

Supporting Information

Assessment of the Activity of Nitroisoxazole Derivatives against *Trypanosoma cruzi*

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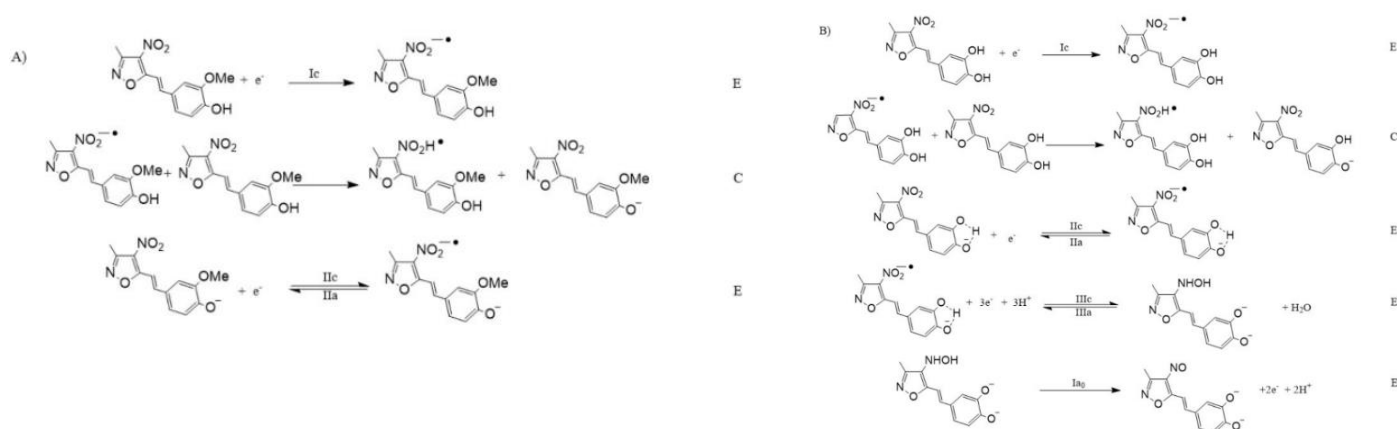
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Table S1. Hyperfine coupling constants of compounds **1–17** using ESR-electrochemical.

C	aN1/NO ₂	aN2	aN3	aH1	aH2	aH2'	aH2''	aH3'	aH3''	aH4'	aF4'	aF34'	aBr
1	2.55	1.19	0.87	4.30	3.34								
2	4.08	1.43		5.01	2.05								
3	3.48	1.52	1.23	5.56	3.14								
4	4.74	1.24		5.37	1.93	0.71	0.71	0.50	0.50	0.66			
5	2.14	0.76		5.55	3.45	2.51	2.51	0.80	0.80		1.53		
6	4.74	0.92		6.15	3.19	1.77	1.77	1.36	1.36			0.83	
7	4.91	0.94	2.01	6.66	3.02	1.30	1.30	1.25	1.25				
8	2.31	0.82		5.68	3.45	2.63	1.11	1.06					
9	2.02	0.90		4.09	3.01	0.88	0.79	0.73					
10	4.36	1.59		5.18	2.22	0.71		0.49		0.20			
11	1.43	0.87	1.68	5.57	4.66	2.48*	1.83**	0.84***	0.92****				
15	2.27	2.30		3.43	3.41	1.20	1.22	1.10	1.10				3.91
16	2.29	2.27		3.51	3.48	1.24	1.20	0.94					3.95
17	2.30	2.38		3.56	3.49	1.18	1.18	1.10	1.10				3.99
C	aN1/NO ₂	aN2	aH1	aH2	Indole				Aril				aCl
					aN1'	aH2'	aH3'	aH2''	aH3''	aH4'	aH5'	aH6'	
12	3.38	2.50	3.90	3.85	2.51	2.54	1.49	1.00	1.53	1.51	1.53	1.00	
13	2.51	2.53	3.98	3.93	2.51	2.47	1.44	1.04	1.50		1.50	1.04	1.75
14	2.62	2.61	4.18	4.30	2.63	2.57	1.55	1.03	1.65		1.65	1.03	

C: compound. In the coumarin position: *4, ** 5, ***7 y **** 8



Scheme S1. A reduction mechanism was proposed for **A)** compound **9** and **B)** compound **8**, in both cases with labile hydrogens in their structure; electrochemical (E) and chemical (C) steps are indicated.

Table S2: ADME parameters.

C	Canonical SMILES	Formula	MW	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp ³	#Rotatable bonds	#H-bond acceptors	#H-bond donors
1	<chem>CN(/C=C/c1onc(c1[N+](=O)[O-])C)C</chem>	C ₈ H ₁₁ N ₃ O ₃	197,19	14	5	0,38	3	4	0
2	<chem>Cc1noc(c1[N+](=O)[O-])/C=C/N1CCCC1</chem>	C ₁₀ H ₁₃ N ₃ O ₃	223,23	16	5	0,5	3	4	0
3	<chem>[O-][N+](=O)c1c(/C=C/N2CCC(CC2)onc1C</chem>	C ₁₁ H ₁₅ N ₃ O ₃	237,26	17	5	0,55	3	4	0
4	<chem>[O-][N+](=O)c1c(C)noc1/C=C/c1cccc1</chem>	C ₁₂ H ₁₀ N ₂ O ₃	230,22	17	11	0,08	3	4	0
5	<chem>Fc1ccc(cc1)/C=C/c1onc(c1[N+](=O)[O-])C</chem>	C ₁₂ H ₉ FN ₂ O ₃	248,21	18	11	0,08	3	5	0
6	<chem>[O-][N+](=O)c1c(/C=C/c2ccc(cc2)C(F)(F)F)onc1C</chem>	C ₁₃ H ₉ F ₃ N ₂ O ₃	298,22	21	11	0,15	4	7	0
7	<chem>[O-][N+](=O)c1ccc(cc1)/C=C/c1onc(c1[N+](=O)[O-])C</chem>	C ₁₂ H ₉ N ₃ O ₅	275,22	20	11	0,08	4	6	0
8	<chem>[O-][N+](=O)c1c(/C=C/c2ccc(c(c2)O)O)onc1C</chem>	C ₁₂ H ₁₀ N ₂ O ₅	262,22	19	11	0,08	3	6	2
9	<chem>COc1cc(/C=C/c2onc(c2[N+](=O)[O-])C)ccc1O</chem>	C ₁₃ H ₁₂ N ₂ O ₅	276,24	20	11	0,15	4	6	1
10	<chem>[O-][N+](=O)c1c(/C=C/c2ccc(c2)onc1C</chem>	C ₁₀ H ₈ N ₂ O ₄	220,18	16	10	0,1	3	5	0
11	<chem>CCN(c1ccc2c(c1)oc(=O)c(c2)/C=C/c1onc(c1[N+](=O)[O-])C)CC</chem>	C ₁₉ H ₁₉ N ₃ O ₅	369,37	27	15	0,26	6	6	0
12	<chem>[O-][N+](=O)c1c(/C=C/c2cn(c3c2cccc3)c2cccc2)onc1C</chem>	C ₂₀ H ₁₅ N ₃ O ₃	345,35	26	20	0,05	4	4	0
13	<chem>Clc1ccc(cc1)n1cc(c2c1cccc2)/C=C/c1onc(c1[N+](=O)[O-])C</chem>	C ₂₀ H ₁₄ ClN ₃ O ₃	379,8	27	20	0,05	4	4	0
14	<chem>Cc1ccc(cc1)n1cc(c2c1cccc2)/C=C/c1onc(c1[N+](=O)[O-])C</chem>	C ₂₁ H ₁₇ N ₃ O ₃	359,38	27	20	0,1	4	4	0
15	<chem>Brc1cccc1/C=C/c1onc(c1[N+](=O)[O-])C</chem>	C ₁₂ H ₉ BrN ₂ O ₃	309,12	18	11	0,08	3	4	0
16	<chem>Brc1cccc(c1)/C=C/c1onc(c1[N+](=O)[O-])C</chem>	C ₁₂ H ₉ BrN ₂ O ₃	309,12	18	11	0,08	3	4	0
17	<chem>Brc1ccc(cc1)/C=C/c1onc(c1[</chem>	C ₁₂ H ₉ BrN ₂ O ₃	309,12	18	11	0,08	3	4	0

	N+](=O)[O-])C								
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C	MR	TPSA	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P	ESOL Log S
1	52,89	75,09	1,84	1,18	1,31	-0,59	-0,85	0,58	-1,87
2	64,31	75,09	2,16	1,67	1,47	0,03	-0,04	1,06	-2,31
3	69,11	75,09	2,39	2,03	1,86	0,32	0,2	1,36	-2,61
4	65,66	71,85	2,2	2,9	2,84	1,17	1,18	2,06	-3,38
5	65,62	71,85	2,23	3	3,4	1,58	1,6	2,36	-3,52
6	70,66	71,85	2,49	3,79	5,01	2,1	2,25	3,13	-4,2
7	74,48	117,67	1,93	2,73	2,75	0,25	-0,96	1,34	-3,41
8	69,71	112,31	1,71	2,19	2,26	0,1	0,23	1,3	-3,08
9	74,18	101,31	2,38	2,52	2,56	0,37	0,75	1,72	-3,28
10	57,93	84,99	2,01	2	2,44	-0,17	0,6	1,37	-2,73
11	105,52	105,3	3,16	3,76	3,8	1,61	2,15	2,9	-4,51
12	102,49	76,78	3,11	4,64	4,79	2,51	2,29	3,47	-5,21
13	107,5	76,78	3,36	5,27	5,44	3	2,92	4	-5,8
14	107,46	76,78	3,23	5	5,1	2,73	2,81	3,77	-5,5
15	73,36	71,85	2,51	3,59	3,61	1,84	1,86	2,68	-4,27
16	73,36	71,85	2,58	3,59	3,61	1,84	1,86	2,7	-4,27
17	73,36	71,85	2,5	3,59	3,61	1,84	1,86	2,68	-4,27

C	ESOL Solubility (mg/ml)	ESOL Solubility (mol/l)	ESOL Class	Ali Log S	Ali Solubility (mg/ml)	Ali Solubility (mol/l)	Ali Class	Silicos-IT LogSw	Silicos-IT Solubility (mg/ml)	Silicos-IT Solubility (mol/l)	Silicos-IT class
1	2.65e+00	1.34e-02	Very soluble	-2,35	8.76e-01	4.44e-03	Soluble	-1,21	1.21e+01	6.14e-02	Soluble
2	1.09e+00	4.90e-03	Soluble	-2,86	3.07e-01	1.38e-03	Soluble	-1,55	6.29e+00	2.82e-02	Soluble
3	5.83e-01	2.46e-03	Soluble	-3,23	1.38e-01	5.83e-04	Soluble	-1,83	3.53e+00	1.49e-02	Soluble
4	9.70e-02	4.22e-04	Soluble	-4,07	1.96e-02	8.52e-05	Moderately soluble	-3,62	5.51e-02	2.39e-04	Soluble
5	7.44e-02	3.00e-04	Soluble	-4,17	1.67e-02	6.71e-05	Moderately soluble	-3,9	3.14e-02	1.26e-04	Soluble
6	1.88e-02	6.31e-05	Moderately soluble	-4,99	3.03e-03	1.02e-05	Moderately soluble	-4,49	9.65e-03	3.24e-05	Moderately soluble
7	1.07e-01	3.90e-04	Soluble	-4,86	3.84e-03	1.40e-05	Moderat	-2,99	2.80e-01	1.02e-03	Soluble

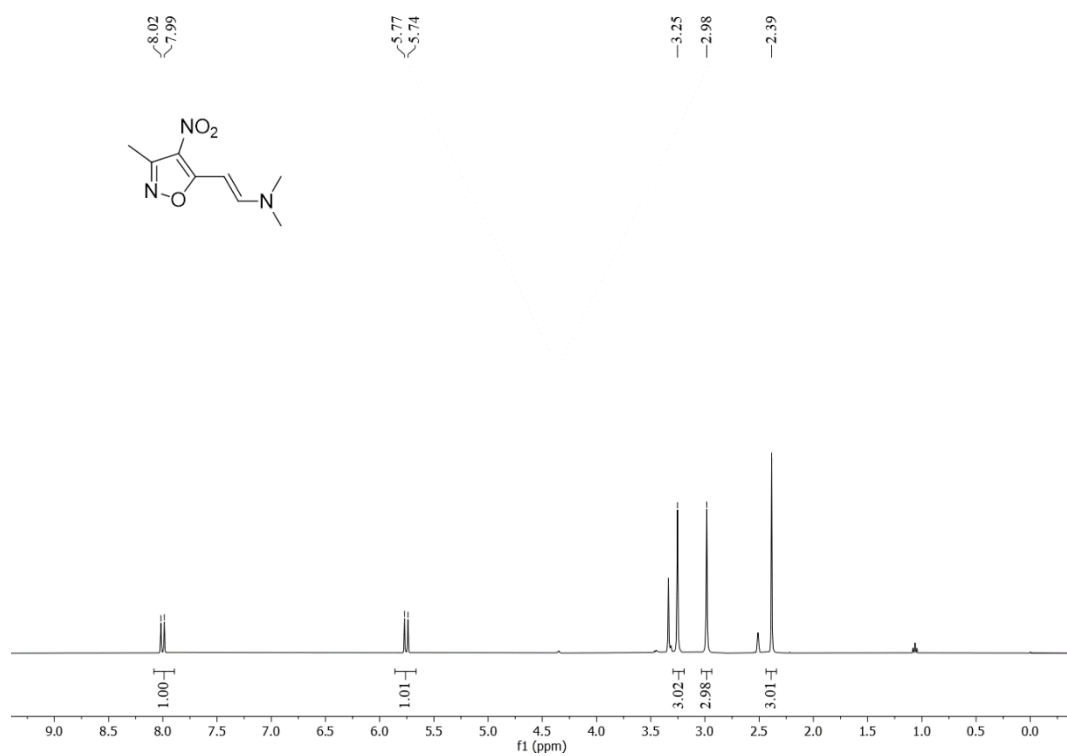
			e				ely soluble				
8	2.20e-01	8.40e-04	Solubl e	-4,18	1.72e-02	6.57e-05	Moderat ely soluble	-2,47	8.97e-01	3.42e-03	Soluble
9	1.44e-01	5.21e-04	Solubl e	-4,29	1.40e-02	5.08e-05	Moderat ely soluble	-3,17	1.89e-01	6.84e-04	Soluble
10	4.10e-01	1.86e-03	Solubl e	-3,41	8.54e-02	3.88e-04	Soluble	-2,83	3.22e-01	1.46e-03	Soluble
11	1.13e-02	3.06e-05	Moder ately solubl e	-5,66	8.00e-04	2.17e-06	Moderat ely soluble	-5,69	7.47e-04	2.02e-06	Moderat ely soluble
12	2.13e-03	6.17e-06	Moder ately solubl e	-5,98	3.63e-04	1.05e-06	Moderat ely soluble	-6,15	2.42e-04	7.01e-07	Poorly soluble
13	6.03e-04	1.59e-06	Moder ately solubl e	-6,63	8.86e-05	2.33e-07	Poorly soluble	-6,75	6.83e-05	1.80e-07	Poorly soluble
14	1.13e-03	3.15e-06	Moder ately solubl e	-6,35	1.60e-04	4.45e-07	Poorly soluble	-6,53	1.06e-04	2.94e-07	Poorly soluble
15	1.65e-02	5.34e-05	Moder ately solubl e	-4,79	5.07e-03	1.64e-05	Moderat ely soluble	-4,45	1.10e-02	3.55e-05	Moderat ely soluble
16	1.65e-02	5.34e-05	Moder ately solubl e	-4,79	5.07e-03	1.64e-05	Moderat ely soluble	-4,45	1.10e-02	3.55e-05	Moderat ely soluble
17	1.65e-02	5.34e-05	Moder ately solubl e	-4,79	5.07e-03	1.64e-05	Moderat ely soluble	-4,45	1.10e-02	3.55e-05	Moderat ely soluble

C	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1	High	No	No	Yes	No	No	No	No
2	High	No	No	Yes	Yes	No	No	No
3	High	No	No	Yes	Yes	No	No	No
4	High	Yes	No	Yes	Yes	No	No	No
5	High	Yes	No	Yes	Yes	No	No	No
6	High	No	No	Yes	Yes	Yes	No	No
7	High	No	No	Yes	Yes	Yes	No	No
8	High	No	No	No	No	No	No	No
9	High	No	No	Yes	Yes	Yes	No	No
10	High	No	No	Yes	No	No	No	No
11	High	No	No	Yes	Yes	Yes	No	Yes
12	High	No	No	Yes	Yes	Yes	No	No
13	High	No	No	Yes	Yes	Yes	No	No
14	High	No	No	Yes	Yes	Yes	No	No
15	High	Yes	No	Yes	Yes	Yes	No	No
16	High	Yes	No	Yes	Yes	Yes	No	No
17	High	Yes	No	Yes	Yes	Yes	No	No

