Electronic Supplementary Information

for

An Innovation for Development of Erlenmeyer–Plöchl Reaction and Synthesis of AT-130 Analogous: A New Application of Continuous-Flow Method

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METHODS:

All chemicals and Nafion-H (5% in ethanol) were purchased from Merck and DuPont companies, respectively. Fe_3O_4 nanocomposite and silica-coated magnetite nanoparticles (SPIONs) was synthesis according to the literature respectively.[29] All known organic products were identified by comparison of their physical and spectral data with those of authentic samples. Thin layer chromatography (TLC) was performed on UV-active aluminum-backed plates of silica gel (TLC Silica gel 60 F254). ^1H, and ^{13}C NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ with chemical shift (δ) given in ppm. Coupling constants are given in Hz. The FT-IR spectra were taken on a Nicolet-Impact 400D spectrophotometer in KBr pellets and reported in cm^{-1}. Melting points were determined using Stuart Scientific SMP2 apparatus and are uncorrected. The sonication was performed in a UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The operating frequency was 24 kHz and the output power was 0–400 Watt through manual adjustment. The TEM images were taken with a Philips CM30 unit operated at 150 kV. The magnetic measurements were performed with a vibrating sample magnetometer (VSM) at Meghnatis Daghigh Kavir Co. TGA curve was obtained with a heating rate of 10 ^oC/min on a TG 50 Mettler thermogravimetric analyzer from 30 ^oC to 600 ^oC.

Preparation of Nafion-H@SPIONs

The catalyst was synthesized via impregnation method. To a mixture of SPIONs (80 mg) in absolute ethanol (10 ml) at 25 °C, 0.4 ml Nafion-H (5% in ethanol) was added and sonicated for 15 minutes. The resulting mixture was stirred for 2h at 100 °C and subsequently calcinated at 120 °C for three hours.

General procedure for the Erlenmeyer-Plöchl reaction in microreactor System..

A microreactor system containing microtube reactor immersed in a water bath, and a syringing pump were used. The syringing pump was equipped with one syringe (1 ml). In the syringe, a solution of 4-chlorobenzaldehyde (0.2 M) and hippuric acid (0.2 M) in acetic anhydride was charged. Next, the mixture was fed into the system by syringe pump (flow rate: 0.72 ml/ h) at 90 °C. After the residence time was reached (50 min), the discharge was collected in a glass vessel equipped with an external permanent magnet. ethanol (5 ml) was added to it and stirred for 10 min until a yellow solid precipitated. The mixture was allowed to stand overnight, and then it was cooled in an ice bath. An aqueous solution (20%) of $NaHCO_3$ (10 ml) was added, the solid products were filtered. The pure products were recrystallized from ethanol in 80-93% yields. Most of the products are known in the literature and were identified by comparison of their FT-IR and NMR with literature data.

General procedure for the synthesis of N-benzoylglycine carbamide catalyzed by Nafion-H@SPIONs in microreactor System

A microreactor system containing a microtube reactor immersed in a water bath, and a syringing pump were used. The syringing pump was equipped with one syringe (1 ml). In the syringe, , a sonicated mixture of an azlactone (1 eq.), a primary or secondary amine (1.0 eq.) and Nafion-H@SPIONs (60 mg containing of 0.35 mol% Nafion-H) in acetonitrile (10 ml) was charged. Next, the mixture was fed into the system by syringe pump (flow rate: 0.48 ml/ h) at 60 °C. After the residence time was reached (75 min), the discharge was collected in a glass vessel equipped with an external permanent magnet. The collected catalyst by the magnet, washed two times with absolute ethanol (2×1 ml), air-dried, and used directly for the next round. After separation of the catalyst from the resulting crude product, the mixture was cooled down to the room temperature, after the addition of water, the related carbamoylbenzamides was filtered off and with the re-crystallization in hot ethanol and the crystalline product isolated. Most of the products are known in the literature and were identified by comparison of their FT-IR and NMR with literature data.

