Supporting Information

Development of New Pyrazole–Thiophene Hybrids: Synthesis, Anticancer Assessment, and Molecular Docking Insights

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^{1}H NMR, ^{13}C NMR, and mass spectra of the new synthesized pyrazole–thiophene hybrids (**3a-c**, **5a-c**, **7a-c**, and **9a,b**)

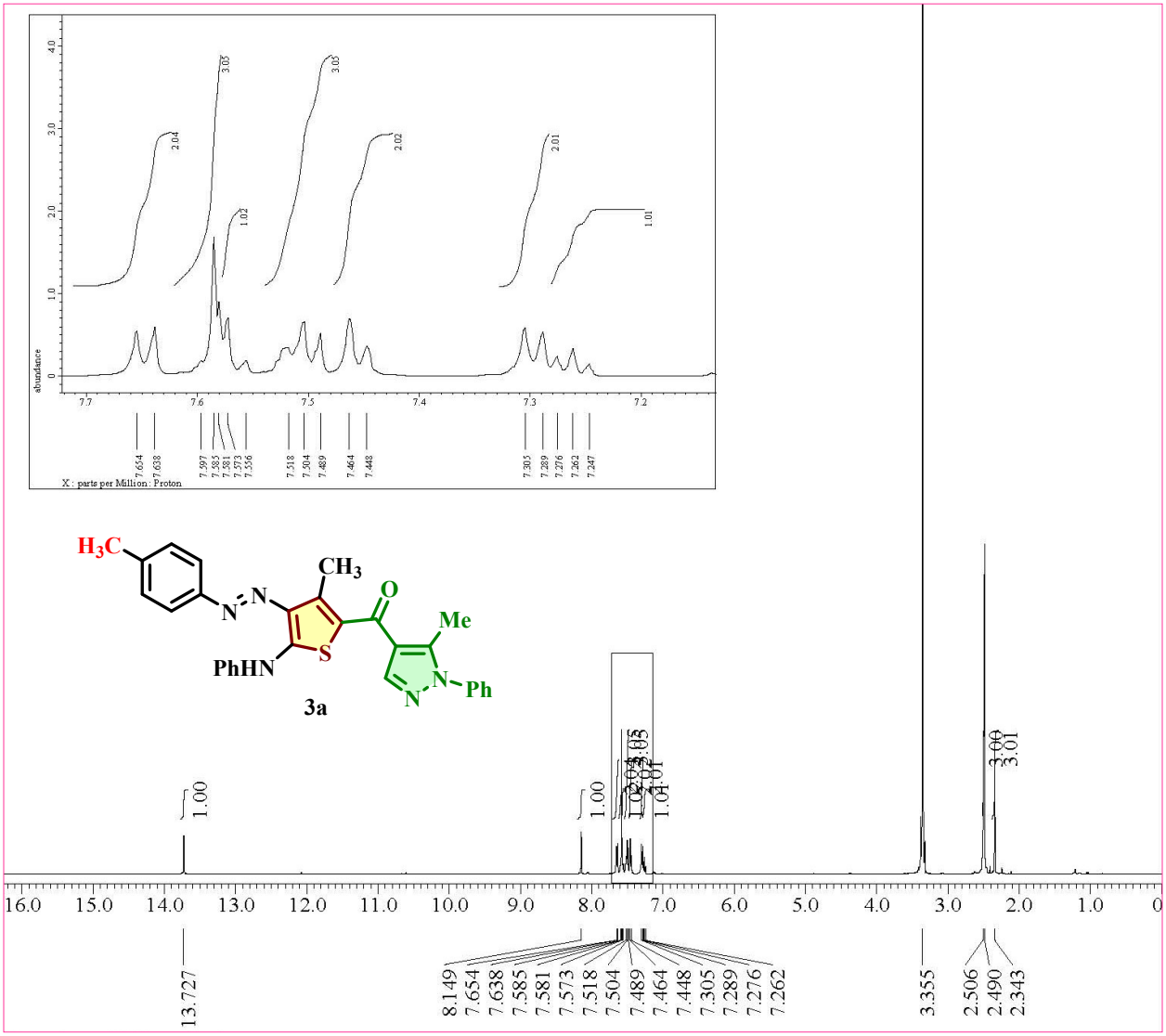


Figure S1. ^{1}H-NMR spectrum of compound **3a**.

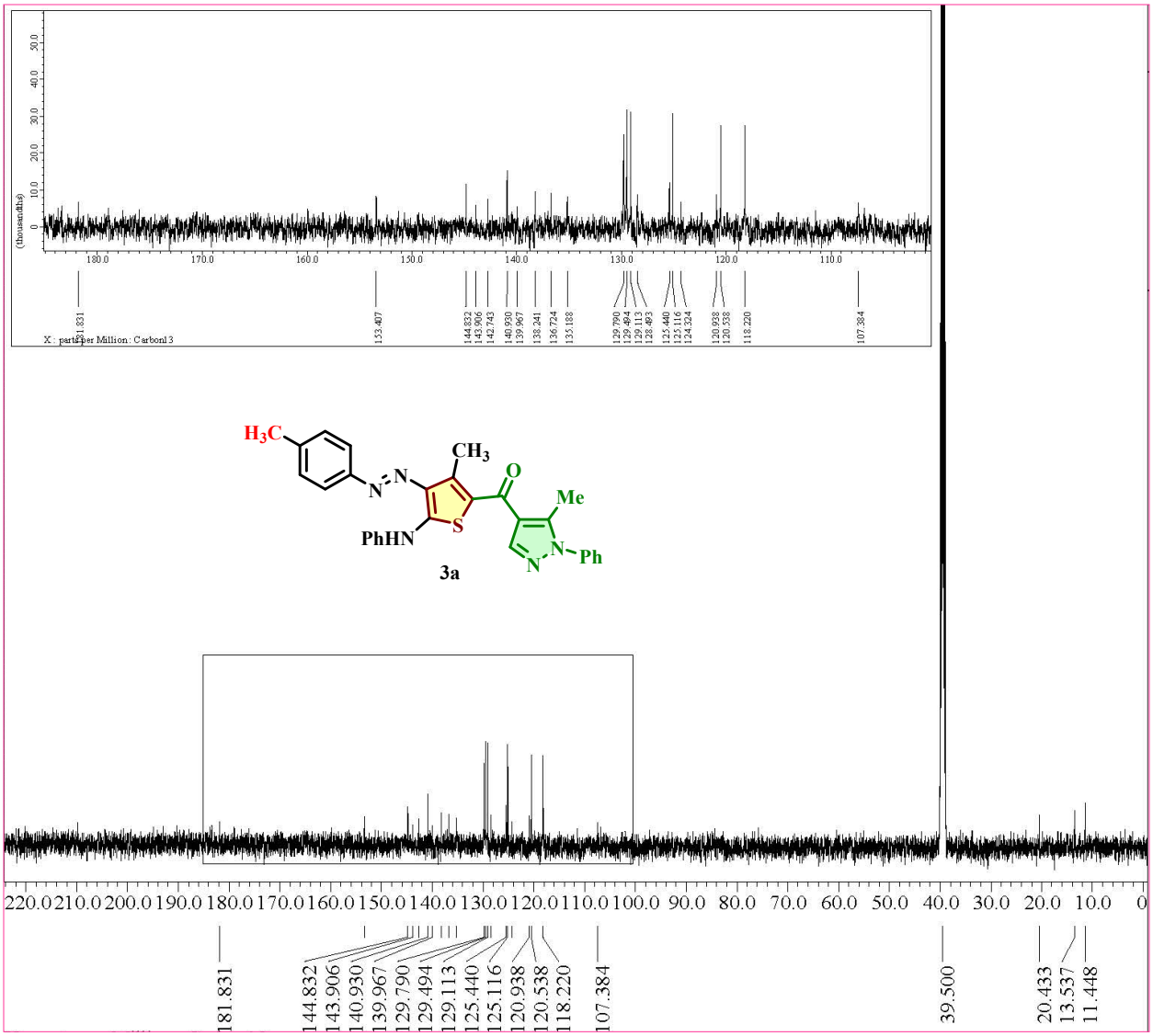


Figure S2. ^{13}C-NMR spectrum of compound **3a**.

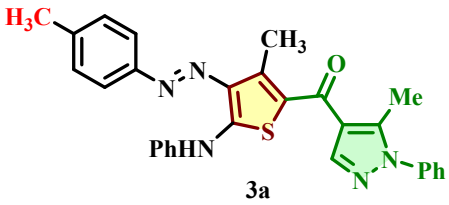


Figure S3. Mass spectrum of compound **3a**.