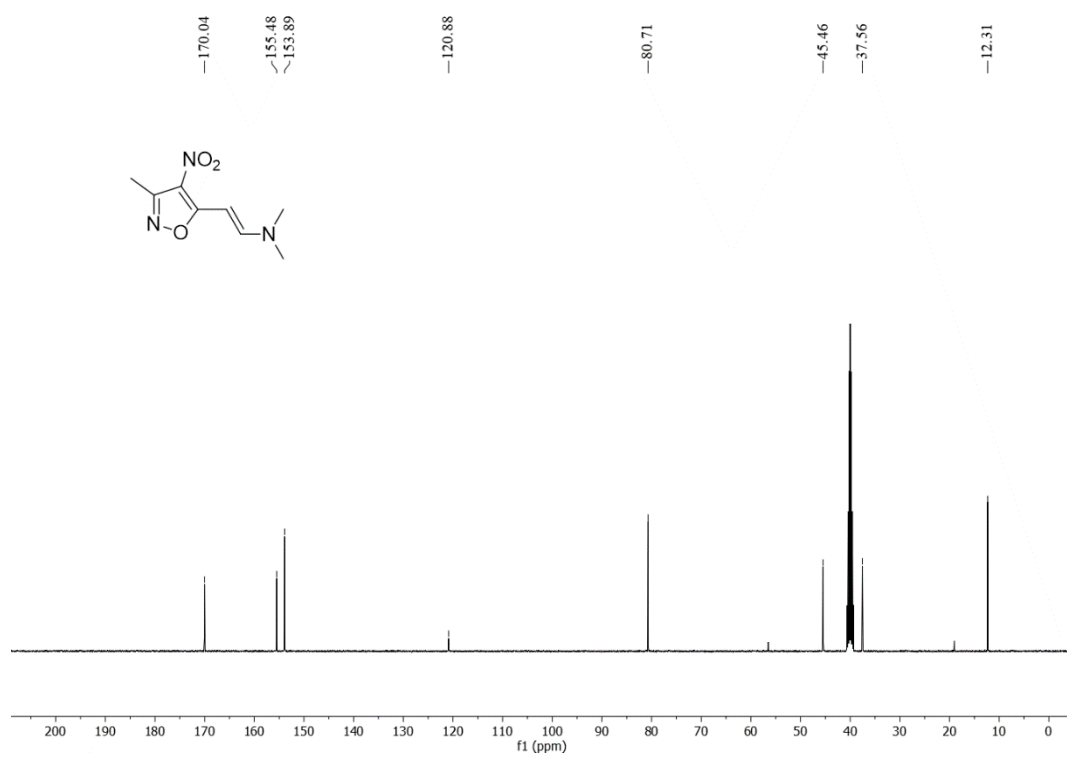
C	log Kp (cm/s)	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
1	-6,67	0	0	0	0	1	0,55	0	2	1	3,34
2	-6,48	0	0	0	0	0	0,55	0	2	1	3,34
3	-6,31	0	0	0	0	0	0,55	0	2	1	3,38
4	-5,65	0	0	0	0	0	0,55	0	2	1	3,19
5	-5,68	0	0	0	0	0	0,55	0	2	1	3,16
6	-5,43	0	0	0	0	0	0,55	0	2	1	3,28
7	-6,04	0	0	0	0	0	0,55	0	2	0	3,17
8	-6,34	0	0	0	0	0	0,55	1	3	0	3,17
9	-6,2	0	0	0	0	0	0,55	0	2	0	3,22
10	-6,22	0	0	0	0	0	0,55	0	2	1	3,22
11	-5,88	0	0	0	0	0	0,55	0	3	2	3,93
12	-5,11	0	0	0	0	0	0,55	0	2	1	3,52
13	-4,88	0	0	0	0	1	0,55	0	2	2	3,49
14	-4,94	0	0	0	0	0	0,55	0	2	2	3,62
15	-5,64	0	0	0	0	0	0,55	0	2	1	3,25
16	-5,64	0	0	0	0	0	0,55	0	2	1	3,21
17	-5,64	0	0	0	0	0	0,55	0	2	1	3,18

