	0.184	0.1969	7.55833	6.6257	7.09022	7.09142	**0.38074912**
Blank	0.0363	0.0357	0.0369	Blank Average		0.0363	Control average		2.77707		

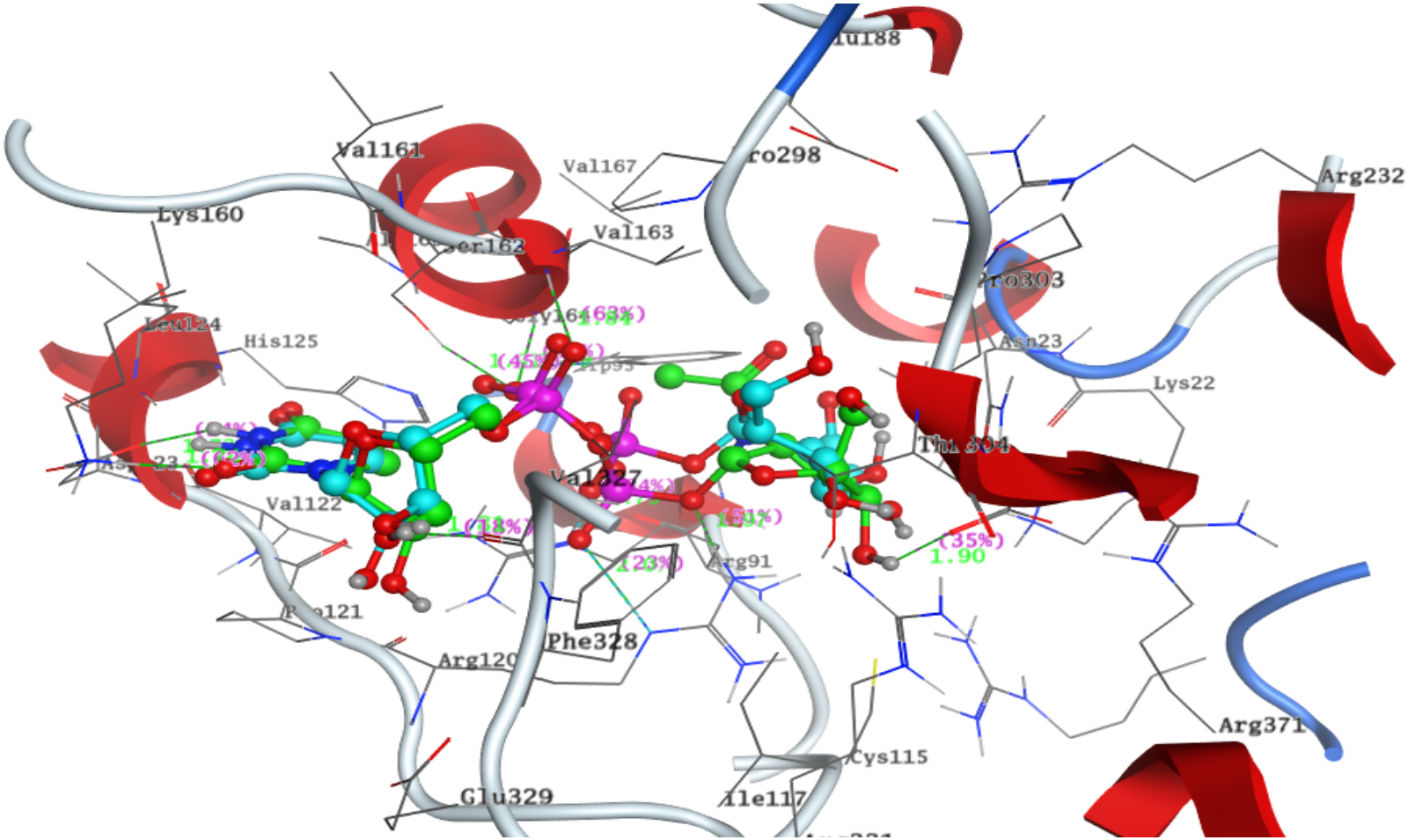
Vero Cell Line:

5a	Raw data			Blank Corrected Data			Viability %				
Conc	1			2			3			Mean	STD
C	2.2275	2.2424	2.2214	2.18967	2.20457	2.18357	100	100	100	100	**0**
0.01	2.2582	2.2145	2.2332	2.22037	2.17667	2.19537	101.266	99.2733	100.126	100.222	**0.81648004**
0.1	2.271	2.1215	2.1788	2.23317	2.08367	2.14097	101.85	95.0318	97.6451	98.1757	**2.80876461**
1	2.1751	2.1102	2.1981	2.13727	2.07237	2.16027	97.4764	94.5164	98.5253	96.8394	**1.69749159**
10	2.1011	2.0982	2.1112	2.06327	2.06037	2.07337	94.1014	93.9691	94.562	94.2108	**0.2541254**
100	1.7391	1.8353	1.8759	1.70127	1.79747	1.83807	77.5913	81.9788	83.8305	81.1335	**2.61631579**
Blank	0.0361	0.0405	0.0369	Blank Average		0.03783	Control average		2.1926		