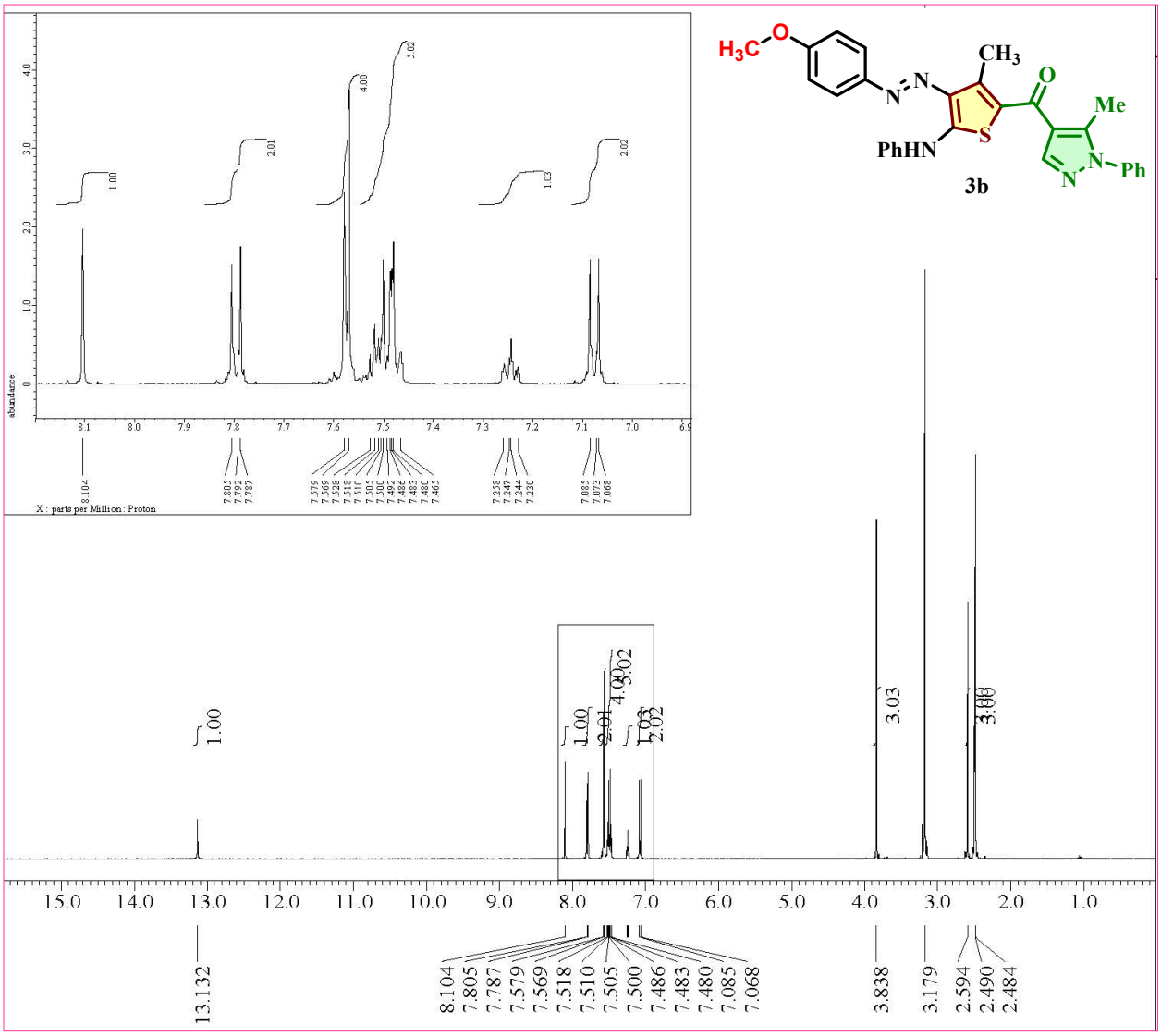


Figure S4. ^{1}H-NMR spectrum of compound **3b**.

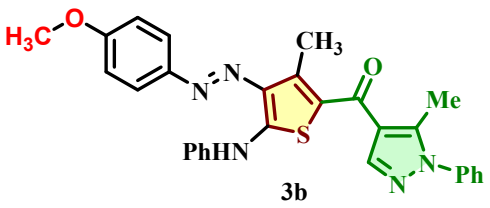


Figure S5. Mass spectrum of compound **3b**.

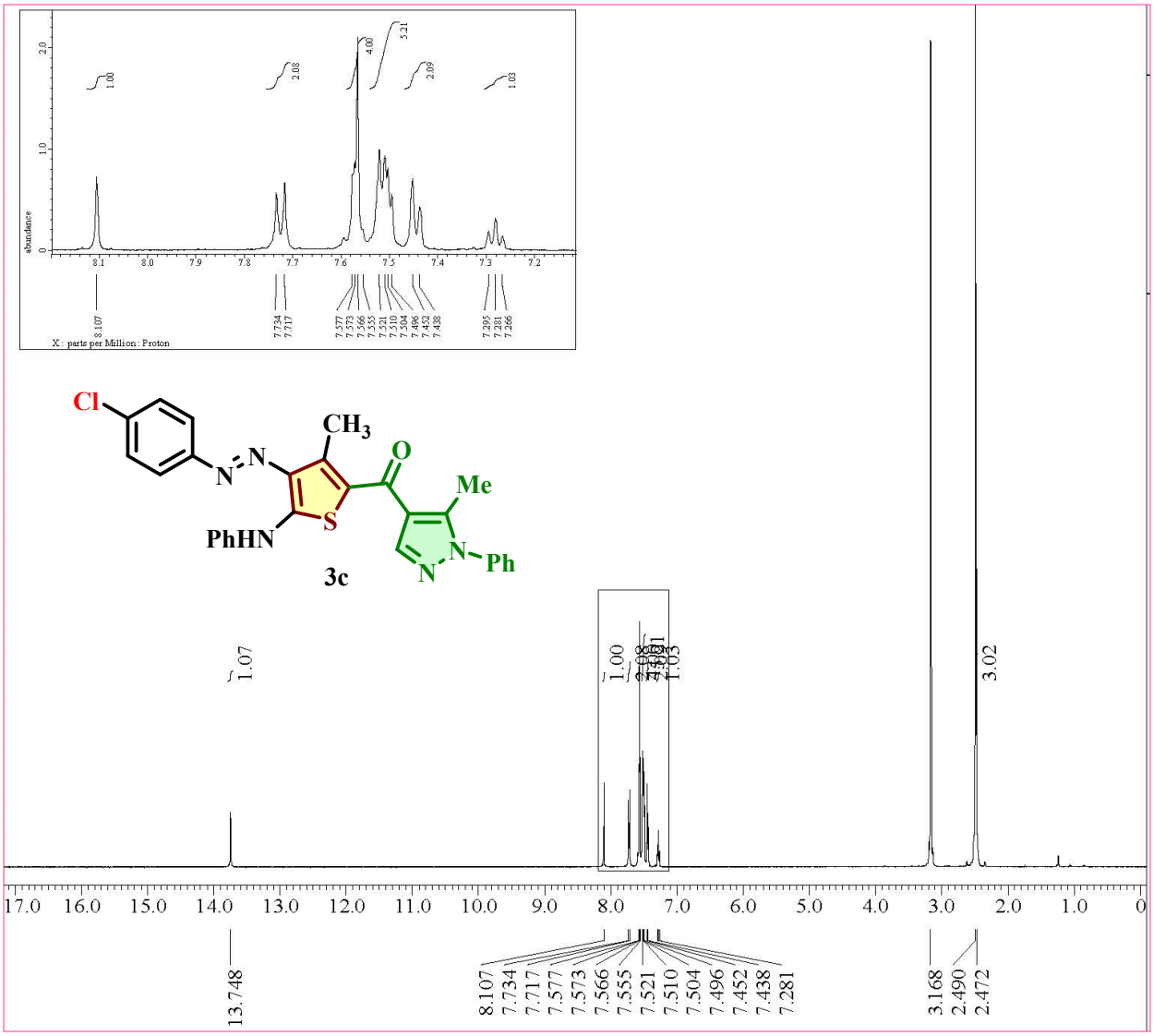


Figure S6. [1]H-NMR spectrum of compound **3c**.

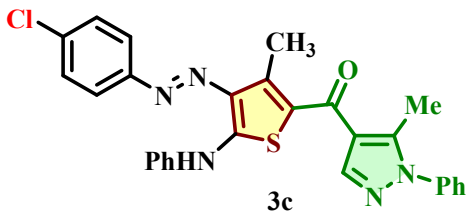


Figure S7. Mass spectrum of compound **3c**.

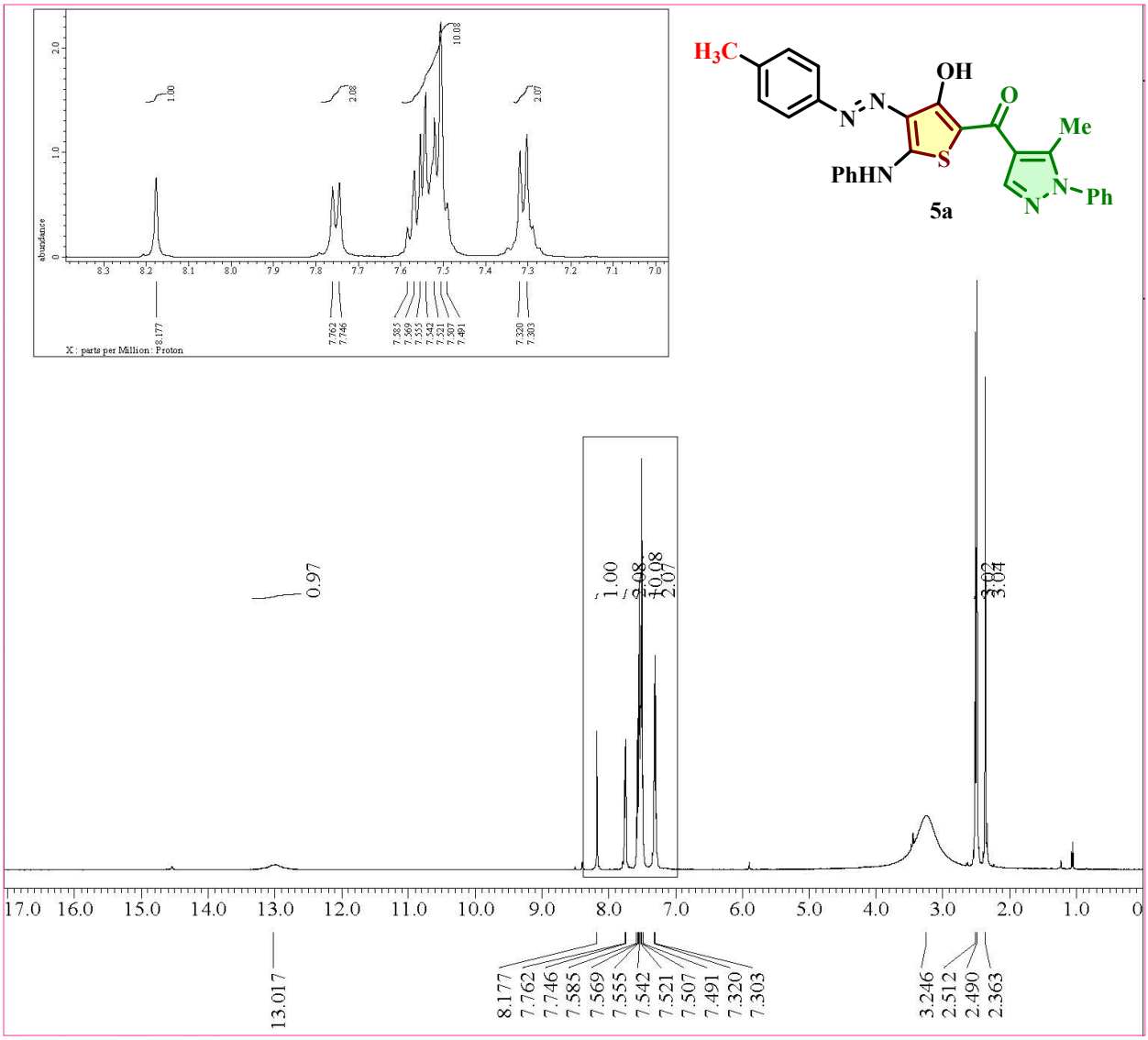


Figure S8. ^{1}H-NMR spectrum of compound **5a**.

