Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.
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New nitazoxanide derivatives: design, synthesis, biological evaluation, and molecular docking studies as antibacterial and antimycobacterial agents

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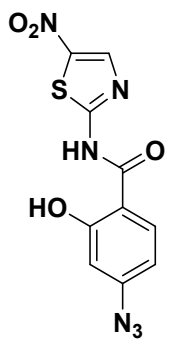

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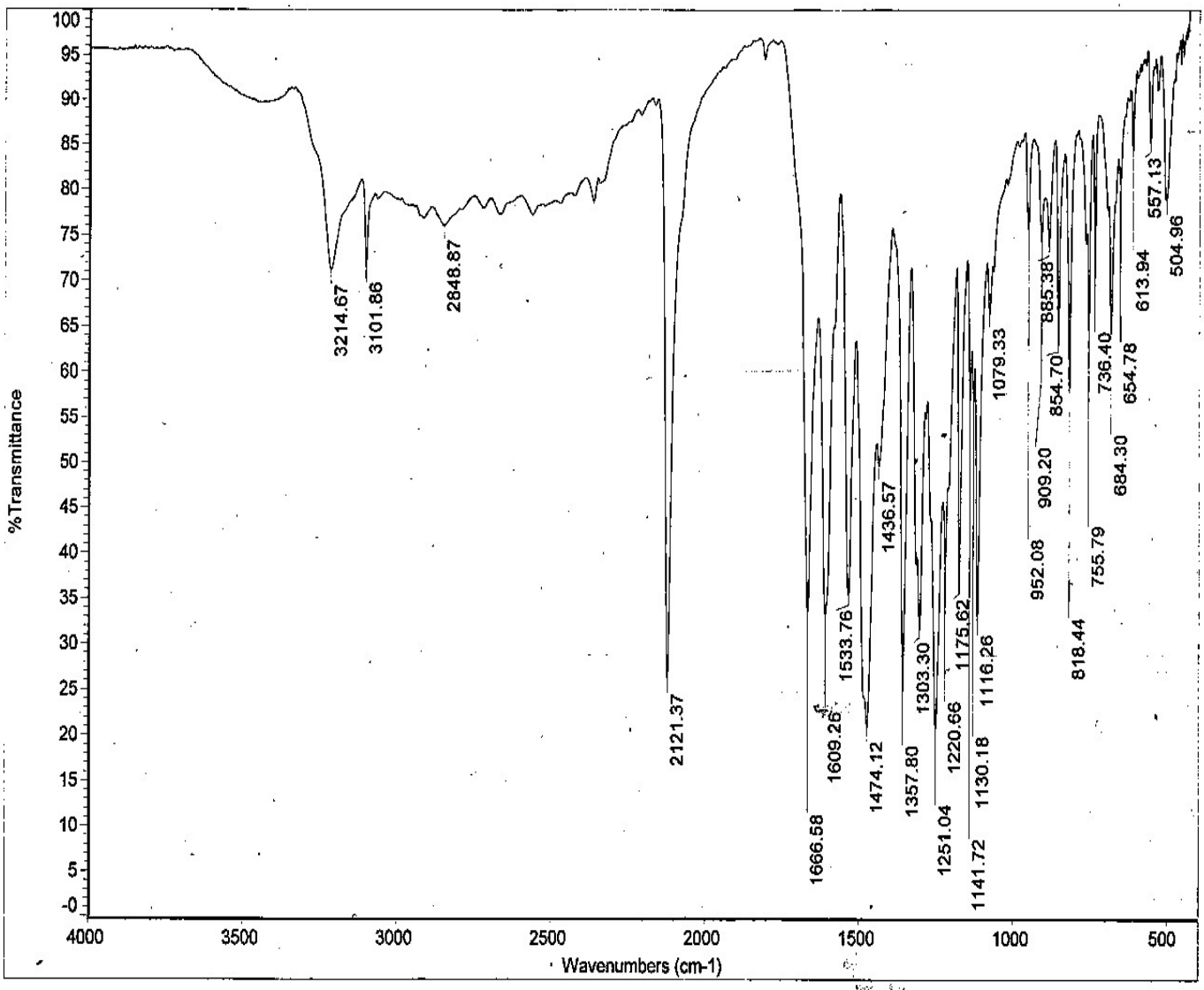

FIGURE S1. FT-IR spectrum of compound 3a.

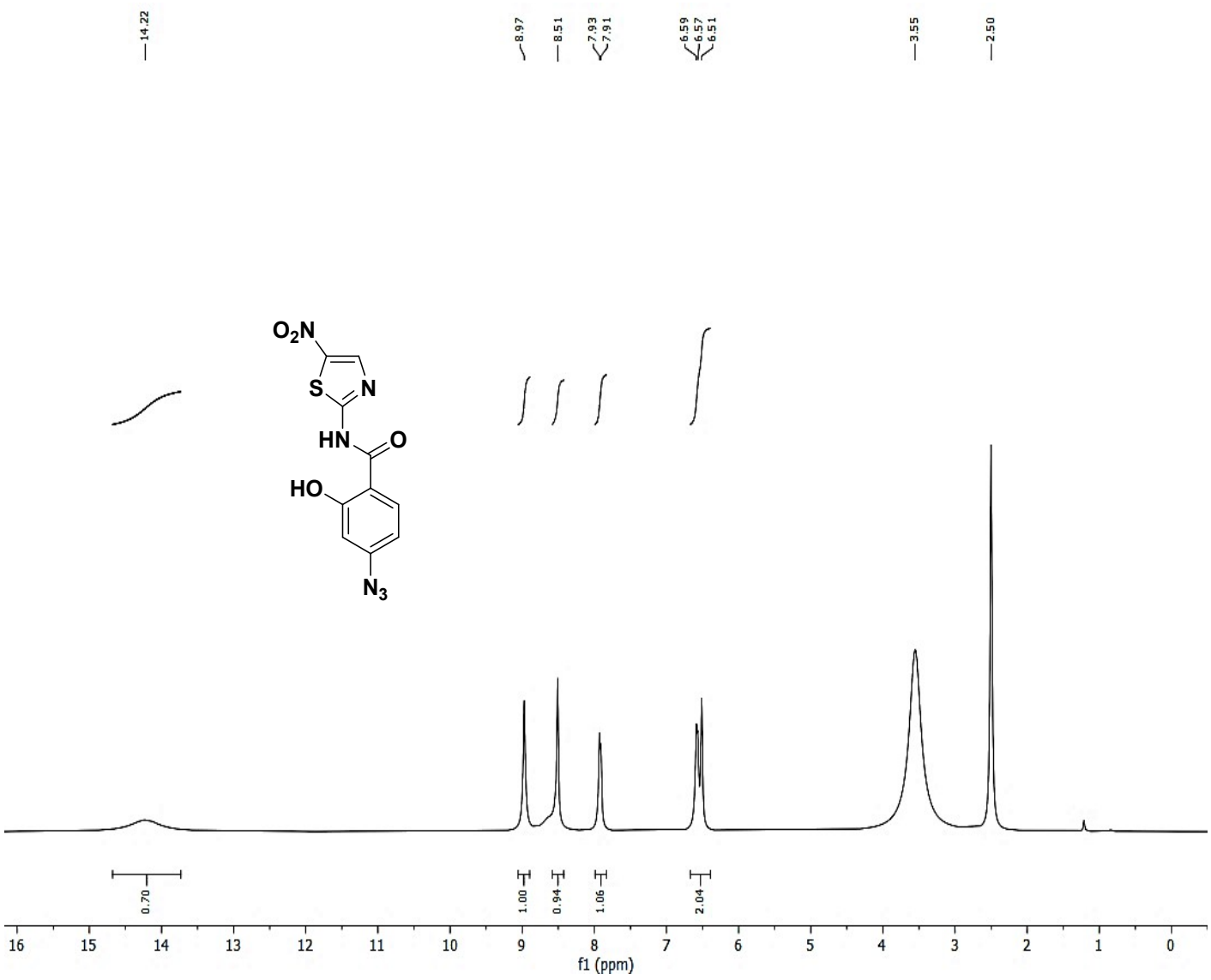

FIGURE S2. [1]H-NMR spectrum of compound 3a.

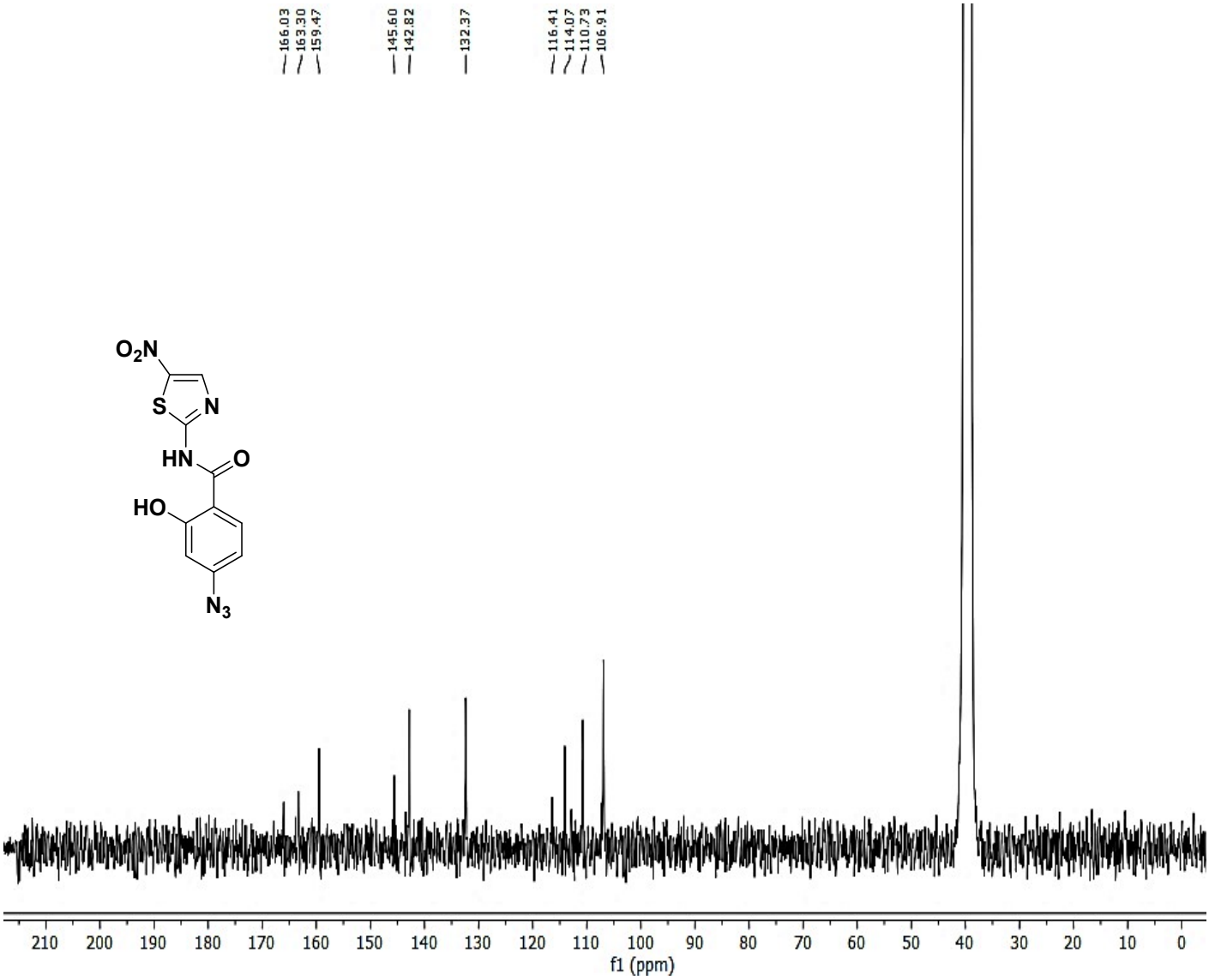

FIGURE S3. ^{13}C-NMR spectrum of compound 3a.

FIGURE S4. ESI-mass spectrum of compound 3a.

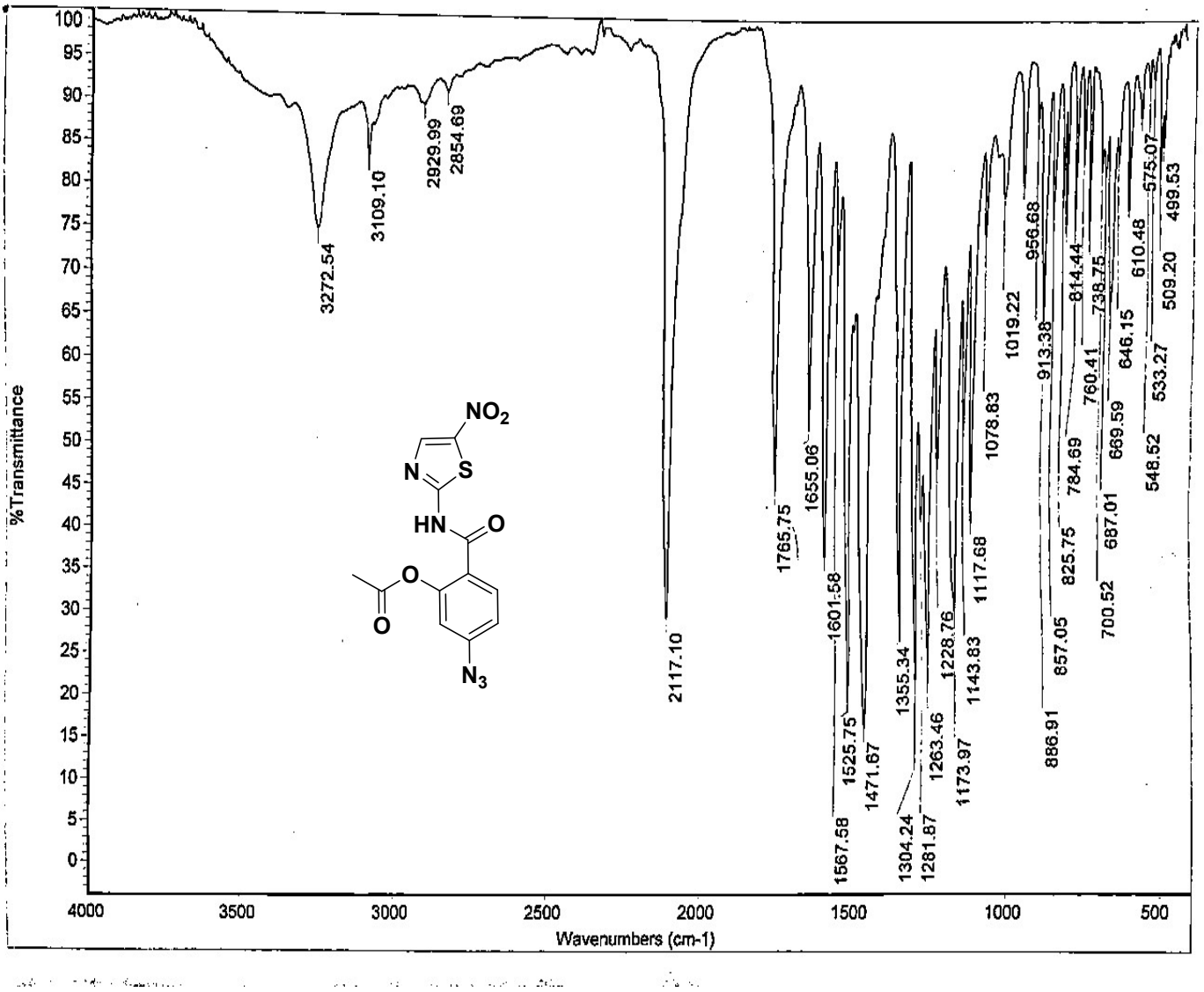

FIGURE S5. FT-IR spectrum of compound 3b.

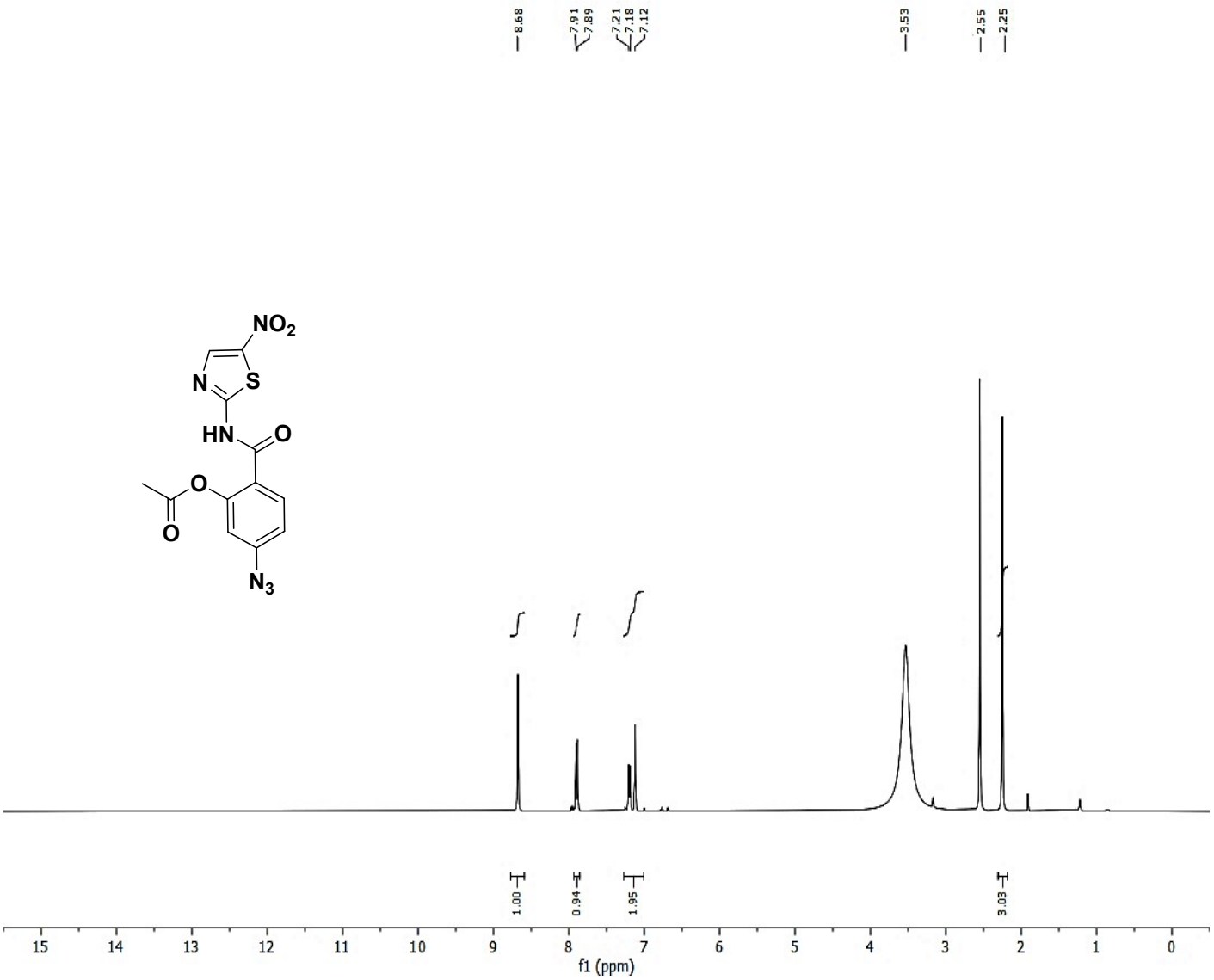

FIGURE S6. [1]H-NMR spectrum of compound 3b.

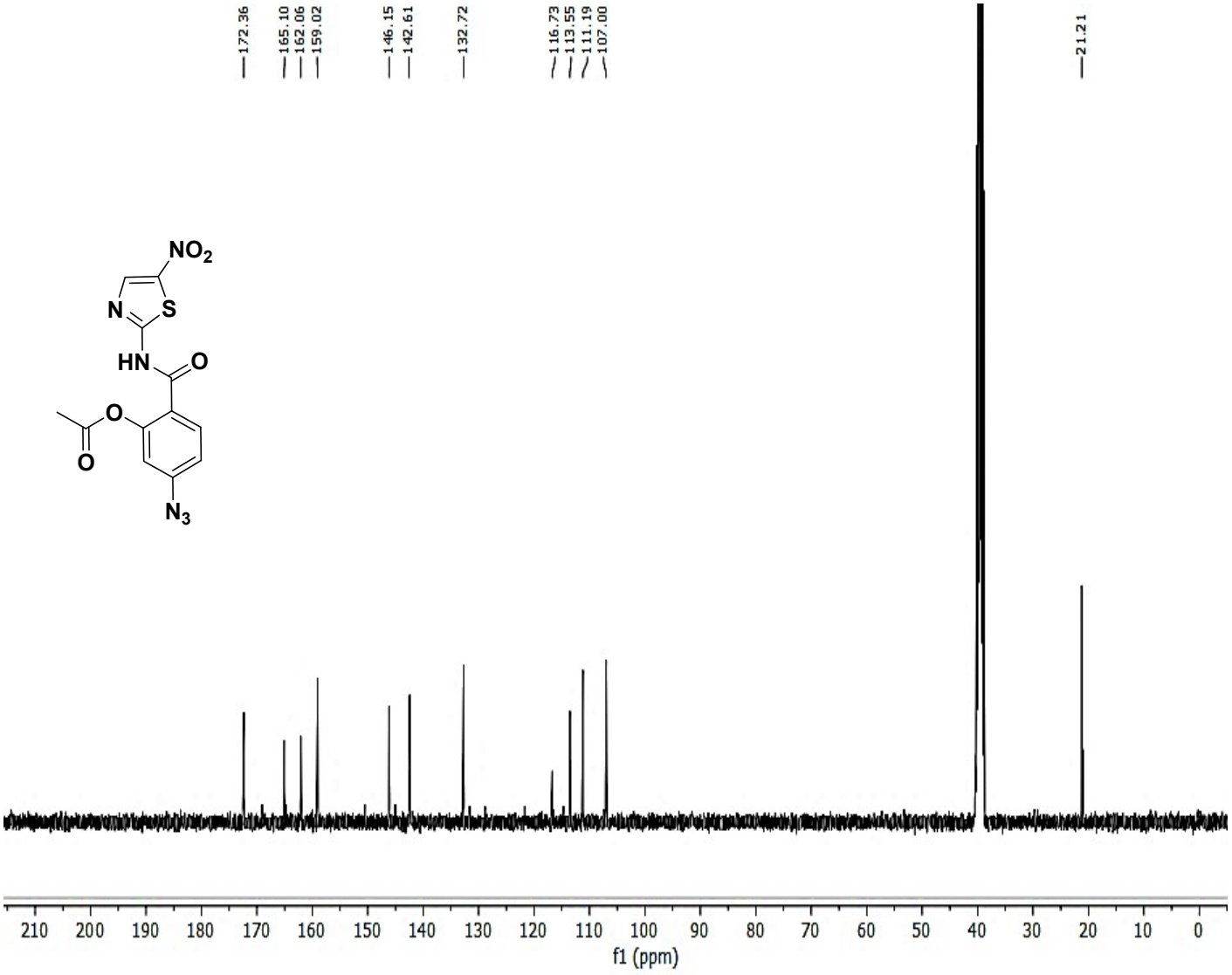

FIGURE S7. ^{13}C-NMR spectrum of compound 3b.

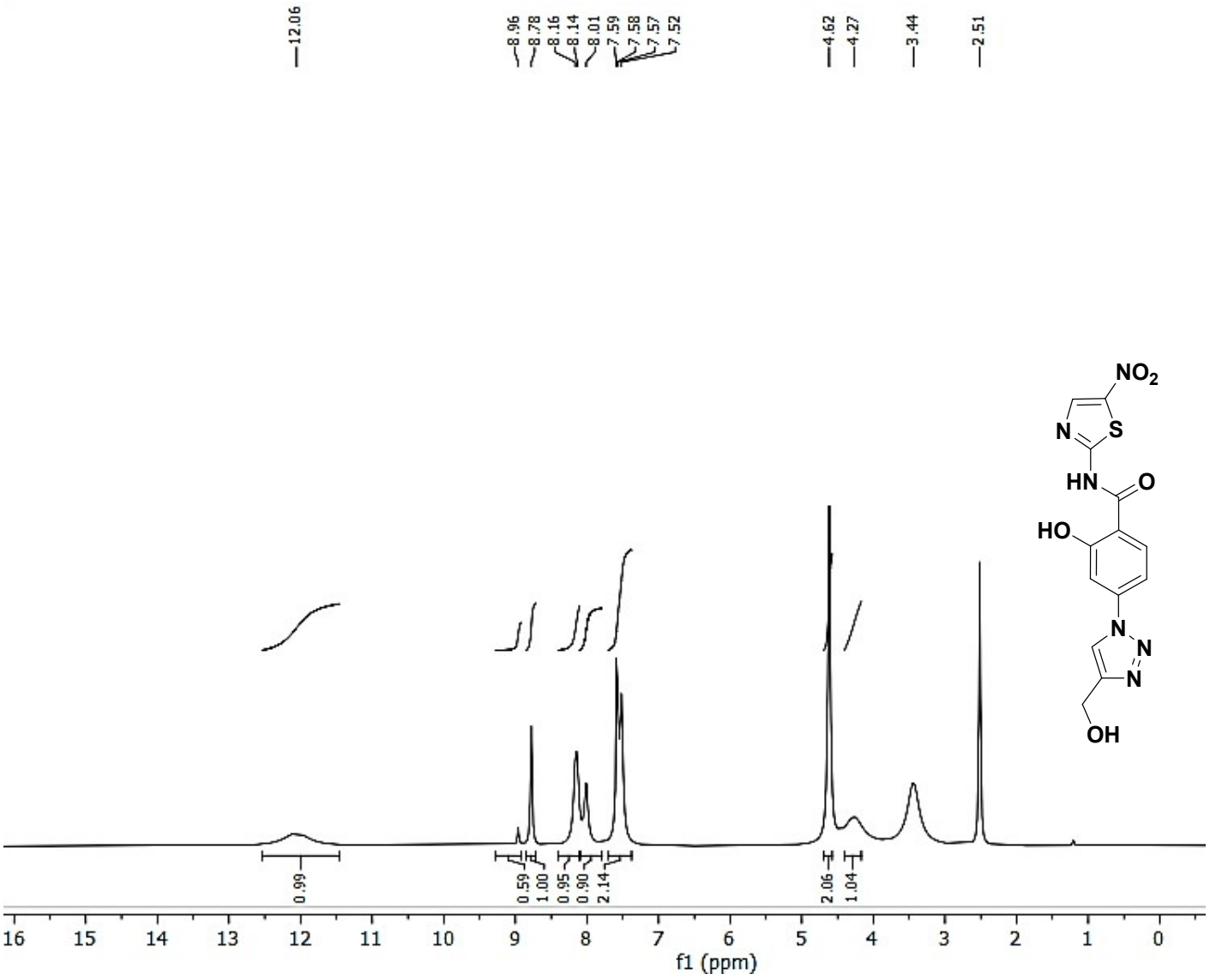

FIGURE S8. [1]H-NMR spectrum of compound 5a.

