Supplementary Information

New Phosphonylation Route of A Series of 2-AlkylBenzimidazole Derivatives: Synthesis, Characterization, Biological Evaluation, ADMET Prediction, Molecular Docking and DFT Studies

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1. ^{1}H and ^{13}C NMR Spectra

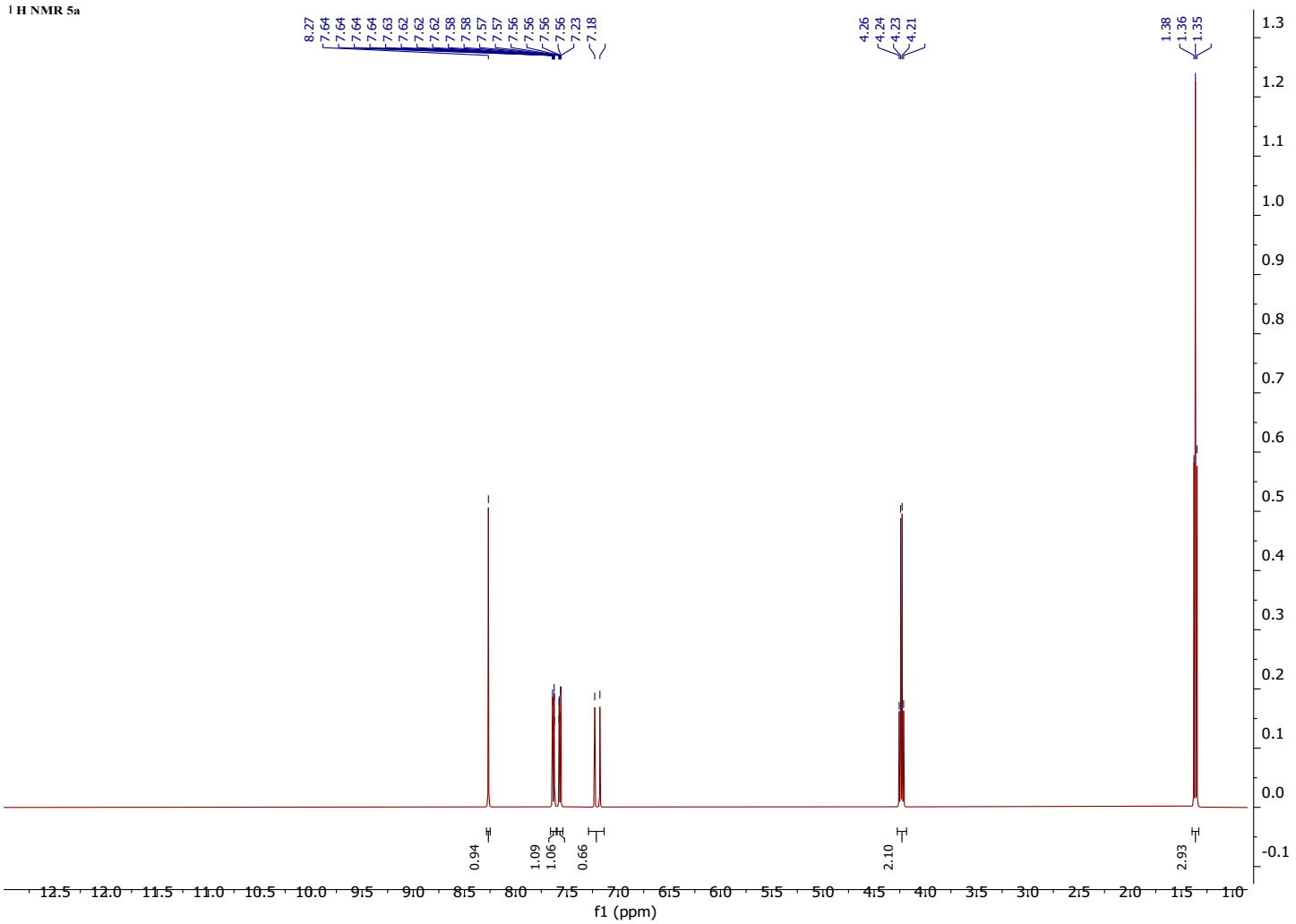

Figure S1a: ^{1}H-NMR spectrum of compound **5a**

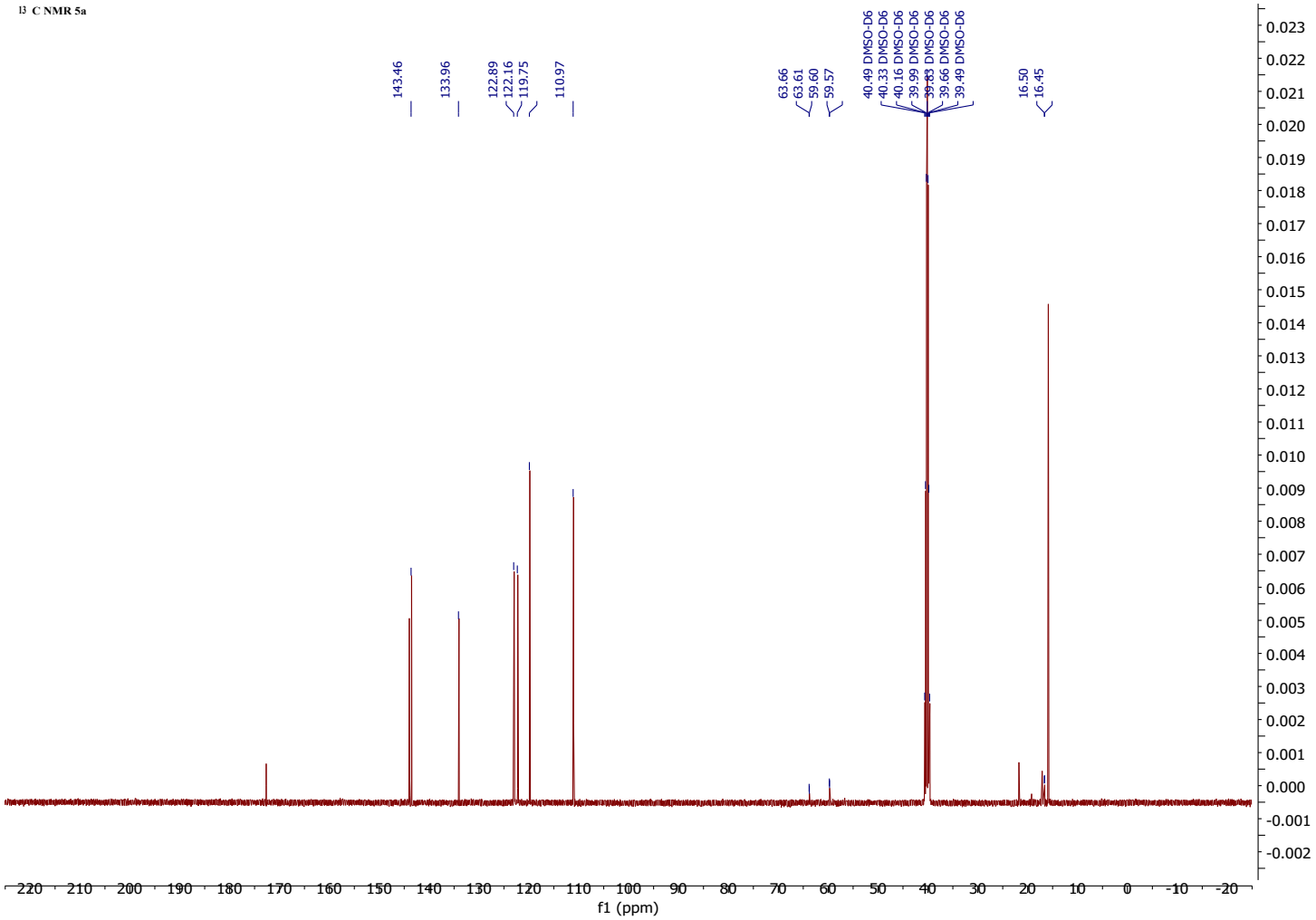

Figure S2a: ^{13}C-NMR spectrum of compound **5a**

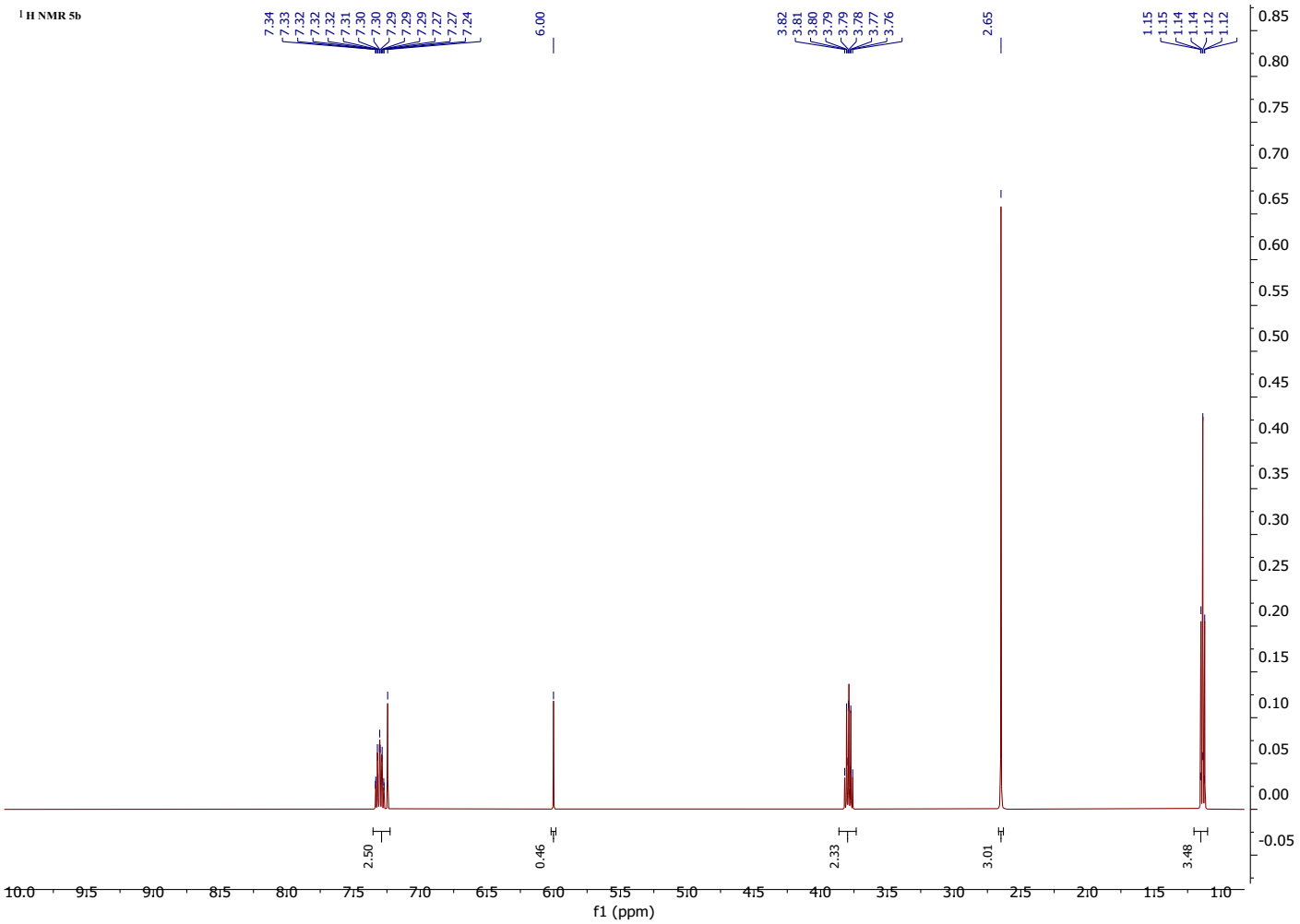

Figure S3b: [1]H-NMR spectrum of compound **5b**

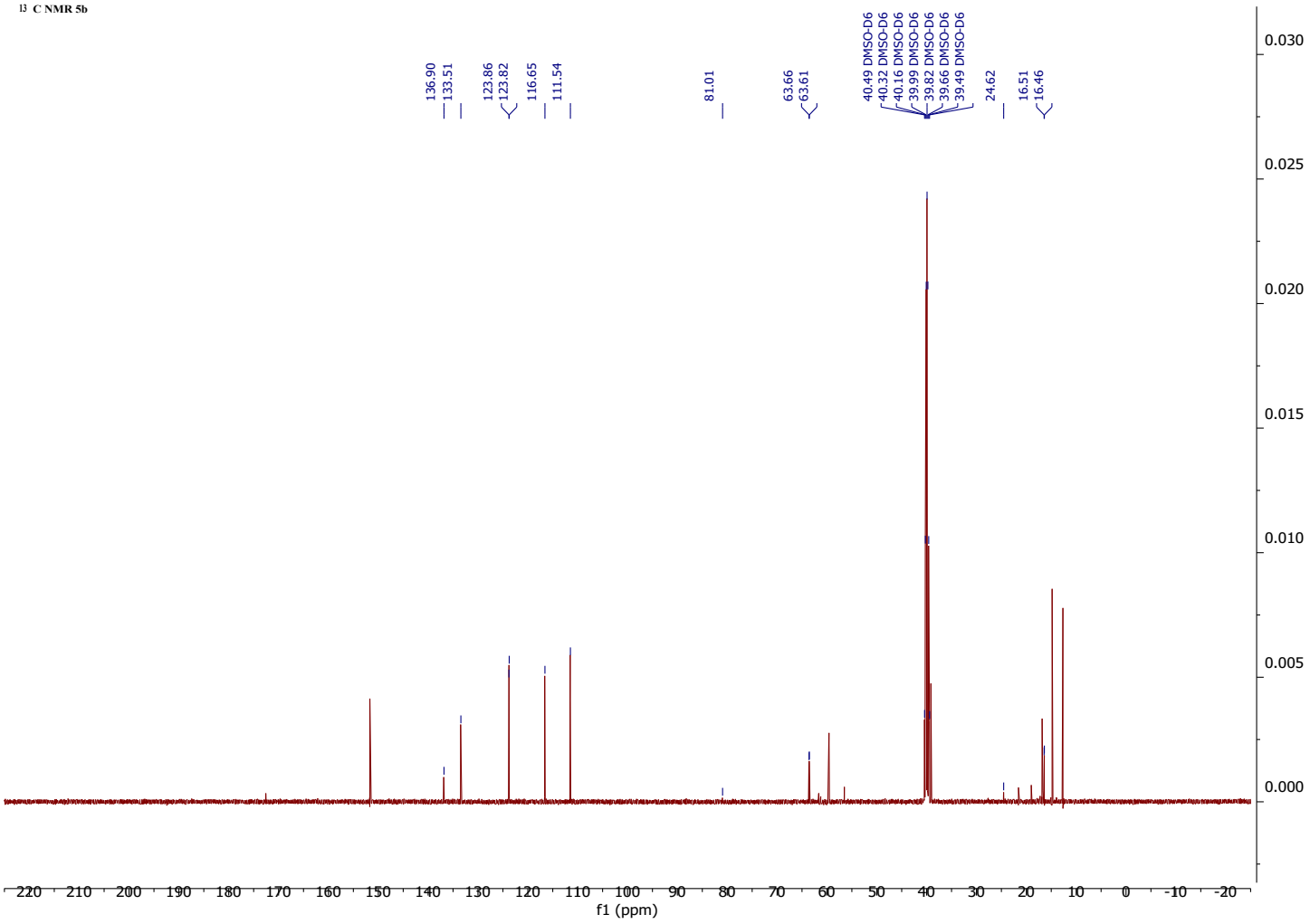

Figure S4b: ^{13}C-NMR spectrum of compound **5b**

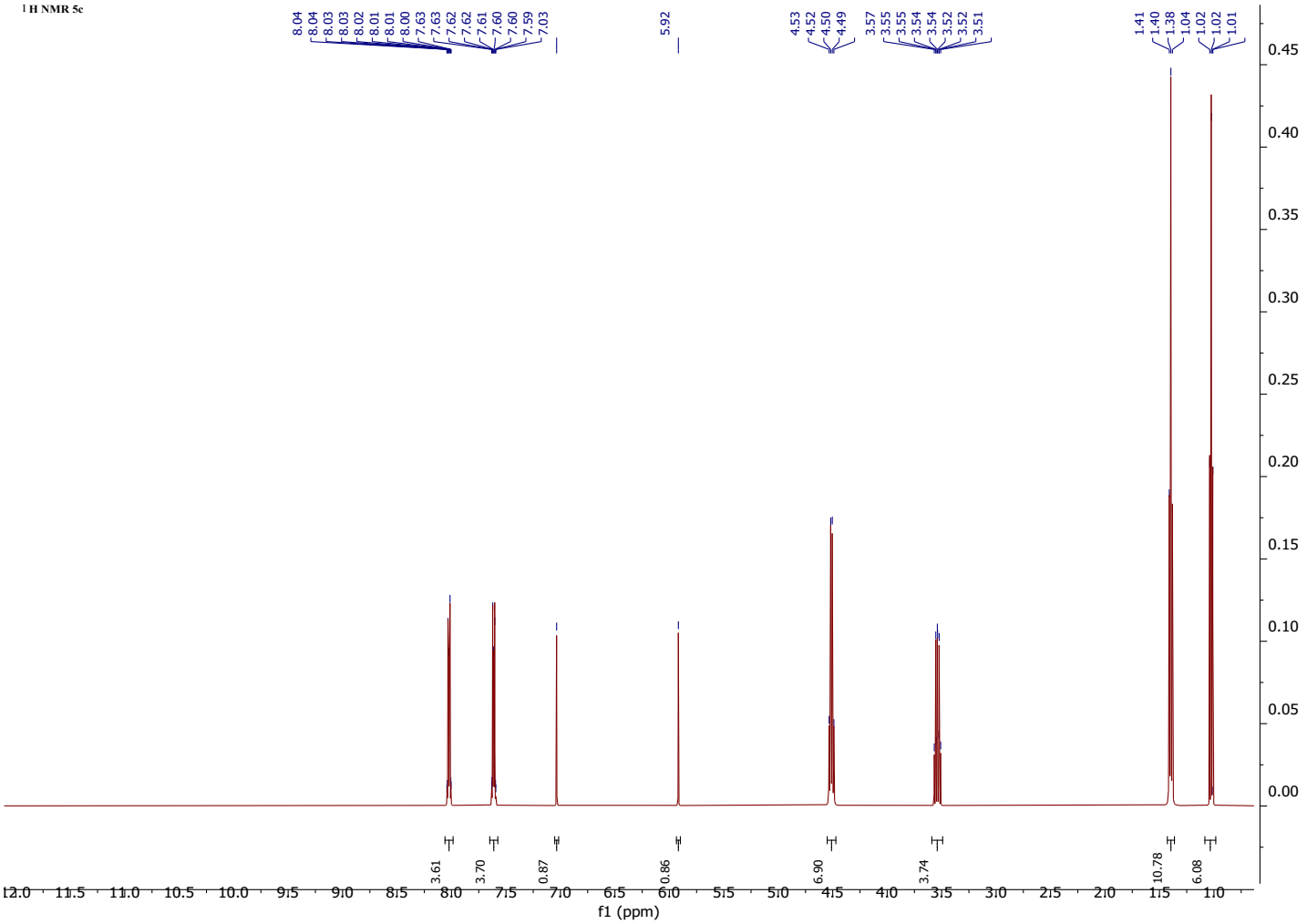

Figure S5c: [1]H-NMR spectrum of compound **5c**

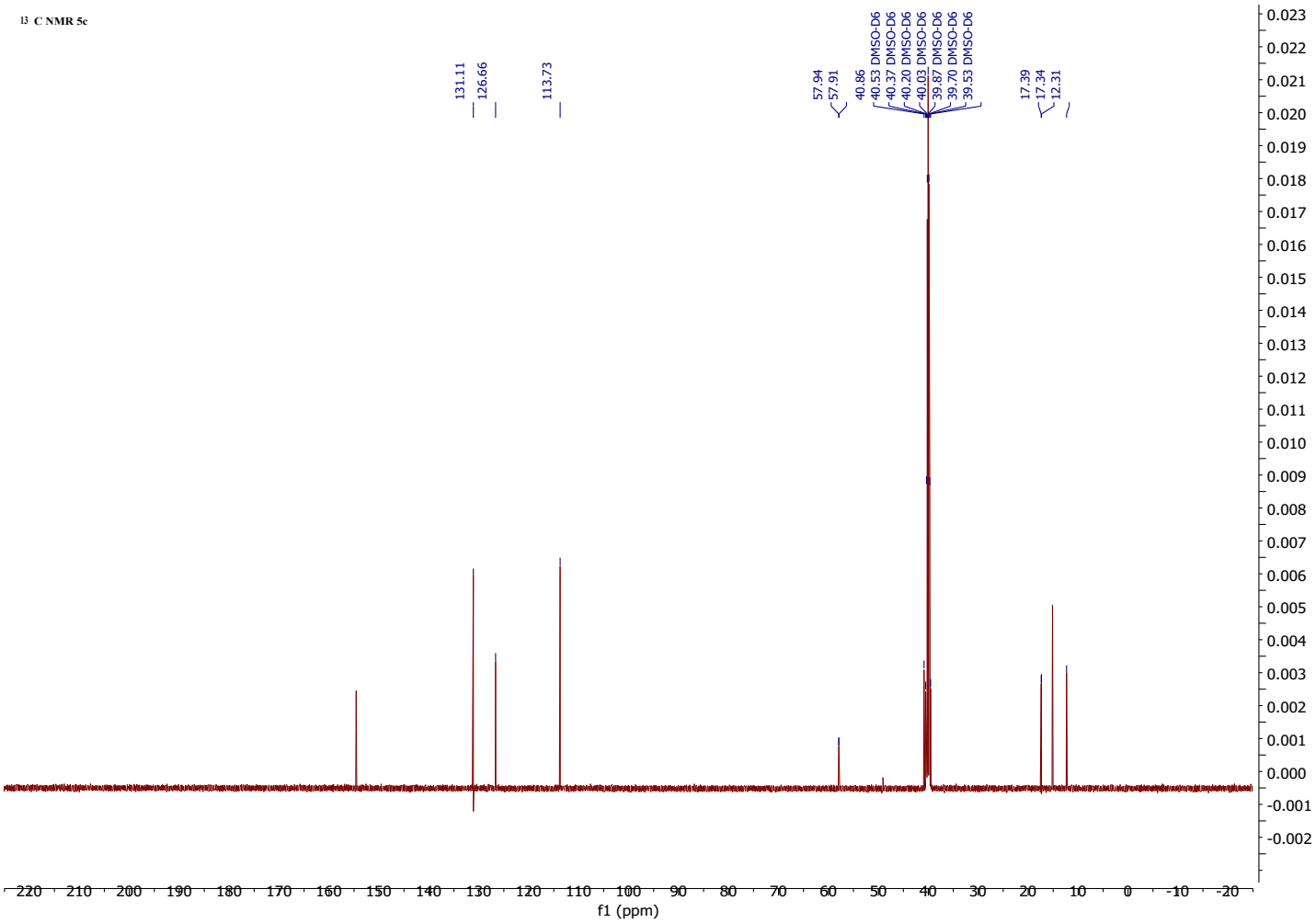

Figure S6c: ^{13}C-NMR spectrum of compound **5c**

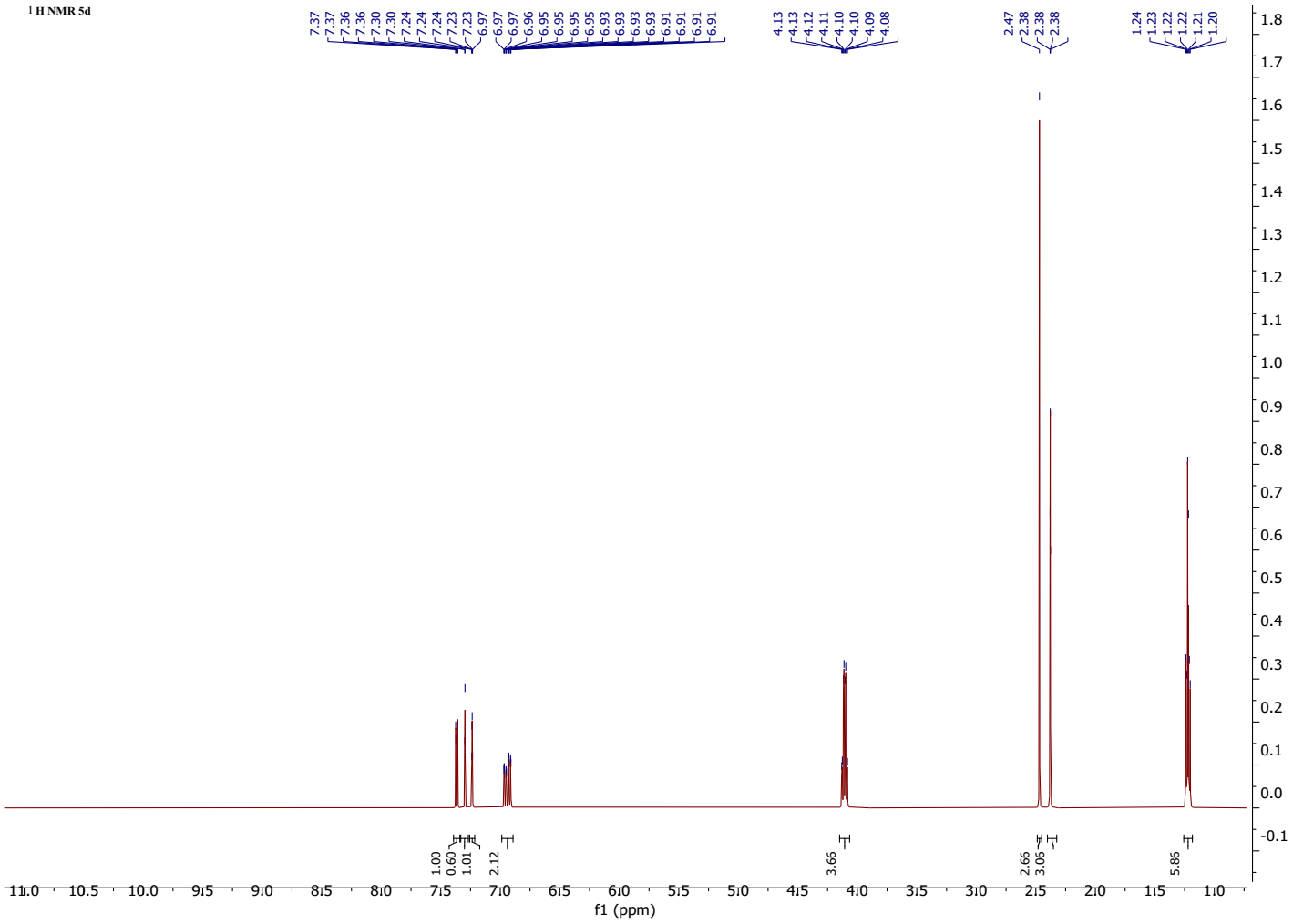

Figure S7d: ^{1}H-NMR spectrum of compound **5d**

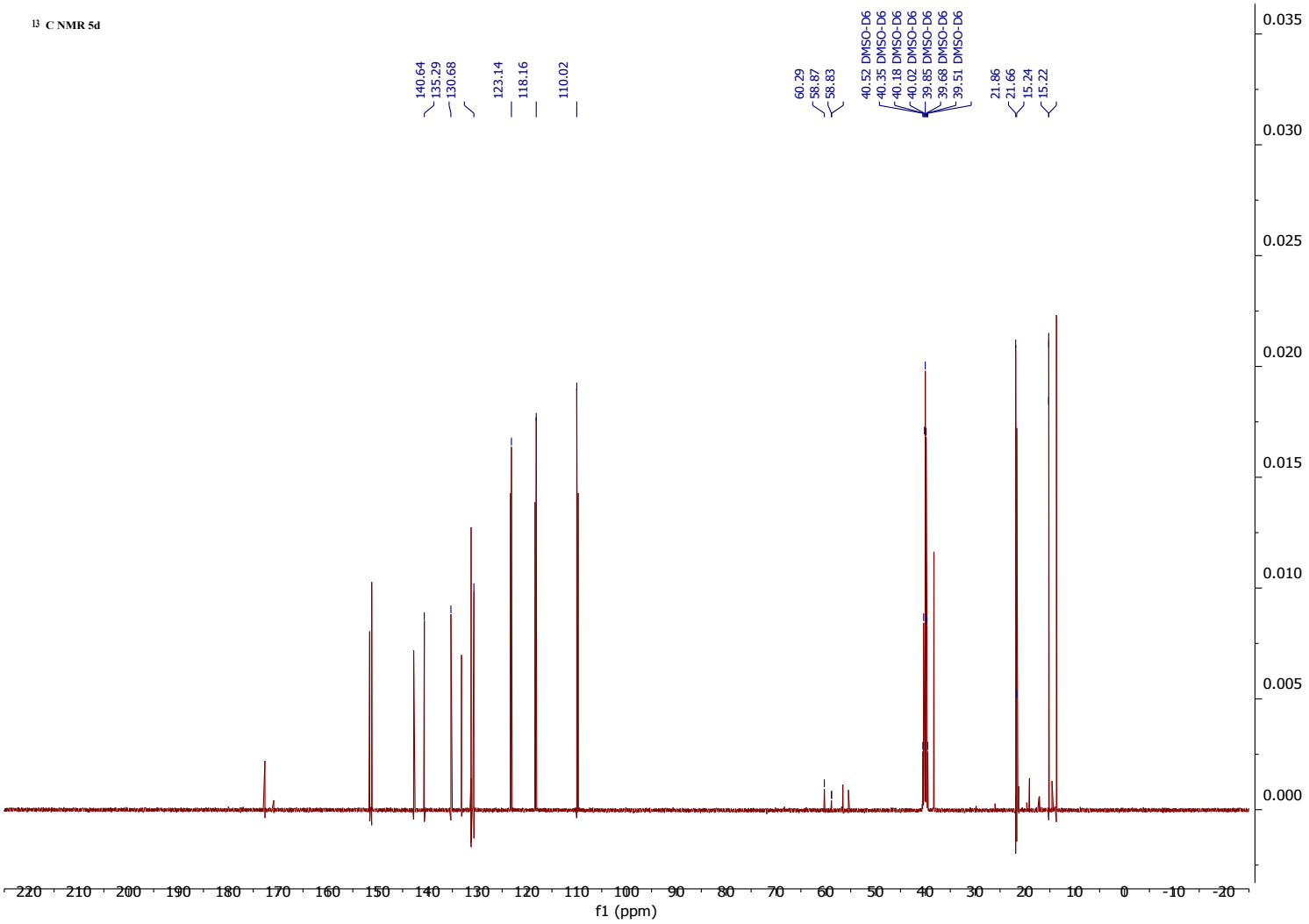

Figure S8d: ^{13}C-NMR spectrum of compound **5d**

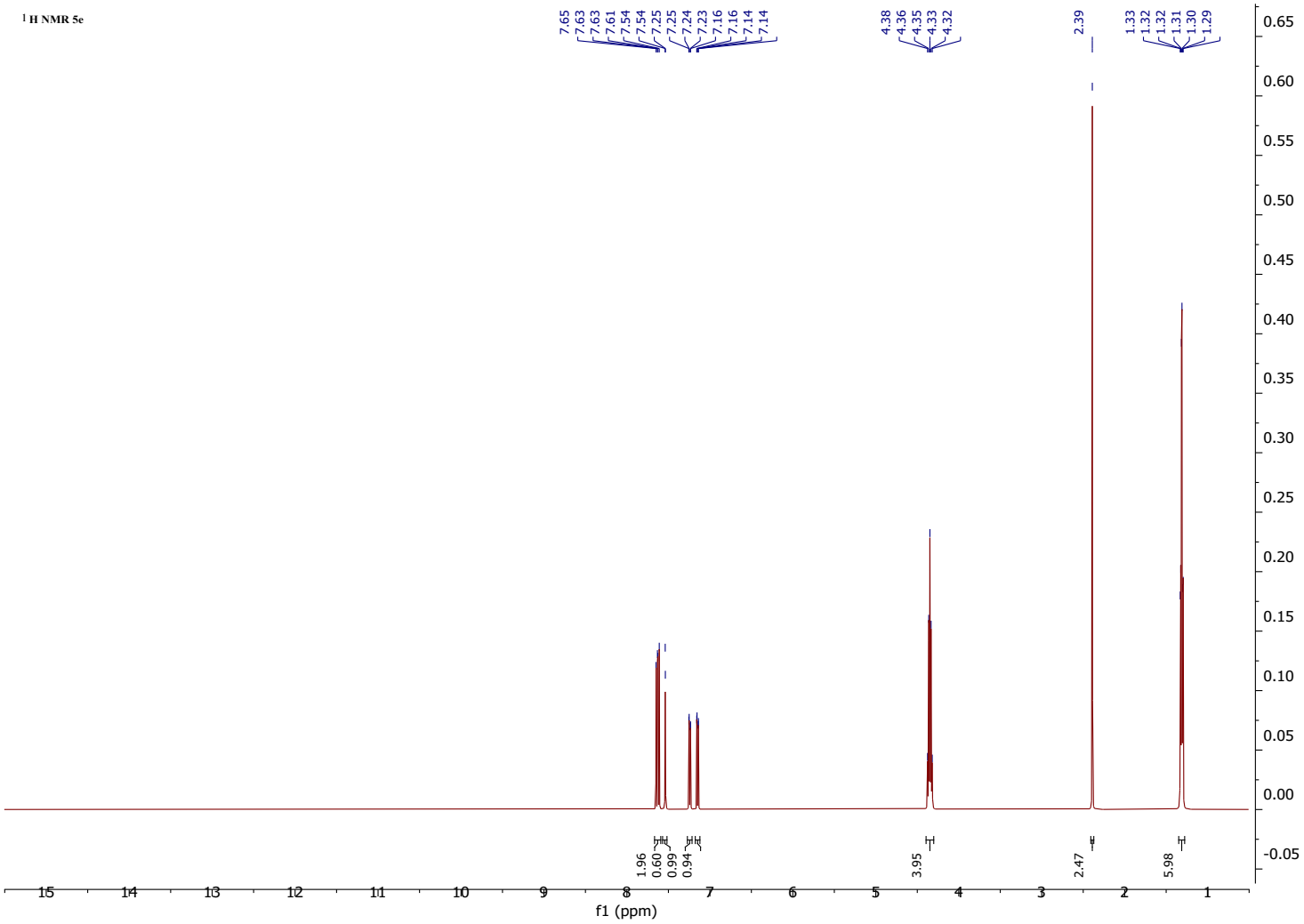

