Electronic Supplementary Material (ESI) for RSC Advances.

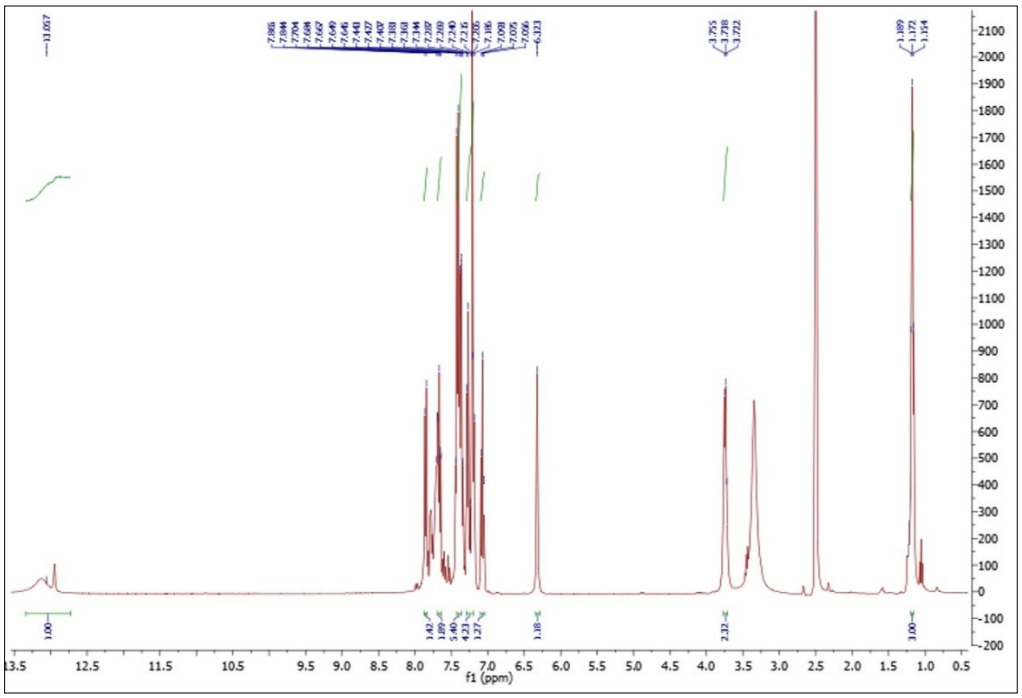
Supplementary material

New pyrazolylindolin-2-one based coumarin derivatives as anti-melanoma agents: Design, synthesis, dual BRAF ^{V600E}/ VEGFR-2 inhibition and computational studies

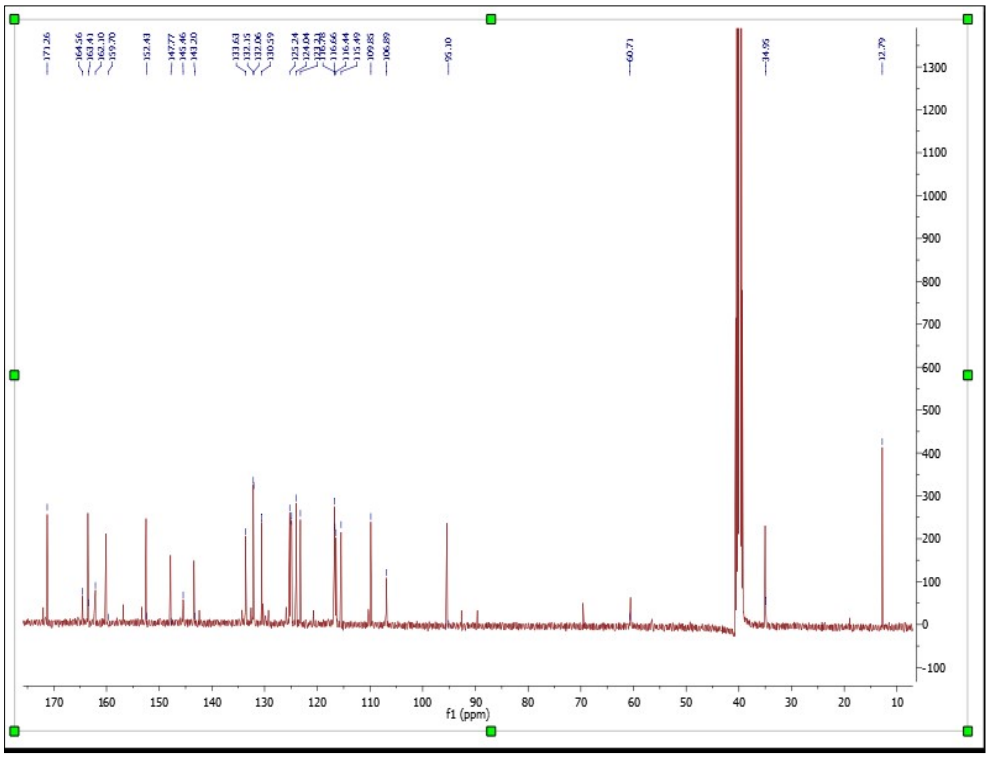
Ahmed Sabt, Mohammed A. Khedr, Wagdy El dehna, Abelsamed I. Elshamy, Mohamed Fayed, Rasha M. Allam, Rasha Z. Batran

- **^{1}HNMR and ^{13}CNMR of the newly synthesized compounds.**
- **Molecular docking study against BRAF^{V600E}**
- **Molecular docking study against VEGFR-2**
- **ADME Prediction Study**

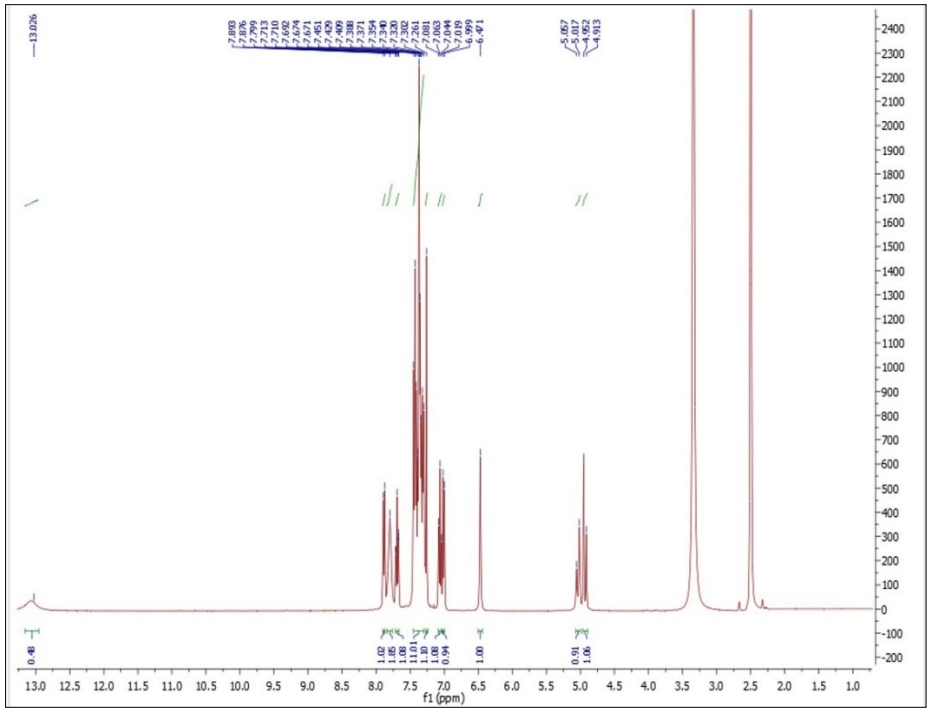
- ^{1}HNMR and ^{13}CNMR of the newly synthesized compounds.



^{1}HNMR of compound 4b



^{13}CNMR of compound 4b



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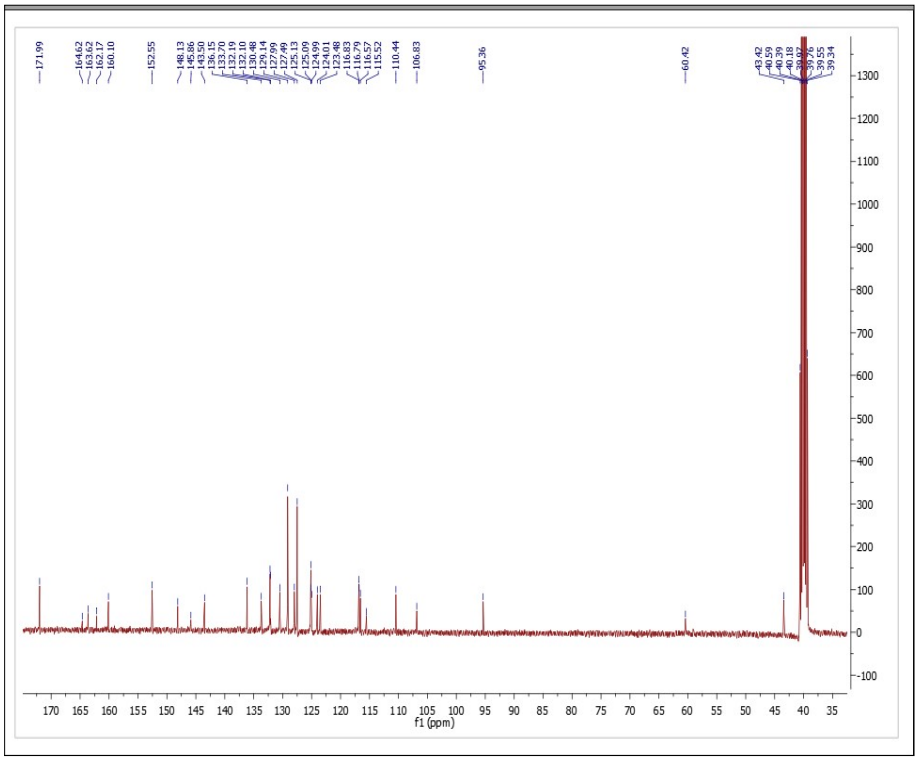

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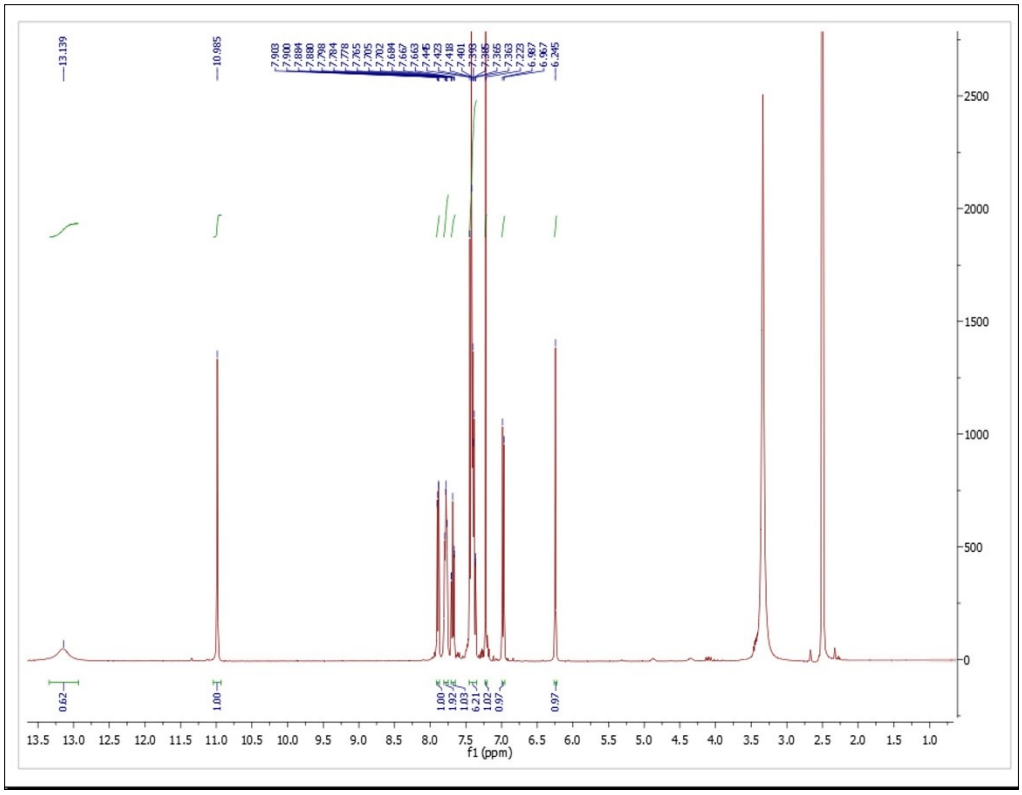

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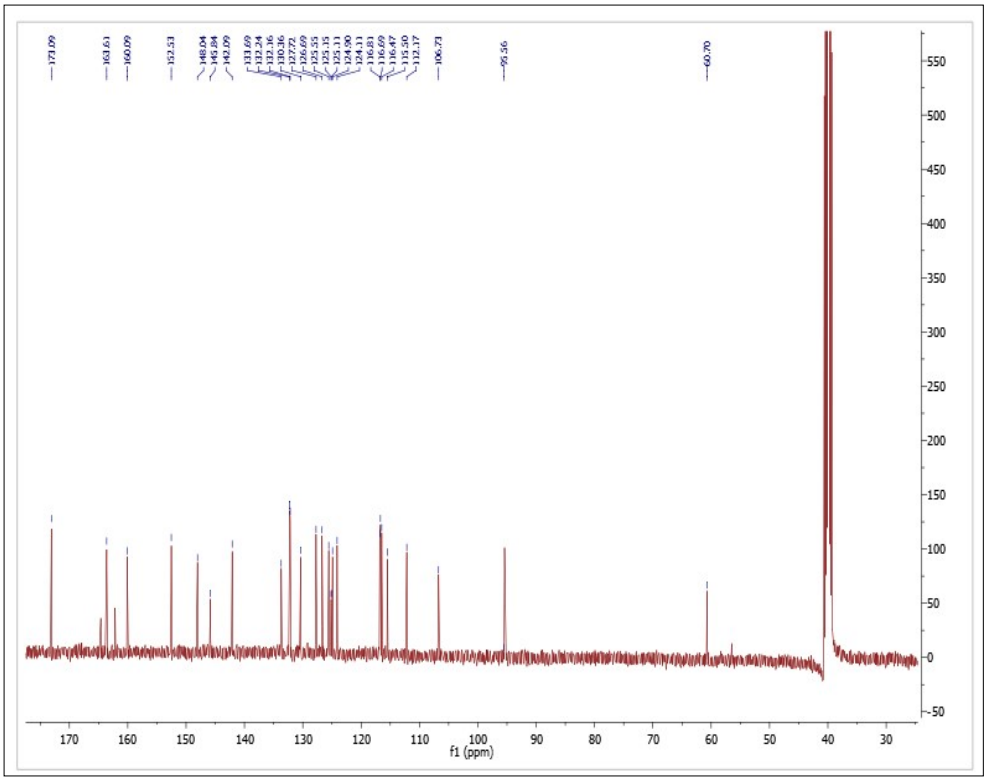

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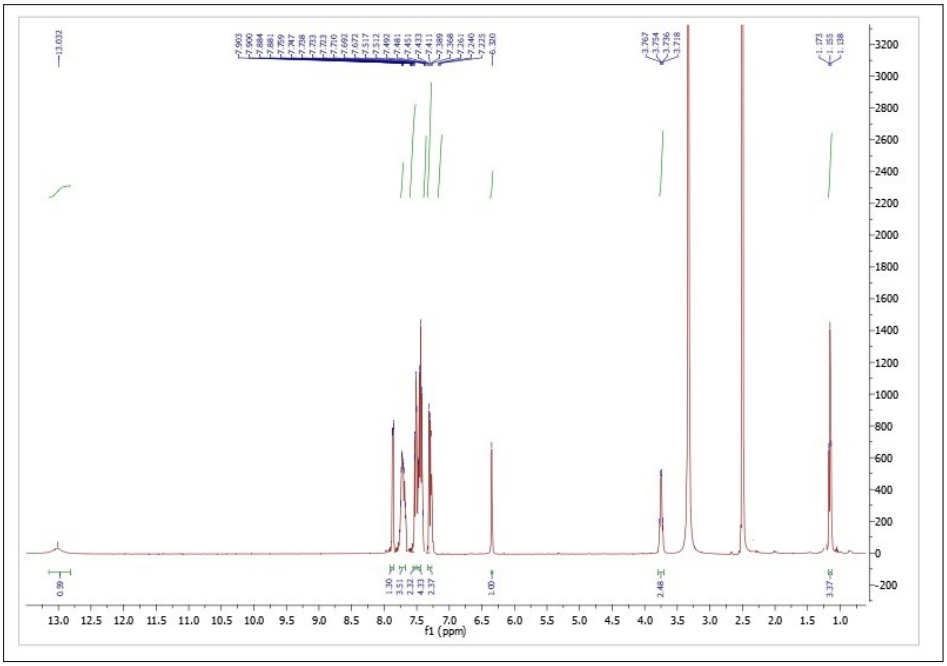

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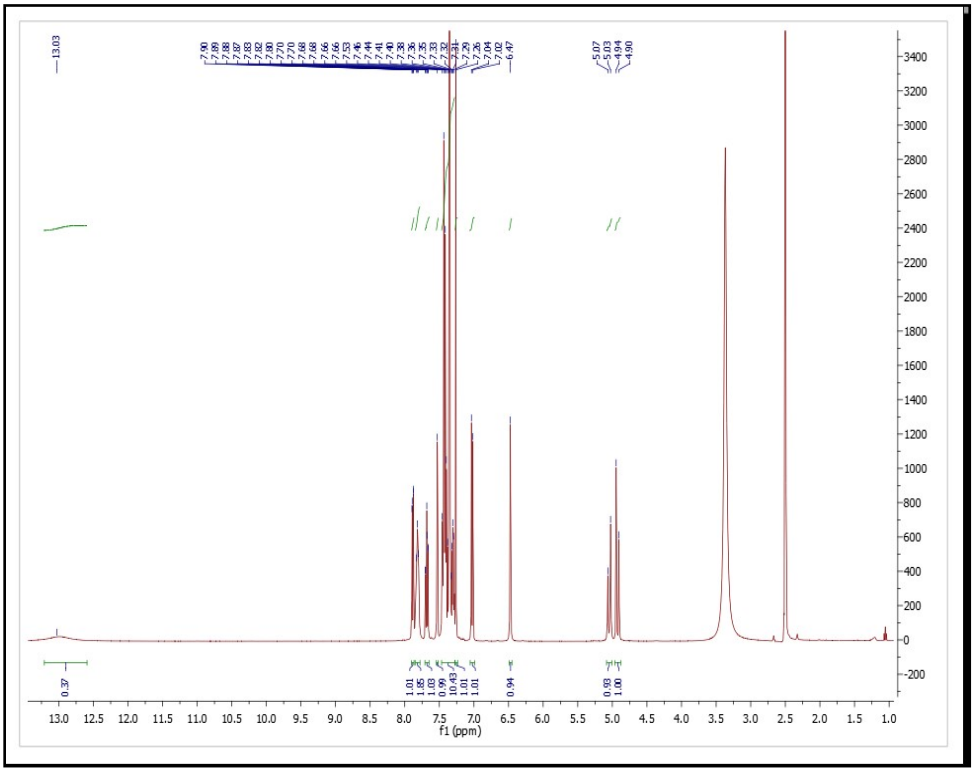