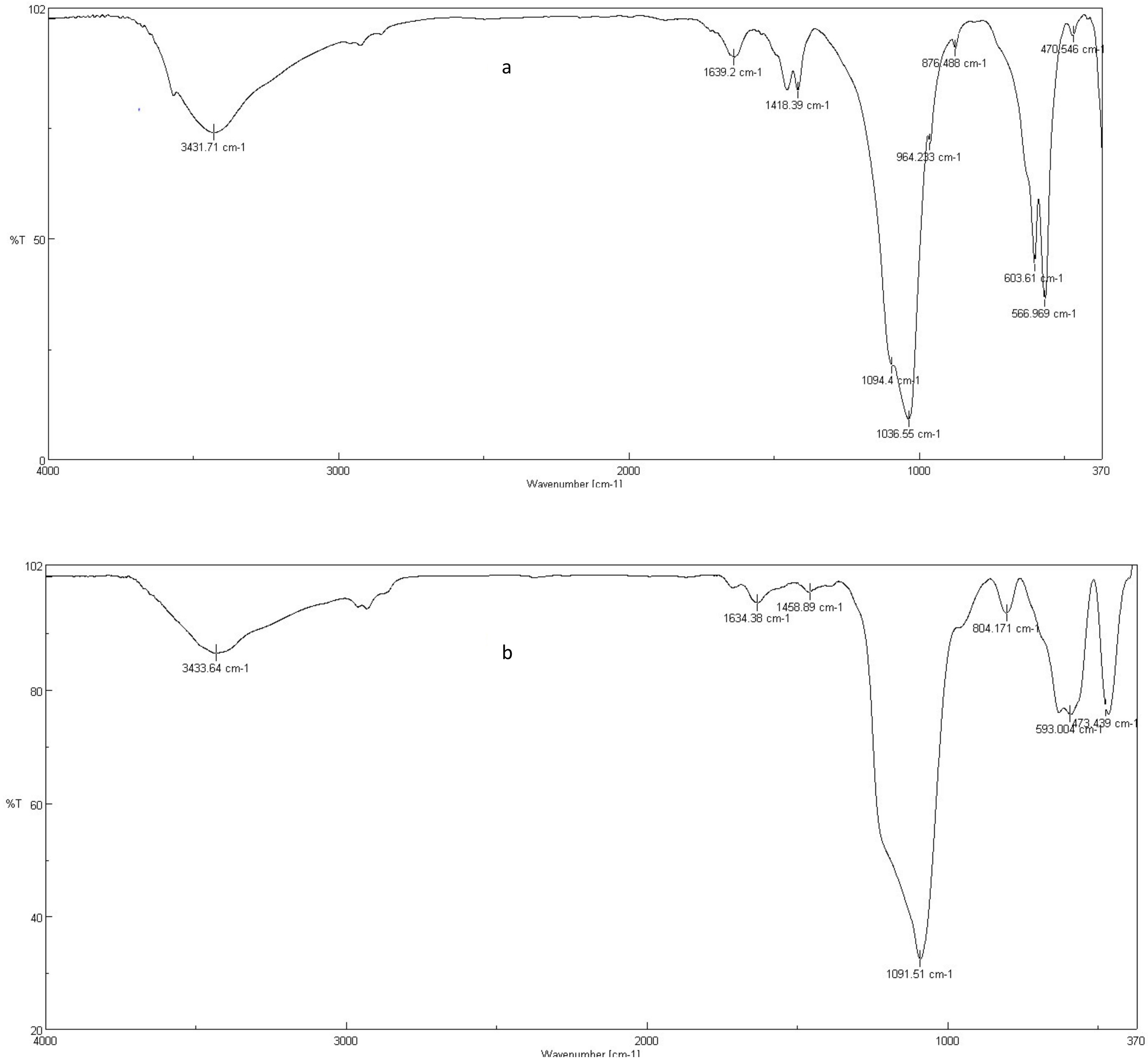


Figure S1: FT-IR spectrums of (a) nano-Fe_3O_4 and (b) SPIONs

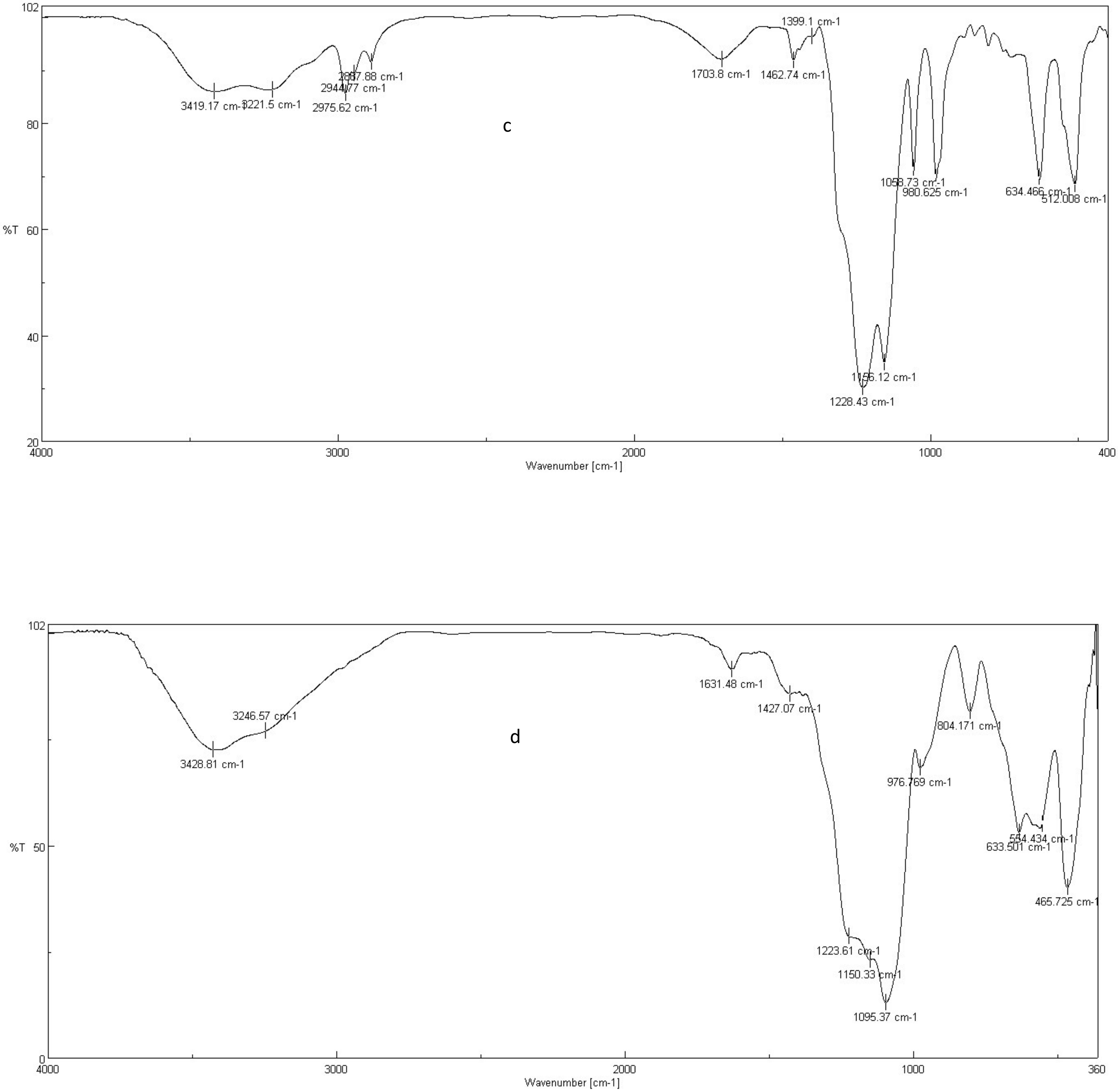


Figure S2: FT-IR spectrums of (c) Nafion-H and (d) Nafion-H@SPIONs

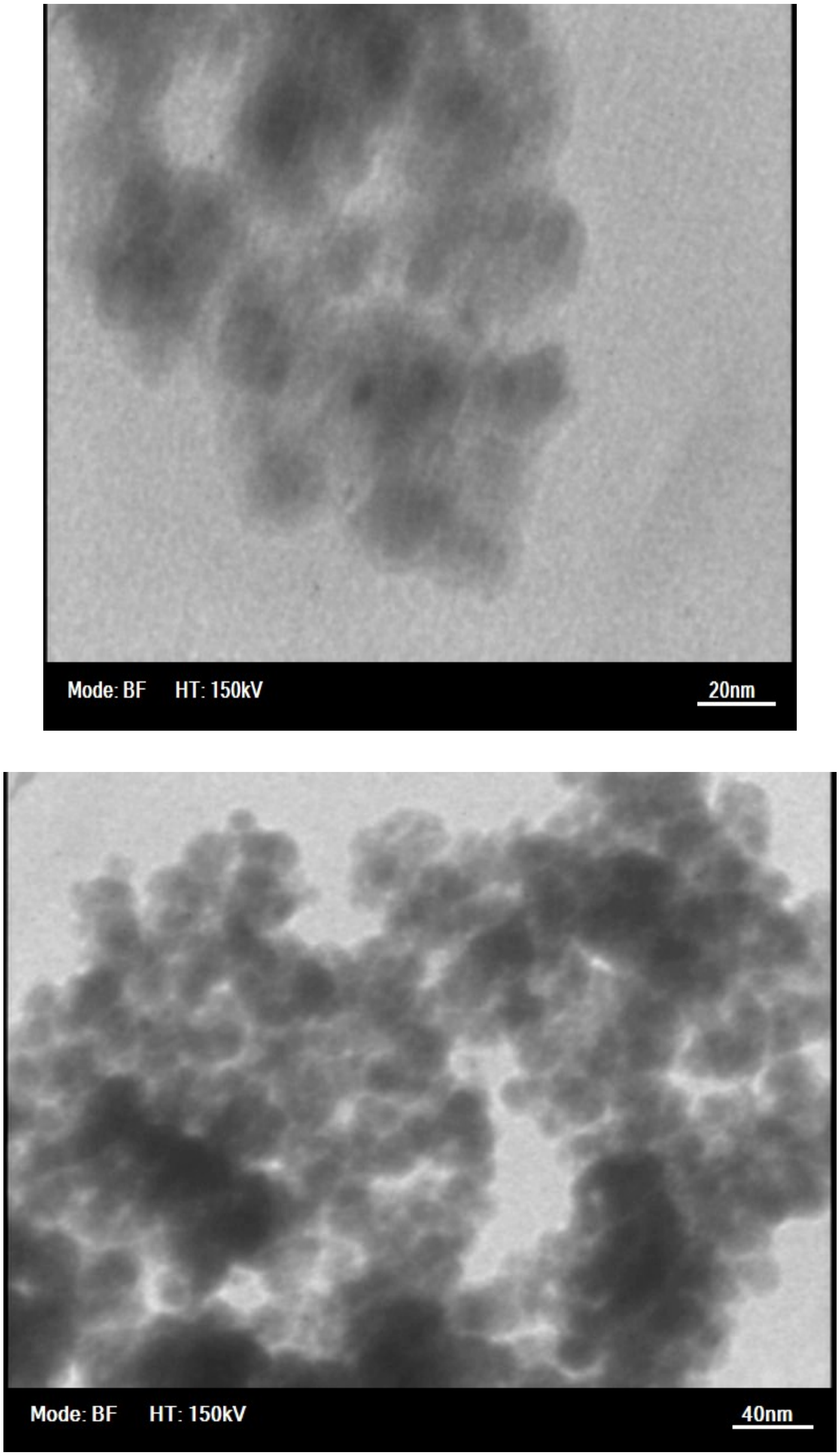


Figure S3: HR-TEM image of Nafion-H@SPIONs (scale bar correspond to 20 and 40 nm respectively)

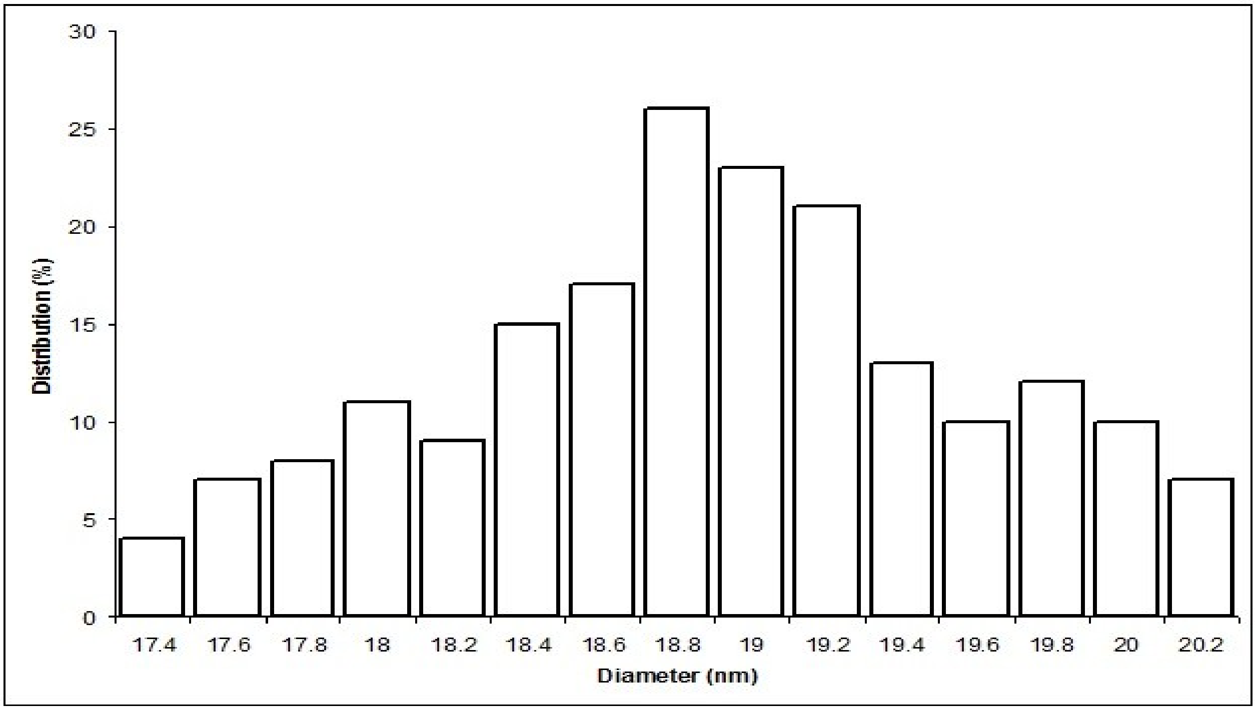


Figure S4: Nafion-H@SPIONs particle size distribution histogram

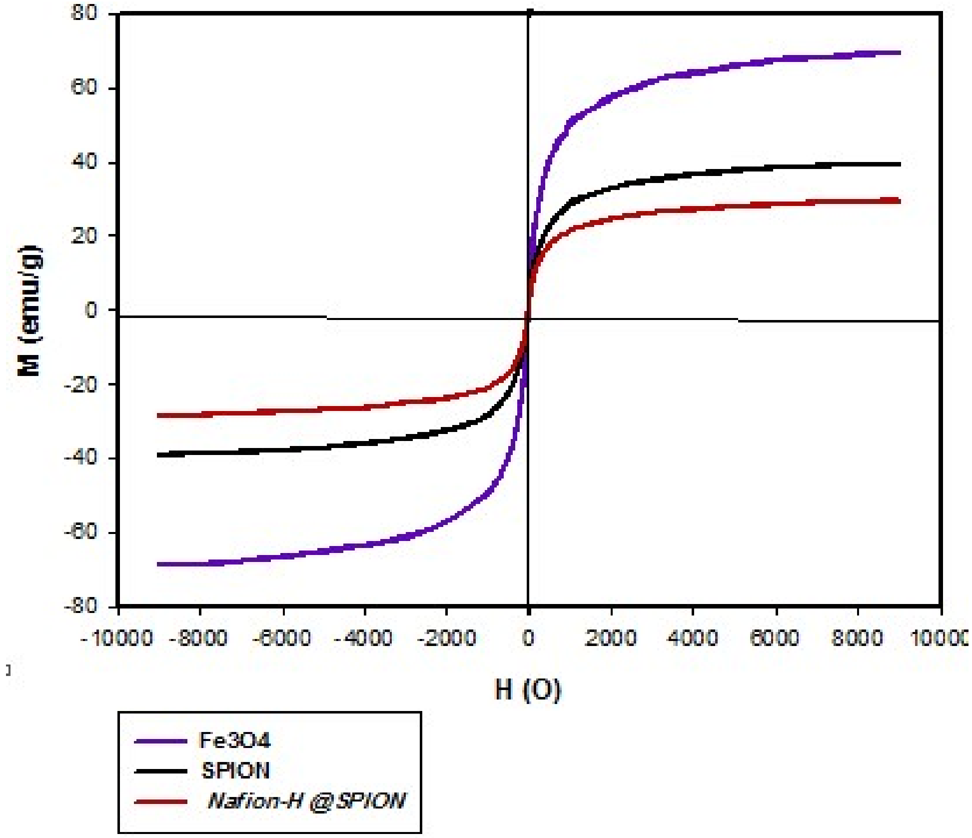
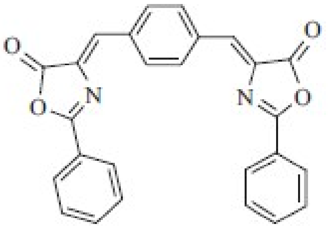


Figure S5: The dc magnetic characterization of the nanoparticles

Figure S6: FT-IR spectrums of (a) Nafion-H@SPIONs after 7 runs and (b) fresh Nafion-H@SPIONs

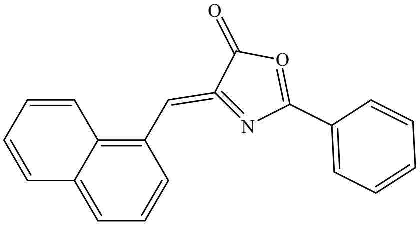
Spectral data for selected compounds:

1. **(Z,Z)-4,4’-(1,4-Phenylenedimethylidyne)bis(2-phenyl-5 (4H)-oxazolone) (C26H16N2O4)**



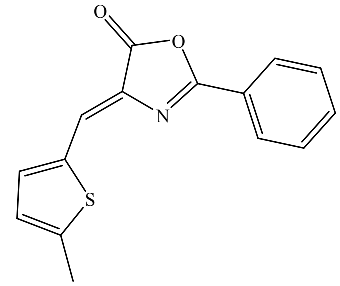
IR (KBr) νmax/cm^{-1}: = 3,039, 1,789, 1,762, 1,653, 1,548, 1,327, 1,159 cm-1; 1H NMR (400 MHz, CDCl$_3$): δ (ppm) : 7.57–7.60 (5H, m), 7.65–7.69 (2H, m), 8.21–8.27 (4H, m), 8.32 (5H, s) ppm; 13C NMR (100 MHz, CDCl$_3$): δ (ppm) : 125.41, 128.60, 129.06, 130.08, 132.68, 133.72, 134.64, 135.86, 164.28, 167.38 ppm; MS (EI): m/z = 420.18, 287.78, 104.89, 76.88.

2 (4Z)-4-((naphthalene-1-yl)methylene)-2-phenyloxazol-5(4H)-one

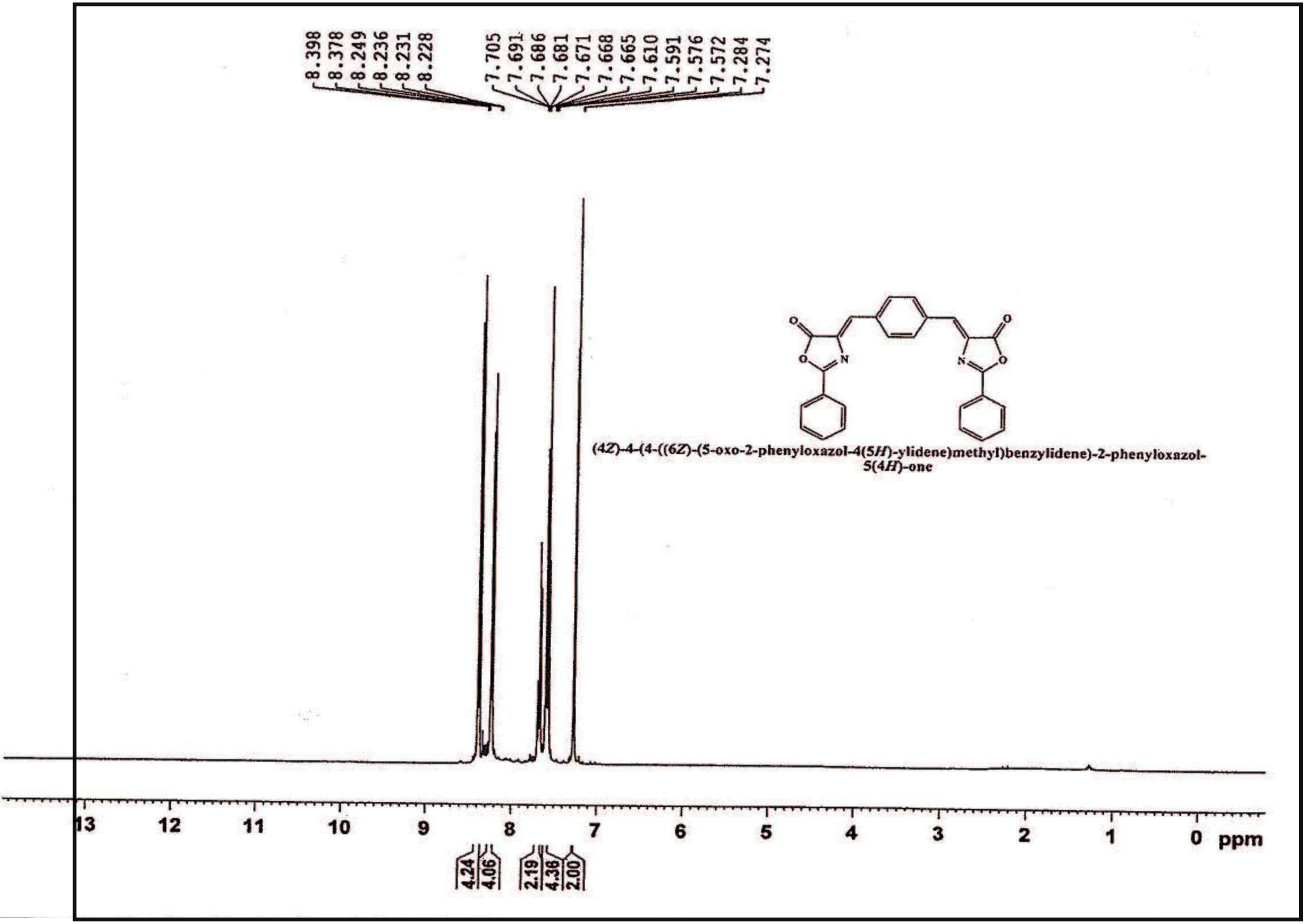


Mp: 163-165 °C. IR (KBr) νmax/cm^{-1}: = 3060, 2923, 1792, 1645, 1549, 1488, 1448, 1323, 1167, 978, 874, 694; 1H NMR (400 MHz, CDCl$_3$): δ (ppm) : 7.57–7.70 (m, 6H, Ar), 7.95 (d, 1H, J=8.00 Hz, Ar), 8.02 (d, 1H, J=8.10 Hz, Ar), 8.19 (s, 1H, C=CH), 8.25-8.26 (m,2H, Ar), 8.36(d, 1H, J=8.50 Hz, Ar), 9.08 (d, 1H, J=7.40 Hz, Ar) ppm; MS (EI): m/z = 299.09, 105, 77.01.