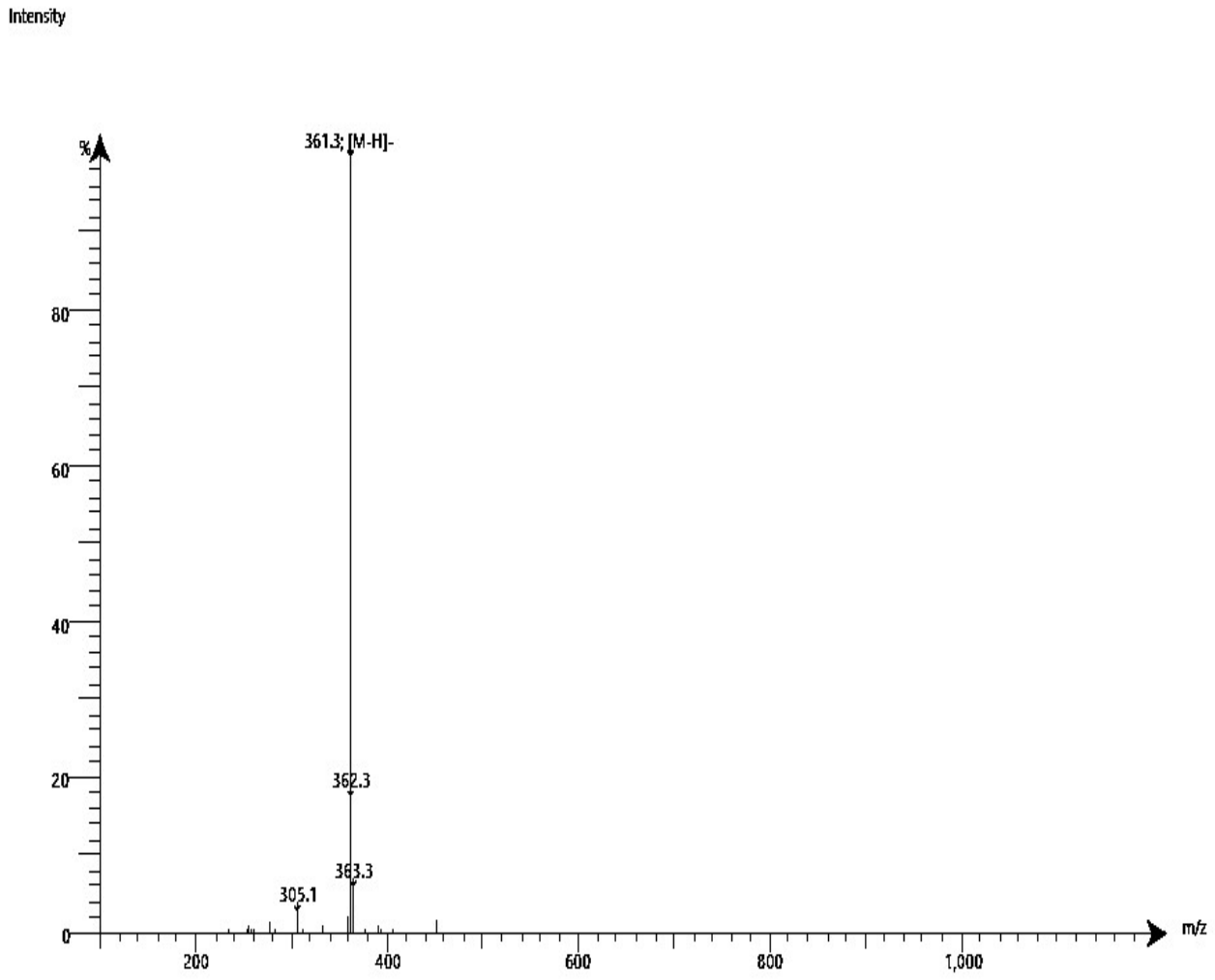

FIGURE S9. ESI-mass spectrum of compound 5a.

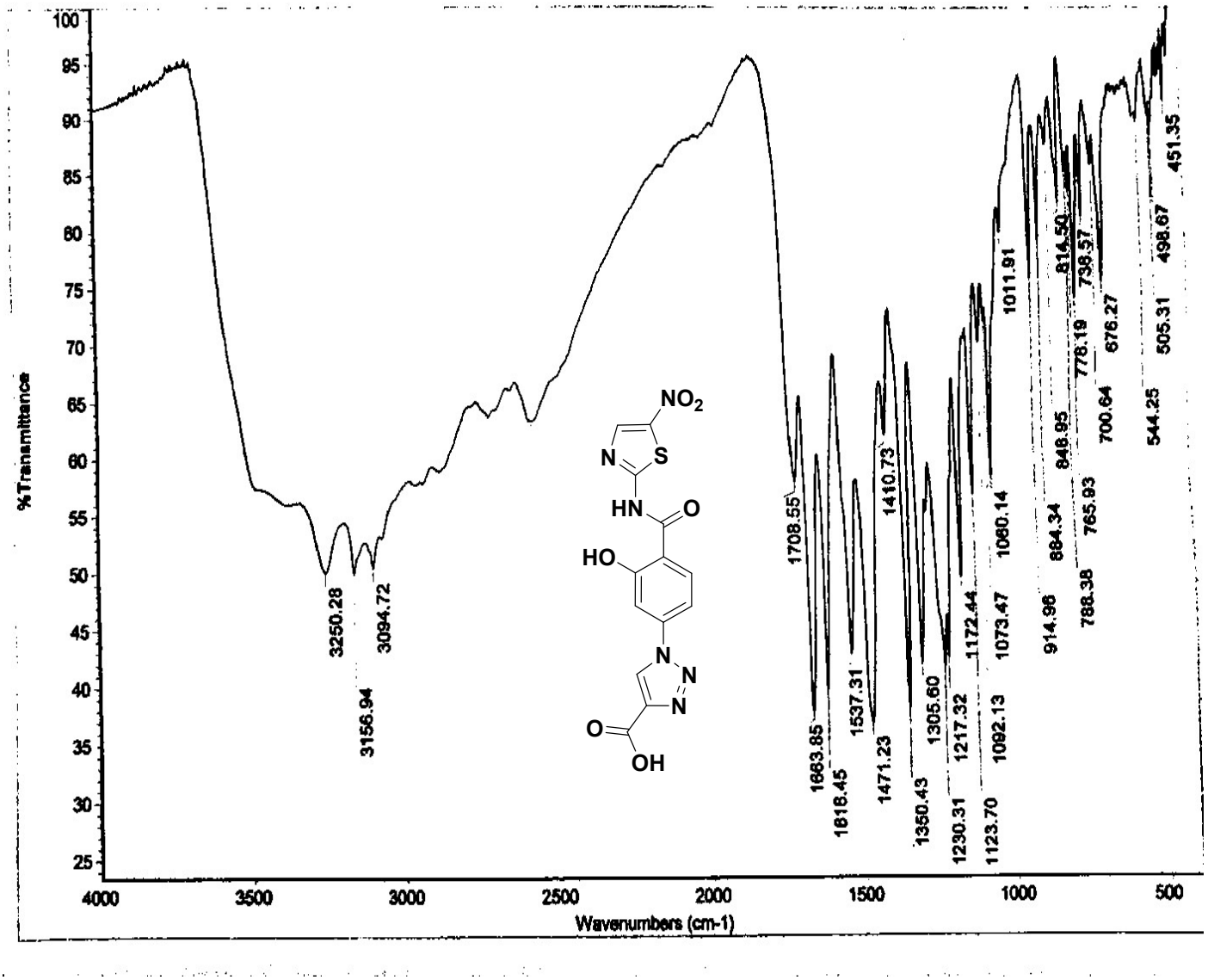

FIGURE S10. FT-IR spectrum of compound 5b.

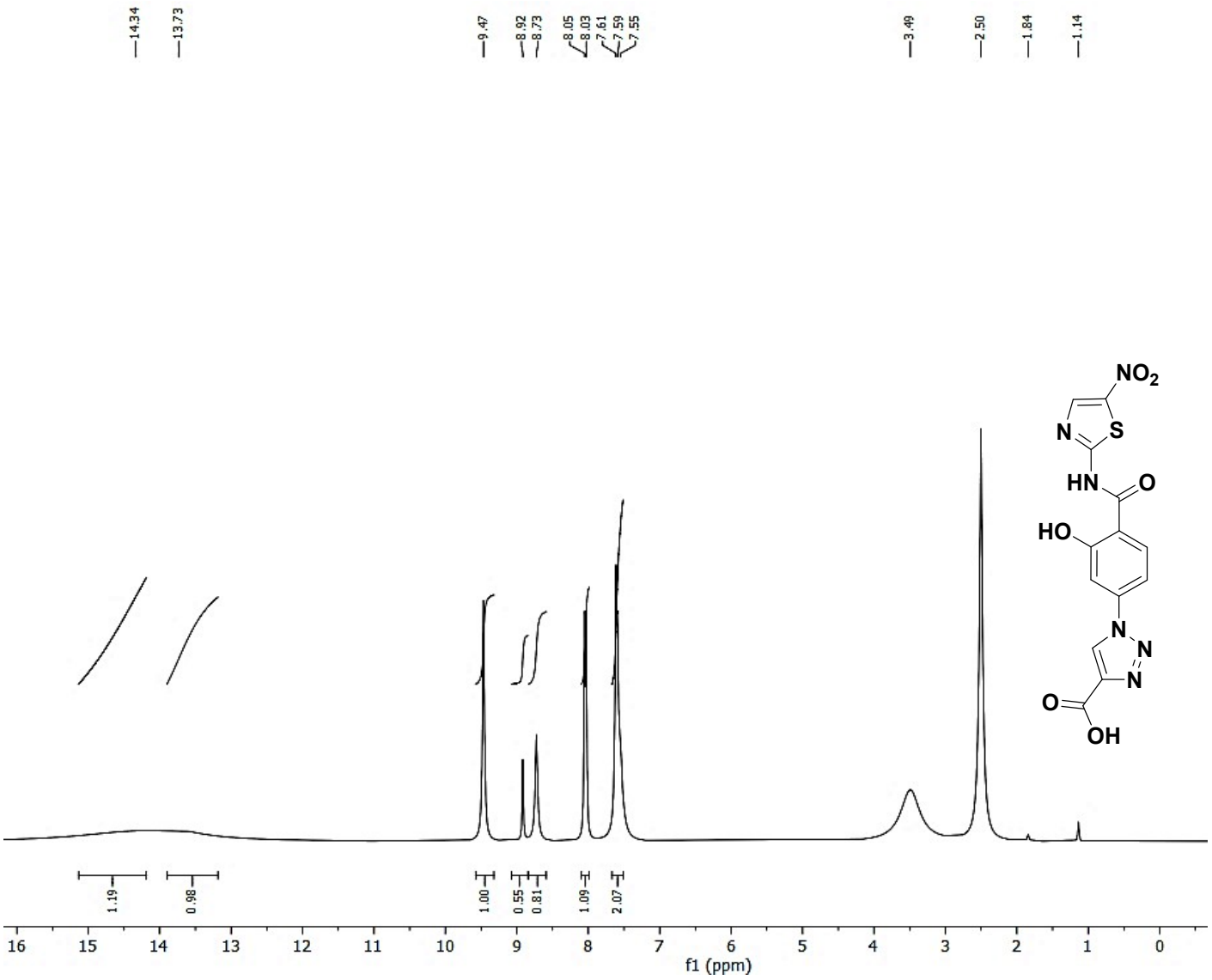

FIGURE S11. ^{1}H-NMR spectrum of compound 5b.

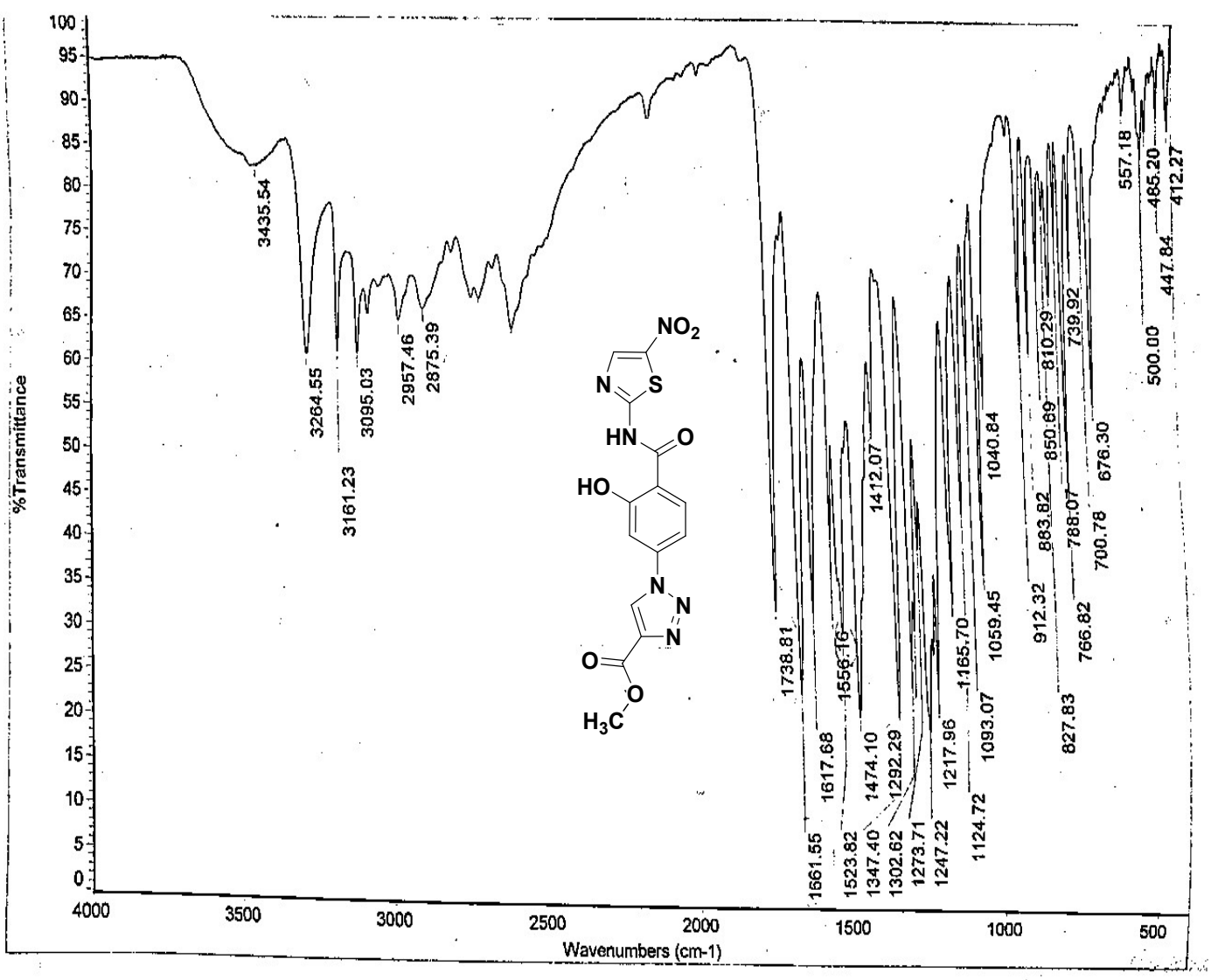

FIGURE S12. FT-IR spectrum of compound 5c.

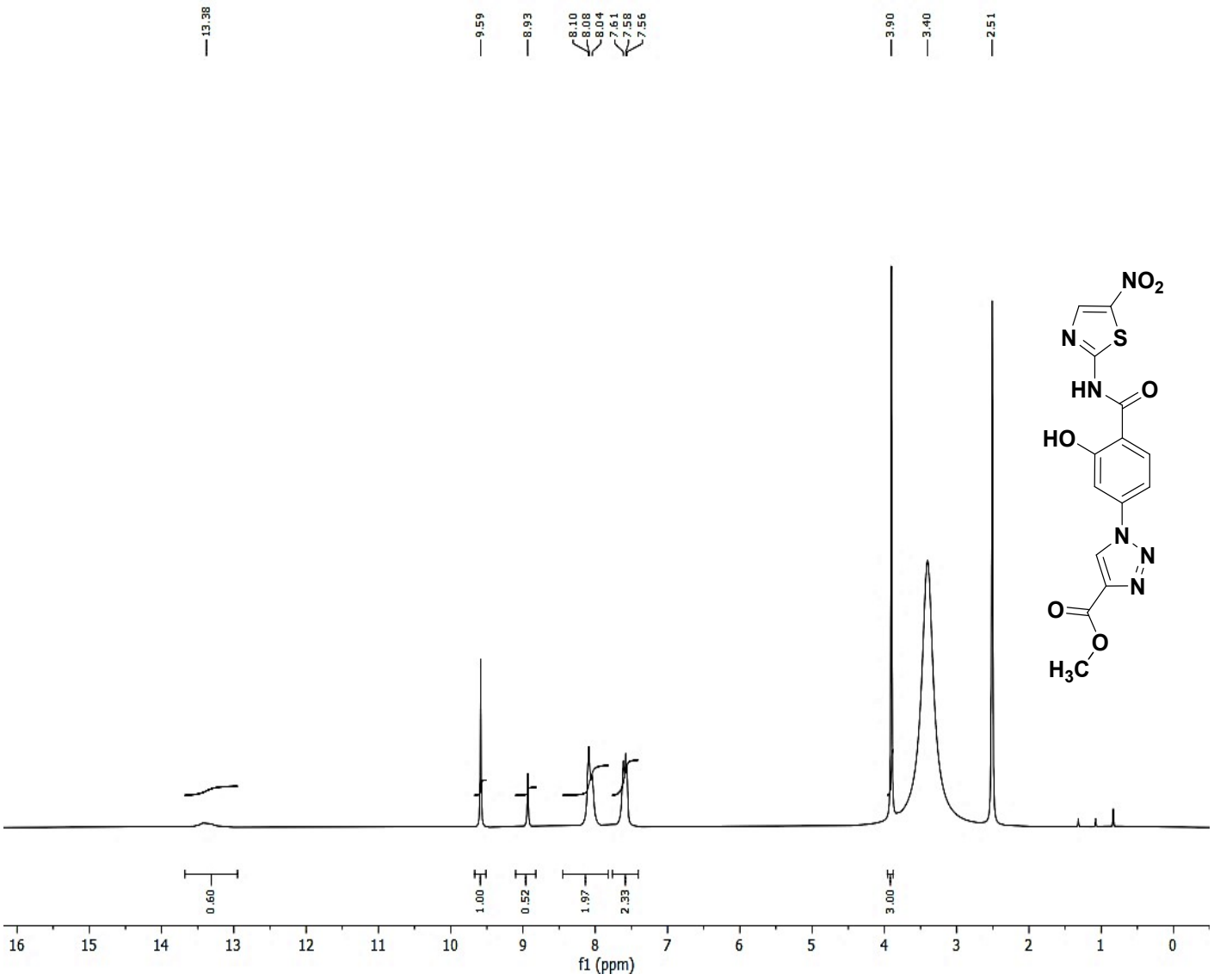

FIGURE S13. ^{1}H-NMR spectrum of compound 5c.

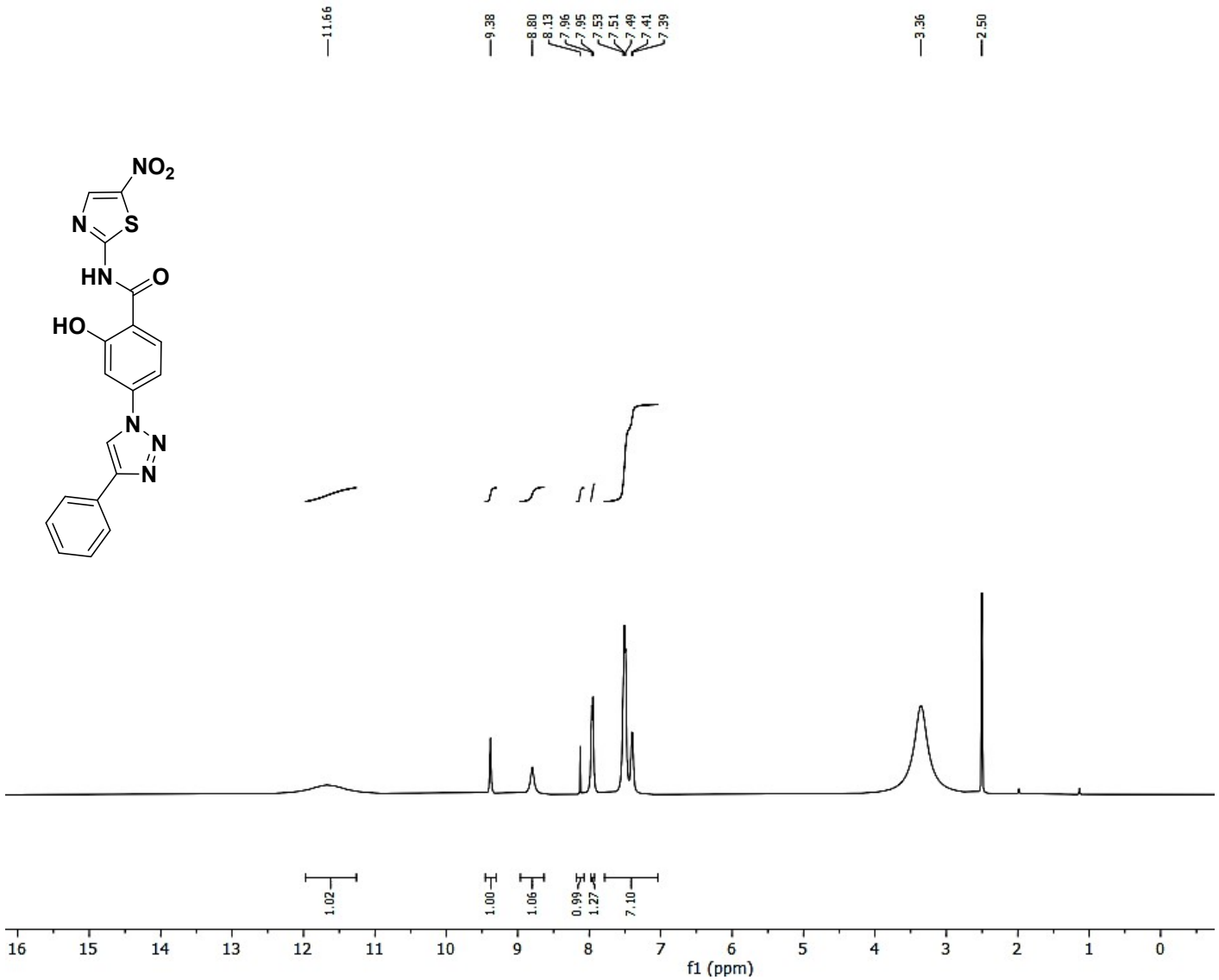

FIGURE S14. ^{1}H- NMR spectrum of compound 5d.

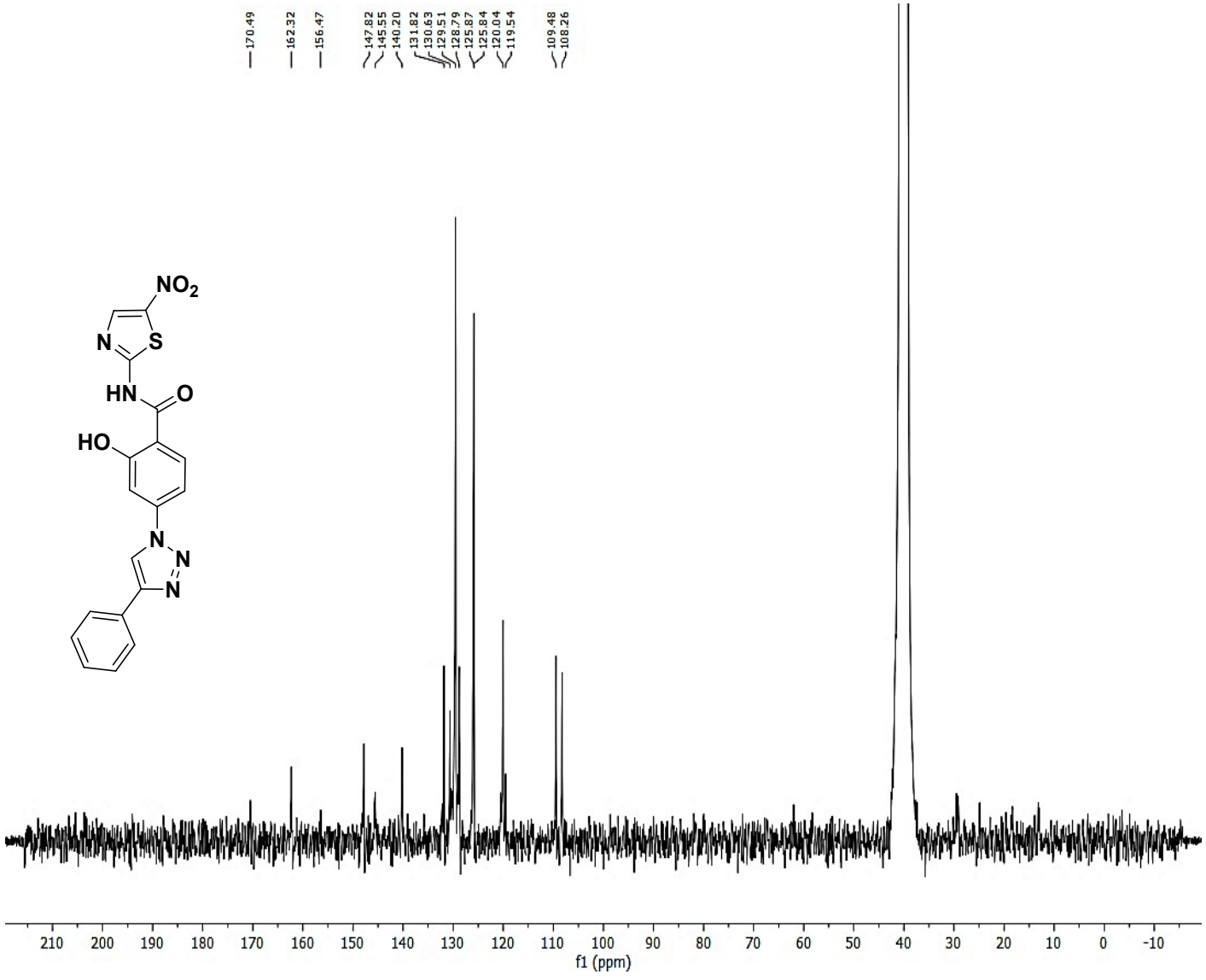

FIGURE S15. ^{13}C- NMR spectrum of compound 5d.

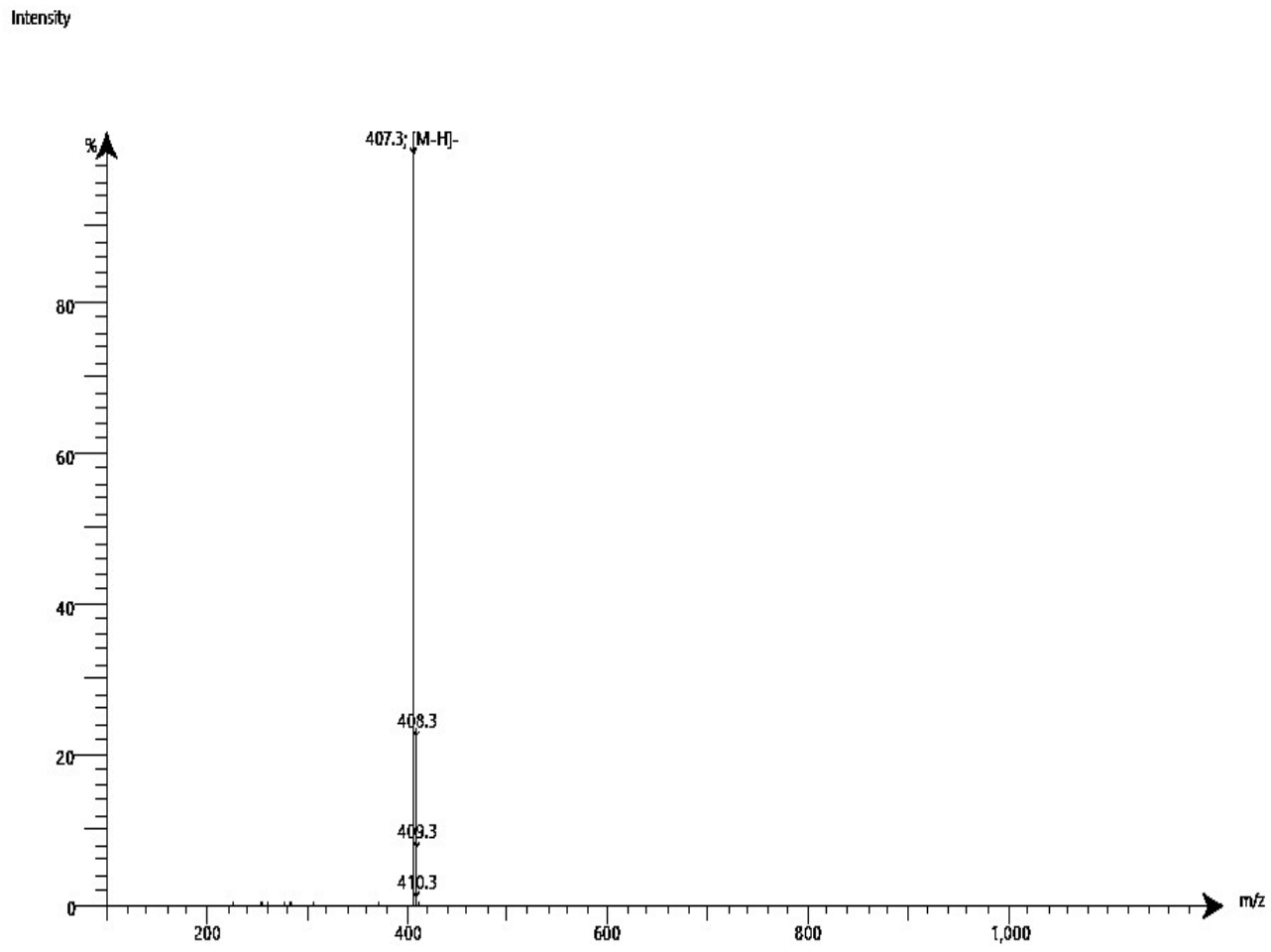

FIGURE S16. ESI-mass spectrum of compound 5d.

