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ChemistryOPEN

Supporting Information

Experimental and Theoretical Approaches in the Study of Phenanthroline-Tetrahydroquinolines for Alzheimer's Disease

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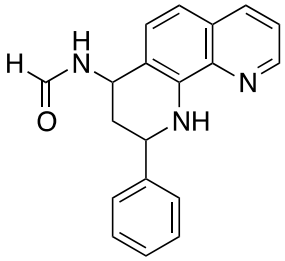
Supporting Information

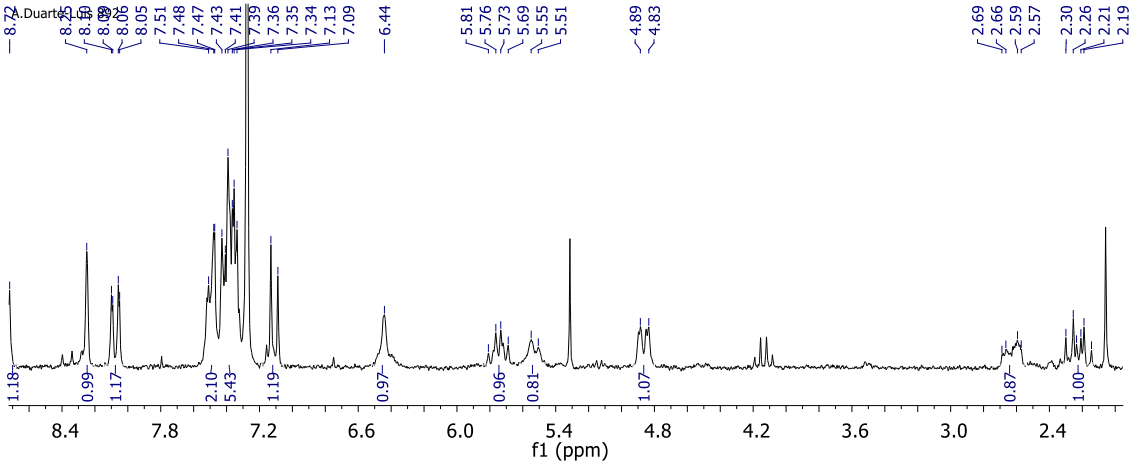
Chemistry

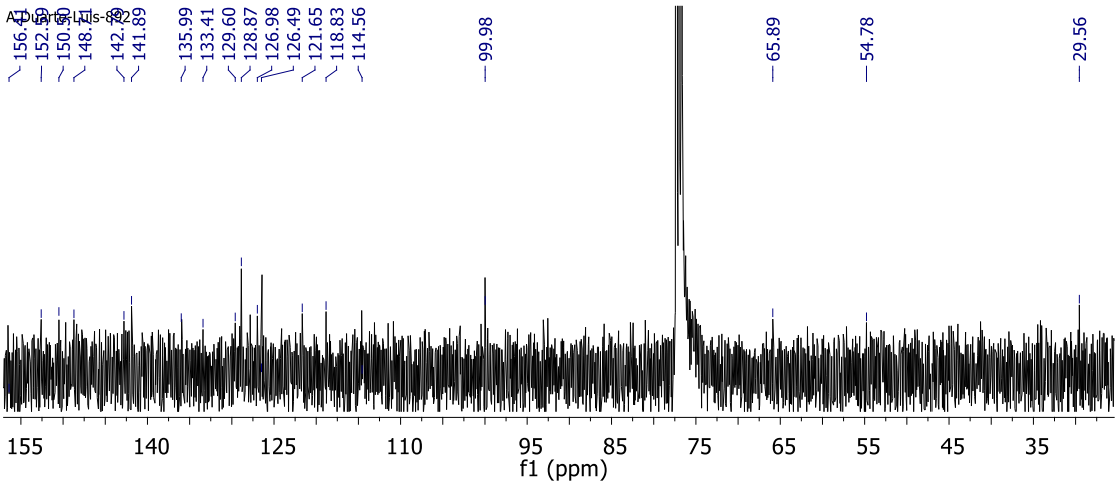
FT-IR spectra were recorded in potassium bromide pellets using a Thermo Nicolet NEXUS 670 FT-IR spectrophotometer, with 0.125 cm^{-1} spectral resolution. ^{1}H NMR (200 MHz) and ^{13}C NMR (101 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6, with a Bruker AMX or a Bruker AM-400 spectrometers. High-resolution mass spectrometry ESI-MS and ESI-MS/MS analyses were conducted in a high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) mass spectrometer (Waters/Micromass Q-TOF micro, Manchester, UK) with a constant nebulizer temperature of 100 °C. The samples were directly infused into the ESI source, via a syringe pump, at flow rates of 5 µL/min, via the instrument's injection valve.