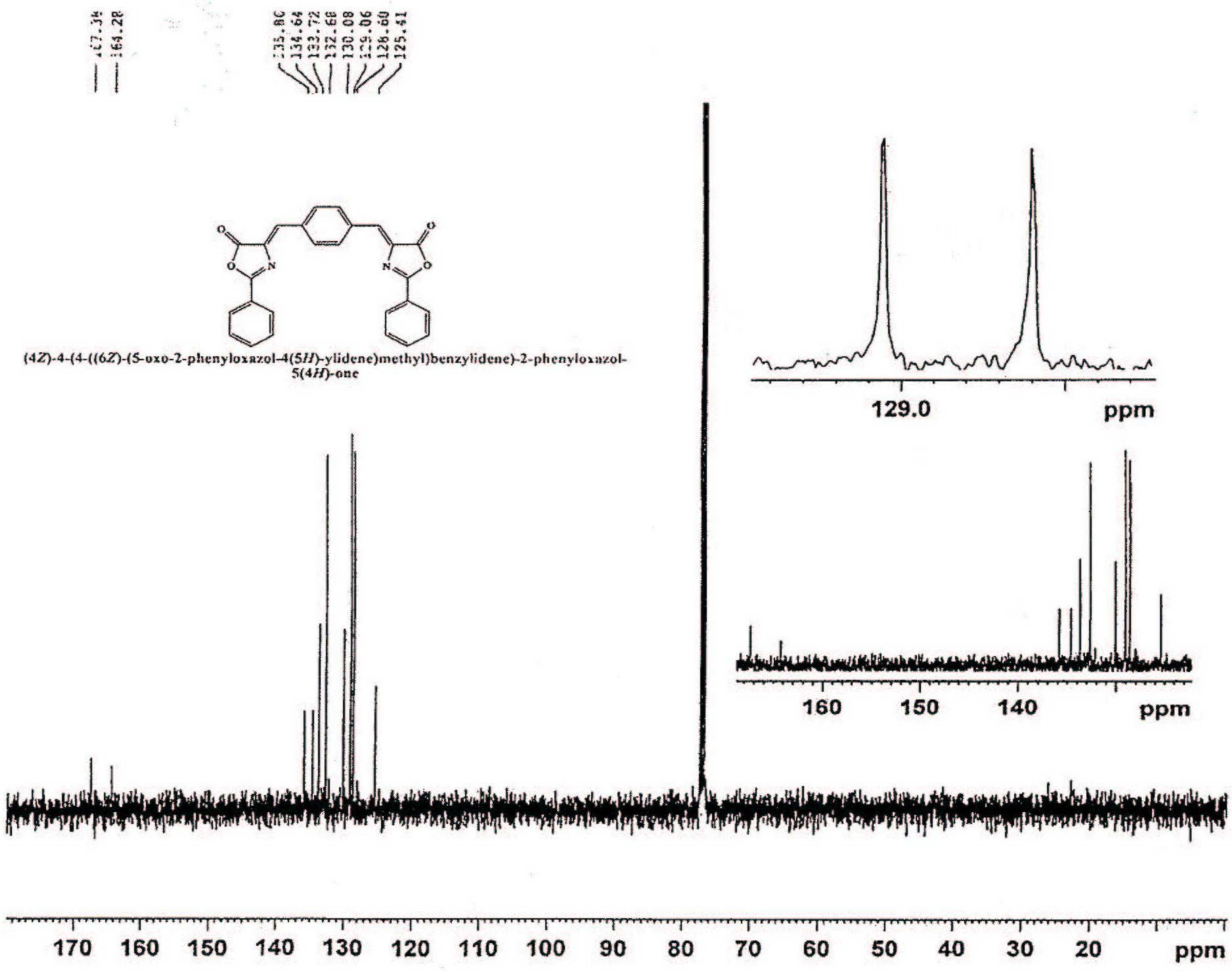
3 (4Z)-4-[(5-Methylthiophen-2-yl)methylene]-2-phenyloxazol-5(4H)-one



Mp: 145–147 °C. IR (KBr) νmax/cm^{-1}: = > 3070, 2922, 2852, 1726, 1639, 1510, 1440, 1375, 1230, 1132, 750;1HNMR (400 MHz, $CDCl_3$), δ (ppm): 2.63(s, 3H), 6.897(s, 1H), 7.44(m, 2H), 7.54(m, 2H), 7.62(m, 1H), 8.17(m, 2H). 13CNMR (100 MHz, $CDCl_3$), δ (ppm): 16.20, 125.55, 125.89, 126.86, 127.60, 128.22, 128.91, 133.00, 135.95, 136.35, 151.58, 160.56, 167.27. MS (EI): m/z (%) = 269.12, 207.11, 105.14, 77.08, 51.14.



(4Z)-4-(4-((6Z)-(5-oxo-2-phenyloxazol-4(5H)-ylidene)methyl)benzylidene)-2-phenyloxazol-5(4H)-one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(4Z)-4-(4-((6Z)-(5-oxo-2-phenyloxazol-4(5H)-ylidene)methyl)benzylidene)-2-phenyloxazol-5(4H)-one
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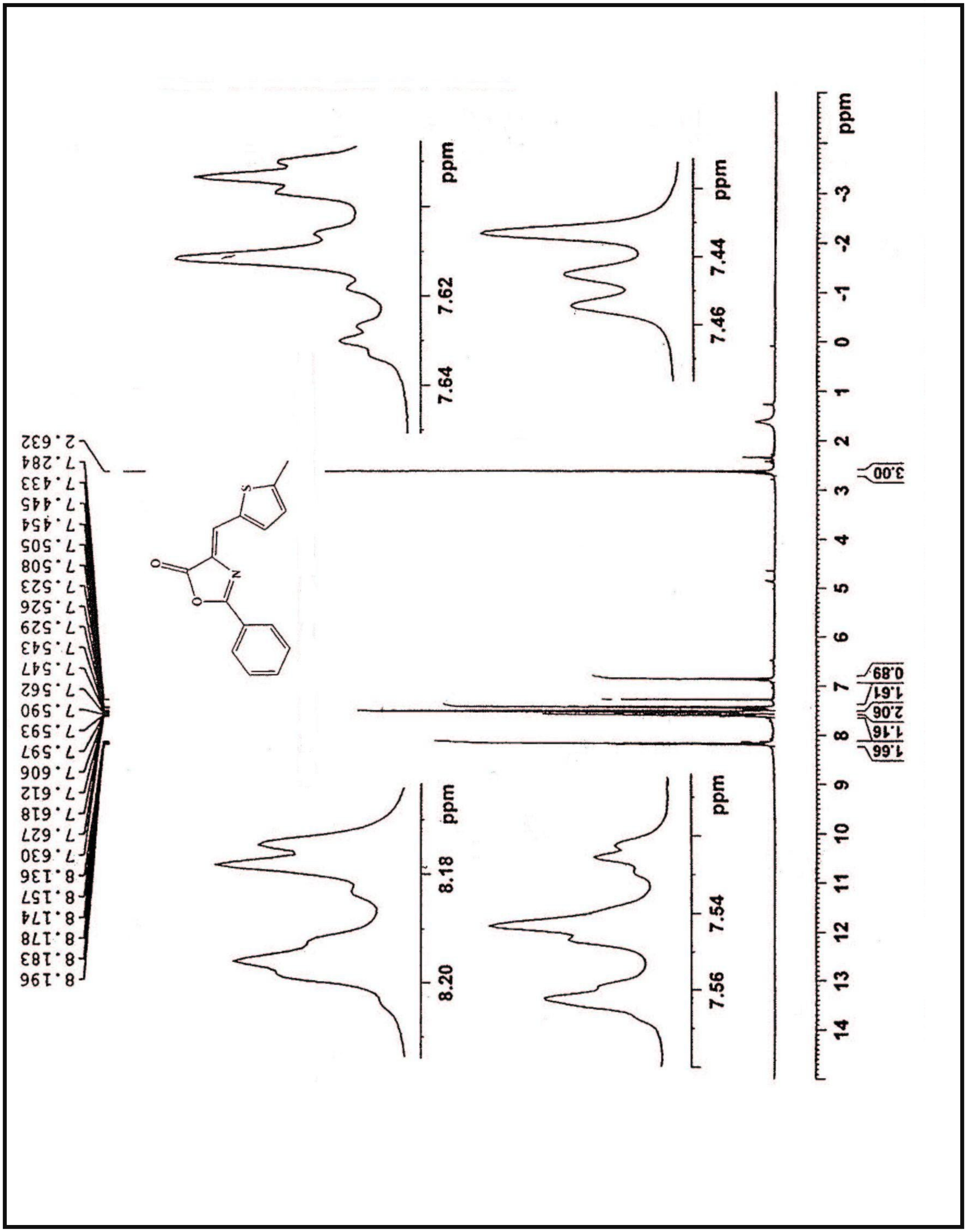
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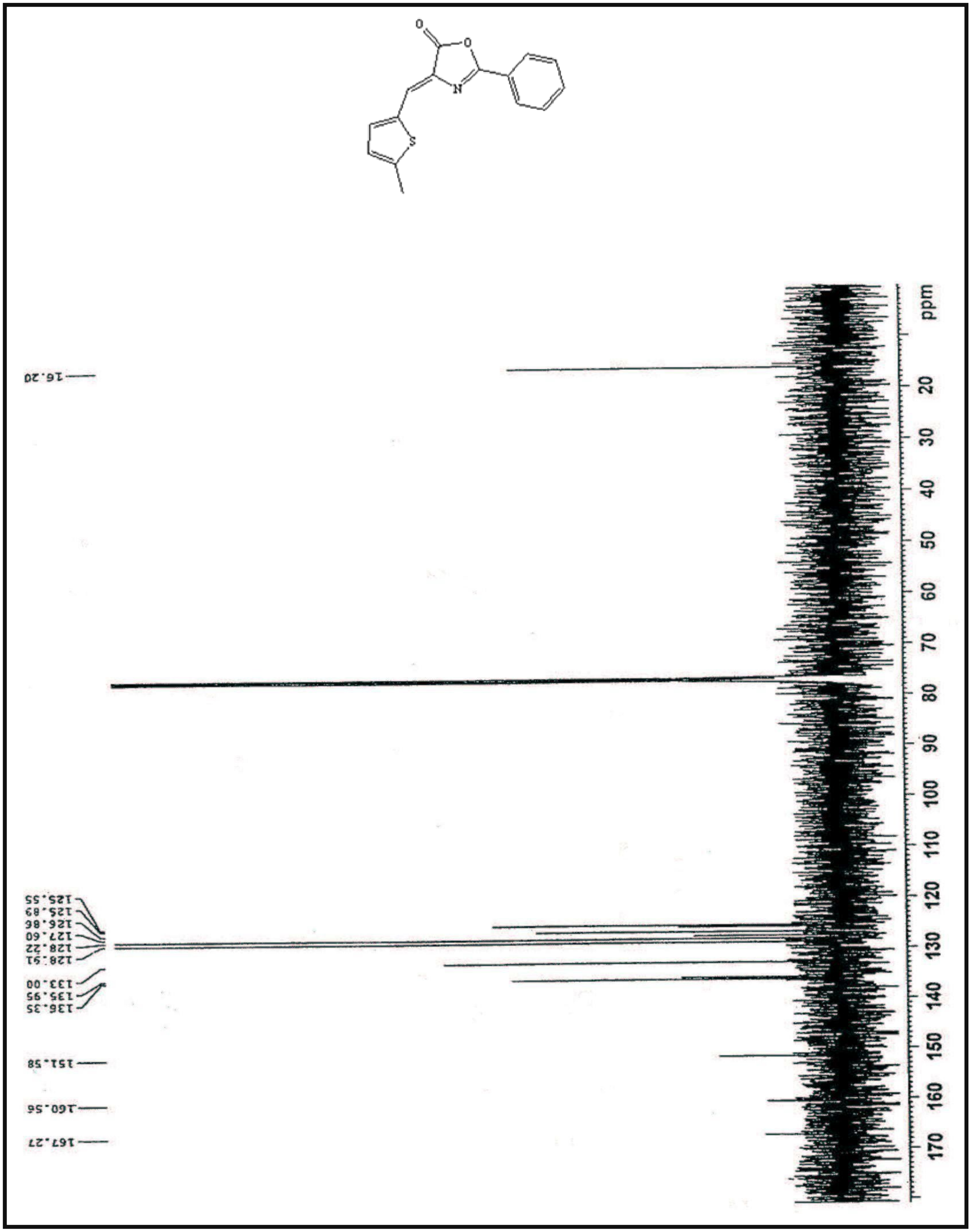
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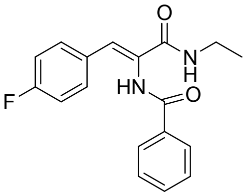
Spectral data for selected compounds:

1.