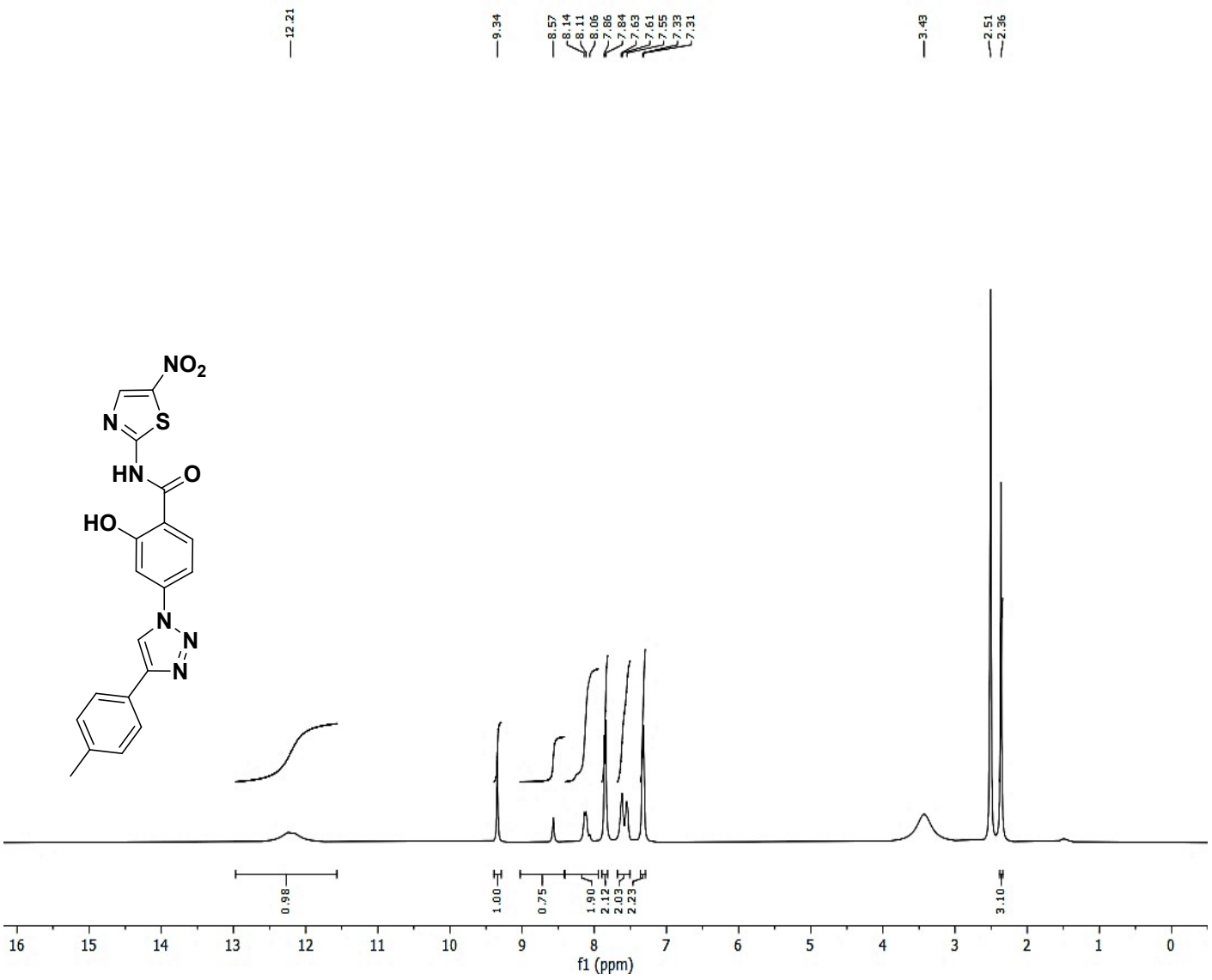

FIGURE S17. ^{1}H-NMR spectrum of compound 5e.

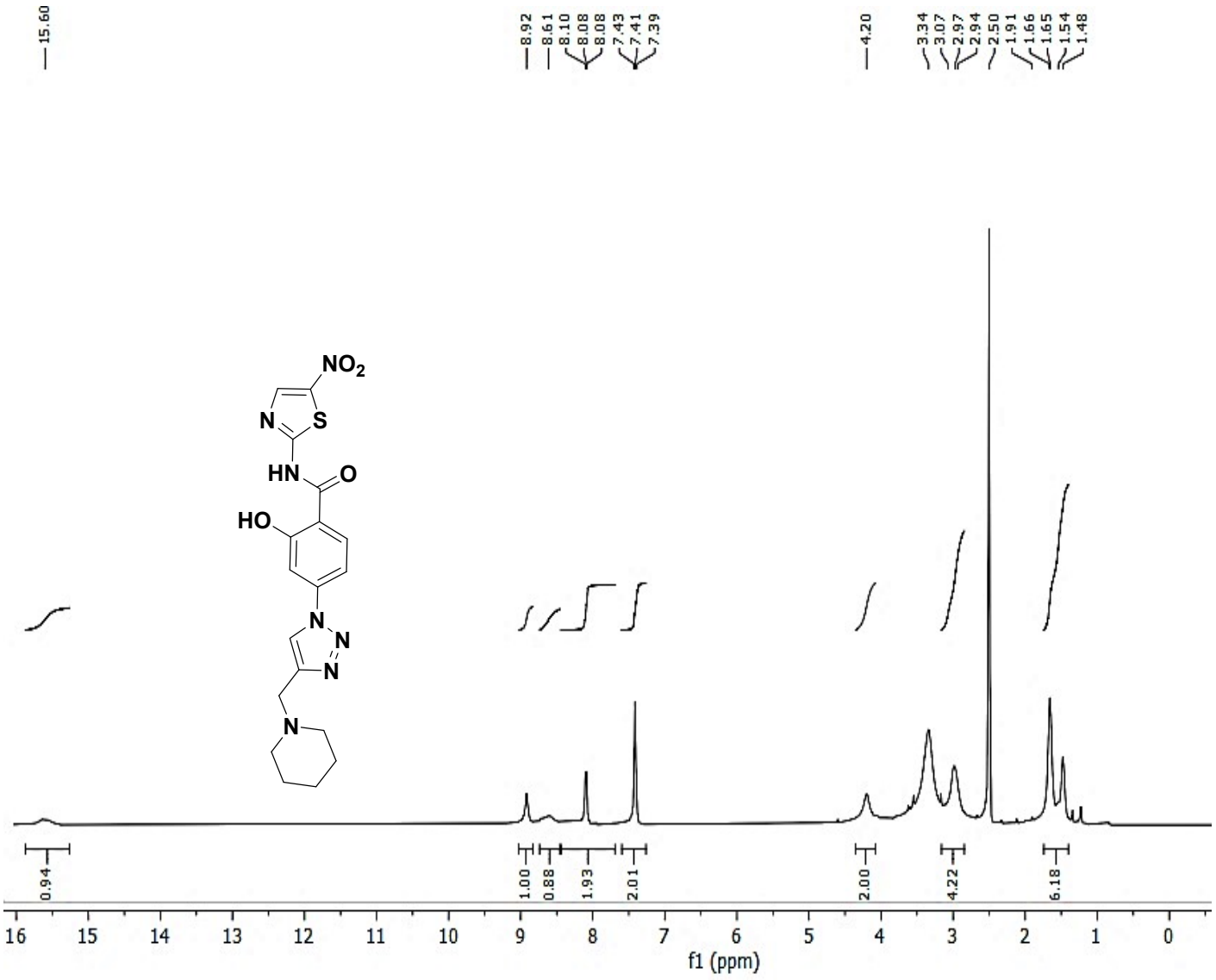

FIGURE S18. ^{1}H-NMR spectrum of compound 5f.

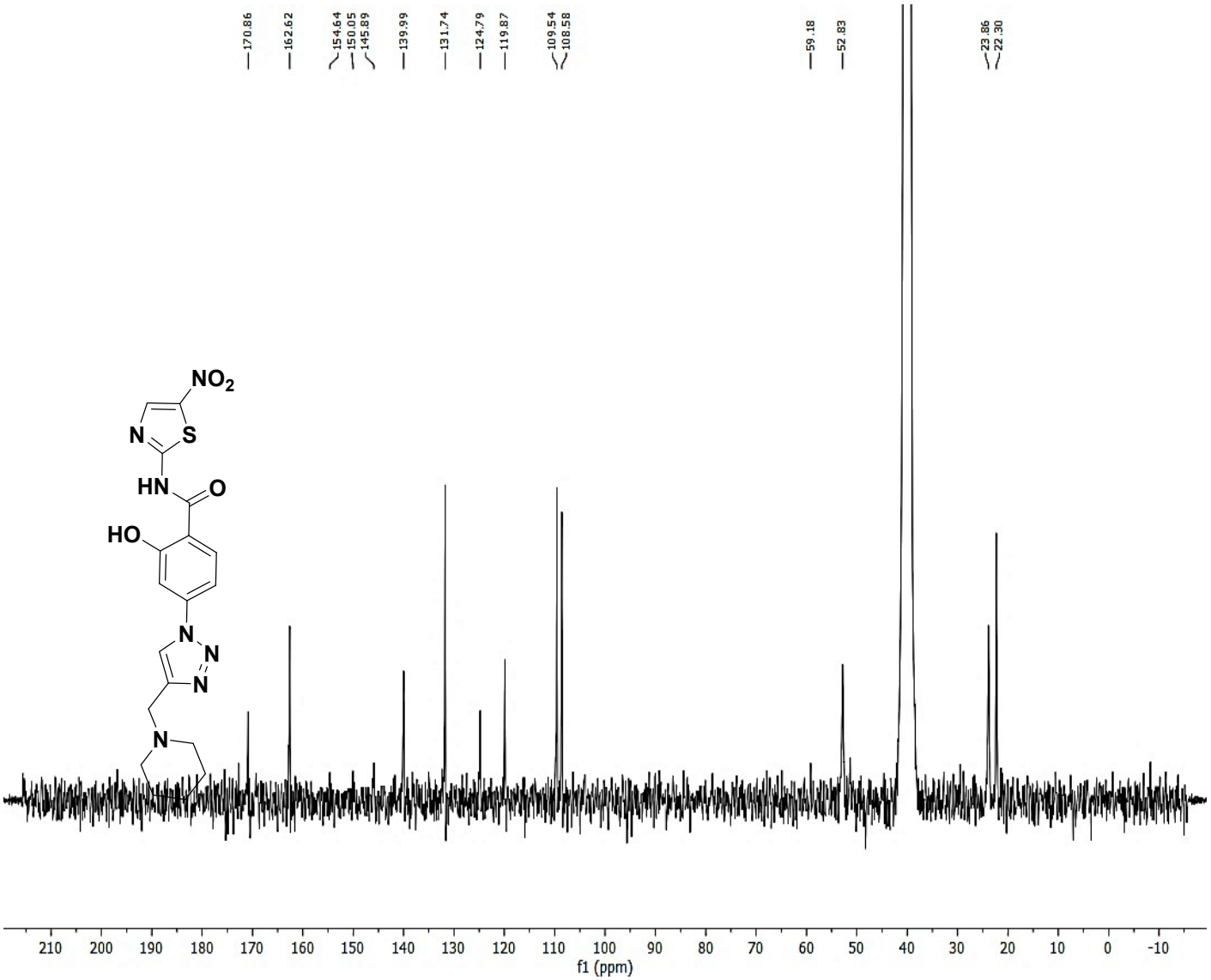
170.86
162.62
154.64
150.05
145.89
139.99
131.74
124.79
119.87
109.54
108.58
59.18
52.83
23.86
22.30
NO2
N
S
HN
O
HO
N
N
N
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

FIGURE S19. ^{13}C-NMR spectrum of compound 5f.

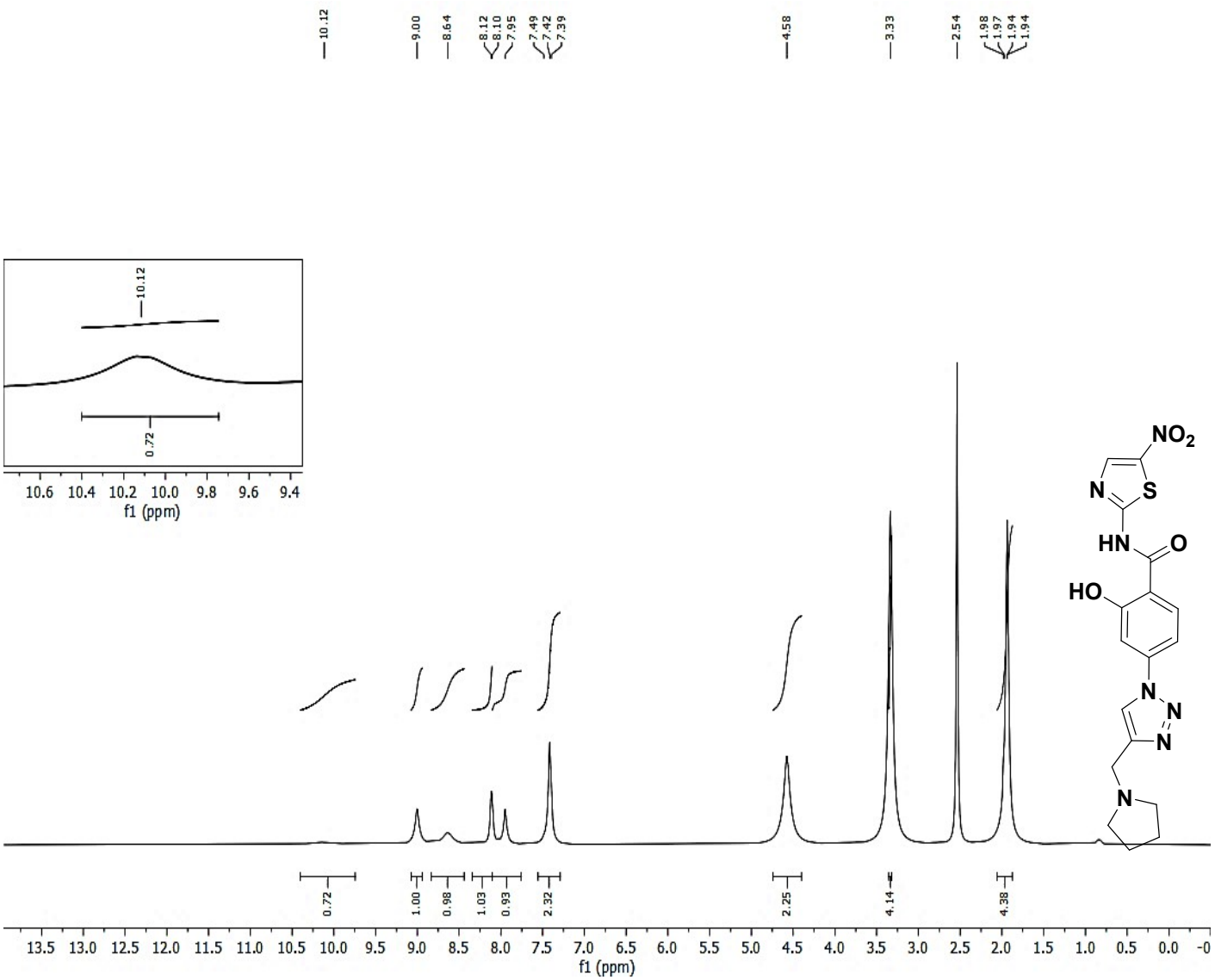

FIGURE S20. ^{1}H-NMR spectrum of compound 5g.

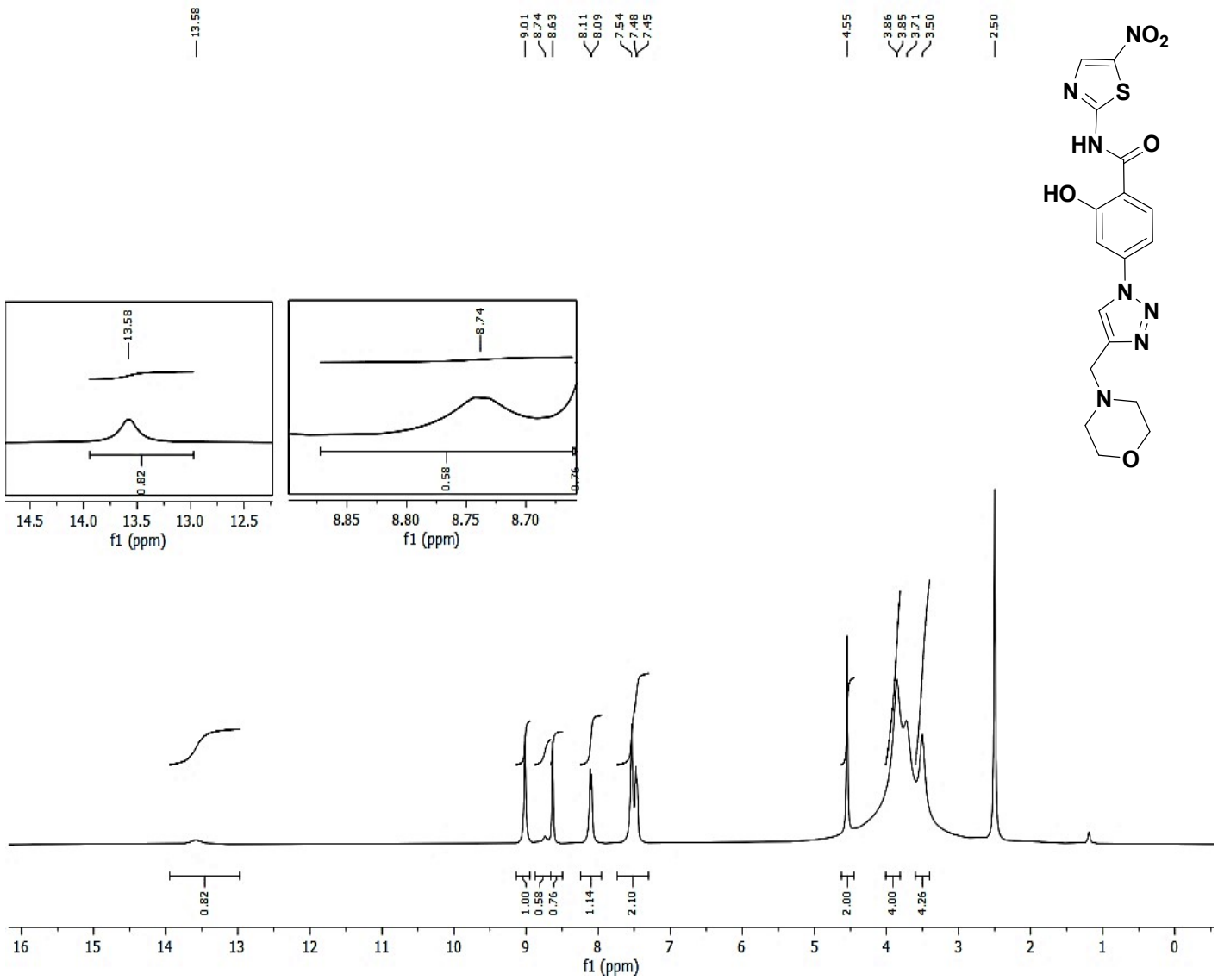

FIGURE S21. ^{1}H-NMR spectrum of compound 5h.

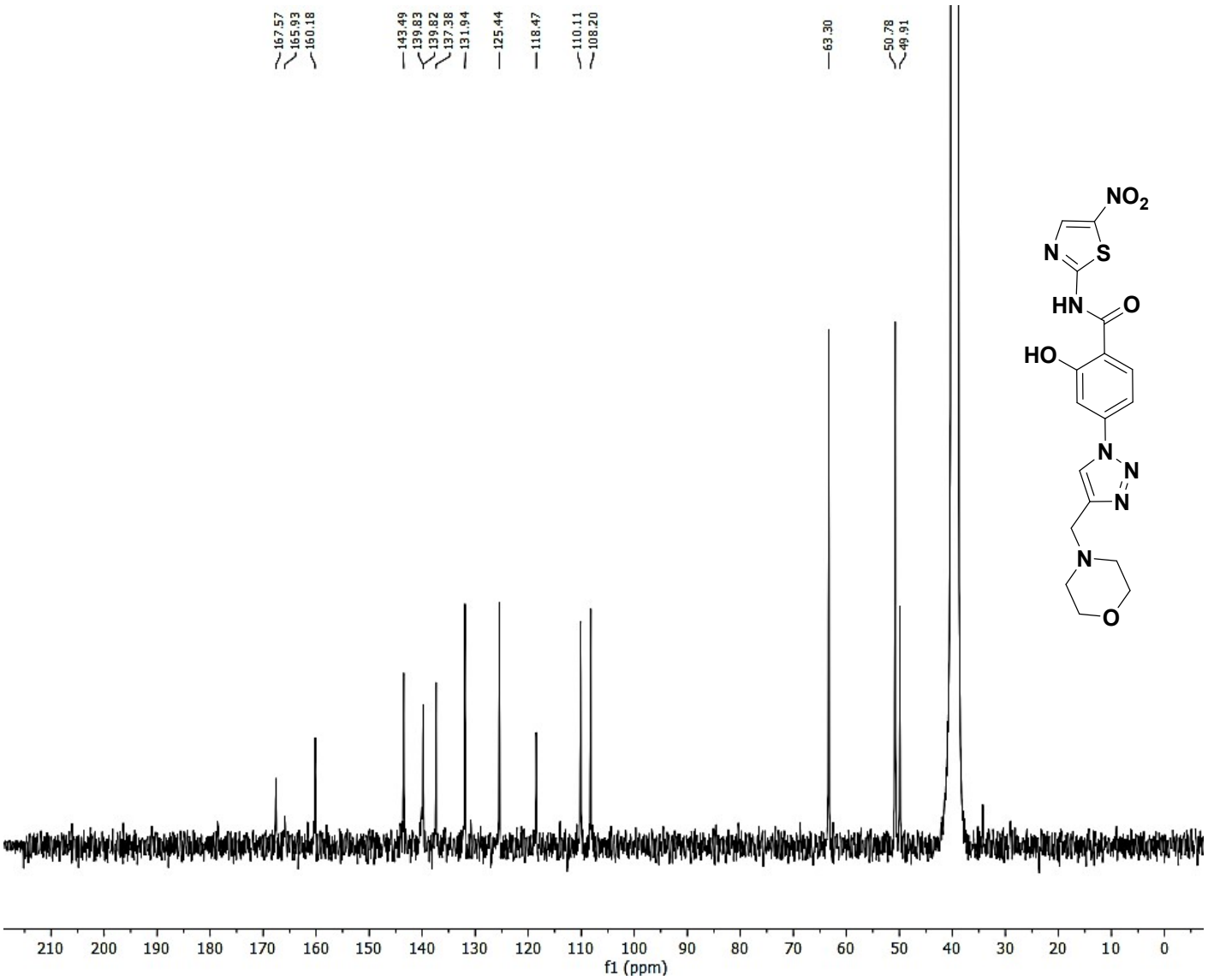

FIGURE S22. ^{13}C-NMR spectrum of compound 5h.

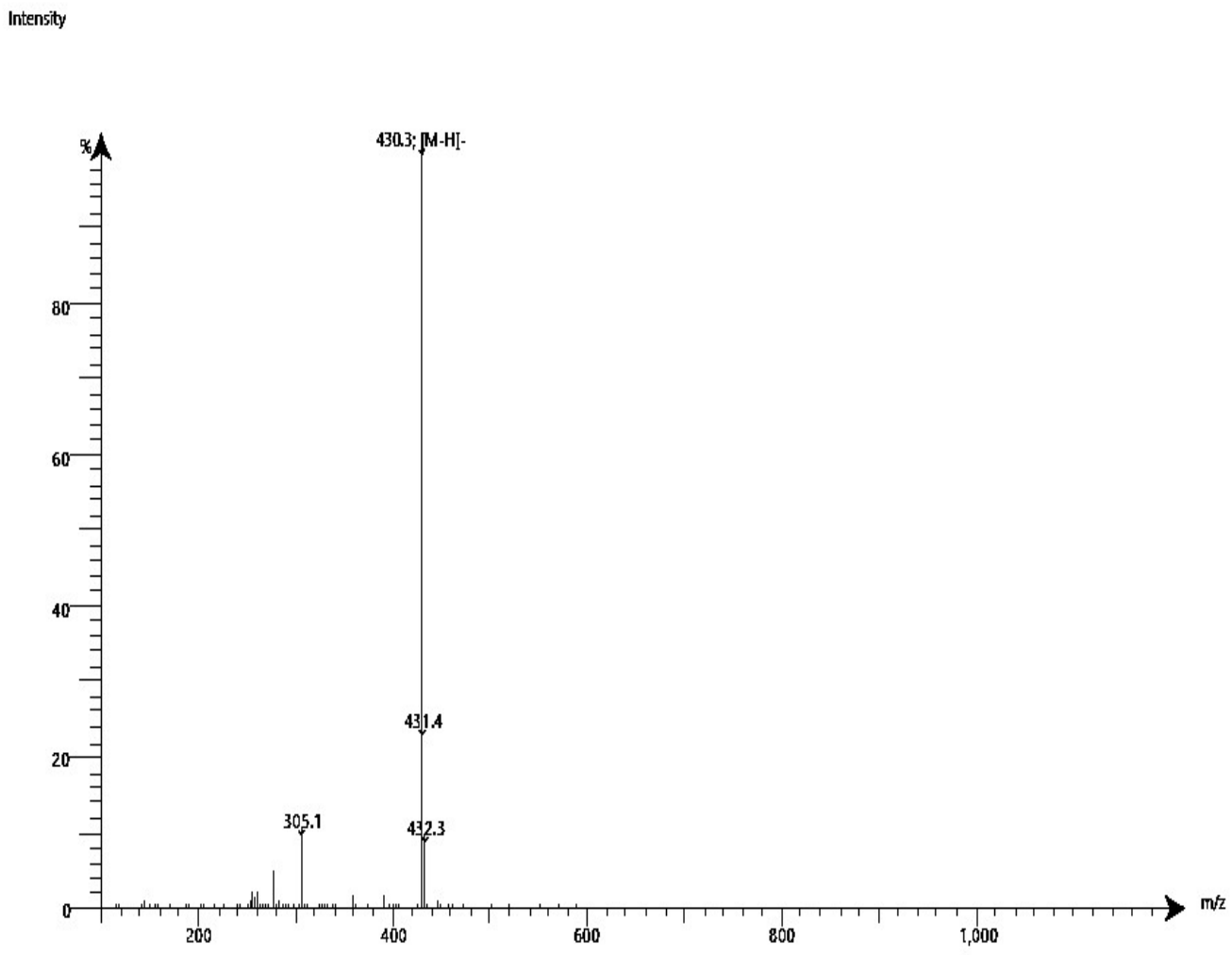

FIGURE S23. ESI-mass spectrum of compound 5h.

