Supplementary Material

Synthesis, In Silico, In Vivo, and Ex Vivo Evaluation of a Boron-Containing Quinolinate Derivative with Presumptive Action on mGluR

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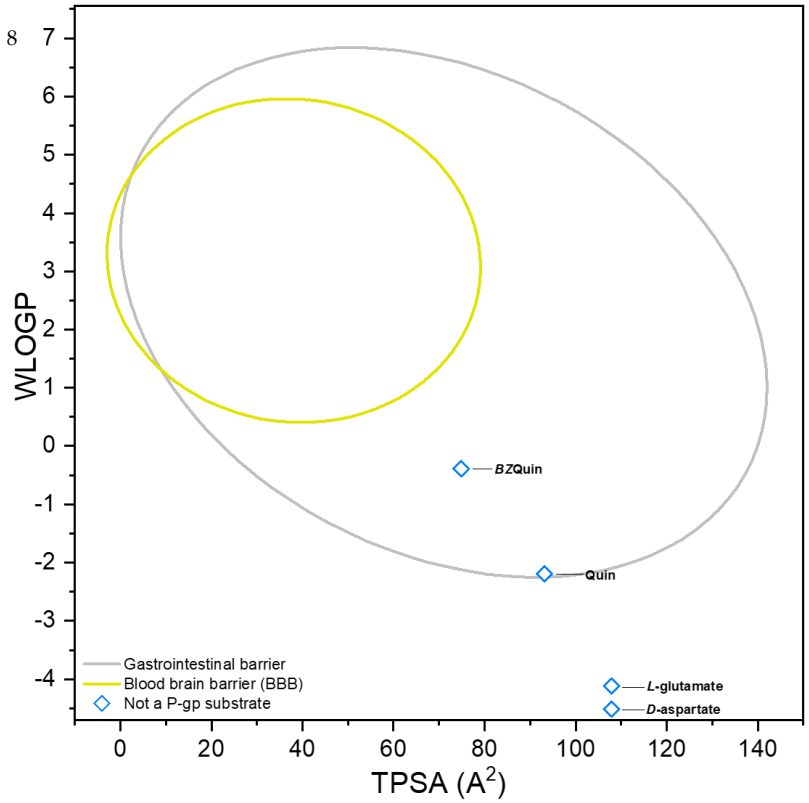

Figure S1. BOILED-Egg graph for BZQuin, Quin, L-glutamate, and D-aspartate. The chemical structures were evaluated while considering the protonation/deprotonation of their groups at physiological pH (7.4).

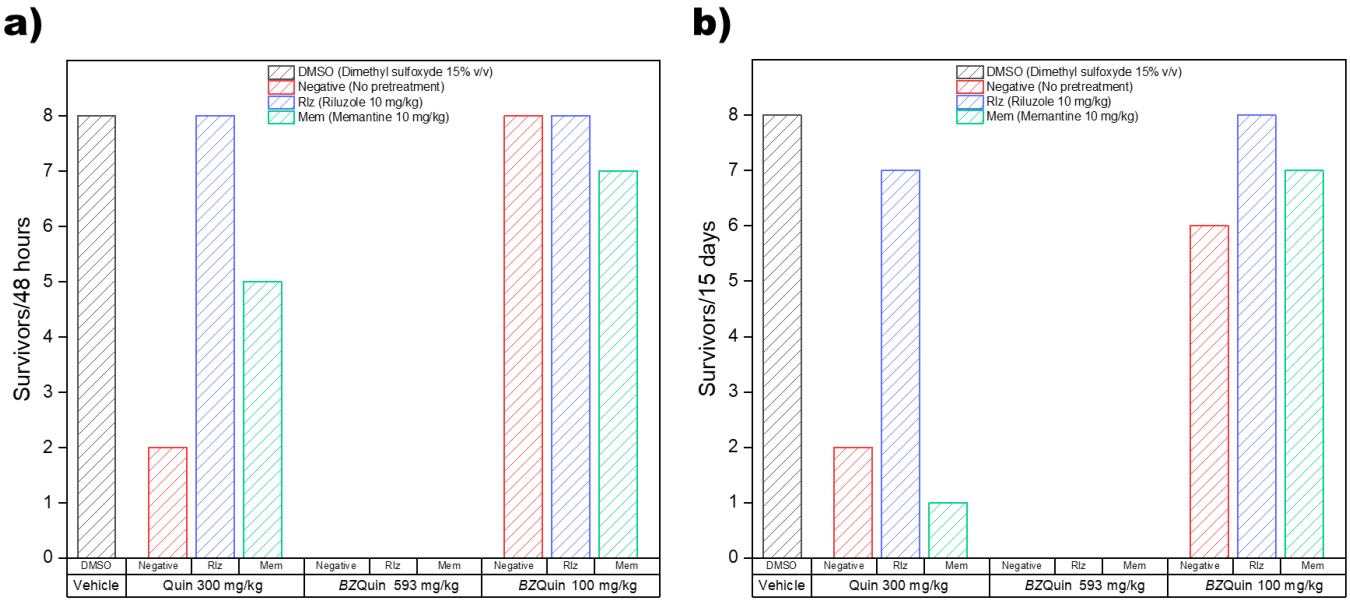

Figure S2. Mice survival at a) 48 hours and b) 15 days after the OFT.

Table S1. Predicted cytochrome inhibition and Lipinski's Rule of Five for *BZQuin*, Quin, *L*-glutamate, and *D*-aspartate. The chemical structures were evaluated while considering the protonation/deprotonation of their groups at physiological pH (7.4).

Metabolism				
Molecule	**CYP1A2 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**
BZQuin	No	No	No	No
Quin	No	No	No	No
L-glutamate	No	No	No	No
D-aspartate	No	No	No	No
Lipinski's Rule of Five				
Molecule	**MW ≤ 500 g/mol**	**MLOGP ≤ 4.15**	**H-bond acceptors ≤ 10**	**H-bond donors ≤ 5**
BZQuin	330.12	2.46	4	0
Quin	165.1	-1.47	5	0
L-glutamate	146.12	-4.64	4	1
D-aspartate	132.09	-5.05	4	1

Table S2. Gibbs energies and binding probabilities of *BZQuin*, Quin, *L*-glutamate, and *D*-aspartate on two isoforms of the NMDA receptor (synaptic and extrasynaptic), two group I mGluRs (mGluR1 & mGluR5), two group II mGluRs (mGluR2 & mGluR3), and two group III (mGluR7 & mGluR8). The chemical structures were evaluated while considering the protonation/deprotonation of their groups at physiological pH (7.4).