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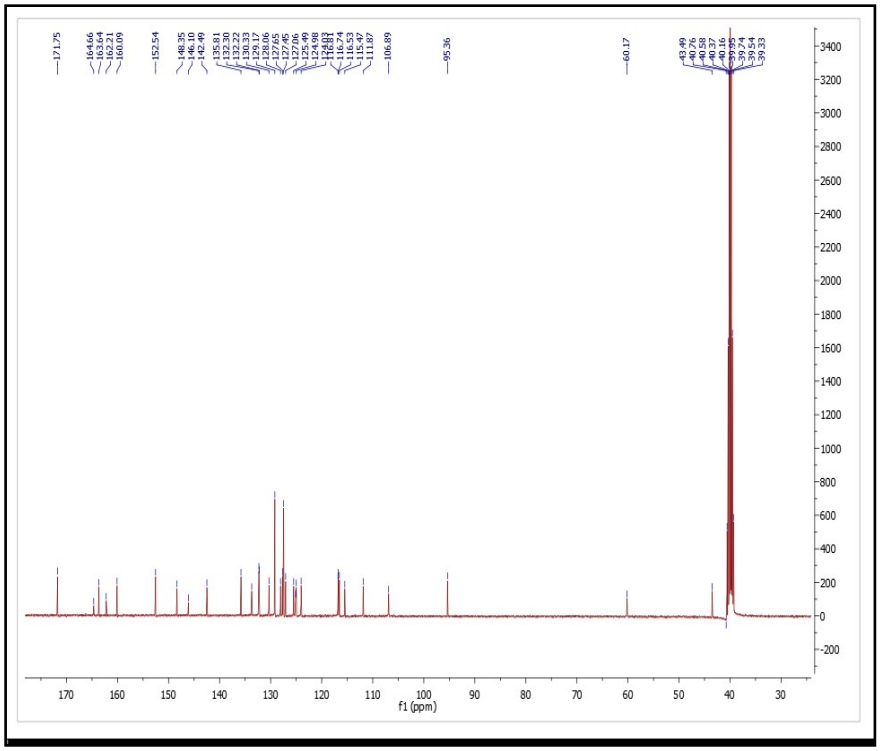

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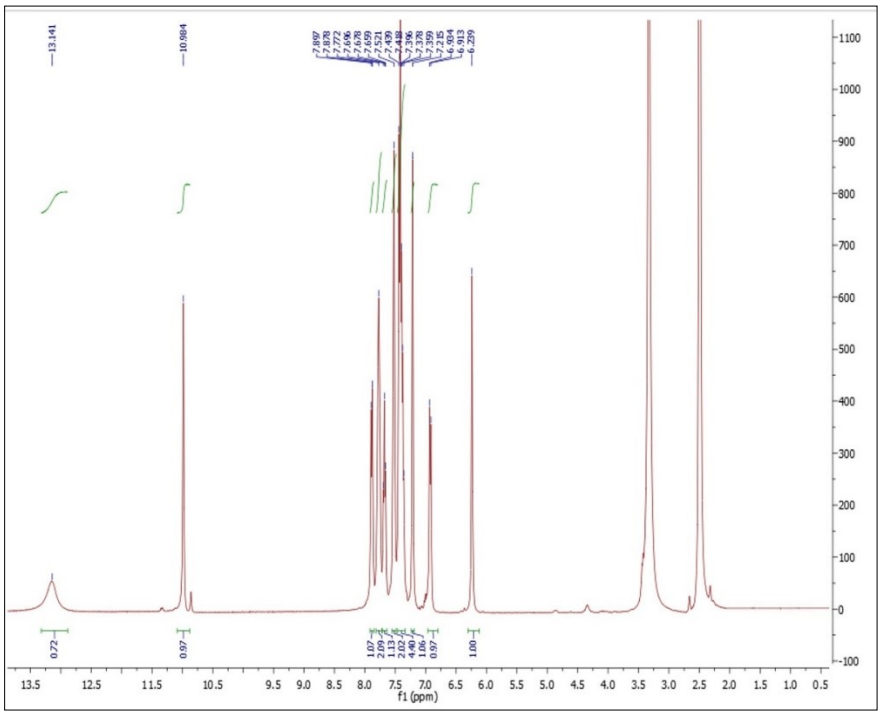

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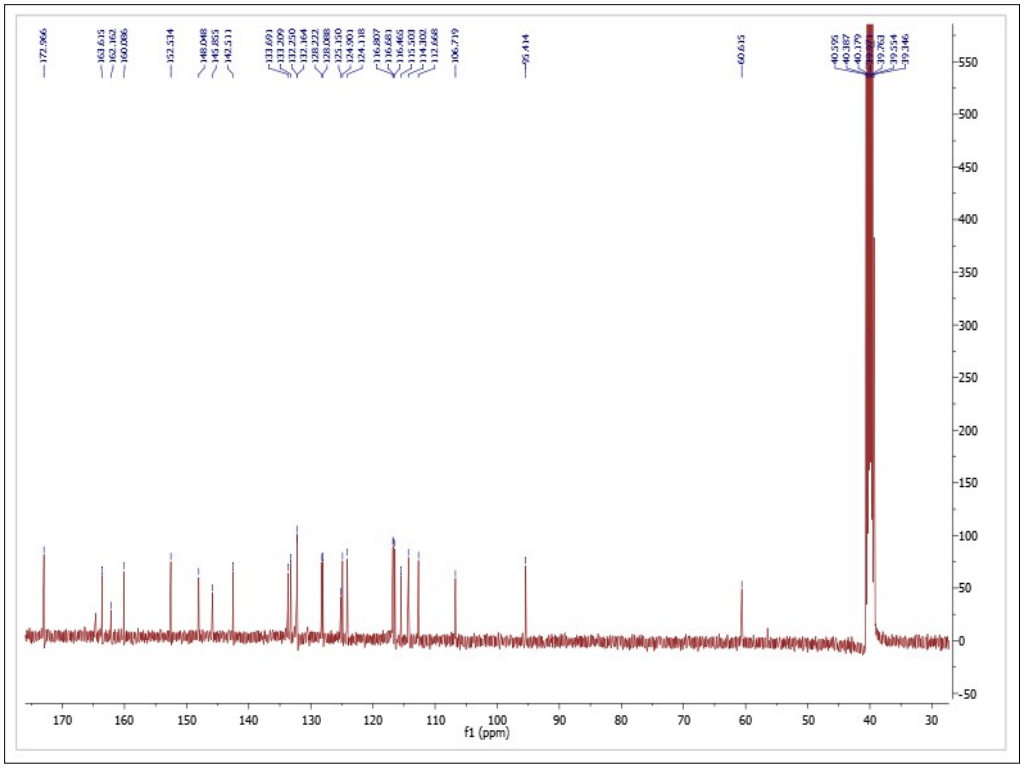

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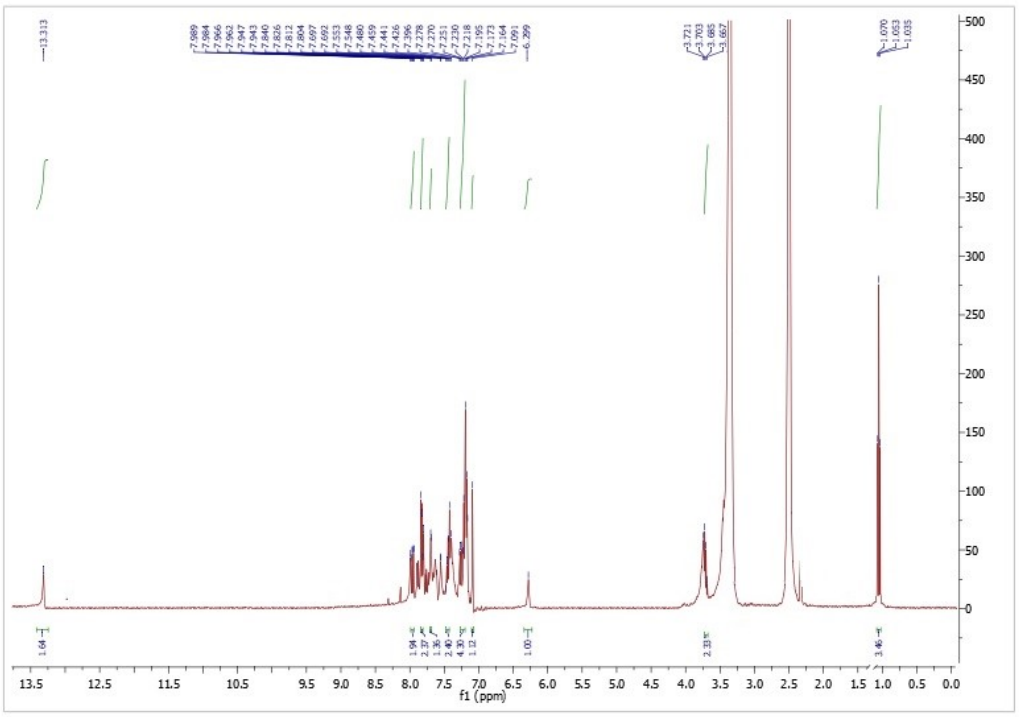

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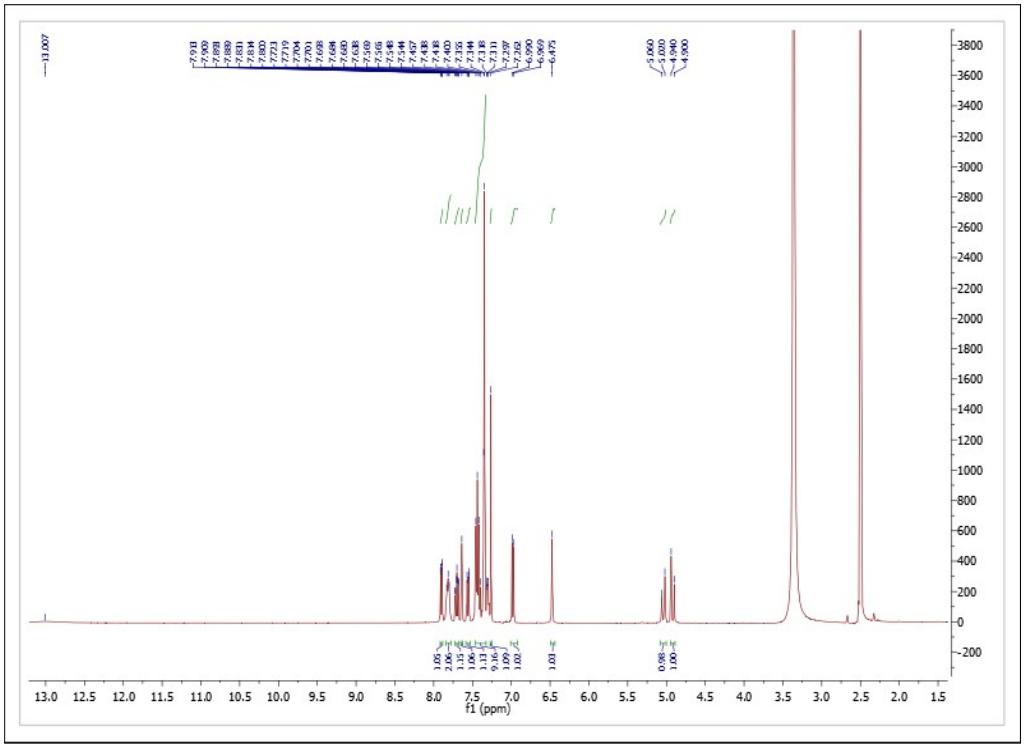

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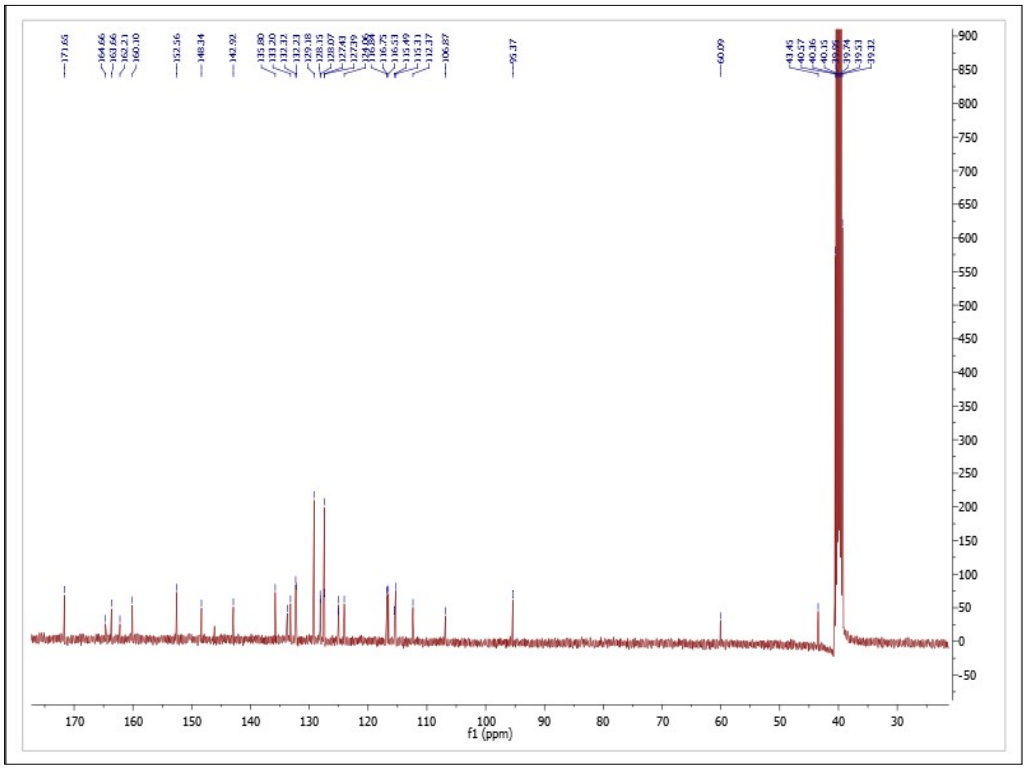

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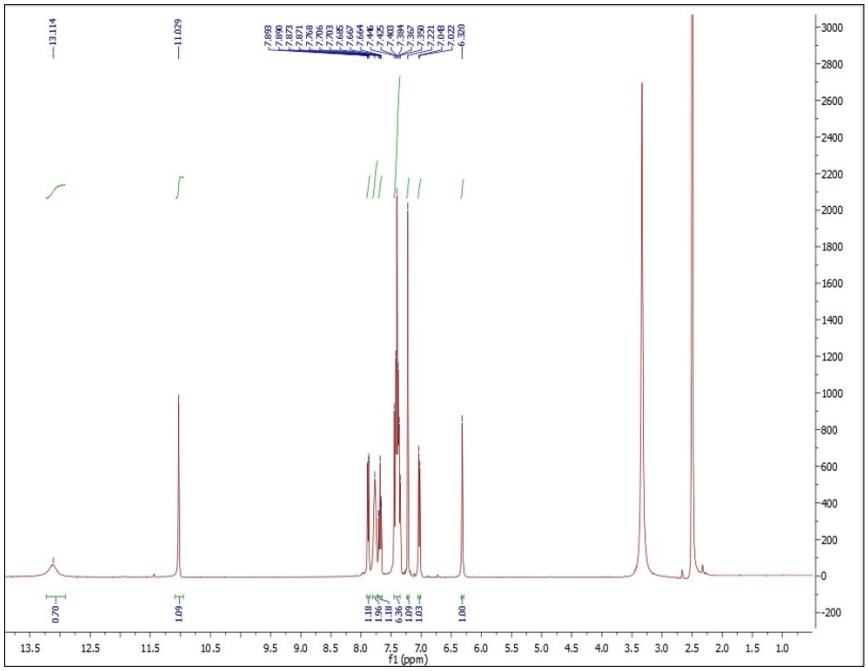

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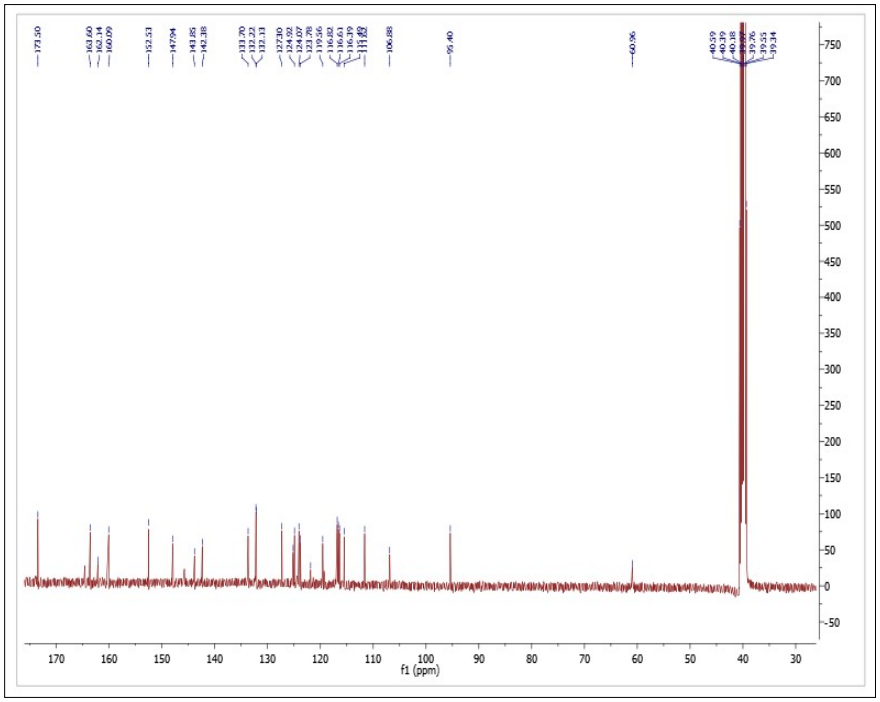

