Supplementary Material

Benzyltriethylammonium chloride (BTEAC) catalyzed efficient synthesis of novel benzofuran-pyrazole hybrids: design, synthesis and in silico evaluation as potential anti-HCV agents

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1) Spectral Data

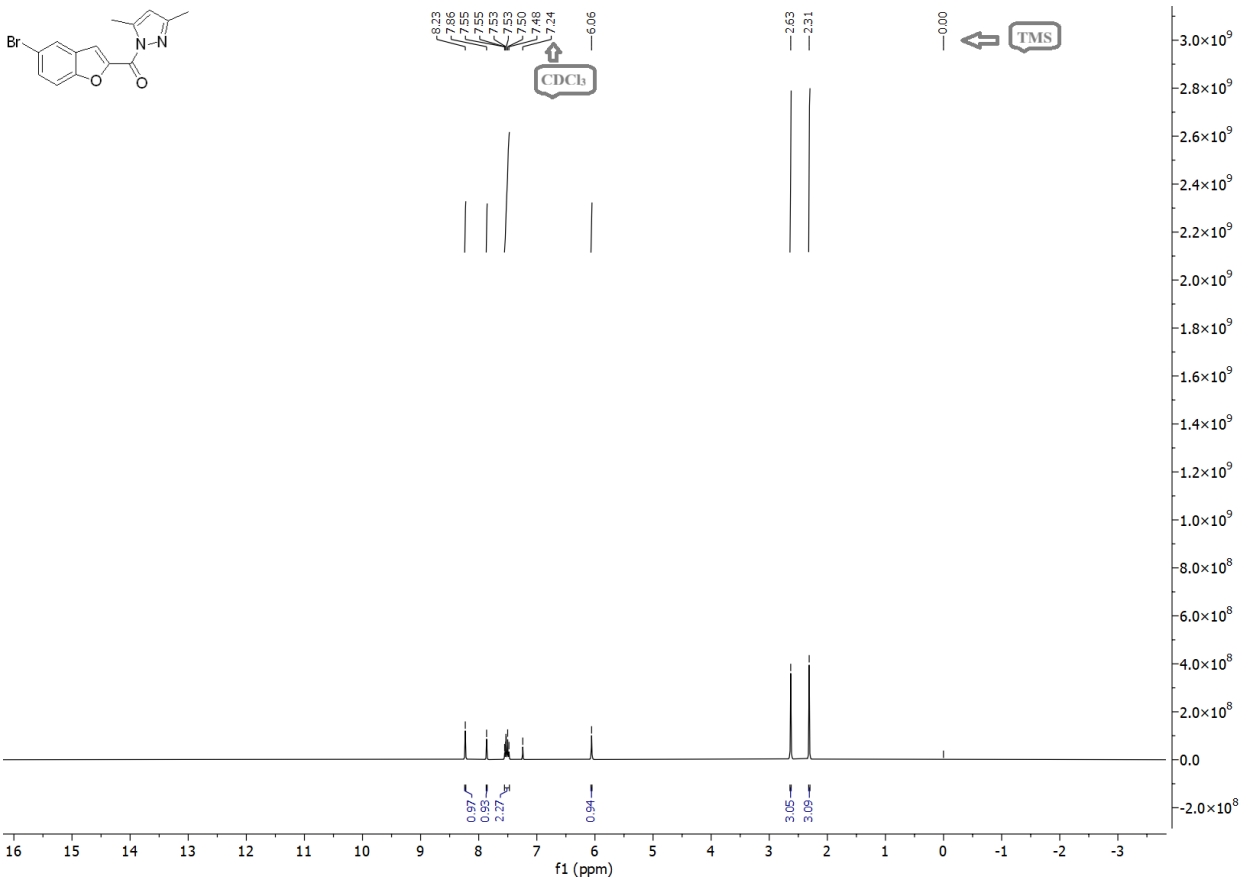

Figure S 1. ^{1}H-NMR Spectra of compound **11a**.

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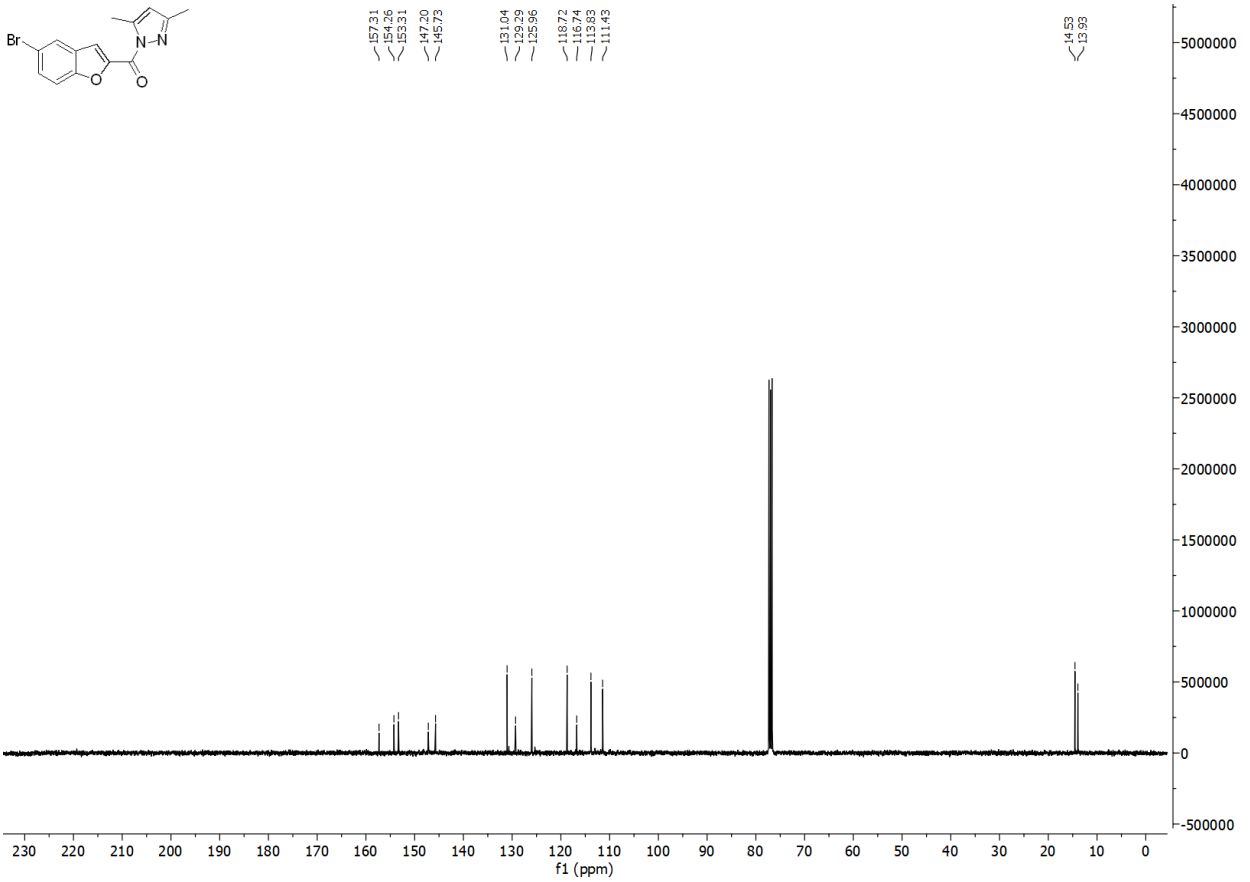

Figure S2. ^{13}C-NMR Spectra of compound **11a**.

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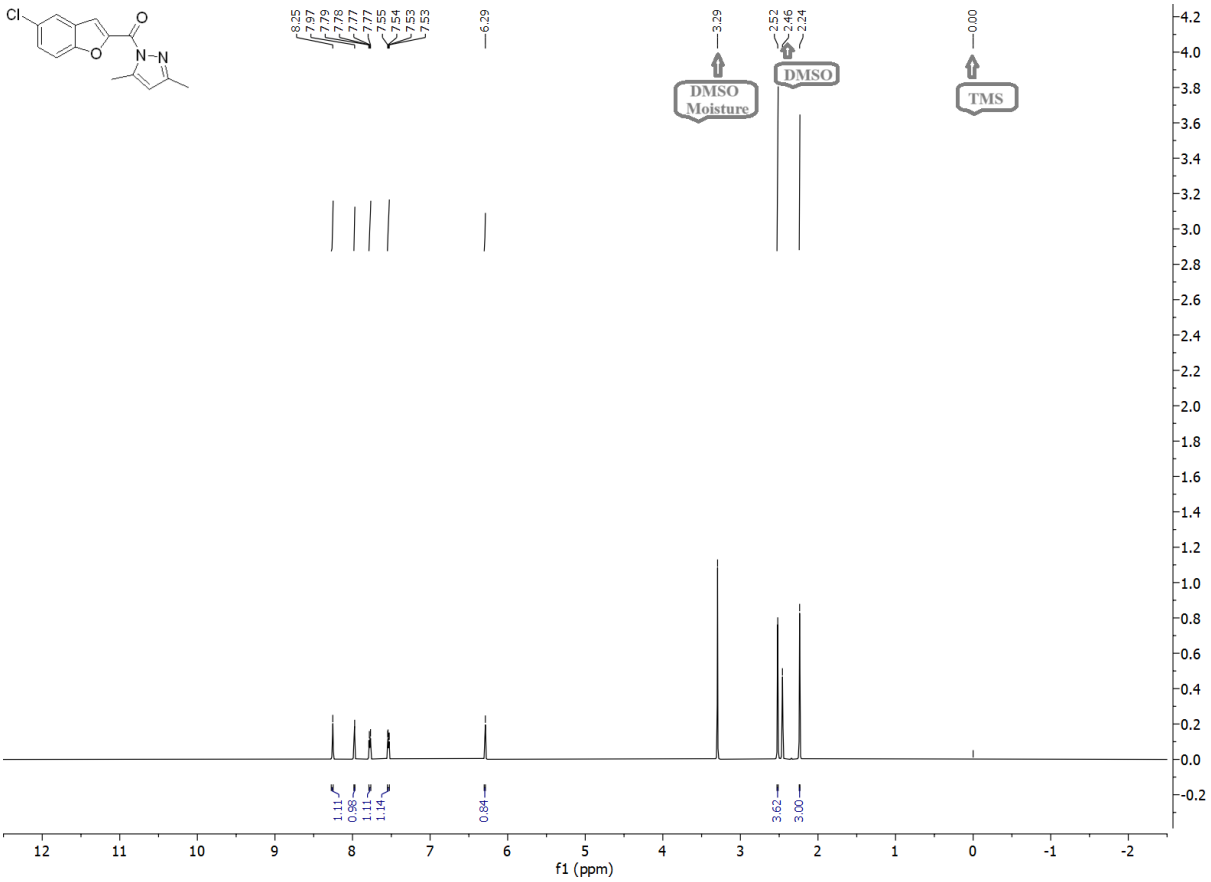

Figure S3. ^{1}H-NMR Spectra of compound **11b**.