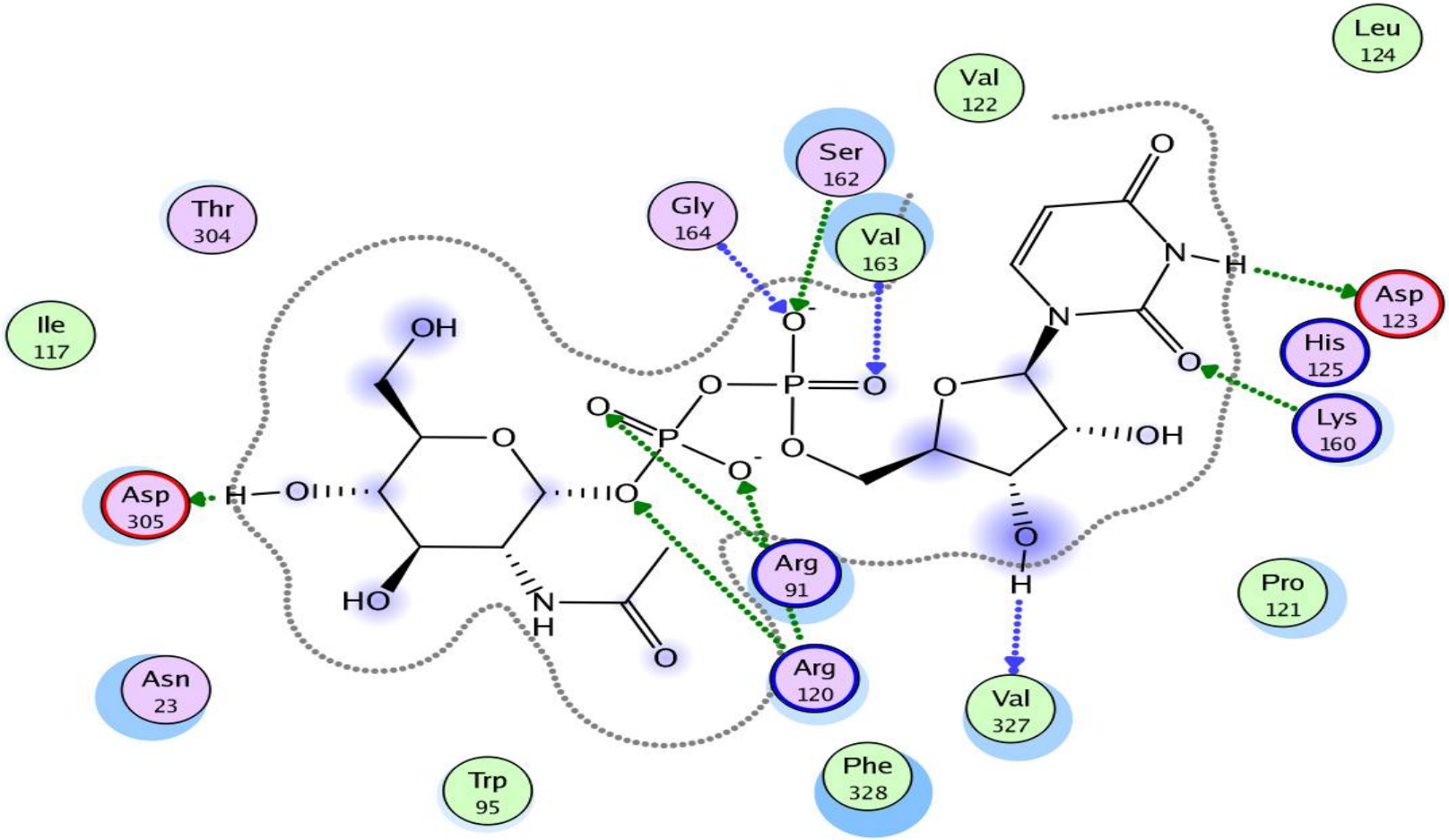
5b	Raw data			Blank Corrected Data			Viability %				
Conc	1			2			3			Mean	STD
C	2.1786	2.187	2.2329	2.14063	2.14903	2.19493	100	100	100	100	**0**
0.01	2.1276	2.221	2.2321	2.08963	2.18303	2.19413	96.6737	100.995	101.508	99.7255	**2.16814043**
0.1	2.1534	2.1253	2.2214	2.11543	2.08733	2.18343	97.8673	96.5673	101.013	98.4826	**1.8664576**
1	2.142	2.1196	2.1599	2.10403	2.08163	2.12193	97.3399	96.3035	98.168	97.2705	**0.76272523**
10	2.1081	2.1141	2.0799	2.07013	2.07613	2.04193	95.7715	96.0491	94.4669	95.4292	**0.68980658**
100	2.1147	2.1149	2.0125	2.07673	2.07693	1.97453	96.0769	96.0861	91.3487	94.5039	**2.23104362**
Blank	0.0379	0.0384	0.0376	Blank Average		0.03797	Control average		2.16153		

Dox	**Raw data**			**Blank Corrected Data**			**Viability %**				
Conc	1			2			3			Mean	STD
C	2.2842	2.1646	2.1727	2.2472	2.1276	2.1357	100	100	100	100	**0**
0.01	2.1596	2.2669	2.2626	2.1226	2.2299	2.2256	97.8082	102.752	102.554	101.038	**2.28550468**
0.1	1.9478	1.93	1.8365	1.9108	1.893	1.7995	88.0485	87.2283	82.9199	86.0656	**2.24940007**
1	0.9495	0.9422	0.9118	0.9125	0.9052	0.8748	42.0475	41.7111	40.3103	41.3563	**0.75227607**
10	0.3061	0.3133	0.2847	0.2691	0.2763	0.2477	12.4	12.7317	11.4139	12.1819	**0.55968729**
100	0.0701	0.0675	0.0608	0.0331	0.0305	0.0238	1.52523	1.40542	1.09669	1.34245	**0.18052834**
Blank	0.0366	0.0365	0.0379	Blank Average		0.037	Control average		2.17017		

