

- Supplementary Information -

A family of substituted hydrazoneisoxazolones with potential biological properties

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Table S1. Selected bond lengths (Å), angles (°) and torsion angles (°) of compounds **4**, **12** y **15**, labelled according to Figure 1.

Bond	(4)	Bond	(12)	Bond	(15a)	Bond	(15b)
N(4)-C(5)	1.294(3)	N(3)-C(2)	1.279(3)	C(2)-N(1)	1.278(4)	C(12)-N(11)	1.293(4)
C(5)-C(1)	1.432(2)	C(1)-C(2) <i>d</i> ₂	1.431(3)	C(2)-C(3) <i>d</i> ₂	1.438(5)	C(12)-C(13) <i>d</i> ₂	1.421(4)
C(1)-N(1)	1.315(2)	N(1)-C(1)	1.296(3)	C(3)-N(3)	1.299(4)	C(13)-N(13)	1.310(4)
N(1)-N(2)	1.313(2)	N(1)-N(2)	1.307(2)	N(3)-N(4)	1.308(3)	N(13)-N(14)	1.306(3)
C(2)-C(1)	1.444(3)	C(1)-C(5)	1.440(3)	C(1)-C(3)	1.445(5)	C(11)-C(13)	1.451(4)
O(2)-C(2)	1.215(2)	O(5)-C(5)	1.207(3)	O(0)-C(1)	1.210(4)	O(10)-C(11)	1.202(4)

N(2)-C(6)	1.419(2)	N(2)-C(21)	1.395(3)	C(4)-N(4)	1.411(4)	C(14)-N(14)	1.416(4)
C(2)-O(3)	1.361(2)	O(4)-C(5)	1.351(3)	C(1)-O(1)	1.343(4)	C(11)-O(11)	1.358(4)
N(4)-O(3)	1.475(2)	O(4)-N(3)	1.470(3)	N(1)-O(1)	1.573(4)	N(11)-O(11)	1.500(3)
Angle	(4)	Angle	(12)	Angle	(15a)	Angle	(15b)
N(1)-C(1)-C(5)	124.09(19)	N(1)-C(1)-C(2)	125.3(2)	N(3)-C(3)-C(1)	130.0(3)	N(13)-C(13)-(11)	130.3(3)
N(2)-N(1)-C(1)	119.45(18)	C(1)-N(1)-N(2)	117.81(18)	C(3)-N(3)-N(4)	120.1(3)	N(14)-N(13)-(13)	119.9(3)
O(2)-C(2)-C(1)	130.89(19)	O(5)-C(5)-C(1)	130.3(2)	O(0)-C(1)-C(3)	129.1(3)	O(10)-(11)-C(13)	131.0(3)
N(1)-N(2)-C(6)	119.71(17)	N(1)-N(2)-(21)	120.2(2)	N(3)-N(4)-C(4)	119.3(3)	N(13)-N(14)-(14)	119.6(3)

Table S2. Chemical shift of signals (δ : ppm) in the ^{13}C -NMR spectra of **1-15**.

	C₁	C₂	C₃	C₄	C₅	C₆, C₇	C₈	C_R
1	10.01	159.72	118.16	163.14	133.53	118.68, 116.02	156.50	---
2	10.35	159.44	120.07	165.55	134.17	117.79, 115.26	158.84	55.80
3	10.34	159.49	120.63	165.30	137.15	130.52, 116.25	138.30	21.20
4	10.36	159.55	121.34	165.11	140.56	129.98, 116.28	126.91	---
5	10.33	159.44	121.97	165.00	139.19	130.13, 117.39	132.20	---
6	10.36	159.45	122.08	164.98	139.67	133.05, 117.67	119.88	---
7	10.08	160.07	122.14	161.97	144.95	130.82 116.47	127.65	166.67
8	10.39	159.51	123.39	164.57	144.03	130.51 115.88	134.98	196.55, 26.67
9	10.37	159.43	124.17	164.31	143.83	134.10, 116.40	118.37	109.50
10	10.11	160.16	123.92	161.39	146.96	125.37, 116.96	144.06	---
	C₁	C₂	C₃	C₄	C₅	C₆, C₇, C₈, C₉	C₁₀	C_R
11	9.85	159.33	120.69	164.28	128.35	127.13, 120.31 115.93, 114.71	146.39	---
12	10.38	159.37	123.47	164.52	137.22	130.15, 128.41	122.23	---

							126.88, 116.28	
13	9.99	159.75	123.08	162.23	131.36		142.65, 134.64 125.00, 115.12	116.12 168.34
14	9.94.	159.73	126.03	162.35	135.35		136.81, 126.00 125.20, 116.88	136.59 ---
	C₁	C₂	C₃	C₄	C₅	C₆, C₇, C₈, C₁₀	C₉	
15	10.38	159.48	122.47	164.80	141.70		130.98, 126.67 116.11, 114.57	136.10 ---

Table S3. Experimental (exp) and calculated (Th.) wavelength (nm), Energy (eV), Oscillator Strength (*f*), Active MOs and their contributions for the vertical excitations from TDDFT for the λ_{max} .

Comp.	C(mol/L)	$\lambda_1(\text{exp})$	$\lambda_1(\text{Th})$	%Orb. Contrib.		eV	<i>f</i>	$\lambda_2(\text{exp})$	$\lambda_2(\text{Th})$	%Orb. Contrib.		eV	<i>f</i>	$\lambda_3(\text{exp})$	$\lambda_3(\text{Th})$	%Orb. Contrib.		eV	<i>f</i>						
1	5.05	427(4.40)	433	57	\rightarrow	58	79	2.86	0.7	300(3.43)	293	55	\rightarrow	58	77	4.23	0.04	252(4.00)	248	53	\rightarrow	58	84	4.99	0.11
2	5.05	405(4.37)	410	57	\rightarrow	58	79	3.03	0.73	260(3.94)	253	57	\rightarrow	59	82	4.9	0.1	253(4.02)	242	53	\rightarrow	58	79	5.11	0.12
3	4.93	421(4.41)	438	61	\rightarrow	62	80	2.83	0.7	303(3.42)	295	59	\rightarrow	62	64	4.2	0.04	252(4.02)	252	57	\rightarrow	62	86	4.91	0.1
4	5.05	396(4.40)	397	53	\rightarrow	54	79	3.12	0.69	255(3.99)	247	53	\rightarrow	55	83	5.03	0.09	249(4.05)	238	49	\rightarrow	54	76	5.21	0.13
5	5.05	397(4.42)	405	61	\rightarrow	62	80	3.06	0.75	258sh(3.95)	257	61	\rightarrow	63	82	4.82	0.09	250(4.05)	249	57	\rightarrow	62	82	4.99	0.12
6	4.95	399(4.45)	410	70	\rightarrow	71	81	3.03	0.77	260(3.97)	259	70	\rightarrow	72	82	4.79	0.09	251(4.06)	258	65	\rightarrow	71	87	4.81	0.1
7	5.05	396(4.50)	396	64	\rightarrow	65	80	3.14	0.87	265sh(4.04)	266	64	\rightarrow	66	73	4.67	0.22	256(4.07)	248	64	\rightarrow	67	65	5	0.01
8	5.05	399(4.36)	399	64	\rightarrow	65	80	3.11	0.91	276(3.89)	278	64	\rightarrow	66	65	4.47	0.16	254(3.89)	252	62	\rightarrow	66	51	4.92	0.01
9	5.05	391(4.50)	394	59	\rightarrow	60	80	3.15	0.89	264sh(4.03)	259	59	\rightarrow	61	64	4.78	0.28	254(4.09)	250	59	\rightarrow	62	73	4.97	0.02
10	5.05	400(4.59)	410	64	\rightarrow	65	82	3.03	0.98	297(3.73)	297	61	\rightarrow	65	82	4.17	0.04	222sh(3.98)	228	58	\rightarrow	65	84	5.44	0.03
11	5	425(4.37)	430	57	\rightarrow	58	79	2.88	0.54	259sh(3.78)	248	57	\rightarrow	59	74	5.01	0.04	245(3.98)	236	53	\rightarrow	58	65	5.27	0.11
12	5.05	395(4.17)	399	61	\rightarrow	62	80	3.11	0.64	260(3.71)	251	61	\rightarrow	63	83	4.93	0.08	252(3.80)	241	56	\rightarrow	62	72	5.15	0
13	5.05	399(4.41)	390	64	\rightarrow	65	79	3.2	0.65	273sh(3.86)	289	61	\rightarrow	65	57	4.3	0.07	264(3.97)	278	60	\rightarrow	65	83	4.5	0.03
14	5.05	410(4.32)	420	64	\rightarrow	65	75	2.95	0.25	343(4.09)	355	64	\rightarrow	66	74	3.5	0.32	281(3.99)	276	62	\rightarrow	66	72	4.49	0.01
15	5	390(4.32)	393	61	\rightarrow	62	79	3.16	0.7	260sh(3.91)	252	61	\rightarrow	63	80	4.91	0.05	252(4.00)	244	57	\rightarrow	62	80	5.09	0.19

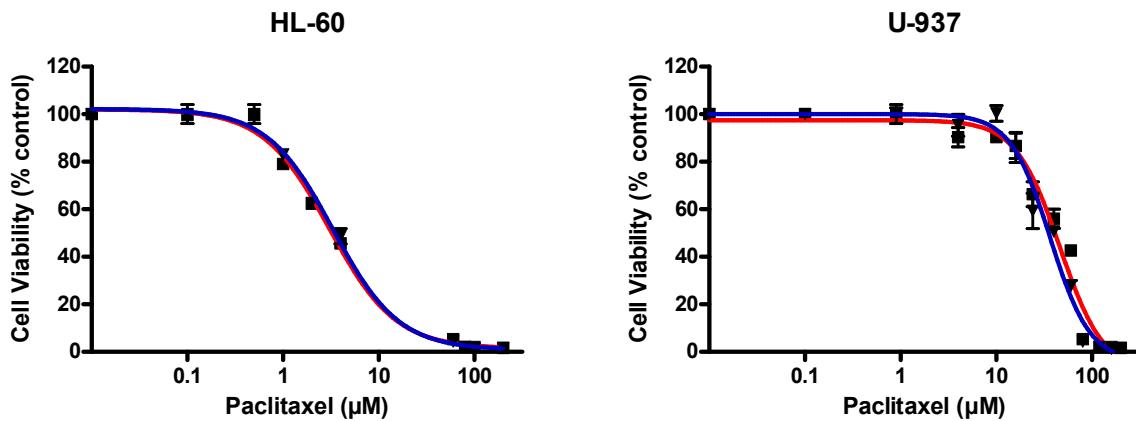


Figure S1. Effect of paclitaxel on cell viability of HL-60 and U937 cells. The cytotoxic effect induced on cell lines HL-60 and U-937 after the exposure to different concentrations of paclitaxel (0 - 200 μ M) by 24 h was expressed as viability percentage change compared to the control sample (untreated cells). The IC₅₀ values were obtained from dose-response curves by no-linear regression using GraphPad Prism software, the IC₅₀values obtained were 3.1 ± 1 and $41 \pm 7 \mu$ M for HL-60 and U-937 cells, respectively. Results shown for each cell line correspond to two independent experiments each in triplicate, and the IC₅₀ values are presented as mean \pm SD.

Paclitaxel (trade names: Taxol®, OnxalTM) is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug, being classified as a "plant alkaloid," a "taxane" and an "antimicrotubule agent." Paclitaxel is used for treatment of breast, ovarian, lung, bladder, prostate, melanoma, esophageal, as well as other types of solid tumor cancers. It has also been used in Kaposi's sarcoma (<http://chemocare.com/chemotherapy/drug-info/Paclitaxel.aspx>)

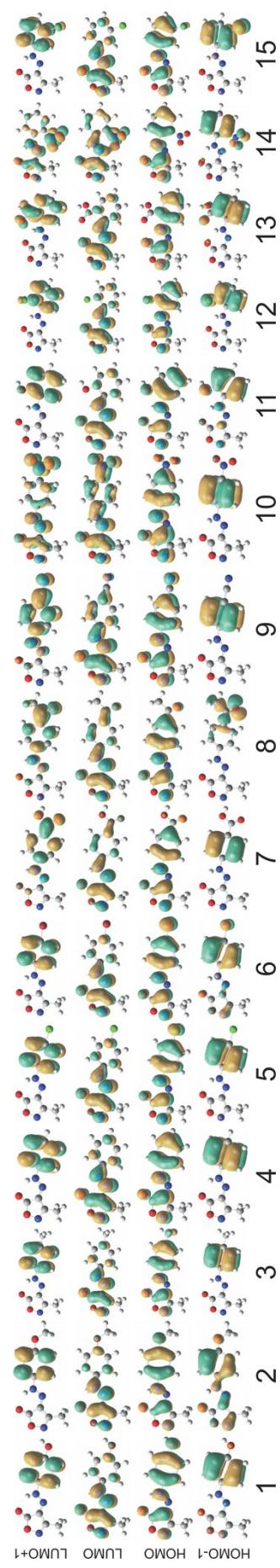
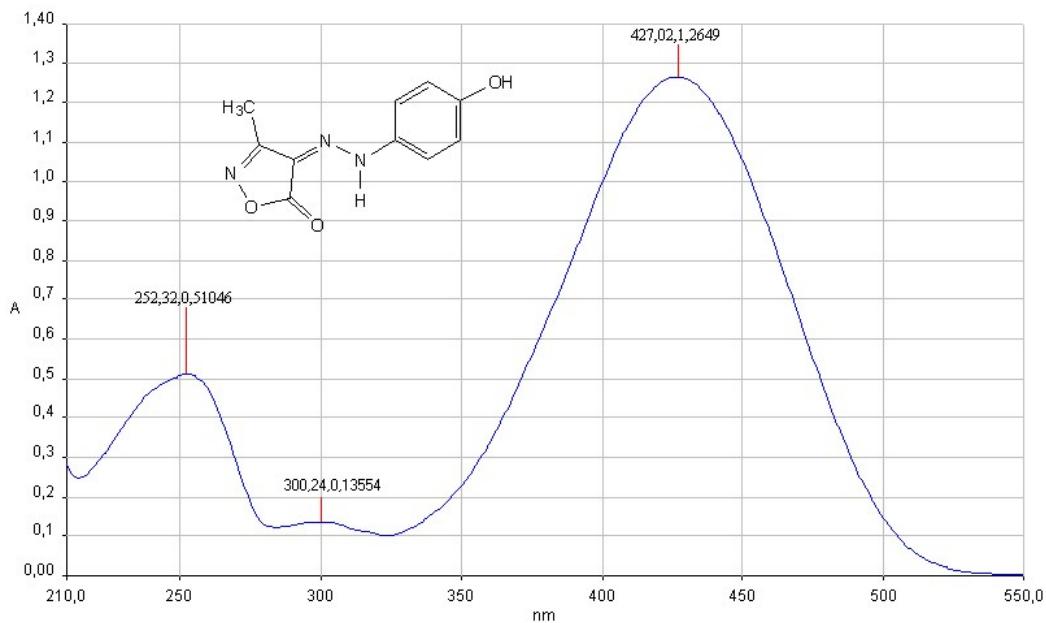
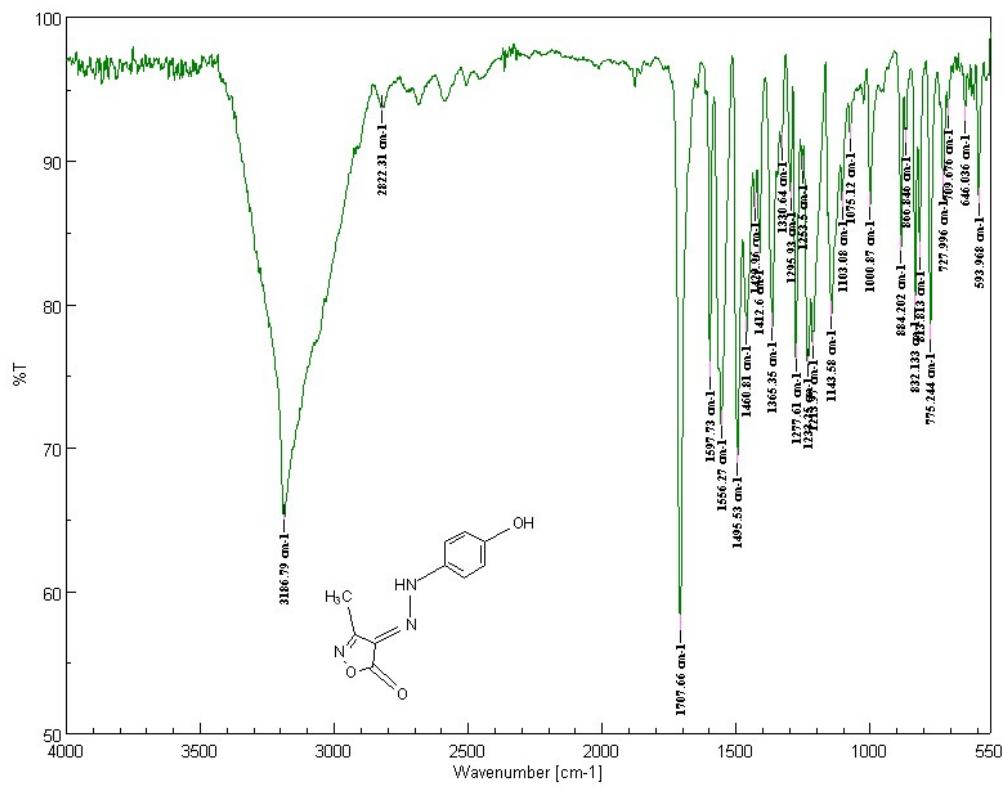


Figure S2. FMOs for all the synthesized compounds.

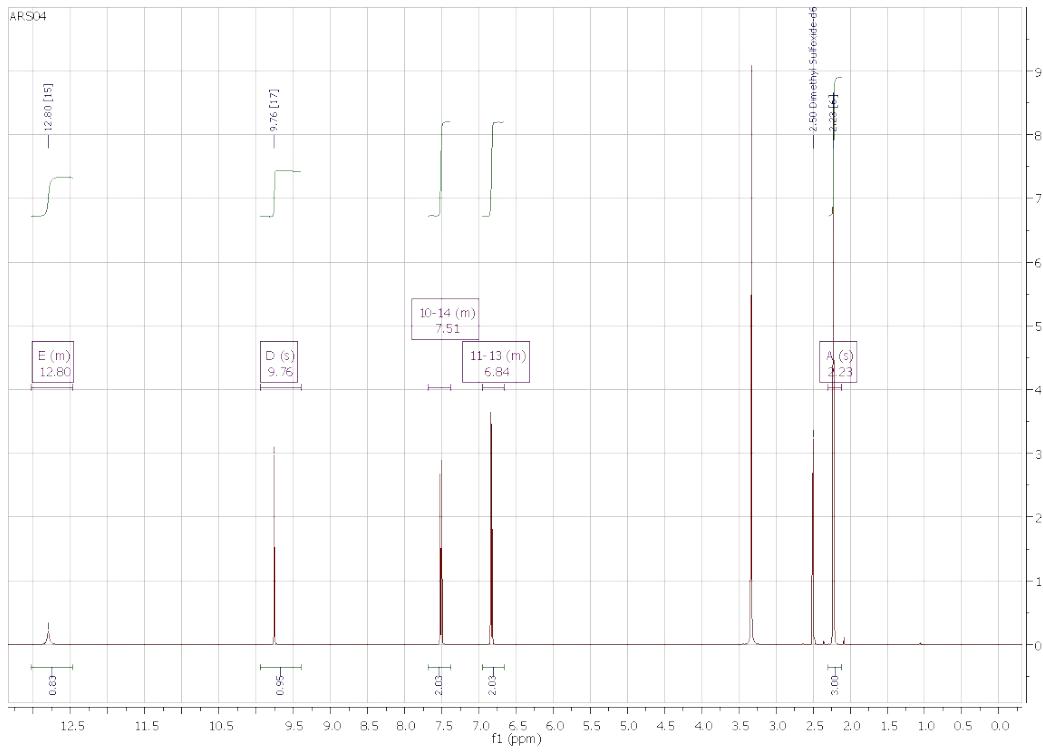
Compound (1)
UV-Vis Spectra



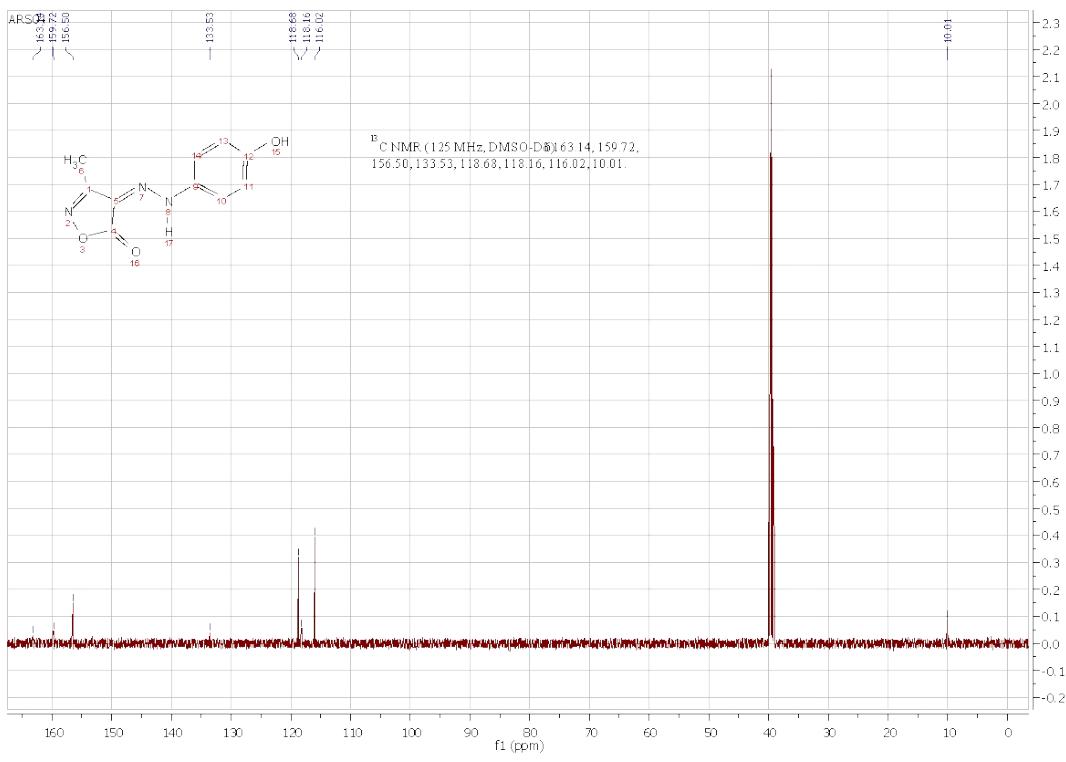
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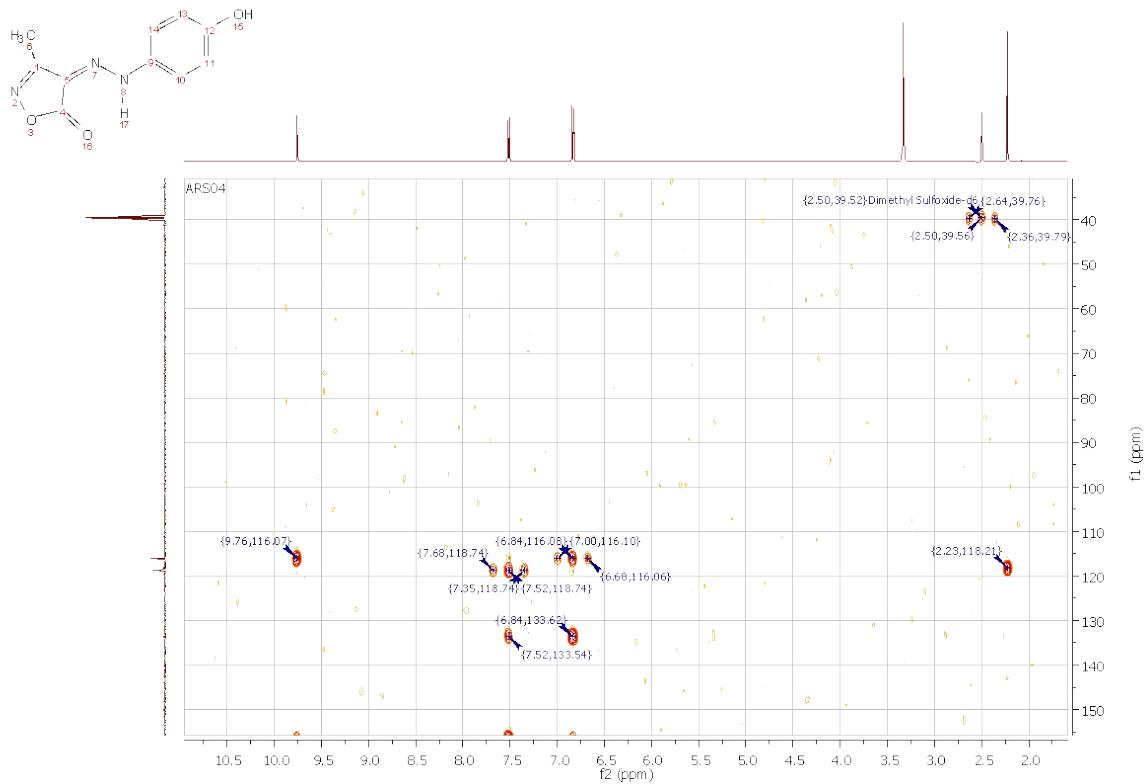
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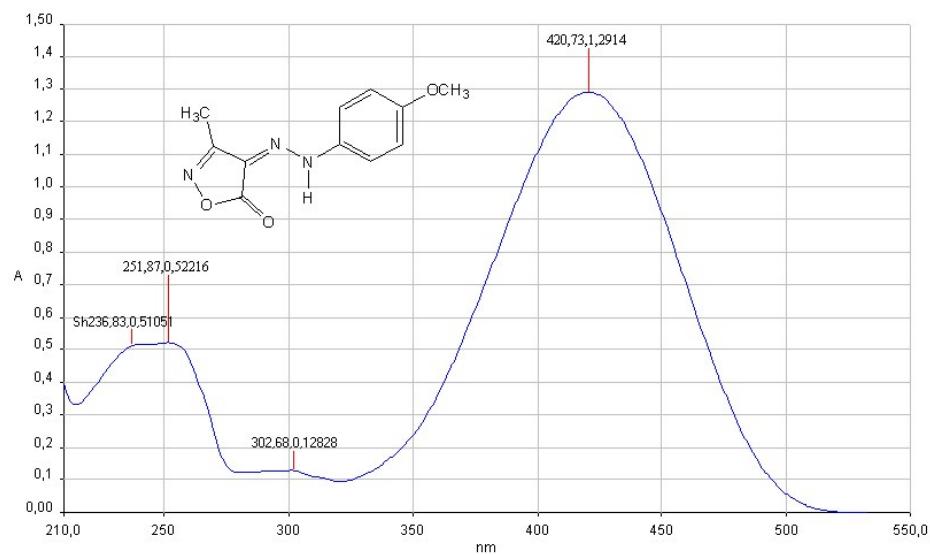
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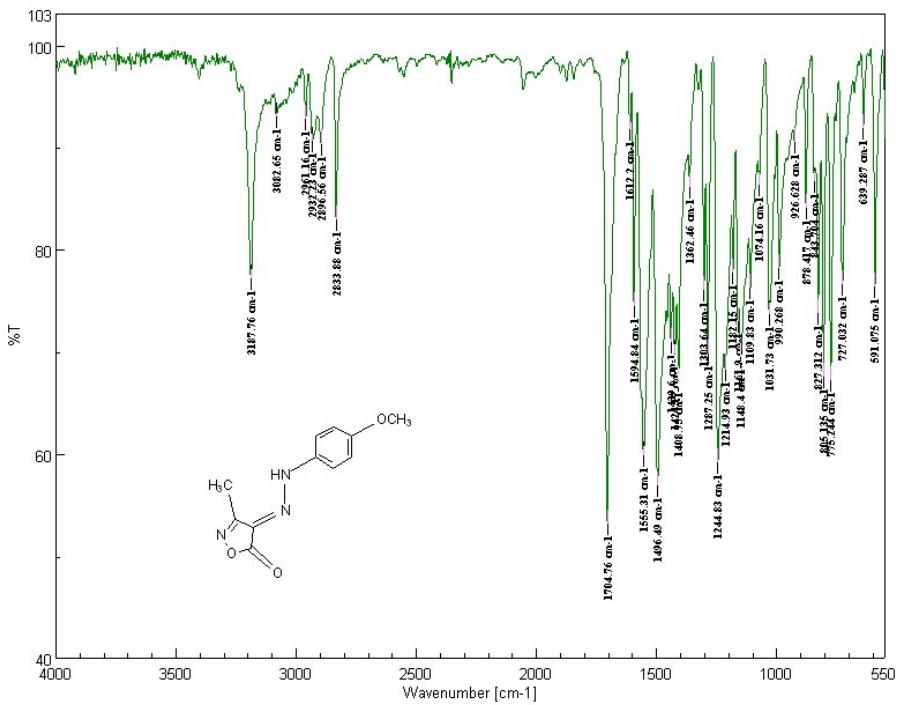
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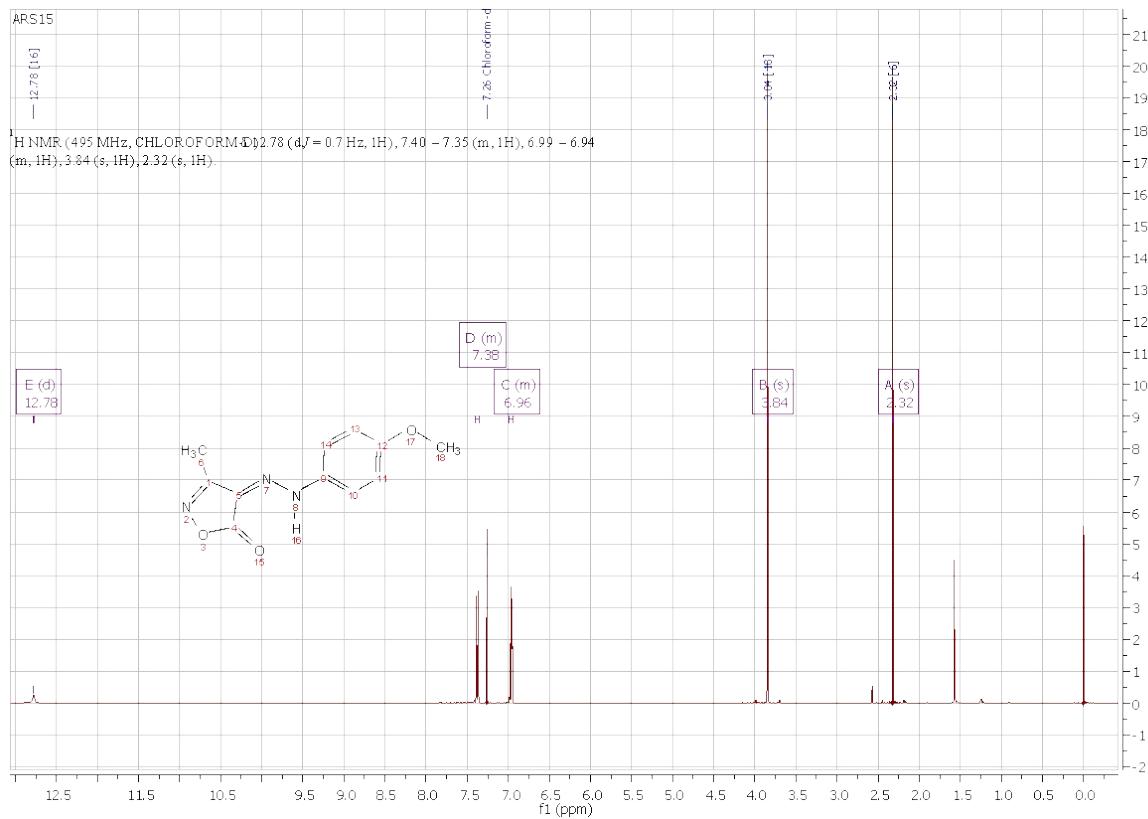
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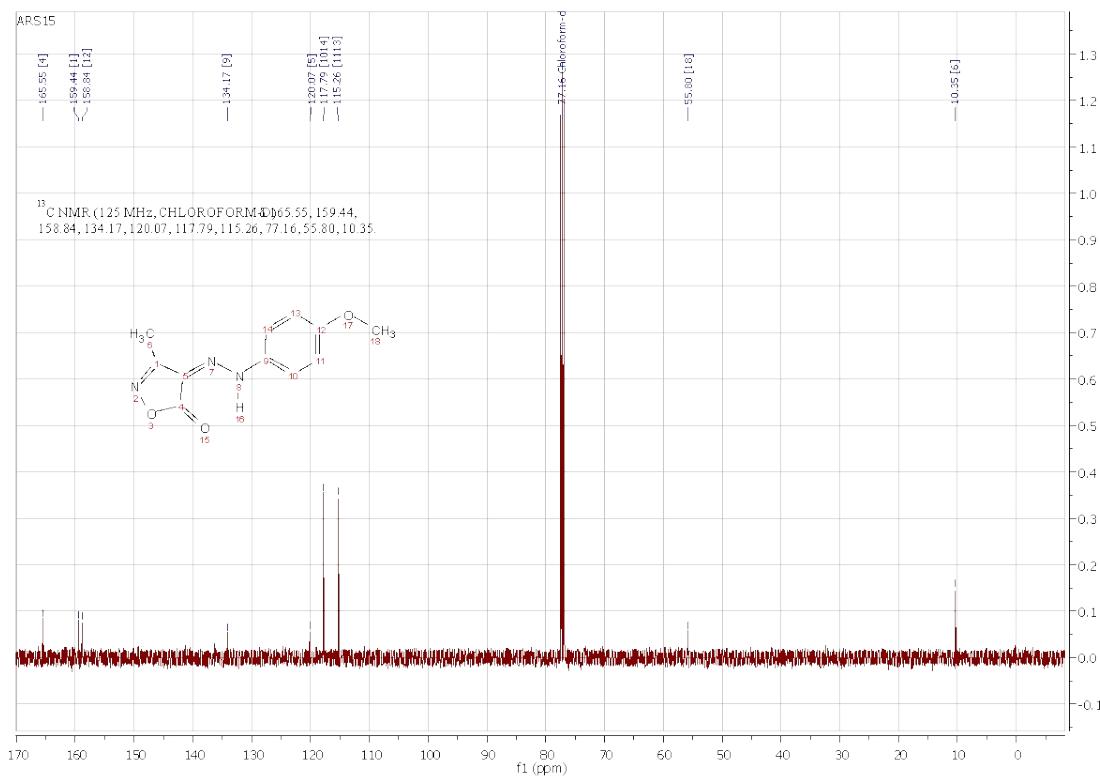
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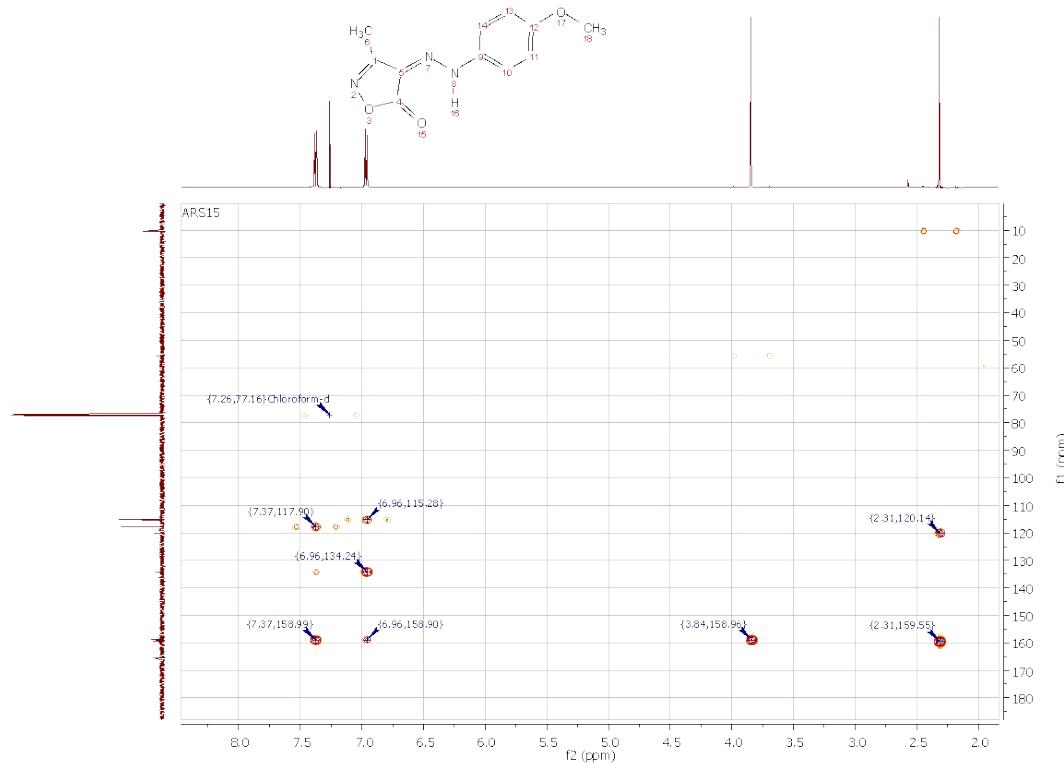
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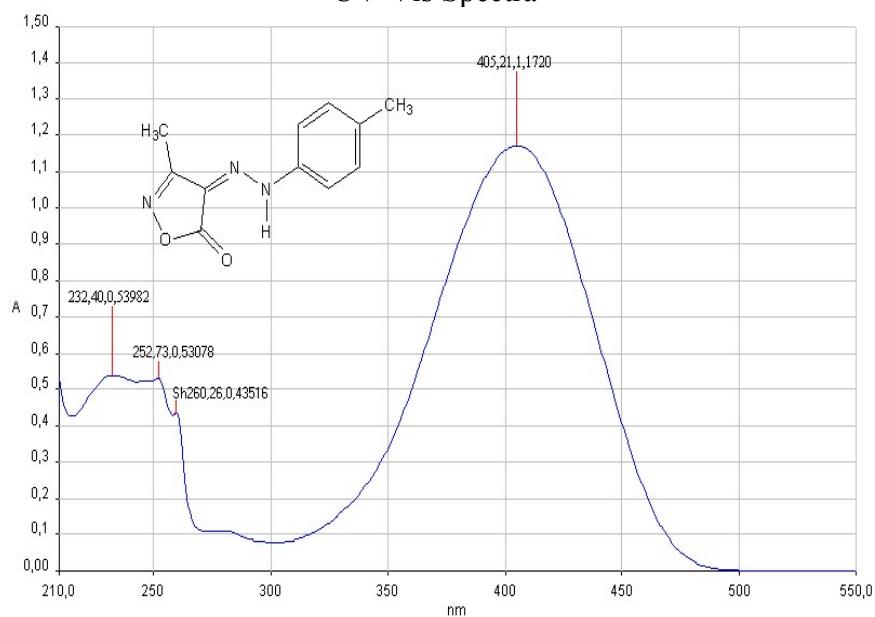


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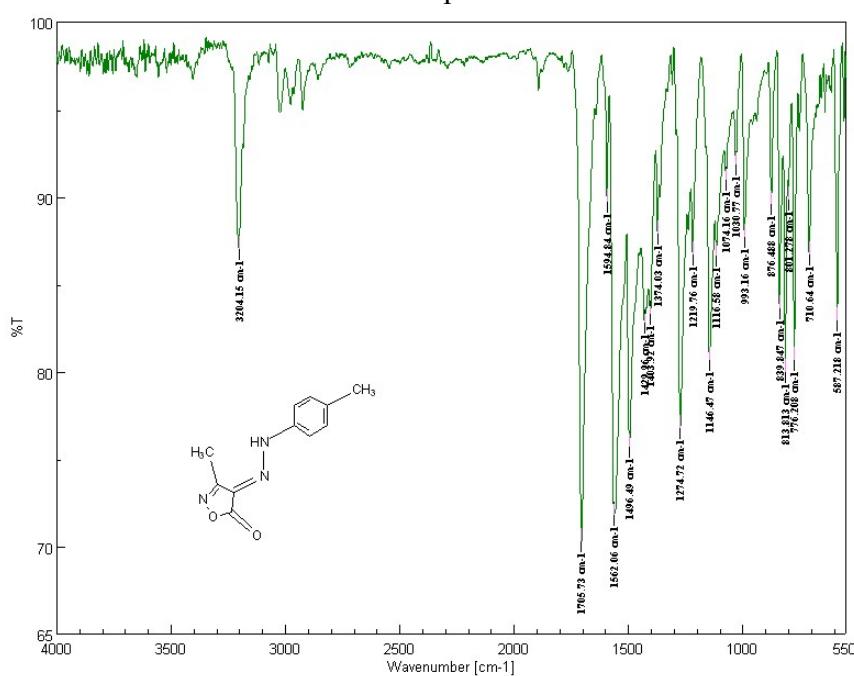


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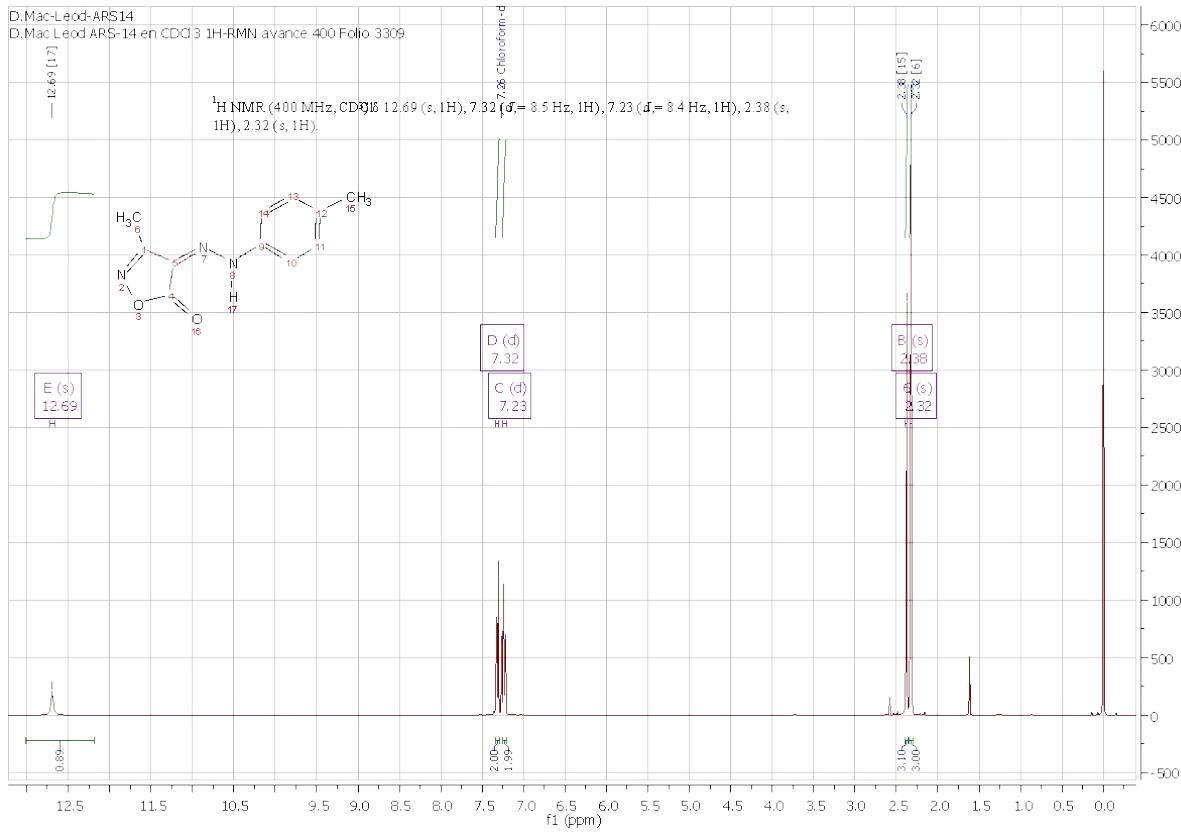
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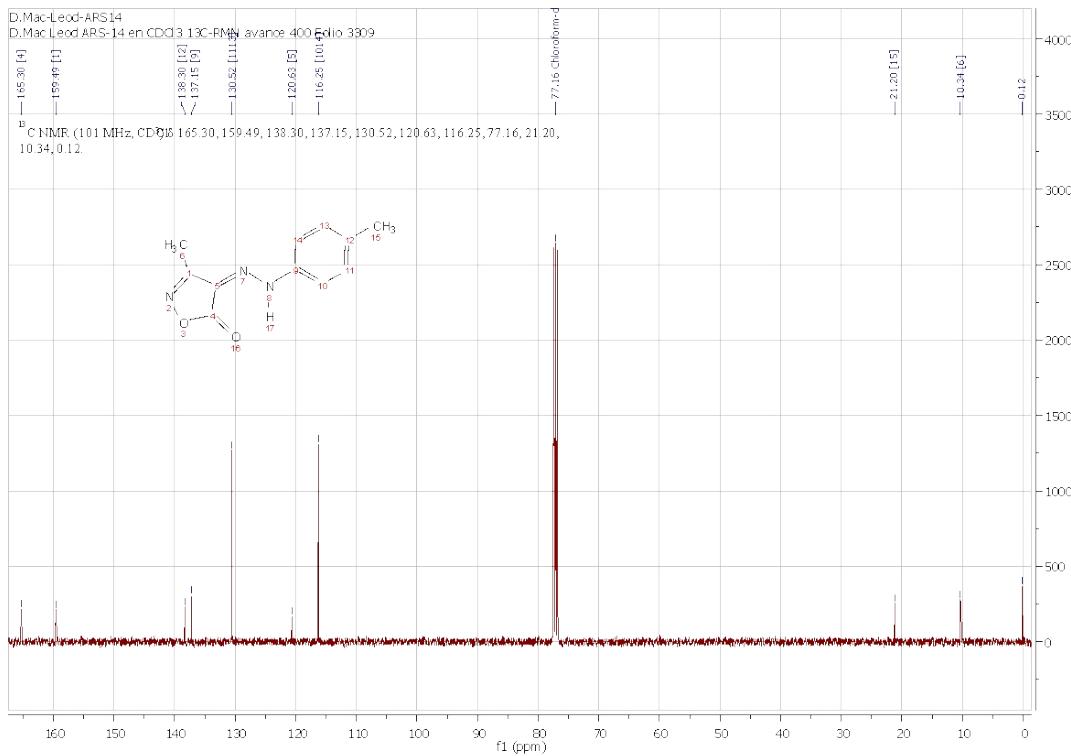
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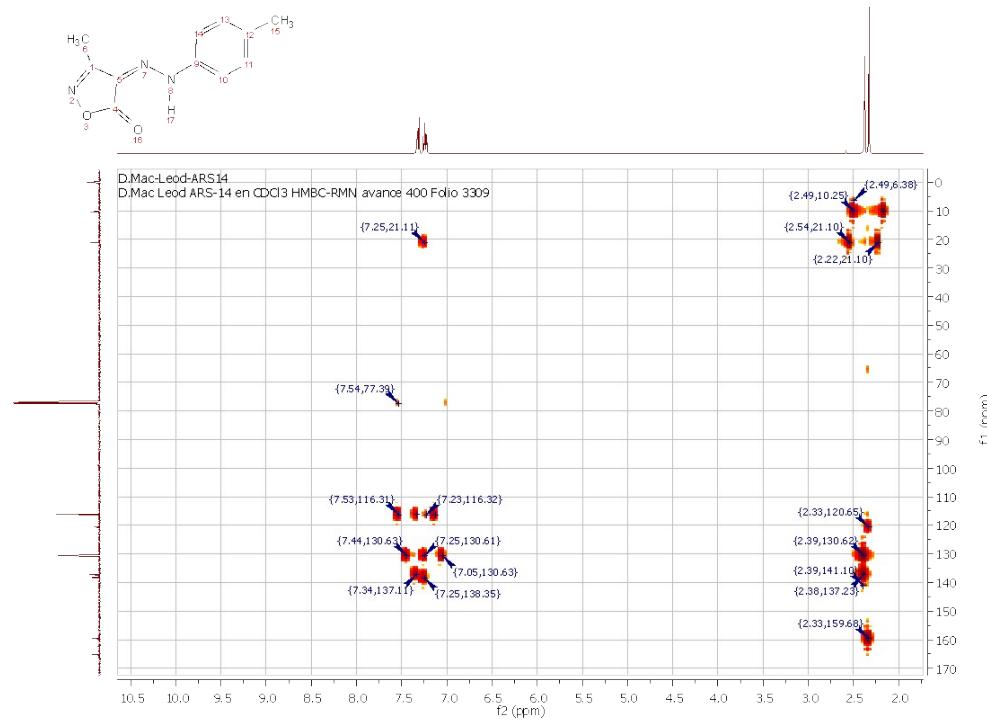
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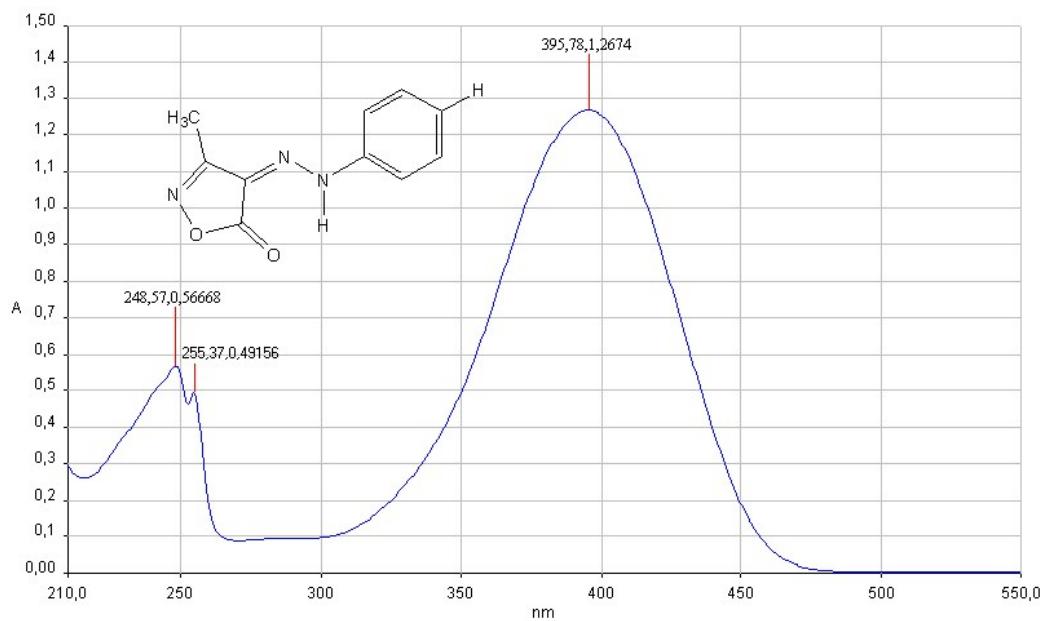
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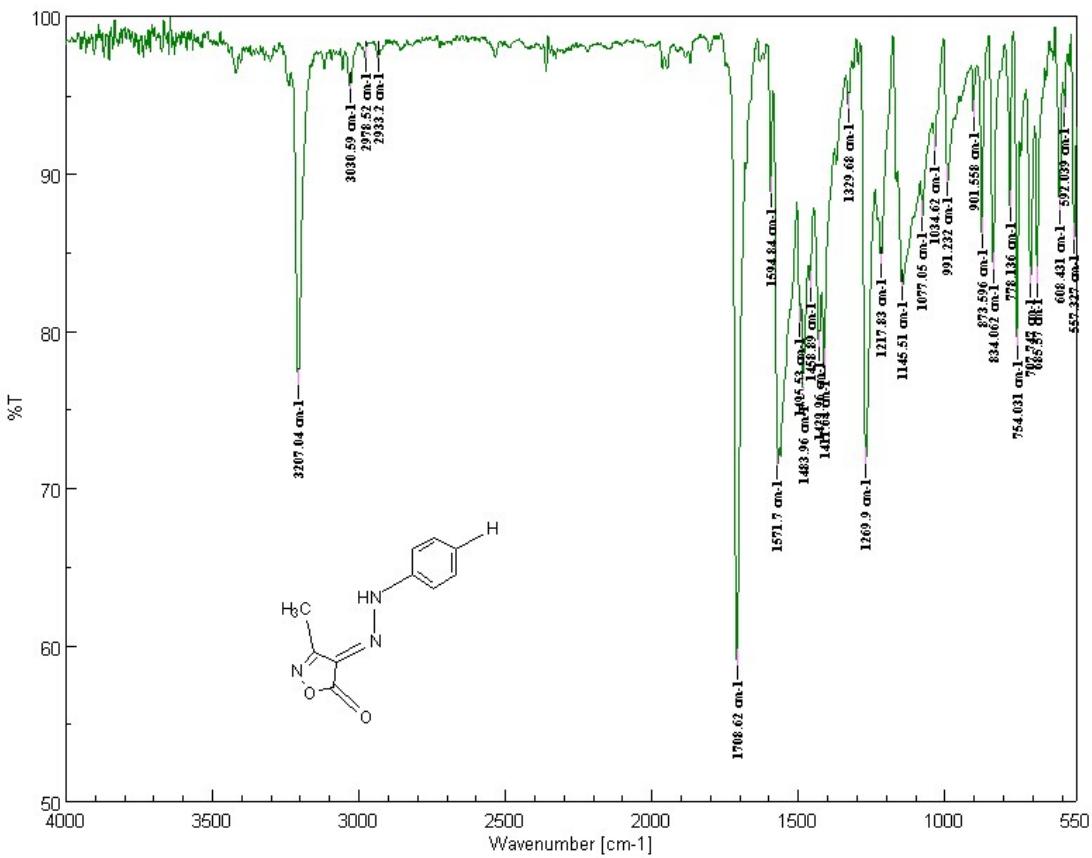
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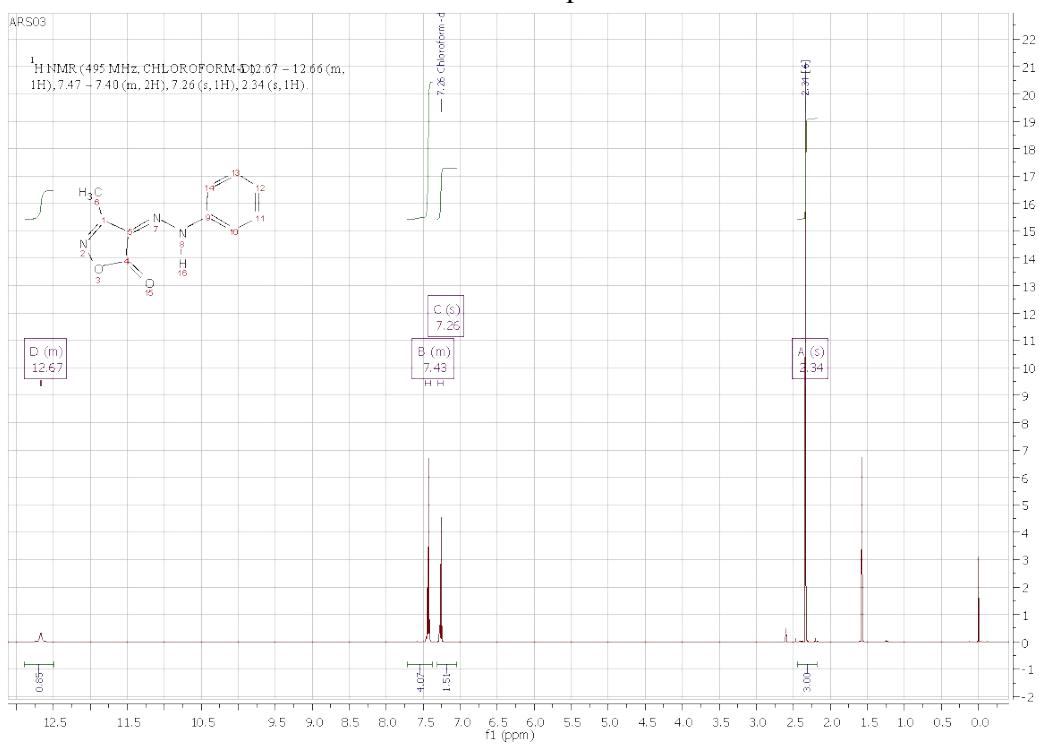
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UV-Vis Spectra



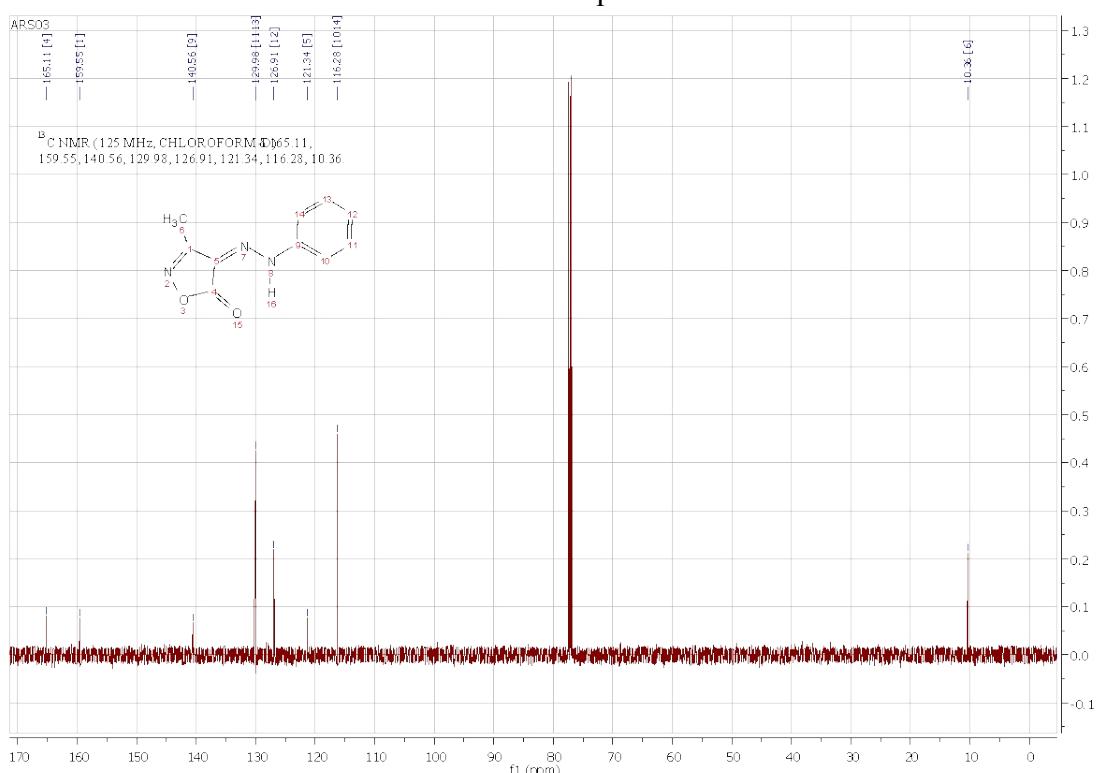
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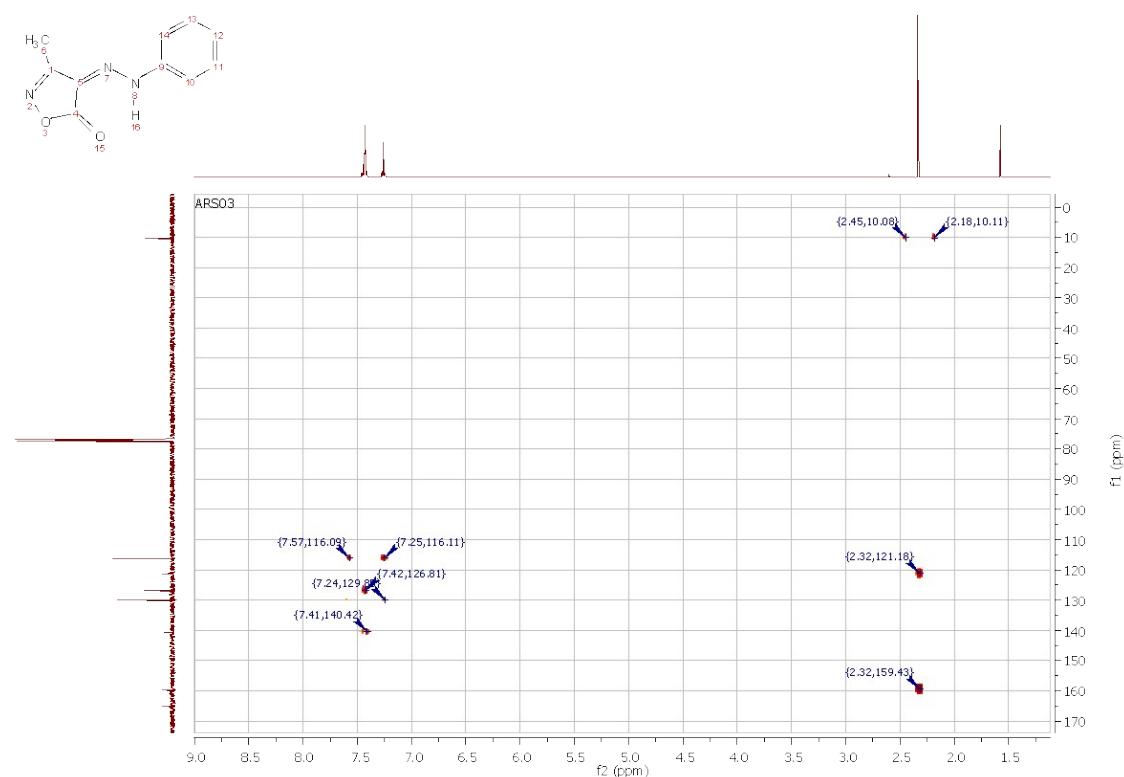
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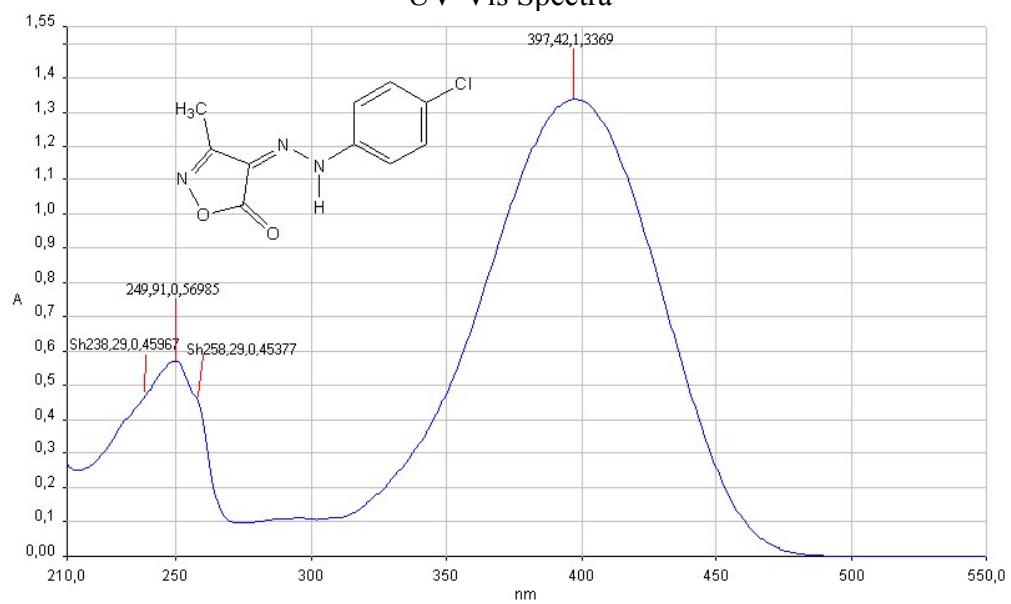


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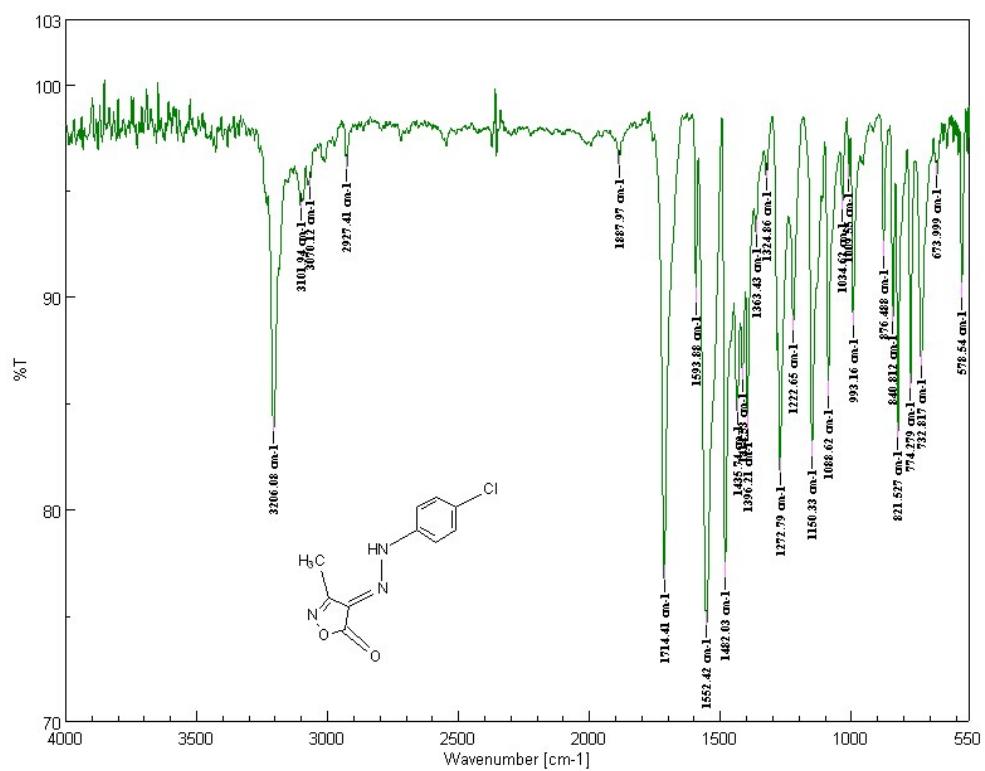


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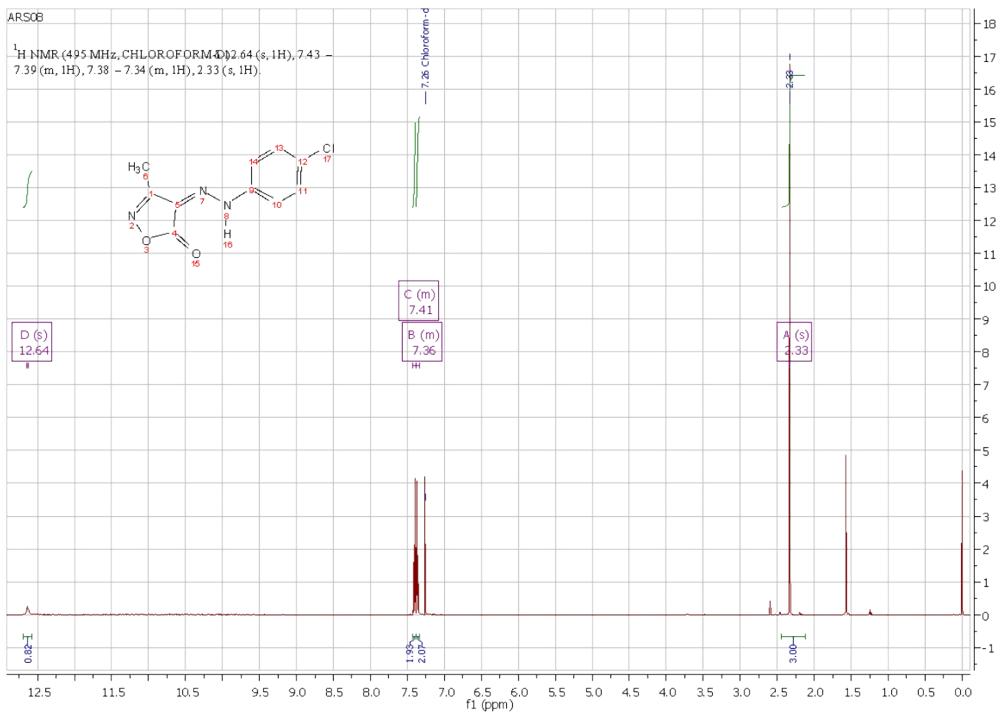
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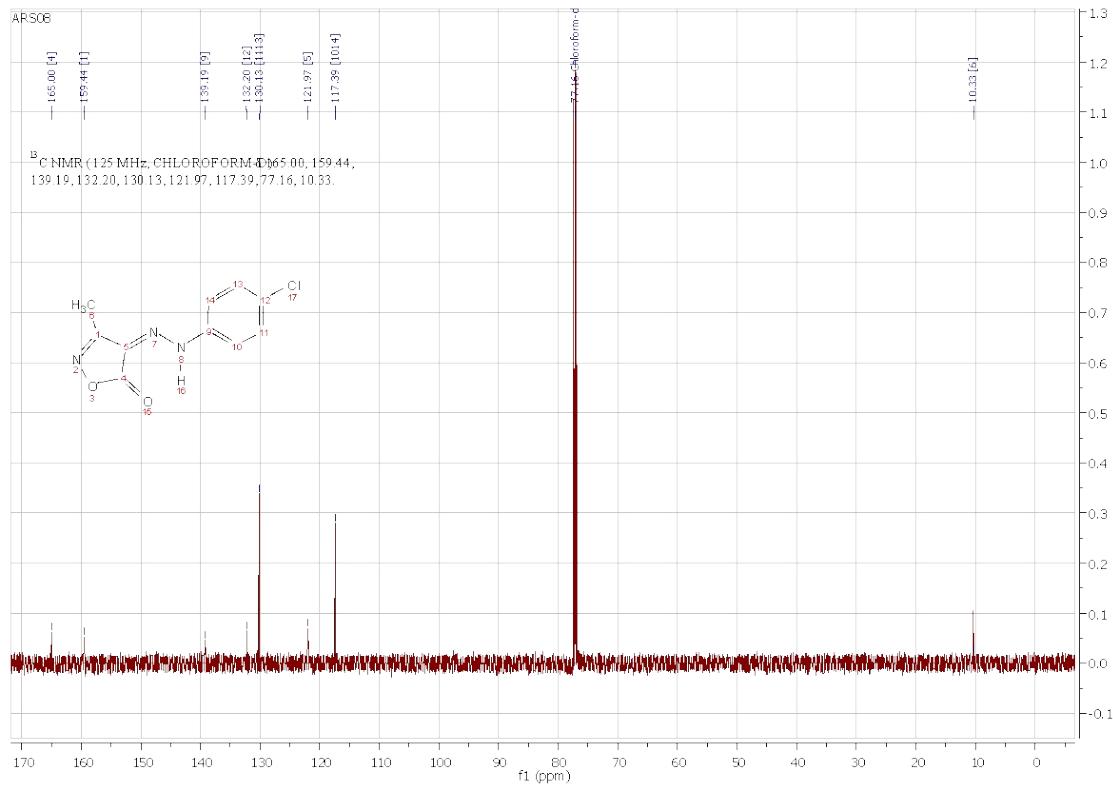
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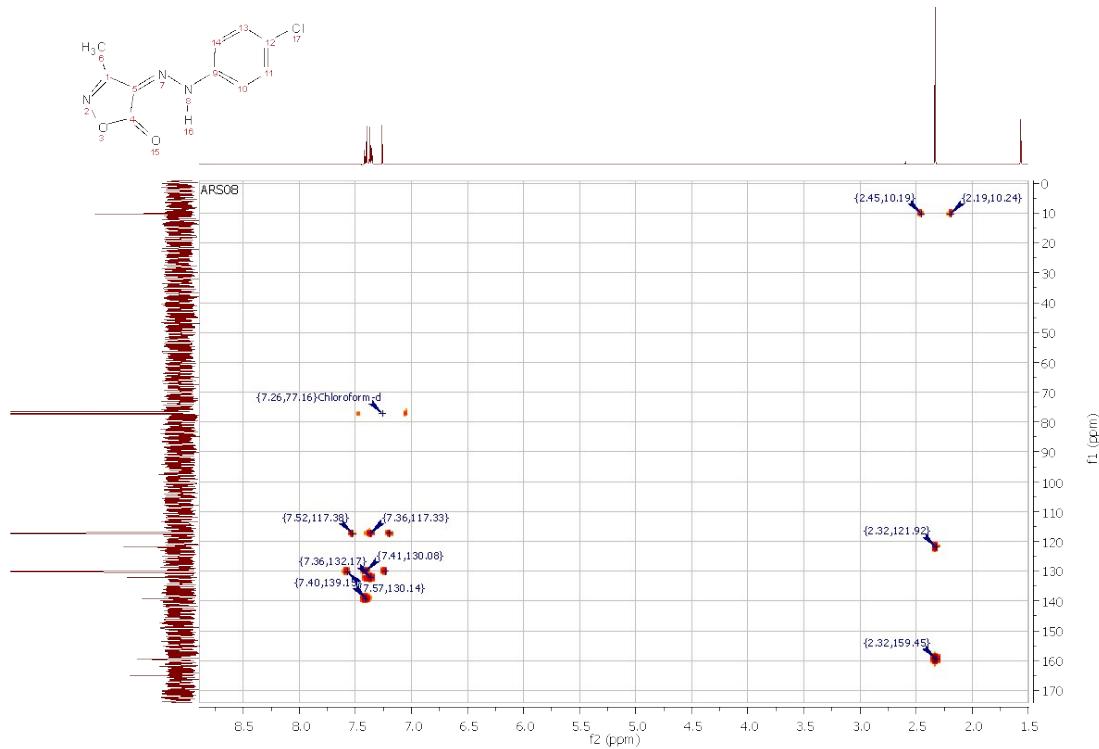
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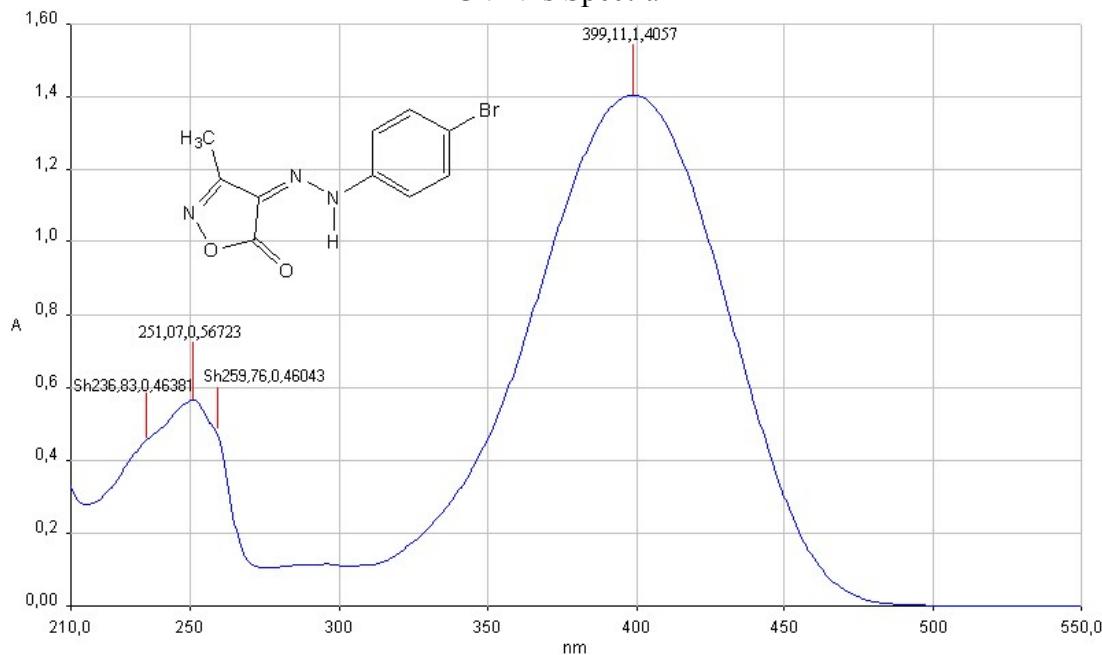
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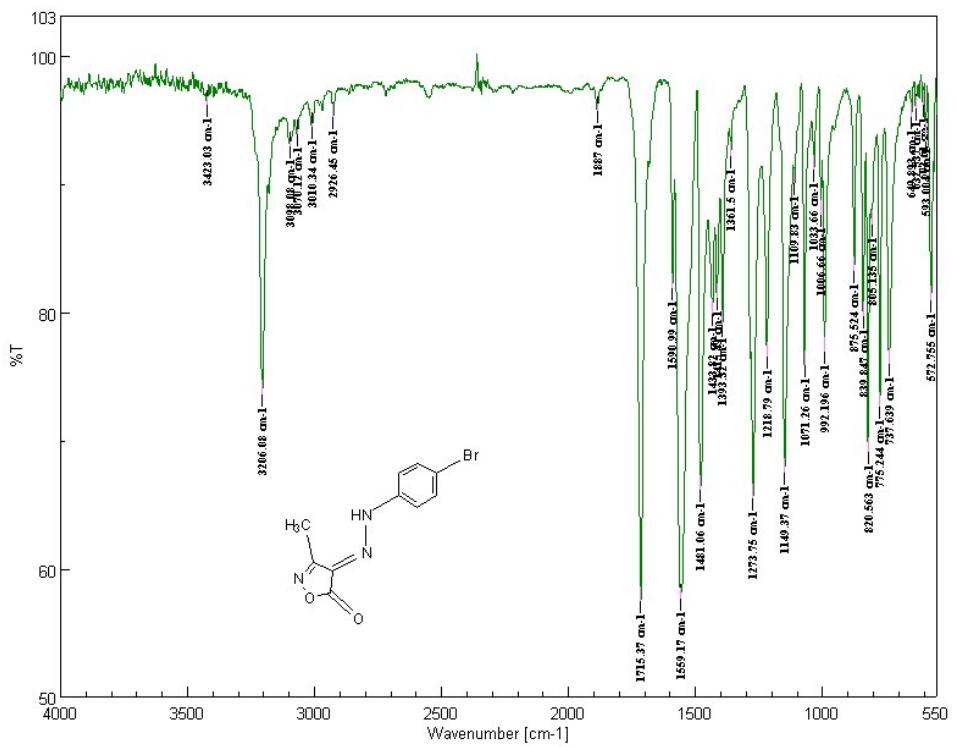
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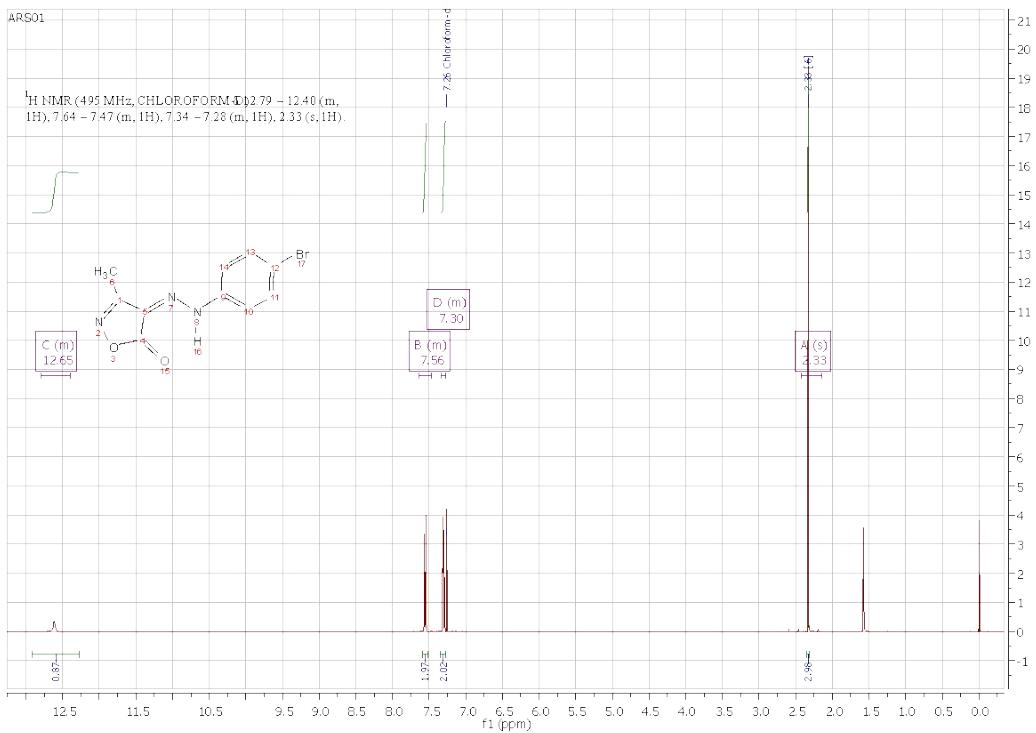
Compound (6)
UV-Vis Spectra



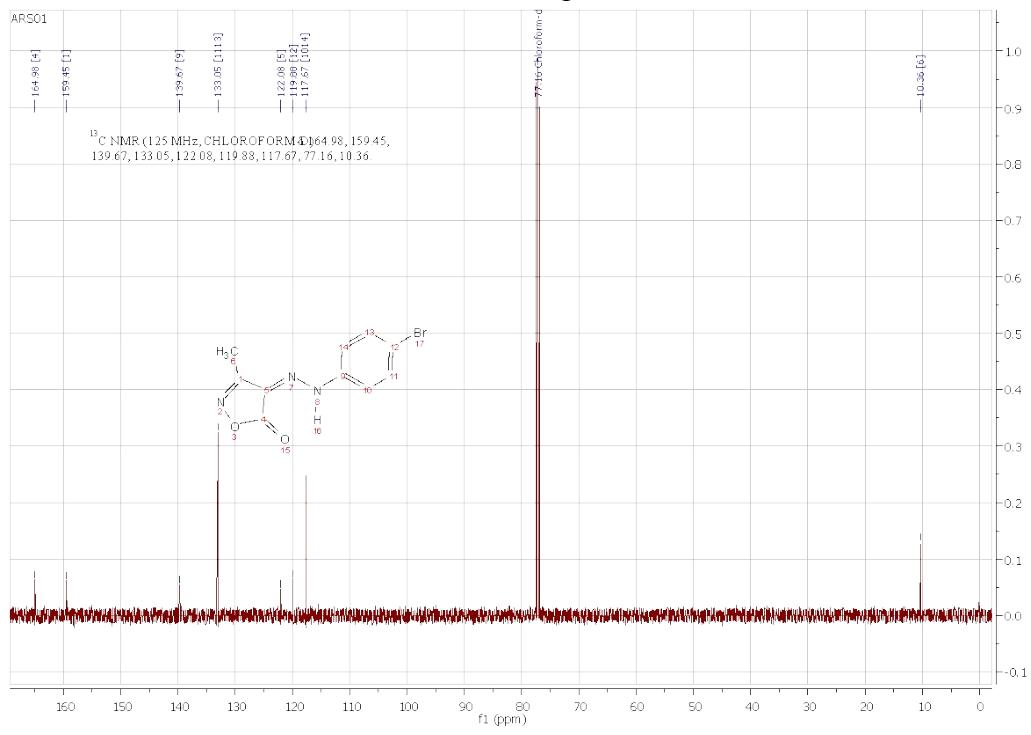
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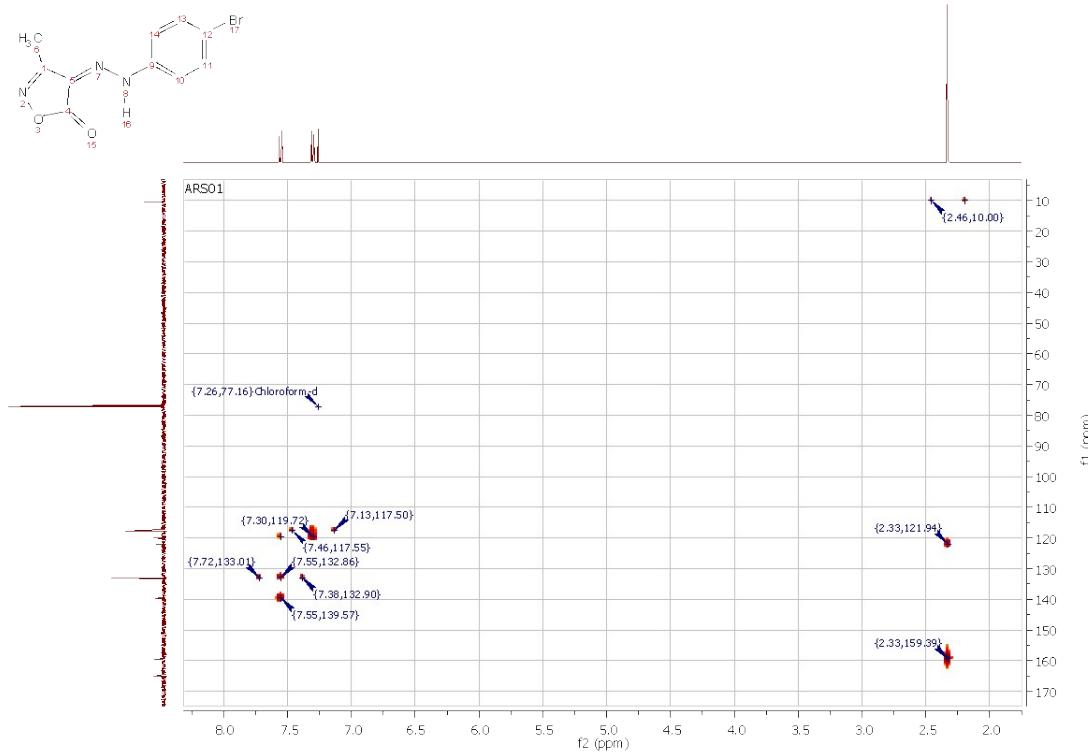
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¹³C-NMR Spectra

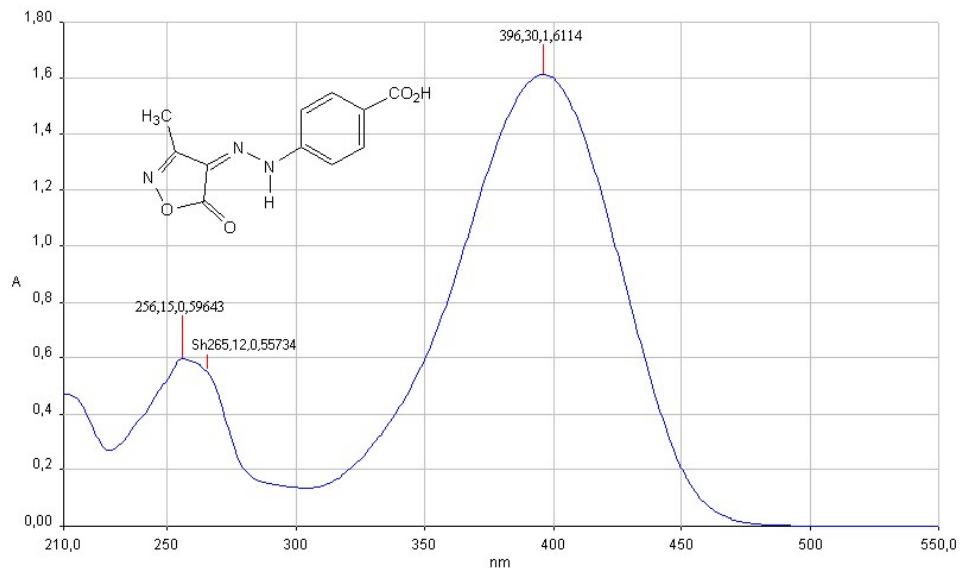


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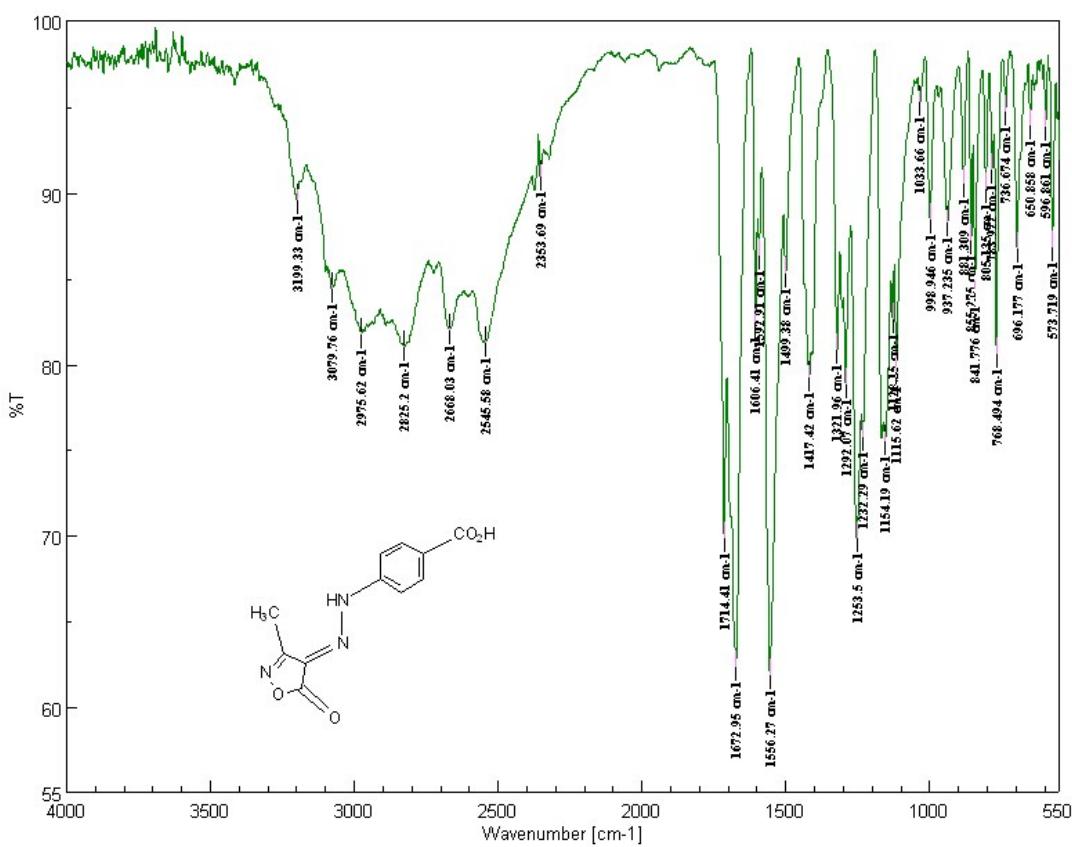


Compound (7)

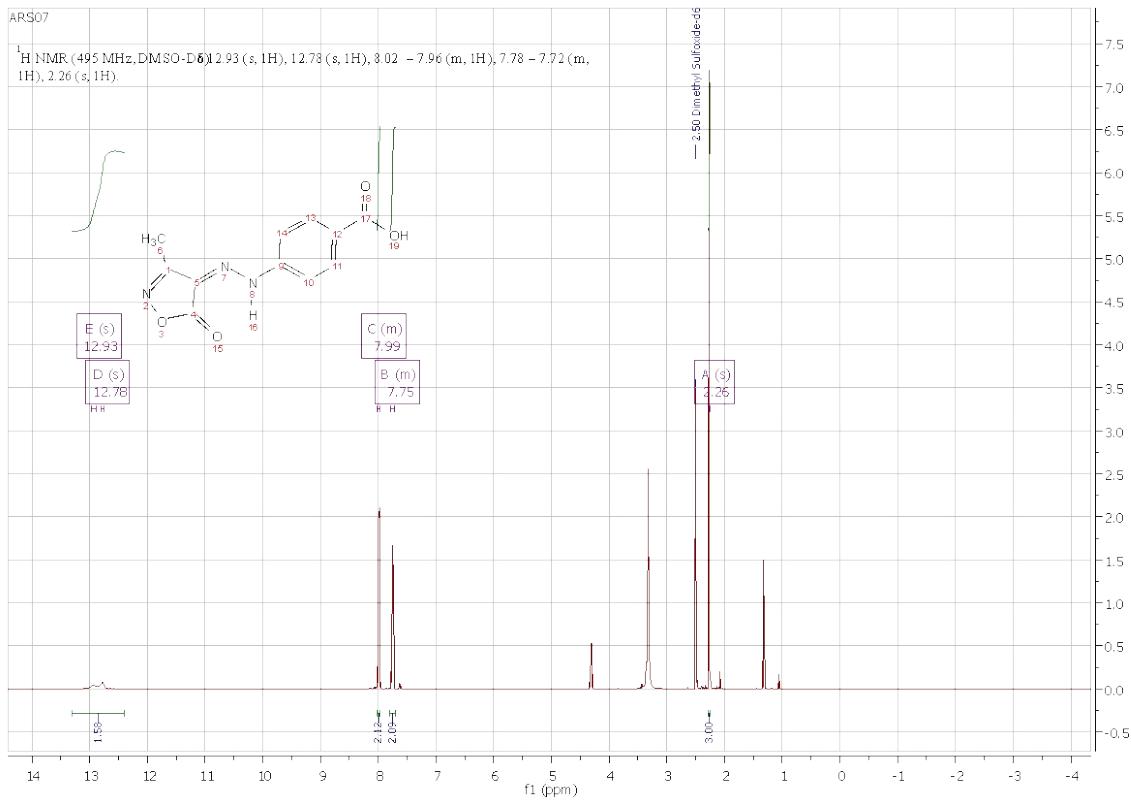
UV-Vis Spectra



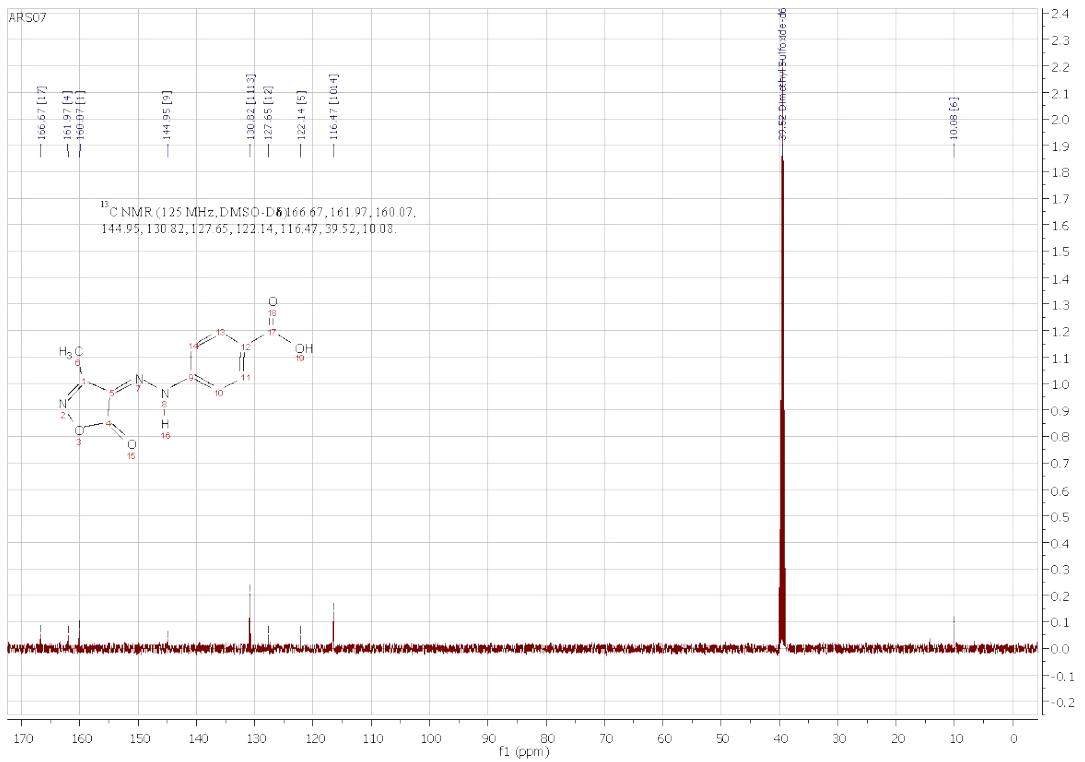
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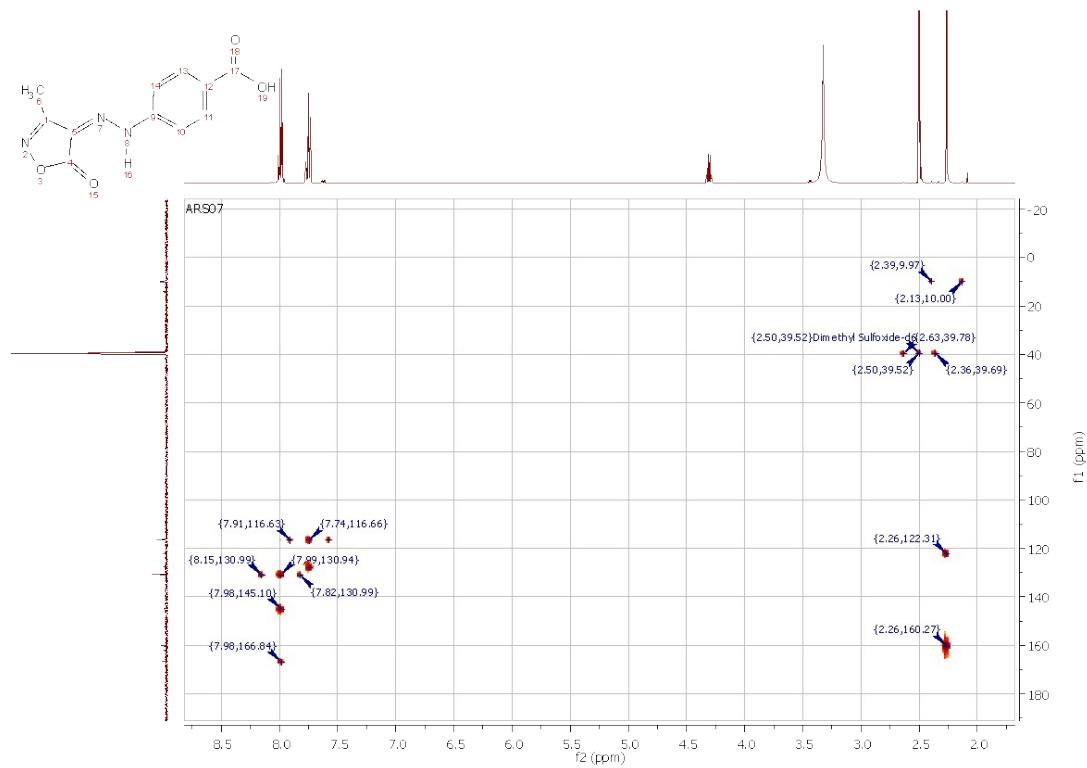
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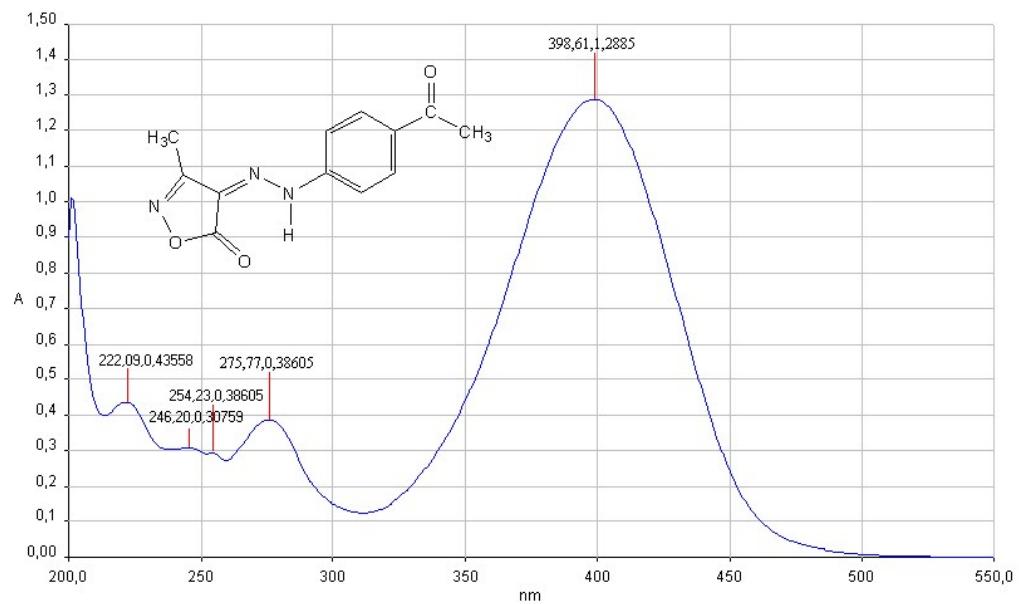
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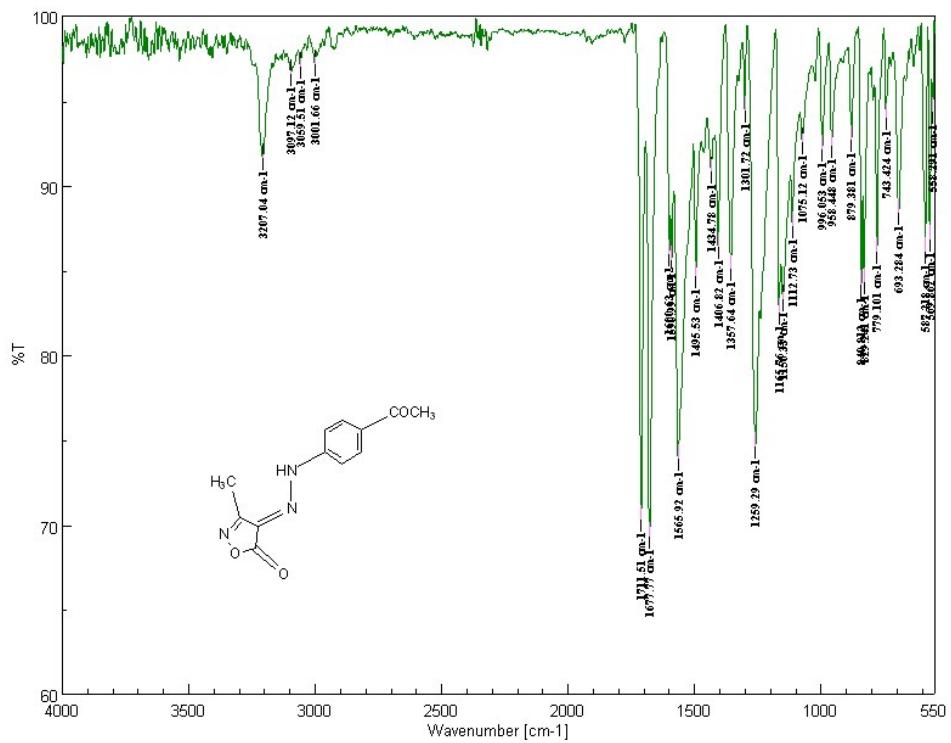
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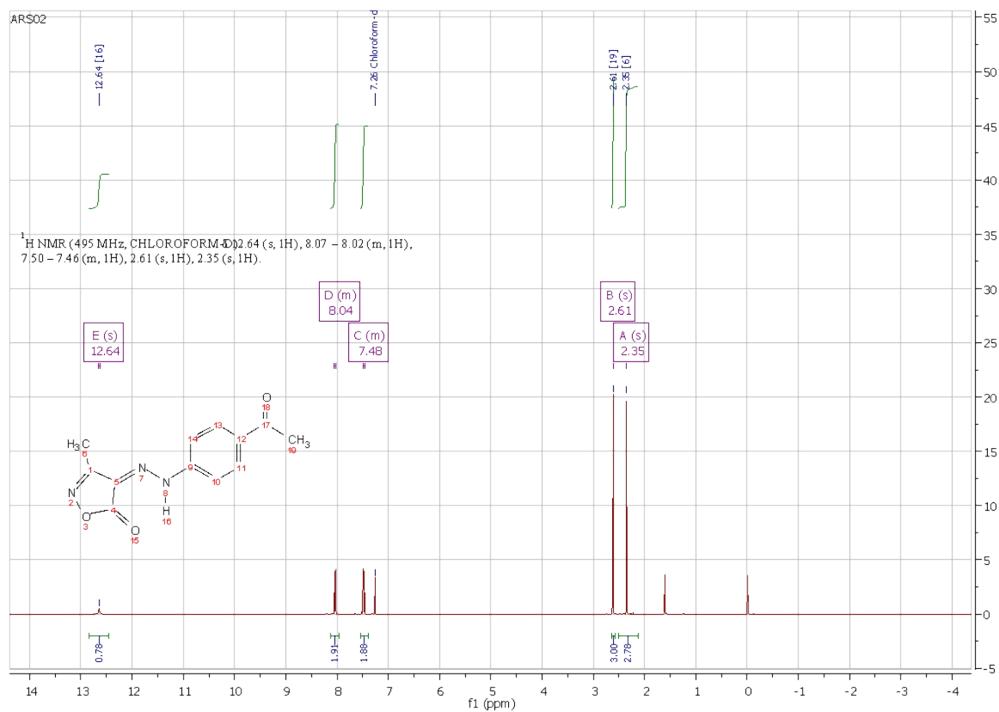
Compound (8)
UV-Vis Spectra



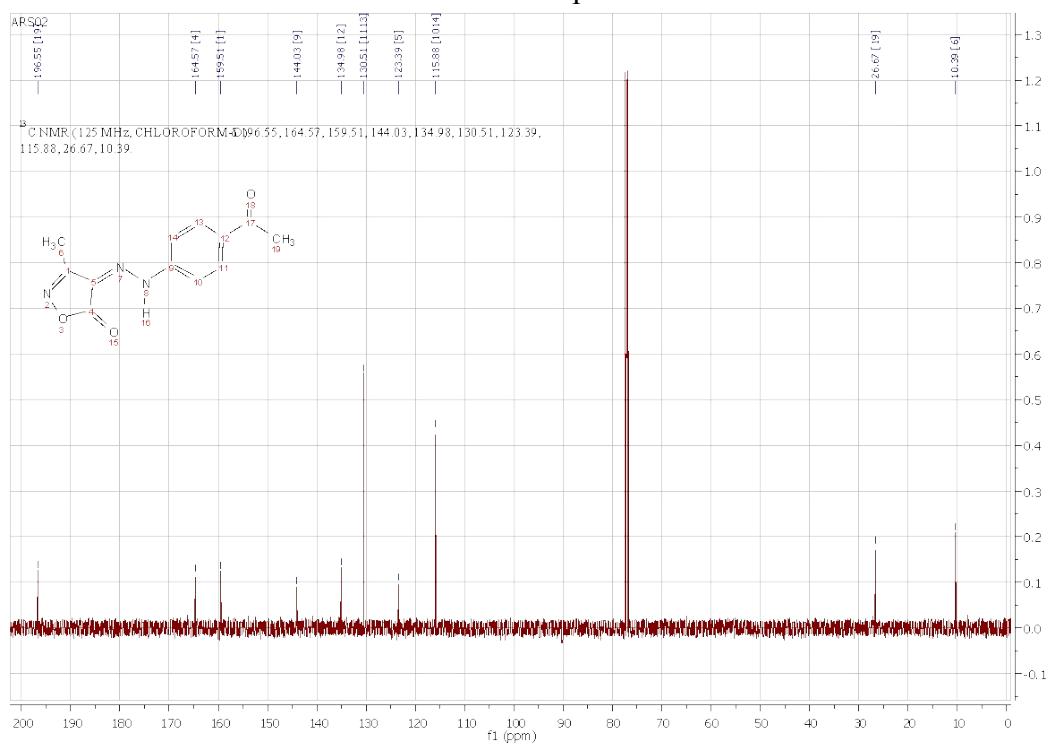
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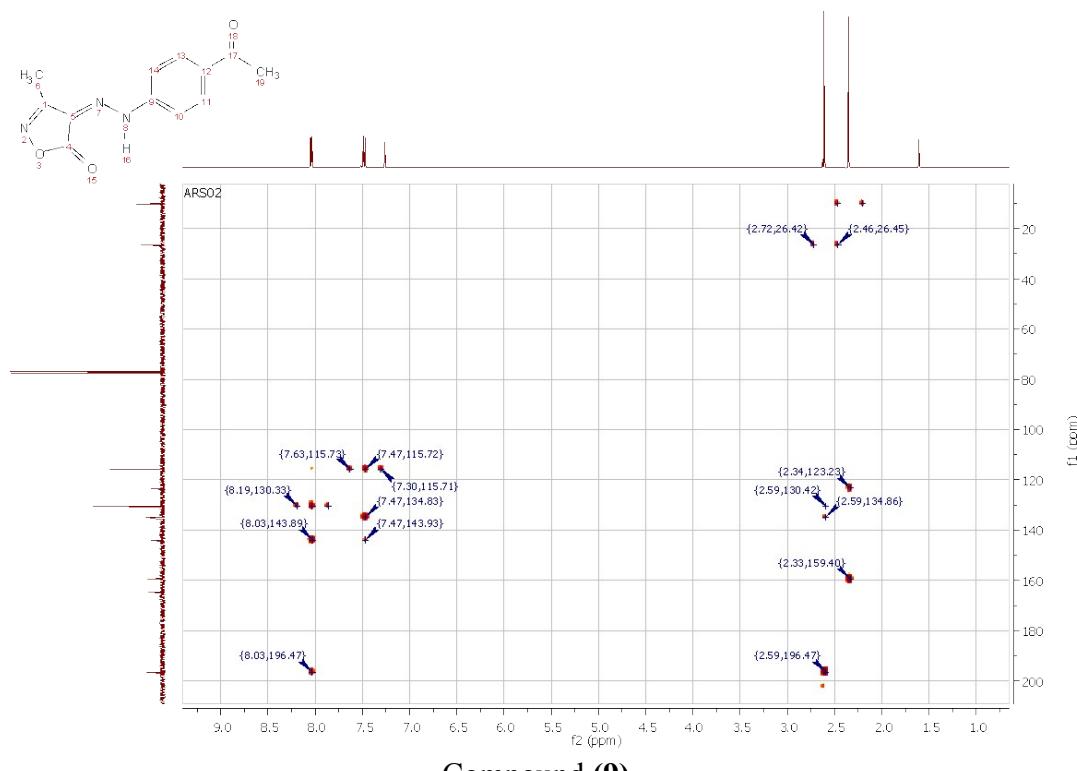
¹H-NMR Spectra



¹³C-NMR Spectra

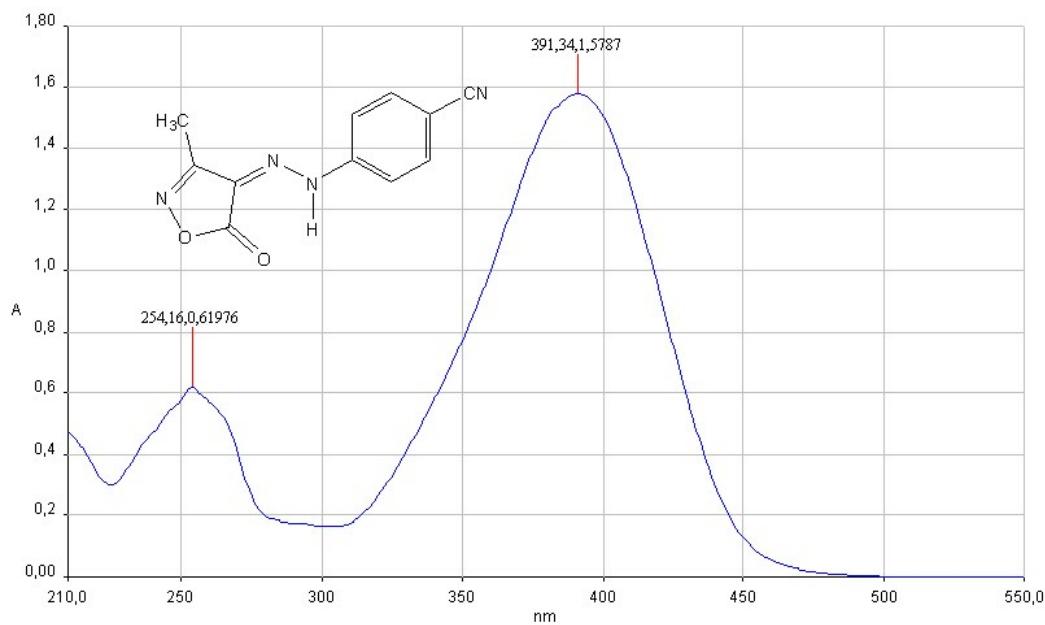


HMBC Spectra

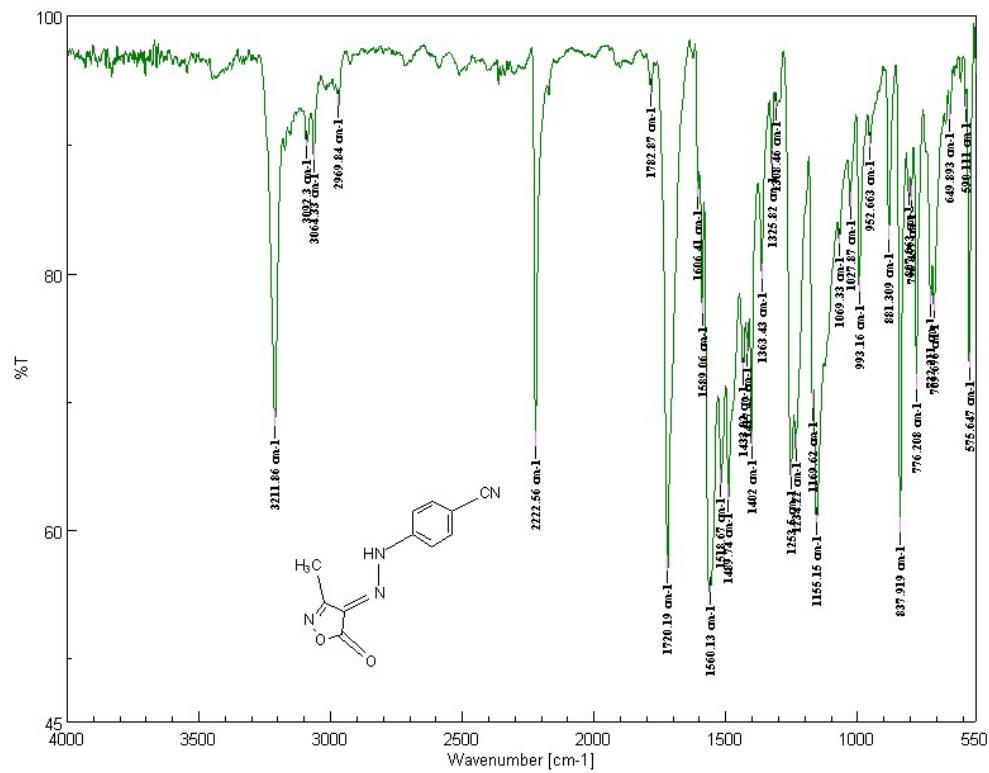


Compound (9)

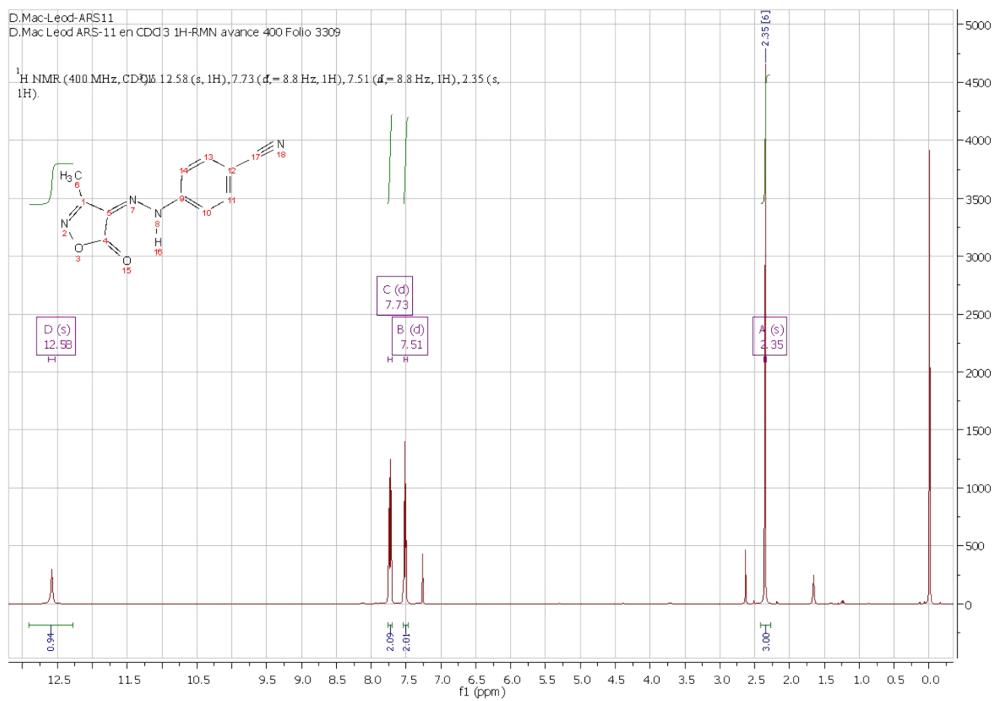
UV-Vis Spectra



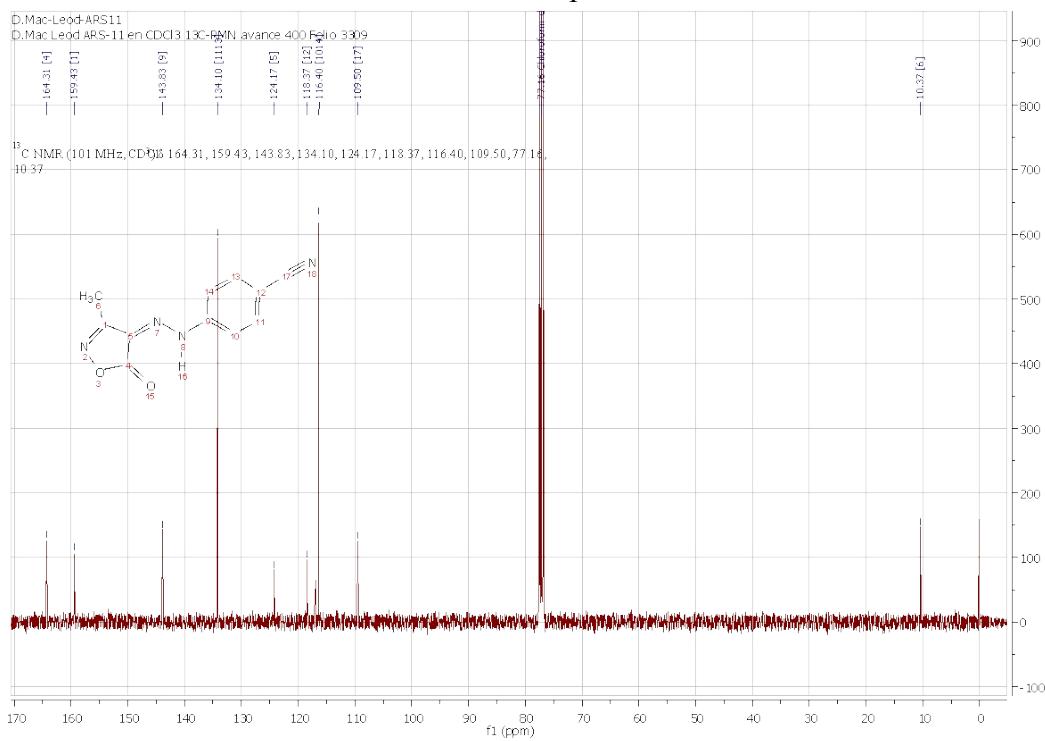
FT-IR Spectra



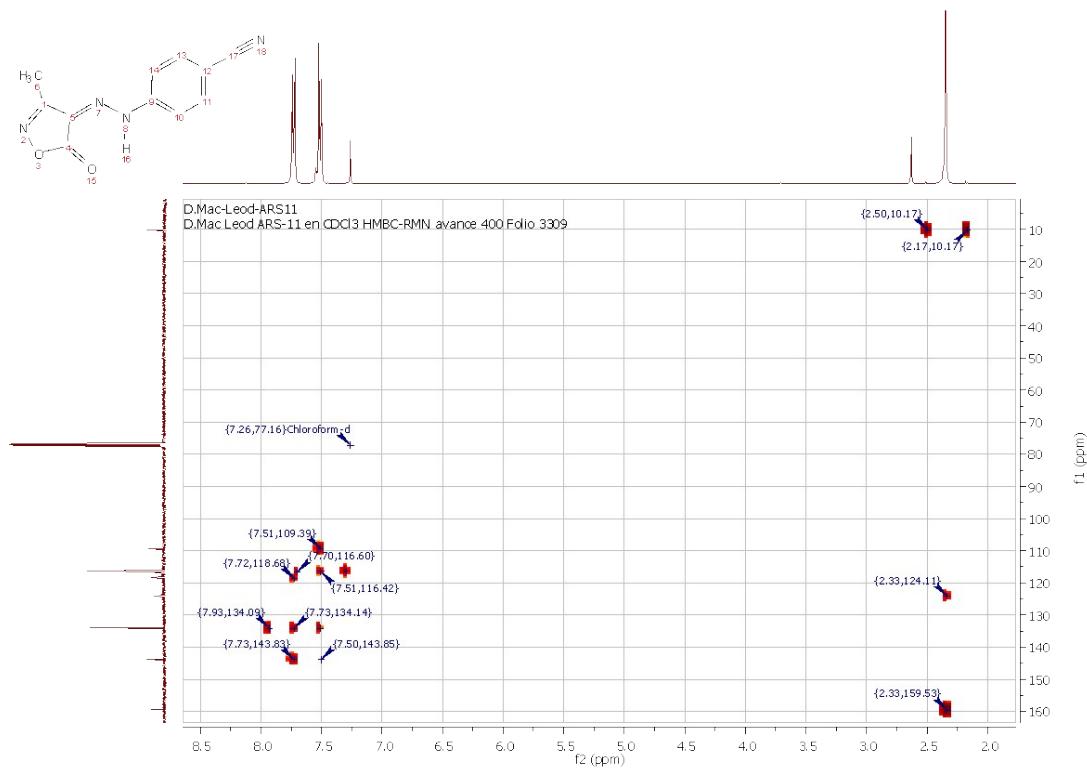
¹H-NMR Spectra



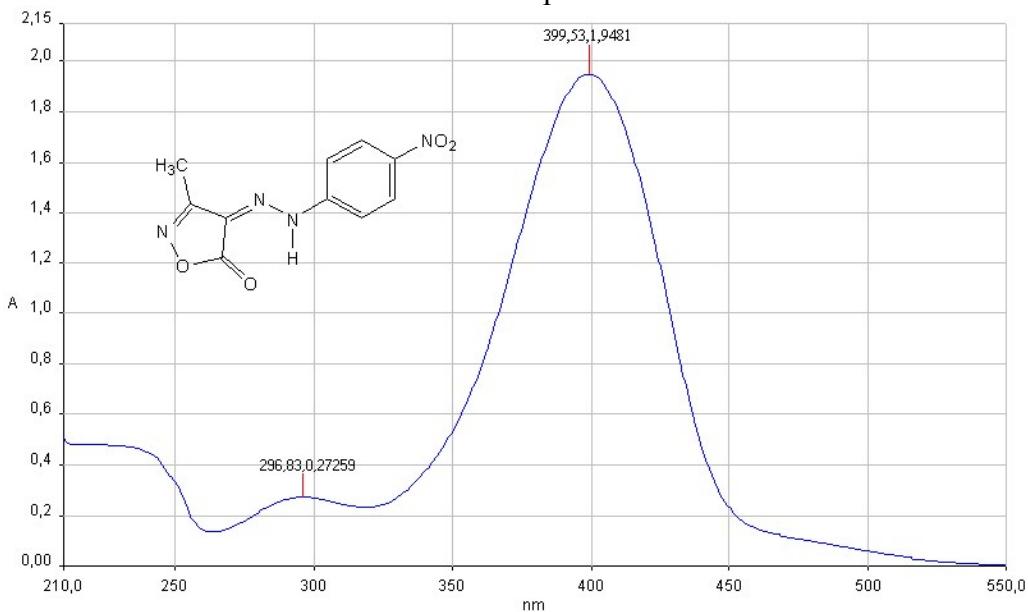
¹³C-NMR Spectra



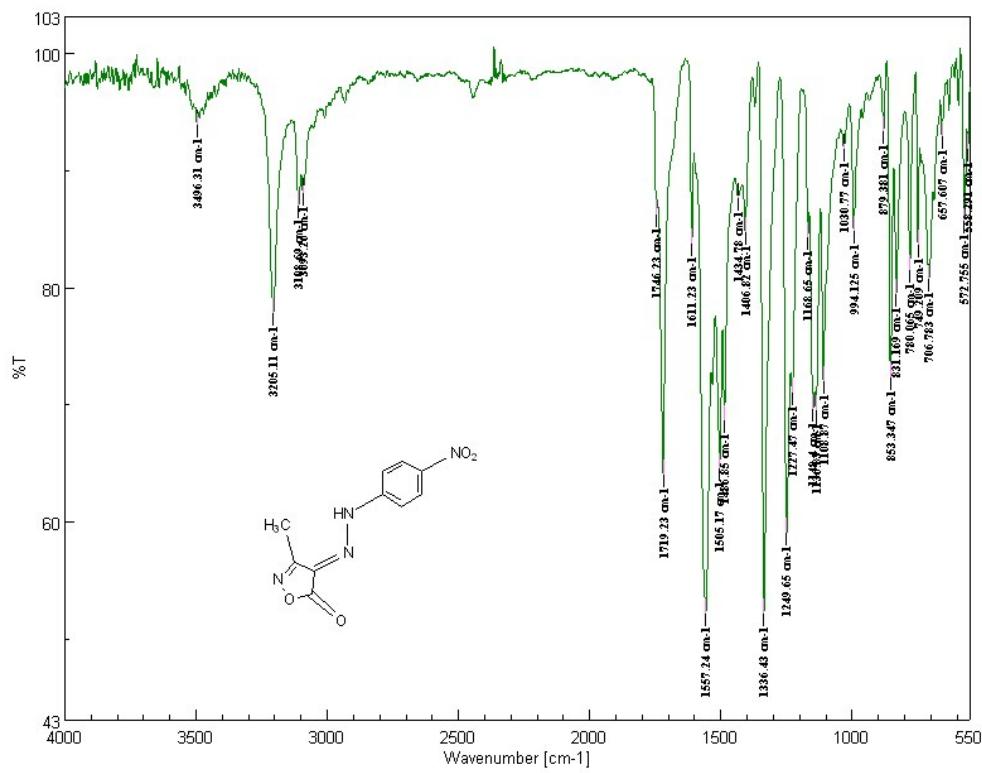
HMBC Spectra



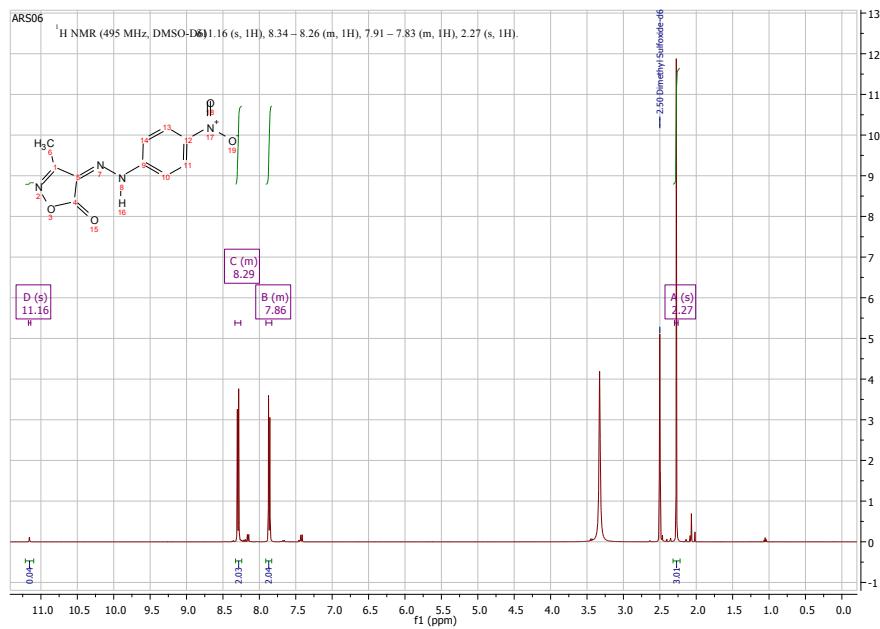
Compound (10) UV-Vis Spectra



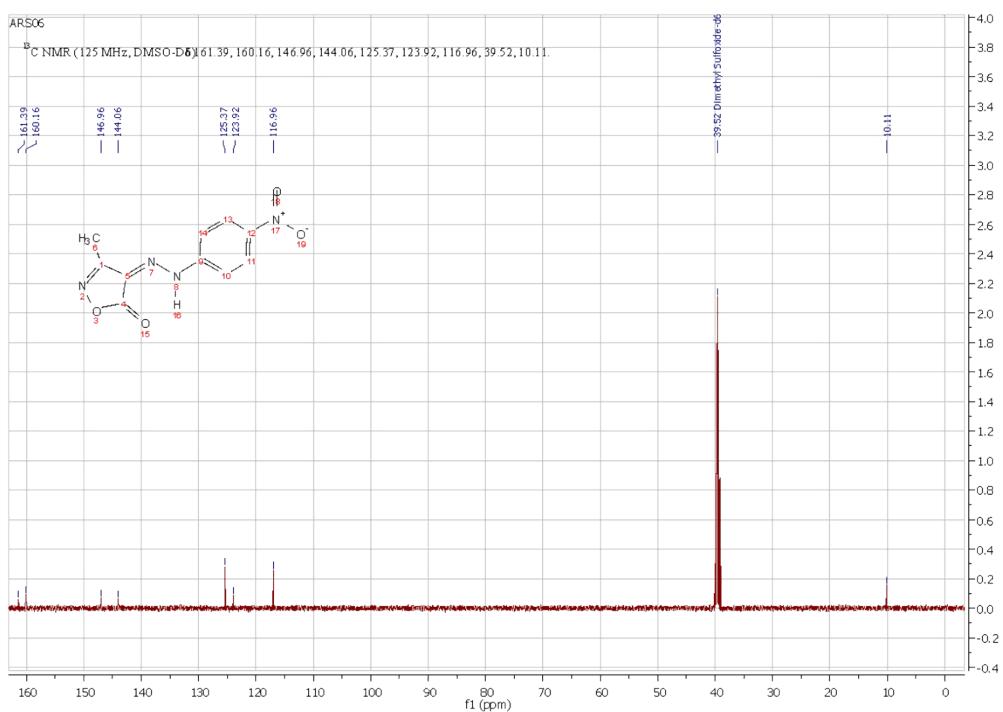
FT-IR Spectra



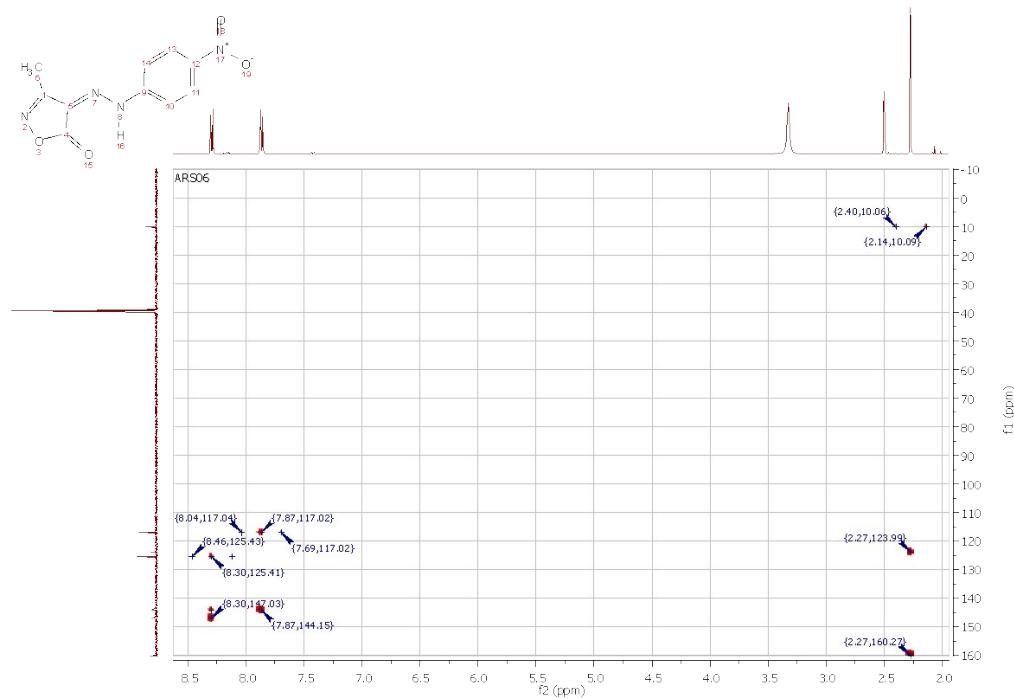
¹H-NMR Spectra



¹³C-NMR Spectra

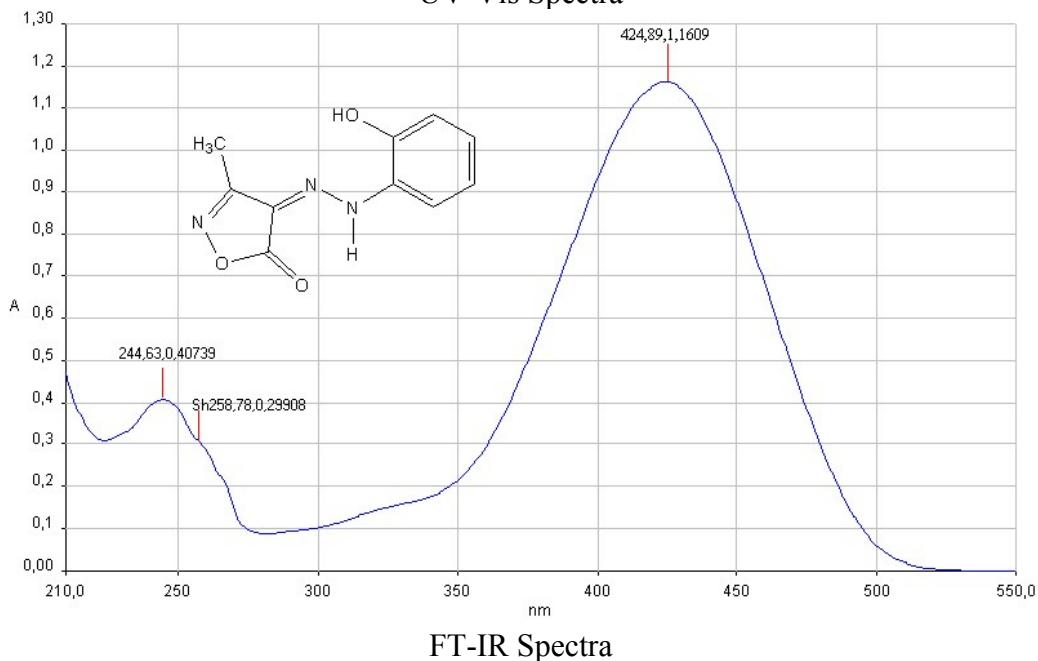


HMBC Spectra

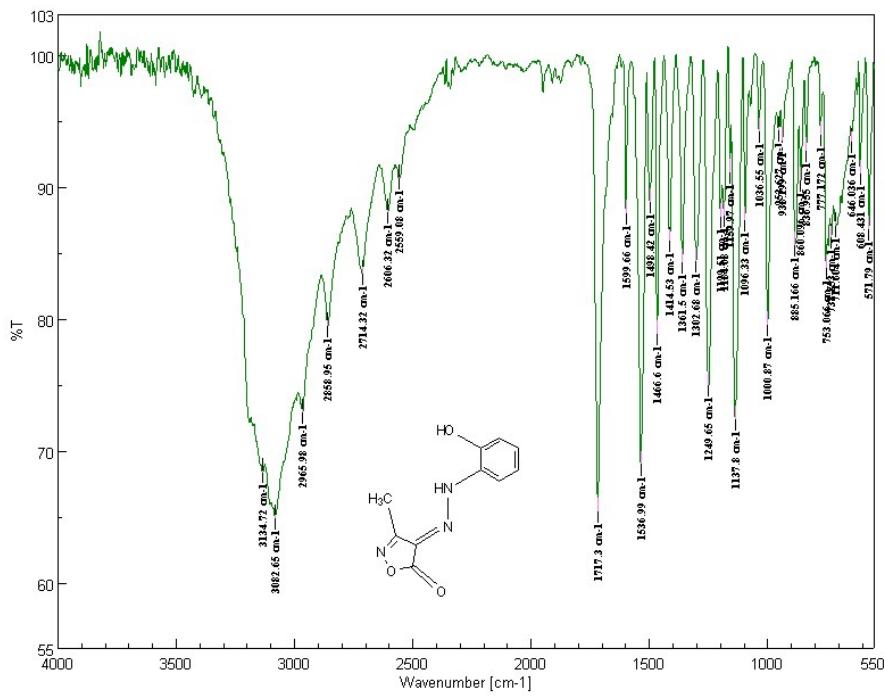


Compound (11)

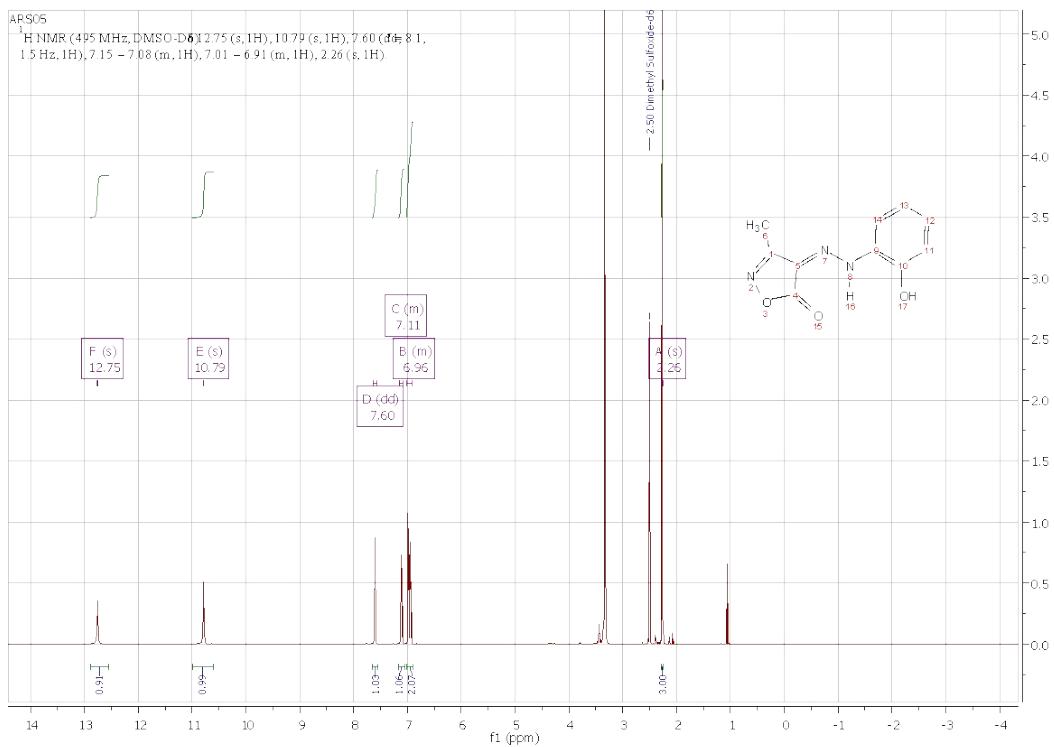
UV-Vis Spectra



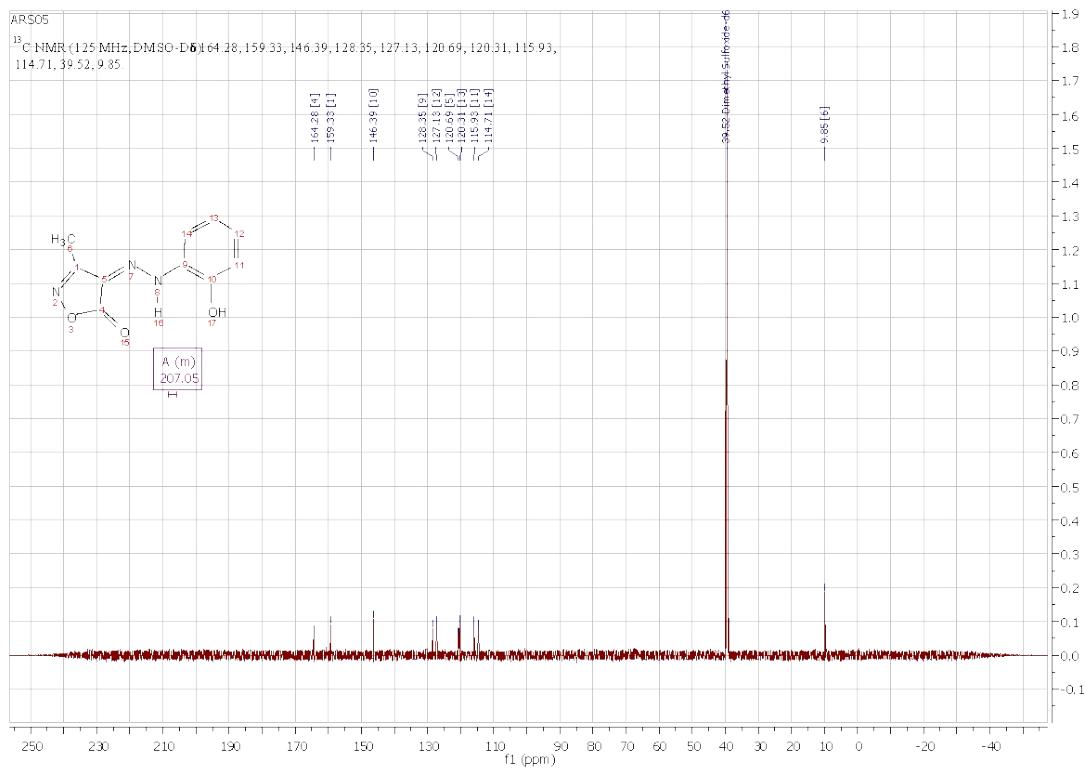
FT-IR Spectra



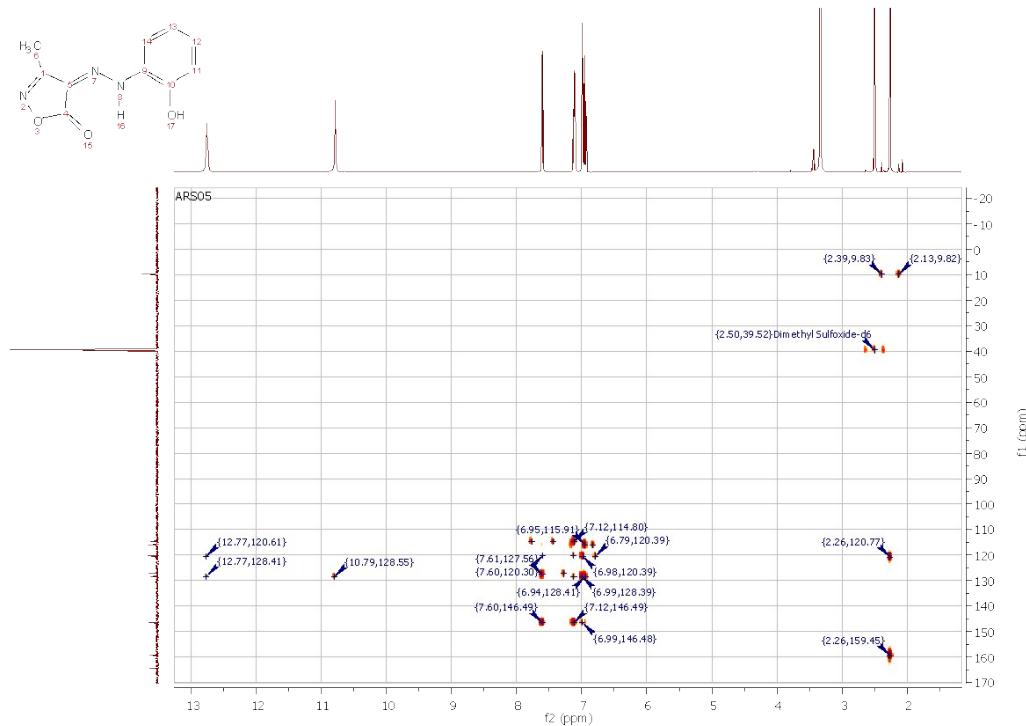
¹H-NMR Spectra



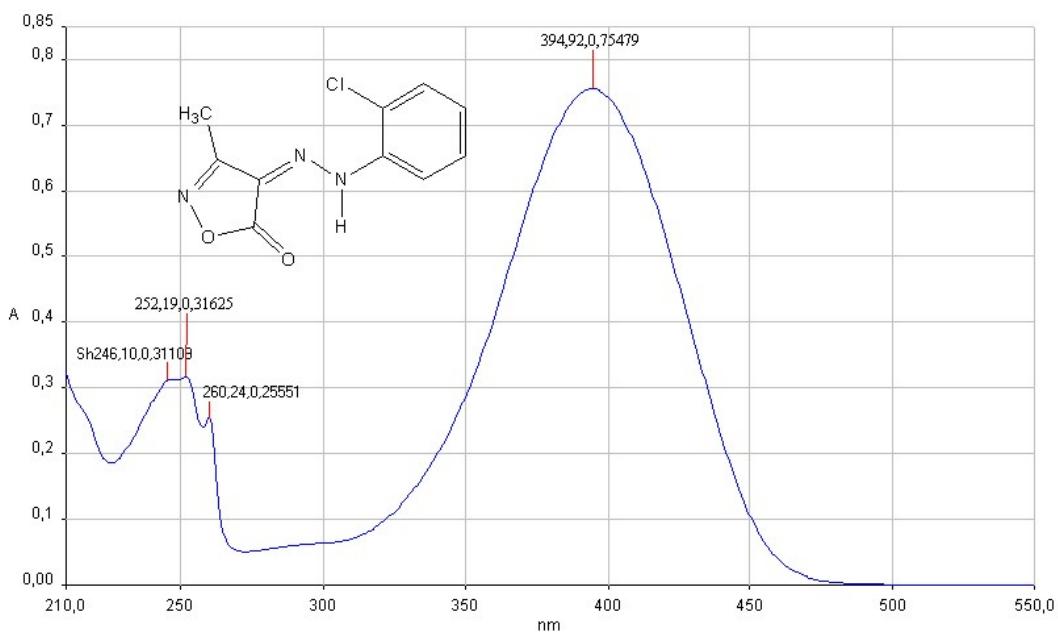
^{13}C -NMR Spectra



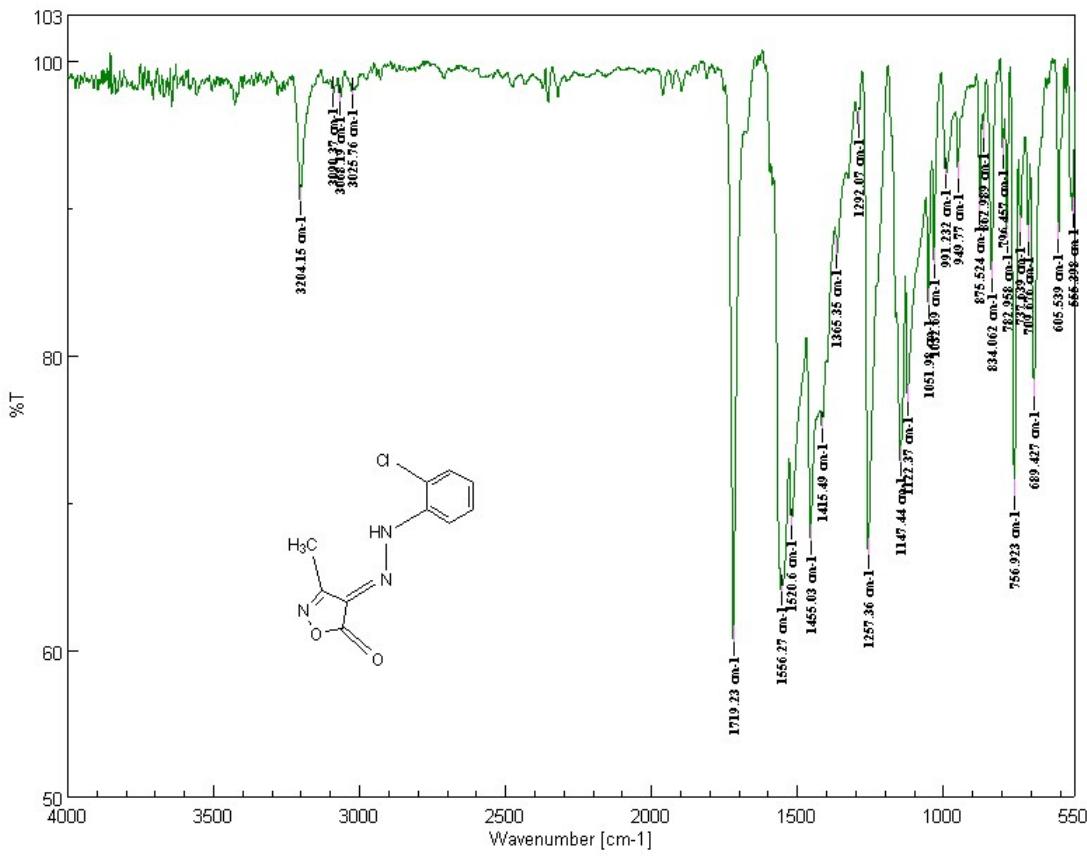
HMBC Spectra



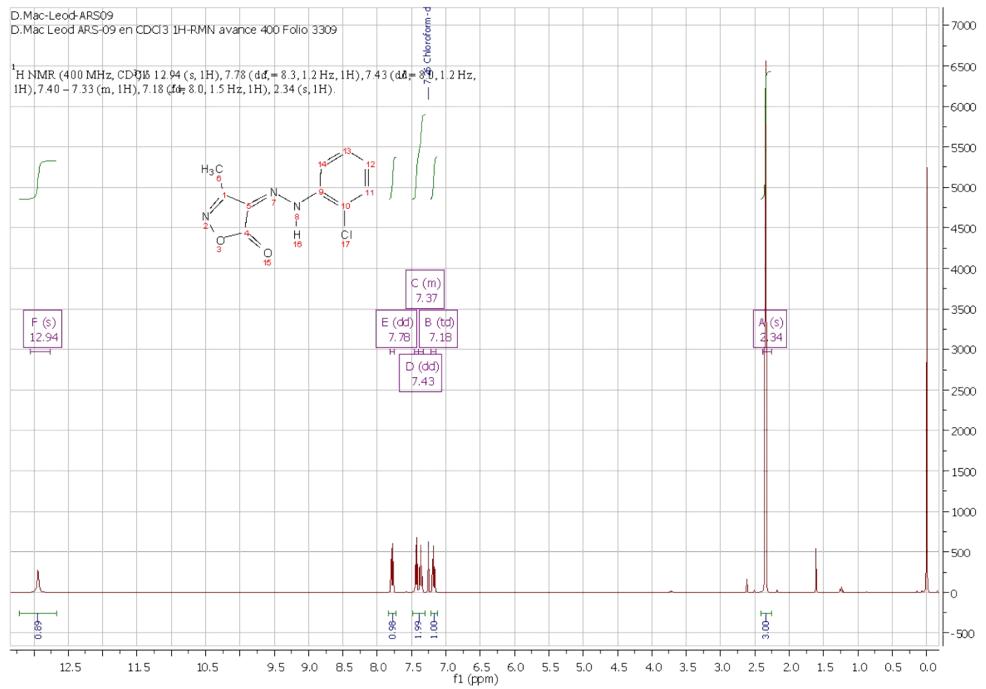
Compound (12) UV-Vis Spectra



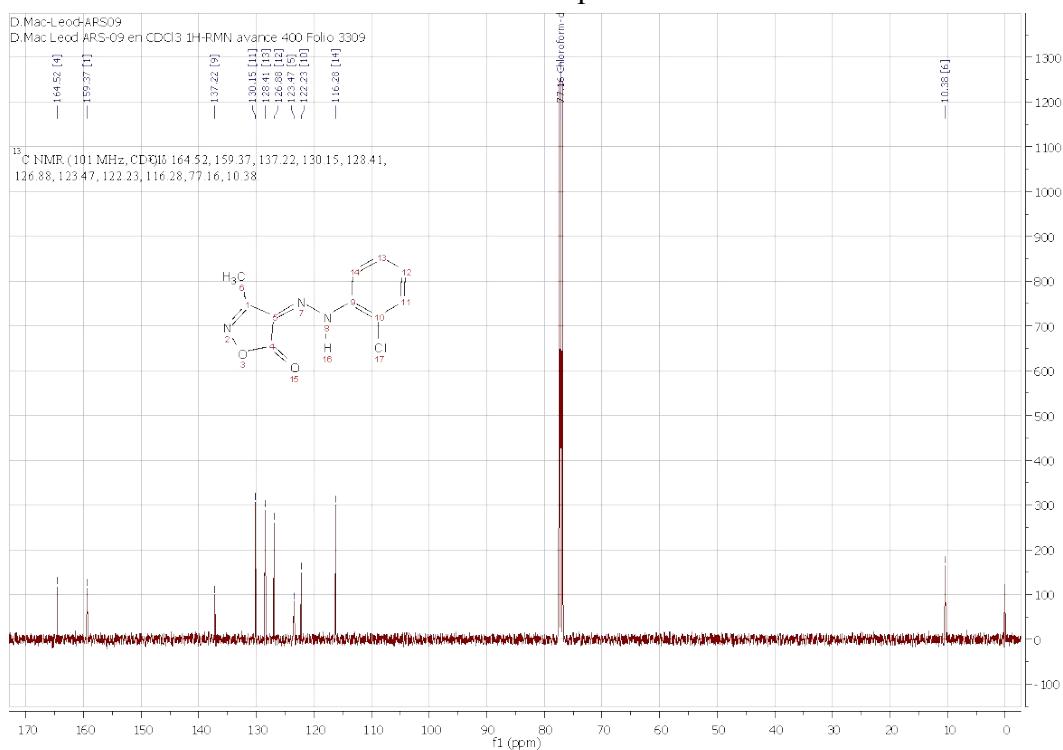
FT-IR Spectra



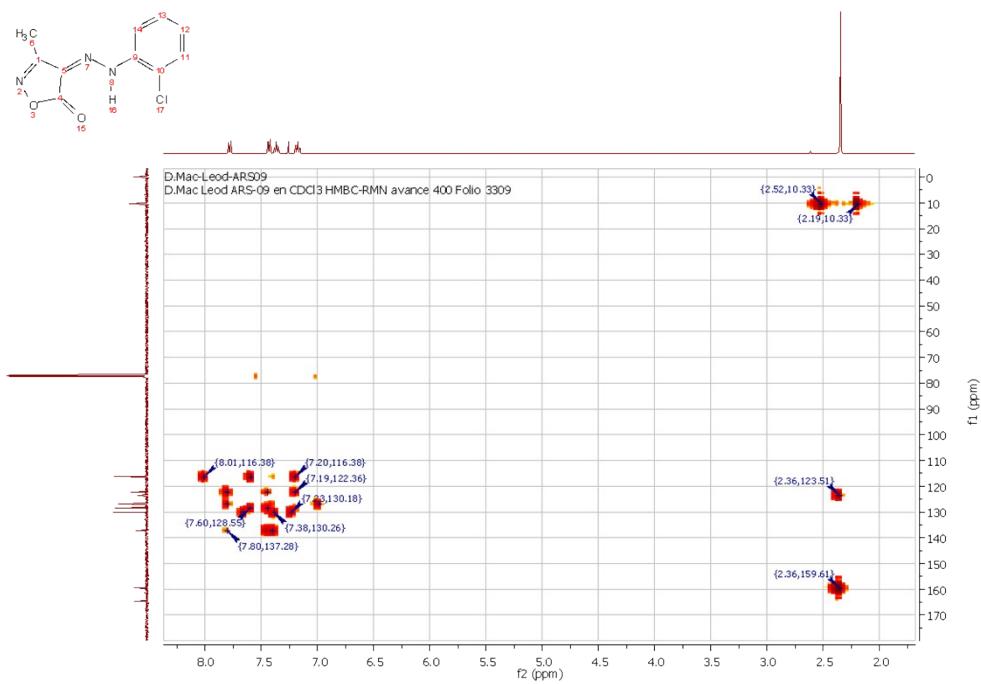
¹H-NMR Spectra



¹³C-NMR Spectra

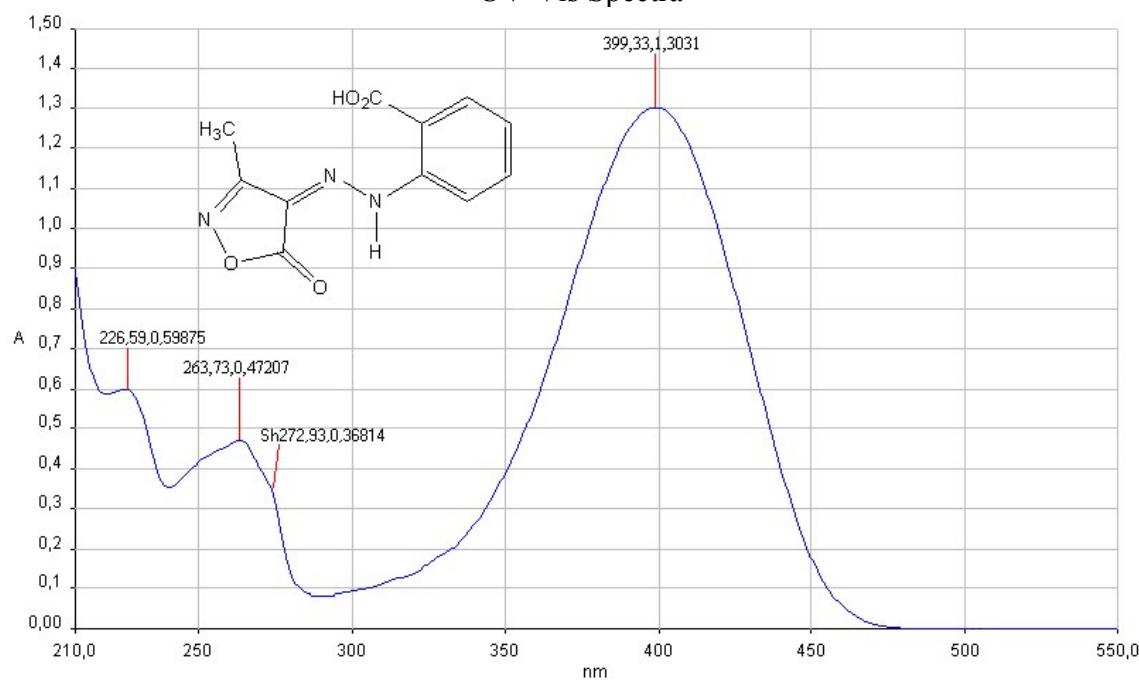


HMBC Spectra

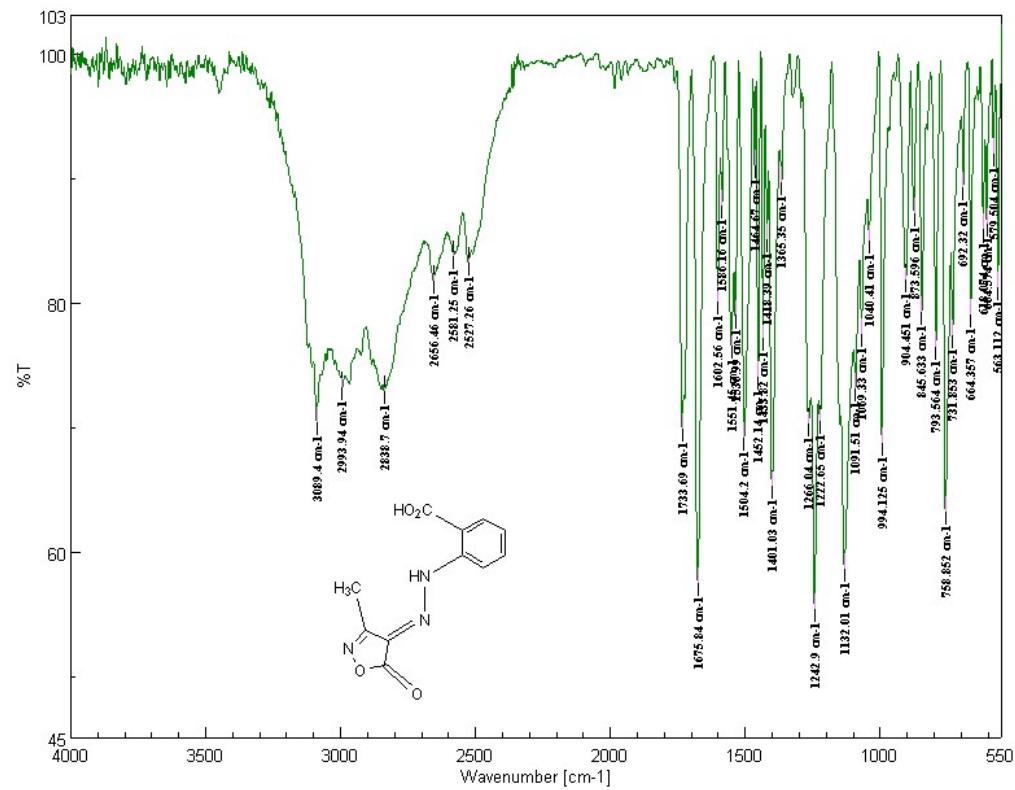


Compound (13)

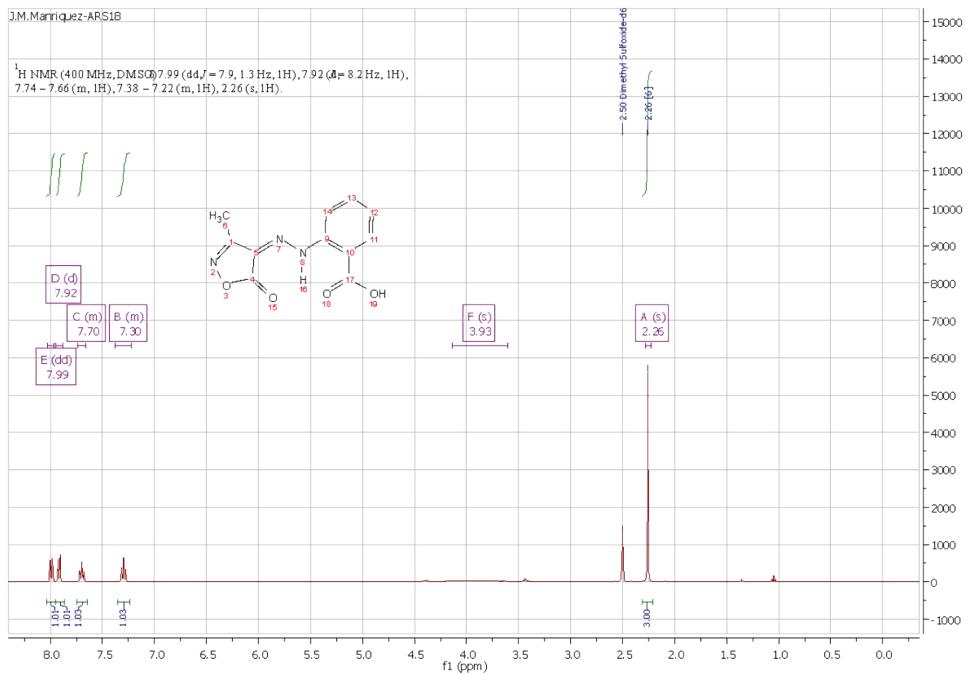
UV-Vis Spectra



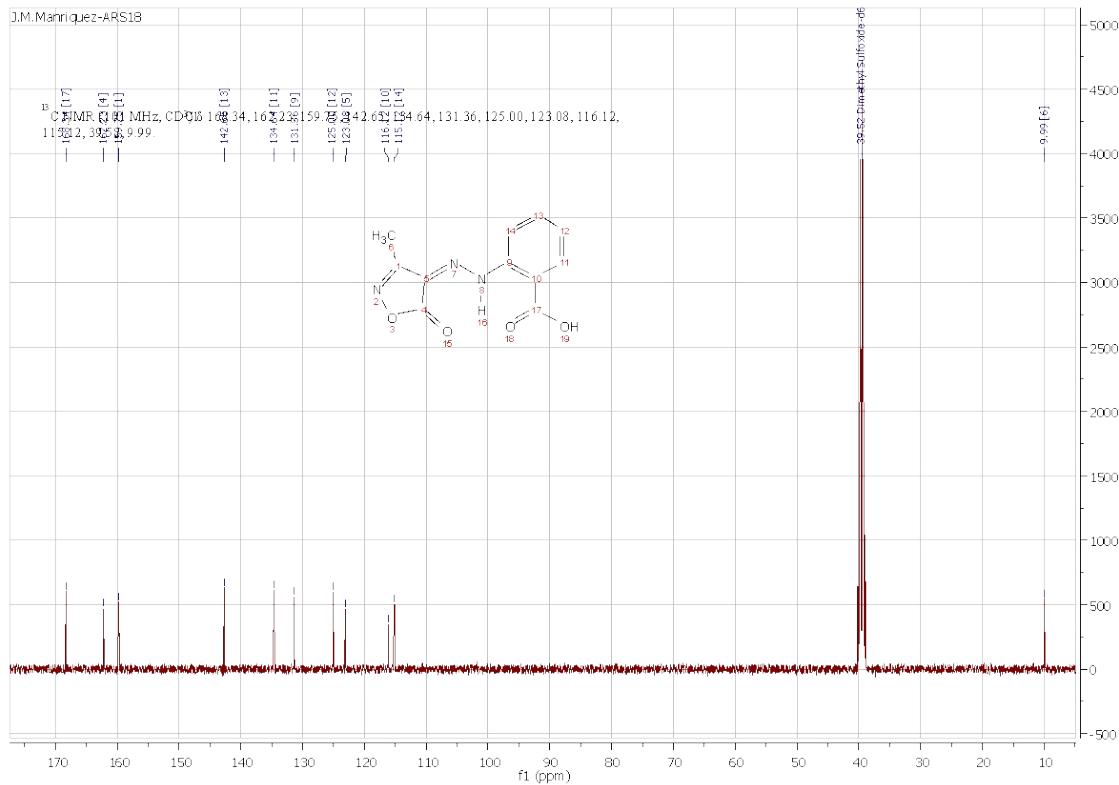
FT-IR Spectra



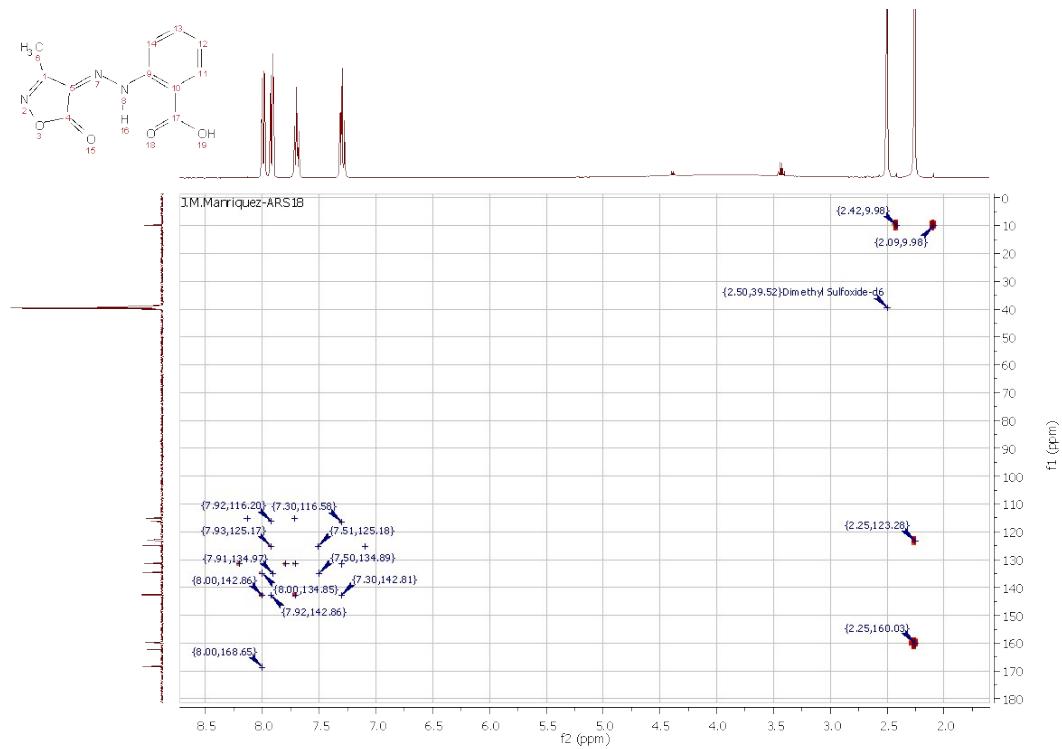
¹H-NMR Spectra



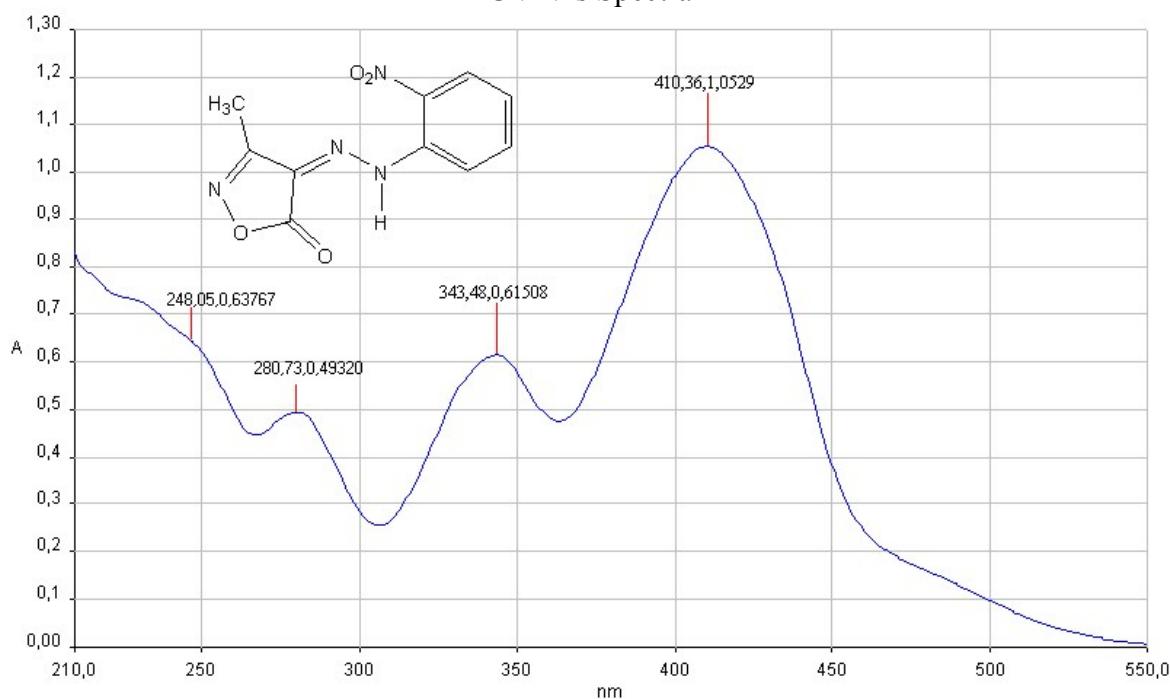
¹³C-NMR Spectra



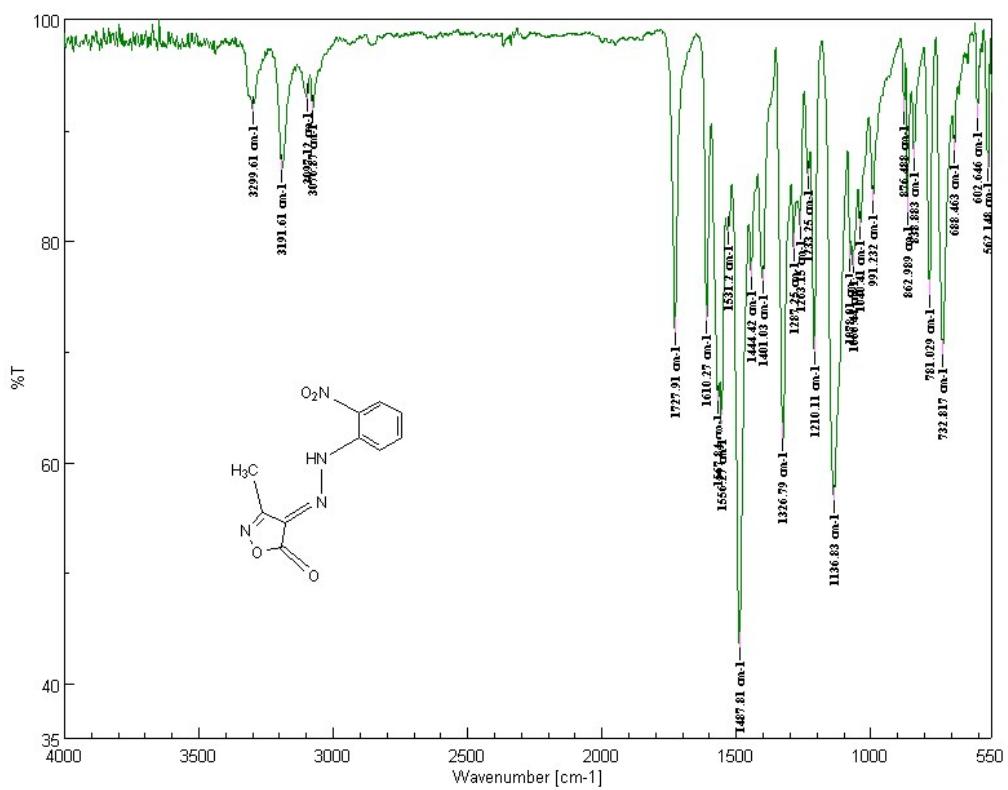
HMBC Spectra



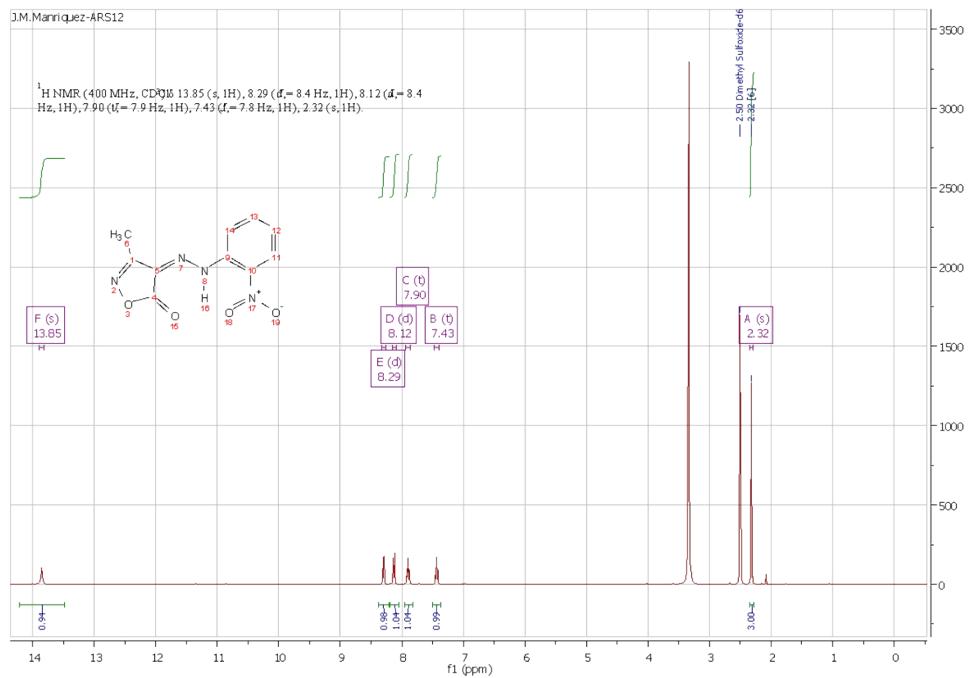
Compound (14) UV-Vis Spectra



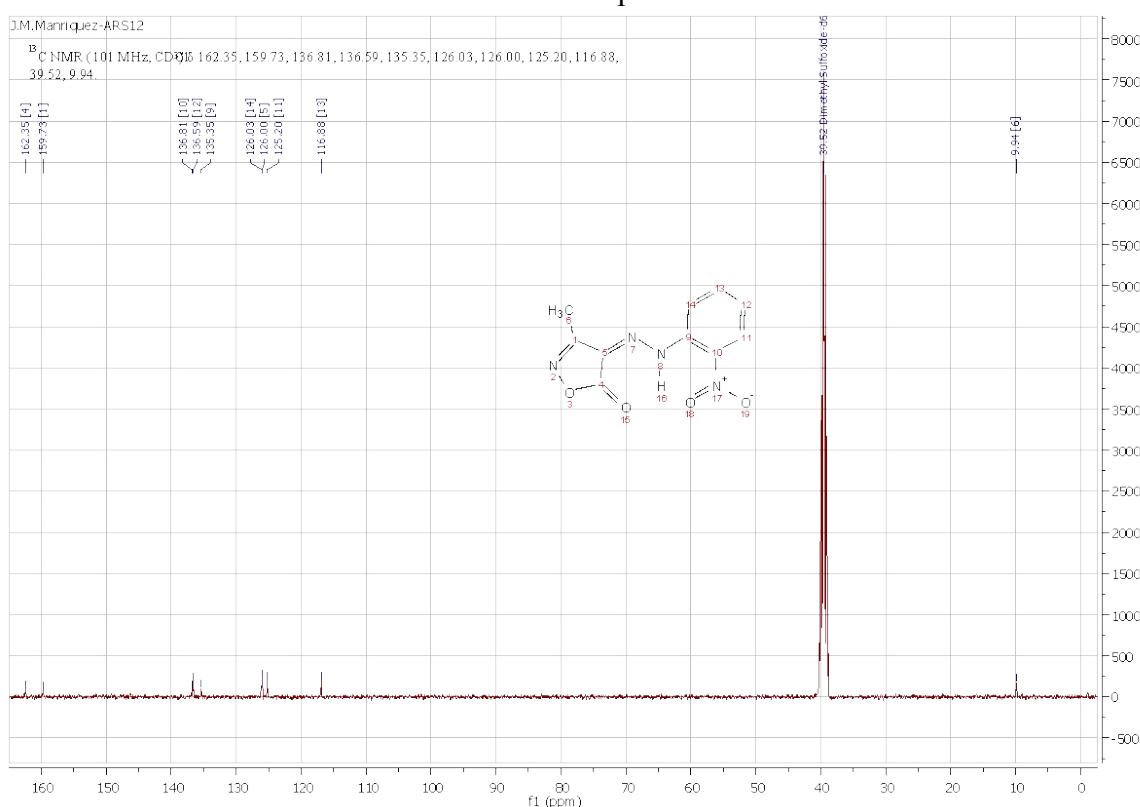
FT-IR Spectra



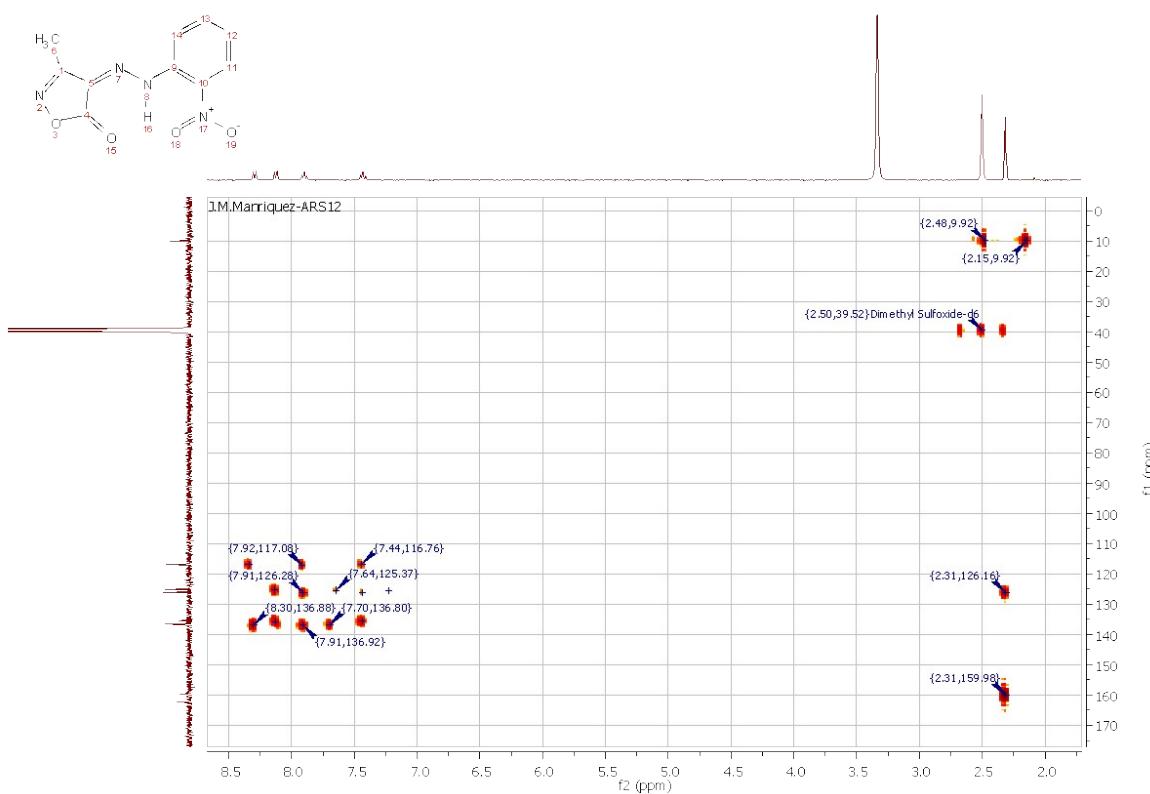
¹H-NMR Spectra



¹³C-NMR Spectra

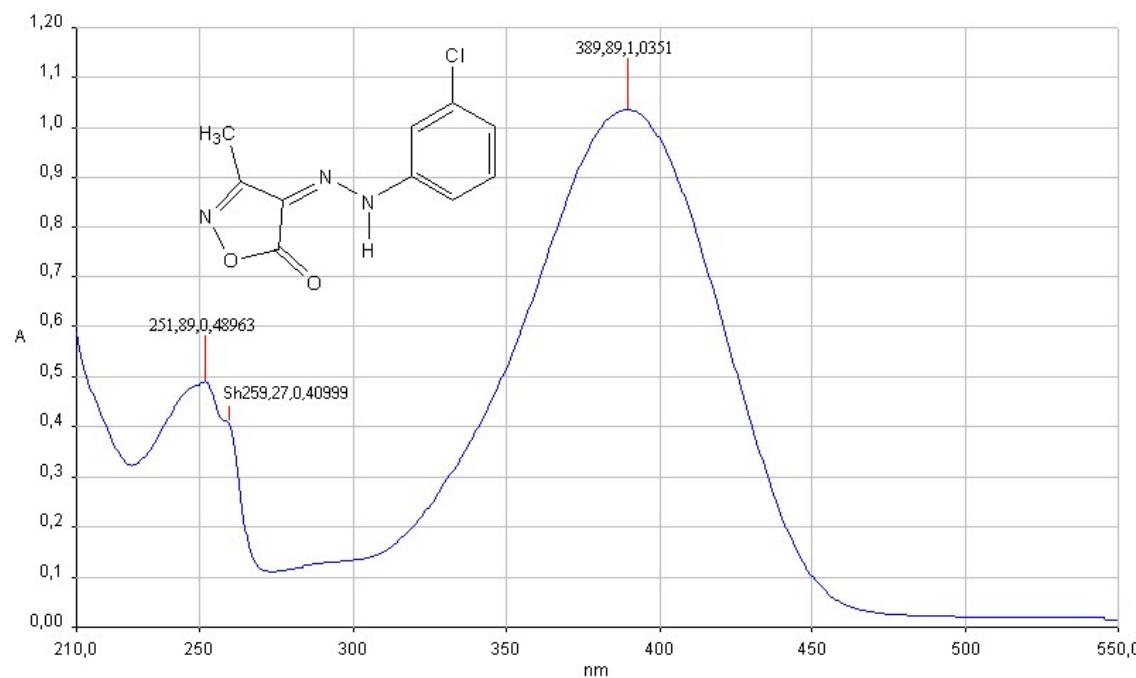


HMBC Spectra

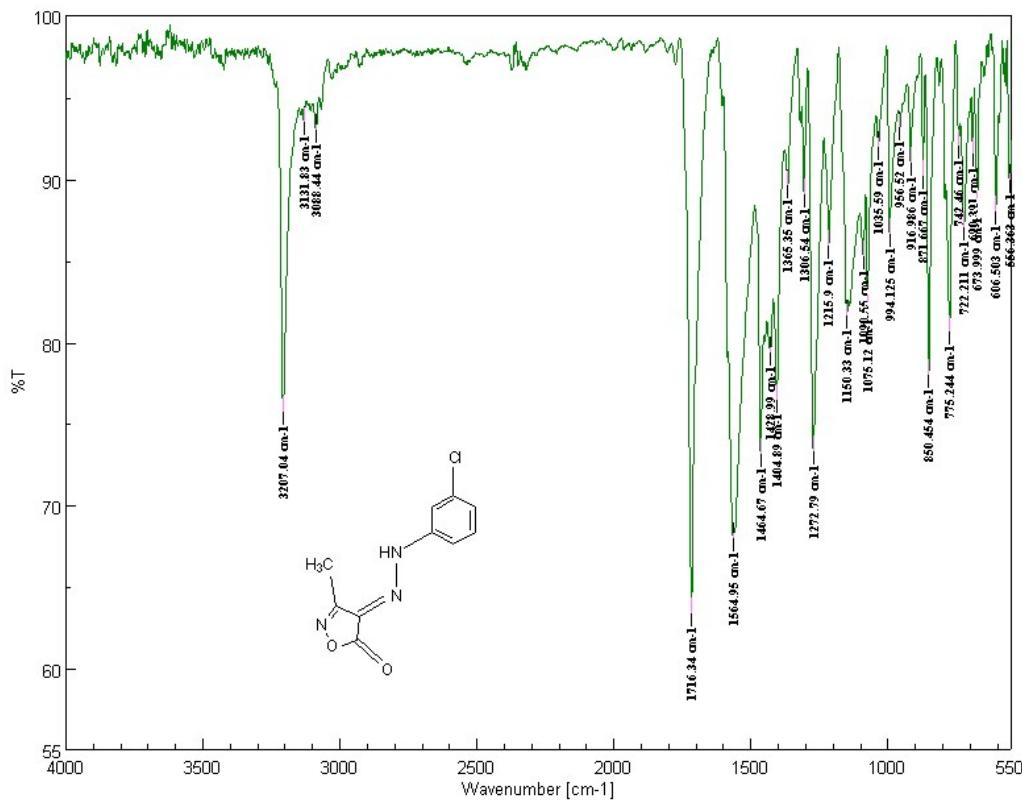


Compound (15)

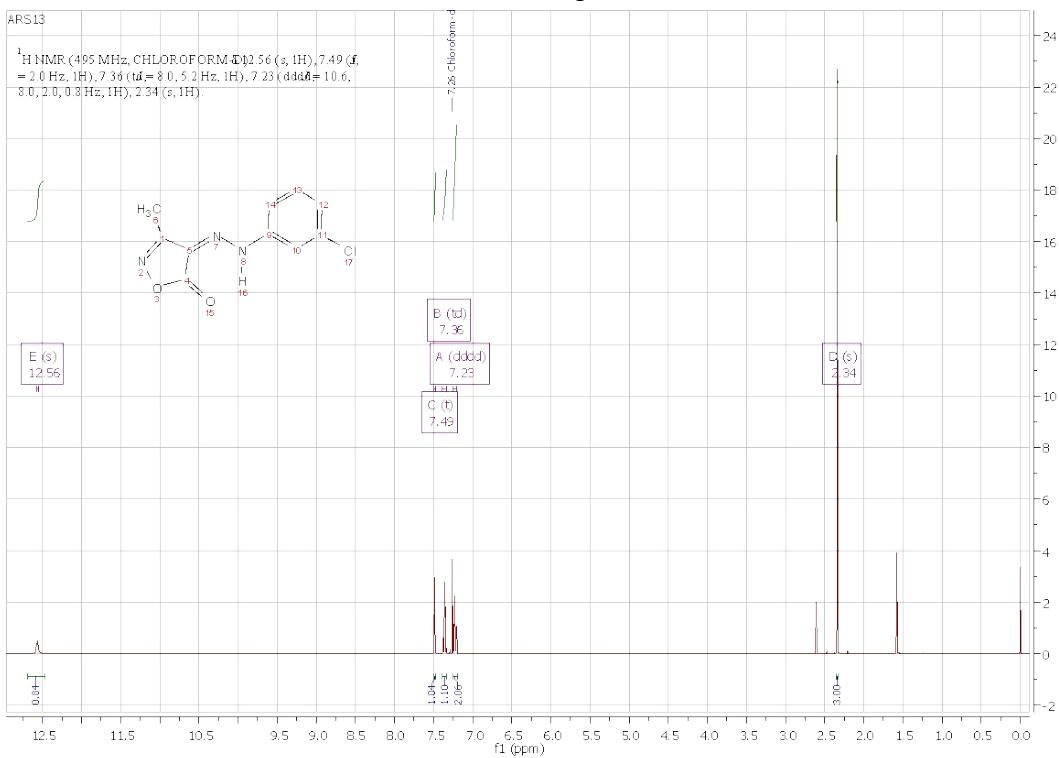
UV-Vis Spectra



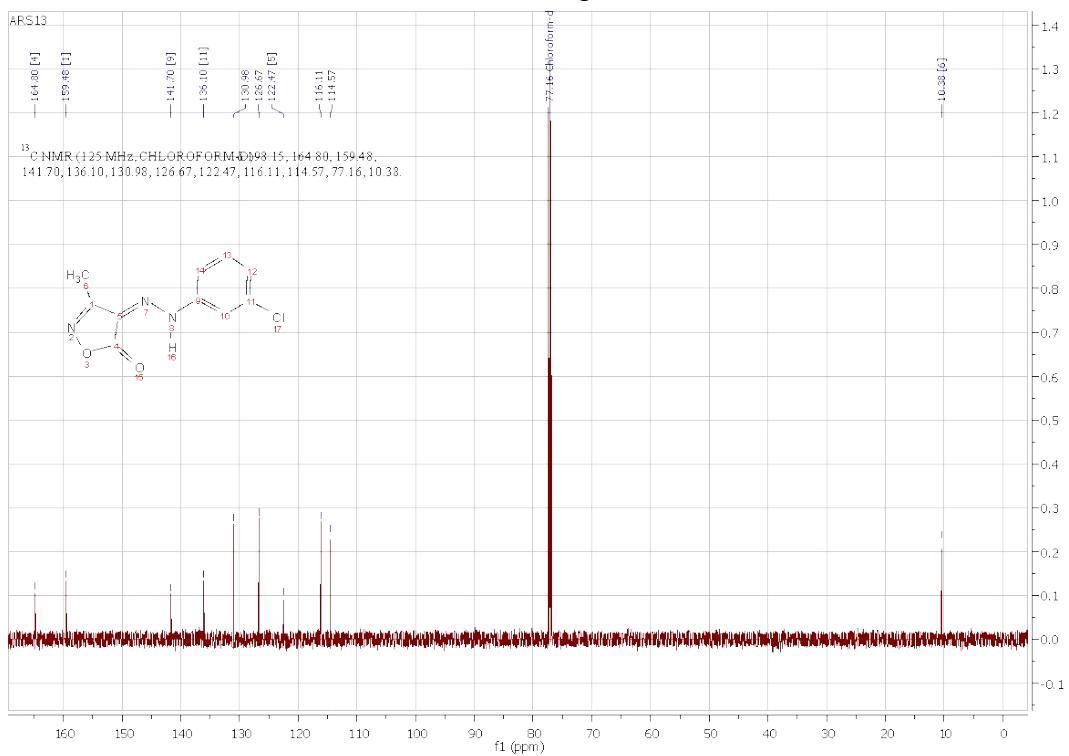
FT-IR Spectra



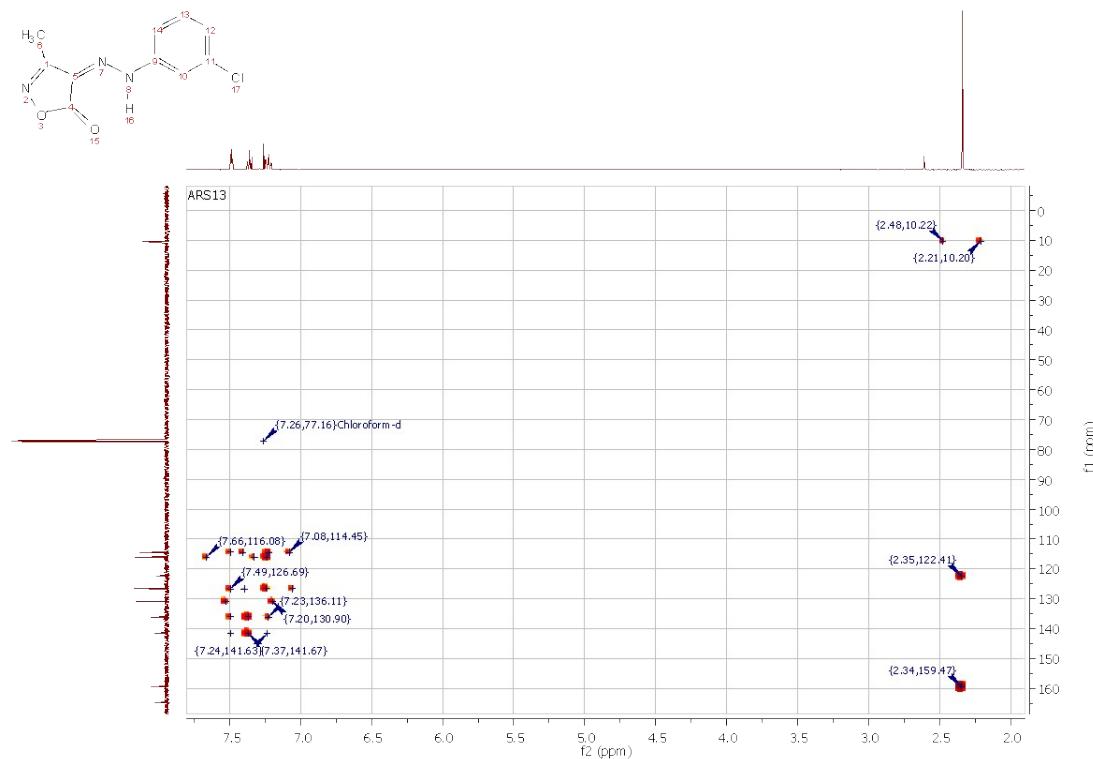
¹H-NMR Spectra



¹³C-NMR Spectra



HMBC Spectra



COMPUESTO (4)

Table S4. Crystal data and structure refinement for **4**.

Identification code	Xv4
Empirical formula	C ₁₀ H ₉ N ₃ O ₂
Formula weight	203.20
Temperature	294(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C 2/c
Unit cell dimensions	a = 11.117(4) Å α= 90°. b = 7.955(2) Å β= 95.76(2)°. c = 21.817(4) Å γ= 90°.
Volume	1919.9(9) Å ³
Z	8
Density (calculated)	1.406 Mg/m ³
Absorption coefficient	0.102 mm ⁻¹
F(000)	848

Crystal size	0.41 x 0.38 x 0.32 mm ³
Theta range for data collection	1.88 to 25.97°.
Index ranges	-13<=h<=13, 0<=k<=9, 0<=l<=26
Reflections collected	1893
Independent reflections	1893
Completeness to theta = 25.97°	100.0 %
Max. and min. transmission	0.9681 and 0.9594
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	1893 / 0 / 122
Goodness-of-fit on F ²	0.981
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.0989
R indices (all data)	R1 = 0.1056, wR2 = 0.1120
Largest diff. peak and hole	0.149 and -0.219 e.Å ⁻³

Table S5. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for (4). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1938(2)	230(3)	6015(1)	38(1)
C(2)	2706(2)	-1236(3)	6029(1)	45(1)
C(5)	1816(2)	650(3)	6644(1)	41(1)
C(6)	1024(2)	1474(3)	4465(1)	37(1)
C(7)	291(2)	2840(3)	4548(1)	45(1)
C(8)	-212(2)	3692(3)	4031(1)	54(1)
C(9)	7(2)	3207(3)	3444(1)	54(1)
C(10)	743(2)	1842(3)	3372(1)	50(1)
C(11)	1256(2)	963(3)	3881(1)	44(1)
C(51)	1120(2)	2049(3)	6875(1)	56(1)
N(1)	1429(2)	1077(2)	5540(1)	39(1)
N(2)	1567(2)	561(2)	4980(1)	42(1)
N(4)	2410(2)	-391(3)	7016(1)	53(1)
O(2)	3084(2)	-2036(2)	5614(1)	59(1)
O(3)	2994(2)	-1616(2)	6634(1)	58(1)

Table S6. Bond lengths [\AA] and angles [$^\circ$] for **4**.

C(1)-N(1)	1.315(2)
C(1)-C(5)	1.432(2)
C(1)-C(2)	1.444(3)
C(2)-O(2)	1.215(2)
C(2)-O(3)	1.361(2)
C(5)-N(4)	1.294(3)
C(5)-C(51)	1.473(3)
C(6)-C(7)	1.380(3)
C(6)-C(11)	1.386(2)
C(6)-N(2)	1.419(2)
C(7)-C(8)	1.385(3)
C(8)-C(9)	1.382(3)
C(9)-C(10)	1.377(3)
C(10)-C(11)	1.387(3)
N(1)-N(2)	1.3133(19)
N(4)-O(3)	1.475(2)
N(1)-C(1)-C(5)	124.09(19)
N(1)-C(1)-C(2)	129.63(18)
C(5)-C(1)-C(2)	106.27(17)
O(2)-C(2)-O(3)	122.7(2)
O(2)-C(2)-C(1)	130.89(19)
O(3)-C(2)-C(1)	106.36(17)
N(4)-C(5)-C(1)	111.2(2)
N(4)-C(5)-C(51)	121.38(19)
C(1)-C(5)-C(51)	127.44(18)
C(7)-C(6)-C(11)	121.17(18)
C(7)-C(6)-N(2)	120.62(16)
C(11)-C(6)-N(2)	118.2(2)
C(6)-C(7)-C(8)	118.33(19)
C(9)-C(8)-C(7)	121.5(2)
C(10)-C(9)-C(8)	119.2(2)
C(9)-C(10)-C(11)	120.5(2)
C(6)-C(11)-C(10)	119.3(2)

N(2)-N(1)-C(1)	119.45(18)
N(1)-N(2)-C(6)	119.71(17)
C(5)-N(4)-O(3)	107.08(16)
C(2)-O(3)-N(4)	109.10(16)

Table S7. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for xv4. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^{*} b^{*} U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	36(1)	37(1)	41(1)	1(1)	5(1)	-2(1)
C(2)	41(1)	46(1)	47(1)	-1(1)	3(1)	-2(1)
C(5)	37(1)	45(1)	42(1)	4(1)	4(1)	-5(1)
C(6)	33(1)	38(1)	39(1)	3(1)	3(1)	-6(1)
C(7)	46(1)	42(1)	45(1)	0(1)	5(1)	3(1)
C(8)	51(2)	50(2)	60(1)	6(1)	1(1)	6(1)
C(9)	56(2)	54(2)	50(1)	11(1)	-6(1)	-3(1)
C(10)	54(2)	55(2)	42(1)	1(1)	4(1)	-8(1)
C(11)	44(1)	42(1)	48(1)	-2(1)	9(1)	-4(1)
C(51)	57(2)	63(2)	50(1)	-12(1)	11(1)	3(1)
O(2)	62(1)	53(1)	63(1)	-8(1)	10(1)	9(1)
O(3)	63(1)	56(1)	55(1)	8(1)	1(1)	16(1)