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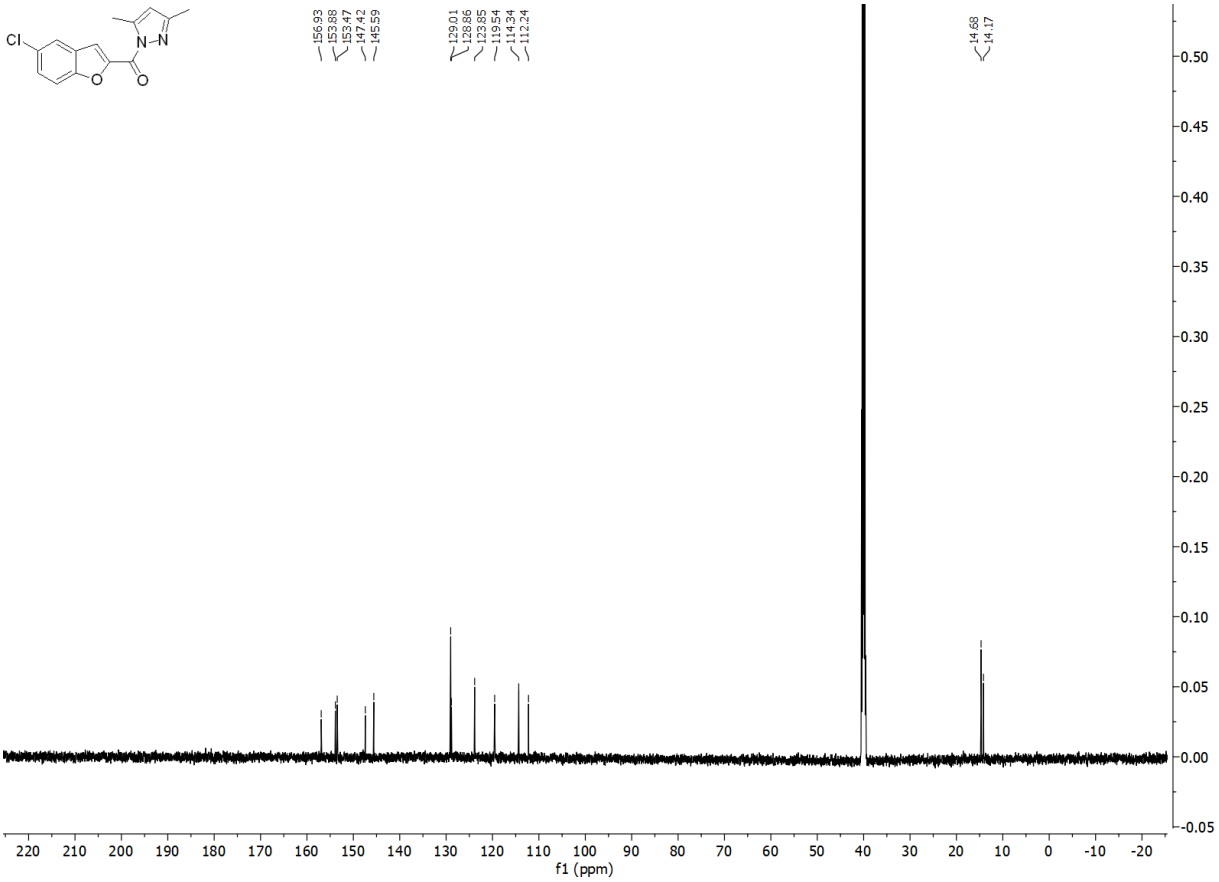

Figure S4. ^{13}C-NMR Spectra of compound **11b**.

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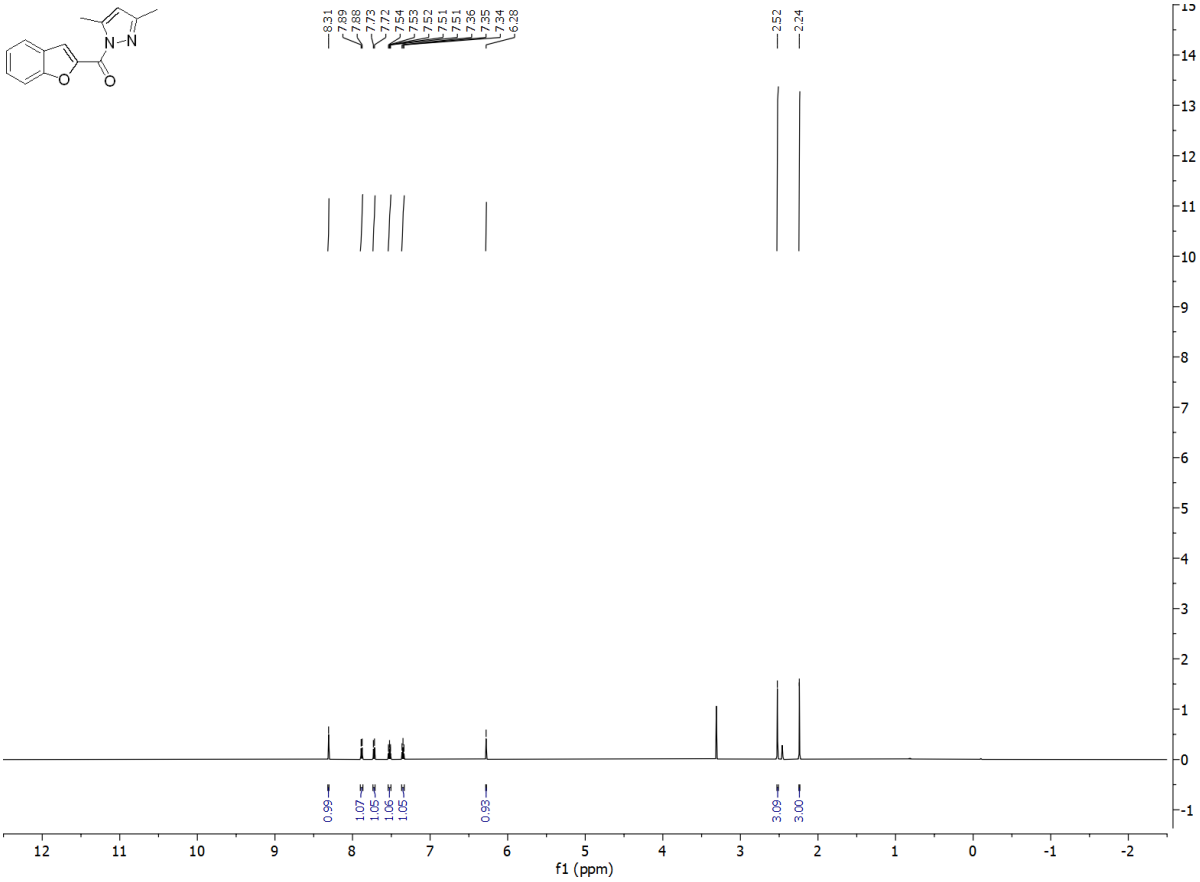

Figure S5. ^{1}H-NMR Spectra of compound **11c**.

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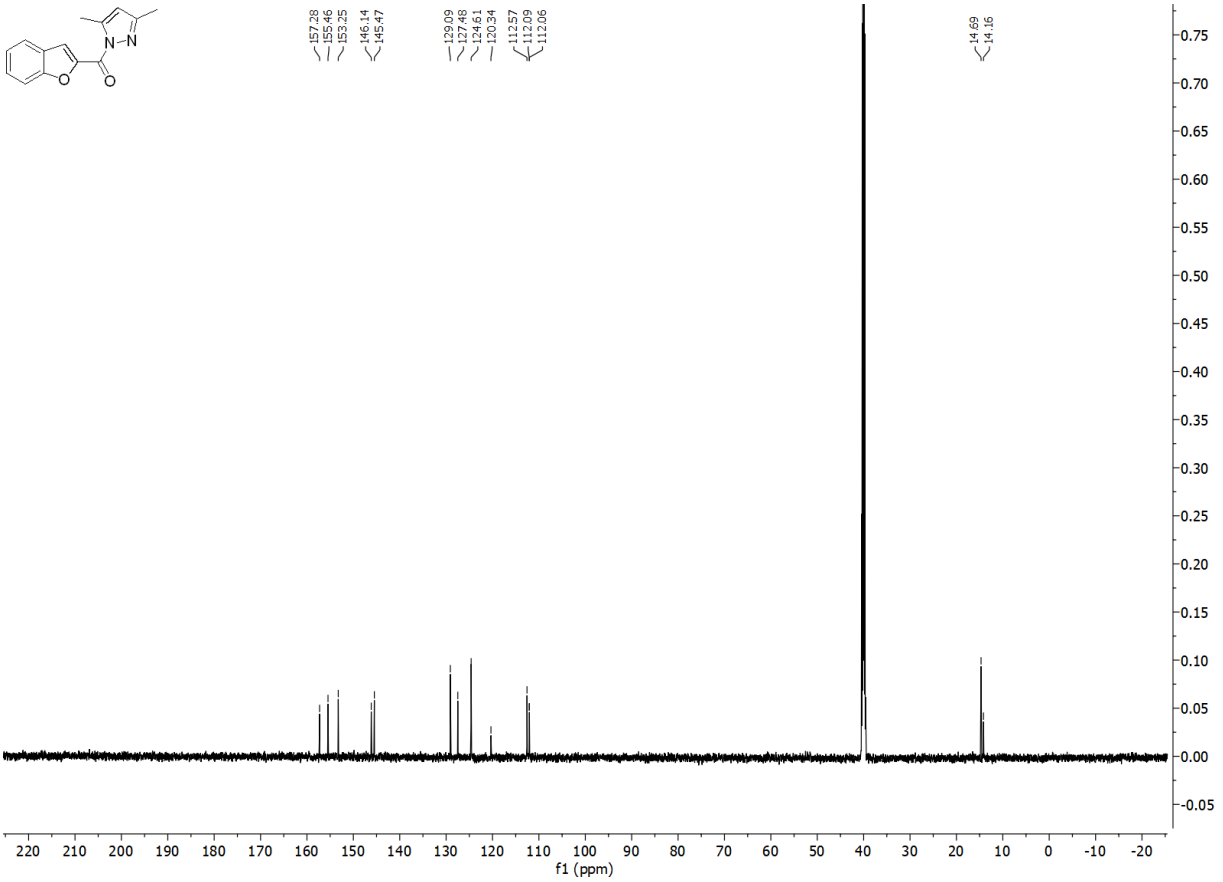

Figure S6. ^{13}C-NMR Spectra of compound **11c**.

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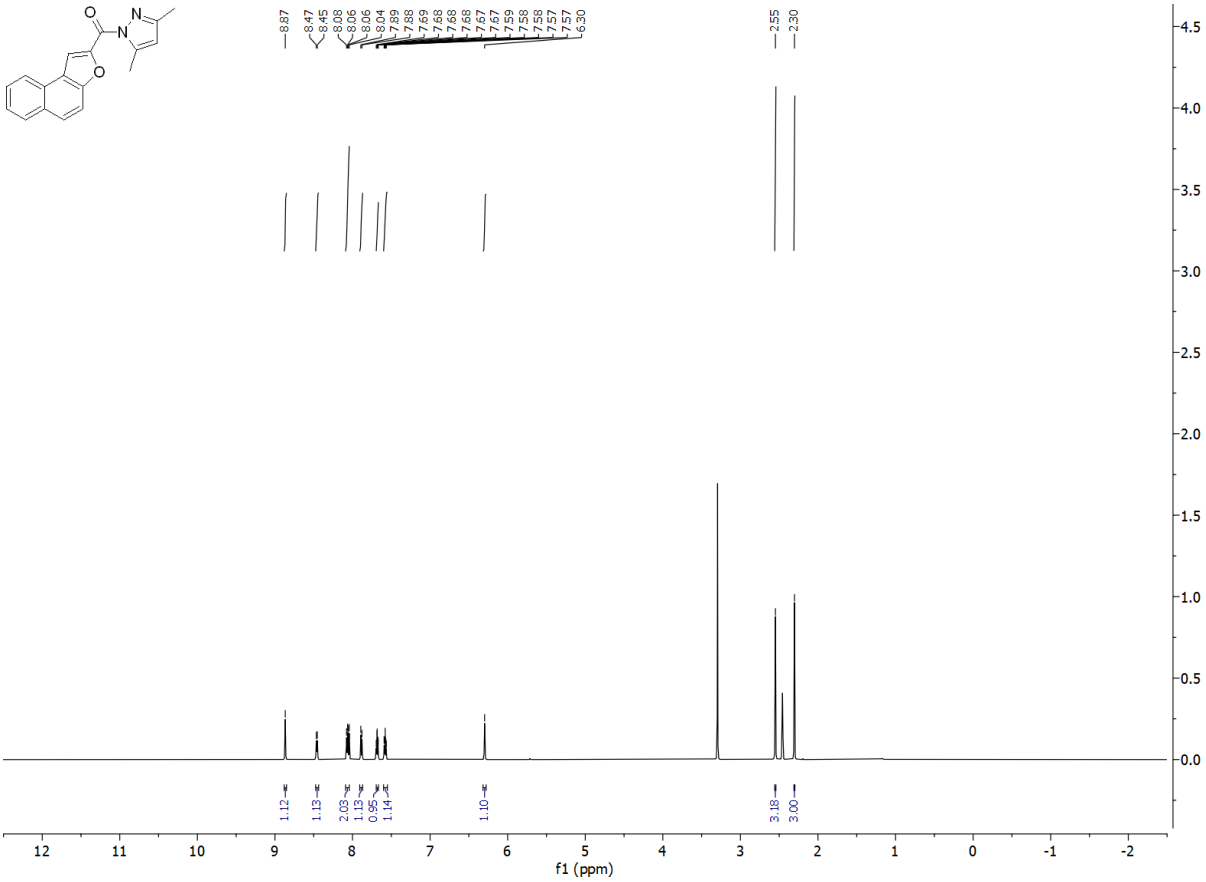

Figure S7. ^{1}H-NMR Spectra of compound **11d**.