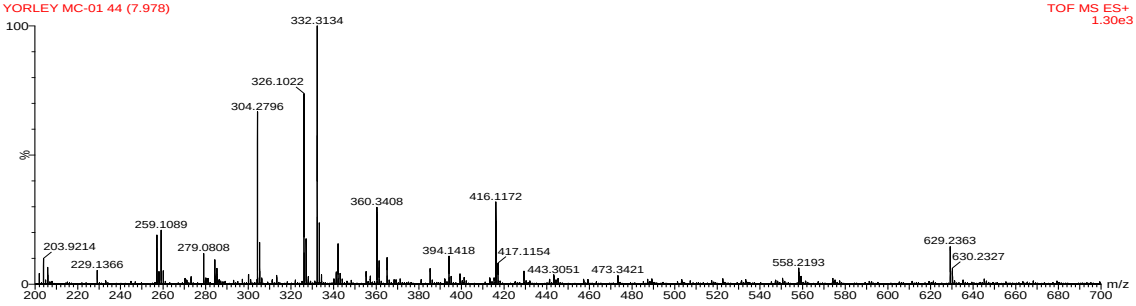
NMR, IR and Mass Spectra for products

Molecule 4a

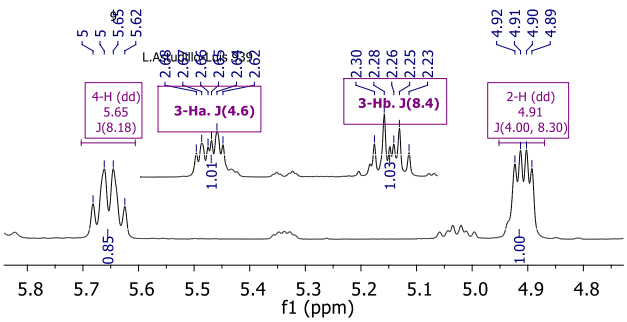




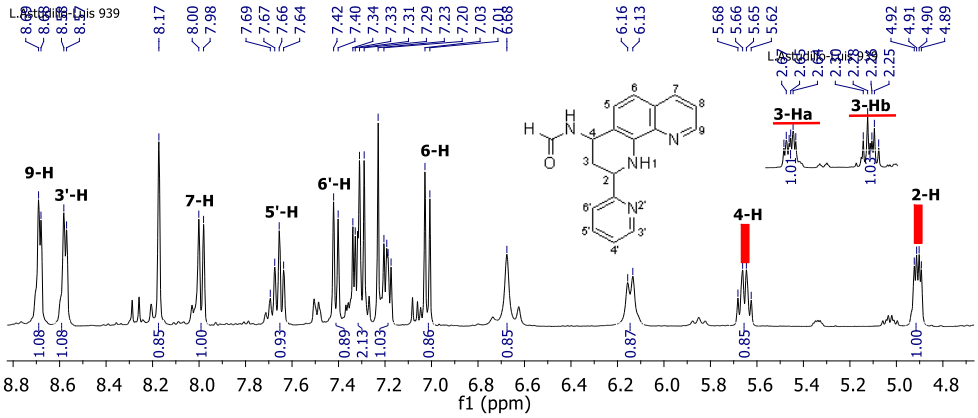




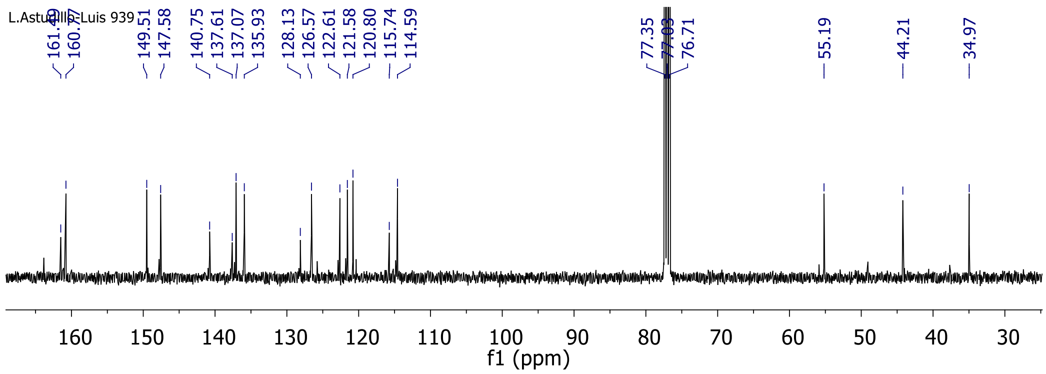
Molecule 4b



^{1}H NMR (400 MHz, CDCl$_3$) δ 2.67 (d, J = 4.6 Hz, 1H), 2.63 (d, J = 5.2 Hz, 1H), 2.29 (d, J = 8.4 Hz, 1H), 2.24 (d, J = 8.2 Hz, 1H).



13C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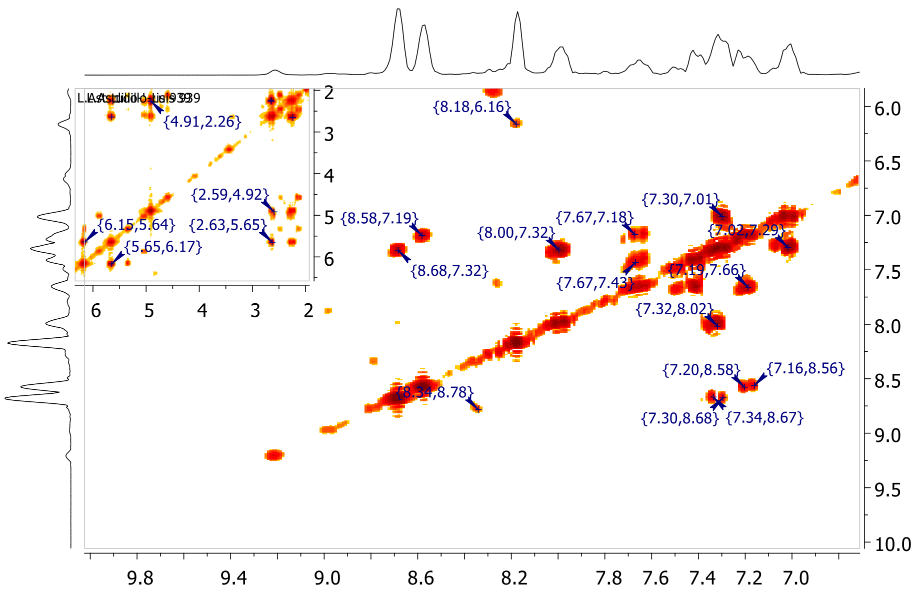
161.40
160.77
149.51
147.58
140.75
137.61
137.07
135.93
128.13
126.57
122.61
121.58
120.80
115.74
114.59
77.35
77.03
76.71
55.19
44.21
34.97
f1 (ppm)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{2.59,4.92}
{6.15,5.64}
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{7.30,7.01}
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{7.19,7.66}
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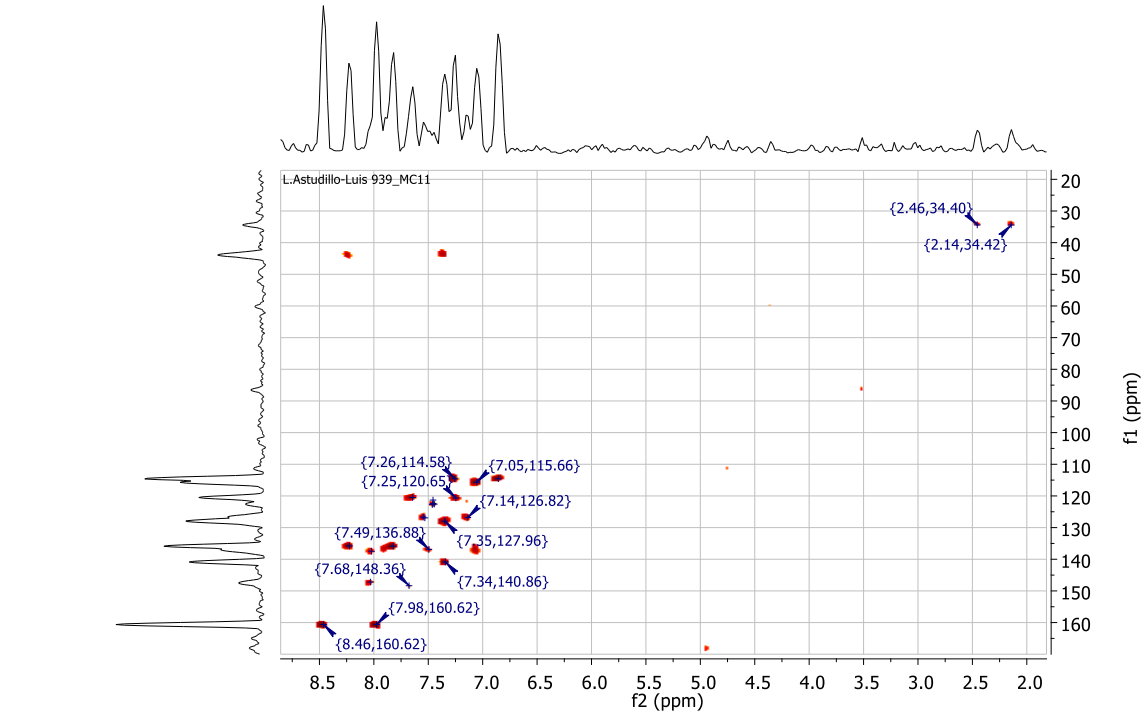
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{7.25,120.65}
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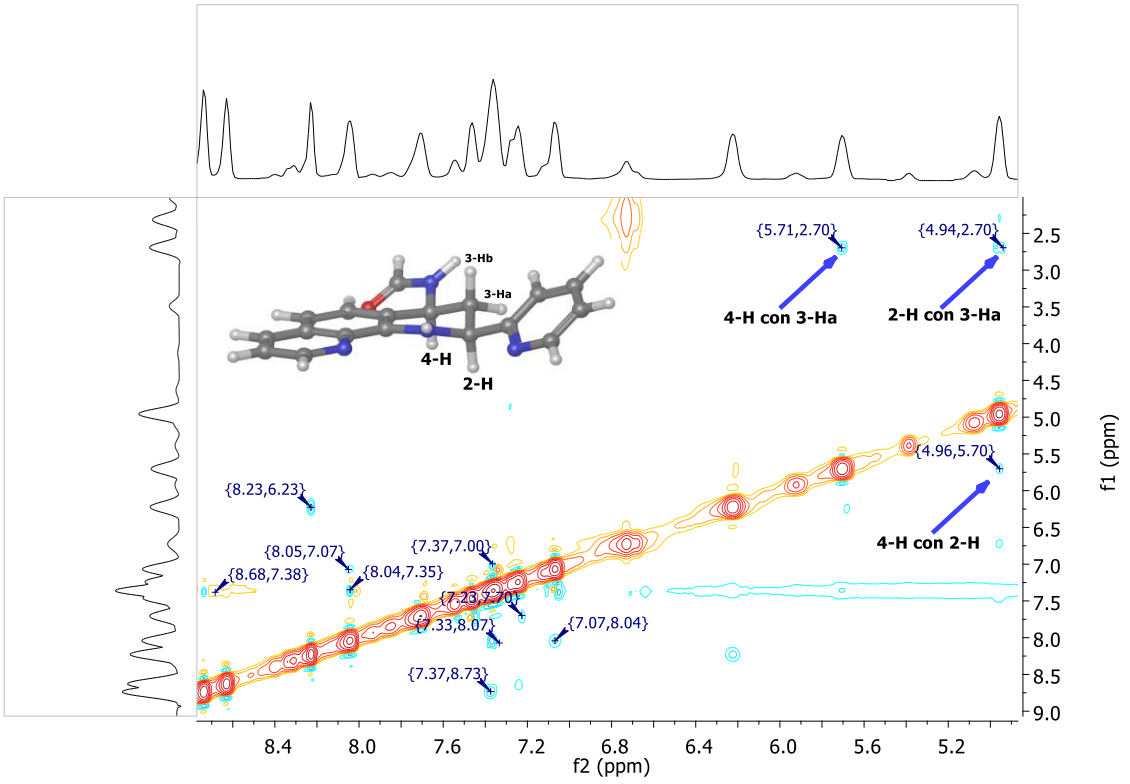
{8.46,160.62}
f2 (ppm)
f1 (ppm)


