SUPPLEMENTARY MATERIALS

Novel hybrid compounds containing benzofuroxan and aminothiazole scaffolds: synthesis and evaluation of their anticancer activity.

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Contents

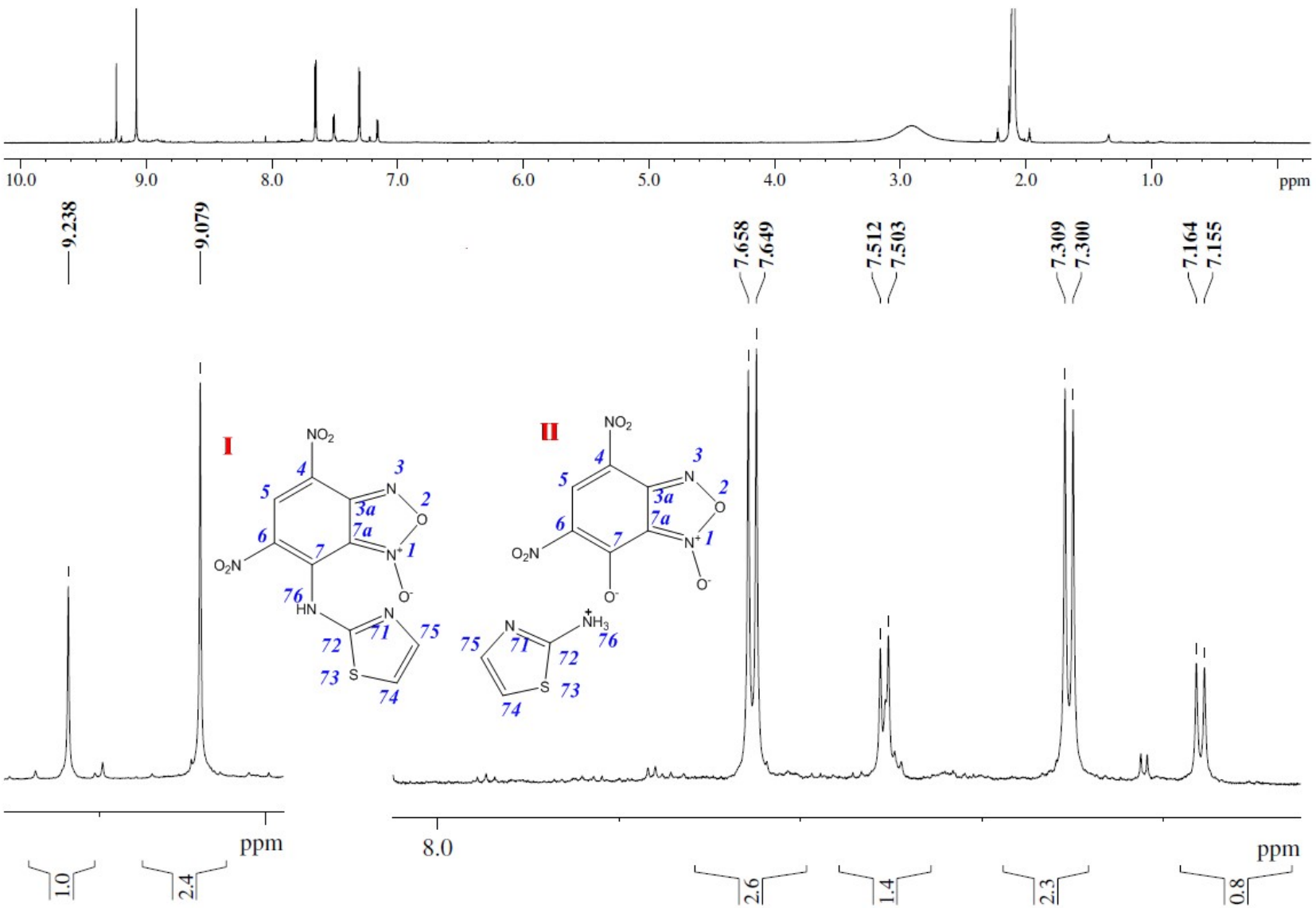


Figure S1. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) mixture of compound **3b** and **6**.

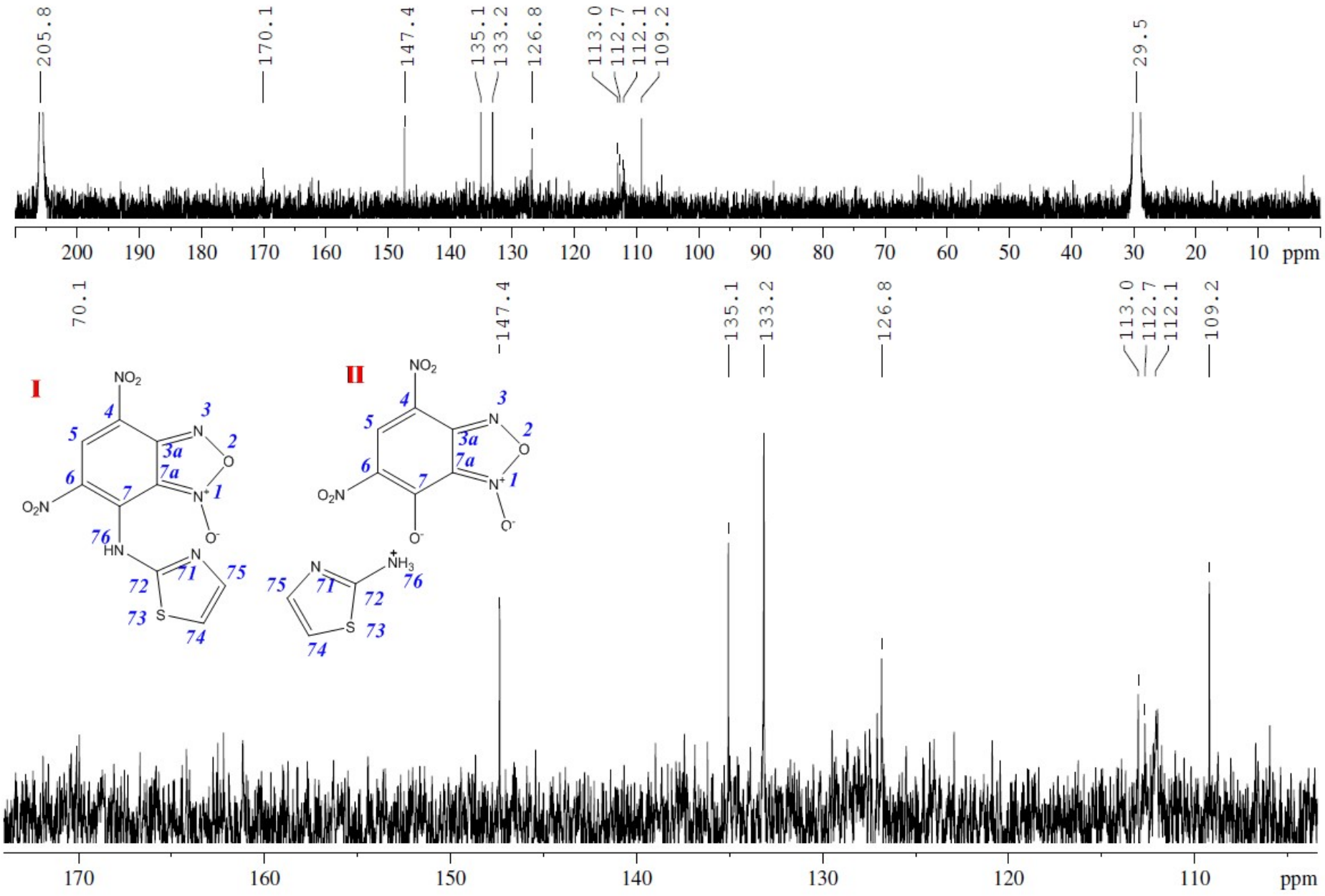


Figure S2. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) mixture of compound **3b** and **6**.

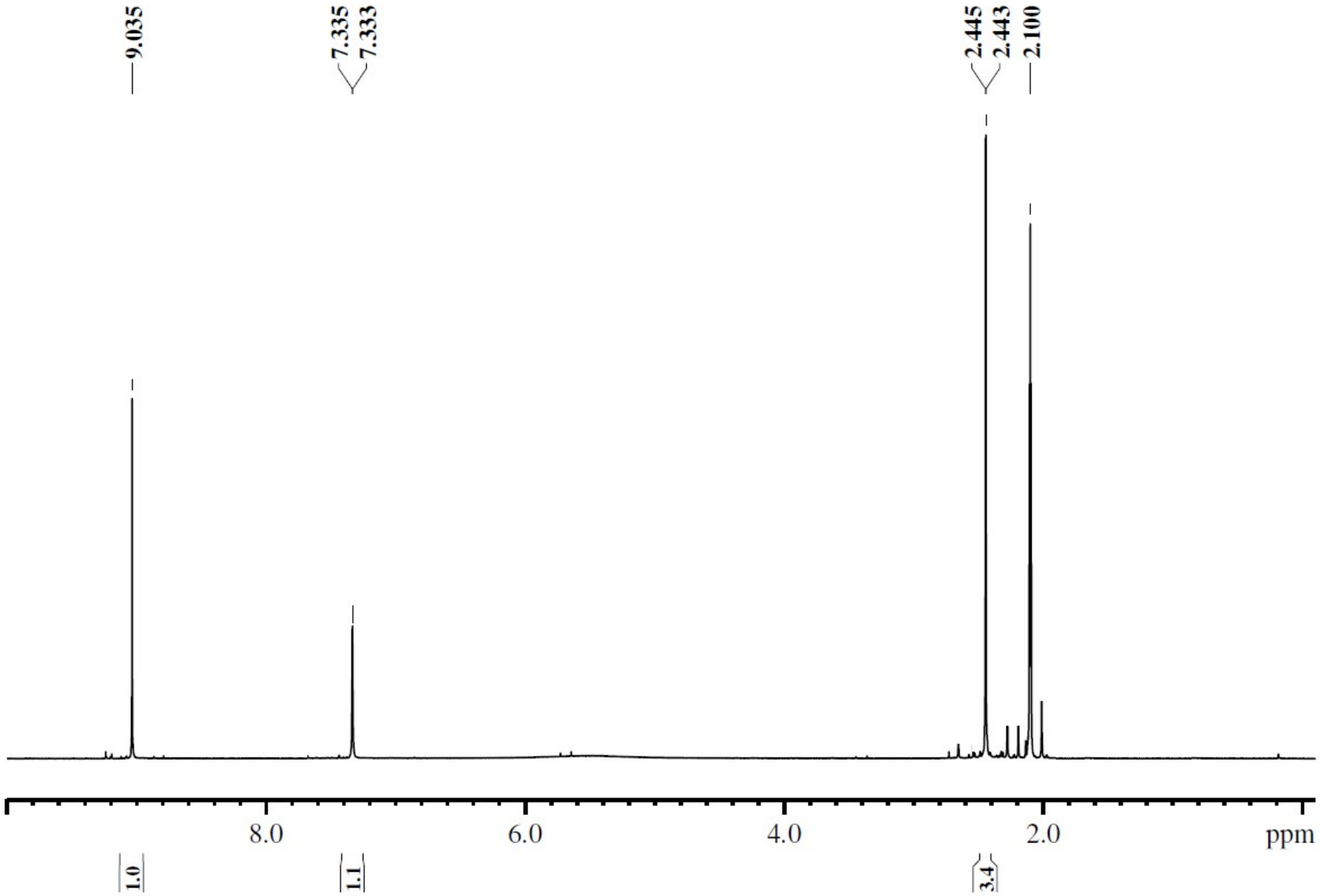


Figure S3. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) of compound **3b**.