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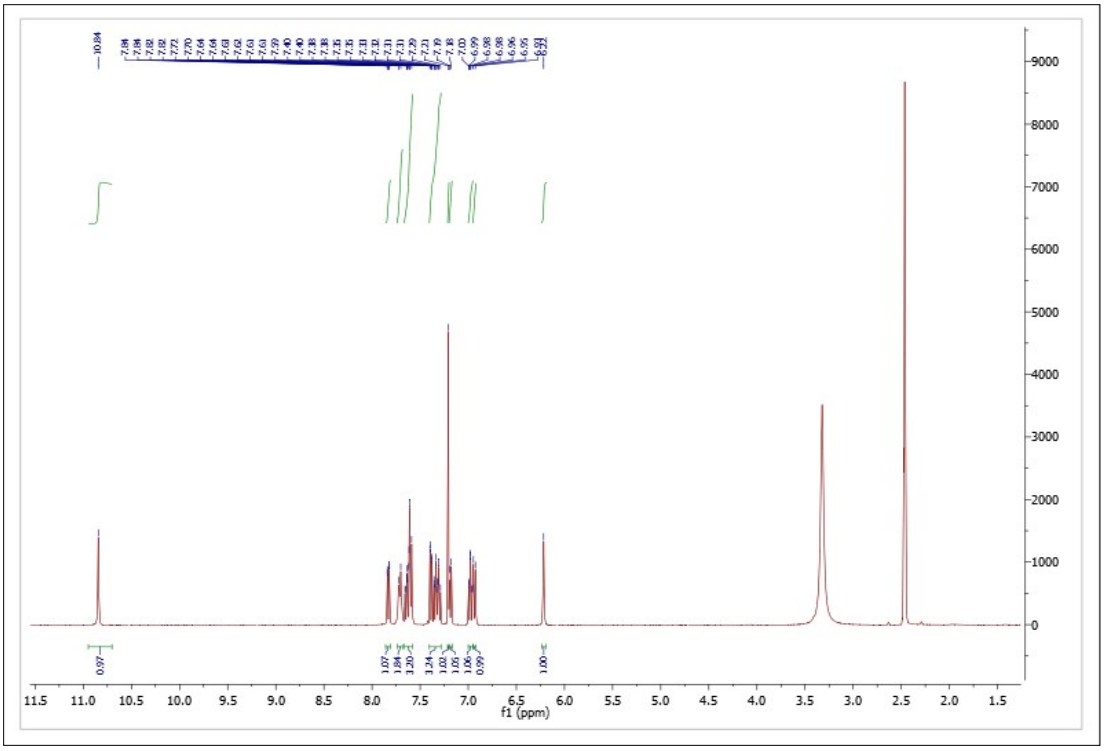

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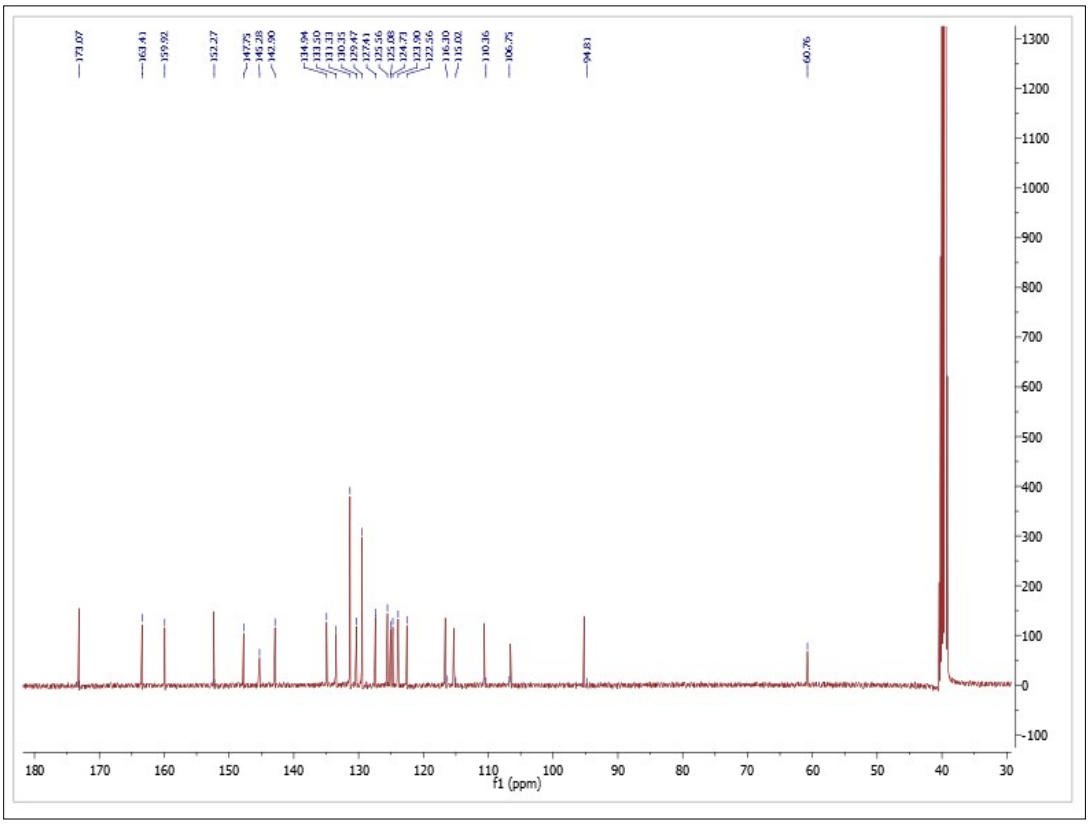

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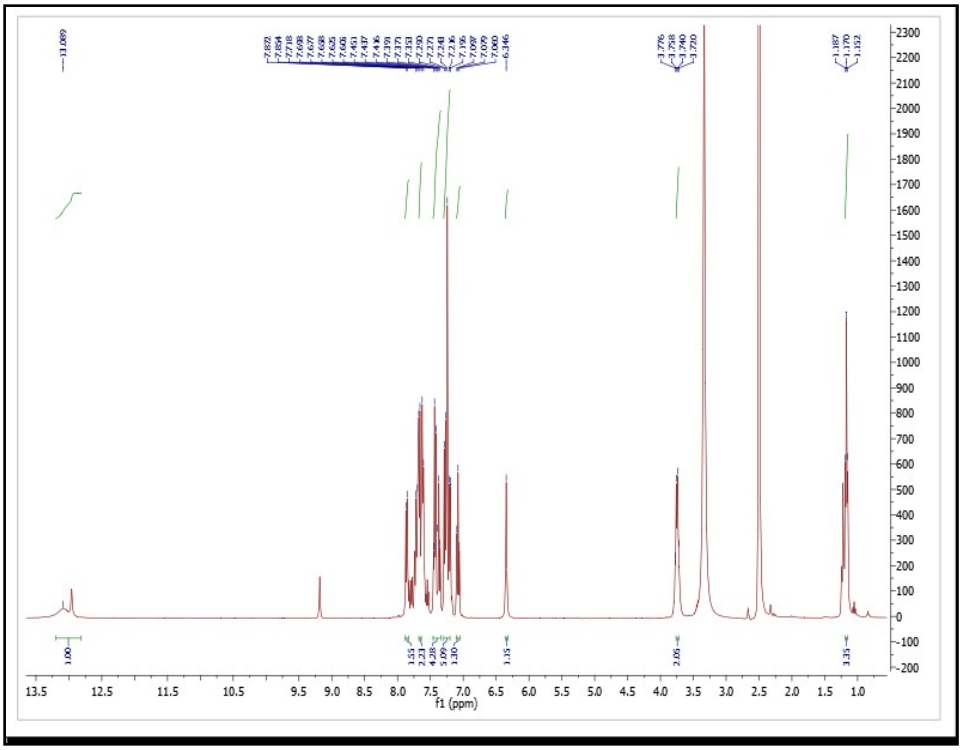

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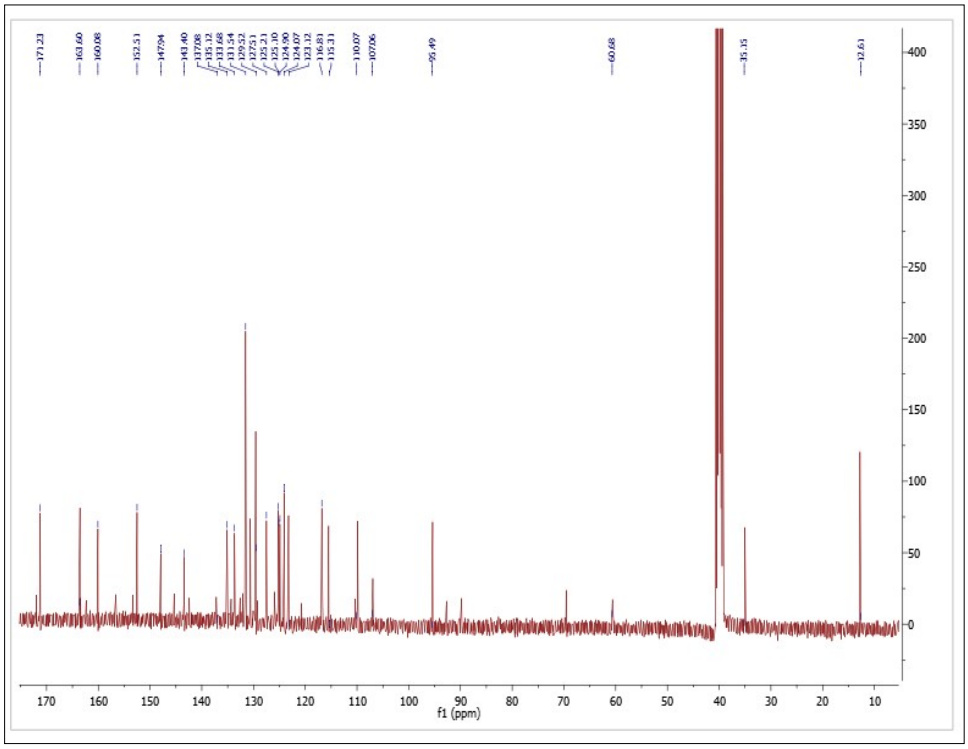

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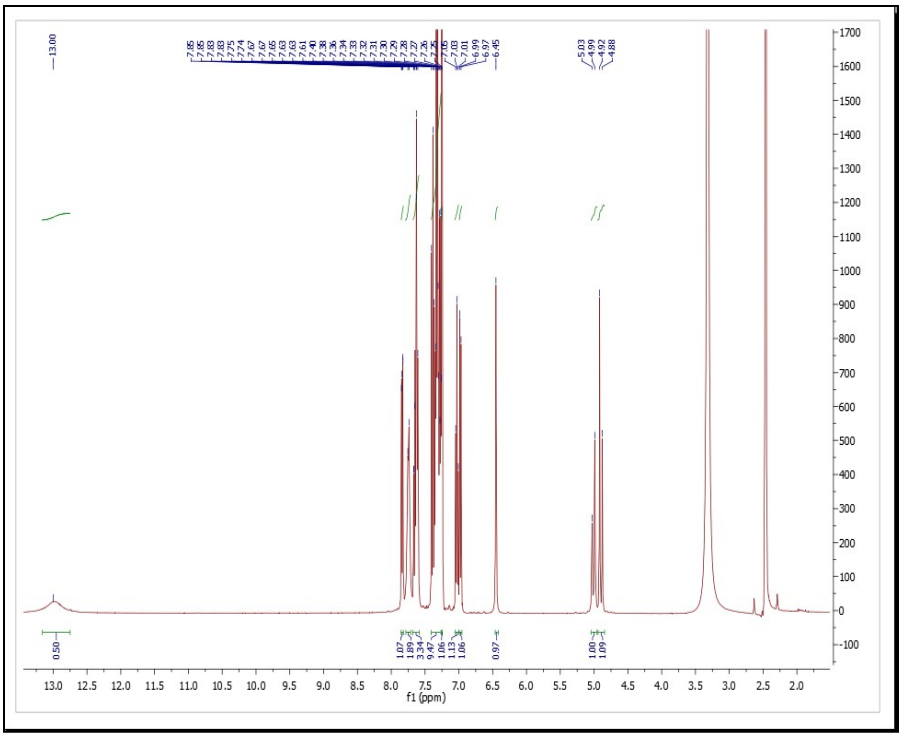

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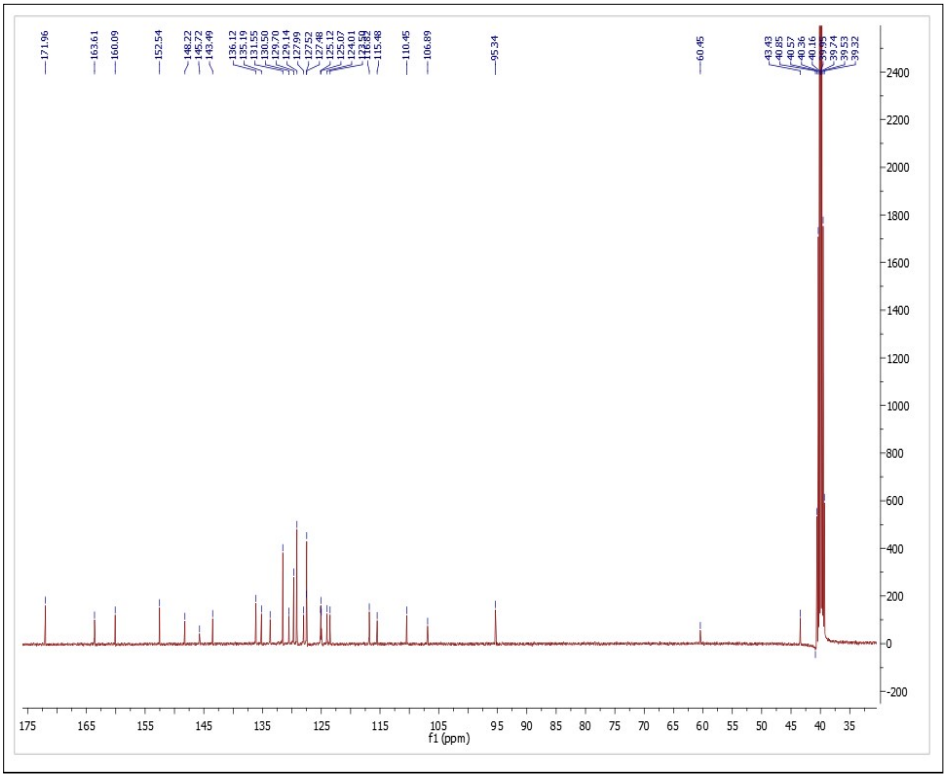

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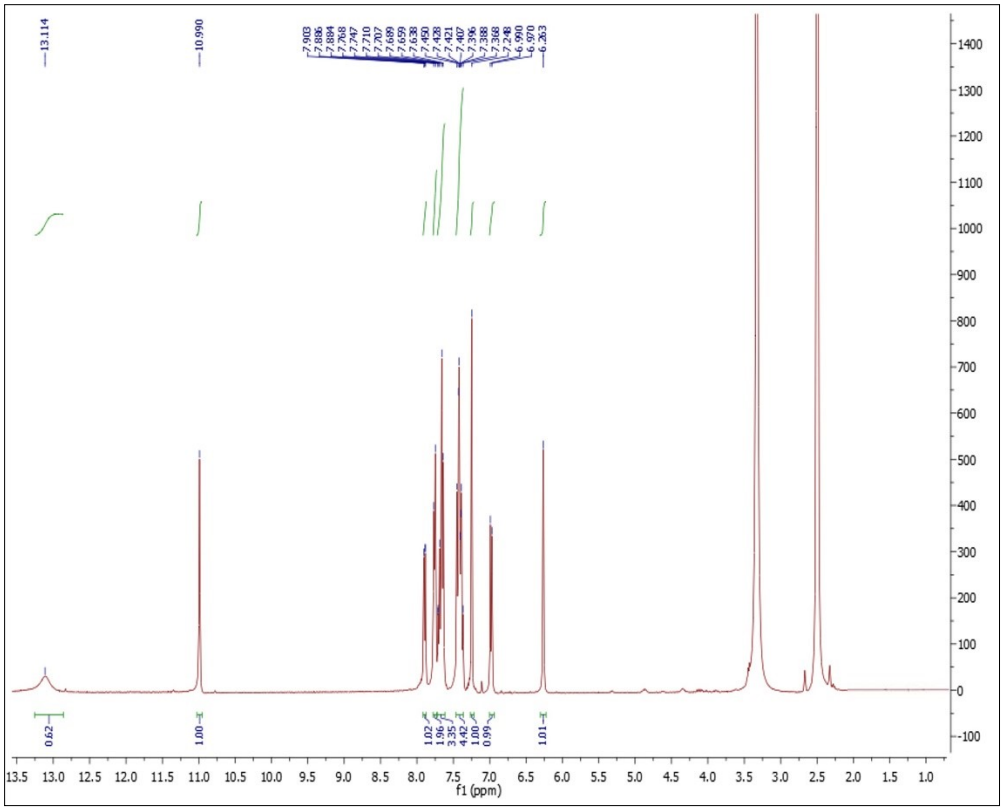