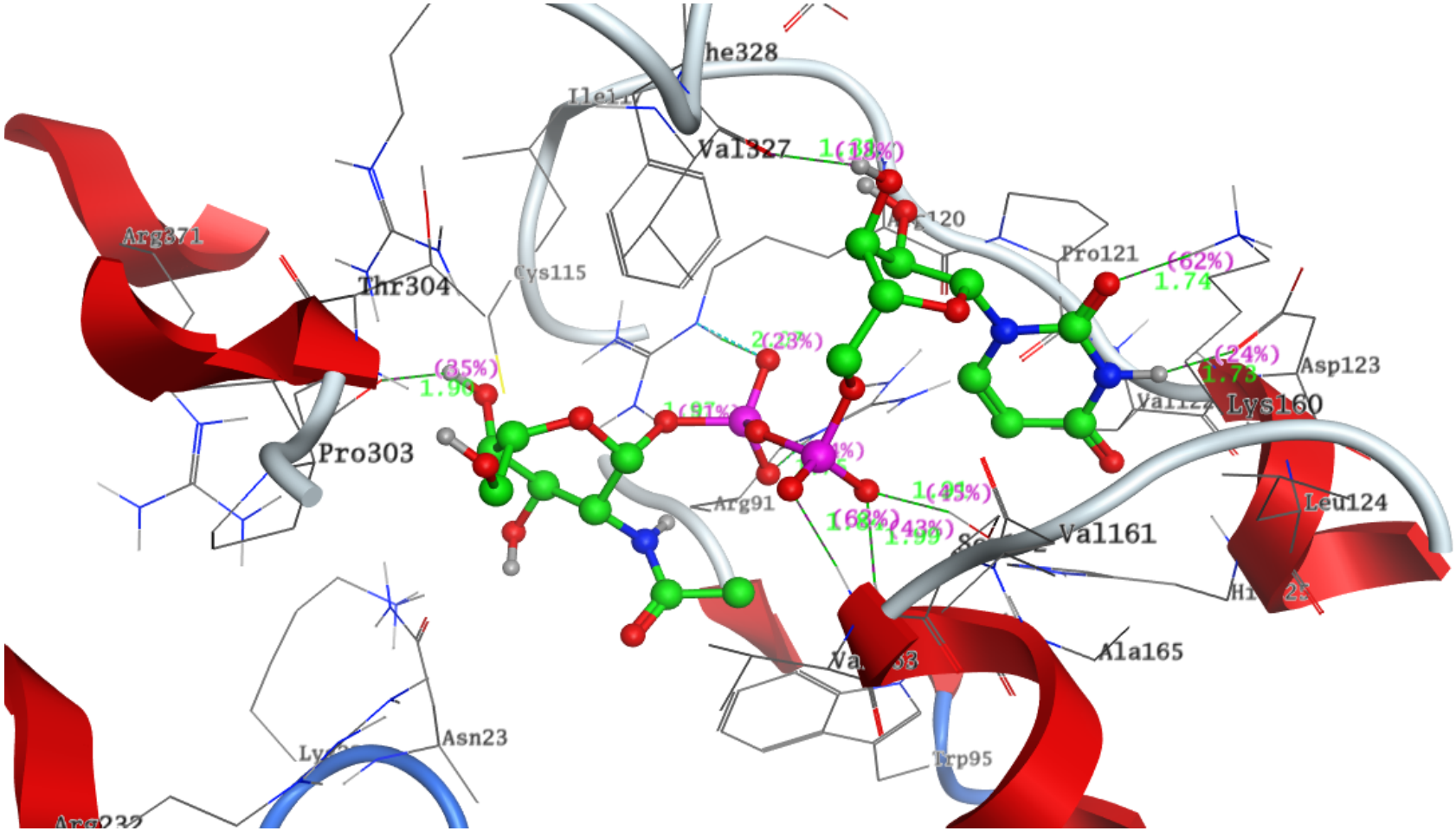
Molecular docking figures



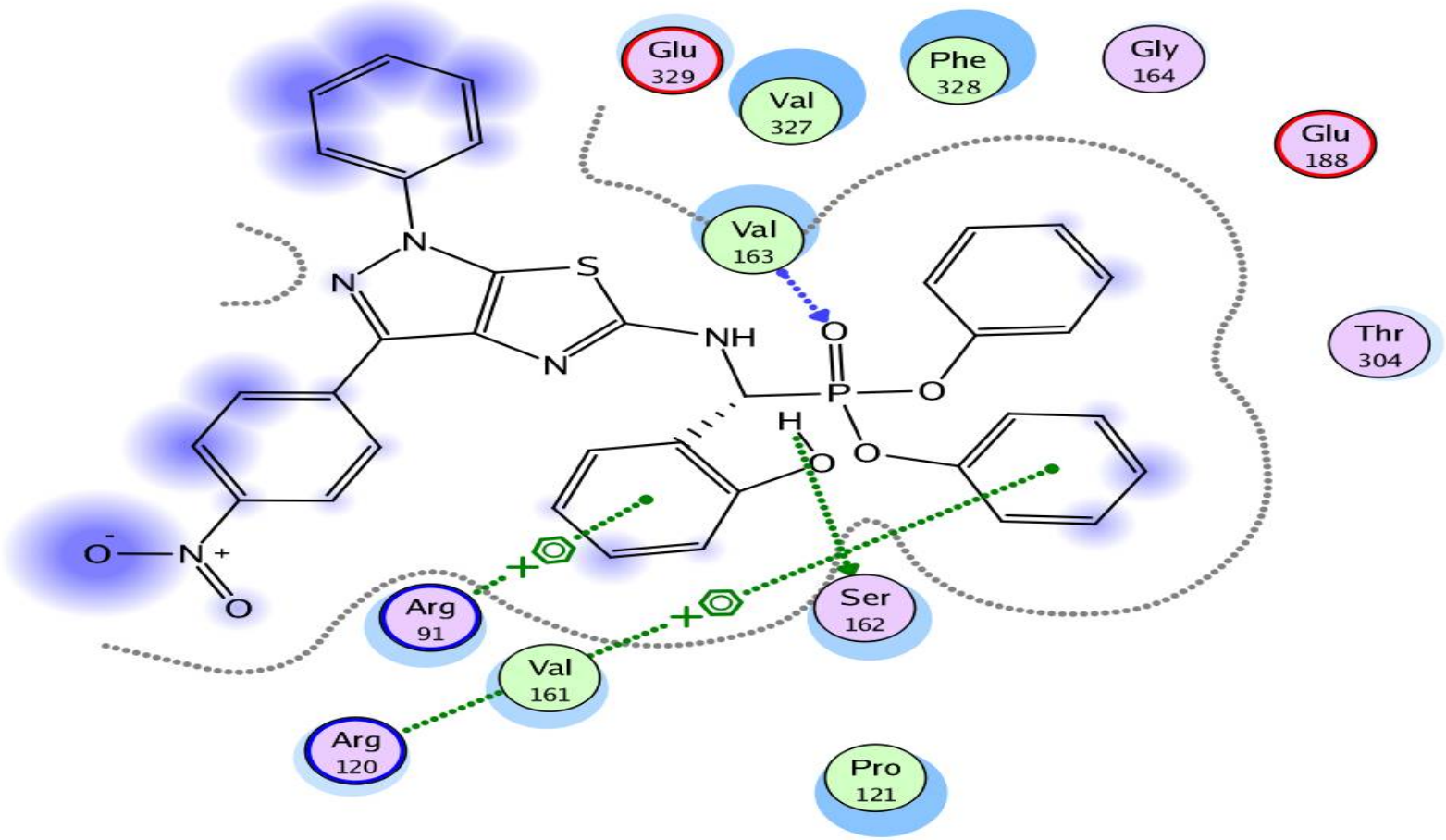
Superimposition of the co-crystallized ligand (**turquoise**) and the re-docked co-crystallized (**green**) through the validation process that exhibited that the co-crystallized ligand showed binding energy S = - 17.69 kcal/mol with RMSD = 1.53 Å.