Figure S9e: ^{1}H-NMR spectrum of compound **5e**

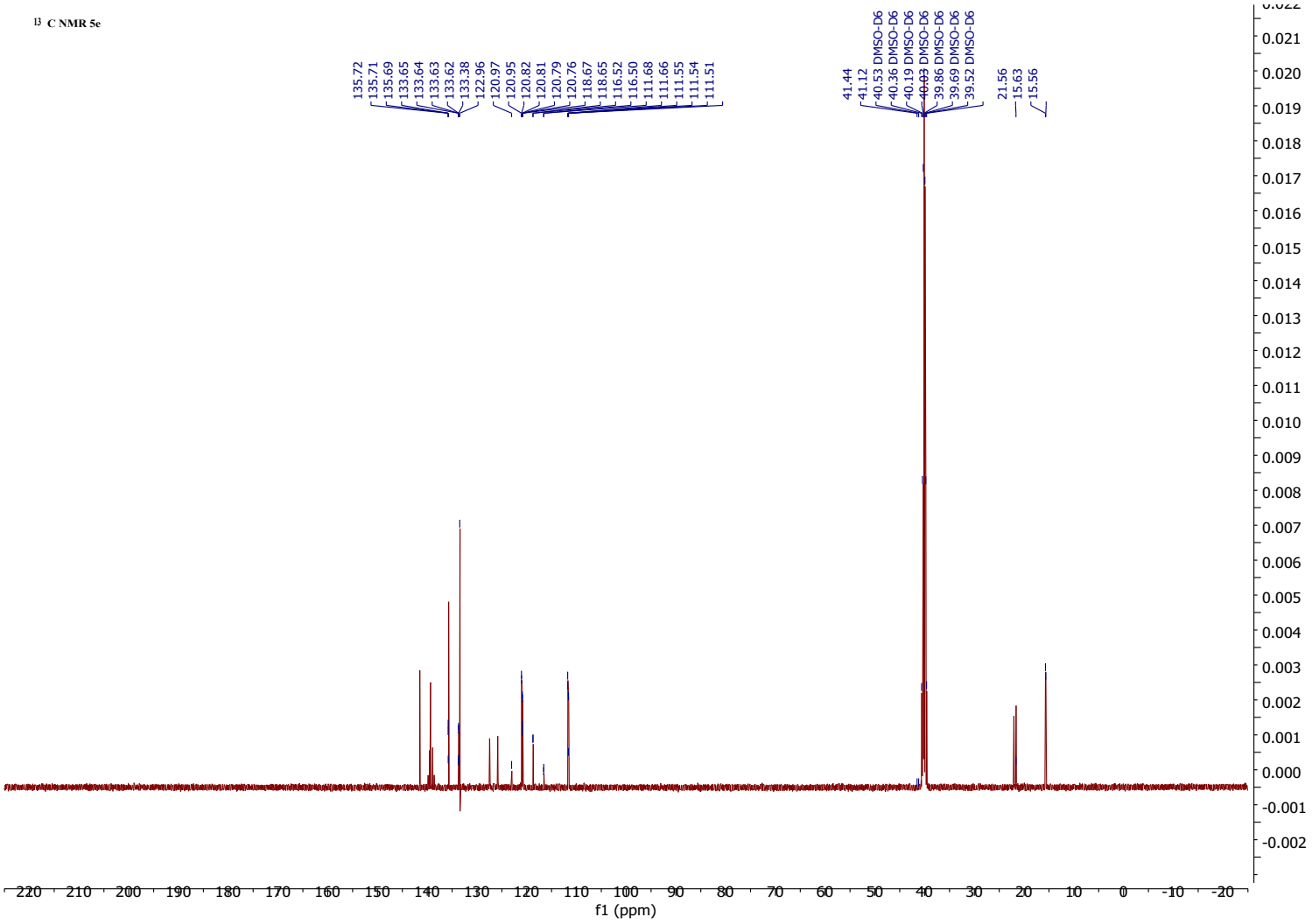

Figure S10e: ^{13}C-NMR spectrum of compound **5e**

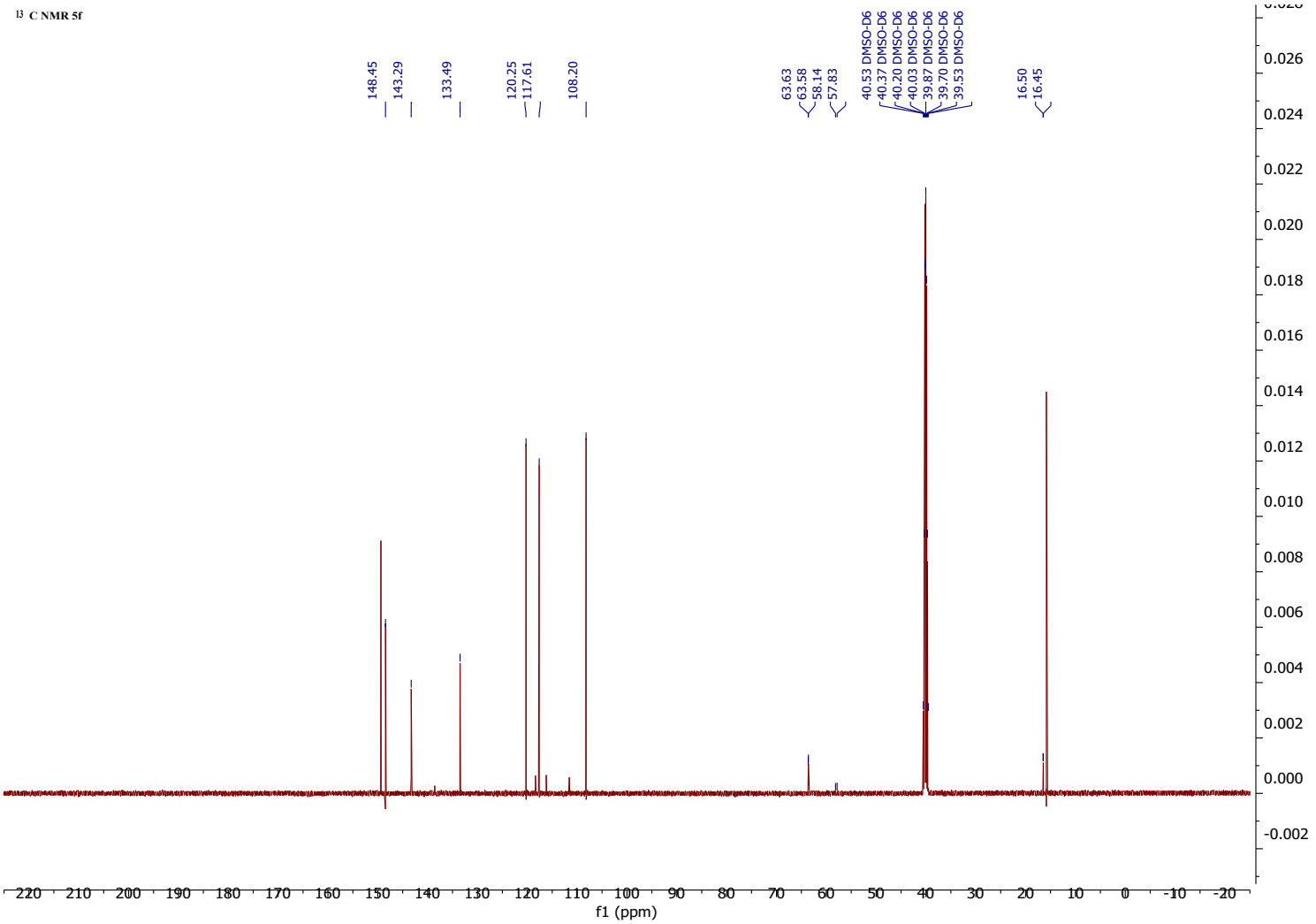

Figure S11f: ^{13}C-NMR spectrum of compound **5f**

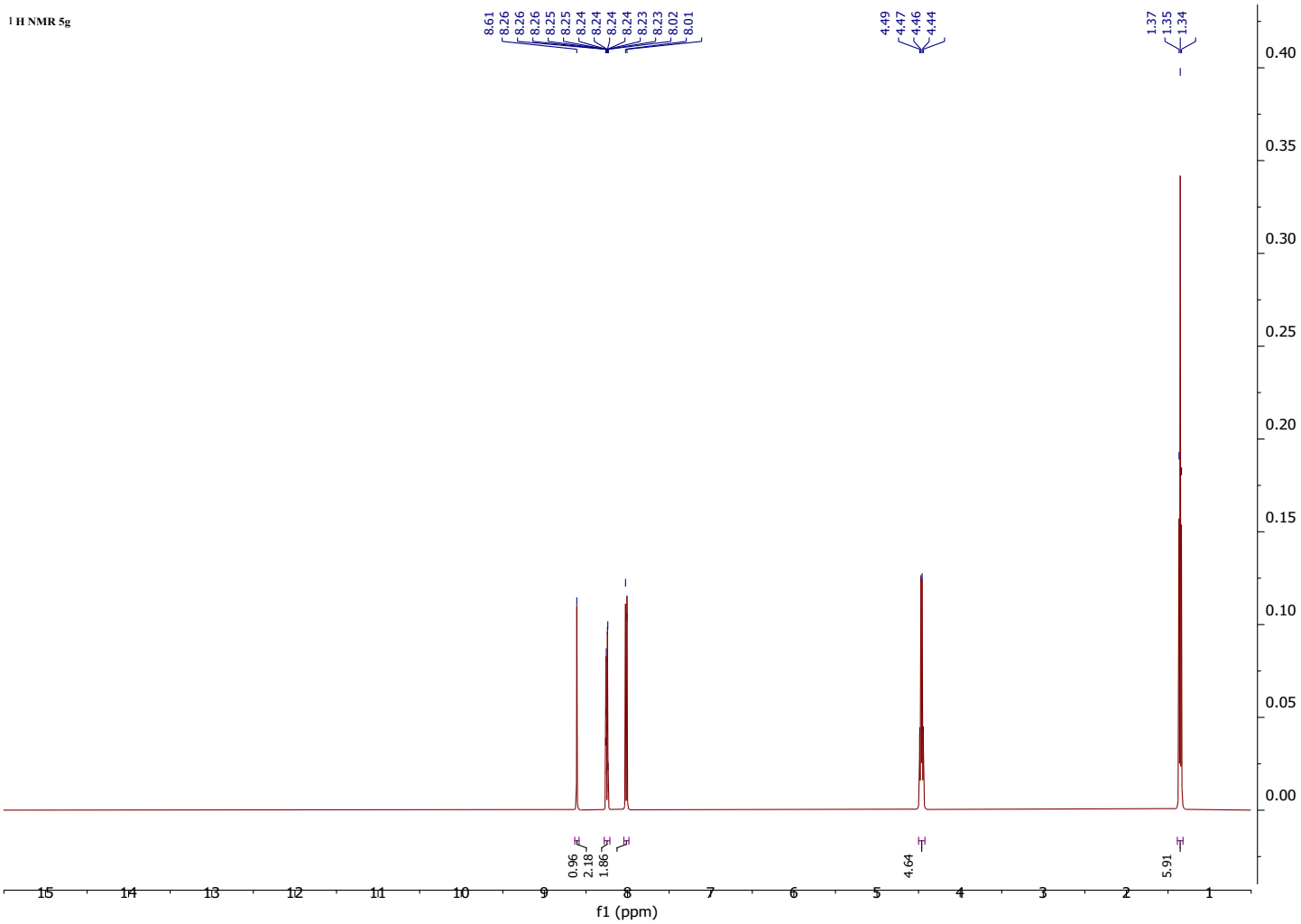

Figure S12g: ^{1}H-NMR spectrum of compound **5g**

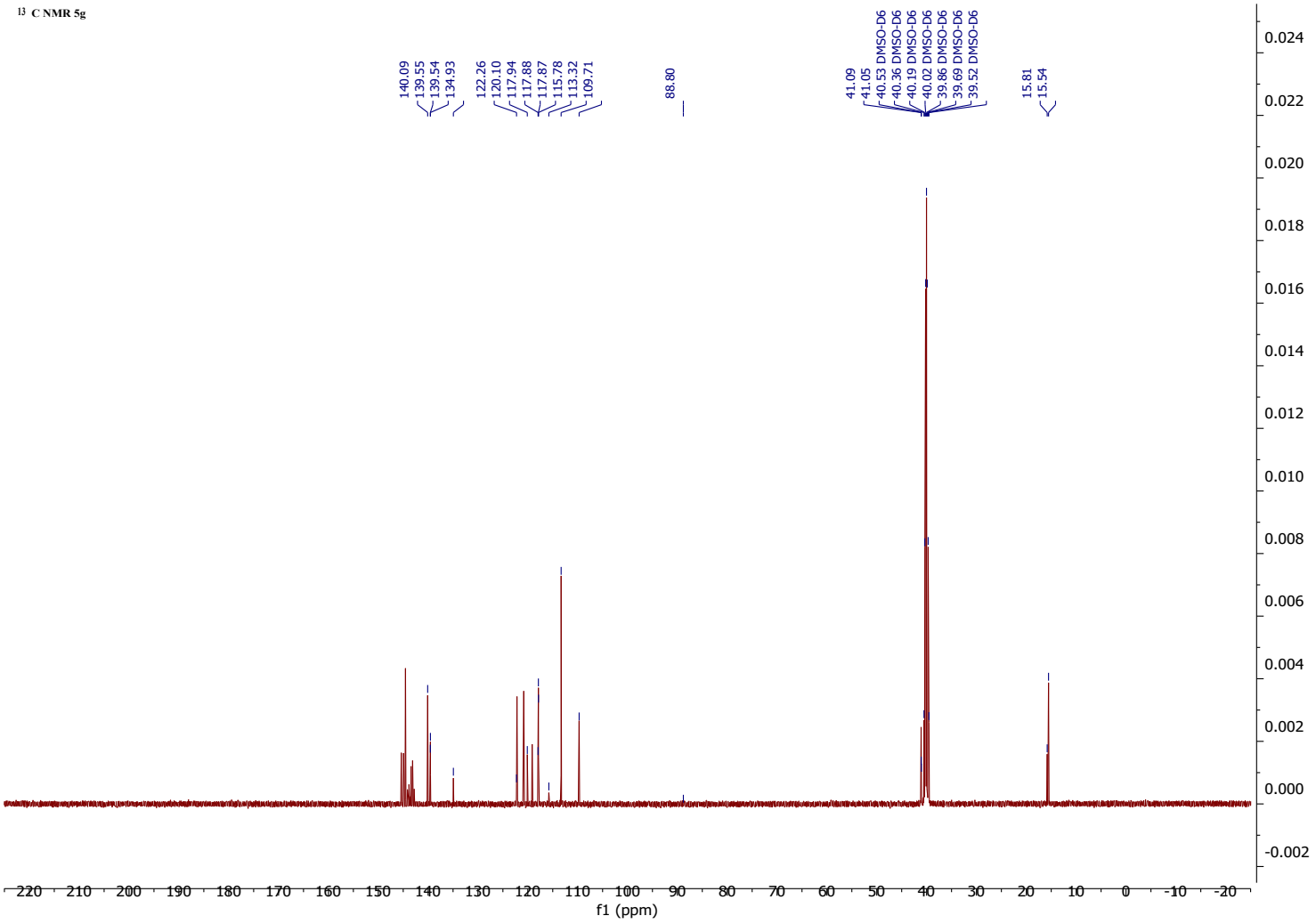

Figure S13g: ^{13}C-NMR spectrum of compound **5g**

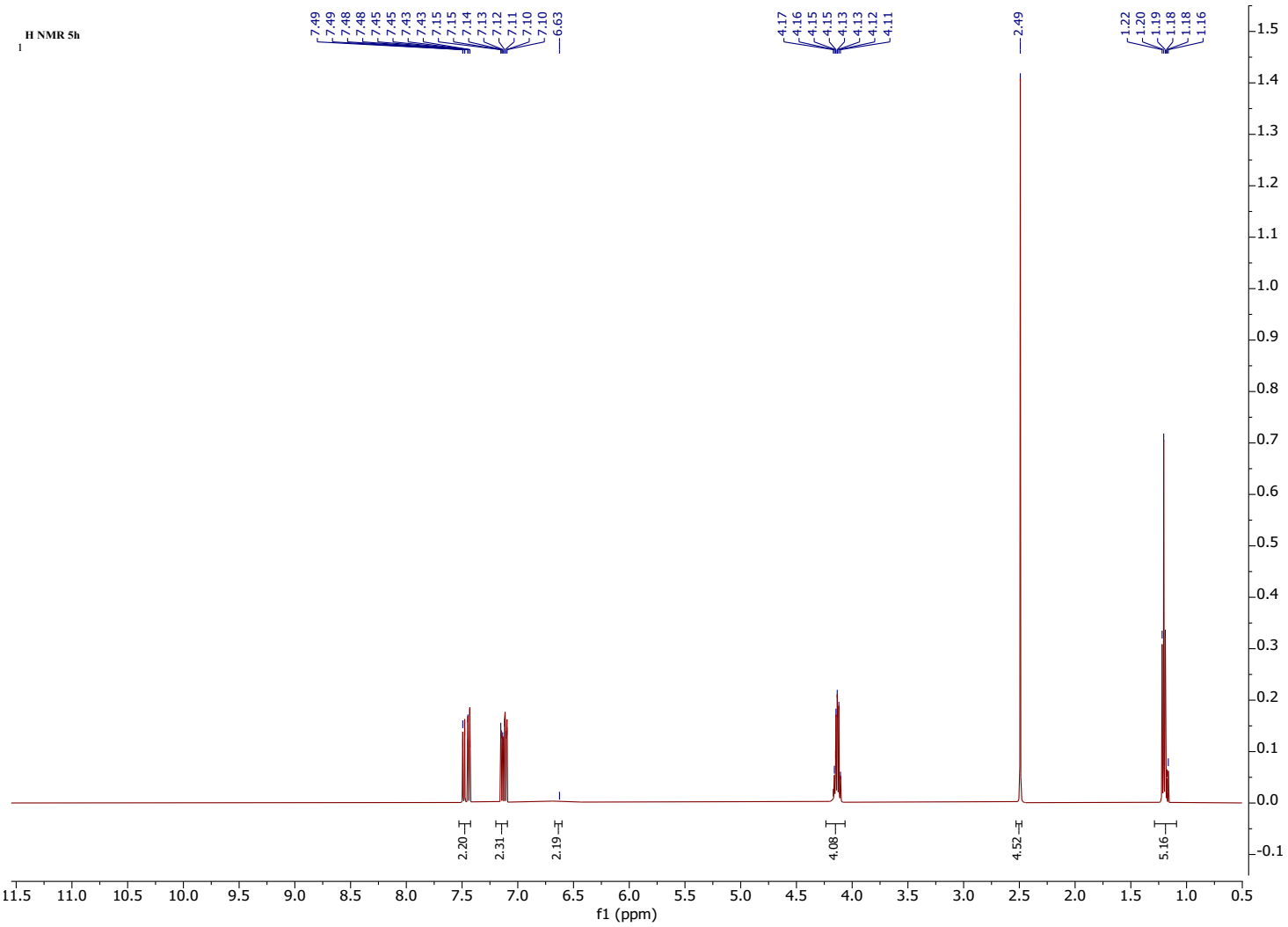

Figure S14h: ^{1}H-NMR spectrum of compound **5h**

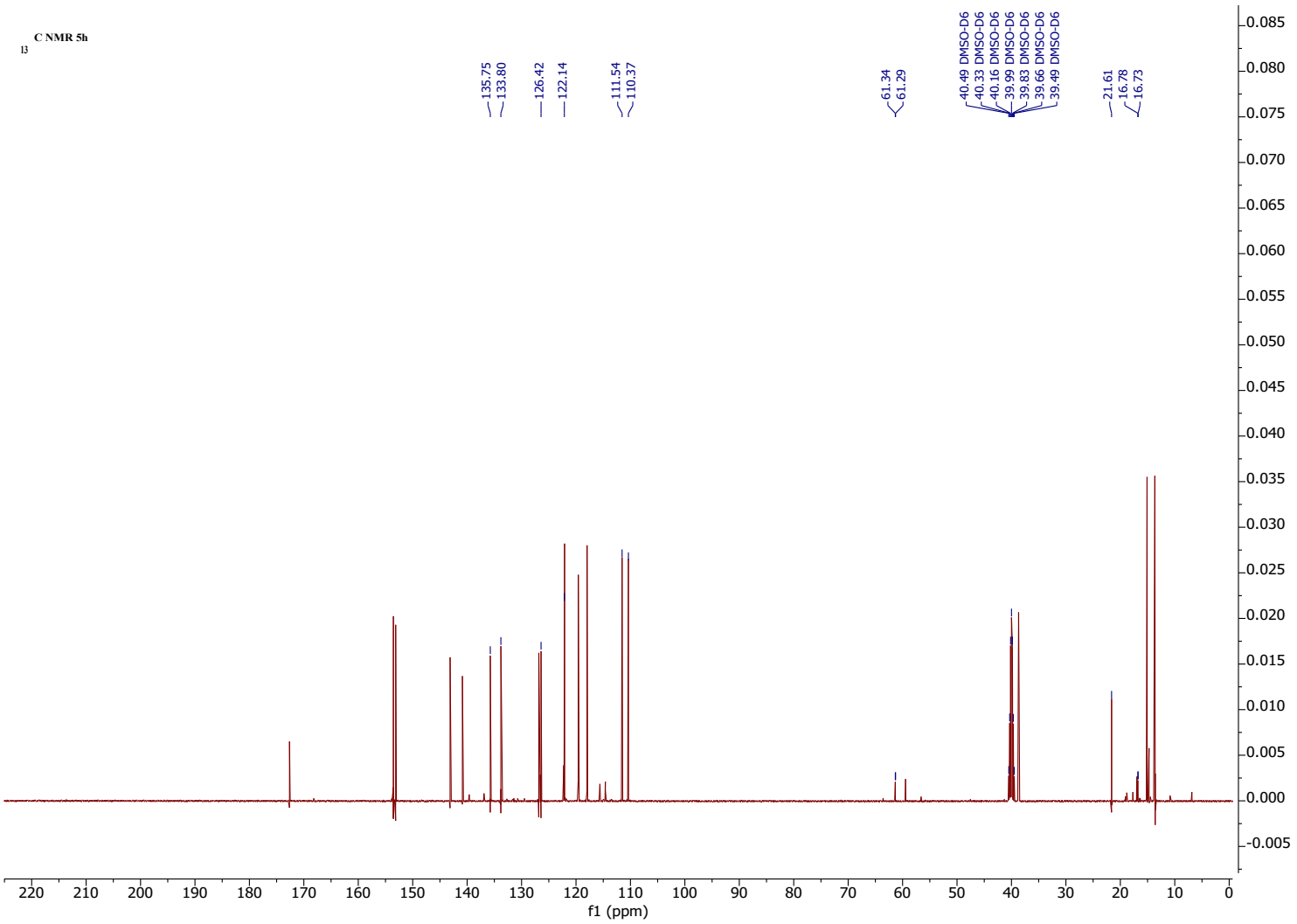

Figure S15h: ^{13}C-NMR spectrum of compound **5h**

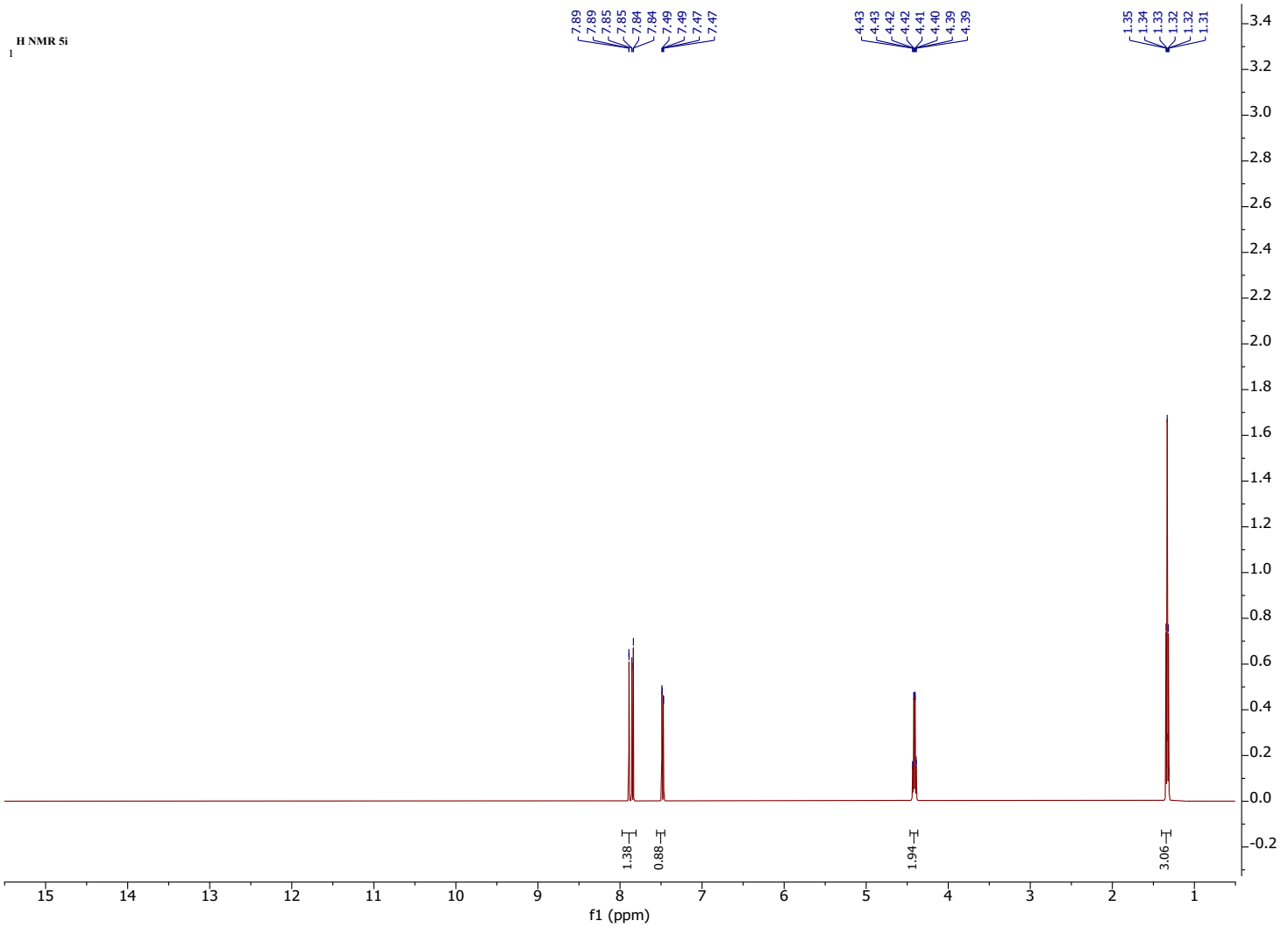

Figure S16i: [1]H-NMR spectrum of compound **5i**

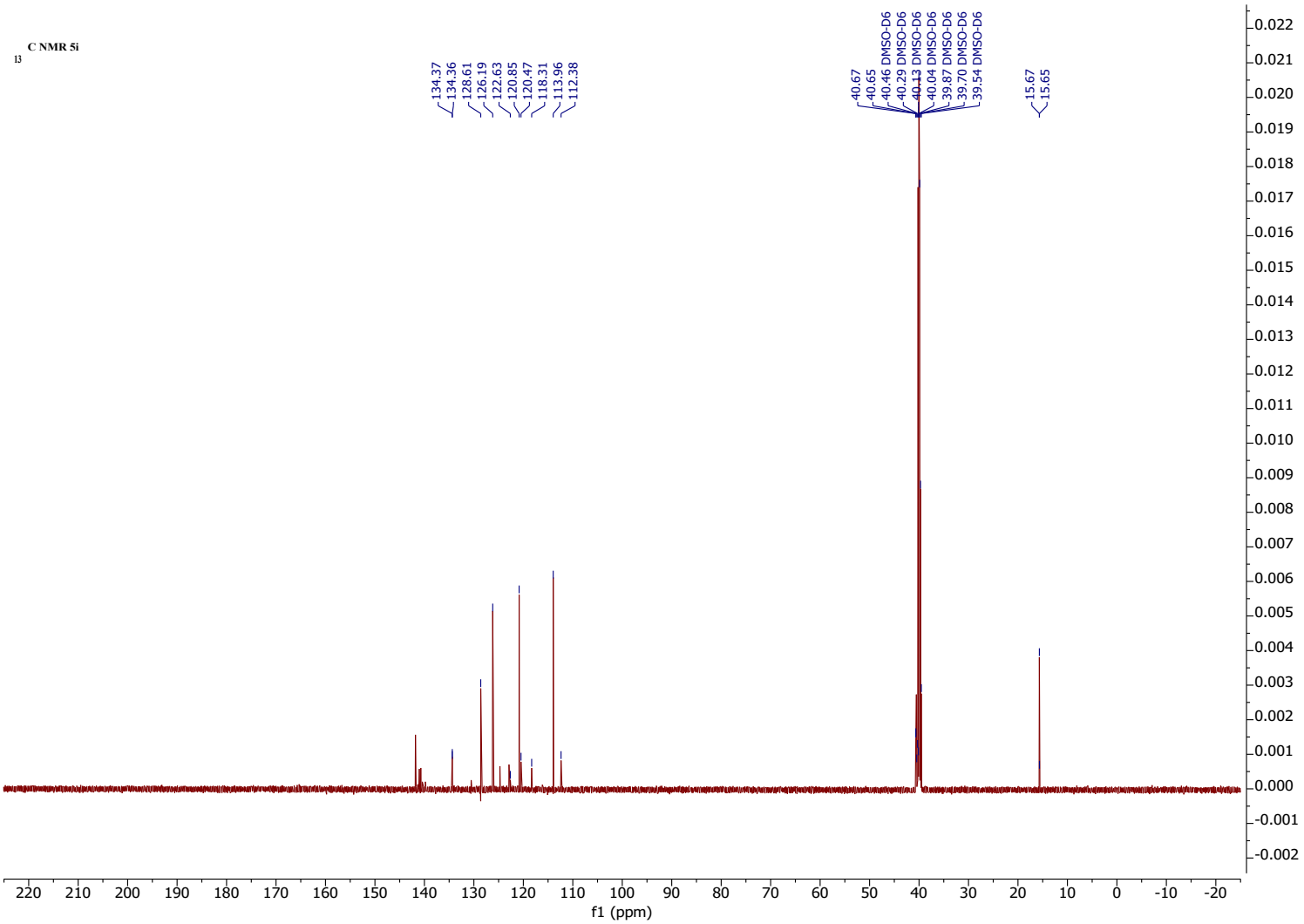

Figure S17i: ^{13}C-NMR spectrum of compound **5i**

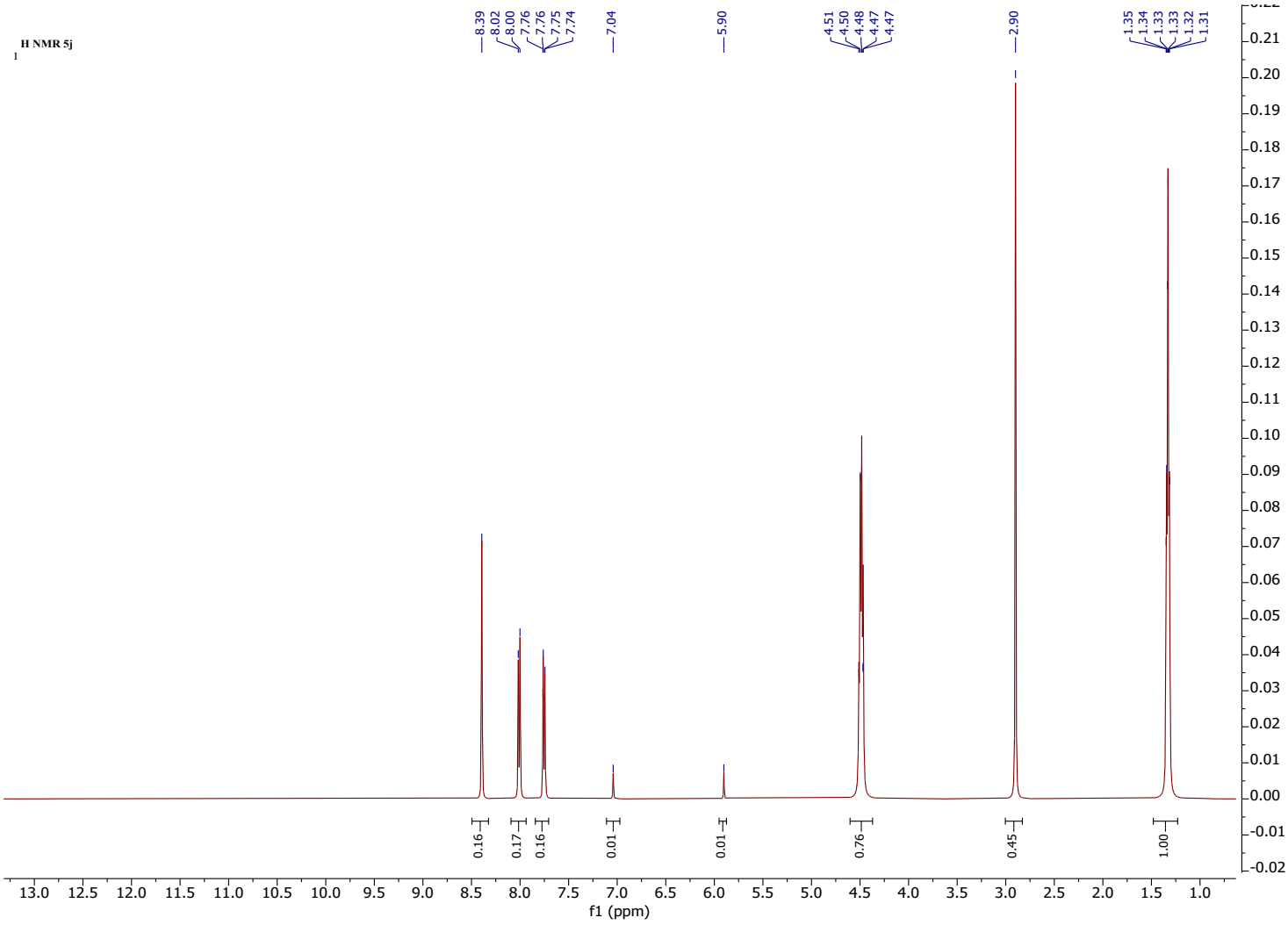

Figure S18j: ^{1}H-NMR spectrum of compound **5j**

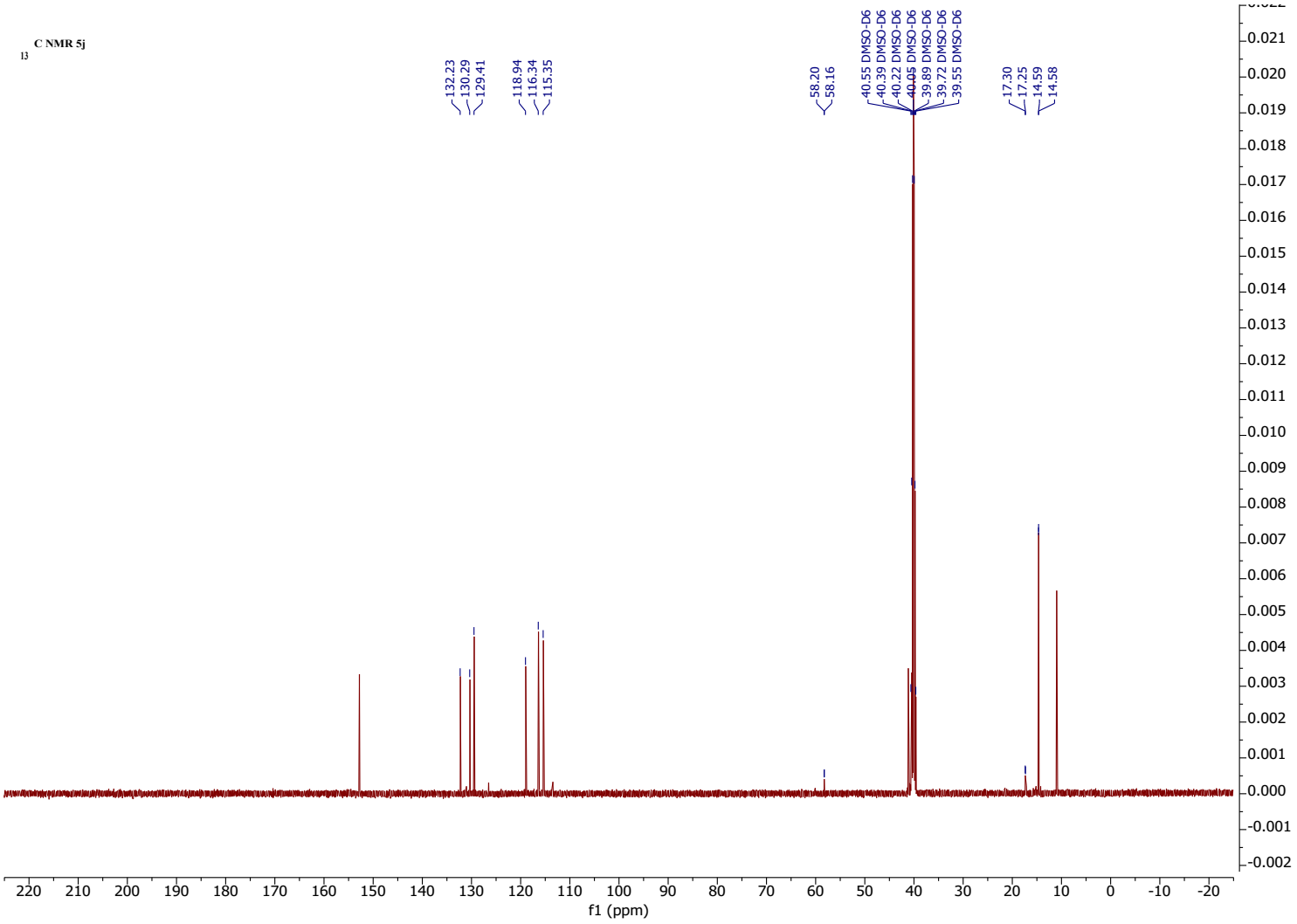

Figure S19j: ^{13}C-NMR spectrum of compound **5j**

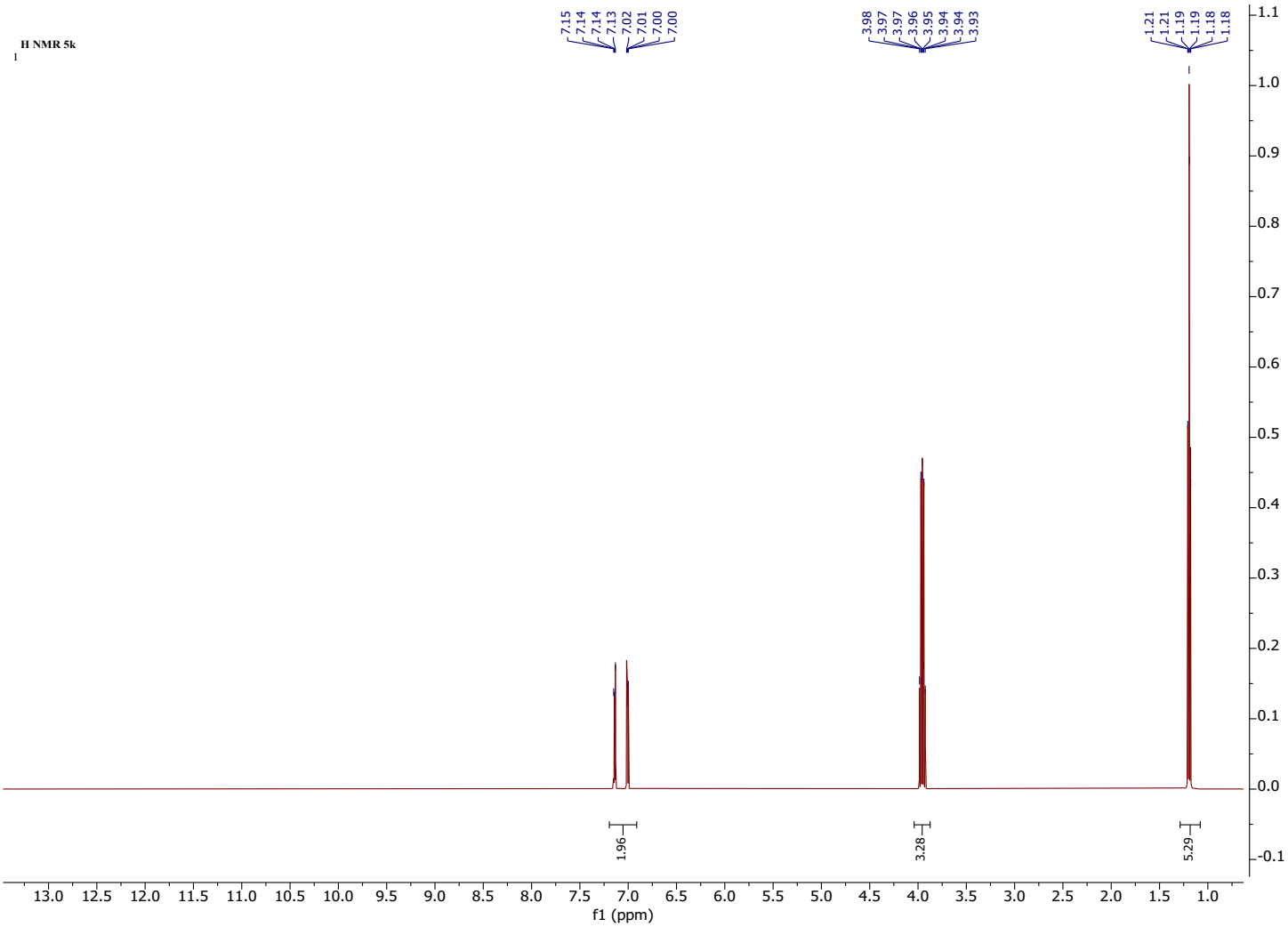

Figure S20k: [1]H-NMR spectrum of compound **5k**