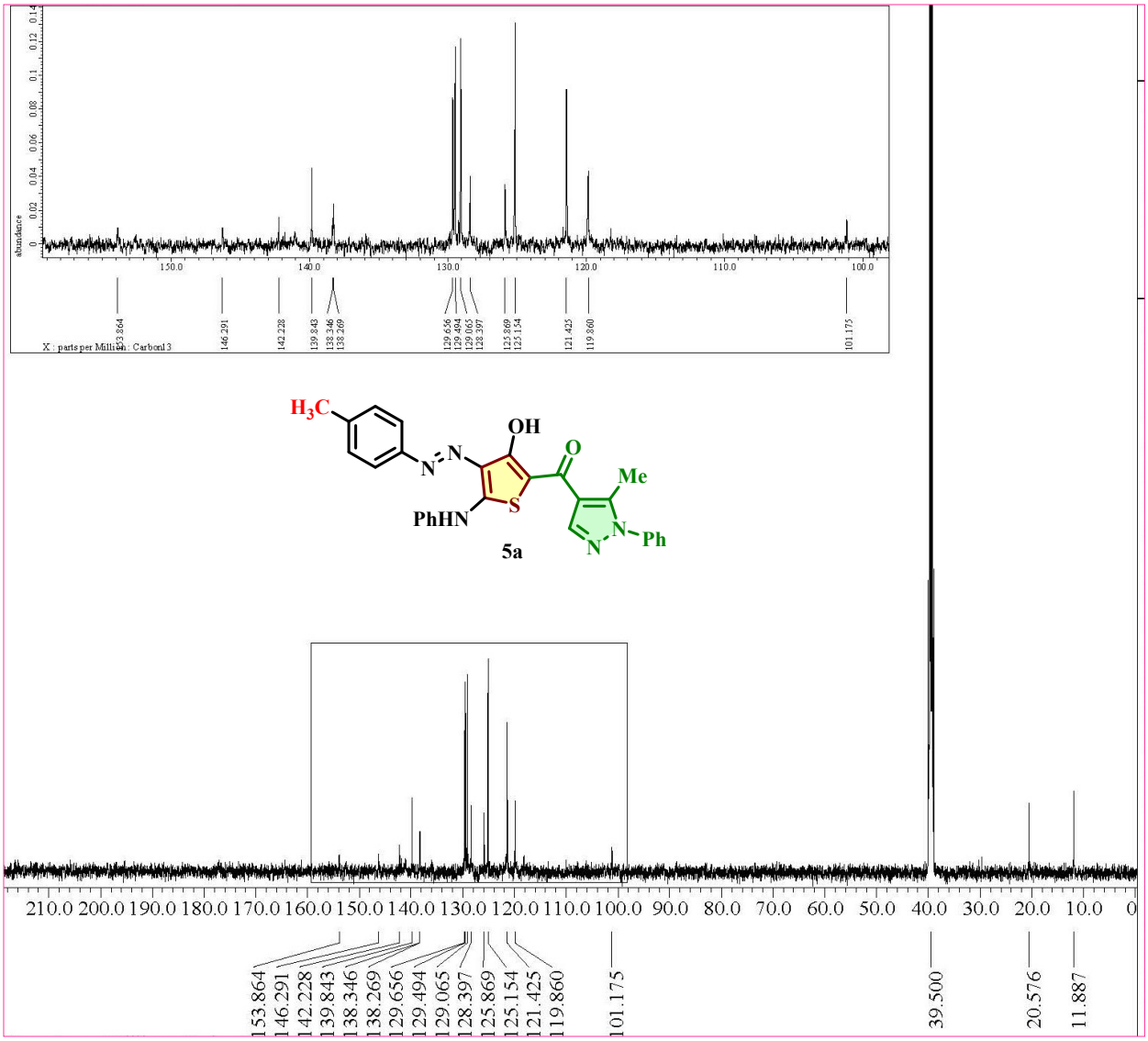


Figure S9. ^{13}C-NMR spectrum of compound **5a**.

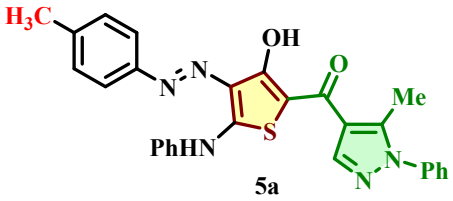


Figure S10. Mass spectrum of compound **5a**.

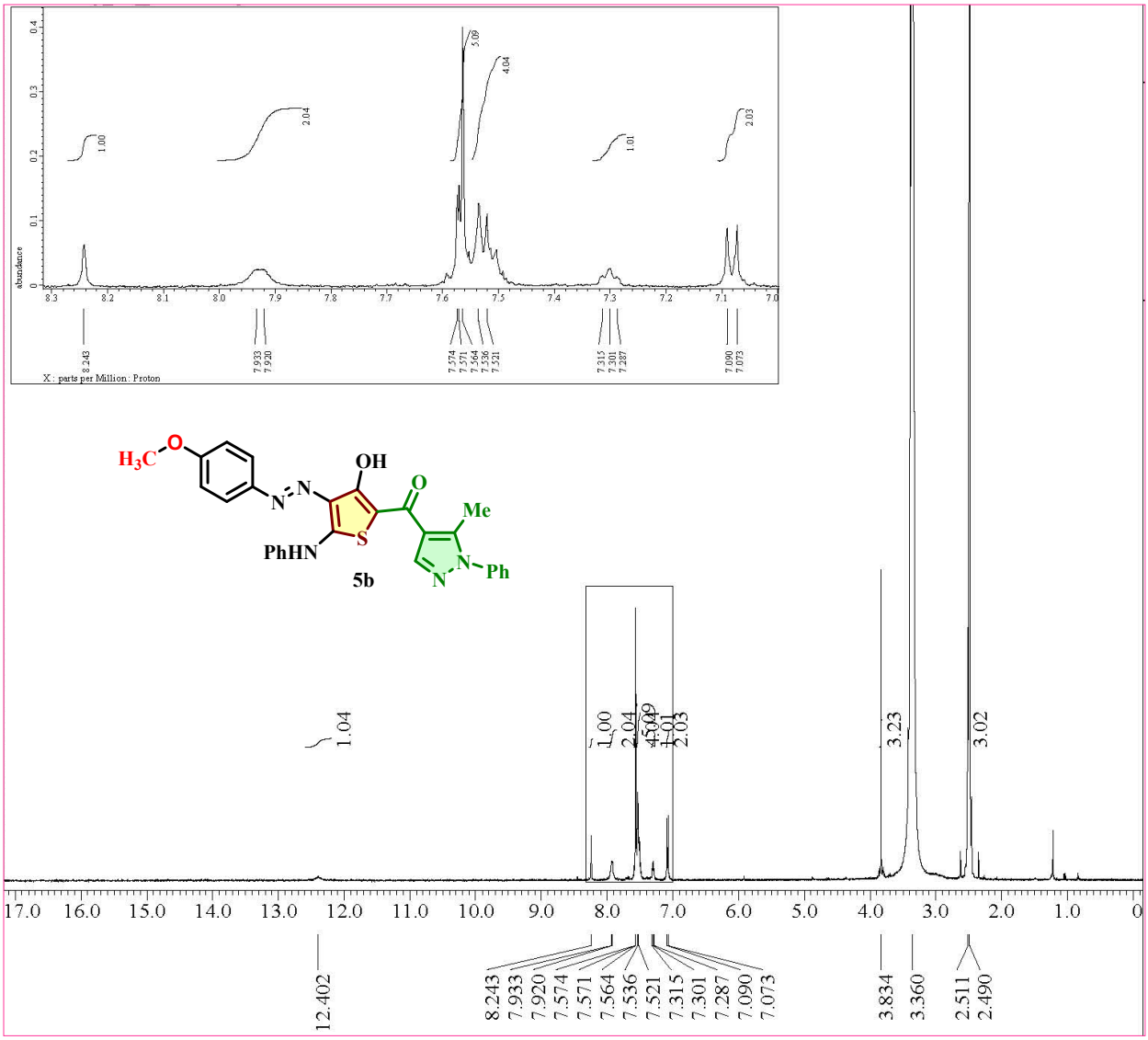


Figure S11. ^{1}H-NMR spectrum of compound **5b**.