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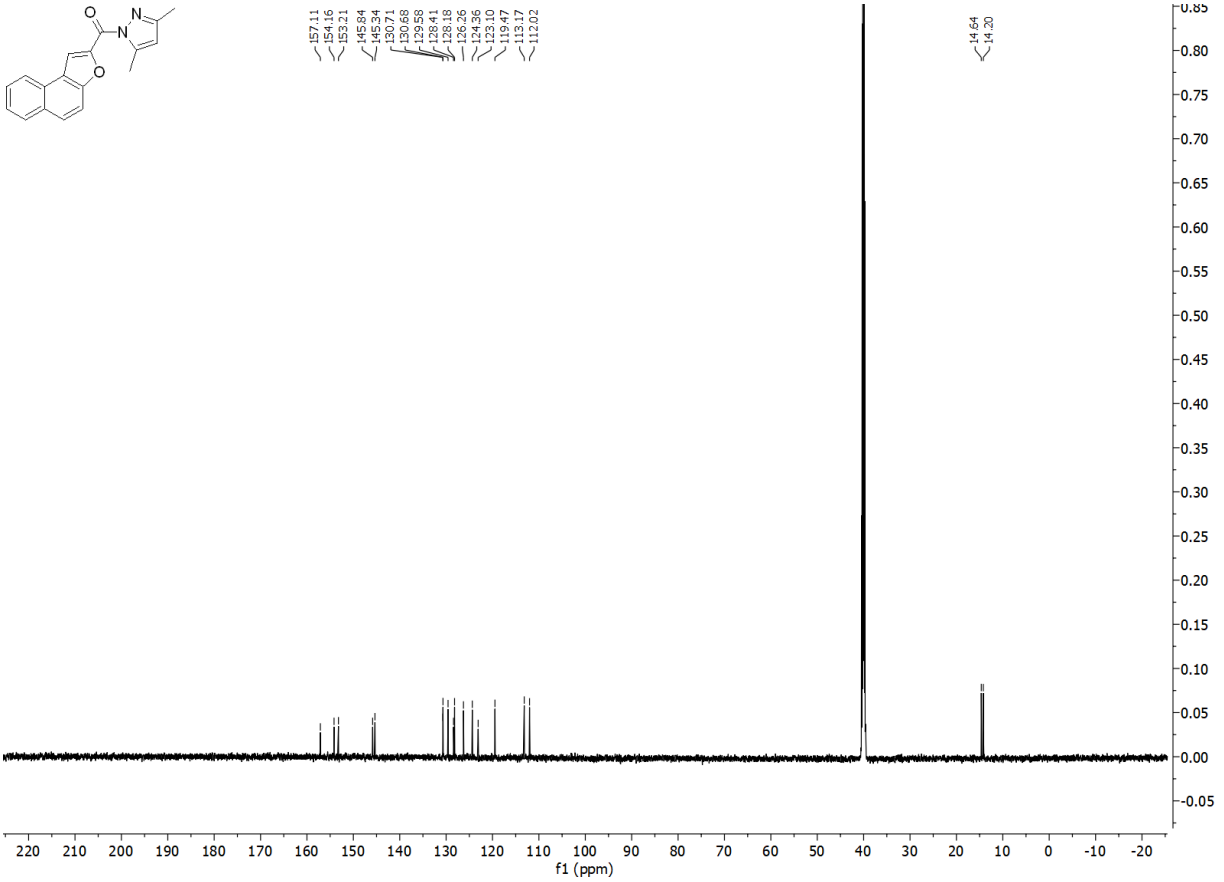

Figure S8. ^{13}C-NMR Spectra of compound **11d**.

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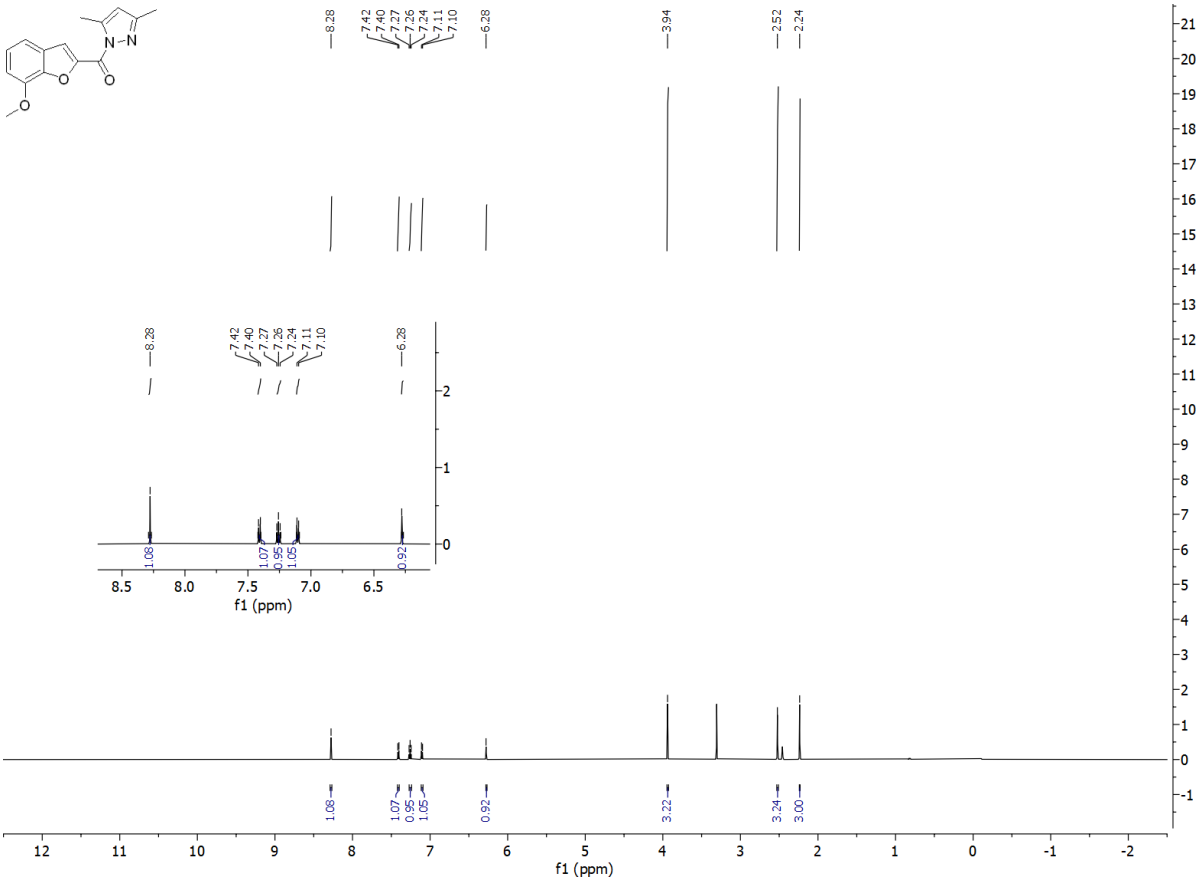

Figure S9. ^{1}H-NMR Spectra of compound **11e**.

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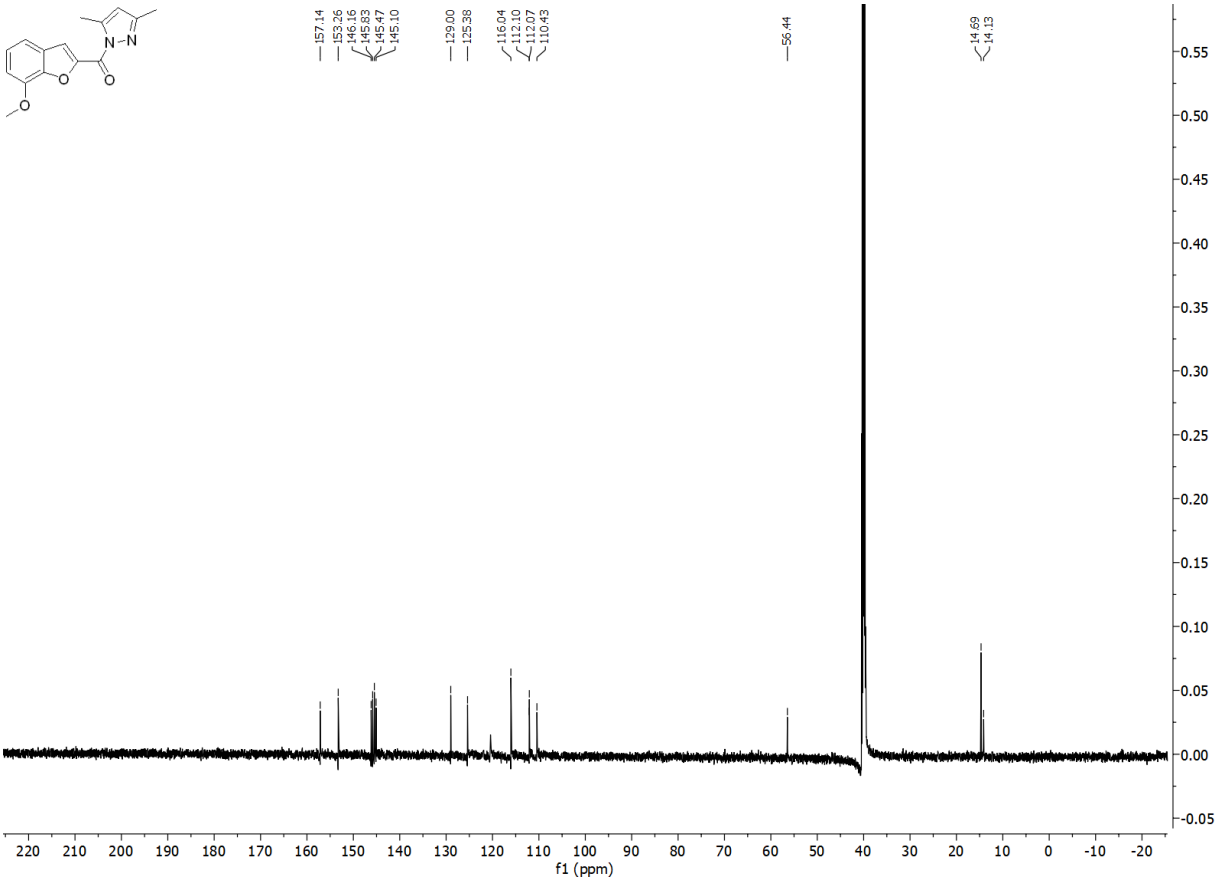

Figure S10. ^{13}C-NMR Spectra of compound **11e**.