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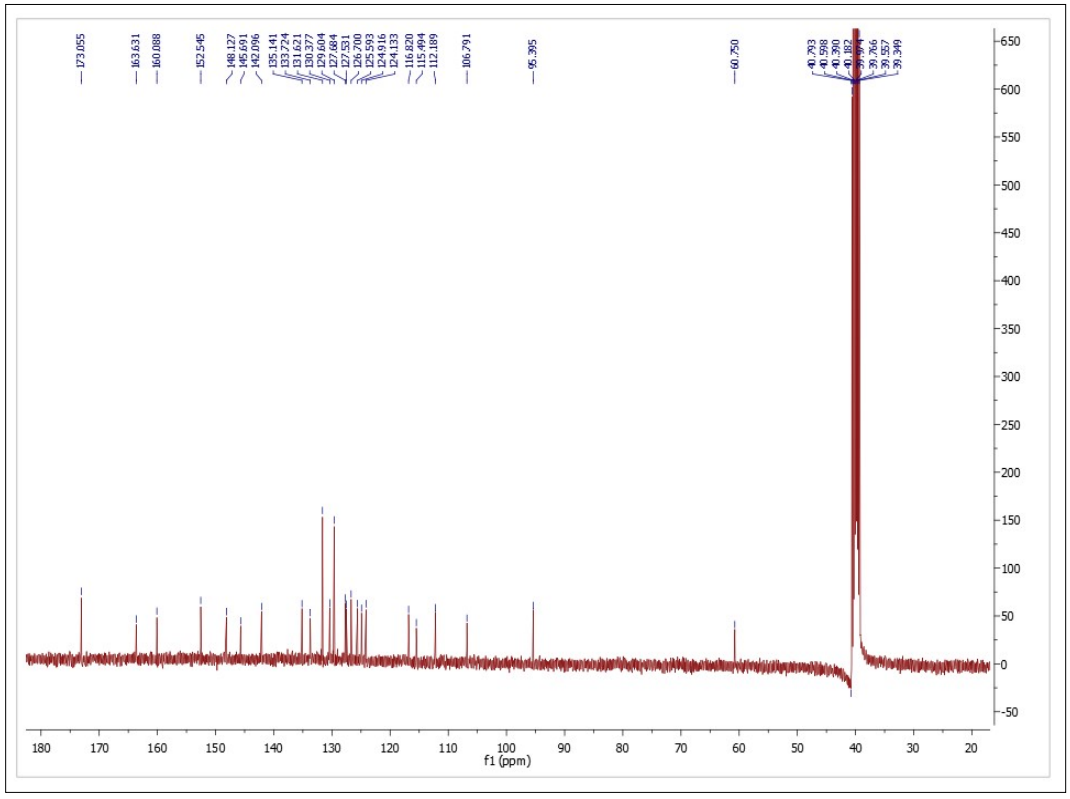

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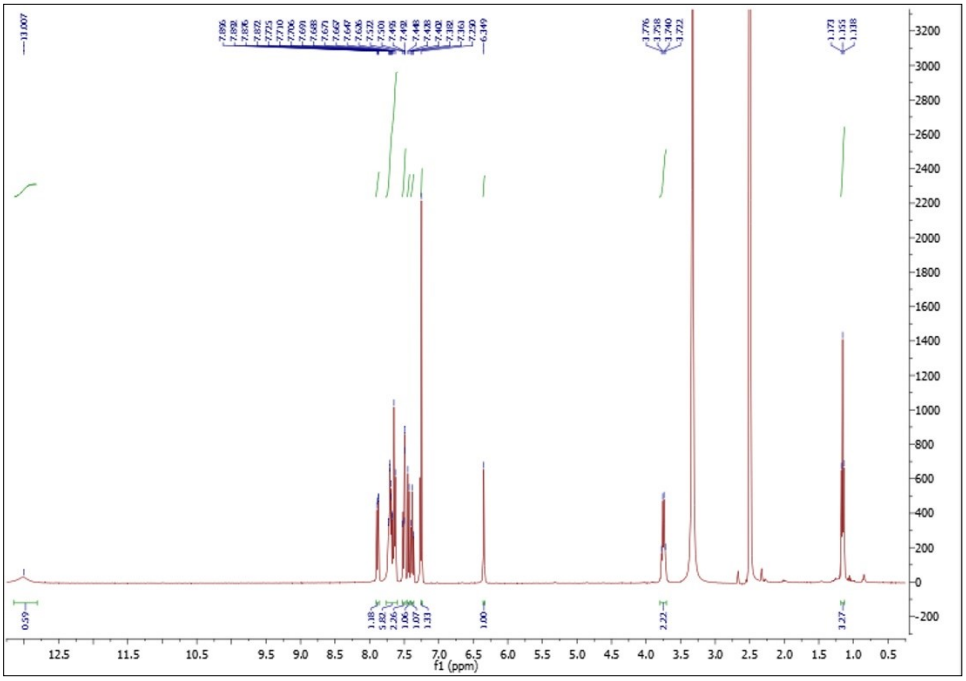

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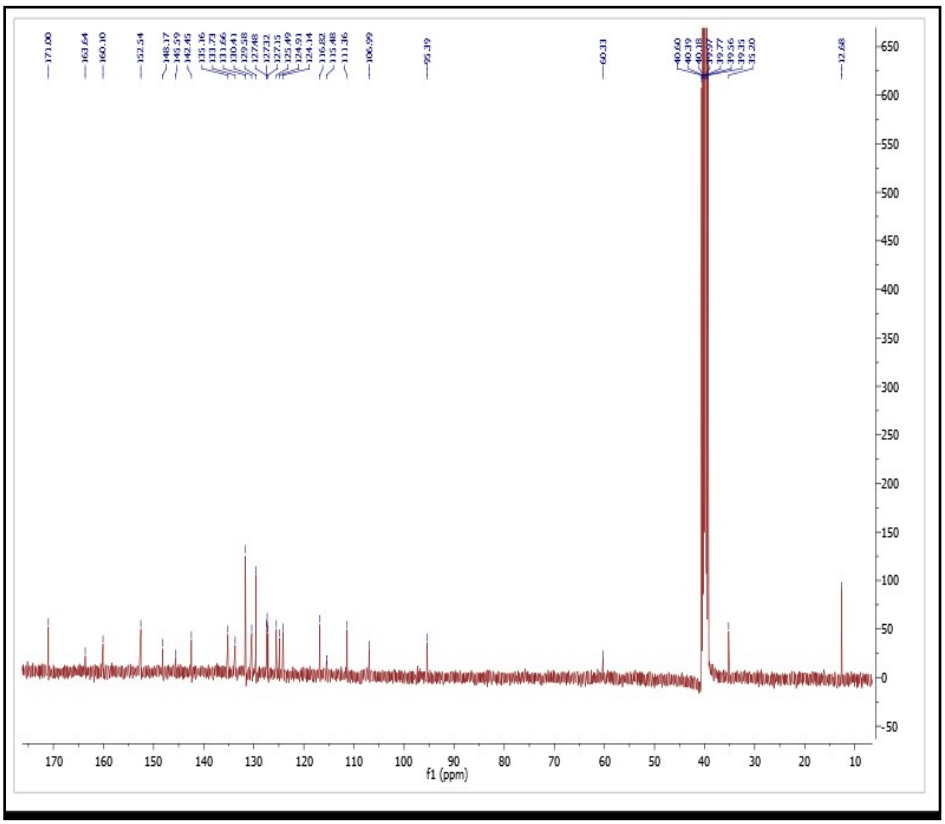

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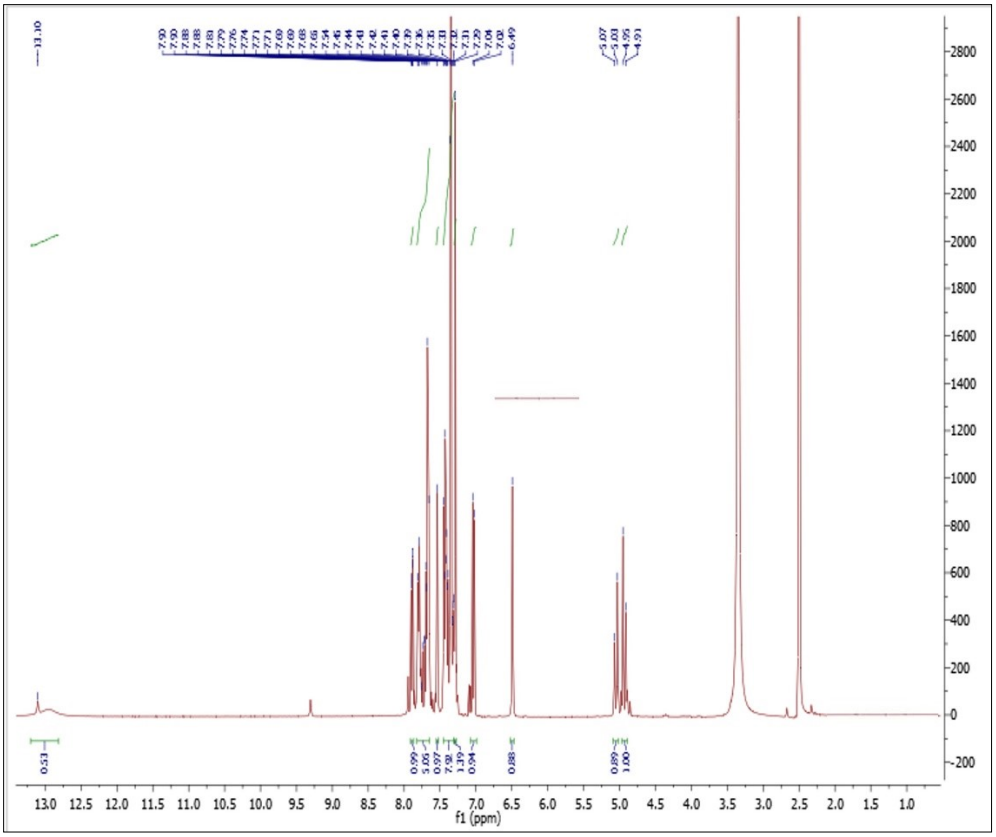

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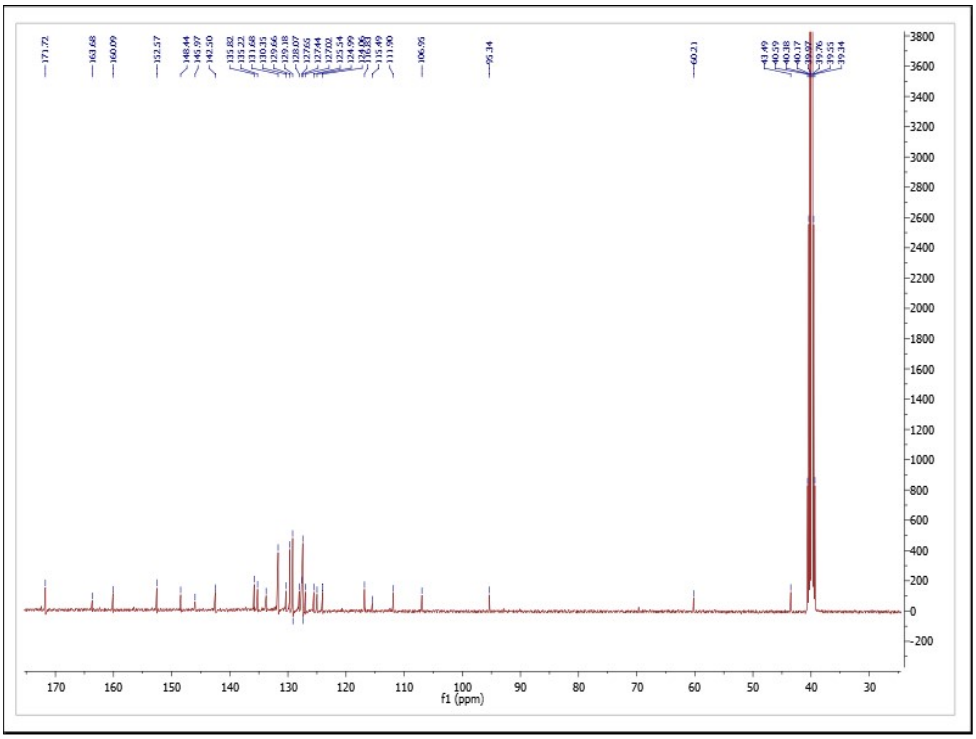

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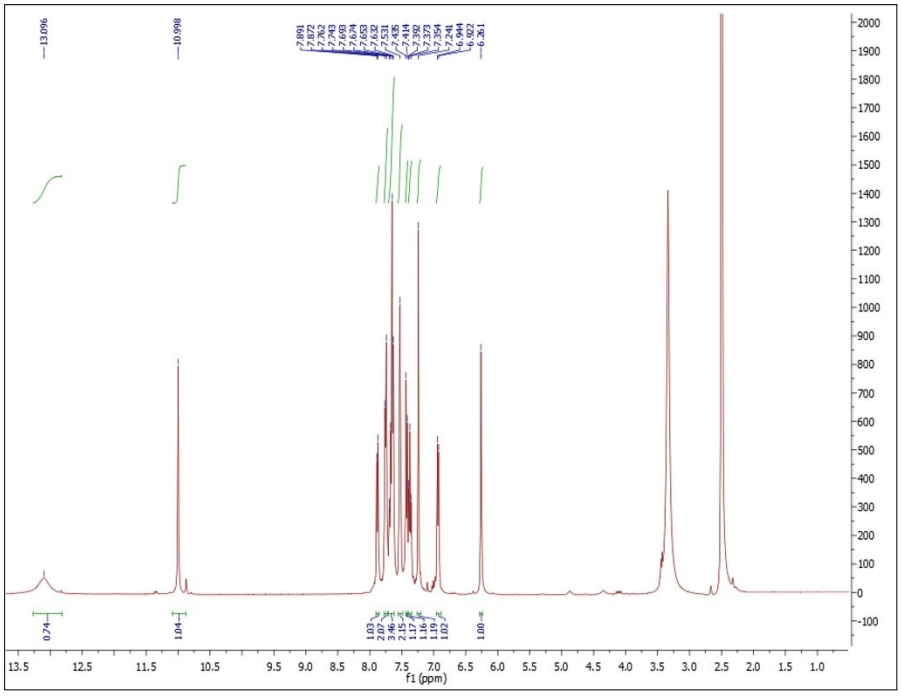

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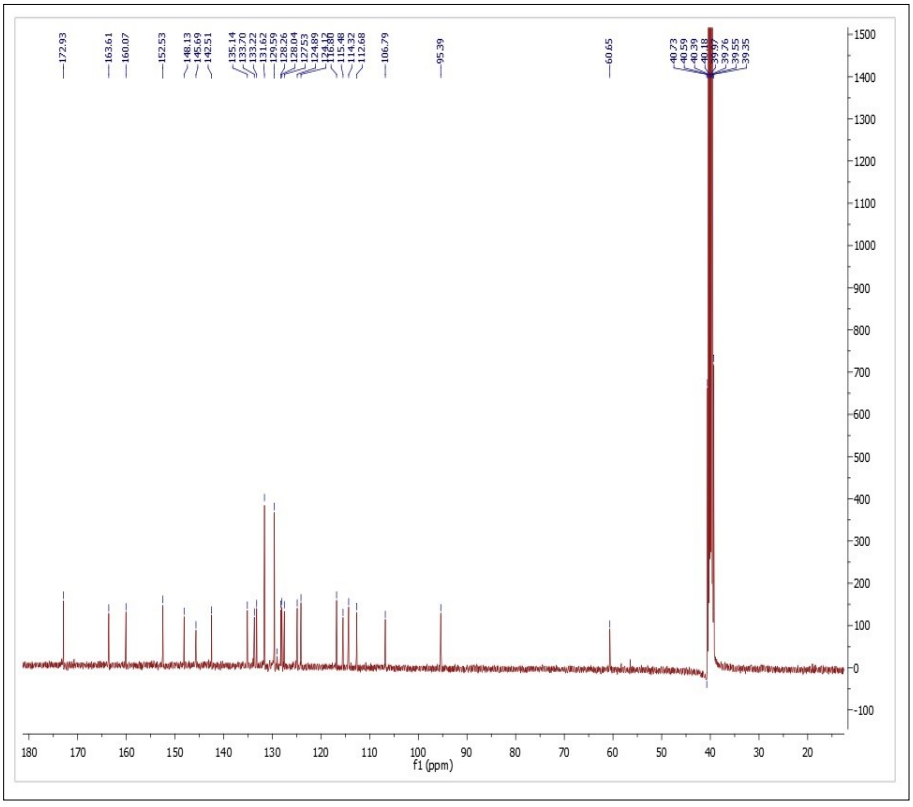

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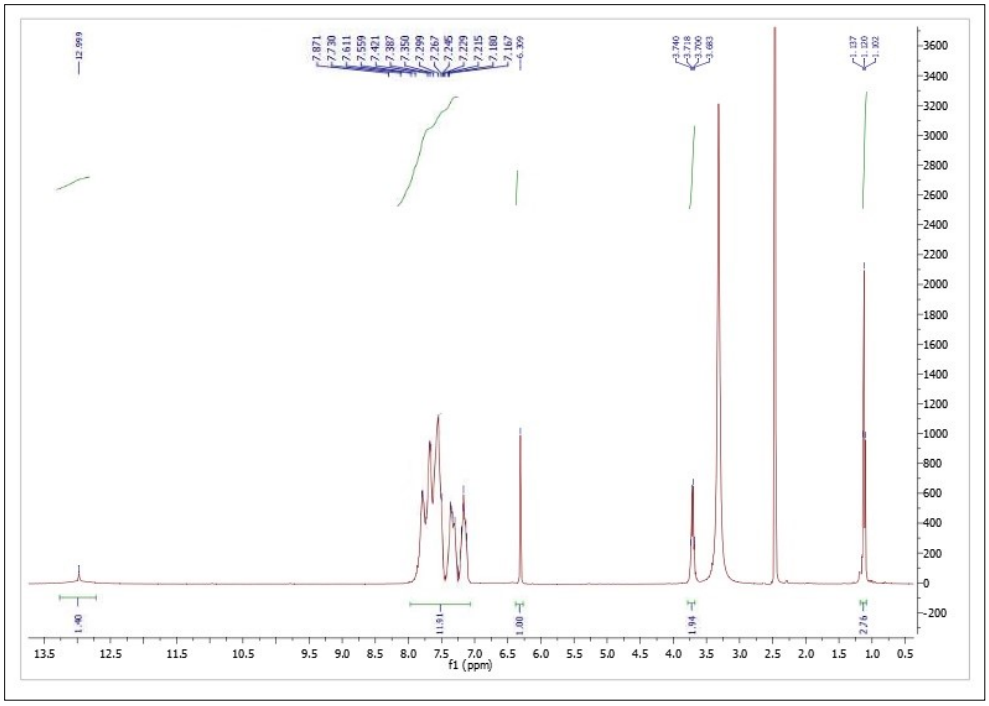