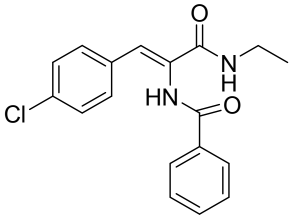
N-((Z)-1-(ethylcarbamoyl)-2-(4-fluorophenyl) vinyl) benzamide



Mp: 233-23°C. IR (KBr) νmax/cm-1: 3232, 3072, 2932, 1630, 1602, 1511, 1481, 1385, 1314, 1275, 1235, 902, 831, 697; ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 1.06 (t, 3H, J=7.0 Hz, CH3), 3.18 (t, 2H, CH2), 7.17 (s, 1H, C=CH), 7.19- 7.21 (m, 2H, Ar), 7.50-7.62 (m, 5H, Ar), 7.99 (d, 2H, J=7.0 Hz, Ar), 8.17 (t, 1H, J=5.0 Hz, NH carbamoyl), 9.88 (s, 1H, NH benzamide); ^{13}C-NMR (100 MHz, DMSO- d6) δ (ppm): 165.7, 164.6, 133.5, 131.6, 131.3, 131.2, 130.1, 128.2, 127.8, 127.5, 115.5, 115.3, 33.9, 14.7.

2.

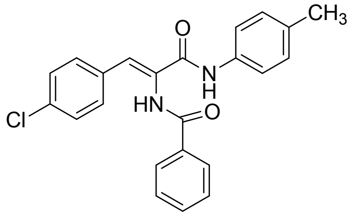
N-((Z)-1-(ethylcarbamoyl)-2-(4-chlorophenyl) vinyl) benzamide



Mp: 216-218°C. IR (KBr) ν_{max}/cm^{-1}: 2926, 2854, 1644, 1482, 1446, 1311, 1093, 713, 526; ^{1}H-NMR (400 MHz, DMSO- d_6) δ (ppm): 9. 86 (s, 1H, NH benzamide), 8.17 (t, 1H. *J*=5.5 Hz, NH carbamoyl), 7.97 (d, 2H, *J*=7.5 Hz. Ar), 7.46-7.59 (m, 7H, Ar), 7.13 (s, 1H, C=CH), 3.14- 3.31 (m, 2H, CH$_{2)}$, 1.05 (t, 3H, CH$_3$); ^{13}C-NMR (100 MHz, DMSO- d_6) δ (ppm): 165.6, 164.5, 133.7, 133.6, 131.6, 131.3, 131.1, 131.0, 128.2, 127.8, 127.0, 121.4, 33.9, 14.6.

3.

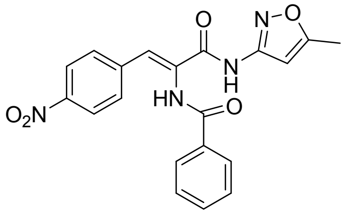
N-((Z)-1-(p-tolylcarbamoyl)-2-(4-chlorophenyl) vinyl) benzamide



Mp: 241-243°C. IR (KBr) νmax/cm-1: 3205, 3046, 1607, 1560, 1513, 1485, 1371, 1294, 1261, 1013, 906, 815, 696, 531, 513; ^{1}H-NMR (400 MHz, DMSO- d6) δ (ppm): 10.11 (s, 1H, NH benzamide), 10.08 (s, 1H, NH carbamoyl), 7.99 (d, 2H, J=7.5 Hz, Ar), 7.58-7.63 (m, 5H, Ar), 7. 52(t, 2H, J=7.7 Hz, Ar), 7. 44 (d, 2H, J=8.5 Hz, Ar), 7. 12 (d, 2H, J=8.3 HZ, Ar), 7.09 (s, 1H, C=CH), 2.28 (s, 3H, CH3); ^{13}C-NMR (100 MHz, DMSO- d6) δ (ppm): 165.8, 163.9, 136.6, 133.3, 132.8, 132.2, 131.7, 130.9, 128.8, 128.4, 128.3, 127.8, 126.4, 120.0, 20.4.

4.

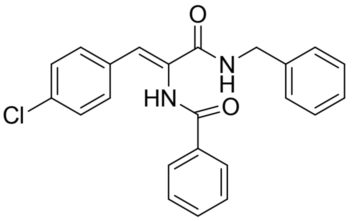
N-((Z)-1-(5-methylisoxsazole-3- carbamoyl)-2-(4nitrophenyl) vinyl) benzamide



Mp: 238-240. IR (KBr) νmax/cm-1: 3257, 3073, 2931, 1655, 1627, 1526, 1471, 1426, 1341, 1280, 699, 525; ^{1}H-NMR (400 MHz, DMSO- d6) δ (ppm): 11.35 (s, 1H, NH benzamide), 10.31 (s, 1H, carbamoyl), 8.23 (d, 2H, J=8.7 Hz, Ar), 7. 98 (d, 2H, J=7.5 Hz, Ar), 7. 84 (d, 2H, J=8.7 Hz, Ar), 7.61 (t, 1H, J=7.2 Hz, Ar), 7.52 (t, 2H, J=7.6 Hz, Ar), 7.22 (s, 1H, C=CH), 6.68 (s, 1H, CH isoxazole), 2.39 (s, 3H, CH3); ^{13}C-NMR (100 MHz, DMSO-d6) δ (ppm): 169.3, 165.9, 163.8, 158.4, 146.6, 141.0, 133.1, 132.9, 131.9, 130.3,128.3, 128.0, 126.3, 123.5, 96.6, 12.0.

5.

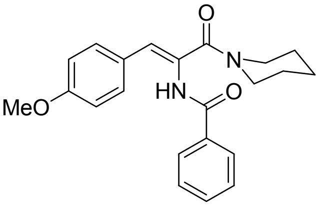
N-((Z)-1-(benzylcarbamoyl)-2-(4-chlorophenyl) vinyl) benzamide



Mp: 194-196. IR (KBr) νmax/cm-1: 3261, 3066, 2923, 1641, 1559, 1516, 1480, 1424, 1370, 1269, 1089, 1012, 694, 523; ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 9.96 (s, 1H, NH benzamide), 8.72 (t, 1H, J=5.9 Hz, NH carbamoyl), 7. 99 (d, 2H, J=5.0 Hz. Ar), 7.57 (d, 3H, J=10.0 Hz, Ar), 7. 50 (t, 2H, J=15.0 HZ, Ar), 7.41 (d, 2H, J=5.0 Hz, Ar), 7.30 (d, 4H, J=5.0 Hz, Ar), 7.18- 7.26 (m, 2H, Ar), 4.38 (d, 2H, J=6.0 Hz, CH2); ^{13}C-NMR (100 MHz, DMSO- d6) δ (ppm): 165.8, 164.8, 139.6, 133.5, 131.6, 131.3, 131.1, 130.9, 128.2, 128 .0, 127.8, 127.8, 127.0, 126.4, 121.6, 42.5.

6.

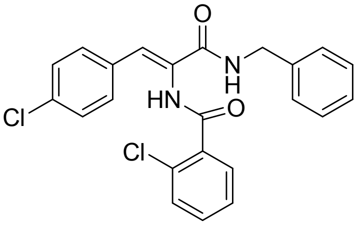
N-((Z)-3-(4- methoxyphenyl)-1-oxo-1-(piperidin-1-yl) prop-2-en-2-yl) benzamide



Mp: 154-157. IR (KBr) νmax/cm-1: 3207, 2939, 2852, 1656, 1614, 1581, 1508, 1478, 1377, 1344, 1281, 1244, 1179, 1133, 692, 530; ^{1}H- NMR (400 MHz, DMSO-d6) δ (ppm): 10.29 (s, 1H, NH benzamide), 7.93 (d, 2H, J=7.4 Hz, Ar), 7.55 (t, 1H, J=7.2 Hz, Ar), 7. 47 (t, 2H, J=7.4 Hz, Ar), 7.17 (d, 2H, J=8.4 Hz, Ar), 6.87 (d, 2H, J=8.4 Hz, Ar), 6.59 (s, 1H, C=CH), 3.72 (s, 3H, OCH3), 3.19 (bs, 4H, aliphatic), 0.6-1.37 (bm, 6H, aliphatic); ^{13}C-NMR (100 MHz, DMSO- d6) δ (ppm): 164.2, 164.1, 158.4, 133.3, 131.7, 130.1, 129.1, 128.2, 127.7, 126. 8, 115. 6, 113.7, 55.1, 46.9, 23.9, 24.8.

7.

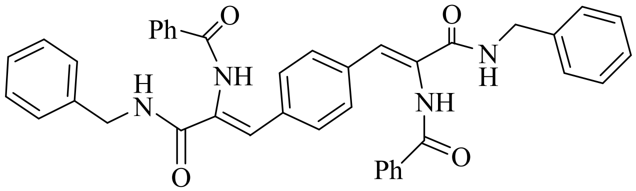
N-((Z)-1-(benzylcarbamoyl)-2-(4-chlorophenyl) vinyl) 2-chlorobenzamide



Mp: 230-233. IR (KBr) νmax/cm^{-1}: 3278, 3074, 2923, 1645, 1623, 1591, 1551, 1489, 1291, 1248, 1084, 915, 819; ^{1}H-NMR (400 MHz, DMSO- d_6) δ (ppm): 4.44 (d, 2H, J=5.8 Hz, CH2), 7.16(s, 1H, C=CH), 7.22- 7.26 (m, 1H, Ar), 7.31- 7.37 (m, 4H, Ar), 7.43- 7.55 (m, 5H, Ar), 7.65- 7.67 (m, 3H, Ar), 8.57 (t, N-H , J=5.9 Hz), 10.1 (s, 1H, NH benzamide); ^{13}C-NMR (100 MHz, DMSO- d_6) δ (ppm): 165.9, 164.7, 139.3, 13.6, 132.9, 131.2, 131.0, 130.2, 130.0, 129.7, 129.3, 128.4, 128.1, 127.2, 127.1, 126.9, 126.6, 30.6.

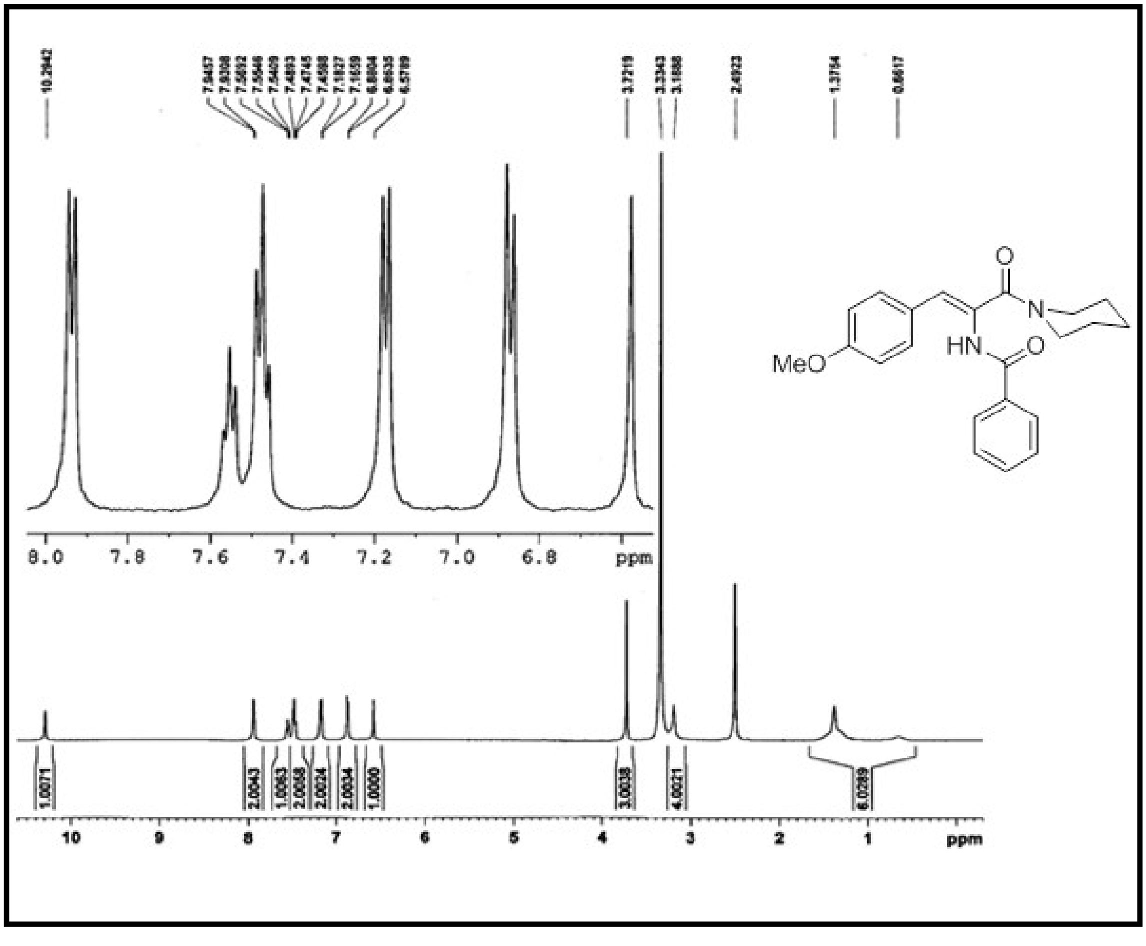
8.

