SUPPORTING INFORMATION

An Iterative *In Silico* and Modular Synthetic Approach to Tercyclic α-Helix Mimetics with Measured Aqueous Solubility

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S1: X-Ray Crystallography Data

Crystal data and structure refinement for compound **7**:

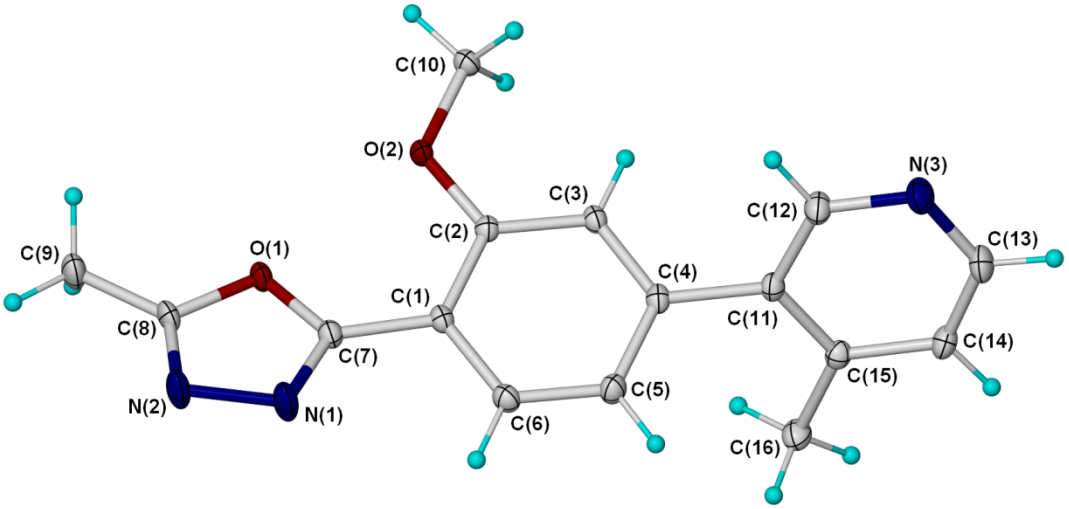


Figure S1.1: Molecular diagram of the X-ray crystal structure of **7**, shown with 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.

Empirical formula	$C_{16}H_{15}N_3O_2$	
Formula weight	281.31	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 21/n	
Unit cell dimensions	a = 12.9066(5) Å	alpha = 90°
	b = 7.1171(2) Å	beta = 101.461(2)°
	c = 15.1189(6) Å	gamma = 90°
Volume	1361.09(8) $Å^3$	
Z, Calculated density	4, 1.373 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	592	

Crystal size	0.25 x 0.13 x 0.10 mm
Theta range for data collection	3.22 to 30.0°
Limiting indices	−16<=h<=18, −10<=k<=5, −21<=l<=20
Reflections collected / unique	11823 / 3961 [R(int) = 0.0178]
Completeness to theta = 27.50	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7460 and 0.7059
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3961 / 0 / 193
Goodness-of-fit on F^2	1.036
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0386$, $wR_2 = 0.1048$
R indices (all data)	$R_1 = 0.0471$, $wR_2 = 0.1118$
Largest diff. peak and hole	0.391 and −0.273 $e \cdot Å^{-3}$

Crystal data and structure refinement for compound **11**:

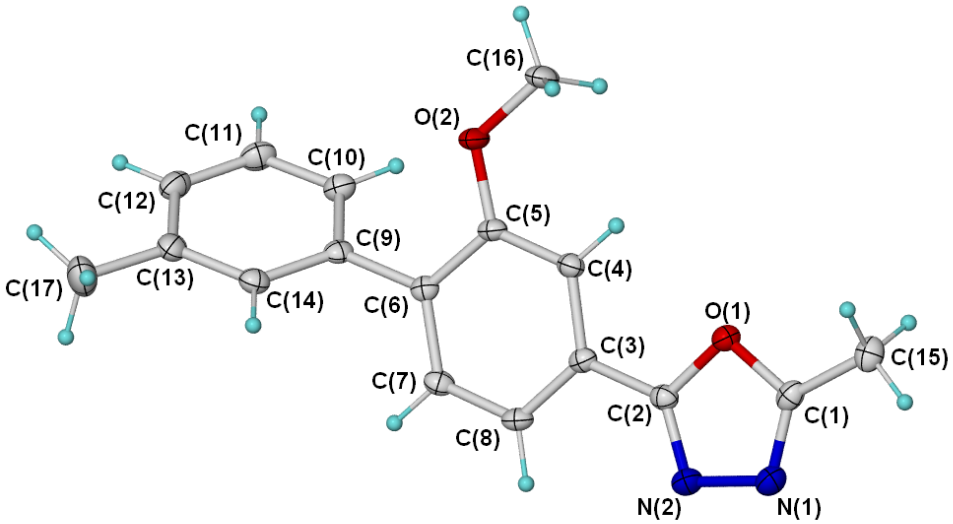


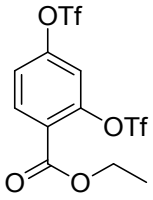
Figure S1.2: Molecular diagram of the X-ray crystal structure of **11**, shown with 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size.

Empirical formula	$C_{17}H_{16}N_2O_2$	
Formula weight	280.32	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 21/c	
Unit cell dimensions	a = 10.8379(25) Å	alpha = 90°
	b = 7.0007(1) Å	beta = 92.548(1)°
	c = 18.8456(3) Å	gamma = 90°
Volume	1428.46(4) $Å^3$	
Z, Calculated density	4, 1.303 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	592	
Crystal size	0.25 x 0.25 x 0.20 mm	
Theta range for data collection	1.88 to 30.0°	
Limiting indices	−14<=h<=14, −9<=k<=9, −24<=l<=23	

Reflections collected / unique	14965 / 3264 [R(int) = 0.0183]
Completeness to theta = 27.50	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.22222 and 0.95108
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3264 / 0 / 193
Goodness-of-fit on F^2	1.042
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0369$, $wR_2 = 0.0964$
R indices (all data)	$R_1 = 0.0418$, $wR_2 = 0.1000$
Largest diff. peak and hole	0.320 and −0.194 $e \cdot Å^{-3}$

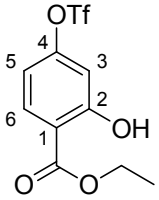
S2: Experimental

Ethyl 2,4-bis(((trifluoromethyl)sulfonyl)oxy)benzoate (29).



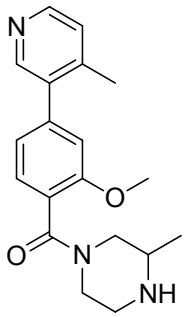
Trifluoromethanesulfonic anhydride (2.00 mL, 11.9 mmol) was added slowly to a stirring mixture of ethyl 2,4-dihydroxybenzoate **16** (2.00 g, 11.0 mmol), triethylamine (2.30 mL, 16.5 mmol) and dry DCM (25 mL) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 18 h, then washed with 1 M HCl (2 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified *via* silica gel chromatography (9:1 hexane/ethyl acetate) to afford the title compound **29** (2.16 g, 44%) as a white crystalline solid. m.p.: 34.2 – 35.6 °C. **^{1}H NMR** ($CDCl_3$): δ 8.22 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 162.6, 151.8, 148.7, 134.6, 125.4, 121.6, 118.84 (q, $J_{C\text{-}F}$ = 318.9 Hz), 118.79 (q, $J_{C\text{-}F}$ = 319.4 Hz), 116.9, 62.9, 14.1. **^{19}F NMR** ($CDCl_3$): δ −72.4, −73.0. **LRMS** (EI+): *m/z* 446.0 $[M]^{\cdot+}$ (14%), 417.9 $[M-C_2H_4]^{\cdot+}$ (86%), 400.9 $[M-C_2H_5O\cdot]^+$ (88%), 268.0, $[M-C_2H_5O-CF_3O_2S\cdot]^+$ (100%). **IR** (neat): ν_{max} 1732m, 1608m, 1430s, 1203s, 1133s, 1073s, 963s, 866s, 845s, 795s, 754s cm^{-1}.

Ethyl 2-hydroxy-4-(trifluoromethylsulfonyloxy)benzoate (17).



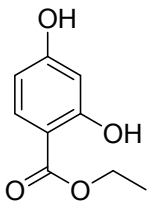
A mixture of *N*-phenyl-bis(trifluoromethanesulfonimide) (1.16 g, 3.26 mmol), ethyl 2,4-dihydroxybenzoate **16** (0.54 g, 2.96 mmol) and pyridine (0.26 mL, 3.26 mmol) in dry DCM (20 mL) was stirred at rt for 24 h. The reaction mixture then washed with 1 M HCl (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified *via* silica gel chromatography (9:1 hexane/ethyl acetate) to afford the title compound **17** (0.37 g, 40%) as a white solid. **^{1}H NMR** ($CDCl_3$): δ 11.11 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.8, 2.4 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H).

(2-Methoxy-4-(4-methylpyridin-3-yl)phenyl)(3-methylpiperazin-1-yl)methanone (5).



A solution of 2-methoxy-4-(4-methylpyridin-3-yl)benzoic acid **22** (90 mg, 0.37 mmol) in thionyl chloride (3 mL) was heated at reflux for 1 h. After 1 h the reaction mixture turned red, and excess thionyl chloride was removed under a flow of nitrogen and volatiles removed *in vacuo*. The reaction vessel was then charged with (±)-2-methylpiperazine (37 mg, 0.37 mmol) and dissolved with dry dichloromethane (10 mL), before cooling to 0 °C. A 1.8 M solution of diethylaluminium chloride in toluene (0.21 mL, 0.37 mmol) was then added and the reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was then diluted with 1 M $HCl_{(aq)}$ (5 mL) and washed with DCM (3 x 15 mL). The aqueous layer was concentrated *in vacuo* before it was purified *via* reverse phase (C_{18}) HPLC with a gradient elution of H_2O/ACN (100/0% to 10/90%) to afford the title compound **5**, a yellow oil (30 mg, 25%), as a mixture of conformers. **^{1}H NMR** (D_2O): δ 8.68 (m, 2H), 8.04 (d, *J* = 6.0 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.25 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.96 (s, 3H), 3.82 – 3.30 (m, 7H), 2.62 (s, 1H), 2.61 (s, 1H), 1.50 – 1.48 (m, 2H), 1.15 – 1.12 (m, 1H).

S3: ^{1}H and ^{13}C NMR Spectra



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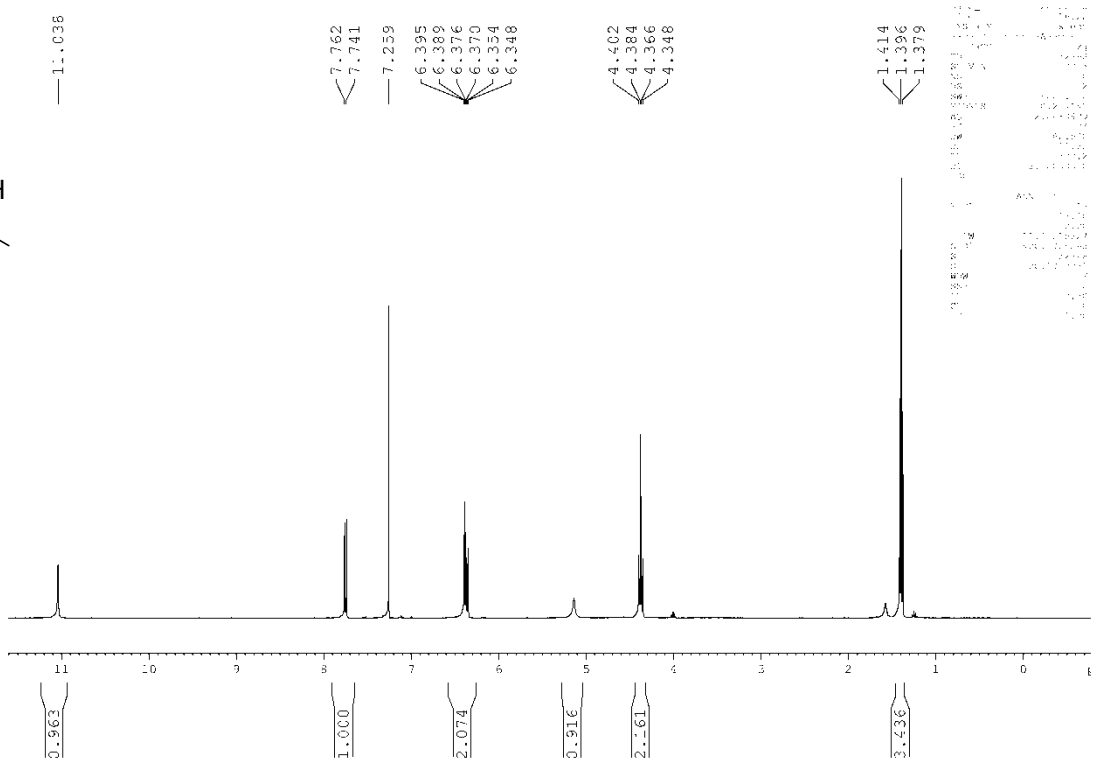

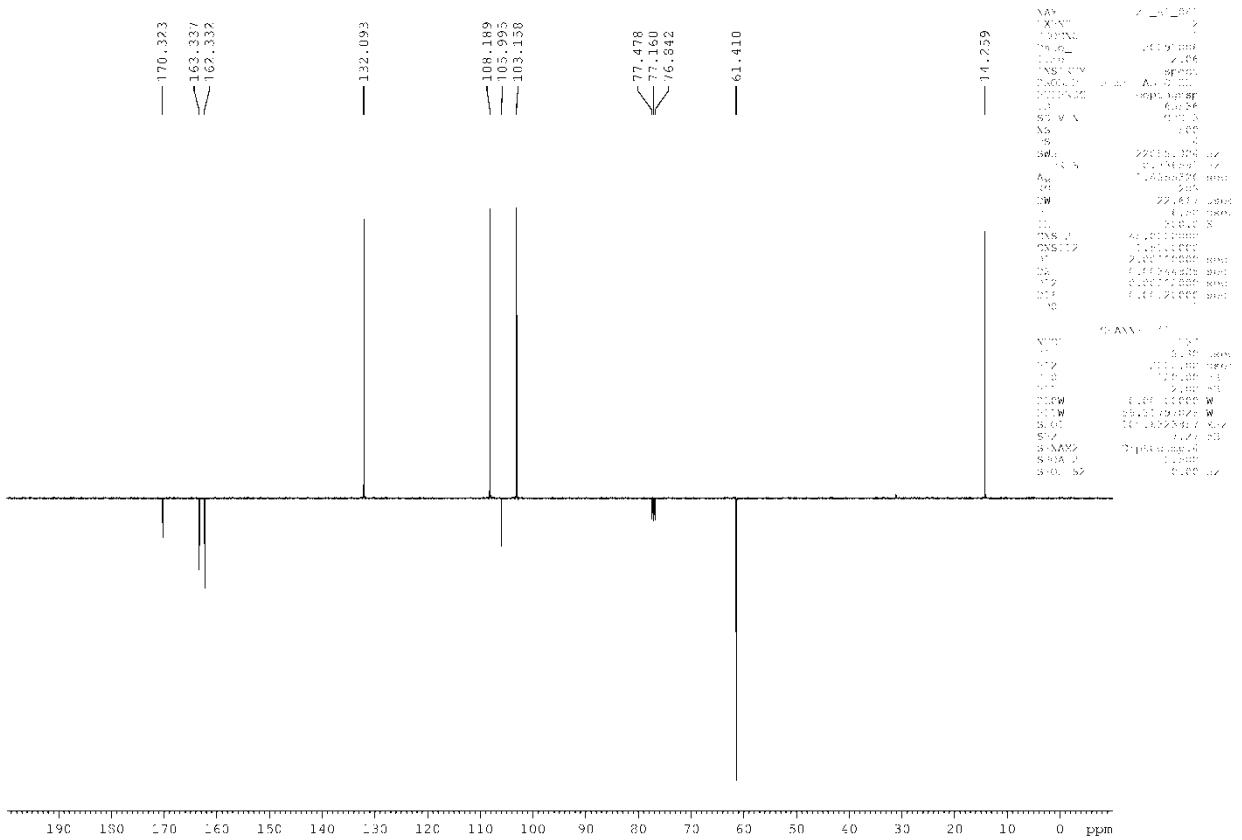

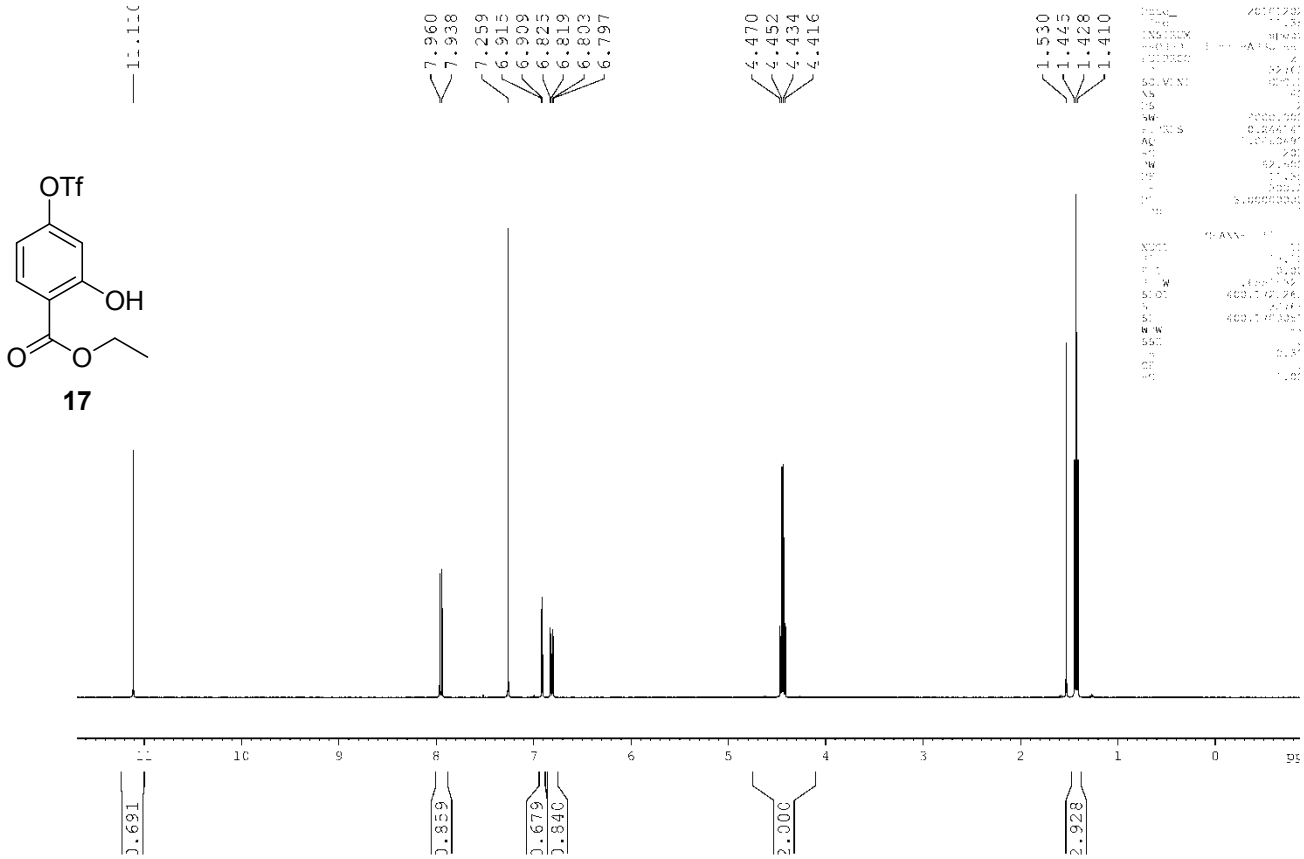
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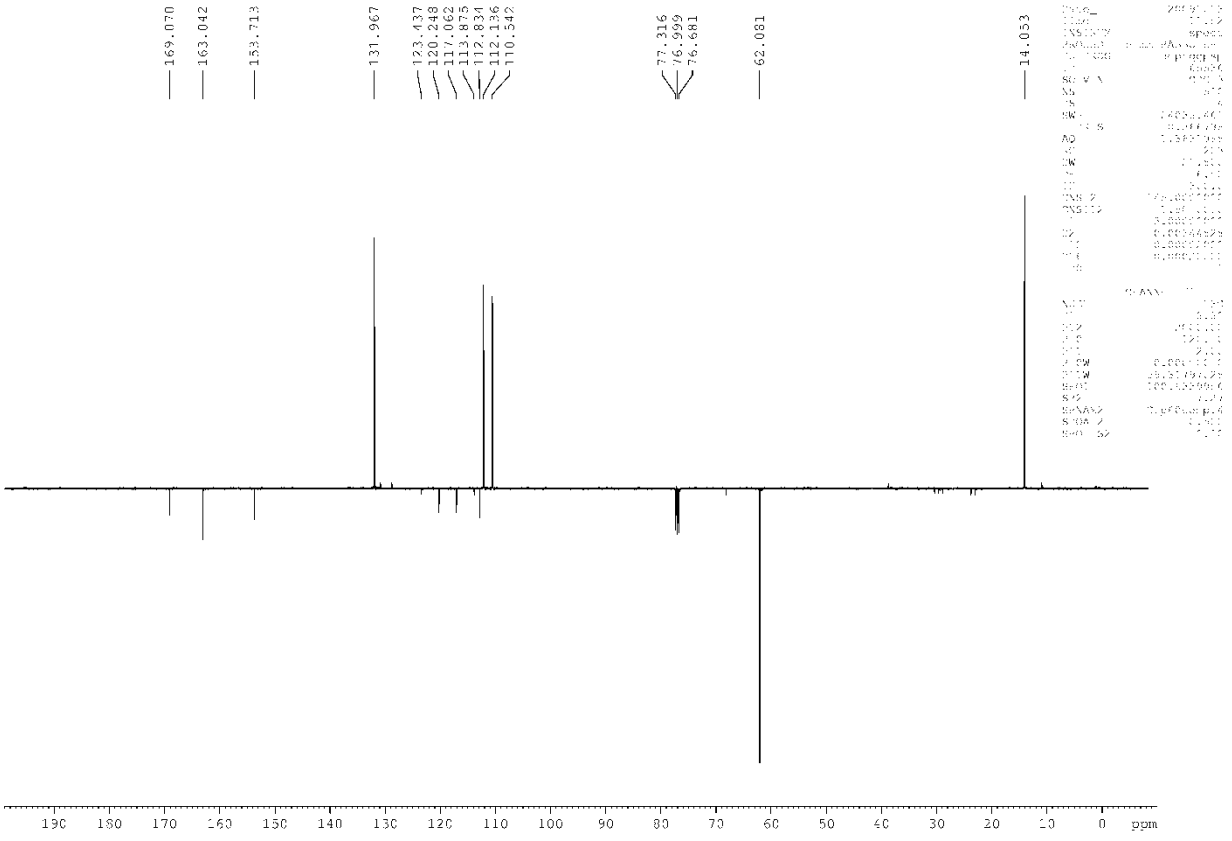
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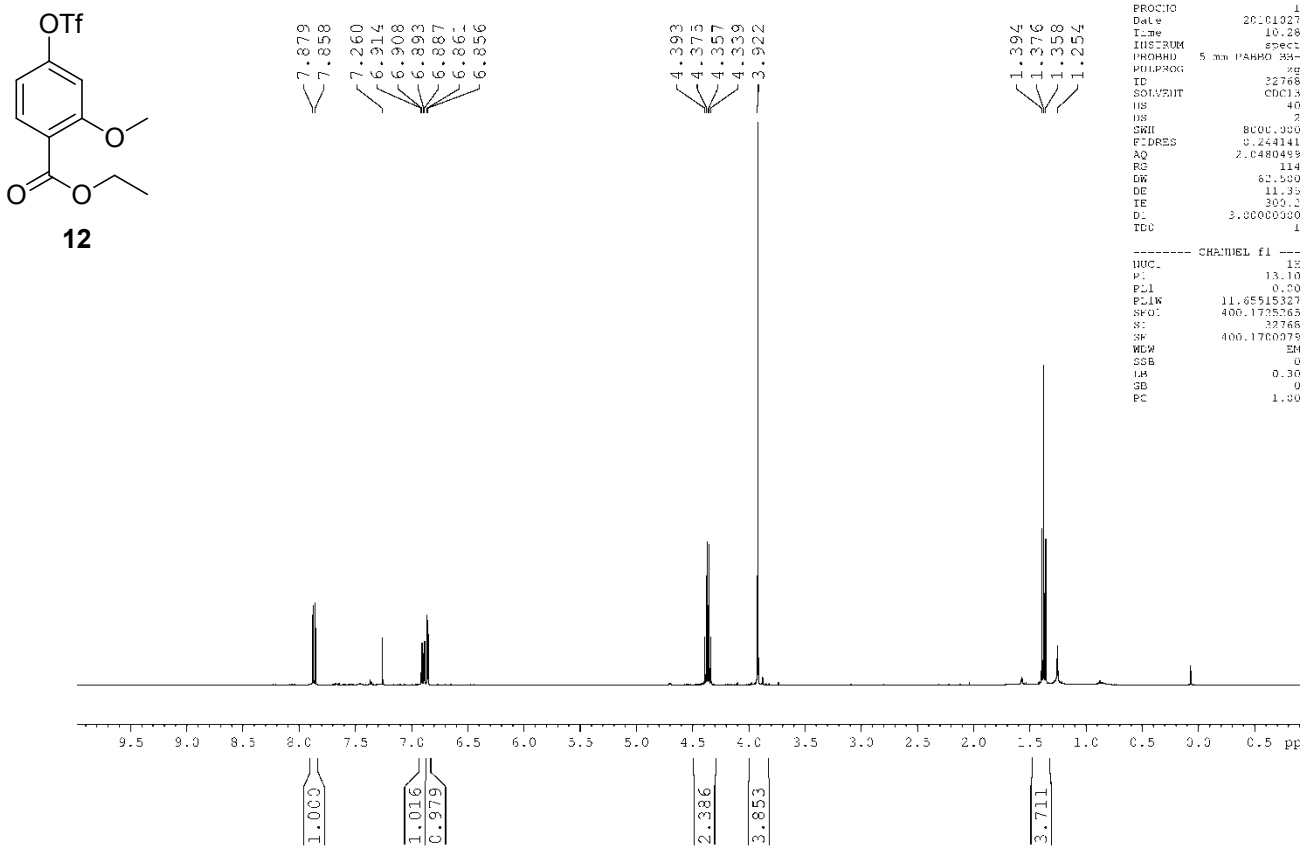
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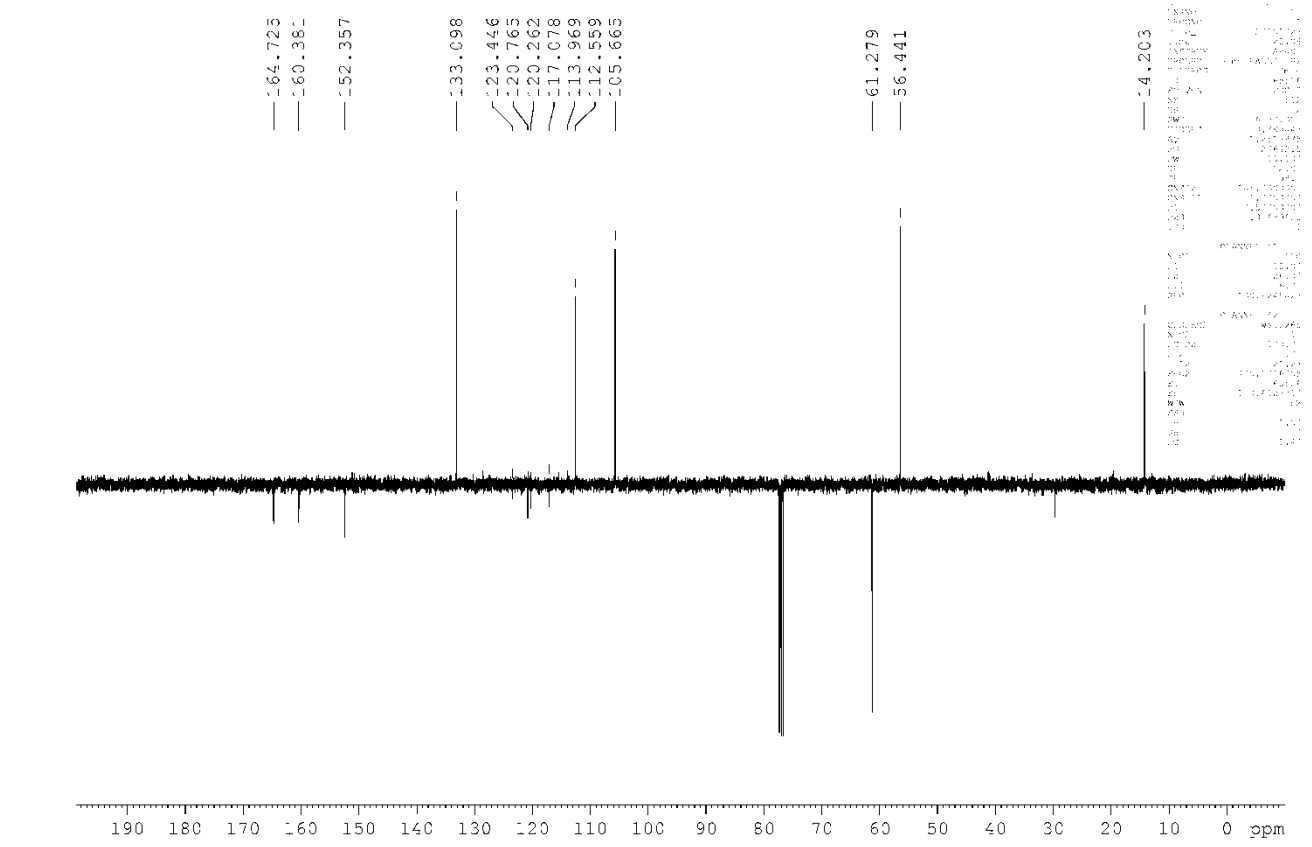
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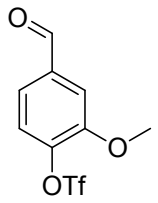
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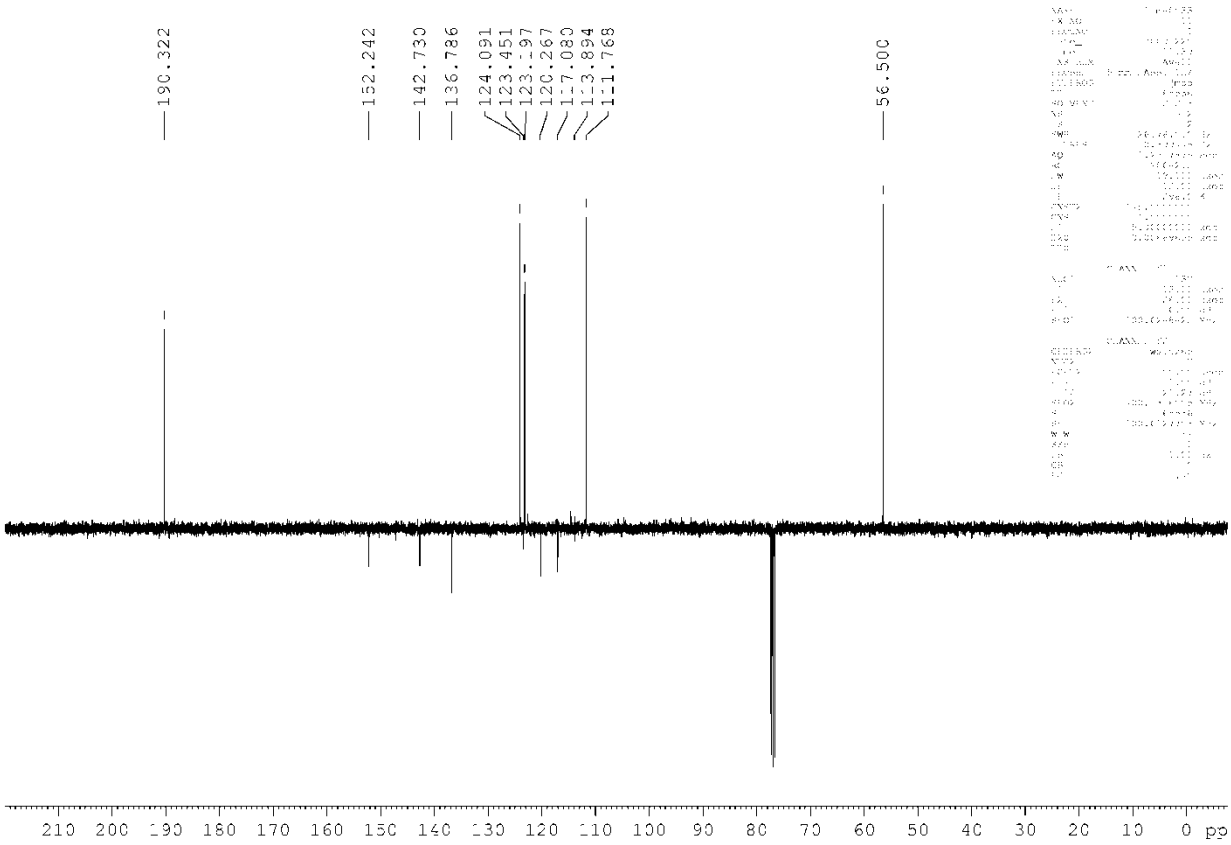
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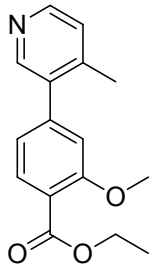