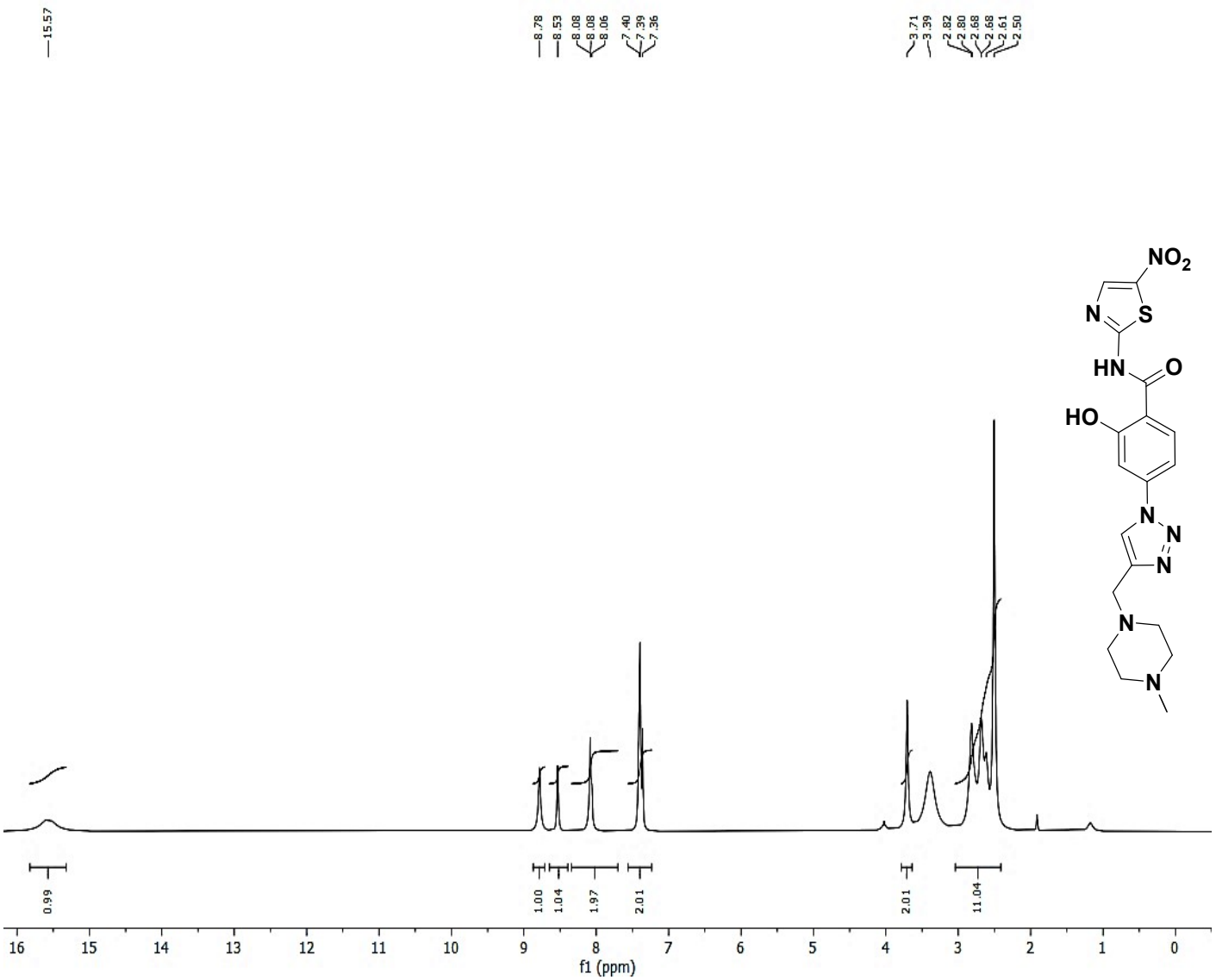

FIGURE S24. ^{1}H-NMR spectrum of compound 5i.

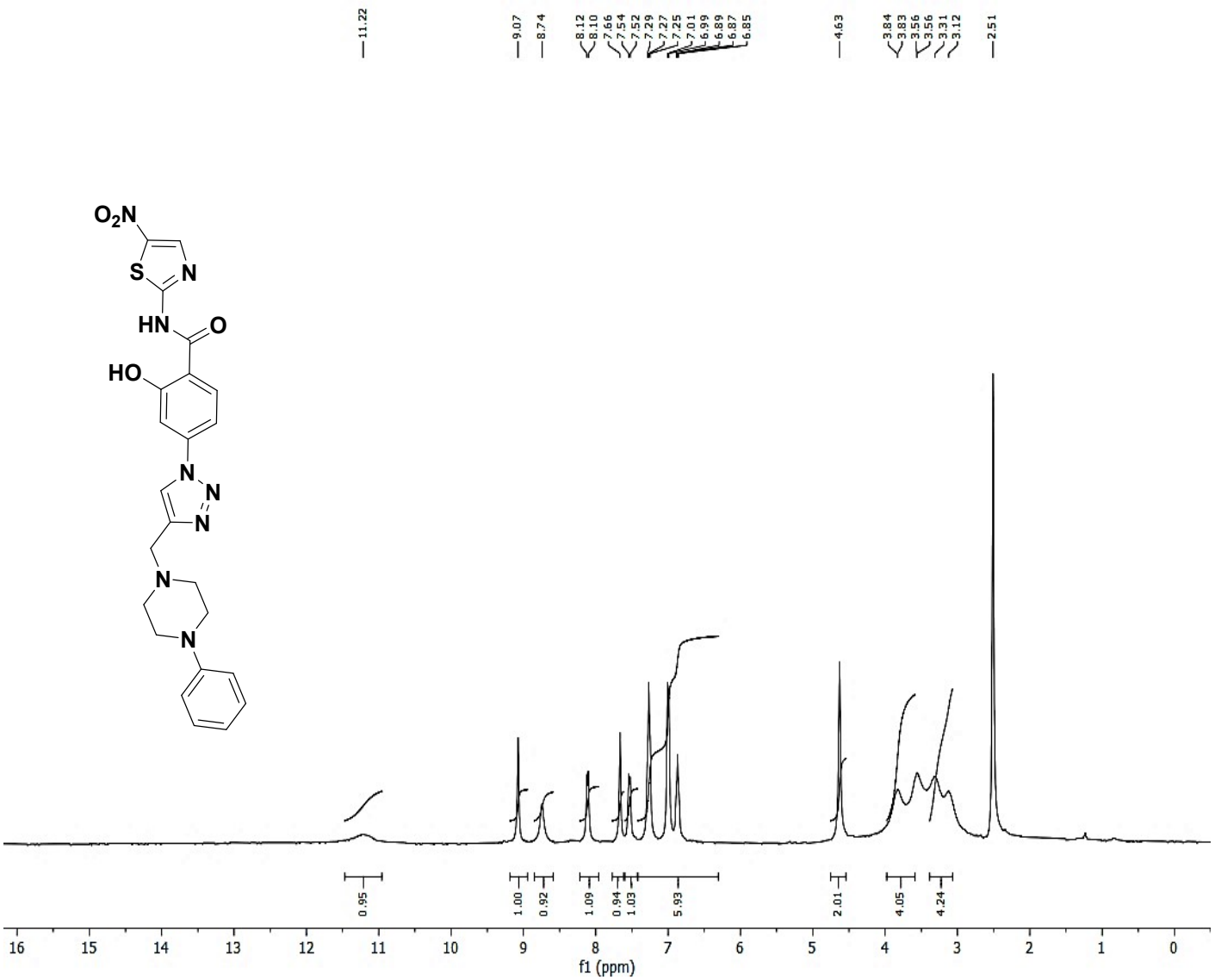

FIGURE S25. ^{1}H-NMR spectrum of compound 5j.

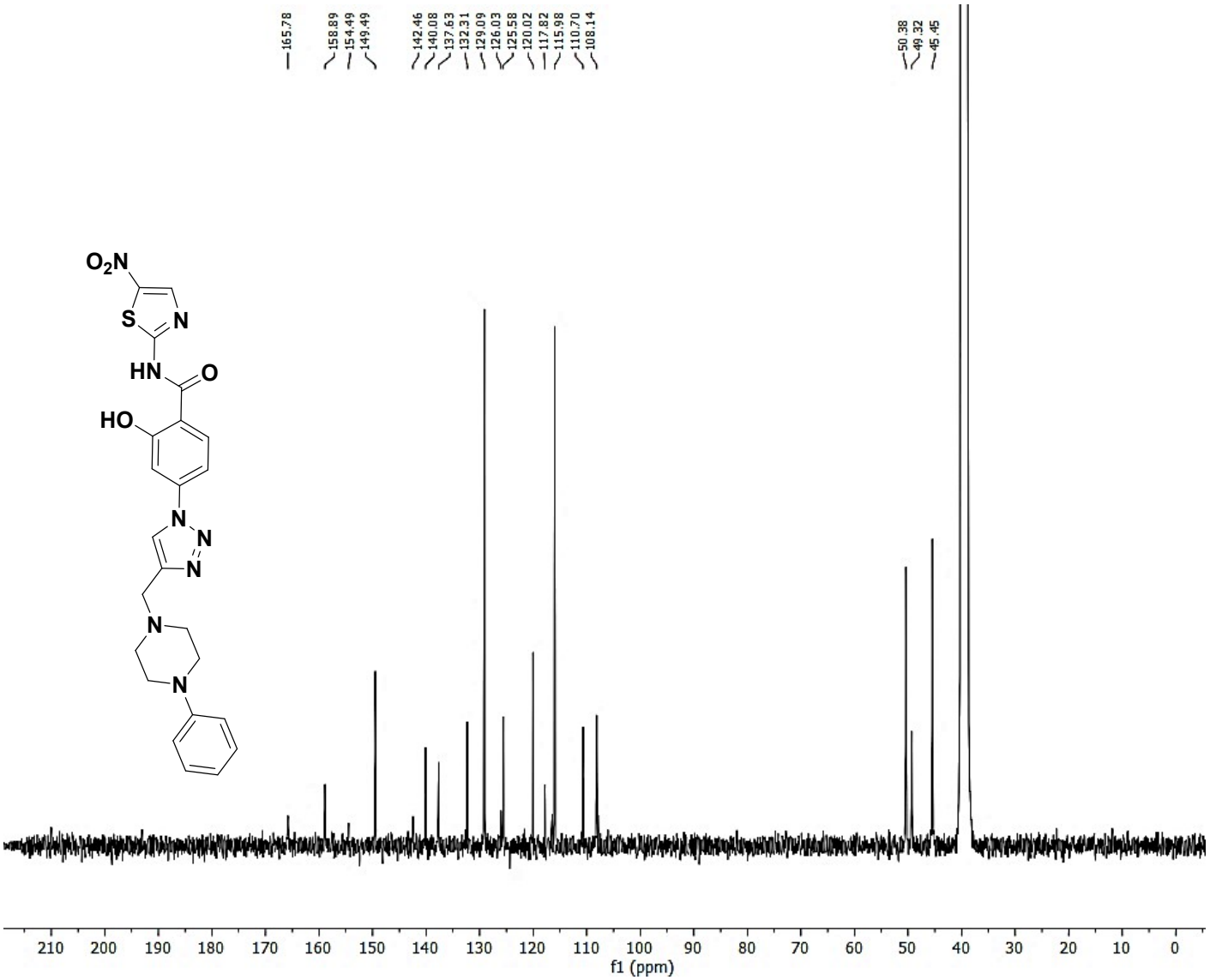

FIGURE S26. ^{13}C-NMR spectrum of compound 5j.

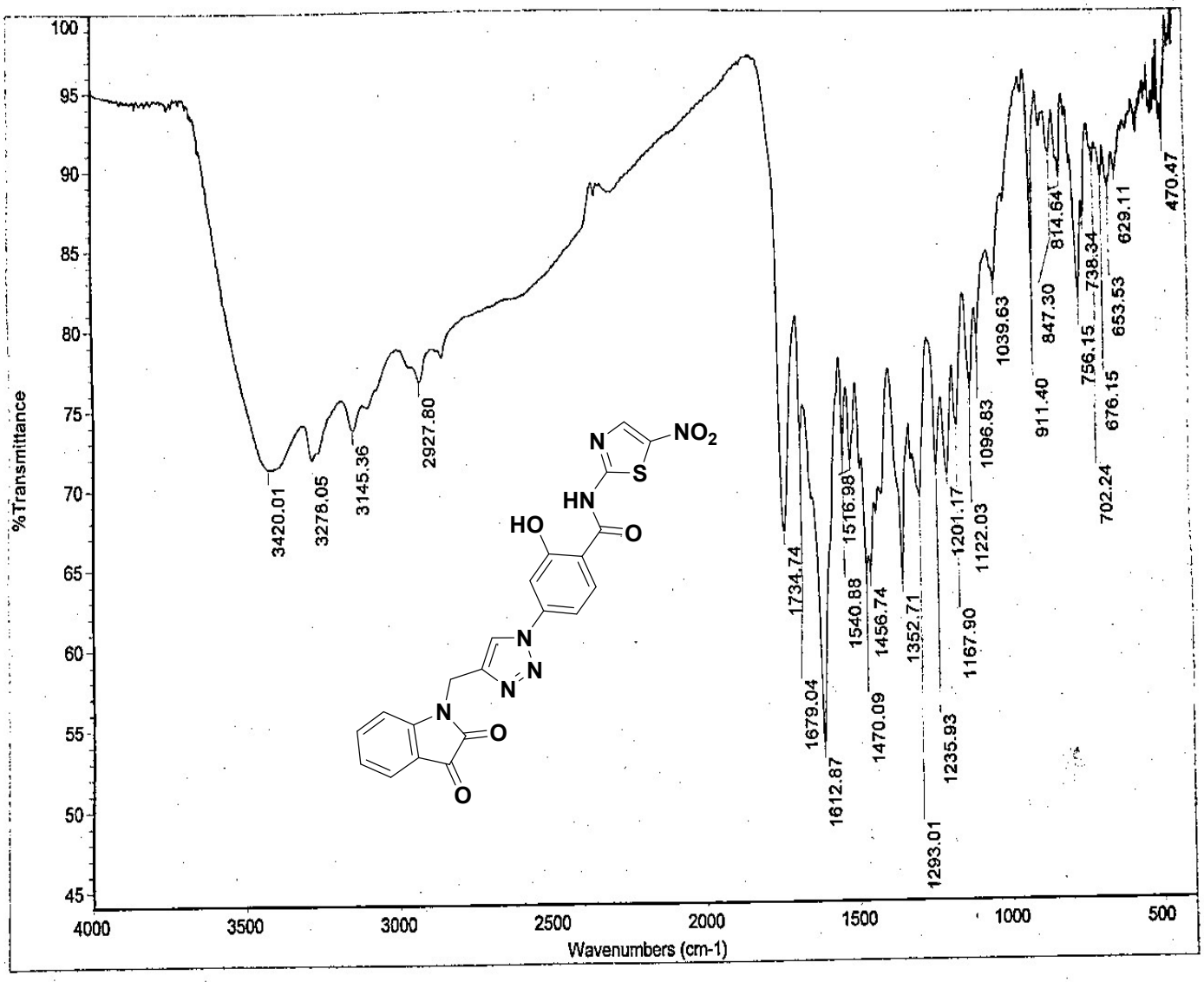

FIGURE S27. FT-IR spectrum of compound 5k.

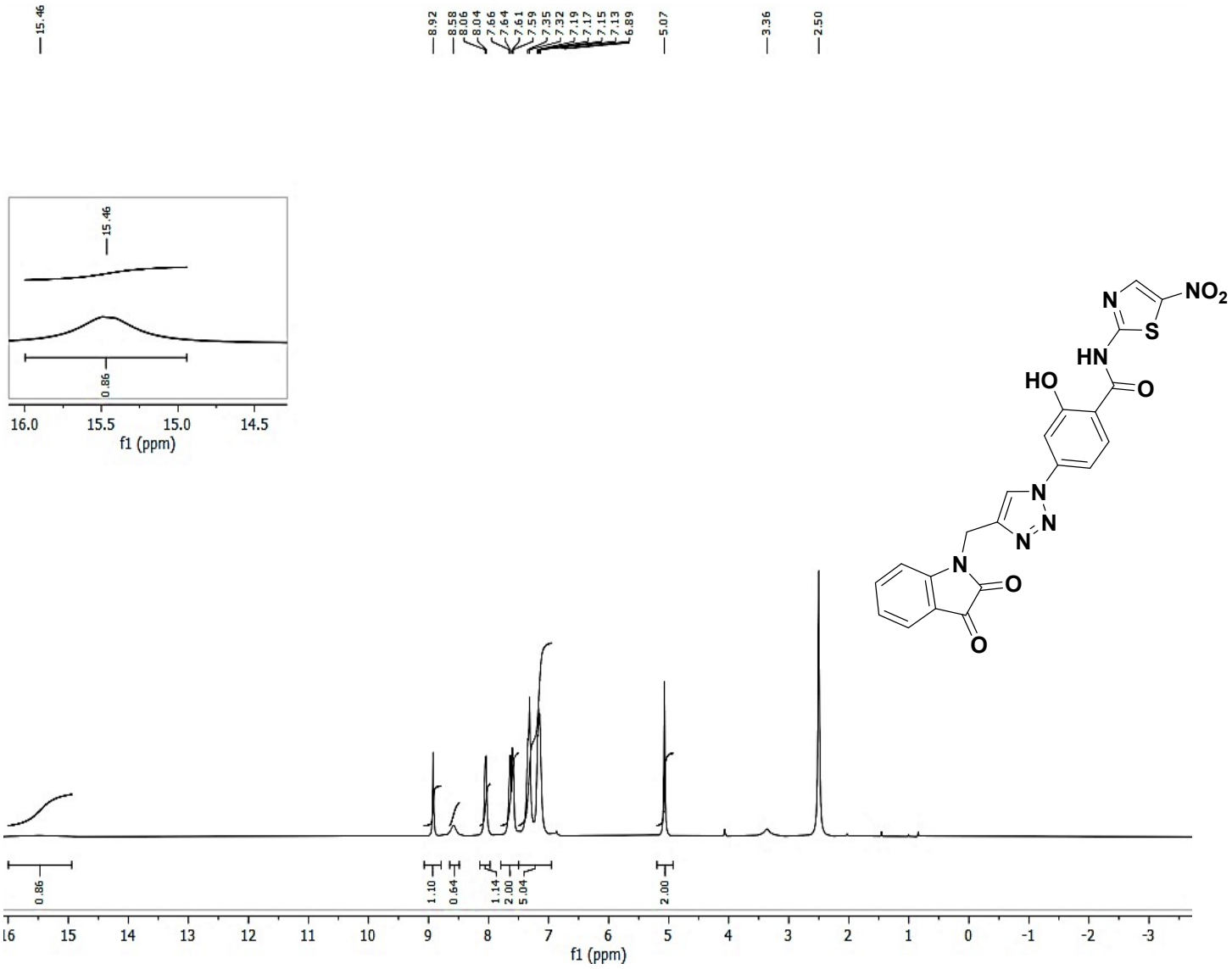

FIGURE S28. [1]H-NMR spectrum of compound 5k.

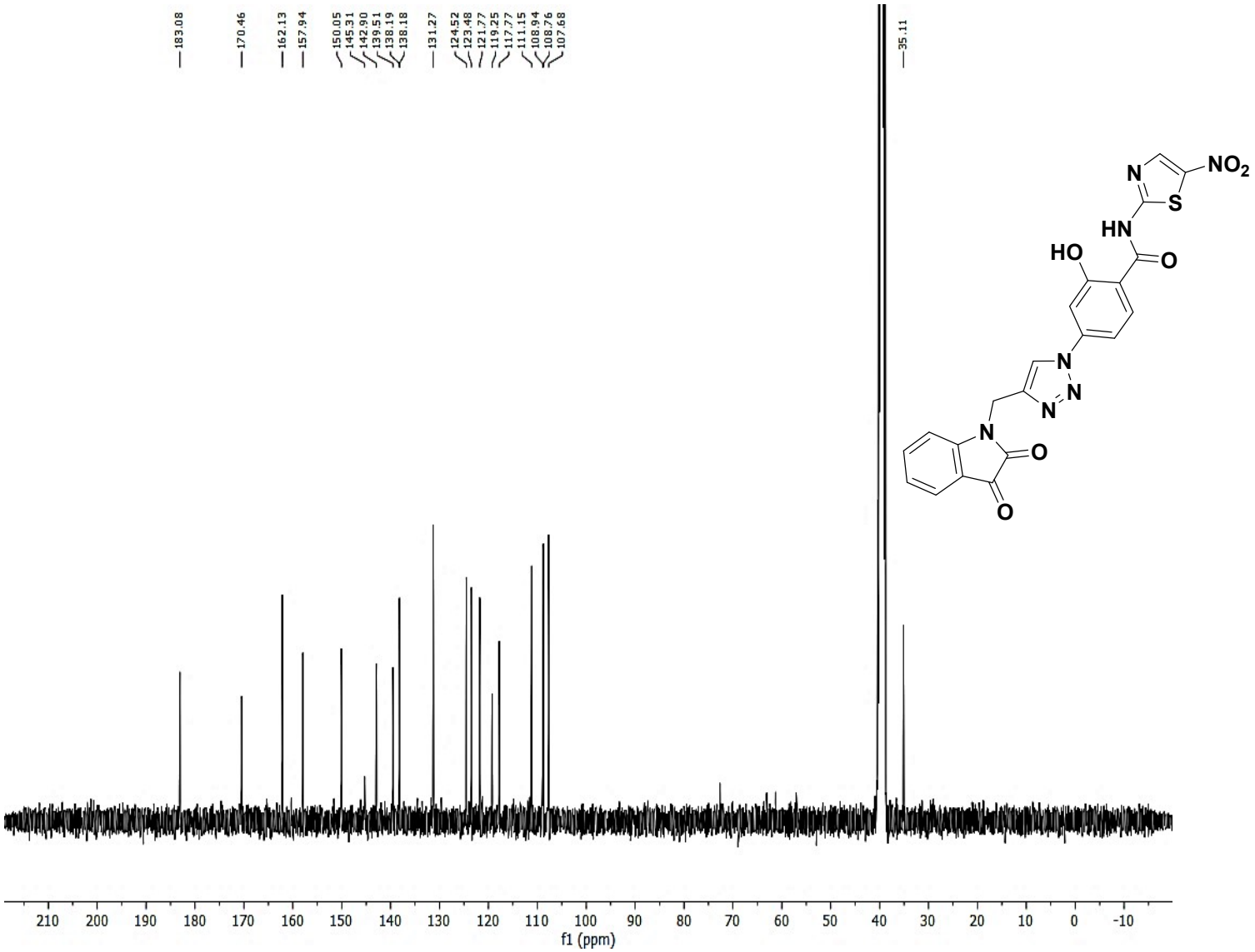

FIGURE S29. ^{13}C-NMR spectrum of compound 5k.

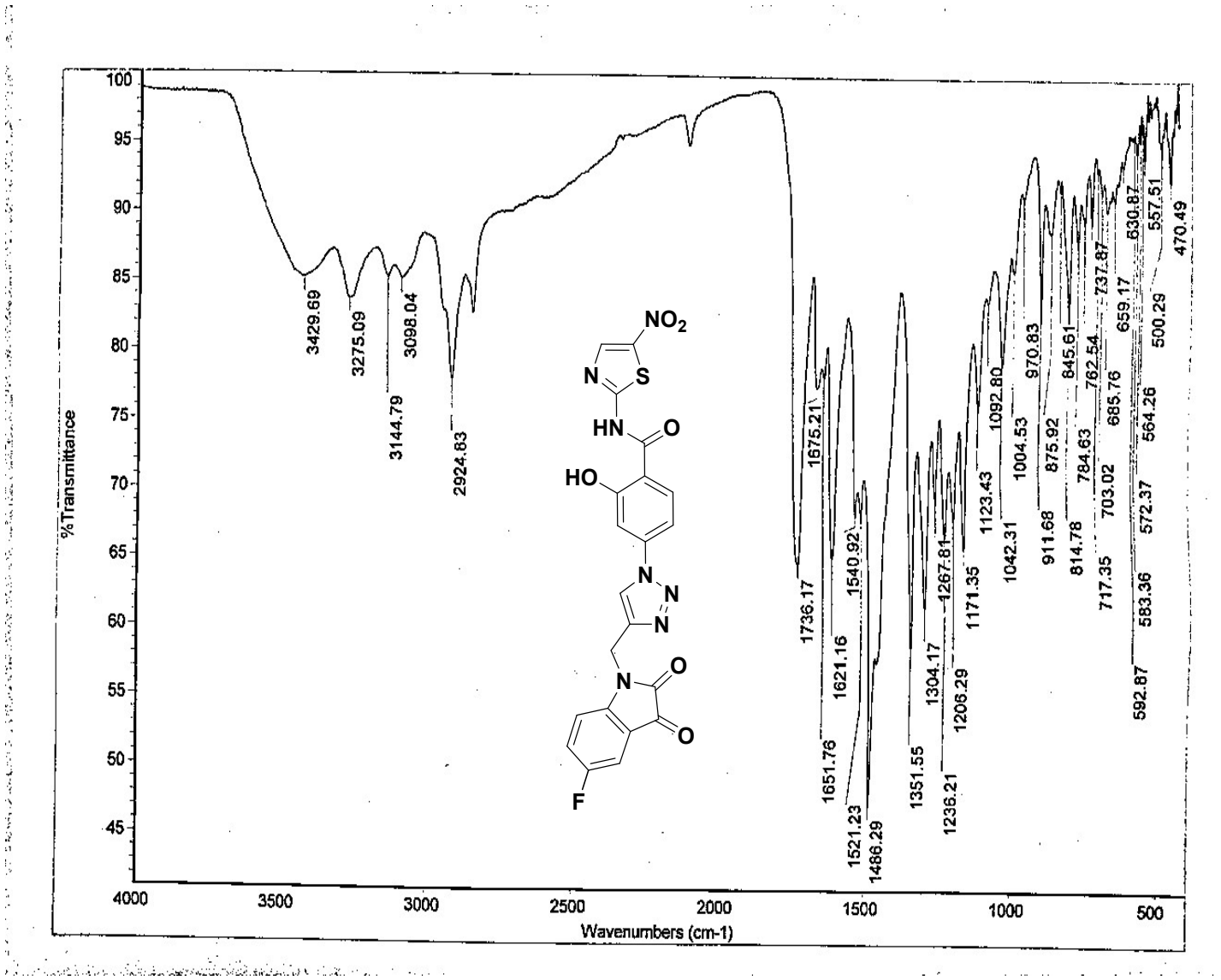

FIGURE S30. FT-IR spectrum of compound 5l.

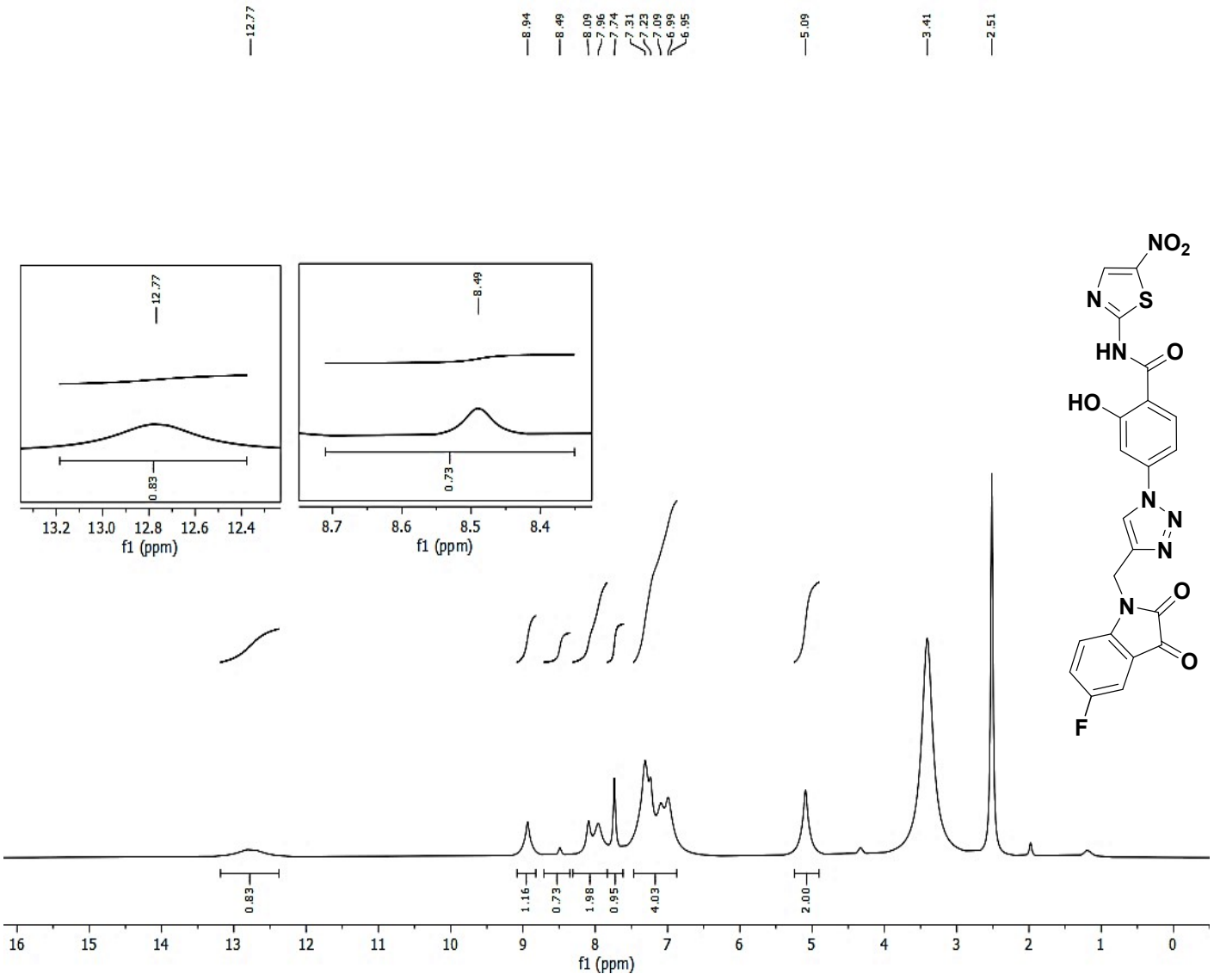

FIGURE S31. ^{1}H-NMR spectrum of compound 5l.