Figure S1: NMR Spectra of compounds

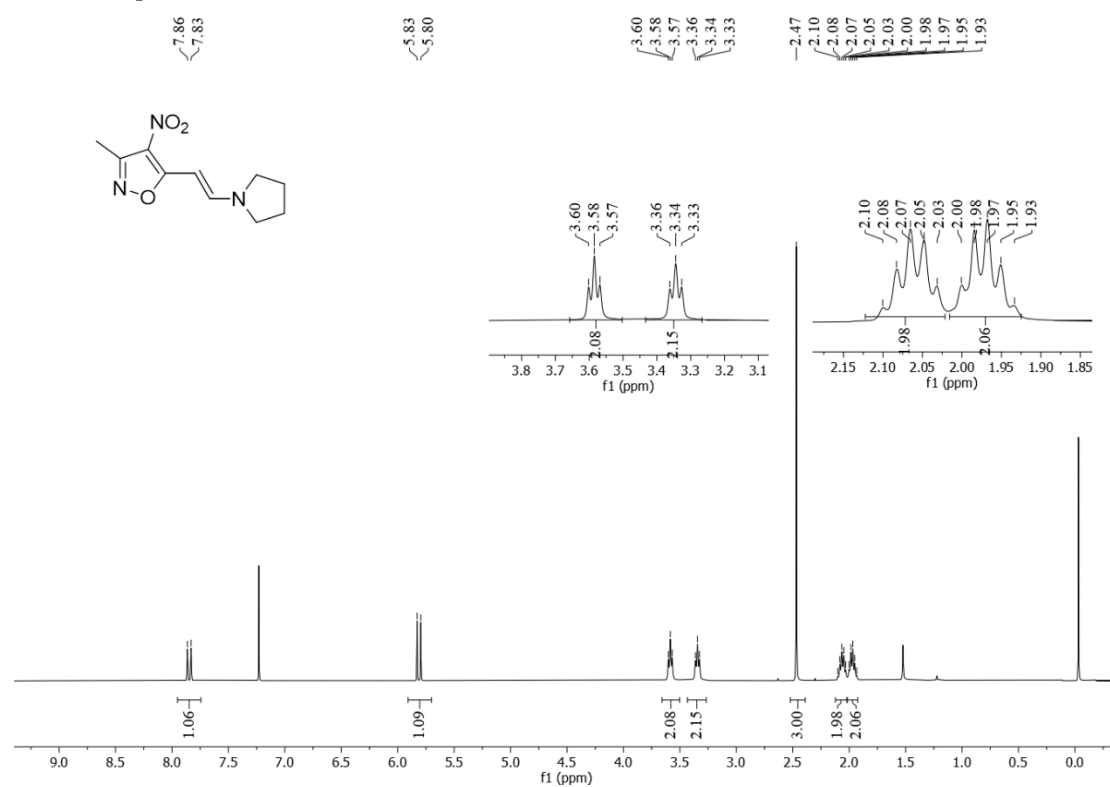
^1H -NMR spectrum of **1**



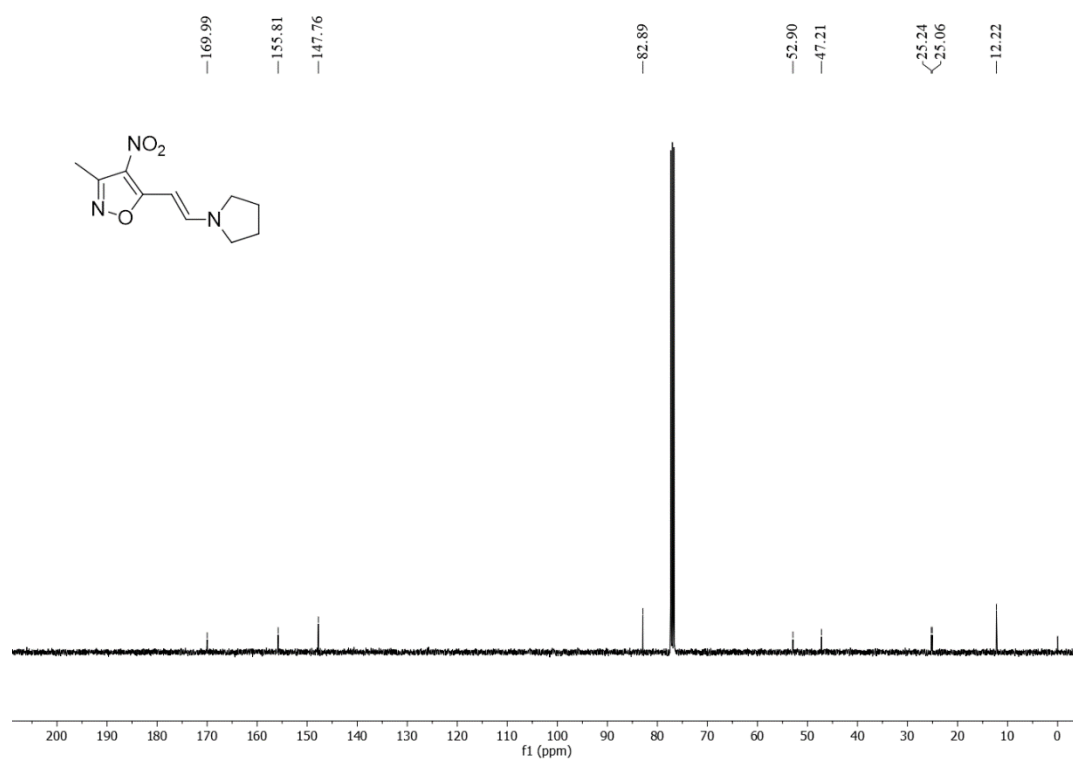
^{13}C -NMR spectrum of **1**



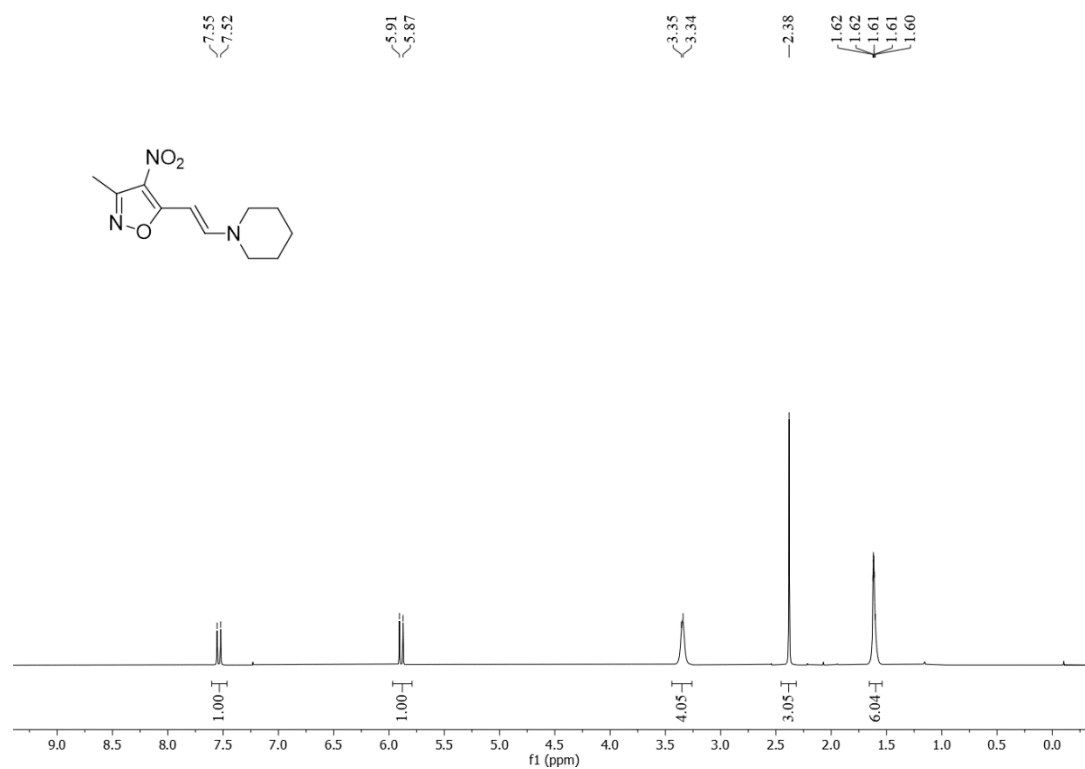
¹H-NMR spectrum of **2**



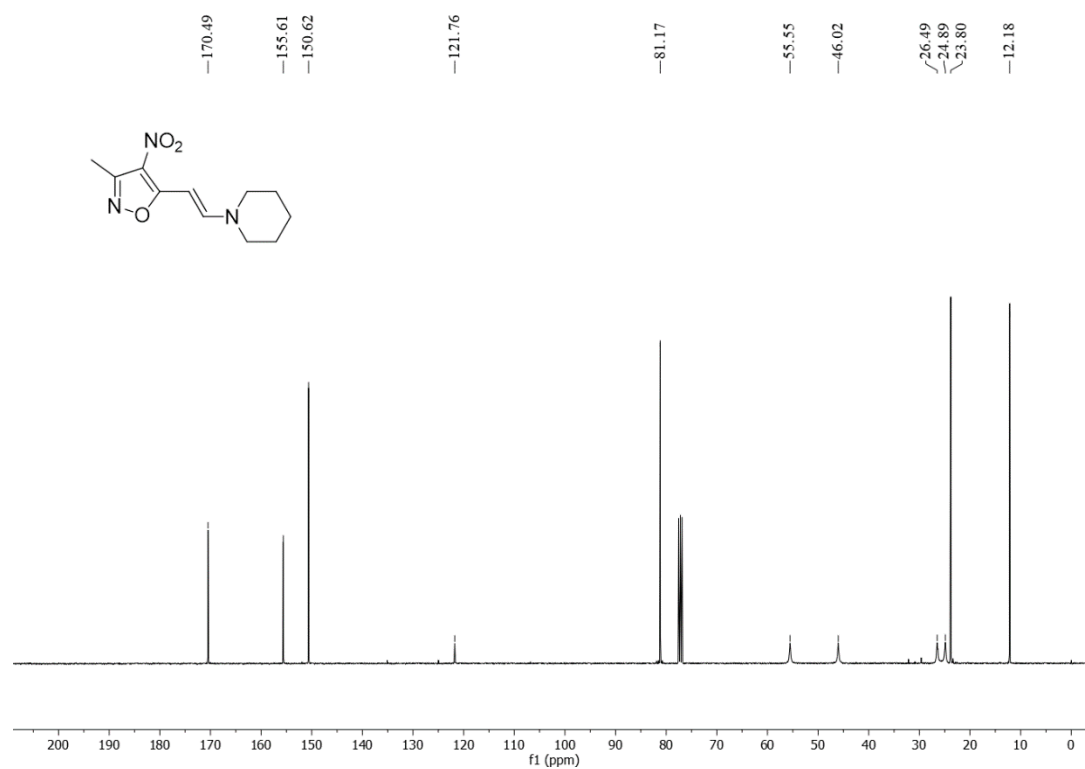
¹³C-NMR spectrum of **2**



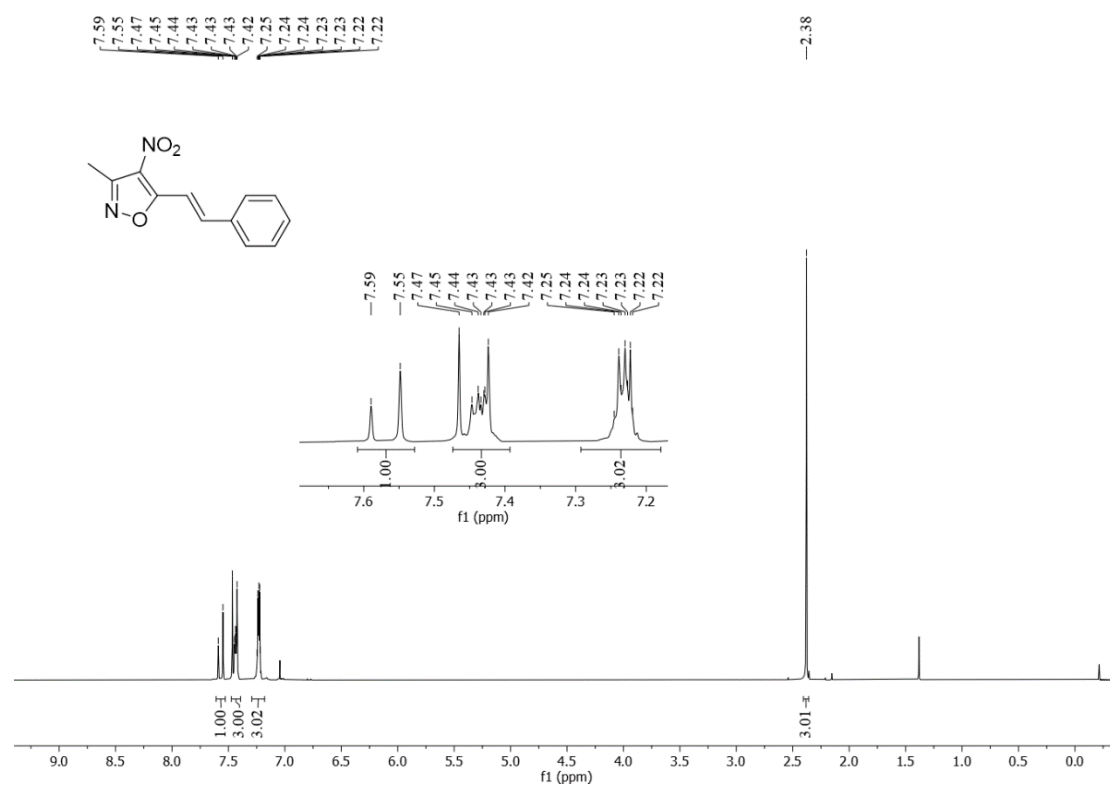
¹H-NMR spectrum of **3**



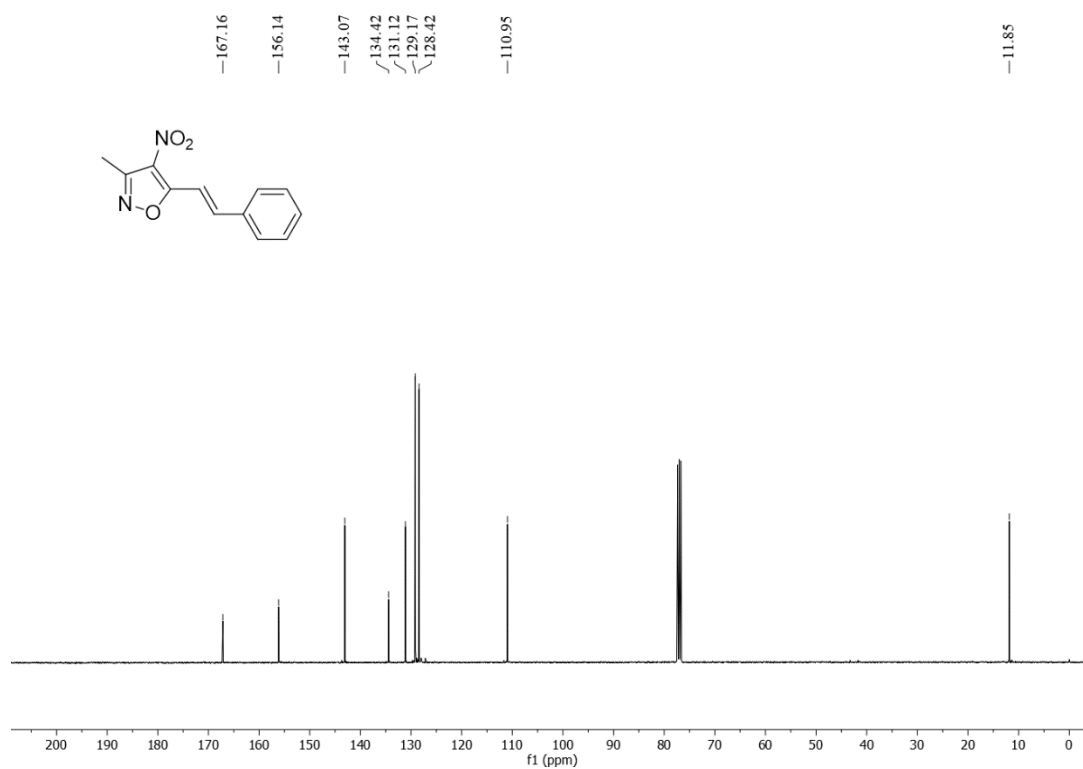
¹³C-NMR spectrum of **3**



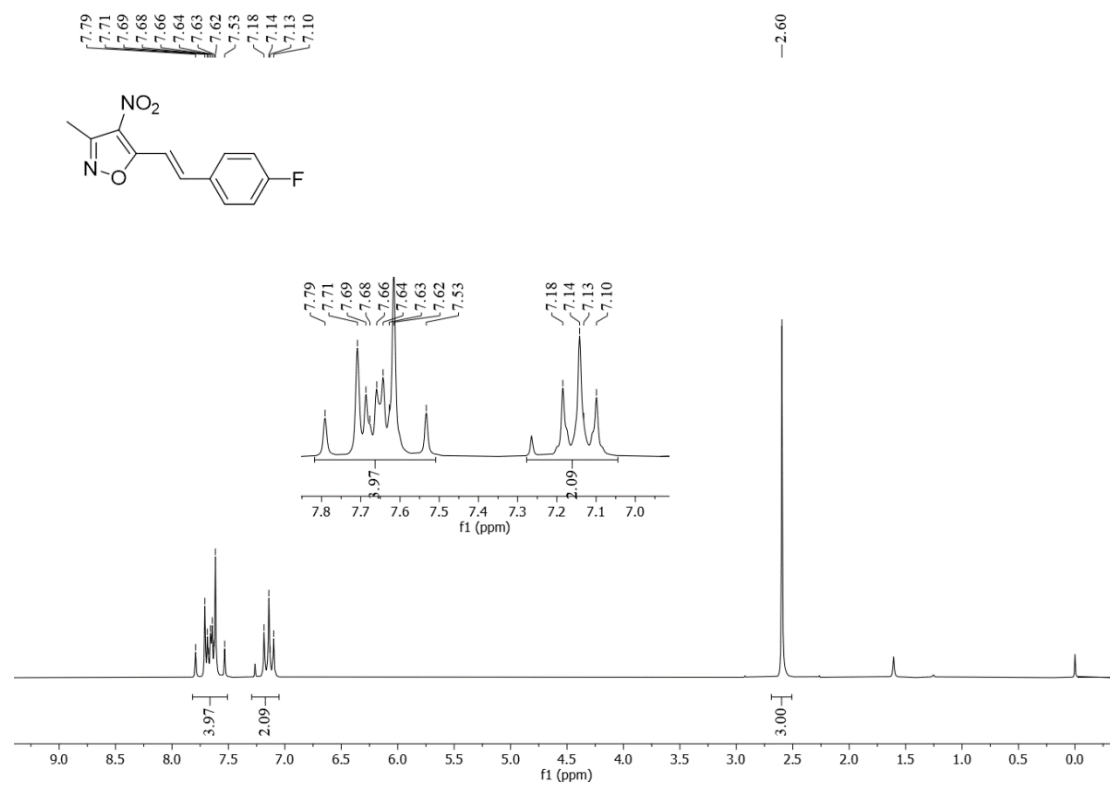
¹H-NMR spectrum of **4**



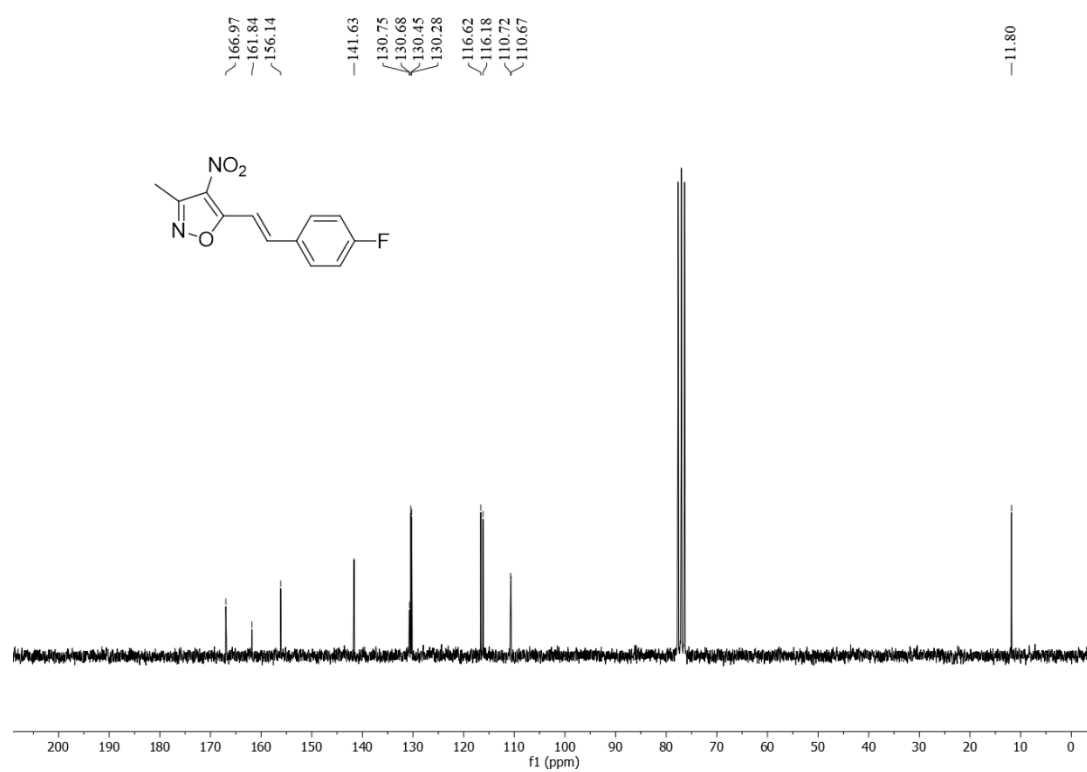
¹³C-NMR spectrum of **4**



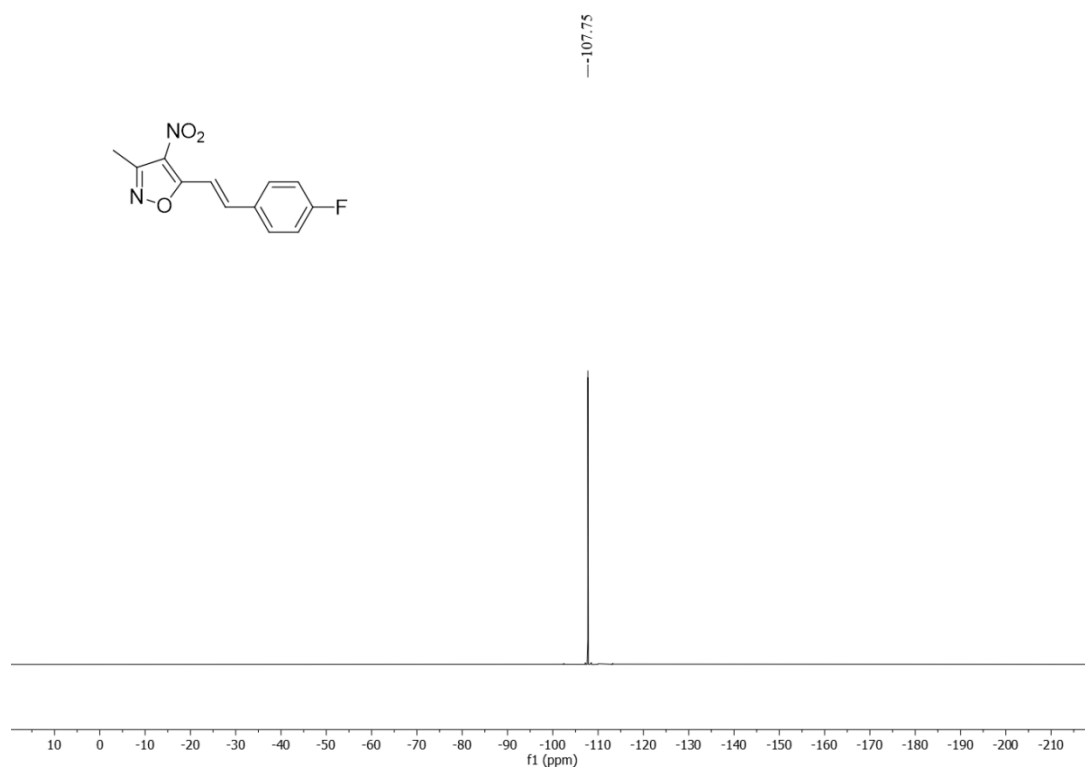
¹H-NMR spectrum of **5**



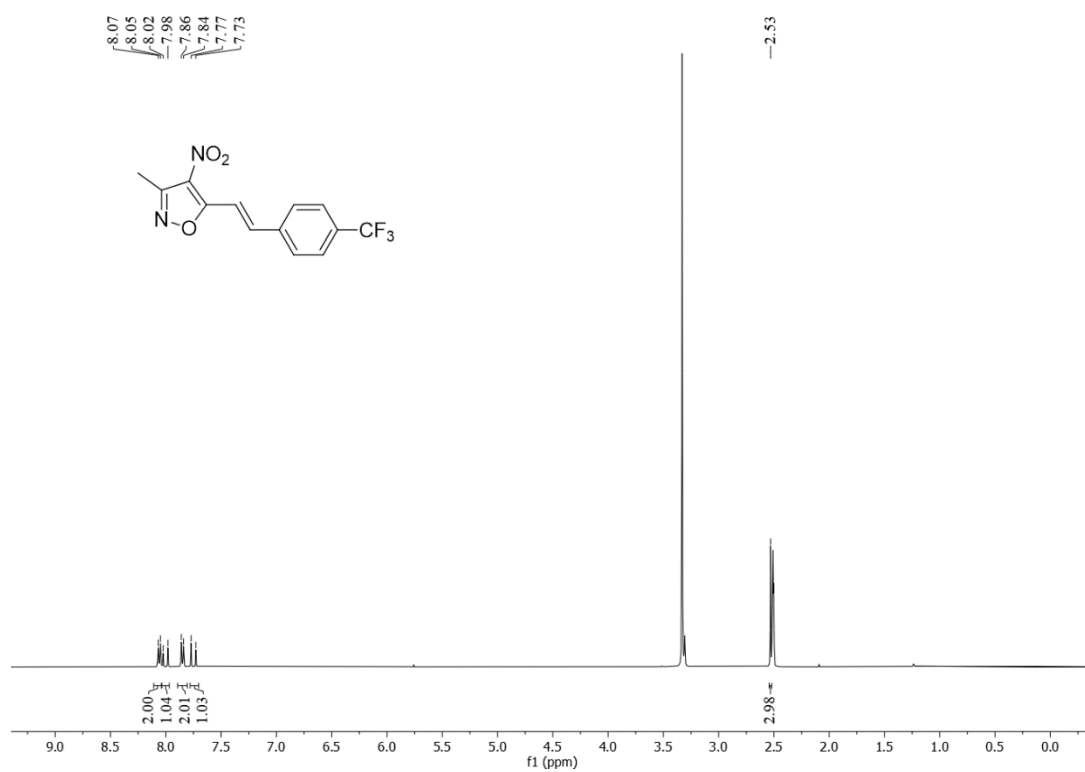