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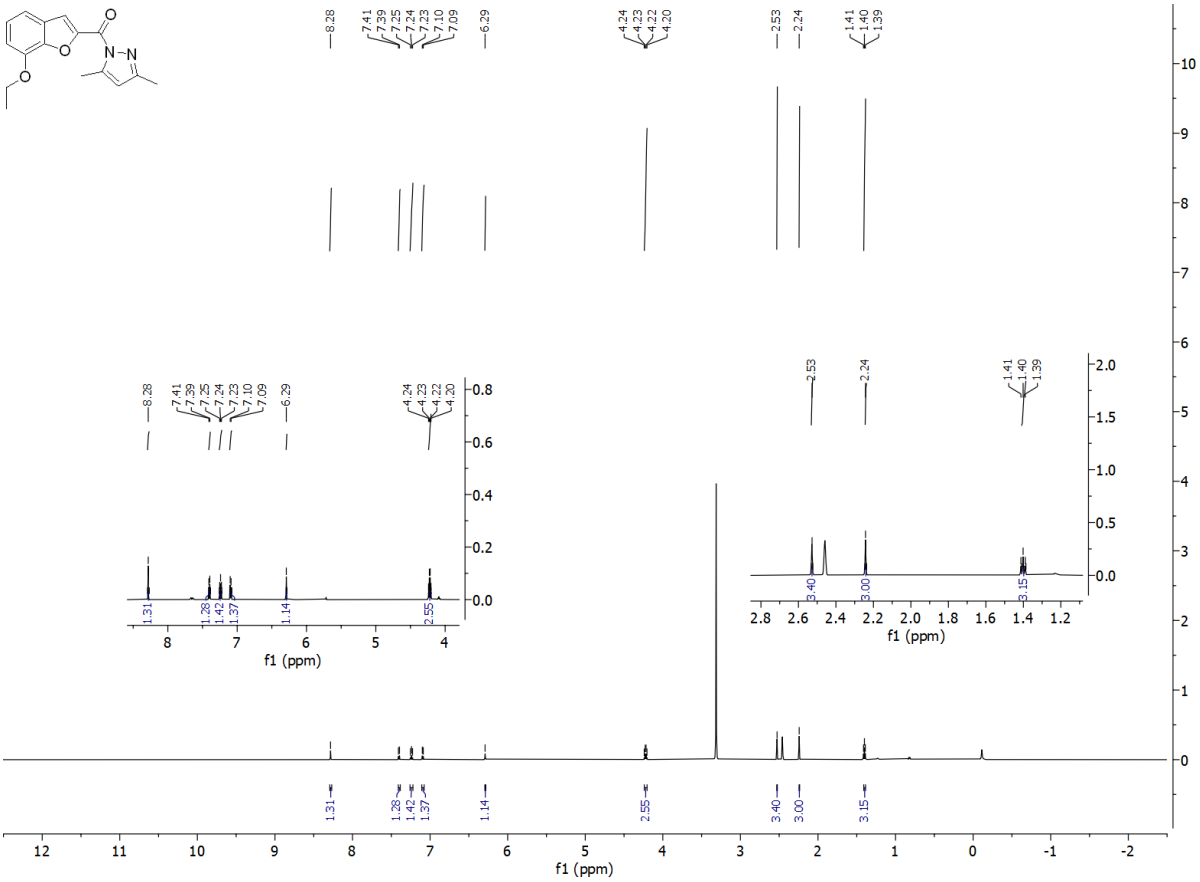

Figure S11. ^{1}H-NMR Spectra of compound **11f**.

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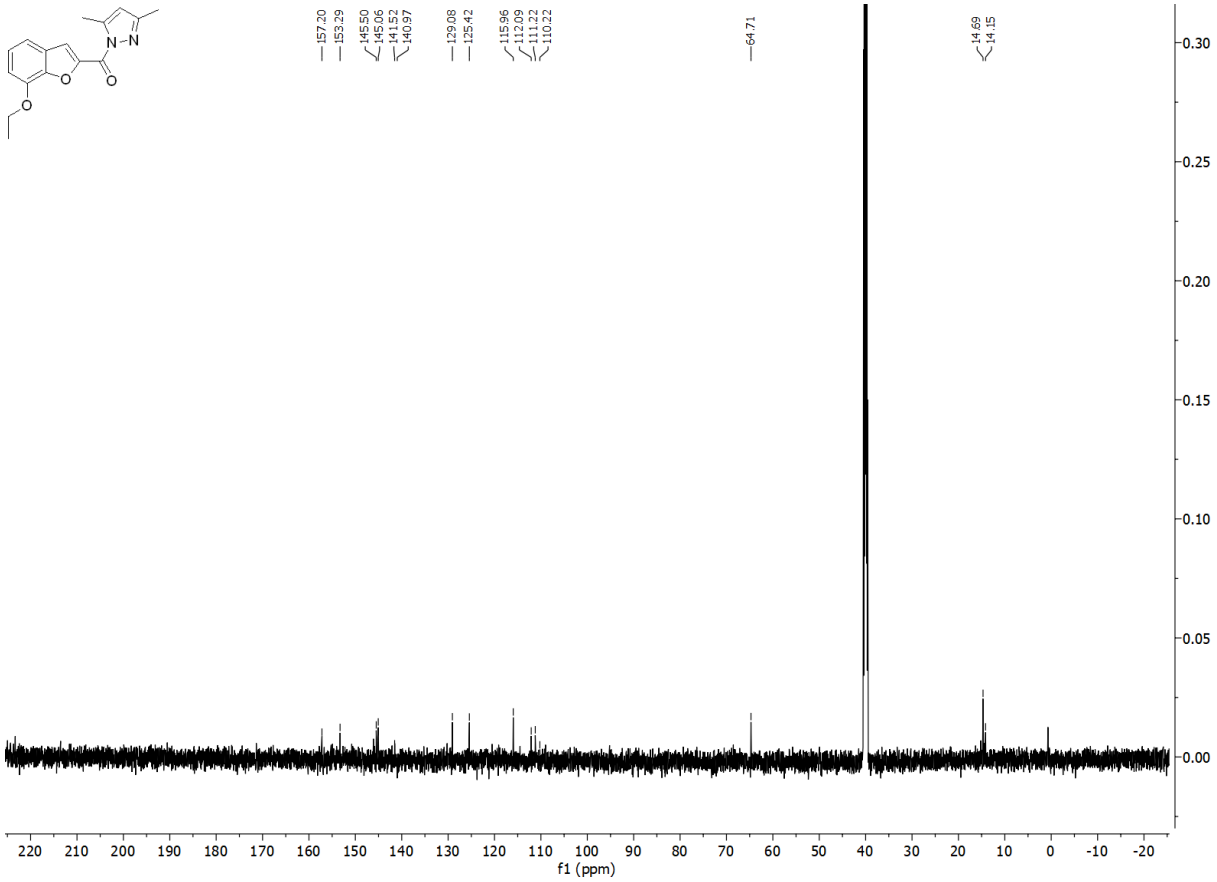

Figure S12. ^{13}C-NMR Spectra of compound **11f**.

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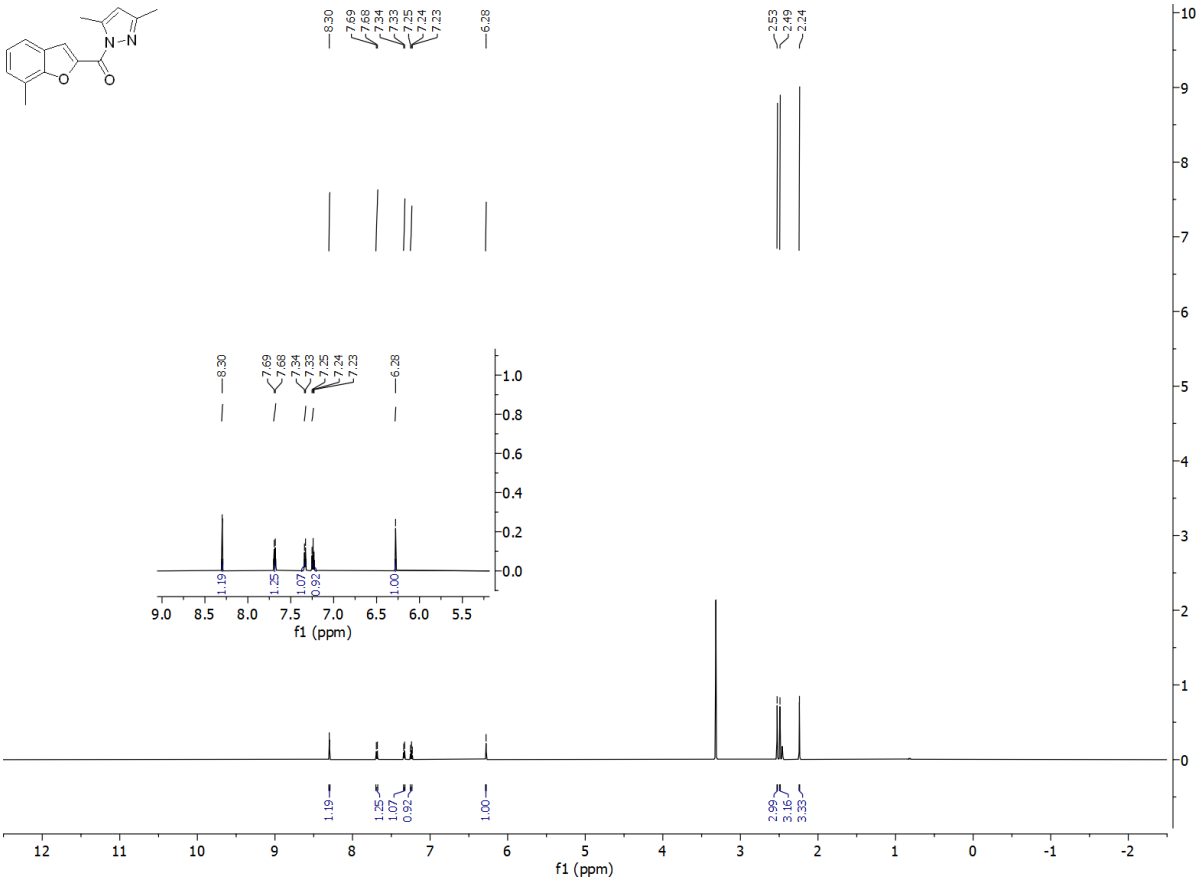

Figure S13. ^{1}H-NMR Spectra of compound **11g**.

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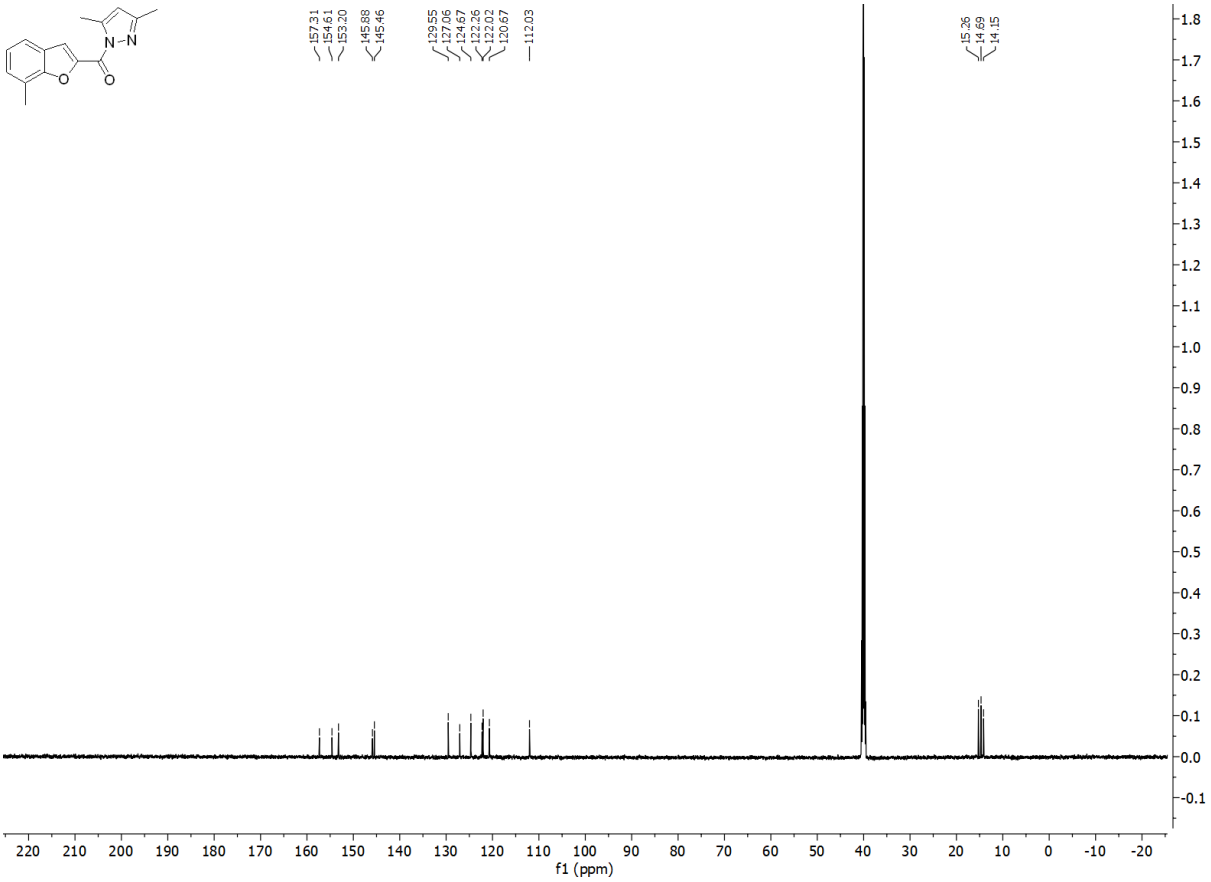

Figure S14. ^{13}C-NMR Spectra of compound **11g**.