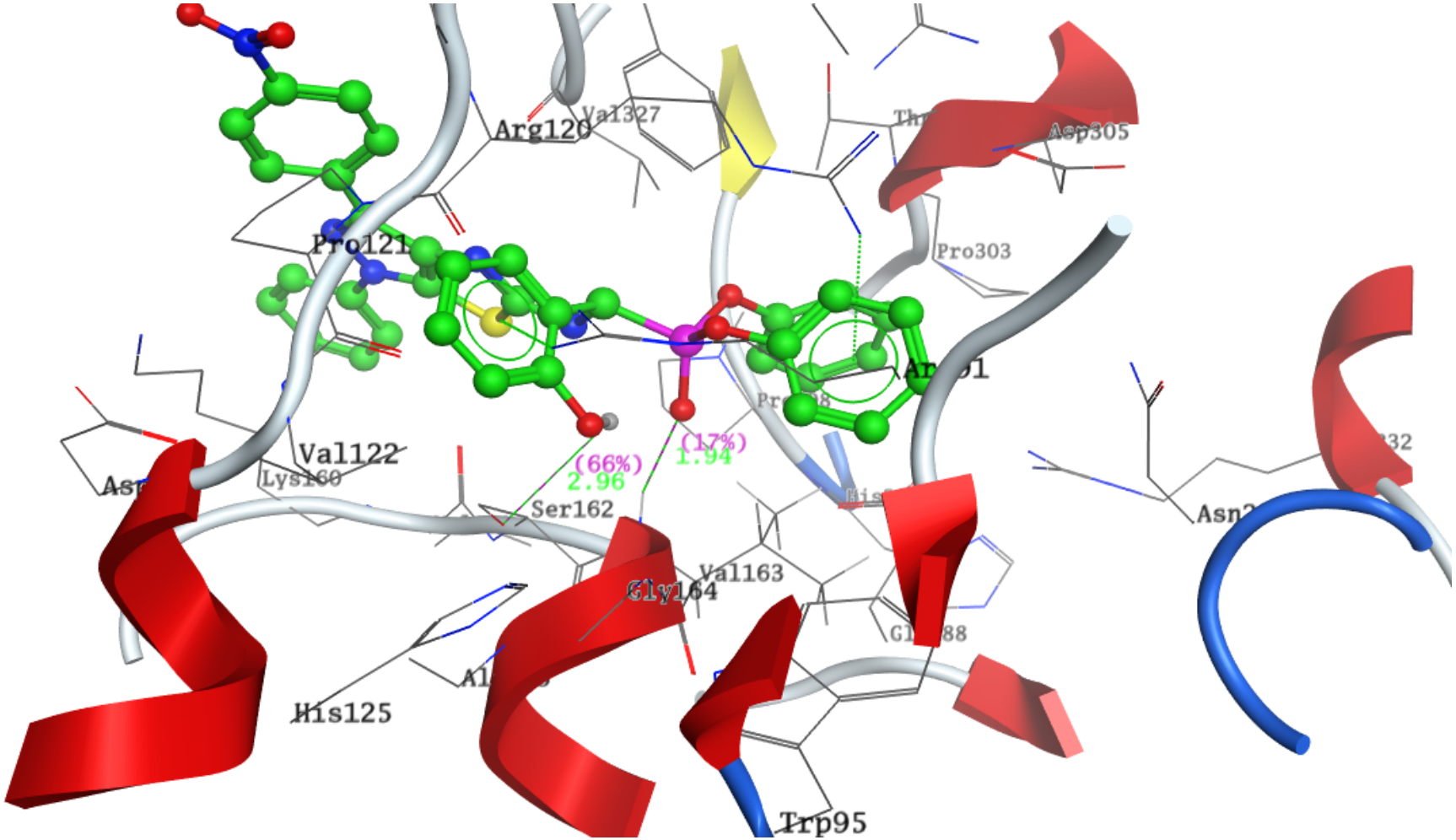
2D structure of **co-crystallized ligand** inside the active site of Mur A (PDB: 1AUE)



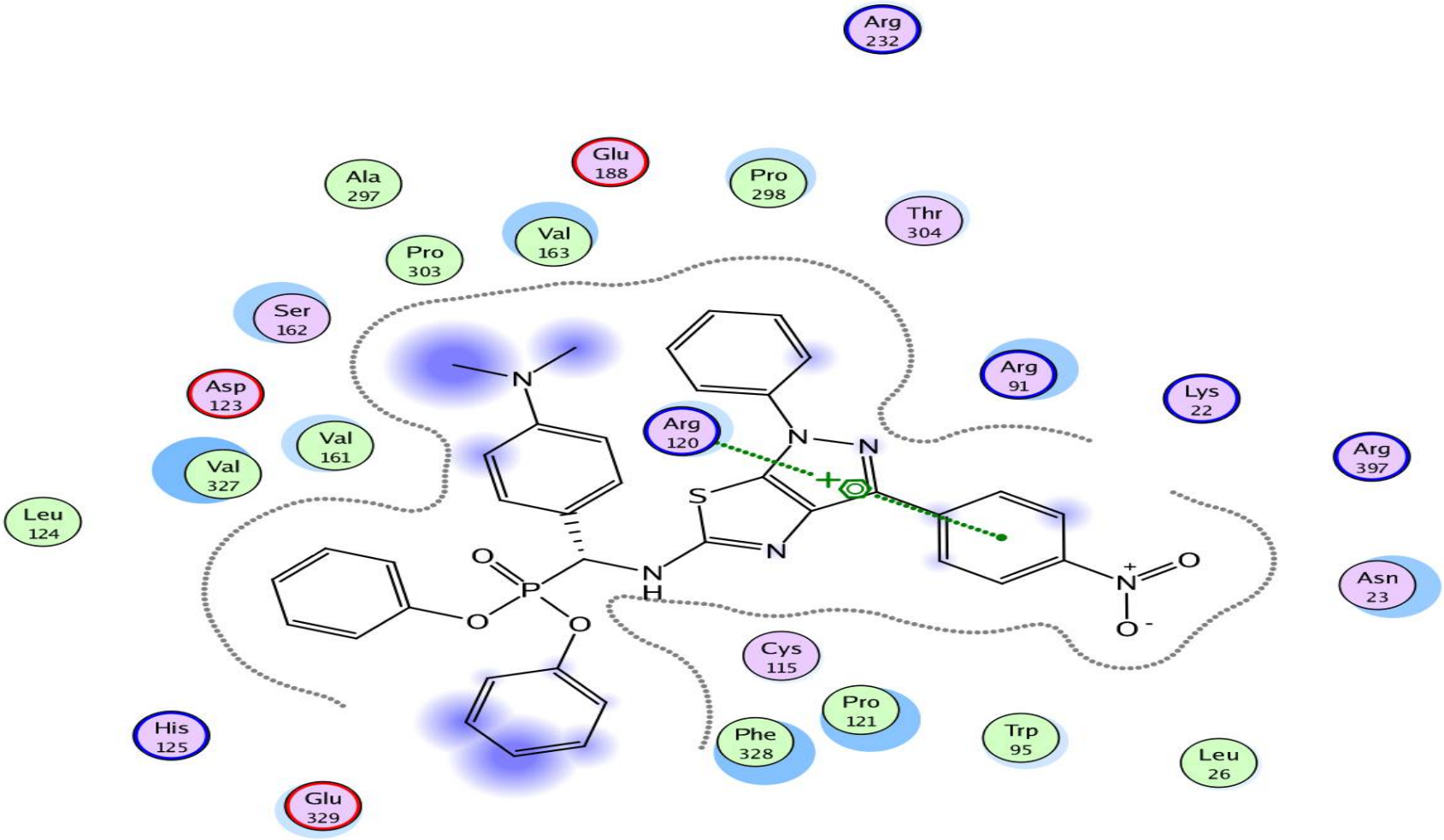
3D structure of **co-crystallized ligand** inside the active site of Mur A (PDB: 1AUE)