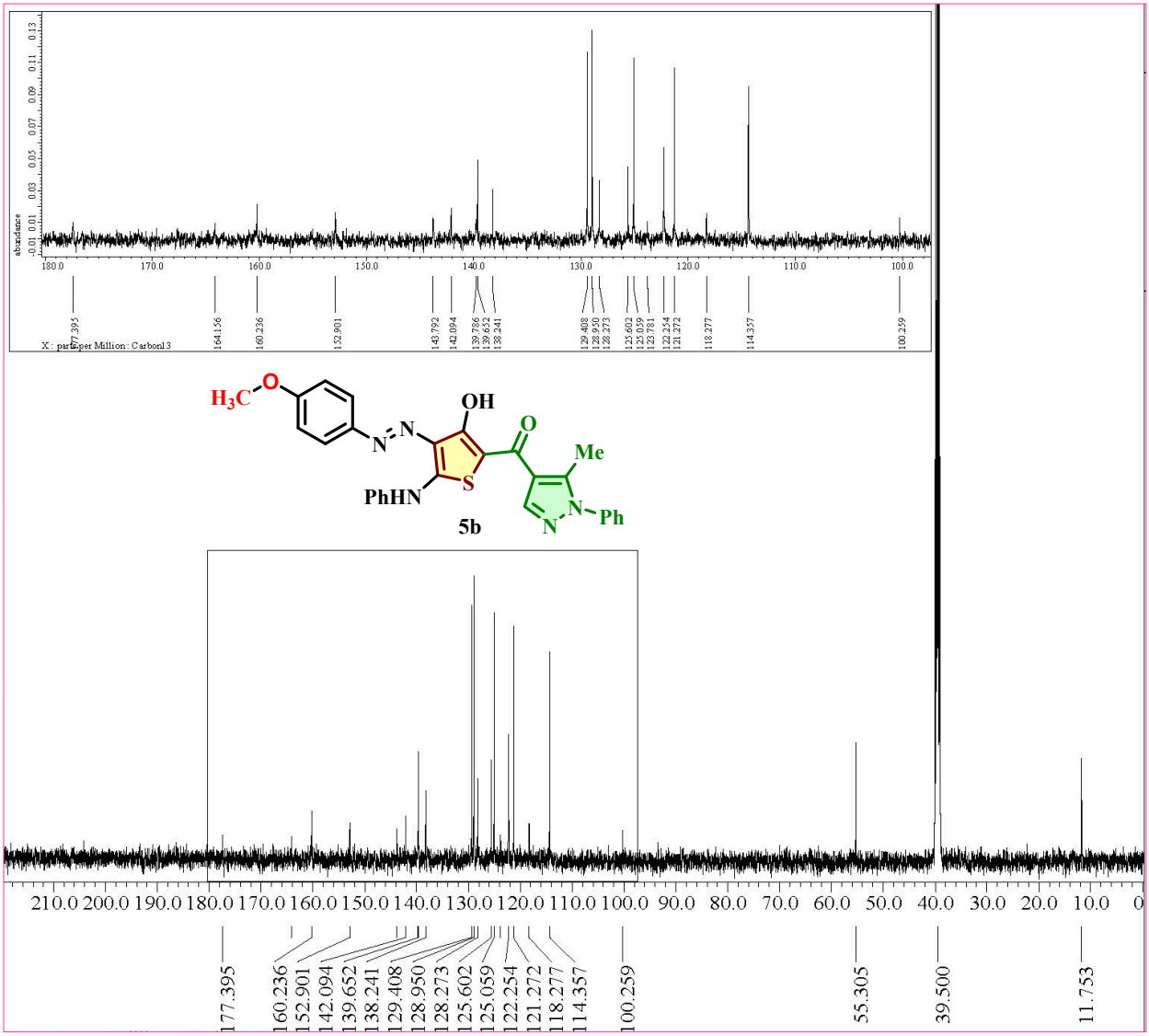
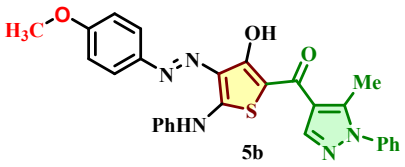


Figure S12. ^{13}C-NMR spectrum of compound **5b**.



5b

Figure S13. Mass spectrum of compound **5b**.

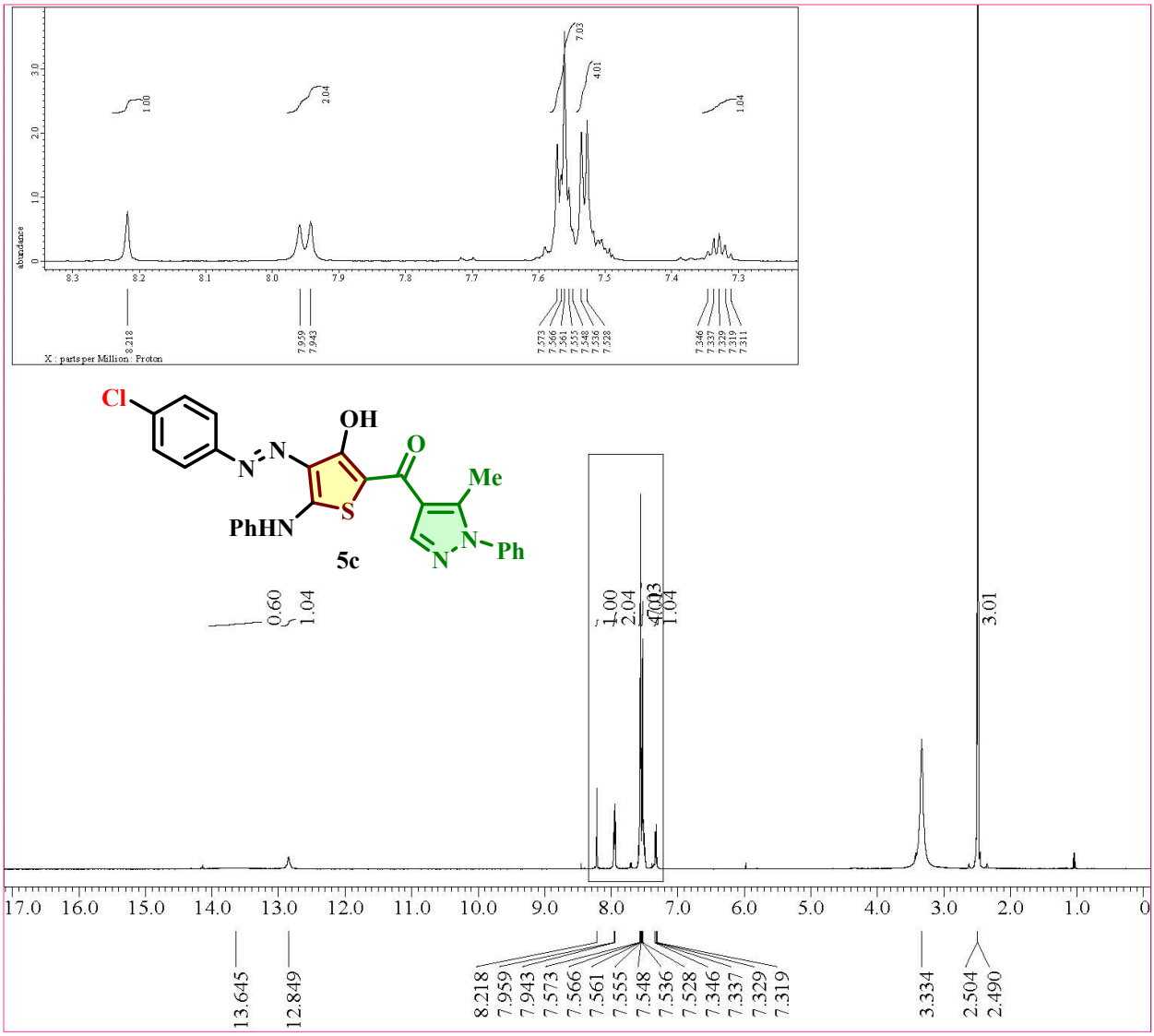


Figure S14. ^{1}H-NMR spectrum of compound **5c**.

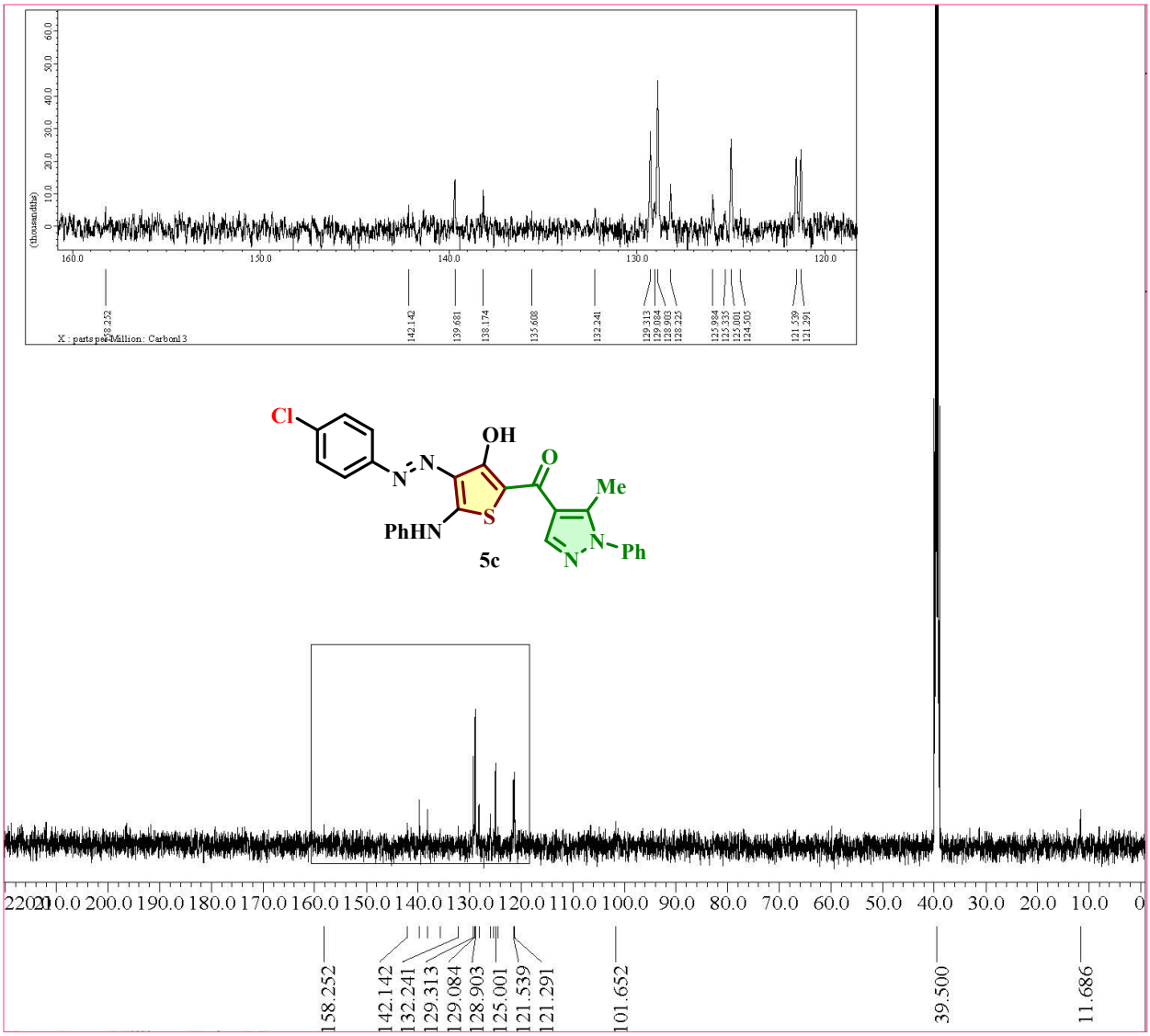


Figure S15. ^{13}C-NMR spectrum of compound **5c**.