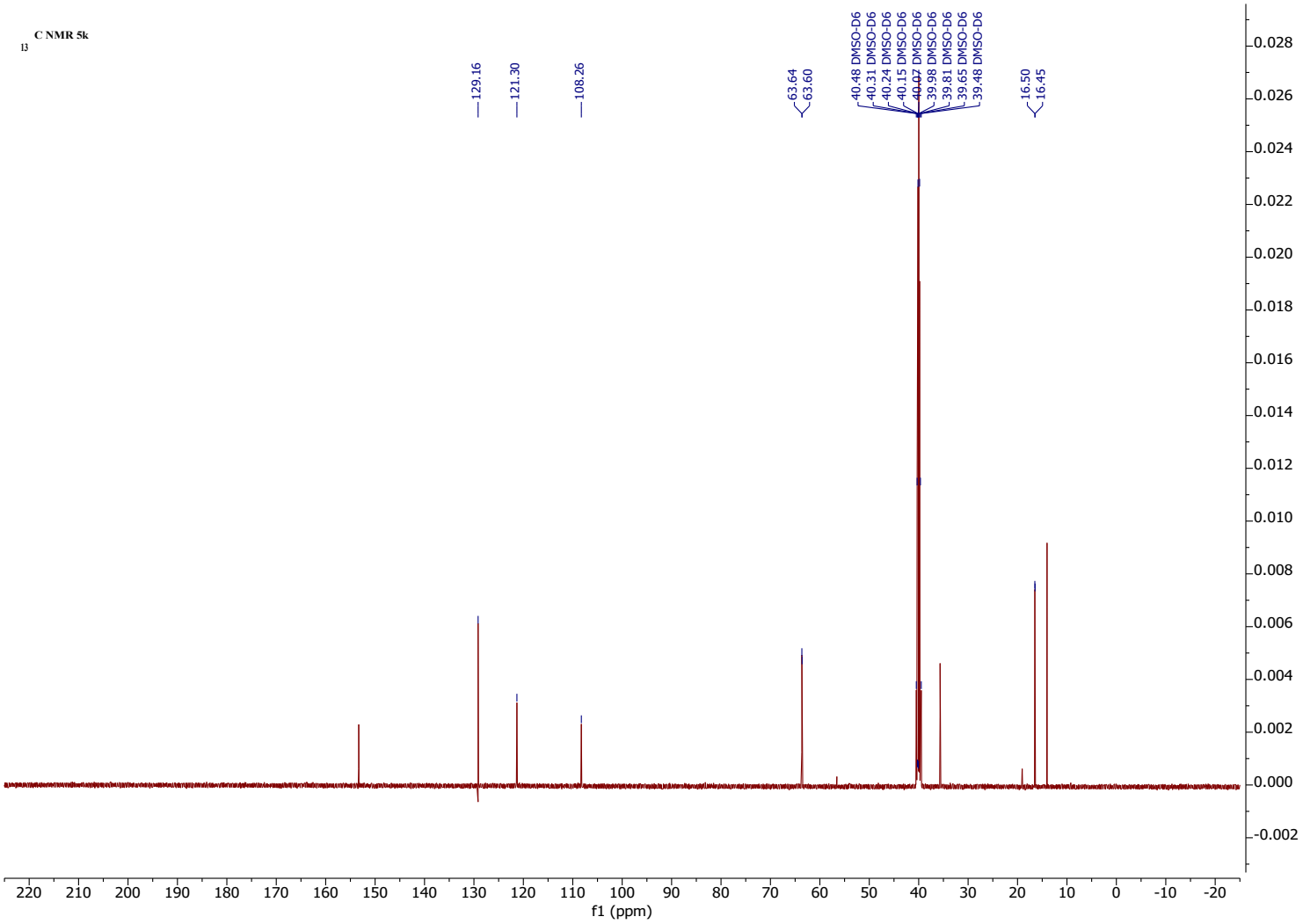

Figure S21k: ^{13}C-NMR spectrum of compound **5k**

2. Computational studies

2.1. ADMET predictions

Table S1. ADMET predicts the absorption for the synthesized compounds

Name of model	5b	5c	5g	5h	5i	Unity
Hydrosolubility	-3.441	-3.436	-4.664	-5.015	-4.192	(log mol/L)
Permeability in $CaCO_2$	1.316	1.342	0.497	1.398	1.338	(log Papp en 10^{-6} cm/s)
Intestinal Absorption (human)	88.078	88.108	83.871	83.888	86.733	(% absorbed)
Skin permeability	-3.231	-3.245	-2.817	-3.141	-3.228	(log Kp)
Substrate of glycoprotein P	No	No	yes	No	yes	
Inhibitor of glycoprotein P I	No	No	yes	No	No	
Inhibitor of glycoprotein P II	No	No	No	No	No	

Table S2. ADMET predicts the distribution for the synthesized compounds

Name of model	5b	5c	5g	5h	5i	Unity
VDss (human)	0.242	0.256	0.135	-0.058	0.172	(log L/kg)
Unbound fraction (human)	0.383	0.336	0.241	0.324	0.368	(Fu)
Permeability of BHE	0.225	0.137	-1.022	0.13	0.181	(log BB)
Permeability of SNC	-2.392	-2.368	-2.418	-3.025	-2.984	(log PS)

Table S3. ADMET predicts metabolism for the synthesized compounds