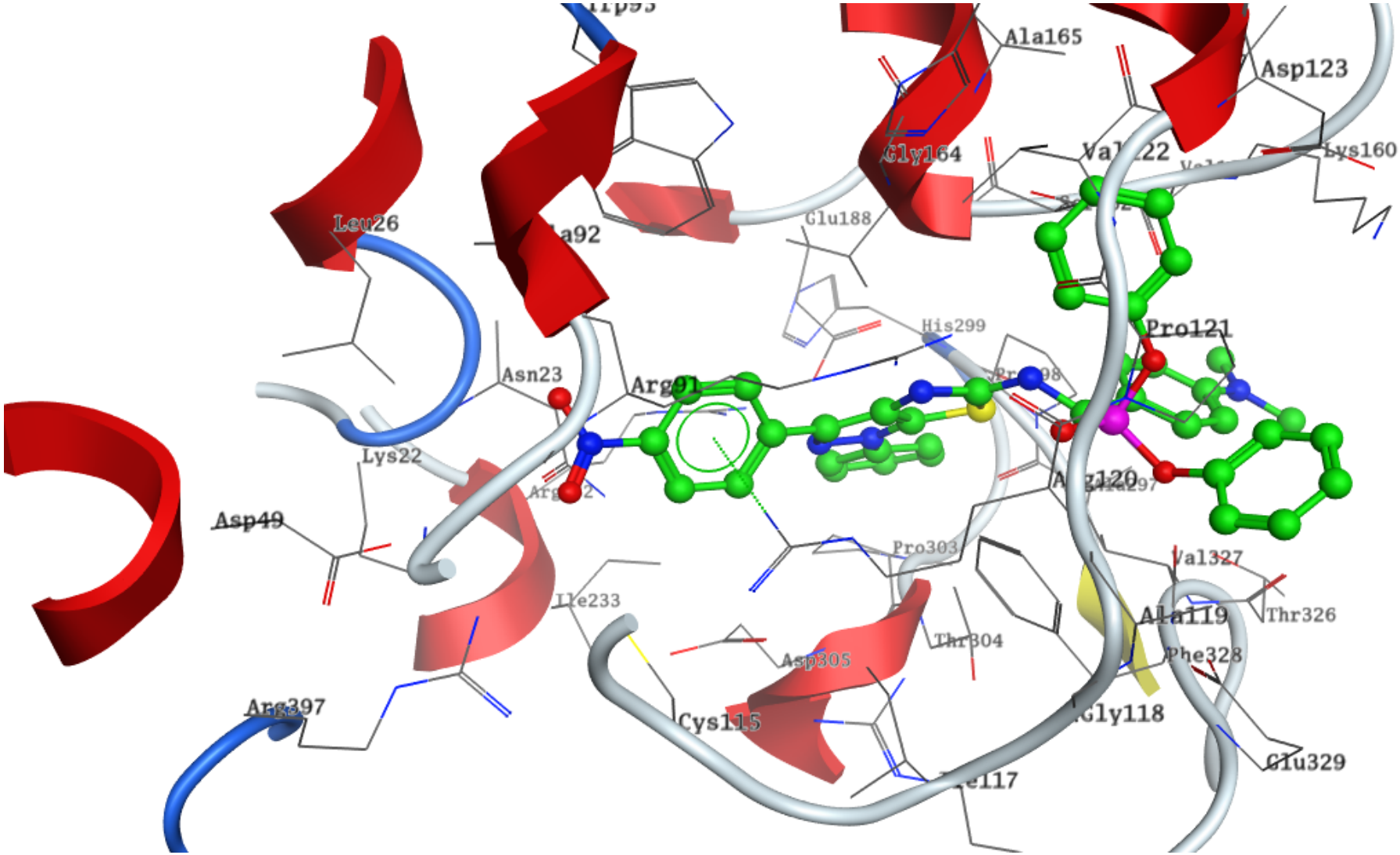
2D structure of most active diphenyl α-aminophosphonate derivatives **5a** inside the active site of Mur A (PDB: 1AUE)