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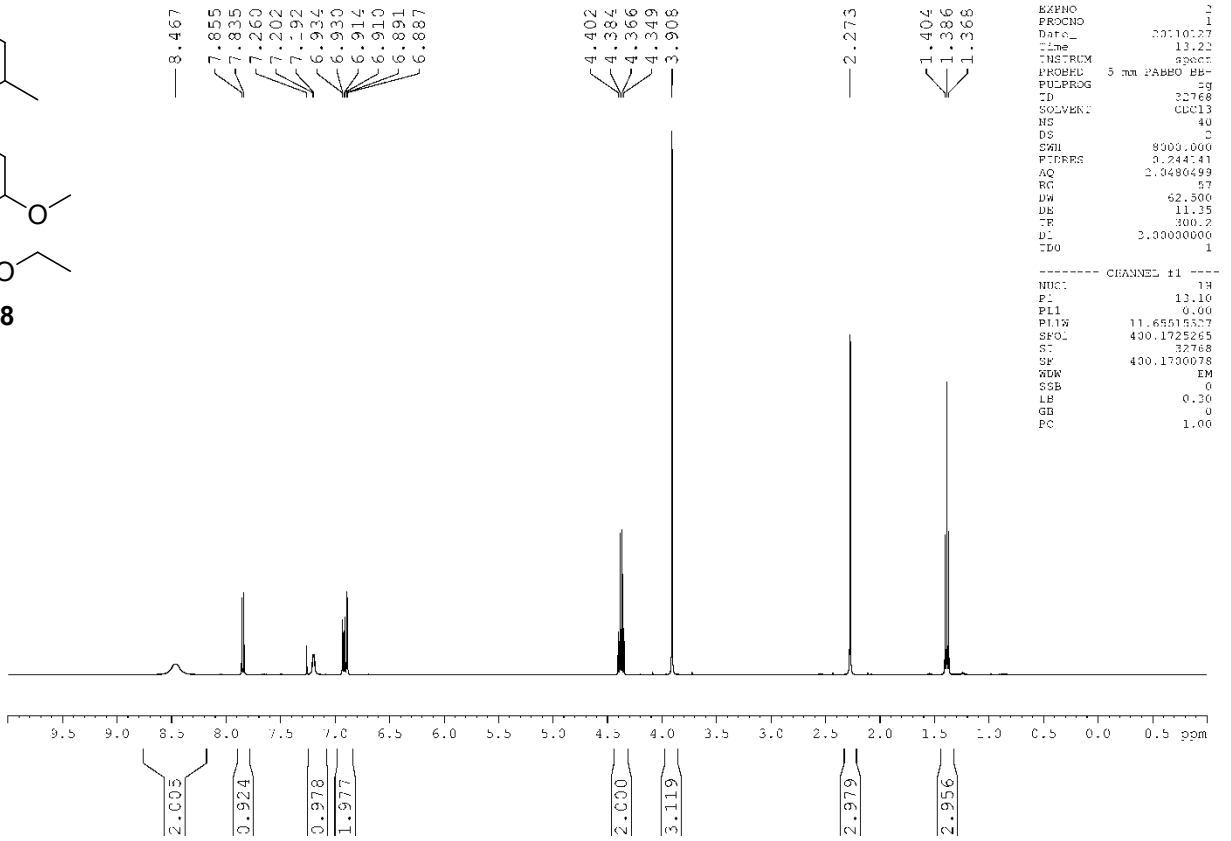
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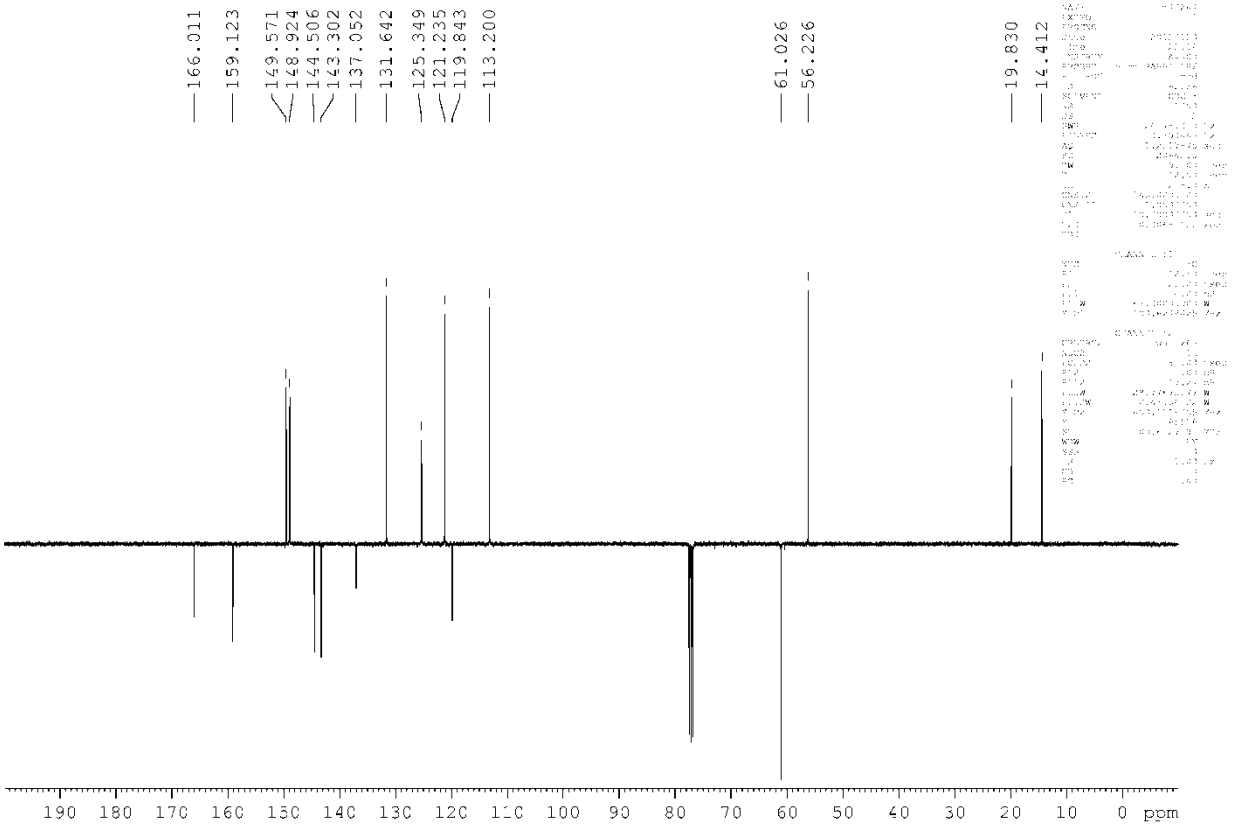
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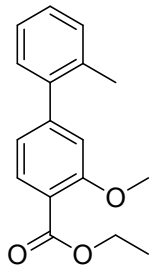

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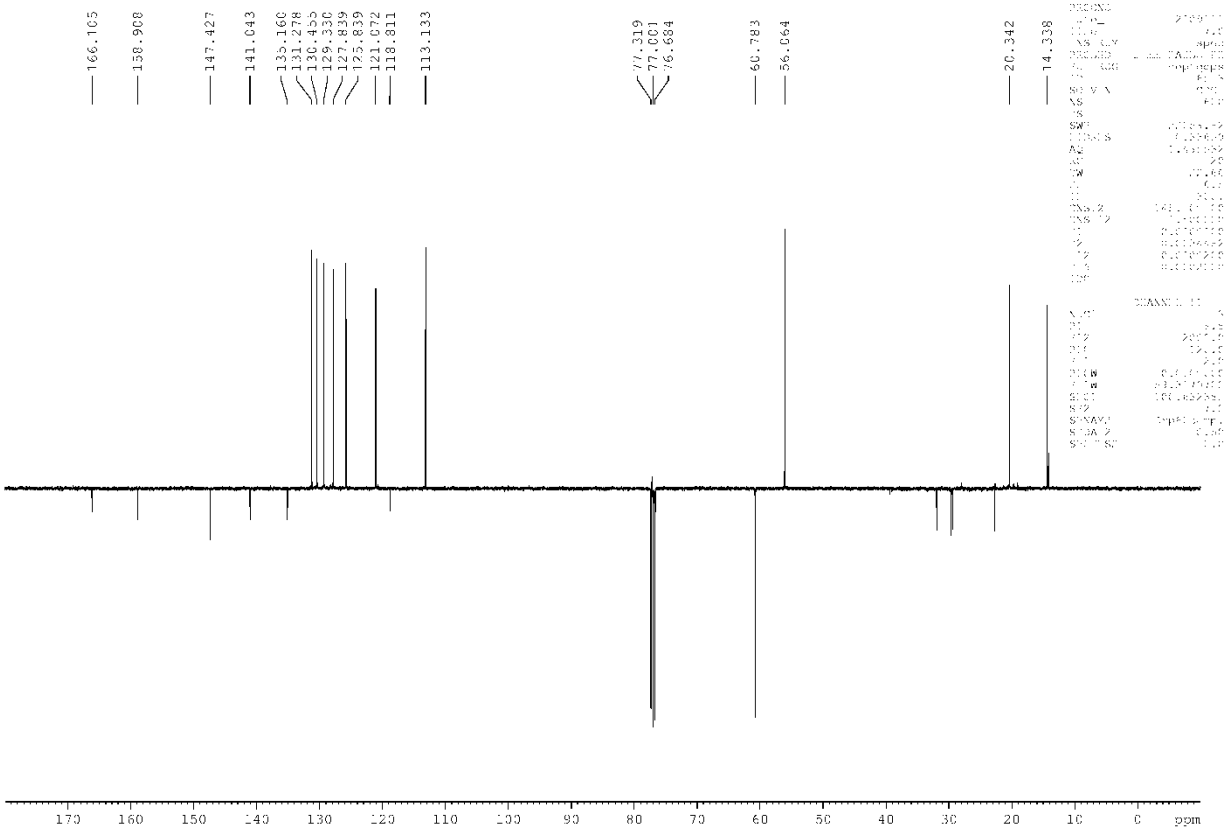

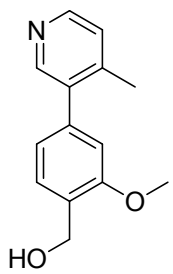
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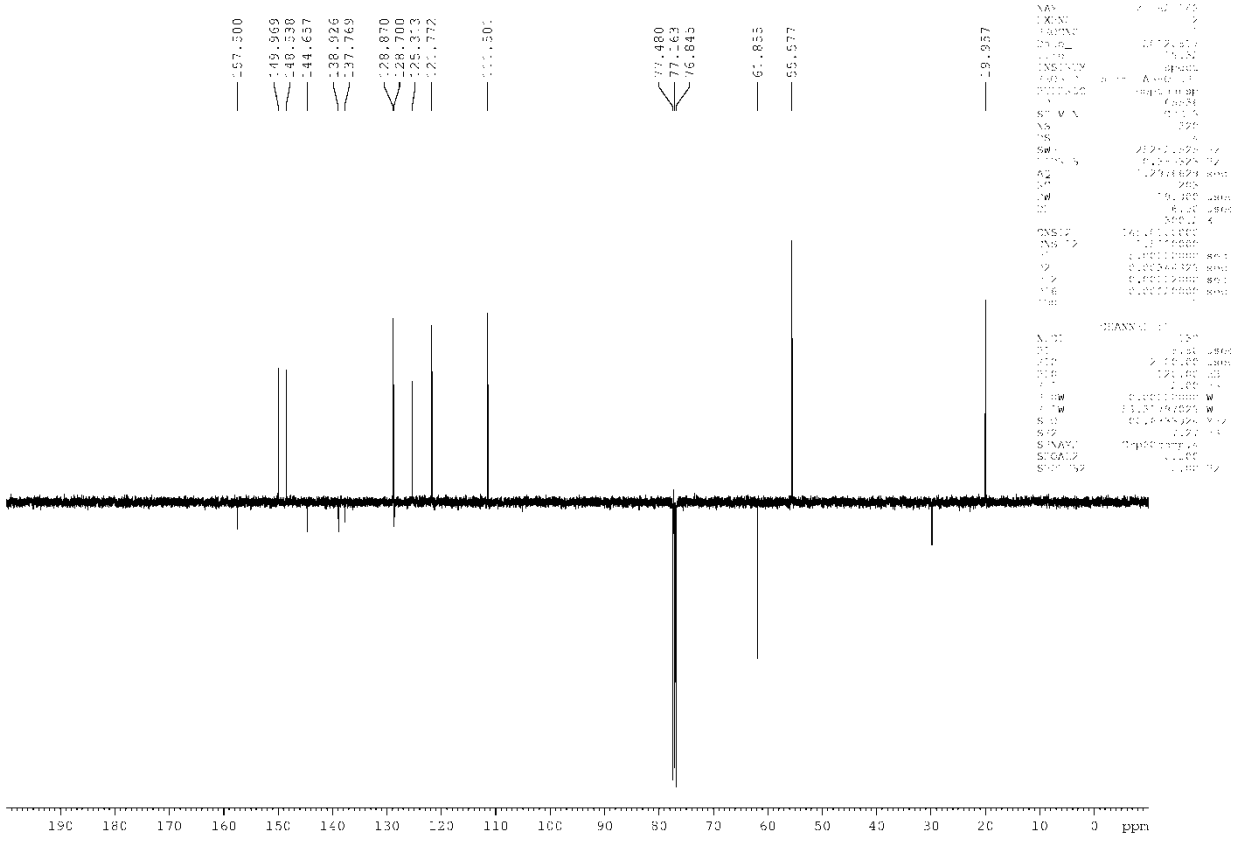
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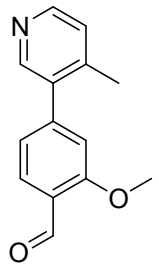