Name of model	5b	5c	5g	5h	5i
Substrat of CYP2D6	No	No	No	No	No
Substrat of CYP3A4	No	No	Yes	No	No
Inhibitor of CYP1A2	Yes	Yes	No	No	Oui
Inhibitor of CYP2C19	Yes	Yes	Yes	Yes	Yes
Inhibitor of CYP2C9	No	No	No	No	No
Inhibitor of CYP2D6	No	No	No	No	No
Inhibitor of CYP3A4	No	No	No	No	No

Table S4. ADMET predicts excretion for the synthesized compounds

Name of model	5b	5c	5g	5h	5i	Unity
Total clearance	0.353	0.398	0.612	0.388	0.288	(log ml/min/kg)
Renal substrate OCT2	No	No	No	No	No	(Oui/Non)

Table S5. ADMET Predicts the toxicity for the synthesized compounds

Name of model	5b	5c	5g	5i	5h	Unity
Toxicity of l'AMES	No	No	yes	No	No	Yes/No
Maximum tolerated dose (human)	0.052	-0.164	0.047	-0.037	0.176	(log mg/kg/jour)
Inhibitor of hERG I	No	No	No	No	No	Yes/No
Inhibitor of hERG II	No	No	No	No	No	Yes/No

Acute oral toxicity in rats (DL50)	**2.624**	**2.921**	**3.491**	**3.09**	**2.674**	**(mol/kg)**
Chronic oral toxicity in rats (DMENO)	**0.982**	**0.877**	**1.255**	**0.845**	**0.909**	**(log mg/kg_bw/jour)**
Hepatotoxicity	**yes**	**yes**	**yes**	**yes**	**yes**	**Yes/No**