¹³C-NMR spectrum of **5**



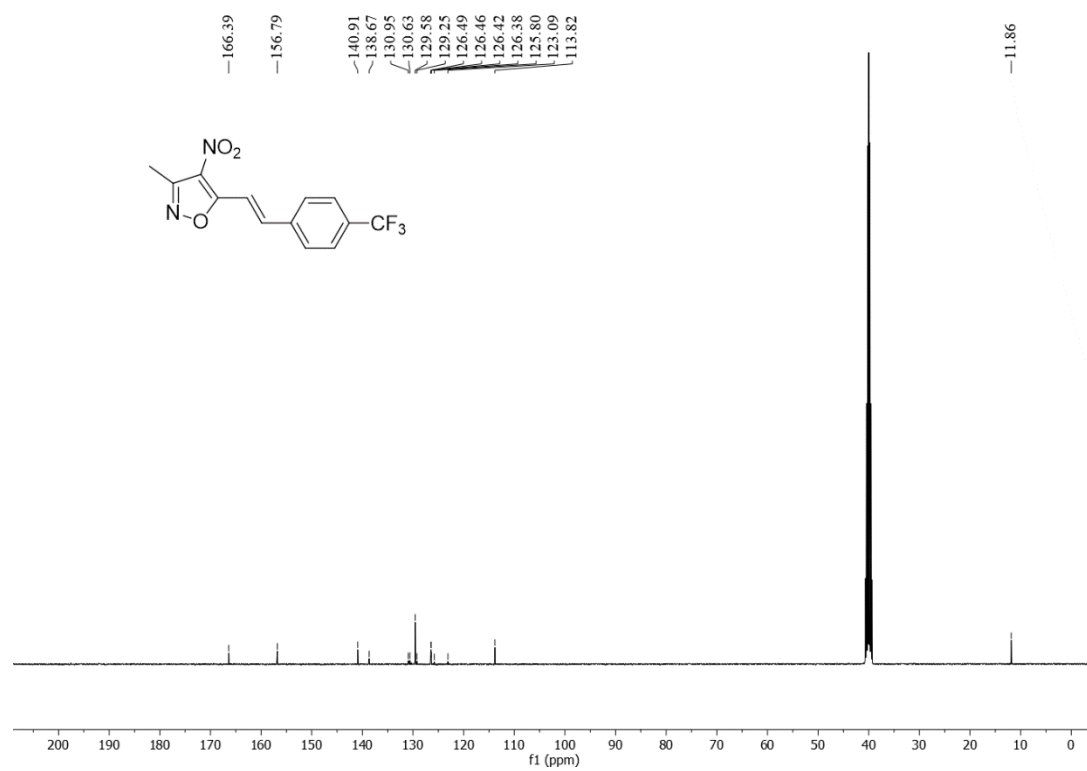
^{19}F -NMR spectrum of **5**



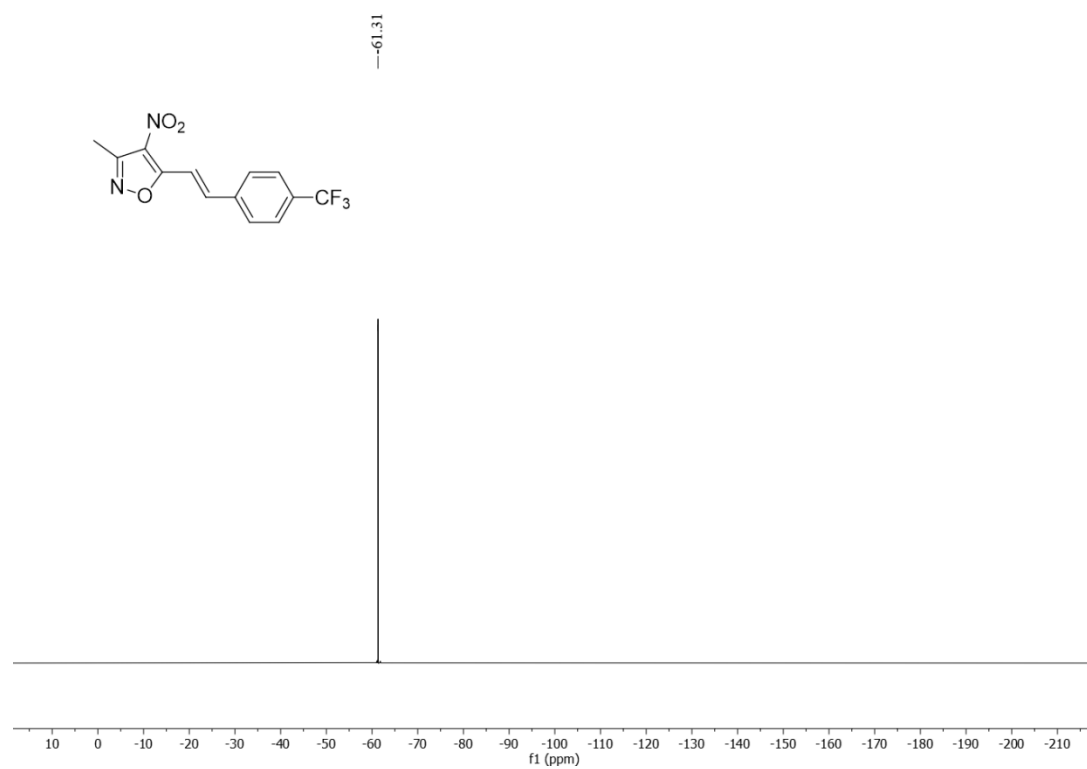
^1H -NMR spectrum of **6**



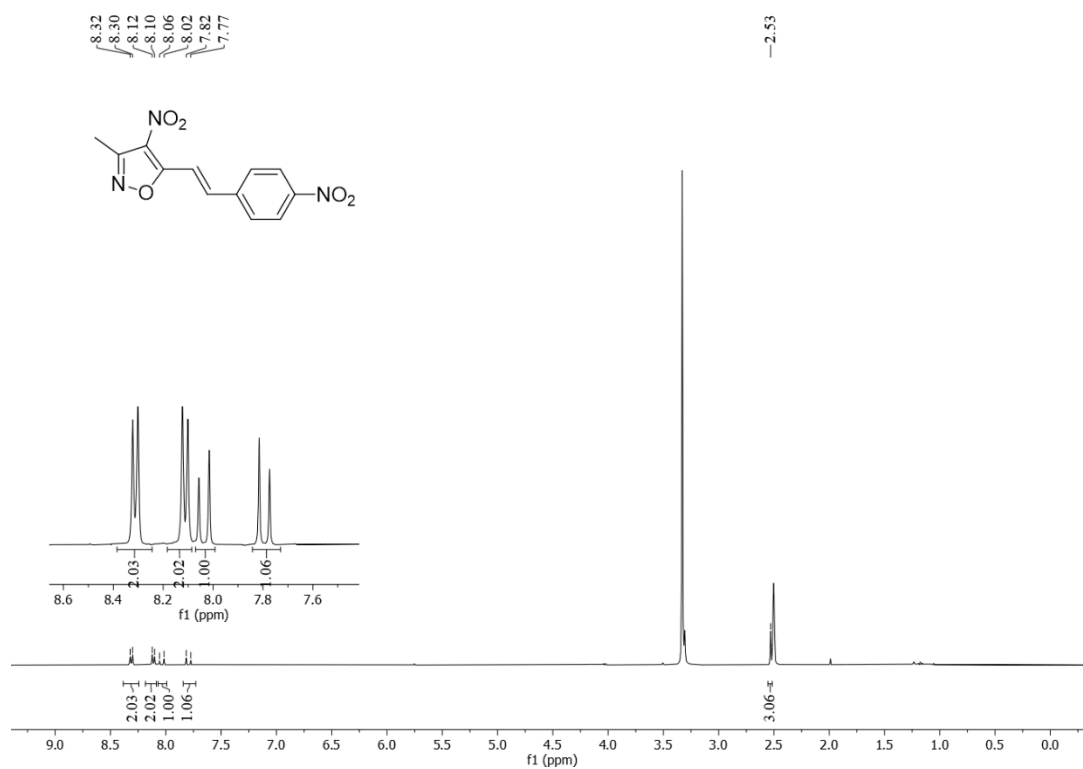
¹³C-NMR spectrum of **6**



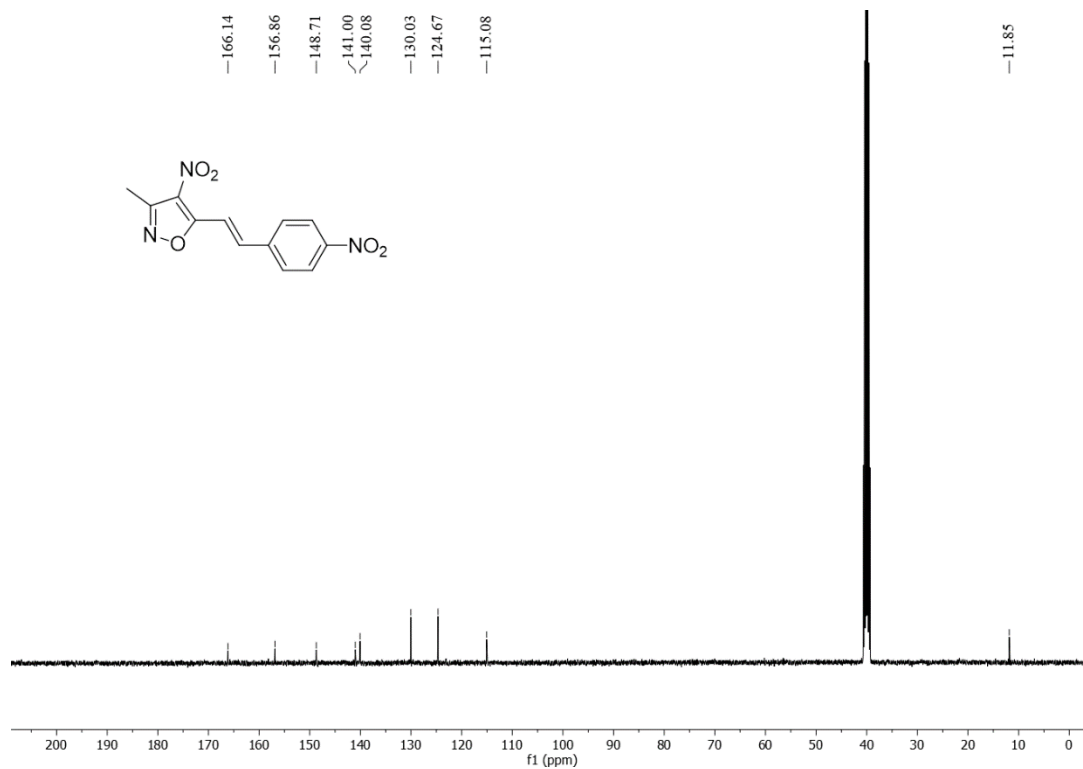
¹⁹F-NMR spectrum of **6**



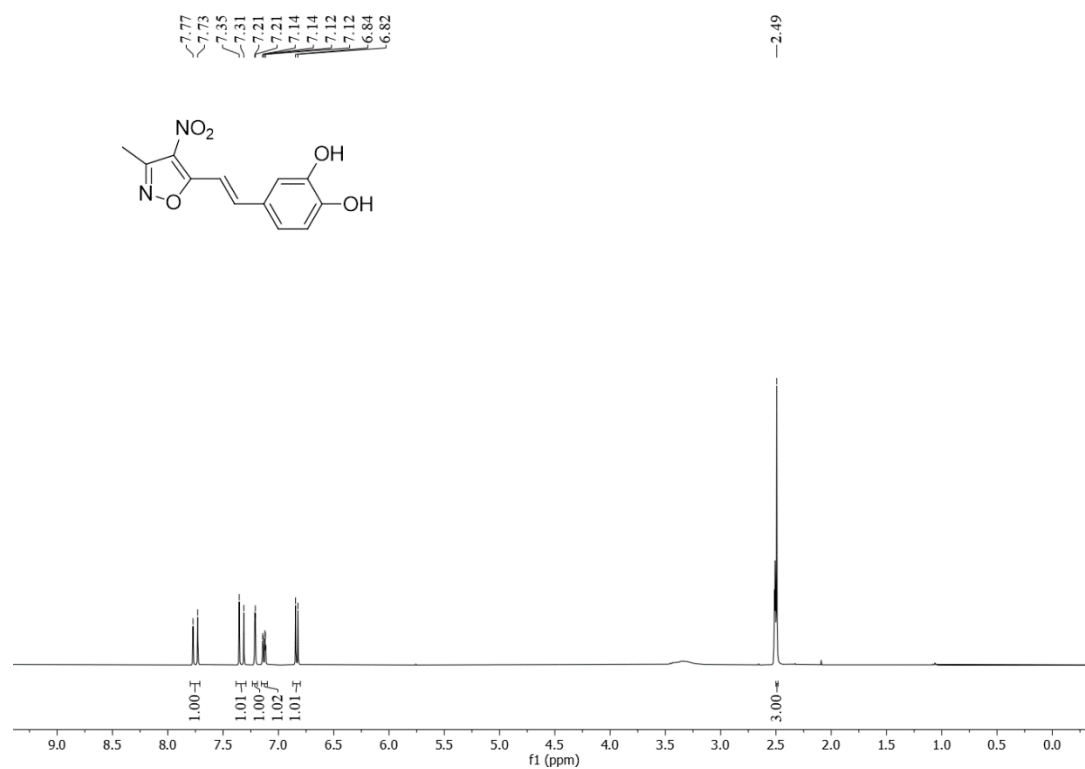
^1H -NMR spectrum of **7**



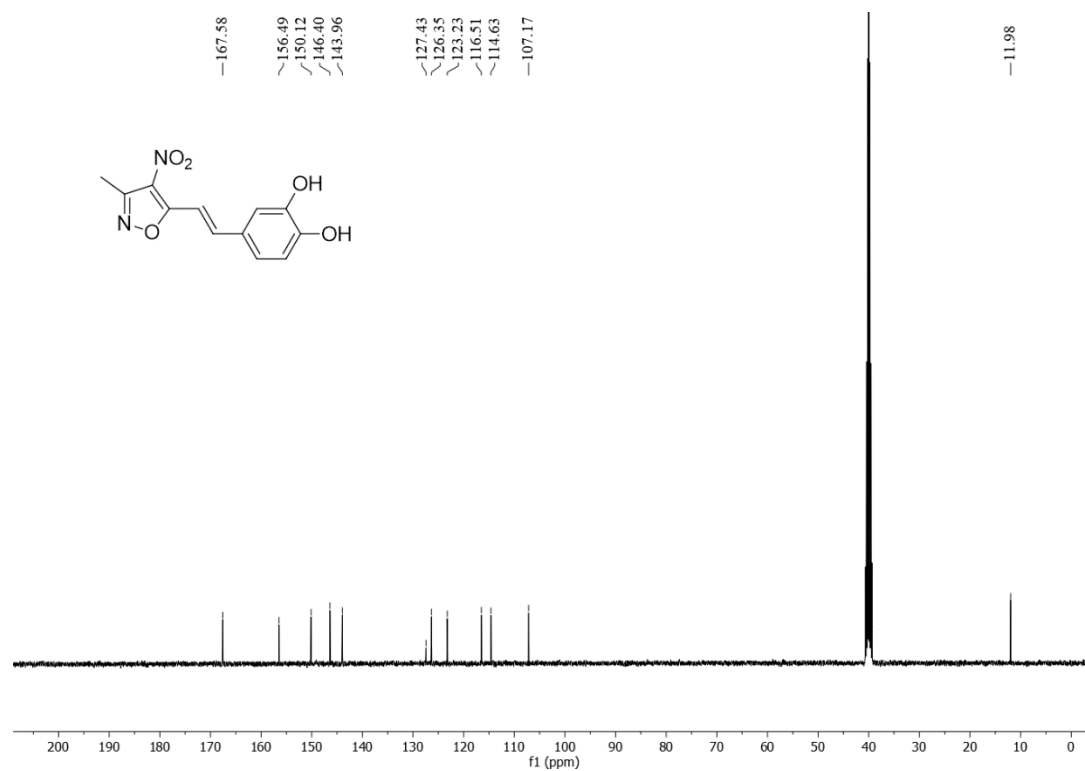
^{13}C -NMR spectrum of **7**



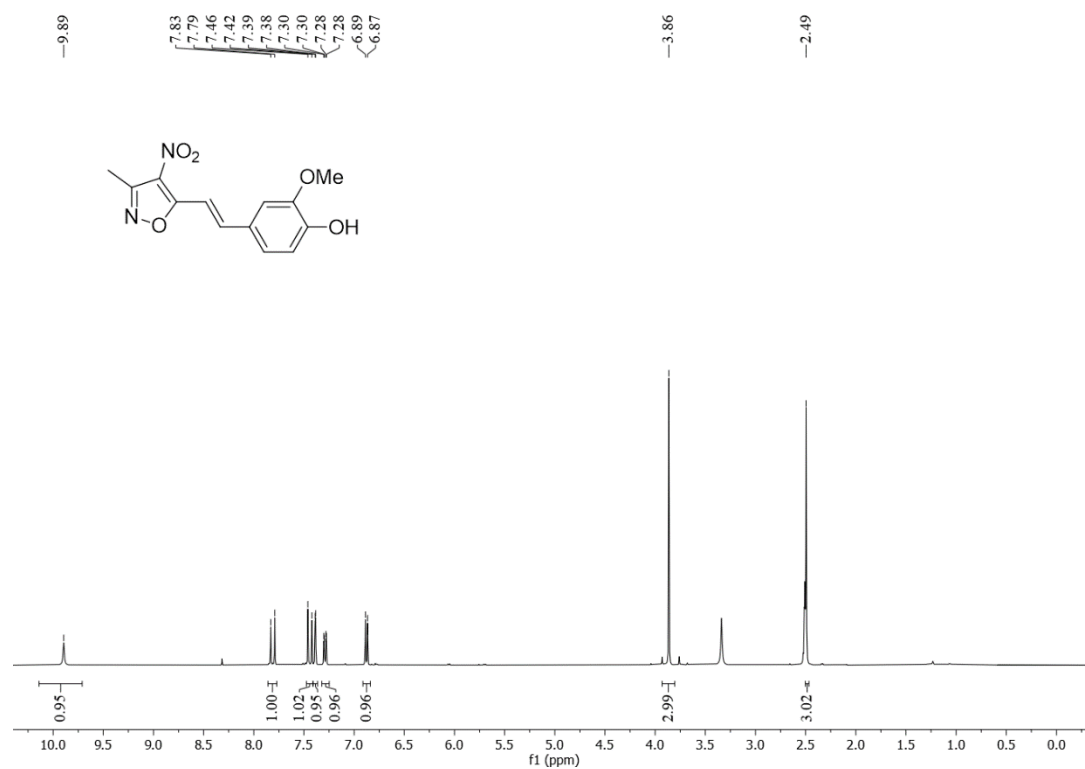
¹H-NMR spectrum of **8**



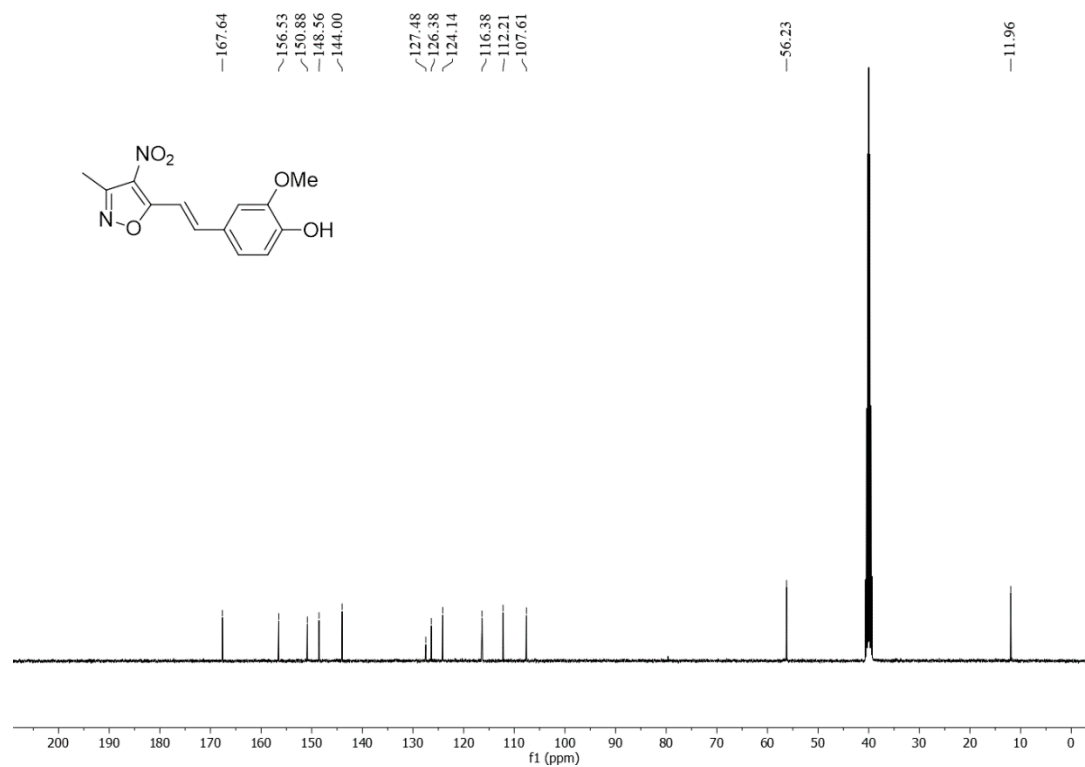
¹³C-NMR spectrum of **8**



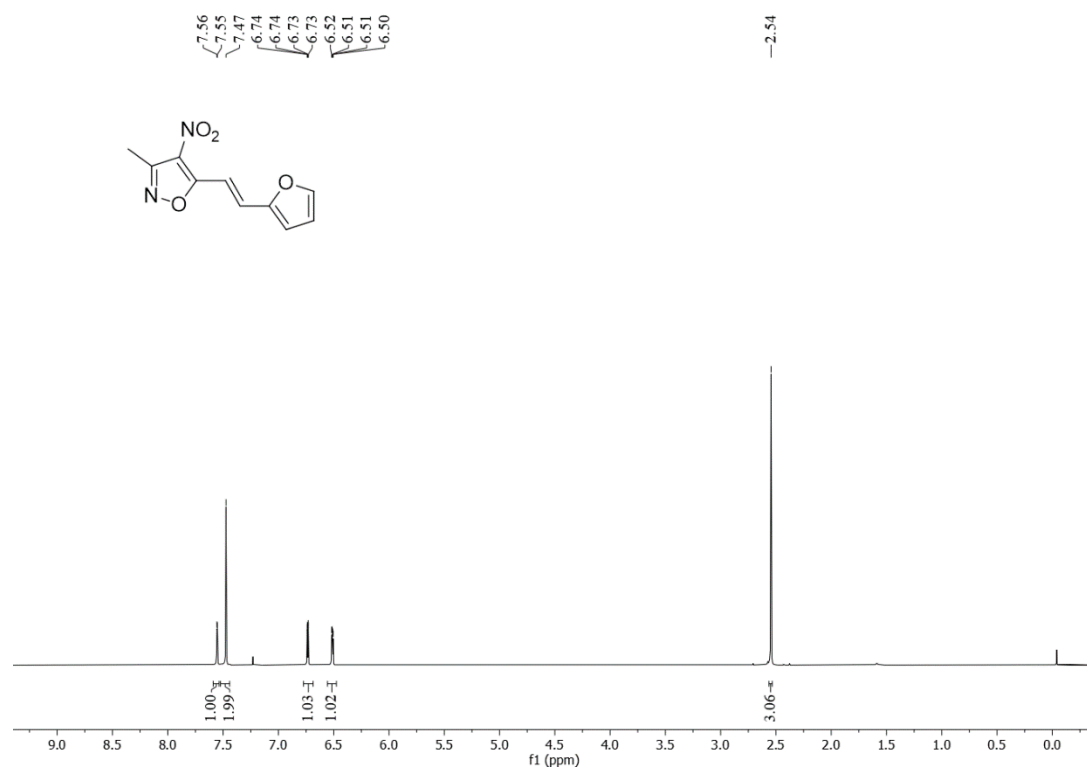
¹H-NMR spectrum of **9**