3-Hb
3-Ha
4-H
2-H
{5.71,2.70}
{4.94,2.70}
4-H con 3-Ha
2-H con 3-Ha
{4.96,5.70}
4-H con 2-H
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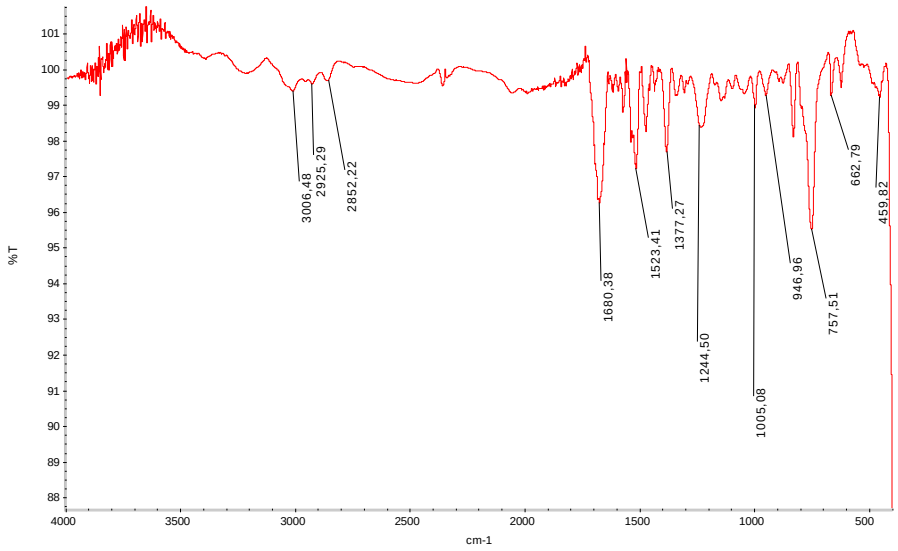
{7.37,8.73}
f2 (ppm)
f1 (ppm)


%T
cm-1
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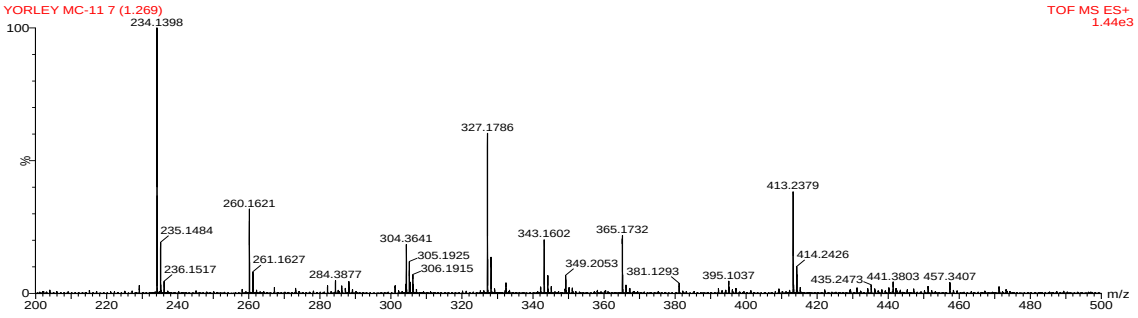
1244.50
1005.08
946.96
757.51
662.79
459.82


YORLEY MC-11 7 (1.269)
TOF MS ES+
1.44e3
%
m/z
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327.1786
413.2379
260.1621
235.1484
304.3641
343.1602
365.1732
261.1627
305.1925
414.2426
236.1517
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349.2053
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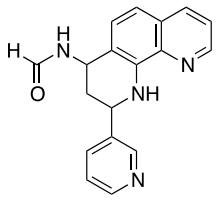
381.1293
395.1037
435.2473
441.3803
457.3407

Molecule 4c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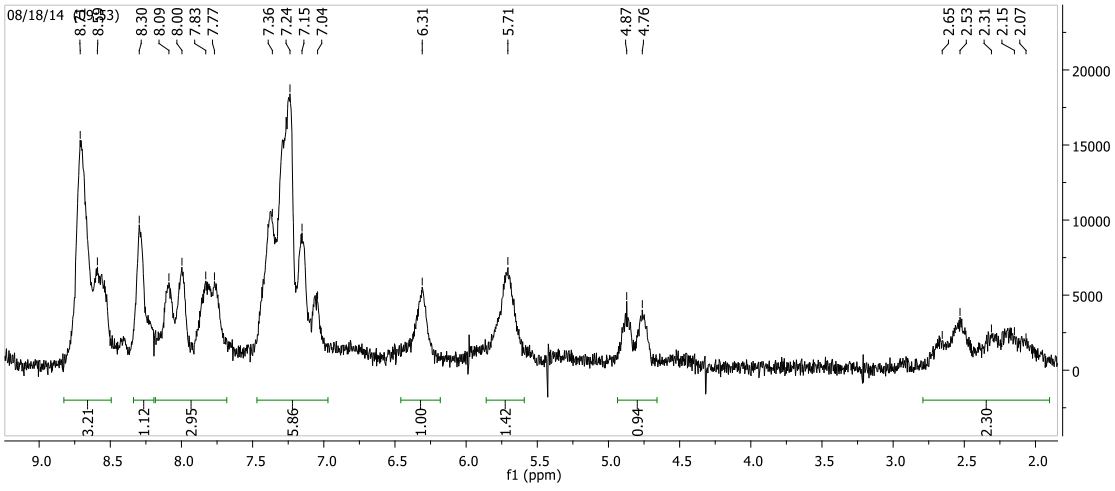
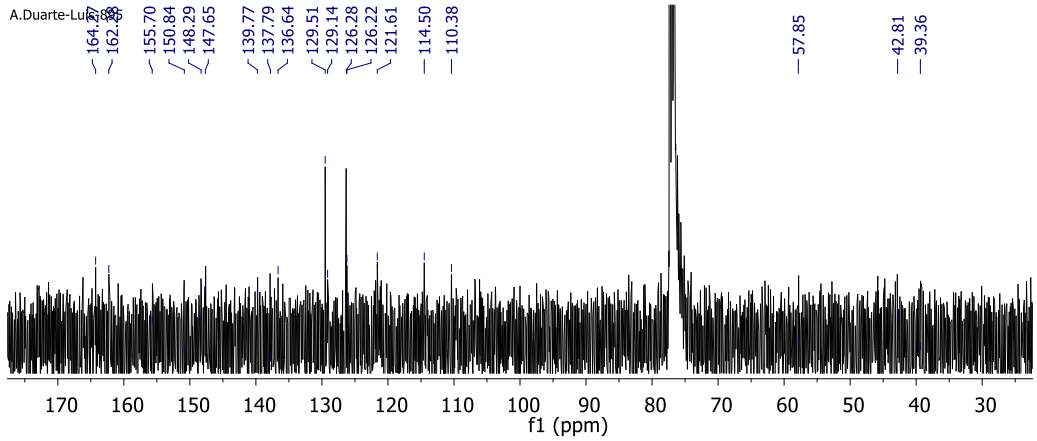
N
O
NH
N
N