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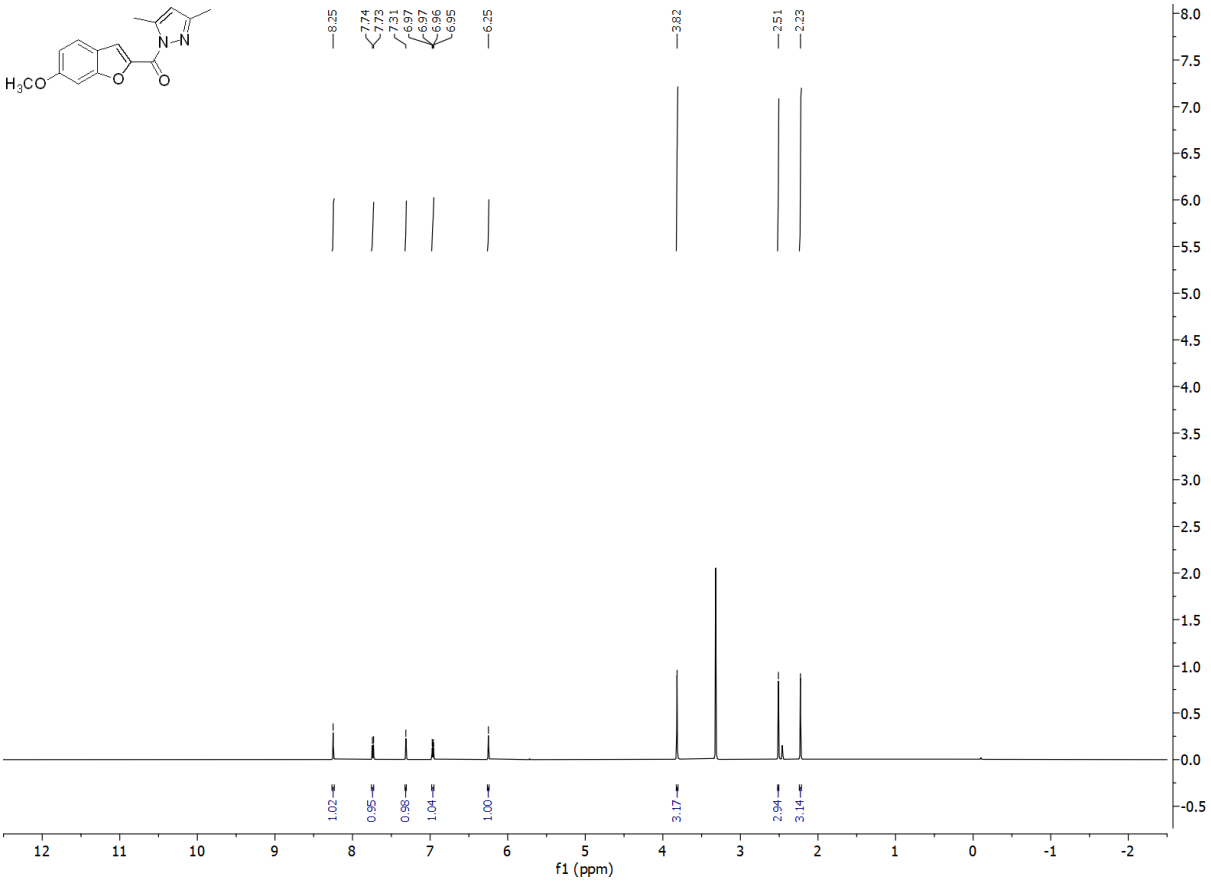

Figure S15. ^{1}H-NMR Spectra of compound **11h**.

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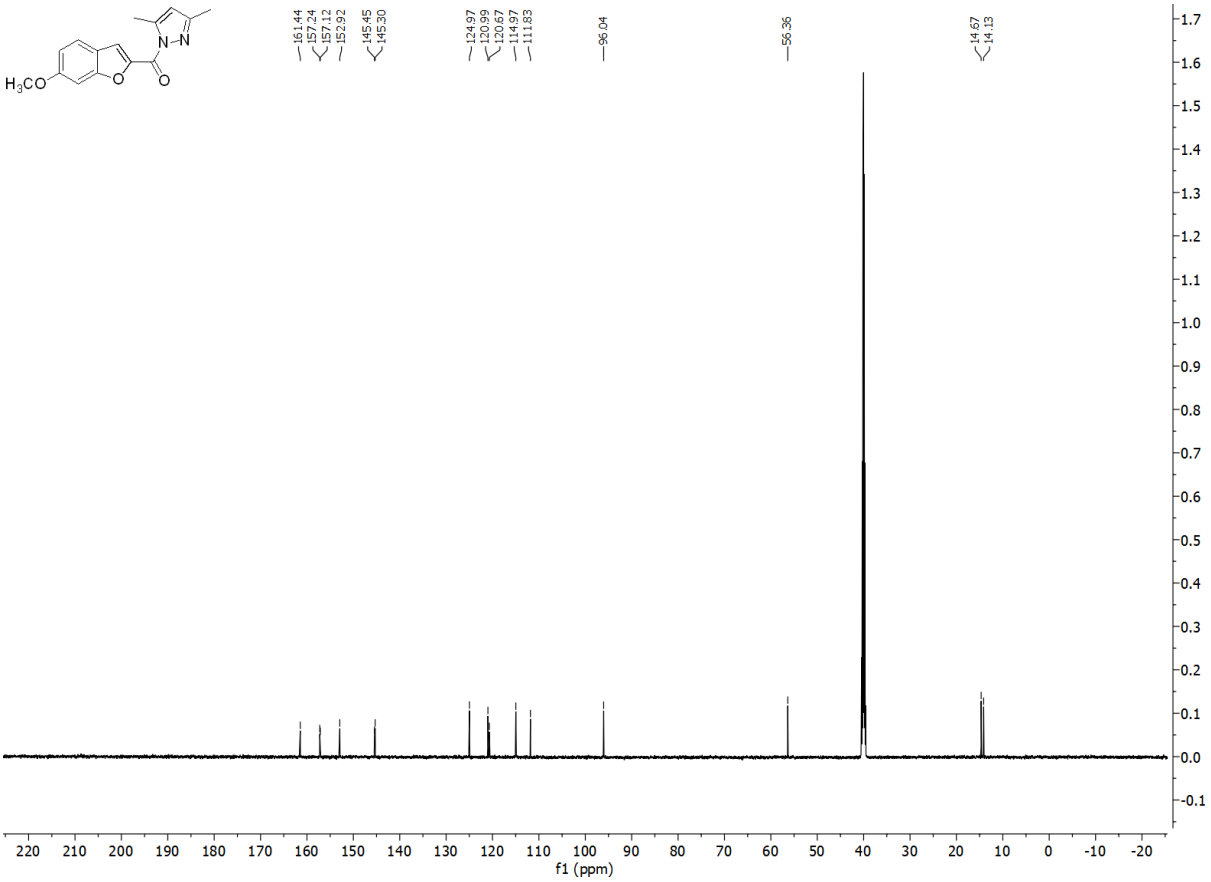

Figure S16. ^{13}C-NMR Spectra of compound **11h**.

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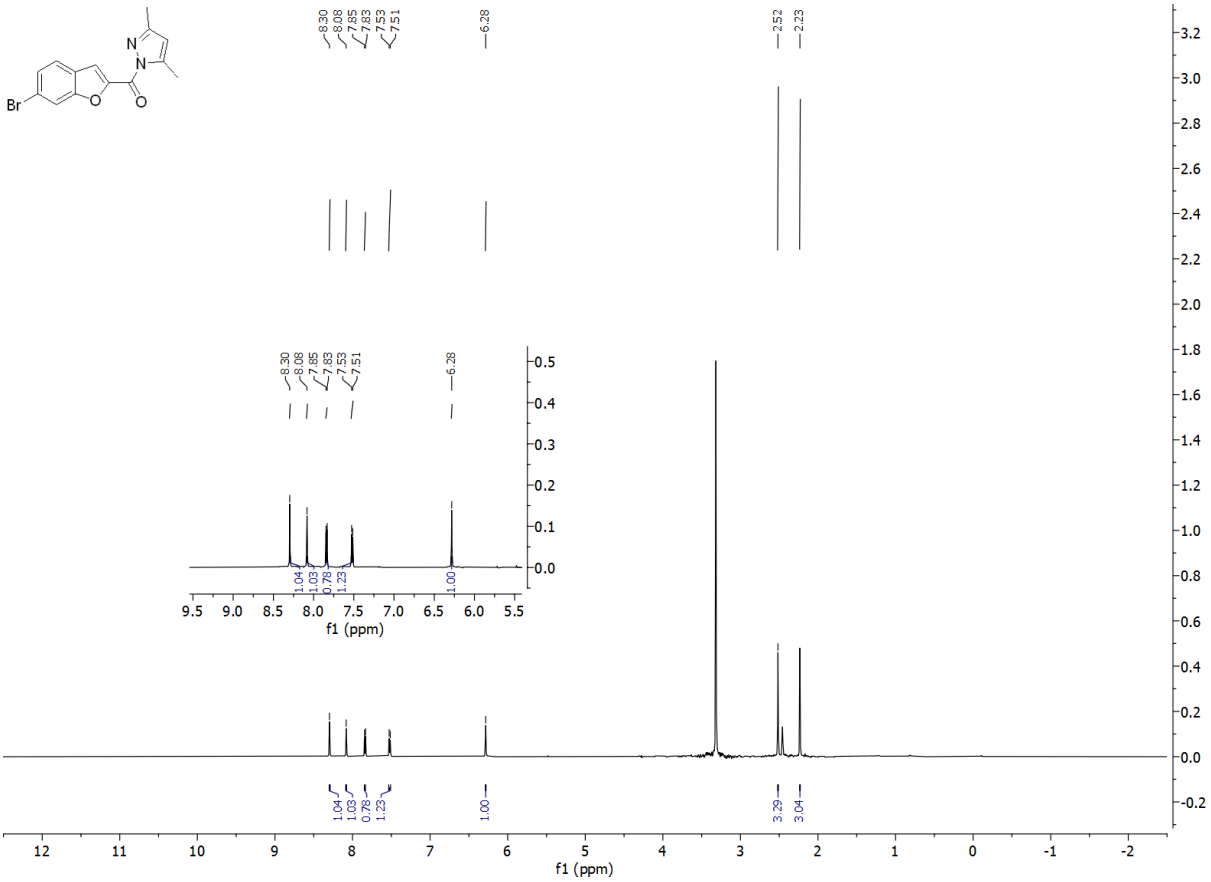

Figure S17. ^{1}H-NMR Spectra of compound **11i**.