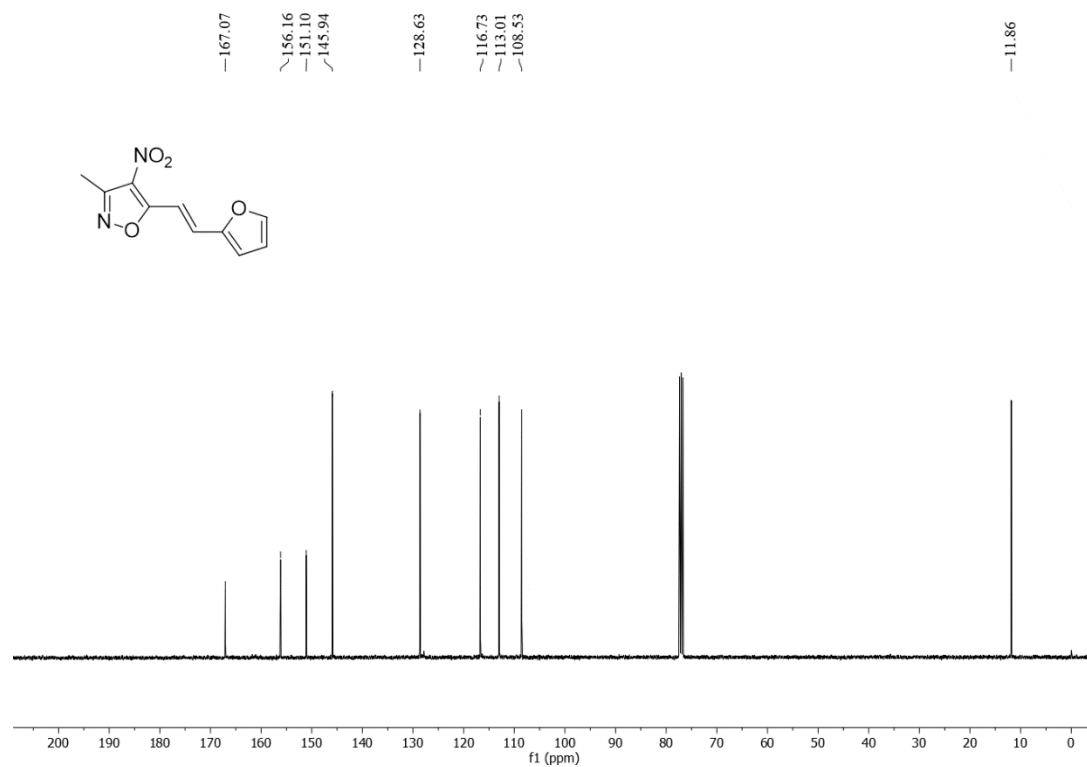
¹³C-NMR spectrum of **9**



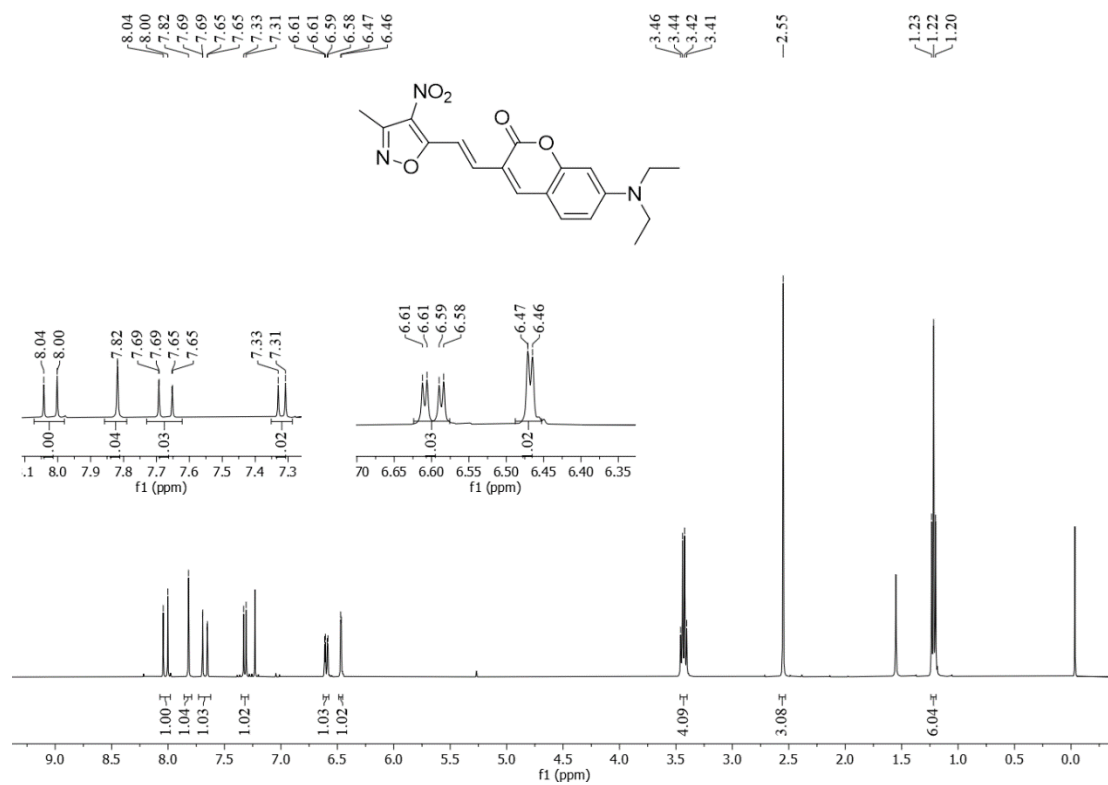
¹H-NMR spectrum of **10**



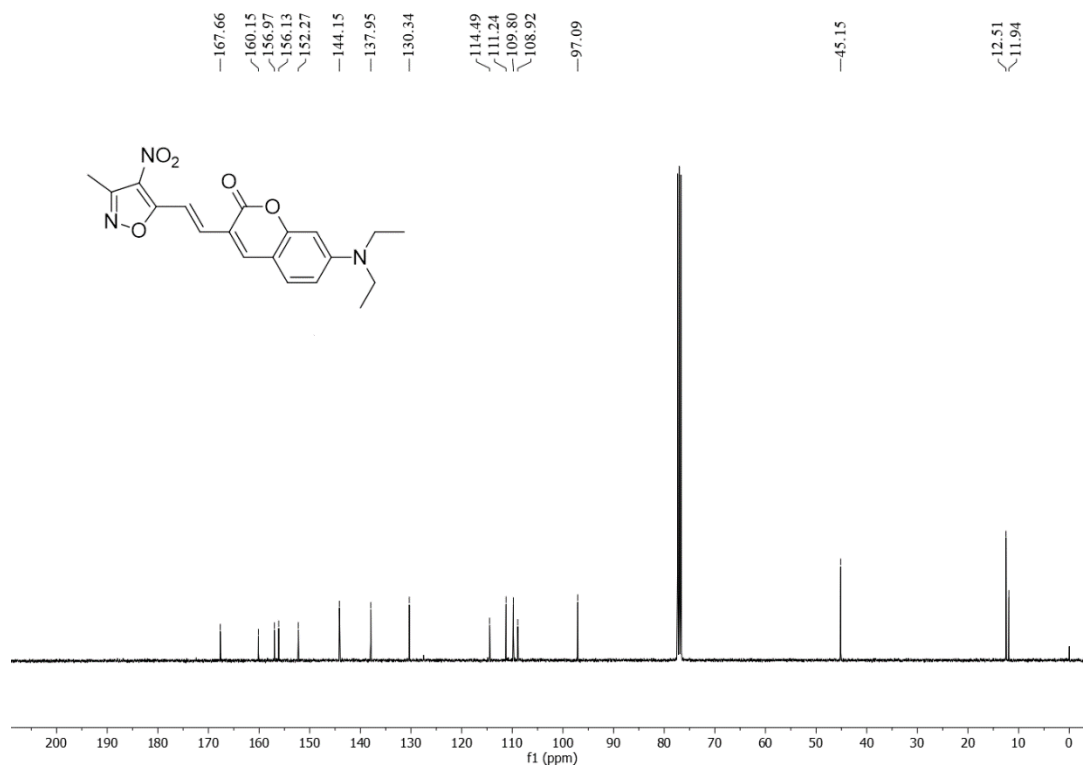
¹³C-NMR spectrum of **10**



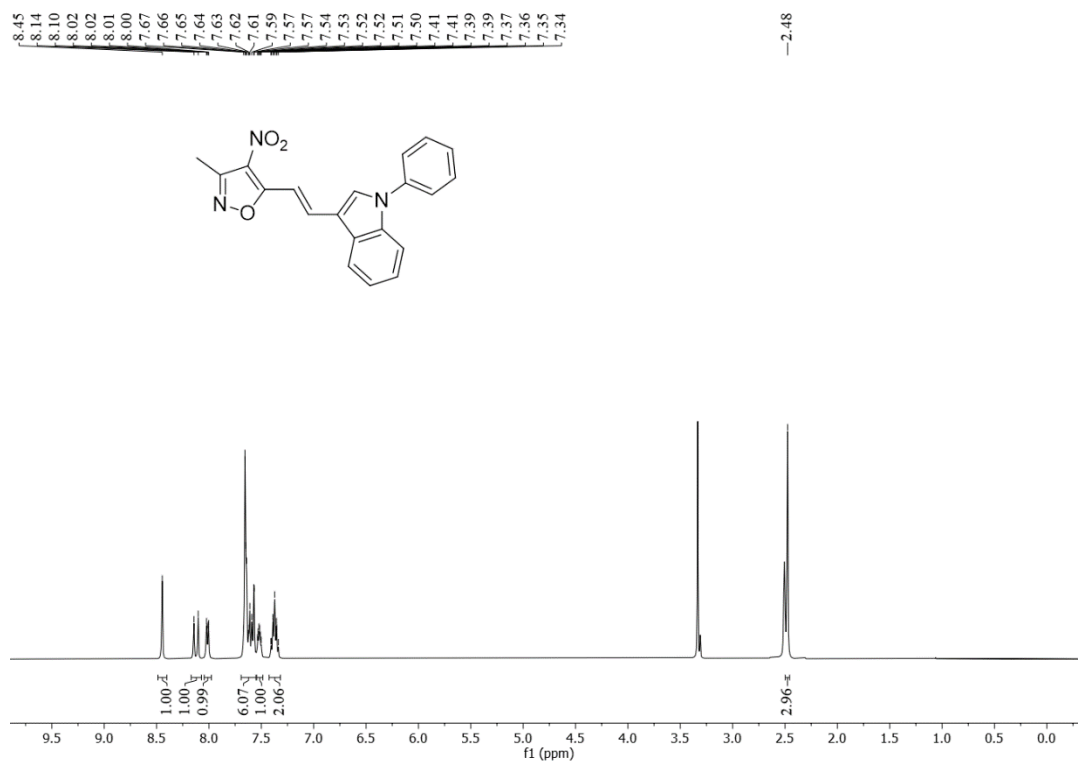
¹H-NMR spectrum of **11**



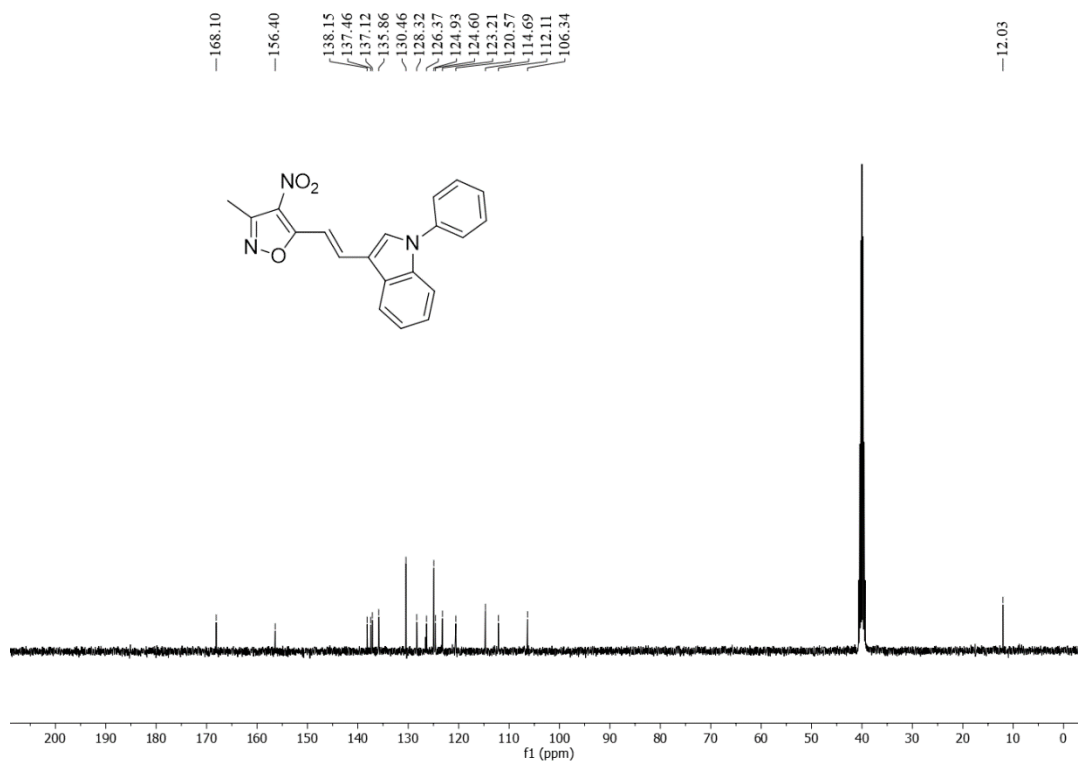
¹³C-NMR spectrum of **11**



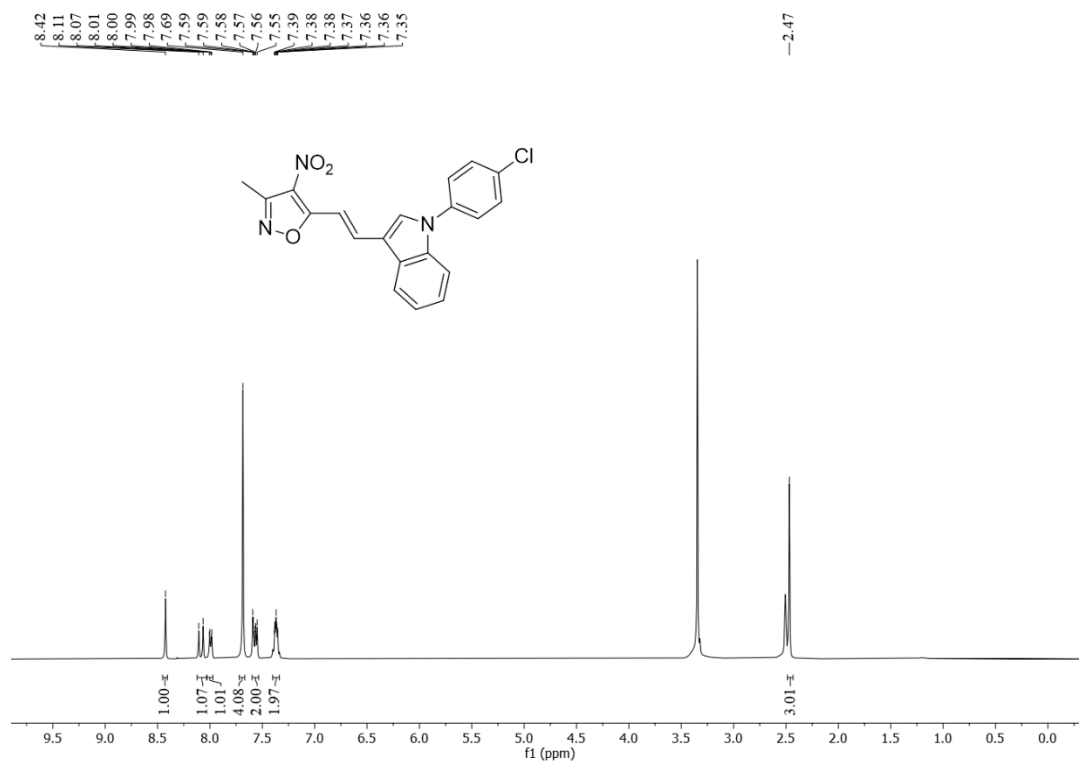
¹H-NMR spectrum of **12**



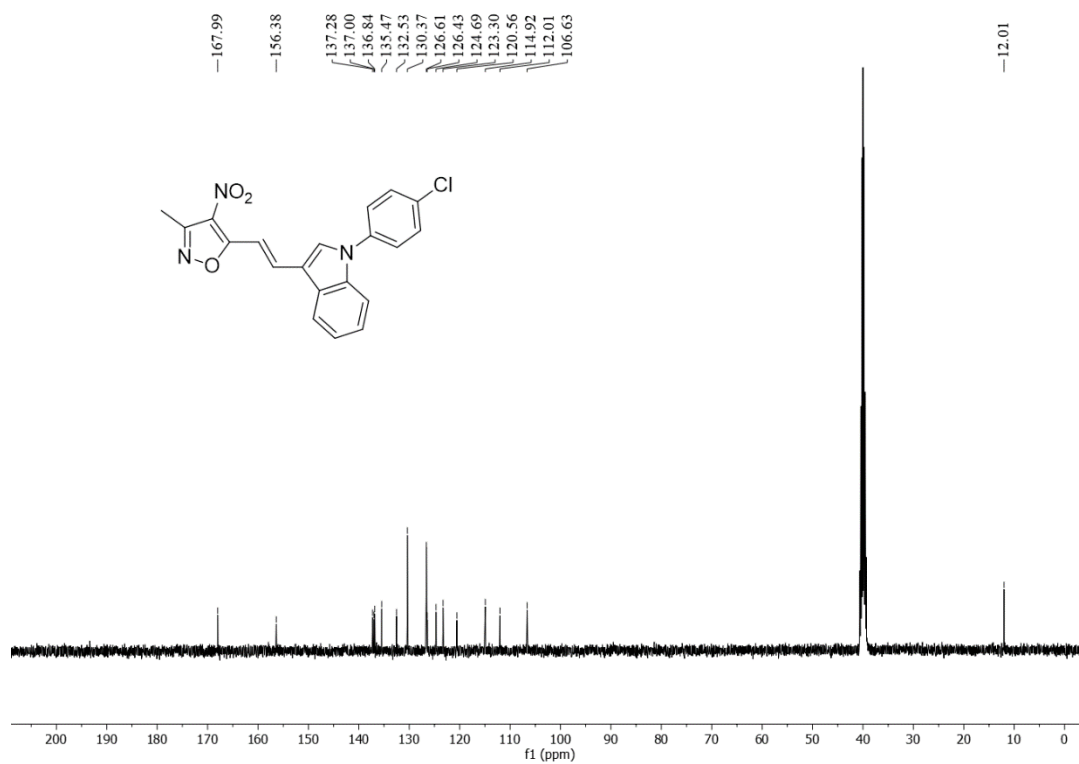
¹³C-NMR spectrum of **12**



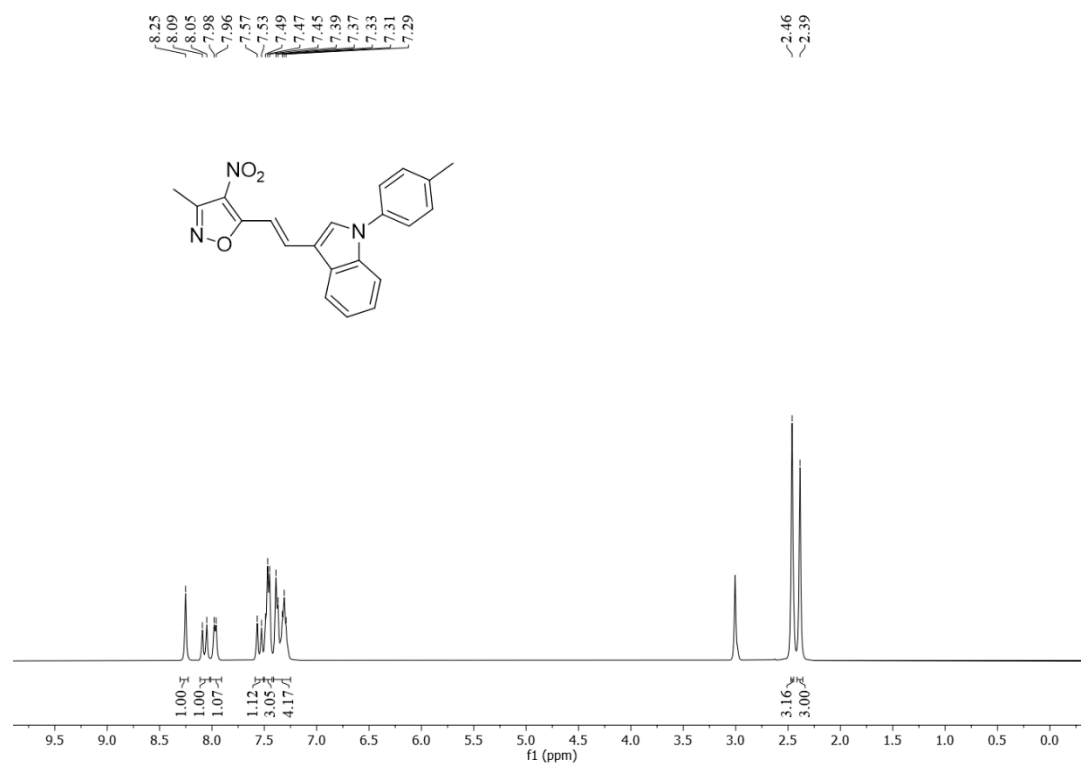
¹H-NMR spectrum of **13**



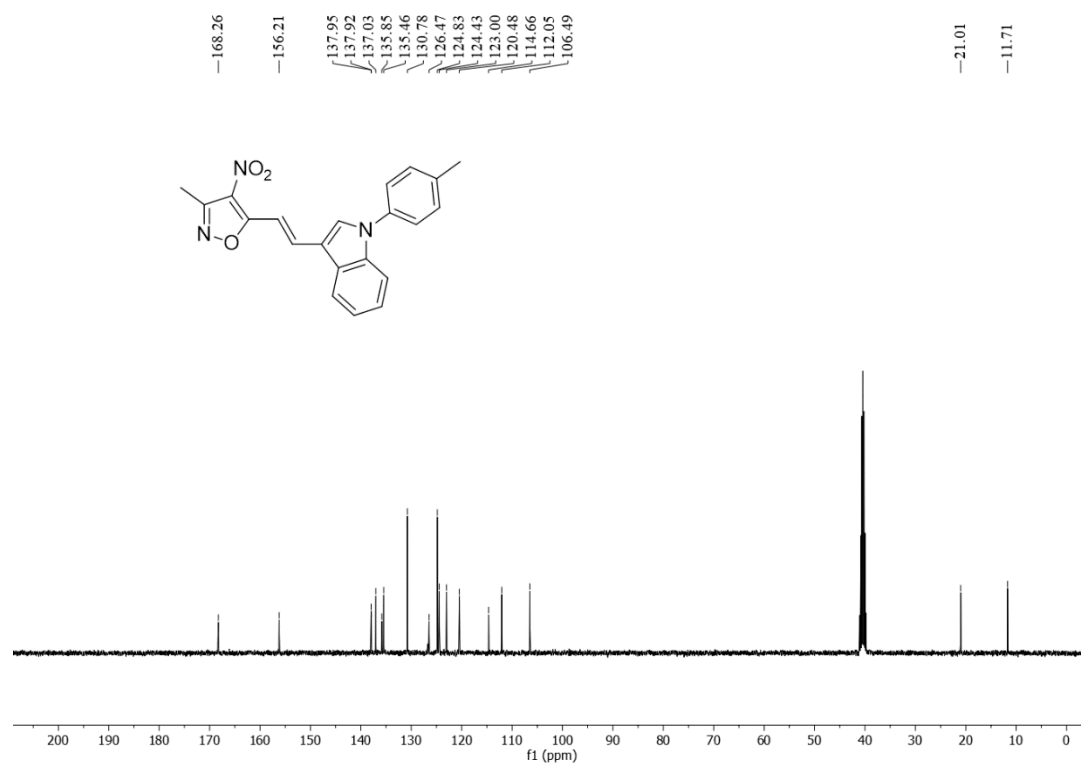
¹³C-NMR spectrum of **13**



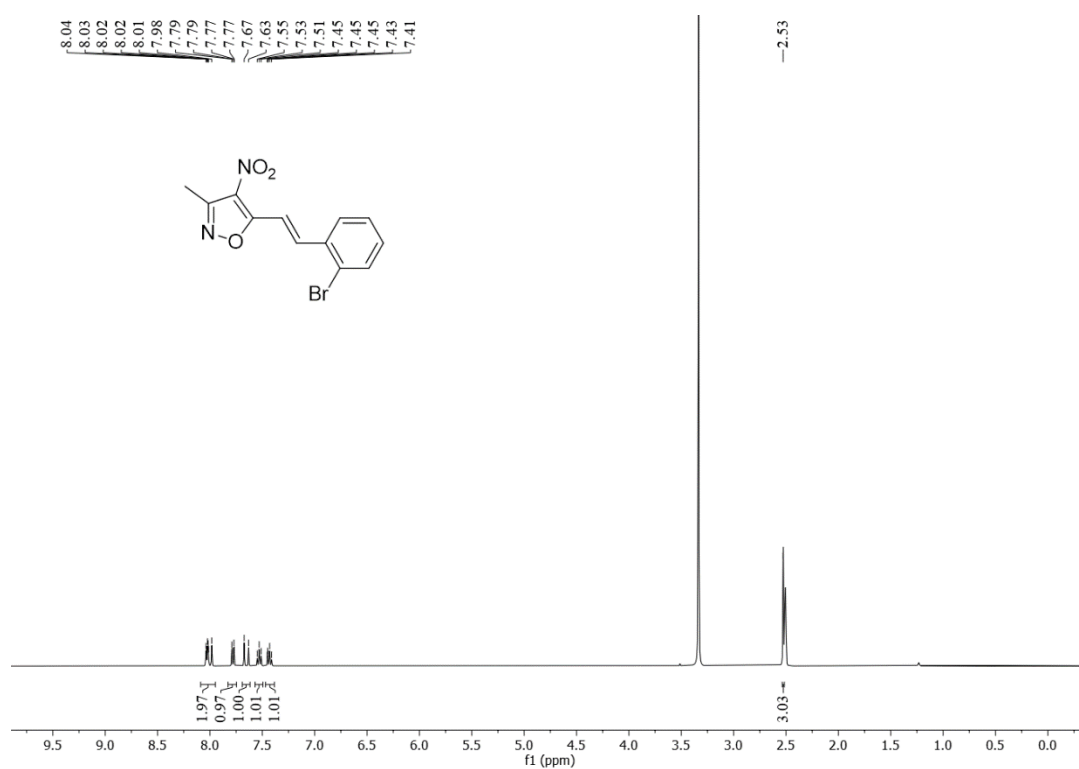
¹H-NMR spectrum of **14**