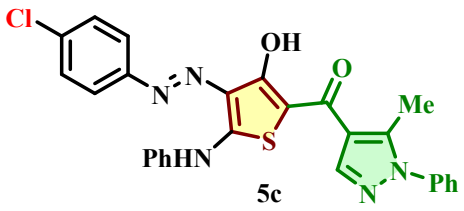


Figure S16. Mass spectrum of compound **5c**.

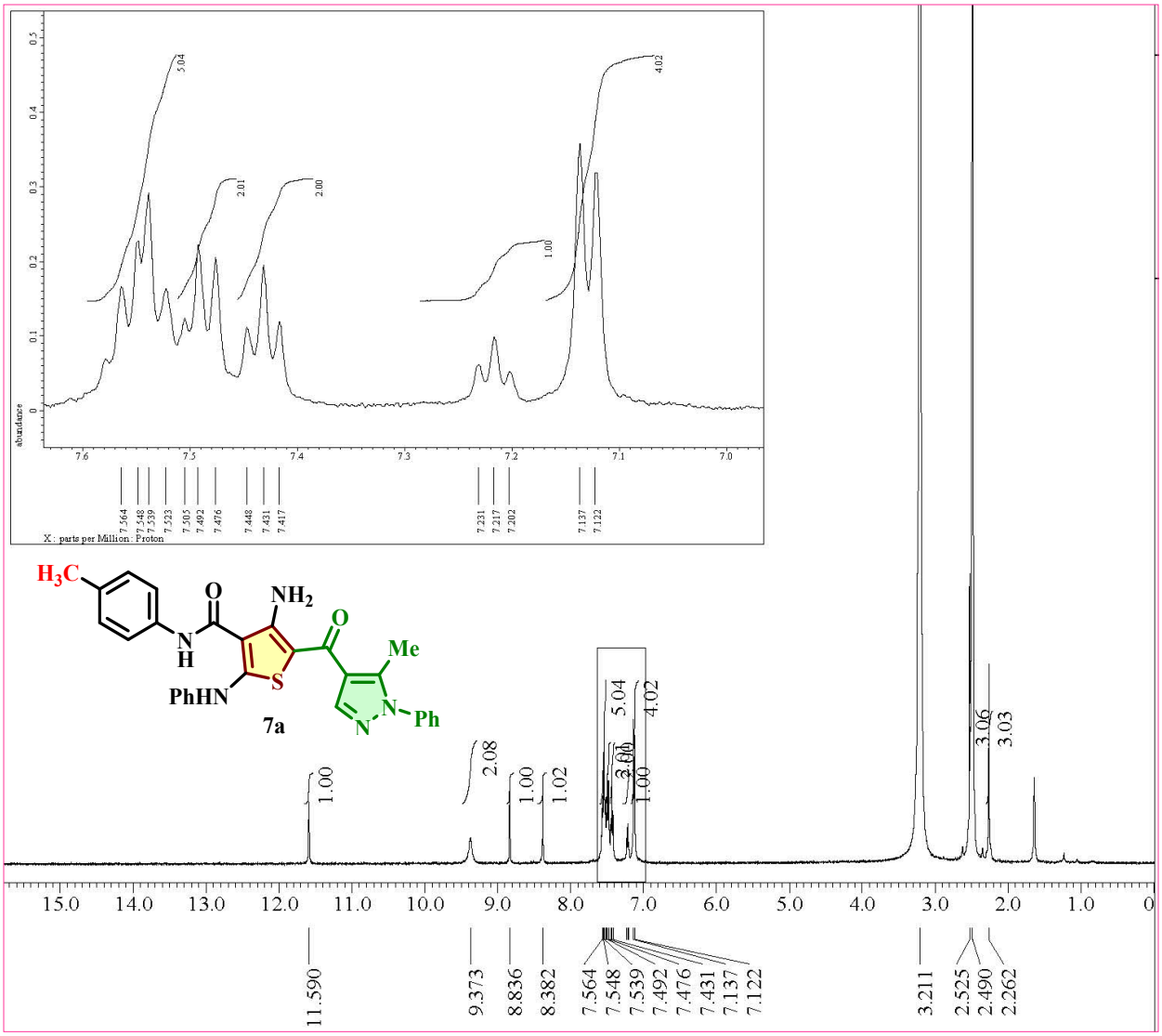


Figure S17. ^{1}H-NMR spectrum of compound **7a**.

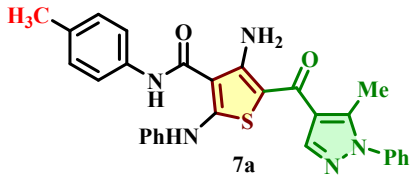


Figure S18. Mass spectrum of compound **7a**.

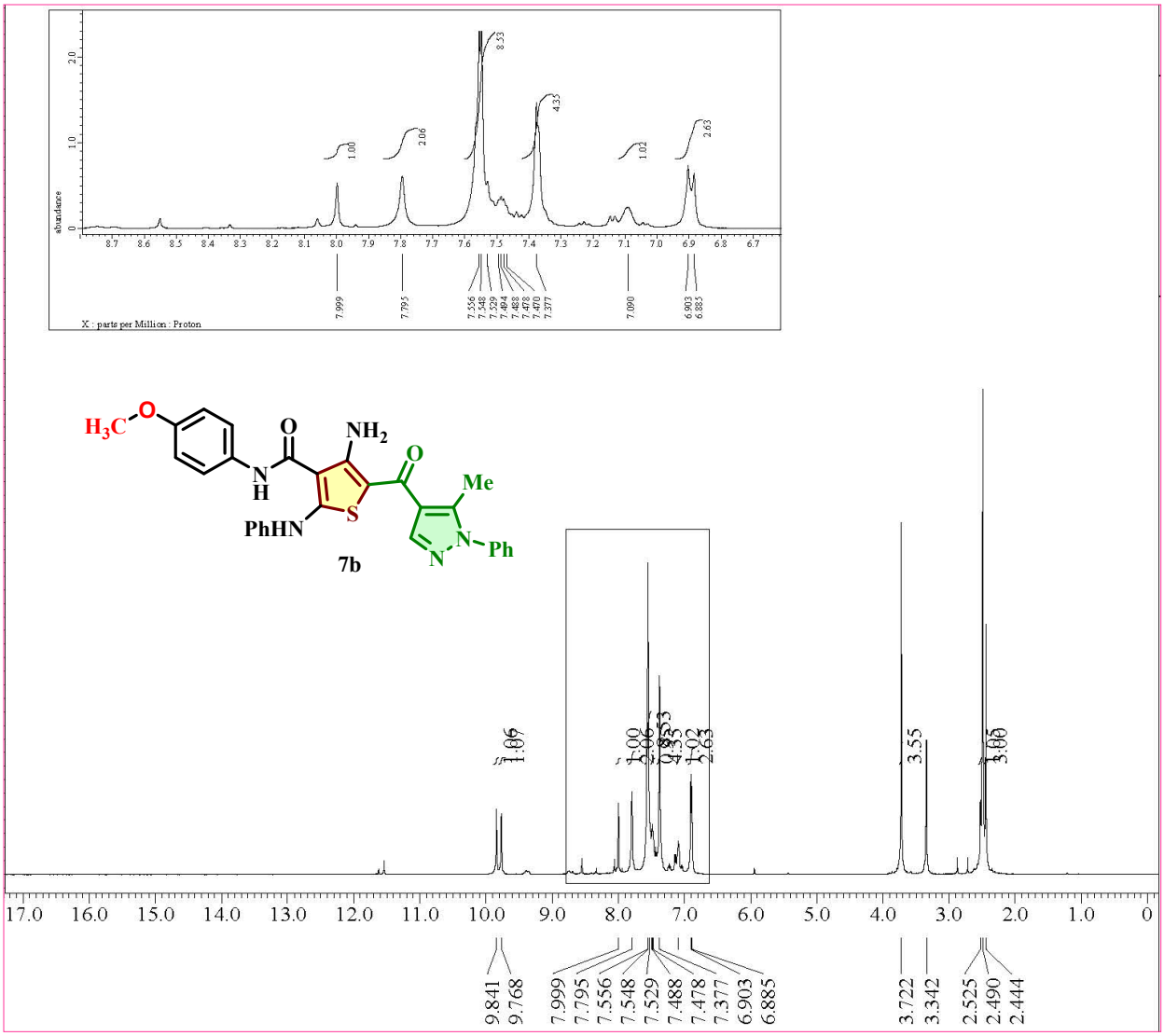


Figure S19. ^{1}H-NMR spectrum of compound **7b**.