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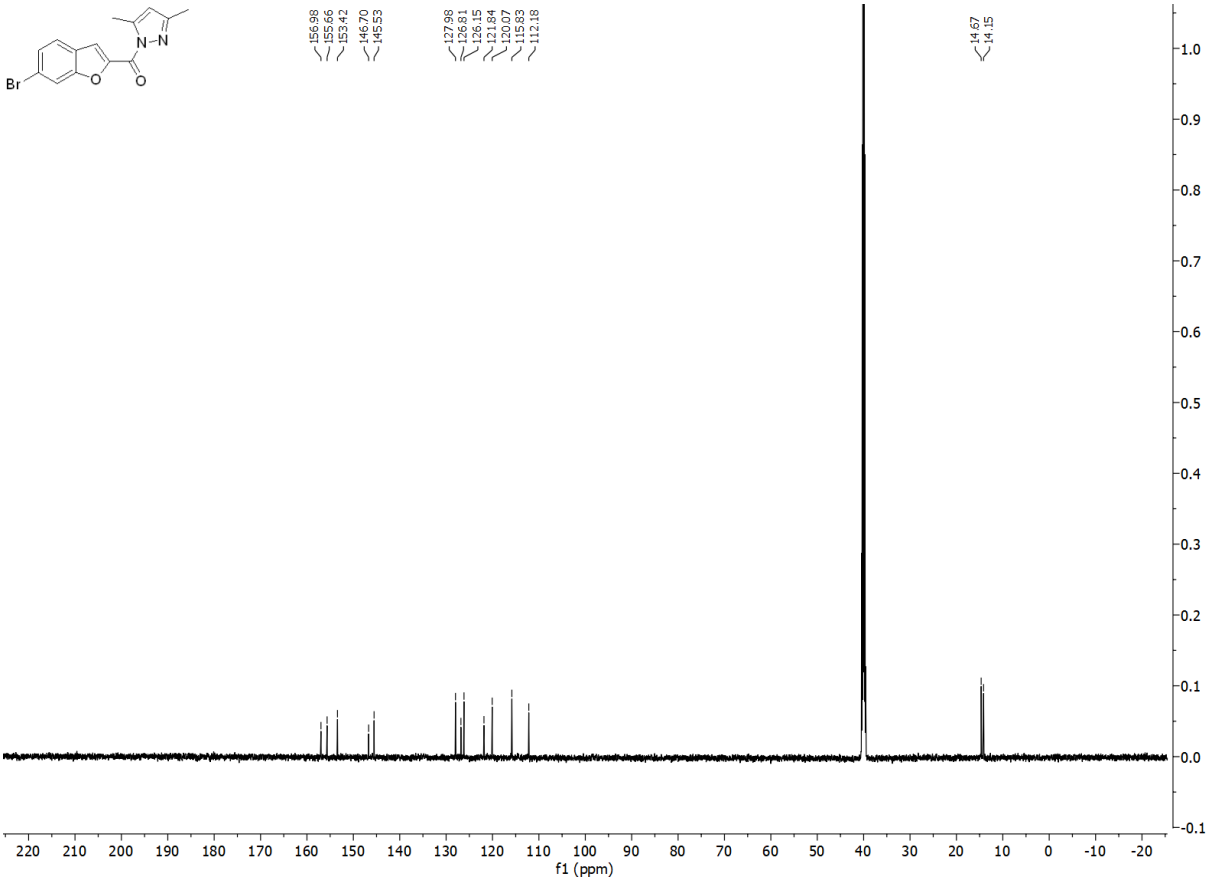

Figure S18. ^{13}C-NMR Spectra of compound **11i**.

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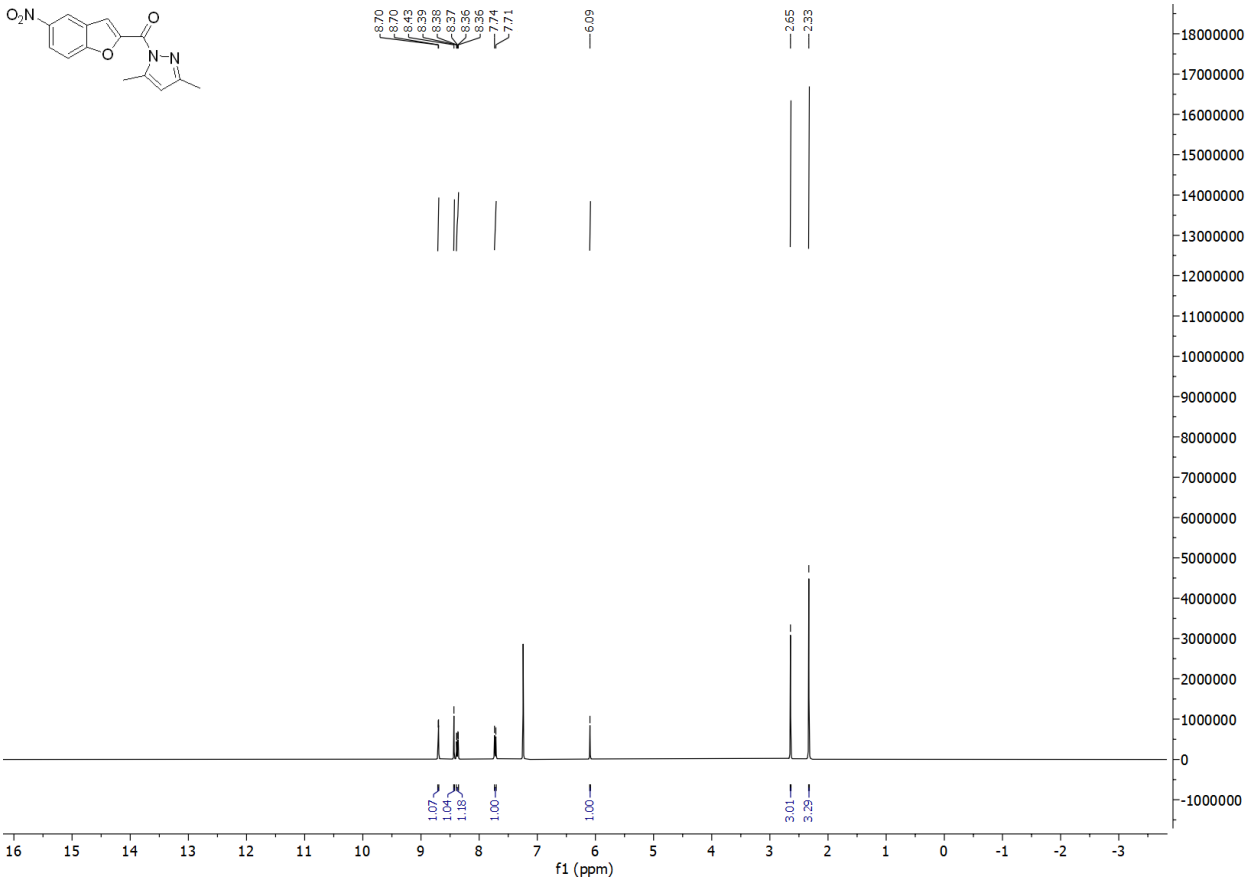

Figure S19. ^{1}H-NMR Spectra of compound **11j**.

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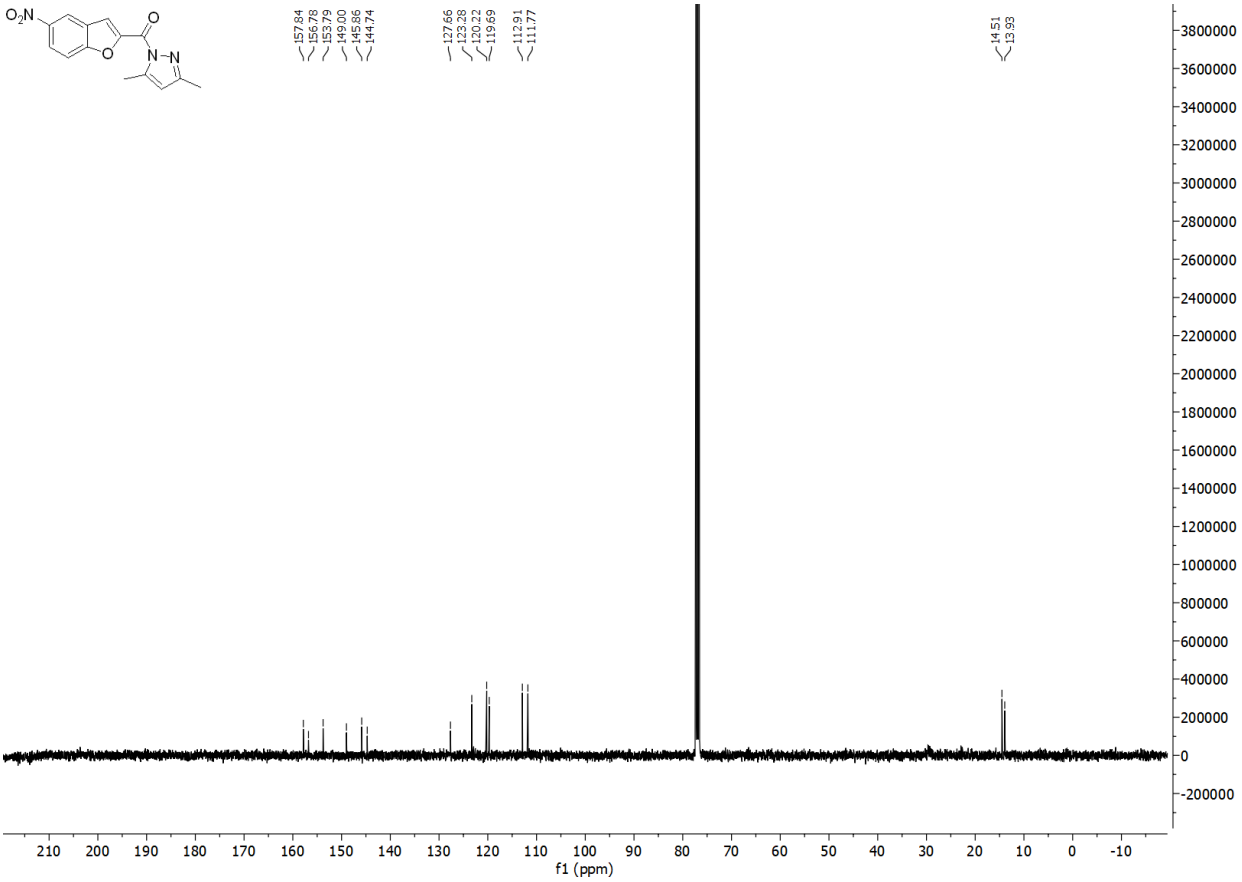

Figure S20. ^{13}C-NMR Spectra of compound **11j**.

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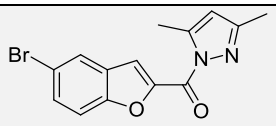
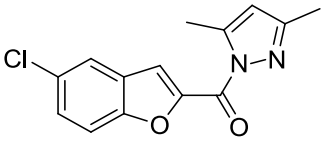
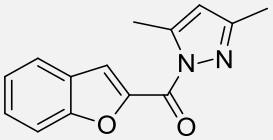
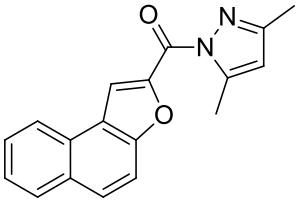
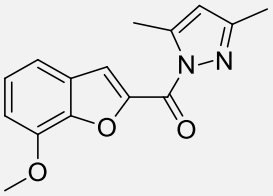
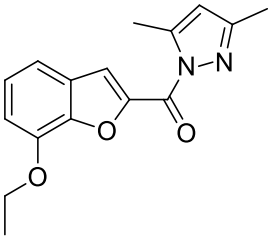
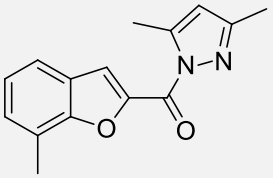
2) Docking interaction analysis data

Table S1. Interaction analysis of synthesized benzofuran-pyrazole derivatives **11(a-i)** within the active site of NS5A

Compound	Structure	Docking score	Interaction types	Interacting Residues
11a		-8.8	Conventional H-bond, pi-pi T-shaped, alkyl, pi-alkyl	Tyr 161, Arg 160, His 159, Phe 149, Pro 145, Trp 111
11b		-9.1	Pi-cation, pi-pi stacked, pi-alkyl, alkyl	Arg 160, Pro 100, Tyr 161, His 159
11		-8.4	Conventional H-bond, C-H bond, pi-alkyl, alkyl, pi-cation, pi-pi stacked, pi-pi T-shaped	Tyr 161, His 159, Arg 112, Phe 149, Trp 111
11d		-10.6	Conventional H-bond, amide-pi stacked, pi-alkyl, pi-pi T-shaped, alkyl	Val 144, Pro 141, His 159, Phe 149, Arg 112, Pro 145
11e		-8.9	Conventional H-bond, C-H bond, pi-alkyl, pi-cation, pi-pi T-shaped, alkyl	His 159, Arg 160, Tyr 161, Arg 112, Phe 149, Pro 145, Trp 111
11f		-8.8	Conventional H-bond, Carbon hydrogen bond, alkyl, pi-alkyl, pi-pi T-shaped	His 159, Pro 145, Trp 111, Phe 149, Tyr 161, Arg 160, Arg 112
11g		-8.9	Conventional H-bond, pi-alkyl, pi-cation, pi-sigma, pi-pi T-shaped	Tyr 161, Arg 112, His 159, Phe 149, Trp 111