08/18/14
8.79
8.53
8.30
8.09
8.00
7.83
7.77
7.36
7.24
7.15
7.04
6.31
5.71
4.87
4.76
2.65
2.53
2.31
2.15
2.07
3.21
1.12
2.95
5.86
1.00
1.42
0.94
2.30
f1 (ppm)


A.Duarte-Luz-2-25
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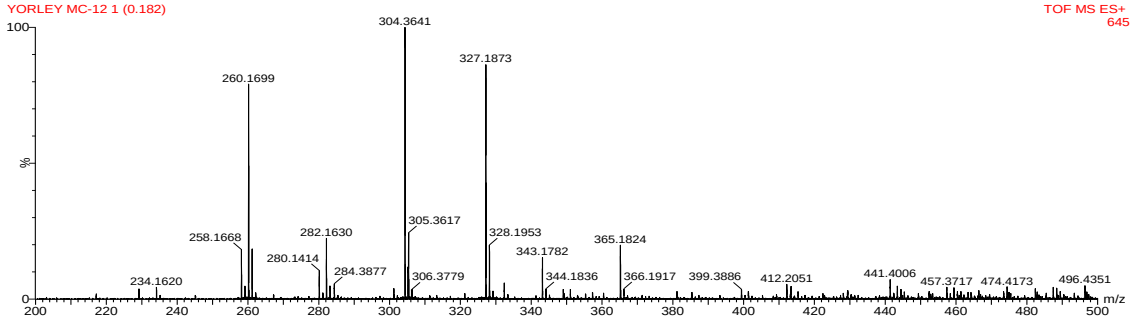
162.88
155.70
150.84
148.29
147.65
139.77
137.79
136.64
129.51
129.14
126.28
126.22
121.61
114.50
110.38
57.85
42.81
39.36
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)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TOF MS ES+
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100
%
0
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260.1699
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280.1414
284.3877
305.3617
306.3779
328.1953
343.1782
365.1824
234.1620
344.1836
366.1917
399.3886
412.2051
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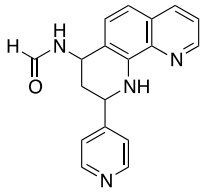
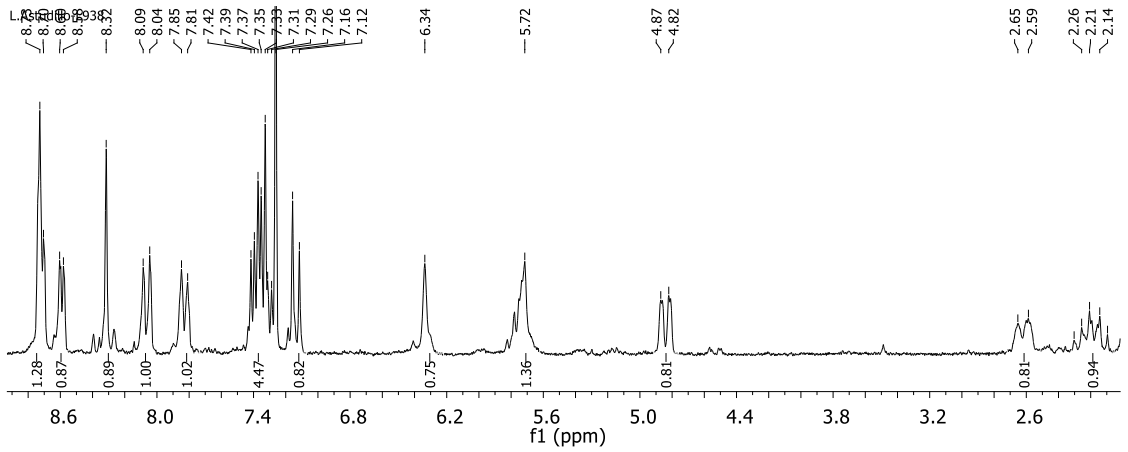
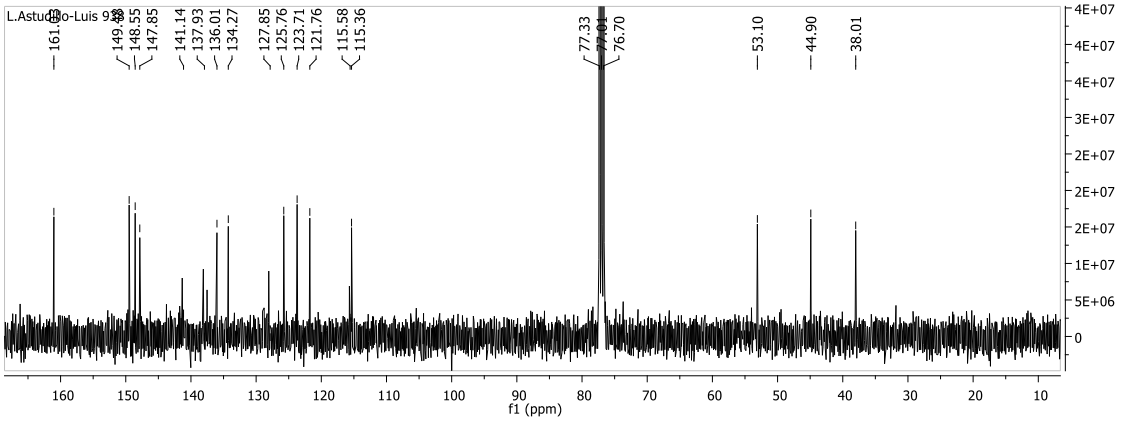
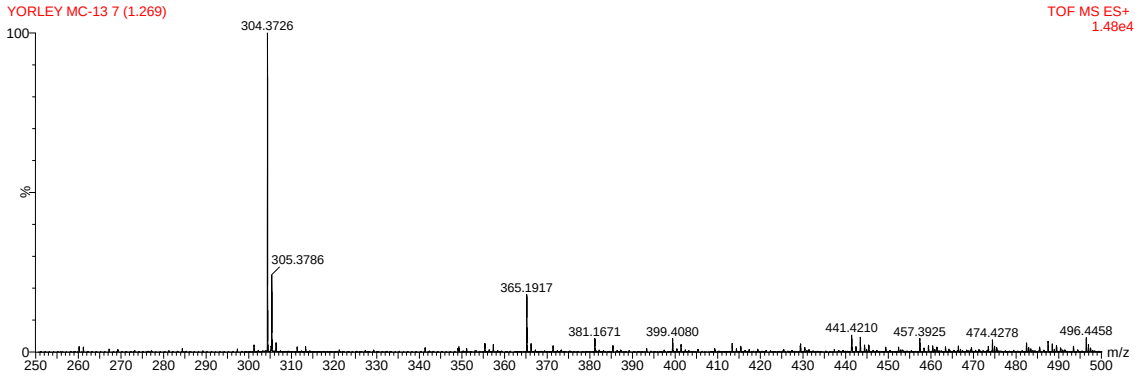
457.3717
474.4173
496.4351
200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500
m/z