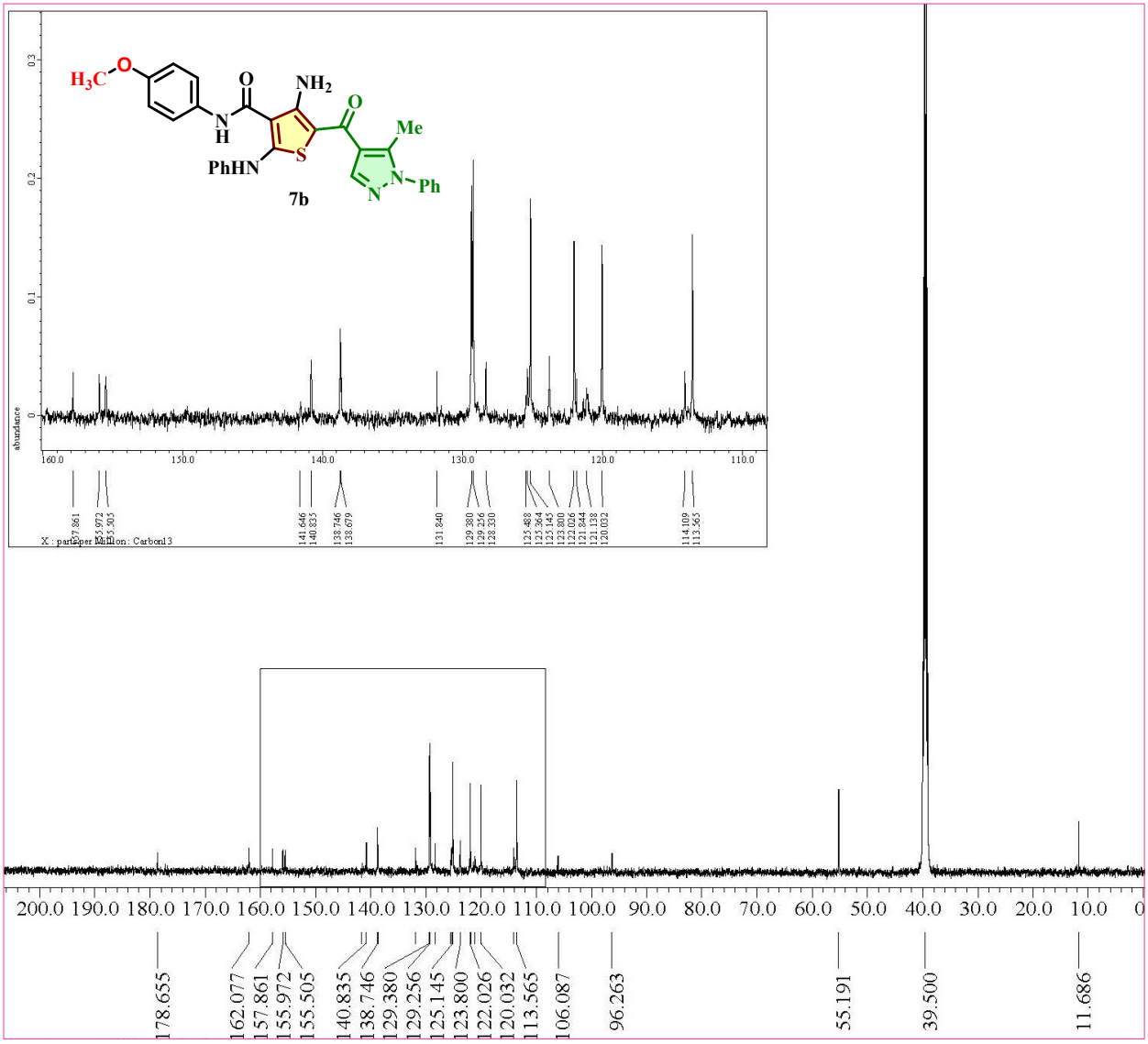


Figure S20. ^{13}C-NMR spectrum of compound **7b**.

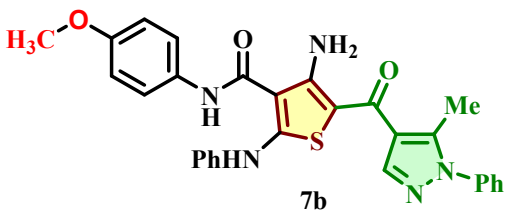


Figure S21. Mass spectrum of compound **7b**.

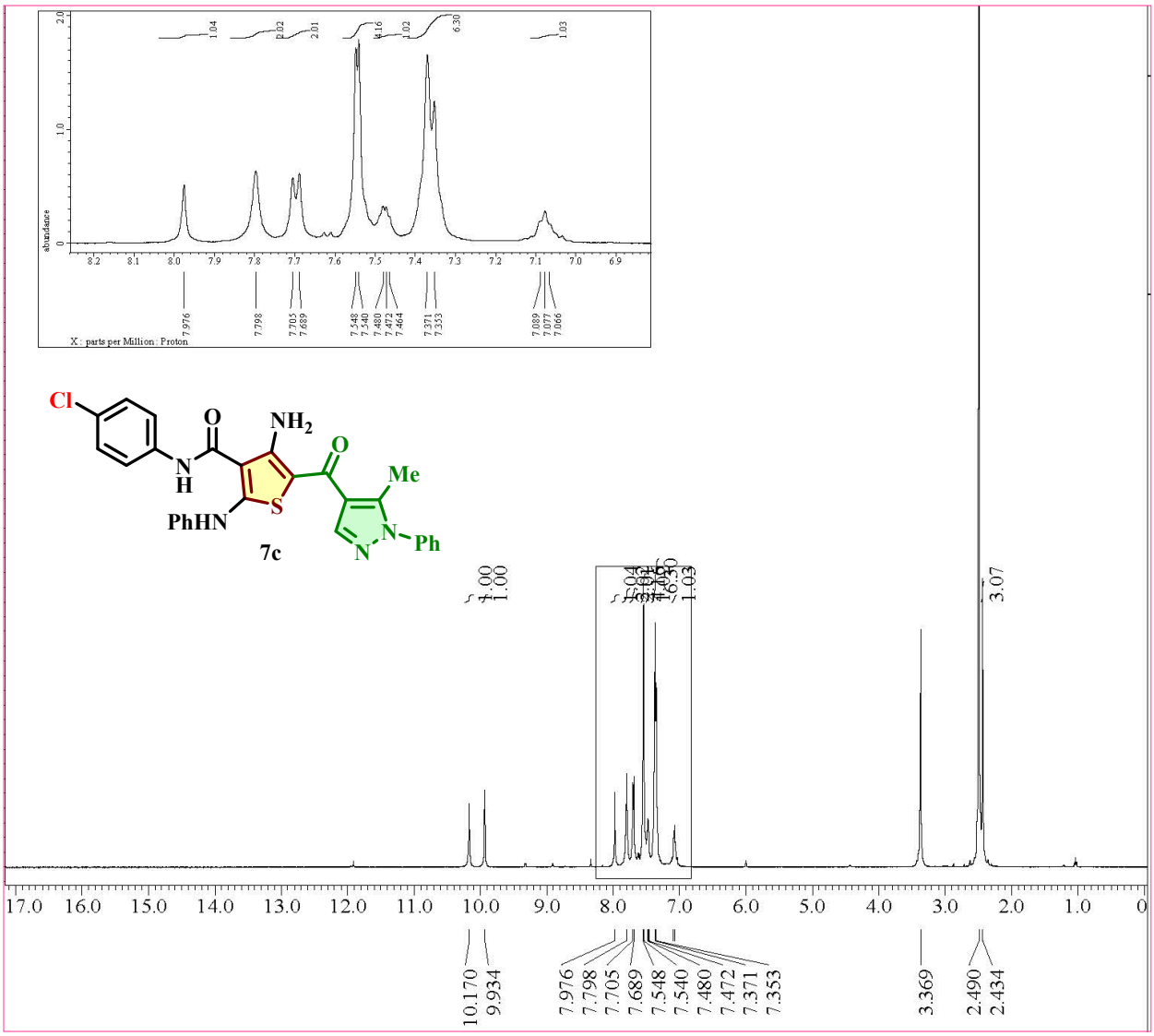


Figure S22. ^{1}H-NMR spectrum of compound **7c**.

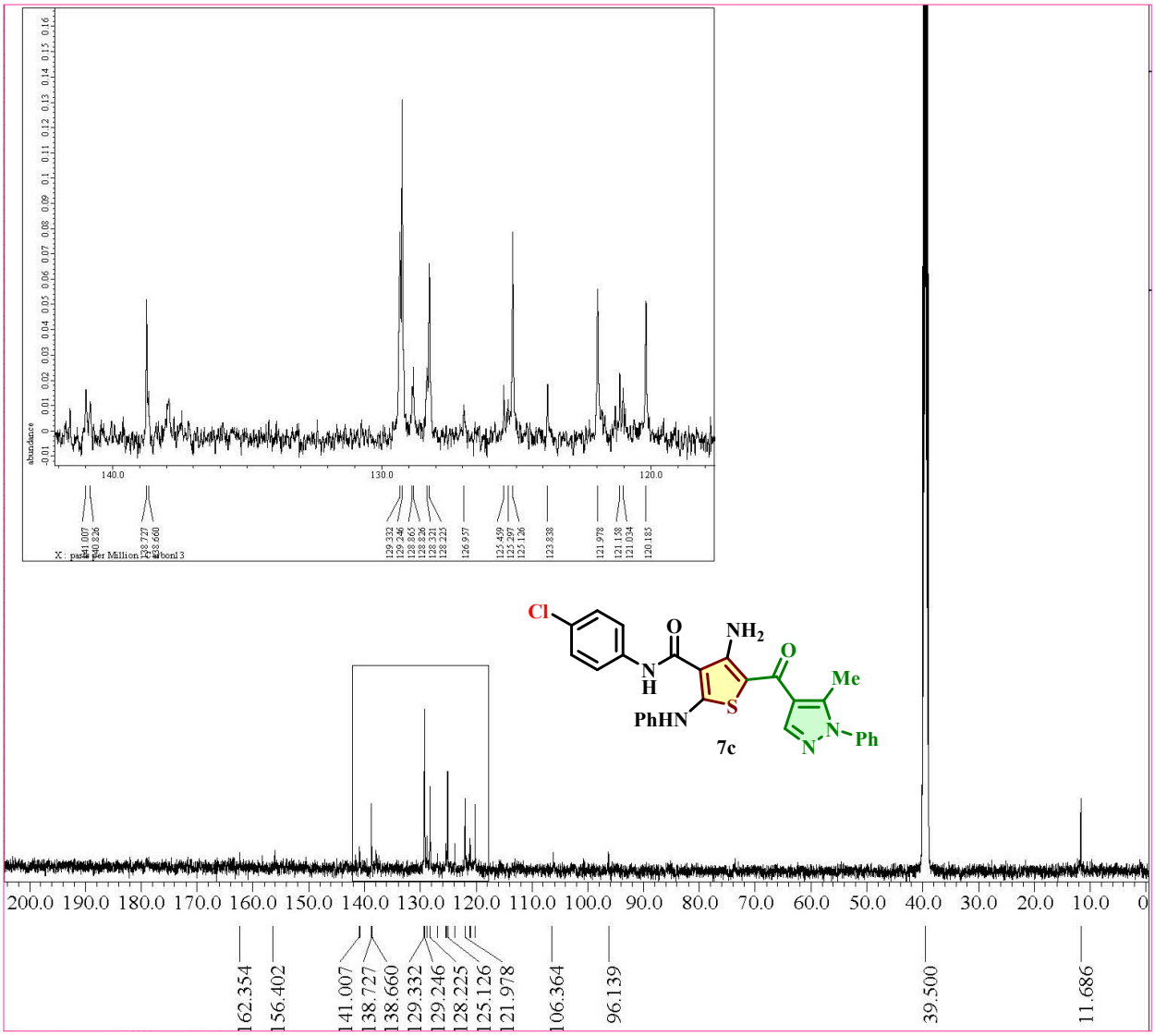


Figure S23. ^{13}C-NMR spectrum of compound **7c**.

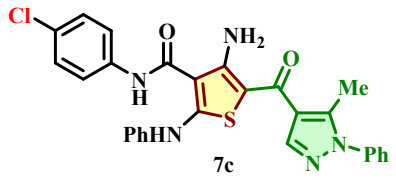


Figure S24. Mass spectrum of compound **7c**.