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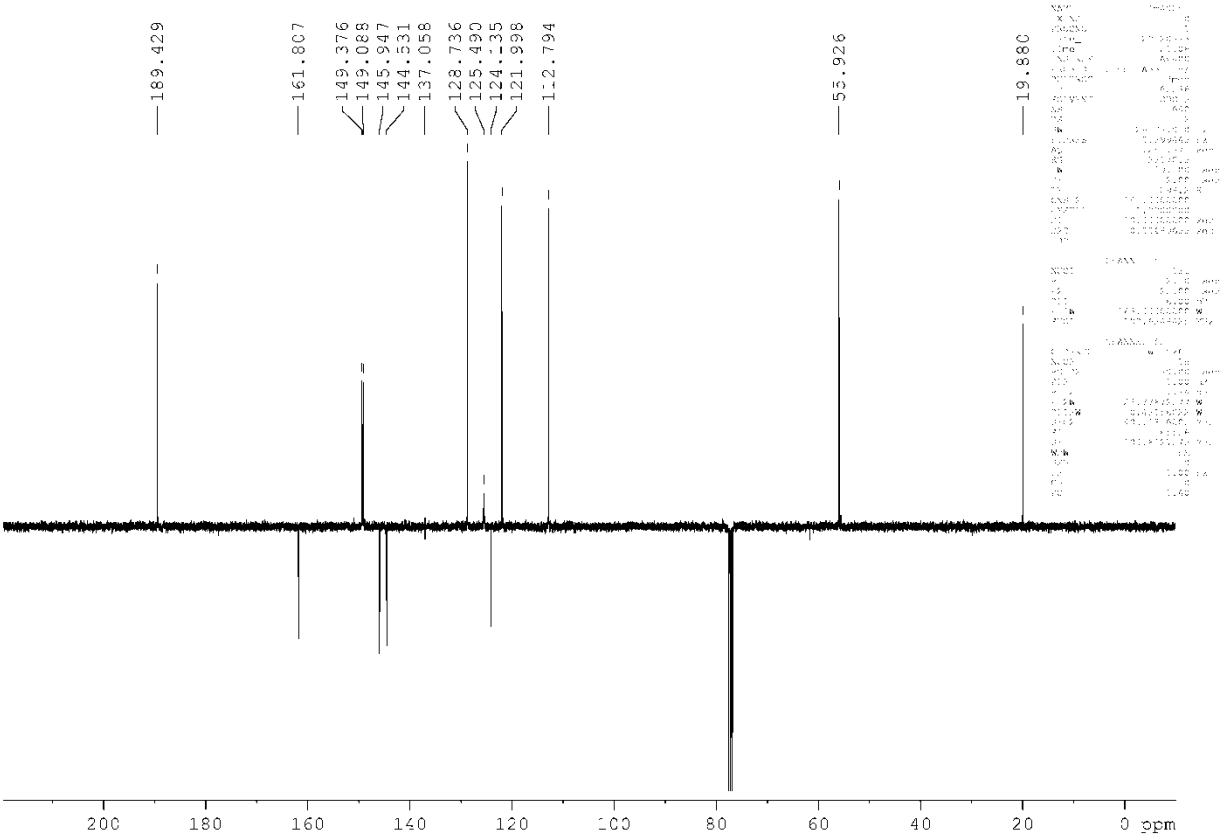
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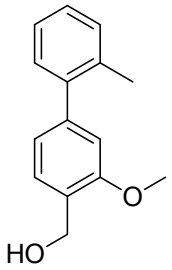
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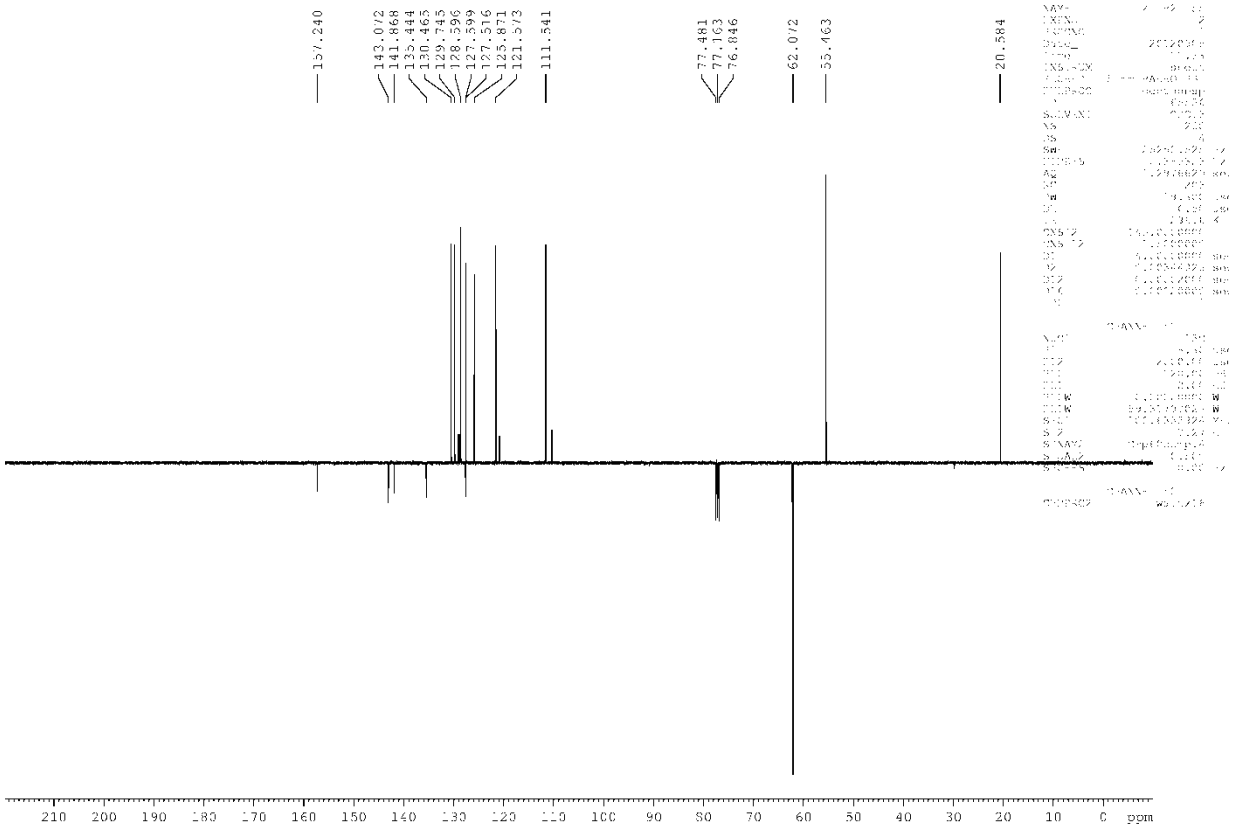
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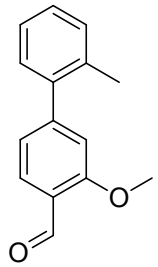
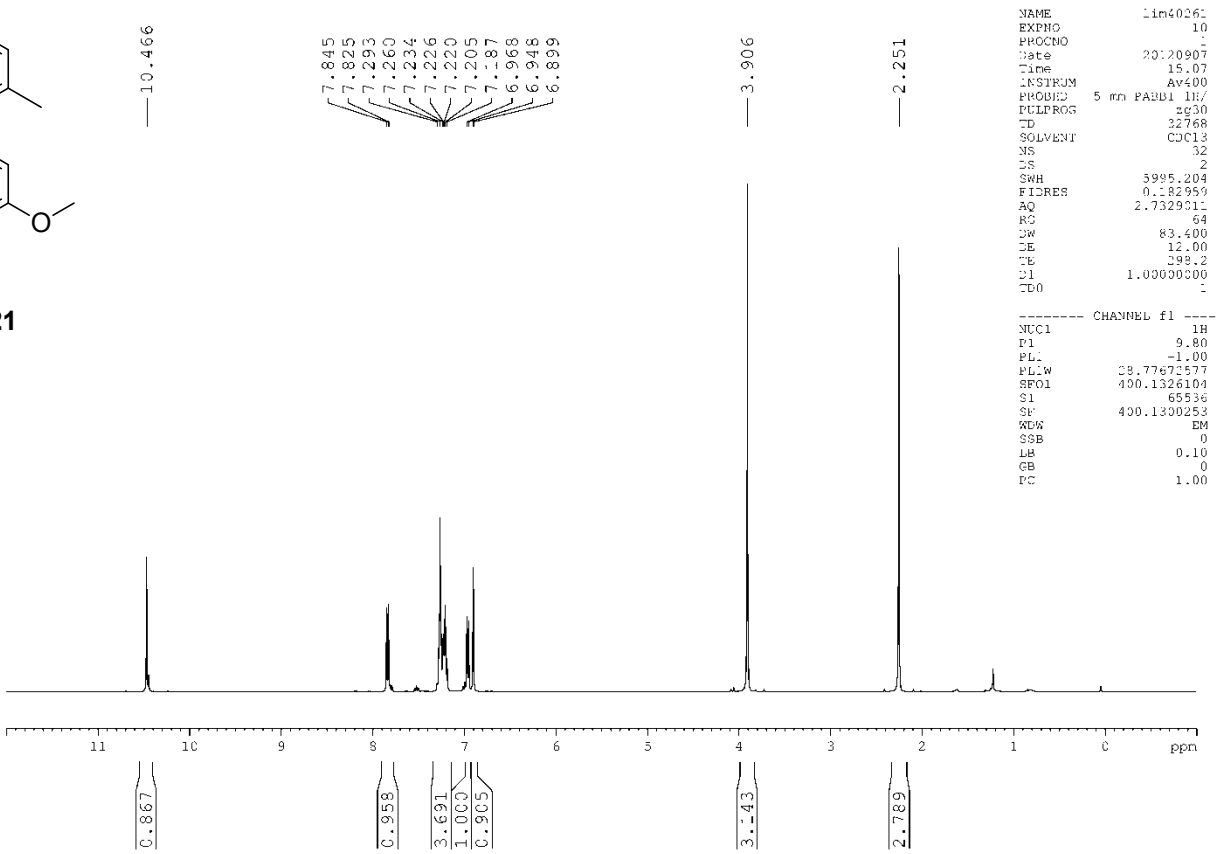
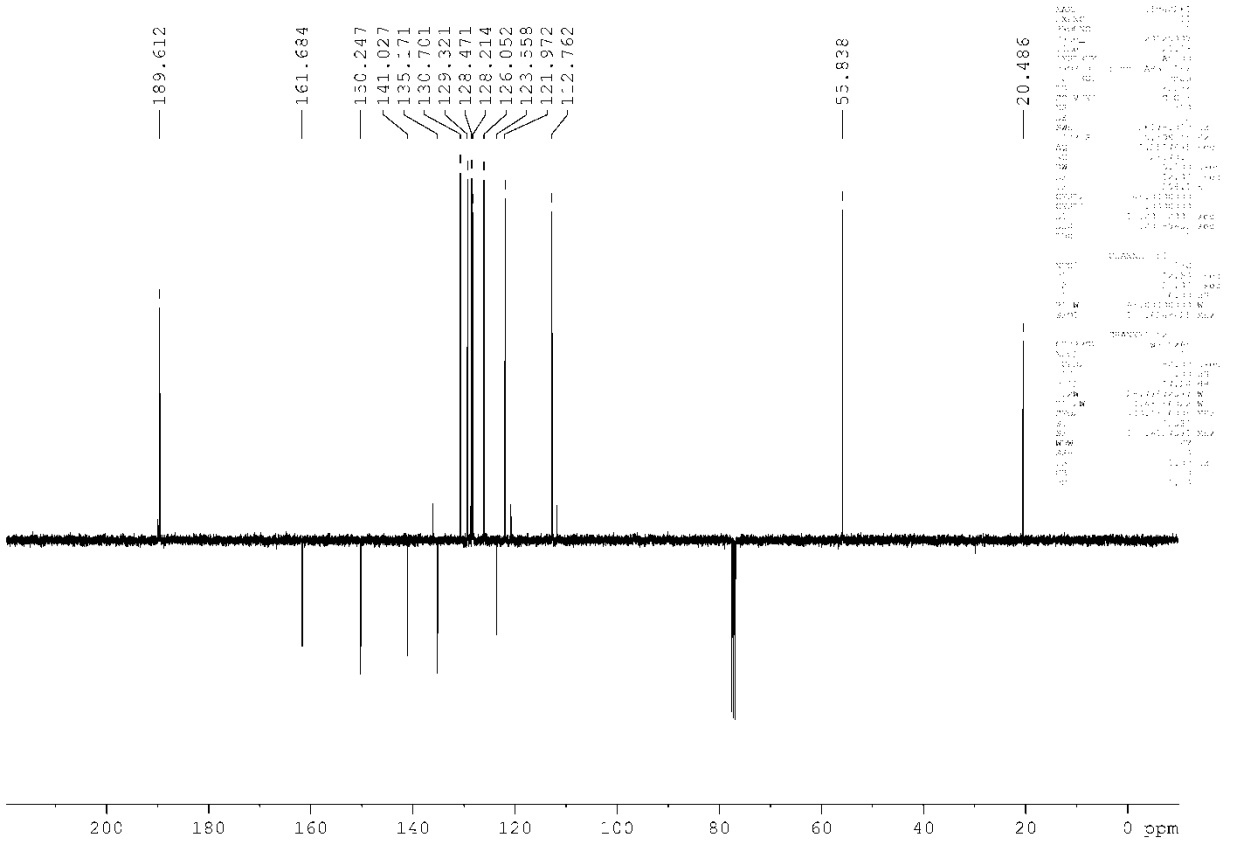
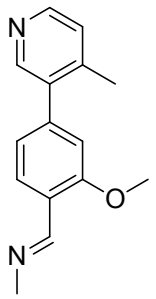
20.584
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



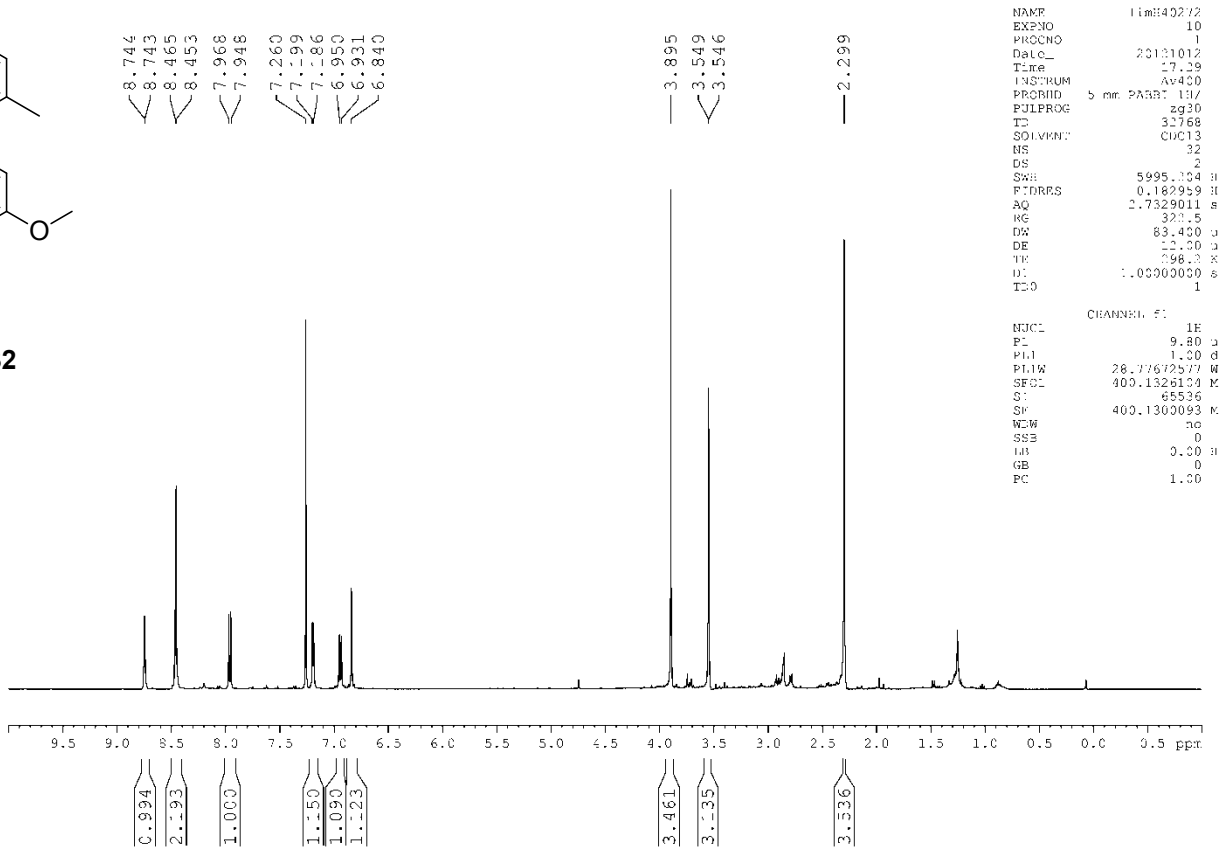
21

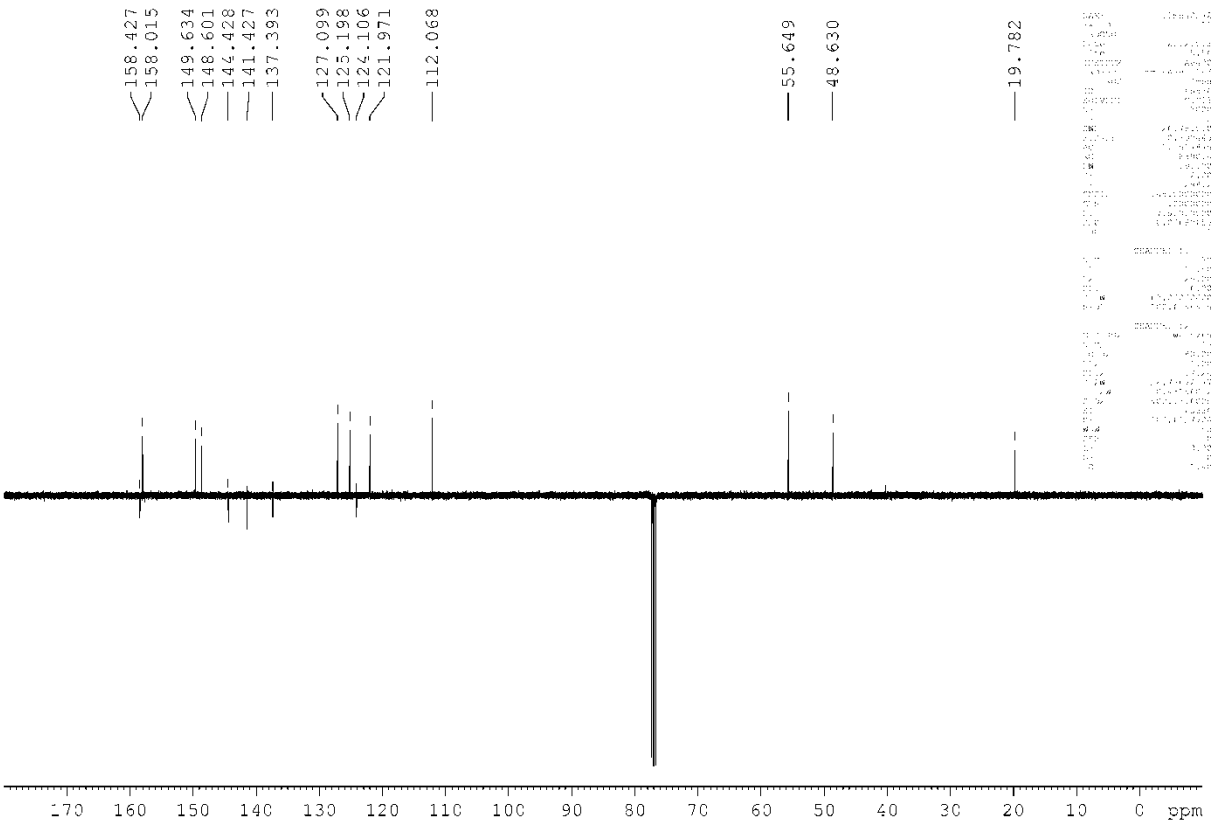

10.466
7.845
7.825
7.293
7.260
7.234
7.226
7.220
7.205
7.187
6.968
6.948
6.899
3.906
2.251
NAME 1im40261
EXPNO 10
PROCNO 1
Date 20120907
Time 15.07
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5995.204
FIDRES 0.182959
AQ 2.7329011
RG 64
DW 83.400
DE 12.00
TE 298.2
D1 1.00000000
TD0 1
CHANNEL f1
NUC1 1H
P1 9.80
PL1 -1.00
PL1W 38.77672577
SFO1 400.1326104
SI 65536
SW 400.1300253
WDW EM
SSB 0
LB 0.10
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.867
0.958
3.691
1.000
0.905
3.143
2.789

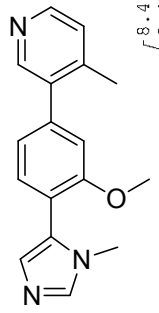

189.612
161.684
130.247
141.027
135.171
130.701
129.321
128.471
128.214
126.052
123.558
121.972
112.762
55.838
20.486
200 180 160 140 120 100 80 60 40 20 0 ppm



32

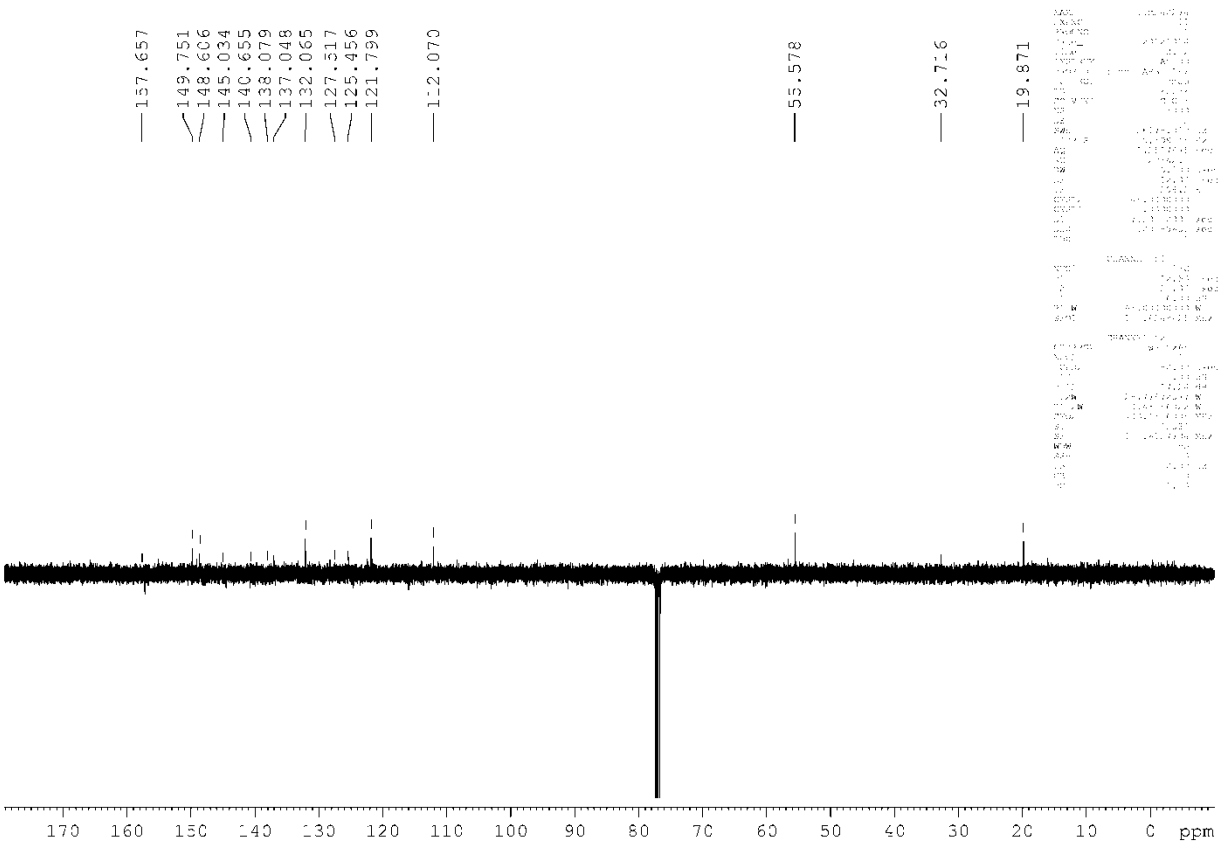

8.744
8.743
8.465
8.453
7.968
7.948
7.260
7.199
7.186
6.950
6.931
6.840
3.895
3.549
3.546
2.299
0.994
2.193
1.000
1.150
1.090
1.123
3.461
3.135
3.536
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

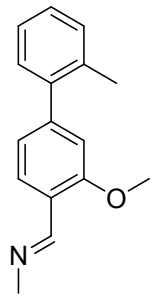

158.427
158.015
149.634
148.601
144.428
141.427
137.393
127.099
125.198
124.106
121.971
112.068
55.649
48.630
19.782
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



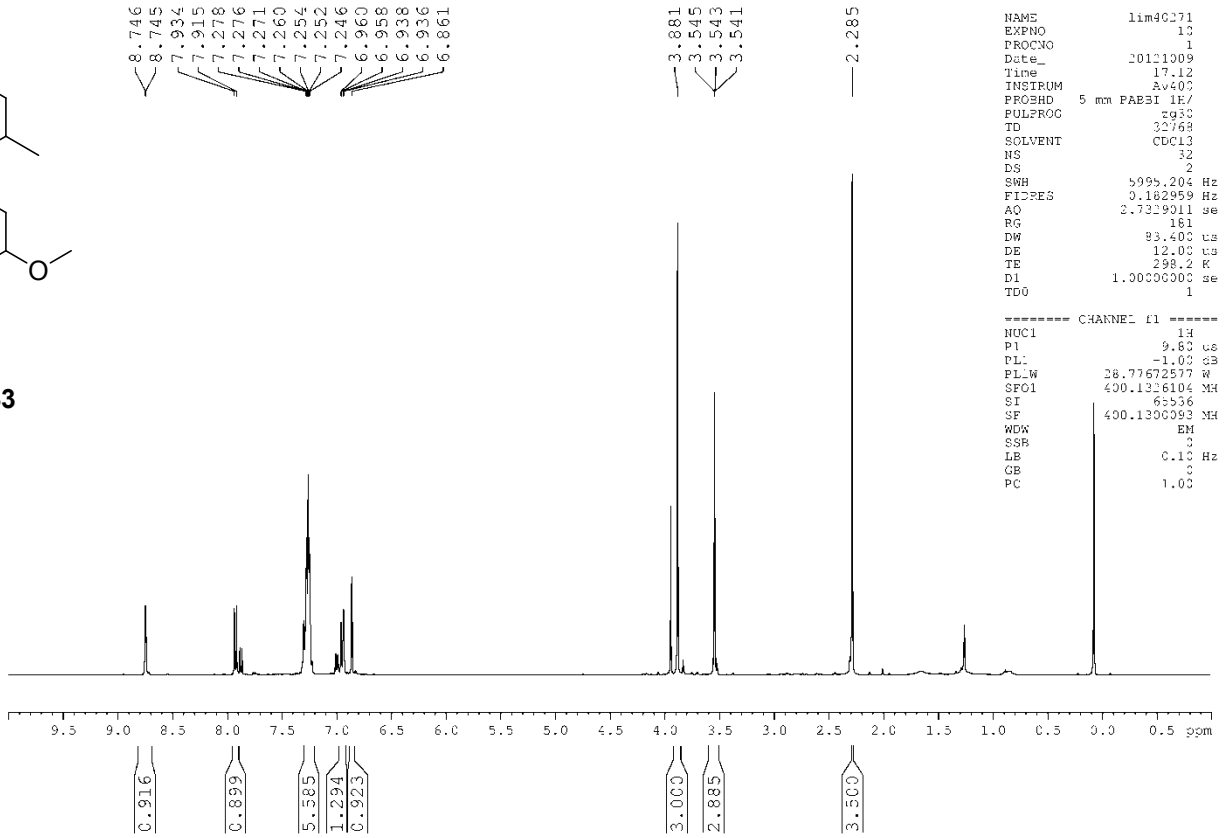
3

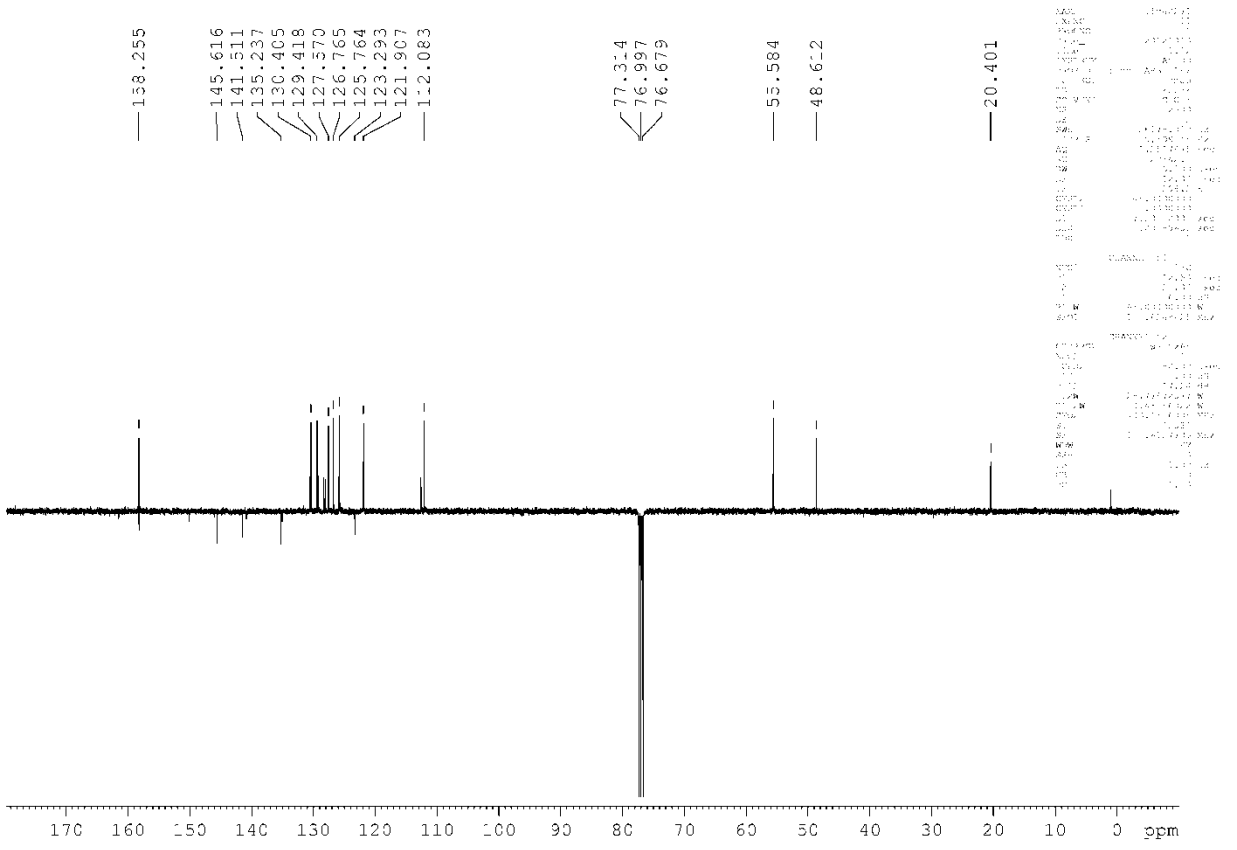
8.490
8.473
8.450
7.536
7.518
7.506
7.486
7.336
7.317
7.260
7.230
7.218
7.190
7.179
6.988
6.969
6.910
6.813
6.793
3.841
3.587
2.353
NAME TimH40274
EXPNO 10
PROCNO 1
Date_ 20131023
Time 18.24
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 5995.204 H
FIDRES 0.182959 H
AQ 2.7329011 s
RG 512
DW 83.400 u
DE 12.20 u
TE 298.2 K
D1 1.00000000 s
TD0 1
CHANNEL f1
NUC1 1H
P1 9.80 u
PL1 1.00 d
PL1W 28.77672577 W
SFO1 400.1326104 M
SI 65536
SW 400.1300093 M
WDW no
SSB 0
LB 0.30 H
GB 0
PC 1.00
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 0.0 -0.5 ppm
1.276
0.518
1.257
0.865
1.245
1.247
1.848
3.000
2.639
3.242

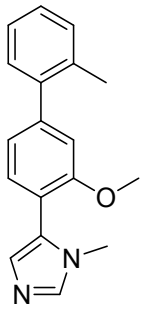

157.657
149.751
148.606
145.034
140.655
138.079
137.048
132.065
127.317
125.456
121.799
112.070
55.578
32.716
19.871
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