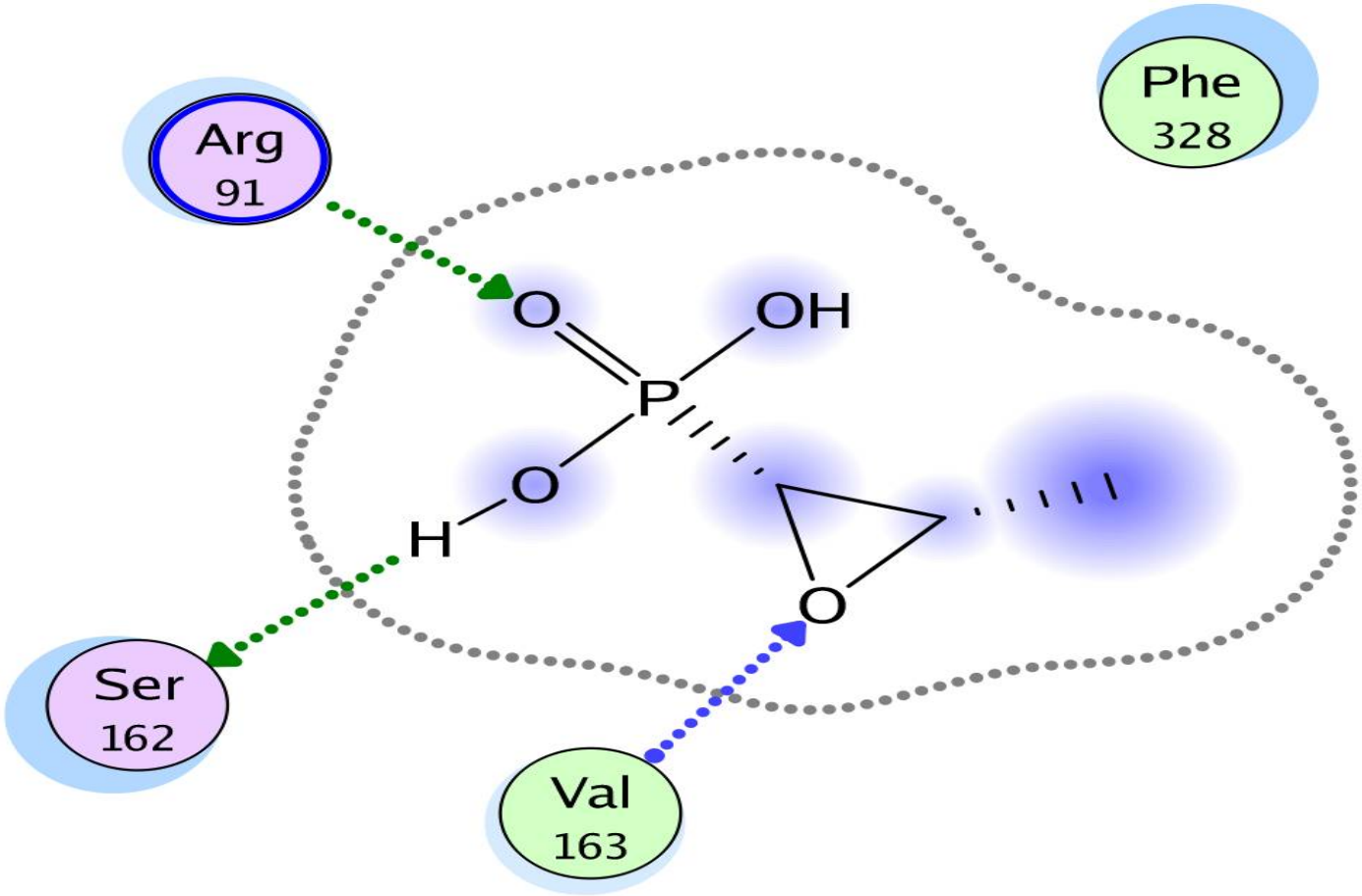
3D structure of most active diphenyl α-aminophosphonate derivatives **5a** inside the active site of Mur A (PDB: 1AUE)



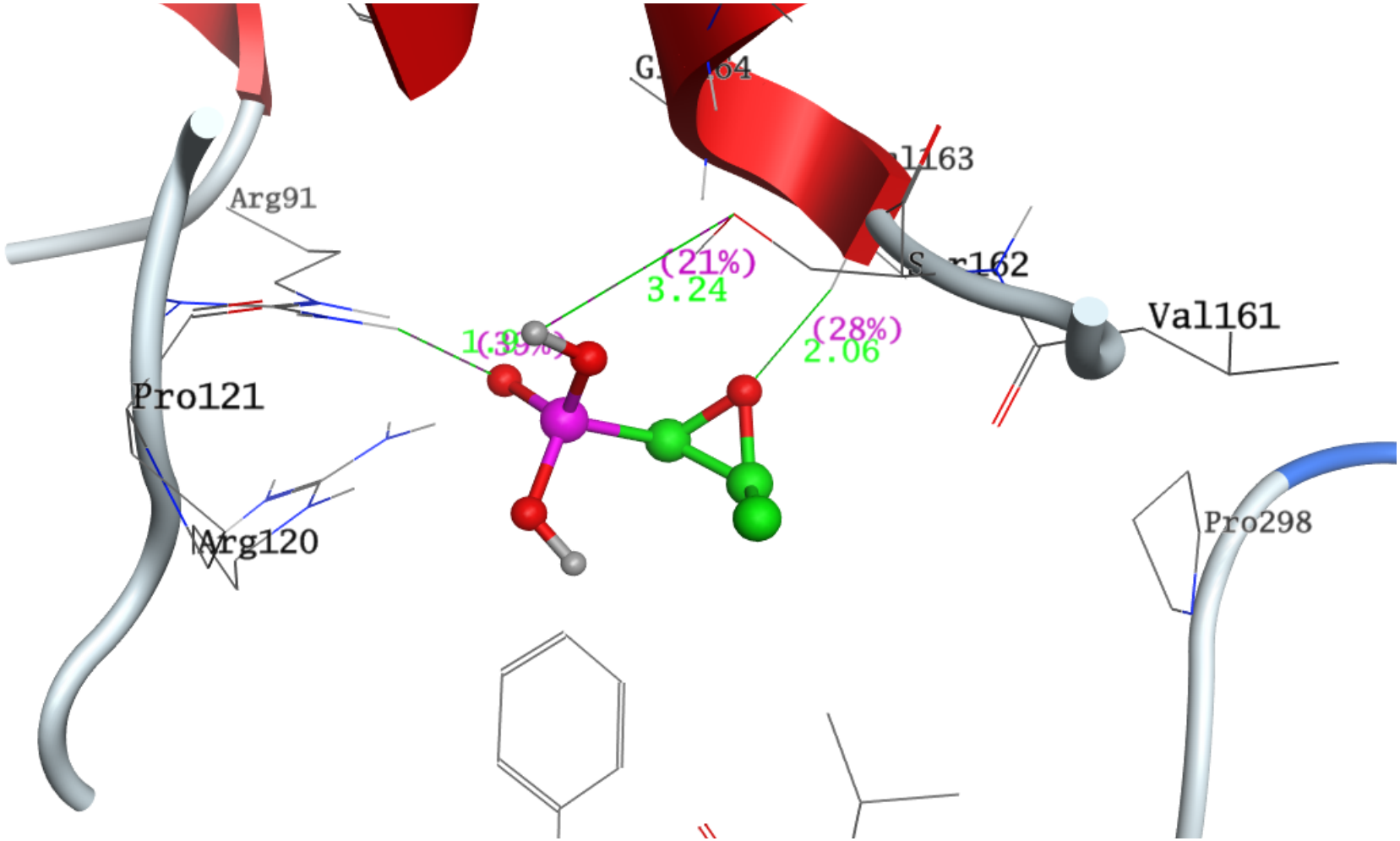
2D structure of most active diphenyl α-aminophosphonate derivatives **5b** inside the active site of Mur A (PDB: 1AUE)