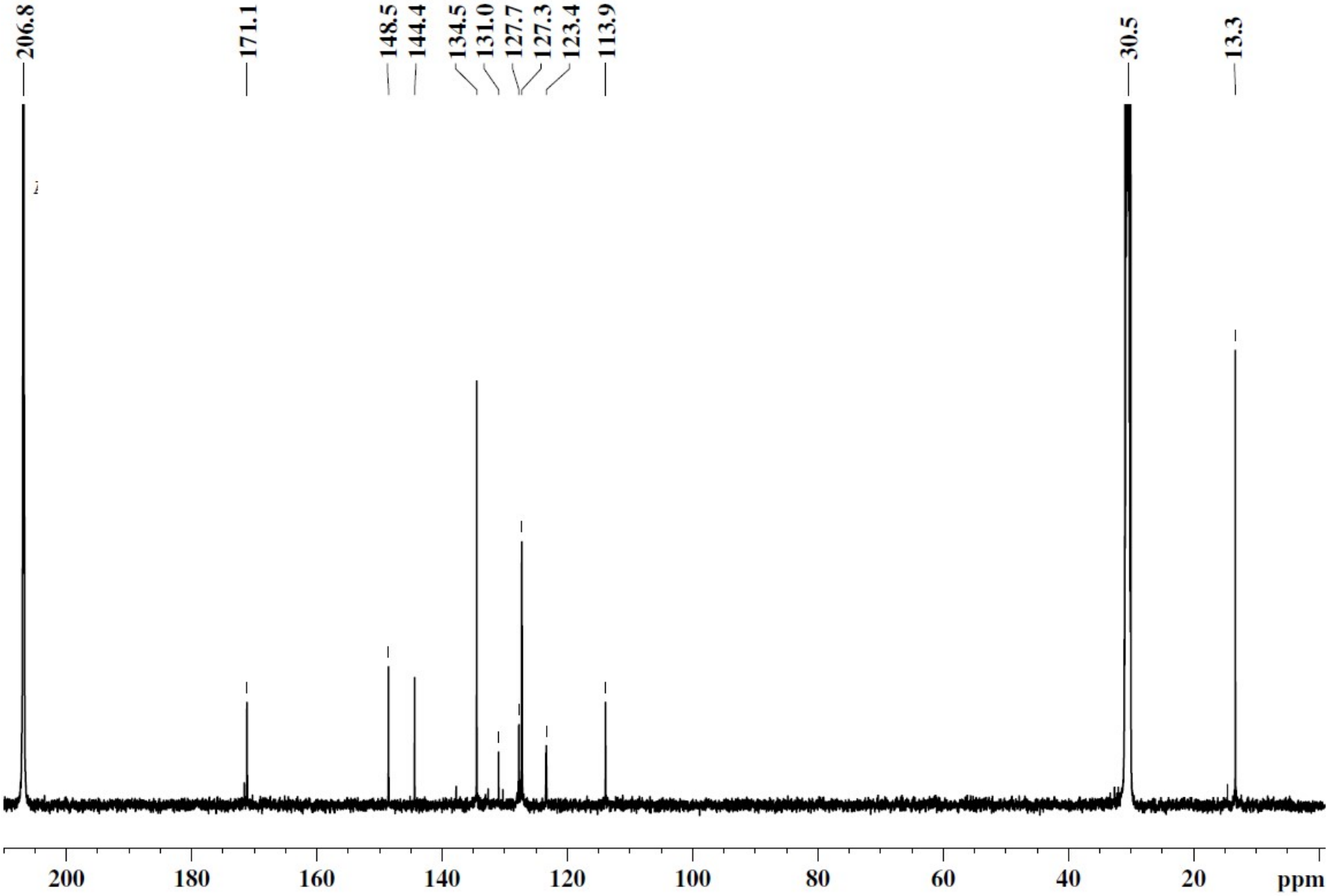


Figure S4. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) of compound **3b**.

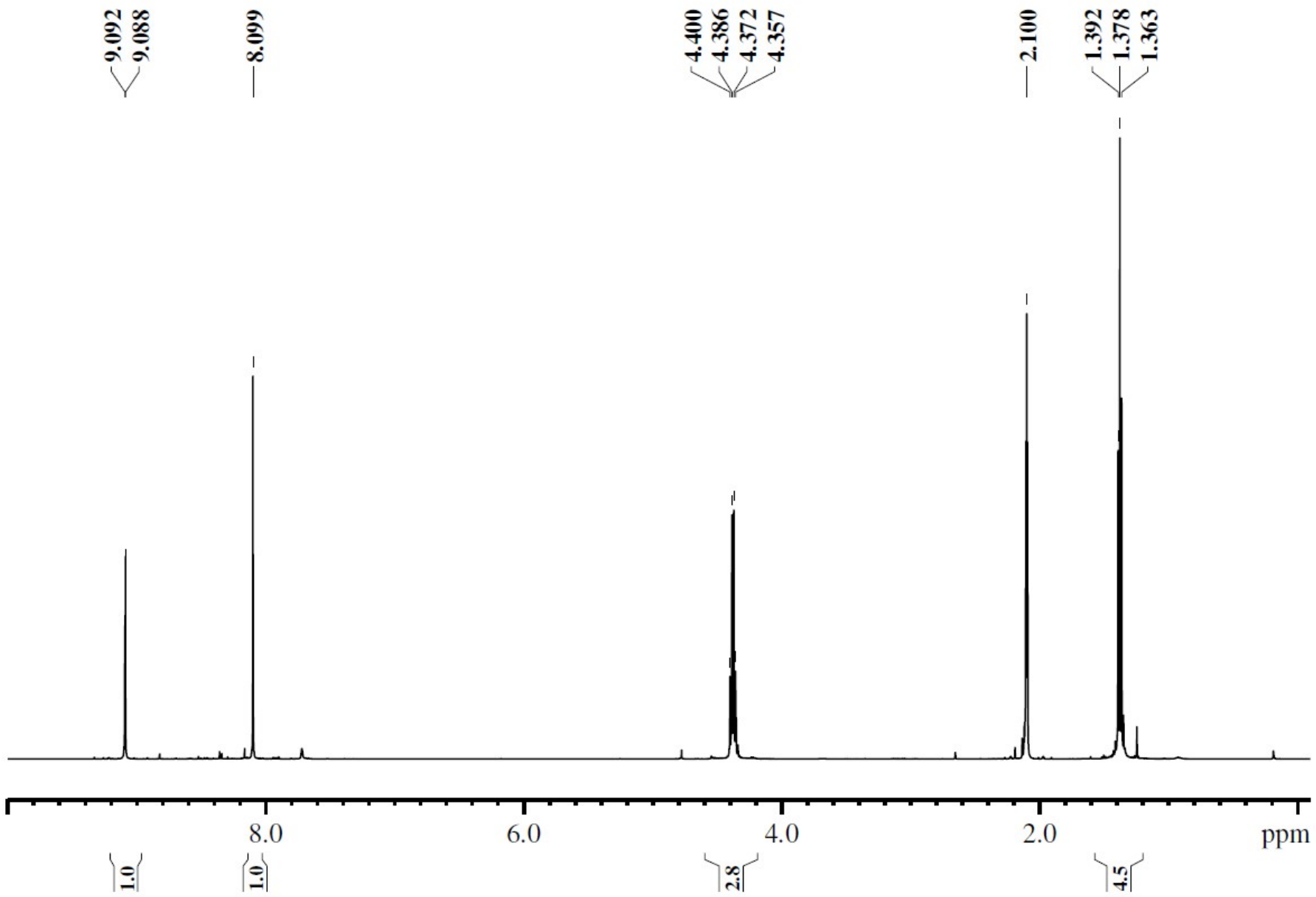


Figure S5. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) of compound **3c**.