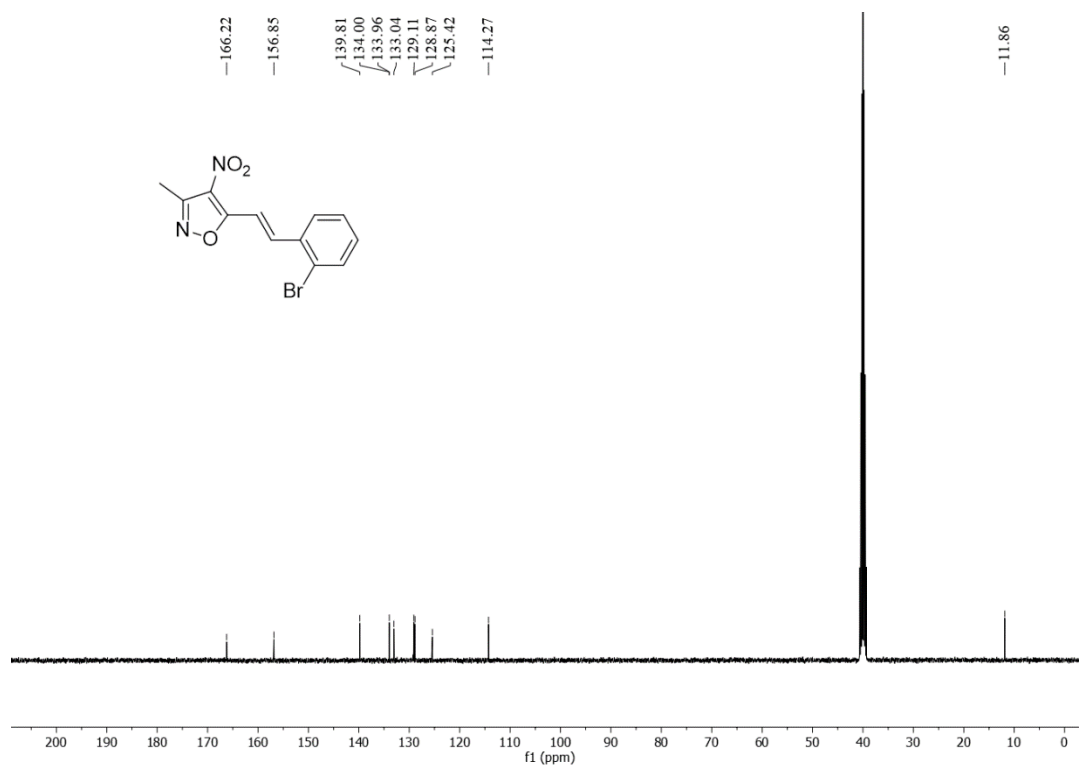
¹³C-NMR spectrum of **14**



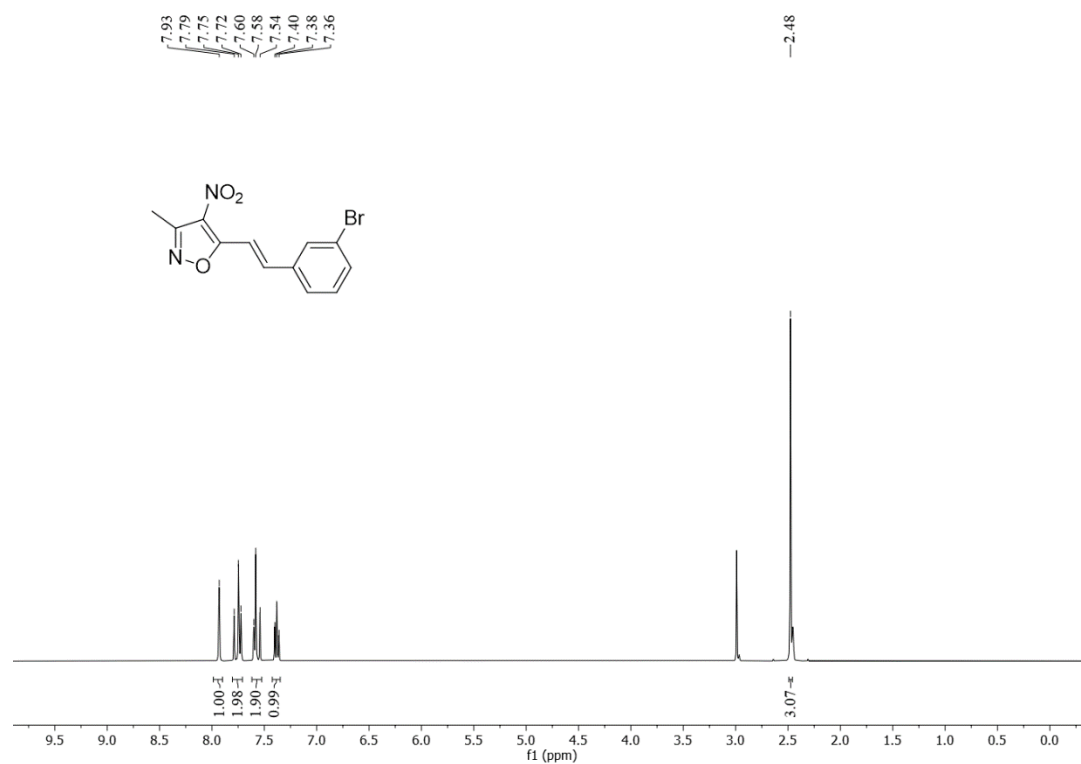
¹H-NMR spectrum of **15**



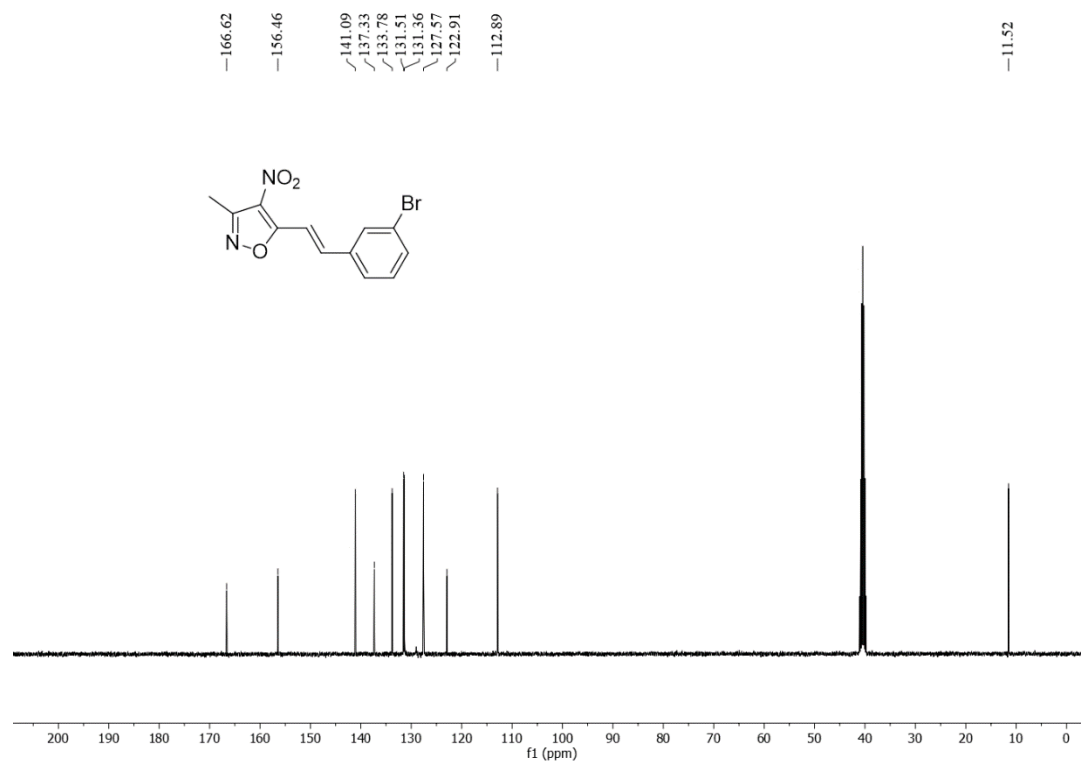
¹³C-NMR spectrum of **15**



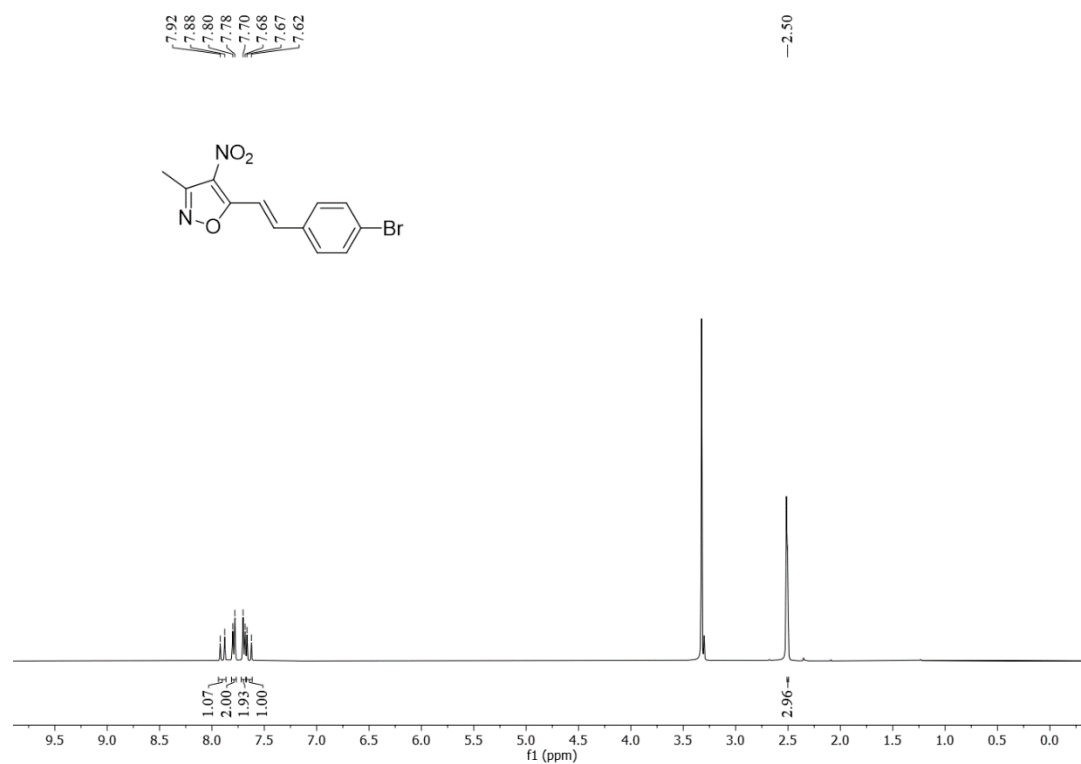
¹H-NMR spectrum of **16**



¹³C-NMR spectrum of **16**



^1H -NMR spectrum of **17**



^{13}C -NMR spectrum of **17**

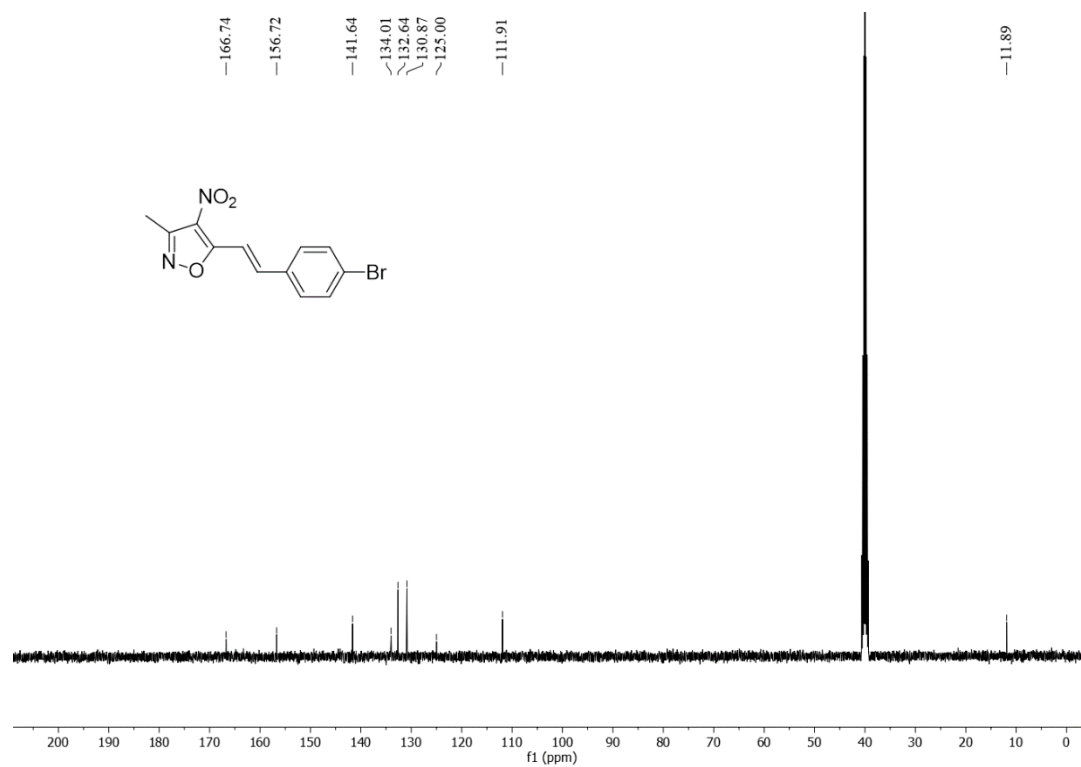
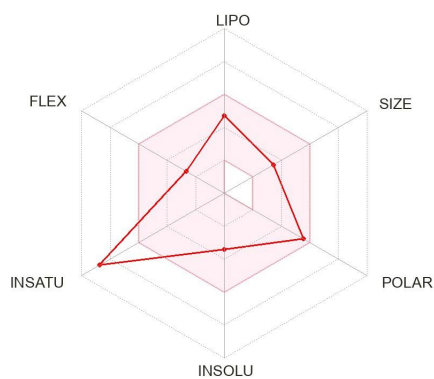
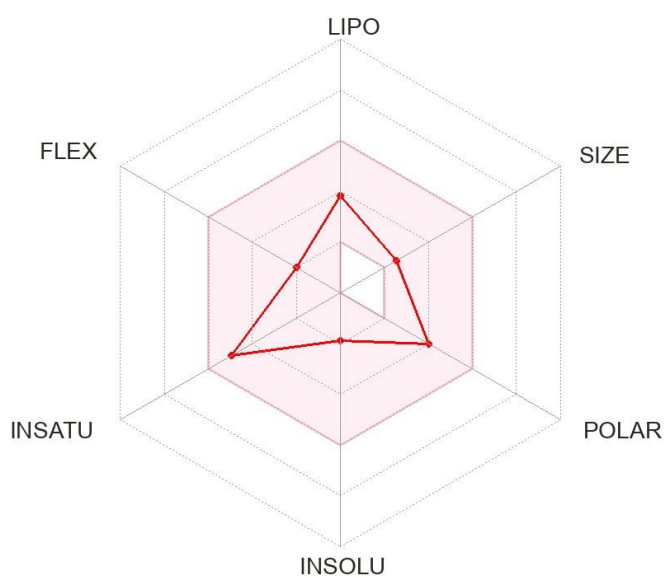


Figure S2: Profile Physicochemical properties

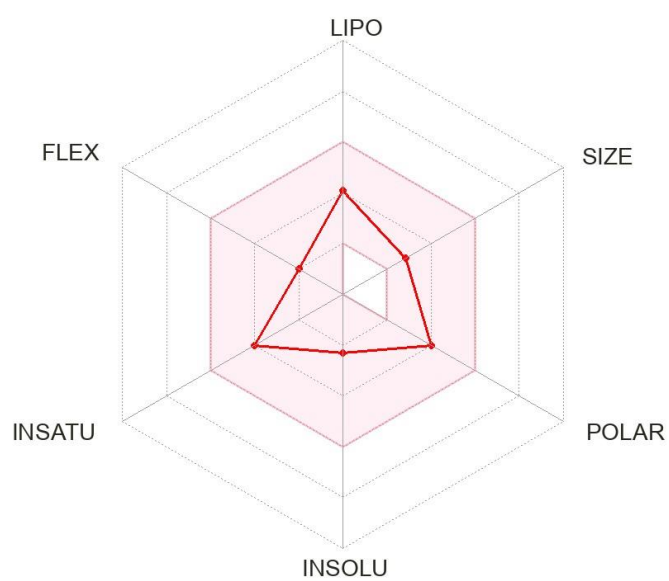
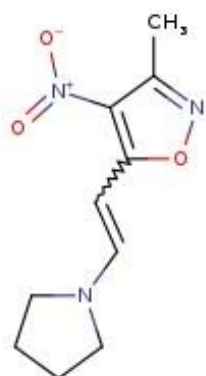