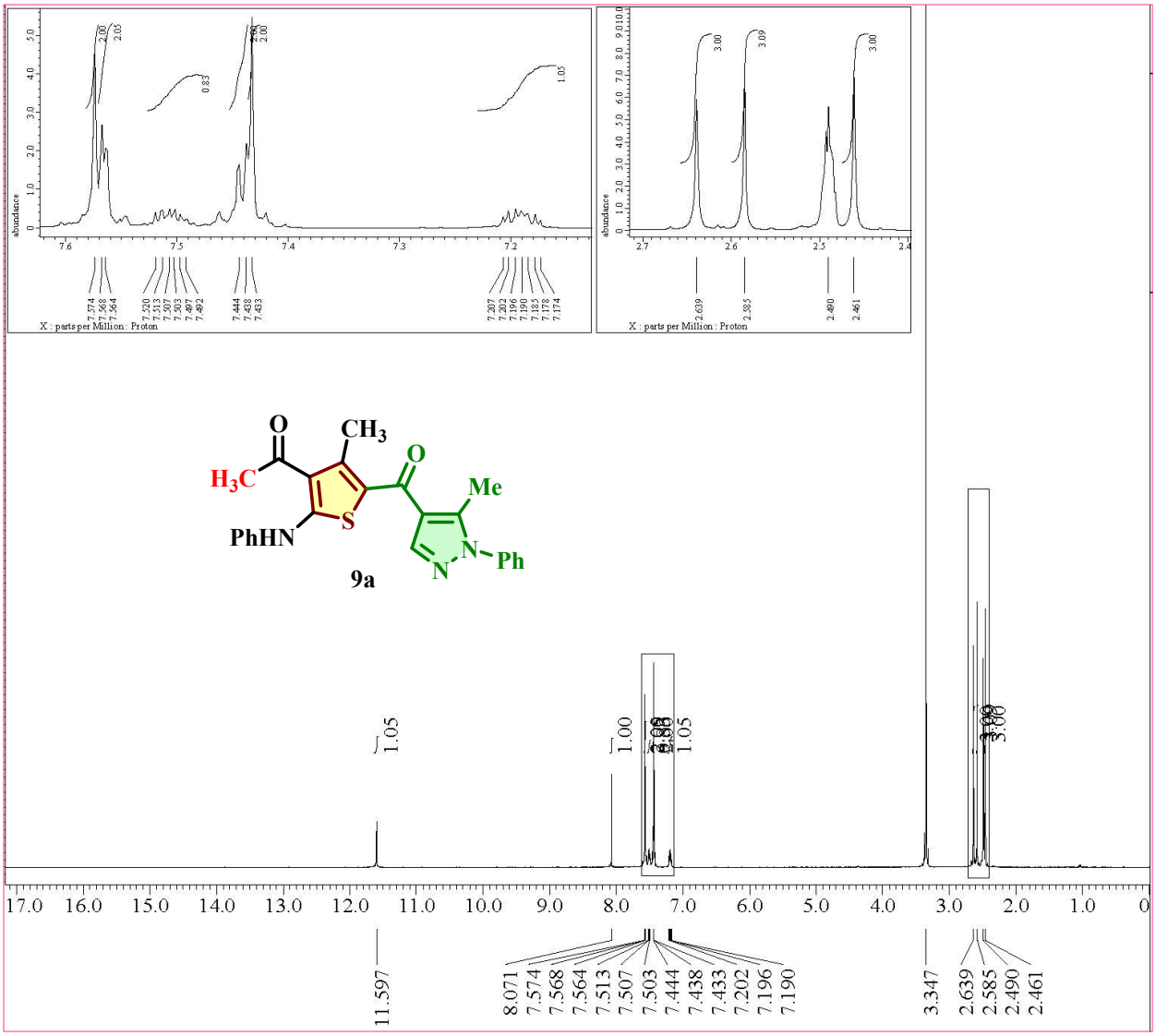


Figure S25. [1]H-NMR spectrum of compound **9a**.

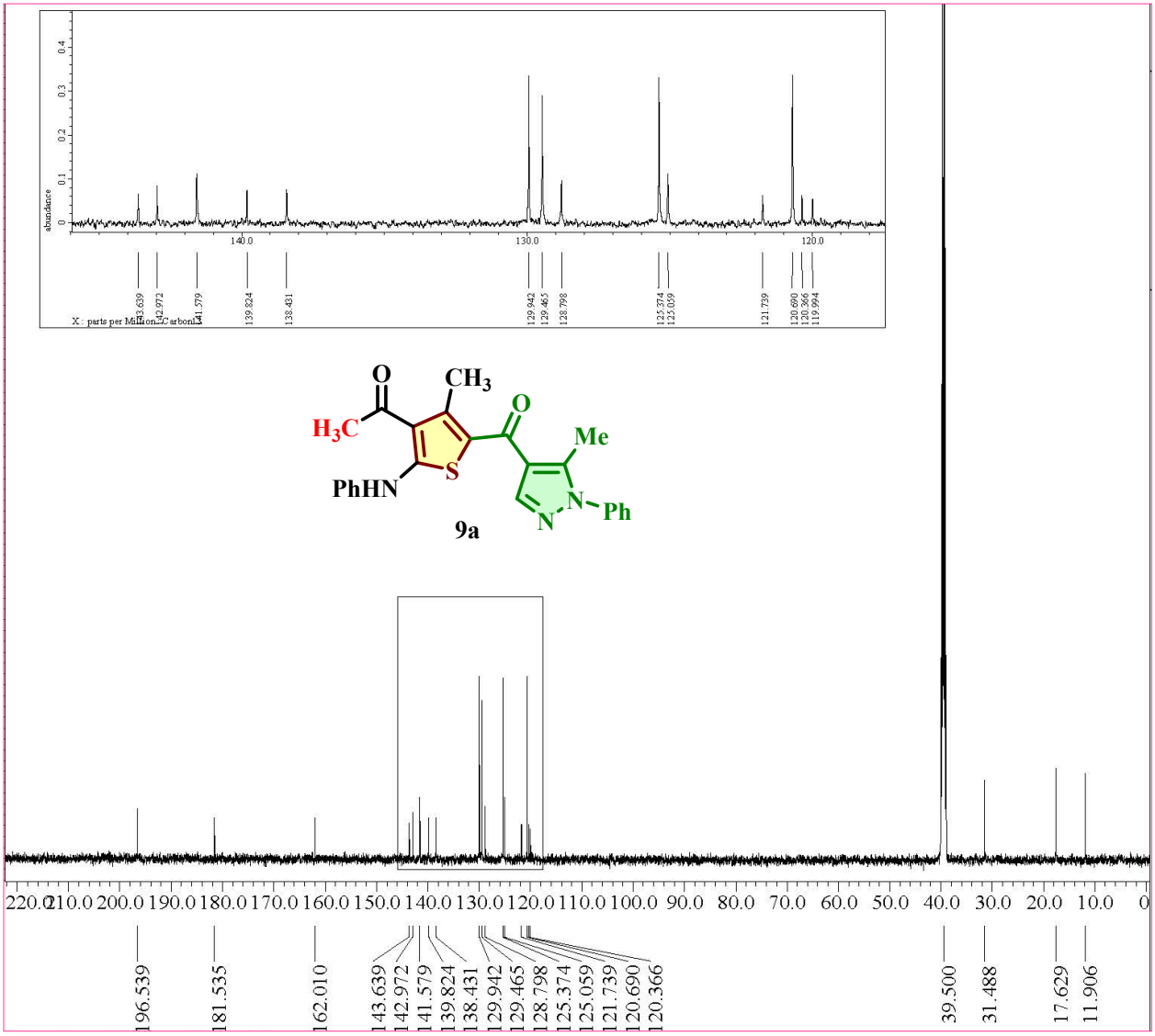


Figure S26. ^{13}C-NMR spectrum of compound **9a**.

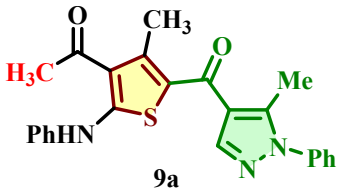


Figure S27. Mass spectrum of compound **9a**.