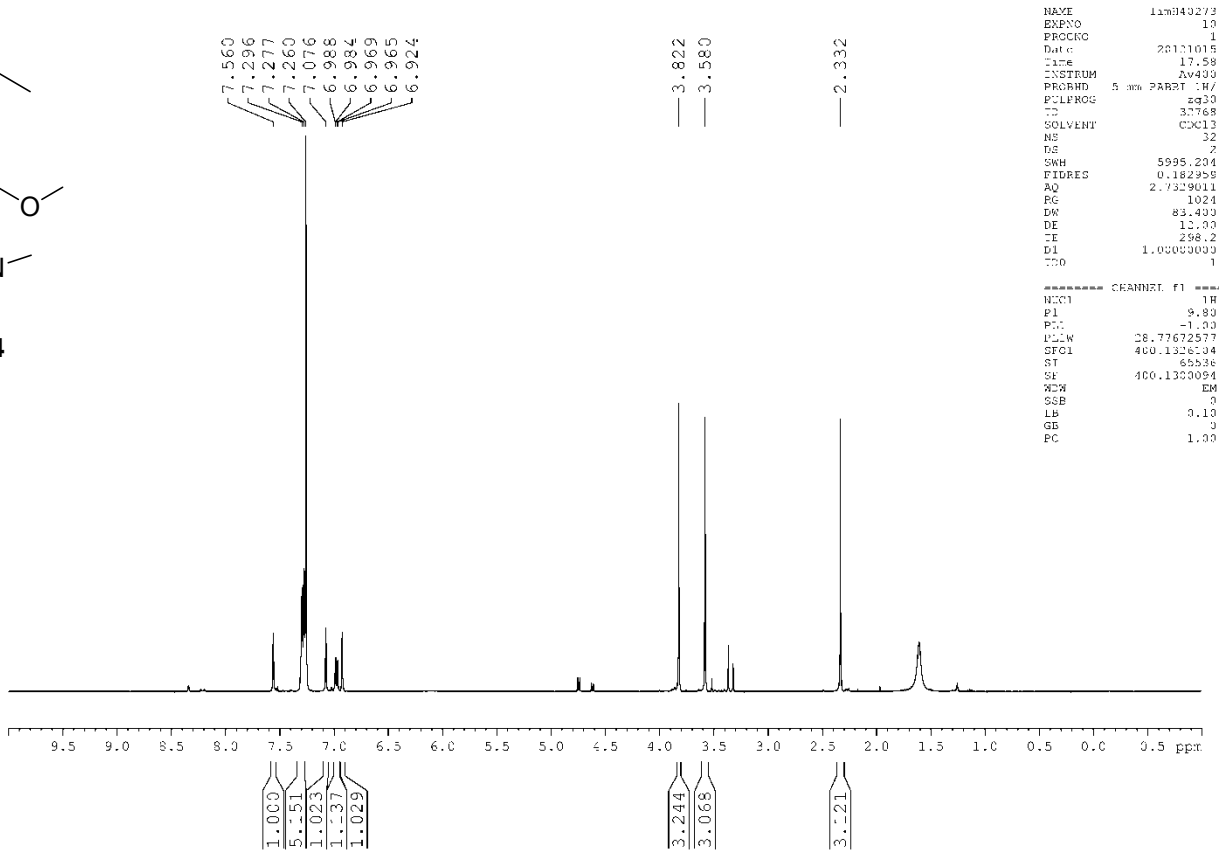
33

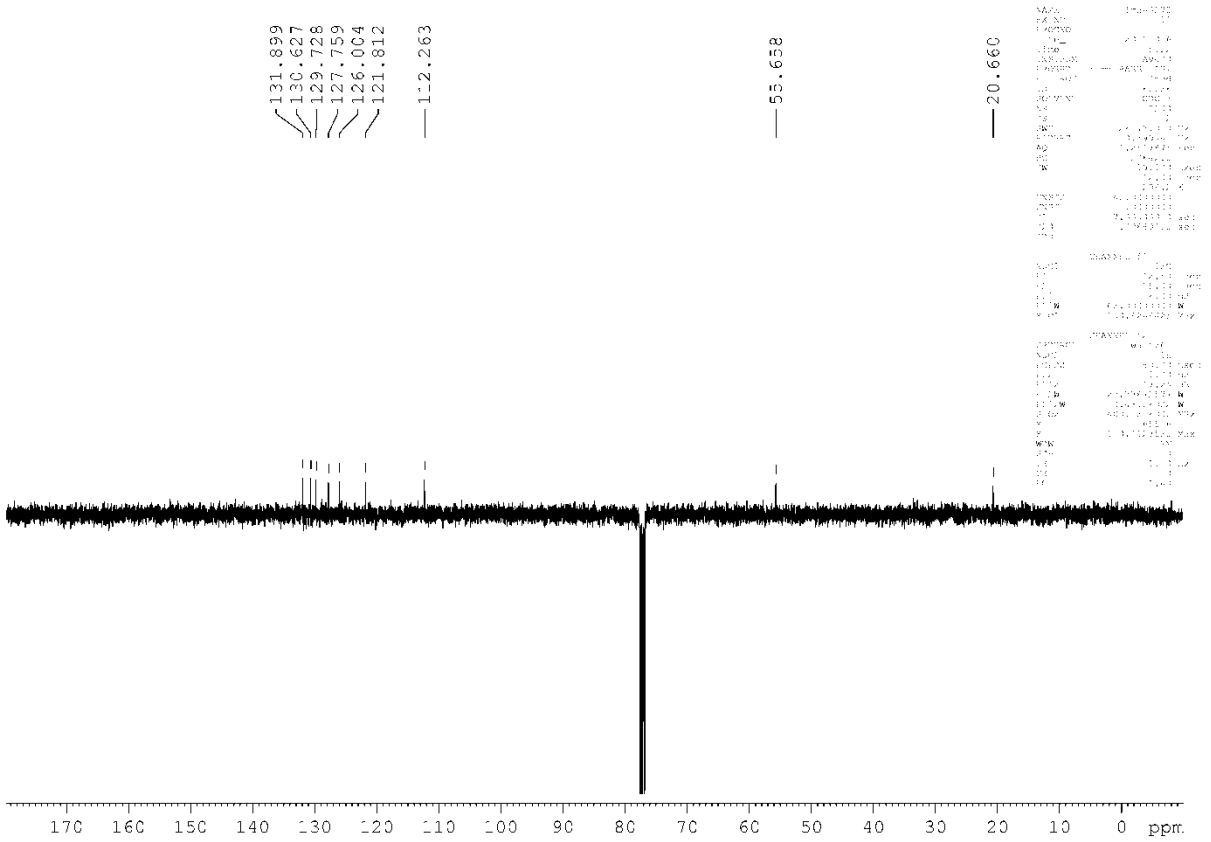

8.746
8.745
7.934
7.915
7.278
7.276
7.271
7.260
7.254
7.252
7.246
6.960
6.958
6.938
6.936
6.861
3.881
3.545
3.543
3.541
2.285
NAME lim40271
EXPNO 10
PROCNO 1
Date_ 20121009
Time 17.12
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 se
RG 161
DW 83.400 us
DE 12.00 us
TE 298.2 K
D1 1.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 9.80 us
PL1 -1.00 dB
PL1W 28.77672577 W
SFO1 400.1316104 MH
SI 65536
SF 400.1300093 MH
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
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 0.0 0.5 ppm
0.916
0.899
5.385
1.294
0.923
3.000
2.885
3.500

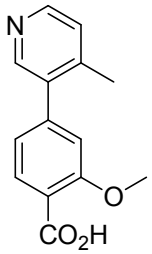

138.255
145.616
141.511
135.237
130.405
129.418
127.570
126.765
125.764
123.293
121.907
112.083
77.314
76.997
76.679
55.584
48.622
20.401
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



4

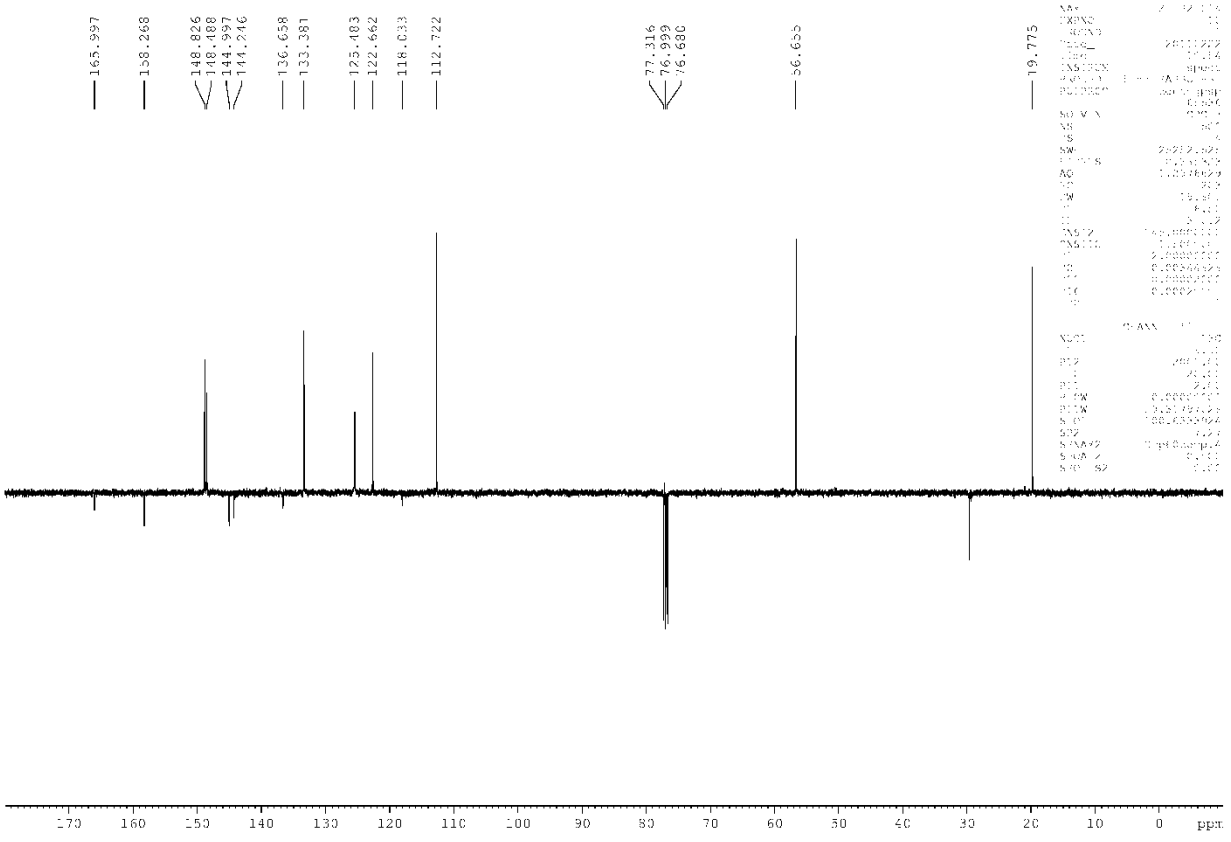

7.560
7.296
7.277
7.260
7.076
6.988
6.984
6.969
6.965
6.924
3.822
3.580
2.332
NAME 1amB40279
EXPNO 10
PROCNO 1
Date 20101015
Time 17.58
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5995.204
FIDRES 0.182959
AQ 2.7329011
RG 1024
DW 83.400
DE 12.00
TE 298.2
D1 1.00000000
TD0 1
CHANNEL f1
NUC1 1H
P1 9.80
PL1 -1.00
PLW 28.77672577
SFO1 400.1316004
ST 65536
SF 400.1300094
WDW EM
SSB 0
LB 0.10
GB 0
PC 1.00
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 0.0 -0.5 ppm
1.000
5.151
1.023
1.137
1.029
3.244
3.068
3.121

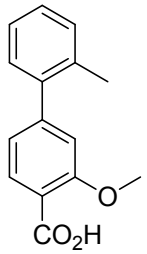

131.899
130.627
129.728
127.759
126.004
121.812
112.263
55.658
20.660
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



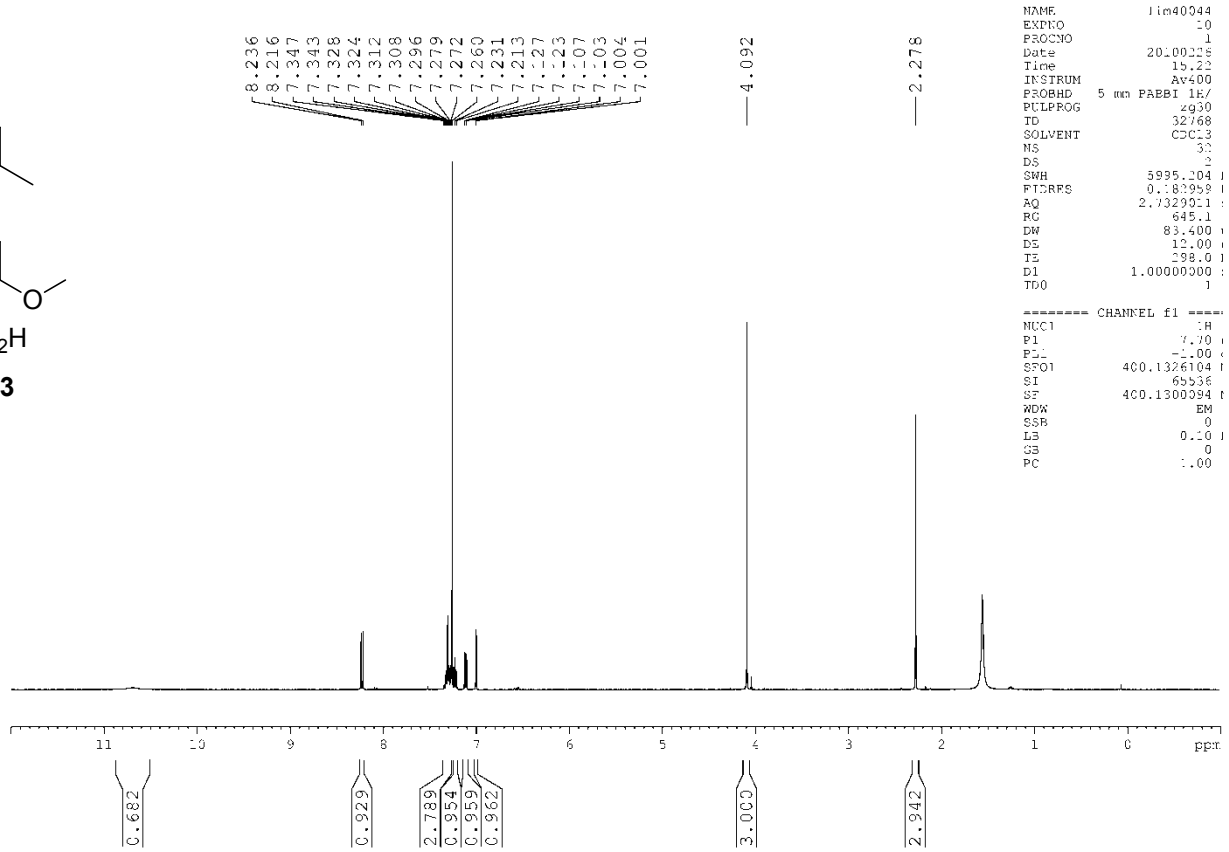
22

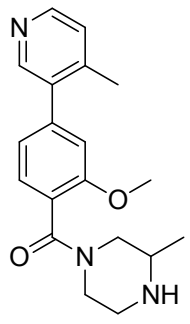
8.517
8.506
8.461
8.208
8.188
7.260
7.253
7.240
7.087
7.084
7.067
7.064
6.980
6.976
4.074
2.305
EXPNO 11
PROCNO 1
Date 20110222
Time 12.52
INSTRUM spect
PROBHD 5 mm PABBO BB
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 8000.000
FIDRES 0.244141
AQ 2.0480493
RG 114
DW 62.500
DE 11.35
TE 300.2
D1 3.00000000
TD0 1
CHANNEL f1
NUC1 1H
P1 13.10
PL1 0.00
PL1W 11.65515327
SFO1 400.7235265
SI 32768
SF 400.7200078
WDW EM
SSB 0
LB 0.30
GB 0
PC 1.00
ppm
1.070
1.308
1.025
0.901
1.003
1.000
3.299
3.182


165.997
158.268
148.826
148.488
144.997
144.246
136.658
133.381
123.483
122.662
118.033
112.722
77.316
76.999
76.680
56.655
19.775
ppm


O
CO2H

23

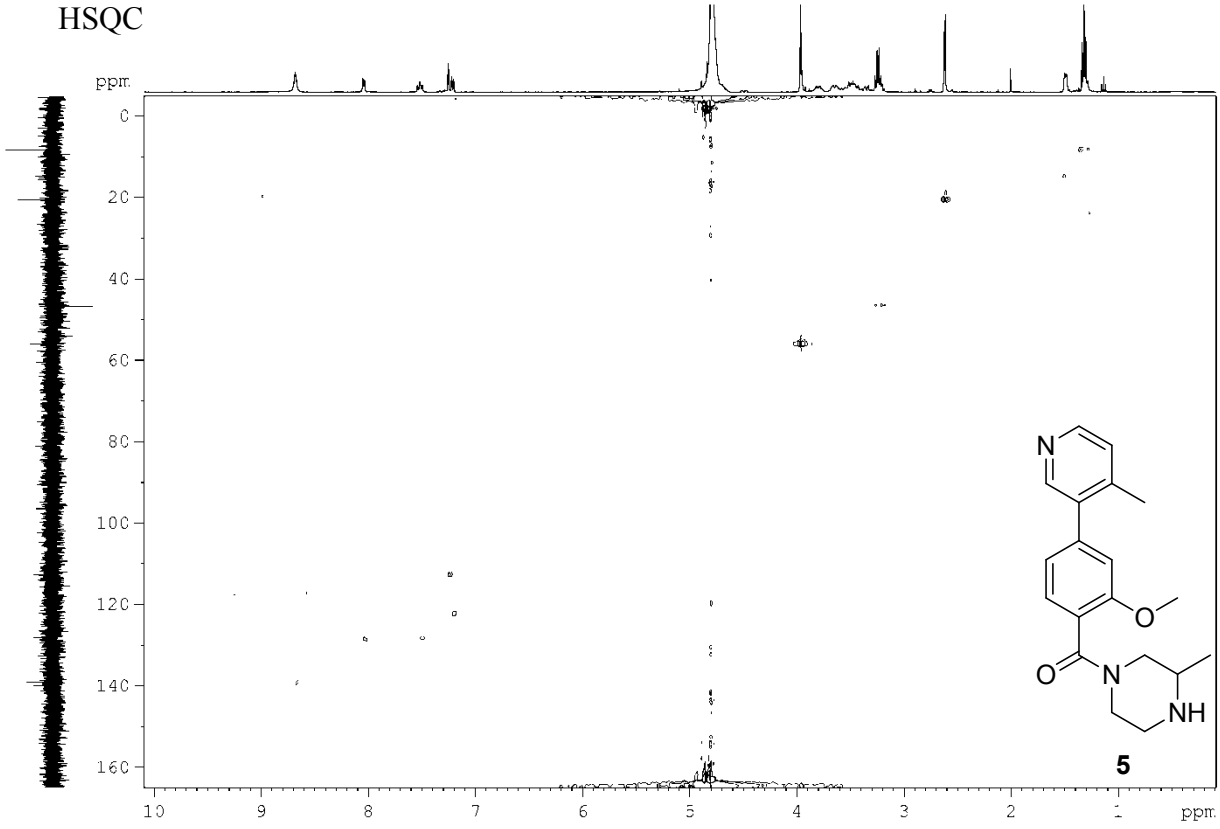

8.236
8.216
7.347
7.343
7.328
7.324
7.312
7.308
7.296
7.279
7.272
7.260
7.231
7.213
4.092
2.276
NAME Tim40044
EXPNO 10
PROCNO 1
Date 20100225
Time 15.22
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
SWH 5995.204
FIDRES 0.183058
AQ 2.7329011
RG 645.1
DW 83.400
DE 12.00
TE 298.0
D1 1.00000000
TD0 1
CHANNEL f1
NUC1 1H
P1 7.70
PL1 -1.00
SFO1 400.1326104
SI 65536
SF 400.1300094
WDW EM
SSB 0
LB 0.10
GB 0
PC 1.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.682
0.929
2.789
0.954
0.959
0.962
3.000
2.942


N
O
O
N
NH

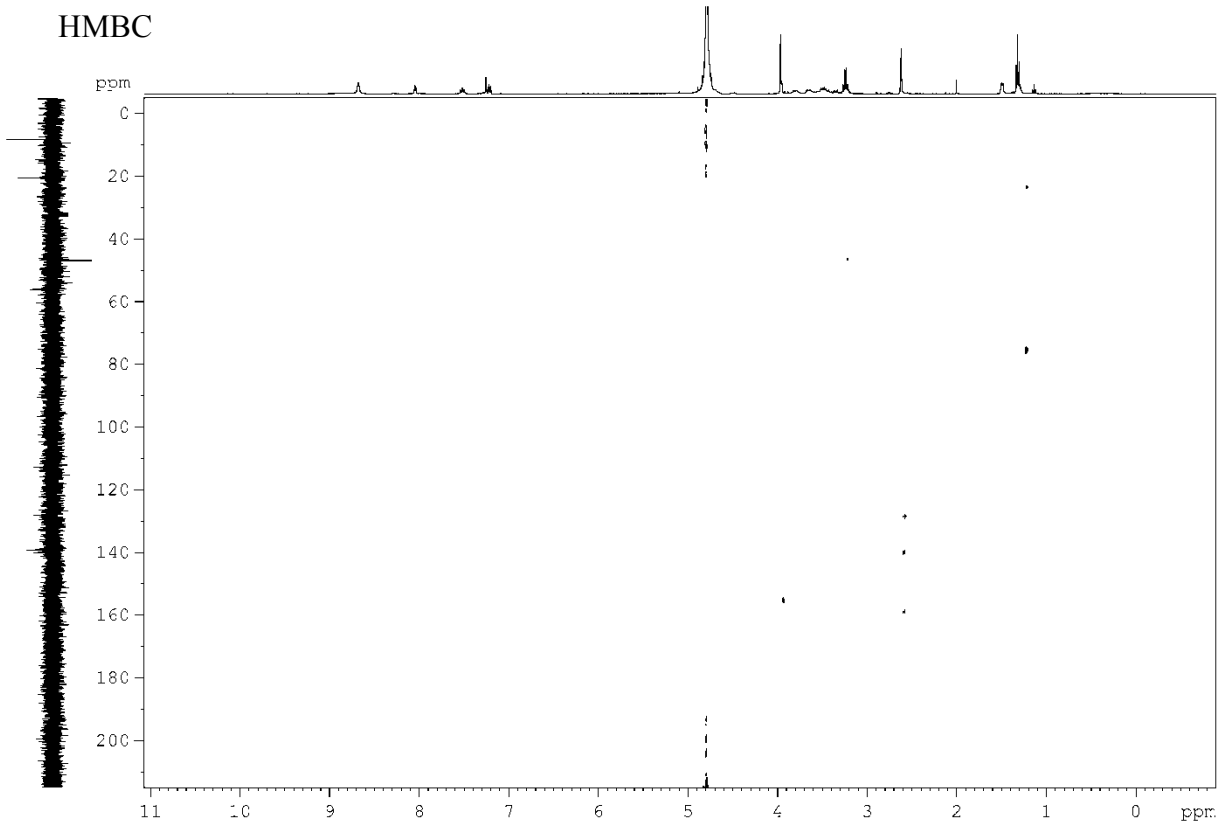
5

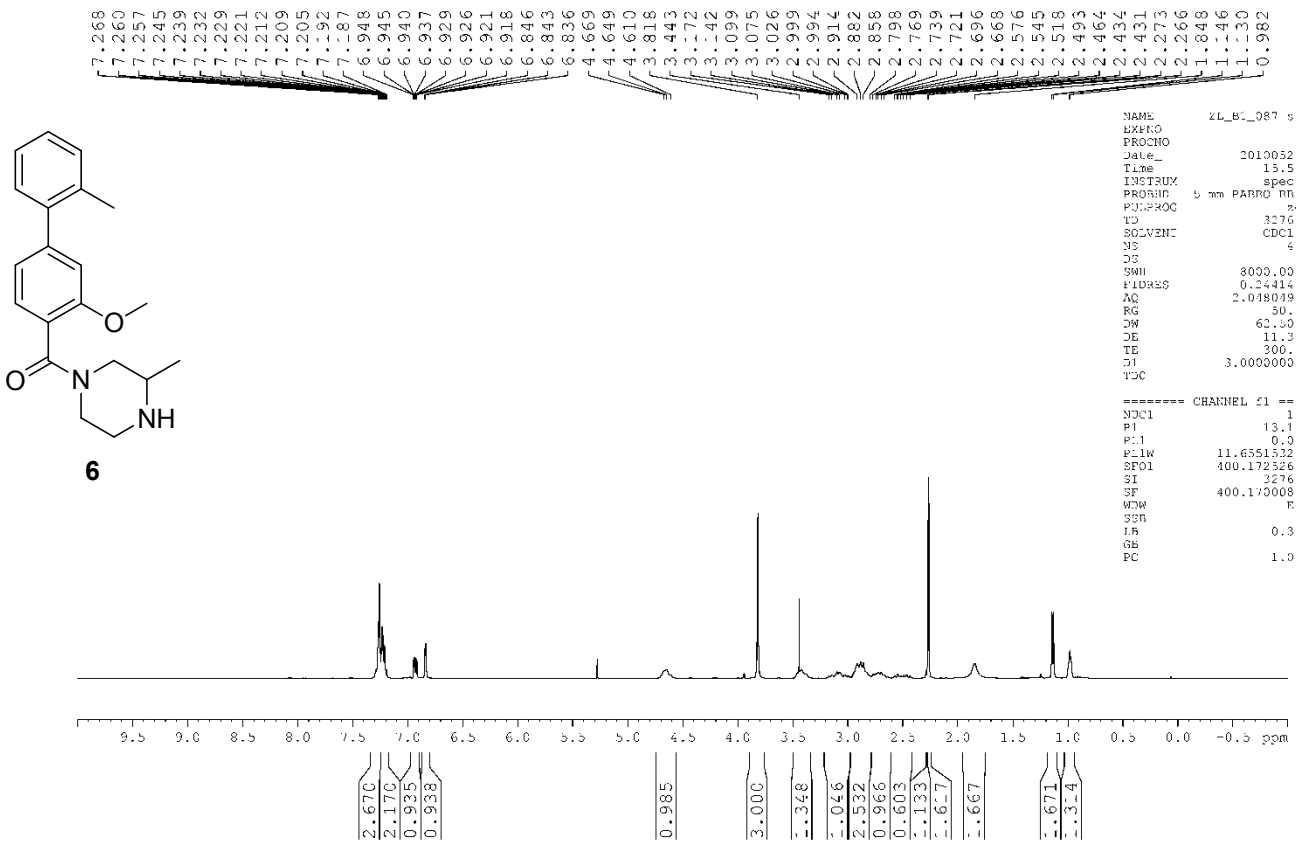
8.680
8.052
8.036
7.254
7.226
7.222
7.206
7.202
3.965
3.816
3.783
3.660
3.635
3.580
3.550
3.514
3.496
3.477
3.463
3.429
3.393
3.370
3.362
3.340
3.270
3.233
3.215
2.624
2.614
1.497
1.489
1.338
1.320
1.302
1.153
1.135
1.116
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5 ppm
2.087
1.000
1.094
1.060
0.990
3.359
3.145
4.178
3.304
2.222
1.687
2.962
0.450