Molecule 4d


H
N
O
NH
N
N


L.A.Duarte-2938
Acetone
8.34
8.32
8.09
8.04
7.85
7.81
7.42
7.39
7.37
7.35
7.33
7.31
7.29
7.26
7.16
7.12
6.34
5.72
4.87
4.82
2.65
2.59
2.26
2.21
2.14
1.28
0.87
0.89
1.00
1.02
4.47
0.82
0.75
1.36
0.81
0.81
0.94
8.6 8.0 7.4 6.8 6.2 5.6 5.0 4.4 3.8 3.2 2.6
f1 (ppm)


L.Astudillo-Luis 93
161.03
149.48
148.55
147.85
141.14
137.93
136.01
134.27
127.85
125.76
123.71
121.76
115.58
115.36
77.33
77.01
76.70
53.10
44.90
38.01
f1 (ppm)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TOF MS ES+
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365.1917
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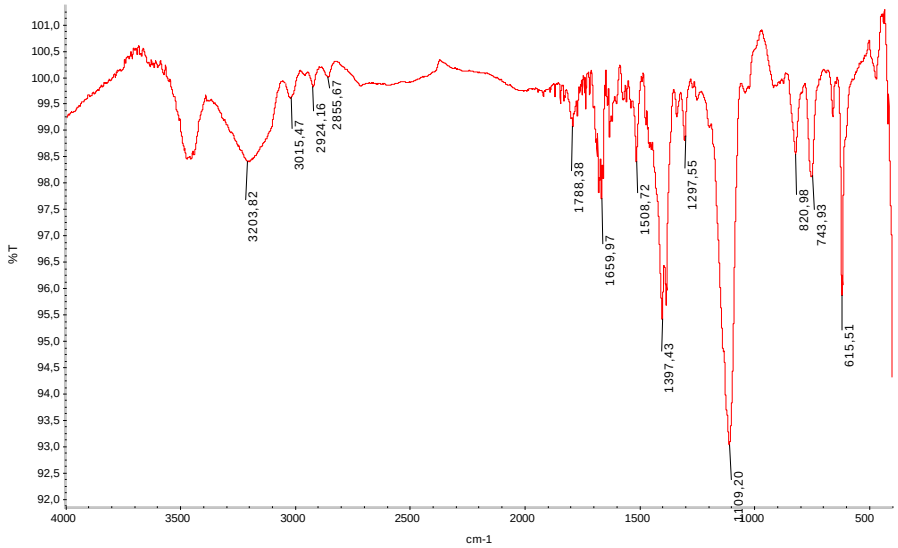
399.4080
441.4210
457.3925
474.4278
496.4458
%
m/z


%T
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3015.47
2924.16
2855.67
1788.38
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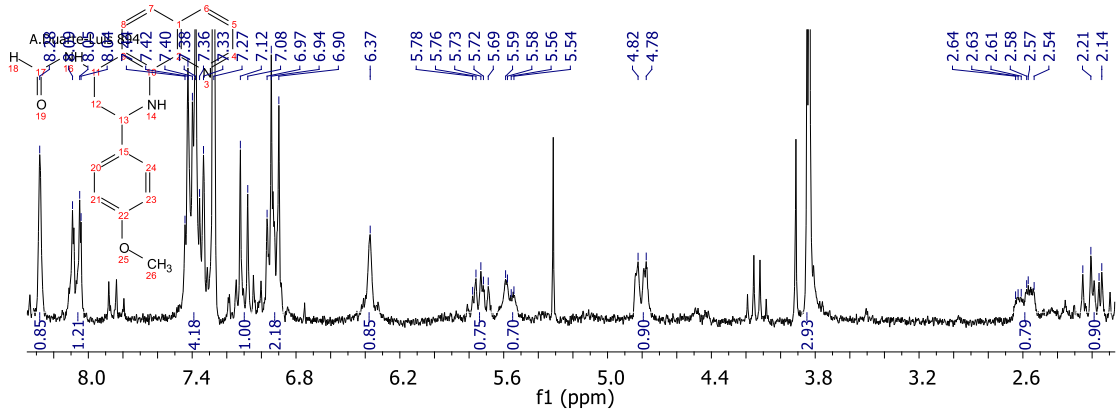
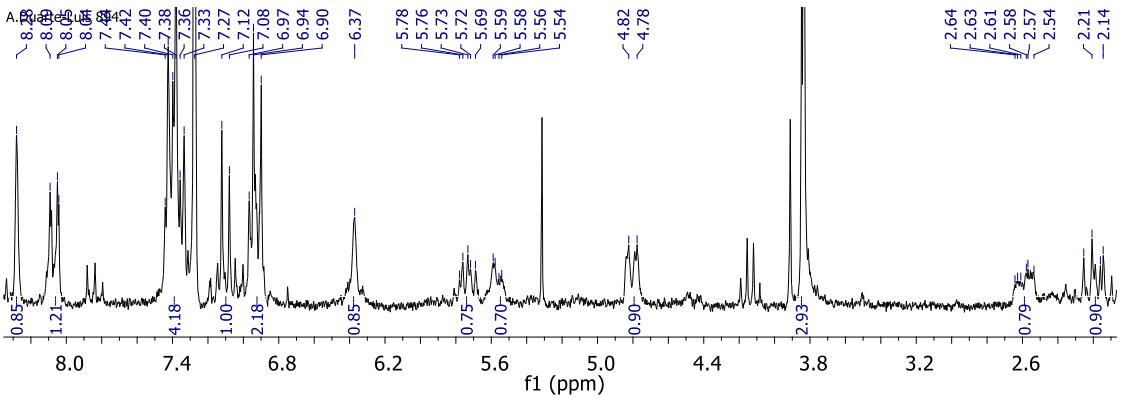
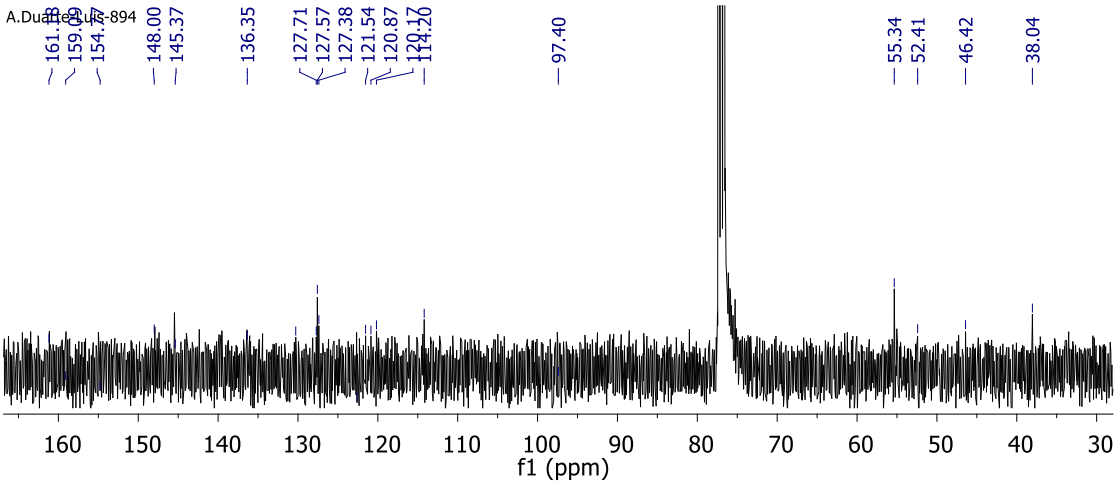
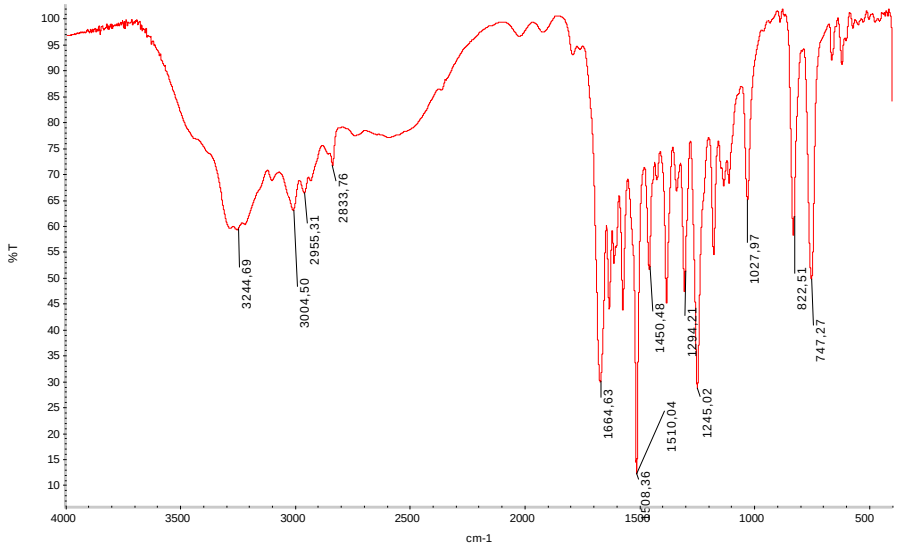
1297.55
1109.20
820.98
743.93
615.51
cm-1