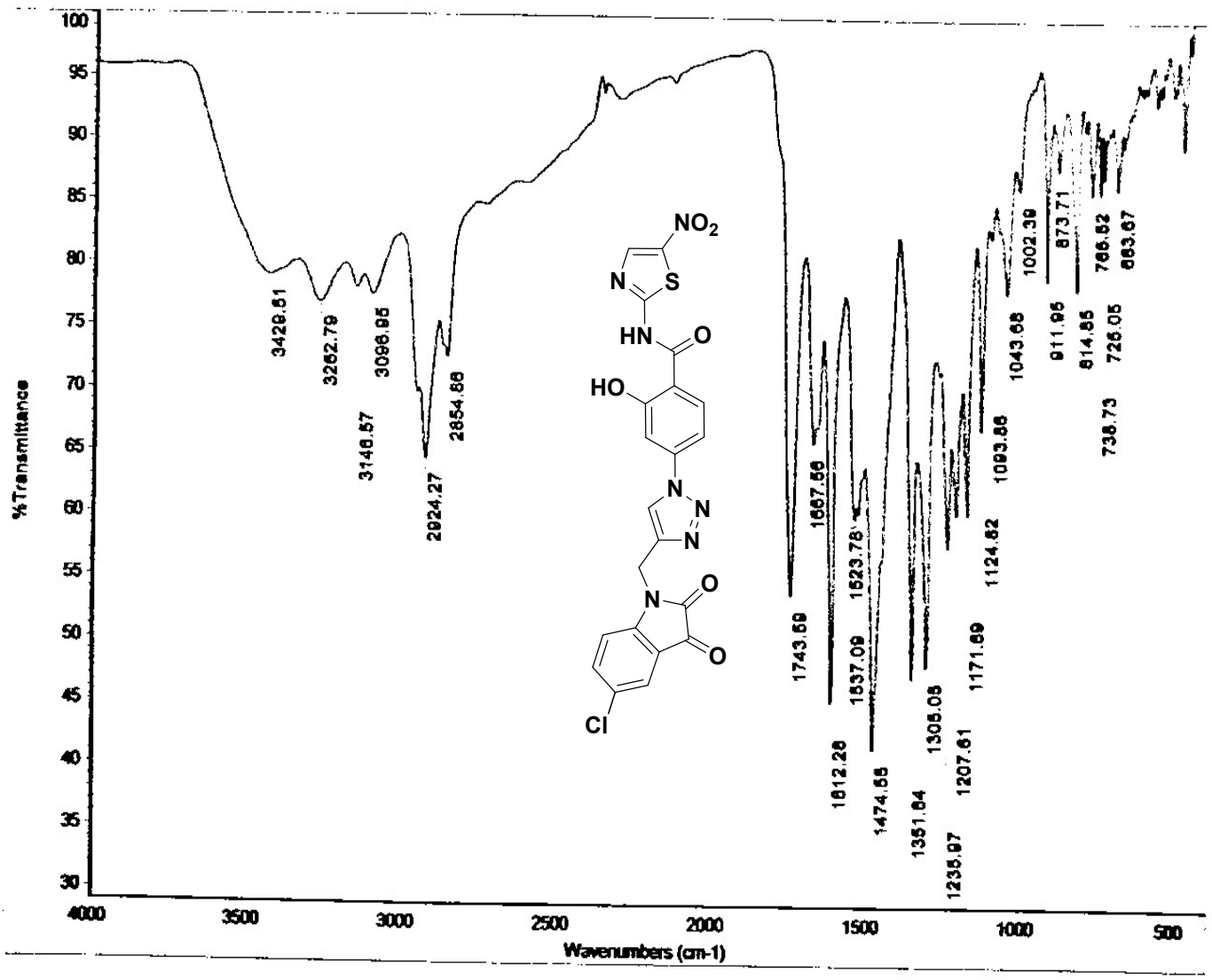

FIGURE S32. FT-IR spectrum of compound 5m.

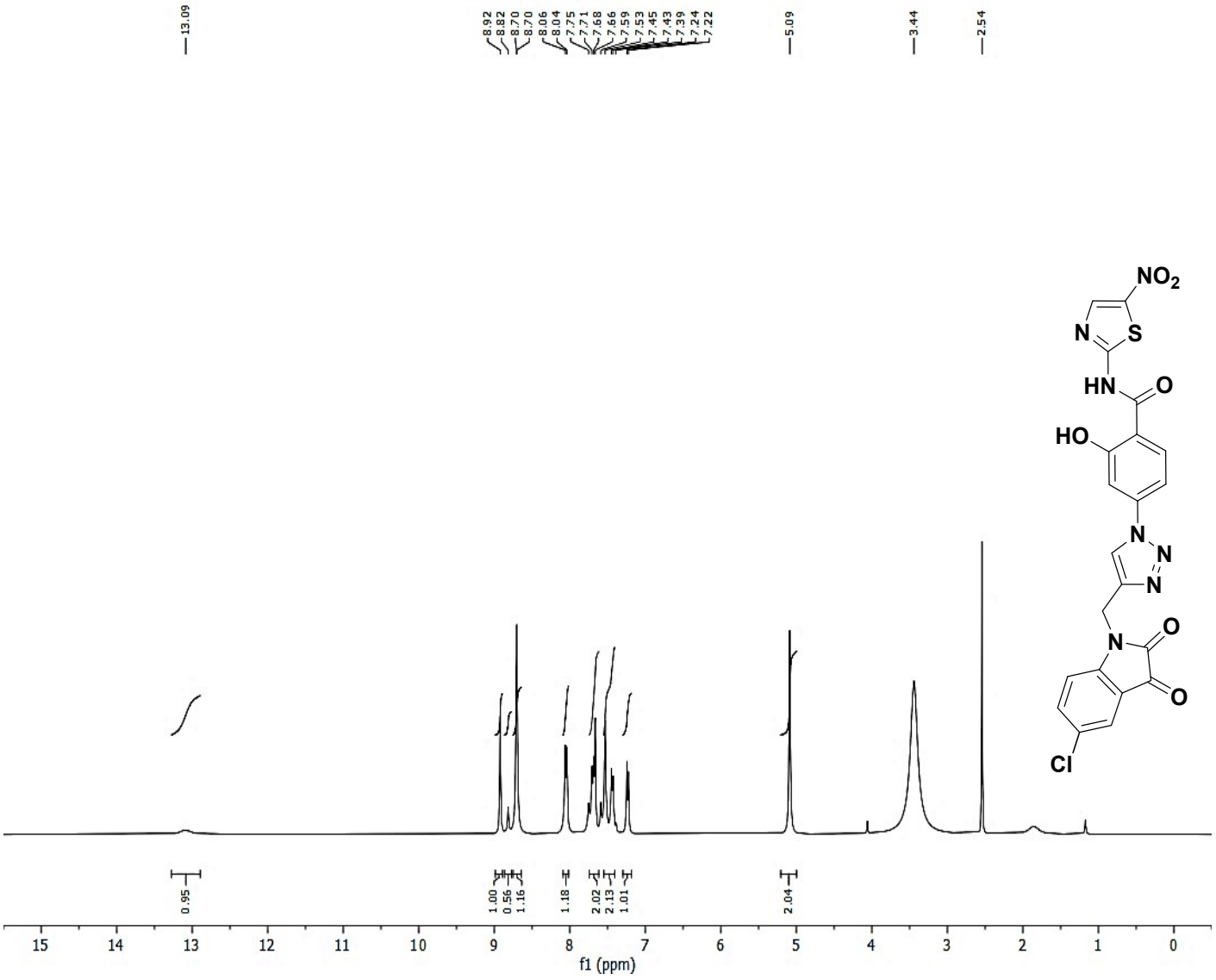

FIGURE S33. ^{1}H-NMR spectrum of compound 5m.

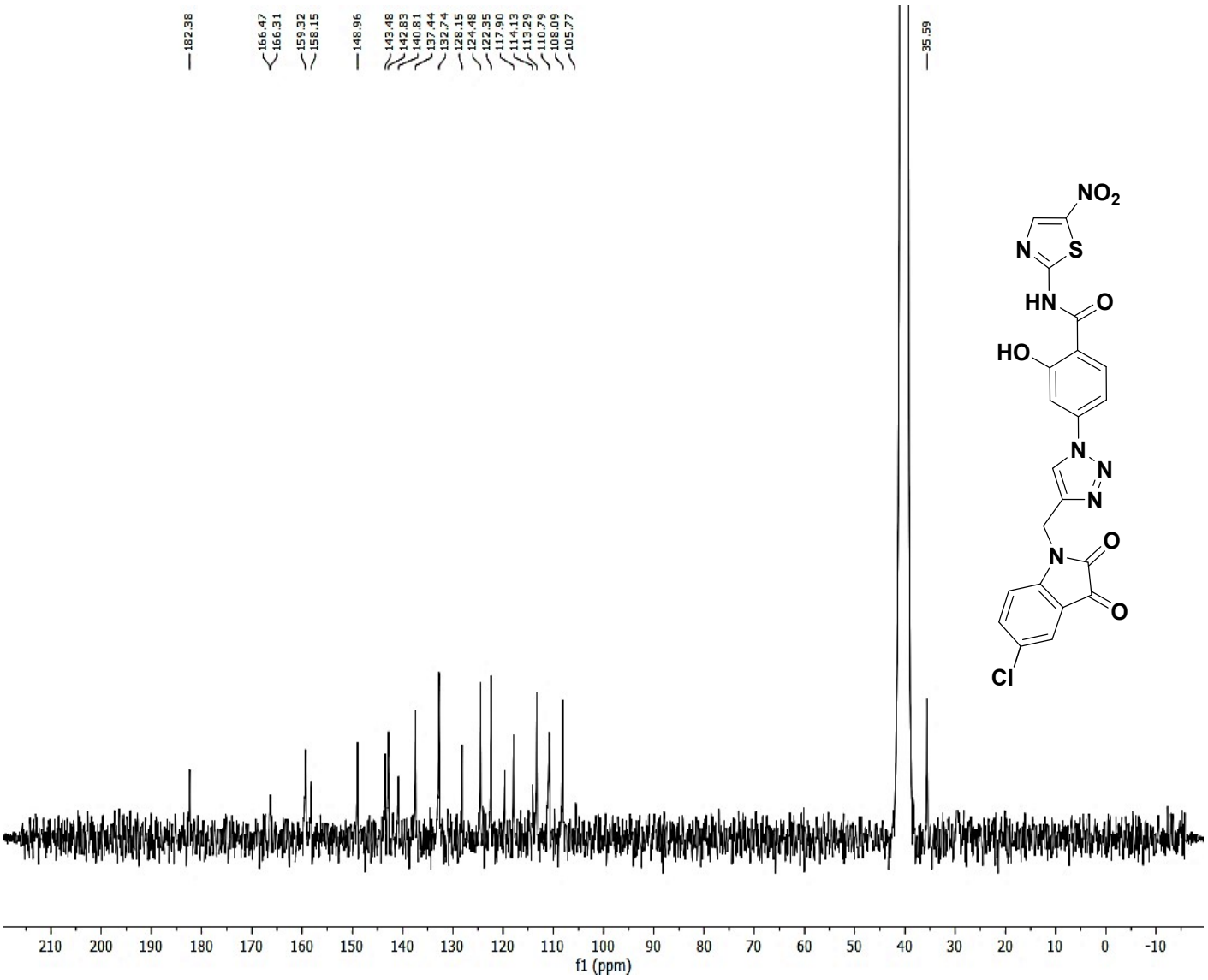

FIGURE S34. ^{13}C-NMR spectrum of compound 5m.

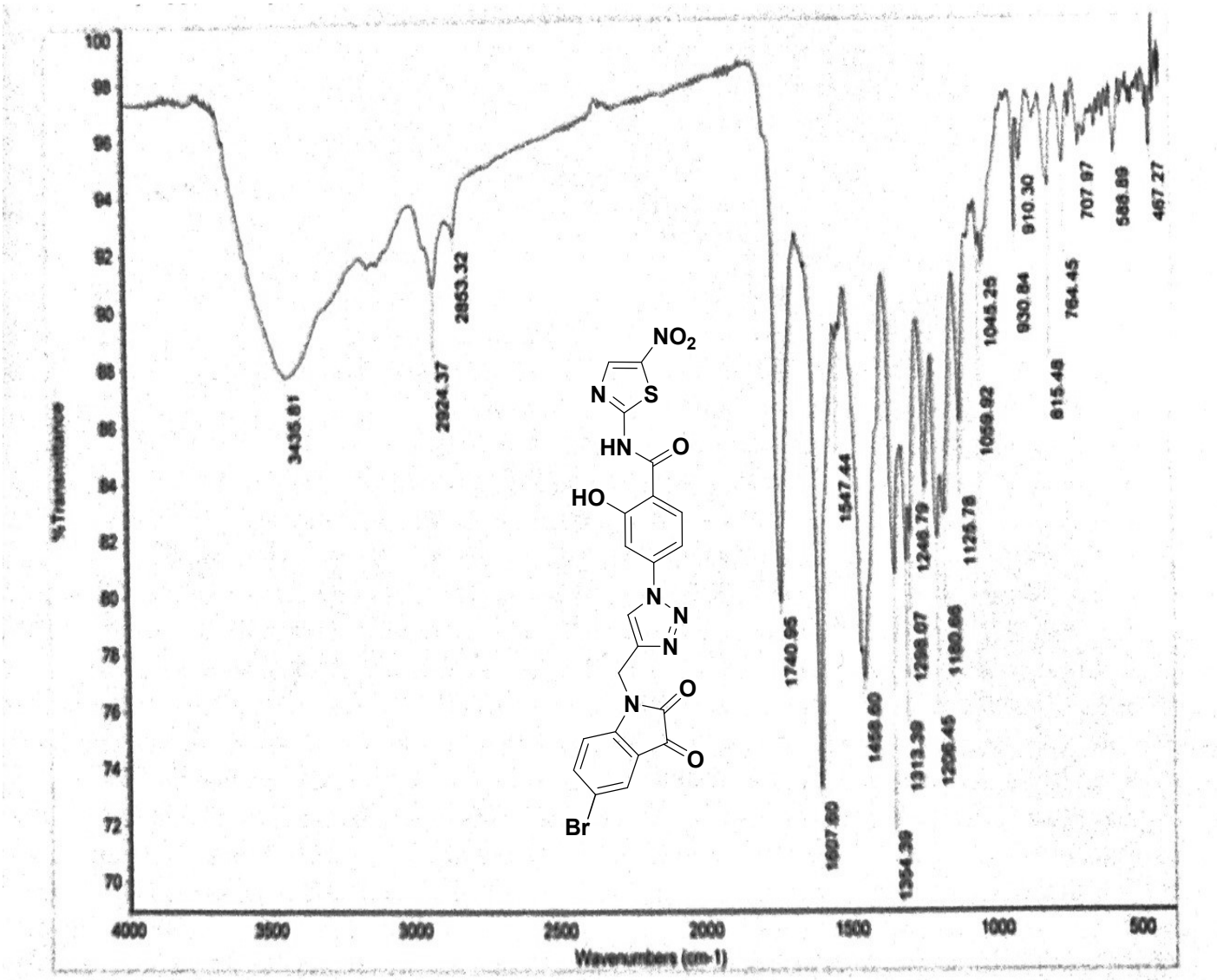

FIGURE S35. FT-IR spectrum of compound 5n.

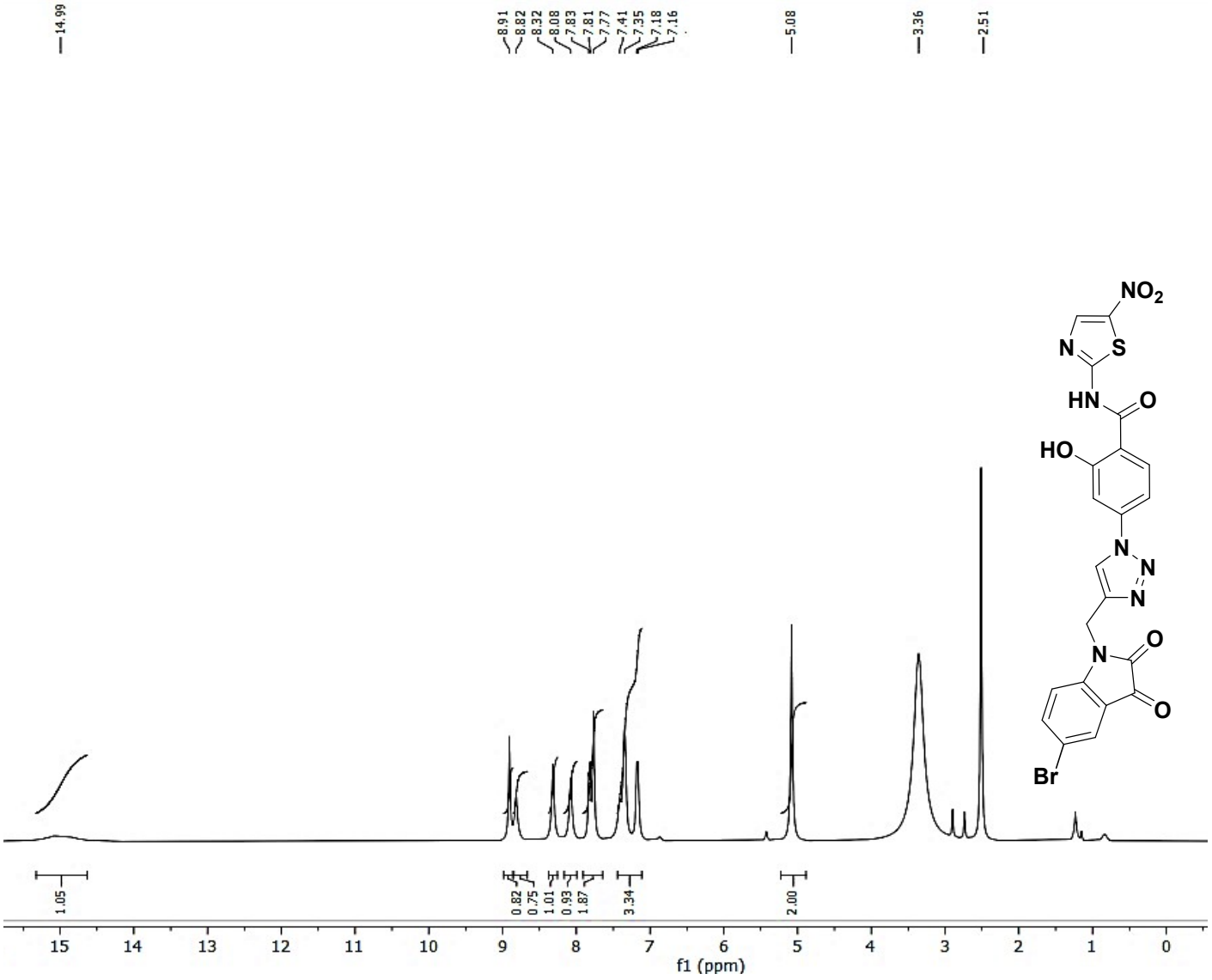

FIGURE S36. [1]H-NMR spectrum of compound 5n.

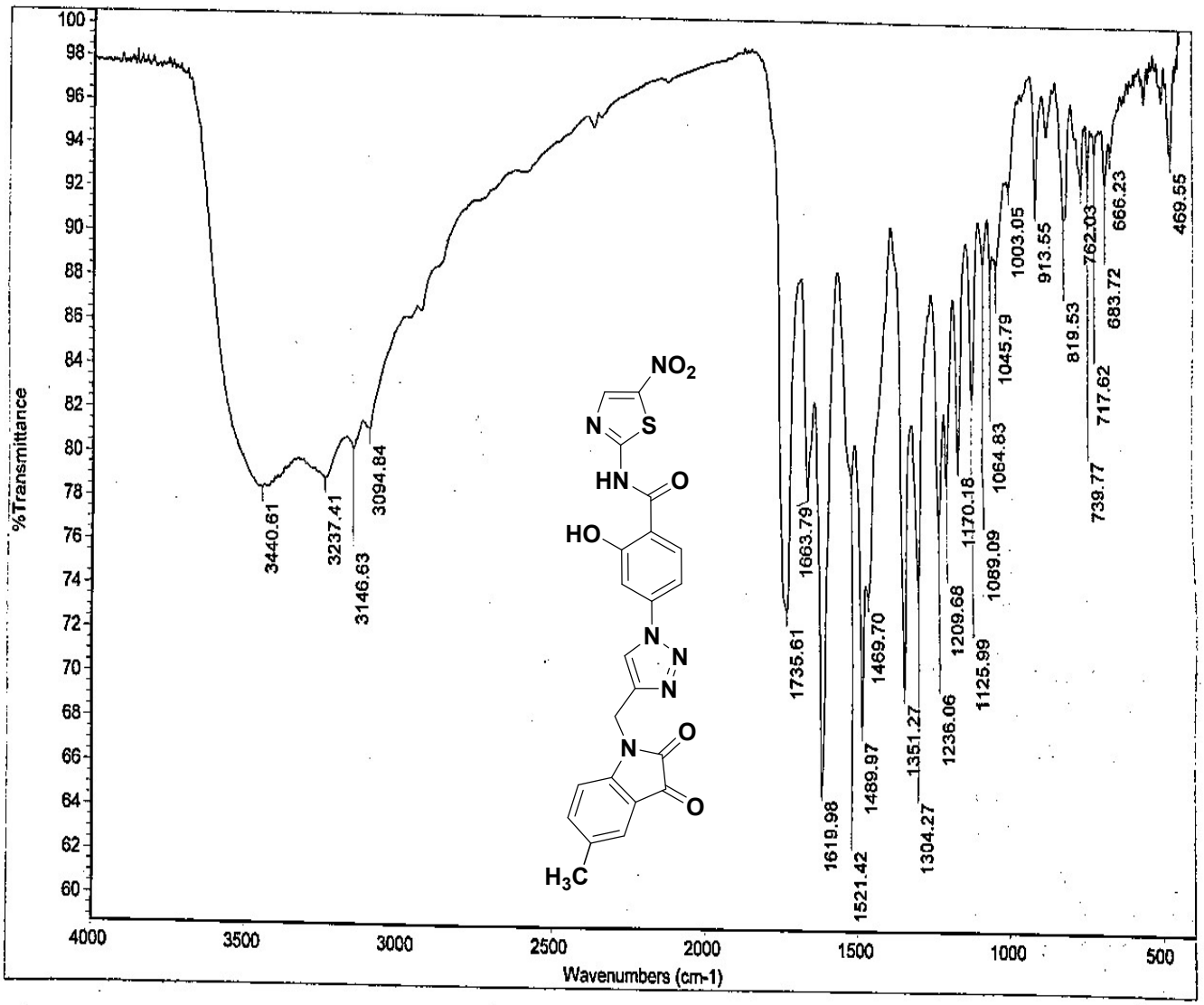

FIGURE S37. FT-IR spectrum of compound 5o.

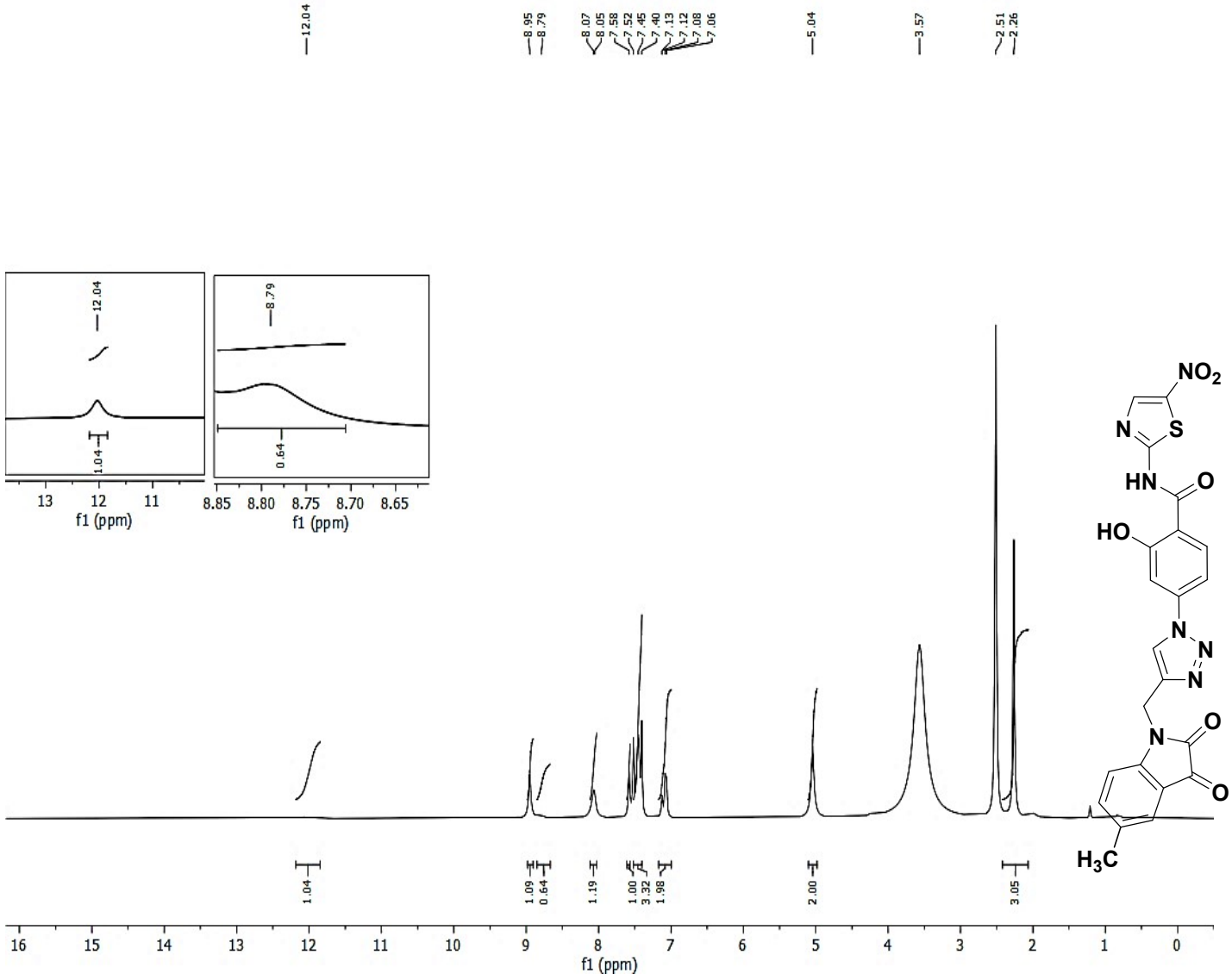

FIGURE S38. [1]H-NMR spectrum of compound 5o.

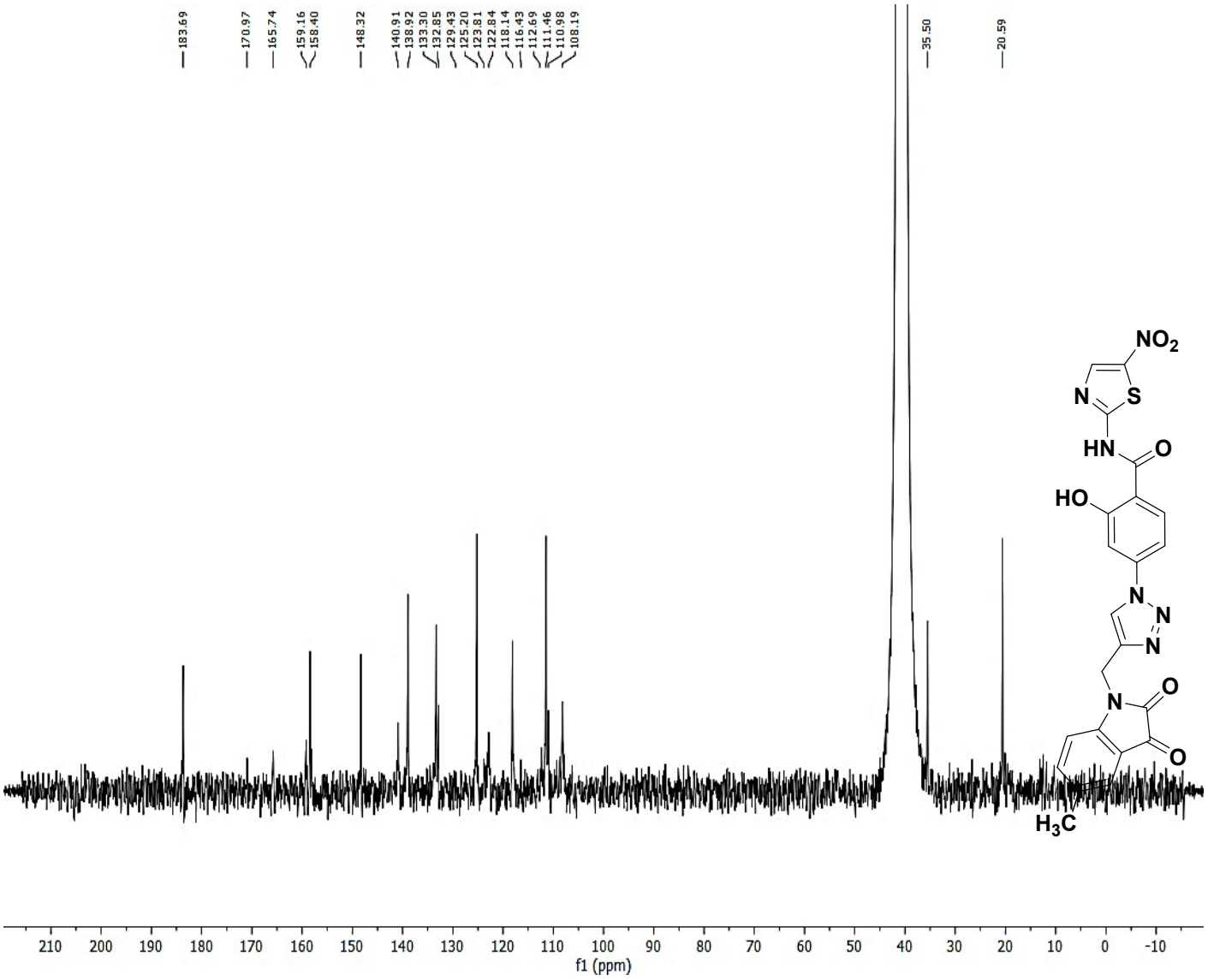
183.69
170.97
165.74
159.16
158.40
148.32
140.91
138.92
133.30
132.85
129.43
125.20
123.81
122.84
118.14
116.43
112.69
111.46
110.98
108.19
35.50
20.59
NO2
N
S
HN
O
HO
N
N
N
N
O
O
H3C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

FIGURE S39. ^{13}C-NMR spectrum of compound 5o.