Representative profile of physicochemical properties of the Nitroisoxazole series, the delimited area represents the optimal range for each property (the limits of each property are: Lipophilicity (expressed from the XLOGP3 variable) between -0.7 and +0.5, Size: between 150 and 500g/mol, polarity (TPSA) between 10 to 130 Å², Solubility (Log S) no greater than 6, unsaturations (fraction of carbons with SP³ hybridization) no greater than 0.25, Flexibility no more than 9 rotatable bonds).

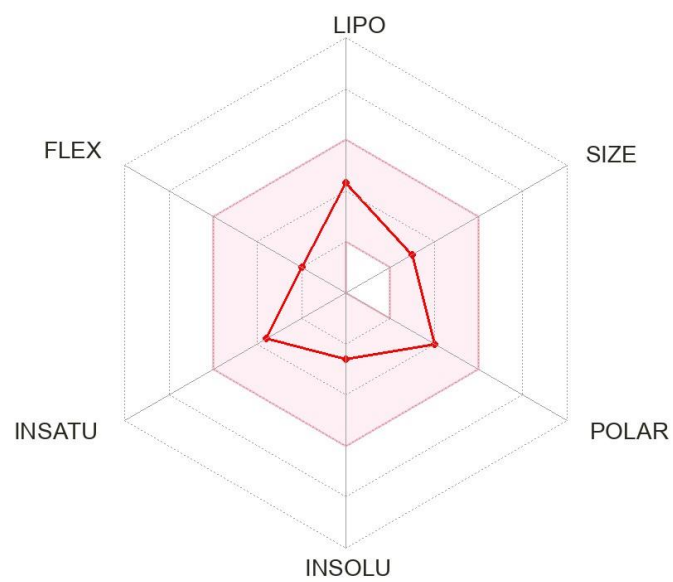
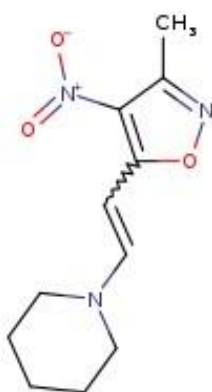
Molecule 1



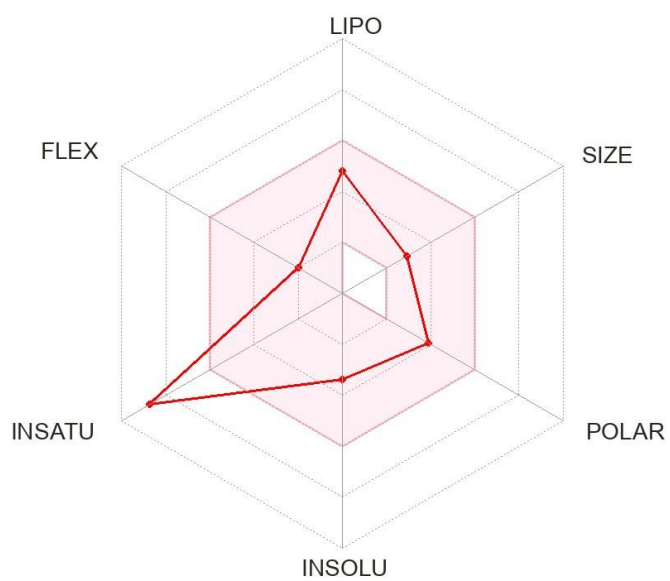
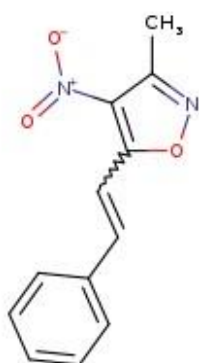
Molecule 2



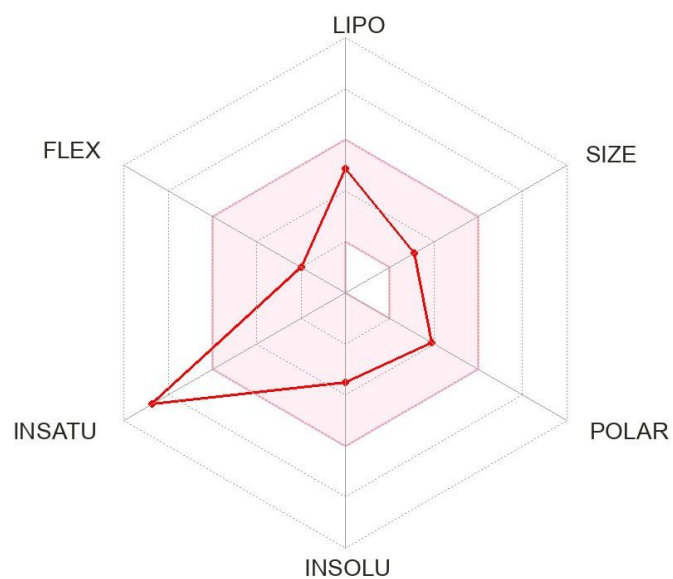
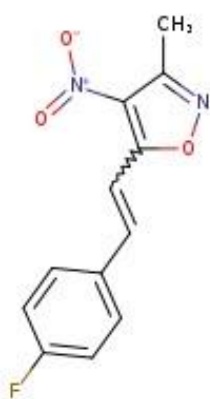
Molecule 3