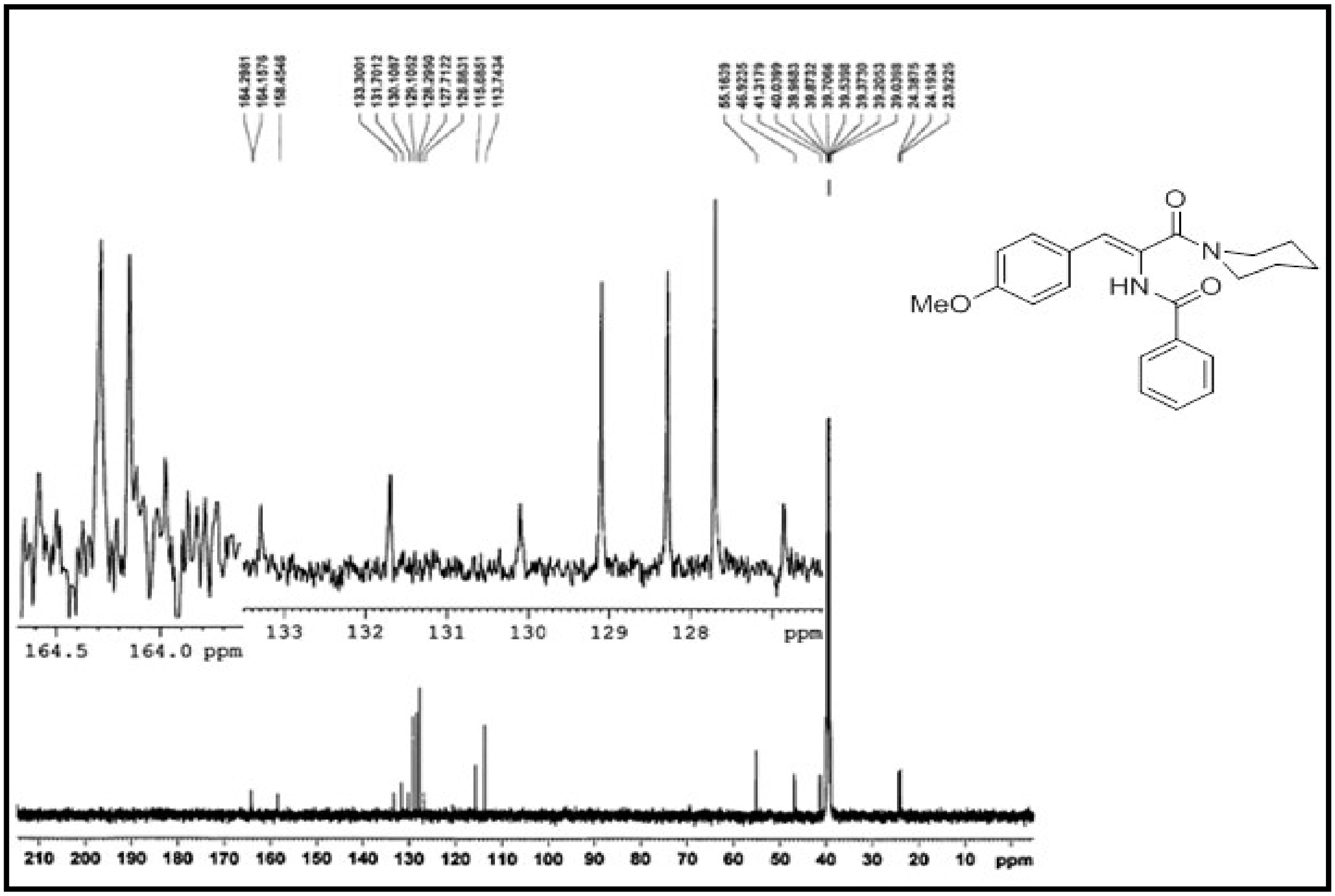
N,N'-(1Z,1'Z)-1,1'-(1,4-phenylene)bis(3-(benzylamino)-3-oxoprop-1-ene-2,1-diyl)dibenzamide



Mp: 228-230. IR (KBr) νmax/cm-1: 3315, 3062, 2924, 1651.7, 1521.6, 1474, 1276, 697; ^{1}H-NMR (400 MHz, DMSO- d6) δ (ppm): 9.98 (s, 2H, benzamide), 8.70-8.72 (t, 2H, J=5.65Hz, carbamoyl), 7.96 (d, 4H, J= 7.45 Hz, Ar), 7.44-7.58 (m, 10H, Ar), 7.20-7.31

(m, 9H, Ar), 7.17-7.20 (m,3H, Ar), 4.36 (d, 4H, J= 5.75 Hz, CH2 benzylic); ^{13}C-NMR (100 MHz, DMSO- d6) δ (ppm): 165.99, 164.89, 139.71, 134.47, 133.79, 131.58, 130.58, 129.35, 128.19, 128.06, 127.86, 127.73, 127.06, 126.49, 42.57.

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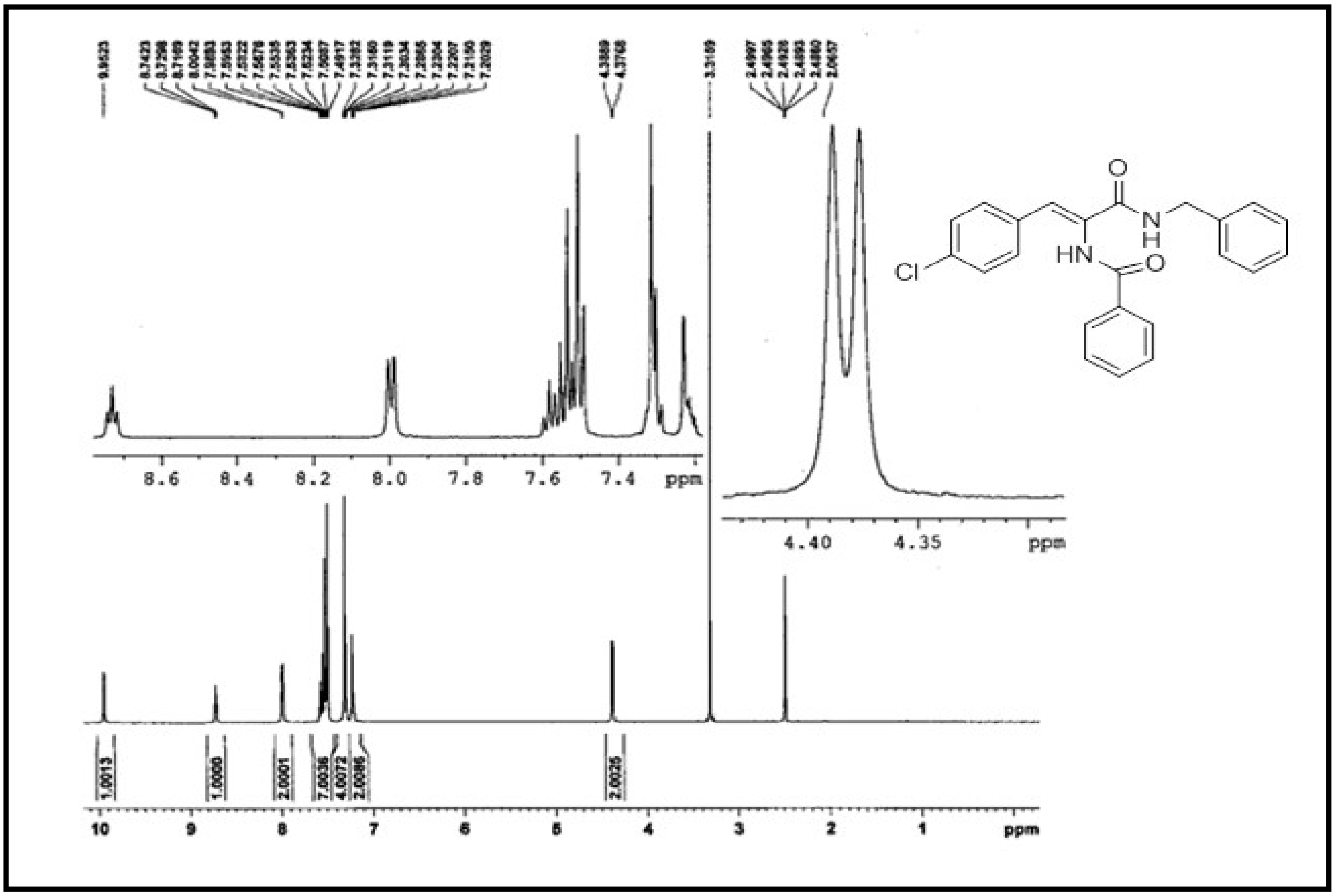
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2.0657
8.6
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8.2
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7.6
7.4
ppm
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4.35
ppm
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H
HN
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Cl
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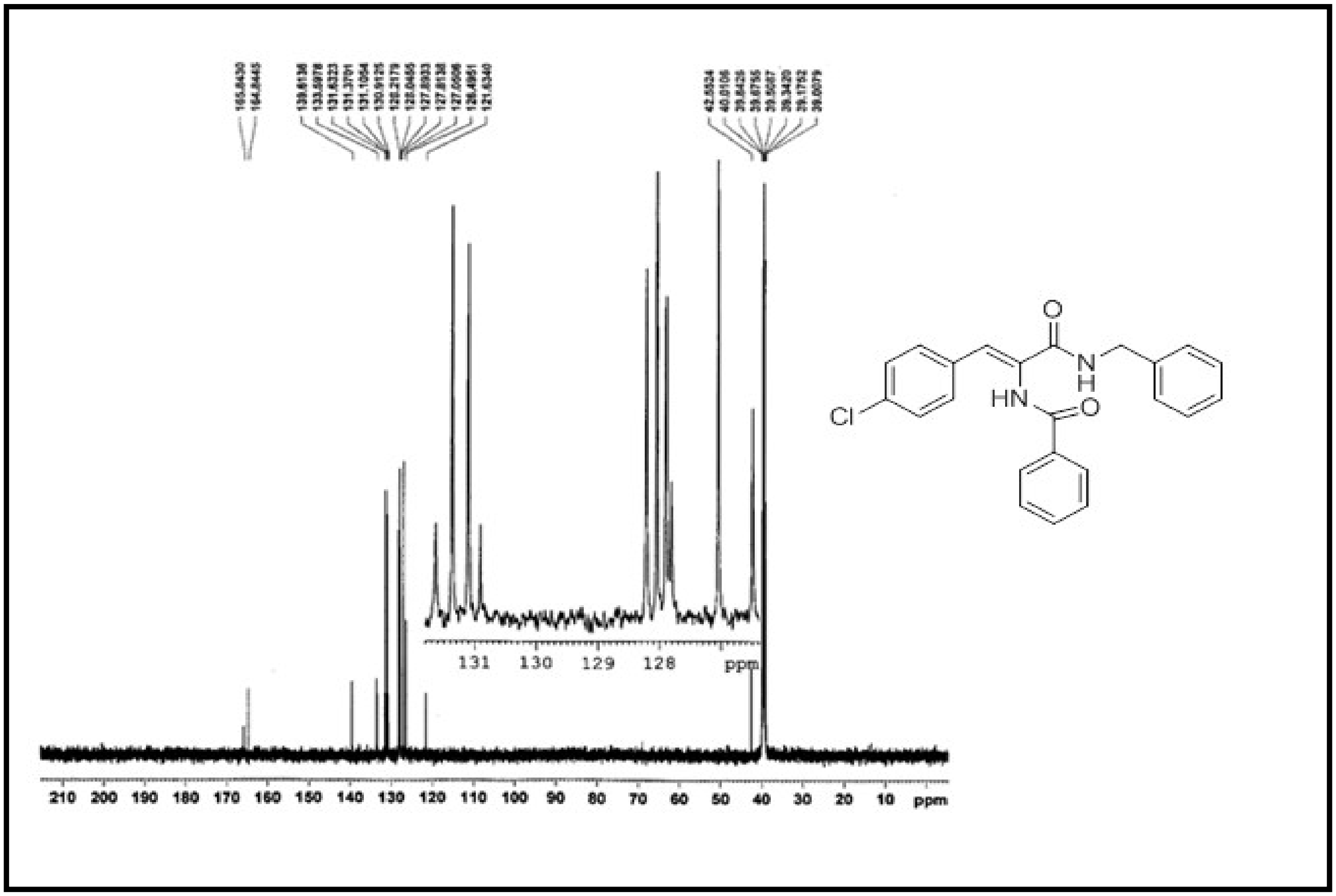
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121.6340
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39.8428
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39.5087
39.3420
39.1752
39.0079
131
130
129
128
ppm
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200
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ppm
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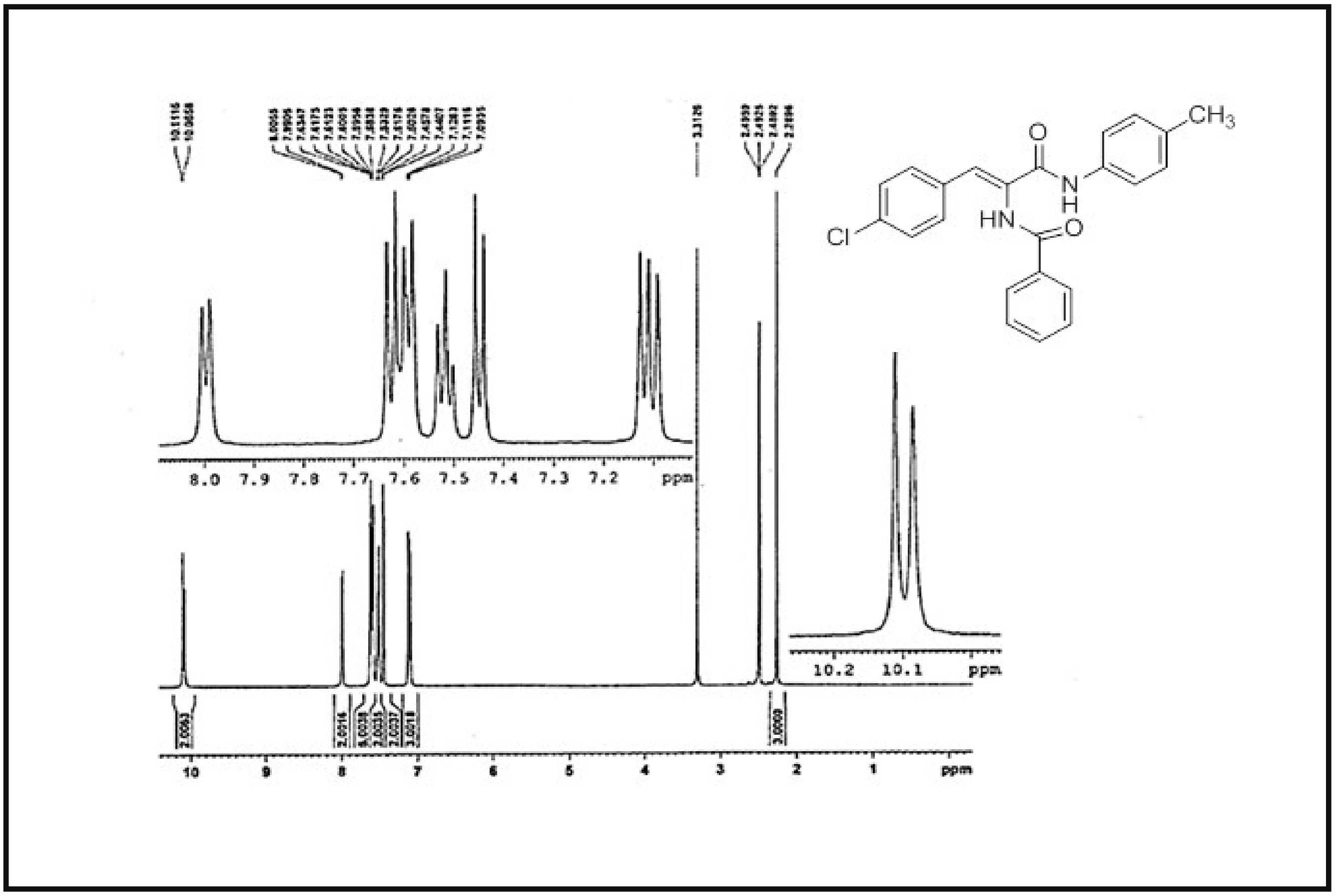