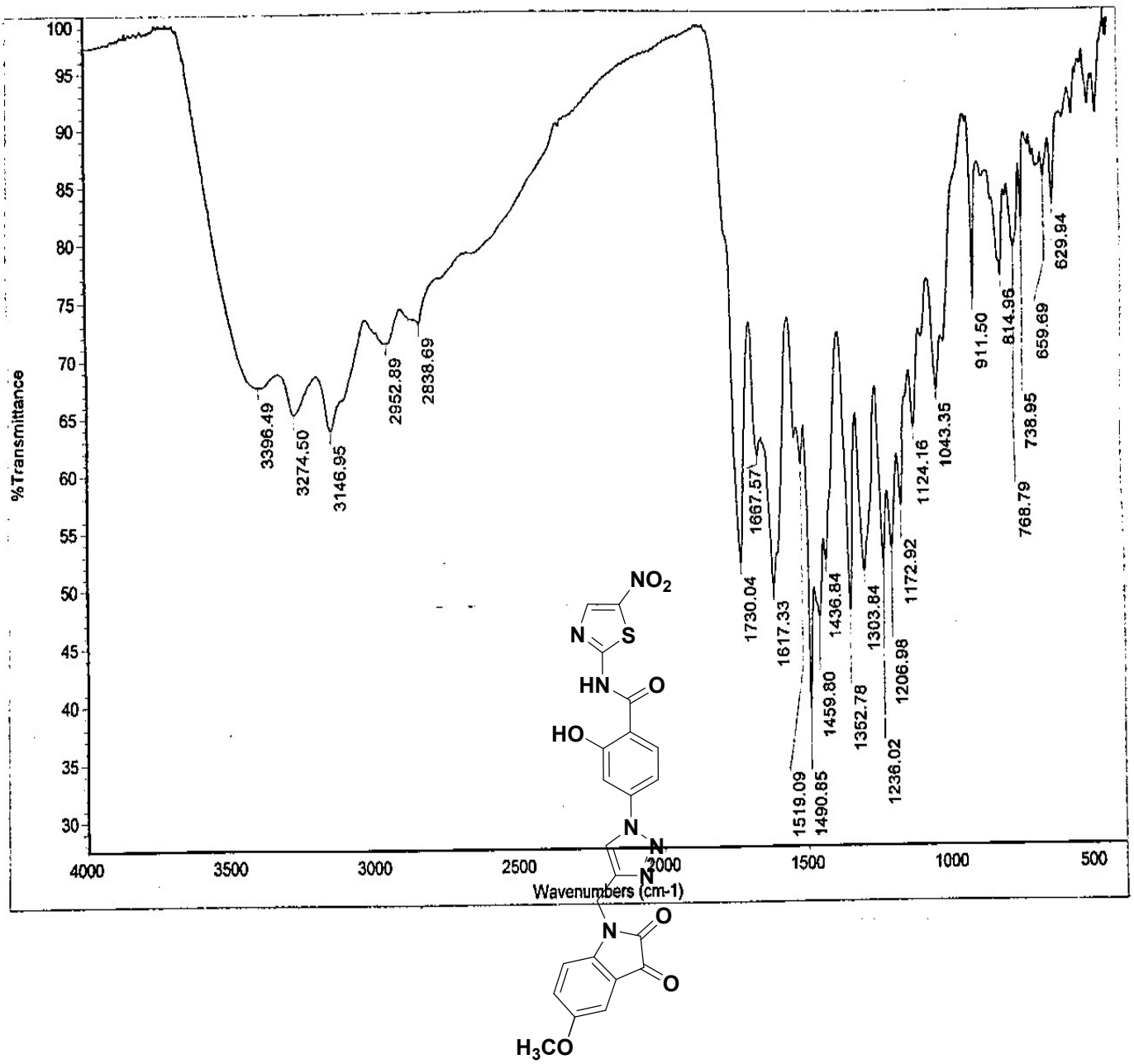

FIGURE S40. FT-IR spectrum of compound 5p.

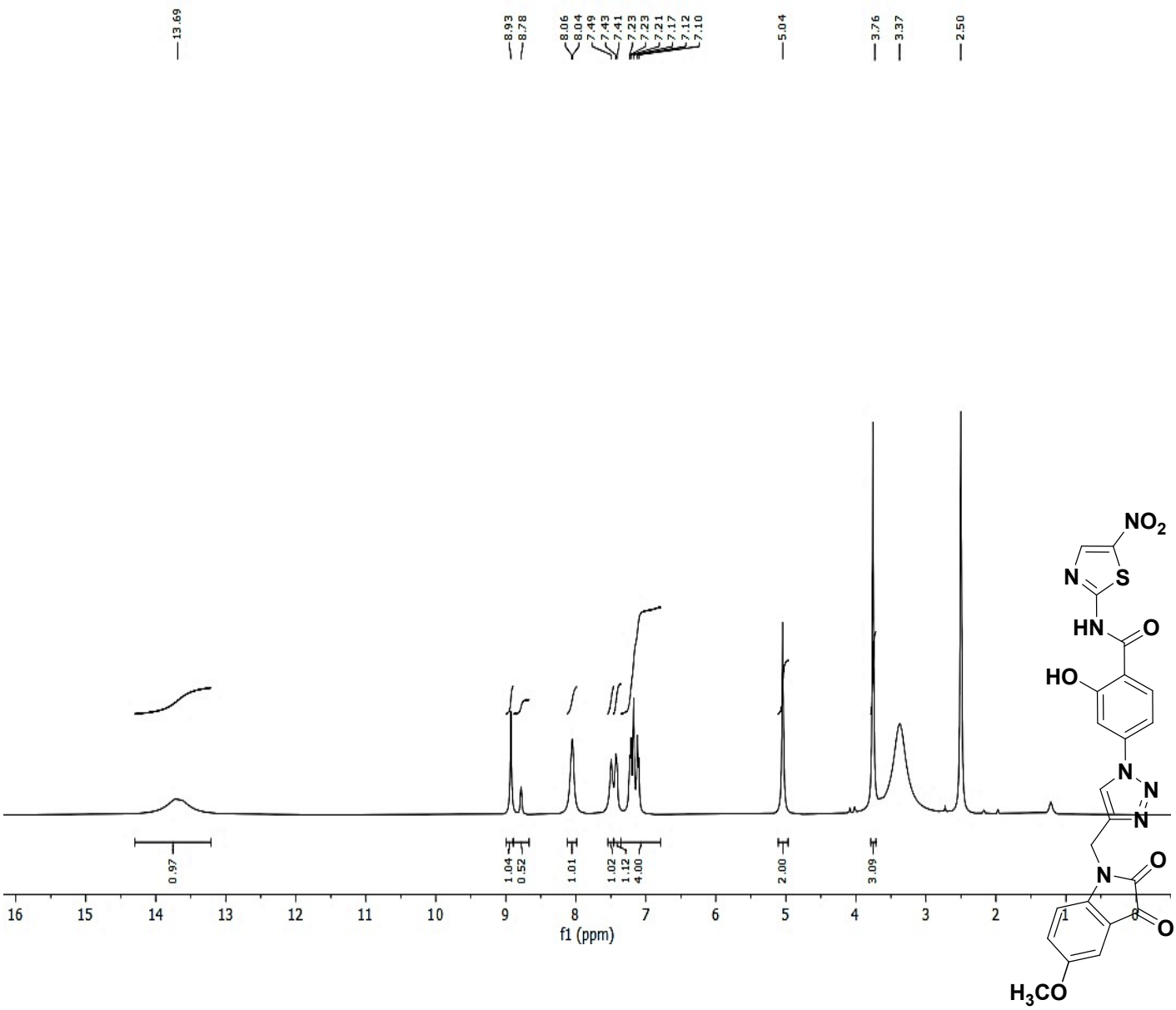
13.69
8.93
8.78
8.06
8.04
7.49
7.43
7.41
7.23
7.21
7.17
7.12
7.10
5.04
3.76
3.37
2.50
0.97
1.04
0.52
1.01
1.02
1.12
4.00
2.00
3.09
f1 (ppm)
NO2
N
S
HN
O
HO
N
N
N
N
O
O
H3CO

FIGURE S41. ^{1}H-NMR spectrum of compound 5p.

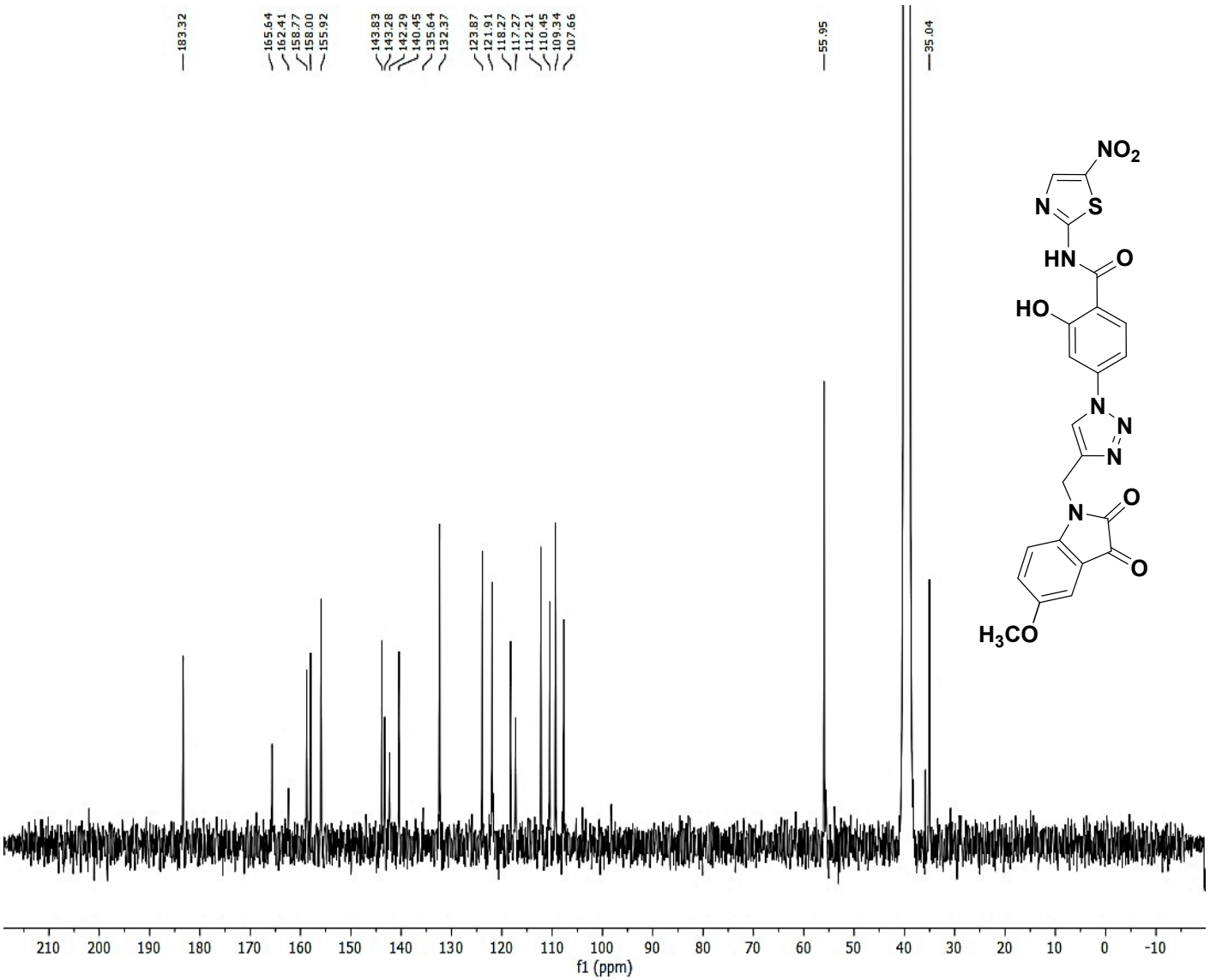

FIGURE S42. ^{13}C-NMR spectrum of compound 5p.

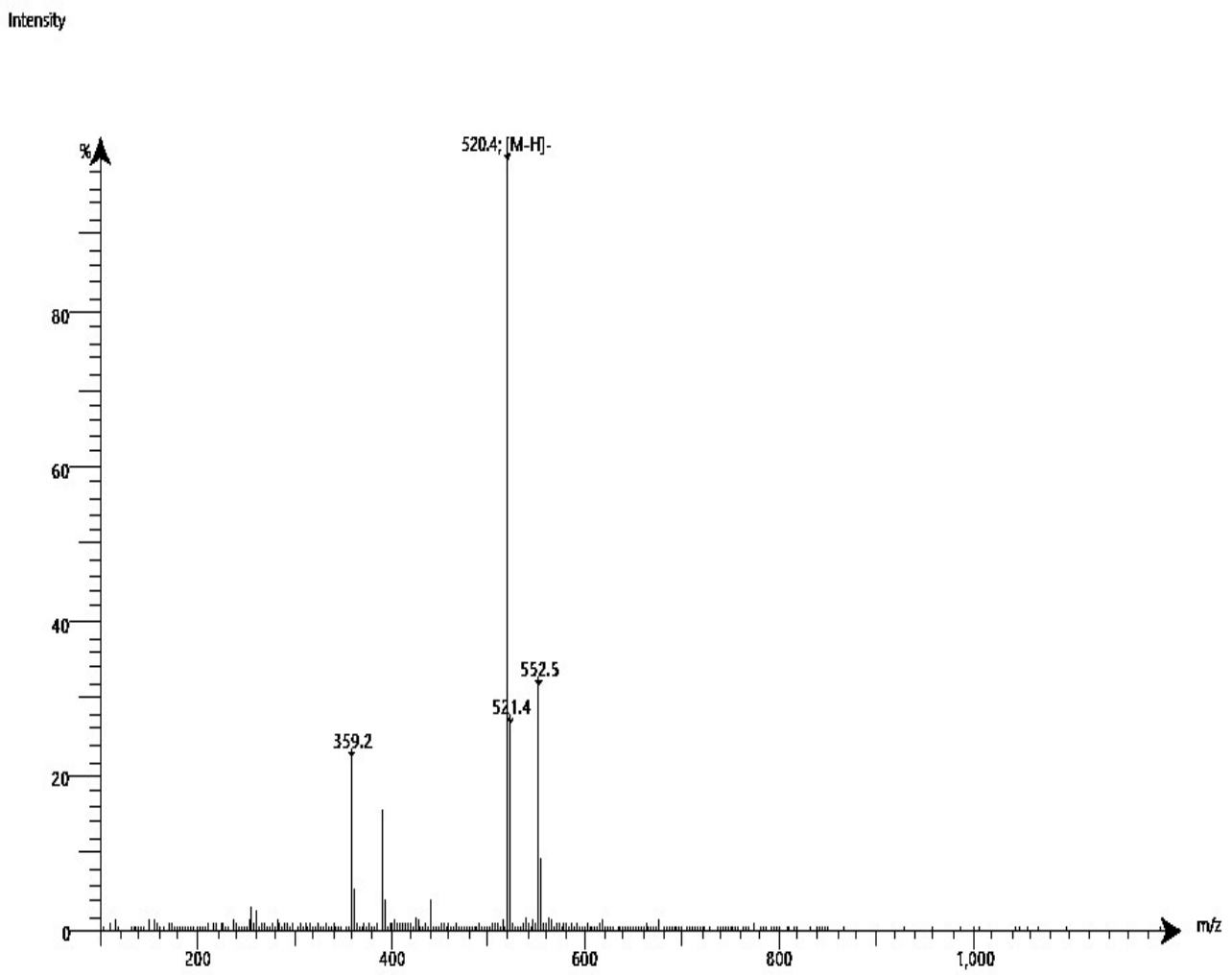

FIGURE S43. ESI-mass spectrum of compound 5p.

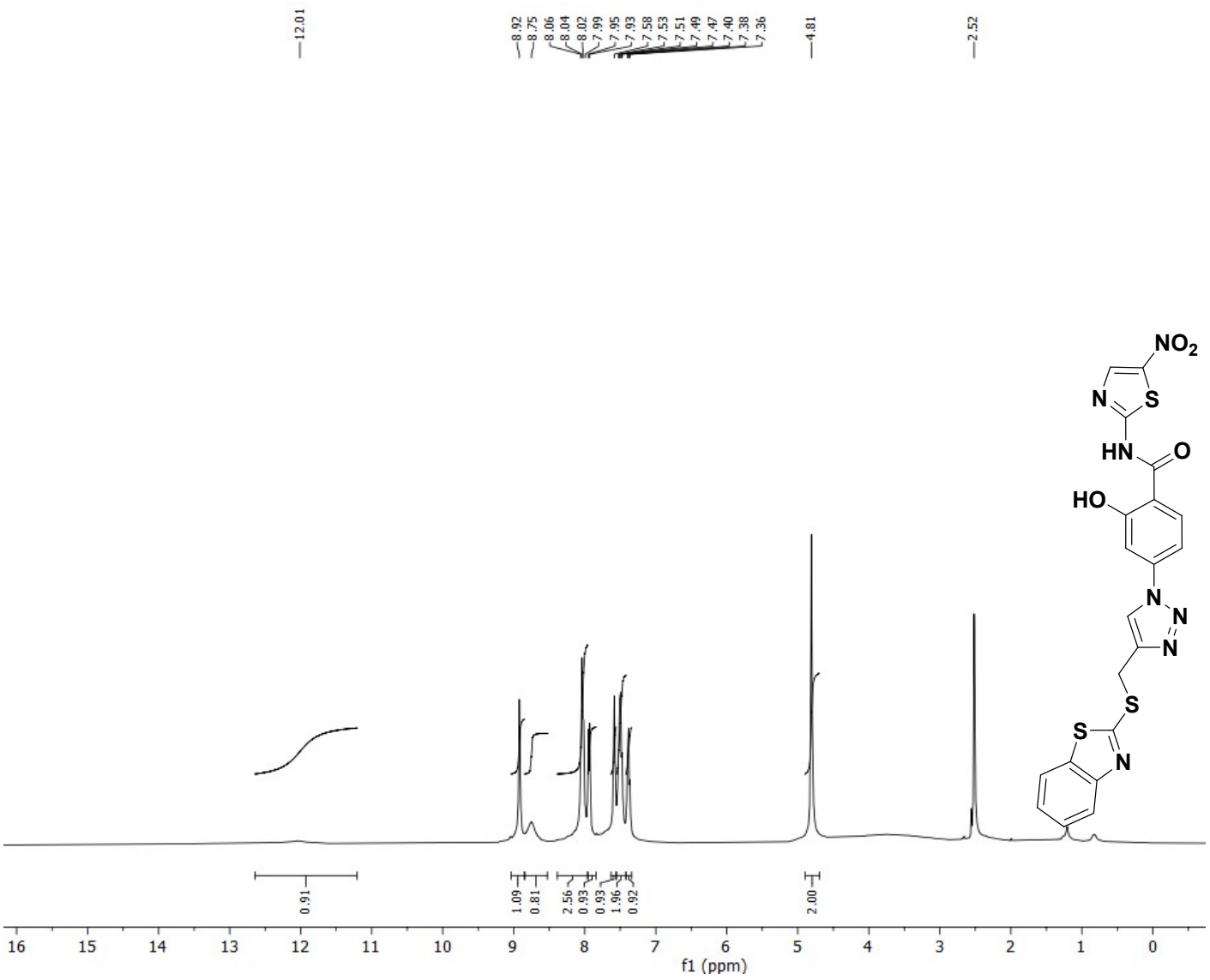

FIGURE S44. ^{1}H-NMR spectrum of compound 5q.

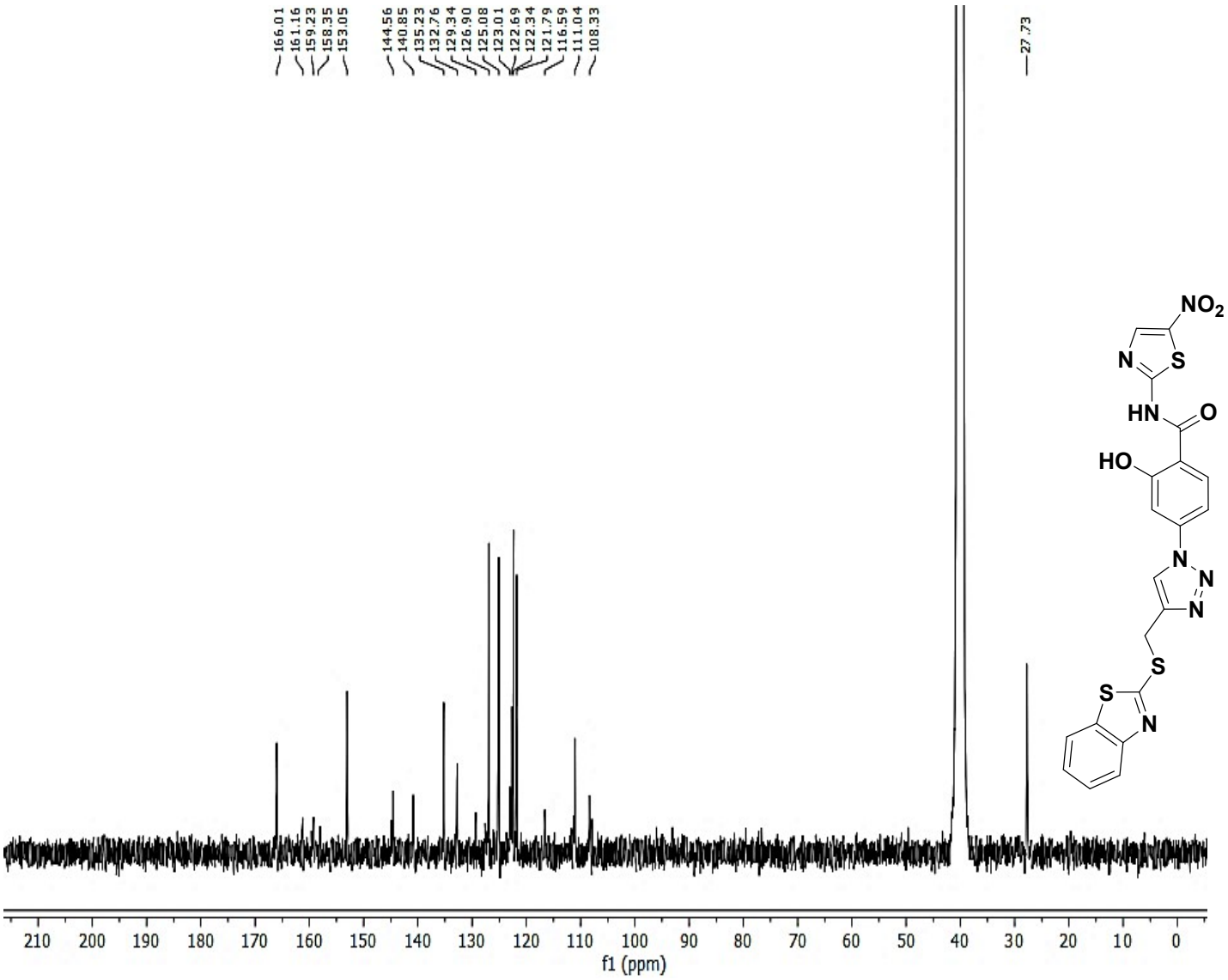

FIGURE S45. ^{13}C-NMR spectrum of compound 5q.

Al-Azhar University

The Regional Center for Mycology and Biotechnology

Requester Data:

Name: Dr. Mahmoud Saleh Mahmoud
Authority: Faculty of Pharmacy, Assuit University

Sample Data:

Nineteen samples had been submitted for elemental analysis.

Analysis Report:

Sample Code	C%	H%	N%	S%
MZ_1	39.49	2.15	27.68	10.50
MZ_2	51.60	2.79	20.19	6.61
MZ_3	50.88	3.14	19.07	6.08
MZ_4	47.15	2.67	19.40	18.59
MZ_5	43.23	3.01	23.45	8.97
MZ_6	43.21	2.69	21.70	8.30
MZ_7	53.15	3.04	20.79	7.96
MZ_8	54.29	3.47	20.04	7.68
MZ_9	50.60	4.52	22.95	7.42
MZ_{10}	41.75	2.27	22.59	8.43
MZ_{11}	44.16	2.36	17.45	5.49
MZ_{12}	47.60	4.15	22.94	7.28
MZ_{13}	54.78	4.50	22.39	6.41
MZ_{14}	48.91	4.68	25.47	7.09
MZ_{15}	52.47	3.15	19.68	6.47
MZ_{16}	48.15	2.47	18.85	5.98
MZ_{17}	49.78	2.43	19.51	6.33
MZ_{18}	49.33	4.29	23.76	7.94
MZ_{19}	41.59	2.47	24.41	9.45

INVESTIGATOR DIRECTOR

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Facebook : RCMB AZHAR P.O. box mail : 11751 Nasr City Cairo, Egypt.

FIGURE S46. Elemental analysis of the synthesized compound 3a, 3b, 5a-q.

Compound No.	experimental code
3a	Mz1
3b	Mz19
5a	Mz5
5b	Mz10
5c	Mz6
5d	Mz7
5e	Mz8
5f	Mz9
5g	Mz18
5h	Mz12
5i	Mz14
5j	Mz13
5k	Mz2
5l	Mz17
5m	Mz16
5n	Mz11
5o	Mz15
5p	Mz3
5q	Mz4

3. Antibacterial activity

Table S1. Antibacterial activity against different bacterial test strains. MIC (in µg/mL) values represent the average of at least two replicate experiments.

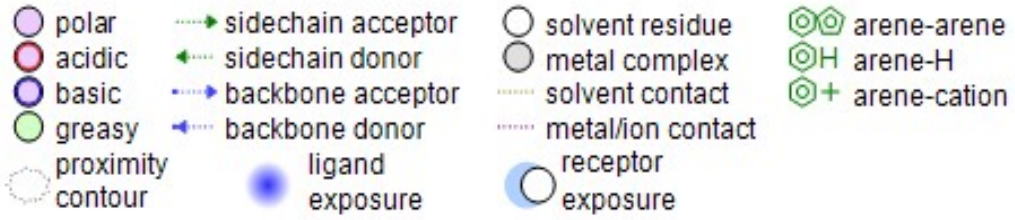
ID	Gram-negative strains			Gram-positive strains		Anaerobe strain
	E. coli ATCC 8739	*P. aeruginosa* ATCC 27853	*K. pneumoniae* ATCC 10031	*S. aureus* ATCC 6538	*E. faecalis* ATCC 19433	*H. pylori* ATCC 700392
TIZ	48	96	64	40	36	3
NTZ	32	128	56	32	48	4
Cipro	0.1	1.5	3	1	2	0.5
3a	1.5	>512	96	3	8	32
3b	3	32	12	4	0.75	4
5a	>512	128	32	>512	48	16
5b	2.5	4	6	32	>512	8
5c	1.5	6	2	4	>512	1.5
5d	>512	>512	16	12	8	6
5e	3	128	>512	512	32	2.5
5f	32	>512	512	4	12	0.75
5g	2.5	3	5	1.5	>512	8
5h	512	64	8	3	>512	4
5i	>512	64	4	2	>512	3
5j	6	1.5	128	256	1	16
5k	>512	8	>512	16	2	64
5l	>512	4	>512	8	2.5	2
5m	256	>512	32	>512	>512	2.5
5n	12	3	2.5	0.5	5	2
5o	0.75	4	2	256	3	1.5
5p	8	>512	256	48	96	5
5q	2	16	12	2	>512	8

4. Molecular docking

Table S2. Ligand-protein complex interactions of the tested compounds 5c, 5e, 5f, 5m, 5n and 5o along with NTZ within the active site of PFOR.