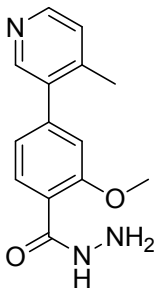
HSQC


ppm
0
20
40
60
80
100
120
140
160
10
9
8
7
6
5
4
3
2
1
ppm
N
O
O
N
NH
5

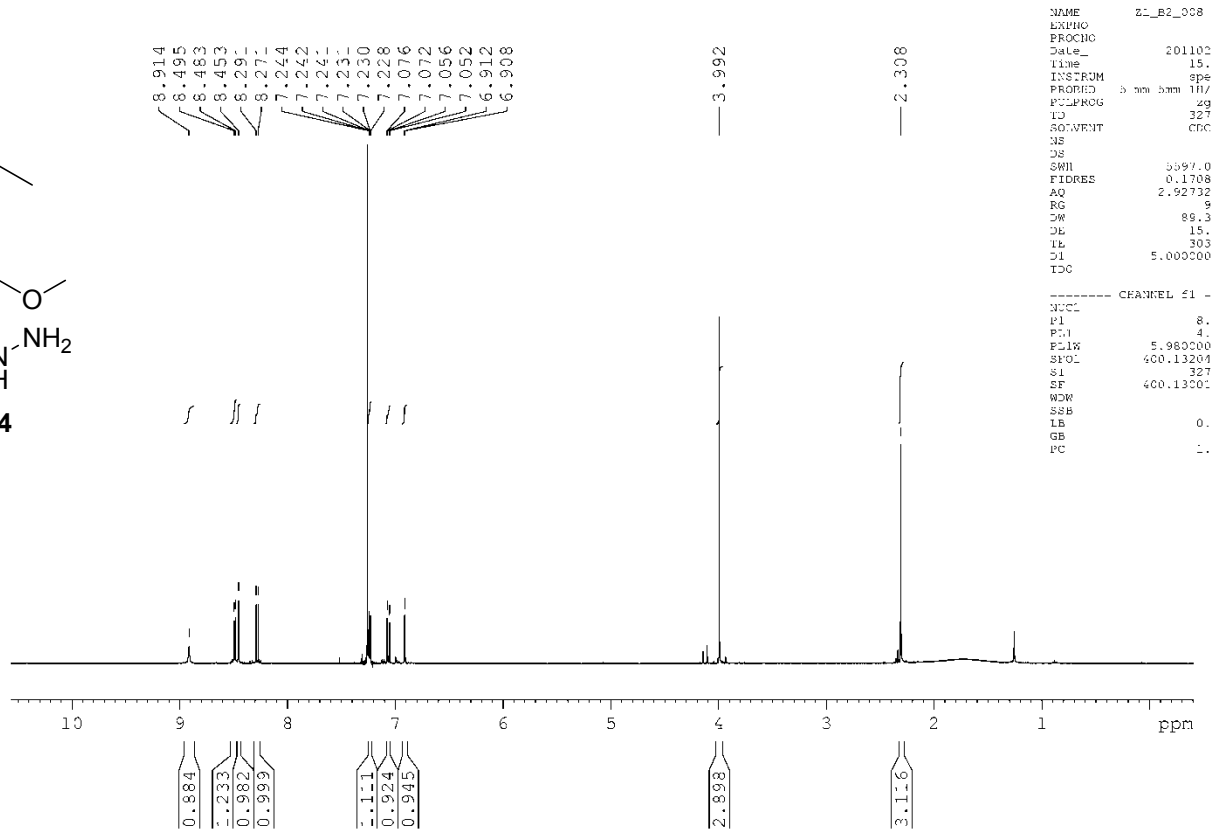
HMBC

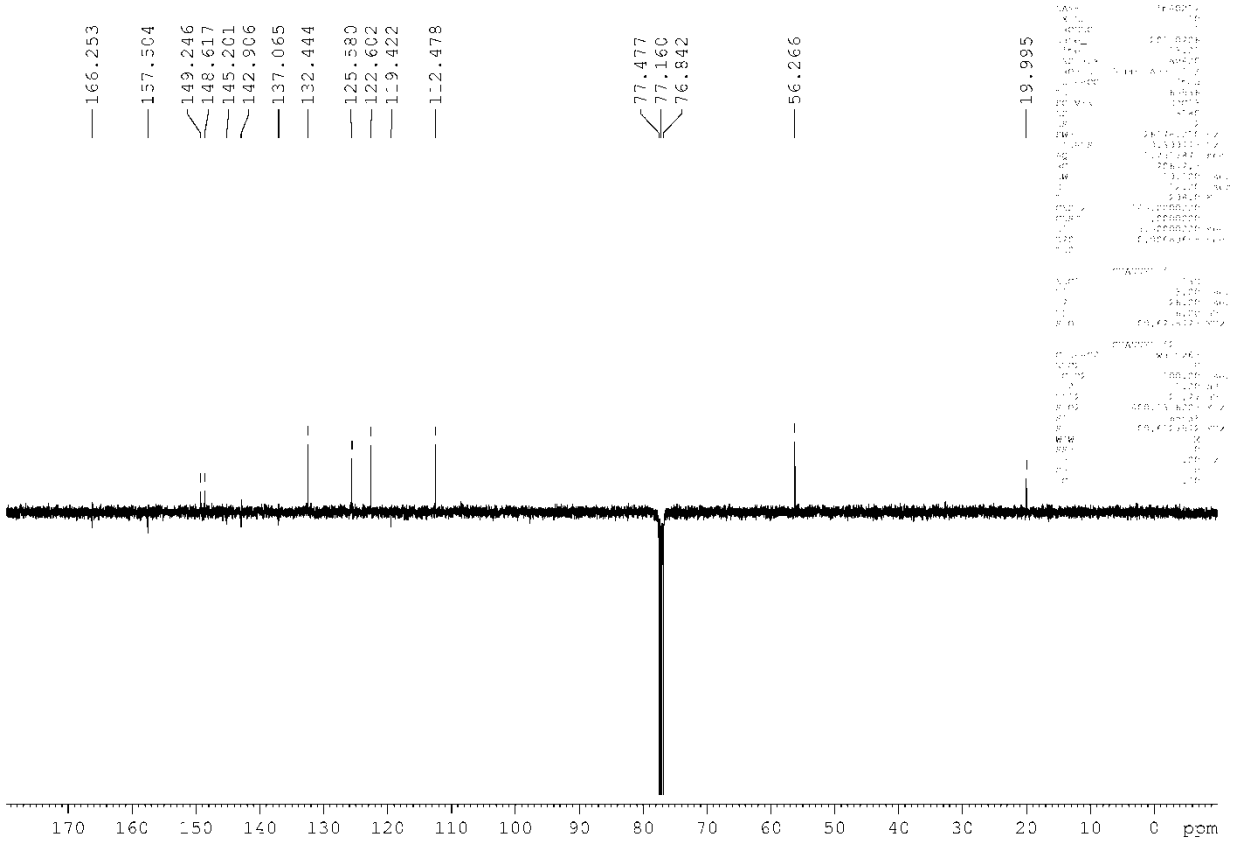

ppm
0
20
40
60
80
100
120
140
160
180
200
11
10
9
8
7
6
5
4
3
2
1
0
ppm

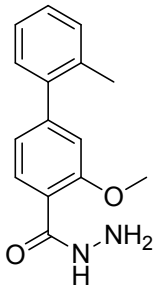

7.268
7.260
7.257
7.245
7.239
7.232
7.229
7.221
7.212
7.209
7.205
7.192
7.187
6.948
6.945
6.940
6.937
6.929
6.926
6.921
6.918
6.846
6.843
6.836
4.669
4.649
4.610
3.818
3.443
3.372
3.142
3.099
3.075
3.026
2.999
2.994
2.914
2.882
2.858
2.798
2.769
2.739
2.721
2.696
2.668
2.576
2.545
2.518
2.493
2.464
2.434
2.431
2.273
2.266
1.848
1.746
1.730
0.982
O
O
N
NH
6
NAME ZL_BI_087 s
EXPNO
PROCNO
Date_ 20100052
Time 15.5
INSTRUM spec
PROBHD 5 mm PABBO BB
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 64
DS
SWH 8000.00
FIDRES 0.24414
AQ 2.0480049
RG 50.
DW 62.50
DE 11.3
TE 300.
D1 3.0000000
TDC
======== CHANNEL f1 ==
NUC1 1
P1 13.1
PL1 0.0
PL1W 11.65551532
SFO1 400.1725256
SI 32768
SF 400.1700008
WDW E
SSB
LB 0.3
GB
PC 1.0
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 0.0 -0.5 ppm
2.670
2.170
0.935
0.938
0.985
3.000
1.348
1.046
2.532
0.966
0.603
1.133
1.167
1.667
1.671
1.314
168.049
167.686
55.133
44.517
41.420
35.377
30.536
30.321
29.616
27.853
27.718
25.893
21.939
12.196
12.122
77.473
77.158
76.840
55.737
55.662
51.216
50.808
50.703
48.975
48.777
48.026
47.163
46.773
45.753
45.572
42.313
42.130
20.538
19.863
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



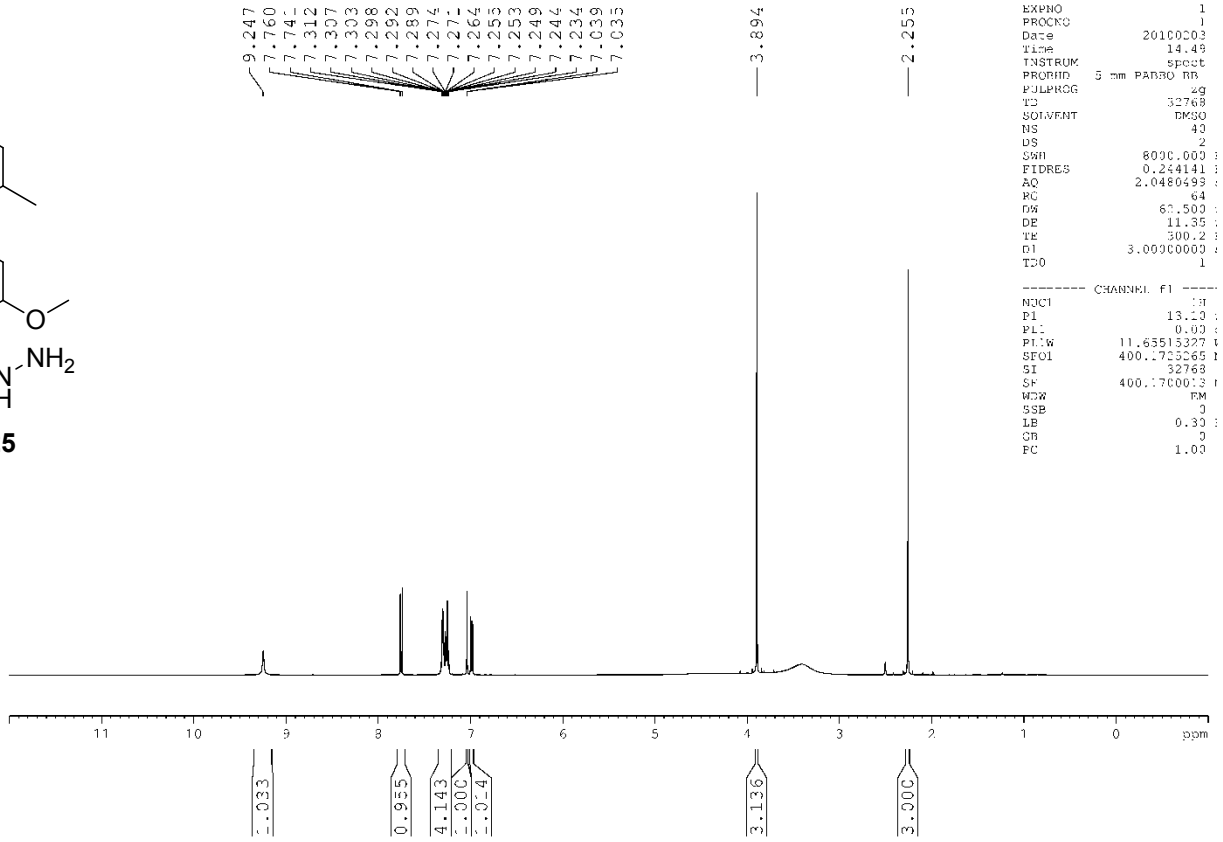
24

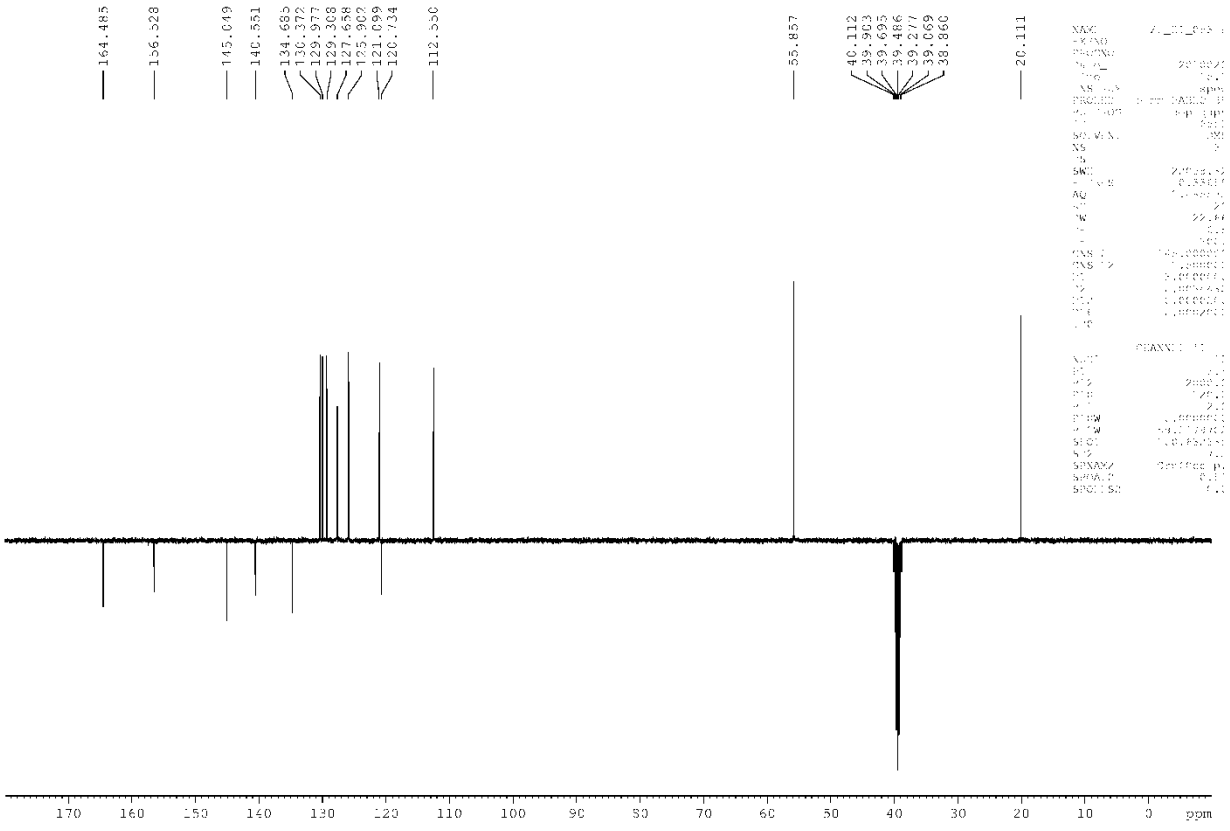

8.914
8.495
8.483
8.453
7.244
7.242
7.230
7.228
7.076
7.072
7.056
7.052
6.912
6.908
3.992
2.308
NAME zz_B2_008
Date_ 201102
Time 15.
INSTRUM spe
PROBHD 5 mm 5mm 1H/
PULPROG zg
TD 327
SOLVENT CDC
SWH 5597.0
FIDRES 0.1708
AQ 2.92732
RG 9
DW 89.3
DE 15.
TE 303
D1 5.000000
TDC
-------- CHANNEL f1 -
NUC1
P1 8.
PL1 4.
PL1W 5.980000
SFO1 400.13204
SI 327
SF 400.13001
WDW
SSB
LB 0.
GB
PC 1.
10
9
8
7
6
5
4
3
2
1
ppm
0.884
2.233
0.982
0.999
3.111
0.924
0.945
2.898
3.116

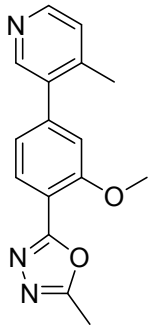

166.253
157.504
149.246
148.617
145.201
142.906
137.065
132.444
125.580
122.602
119.422
112.478
77.477
77.160
76.842
56.266
19.995
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O
NH2
N
H
O

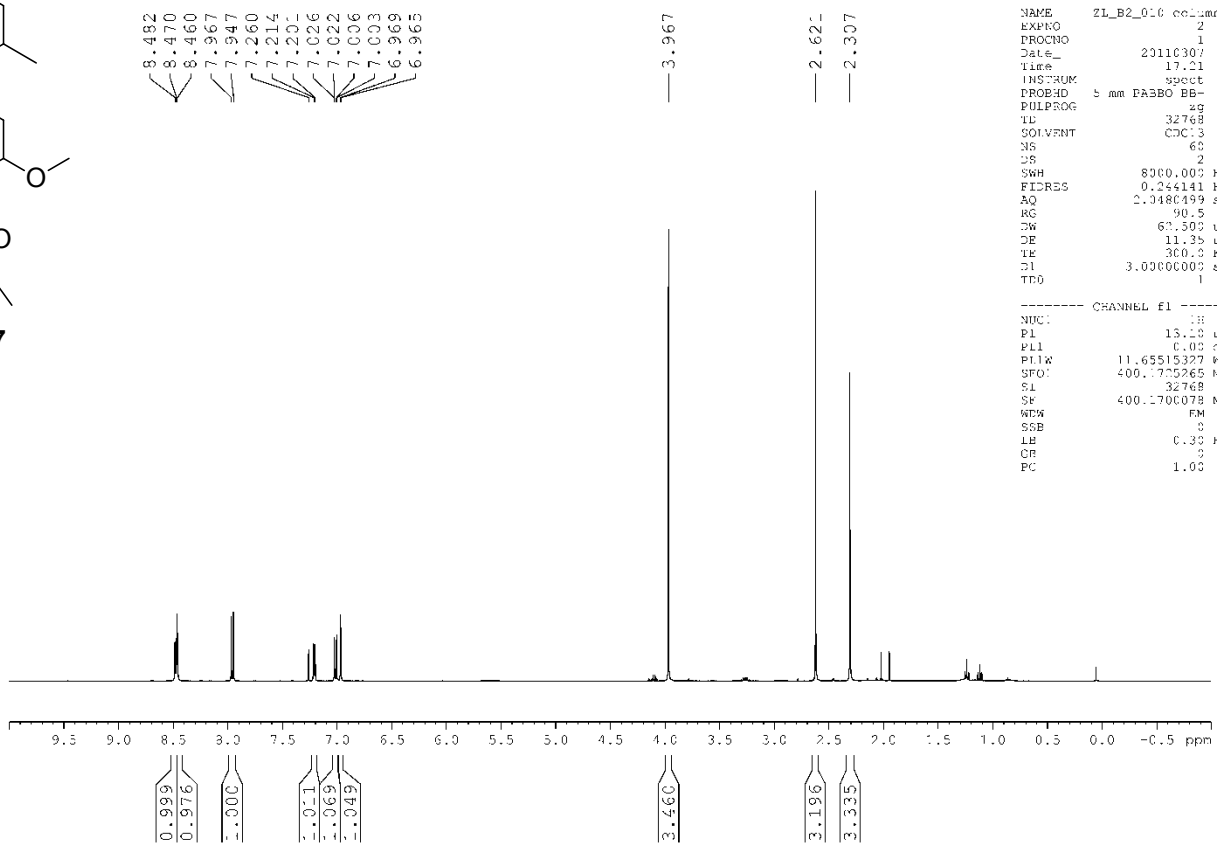
25

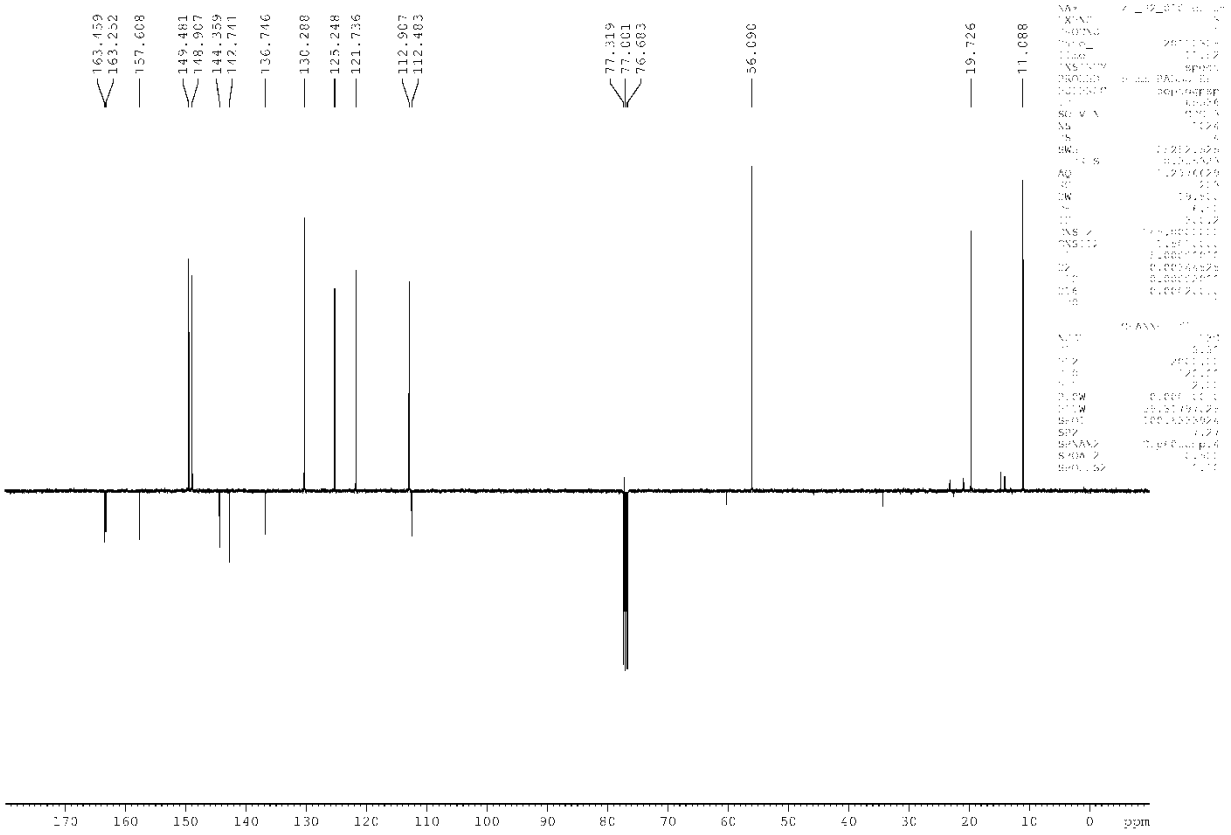

9.247
7.760
7.312
7.307
7.303
7.298
7.292
7.289
7.274
7.271
7.264
7.253
7.249
7.244
7.234
7.039
7.035
3.894
2.255
EXPNO 1
PROCNO 1
Date 20100203
Time 14.49
INSTRUM spect
PROBHD 5 mm PABBO BB
PULPROG zg
TD 32768
SOLVENT DMSO
NS 40
DS 2
SWH 8000.000
FIDRES 0.244141
AQ 2.0480493
RG 64
DW 62.500
DE 11.35
TE 300.2
D1 3.00000000
TD0 1
CHANNEL f1
NUC1 1H
P1 13.20
PLW 11.65513277
SFO1 400.1723265
SI 32768
SF 400.1700013
WDW EM
SSB 0
LB 0.30
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.033
0.955
4.143
1.000
1.014
3.136
3.000

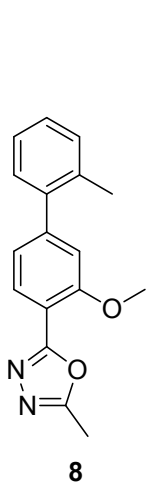

164.485
156.528
145.049
140.551
134.685
130.372
129.977
129.308
127.658
125.902
121.699
120.734
112.360
55.857
40.112
39.903
39.695
39.486
39.277
39.069
38.860
20.111
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



7

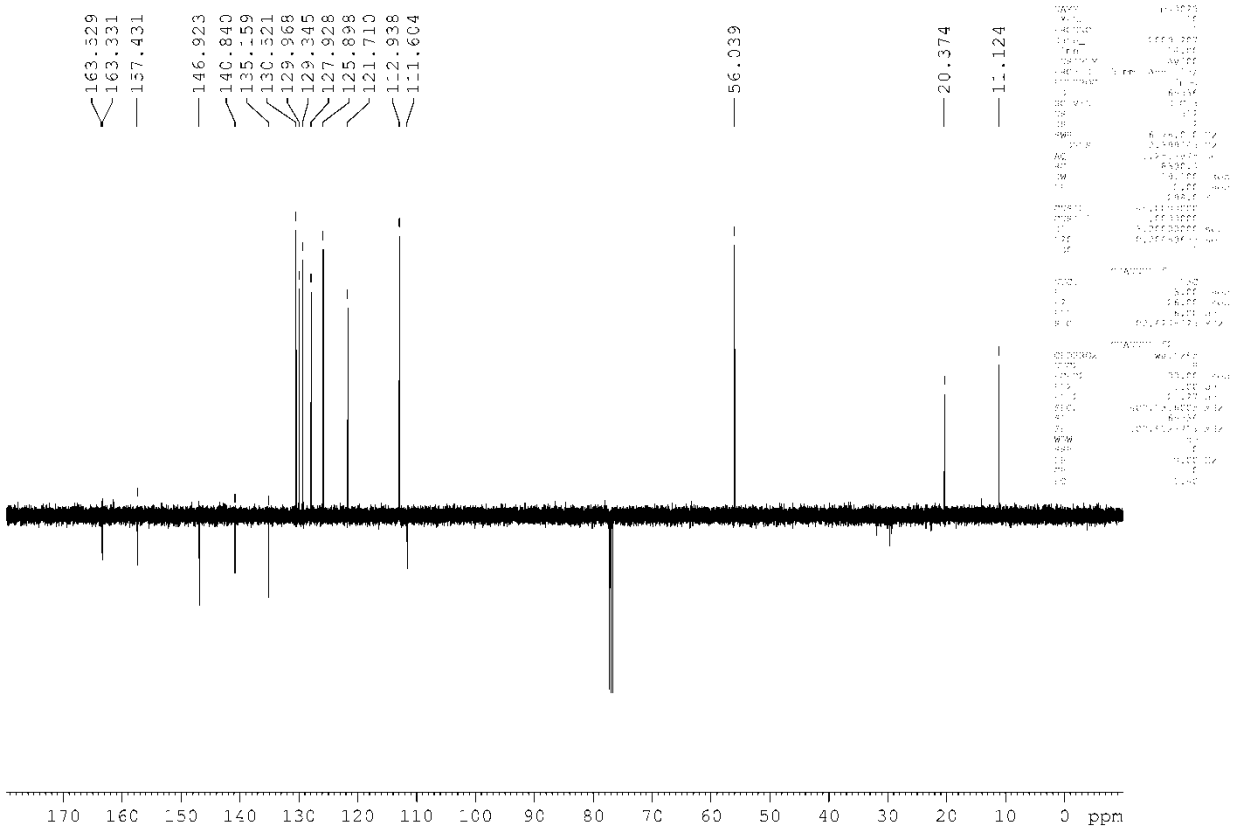

8.482
8.470
8.460
7.967
7.947
7.260
7.214
7.205
7.026
7.022
7.006
7.003
6.969
6.963
3.967
2.622
2.307
0.999
0.976
3.460
3.196
3.335
ppm