Molecule 4f


A.DuarteLuis-894
f1 (ppm)


A.DuarteLuis-894
f1 (ppm)


A.DuarteLuis-894
f1 (ppm)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cm-1
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3004,50
2955,31
2833,76
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1508,36
1510,04
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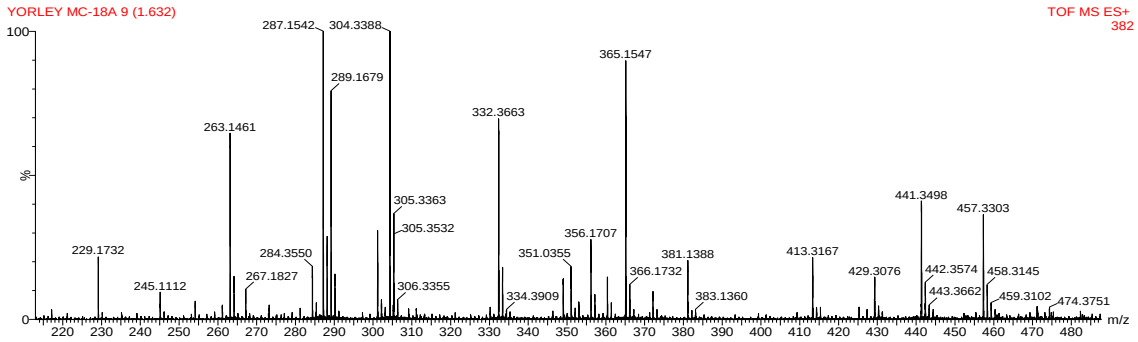
1245,02
1027,97
822,51
747,27


YORLEY MC-18A 9 (1.632)
TOF MS ES+
382
%
m/z
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304.3388
289.1679
365.1547
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332.3663
305.3363
305.3532
441.3498
457.3303
229.1732
356.1707
351.0355
381.1388
413.3167
284.3550
366.1732
429.3076
442.3574
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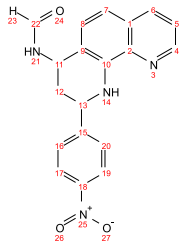
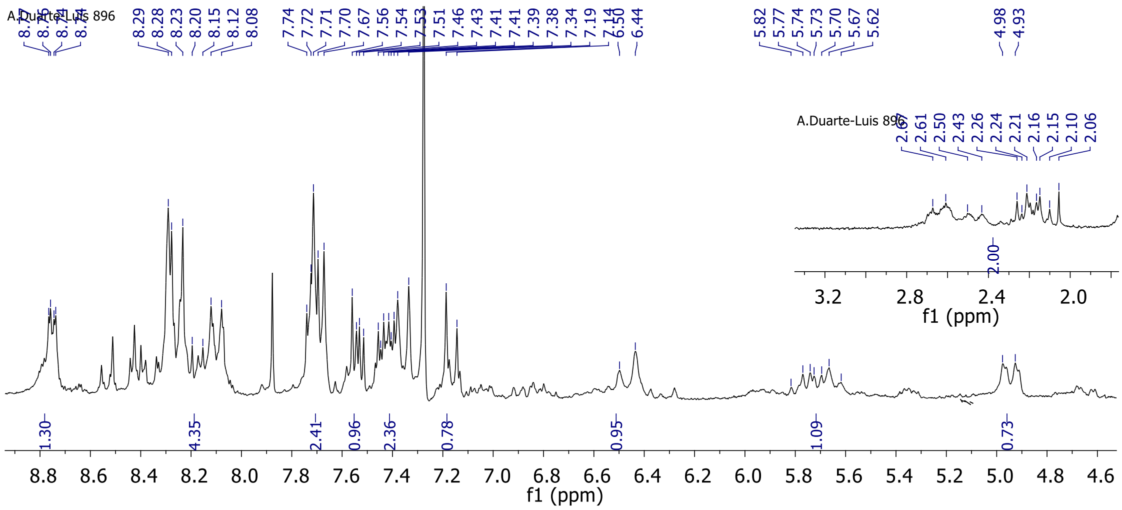
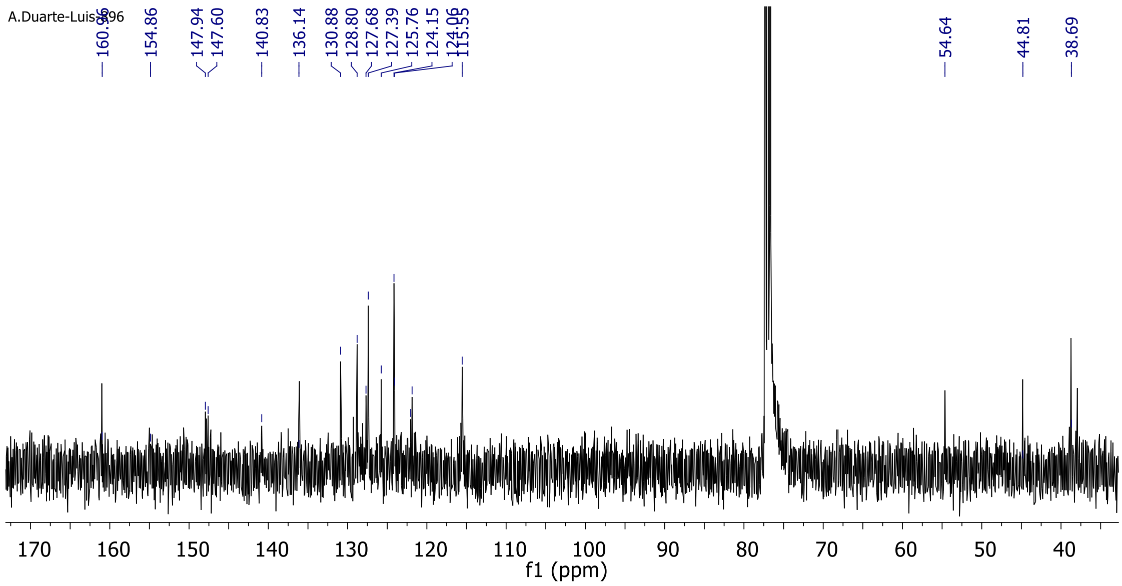
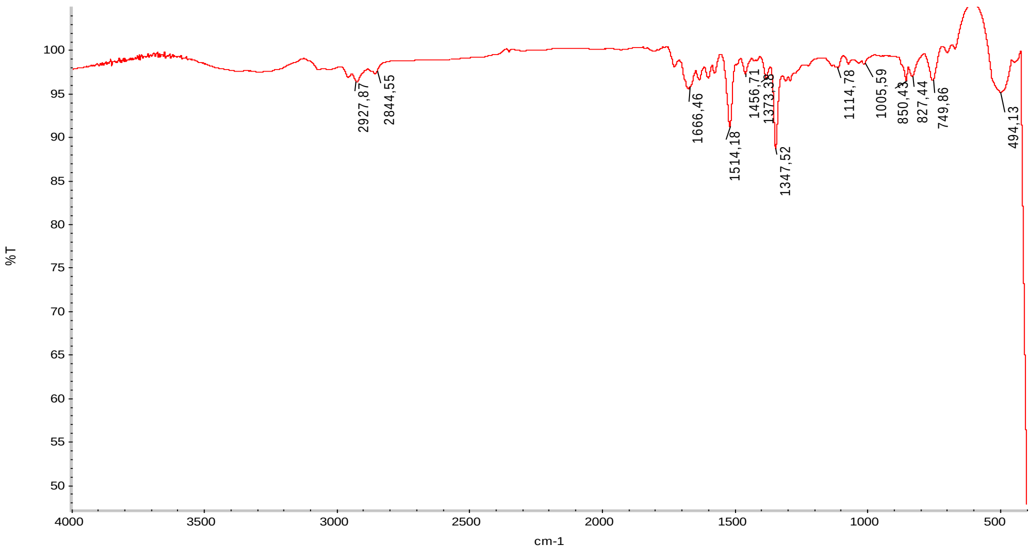
443.3662
459.3102
474.3751