Interaction with PFOR (2C42)			
Compd.	**Score kcal/mol**	**H-bond interactions (Å)**	**Other interactions (Å)**
Co-crystallized Pyruvate	**-4.45**	**Thr31 (2.94, 3.06) Arg114 (2.97, 2.98, 3.40)**	**Arg114 (2.98) Ionic interaction**
NTZ	**-7.39**	**Arg114 (3.37) Thr31 (2.77) Asn 996 (2.99)**	**-**
5c	**-8.72**	**Thr838 (3.51) Asn996 (3.05) Gly839 (3.44)**	**Arg114 (3.96) pi-H Tyr994 (4.56) pi-H Thr31 (4.74) pi-H Arg114 (3.94) pi-cation Phe869 (3.53) pi-pi**
5e	**-8.64**	**Pro29 (3.27) Asn996 (3.13) Thr997 (3.49) Thr31 (2.74)**	**Cys840 (3.70, 4.54) pi-H Ser841 (4.89) pi-H Asn996 (4.30) pi-H Phe869 (3.71) pi-pi**
5f	**-8.87**	**Arg 114 (3.42) Thr 31 (3.72) Asn 996 (3.02)**	**Tyr 994 (4.35) pi-H Phe 969 (3.80) pi-pi**

5m	**-7.78**	**Trp 965 (3.19) Tyr994 (3.24) Ser995 (3.53) Arg114 (2.91) Ser841 (2.72)**	**Tyr994 (3.31) pi-H Arg114 (4.20) pi-cation Ile123 (4.59) pi-H Ser995 (4.67) pi-H**



5n	**-8.05**	**Thr997 (3.20) Thr838 (2.89) Met989 (3.26) Gly964 (2.78) Ser995 (2.90) Arg114 (2.85) Ser841 (2.69, 2.90)**	**Arg114 (4.15) pi-cation Ile123 (4.48) pi-H Glu817 (3.33) pi-H Gly962 (3.50) pi-H Asn996 (3.55, 4.54)**
5o	**-8.37**	**Arg 114 (3.00) Thr 997 (3.46) Gly964 (2.78) Tyr994 (3.17) Ser995 (2.94)**	**Phe869 (3.59) pi-H Tyr994 (4.44) pi-H**

FIGURE S47. Color scheme for the 2D representations of the interactions between the docked ligands and the active site of the enzyme.

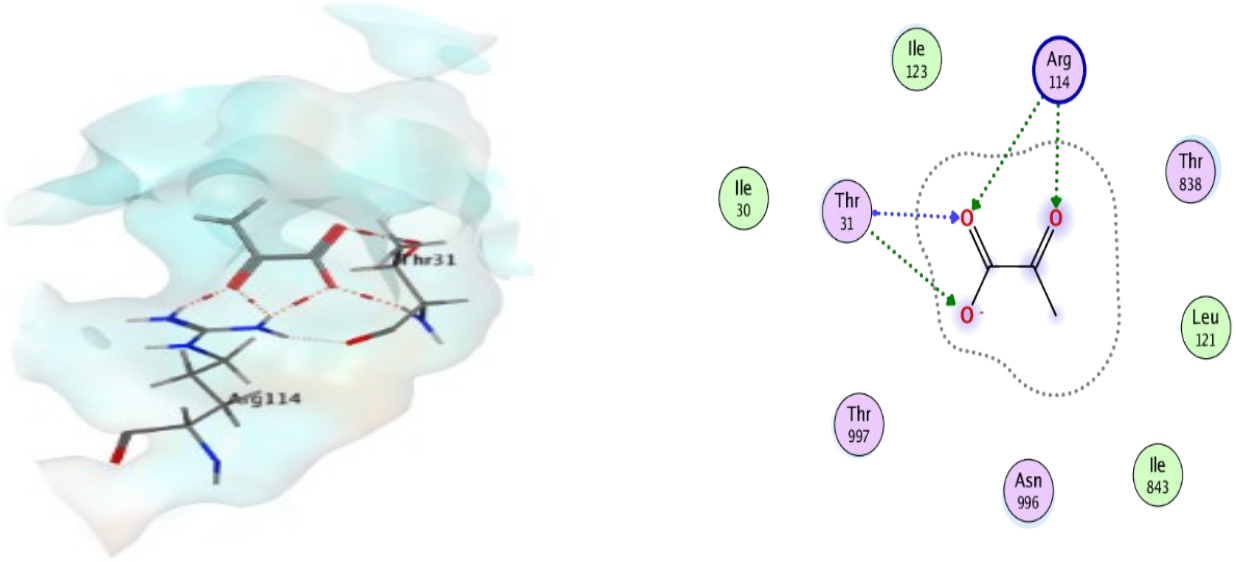


FIGURE S48. Redocking of co-crystallized pyruvate within the active site of PFOR (2C42).

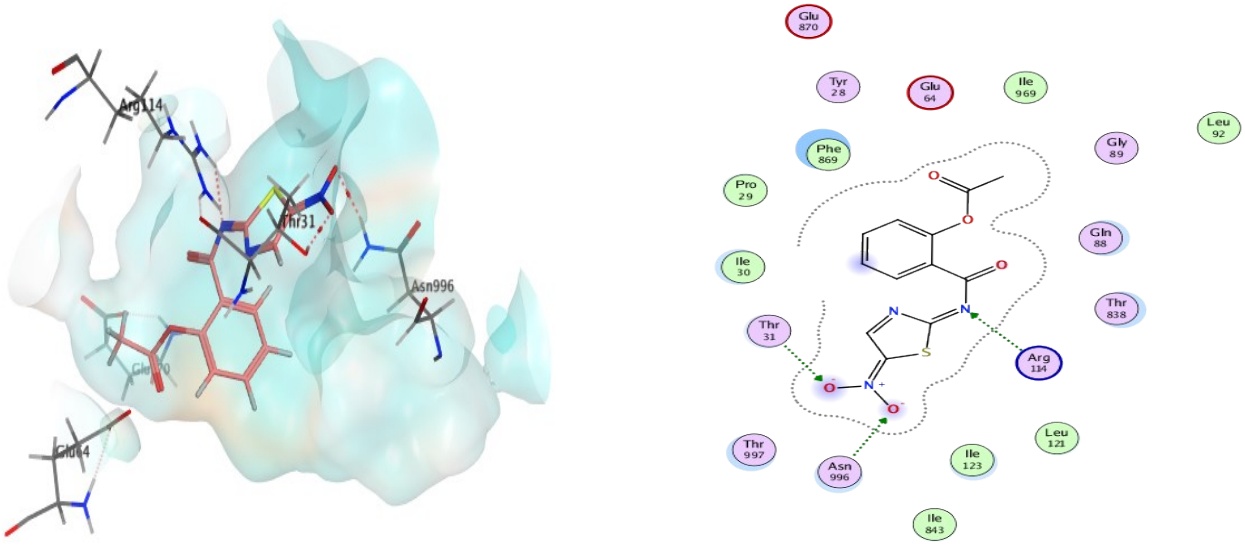


FIGURE S49. Interaction of NTZ with the active site of PFOR (2C42).

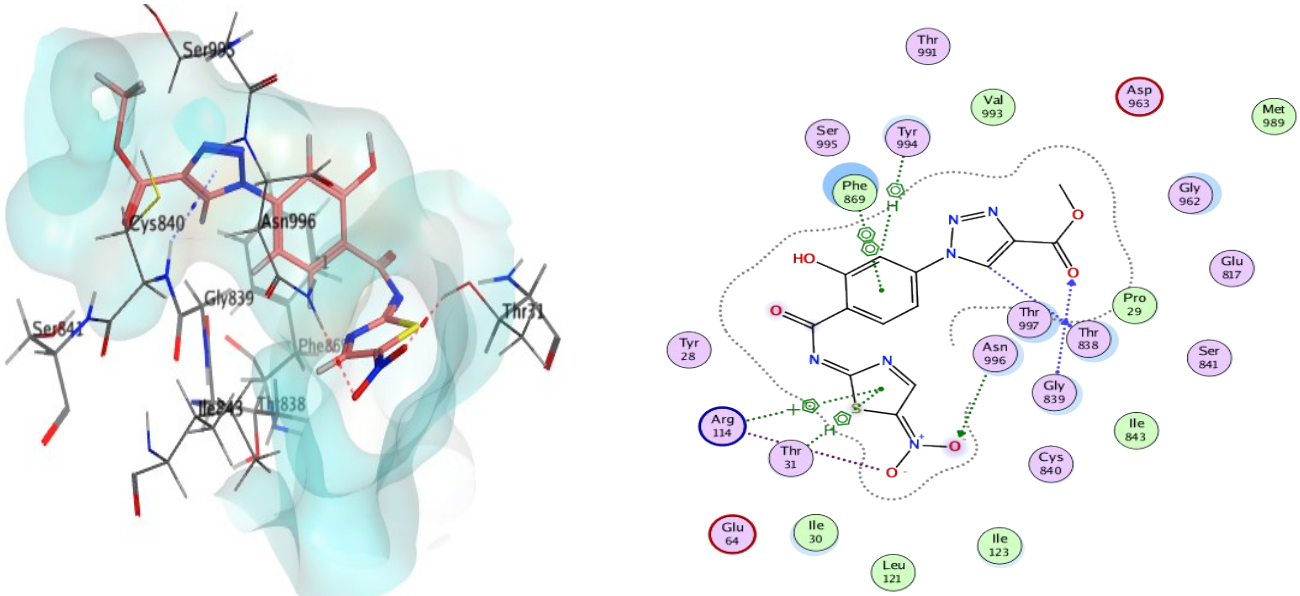


FIGURE S50. Interaction of 5c with the active site of PFOR (2C42).

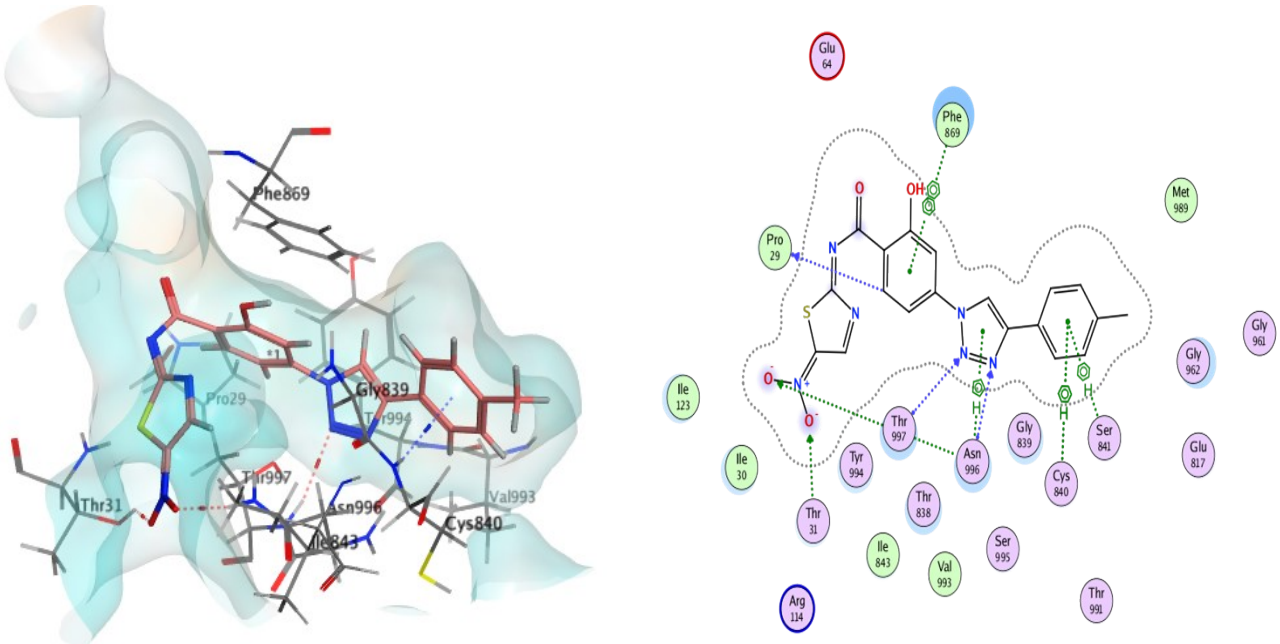


FIGURE S51. Interaction of 5e with the active site of PFOR (2C42).

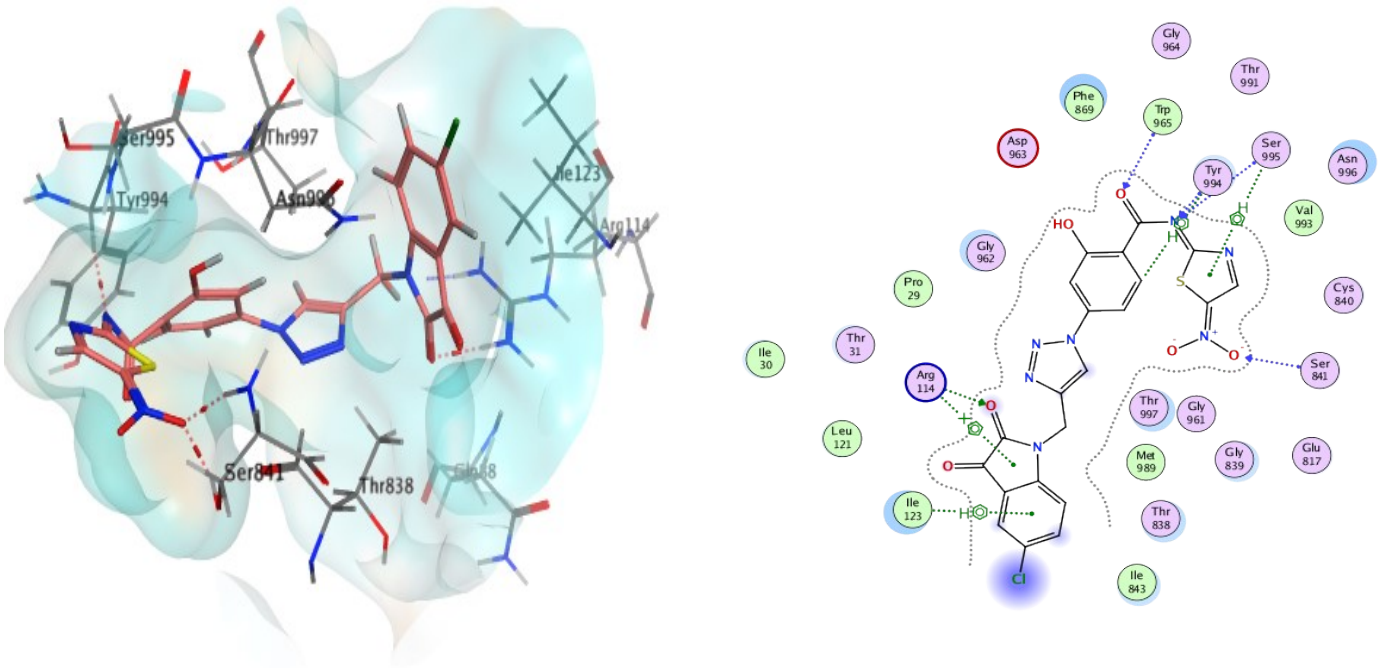


FIGURE S52. Interaction of 5m with the active site of PFOR (2C42).

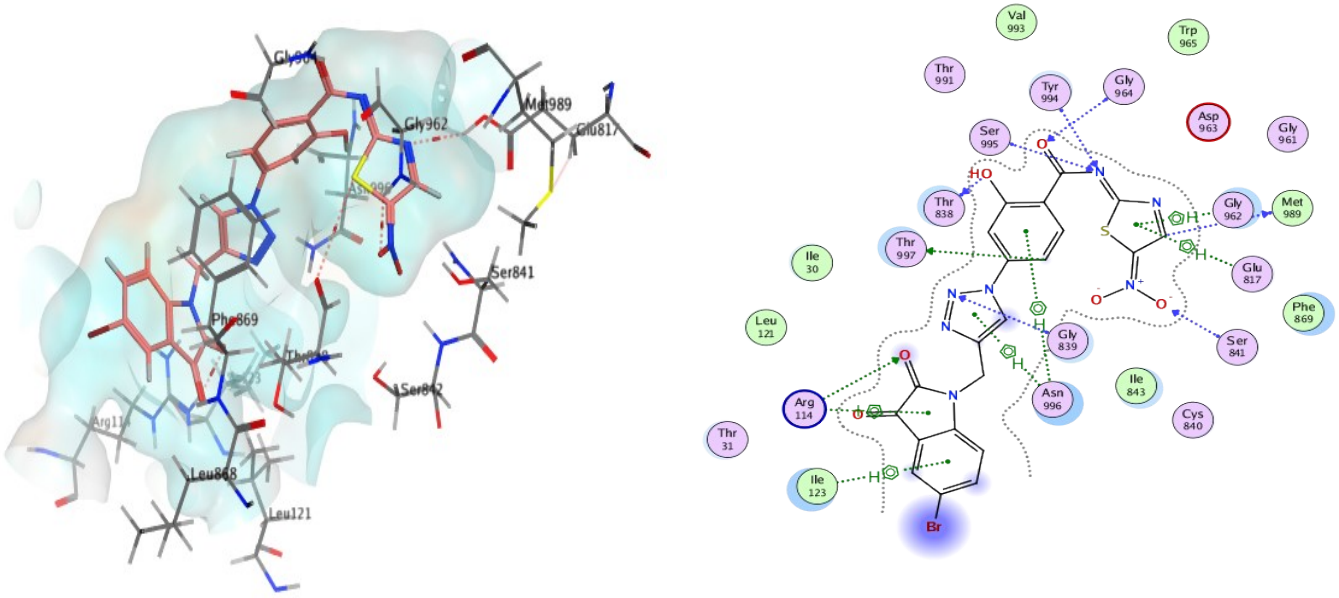


FIGURE S53. Interaction of 5n with the active site of PFOR (2C42).

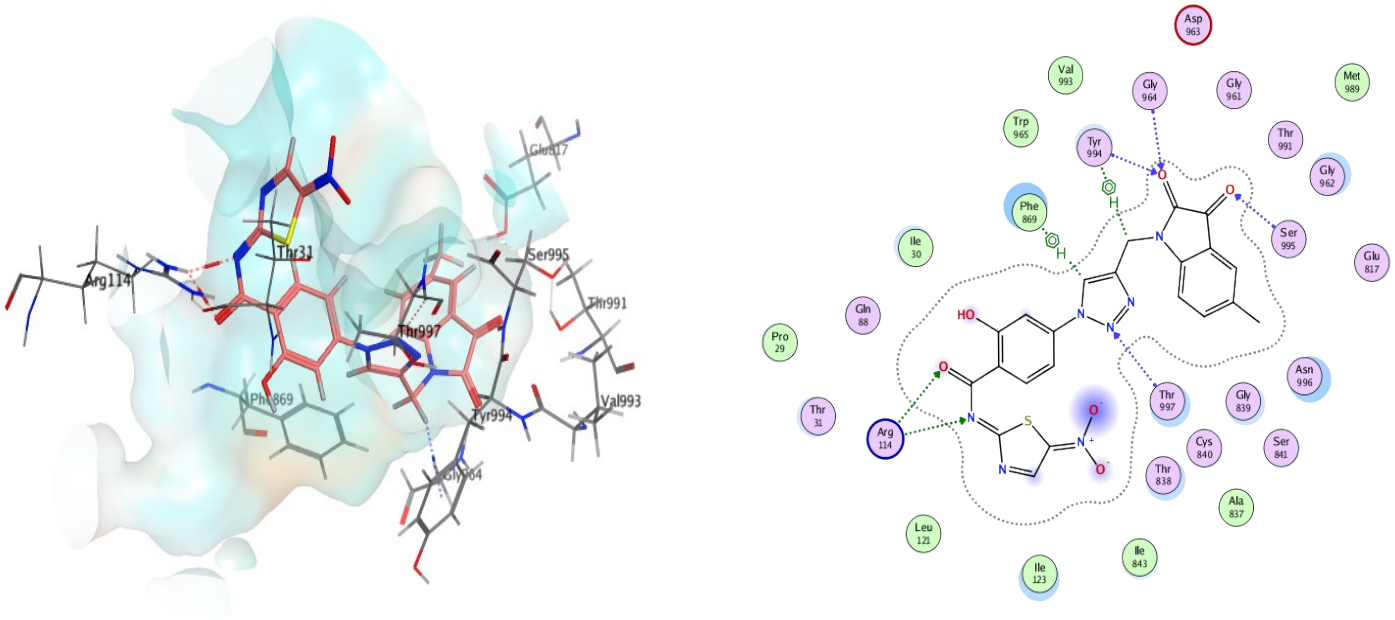


FIGURE S54. Interaction of 5o with the active site of PFOR (2C42).

Table S3. Ligand-protein complex interactions of the tested compounds 3, 4, 5c, 5n, 5o and 5q along with NTZ within the active site of G6PS (2J6H).

Interaction with G6PS (2J6H)			
Compd.	**Score kcal/mol**	**H-bond interactions (Å)**	**Other interactions (Å)**
co-crystallized ligand (G6P)	**-6.22**	**Ser303 (2.69) Ser349 (2.78, 2.92) Ser347 (2.86) Thr352 (2.51) Glu488 (2.54) Thr302 (3.10, 3.16, 3.19) Lys485 (3.25)**	**-**
NTZ	**-7.06**	**Ser303 (2.92, 3.08) Ser347 (3.10, 3.31) Gln348 (3.04) Ser401 (4.23, 3.33, 3.43) Ser349 (2.76, 2.95)**	**-**
3a	**-7.10**	**Ala602 (3.27, 3.46) Ser401 (3.09, 3.46) Lys485 (3.78) Ser347 (2.90, 3.27) Ser349 (3.03, 3.49) Thr352 (2.89)**	**-**
3b	**-7.23**	**Lys603 (2.93) Ser347 (2.90) Thr352 (2.77) Cys300 (2.87) Ser604 (3.37) Val605 (3.06)**	**-**
5c	**-7.48**	**Ala602 (3.45, 3.71) Lys603 (2.79) Ser401 (3.14, 3.47) Lys485 (3.65) Ser347 (2.98) Ser349 (3.19, 3.32)**	**Leu601 (3.61) pi-H**
5n	**-7.99**	**Ala602 (3.41, 3.65) Lys603 (2.78) Ser401 (3.10, 3.35) Thr352 (2.90) Ser347 (2.97) Ser349 (3.17, 3.30)**	**Leu601 (3.64) pi-H**

5o	**-8.15**	**Ser401 (3.49) Ser347 (2.90, 3.35) Ser349 (3.11) Thr352 (2.88)**	**Leu601 (3.38) pi-H Val605 (3.94, 4.48) pi-H**
5q	**-8.49**	**Thr 302 (3.06) Lys603 (2.90) Cys300 (2.88) Ser347 (2.92) Thr352 (2.81)**	**Leu484 (3.86) pi-H Lys487 (3.68) pi-pi**

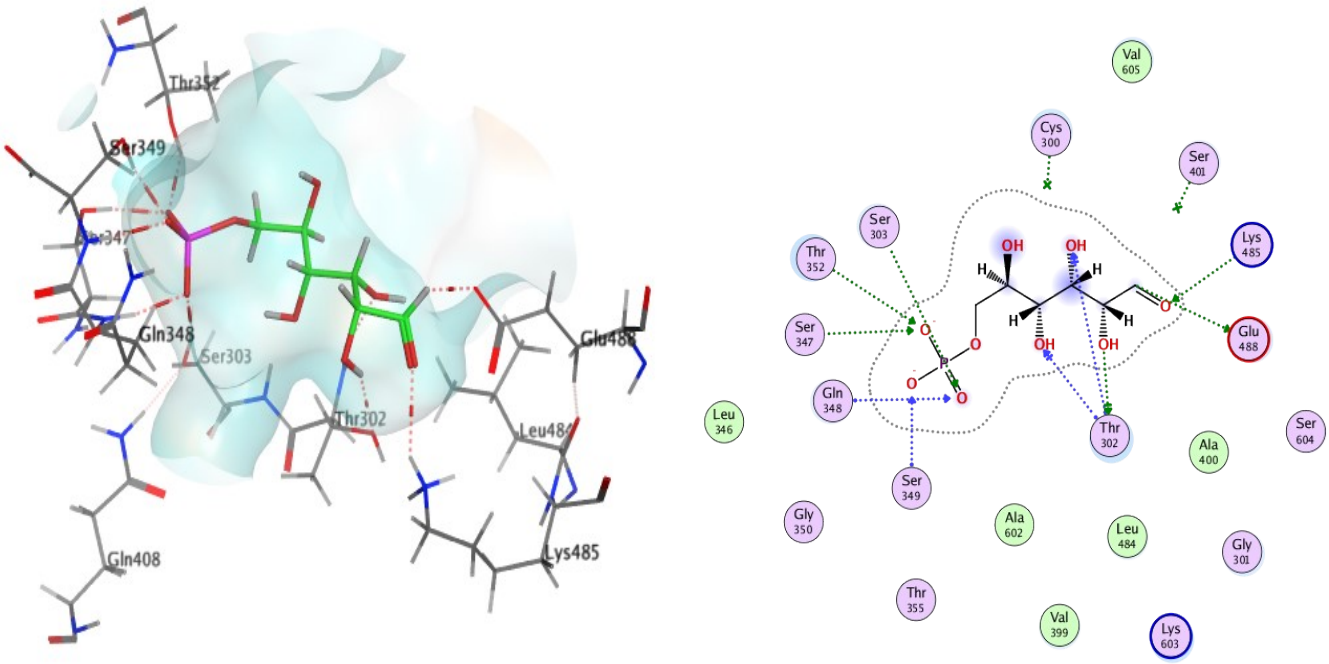


FIGURE S55. Interaction of co-crystallized ligand to the active site of G6PS (2J6H).