Skin sensitization	**No**	**No**	**No**	**No**	**No**	**Yes/No**
Toxicity of T.Pyriformis	**0.438**	**0.933**	**1.039**	**0.843**	**0.539**	**(log ug/L)**
Toxicity of vairon	**0.395**	**0.432**	**1.553**	**0.706**	**0.388**	**(log mM)**

2.2. Molecular docking

i. Study of the activity of the synthesized products with *Candida albicans* (Ligand-4ydo interaction study)

Table S6. Activity of the synthesized products with *Candida albicans*

Ligands	Affinity energies	Amino acids	Interactions	Distances(A°)
5b	-6,6	LYS B : 427	Van der Waals	-
		HIS B : 415	Pi –Cation	4,90
			Pi-Donor Hydrogen Bond	3,00
			Pi-Sigma	3,89
		ARGA: 292	Conventional Hydrogen Bond	2,52
		PHE A : 259	Pi -Alkyl	4,68
		ASP B : 422	Attractive charge	5,44
		ASN B : 426	Amide-Pi stacked	5,10
5c	-6.3	GLN A :110	Conventional Hydrogen Bond	2,35
		MET B :308	Conventional Hydrogen Bond	2,29
			Alkyl	4,52
		GLY B :306	Carbon Hydrogen Bond	4,74
		GLU B :307	Carbon Hydrogen Bond	3,59
		ILE B : 362	Alkyl	5,05
			Pi -Alkyl	4,58
		LEU A :111	Alkyl	4,74
			Conventional Hydrogen Bond	2,86