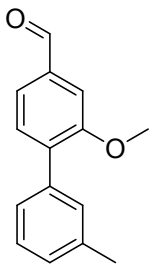

163.459
163.252
157.608
149.481
148.907
144.359
142.741
136.746
130.288
125.248
121.736
112.967
112.483
77.319
77.001
76.683
56.090
19.726
11.088
ppm



8

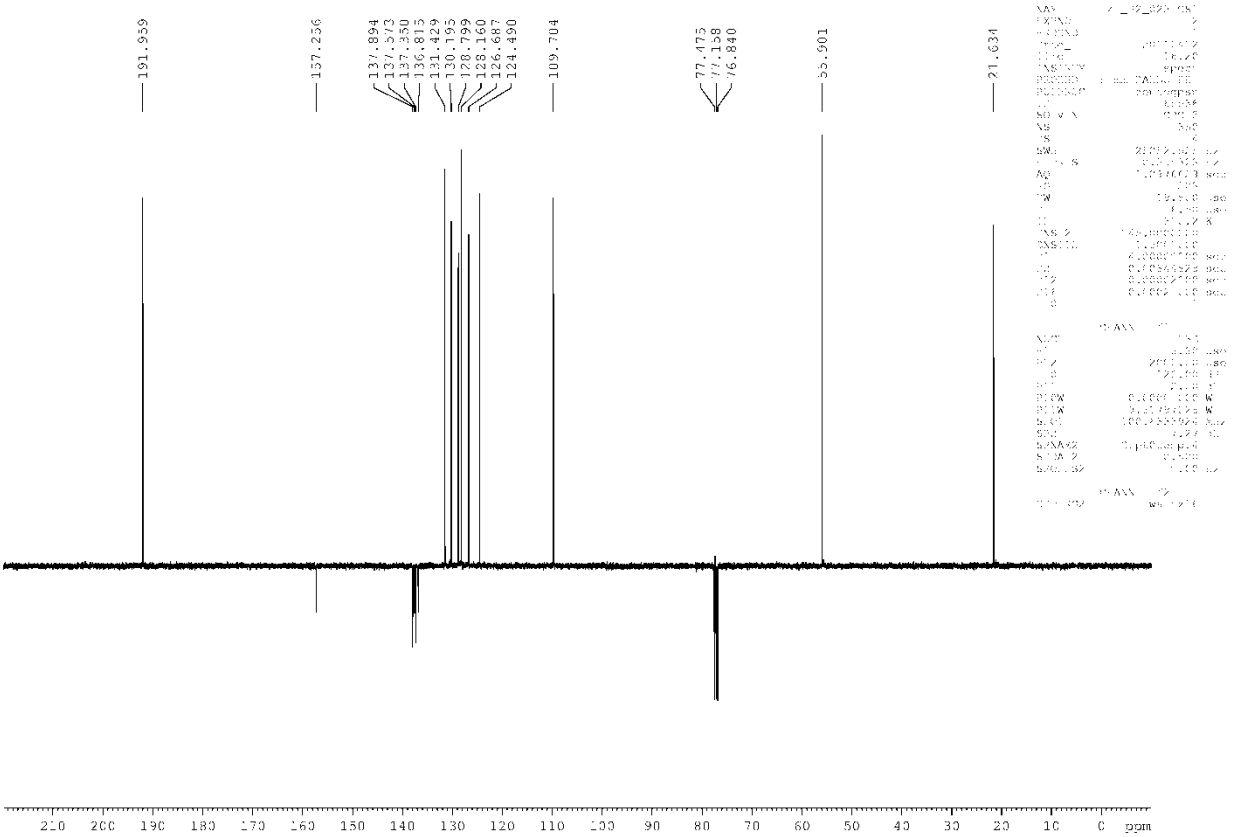
7.939
7.919
7.317
7.308
7.299
7.290
7.279
7.271
7.268
7.260
7.043
7.039
7.023
7.019
6.997
6.993
3.969
2.635
2.301
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm
0.962
2.063
1.393
1.042
1.177
2.996
3.000
3.171

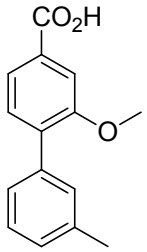

163.329
163.331
157.431
146.923
140.840
135.159
130.321
129.968
129.345
127.928
125.898
121.710
112.938
111.604
56.039
20.374
15.124
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



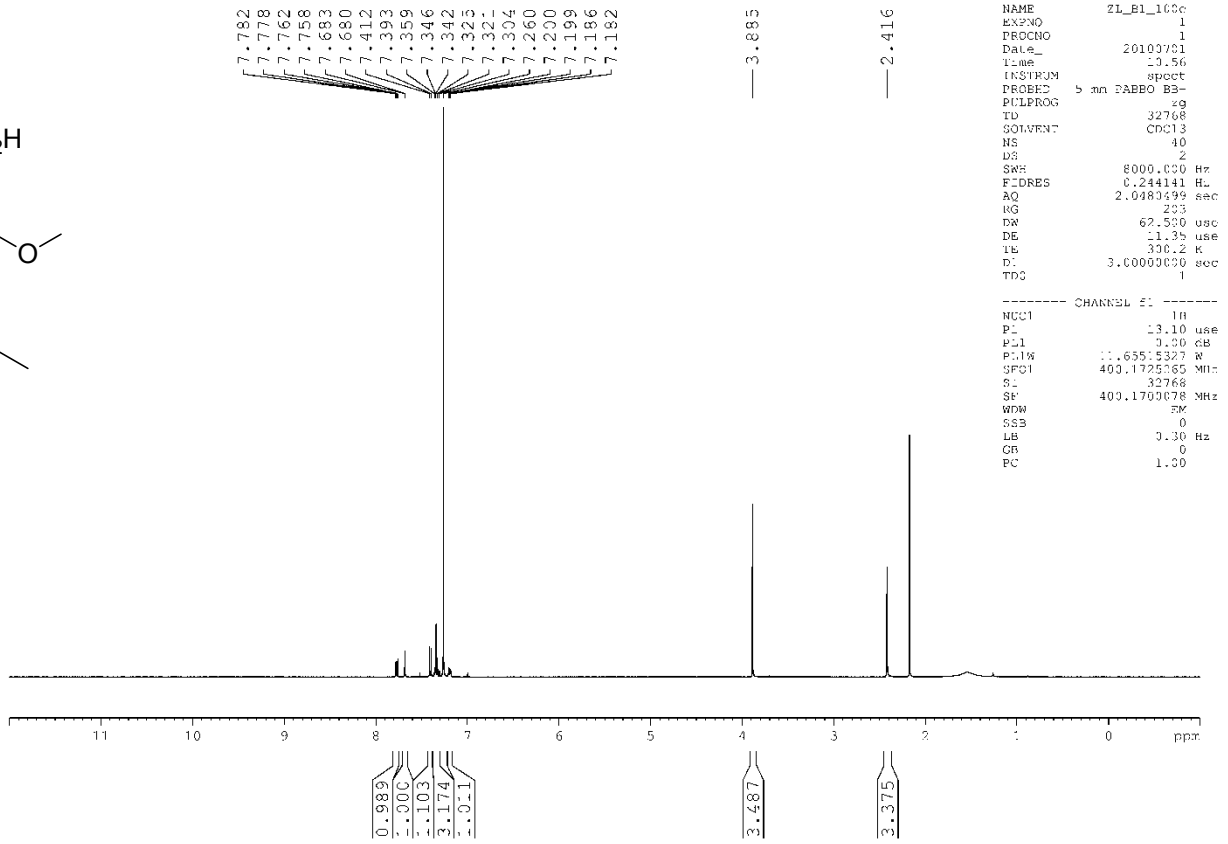
26

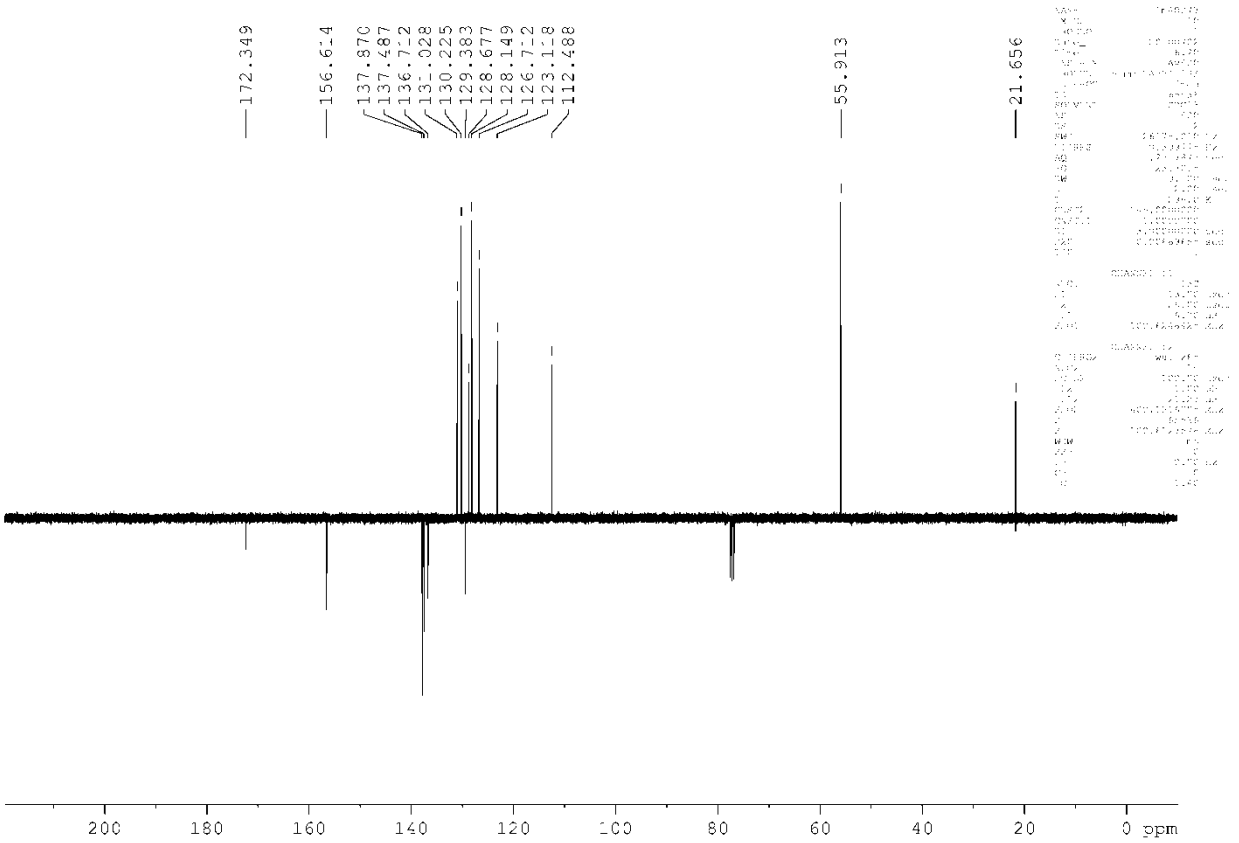
10.014
7.538
7.534
7.519
7.516
7.502
7.499
7.490
7.471
7.372
7.367
7.353
7.337
7.332
7.320
7.315
7.260
7.221
7.216
7.214
7.212
7.209
7.203
7.199
7.195
3.894
2.425
NAME 2L_B2_323 CS1
EXPNO 1
PROCNO 1
Date_ 20110412
Time 6.59
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 8000.000 Hz
FIDRES 0.244141 Hz
AQ 2.0480499 sec
RG 80.6
DW 62.500 usec
DE 11.35 usec
TE 300.2 K
D1 3.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
PLW1 11.65515327 W
SFO1 400.1725265 MHz
SI 32768
SF 400.1700076 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.984
3.442
3.274
3.006
3.881
3.581

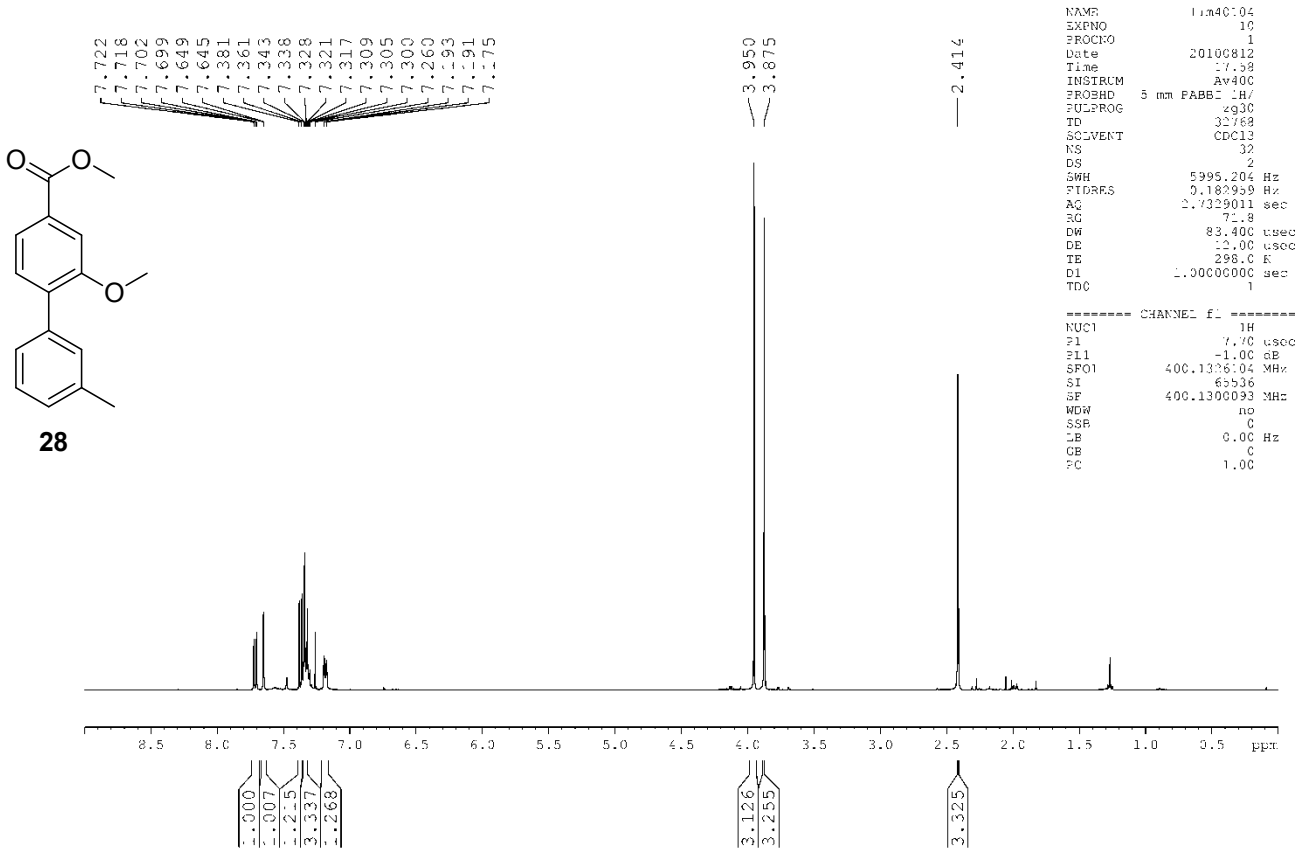

191.959
157.256
137.894
137.573
137.350
136.815
131.429
130.195
128.799
128.160
126.687
124.490
109.704
77.475
77.158
76.840
55.901
21.634
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


CO2H
O

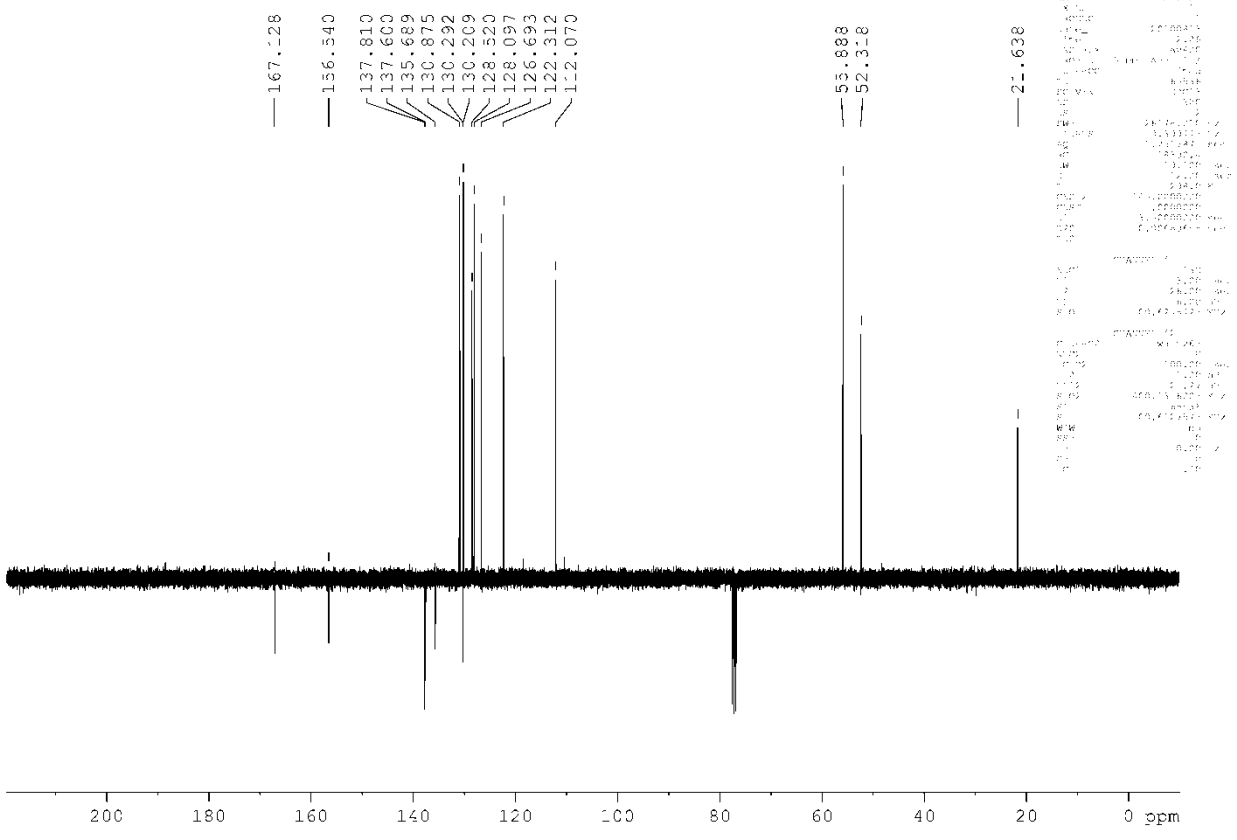
27

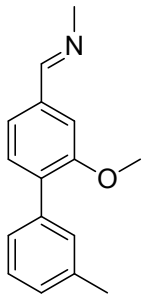

7.782
7.778
7.762
7.758
7.683
7.680
7.412
7.393
7.359
7.346
7.342
7.325
7.304
7.260
7.200
7.199
7.186
7.182
3.885
2.416
NAME ZL_B1_100c
EXPNO 1
PROCNO 1
Date_ 20100701
Time 10.56
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 8000.000 Hz
FIDRES 0.244141 Hz
AQ 2.0480499 sec
RG 203
DW 62.500 usec
DE 11.35 usec
TE 300.2 K
D1 3.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
PLW1 11.65515327 W
SFO1 400.1725065 MHz
SI 32768
SF 400.1700078 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.989
2.000
2.103
3.174
3.021
3.487
3.375


172.349
156.614
137.870
137.487
136.712
130.028
130.225
129.383
128.677
128.149
126.712
123.118
112.488
55.913
21.656
200 180 160 140 120 100 80 60 40 20 0 ppm

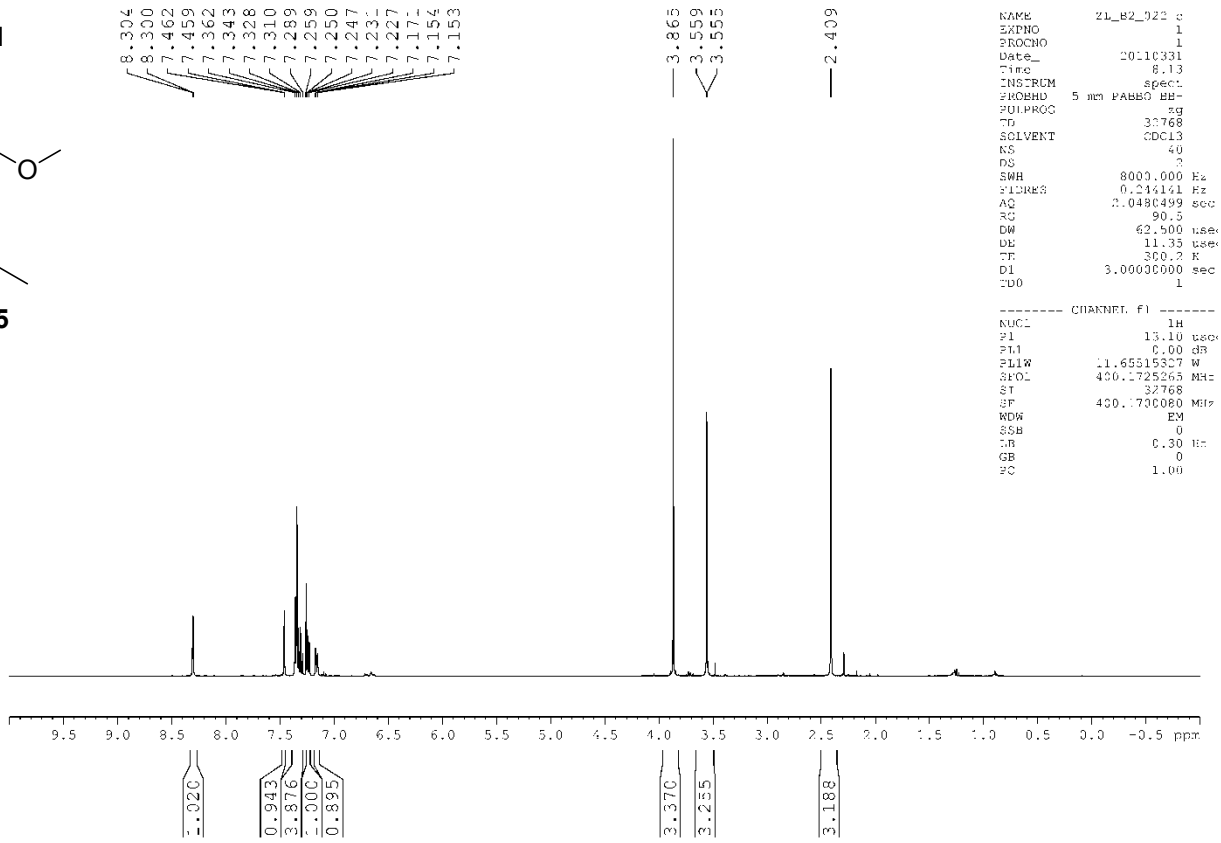

7.722
7.718
7.702
7.699
7.649
7.645
7.381
7.361
7.343
7.338
7.328
7.321
7.317
7.309
7.305
7.300
7.260
7.193
7.191
7.175
3.950
3.875
2.414
NAME tim40104
EXPNO 10
PROCNO 1
Date 20100812
Time 17.58
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 71.8
DW 83.400 usec
DE 12.00 usec
TE 298.0 K
D1 1.00000000 sec
TDC 1
======== CHANNEL f1 ========
NUC1 1H
P1 7.70 usec
PL1 -1.00 dB
SFO1 400.1336104 MHz
SI 65536
SF 400.1300093 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
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
1.000
1.007
2.215
3.337
2.268
3.126
3.255
3.325

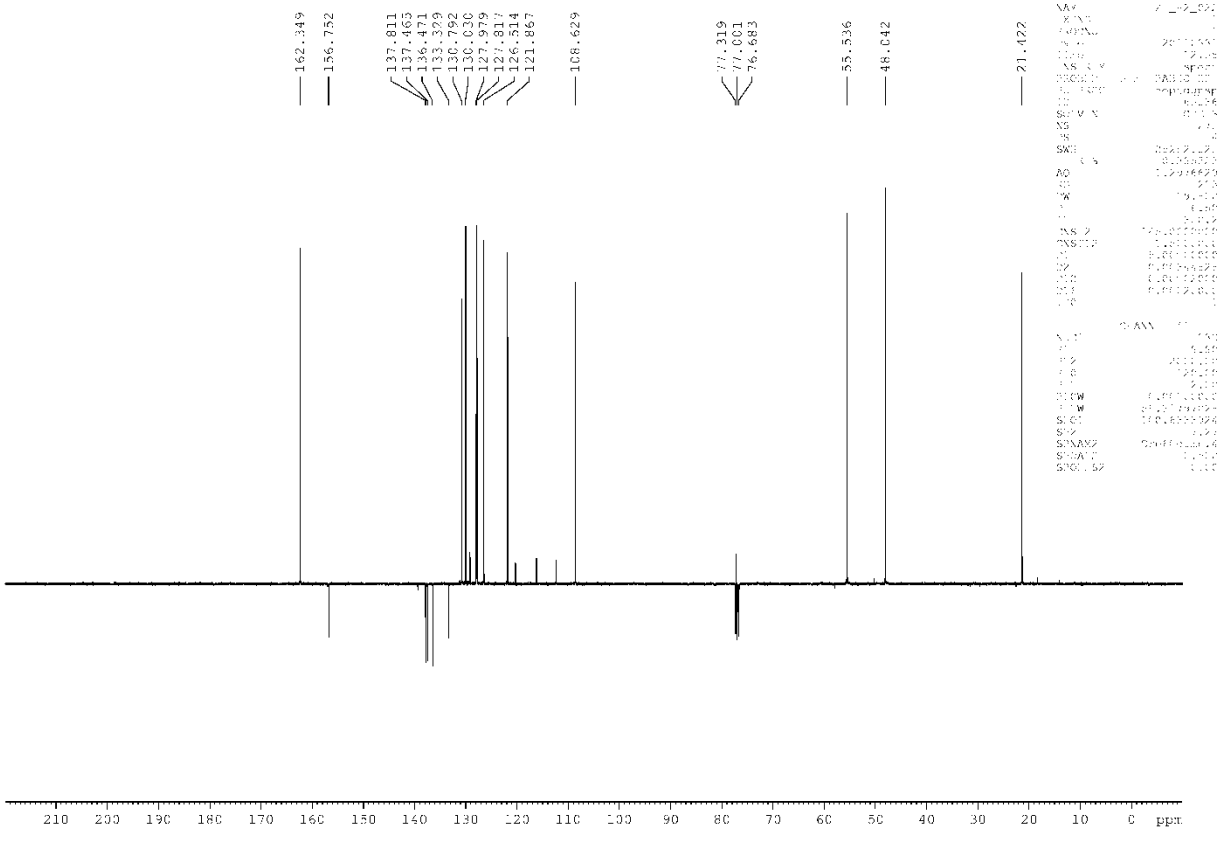
28

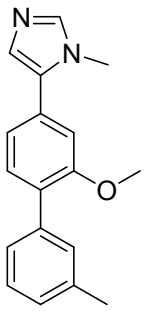

167.128
156.540
137.810
137.600
135.689
130.875
130.292
130.209
128.520
128.097
126.693
122.312
112.070
55.888
52.328
21.638
200
180
160
140
120
100
80
60
40
20
0 ppm