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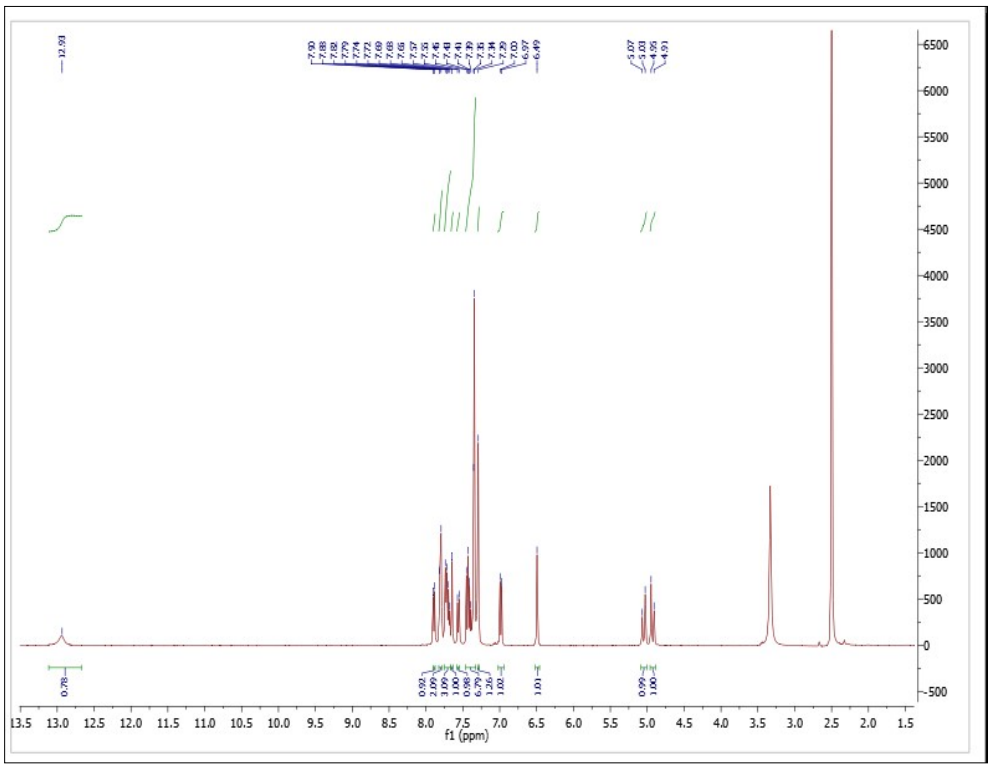

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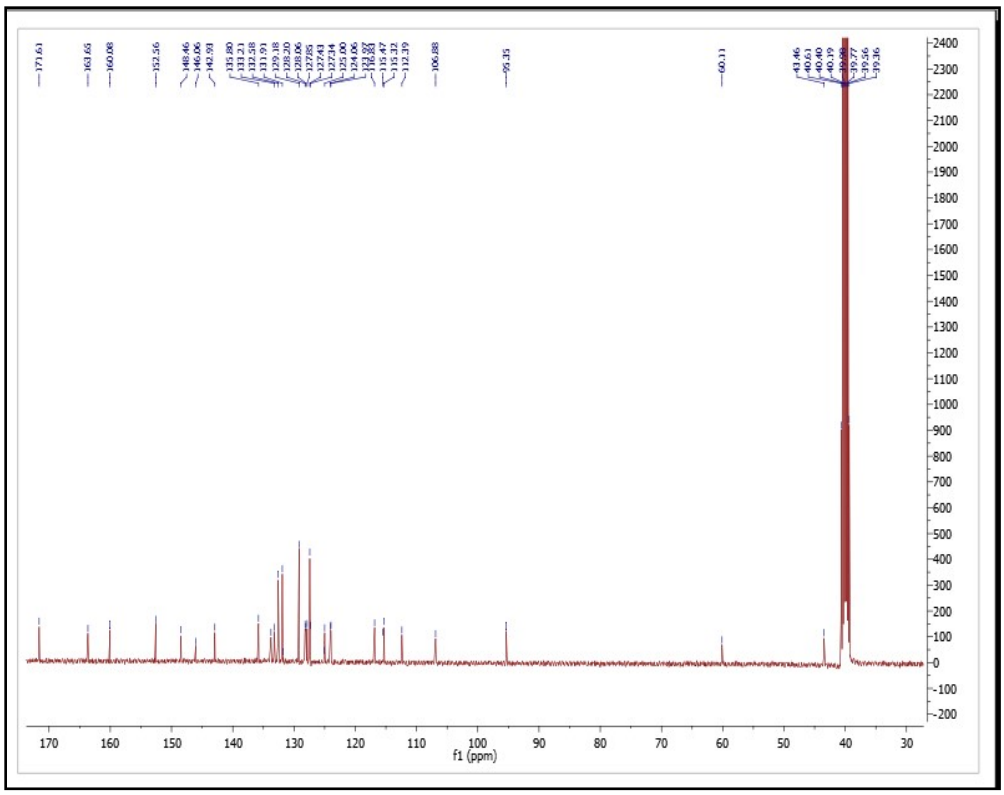

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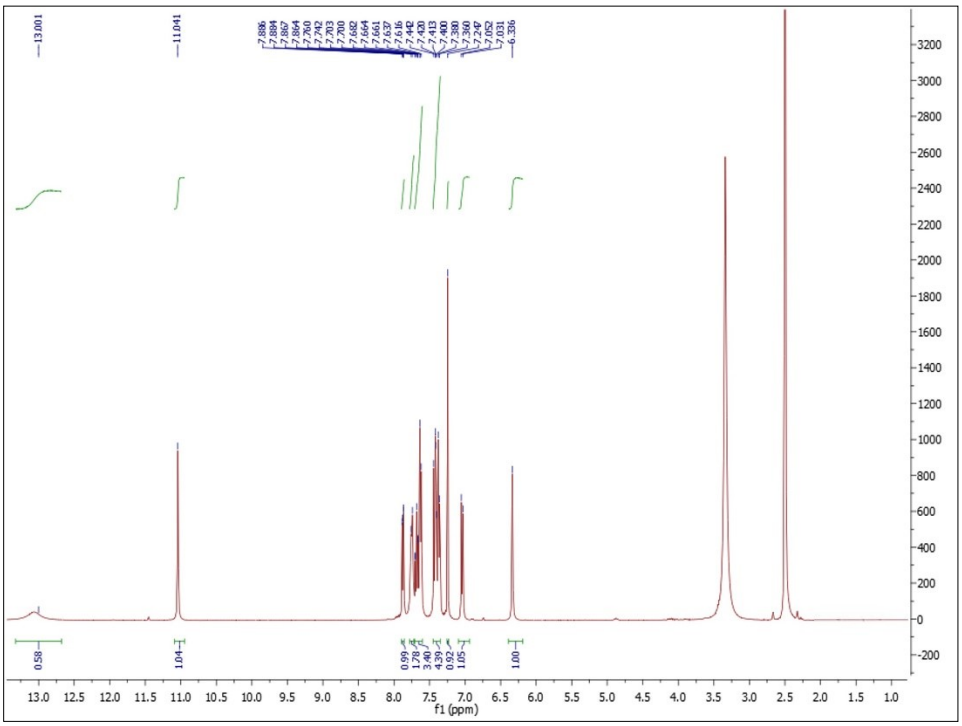

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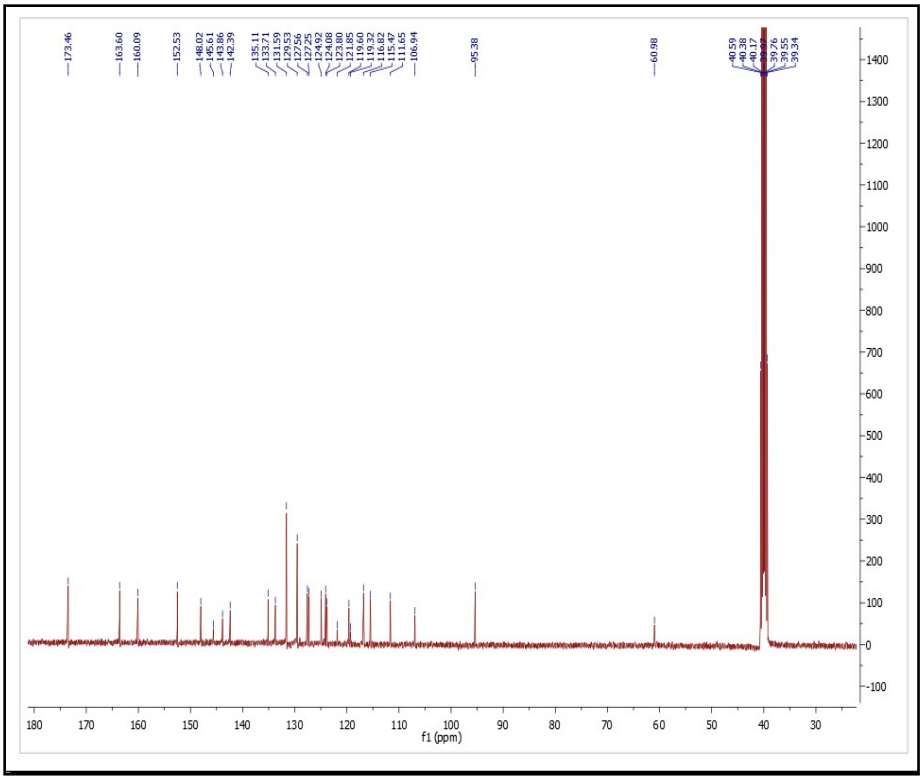

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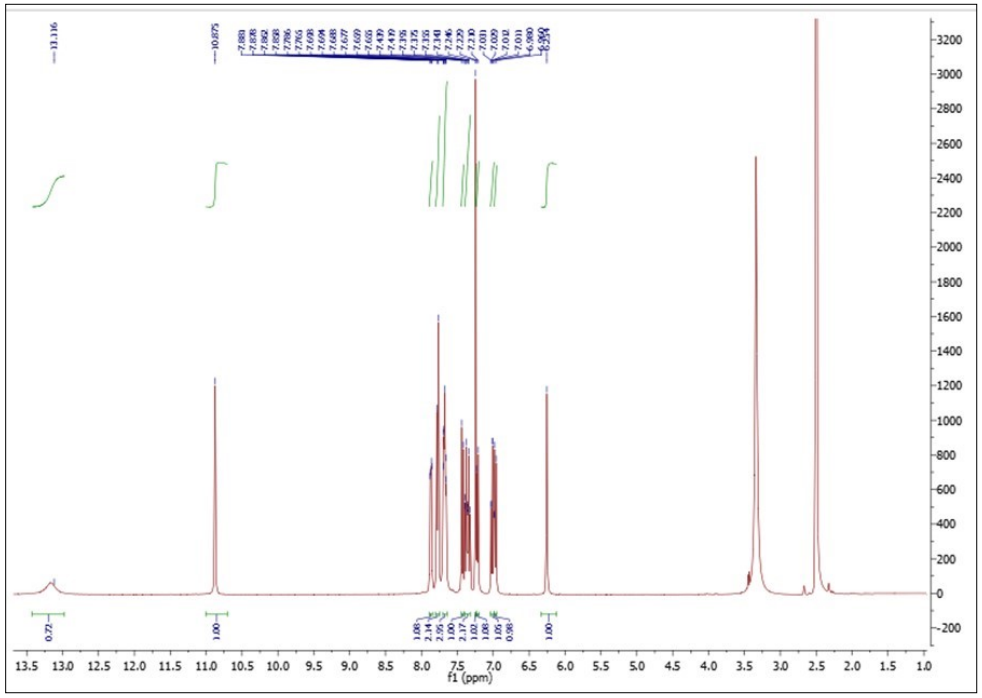

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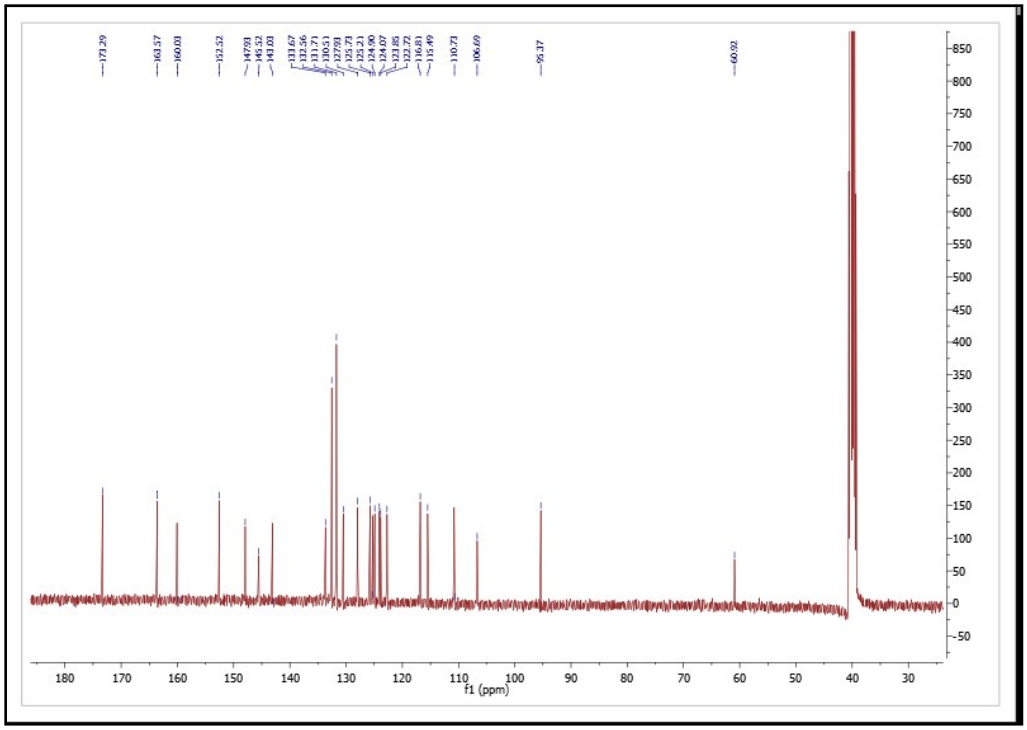

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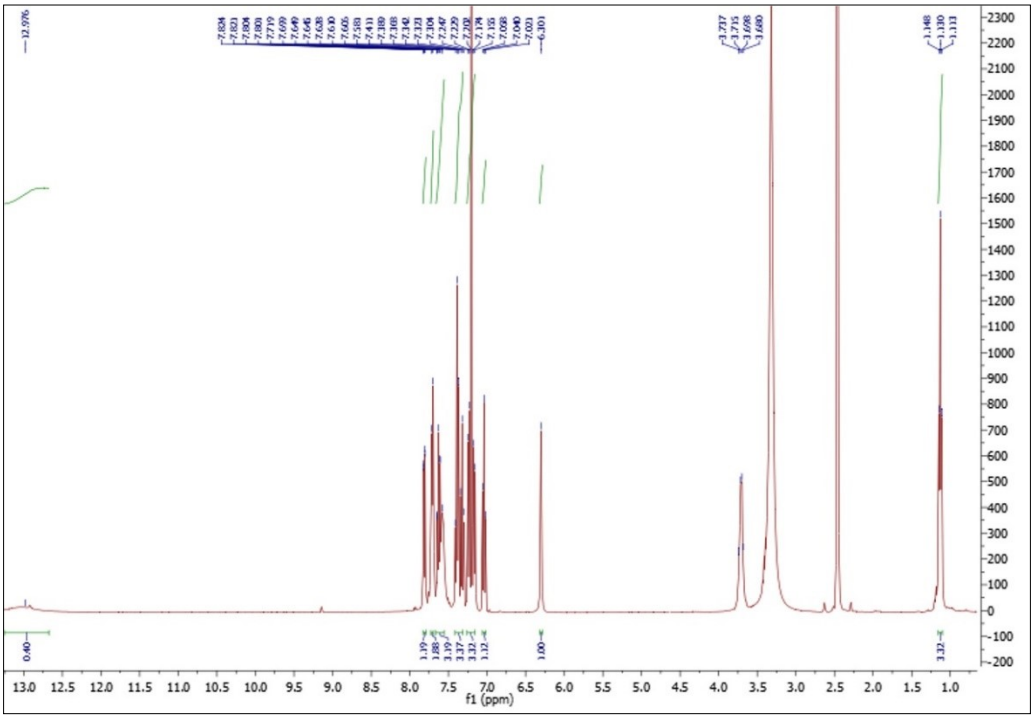

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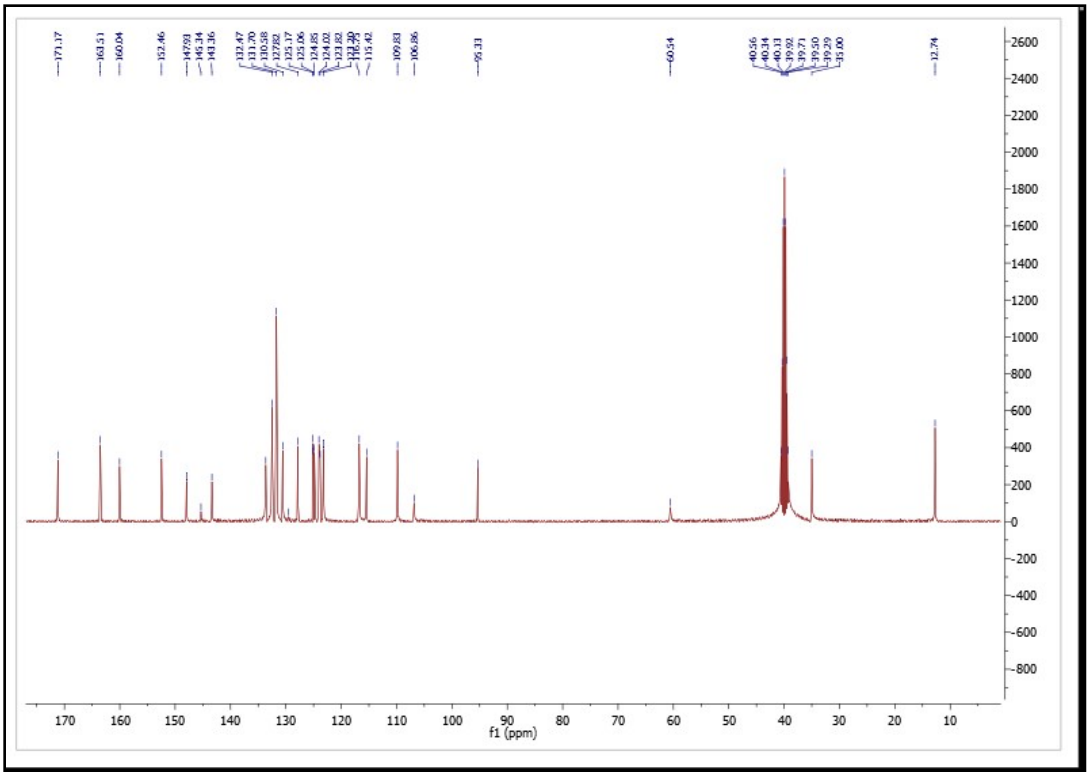