Molecule 4g


H
O
HN
N
NH
O
N
O


A.Duarte-Luis 896
f1 (ppm)


A.Duarte-Luis 896
f1 (ppm)


%T
cm-1
2927,87
2844,55
1666,46
1514,18
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1347,52
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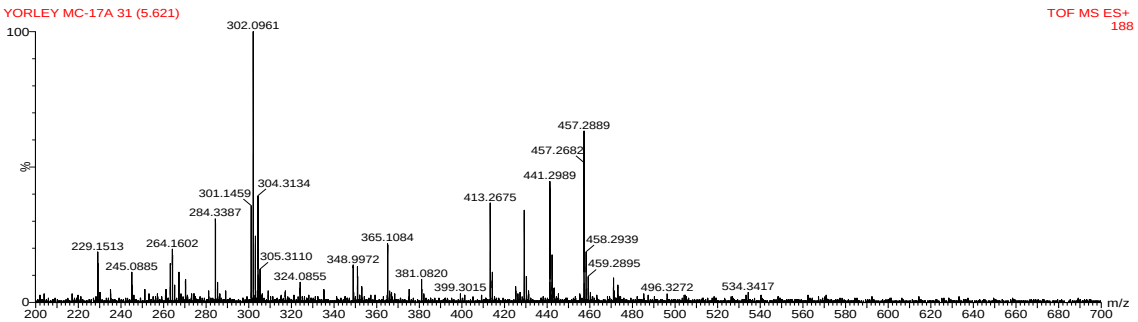
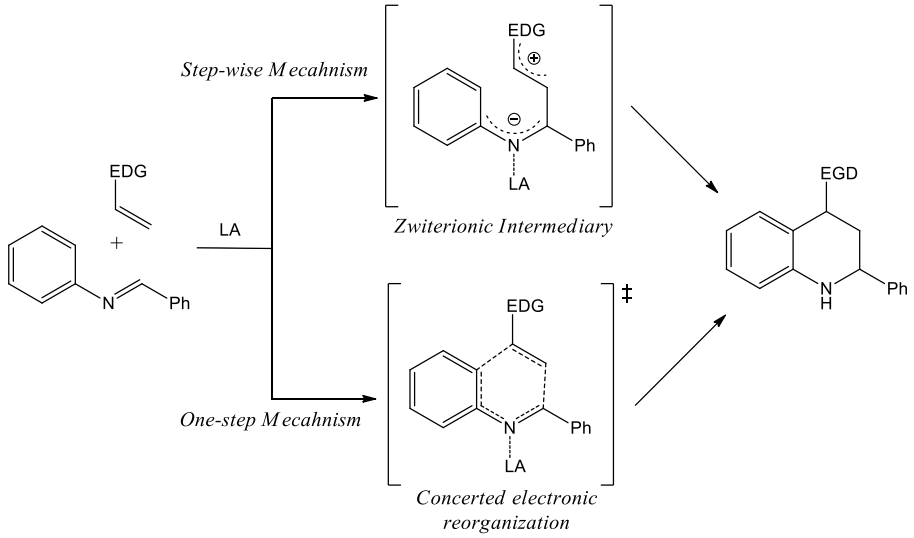
1005,59
850,43
827,44
749,86
494,13



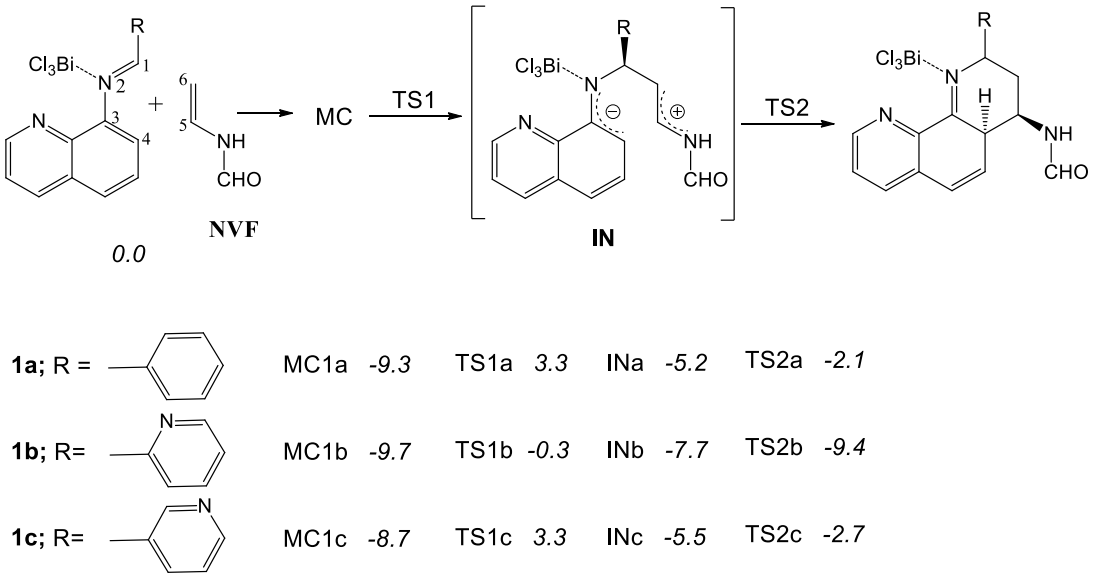
Theoretical Study

Computational study



Scheme 1. Possible Mechanisms for the iDA Reaction, one-step and step-wise mechanism.