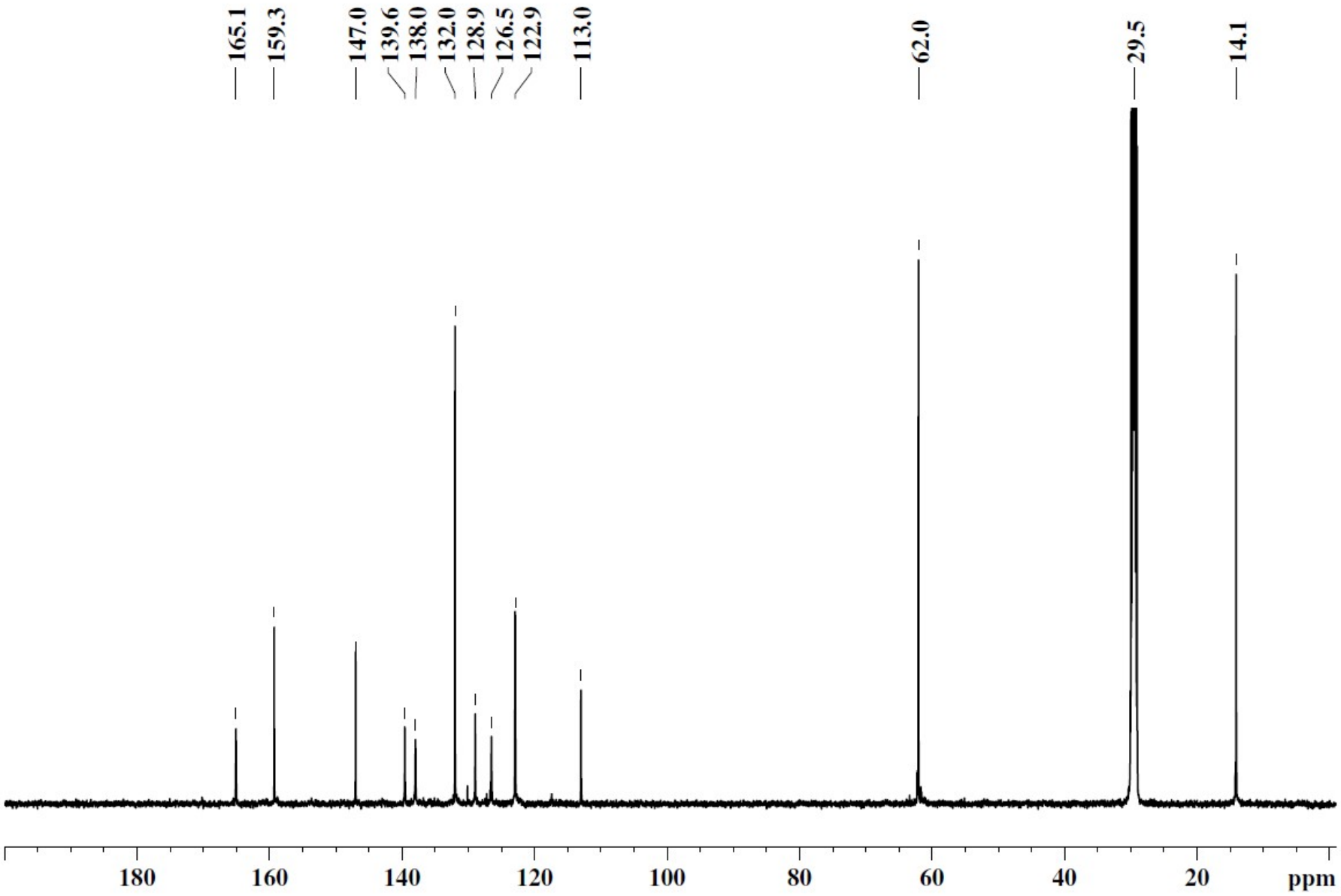


Figure S6. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) of compound **3c**.

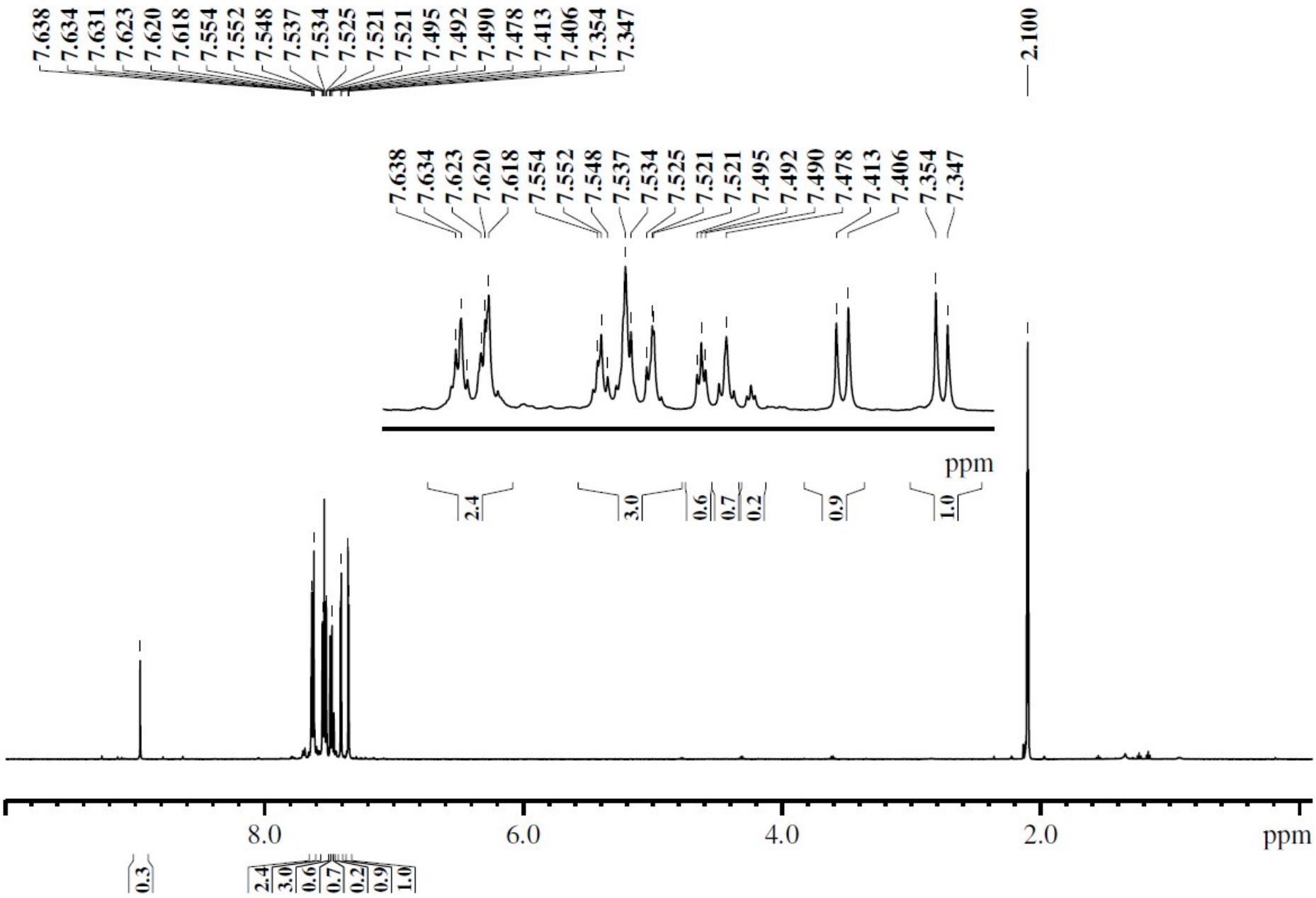


Figure S7. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) of compound **3d**.

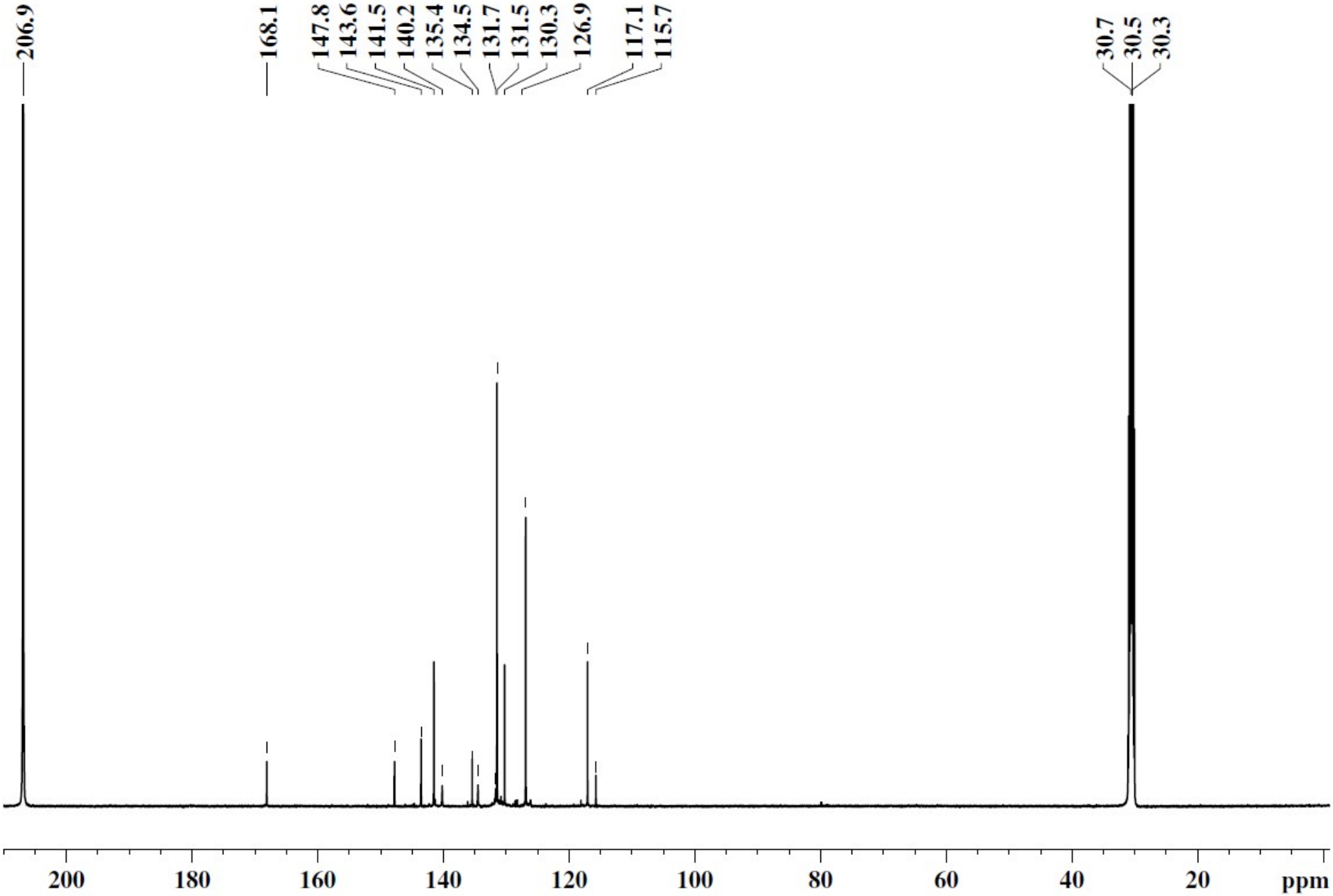


Figure S8. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) of compound **3d**.

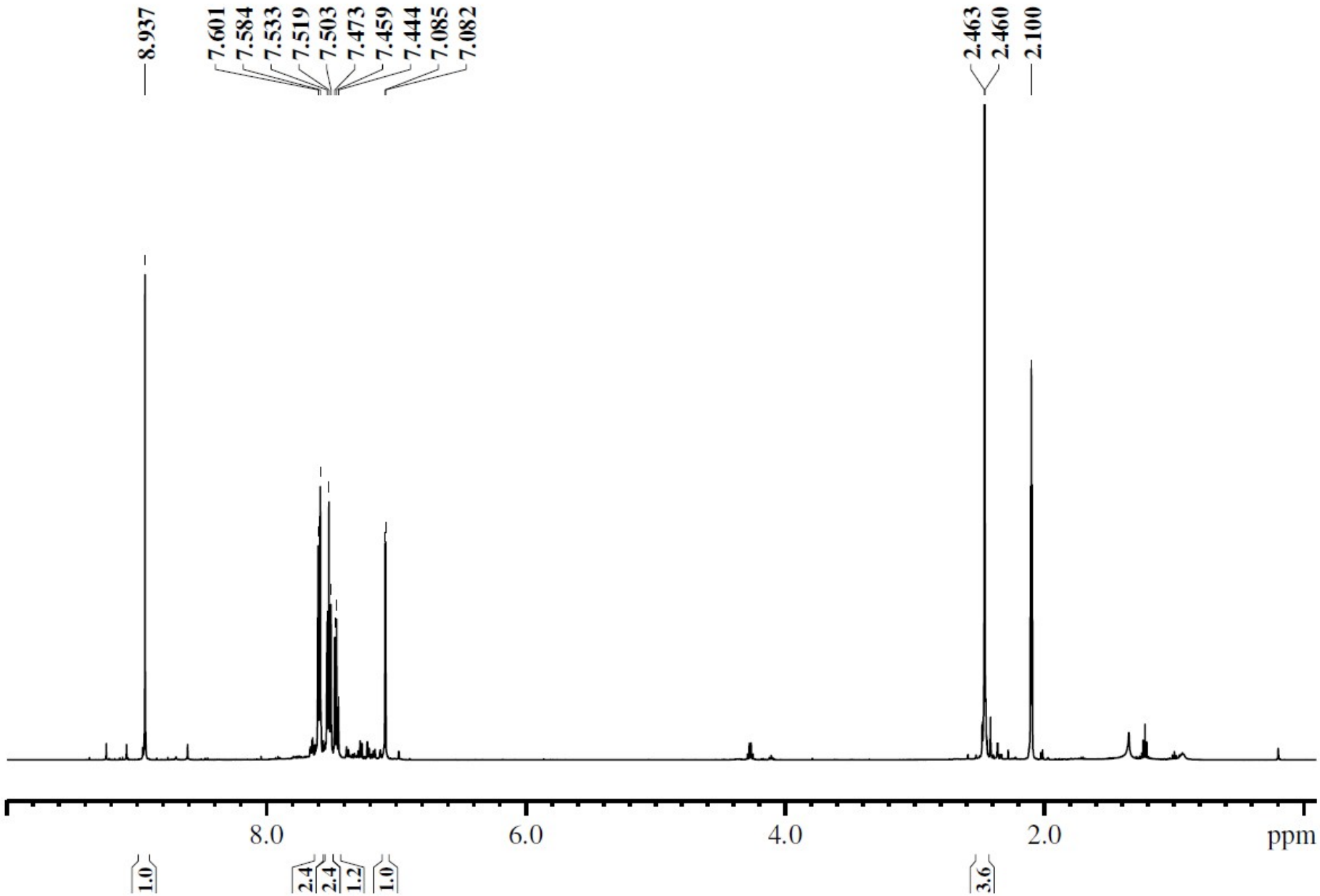


Figure S9. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) of compound **3e**.

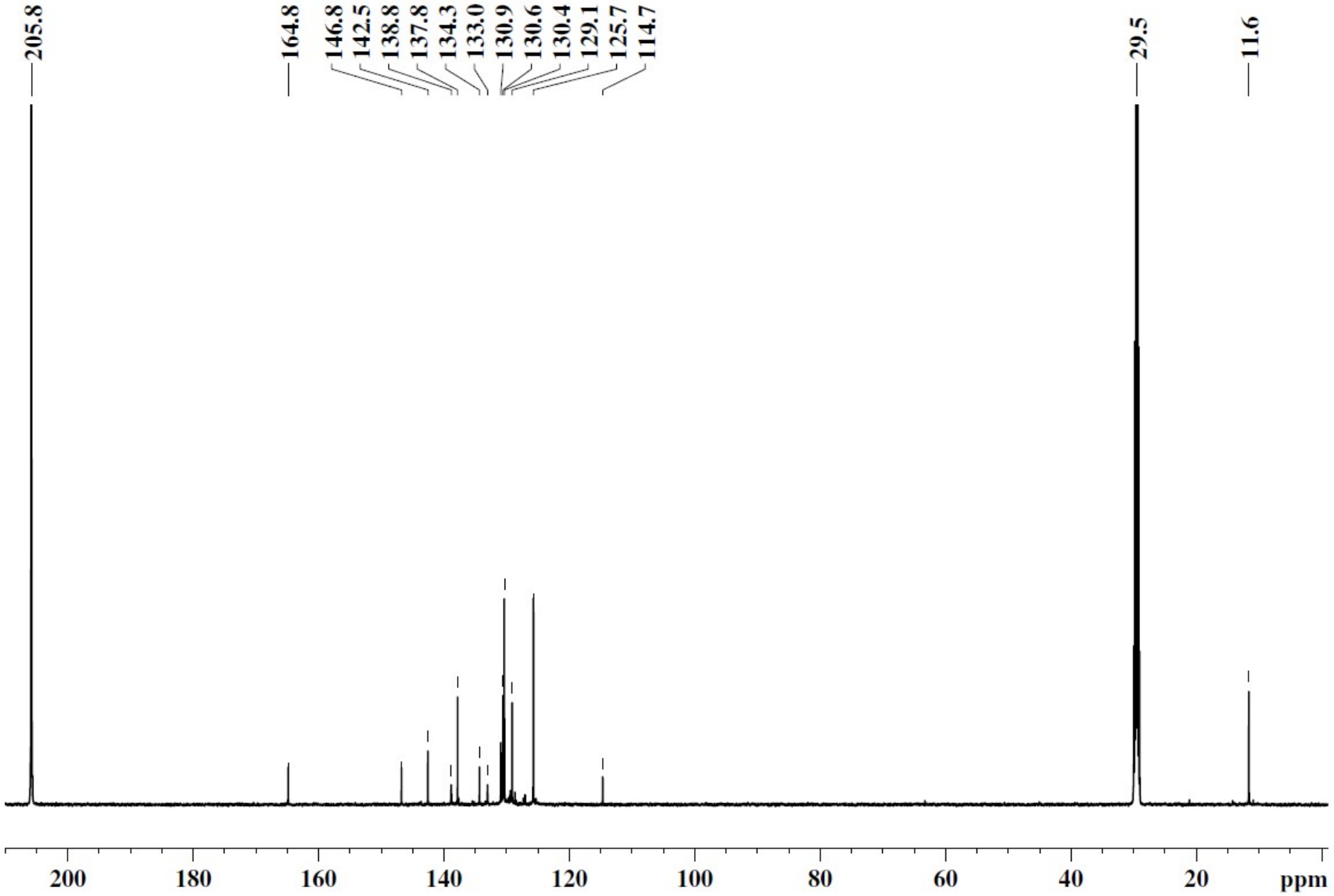


Figure S10. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) of compound **3e**.

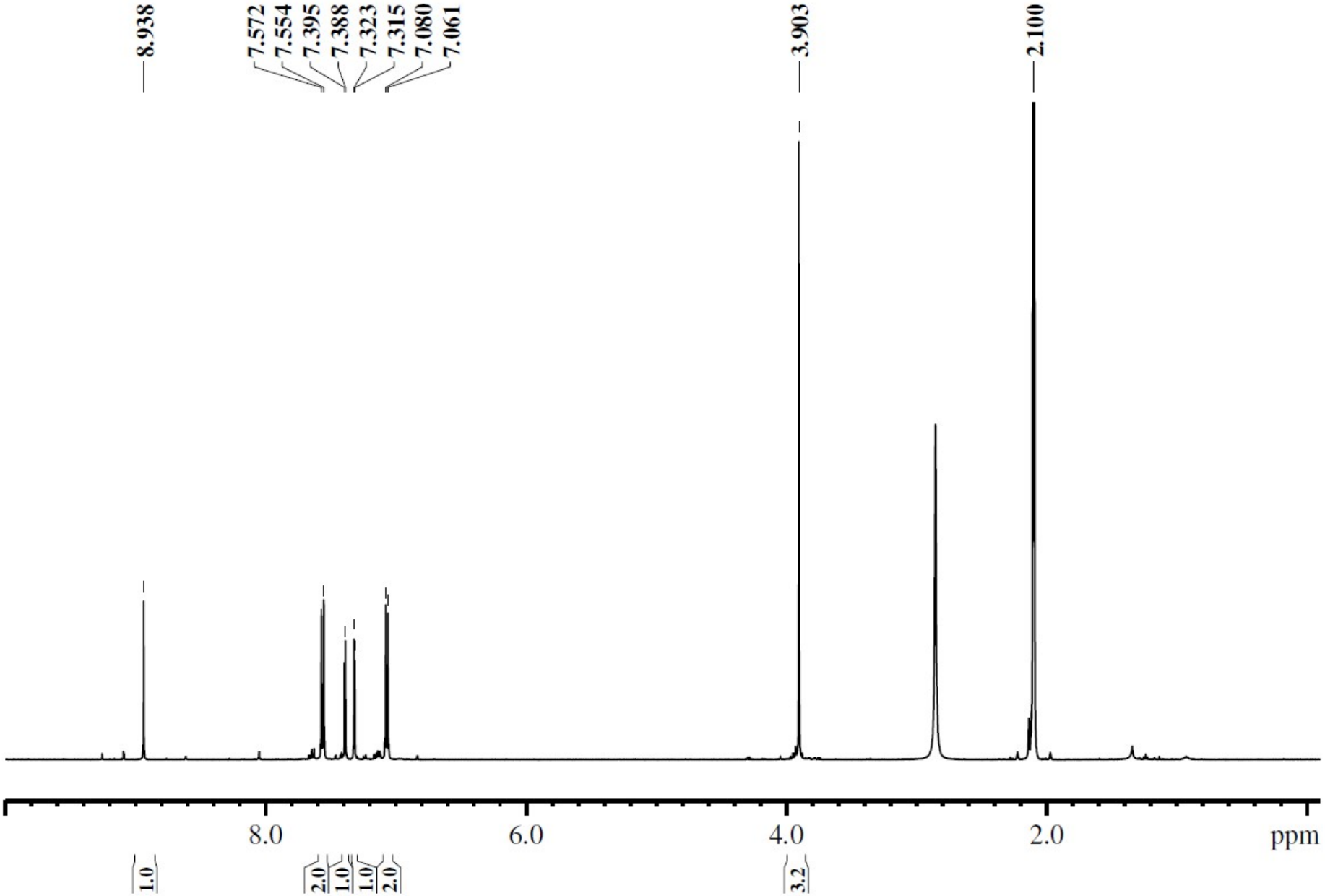


Figure S11. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) of compound **3f**.

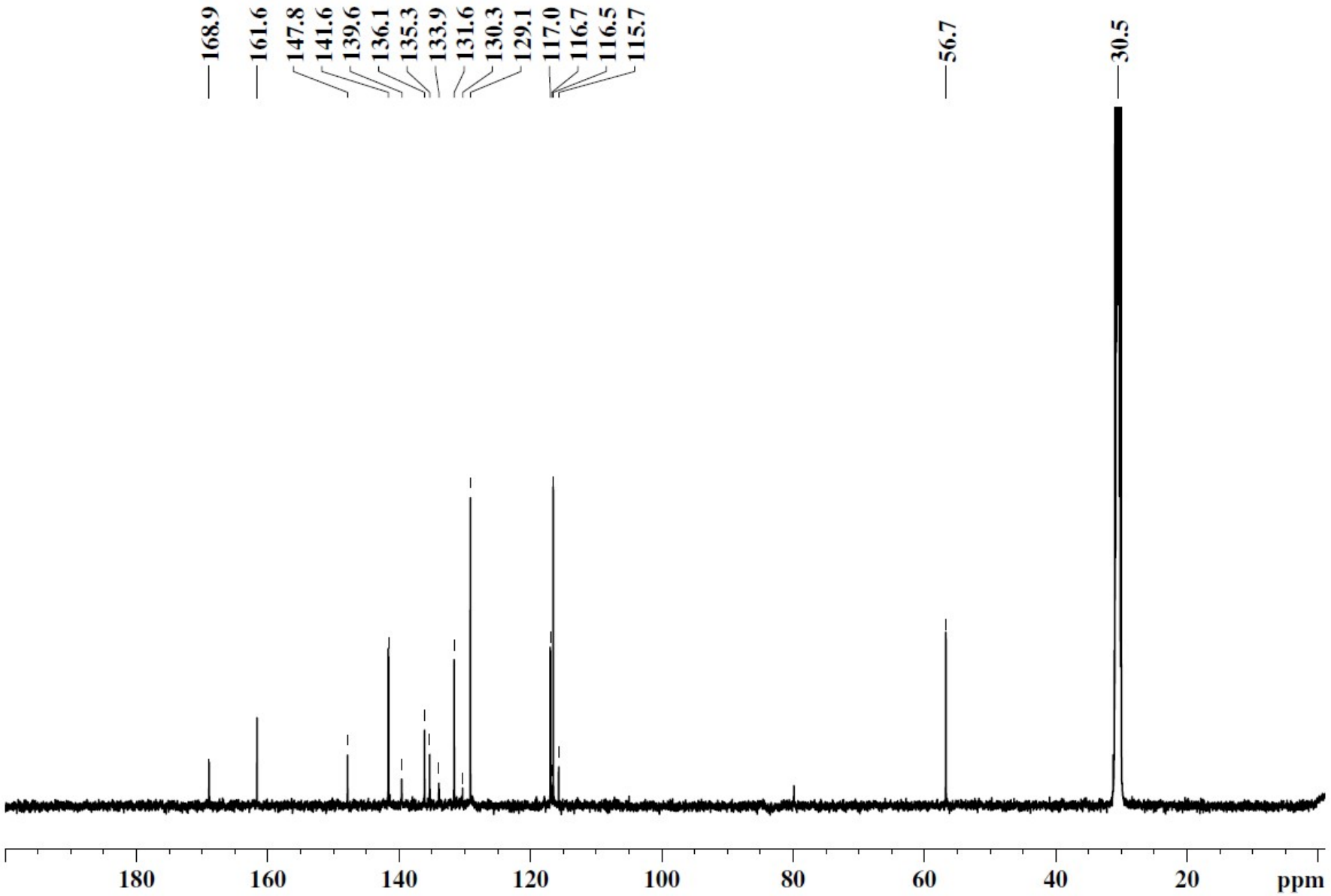


Figure S12. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) of compound **3f**.

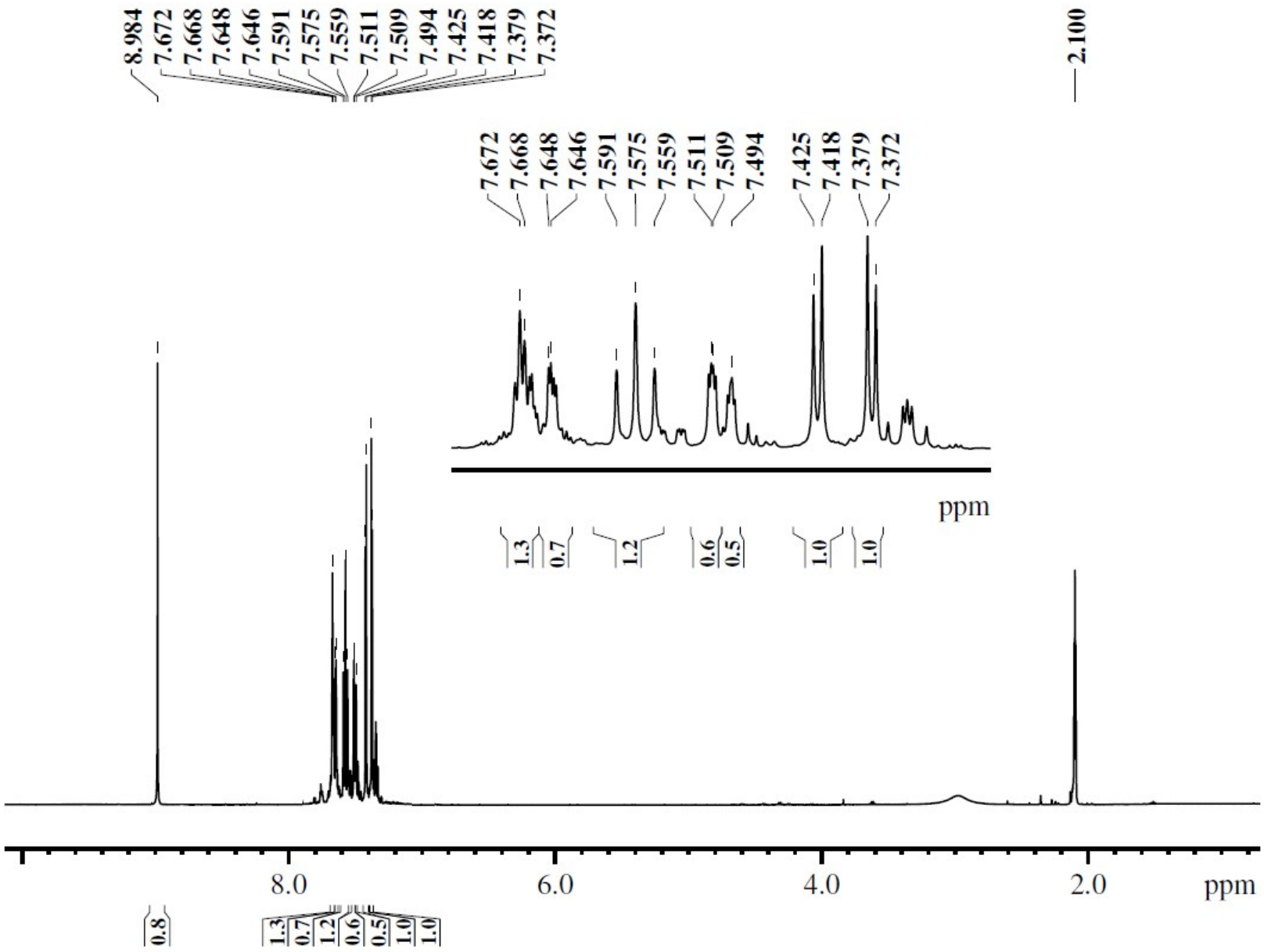


Figure S13. ^{1}H NMR (acetone-d_6, 500 MHz, 303 K) of compound **3g**.

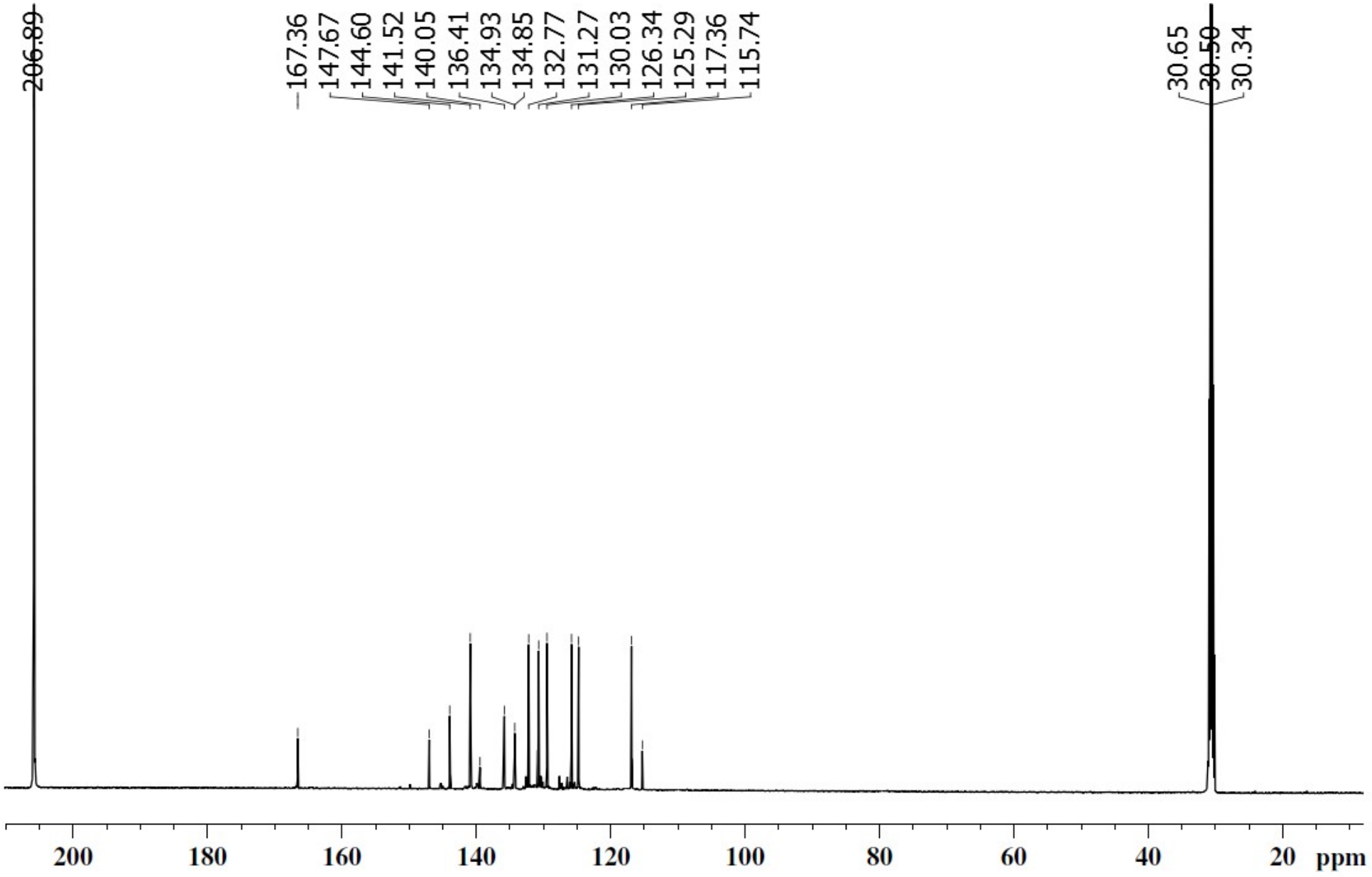


Figure S14. $^{13}C\{1H\}$ NMR (acetone-d_6, 126 MHz, 303 K) of compound **3g**.

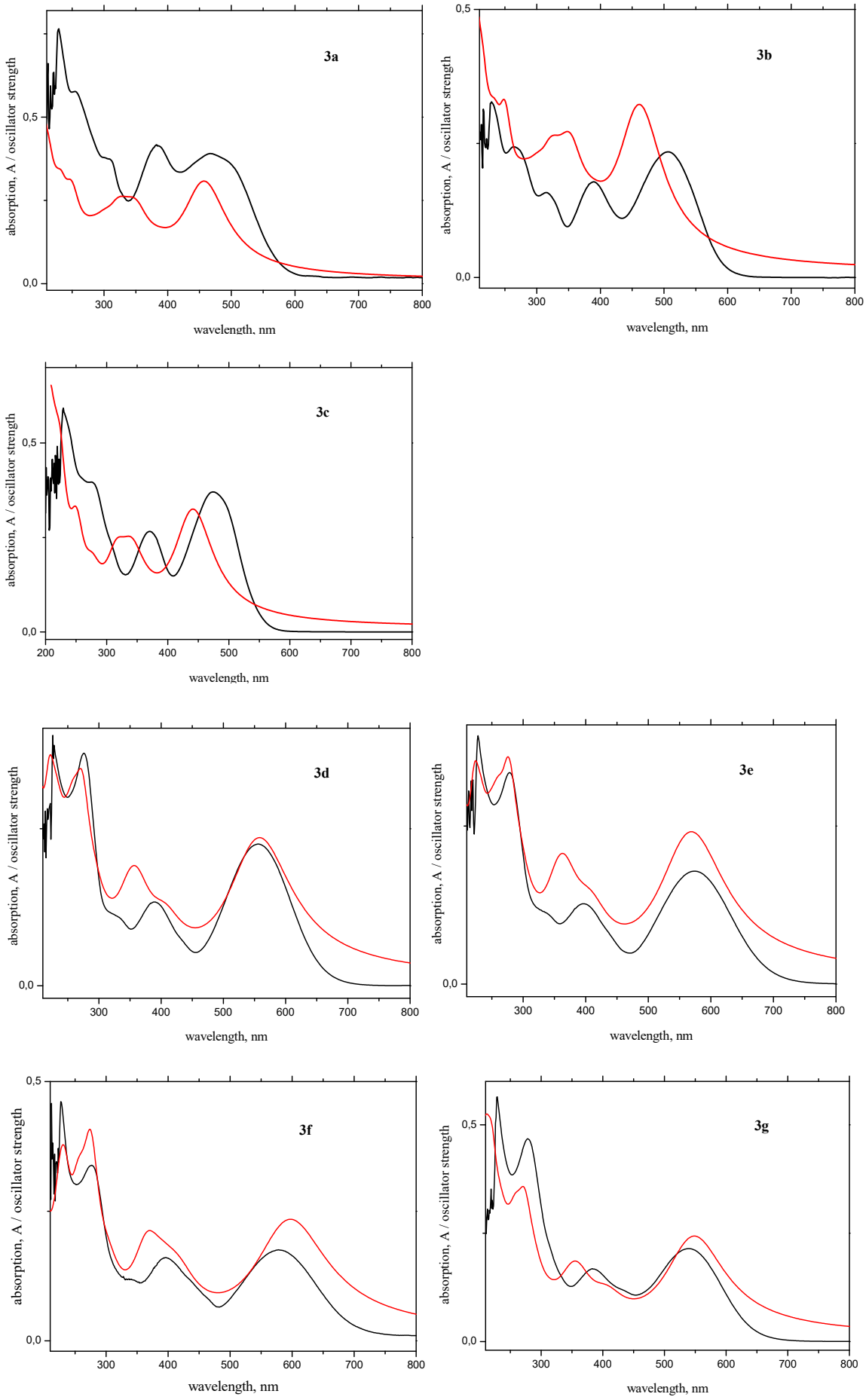


Figure S15. Experimental (black) vs theoretical (red) UV/Vis spectra of **3a** – **3g**.

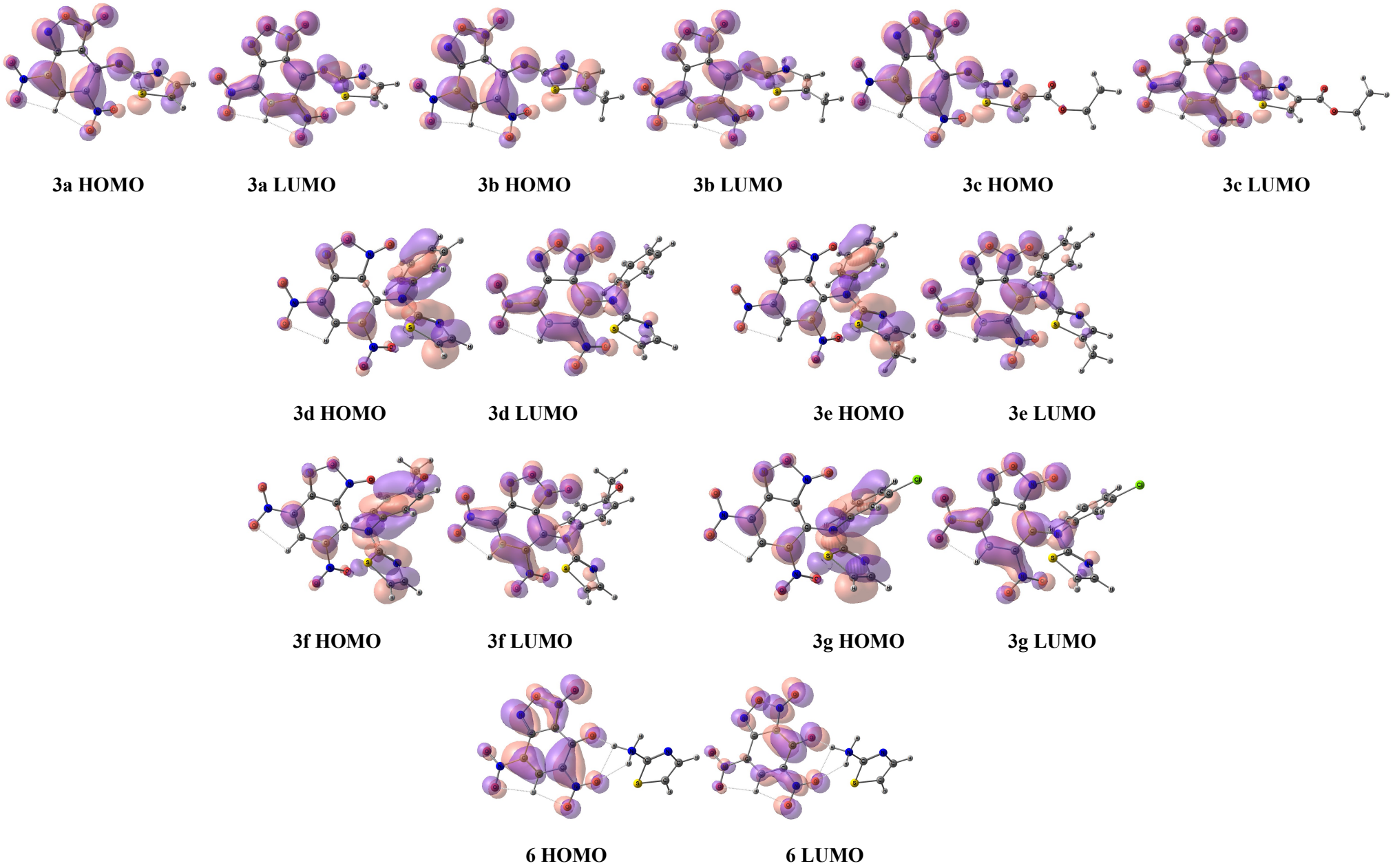


Figure S16. Frontier orbitals of **3a** – **3g** and **6**.

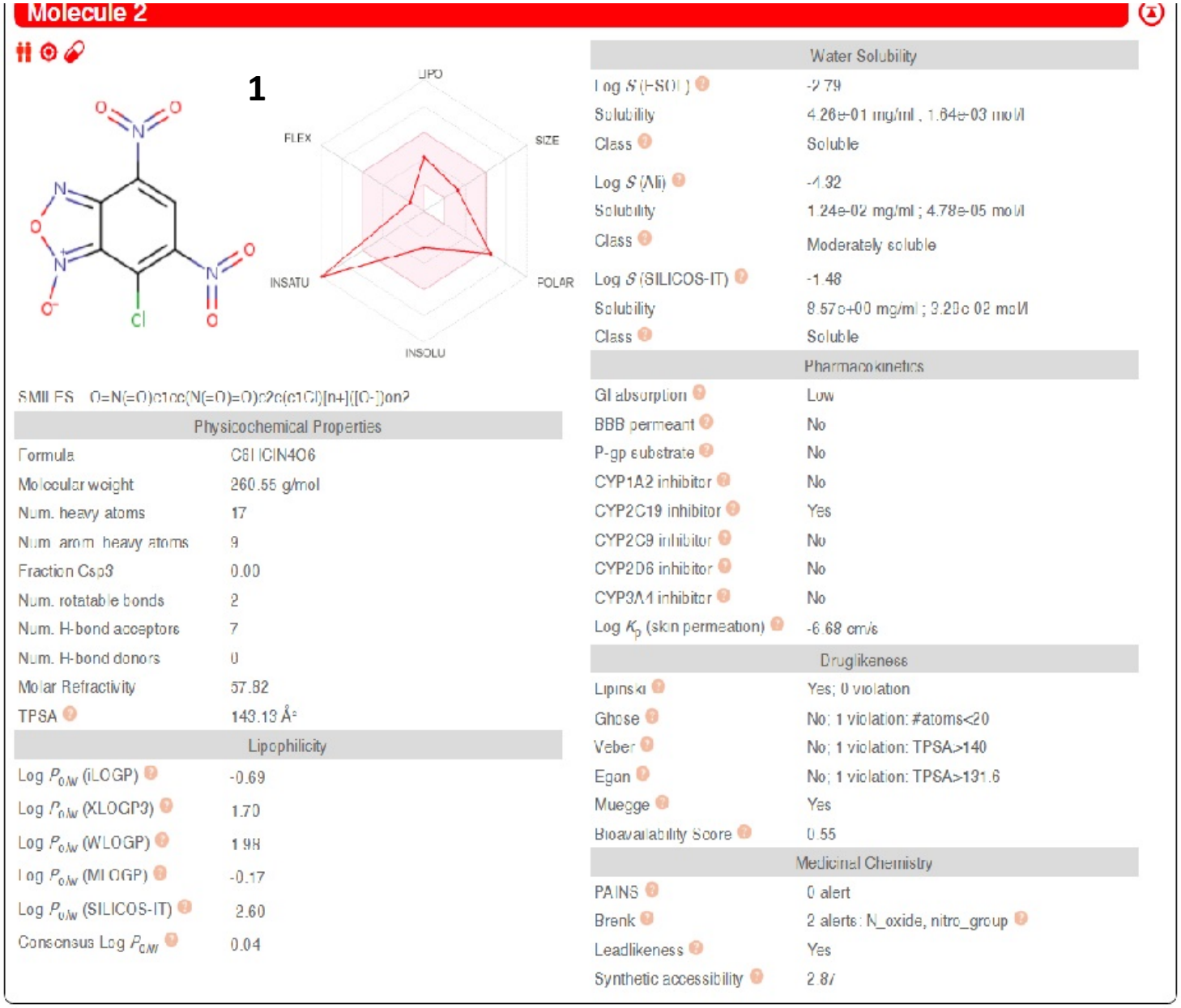


Figure S17. ADMET prediction for compound **1**

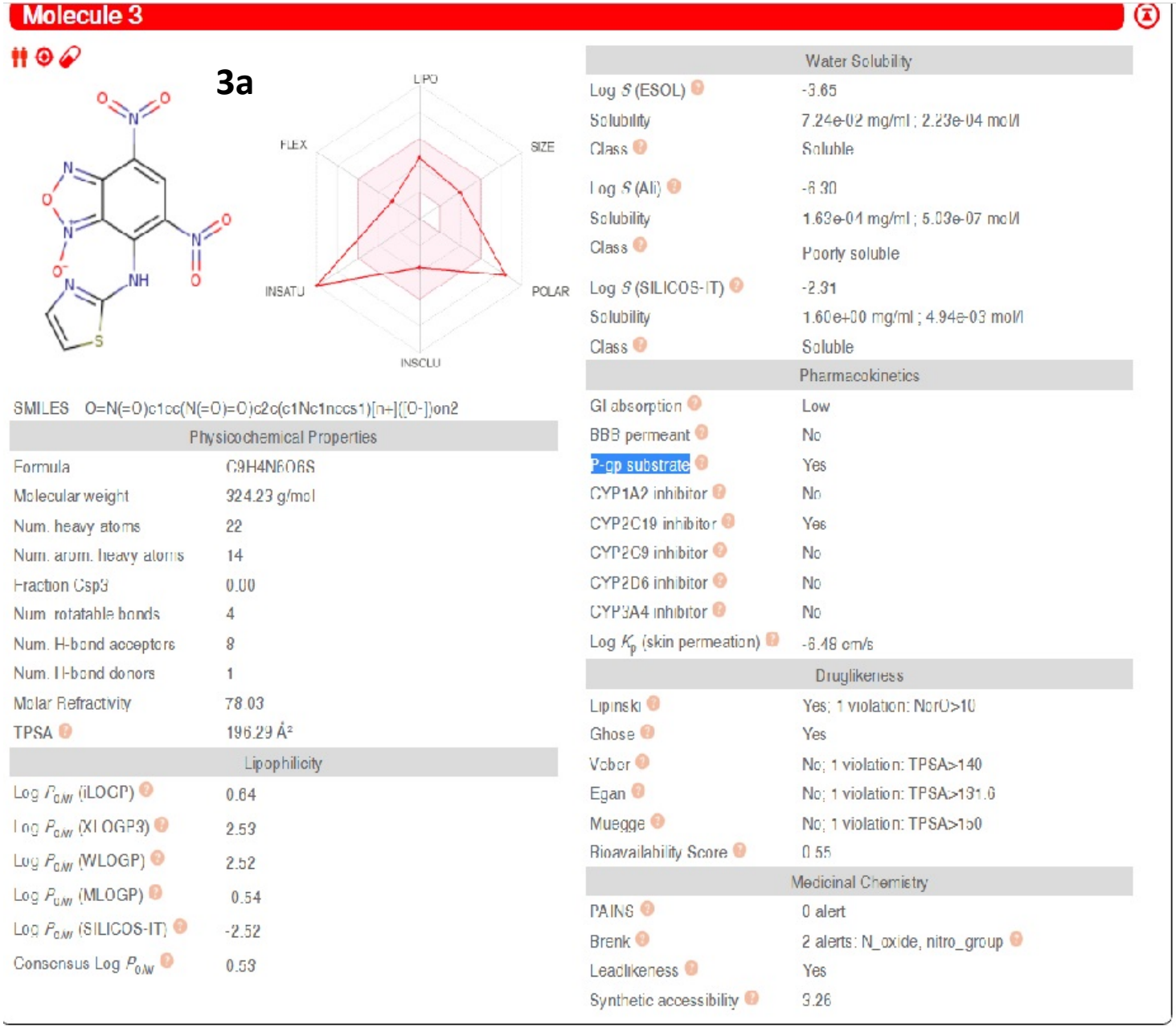
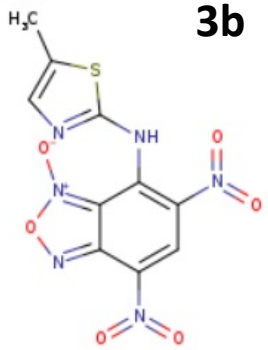
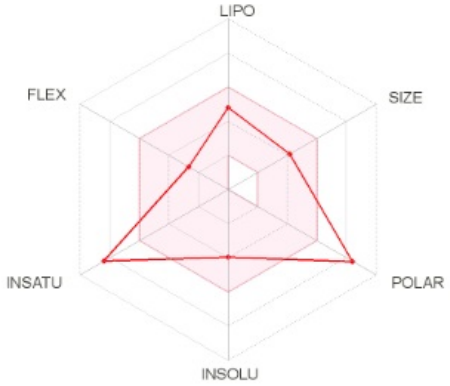


Figure S18. ADMET prediction for compound **3a**

Molecule 4

3b





SMILES Cc1cnc(s1)Nc1c(cc(c2c1[n+]([O-])on2)N(=O)=O)N(=O)=O

Physicochemical Properties	
Formula	C10H6N6O6S
Molecular weight	338.26 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	14
Fraction Csp3	0.10
Num. rotatable bonds	4
Num. H-bond acceptors	8
Num. H-bond donors	1
Molar Refractivity	83.00
TPSA	196.29 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.99
Log $P_{o/w}$ (XLOGP3)	2.93
Log $P_{o/w}$ (WLOGP)	2.83
Log $P_{o/w}$ (MLOGP)	-0.24
Log $P_{o/w}$ (SILICOS-IT)	-2.07
Consensus Log $P_{o/w}$	0.89

Water Solubility	
Log S (ESOL)	-3.97
Solubility	3.63e-02 mg/ml ; 1.07e-04 mol/l
Class	Soluble
Log S (Ali)	-6.71
Solubility	6.54e-05 mg/ml ; 1.93e-07 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-2.69
Solubility	6.99e-01 mg/ml ; 2.07e-03 mol/l
Class	Soluble

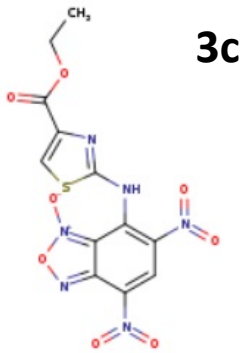
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.28 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55