3D structure of most active diphenyl α-aminophosphonate derivatives **5b** inside the active site of Mur A (PDB: 1AUE)

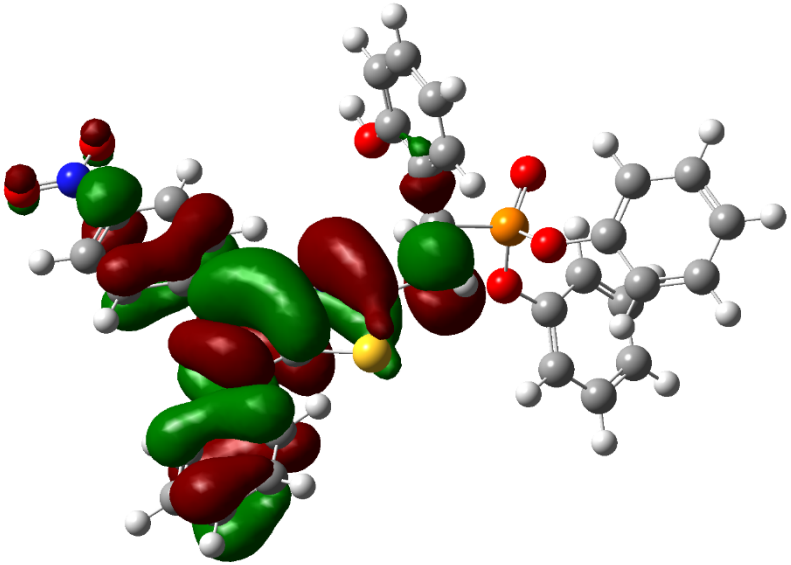
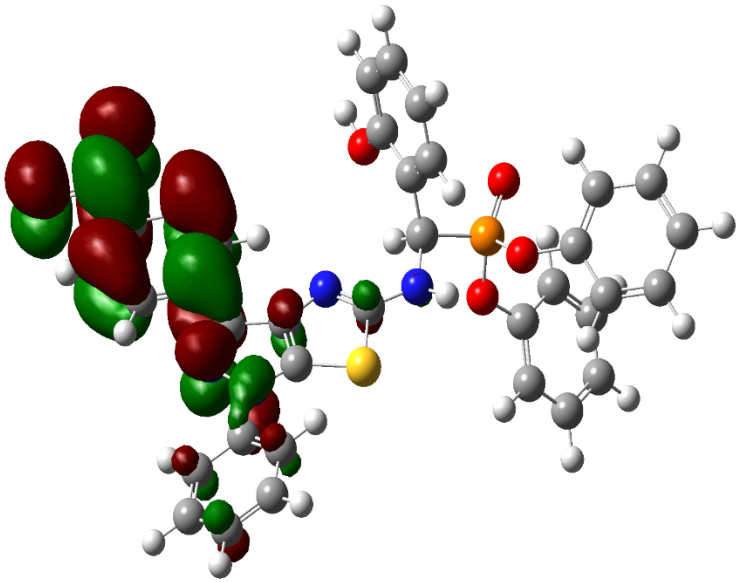


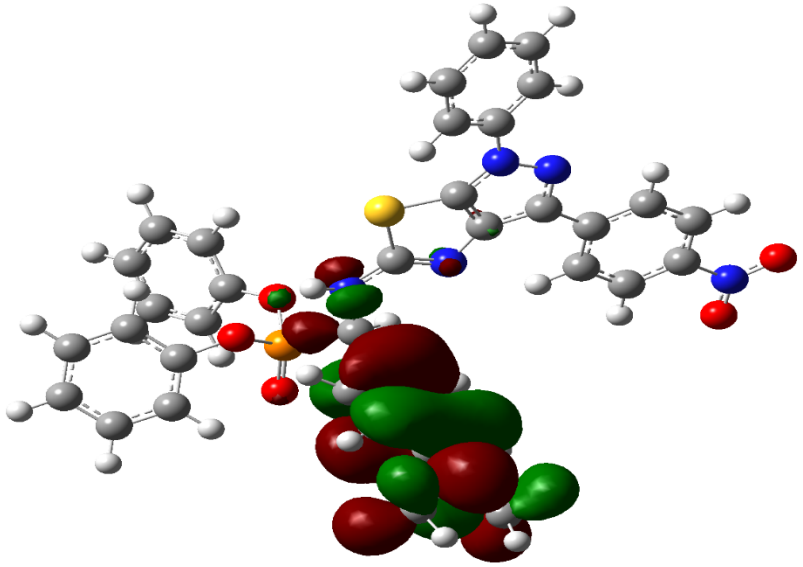
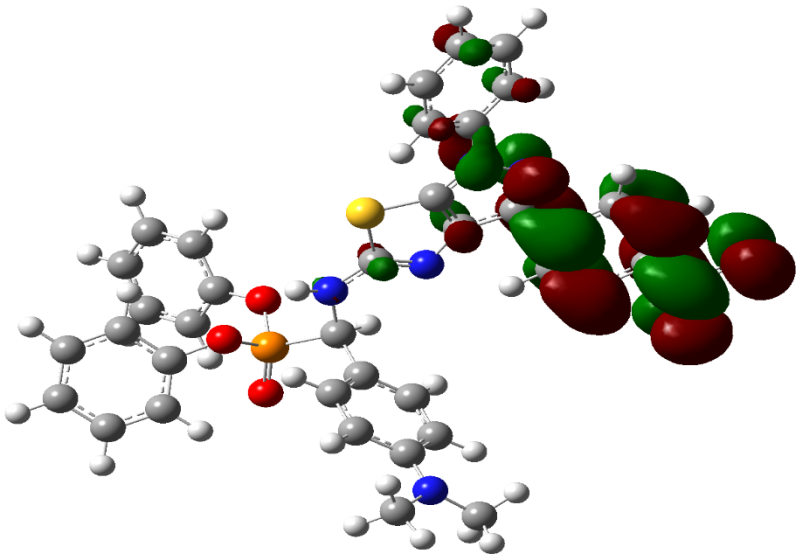
2D structure of most active diphenyl α-aminophosphonate derivatives **Fosfomycin** inside the active site of Mur A (PDB: 1AUE)