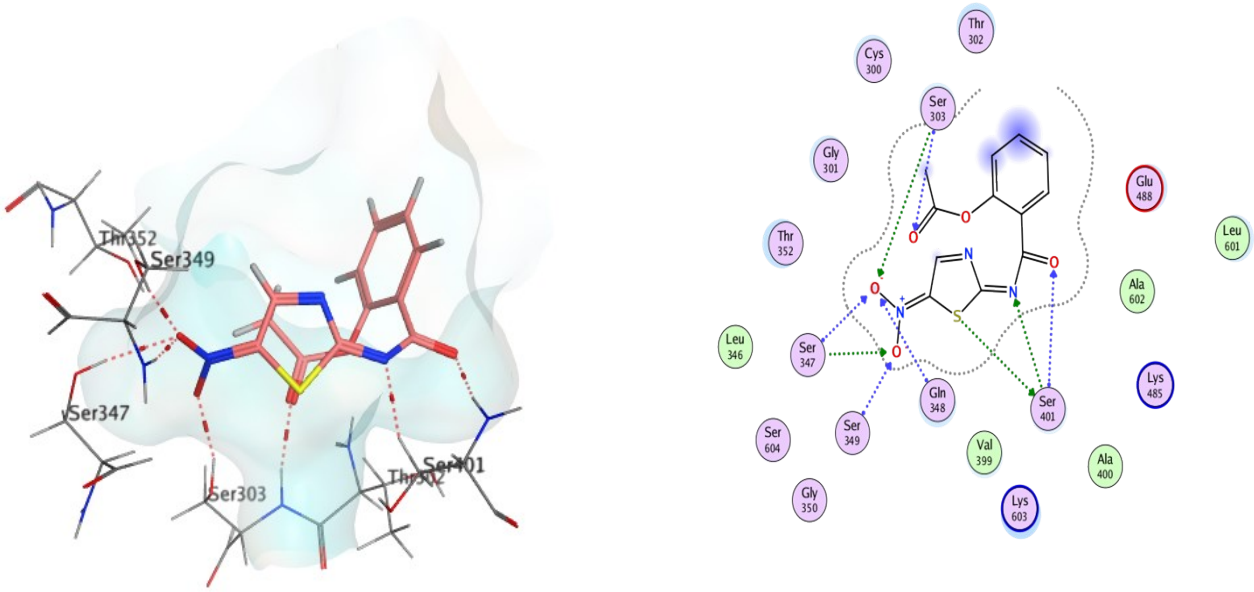
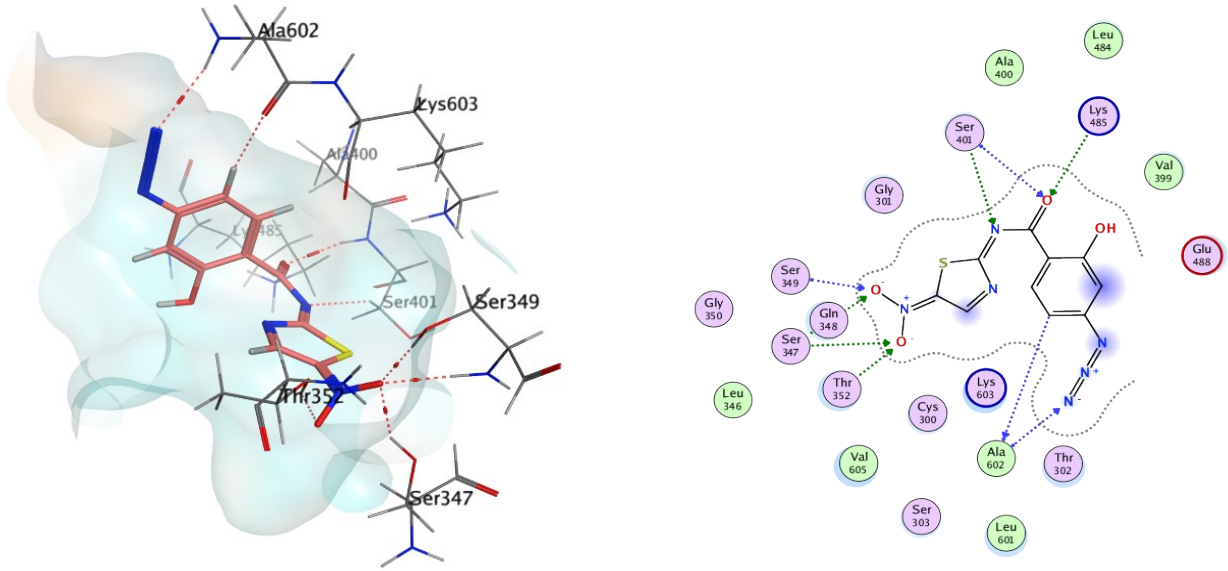


FIGURE S56. Interaction of NTZ with the active site of G6PS (2J6H).



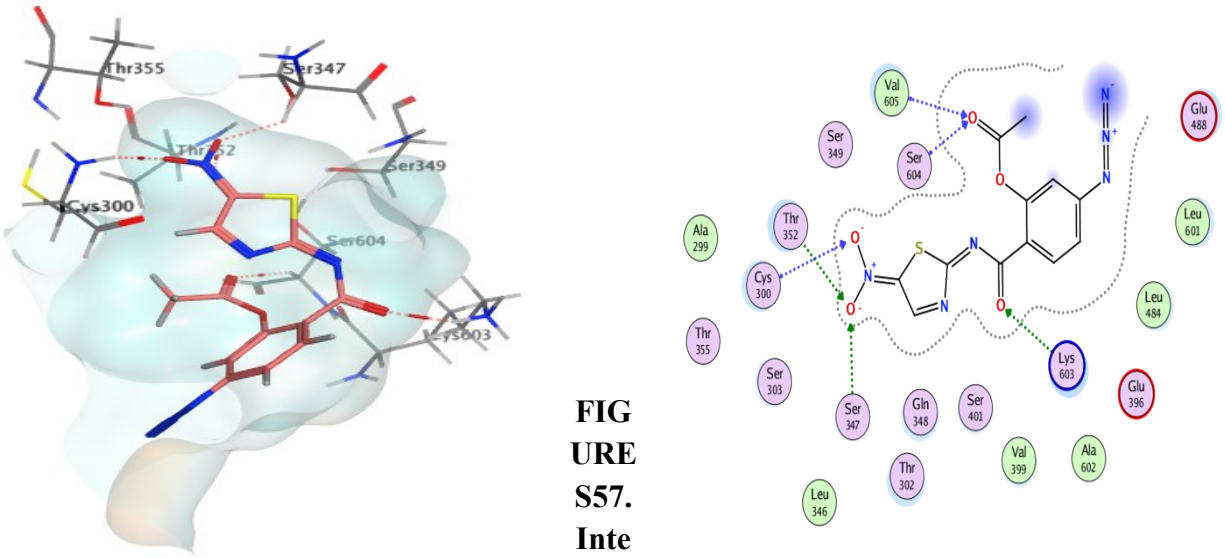


FIGURE S57. Interaction of compound 3a with the active site of G6PS (2J6H).

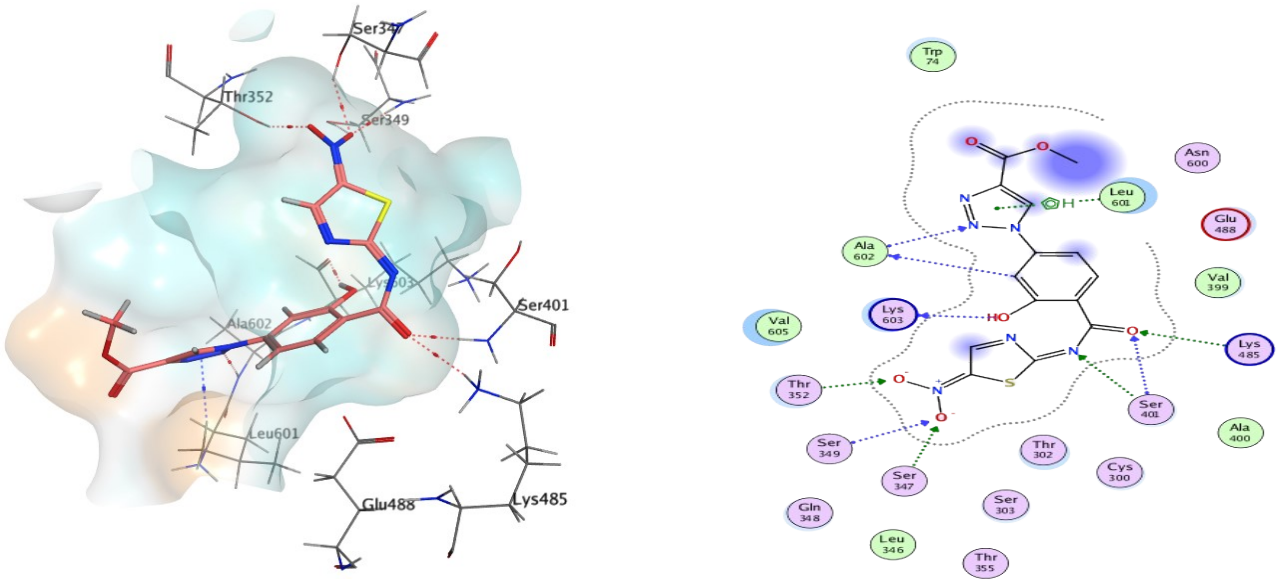


FIGURE S58. Interaction of compound 3b with the active site of G6PS (2J6H).

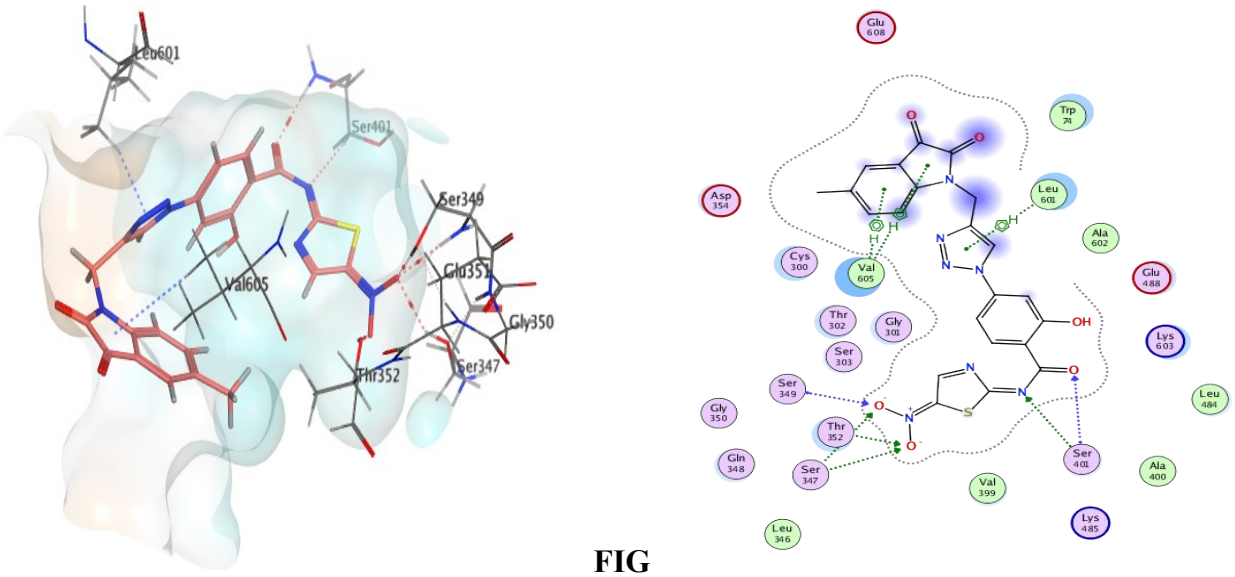
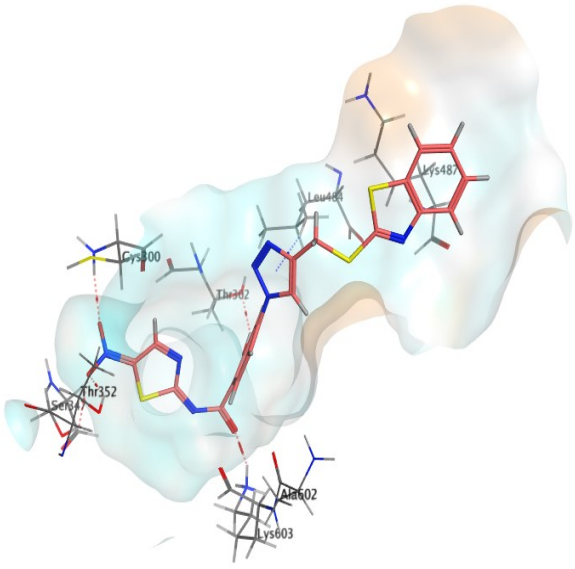


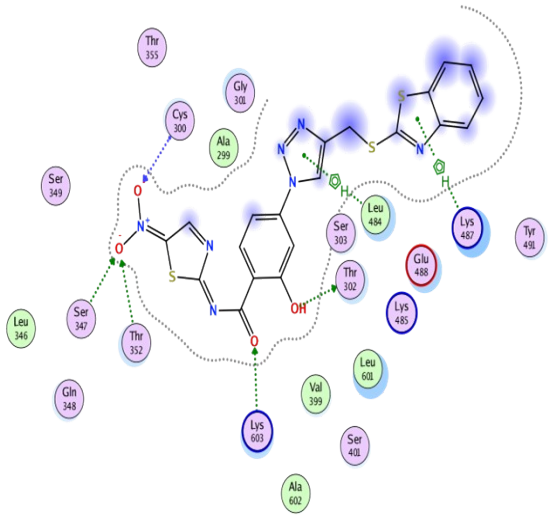
FIG URE S59. Interaction of compound 5c with the active site of G6PS (2J6H).

FIGURE S60. Interaction of compound 5o with the active site of G6PS(2J6H).

FIGURE S61. Interaction of compound 5q with the active site of G6PS (2J6H).

Table S4. Ligand-protein complex interactions of the tested compounds 3, 4, 5b and 5e along with NTZ within the active site of Mtb DHFR (6DDW).





Interaction with Mtb DHFR (6DDW)			
Compd.	**Score kcal/mol**	**H-bond interactions (Å)**	**Other interactions (Å)**

Co-crystallized Ligand (G7D)	**-8.33**	**Ile94 (3.20) Asp27 (2.59, 3.04, 3.34) Arg60 (2.83, 2.87)**	**Arg32 (3.30, 3.41) Ionic interaction Arg60 (2.83, 2.87, 3.81, 3.42) Ionic interaction Phe 31 (4.31)**
NTZ	**-6.14**	**Arg60 (3.06) Gln 28 (3.55)**	**Arg60 (3.06, 3.60) Ionic interaction Gln28 (4.60) Pi-H interaction**
3a	**-6.35**	**Arg 60 (2.94, 2.99) Trp 6 (4.16)**	**Arg 60 (2.94, 2.99, 3.97) Ionic interaction Gln 28 (4.59) Pi-H interaction**
3b	**-6.68**	**Gln28 (3.54) Arg32 (3.40) Arg60 (2.98, 3.46) Ile20 (3.85) Thr46 (3.78)**	**Arg60 (3.46, 2.98, 3.79) Ionic interaction Gln 28 (4.63) Pi-H**
5b	**-6.65**	**Arg32 (3.40) Thr 46 (3.93) Ser49 (4.18) Arg60 (2.98)**	**Arg60 (2.98, 3.75) Ionic interaction Arg32 (3.28, 3.69) Ionic interaction Ile20 (3.55) pi-H Gln28 (4.39) pi-H Phe31 (4.19) pi-H**
5e	**-7.43**	**Gln28 (3.29) Arg60 (2.83, 4.24)**	**Arg60 (2.83, 3.24, 3.48, 3.98) Ionic interaction Ile20 (3.66) pi-H Gln28 (4.52) pi-H Val54 (4.87)**

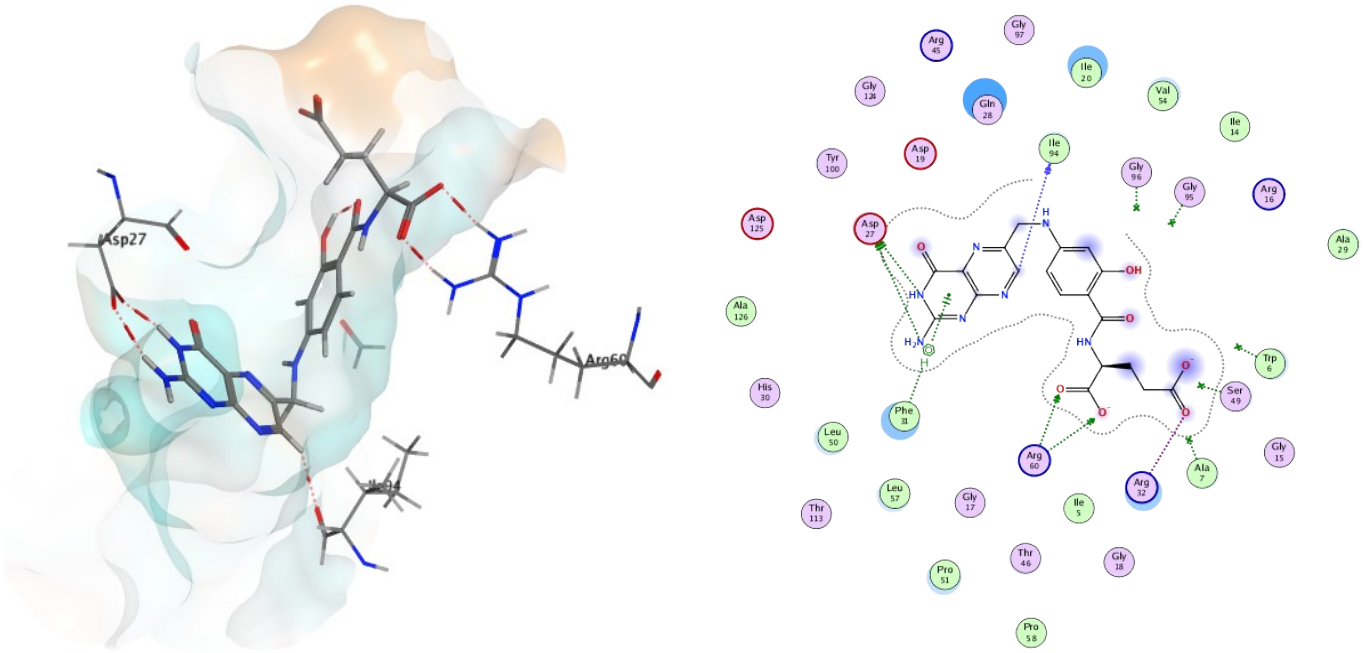


FIGURE S62. Interaction of co-crystallized ligand with the active site of DHFR (6DDW).

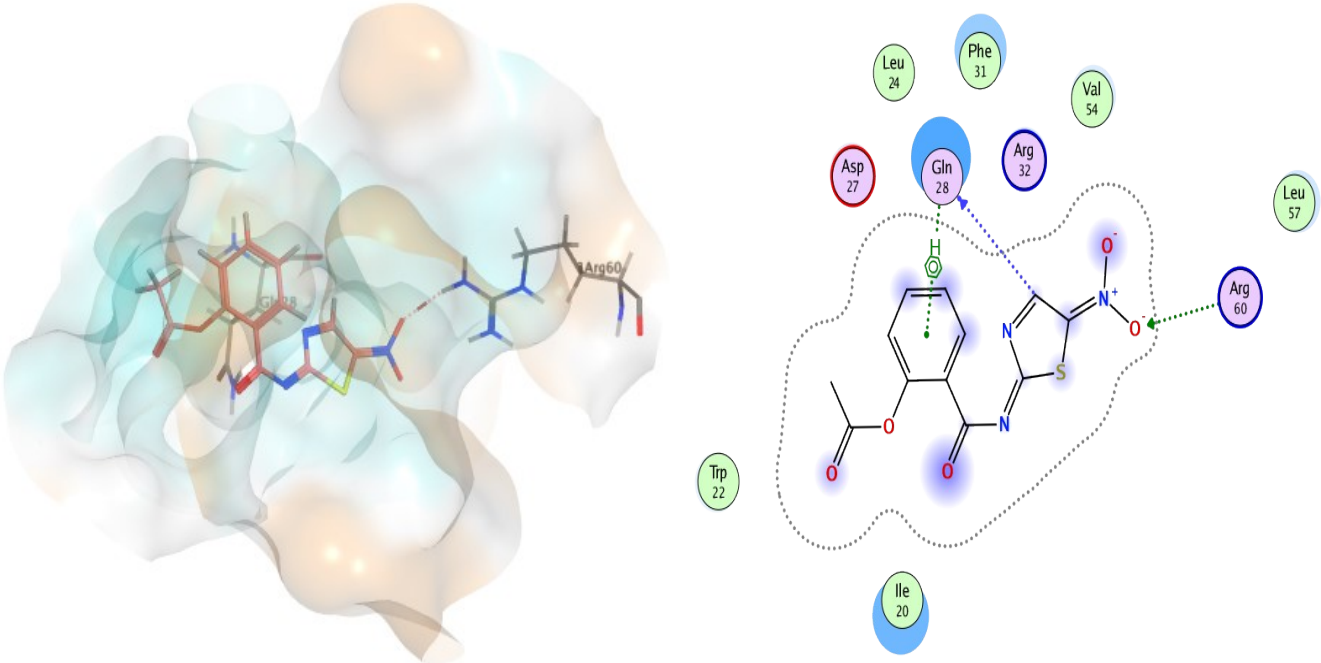


FIGURE S63. Interaction of NTZ with the active site of DHFR (6DDW).

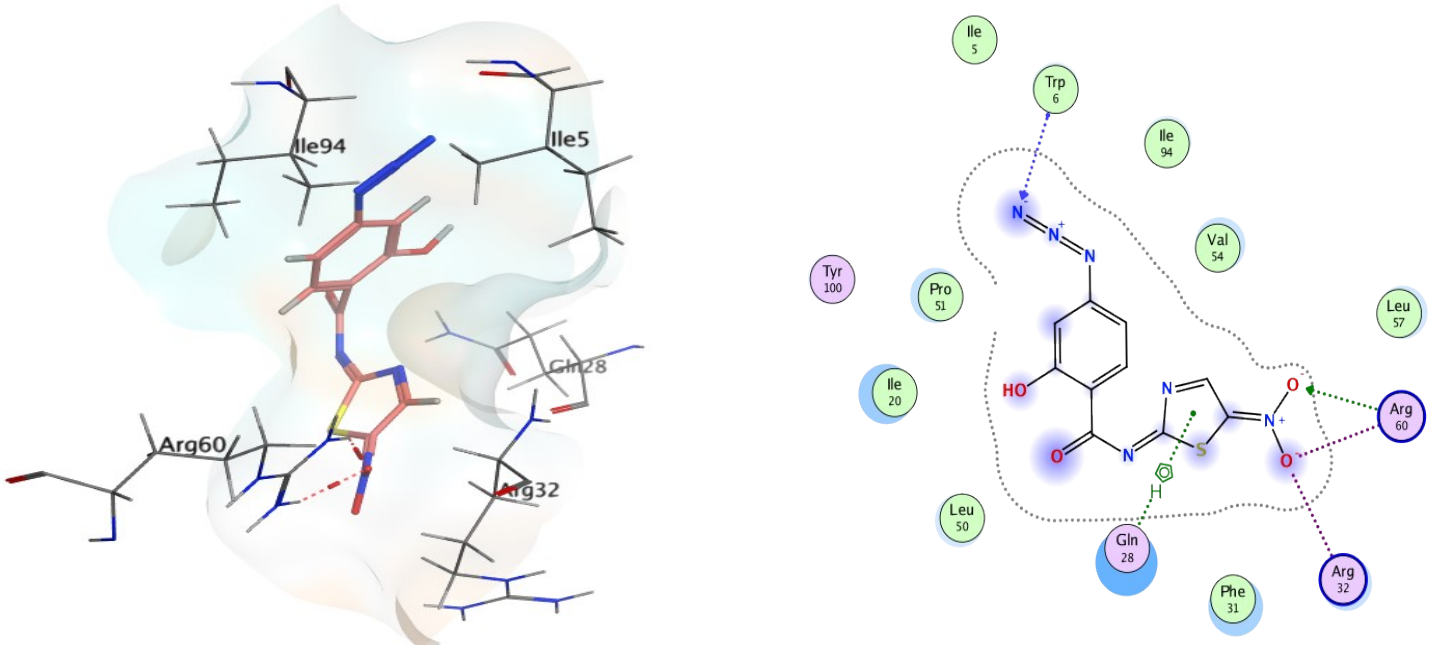


FIGURE S64. Interaction of compound 3a with the active site of DHFR (6DDW).

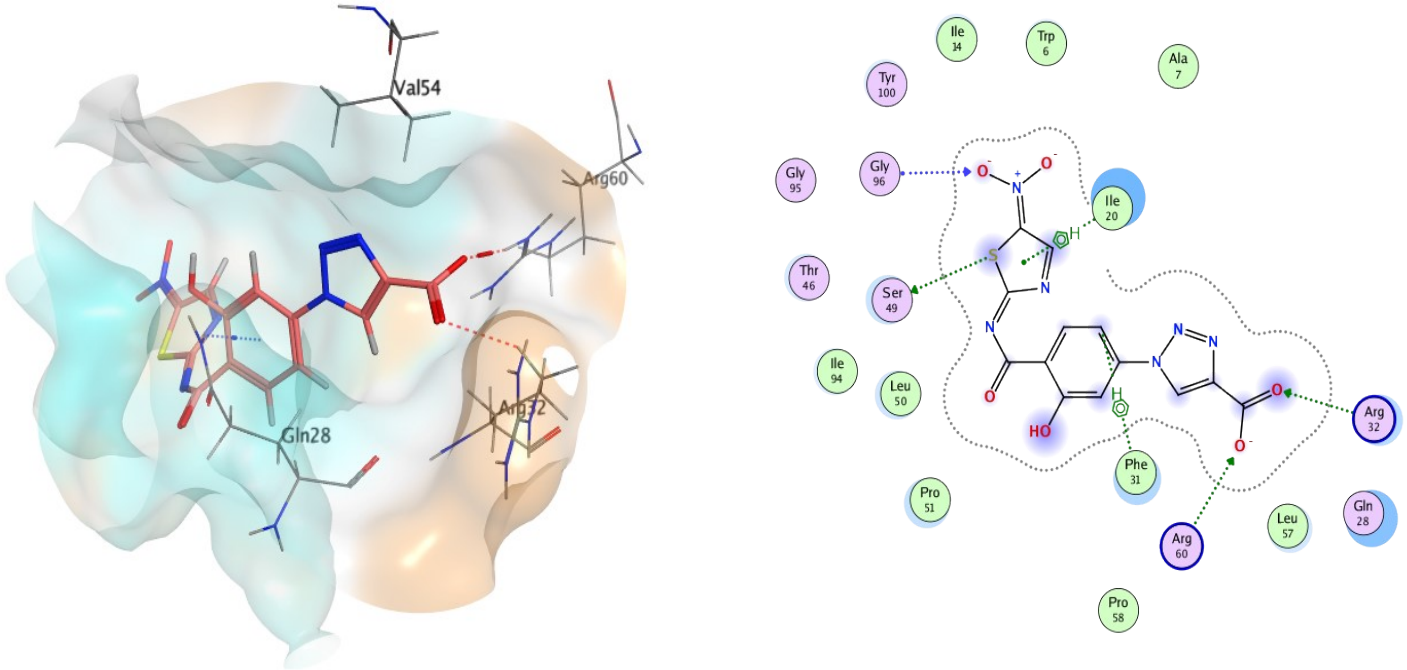


FIGURE S65. Interaction of compound 5b with the active site of DHFR (6DDW).

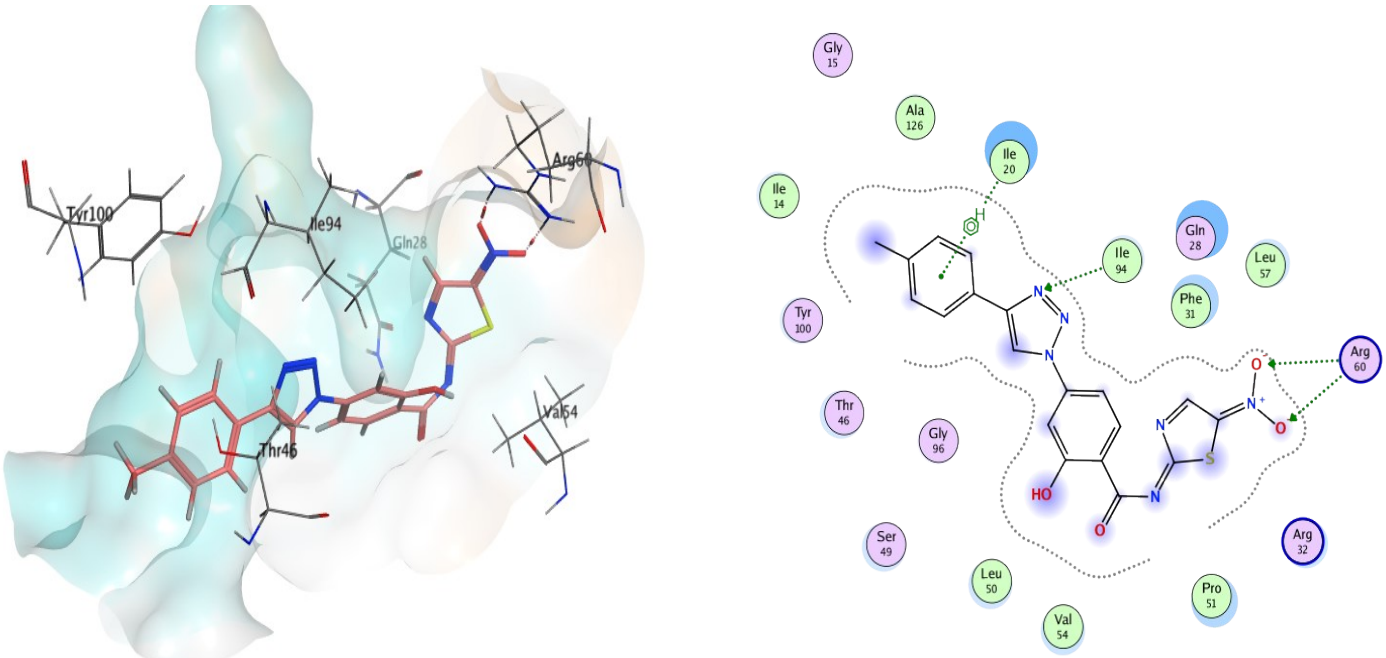


FIGURE S66. Interaction of compound 5e with the active site of DHFR (6DDW).