***Energy aspects*:**



Scheme 2: iDA reaction between *N*-aryl imine and NVF using M06-2X/6-311G** level of theory. The relative energies are in kcal mol^{-1}.

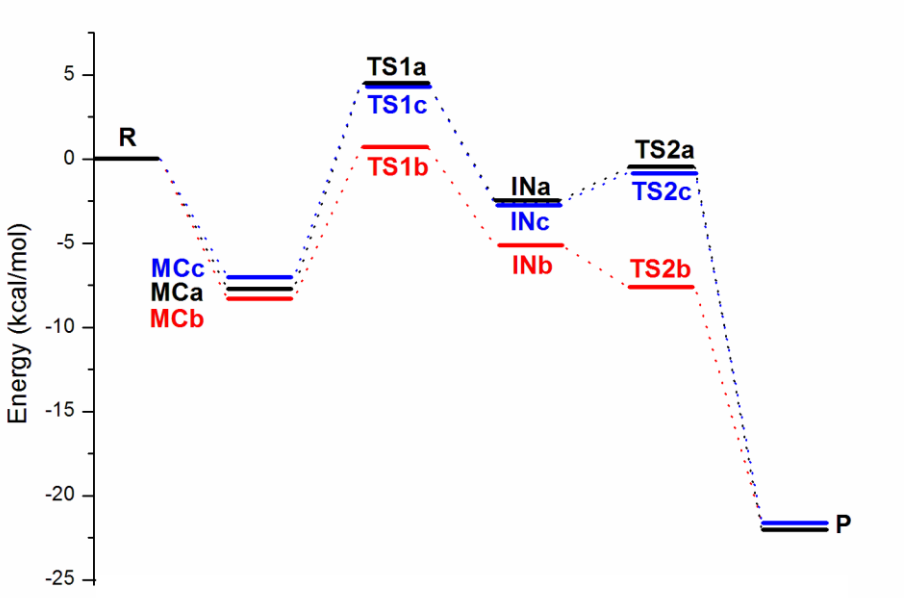


Figure 1. Relative Energy profile (ΔE in kcal mol^{-1}) of the iDA reaction between N-aryl imine and NVF.

***Reactivity index analysis*:**

Table 1. *Reactivity index analysis*: M06-2X/6-311G** level of theory. Electronic chemical potential μ, hardnesses η, global electrophilicity ω, and global nucleophilicity

N indices, for the reagents and compounds involved in iDA reactions for phenanthroline-THQ.

Compounds	μ	η	ω	N	$\Delta\omega$
NVF	-0.1545	0.3273	0.99	2.91	
1a	-0.1802	0.1988	2.22	2.71	1.23
1b	-0.1848	0.1822	2.55	2.65	1.59
1c	-0.1891	0.2251	2.16	2.62	1.17

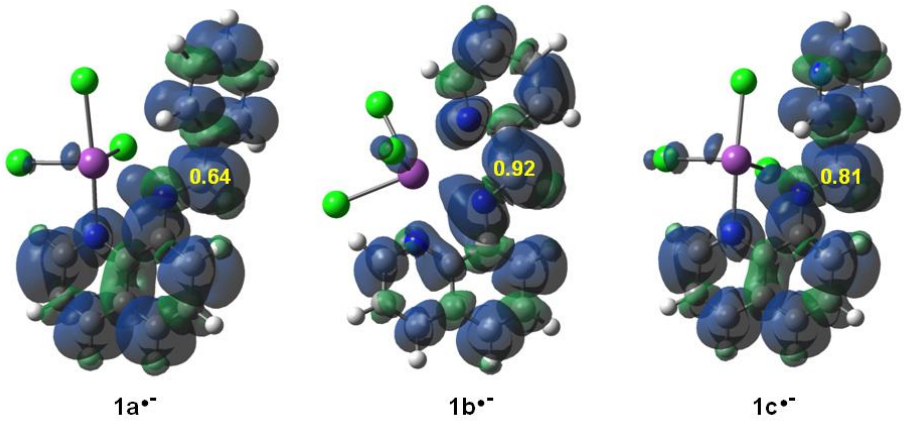


Figure 2. M06-2X/6-311G** 3D Maps of the ASD (Atomic Spin Densities) and electrophilic P+k Parr functions of 1a, 1b and 1c compounds.

Table 2. *Reactivity index analysis*: M06-2X/6-311G** level of theory. Electronic chemical potential μ, hardnesses η, global electrophilicity ω, and global nucleophilicity N indices, for the intermediaries involved in iDA reactions for phenanthroline THQ.

Compounds	μ	η	ω	N
INa	-0.1797	0.1757	2.50	3.54
INb	-0.1814	0.1773	2.52	3.47
INc	-0.1808	0.1759	2.53	3.51

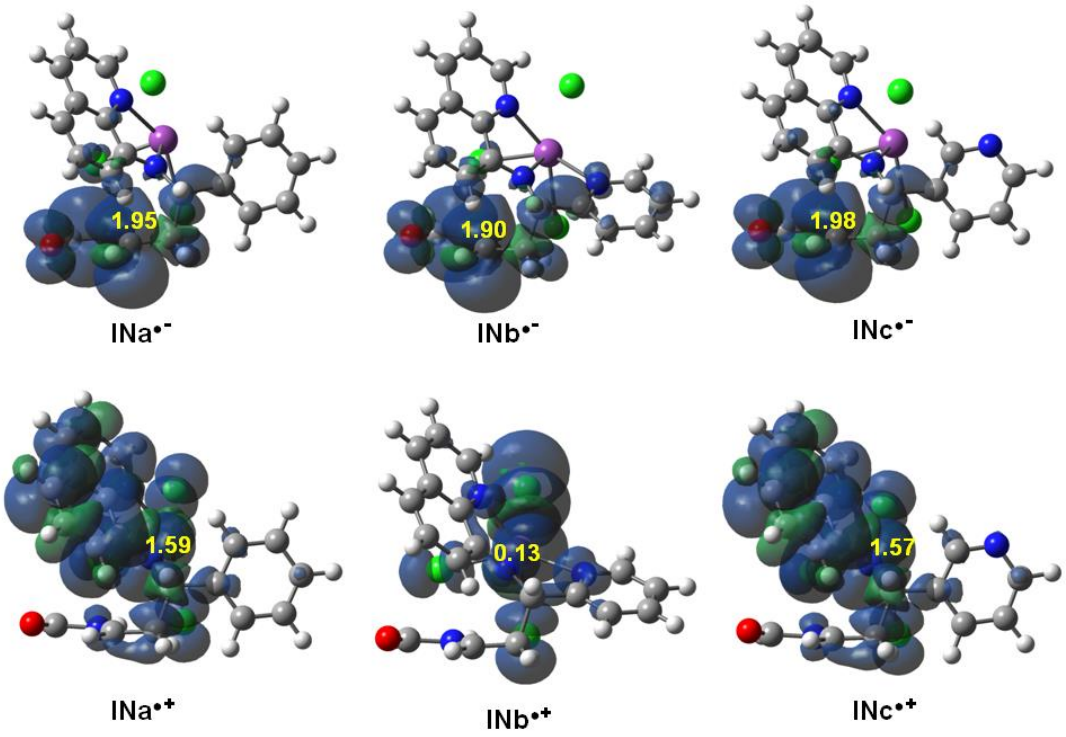


Figure 3. M06-2X/6-311G** 3D Maps of the ASD (Atomic Spin Densities) and electrophilic P+k Parr functions of intermediaries 1a, 1b and 1c involved in iDA reaction.

This result suggests that the polarity of the process depends mostly on a high electrophilicity value at any of both fragments, thereby suggesting that during an electrophile–nucleophile interaction the effect of electrophilicity outweigh the effect of nucleophilicity.