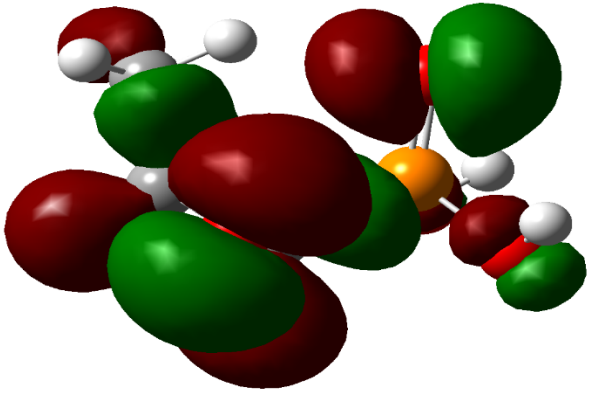
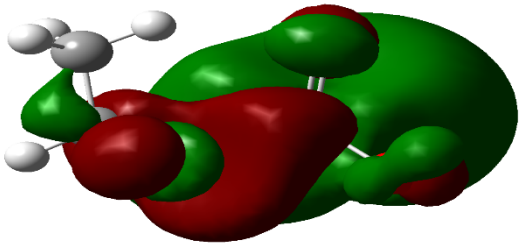


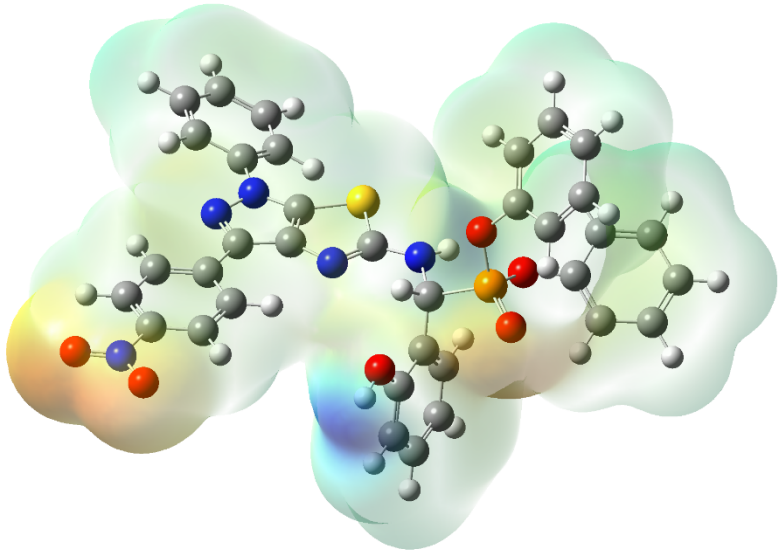
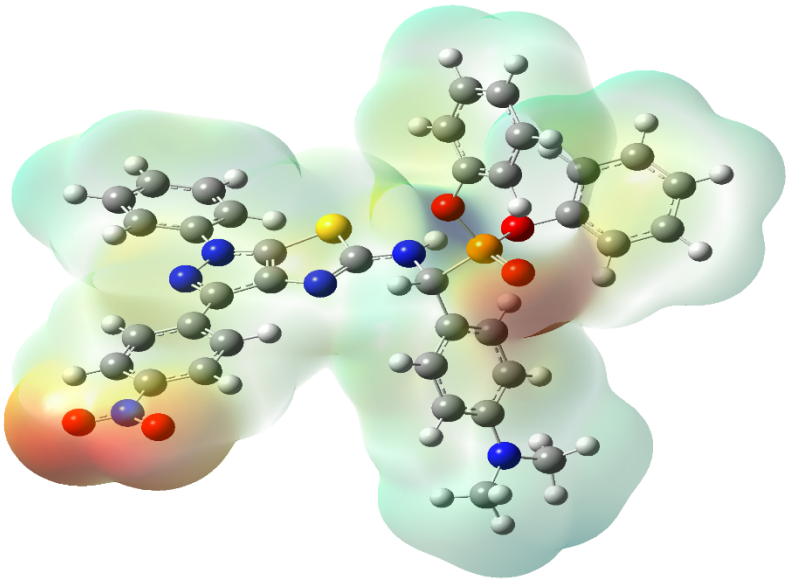
3D structure of most active diphenyl α-aminophosphonate derivatives **Fosfomycin** inside the active site of Mur A (PDB: 1AUE)

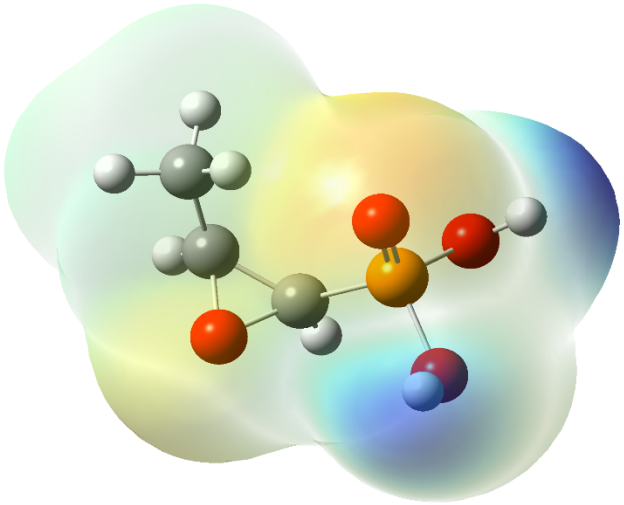
DFT calculations Figures

	
5a HOMO	**5a LUMO**

	
5b HOMO	**5b LUMO**

	
Fosfomycin HOMO	**Fosfomycin HUMO**

	
MEP maps 5a	**MEP maps 5b**



Fosfomycin MEP maps