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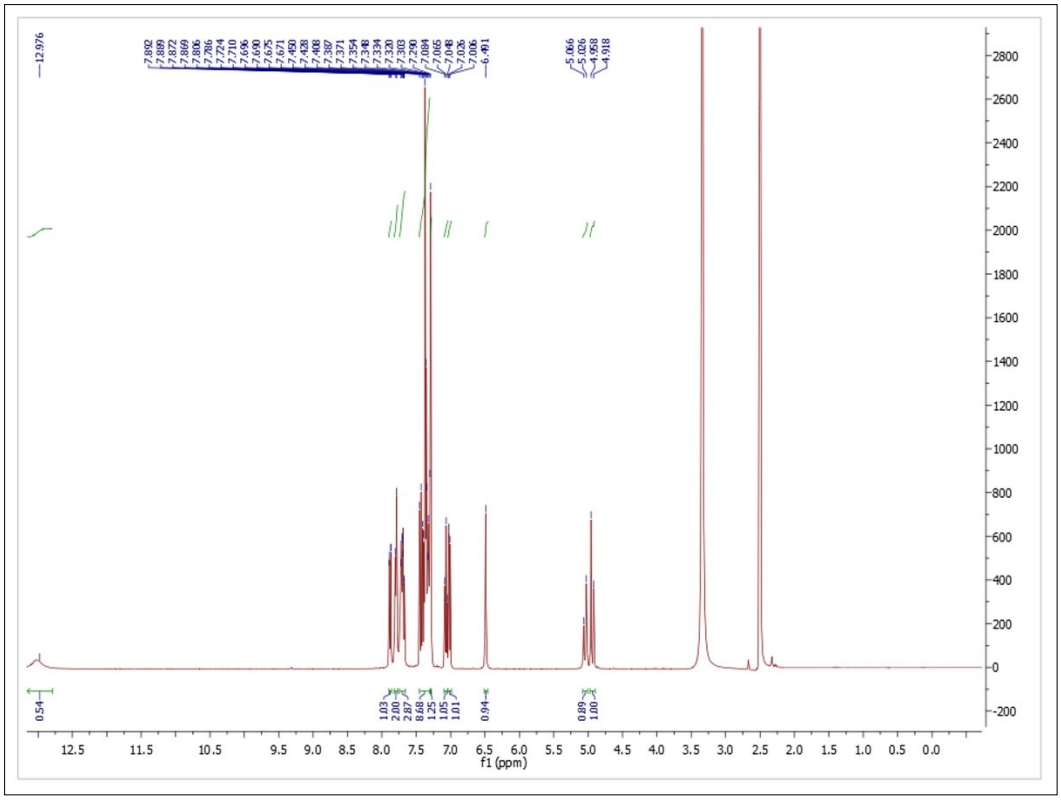

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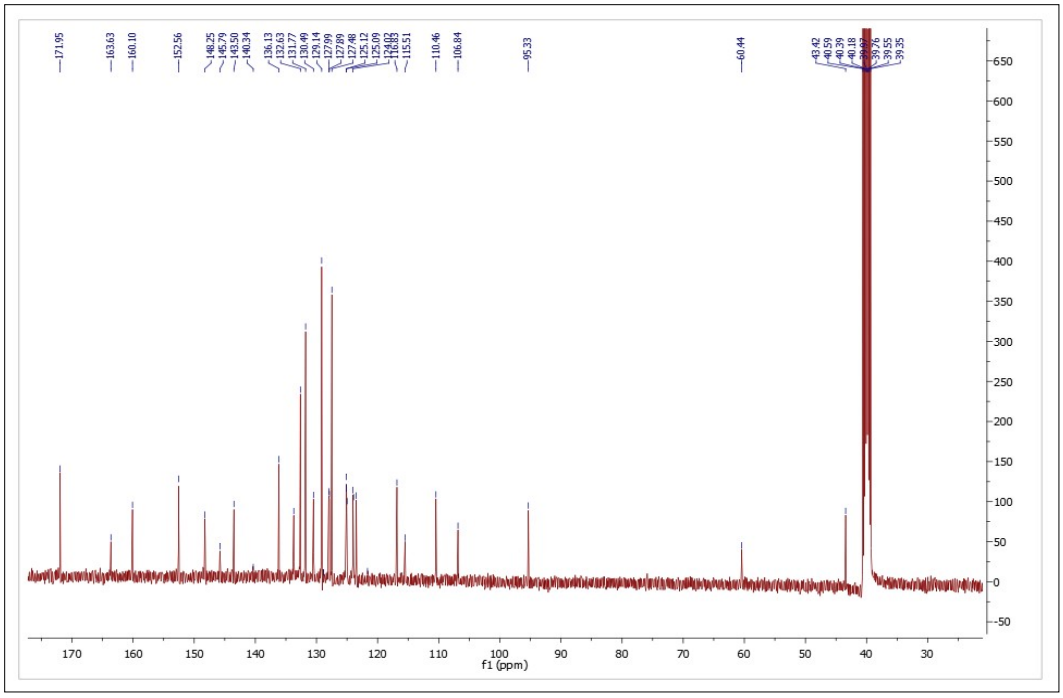

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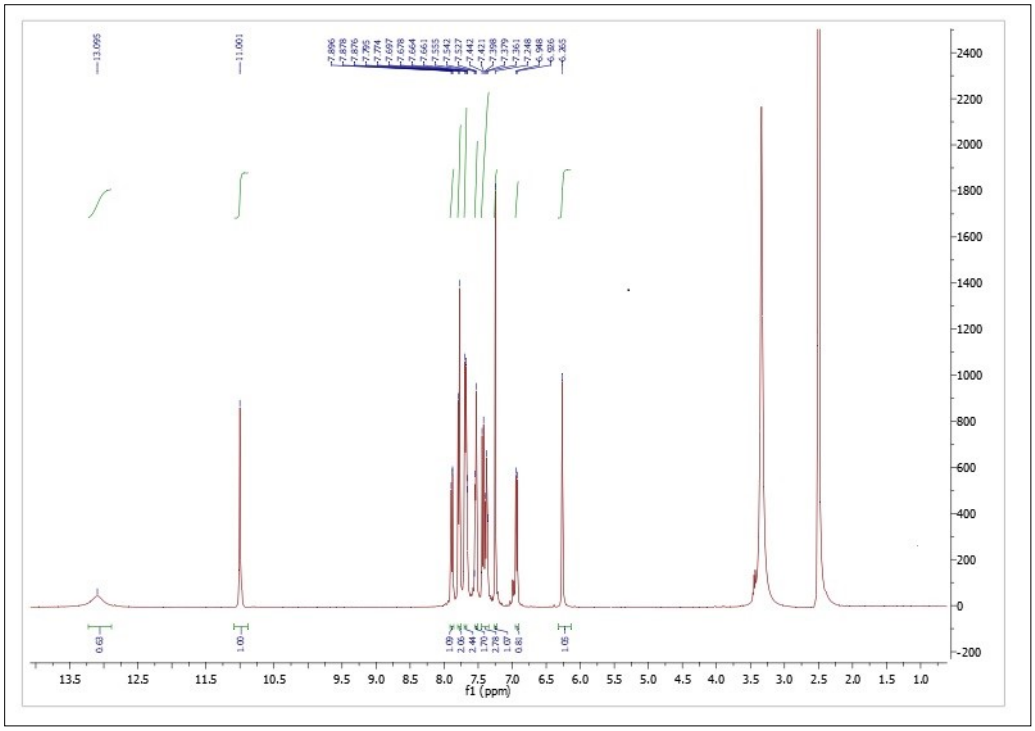

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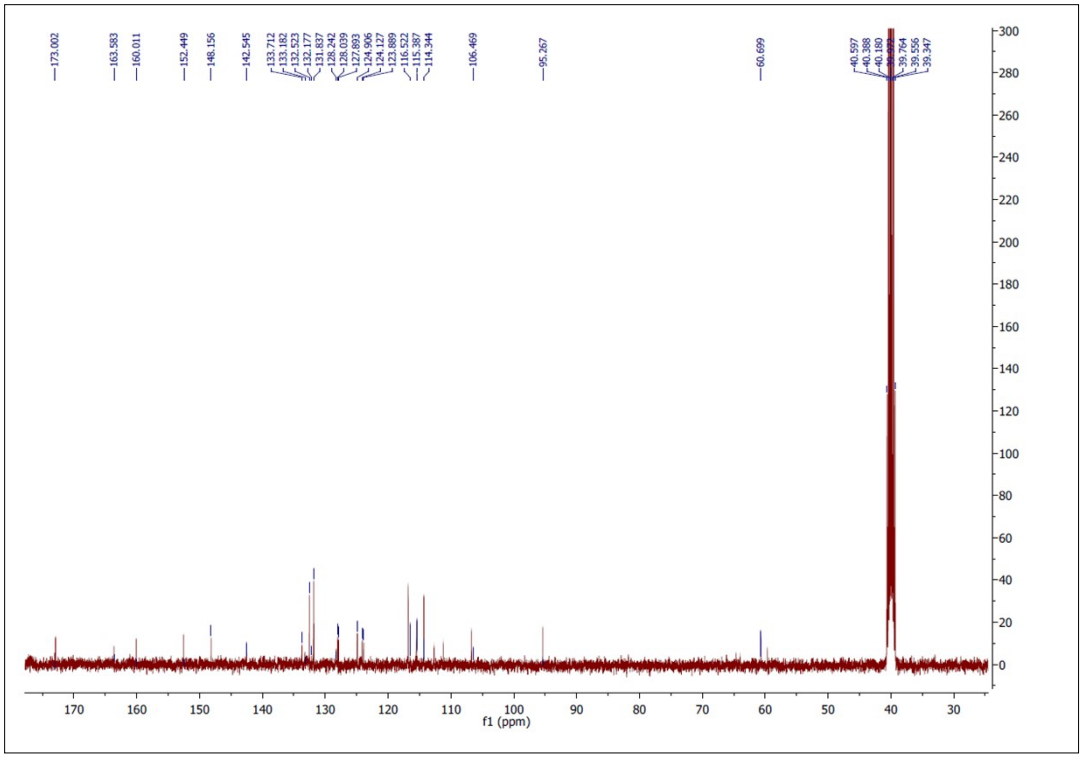

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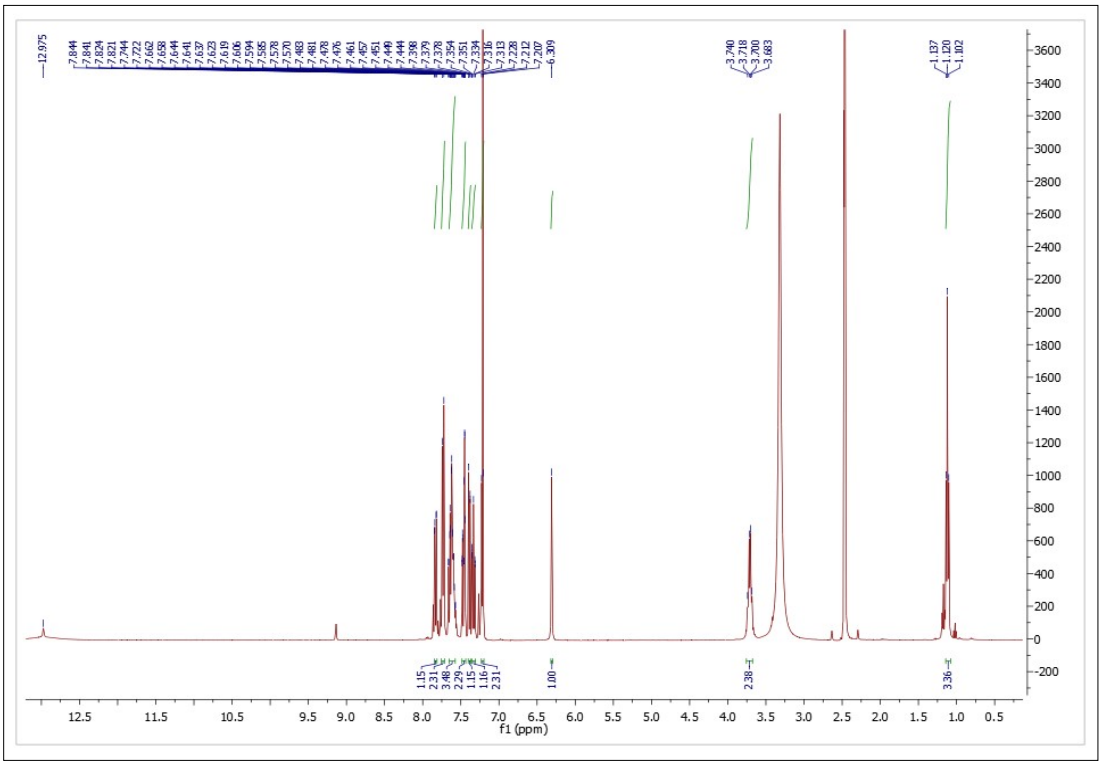

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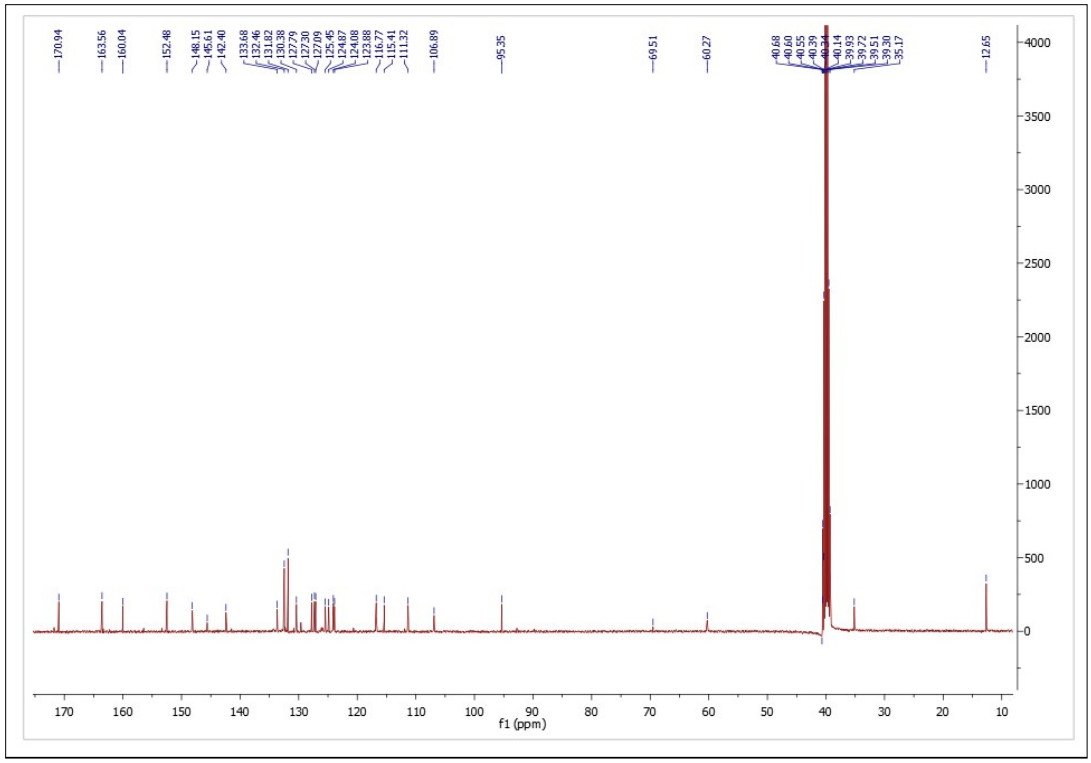

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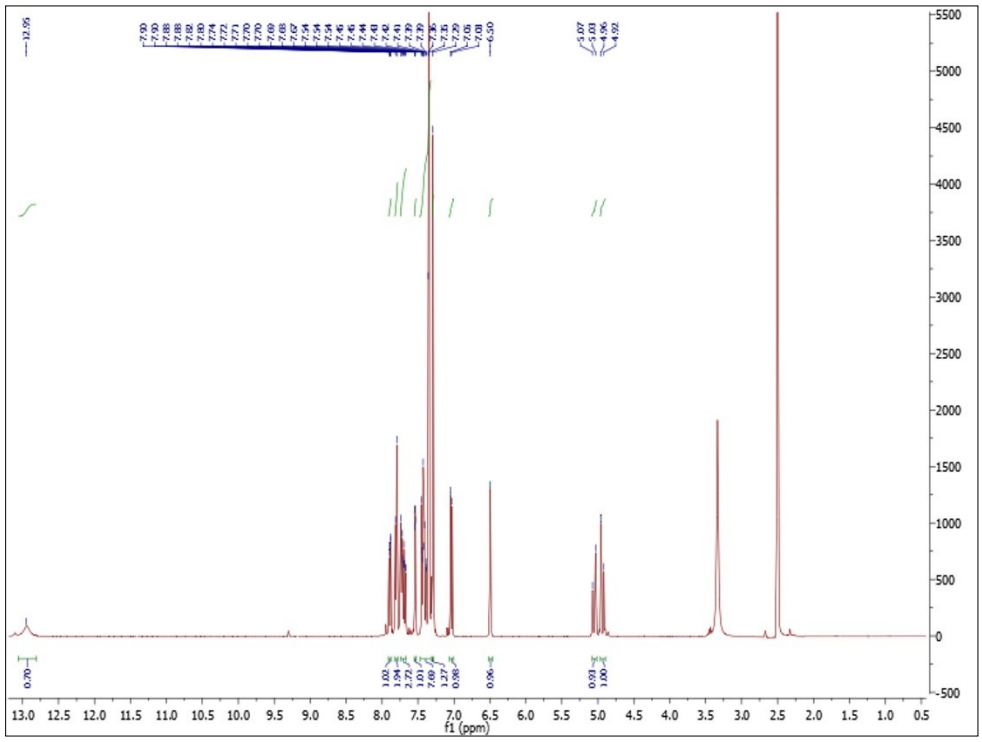