5g	-7.7	GLN A : 110	Conventional Hydrogen Bond	2,77
			Carbon Hydrogen Bond	3,73
		CYS B :294	Conventional Hydrogen Bond	2,76
		MET B :308	Conventional Hydrogen Bond	2,31
			Conventional Hydrogen Bond	2,64
			Halogen (Fluorine)	3,04
		ILE B :362	Pi -Alkyl	4,48
5h	-5.8	ASN B :193	Conventional Hydrogen Bond	2,34
		TYR A :103	Conventional Hydrogen Bond	2,39
		TYR B :495	Pi-Pi T-stacked	5,40
			Pi -Alkyl	4,47
		ARG B :311	Conventional Hydrogen Bond	2,17
			Conventional Hydrogen Bond	2,27
			Unfavorable positive-positive	3,90
		TRP B :200	Pi-Pi T-shaped	4,85
		TRP B :196	Pi -Alkyl	4,57
		HIS B :254	Pi -Alkyl	4,21
		ALA B :256	Alkyl	4,16
5i	-7.0	MET B :308	Conventional Hydrogen Bond	2,33
			Conventional Hydrogen Bond	2,61
			Halogen (Fluorine)	2,91
		ILE B :362	Pi -Sigma	3,94
Fluconazole	**-7.3**	B: ARG 413	Conventional Hydrogen Bond	2,095
			Pi-Cation;Pi-Donor Hydrogen Bond	3,94
		ARG A:292	Pi-Cation	4,83
		GLU B: 416	ConventionalHydrogenBond;Halogen (Fluorine)	2,52
		GLN B: 127	Carbon Hydrogen Bond	3,45
		ASP B:422	Carbon Hydrogen Bond	3,73
		ASP A: 289	Halogen (Fluorine)	3,16
		PRO A: 220	Pi-Alkyl	4,18

ii. Visual analysis of ligand-4ydo interactions

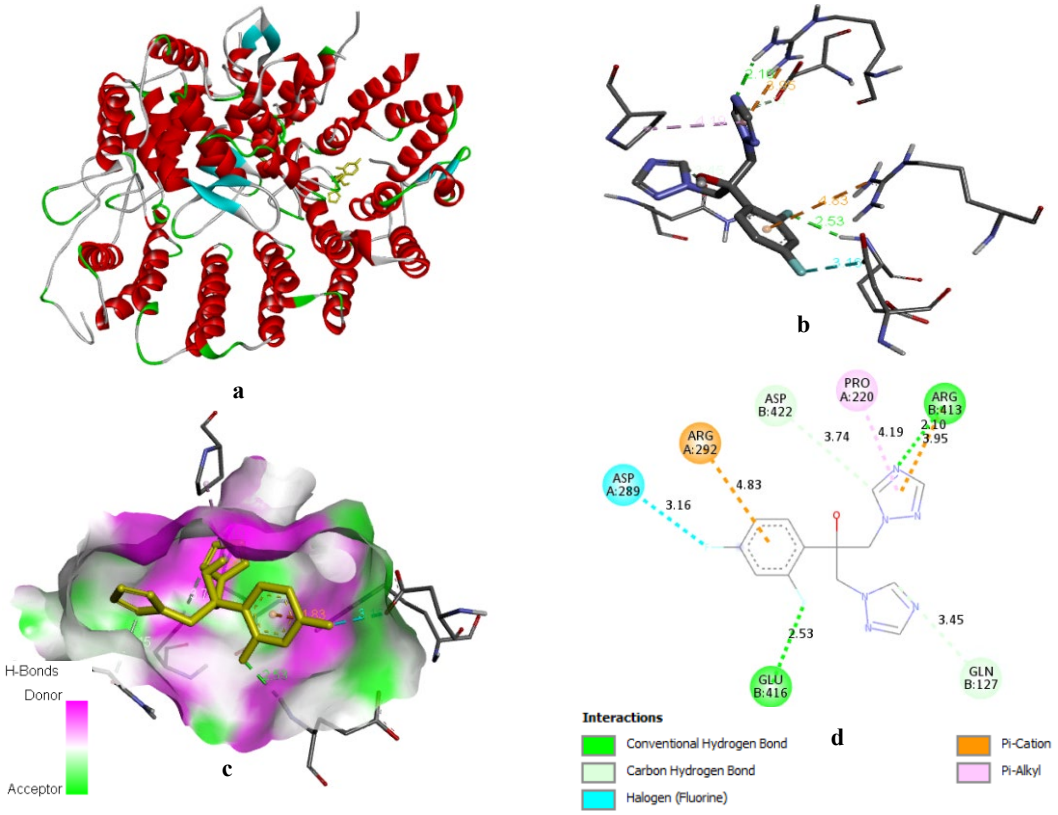

Figure S2. a : The position of ligand **Fluconazol** within the active site of 4ydo and b, c, d: Shows the (2D) and (3D) visualization of the interactions between **Fluconazol** and the amino acids of 4ydo, as well as the nature of these interactions

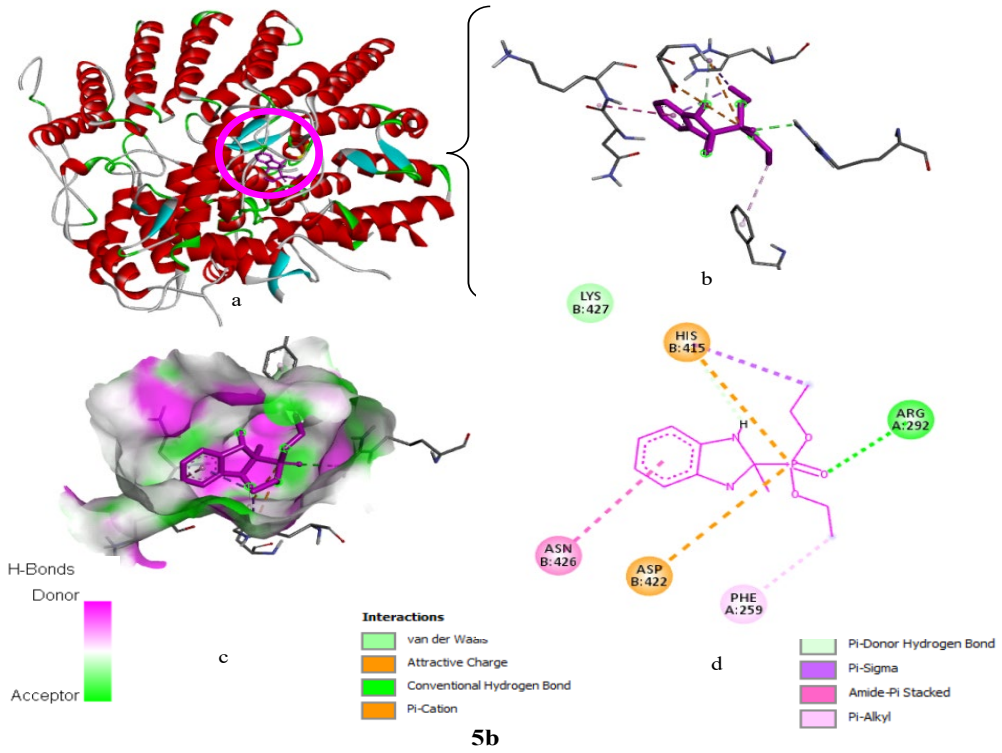

Figure S2. a : The position of ligand **5b** within the active site of 4ydo and b, c, d: Shows the (2D) and (3D) visualization of the interactions between ligand **5b** and the amino acids of 4ydo, as well as the nature of these interactions

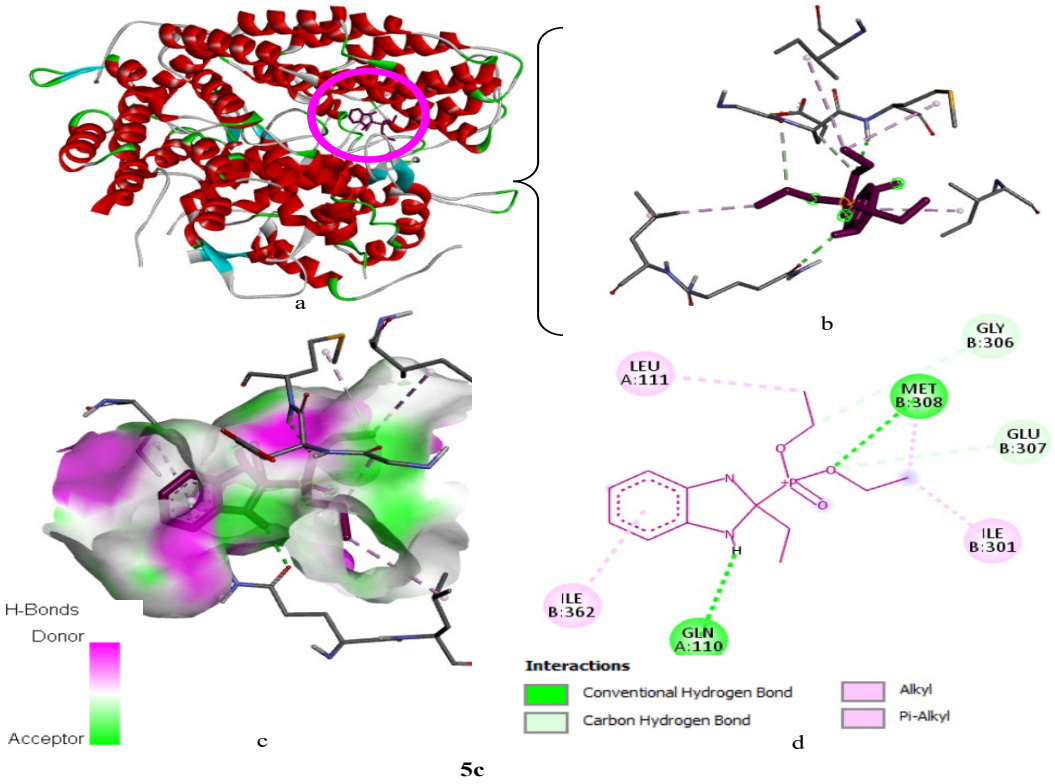

Figure S3. a : The position of ligand **5c** within the active site of 4ydo and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5c** and the amino acids of 4ydo, as well as the nature of these interactions

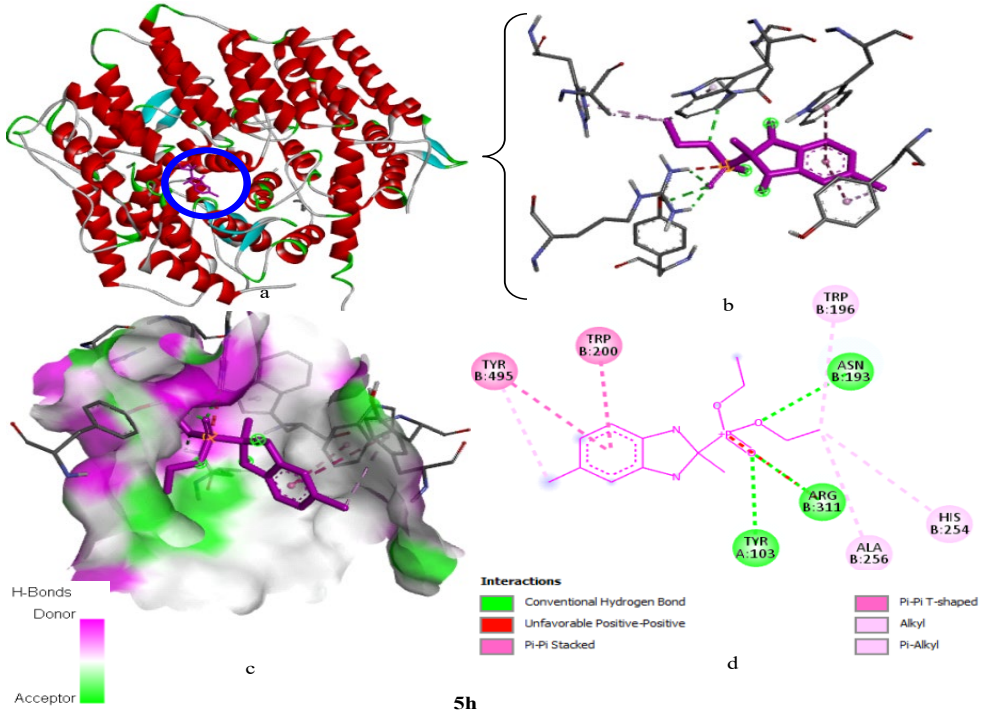

Figure S4. a : The position of ligand **5h** within the active site of 4ydo and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5h** and the amino acids of 4ydo, as well as the nature of these interactions

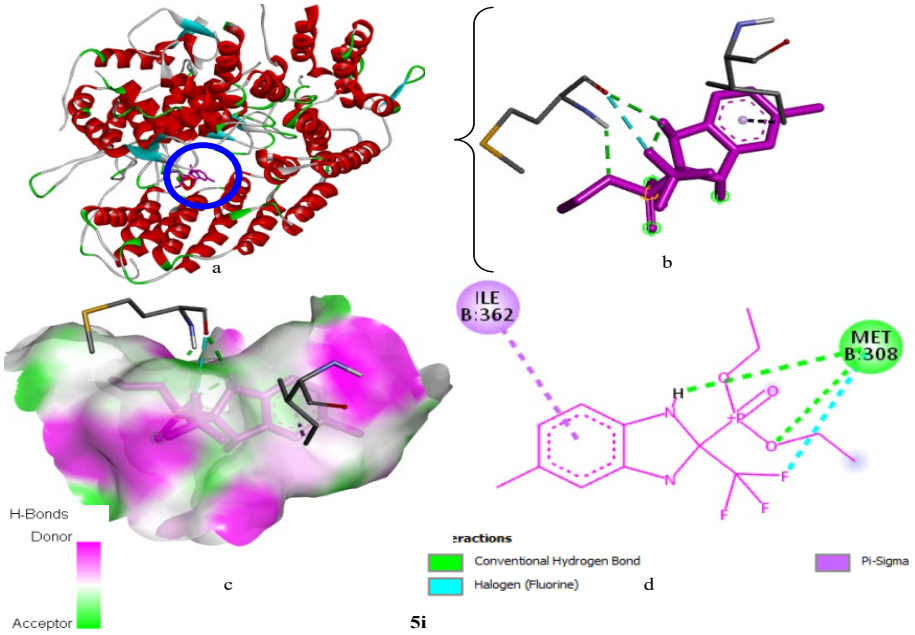

Figure S5. a : The position of ligand **5i** within the active site of 4ydo and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5i** and the amino acids of 4ydo, as well as the nature of these interactions

iii. Study of the activity of the synthesized products with *Escherichia coli* (Ligand-6gj1 interaction study)

Table S7. Activity of the synthesized products with *Escherichia coli*

Ligands	Affinity Energies	Amino-Acids	Interactions	Distances (A°)
5b	-7,1	ASN B :474	Conventional Hydrogen Bond	2,08
			Conventional Hydrogen Bond	2,72
			Unfavorable Donor- Donor	1,47
		CYS C :169	Alkyl	4,59
		MET B :475	Alkyl	4,90
		LEU B ;476	Alkyl	5,06
		HIS B :467	Pi – Alkyl	5,16
		PRO C 190	Alkyl	4,21
		ASN B :474	Conventional Hydrogen Bond	1,91
			Conventional Hydrogen Bond	2,52
		VAL C : 284	Conventional Hydrogen Bond	2,21
		ARG C : 289	Conventional Hydrogen Bond	2,70
			Unfavorable positive-positive	4,19
		GLY B :471	Carbon Hydrogen Bond	3,48
			Halogen (Fluorine)	2,85

5g	-7,7	MET C : 187	Halogen (Fluorine)	3,17
		LEU C : 164	Halogen (Fluorine)	3,61
			Halogen (Fluorine)	3,28
		PHE B : 472	Pi –Cation	4,91
			Pi – Alkyl	4,59
		PRO C ; 190	Alkyl	4,18
5h	-7,0	ARG A : 459	Carbon Hydrogen Bond	3,51
		ARG A :463	Alkyl	3,54
		TRP A :462	Carbon Hydrogen Bond	3,32
			Pi –Cation	4,29
			Pi-Pi -stacked	5,26
		GLU A :73	Pi –Anion	3,97
			Pi –Sigma	3,94
5i	-7,1	HIS B :375	Conventional Hydrogen Bond	2,95
		HIS A : 461	Pi – Alkyl	4,18
		HIS A : 467	Pi – Alkyl	3,94
		ARG B :361	Halogen (Fluorine)	3,32
			Pi – Alkyl	5,26
		PHE B : 358	Halogen (Fluorine)	3,23
		SER B : 357	Halogen (Fluorine)	3,18
		MET B :78	Pi –Sigma	3,94
			Pi –Sulfur	4,44
			Alkyl	4,73
		VAL A :464	Pi –Sigma	3,89
			Alkyl	3,77
			Alkyl	5,03
Ciprofloxacin	-7.9	ARG B:85	Conventional Hydrogen Bond	2,45
			Conventional Hydrogen Bond	2,25
		ARG B: 359	Alkyl	5,31
		SER B: 74	CarbonHydrogen Bond	3,68
		HIS B:82	Pi-Cation	4,71
			Pi-Cation	4,26