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7.5329
7.5176
7.5026
7.4578
7.4407
7.1263
7.1116
7.0935
3.3126
2.4592
2.4525
2.4492
2.2896
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 ppm
10.2 10.1 ppm
2.0063
2.0016
6.0038
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2.0037
3.0018
3.0000
10 9 8 7 6 5 4 3 2 1 ppm
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CH3
Cl
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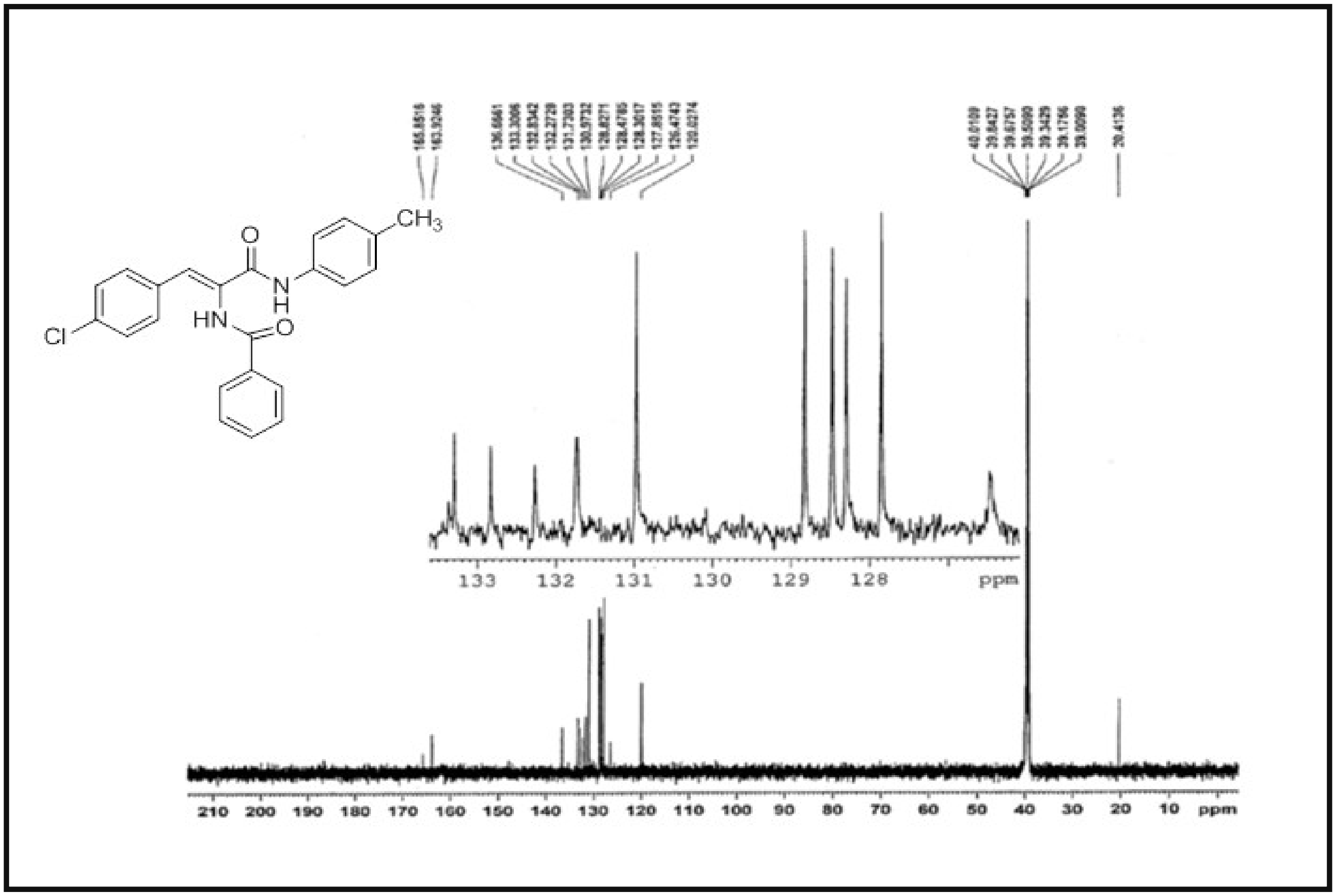
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127.8815
126.4743
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40.0109
39.8427
39.6757
39.5090
39.3429
39.1756
39.0090
20.4136
CH3
O
N
H
Cl
HN
O
133
132
131
130
129
128
ppm
210
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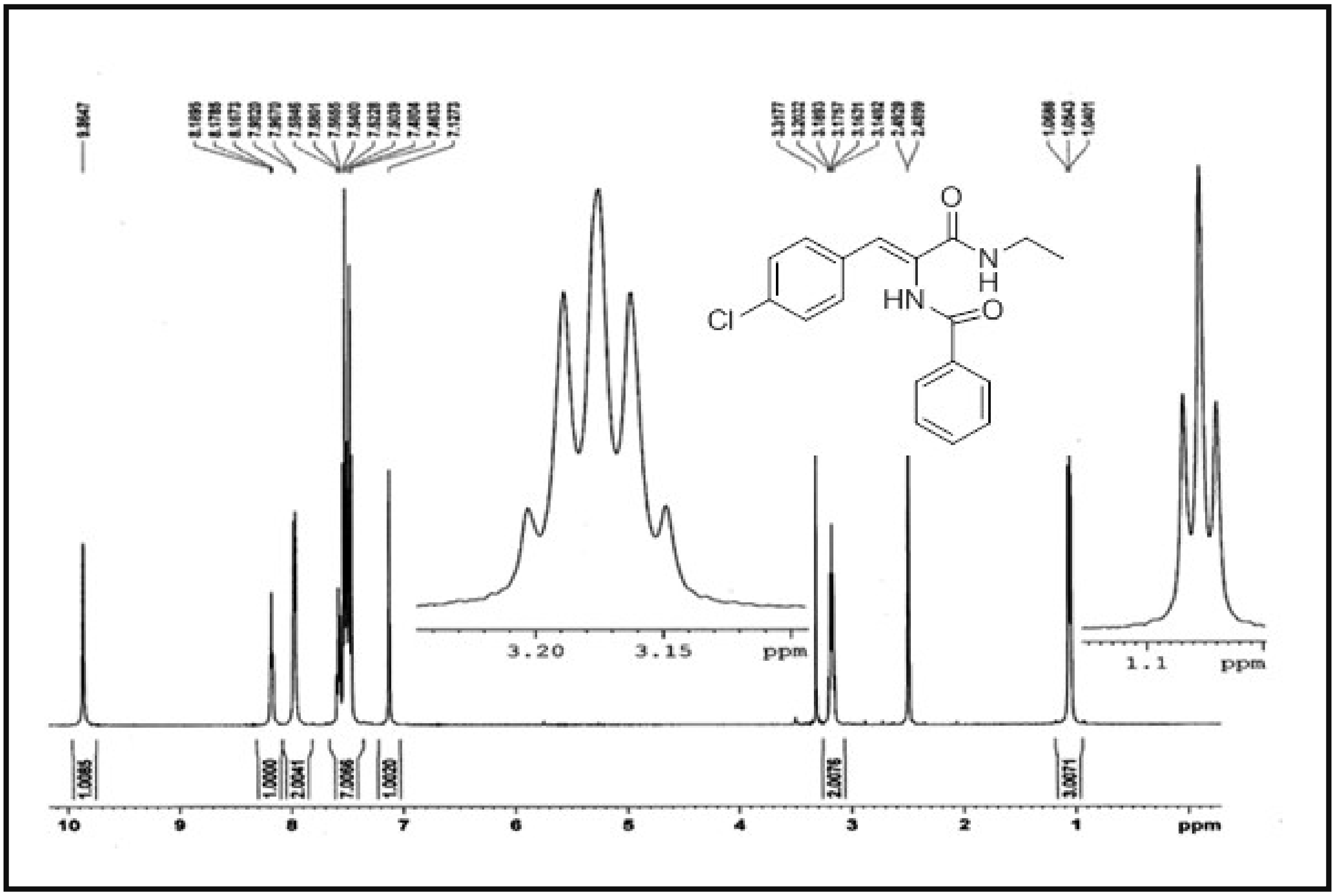