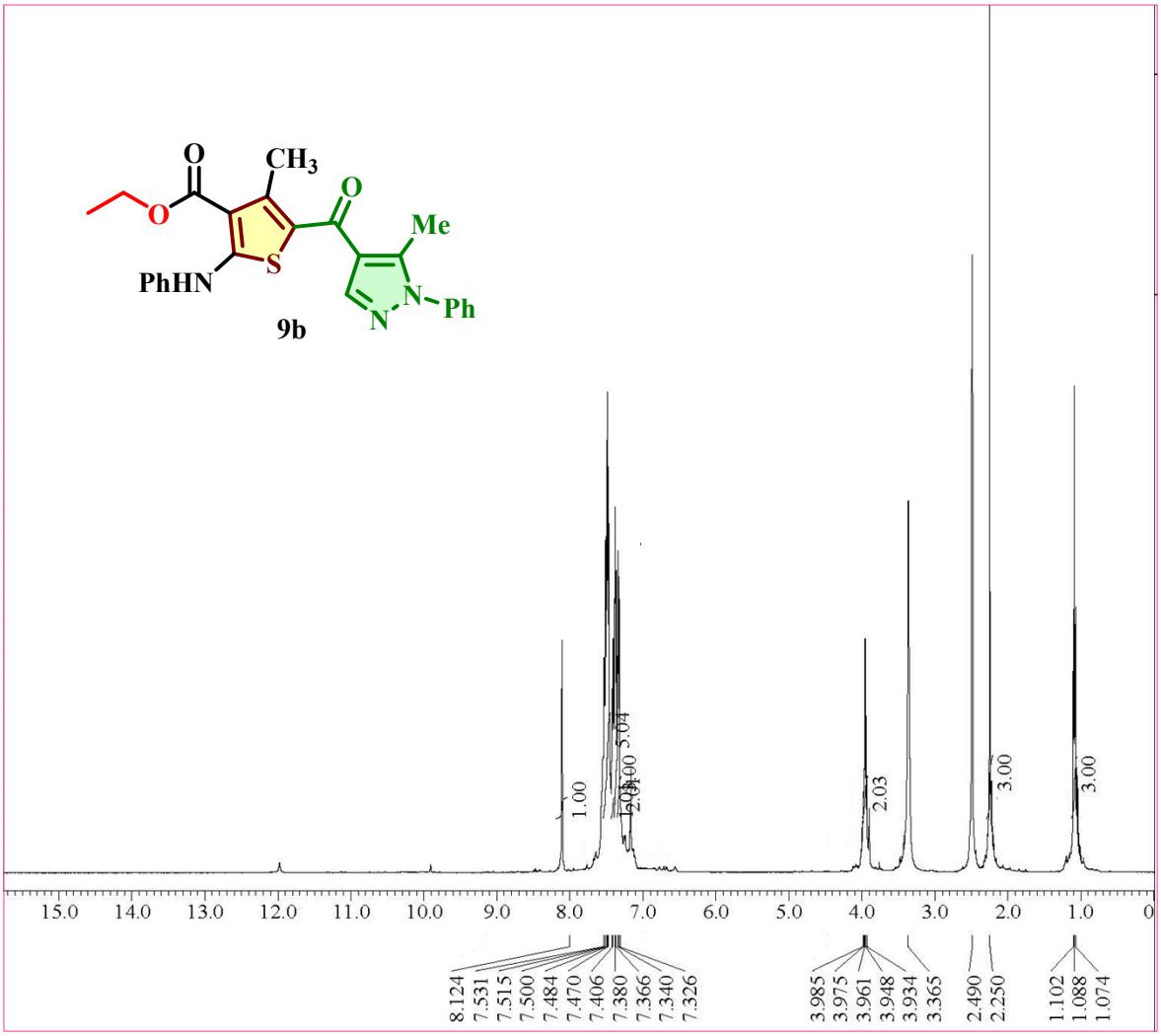


Figure S28. ^{1}H-NMR spectrum of compound **9b**.

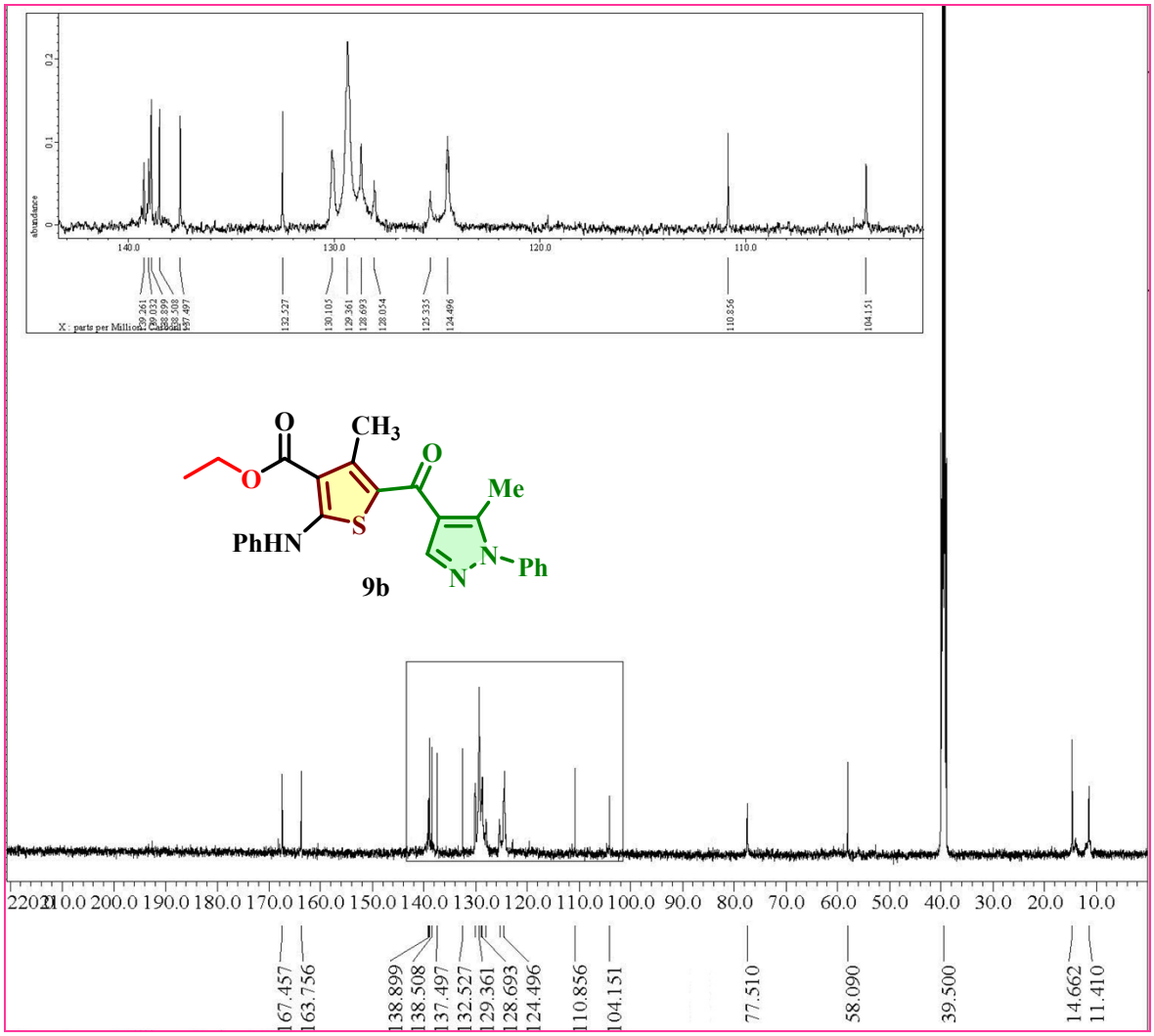


Figure S29. ^{13}C-NMR spectrum of compound **9b**.

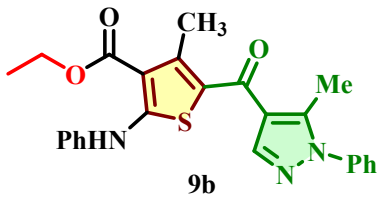


Figure S30. Mass spectrum of compound **9b**.

Anticancer Activity

Table S1. Cell viability and growth inhibition percent after treatment of cells with 500 µM of the tested compounds.

Cpd. No.	HEPG2		MCF7	
	Cell viability (%)	Growth Inhibition (%)	Cell viability (%)	Growth Inhibition (%)
3a	5.55	94.45	3.26	96.74
3b	33.17	66.83	25.90	74.10
3c	15.46	84.54	5.74	94.26
5a	16.64	83.36	9.99	90.01
5b	7.80	92.20	4.80	95.20
5c	11.80	88.20	7.39	92.61
7a	16.19	83.81	13.13	86.87
7b	9.12	90.88	3.87	96.13
7c	10.57	89.43	7.17	92.83
9a	3.94	96.06	11.98	88.02
9b	5.81	94.19	6.05	93.95
VLB.	5.36	94.64	3.23	96.77

Molecular Docking

Table S2. Docking results of the synthesized pyrazole thienyl ketones.

Compound no.	S (Kcal/mol)	RMSD	ligand bindings with the amino acid residues	Binding types	Bond Length (Å)
3a	-6.6225	1.8953	Toluyl-ring with Arg105	pi-cation	3.99
3b	-6.3945	1.5594	N14 with Gly104	H-acceptor	3.68
			The phenyl-ring with Arg68	pi-cation	4.51
			The anisyl-ring with Arg105	pi-cation	4.38
3c	-6.8042	1.2834	Cl16 with Glu119	H-donor	3.68
			N3 of the pyrazole-ring with Arg105	H-acceptor	3.59
			The aniline-ring with Arg68	pi-cation	4.03
			The pyrazole-ring with Arg105	pi-cation	4.03
5a	-6.2690	1.0757	S11 of the thiophene-ring with Glu119	H-donor	4.25
			The toluyl-ring with Ala72	pi-H	3.92
5b	-6.6781	1.8756	N29 of the aniline-ring with Tyr67	H-donor	3.23
			The anisyl-ring with Arg66	pi-cation	3.78
5c	-6.6810	1.5959	O8 of the hydroxyl group with Ala72	H-donor	2.88
7a	-7.1000	1.5746	O7 of the amide group with Arg105	H-acceptor	3.24
			C26 of the phenyl-ring with Phe71	H-pi	4.45
			The pyrazole-ring with Arg66	pi-cation	4.02
			The aniline-ring with Gly104	pi-H	3.59
7b	-6.8632	1.4385	The aniline-ring with Arg68	pi-H	3.64
7c	-7.3575	1.5156	O7 of the amide group with Arg66	H-acceptor	3.35
			The aniline-ring with Arg68	pi-cation	3.53
			The pyrazole-ring Arg105	pi-cation	3.71
9a	-6.1589	1.9037	O1 of the acetyl group with Arg68	H-acceptor	3.30
9b	-6.0251	1.2354	The phenyl-ring with Gly104	pi-H	3.89
Vinblastine	-5.9584	1.2016	O20 of the hydroxyl group with Gly104	H-acceptor	2.87

Pharmacokinetic Character

Table S3. *In Silico* pharmacokinetic properties of the synthesized compounds.

Compound no.	MW [a]	Log P [b]	ESOL Class	GI Absorption	BBB Permeant	CYP Inhibition	Lipinski Violations	PAINS Alerts	Synthetic Accessibility
3a	491.61	6.57	Poor	Low	No	None	1	1	4.12
3b	507.61	6.24	Poor	Low	No	None	1	1	4.12
3c	512.03	6.77	Poor	Low	No	None	2	1	3.99
5a	493.58	5.98	Poor	Low	No	None	0	2	4.14
5b	509.58	5.65	Poor	Low	No	2C9	1	2	4.14
5c	514.00	6.15	Poor	Low	No	None	1	2	4.01
7a	507.61	5.14	Poor	Low	No	2C19,2C9, 2D6	1	0	4.11
7b	523.61	4.82	Poor	Low	No	2C19,2C9, 2D6	1	0	4.12
7c	528.02	5.34	Poor	Low	No	2C19, 2C9	1	0	3.99
9a	415.51	4.83	Poor	**High**	No	2C9, 3A4	0	0	3.60
9b	445.53	5.11	Poor	Low	No	2C9, 3A4	0	0	3.88

[a] MW: Molecular Weight (g/mol); [b] Consensus Log P: Partition coefficient (lipophilicity); ESOL class: Estimated aqueous solubility; Cytochrome P450 isoforms.