HIS B: 82	Pi-Pi T-shaped	5,15
	Pi-Pi T-shaped	4,68
HISB:375	Pi-Alkyl	5,22
VALB:378	Pi-Sigma	3,96
	Pi-Sigma	3,89
PHE B:358	Pi-Alkyl	5,16

iv. Visual analysis of ligand-6gj1 interactions

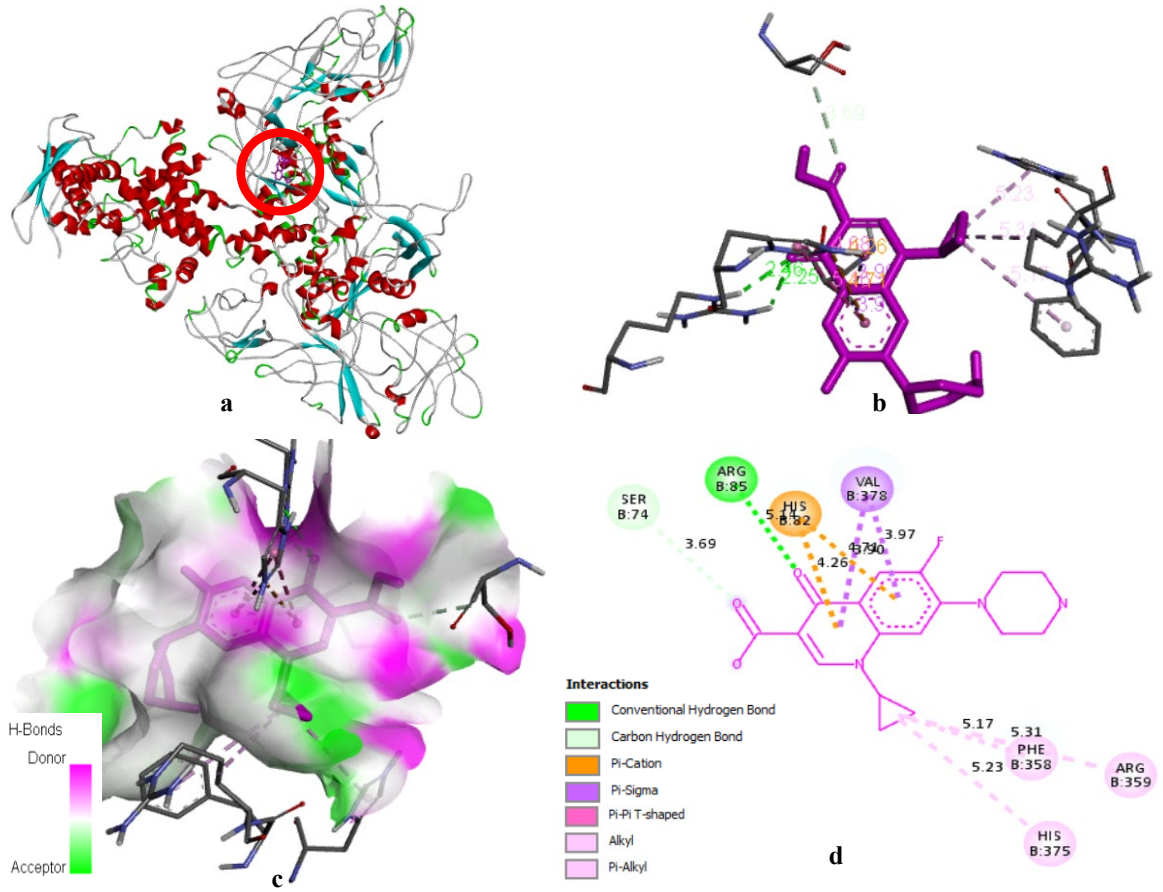

Figure S6. a : The position of ligand **Ciprofloxacin** within the active site of 6gj1 and b, c, d: Shows the 2D and 3D visualization of the interactions between **Ciprofloxacin** and the amino acids of 6gj1, as well as the nature of these interactions

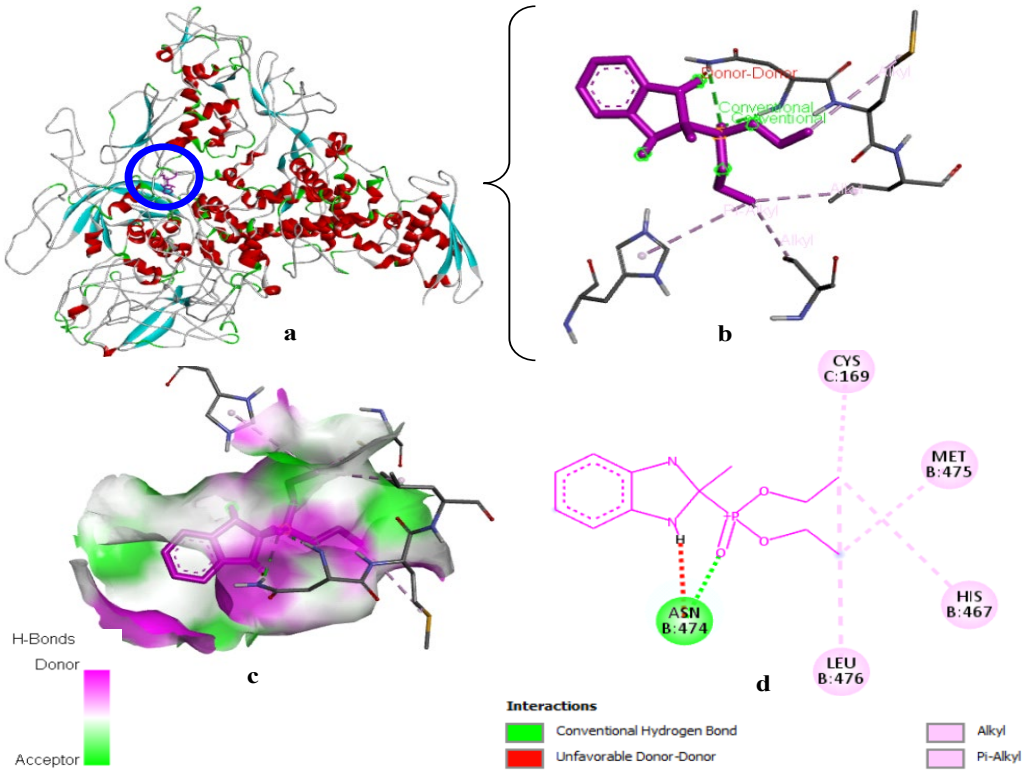

Figure S7. a : The position of ligand **5b** within the active site of 6gj1 and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5b** and the amino acids of 6gj1, as well as the nature of these interactions

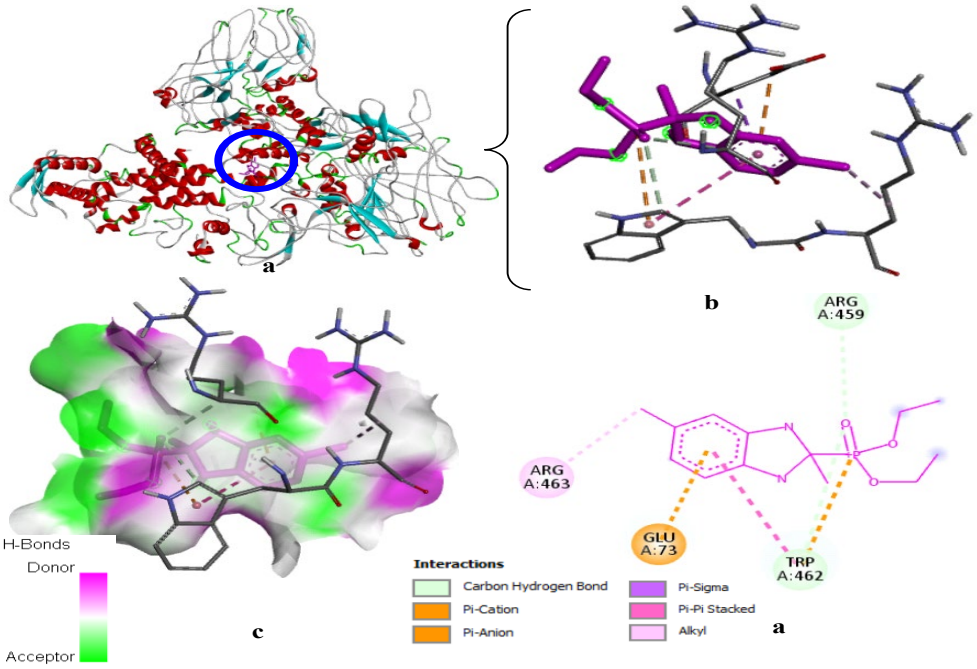

Figure S8. a: The position of ligand **5h** within the active site of 6gj1 and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5h** and the amino acids of 6gj1, as well as the nature of these interactions

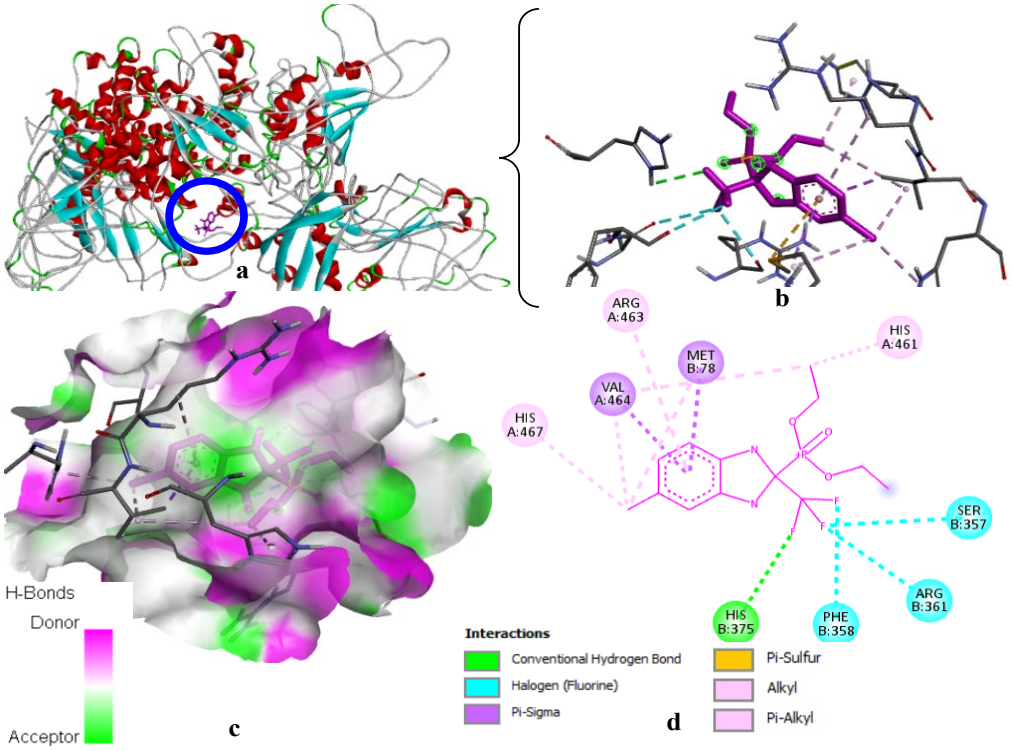

Figure S9. a : The position of ligand **5i** within the active site of 6gj1 and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5i** and the amino acids of 6gj1, as well as the nature of these interactions

v. Study of the activity of the synthesized products with *Pseudomonas aeroginsa* (Ligand-7xg0 interaction study)

Table S8. Activity of the synthesized products with *Pseudomonas aeroginsa*

Ligands	Affinity energies	Amino acids	Interactions	Distances(A°)
5b	-6,1	ALA E :16	Conventional Hydrogen Bond	2,61
		ARG E :44	Unfavorable positive-positive	4,37
		ARG D :180	Unfavorable positive-positive	4,57
		PHE D :246	Pi-Pistacked	4,17
		PRO E :18	Pi – Alkyl	4,95
5g	-7,2	ARG E :71	Conventional Hydrogen Bond;Fluorine	2,32
			Halogen (Fluorine)	3,70
			Conventional Hydrogen Bond	3,07
		ARG E :75	Conventional Hydrogen Bond;Fluorine	2,00
			Conventional Hydrogen Bond;Fluorine	1,94
			Conventional Hydrogen Bond	2,70
			Unfavorable positive-positive	4,35
		ASN D :187	Conventional Hydrogen Bond	2,91

			Conventional Hydrogen Bond	3,00
			Conventional Hydrogen Bond	2,60
		ASN E :68	Halogen (Fluorine)	2,91
			Halogen (Fluorine)	3,10
		MET D :182	Pi-sulfur	5,72
		ARG D :180	Conventional Hydrogen Bond	2,14
			Conventional Hydrogen Bond	2,20
			Unfavorable positive-positive	4,27
		ARG D :181	Alkyl	4,57
5h	-7,0		Pi –Alkyl	5,03
		THR E :69	Conventional Hydrogen Bond	1,98
		ALA E : 288	Alkyl	4,27
		PRO E :66	Alkyl	4,45
		MET D :182	Pi-sulfur	5,81
			Conventional Hydrogen Bond	2,37
			Conventional Hydrogen Bond	2,87
		ARG E :44	Conventional Hydrogen Bond;Fluorine	2,22
			Unfavorable positive-positive	4,24
			Conventional Hydrogen Bond;Fluorine	2,85
		ARG D :180	Unfavorable positive-positive	5,12
			Pi –Alkyl	4,96
5i	-7,2		Conventional Hydrogen Bond	2,72
		THR E :69	Pi-Donor Hydrogen Bond	3,06
		SER E :15	Conventional Hydrogen Bond	2,81
			Carbon Hydrogen Bond	3,20
		ALA D :179	Halogen (Fluorine)	3,57
		TRP D :178	Halogen (Fluorine)	3,45
			Alkyl	4,34
		MET D :180	Pi-sulfur	5,56
		ARG F: 71	Conventional Hydrogen Bond	2,24
			Conventional Hydrogen Bond	2,13
Ciprofloxacin		ARG F: 75	Conventional Hydrogen Bond	2,82
	-7.9		Conventional Hydrogen Bond	2,51

	GLY F: 134	Conventional Hydrogen Bond	2,61
	GLY F:142	Conventional Hydrogen Bond	2,27
	LEU F: 140	Conventional Hydrogen Bond	2,11
	ASN F: 68	Halogen (Fluorine)	3,43

vi. Visual analysis of ligand-7xg0 interactions

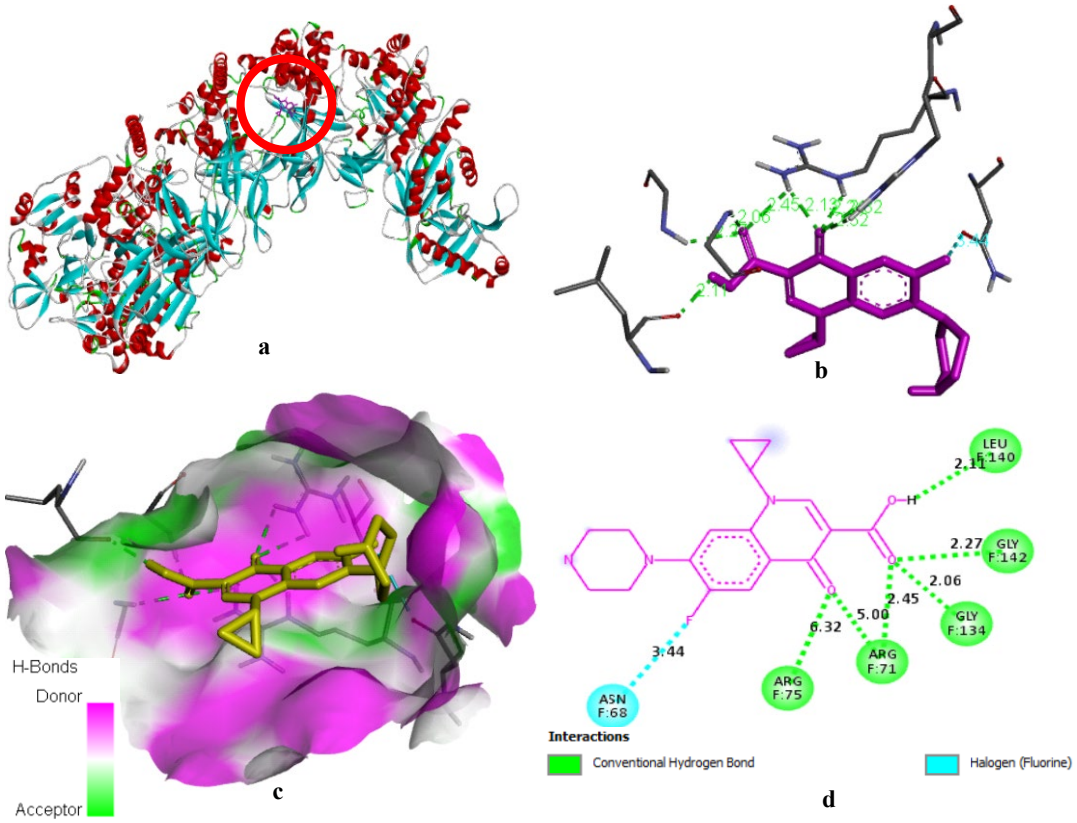

Figure S10. a : The position of ligand **Ciprofloxacin** within the active site of 7xg0 and b, c, d: Shows the 2D and 3D visualization of the interactions between **Ciprofloxacin** and the amino acids of 7xg0, as well as the nature of these interactions

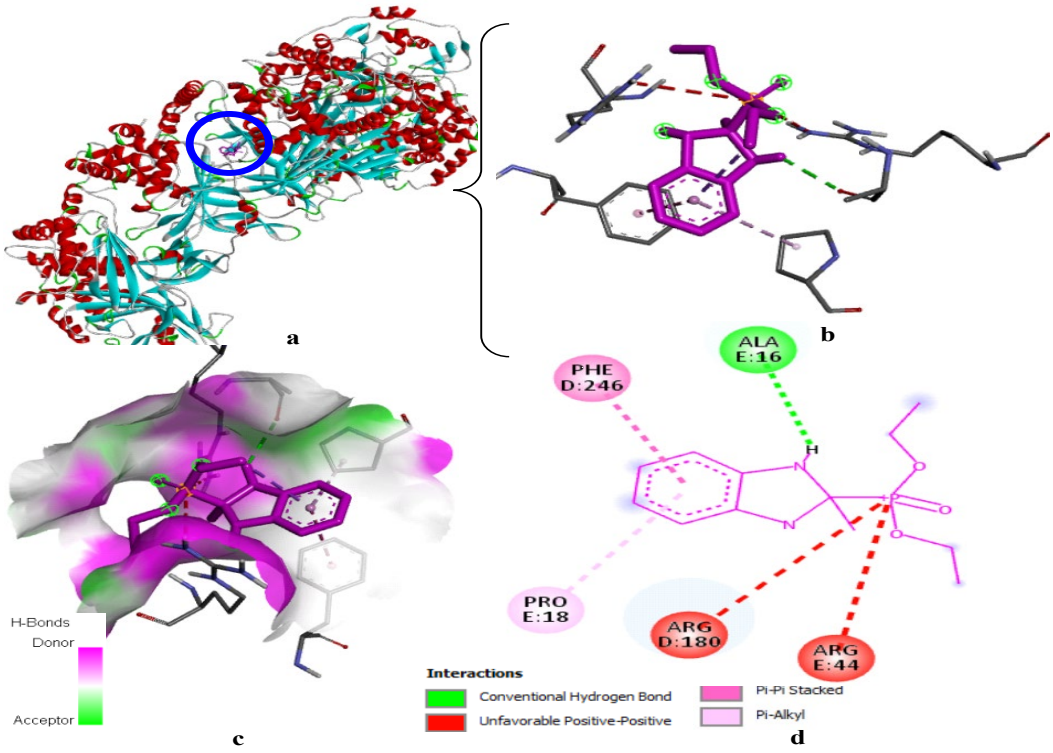

Figure S11. a : The position of ligand **5b** within the active site of 7xg0 and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5b** and the amino acids of 7xg0, as well as the nature of these interactions