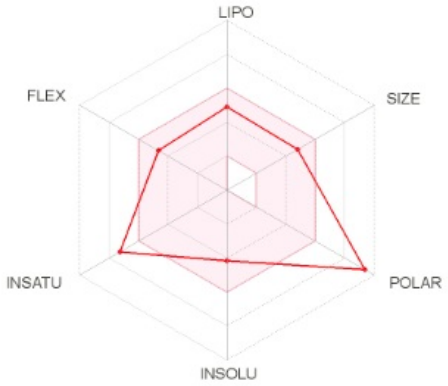
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: N_oxide, nitro_group
Leadlikeness	Yes
Synthetic accessibility	3.33

Figure S19. ADMET prediction for compound **3b**

Molecule 5



3c



SMILES CCOC(=O)c1csc(n1)Nc1c(cc(c2c1[n+]([O-])on2)N(=O)=O)N(=O)=O

Physicochemical Properties	
Formula	C12H8N6O8S
Molecular weight	396.29 g/mol
Num. heavy atoms	27
Num. arom. heavy atoms	14
Fraction Csp3	0.17
Num. rotatable bonds	7
Num. H-bond acceptors	10
Num. H-bond donors	1
Molar Refractivity	94.12
TPSA	222.59 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.12
Log $P_{o/w}$ (XLOGP3)	3.08
Log $P_{o/w}$ (WLOGP)	2.70
Log $P_{o/w}$ (MLOGP)	-0.15
Log $P_{o/w}$ (SILICOS-IT)	-2.25
Consensus Log $P_{o/w}$	0.90

Water Solubility	
Log *S* (ESOL)	-4.16
Solubility	2.75e-02 mg/ml ; 6.93e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.42
Solubility	1.50e-05 mg/ml ; 3.79e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-2.74
Solubility	7.28e-01 mg/ml ; 1.84e-03 mol/l
Class	Soluble

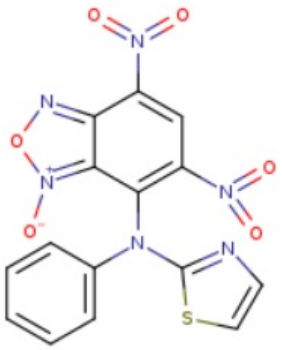
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.53 cm/s

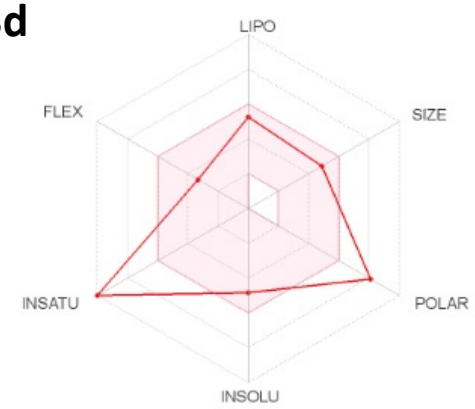
Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: N_oxide, nitro_group
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.60

Figure S20. ADMET prediction for compound **3c**

3d





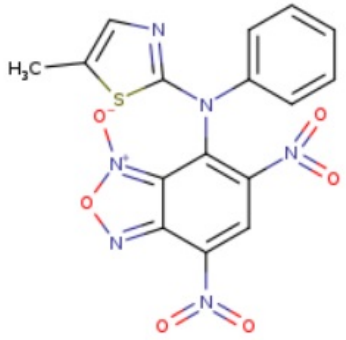
SMILES O=N(=O)c1cc(N(=O)=O)c2c(c1N(c1nccs1)c1ccccc1)[n+]([O-])on2

Physicochemical Properties	
Formula	C15H8N6O6S
Molecular weight	400.33 g/mol
Num. heavy atoms	28
Num. arom. heavy atoms	20
Fraction Csp3	0.00
Num. rotatable bonds	5
Num. H-bond acceptors	8
Num. H-bond donors	0
Molar Refractivity	103.17
TPSA	187.50 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.26
Log $P_{o/w}$ (XLOGP3)	3.68
Log $P_{o/w}$ (WLOGP)	4.25
Log $P_{o/w}$ (MLOGP)	1.19
Log $P_{o/w}$ (SILICOS-IT)	-1.75
Consensus Log $P_{o/w}$	1.73

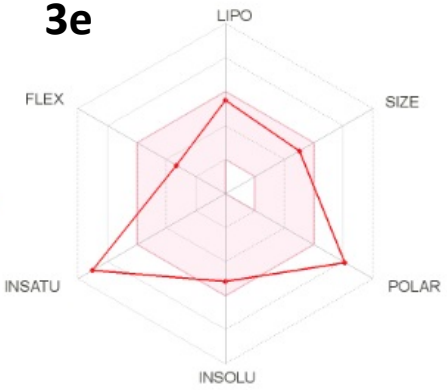
Water Solubility	
Log S (ESOL)	-4.84
Solubility	5.80e-03 mg/ml ; 1.45e-05 mol/l
Class	Moderately soluble
Log S (Ali)	-7.31
Solubility	1.97e-05 mg/ml ; 4.93e-08 mol/l
Class	Poorly soluble
Log S (SILICOS-IT)	-4.05
Solubility	3.55e-02 mg/ml ; 8.87e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.13 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: N_oxide, nitro_group
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.69

Figure S21. ADMET prediction for compound **3d**

Molecule 9



3e



SMILES Cc1cnc(s1)N(c1c(cc(c2c1[n+]([O-])on2)N(=O)=O)N(=O)=O)c1ccccc1

Physicochemical Properties	
Formula	C16H10N6O6S
Molecular weight	414.35 g/mol
Num. heavy atoms	29
Num. arom. heavy atoms	20
Fraction Csp3	0.06
Num. rotatable bonds	5
Num. H-bond acceptors	8
Num. H-bond donors	0
Molar Refractivity	108.14
TPSA	187.50 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.60
Log $P_{o/w}$ (XLOGP3)	4.08
Log $P_{o/w}$ (WLOGP)	4.56
Log $P_{o/w}$ (MLOGP)	1.44
Log $P_{o/w}$ (SILICOS-IT)	-1.25
Consensus Log $P_{o/w}$	2.08

Water Solubility	
Log *S* (ESOL)	-5.16
Solubility	2.87e-03 mg/ml ; 6.92e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.72
Solubility	7.85e-06 mg/ml ; 1.89e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-4.43
Solubility	1.55e-02 mg/ml ; 3.74e-05 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.93 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: N_oxide, nitro_group
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.76

Figure S22. ADMET prediction for compound **3e**

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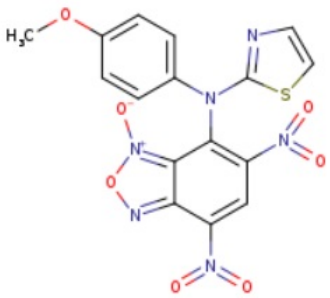
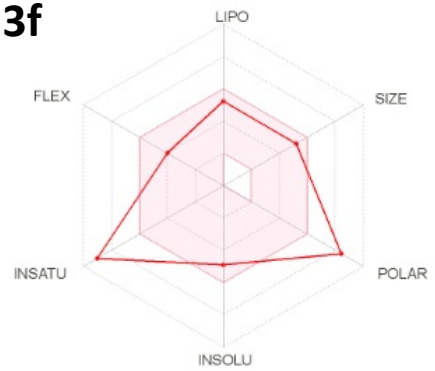
Molecule 1

3f





SMILES COc1ccc(cc1)N(c1c(cc(c2c1[n+]([O-])on2)N(=O)=O)N(=O)=O)c1nccs1

Physicochemical Properties	
Formula	C16H10N6O7S
Molecular weight	430.35 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	20
Fraction Csp3	0.06
Num. rotatable bonds	6
Num. H-bond acceptors	9
Num. H-bond donors	0
Molar Refractivity	109.66
TPSA	196.73 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.51
Log $P_{o/w}$ (XLOGP3)	3.65
Log $P_{o/w}$ (WLOGP)	4.26
Log $P_{o/w}$ (MLOGP)	0.95
Log $P_{o/w}$ (SILICOS-IT)	-1.70
Consensus Log $P_{o/w}$	1.74

Water Solubility	
Log *S* (ESOL)	-4.91
Solubility	5.36e-03 mg/ml ; 1.24e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.47
Solubility	1.46e-05 mg/ml ; 3.39e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-4.15
Solubility	3.03e-02 mg/ml ; 7.03e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.33 cm/s

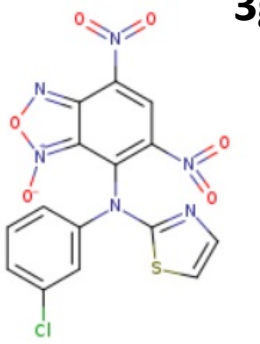
Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55

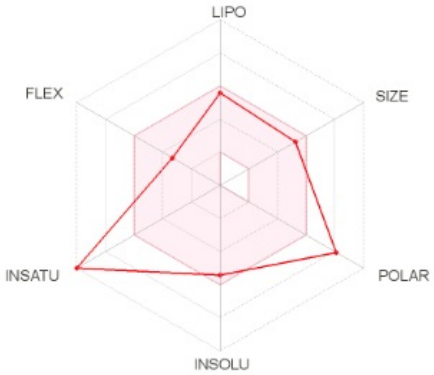
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: N_oxide, nitro_group
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.68

Figure S23. ADMET prediction for compound **3f**

Molecule 8

3g





SMILES Clc1cccc(c1)N(c1c(cc(c2c1[n+]([O-])on2)N(=O)=O)N(=O)=O)c1nccs1

Physicochemical Properties	
Formula	C15H7ClN6O6S
Molecular weight	434.77 g/mol
Num. heavy atoms	29
Num. arom. heavy atoms	20
Fraction Csp3	0.00
Num. rotatable bonds	5
Num. H-bond acceptors	8
Num. H-bond donors	0
Molar Refractivity	108.18
TPSA	187.50 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.76
Log $P_{o/w}$ (XLOGP3)	4.30
Log $P_{o/w}$ (WLOGP)	4.90
Log $P_{o/w}$ (MLOGP)	1.70
Log $P_{o/w}$ (SILICOS-IT)	-1.10
Consensus Log $P_{o/w}$	2.11

Water Solubility	
Log *S* (ESOL)	-5.42
Solubility	1.63e-03 mg/ml ; 3.76e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.95
Solubility	4.87e-06 mg/ml ; 1.12e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-4.64
Solubility	1.00e-02 mg/ml ; 2.31e-05 mol/l
Class	Moderately soluble

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.90 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	Yes
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: N_oxide, nitro_group
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.64

Figure S24. ADMET prediction for compound **3g**