35


8.334
8.330
7.462
7.459
7.362
7.343
7.328
7.310
7.289
7.259
7.250
7.247
7.231
7.227
7.177
7.154
7.153
3.865
3.559
3.555
2.409
NAME ZL_B2_022 c
EXPNO 1
PROCNO 1
Date_ 20110331
Time 8.13
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 8000.000 Hz
FIDRES 0.244141 Hz
AQ 2.0480499 sec
RG 90.5
DW 62.500 use
DE 11.35 use
TE 300.2 K
D1 3.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 13.10 use
PL1 0.00 dB
PL1W 11.65515327 W
SFO1 400.1725265 MHz
SI 32768
SF 400.1700080 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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 0.0 -0.5 ppm
2.020
0.943
3.876
2.000
0.895
3.370
3.255
3.188


162.349
156.752
137.811
137.465
136.471
133.329
130.792
130.030
127.979
121.867
108.629
77.319
77.001
76.683
55.536
48.042
21.422
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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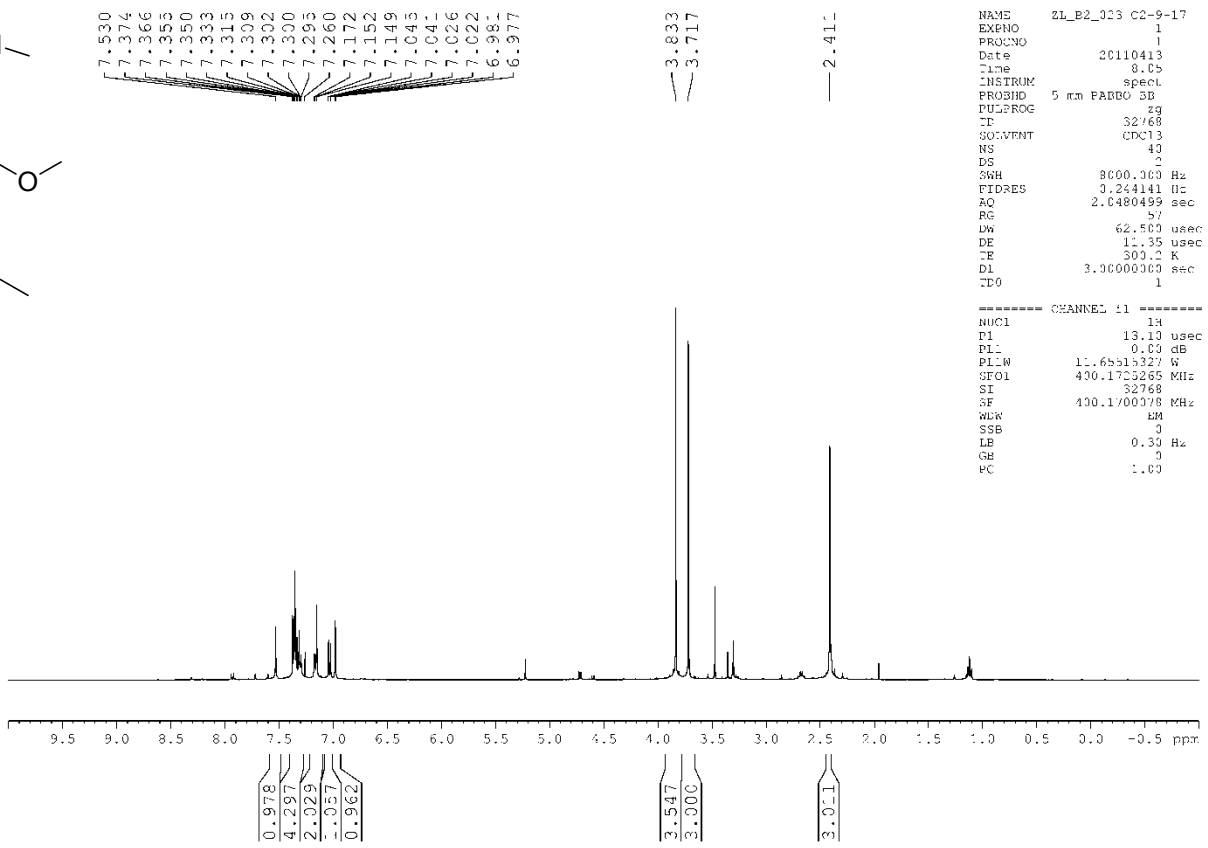
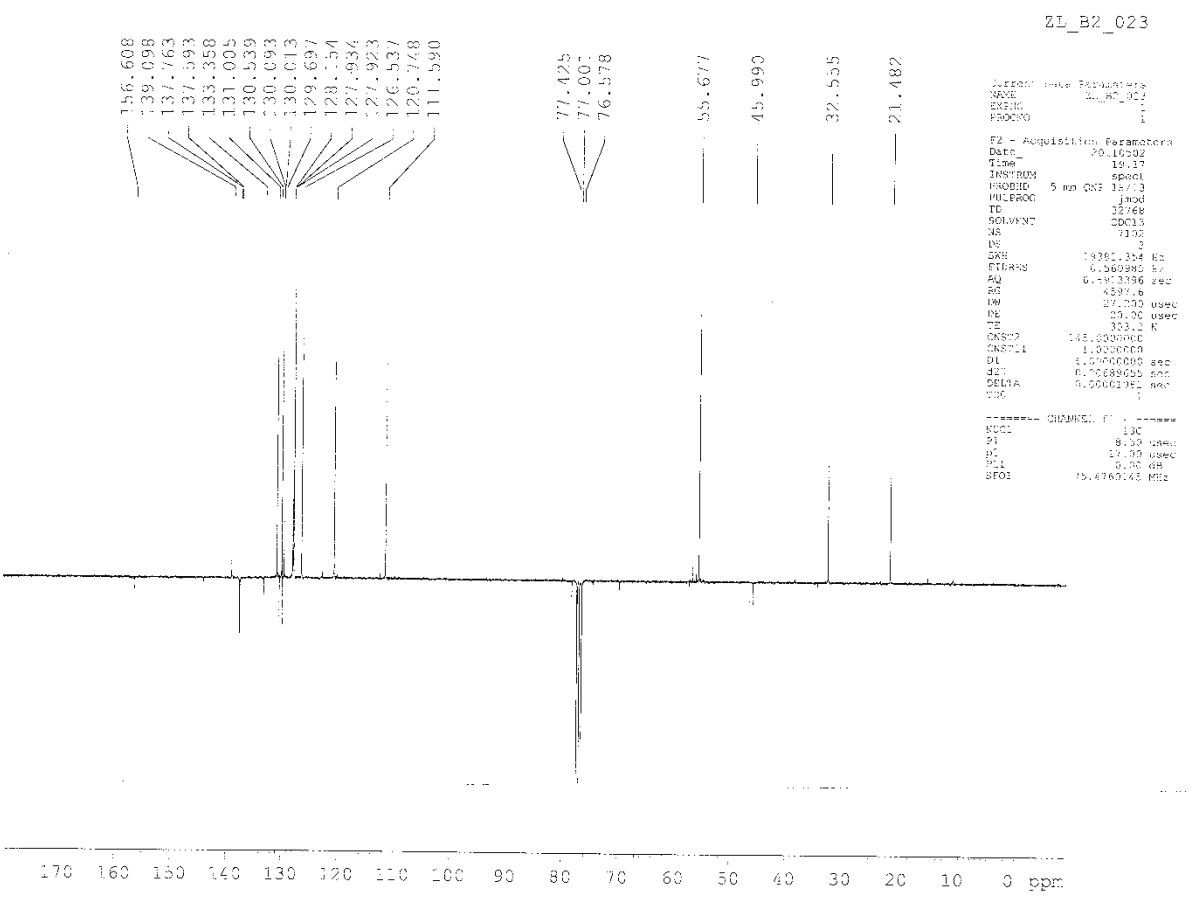
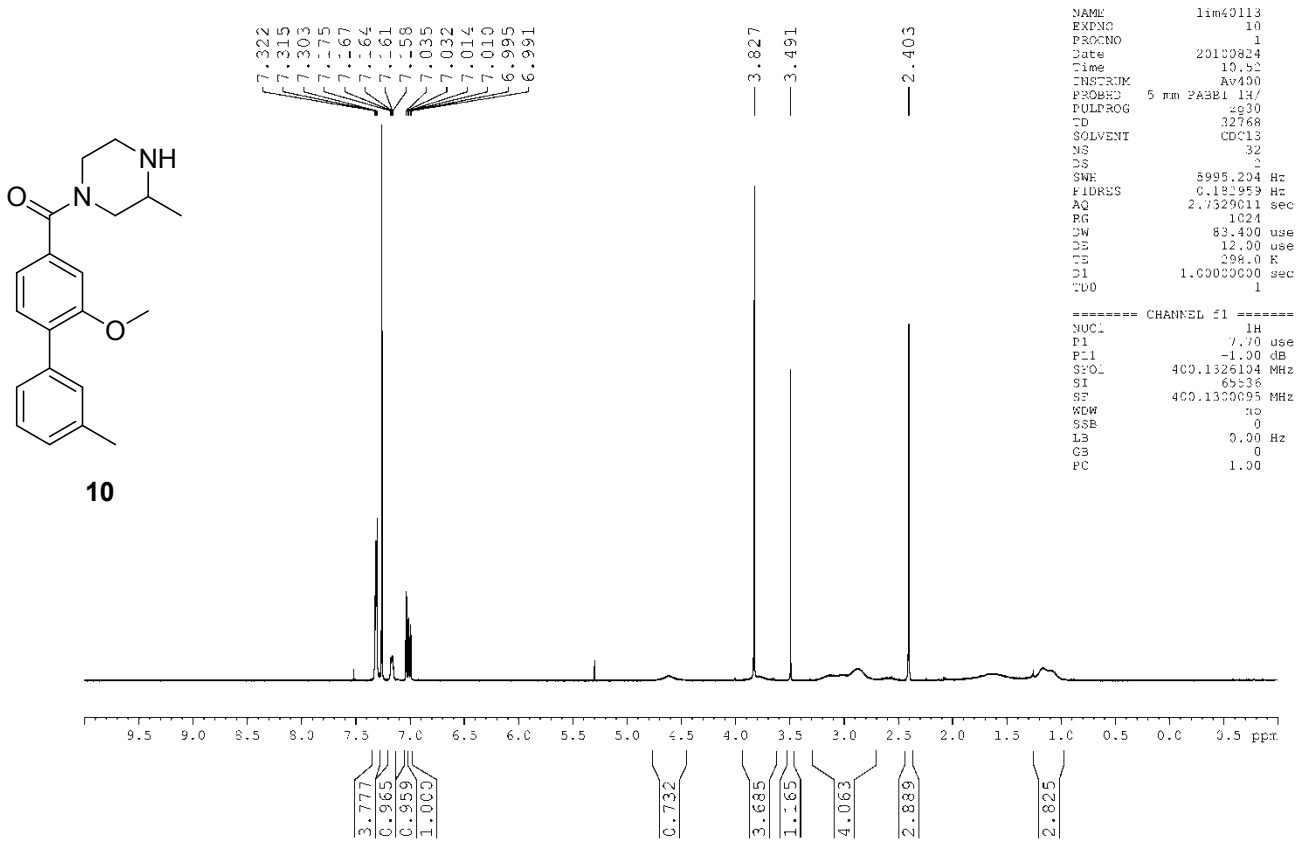
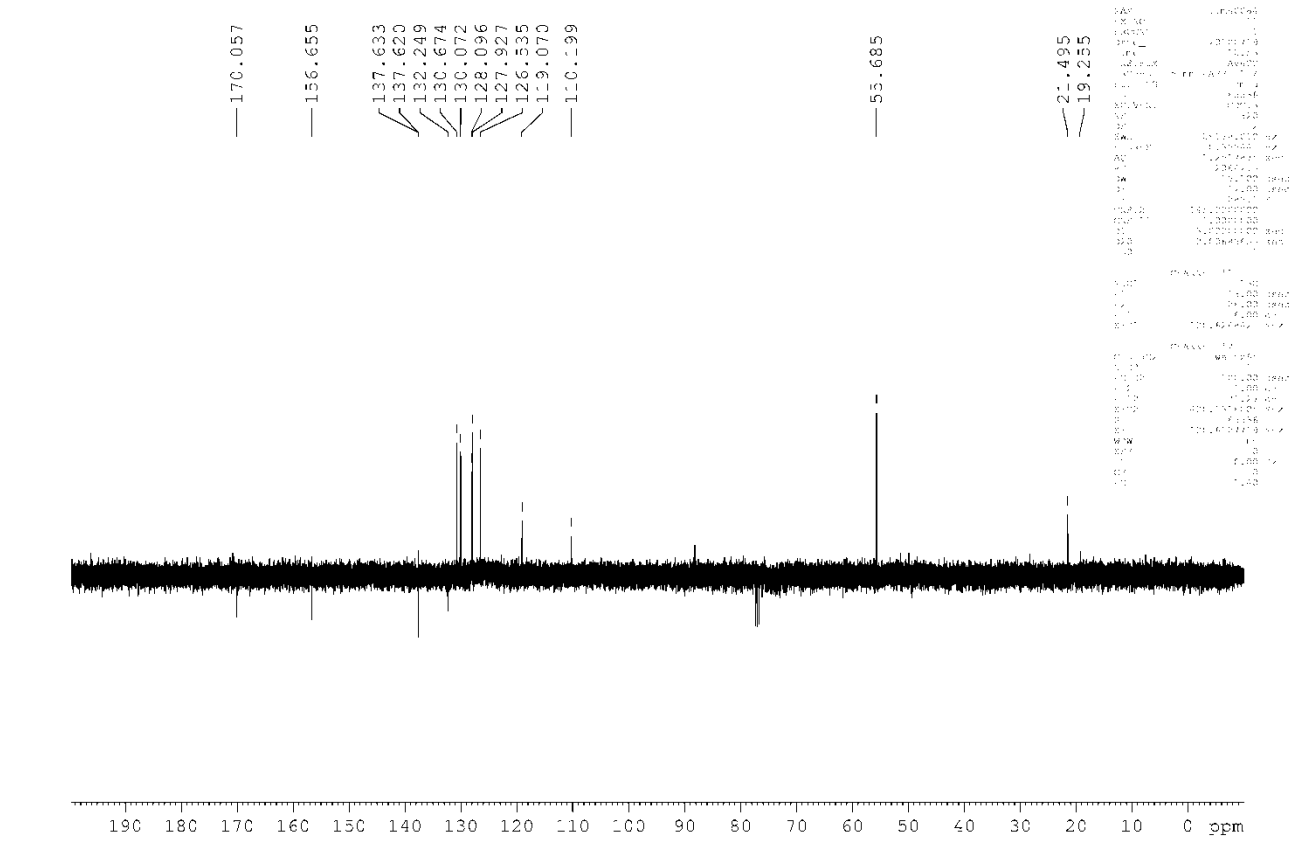
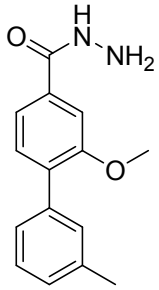

7.530
7.374
7.366
7.355
7.350
7.333
7.315
7.309
7.302
7.300
7.295
7.260
7.172
7.152
7.149
7.045
7.041
7.026
7.022
6.982
6.977
3.833
3.717
2.411
NAME ZL_B2_023 C2-9-17
EXPNO 1
PROCNO 1
Date 20110413
Time 8.05
INSTRUM spect
PROBHD 5 mm PABBO BB
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 8000.000 Hz
FIDRES 0.244141 Hz
AQ 2.0480499 sec
RG 57
DW 62.500 usec
DE 12.35 usec
TE 300.2 K
D1 3.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
PL1W 11.65515327 W
SFO1 400.1725265 MHz
SI 32768
SF 400.1700078 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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 0.0 -0.5 ppm
0.978
4.297
2.029
1.057
0.962
3.547
3.000
3.021


ZL_B2_023
156.608
139.098
137.763
137.393
133.358
131.005
130.539
130.093
130.013
129.697
128.154
127.934
127.923
126.537
120.748
111.590
77.425
77.007
76.578
55.677
49.990
32.555
21.482
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


NH
O
N
O
10
7.322
7.315
7.303
7.175
7.167
7.164
7.161
7.158
7.035
7.032
7.014
7.010
6.995
6.991
3.827
3.491
2.403
NAME lim40113
EXPNO 10
PROCNO 1
Date 20130824
Time 10.52
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 1024
DW 83.400 use
DE 12.00 use
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 =======
NUC1 1H
P1 7.70 use
PL1 -1.00 dB
SFO1 400.1326104 MHz
SI 65536
SF 400.1300095 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
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 0.0 -0.5 ppm
3.777
0.965
0.959
1.000
0.732
3.685
1.265
4.063
2.889
2.825


170.057
156.655
137.633
137.620
132.249
130.674
130.072
128.096
127.927
126.535
119.070
110.199
55.685
21.495
19.255
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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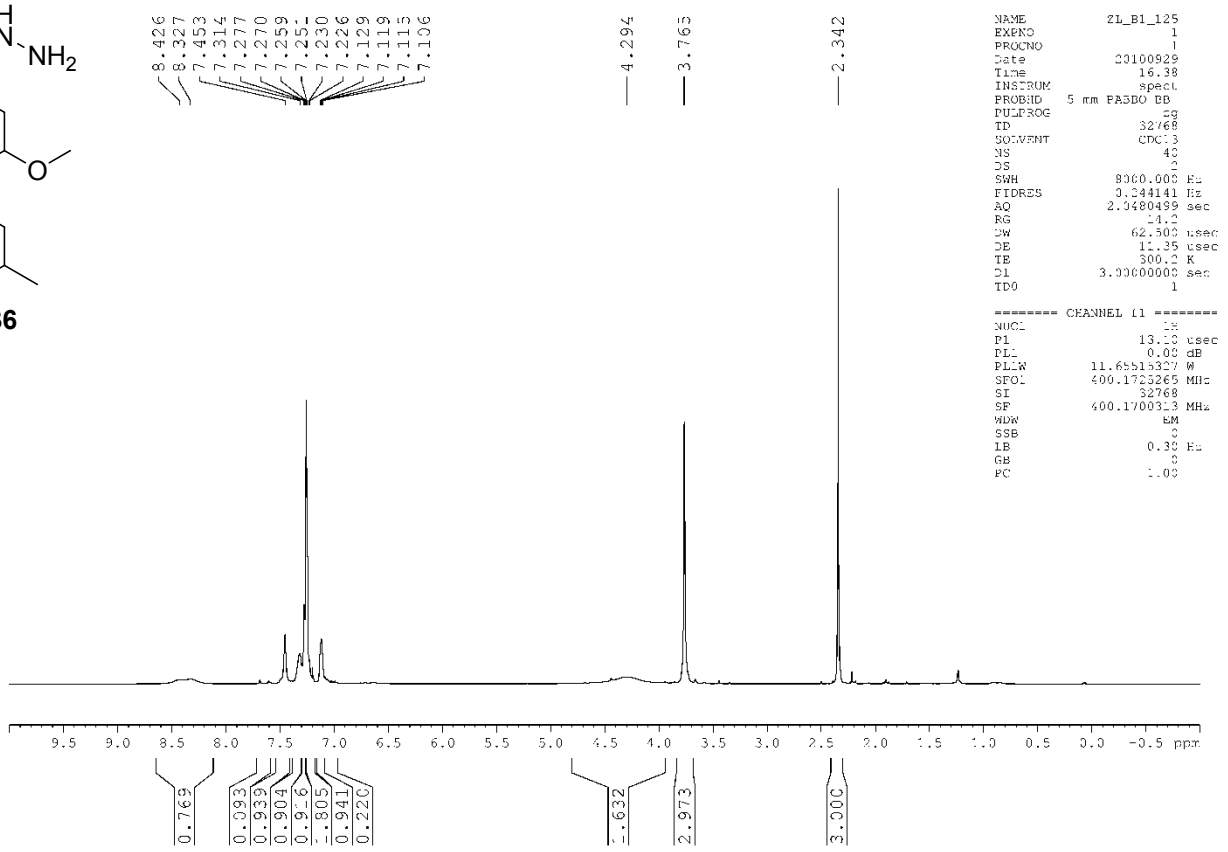
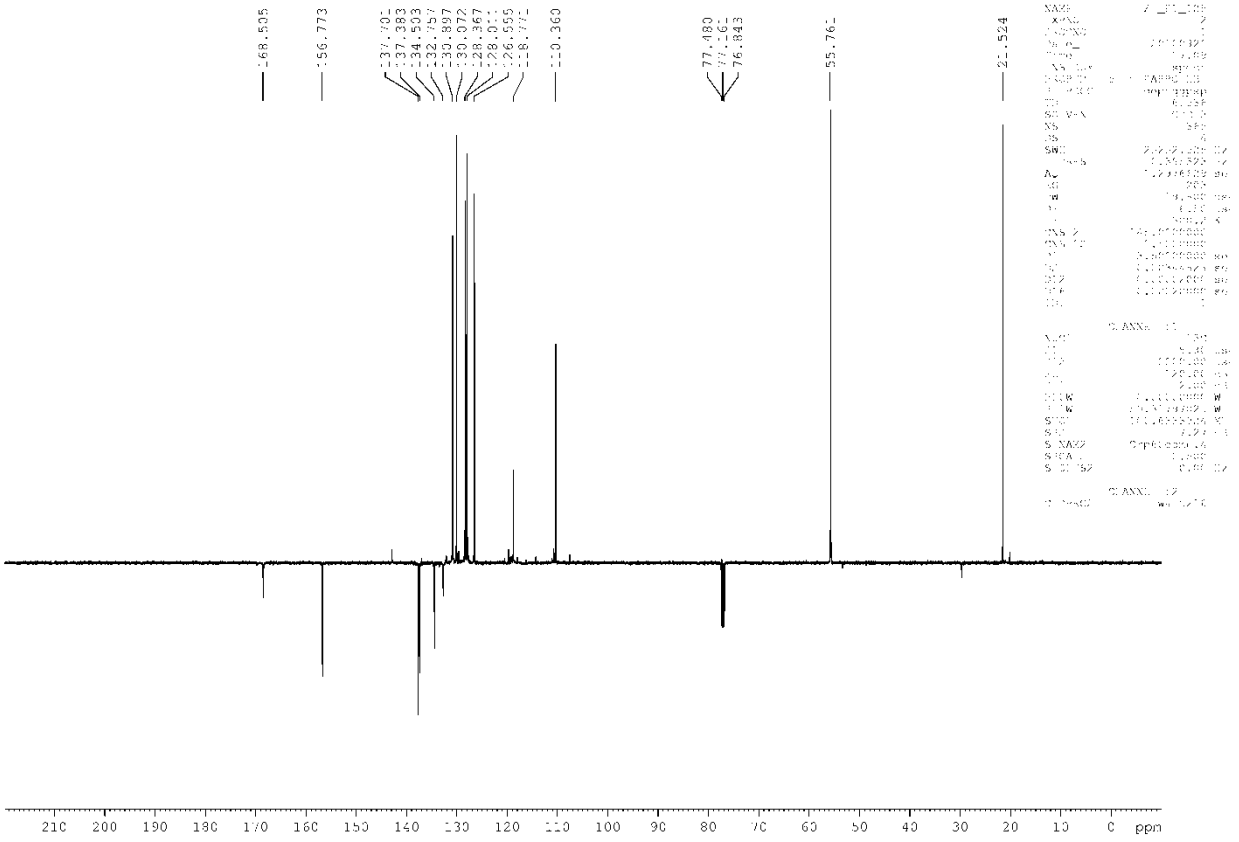
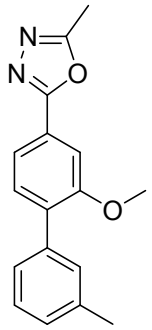
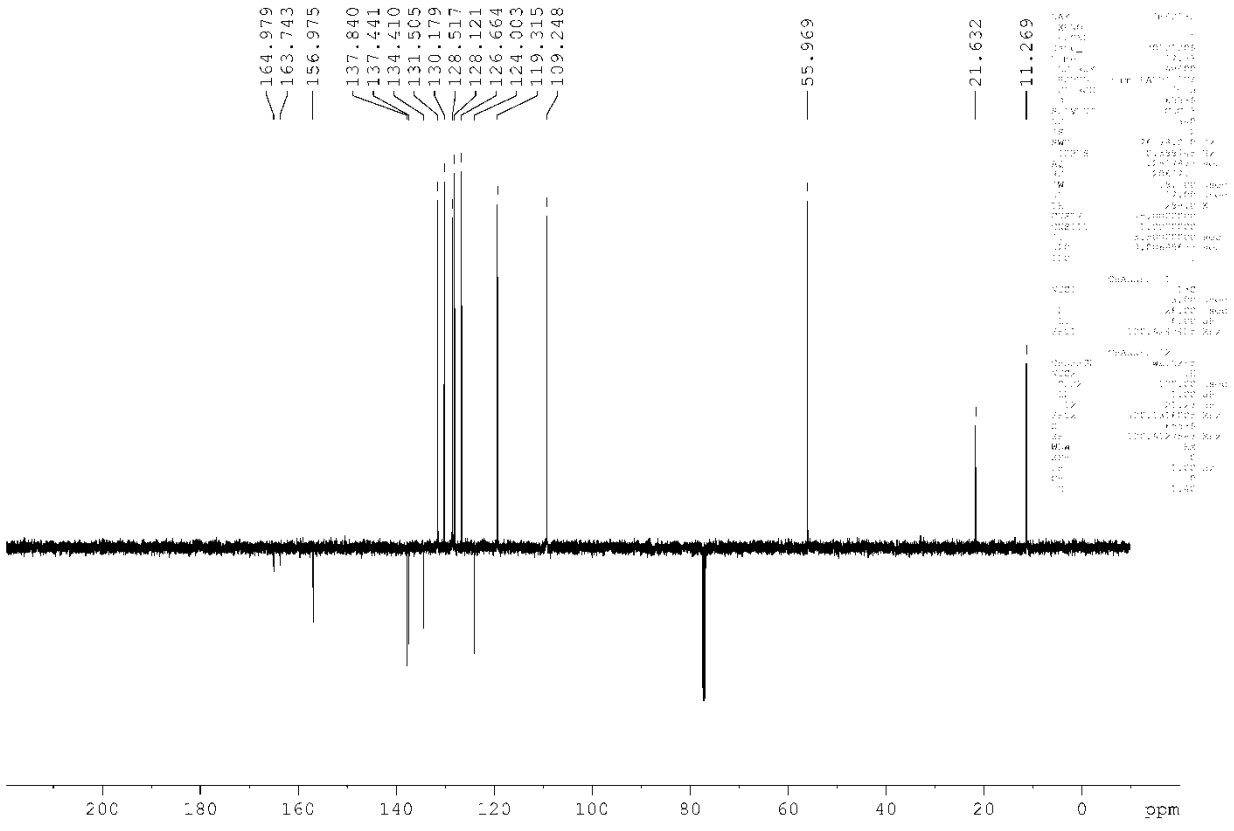