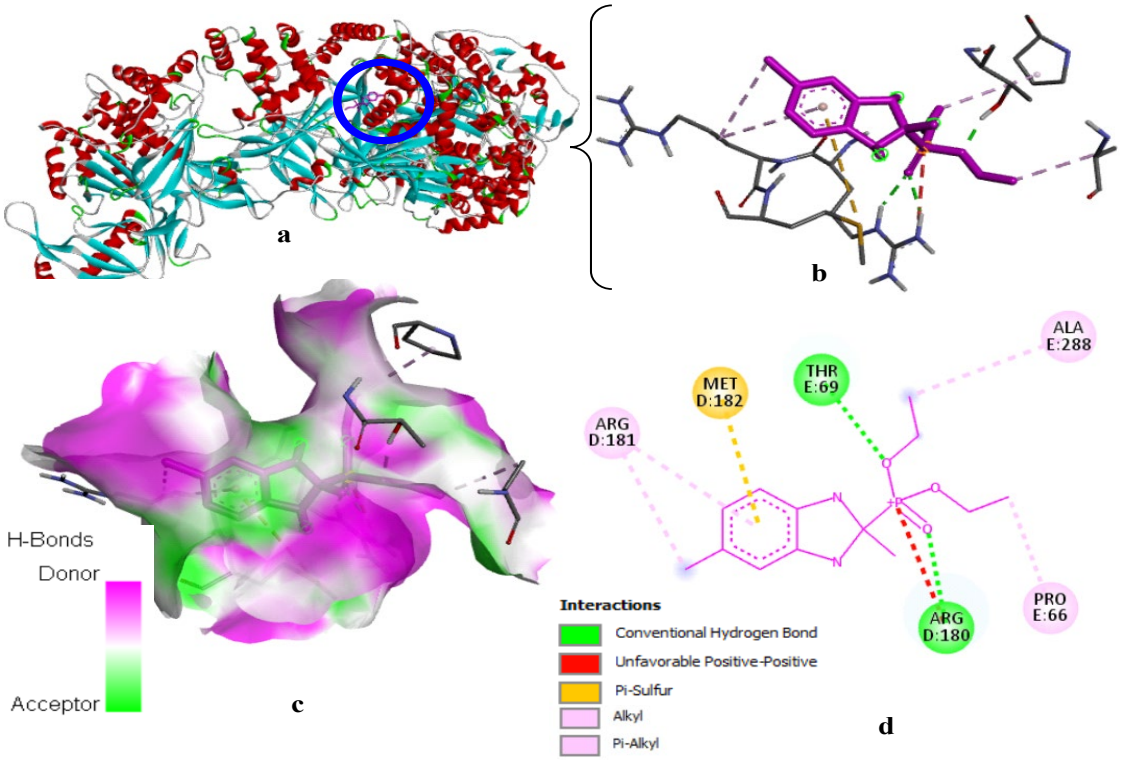

Figure S12. a : The position of ligand **5h** within the active site of 7xg0 and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5h** and the amino acids of 7xg0, as well as the nature of these interactions

vii. Study of the activity of the synthesized products with *Staphyloccocus aureus* (Ligand-5cdp interaction study)

Table S9. Activity of the synthesized products with *Staphyloccocus aureus*

Ligands	Affinity Energies	Amino acids	Interactions	Distances(A°)
5b	-7,2	ARG A :122	Conventional Hydrogen Bond	2,33
			Unfavorable Acceptor- Acceptor	3,64
			Unfavorable Donor- Donor	1,32
		GLU D : 435	Conventional Hydrogen Bond	2,17
			Conventional Hydrogen Bond	2,34
			Attractive charge	3,92
			Attractive charge	4,00
		ASP D : 508	Attractive charge	4,00
			Attractive charge	4,21
			Carbon Hydrogen Bond	3,13
			Attractive charge	4,20
			Attractive charge	5,52
			Carbon Hydrogen Bond	3,15
		HIS C : 81	Pi –Alkyl	4,69
		PHE A : 123	Pi-Pi T-shaped	4, 94
5g	-8,3	ARG A :122	Conventional Hydrogen Bond	2,78
			Conventional Hydrogen Bond	2,48
			Unfavorable positive-positive	3,71
			Unfavorable Donor- Donor	1,30
		SER D :438	Conventional Hydrogen Bond	2,91
		GLU D :435	Conventional Hydrogen Bond	1,99
			Conventional Hydrogen Bond	2,15
			Attractive charge	3,92
			Attractive charge	4,04
			Halogen (Fluorine)	3,18
			Halogen (Fluorine)	3,34
			Halogen (Fluorine)	3,27
			Halogen (Fluorine)	3,30
		ASP D : 508	Attractive charge	4,04
			Attractive charge	4,24
			Carbon Hydrogen Bond	3,18

		ASP D : 510	Attractive charge	4,07
			Attractive charge	5,39
			Carbon Hydrogen Bond	3,19
		GLY D : 459	Carbon Hydrogen Bond	3,32
		PHE A :123	Pi-Pi T-shaped	4,86
			Pi –Alkyl	5,08
5h	-7,4	ARG A :122	Conventional Hydrogen Bond	2,70
			Conventional Hydrogen Bond	2,42
			Unfavorable positive-positive	3,65
			Unfavorable Donor- Donor	1,32
		GLU D : 435	Conventional Hydrogen Bond	2,10
			Conventional Hydrogen Bond	2,27
			Attractive charge	3,96
			Attractive charge	4, 04
		ASP D : 508	Attractive charge	4,13
			Attractive charge	4,30
			Carbon Hydrogen Bond	3,18
		ASP D : 510	Attractive charge	4,18
			Attractive charge	5,50
			Carbon Hydrogen Bond	3,18
		PHE A : 123	Pi-Pi T-shaped	4,90
			Pi –Alkyl	5,03
5i	-8,0	ARG A :122	Conventional Hydrogen Bond	2,69
			Conventional Hydrogen Bond	2,60
			Conventional Hydrogen Bond	2,97
			Unfavorable positive-positive	3,70
			Unfavorable Donor- Donor	1,25
		GLU D : 435	Conventional Hydrogen Bond	2,06
			Conventional Hydrogen Bond	2,22
			Attractive charge	3,93
			Attractive charge	4,02
			Halogen (Fluorine)	3,27
			Halogen (Fluorine)	3,42
			Halogen (Fluorine)	3,21

			Halogen (Fluorine)	3,26
		ASP D : 508	Attractive charge	4,04
			Attractive charge	4,25
			Carbon Hydrogen Bond	3,32
		ASP D :510	Attractive charge	4,08
			Attractive charge	5,40
			Carbon Hydrogen Bond	3,16
		GLY D : 459	Carbon Hydrogen Bond	3,43
		PHE	Pi-Pi T-shaped	4,92
			Pi –Alkyl	4,90
Ciprofloxacin	-8.4	GLUD:435	Conventional Hydrogen Bond	2,81
		ASPD:508	Conventional Hydrogen Bond	2,80
			Conventional Hydrogen Bond	2,21
		ARGA:122	Pi-Cation	4,42
			Pi-Cation	4,20
		GLUD:435	Pi-Anion	3,90
			Pi-Anion	3,97
		LYSD:460	Alkyl	4,99

viii. Visual analysis of ligand-5cdp interactions

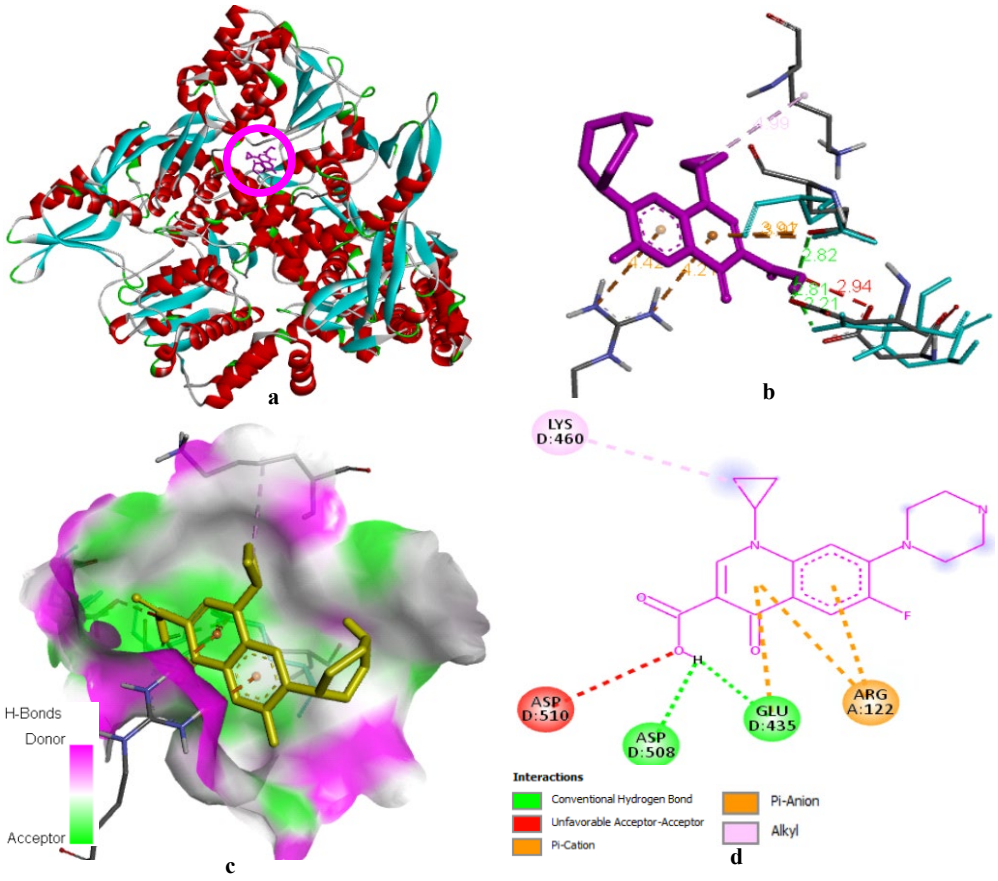

Figure S13. a : The position of ligand **Ciprofloxacin** within the active site of 5cdp and b, c, d: Shows the 2D and 3D visualization of the interactions between **Ciprofloxacin** and the amino acids of 5cdp, as well as the nature of these interactions

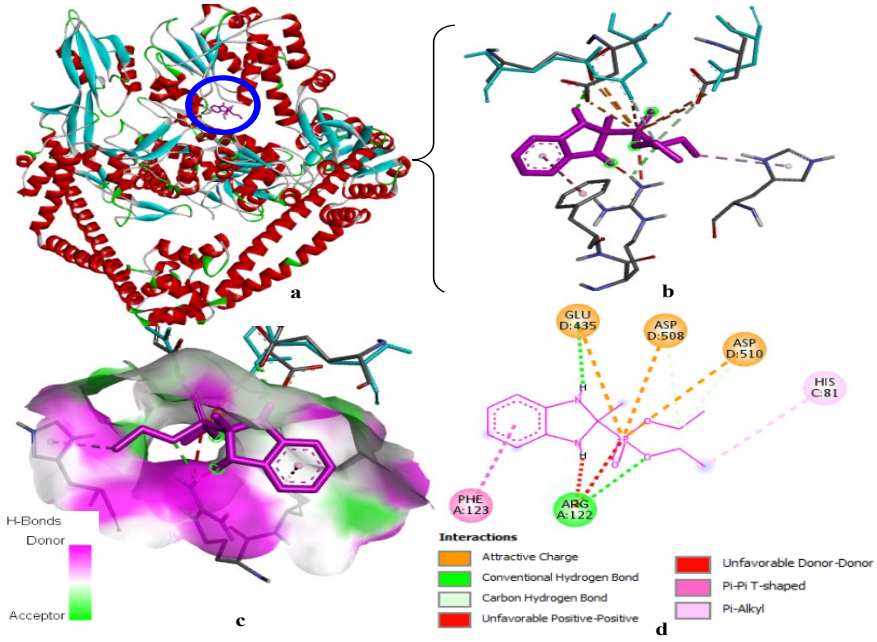

Figure S14. a : The position of ligand **5b** within the active site of 5cdp and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5b** and the amino acids of 5cdp, as well as the nature of these interactions

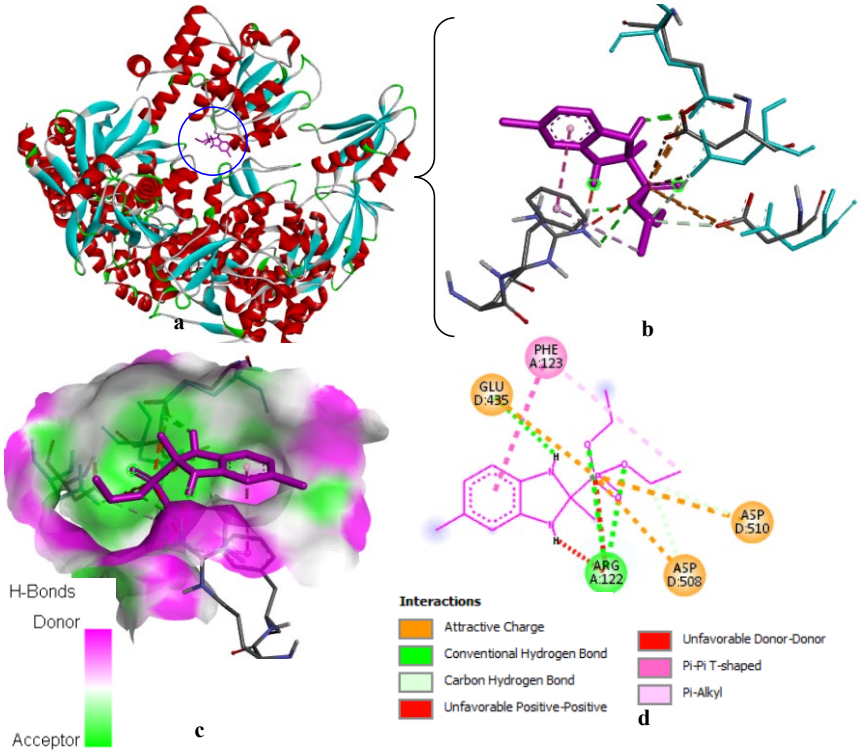

Figure S15. a : The position of ligand **5h** within the active site of 5cdp and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand **5h** and the amino acids of 5cdp, as well as the nature of these interactions

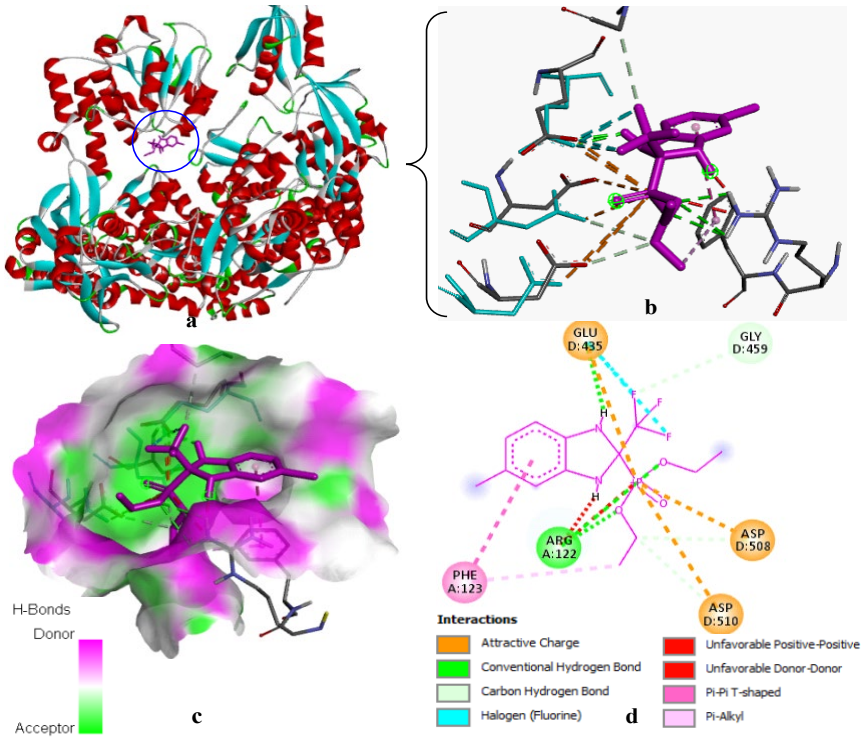

Figure S16. a : The position of ligand 5i within the active site of 5cdp and b, c, d: Shows the 2D and 3D visualization of the interactions between ligand 5i and the amino acids of 5cdp, as well as the nature of these interactions