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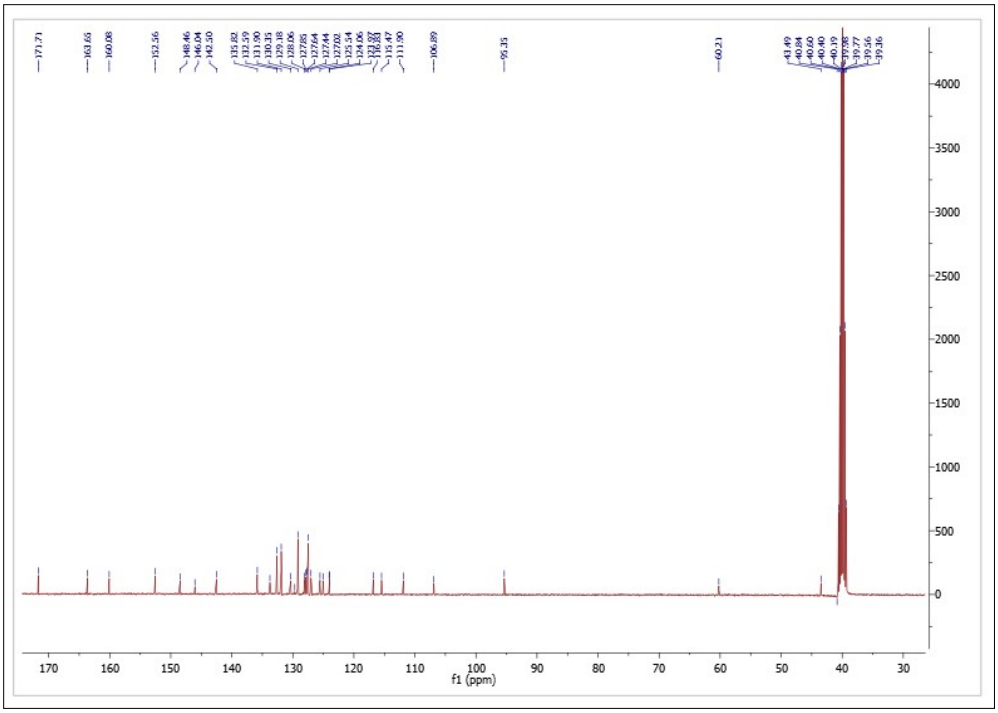

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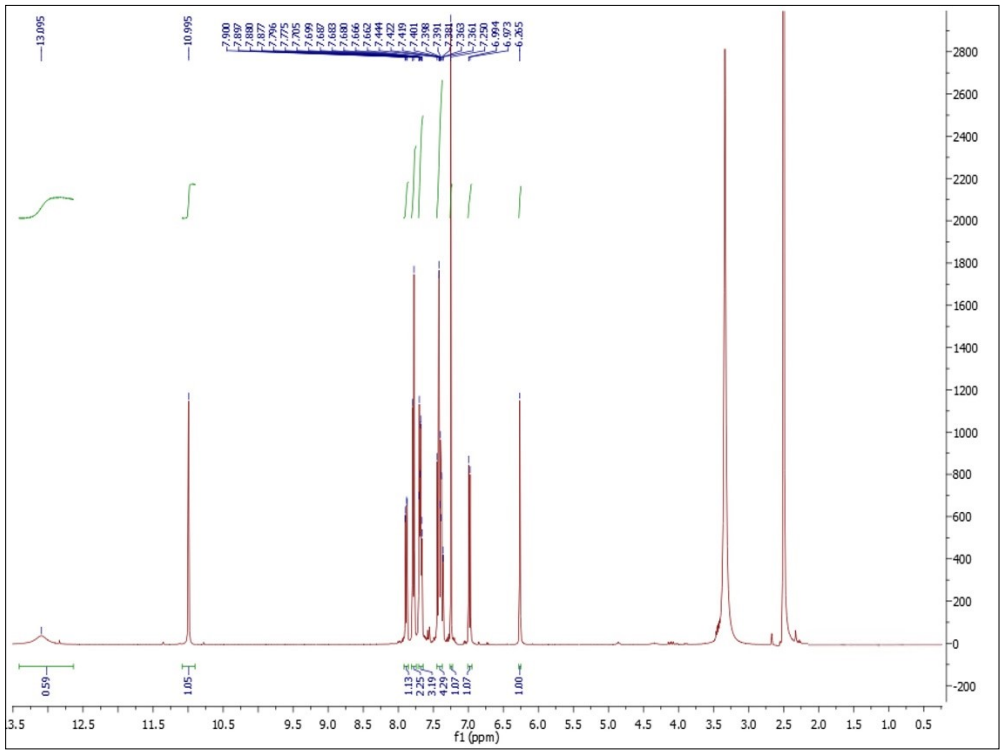

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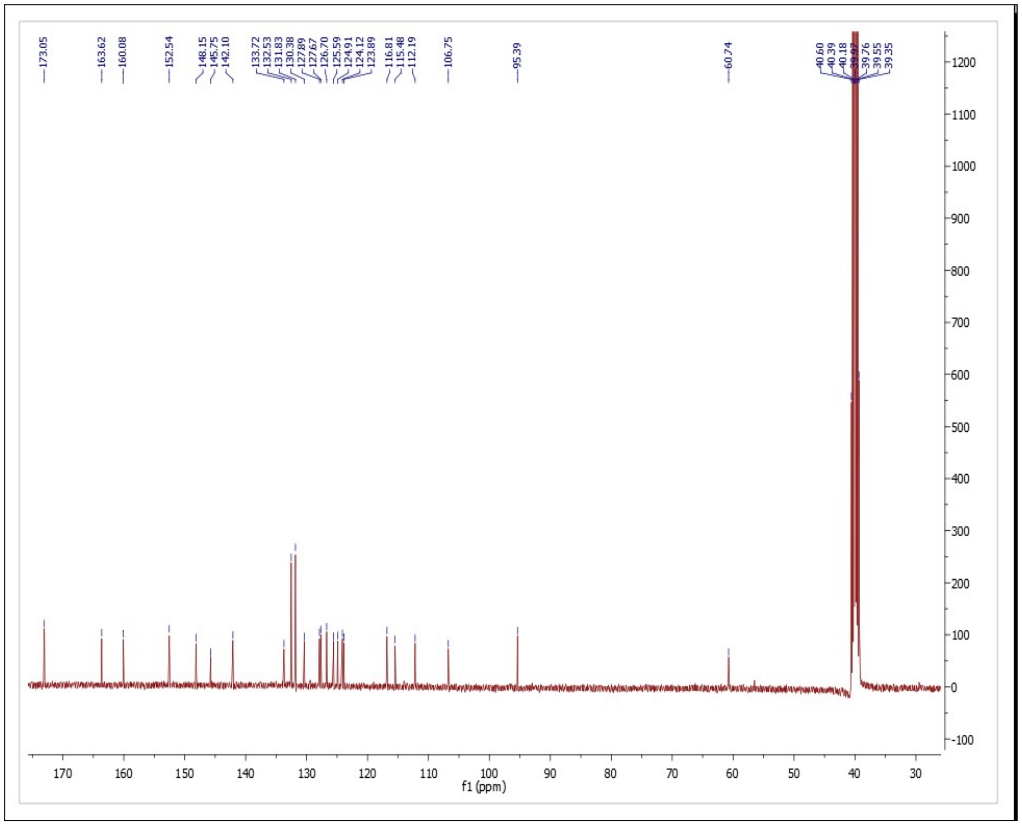

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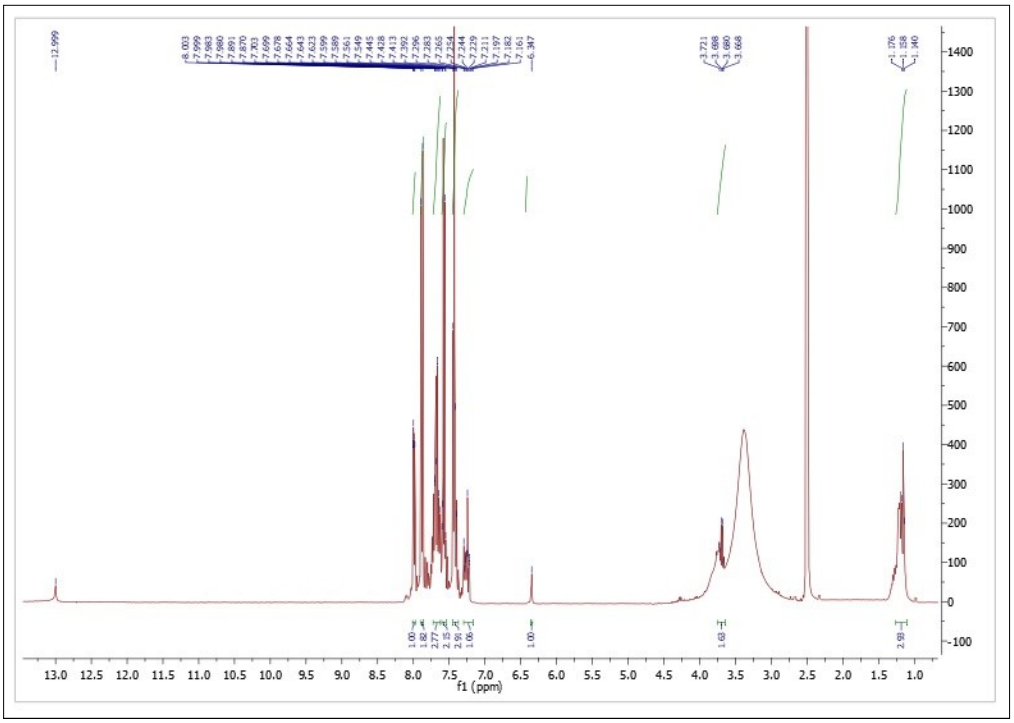

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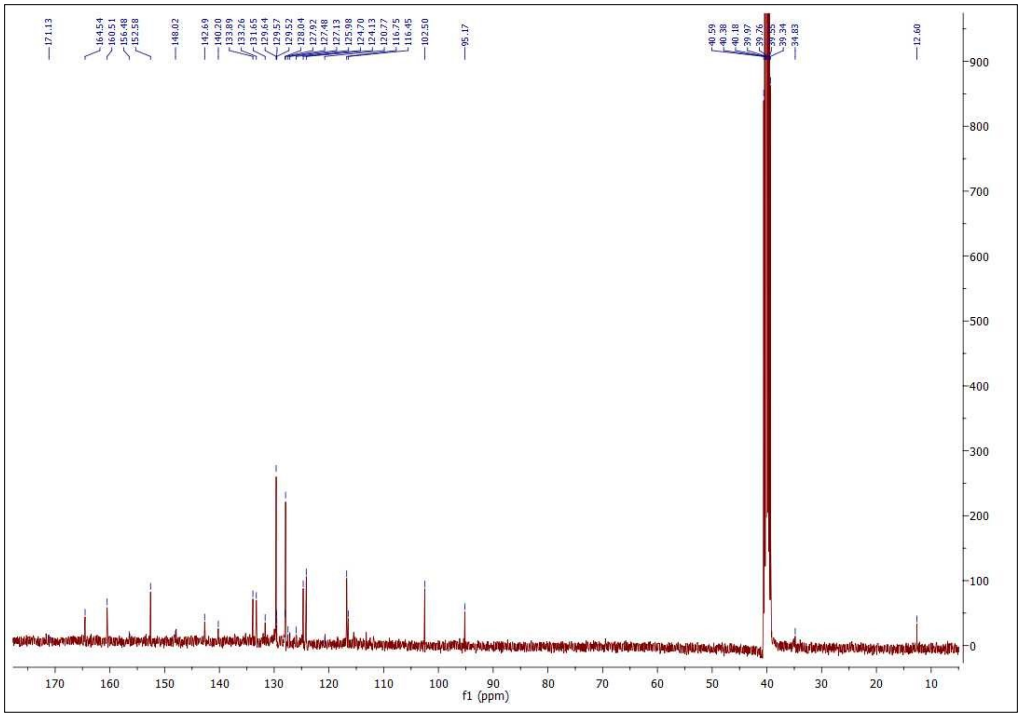

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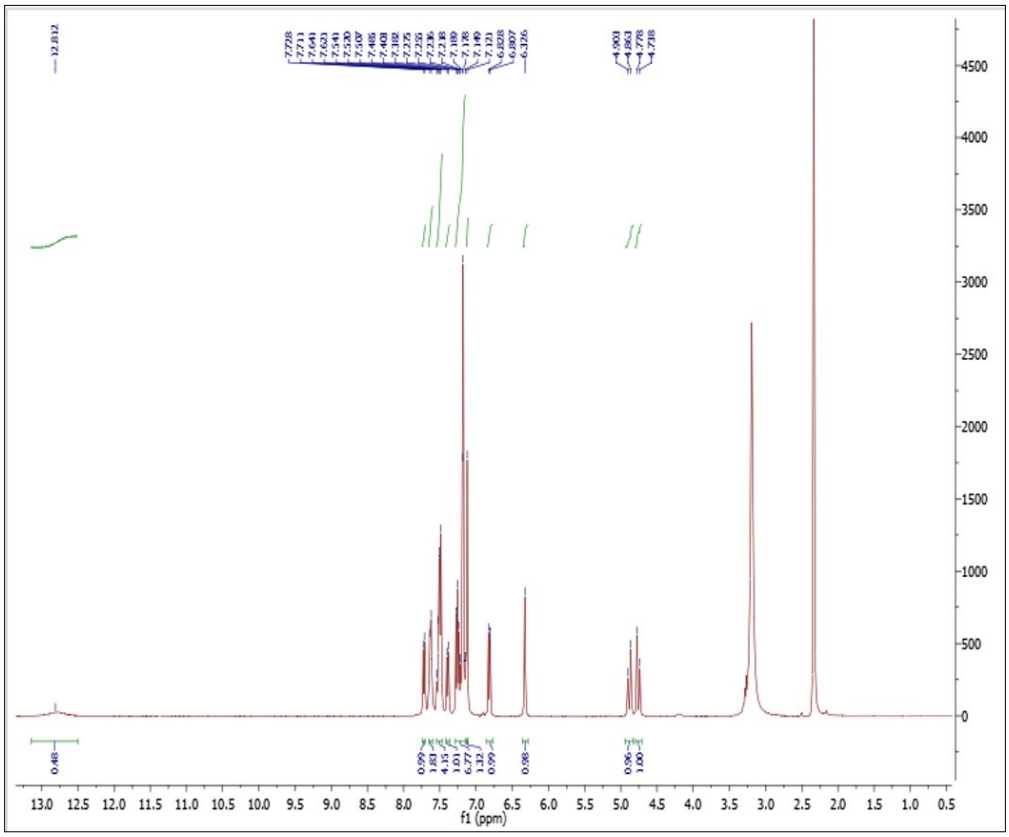

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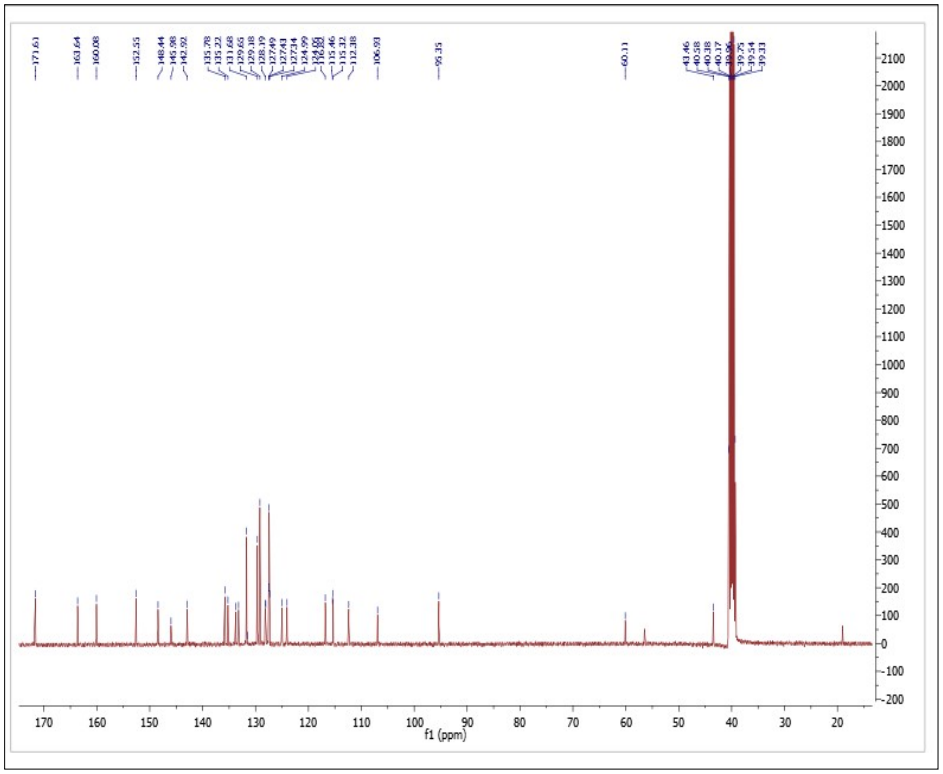

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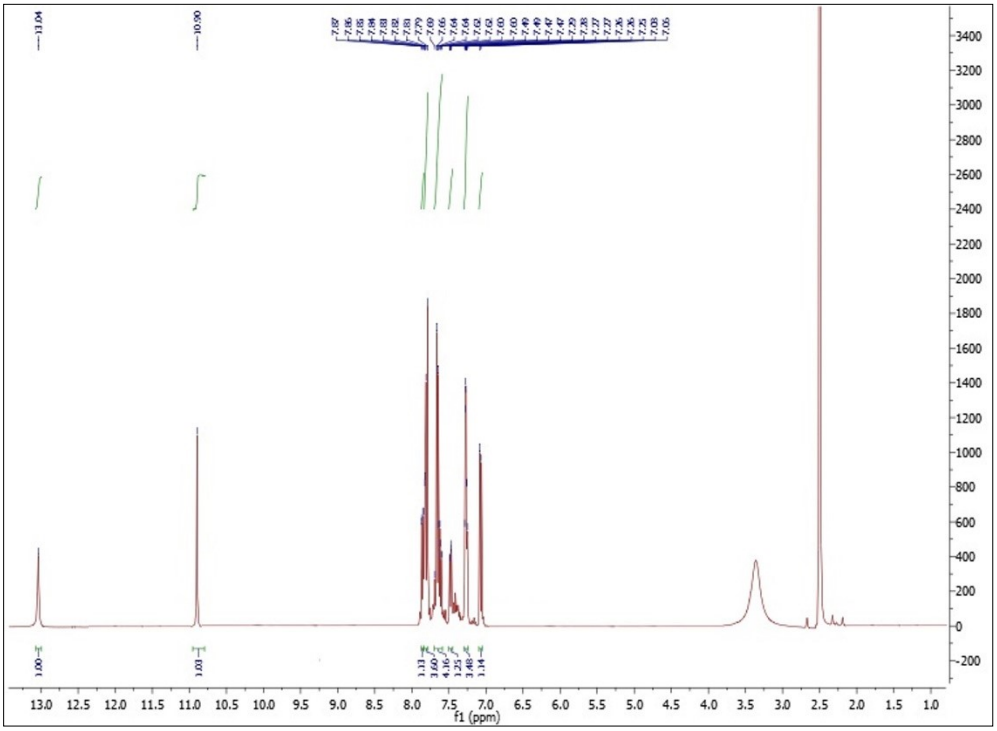

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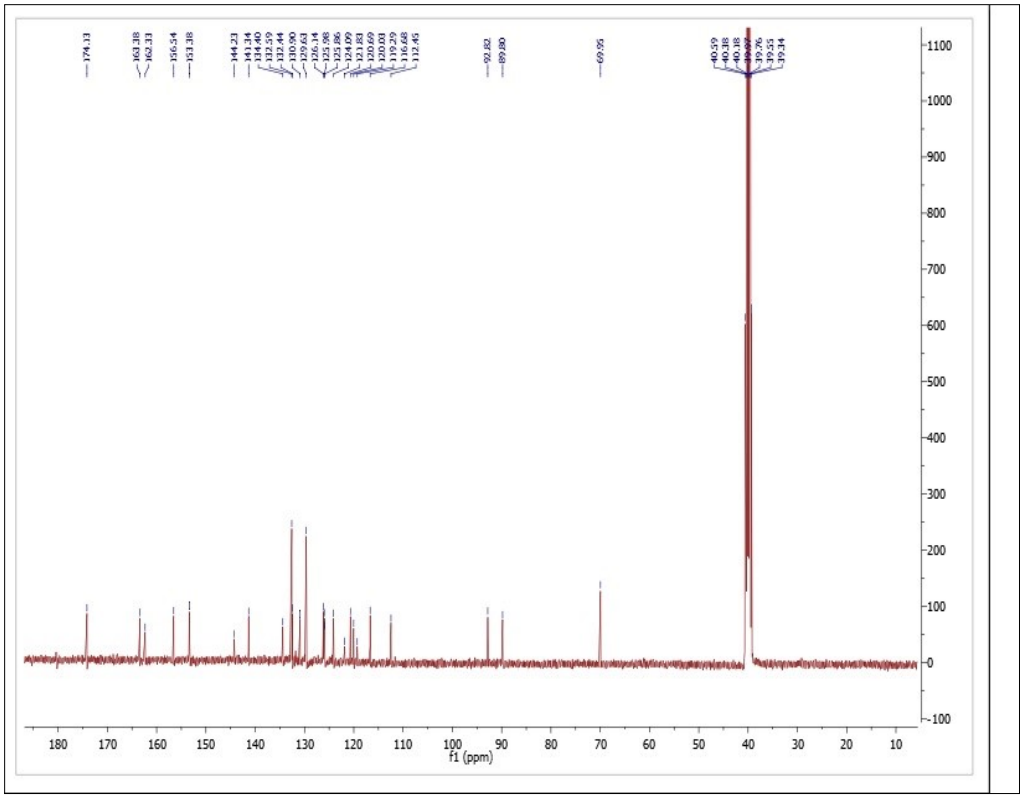

^{13}CNMR of compound 6j

- **Molecular docking study against BRAF^{V600E}**

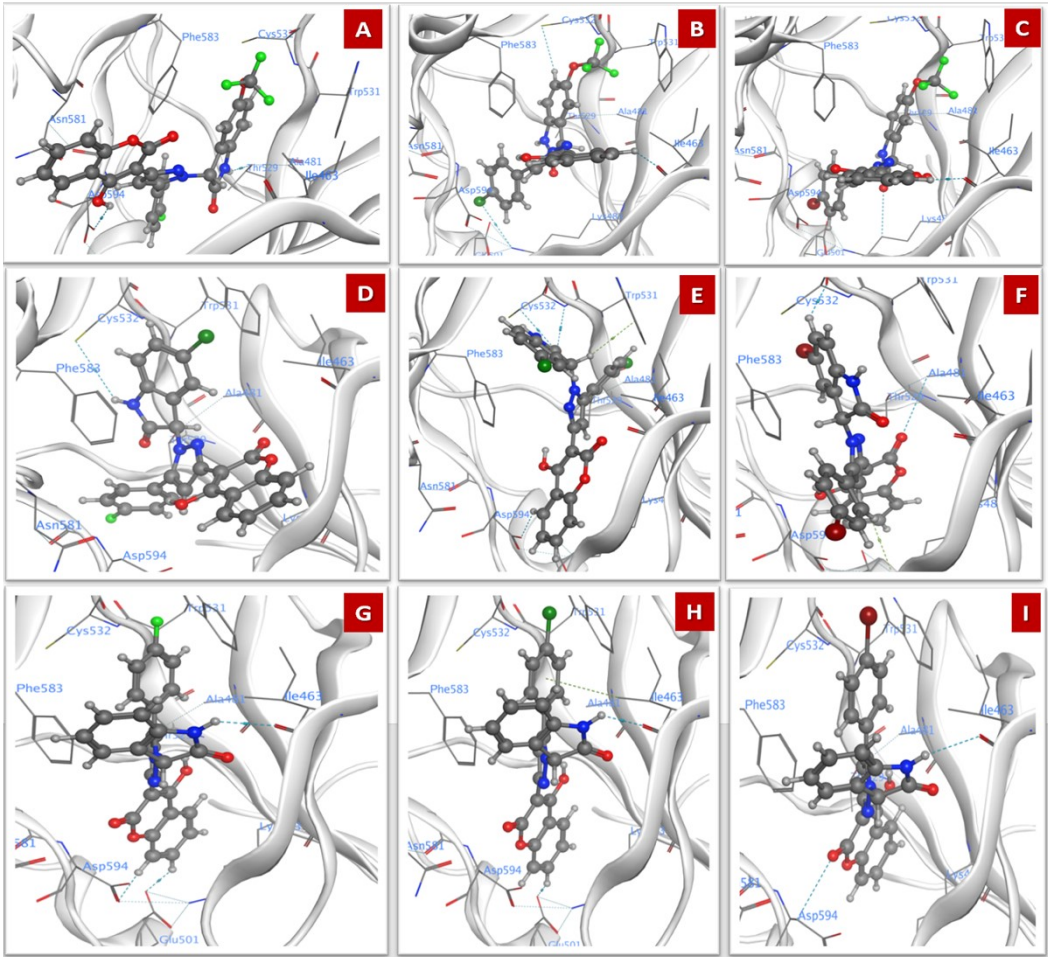

Figure S1. Docking of class I compounds with no substitution at N1-indoline (R1=H) against BRAF^{V600E}: A) **4j**, B) **5j**, C) **6j**, D) **4d**, E) **5d**, F) **6g**, G) **4a**, H) **5a**, I) **6a**.

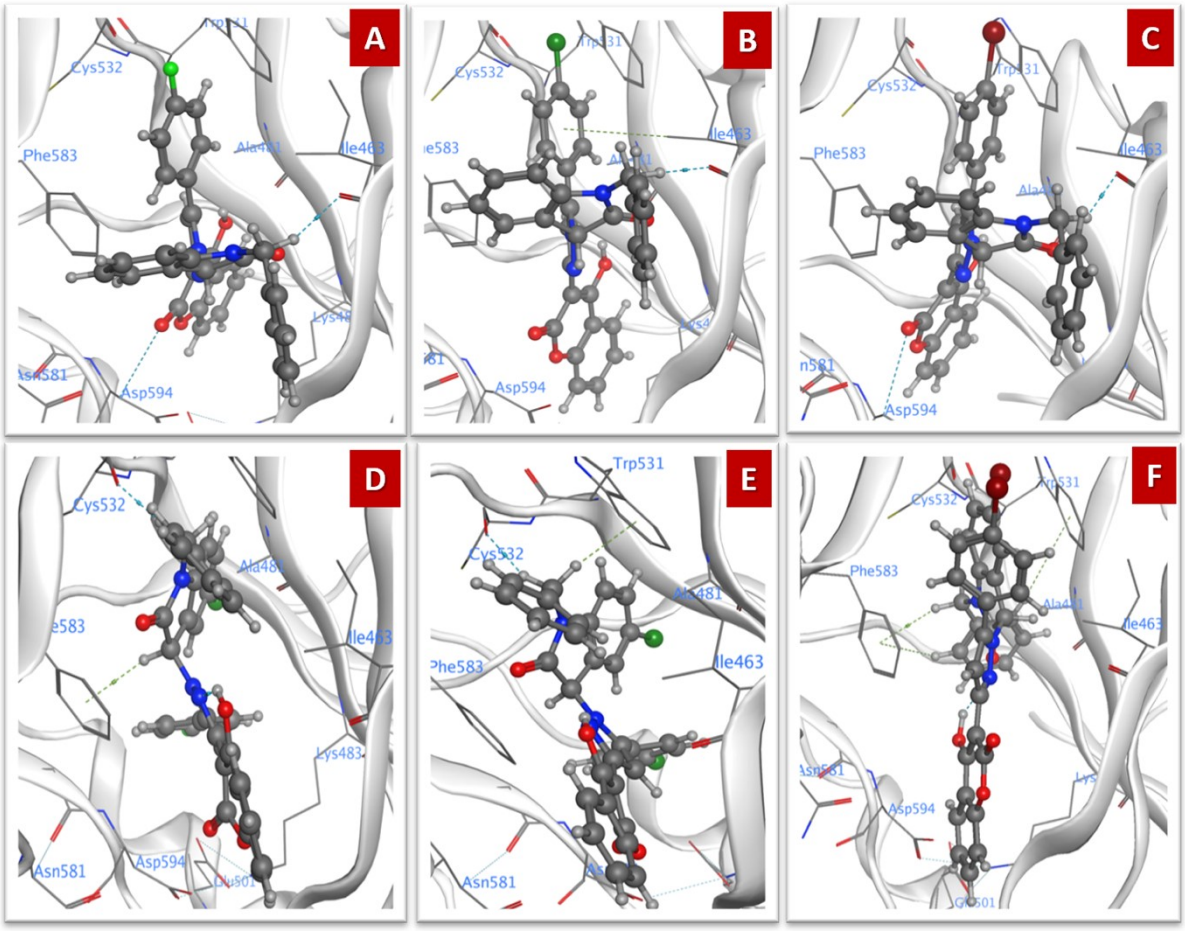

Figure S2. Docking of Class II compounds with N-benzylindoline against $BRAF^{V600E}$; A) **4c**, B) **5c**, C) **6c**, D) **4f**, E) **5f**, F) **6i.**

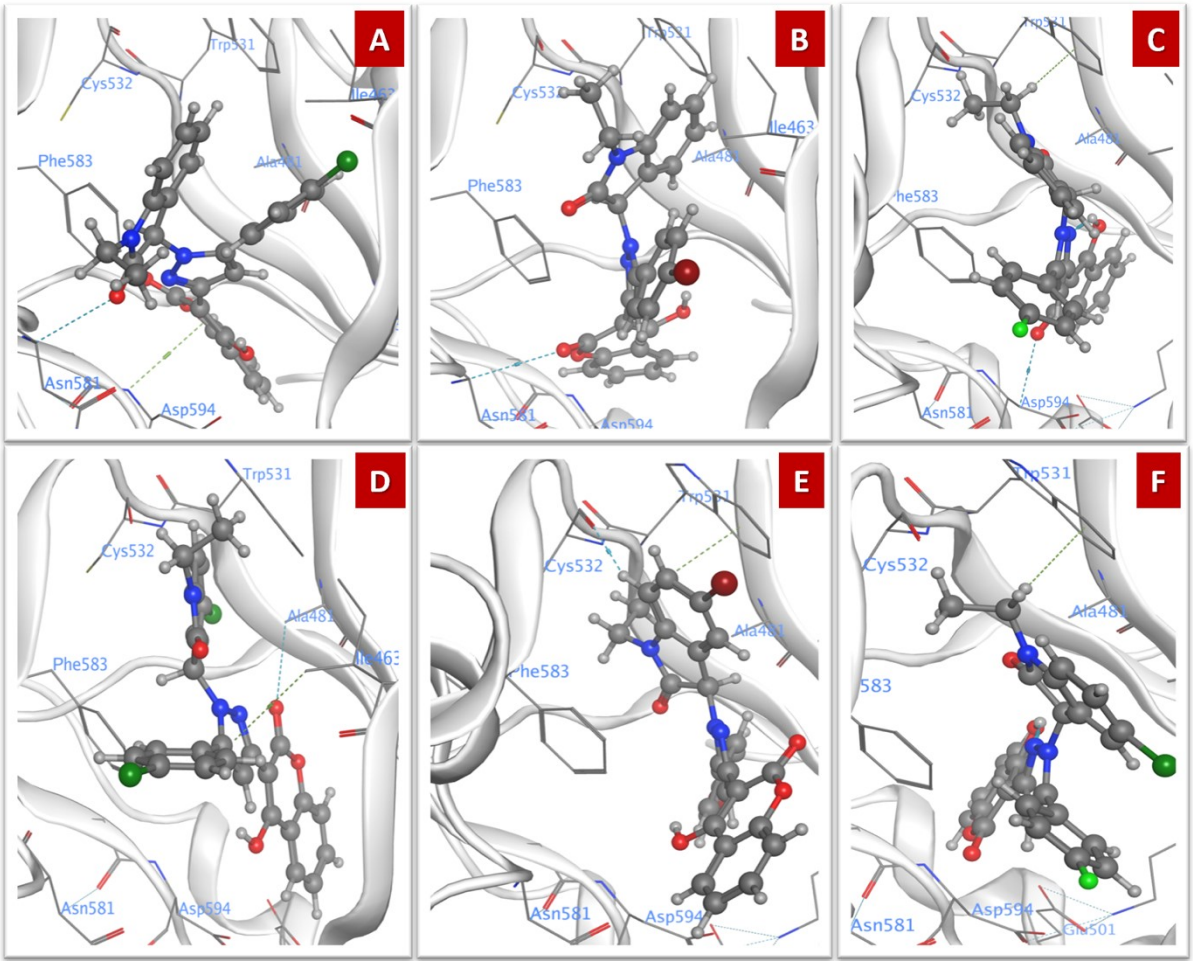

Figure S3. Docking of class III compounds with N-ethylindoline moiety against $BRAF^{V600E}$, A) **5b**, B) **6b**, C) **4b**, D) **5e**, E) **6h**, F) **4e**

- **Molecular docking study against VEGFR-2**

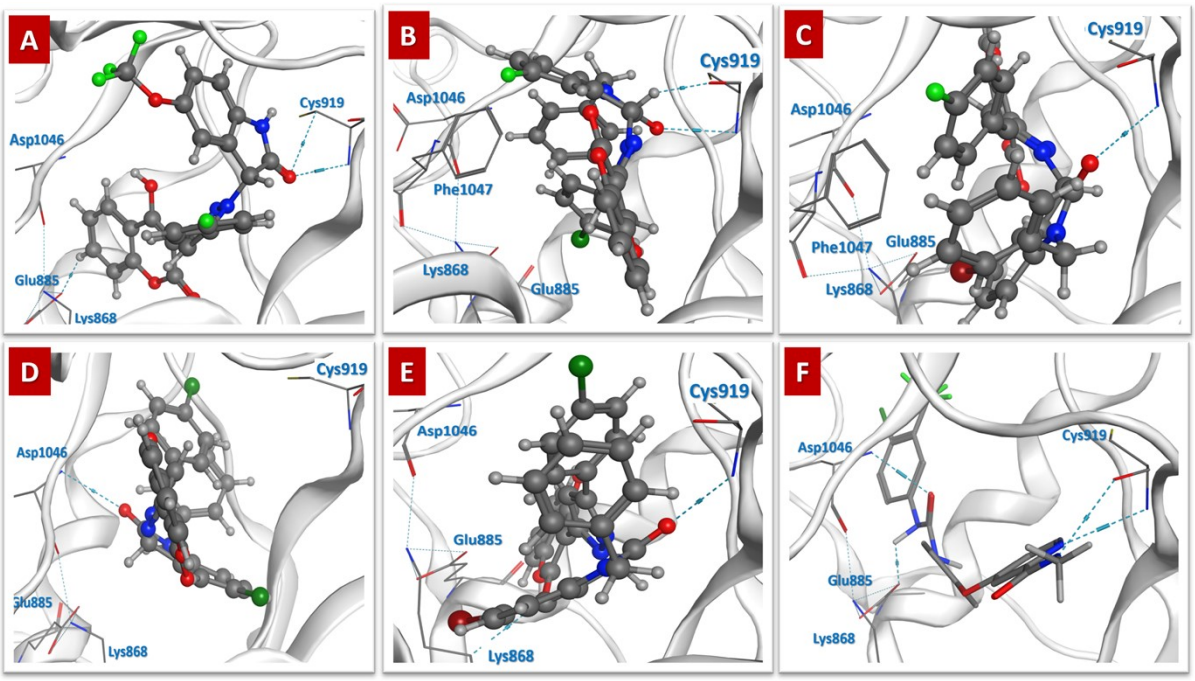

Figure S4. Best docking poses against VEGFR-2, A) Compound **4j**, B) Compound **4f**, C) Compound **4i**, D) Compound **5f**, E) Compound **5i**, F) Sorafenib.

- **ADME Prediction Study**

Table S1: Predicted ADME properties for compounds 4j, 4f, 4i, 5f, and 5i

Property	Model Name	Predicted value				
		4j	4f	4i	5f	5i
Absorption	Caco2 permeability (log cm/s)	-5.01	-5.11	-5.11	-5.11	-5.09
	Intestinal absorption (% absorbed)	100%	97.102%	97.035%	96.118 %	95.984%
	Skin Permeability (log Kp)	-2.735	-2.735	-2.735	-2.735	-2.735
	P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes
	P-glycoprotein I inhibitor	Yes	Yes	Yes	Yes	Yes
	P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes	Yes
Distribution	The volume of distribution (VD) (L/kg)	0.435	0.284	0.342	0.214	0.341
	Plasma protein binding	100%	101.39%	101.240%	101.746%	101.69%
	The fraction unbound in plasma	0.742%	0.783%	1.006 %	0.816%	0.988%
Metabolism	CYP2D6 substrate	No	No	No	No	No
	CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes
	CYP1A2 inhibitior	No	No	No	No	No
	CYP2C19 inhibitior	No	No	No	No	No
	CYP2C9 inhibitior	Yes	Yes	Yes	Yes	Yes
	CYP2D6 inhibitior	No	No	No	No	No
	CYP3A4 inhibitior	No	No	No	No	No
Excretion	Total Clearance (ml/min/kg)	2.8	2.409	1.359	2.098	1.056
	Renal OCT2 substrate	No	No	No	No	No
	The half-life ($T_{1/2}$)	0.009 hr	0.002 hr	0.002 hr	0.002 hr	0.002 hr
Toxicity	AMES Toxicity	No	No	No	No	No
	Skin Sensitization	No	No	No	No	No
	Carcinogencity	No	No	No	No	No
	Eye Corrosion / Irritation	No	No	No	No	No