8.426
8.327
7.453
7.314
7.277
7.270
7.259
7.251
7.230
7.226
7.129
7.119
7.115
7.106
4.294
3.765
2.342
NAME ZL_B1_125
EXPNO 1
PROCNO 1
Date 20100929
Time 16.38
INSTRUM spect
PROBHD 5 mm PABBO BB
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 40
DS 2
SWH 8000.000 Hz
FIDRES 0.244141 Hz
AQ 2.0480499 sec
RG 14.2
DW 62.500 usec
DE 11.35 usec
TE 300.2 K
D1 3.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.10 usec
PL1 0.00 dB
PL1W 11.65515327 W
SFO1 400.1725265 MHz
SI 32768
SF 400.1700313 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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 0.0 -0.5 ppm
0.769
0.093
0.939
0.904
0.916
1.805
0.941
0.220
1.632
2.973
3.000


168.535
156.773
137.701
137.383
134.503
132.757
130.897
130.372
128.867
128.011
126.555
118.772
110.360
77.480
77.161
76.843
55.761
21.524
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



11

7.656
7.634
7.630
7.431
7.412
7.370
7.366
7.353
7.343
7.325
7.309
7.304
7.194
7.177
3.902
2.638
2.416
NAME 11m40135
EXPNO 10
PROCNO 1
Date 20101006
Time 12.23
INSTRUM Av400
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 32
DS 2
SWH 5995.204 H
FIDRES 0.182959 H
AQ 2.7329011 s
RG 71.8
DW 83.400 u
DE 12.00 u
TE 298.0 K
D1 1.00000000 s
TD0 1
======== CHANNEL f1 =====
NUC1 1H
P1 7.70 u
PL1 -1.00 d
SFO1 400.1326104 M
SI 65536
SF 400.1300093 M
WDW EM
SSB 0
LB 0.10 H
GB 0
PC 1.00
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
1.943
1.000
3.034
0.969
3.085
3.024
3.040


164.979
163.743
156.975
137.840
137.441
134.410
131.505
130.179
128.517
128.121
126.664
124.003
119.315
109.248
55.969
21.632
11.269
200 180 160 140 120 100 80 60 40 20 0 ppm

S4: NOESY NMR Spectra

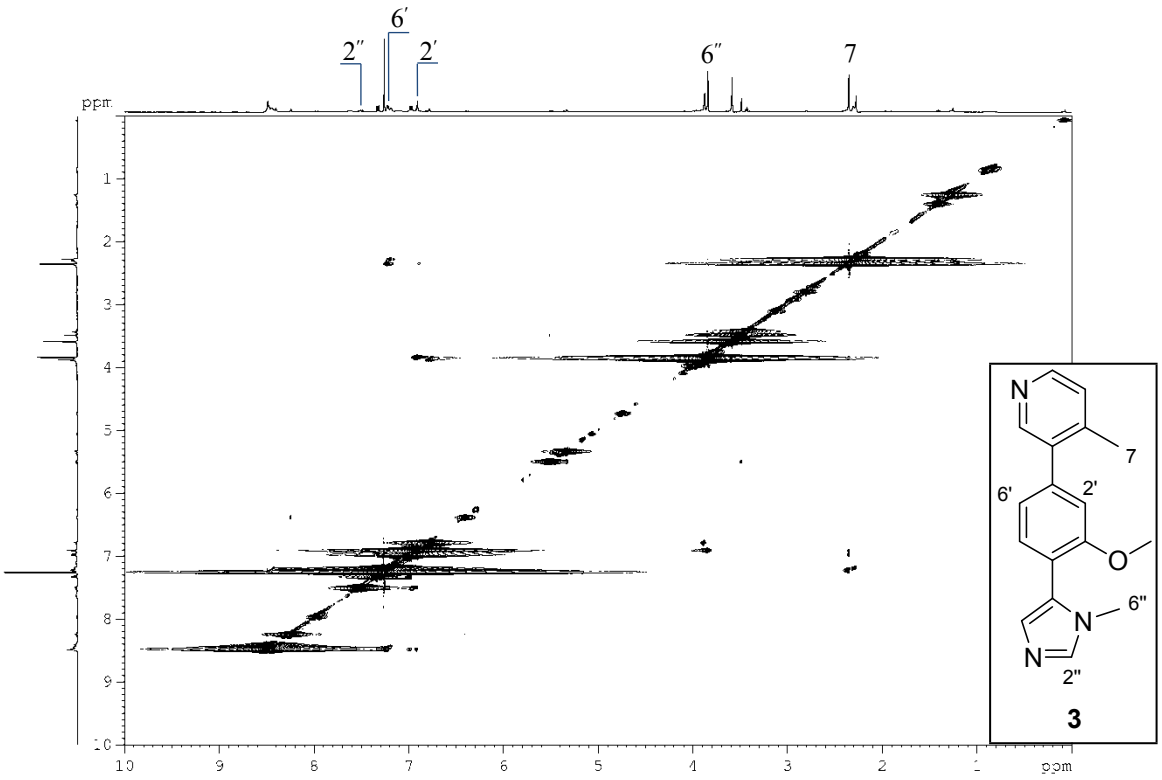


Figure S4.1: NOESY NMR spectrum of the pyridyl-phenyl-imidazole **3**.

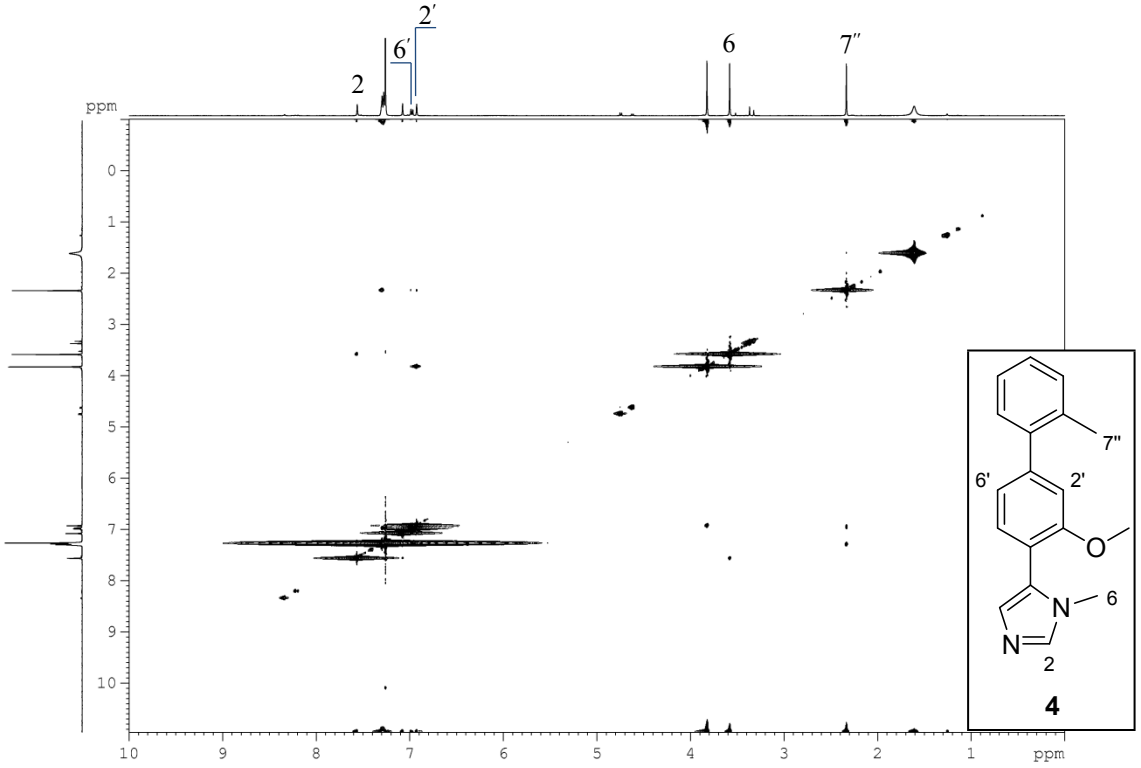


Figure S4.2: NOESY NMR spectrum of the phenyl-phenyl-imidazole **4**.

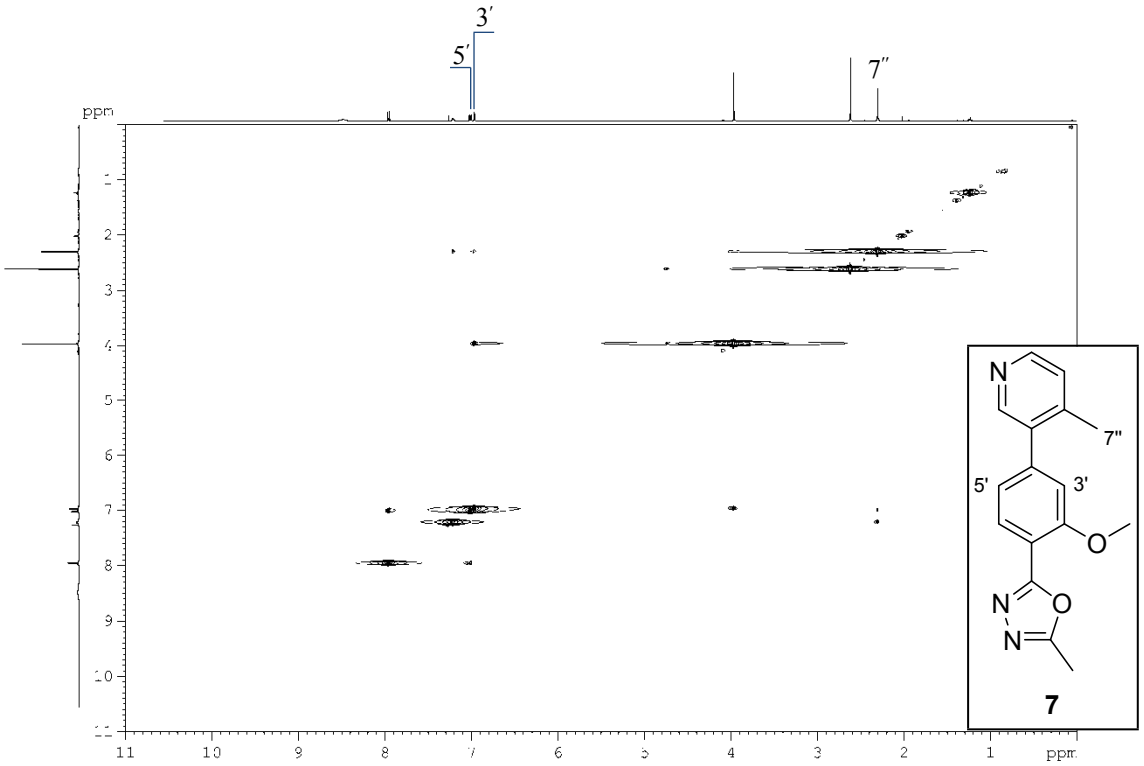


Figure S4.3: NOESY NMR spectrum of the pyridyl-phenyl-oxadiazole **7**.

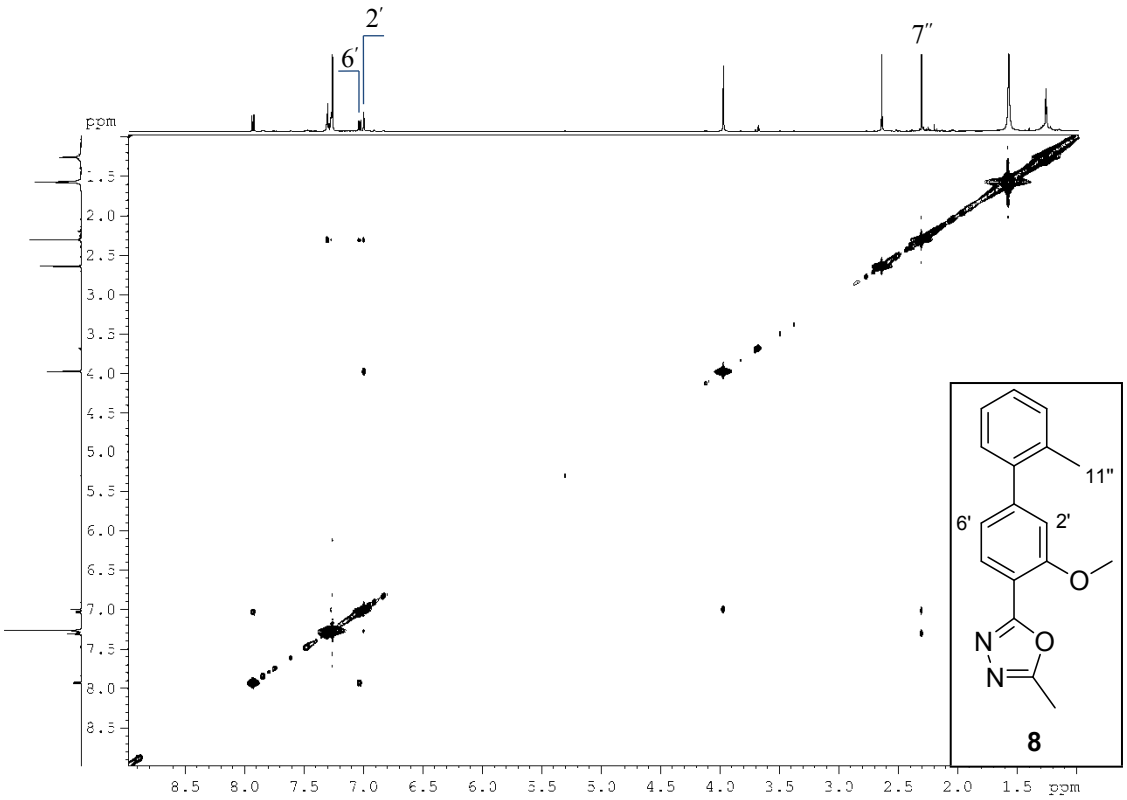


Figure S4.4: NOESY NMR spectrum of the phenyl-phenyl-oxadiazole **8**.

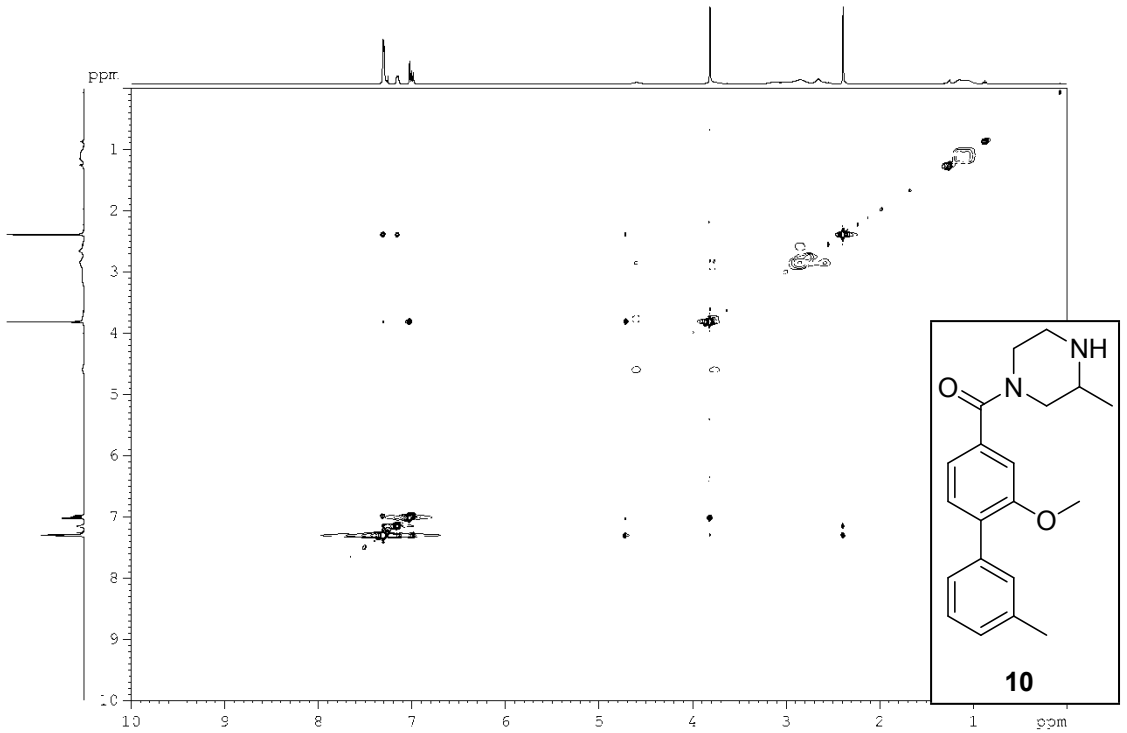
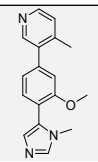
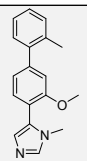
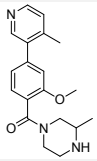
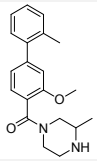
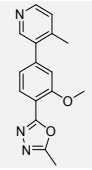
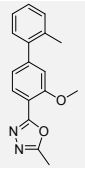
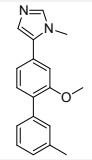
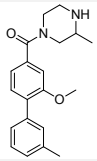
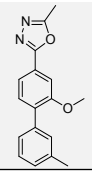
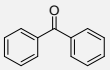


Figure S4.5: NOESY NMR spectrum of the piperazine-phenyl-phenyl **10**.

S5: Aqueous Solubility Summary

Table S5: Aqueous Solubility Summary.

Compound	Structure	Solubility	Compound	Structure	Solubility
3		> 500 µg/mL (1.8 mM)	**4**		169 µg/mL (0.6 mM)
5		> 500 µg/mL (1.5 mM)	**6**		> 500 µg/mL (1.8 mM)
7		> 500 µg/mL (1.8 mM)	**8**		> 500 µg/mL (1.8 mM)
9		104 µg/mL (0.4 mM)	**10**		> 500 µg/mL (1.5 mM)
11		> 500 µg/mL (1.8 mM)	**Reference Standard**		146 µg/mL (0.8 mM)

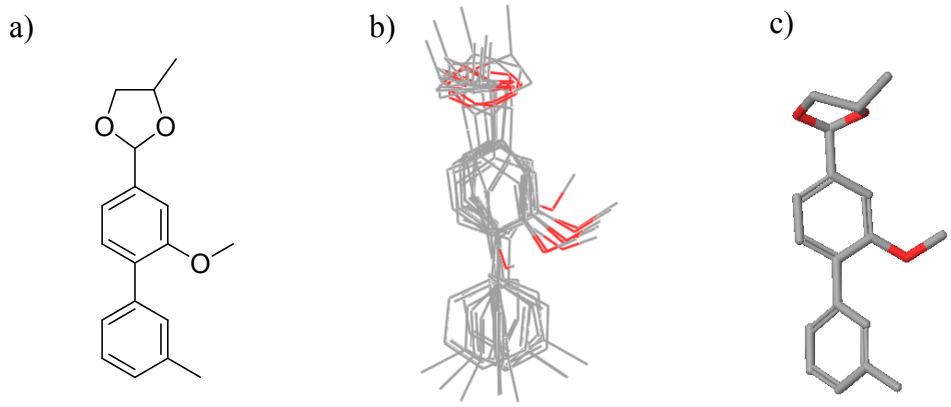


Figure S1.1: Unsuitable dioxolane-phenyl-phenyl structure: a) Schematic of the dioxolane-phenyl-phenyl scaffold; b) low energy conformers determined by MM conformational search; c) *ab initio* optimised low energy conformer.

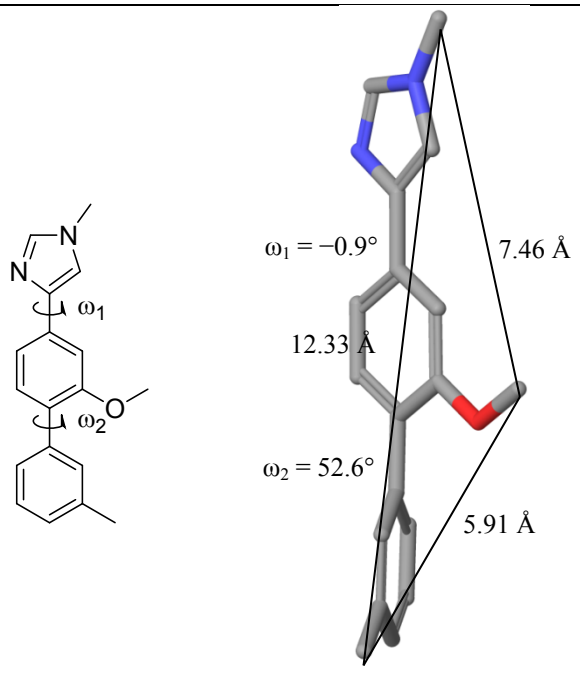


Figure S1.4: Unsuitable 1,3-imidazole-phenyl-phenyl structure.

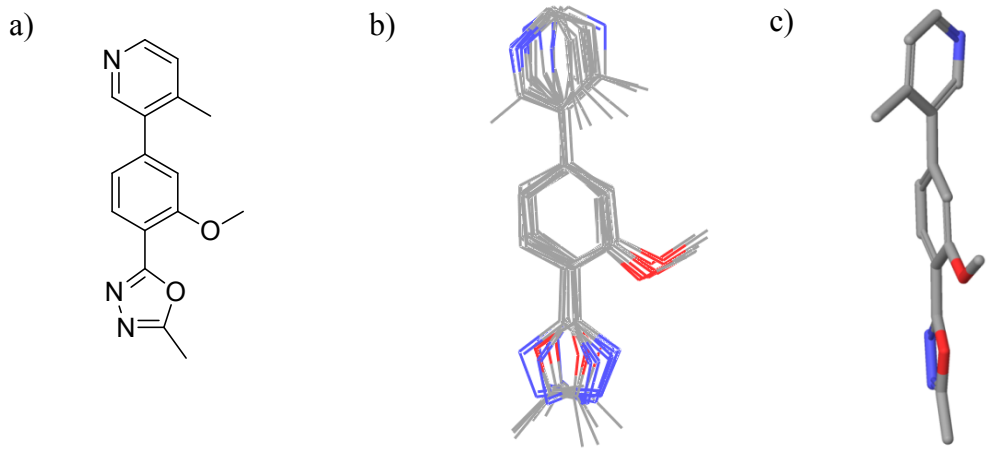


Figure S1.5: Suitable pyridyl-phenyl-oxadiazole structure: a) Schematic of the pyridyl-phenyl-oxadiazole scaffold; b) low energy conformers determined by MM conformational search; c) *ab initio* optimised low energy conformer.

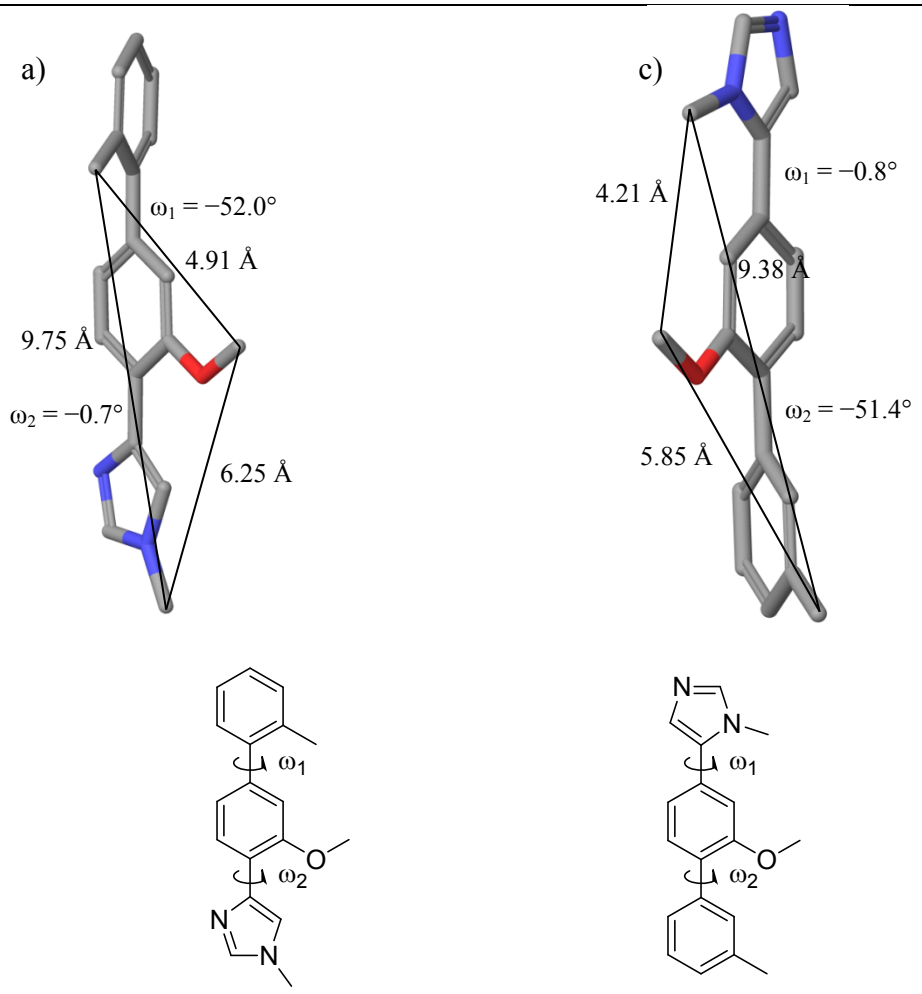


Figure S1.6: Suitable phenyl imidazole structures: a) phenyl-phenyl-1,4-imidazole scaffold; b) 1,5-imidazole-phenyl-phenyl scaffold.