Molecule	**NMDA receptor**							
	Synaptic (GluN1/GluN2A)				**Extrasynaptic (GluN1/GluN2B)**			
	***L*-glutamate site (PDB: 5H8N)**		**2A-selective NAMs/PAMs site (PDB: 5H8N)**		***L*-glutamate site (PDB: 4PE5)**		**Ifenprodil site (PDB: 4PE5)**	
	ΔG (kcal/mol)	**Probability**	**ΔG (kcal/mol)**	**Probability**	**ΔG (kcal/mol)**	**Probability**	**ΔG (kcal/mol)**	**Probability**
BZQuin	0	0	0	0	0	0	0	0
Quin	-6.786	0.082	0	0	-6.300	0.003	-6.600	0.001
L-glutamate	-6.506	0.081	0	0	-5.700	0.003	-6.018	0.134
D-aspartate	-5.633	0.006	0	0	-5.980	0.148	-5.482	0.039
Molecule	**mGluRs Group I**							
	mGluR1				**mGluR5**			
	***L*-glutamate site (PDB: 3KS9)**		**NAMs site (PDB: 4OR2)**		***L*-glutamate site (PDB: 3LMK)**		**NAMs site (PDB: 6FFH)**	
	ΔG (kcal/mol)	**Probability**	**ΔG (kcal/mol)**	**Probability**	**ΔG (kcal/mol)**	**Probability**	**ΔG (kcal/mol)**	**Probability**
BZQuin	-8.667	1.000	0	0	0	0	0	0
Quin	-6.000	1.000	-6.699	0.982	0	0	0	0
L-glutamate	-5.766	0.943	-6.041	0.935	-6.598	0.084	-6.025	0.520
D-aspartate	-4.900	0.866	-5.378	0.952	-5.700	0.120	-5.839	0.753
Molecule	**mGluRs Group II**				**mGluRs Group III**			
	mGluR2		**mGluR3**		**mGluR7**		**mGluR8**	
	***L*-glutamate site (PDB: 5CNJ)**		***L*-glutamate site (PDB: 5CNK)**		***L*-glutamate site (PDB: 3MQ4)**		***L*-glutamate site (PDB: 6BT5)**	
	ΔG (kcal/mol)	**Probability**	**ΔG (kcal/mol)**	**Probability**	**ΔG (kcal/mol)**	**Probability**	**ΔG (kcal/mol)**	**Probability**
BZQuin	-10.490	0.380	0	0	-8.264	1.000	0	0
Quin	-6.800	1.000	-7.594	0.895	0	0	0	0
L-glutamate	-6.690	0.999	-7.149	0.597	-5.098	0.198	-6.018	0.787
D-aspartate	-6.096	1.000	-6.880	0.940	-4.596	0.233	-5.897	0.998

Table S3. Modified Lorke's method results for the LD_{50} estimation of *BZQuin*.

Modified Lorke's method					
Diphenylboroxazolidone derived from quinolinate (*BZQuin*) intraperitoneal 0.5 mL injection on male CD-1 mice.					
Phase I			**Phase II**		
Group	**Dose**	**Deaths**	**Group**	**Dose**	**Deaths**
1	10^{1} mg/kg	0/3	1	$10^{2.25}$ mg/kg	1/3
2	10^{2} mg/kg	0/3	2	$10^{2.50}$ mg/kg	3/3
3	10^{3} mg/kg	3/3	3	$10^{2.75}$ mg/kg	3/3

Table S4. Least square means and their SEMs per pre-treatment and stimulating agent for global comparisons of locomotor activity.

Least square means	
Pre-treatment	
Negative	1555.47 ± 104.72
Rlz 10 mg/kg	1509.86 ± 104.72
Mem 10 mg/kg	1571.20 ± 104.72
Stimulating agent	
Quin 300 mg/kg	470.50 ± 72.44
BZQuin 593 mg/kg	1408.79 ± 72.44
BZQuin 100 mg/kg	2137.41 ± 77.45

Table S5. Least square means and their SEMs per interaction for simple comparisons of locomotor activity.

Least square means			
Stimulating agent	**Pre-treatment**		
	Negative	Rlz 10 mg/kg	Mem 10 mg/kg
Quin 300 mg/kg	627.12 ± 125.48	308.87 ± 125.48	475.50 ± 125.48
BZQuin 593 mg/kg	1662.50 ± 125.48	1815 ± 125.48	748.87 ± 125.48
BZQuin 100 mg/kg	1742 ± 134.14	1923.87 ± 134.14	2746.37 ± 134.14

Table S6. Medians and the respective percentiles of the pre-treatments and stimulating agents for seizure intensity comparison.

Pre-treatment	**P_{50} (Median)**	**P_{25}**	**P_{75}**
Negative	3	2	6.75
Rlz 10 mg/kg	1	0	2
Mem 10 mg/kg	2	0	4
Stimulating agent	**P_{50} (Median)**	**P_{25}**	**P_{75}**
Quin 300 mg/kg	4.50	2.25	6.75
BZQuin 593 mg/kg	2	1	3
BZQuin 100 mg/kg	0	0	2

Table S7. Least square means and their SEMs per pretreatment and neurotoxic agent for global comparisons of neuron counts on the four neuroanatomical structures of interest.

Least square means				
Neuroanatomical structure	**Ventral *hippocampus* (CA1 region)**	**Basal ganglia (*striatum*)**	**Brain cortex (prefrontal cortex)**	**Cerebellum cortex (Purkinje cells)**
Pre-treatment				
Negative	93.50 ± 2.15	127.40 ± 2.46	109.30 ± 1.88	11.20 ± 0.54
Rlz 10 mg/kg	113.80 ± 2.15	176.10 ± 2.46	136.90 ± 1.88	14 ± 0.54
Mem 10 mg/kg	99.10 ± 2.15	141.40 ± 2.46	103.50 ± 1.88	14.60 ± 0.54
Stimulating agent				
Quin 300 mg/kg	95.86 ± 1.75	152.53 ± 2.01	125 ± 1.54	14.40 ± 0.44
BZQuin 100 mg/kg	108.40 ± 1.75	144.06 ± 2.01	108.13 ± 1.54	12.13 ± 0.44

Table S8. Least square means and their SEMs per interaction for simple comparisons of neuron counts on the four neuroanatomical structures of interest.

Least square means			
Ventral *hippocampus* (CA1 region)			
Stimulating agent	**Pre-treatment**		
	Negative	Rlz 10 mg/kg	Mem 10 mg/kg
Quin 300 mg/kg	77.40 ± 3.04	117.60 ± 3.04	92.60 ± 3.04
BZQuin 100 mg/kg	109.60 ± 3.04	110 ± 3.04	105.60 ± 3.04
Basal ganglia (*striatum*)			
Stimulating agent	**Pre-treatment**		
	Negative	Rlz 10 mg/kg	Negative
Quin 300 mg/kg	144.40 ± 3.48	165.40 ± 3.48	147.80 ± 3.48
BZQuin 100 mg/kg	110.40 ± 3.48	186.80 ± 3.48	135 ± 3.48
Brain cortex (prefrontal cortex)			
Stimulating agent	**Pre-treatment**		
	Negative	Rlz 10 mg/kg	Negative
Quin 300 mg/kg	102.60 ± 2.67	150.80 ± 2.67	121.60 ± 2.67
BZQuin 100 mg/kg	116 ± 2.67	123 ± 2.67	85.40 ± 2.67
Cerebellum cortex (Purkinje cells)			
Stimulating agent	**Pre-treatment**		
	Negative	Rlz 10 mg/kg	Negative
Quin 300 mg/kg	12.80 ± 0.76	13 ± 0.76	17.40 ± 0.76
BZQuin 100 mg/kg	9.60 ± 0.76	15 ± 0.76	11.80 ± 0.76

Spectra:

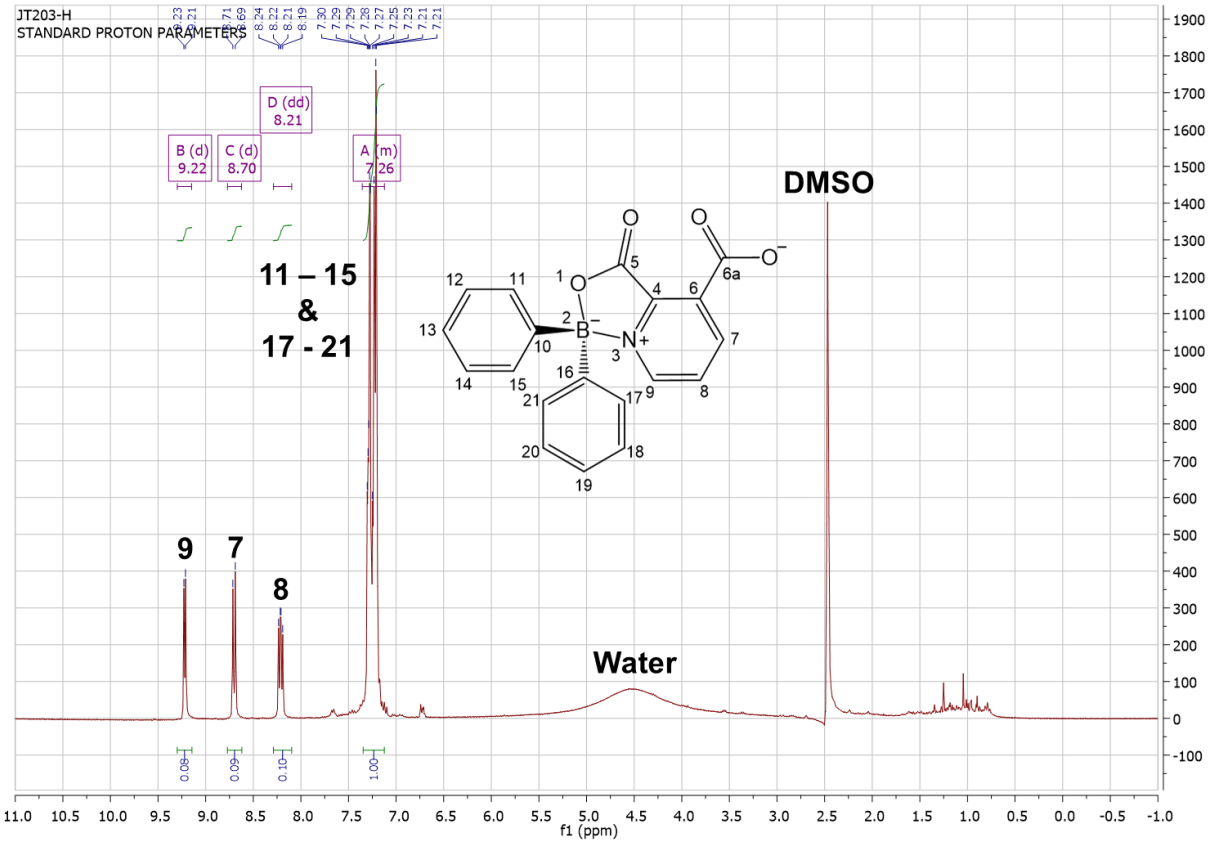

Figure S3. ^{1}H NMR spectrum of *BZQuin*.

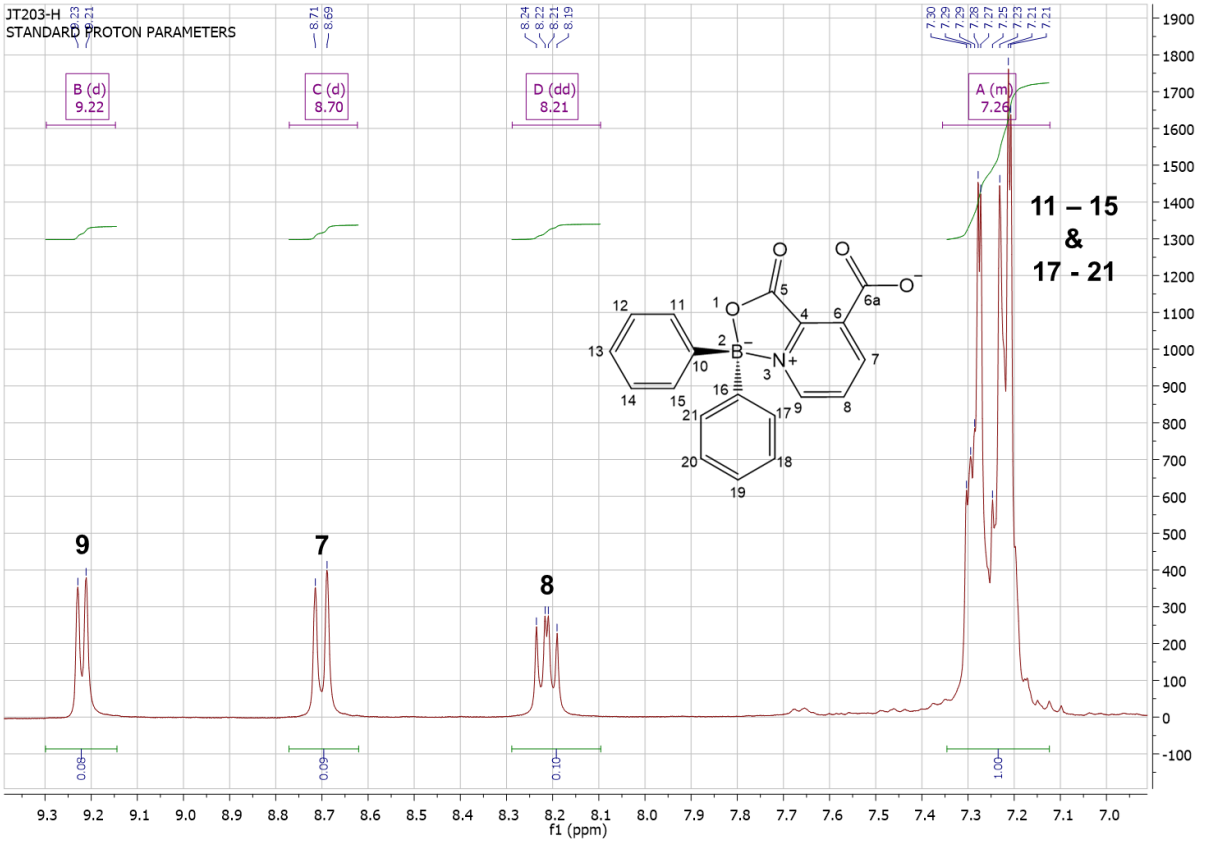

Figure S4. Magnification of the aromatic region of the ^{1}H NMR spectrum of *BZQuin*.