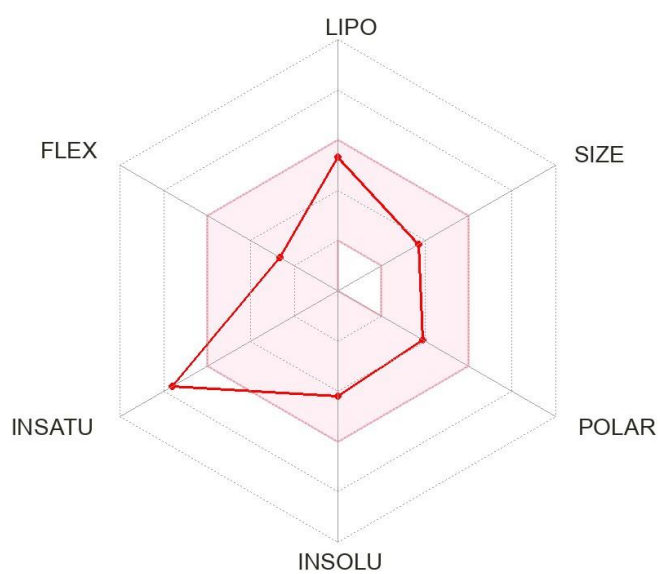
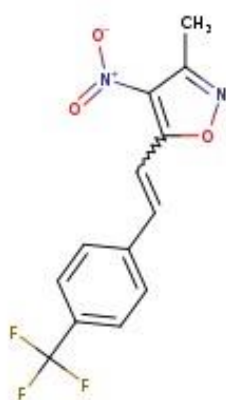
Molecule 4



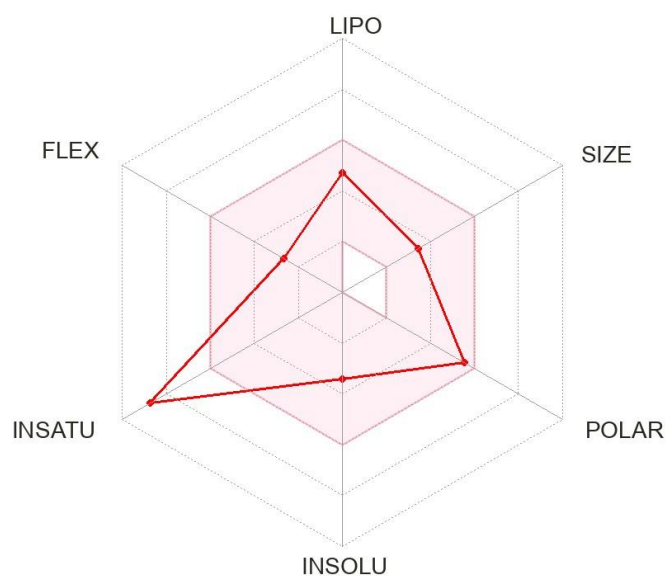
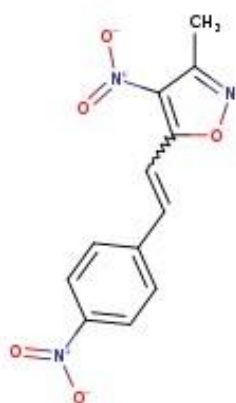
Molecule 5



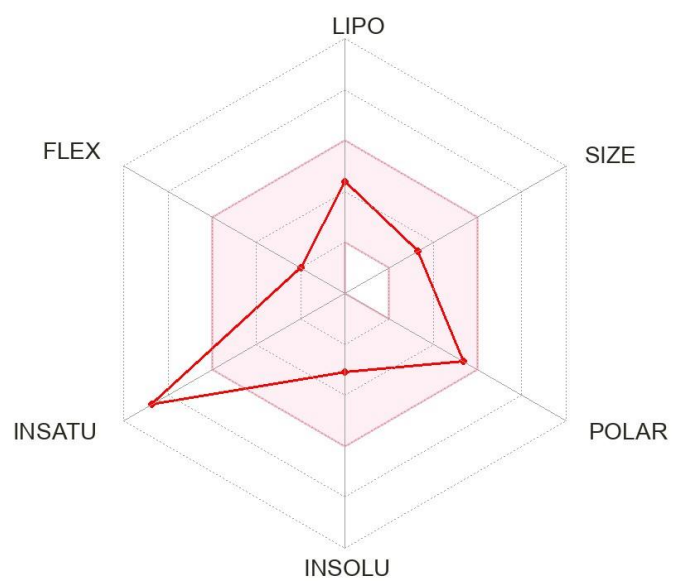
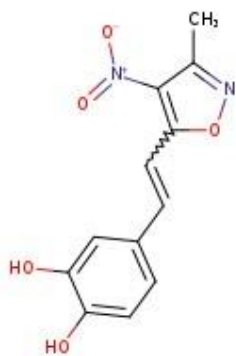
Molecule 6



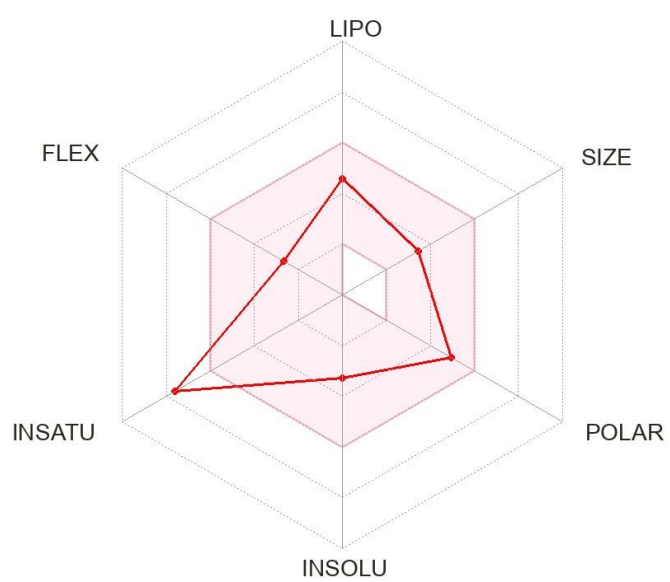
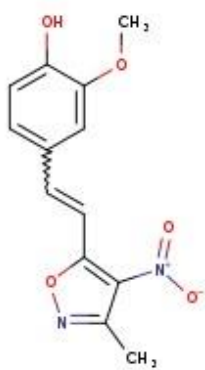
Molecule 7



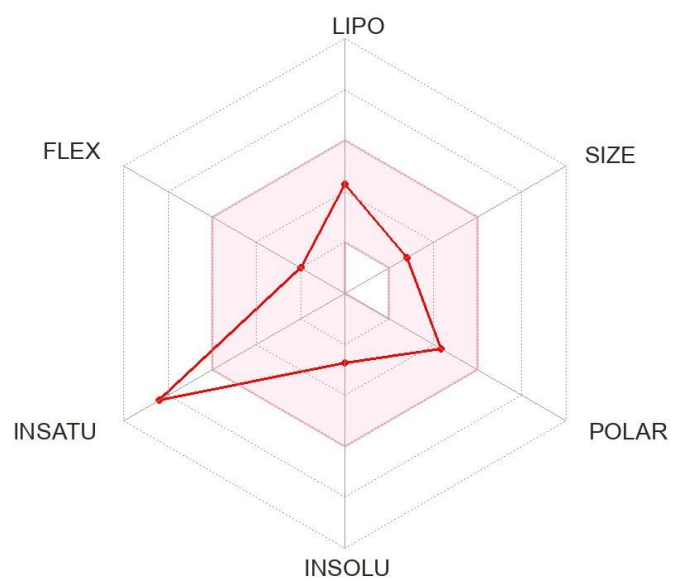
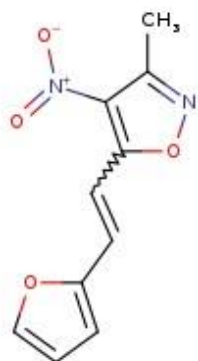
Molecule 8



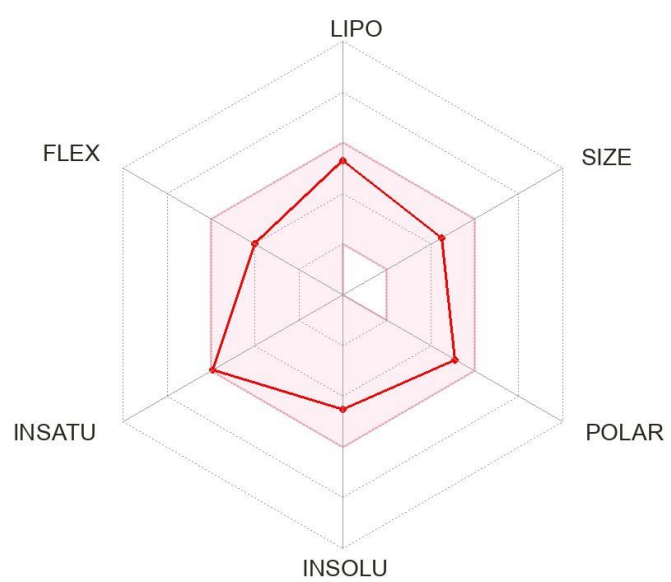
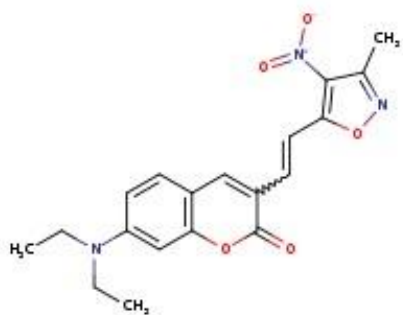
Molecule 9



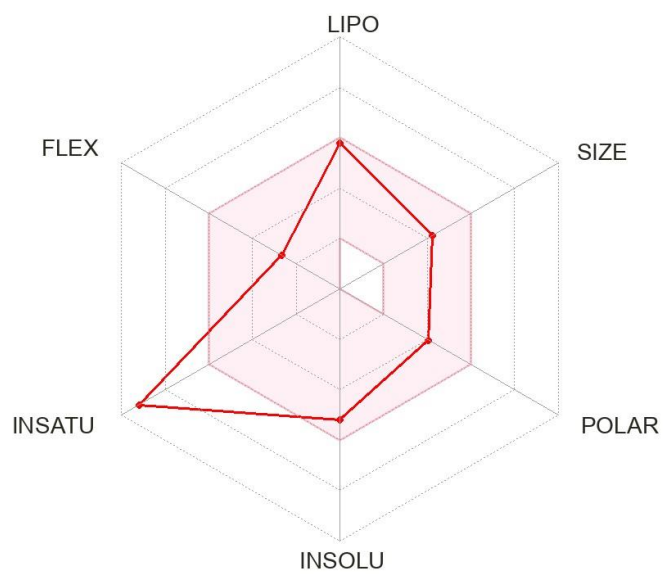
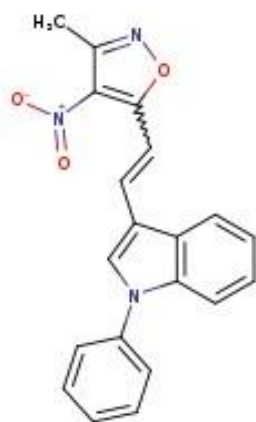
Molecule 10



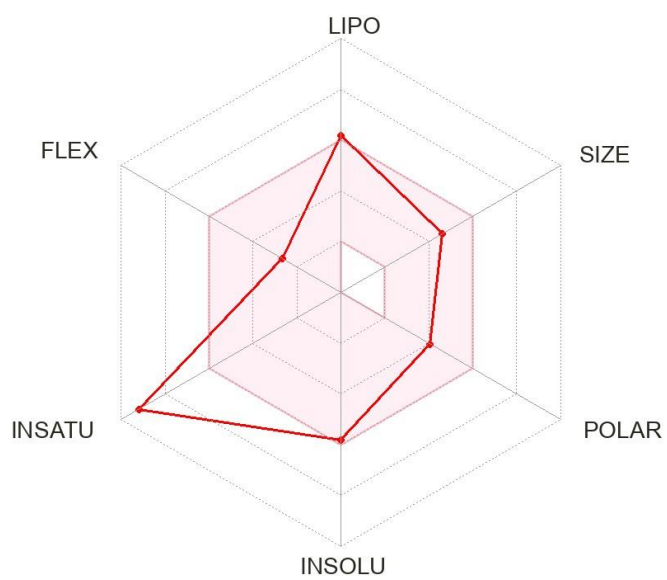
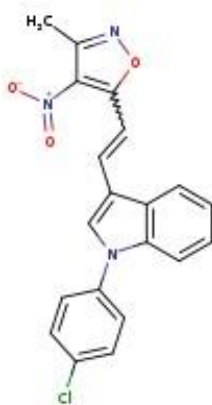
Molecule 11



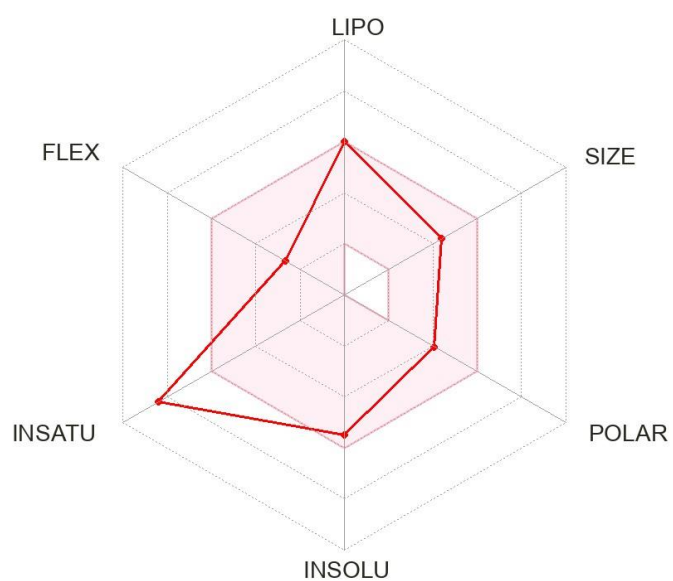
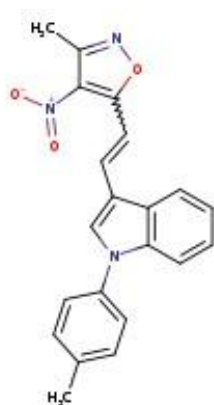
Molecule 12



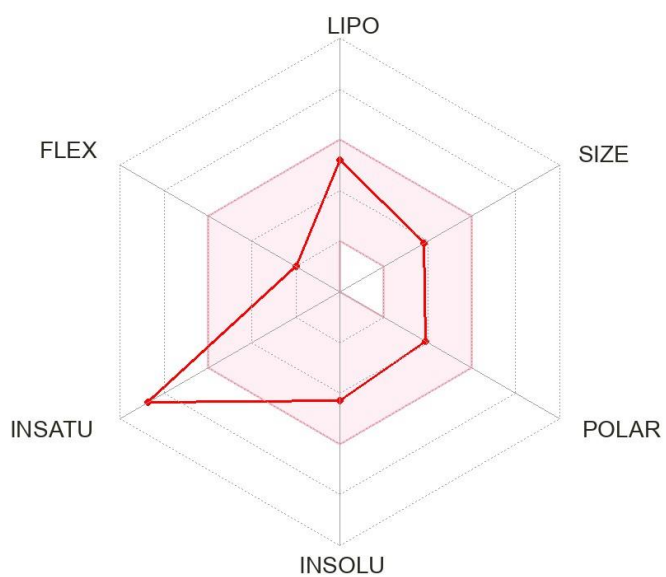
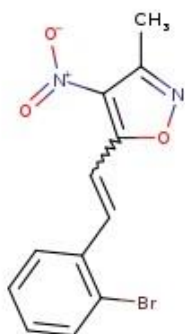
Molecule 13



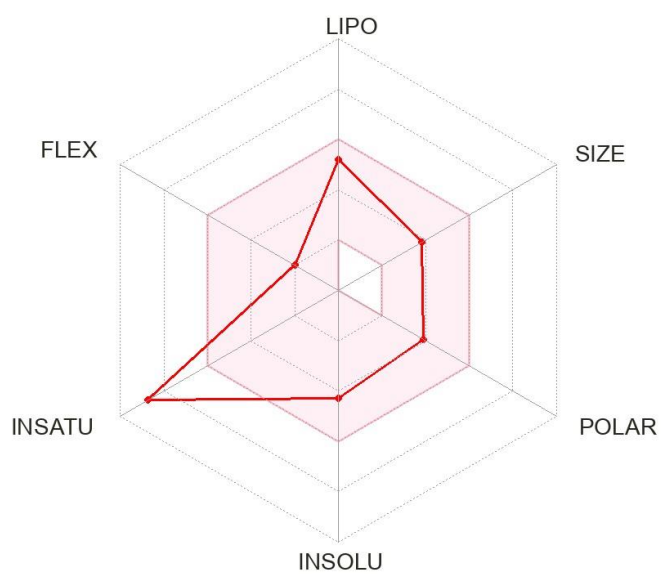
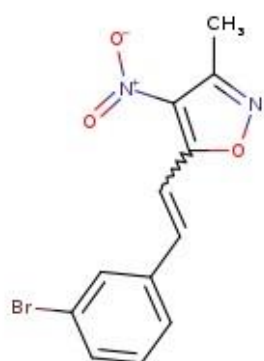
Molecule 14



Molecule 15



Molecule 16



Molecule 17