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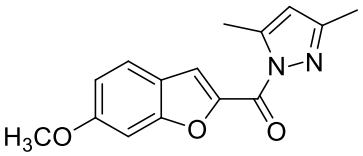
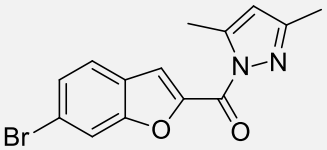
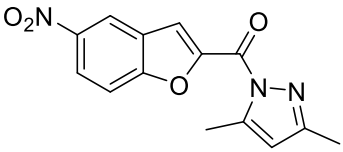
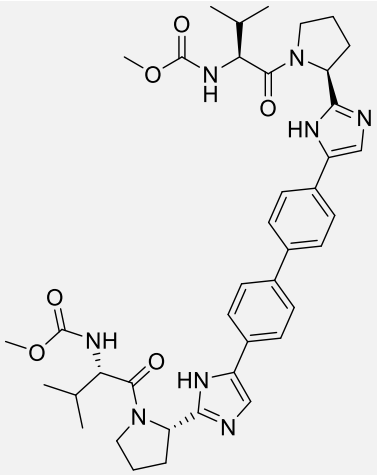
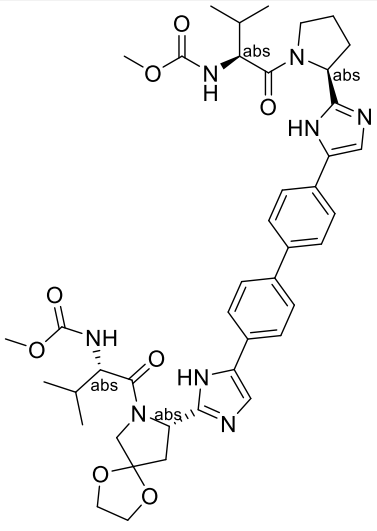
11h		-8.8	Conventional H-bond, pi-cation, pi-sigma, pi-pi T-shaped, pi-alkyl	His 159, Arg 160, Tyr 161, Phe 149, Trp 111, Arg 112
11i		-8.7	Conventional H-bond, Carbon hydrogen bond, alkyl, pi-alkyl, pi-pi T-shaped	Tyr 161, Arg 160, Arg 112, His 159, Phe 149, Trp 111, Pro 145
11j		-9.0	Conventional hydrogen bonding, carbon hydrogen bonding, pi-pi T-shaped, alkyl, pi-alkyl	Tyr 161, His 159, Arg 160, Thr 99, Phe 149, Pro 145, Trp 111
Daclatasvir		-10.4	Conventional H-bond, Carbon hydrogen bond, pi-donor H-bond, alkyl, pi-alkyl, pi-pi T-shaped	Thr 99, His 159, Arg 160, Gln 143, Pro 147, His 128, Pro 145, Pro 141, Phe 149, Glu 148, Tyr 161
GSK-2336805		-9.6	Pi-donor H-bond, pi-alkyl, alkyl, pi-pi T-shaped	Lys 119, Ala 114, Ala 146, Phe 149, Pro 145, Pro 141

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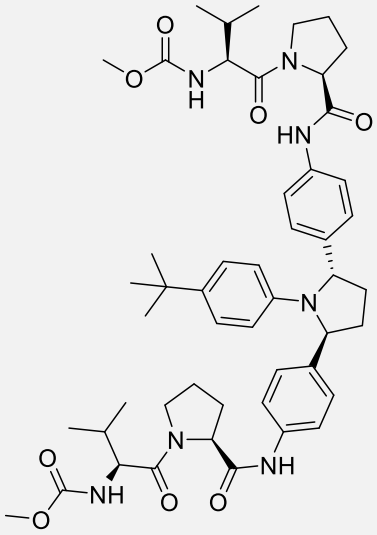
ABT-267		-8.2	Conventional H-bond, C-H bond, Pi-sigma, pi-alkyl, alkyl	Ala 164, Lys 166, Glu 116, Ala 115, Phe 149, Trp 111, Pro 141, Ala 114, Val 118, Glu 116

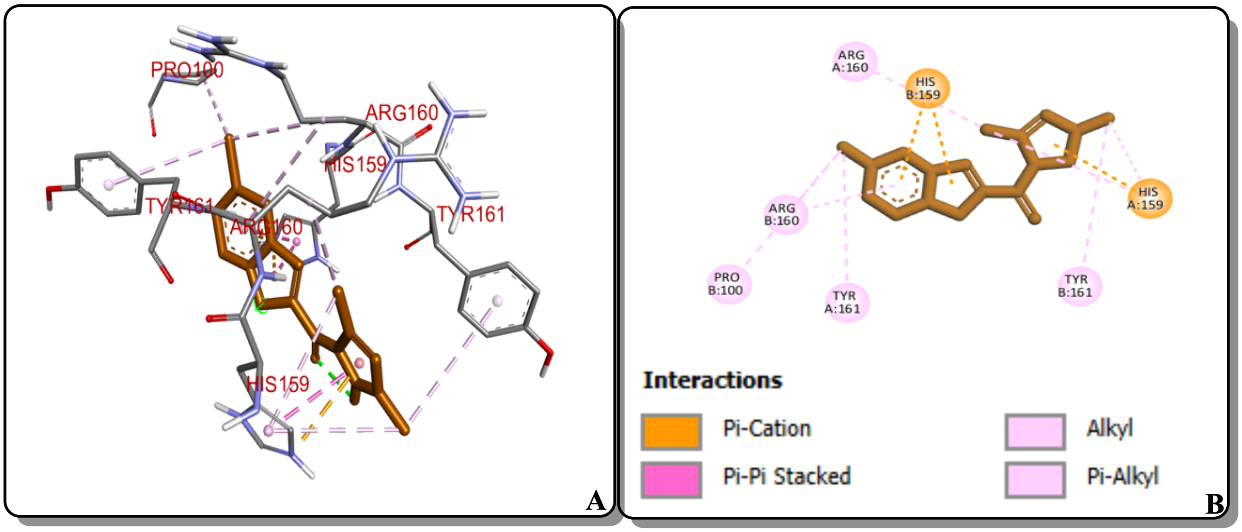


Figure S21. Binding interactions of **11b** with NS5A. A) Ligand surface interaction with protein B) 2D-Interactions.

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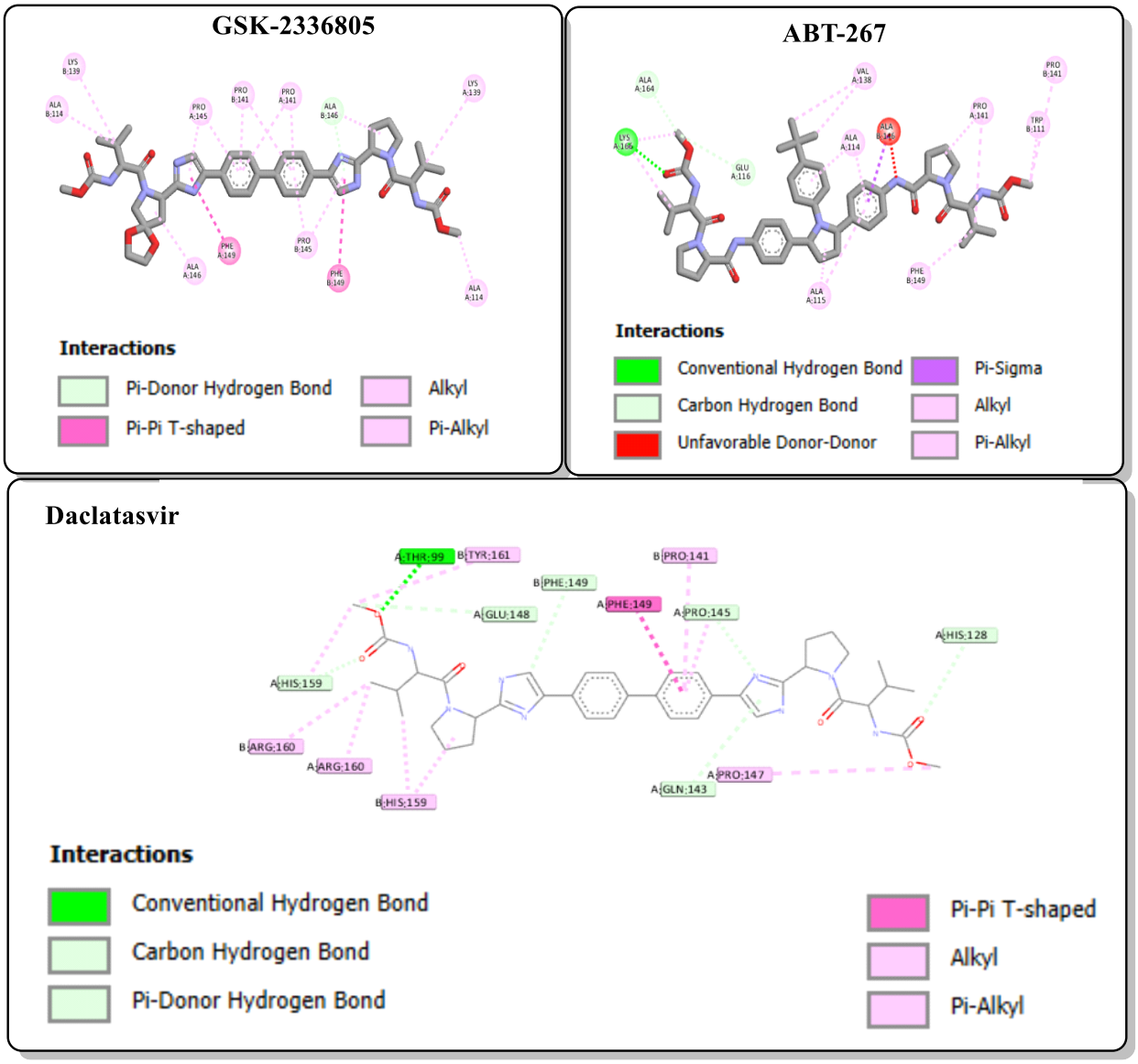

Figure S22. Binding interactions of standards i.e., GSK-2336805, ABT-267 and Daclatasvir with NS5A.

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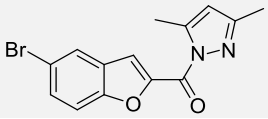
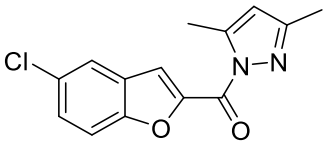
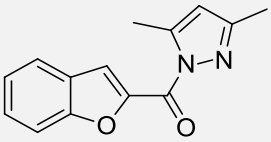
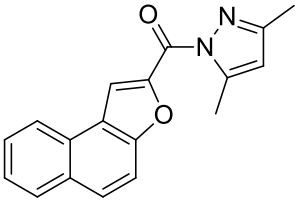
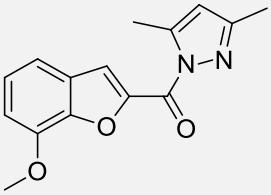
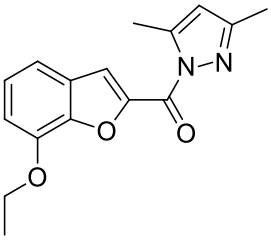
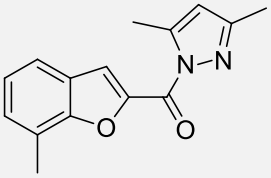
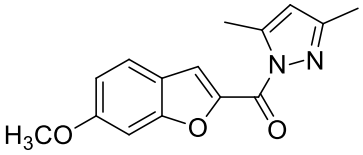
Table S2. Interaction analysis of synthesized benzofuran-pyrazole derivatives **11(a-i)** within the active site of NS5B

Compound	Structure	Docking score	Interaction types	Interacting Residues
11a		-6.3	Pi-anion, pi-sigma, alkyl, pi-alkyl	Leu 127, Glu 111, Glu 258, Ile 262, Tyr 276
11b		-6.9	Pi-cation, pi-anion, pi-sigma, pi-alkyl, alkyl	Leu 60, Lys 79, Asp 244, Val 235, Arg 234, Pro 247
11c		-6.8	Pi-cation, pi-anion, pi-alkyl	Leu 127, Glu 248, Arg 234, Glu 258
11d		-7.6	Attractive charge, conventional H-bond, unfavorable positive-positive, pi-cation, pi-donor hydrogen bond, pi-pi stacked, pi-pi T-shaped, pi-alkyl	Trp 550, Ser 548, Asp 546, His 562, Leu 83, Tyr 176, Leu 91
11e		-6.7	Conventional H-bond, C-H bond, pi-alkyl, pi-pi stacked	Leu 91, Leu 83, Lys 81, Asp 177, Tyr 176, His 562, Trp 550
11f		-6.6	Conventional H-bond, carbon hydrogen bond, pi-alkyl, pi-pi T-shaped, pi-pi stacked	Trp 550, His 562, Leu 83, Asp 177, Leu 91, Lys 81, Tyr 176
11g		-6.8	Pi-pi stacked, pi-pi T-shaped, amide-pi stacked, alkyl, pi-alkyl	Leu 91, Leu 83, Lys 90, Trp 550, Tyr 176, His 562
11h		-6.5	Pi-anion, pi-sigma, pi-pi stacked, alkyl, pi-alkyl	Asp 546, Lys 90, His 562, Leu 91, Leu 83

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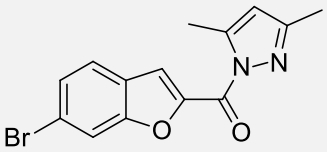
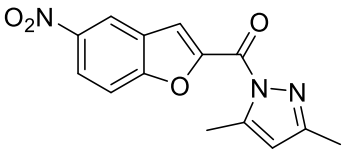
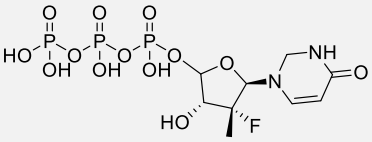
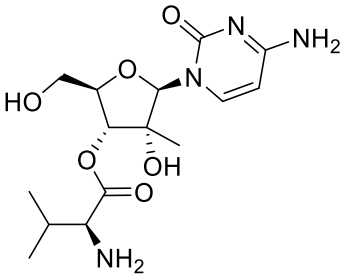
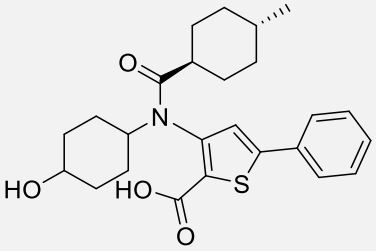
11i		-6.5	Carbon hydrogen bond, pi-cation, pi-anion, pi-sigma, pi-pi stacked, alkyl, pi-alkyl, amide-pi stacked	Leu 91, Leu 83, Lys 90, Ser 563, His 562, Asp 546
11j		-7.0	Conventional H-bond, attractive charge, pi-anion, pi-cation, pi-sigma, pi-alkyl	Arg 254, Arg 250, Asp 244, Lys 79, Val 235, Pro 247, Arg 234
Sofosbuvir triphosphate		-7.1	Conventional H-bond, attractive charge, pi-cation, pi-anion	Arg 234, Tyr 276, Glu 258, Arg 254, Glu 248
Valopicitabine		-6.7	Pi-donor H-bond, pi-anion, alkyl	Asp 546, His 562, Leu 91
VCH-759		-7.4	Conventional H-bond, alkyl, pi-anion	Pro 111, Glu 248, Glu 111, Leu 127, Gln 251, Arg 254, Thr 110

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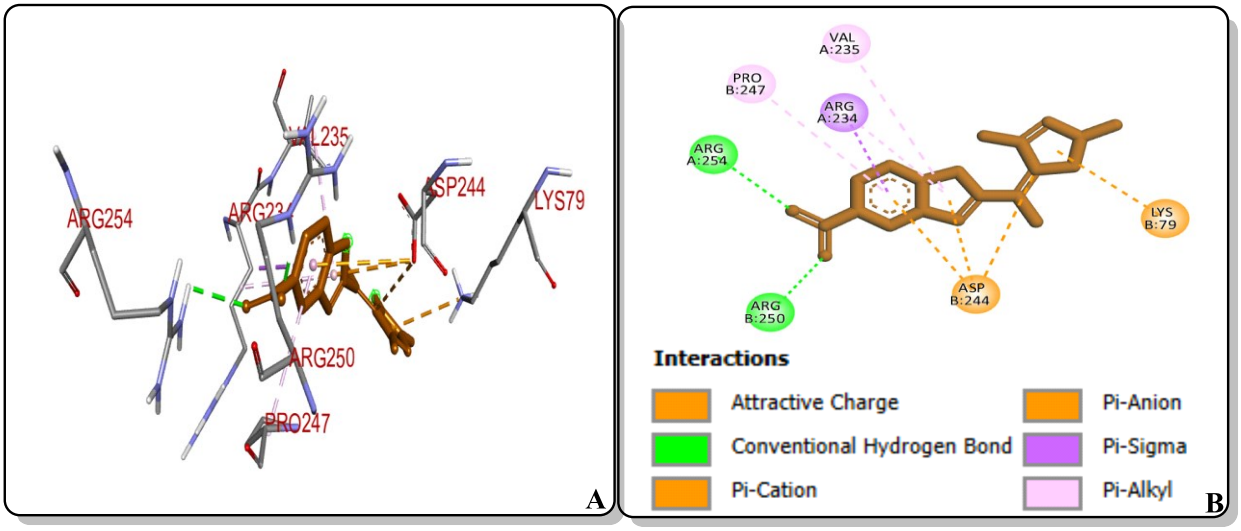

Figure S23. Binding interactions of derivative **11j** with NS5B. A) Ligand surface interaction with protein B) 2D-Interactions.

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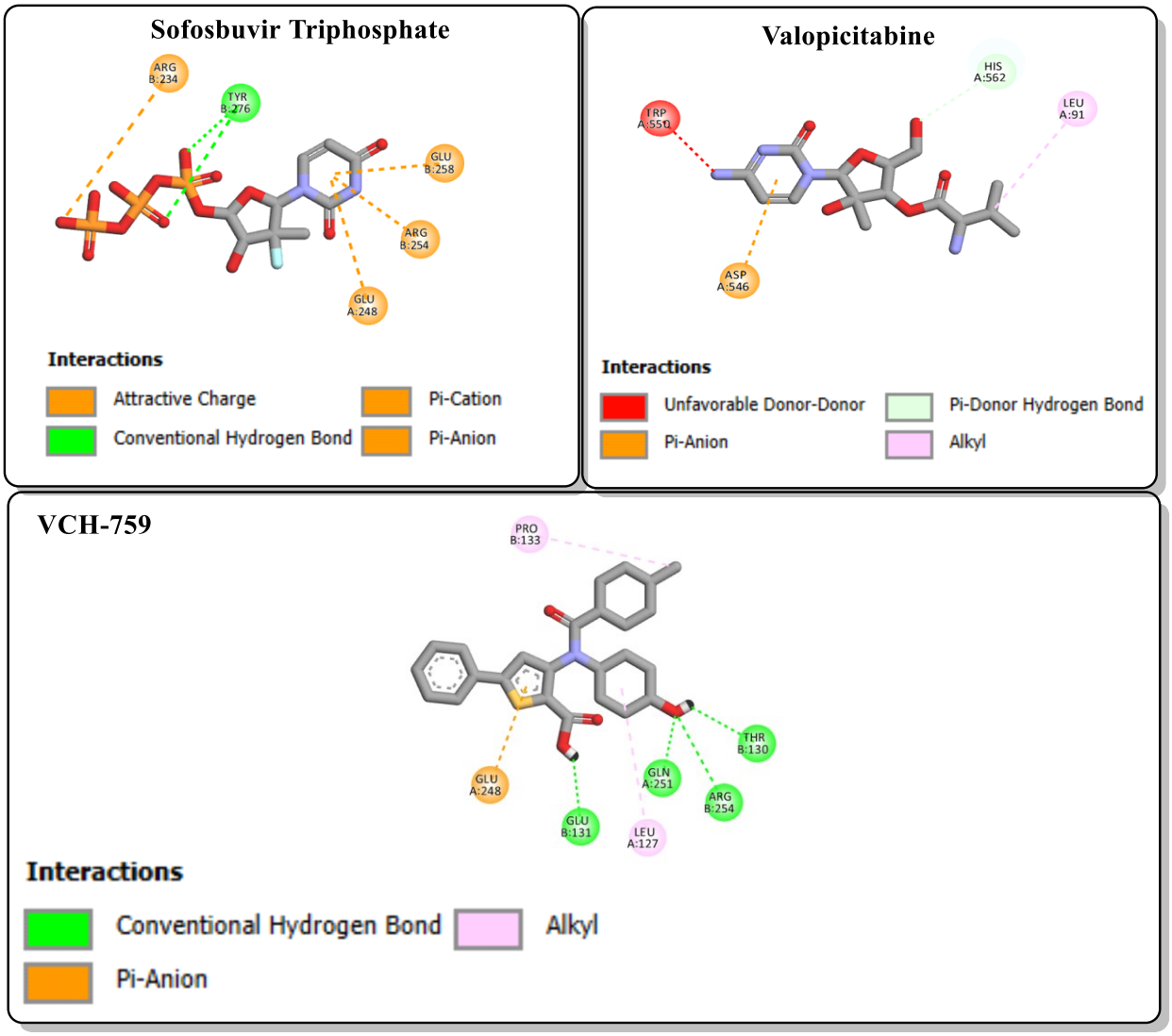

Figure S24. Binding interactions of standards i.e., Sofosbuvir triphosphate, Valopicitabine and VCH-759 with NS5B.

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3) ADMET analysis data

Table S3. ADMET properties of potent synthesized hybrids and standard inhibitors

ADMET Properties	Daclatasvir	VCH-759	11b	11d	11j
Physiochemical and Medicinal Properties					
Molecular Weight	738.39	441.2	274.05	290.11	285.07
nHA	14.0	5.0	4.0	4.0	7.0
nHD	4.0	2.0	0.0	0.0	0.0
LogP	4.417	4.115	3.309	3.718	2.302
nRot	17.0	6.0	2.0	2.0	3.0
TPSA	174.64	77.84	48.03	48.03	91.17
Synthetic Accessibility score	4.22	2.615	2.3	2.0	2.0
Lipinski's Rule	Rejected	Accepted	Accepted	Accepted	Accepted
Distribution and Absorption Properties					
Caco-2 Permeability	-5.405	-5.549	-4.999	-4.803	-5.022
VDss	0.168	-0.048	0.051	0.107	0.084
HIA	0.1	0.003	0.1	0.0	0.0
Pgp-inhibitor	0.999	0.011	0.91	0.75	0.618
Metabolic Properties					
CYP2B6 inhibitor	0.999	0.001	0.1	0.001	0.0
CYP2C19 inhibitor	0.887	0.000	0.537	0.891	0.111
CYP1A2 Inhibitor	0.001	0.000	0.996	0.999	0.966
CYP2D6 Inhibitor	0.1	0.000	0.0	0.0	0.0
CYP3A4 Inhibitor	0.022	0.000	0.153	0.277	0.046
CYP2C9 Inhibitor	0.001	0.016	0.182	0.405	0.048
Excretion and Toxicity Features					
CL_{plasma}	7.631	5.237	5.946	5.971	5.805
AMES Toxicity	0.71	0.374	0.451	0.684	0.913

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Eye corrosion	0.0	0.001	0.234	0.129	0.403
Respiratory Toxicity	0.581	0.415	0.515	0.63	0.773
Rat Oral Acute Toxicity	0.966	0.061	0.497	0.495	0.57
Human Hepatotoxicity	0.61	0.79	0.62	0.65	0.676

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