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HN
O
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ppm
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1.0000
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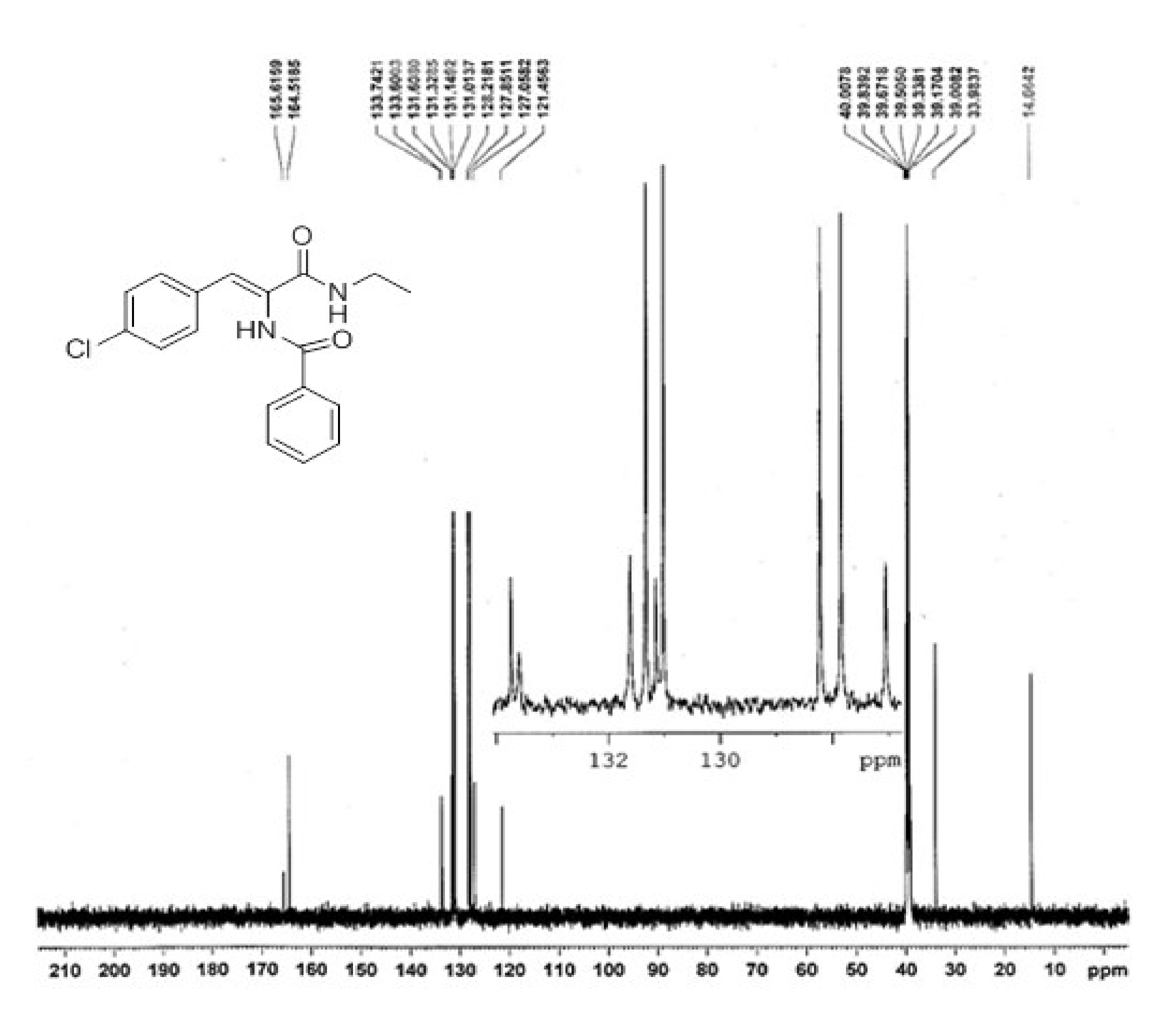
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39.8392
39.6718
39.5050
39.3381
39.1704
39.0082
33.9837
14.6642
O
N
H
HN
O
Cl
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130
ppm
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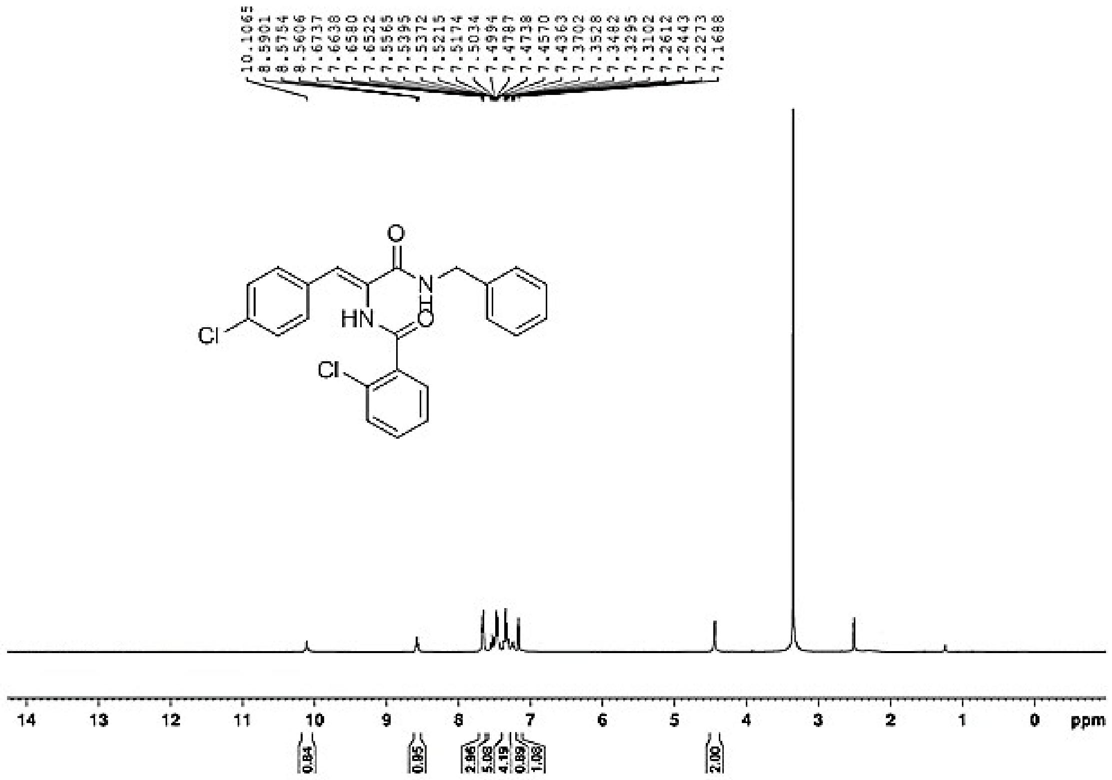
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7.5215
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7.4787
7.4738
7.4570
7.4363
7.3702
7.3528
7.3482
7.3295
7.3102
7.2612
7.2443
7.2273
7.1688
O
N
H
HN
O
Cl
Cl
14
13
12
11
10
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8
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6
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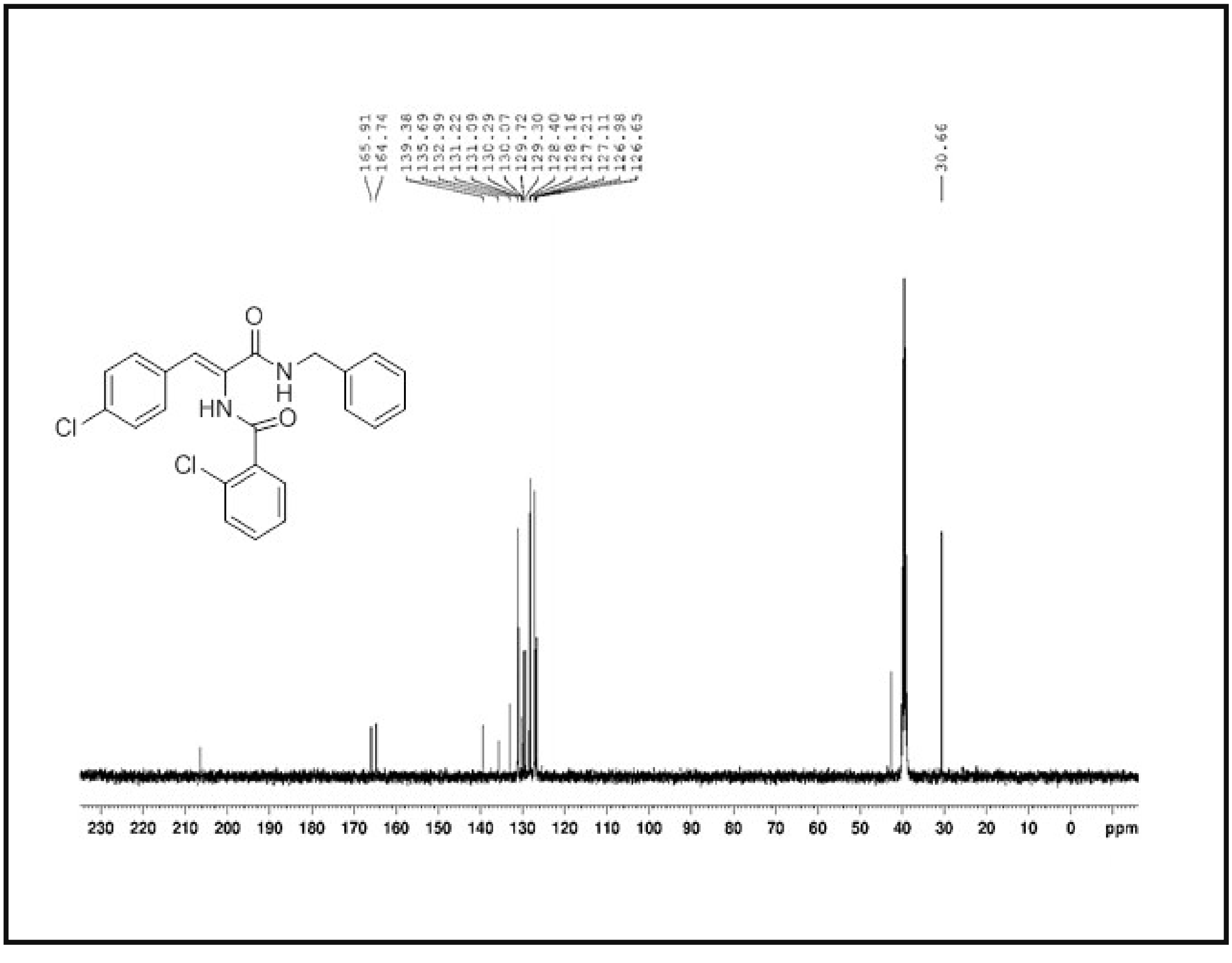
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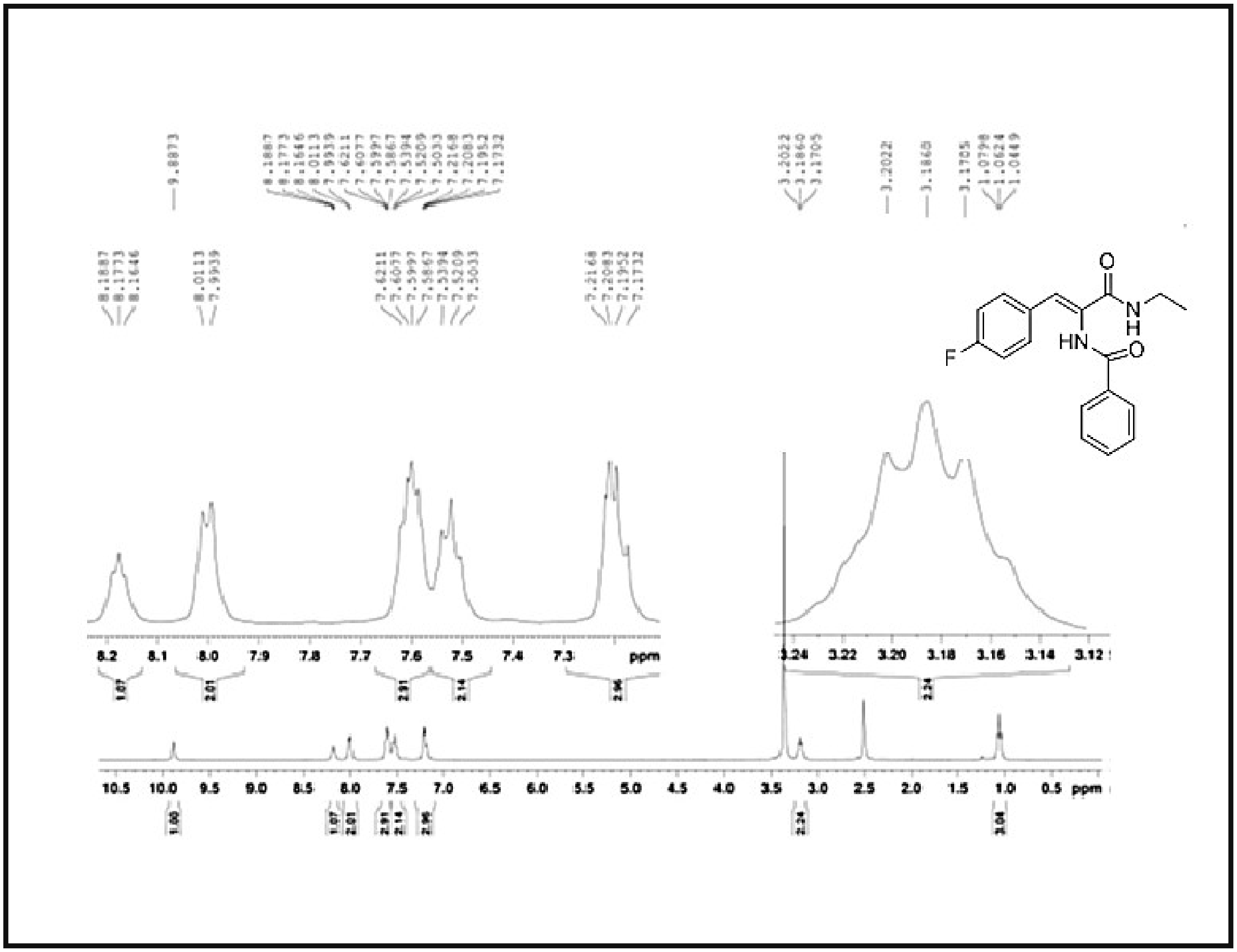
130.29
130.07
129.72
129.30
128.40
128.16
127.21
127.11
126.98
126.65
30.66
O
N
H
HN
O
Cl
Cl
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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7.5209
7.5033
7.2168
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7.1952
7.1732
3.2022
3.1860
3.1705
1.0798
1.0624
1.0449
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
ppm
1.07
2.01
2.91
2.14
2.96
3.24
3.22
3.20
3.18
3.16
3.14
3.12
2.24
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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2.01
2.91
2.14
2.96