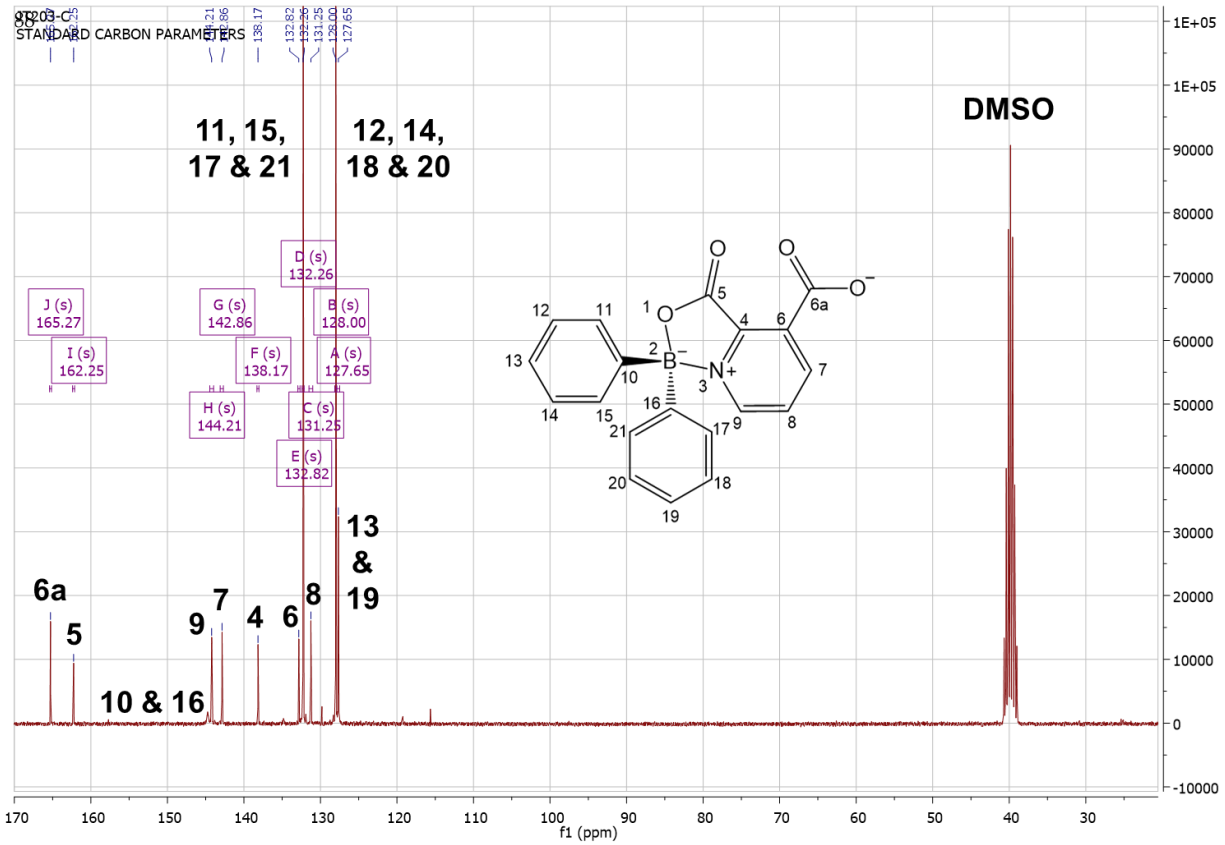

Figure S5. ^{13}C NMR spectrum of *BZQuin*.

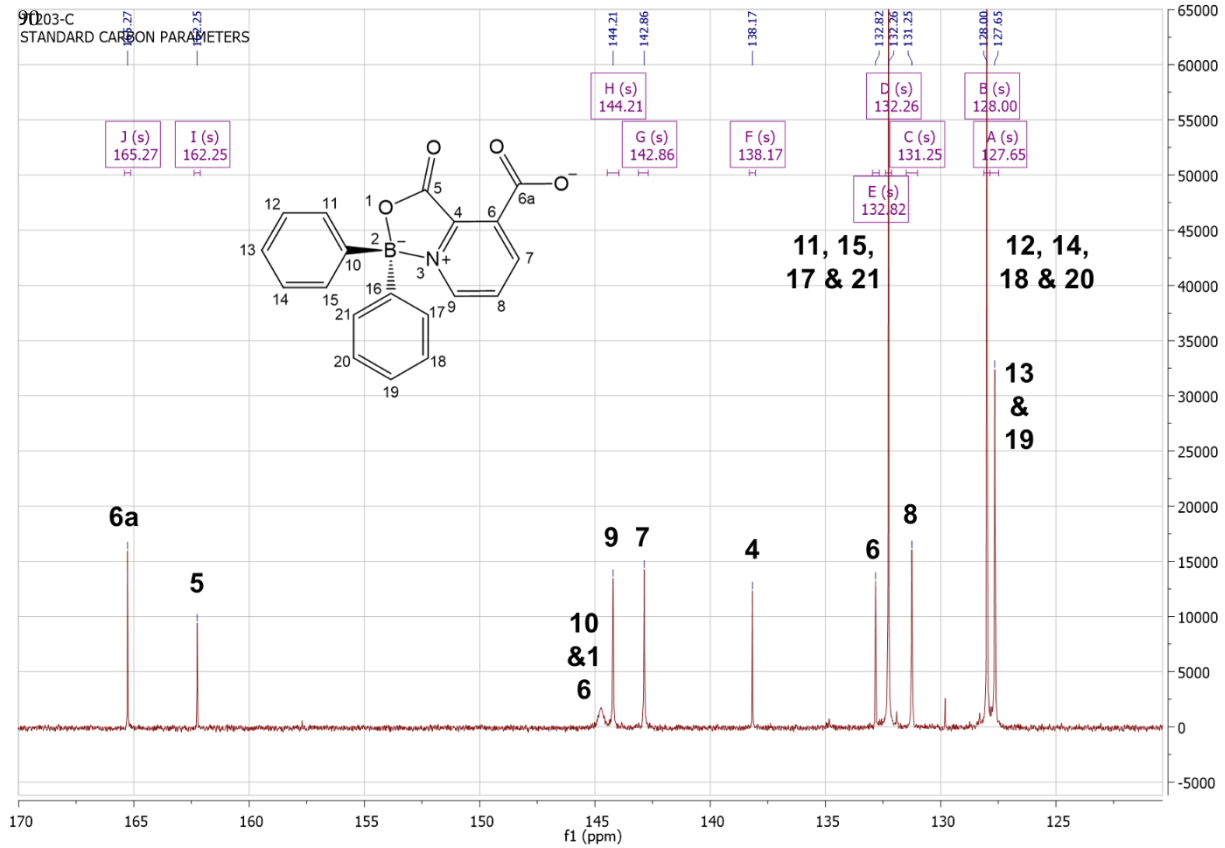

Figure S6. Magnification of the aromatic region of the ^{13}C NMR spectrum of *BZQuin*.

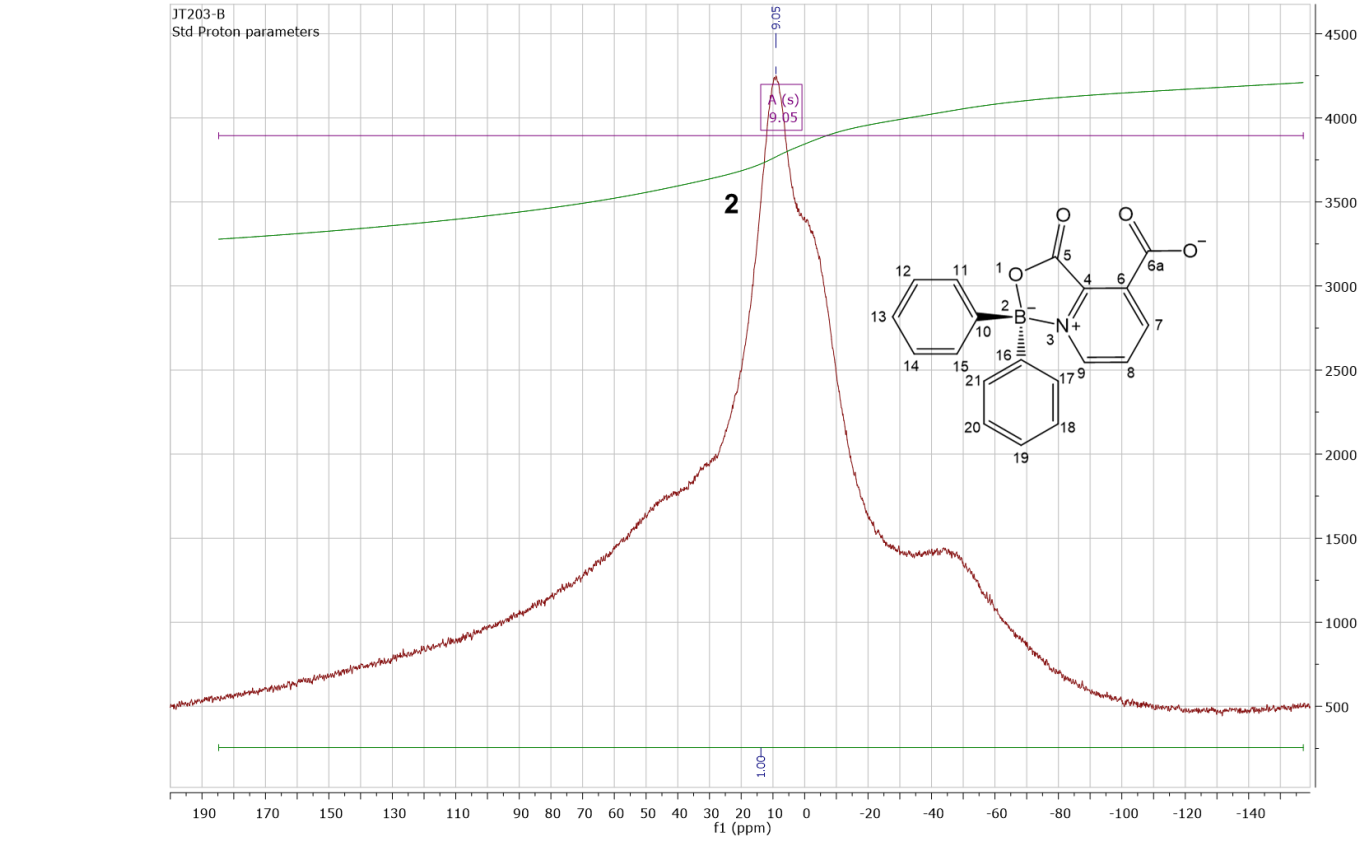

Figure S7. ^{11}B NMR spectrum of *BZQuin*.

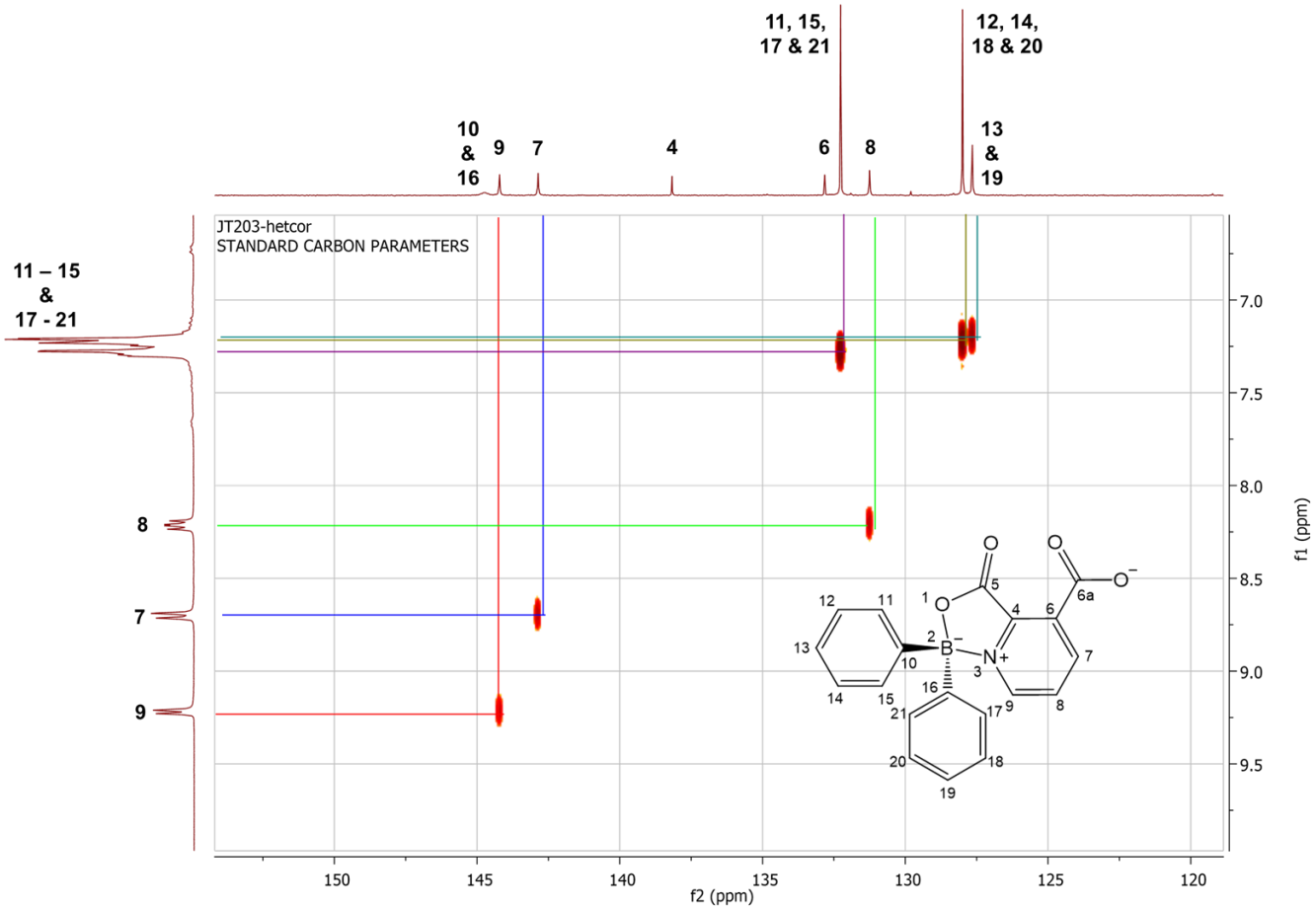

Figure S8. HETCOR 2D NMR experiment for *BZQuin*.

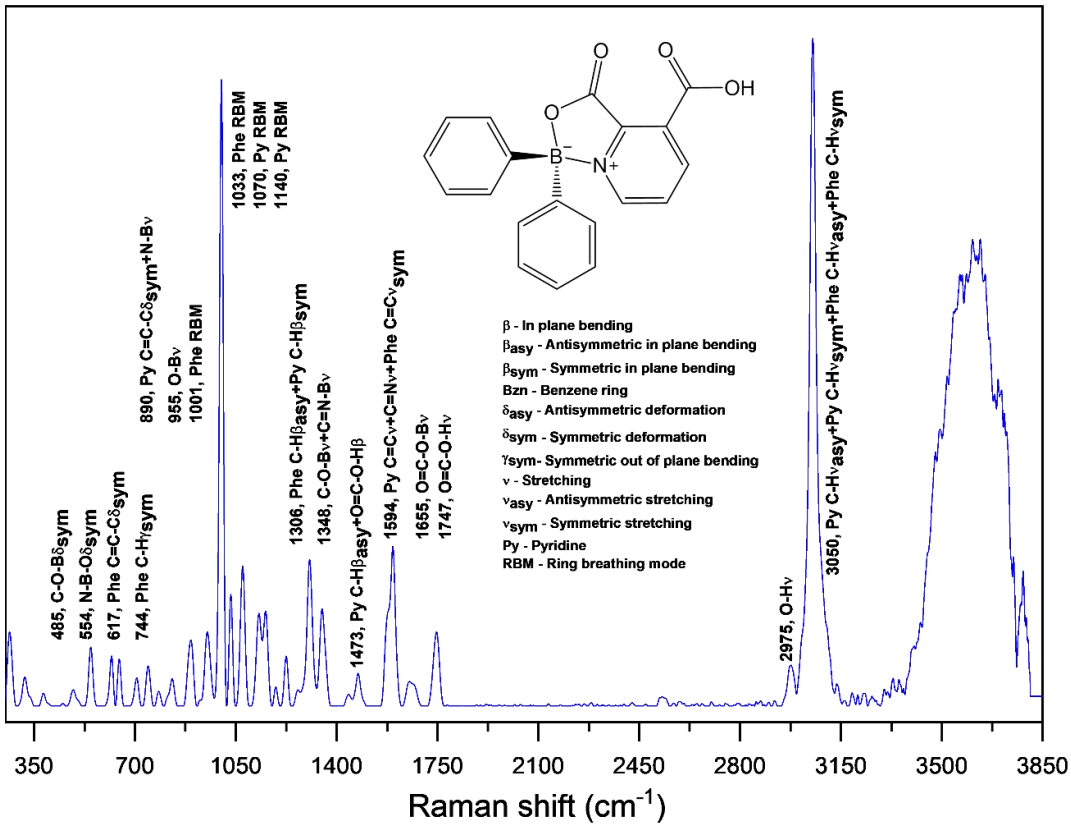

Figure S9. Raman spectrum of *BZQuin* (λ_{laser} = 785 nm at 100 mW).

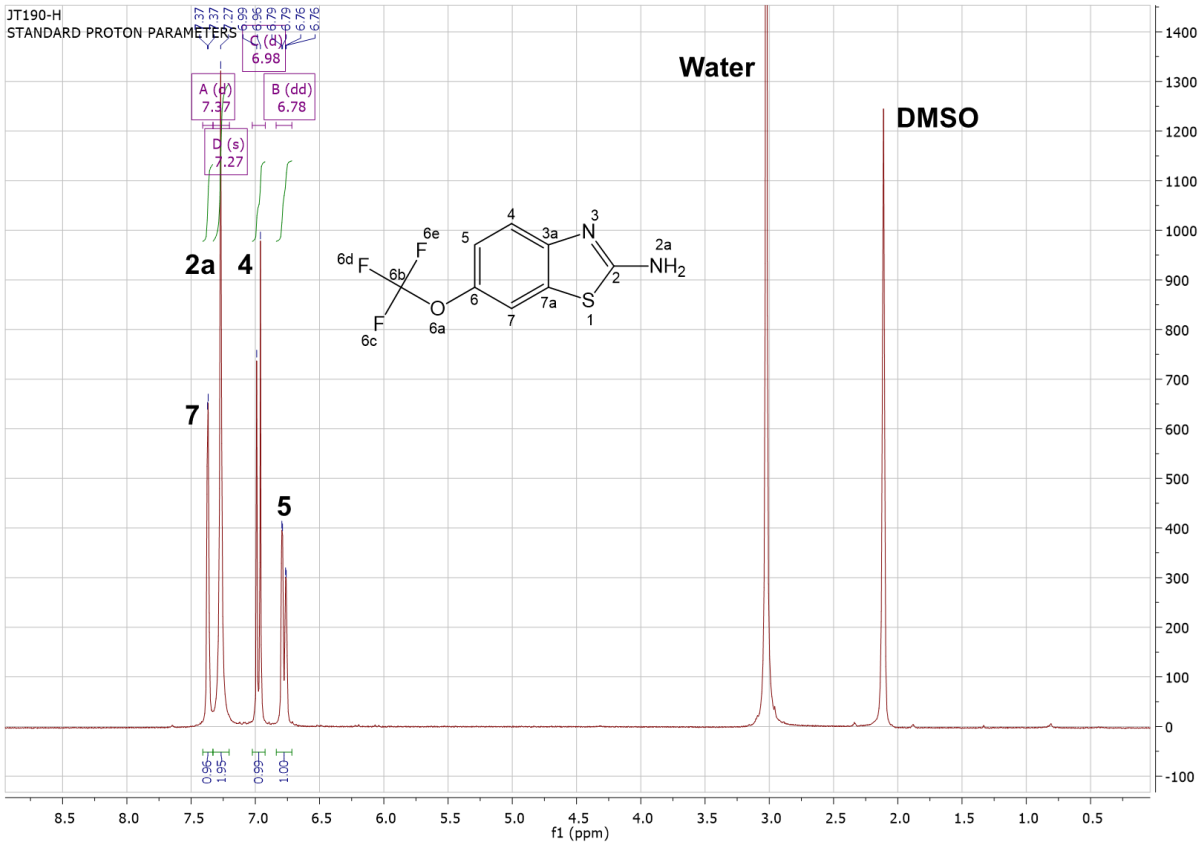

Figure S10. ^{1}H NMR spectrum of Rlz.

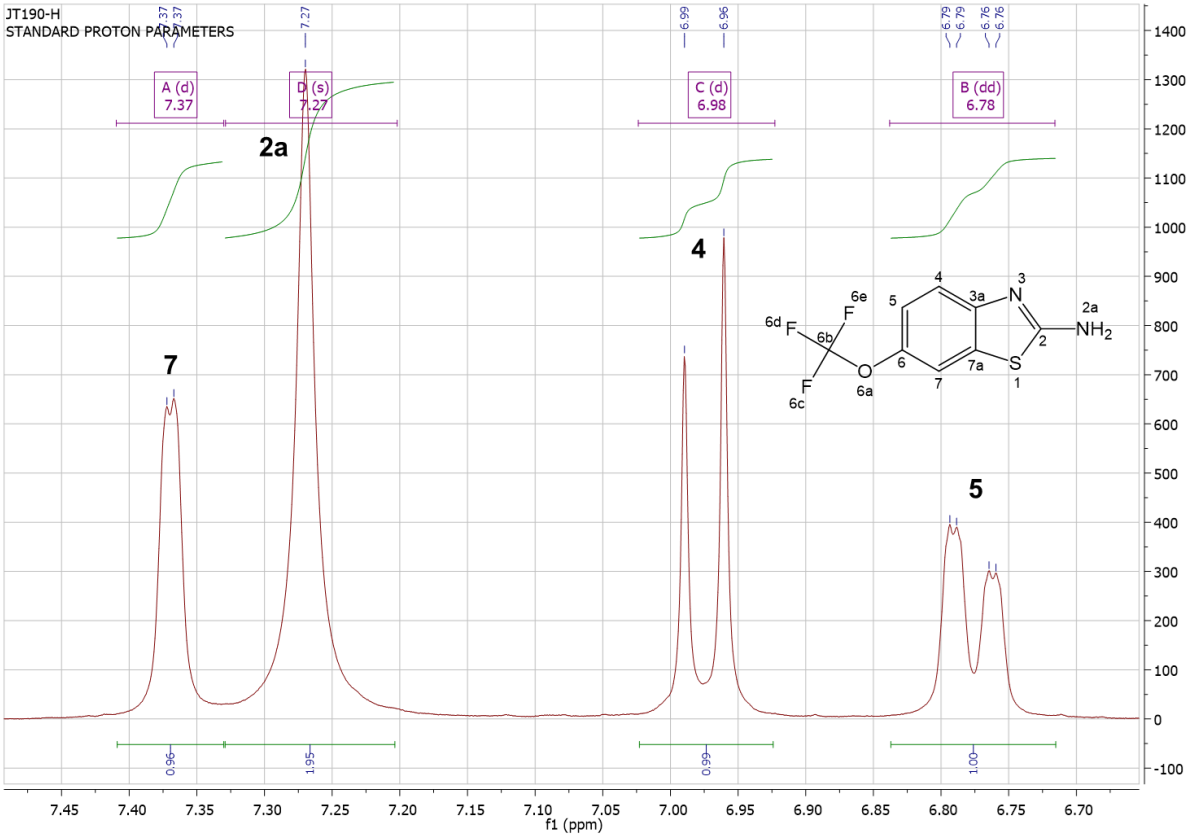

Figure S11. Magnification of the aromatic region of the ^{1}H NMR spectrum of Rlz.

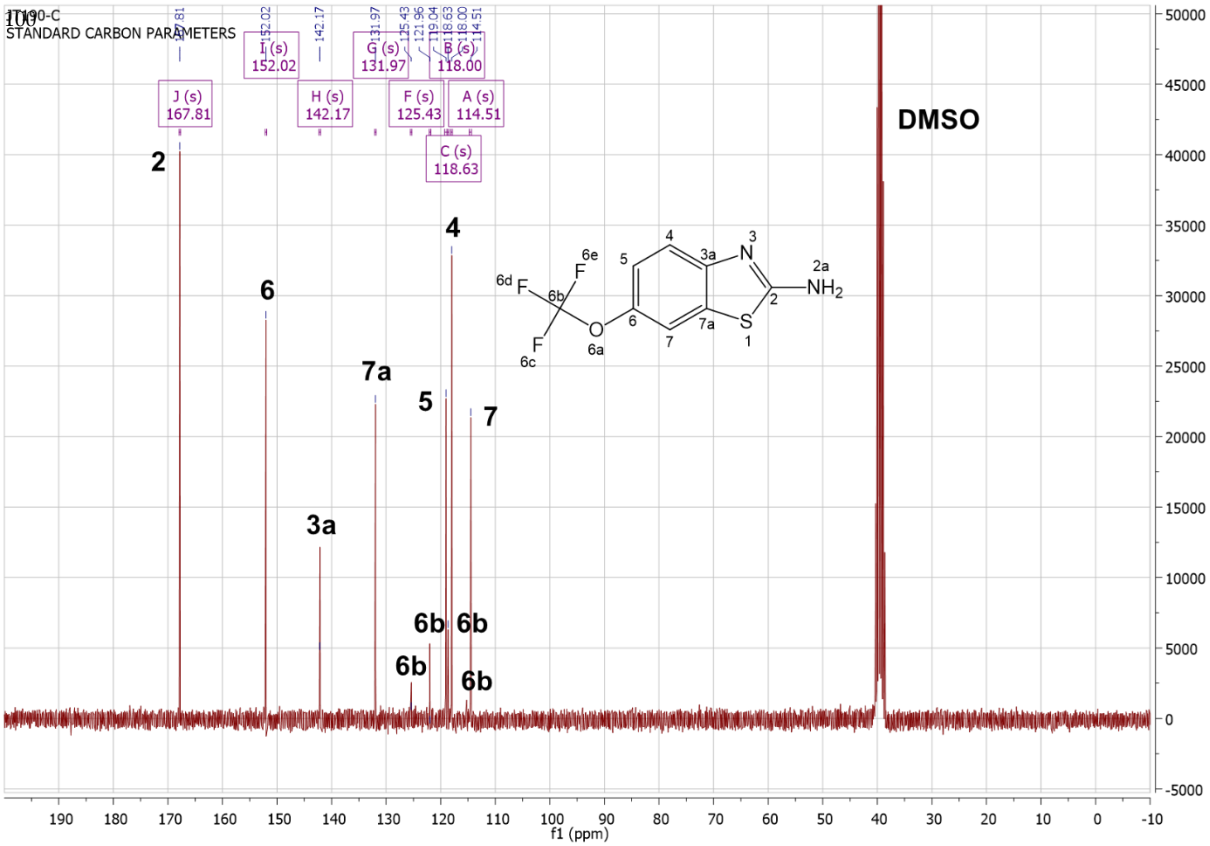

Figure S12. ^{13}C NMR spectrum of Rlz.

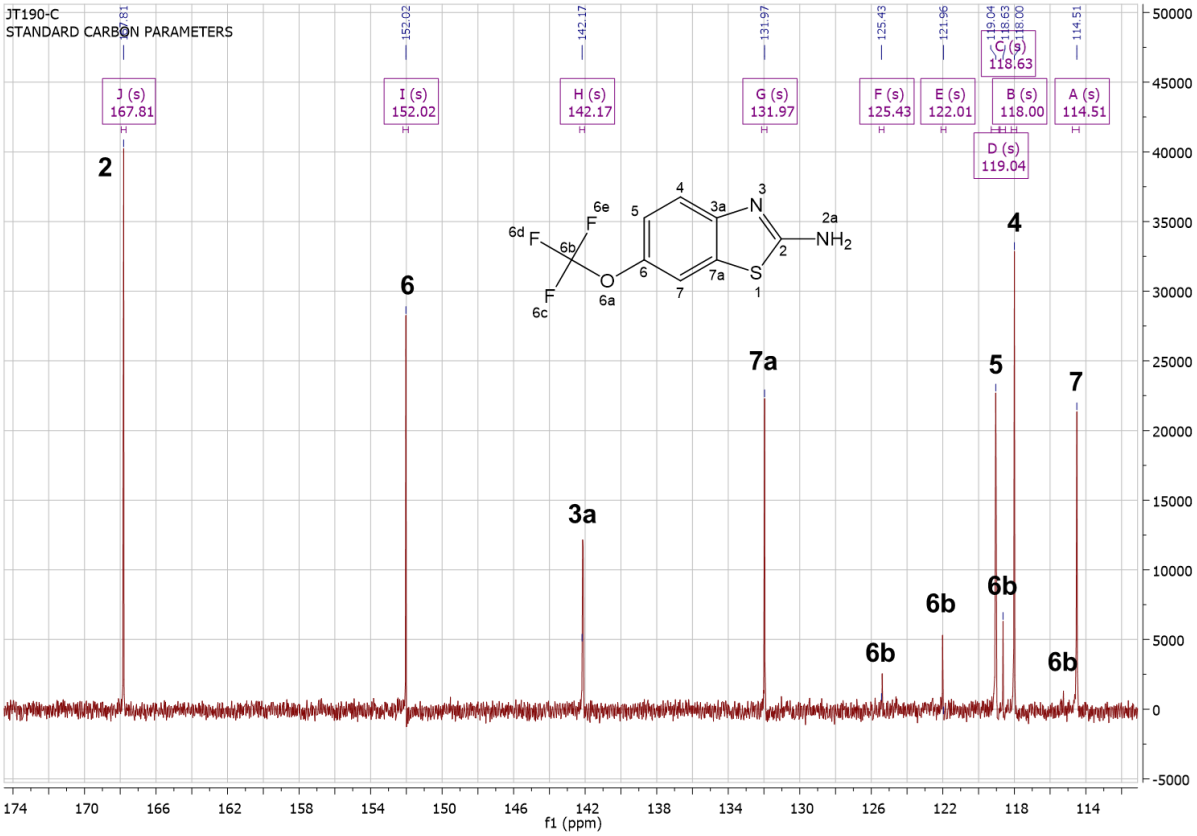

Figure S13. Magnification of the aromatic region of the ^{13}C NMR spectrum of Rlz.

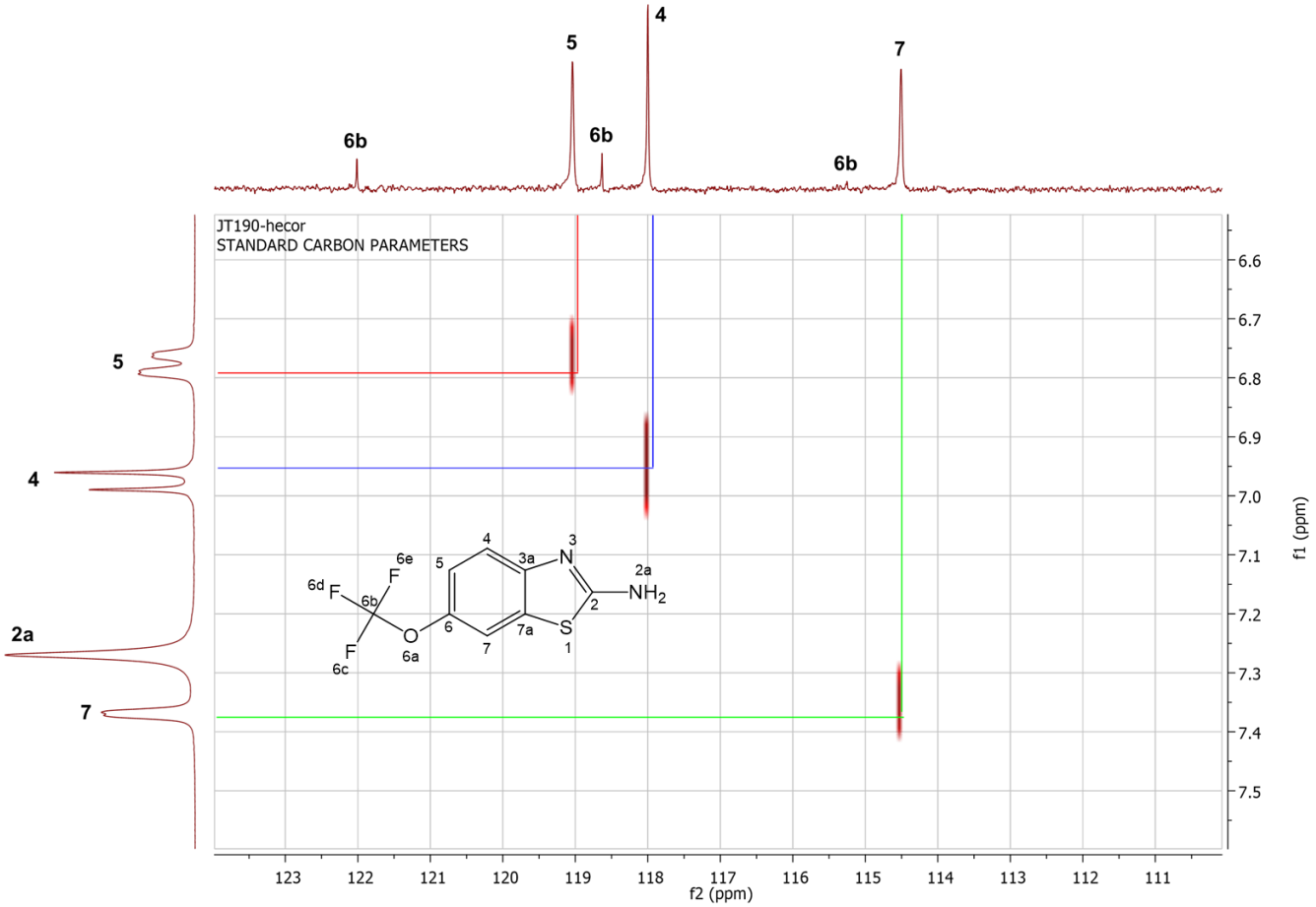

Figure S14. HETCOR 2D NMR experiment for Rlz.

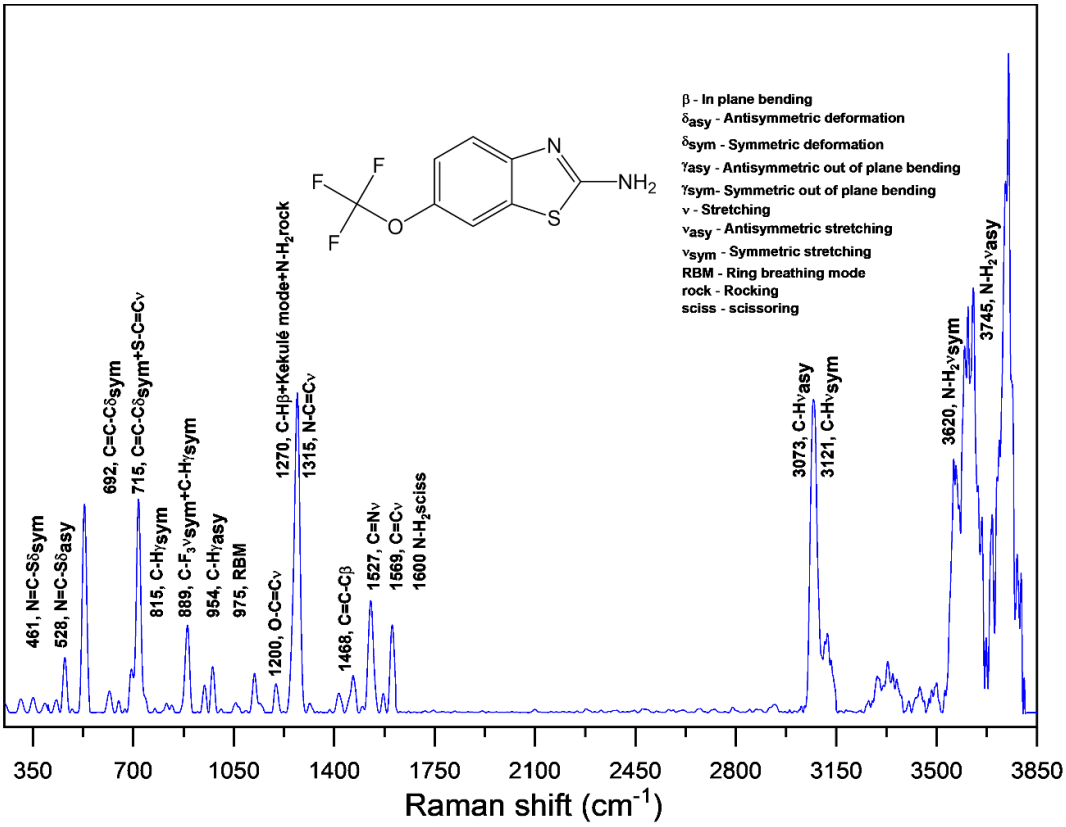

Figure S15. Raman spectrum of Rlz (λ_{laser} = 785 nm at 100 mW).