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3.04
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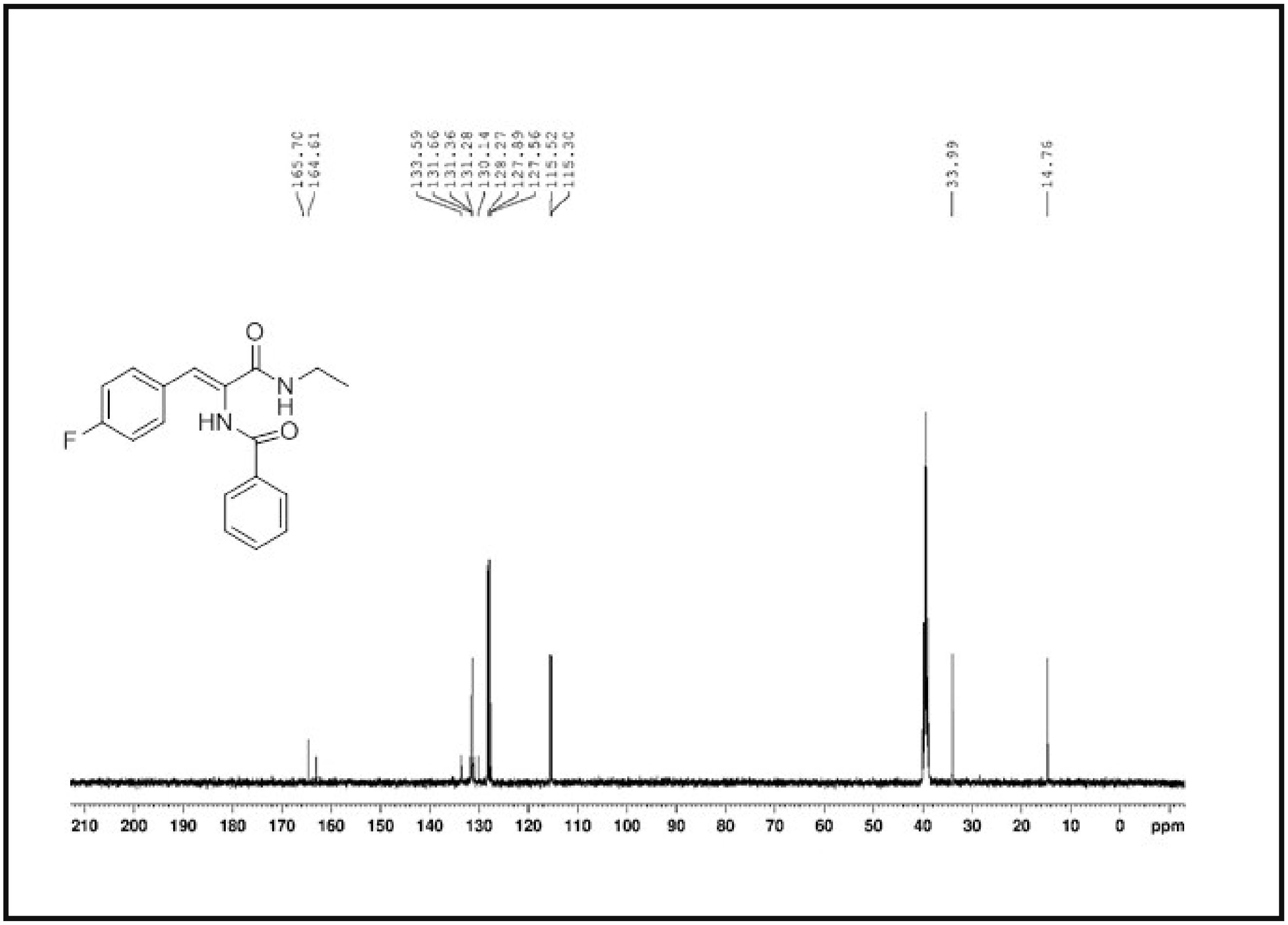
N
H
HN
O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127.56
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115.30
33.99
14.76
O
N
H
F
HN
O
210
200
190
180
170
160
150
140
130
120
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100
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80
70
60
50
40
30
20
10
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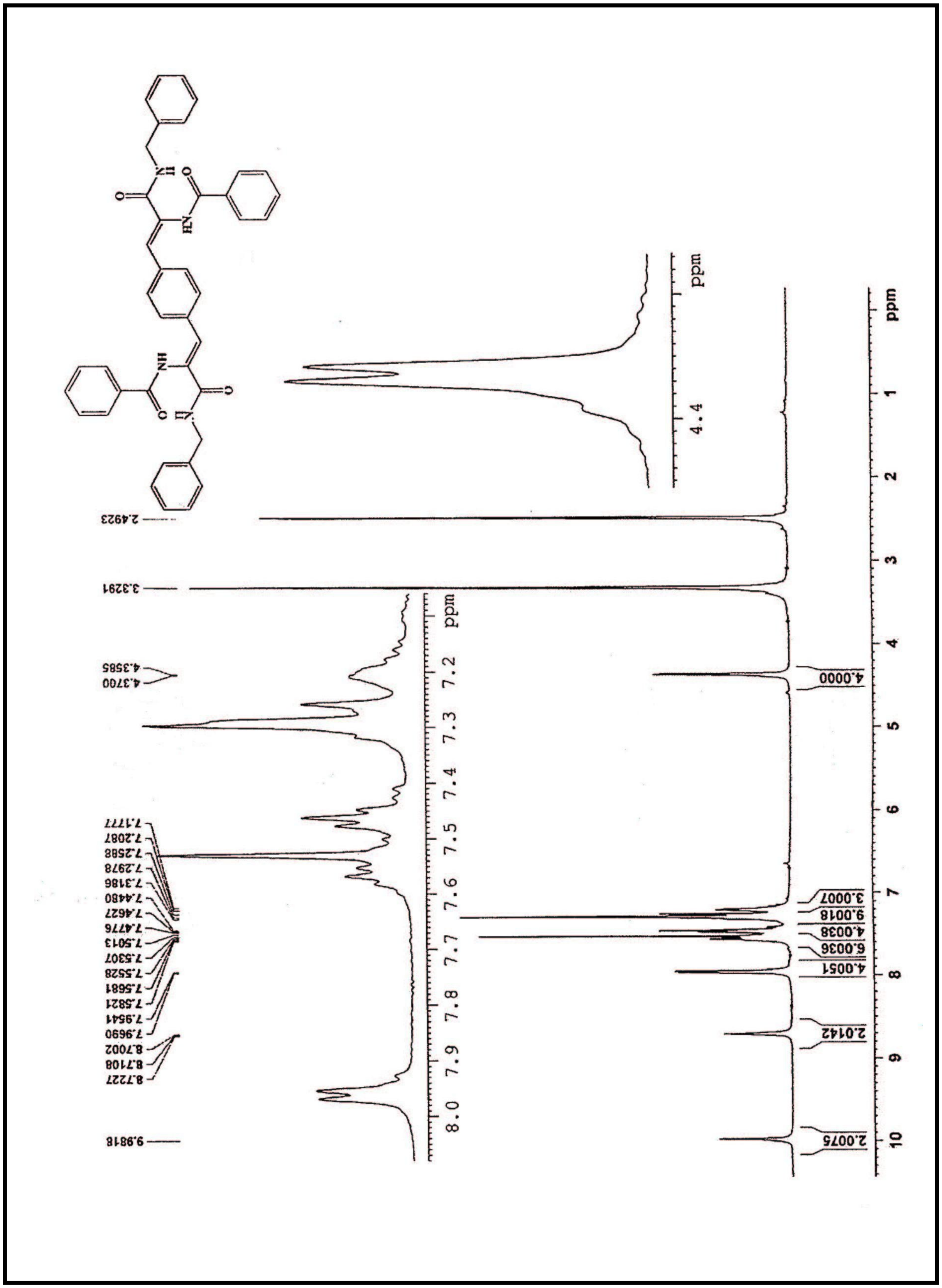
ppm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NH
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O
O
HN
NH
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8.7002
7.9690
7.9541
7.5821
7.5681
7.5528
7.5307
7.5013
7.4776
7.4627
7.4480
7.3186
7.2978
7.2588
7.2087
7.1777
4.3700
4.3585
3.3291
2.4923
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
ppm
4.4
ppm
2.0075
2.0142
4.0051
6.0036
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9.0018
3.0007
4.0000
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9
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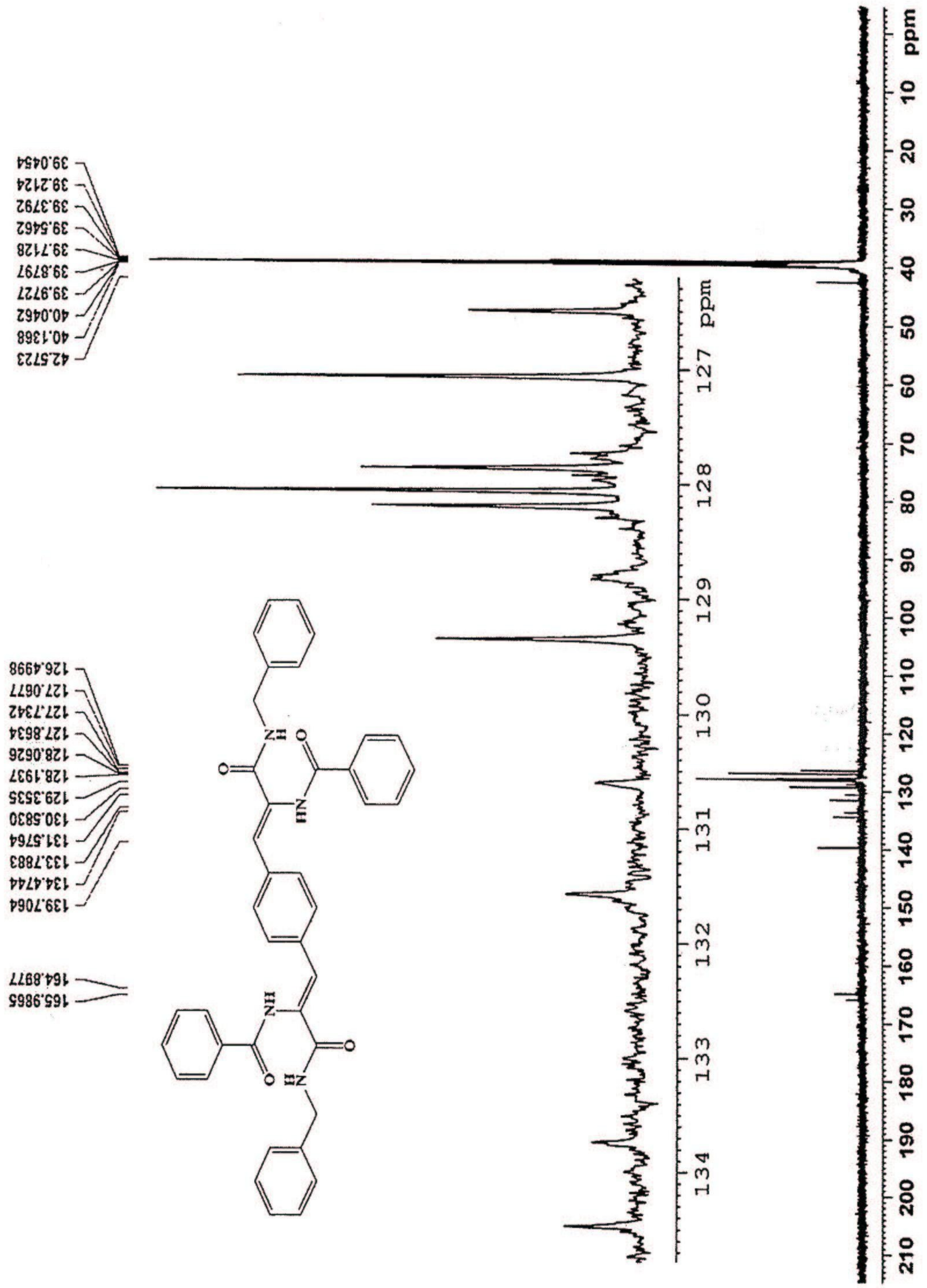
7
6
5
4
3
2
1
ppm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39.9727
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40.1368
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126.4998
127.0677
127.7342
127.8634
128.0626
128.1937
129.3535
130.5830
131.5764
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134.4744
139.7064
164.8977
165.9865
O
NH
HN
O
ppm
127
128
129
130
131
132
133
134
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200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm