

Synthetic studies towards aryl-(4-aryl-4*H*-[1,2,4]triazole-3-yl)-amine from 1,3-diarylthiourea as urea mimetics

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michael_chorev@hms.harvard.edu

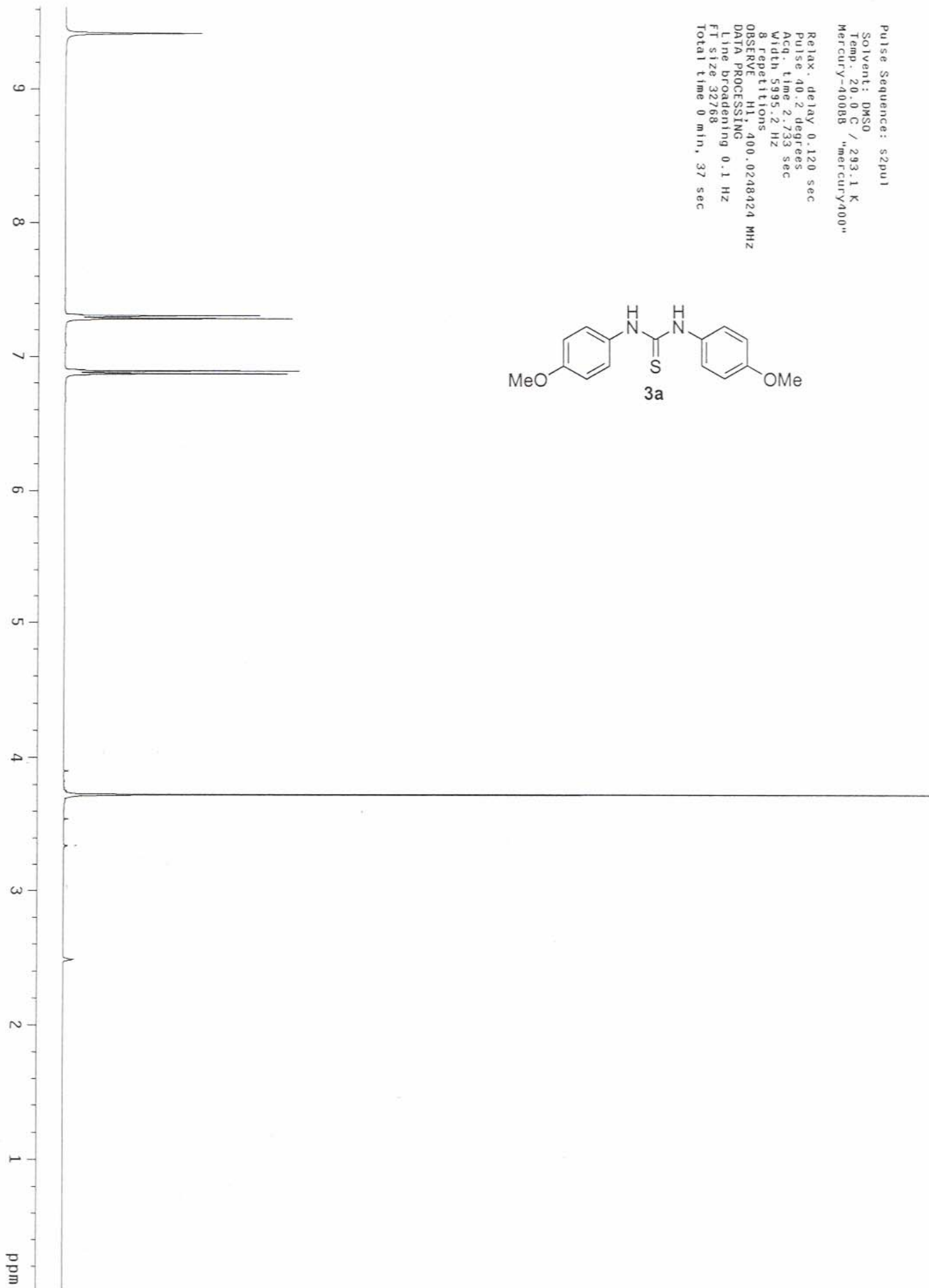
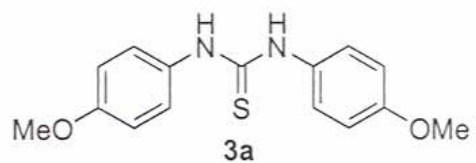
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Pulse Sequence: s2pu1
Solvent: DMSO
Temp. 20.0 C / 293.1 K
Mercury-400BB "mercury400"

Relax. delay 0.120 sec
Pulse 40.2 degrees
Acq. time 2.733 sec
Width 5995.2 Hz
8 repetitions
OBSERVE H1, 400.0248424 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 37 sec



13C OBSERVE

Pulse Sequence: s2pul

Solvent: DMSO

Temp. 22.0 C / 295.1 K

Mercury-400BB "mercury400"

Pulse 42.5 degrees

Acq. time 1.311 sec

Width 25000.0 Hz

Reference

OBSERVE C13, 100.5863026 MHz

DECUPLE H1, 400.0268647 MHz

Power 48 dB

continuously on

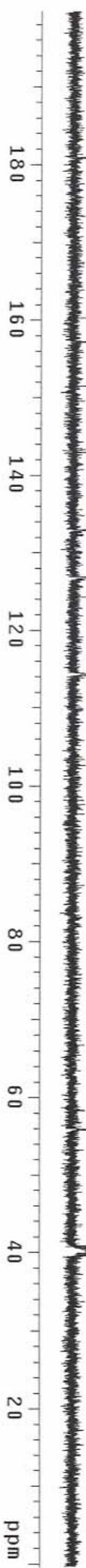
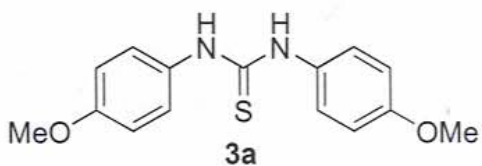
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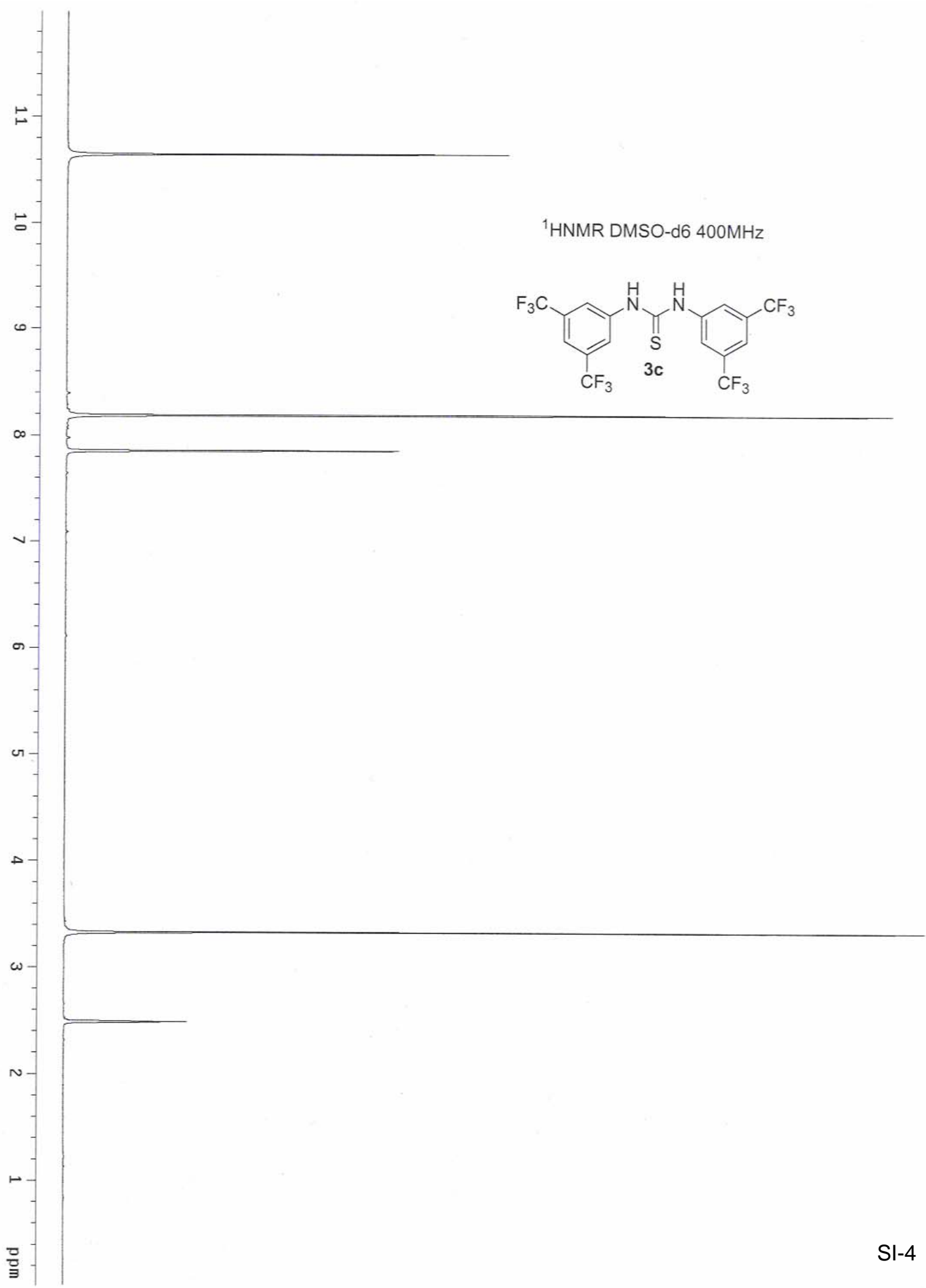
DATA PROCESSING

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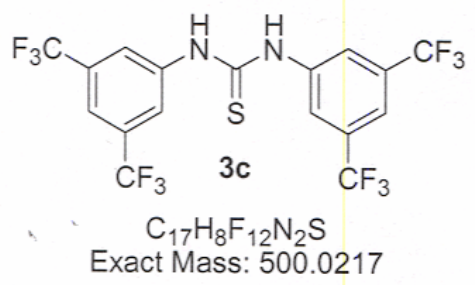
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Total time 5 min, 2 sec





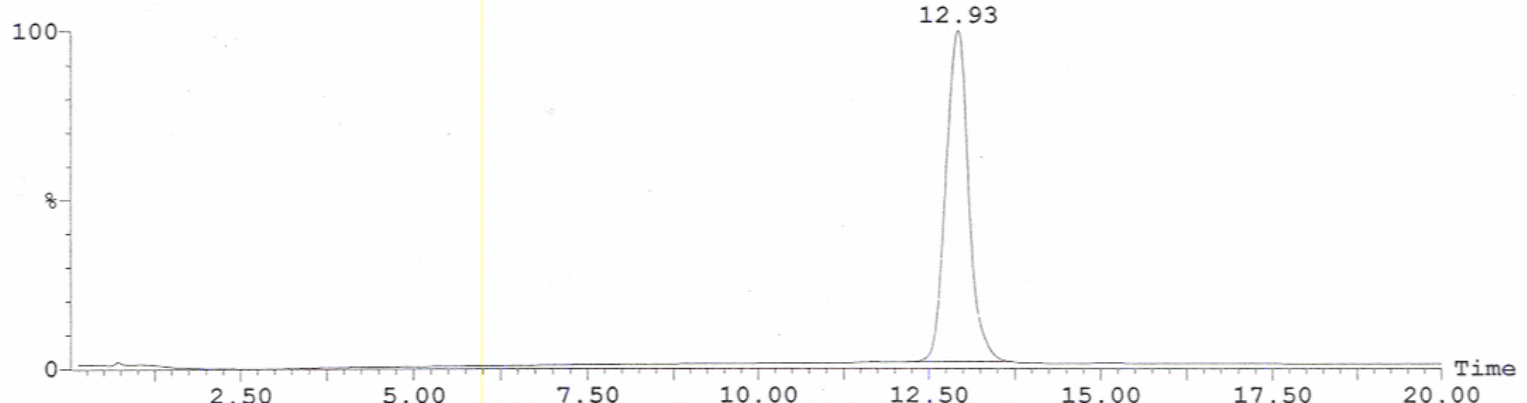
LC - Xterra C18 5 μ M 3.0 \times 100.0 mm column
 APCI positive MS



Solvent A Solvent B	Water Acetonitrile	
Time	% A	% B
0	95	5
15	5	95
20	5	95

DAD: TIC Smooth (Mn, 2x1)

6.1e+007

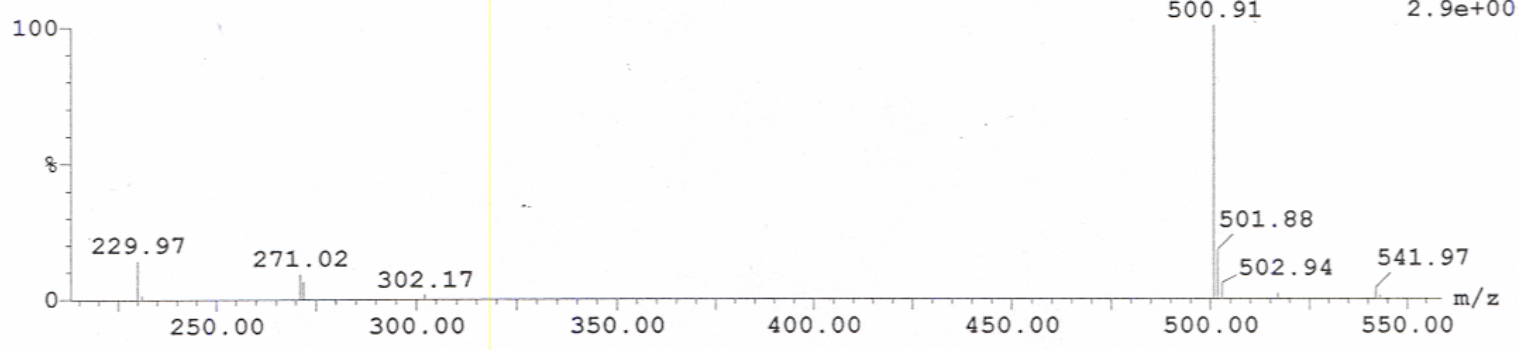


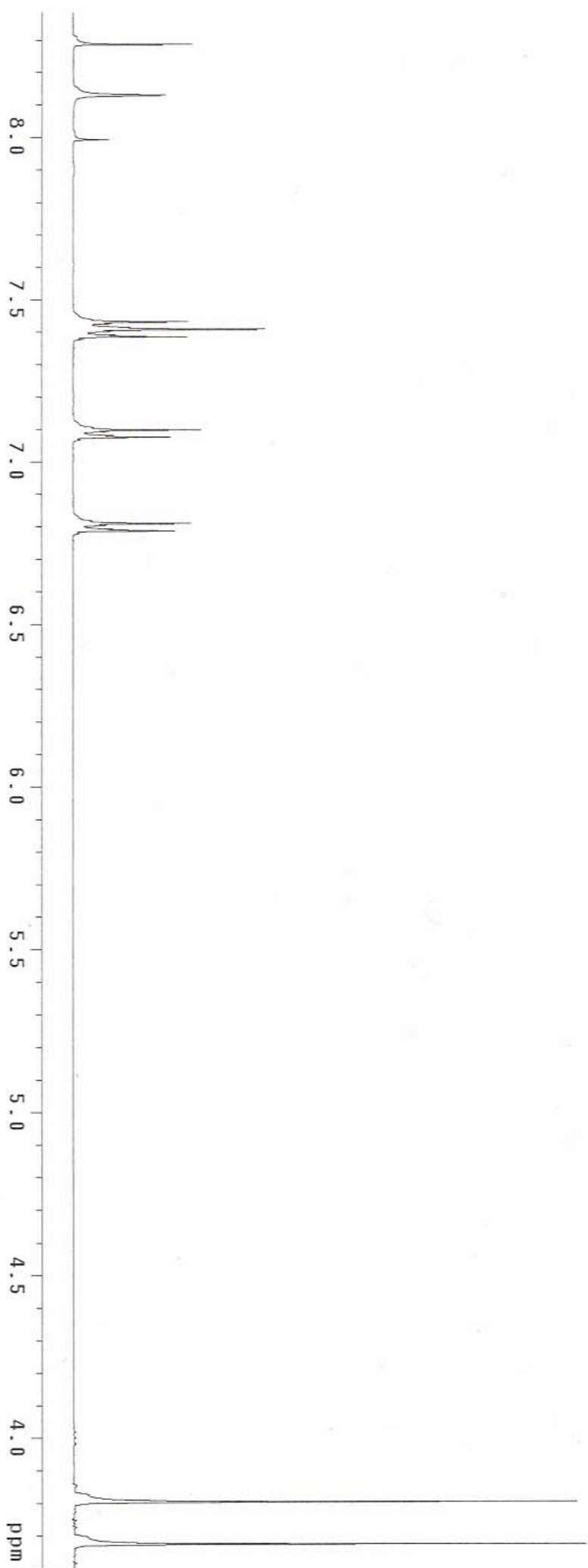
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
3		12.93	2e+007	100.00	2	6e+007	

Peak ID Compound Time Mass Found
 3 12.95

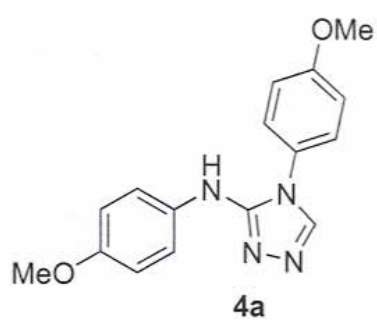
Combine (484:488-(473:474+498:499))

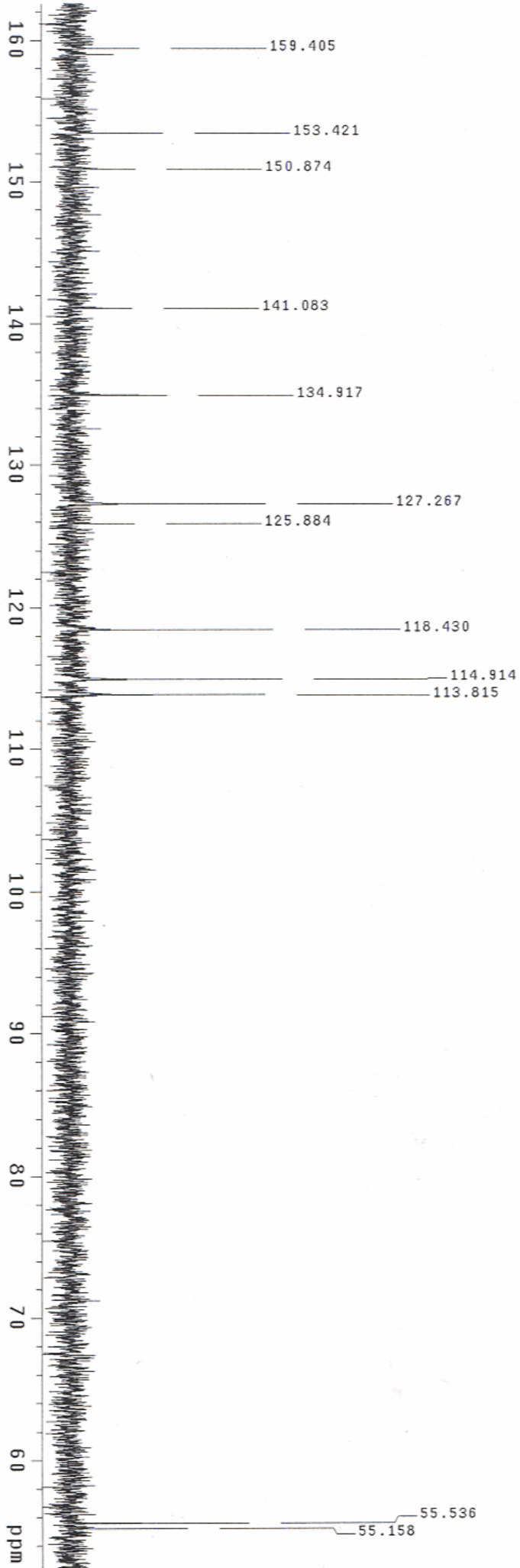
2:MS AP+
 2.9e+006



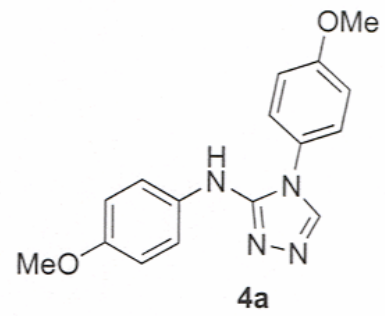


¹H NMR, DMSO-d₆, 400MHz

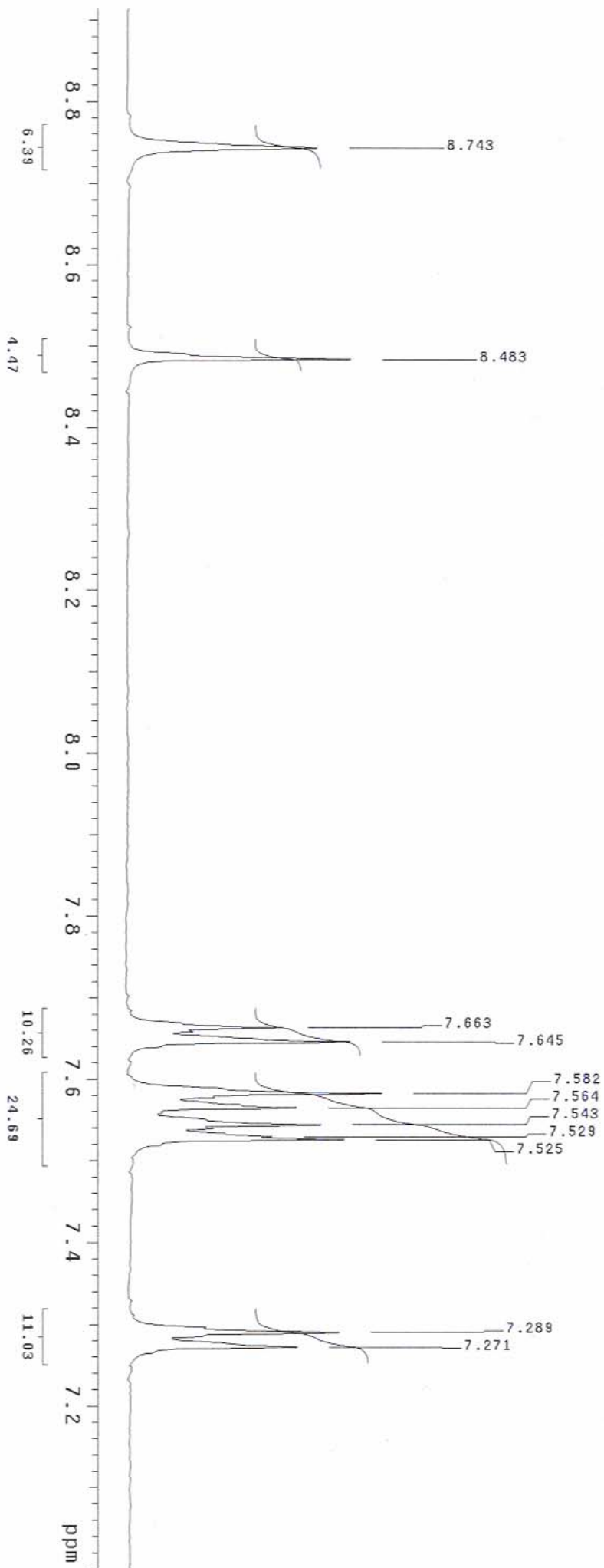
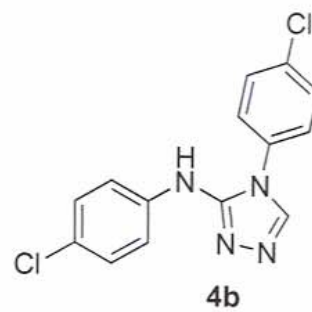




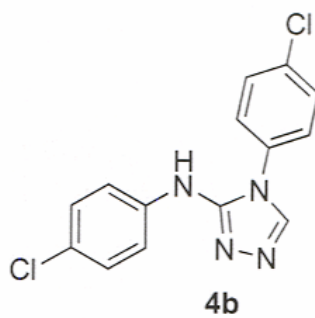
¹³CNMR, DMSO-d₆, 100MHz



¹HNMR, DMSO-d₆, 500MHz



^{13}C NMR, DMSO-d₆, 125MHz



180
160
140
120
100
80
60
40
20
ppm

Pulse Sequence: szpu1

Solvent: DMSO

Temp: 20.0 C / 293.1 K

Mercury-400BB "mercury400"

Relax. delay 0.120 sec

Pulse 62.5 degrees

Acq. time 2.733 sec

Width 5995.2 Hz

16 repetitions

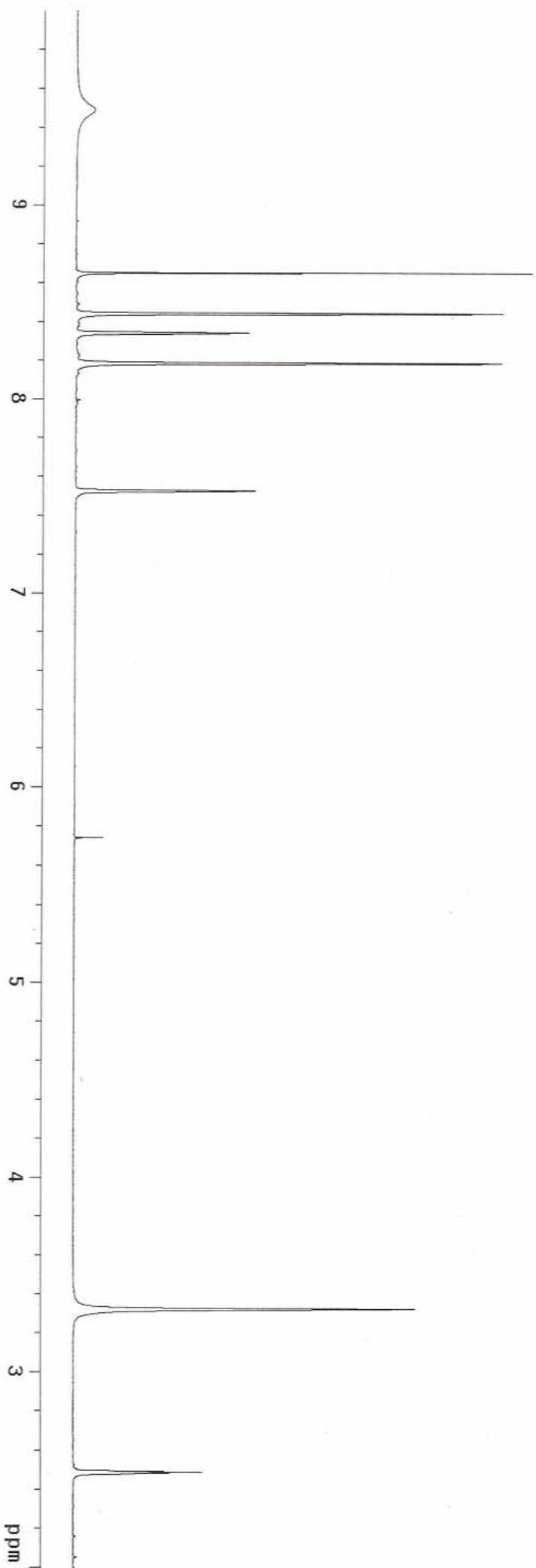
OBSERVE H1, 400.0248424 MHz

DATA PROCESSING

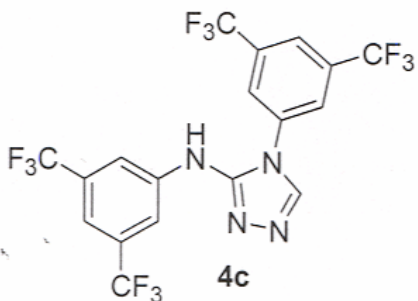
Line broadening 0.1 Hz

FT size 32768

Total time 1 min, 4 sec



LC – Xterra C18 5 μ M 3.0 \times 100.0 mm column
 APCI positive MS



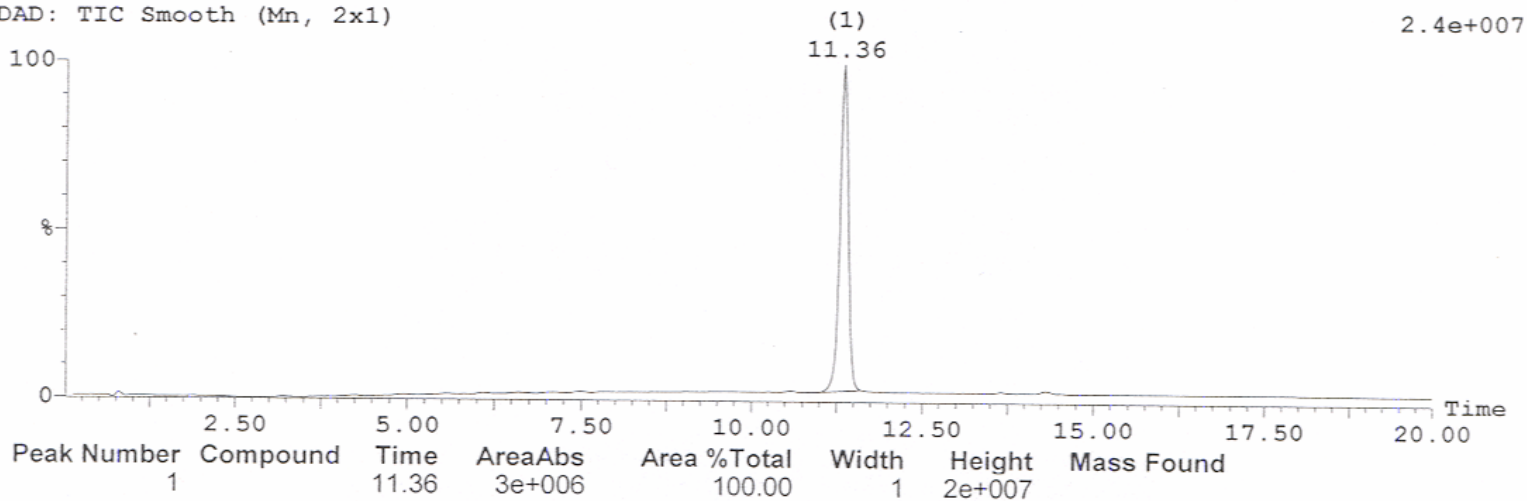
$C_{18}H_8F_{12}N_4$
 Exact Mass: 508.0557

Solvent A
 Solvent B

Water
 Acetonitrile

Time	% A	% B
0	95	5
15	5	95
20	5	95

DAD: TIC Smooth (Mn, 2x1)

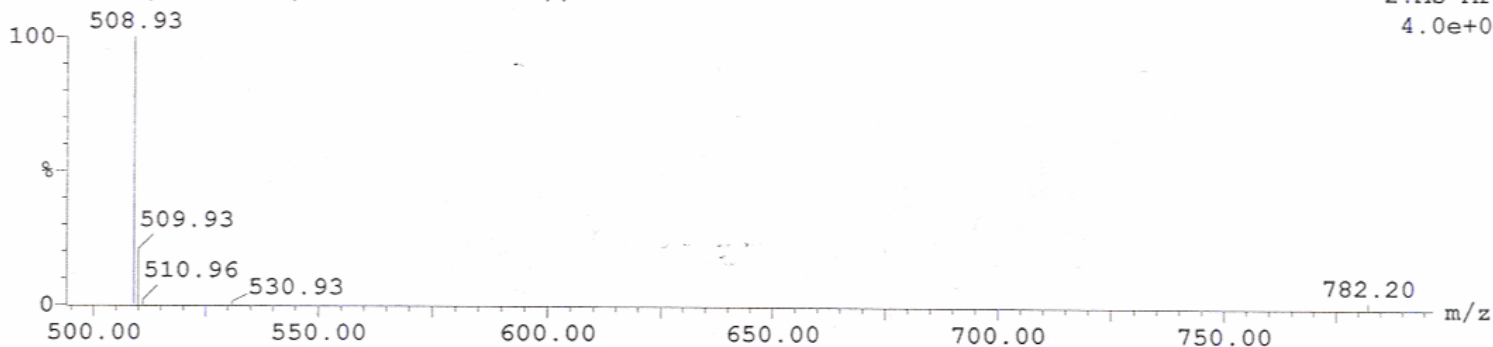


Peak ID Compound Time Mass Found

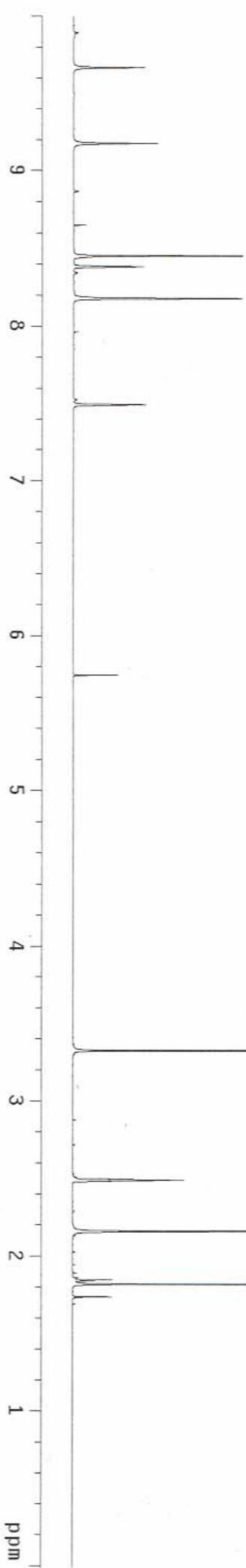
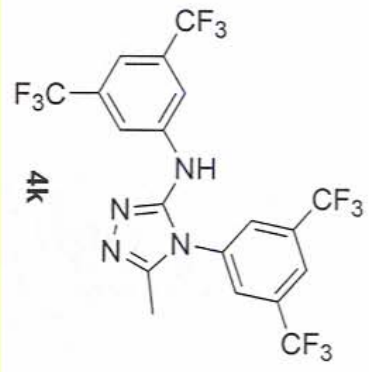
1 11.35

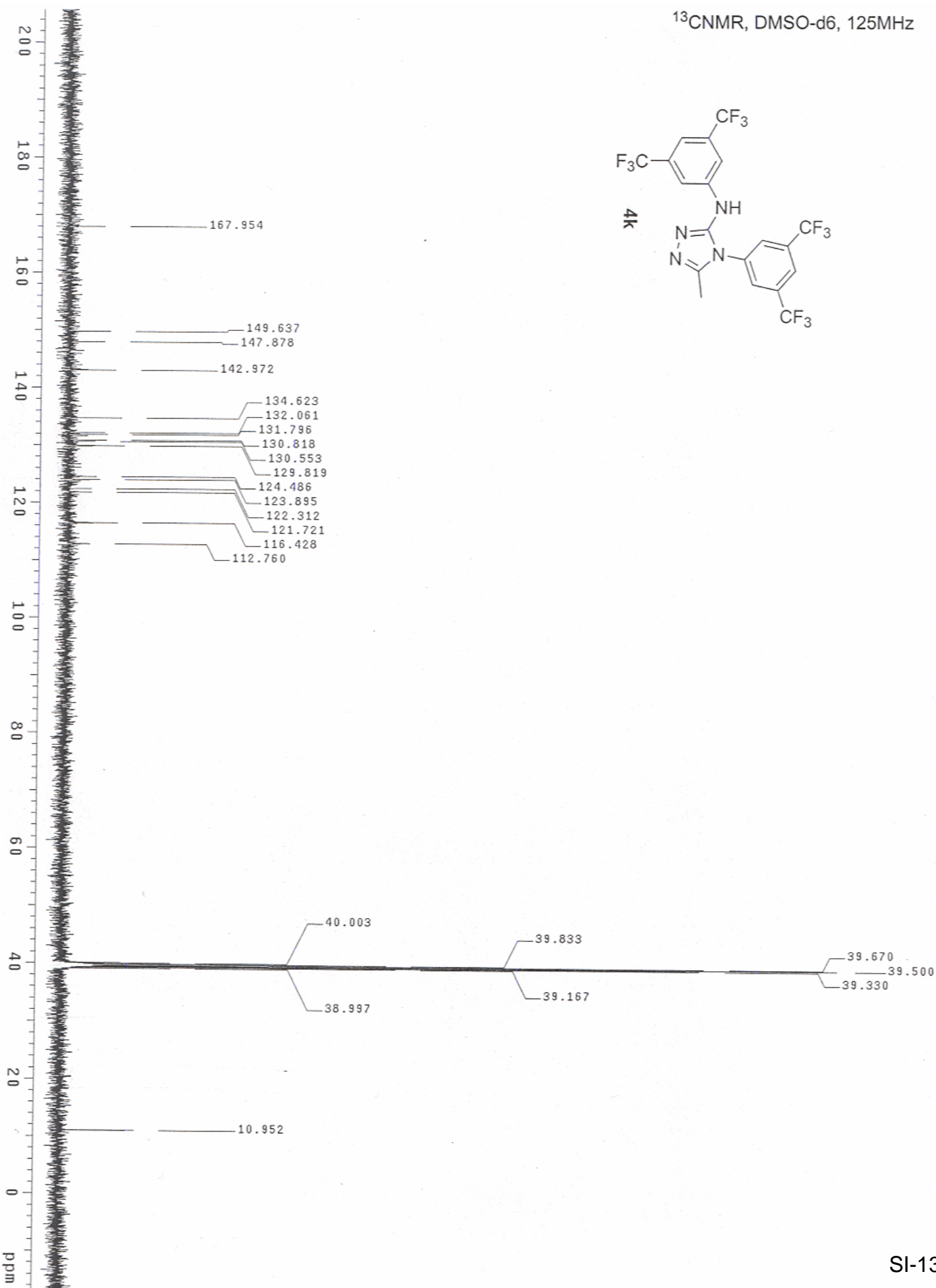
Combine (424:428-(413:414+438:439))

2:MS AP+
 4.0e+007

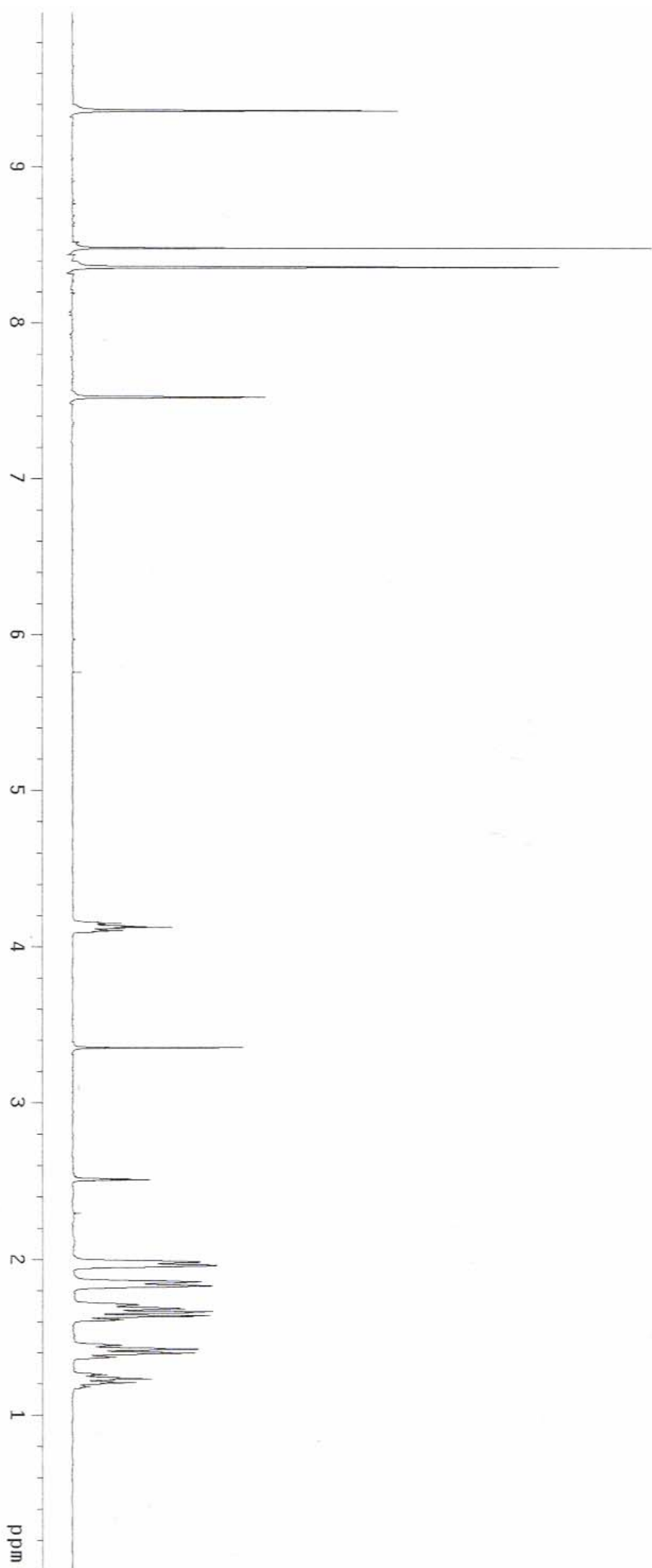
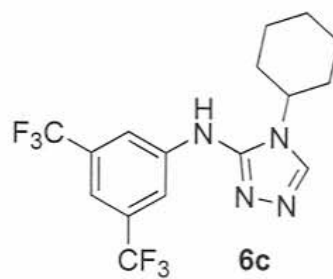


¹HNMR, DMSO-d₆, 500MHz

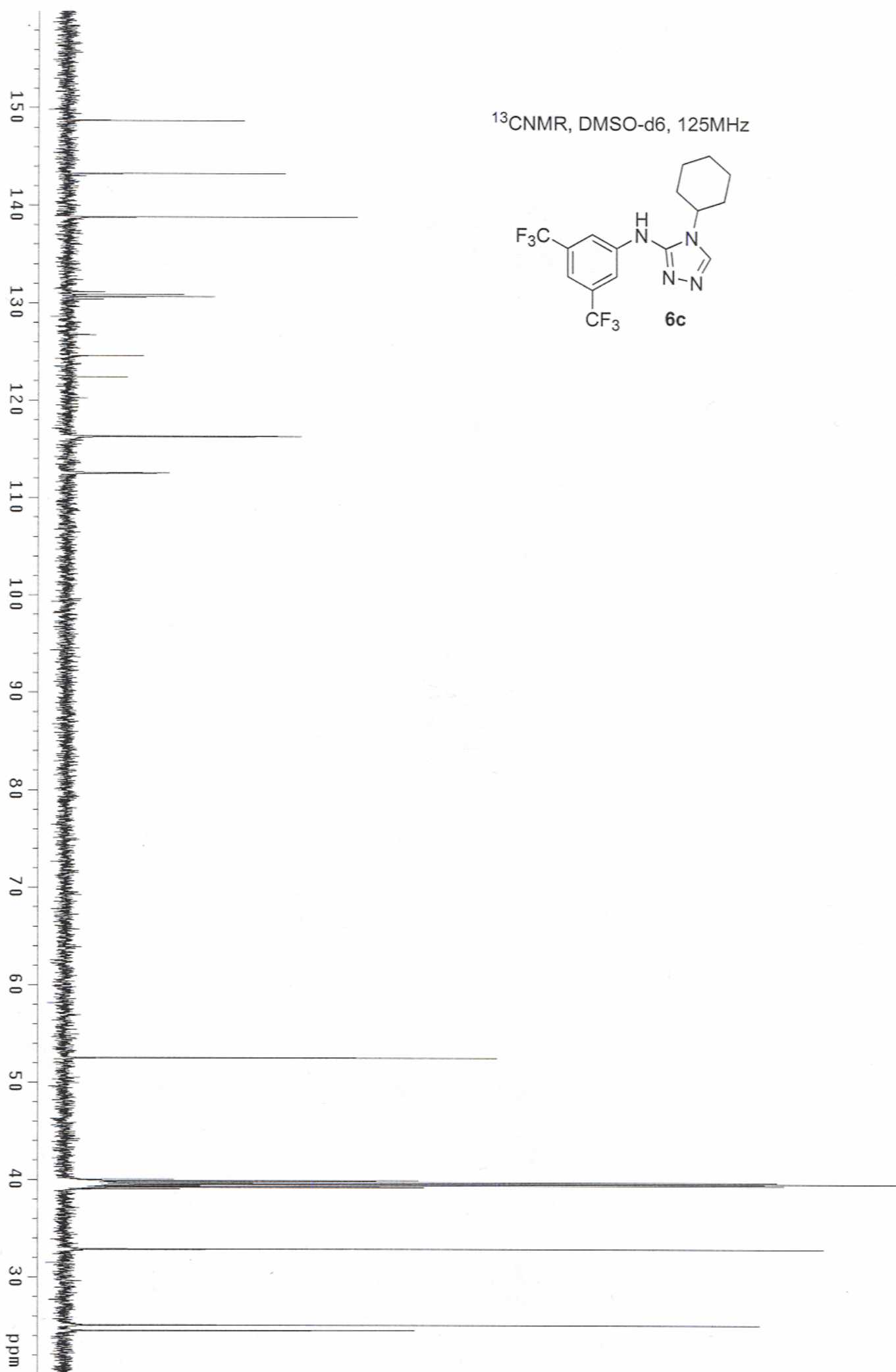
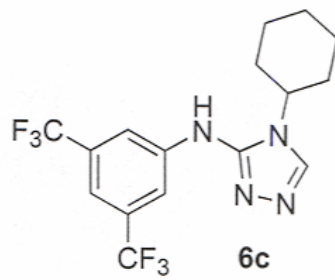




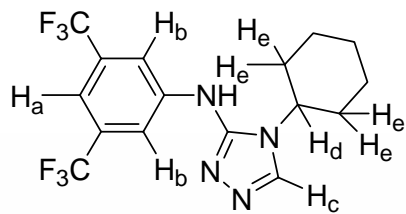
¹HNMR, DMSO-d₆, 500MHz



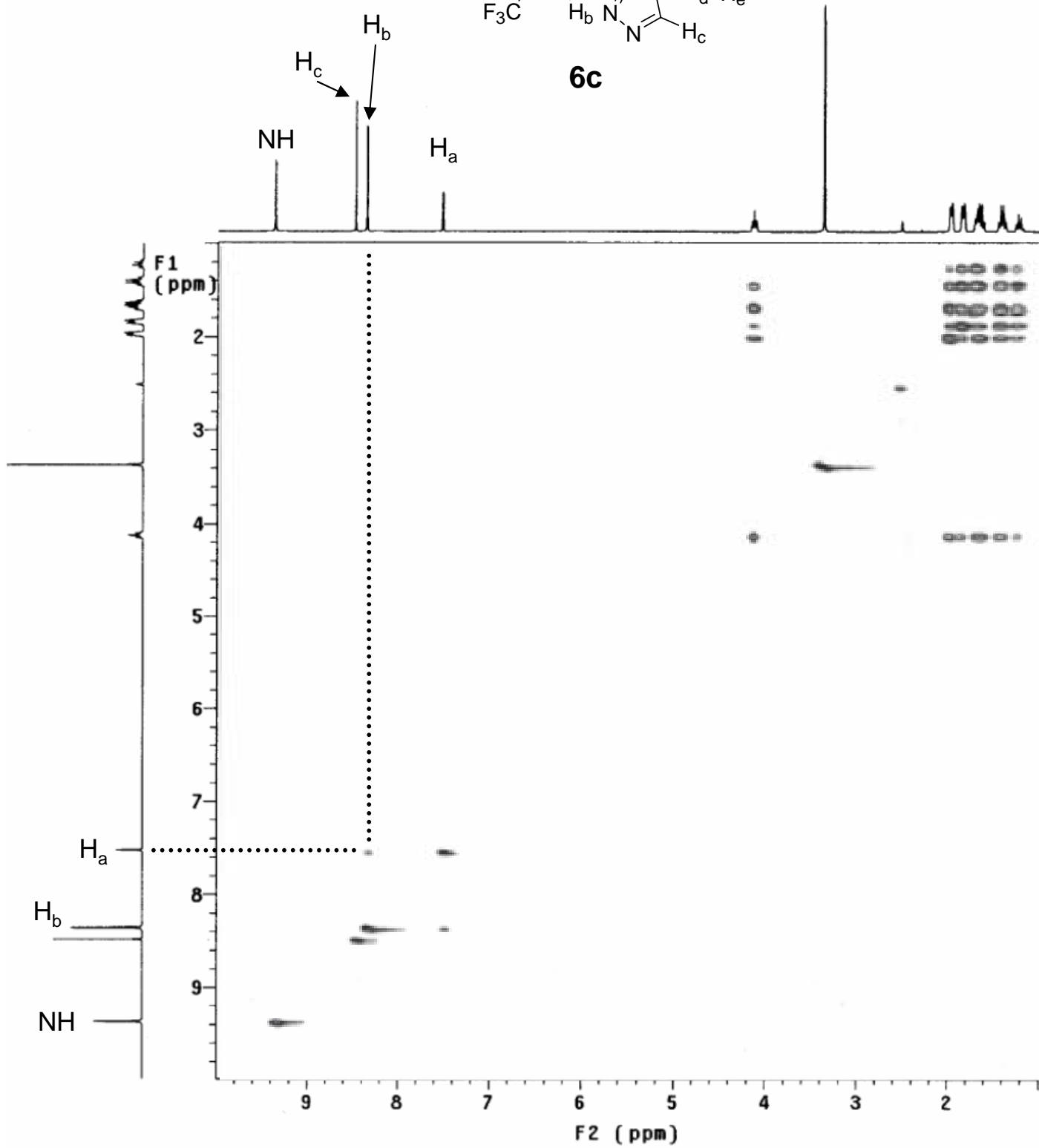
¹³CNMR, DMSO-d₆, 125MHz



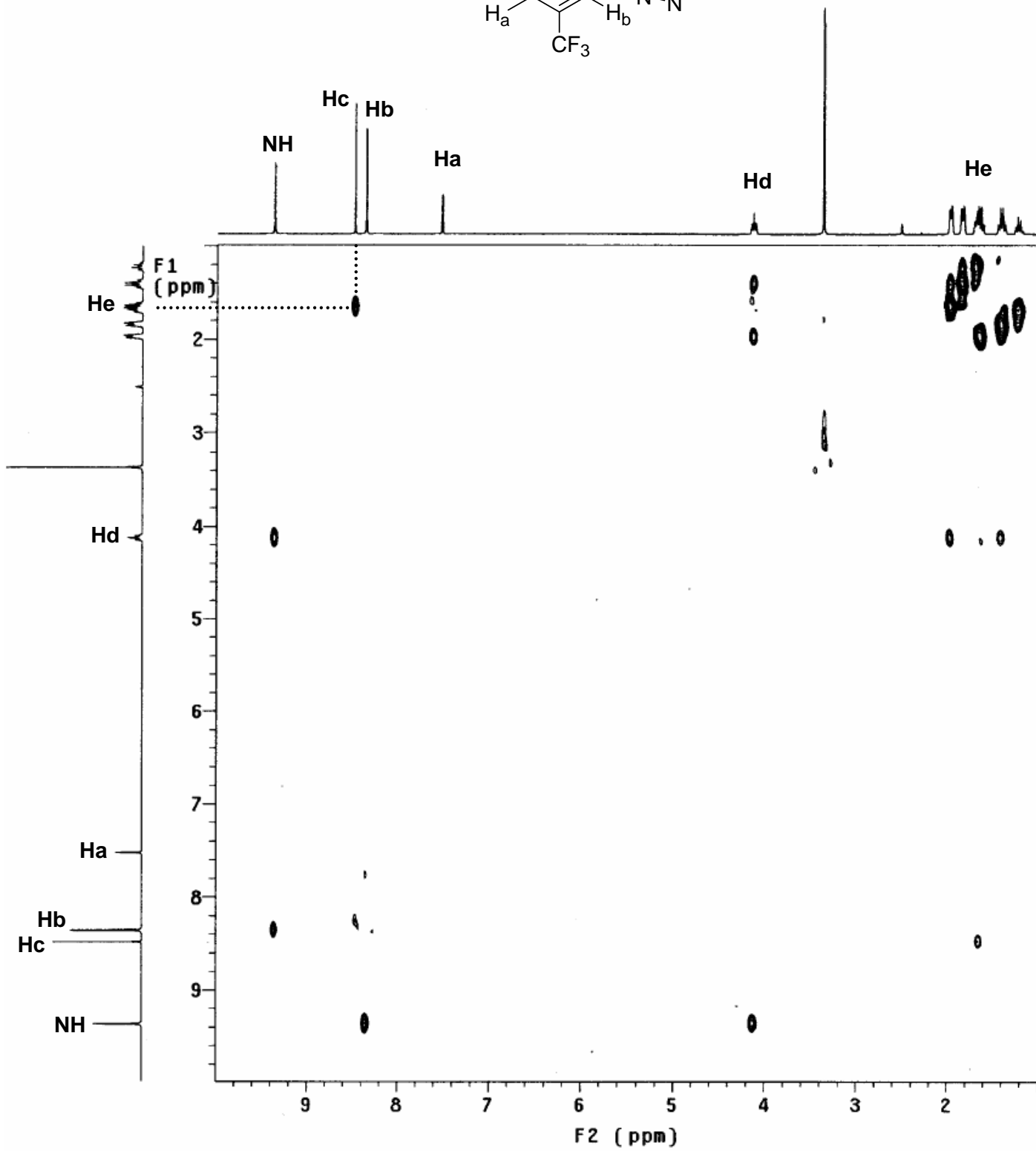
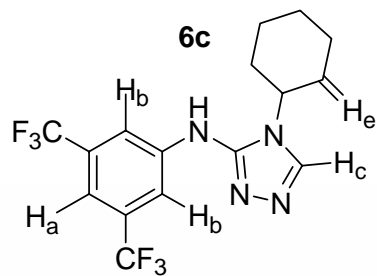
TOCSY



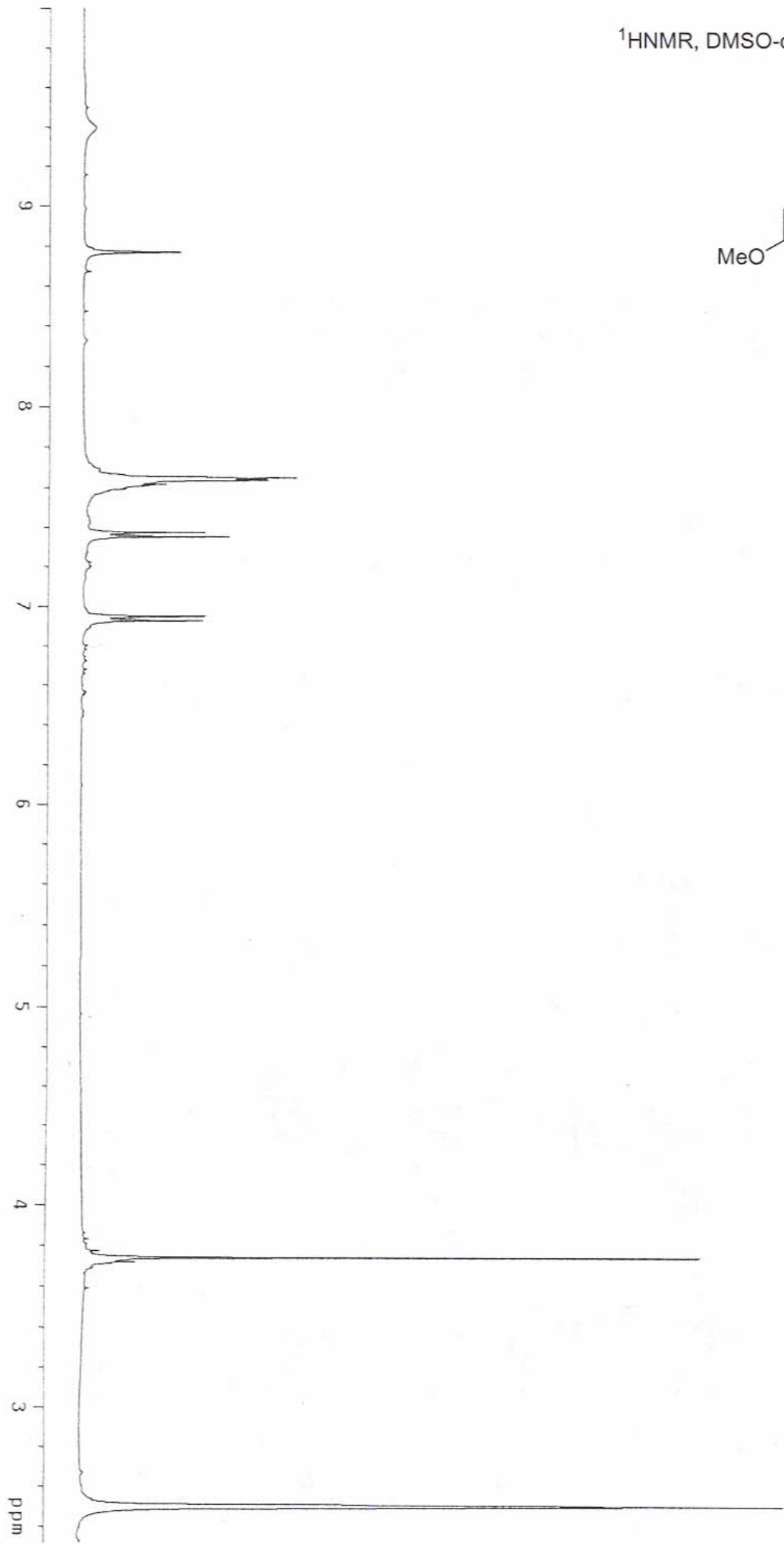
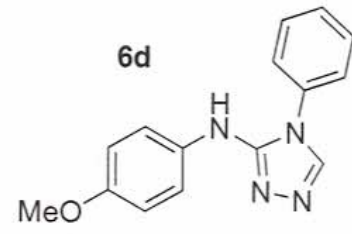
6c



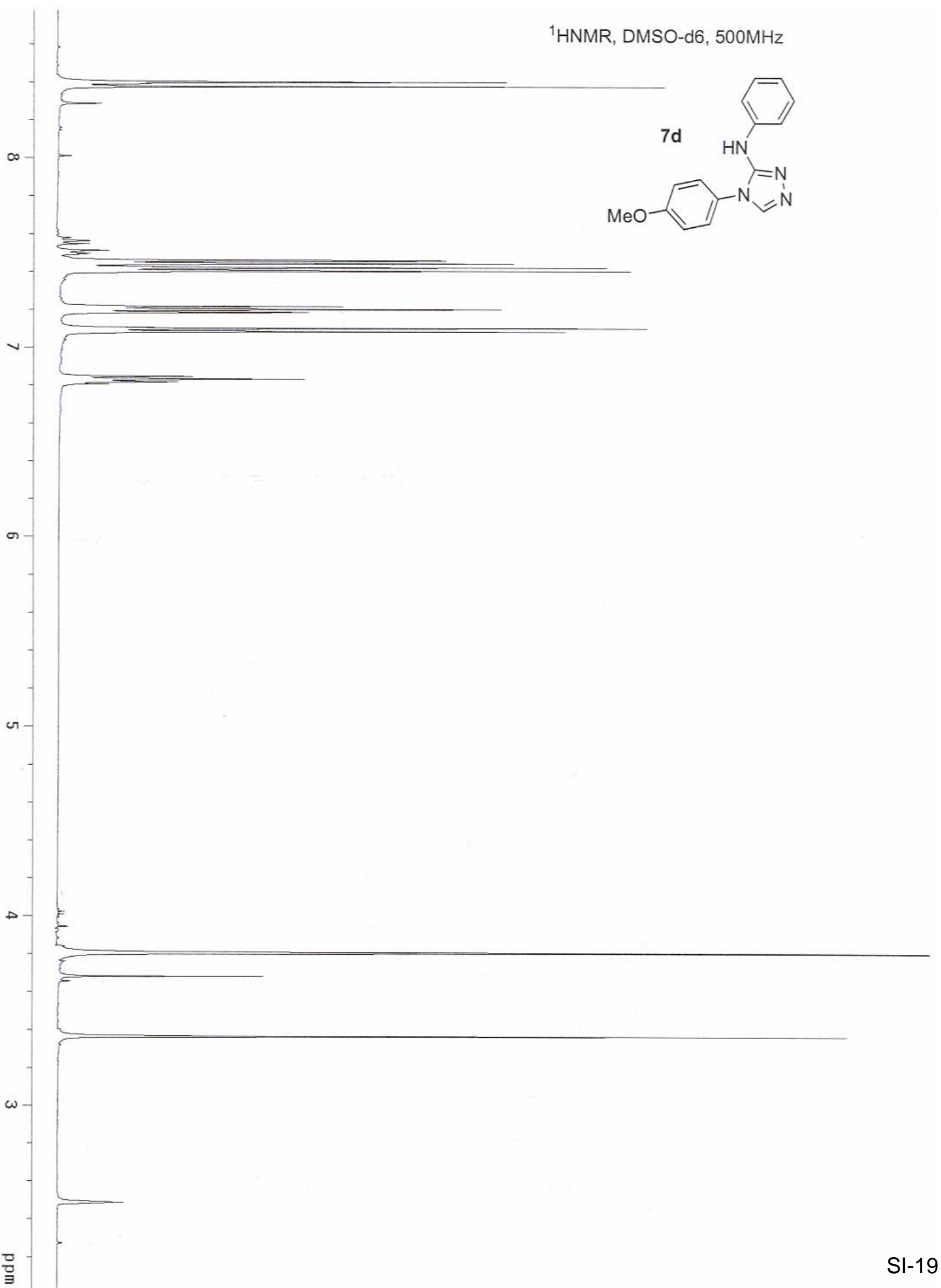
NOESY



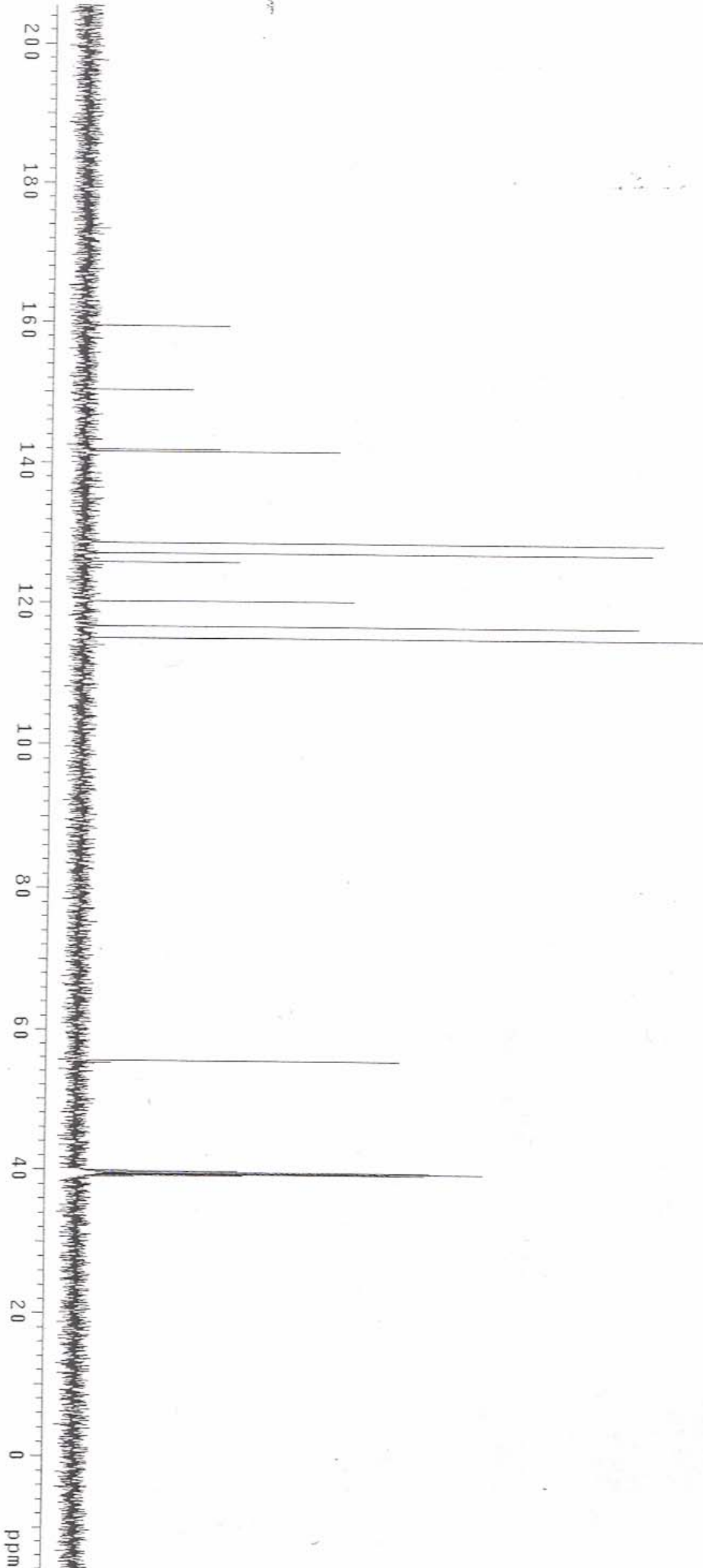
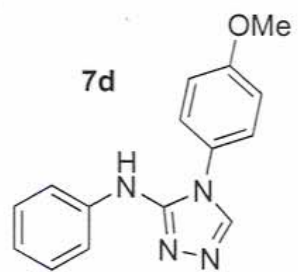
¹HNMR, DMSO-d6, 400MHz



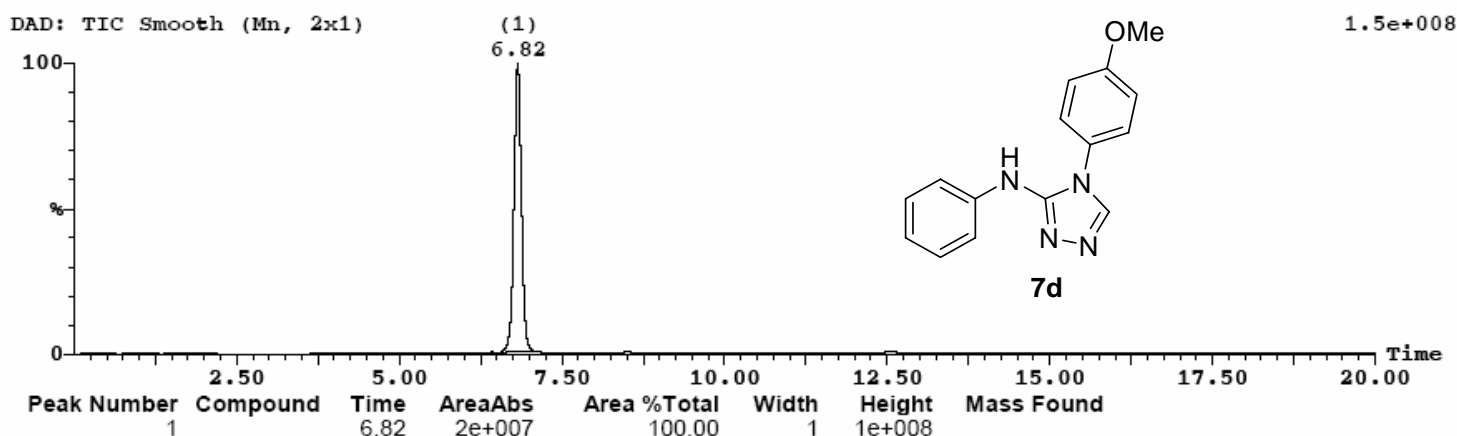
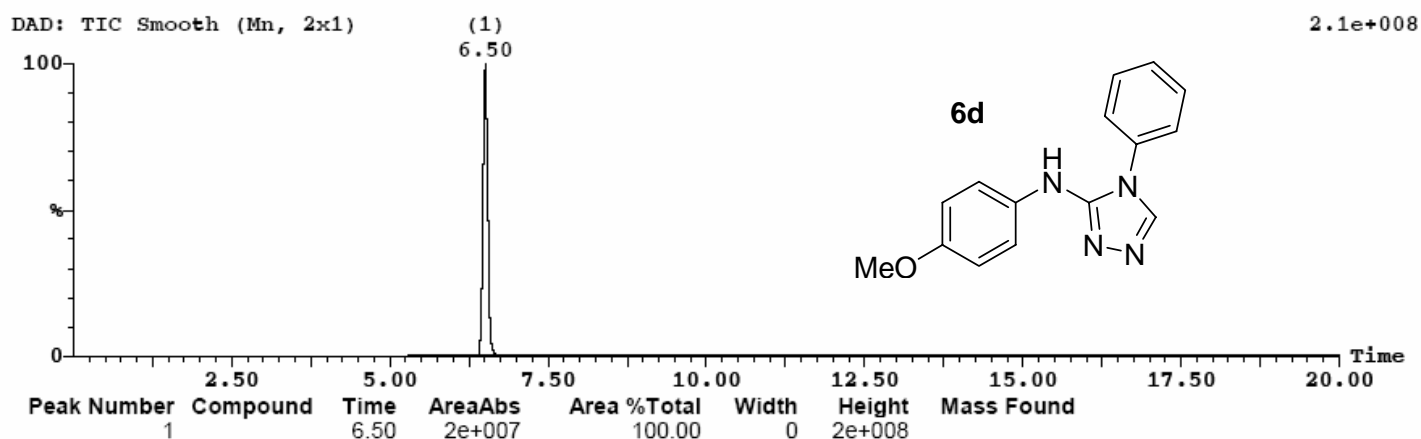
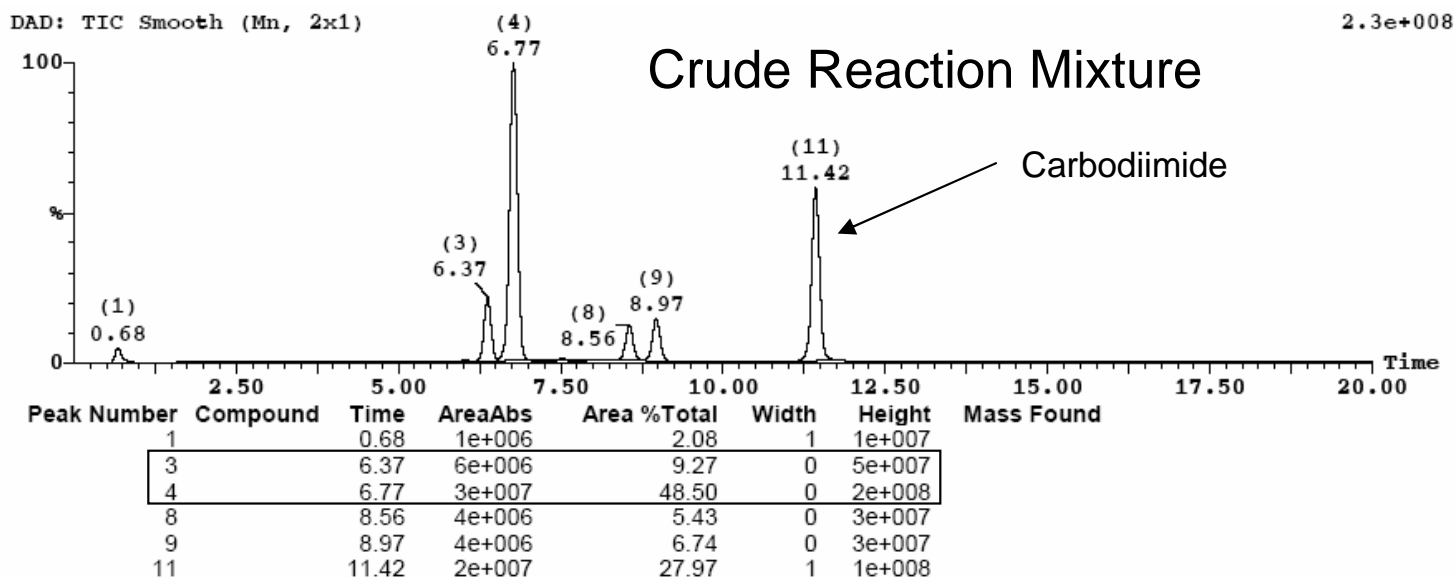
¹HNMR, DMSO-d6, 500MHz



^{13}C NMR, DMSO-d₆, 125MHz

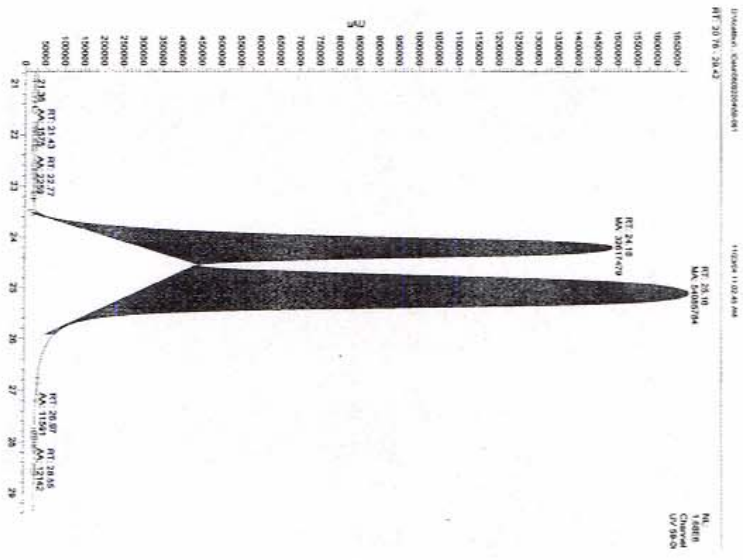
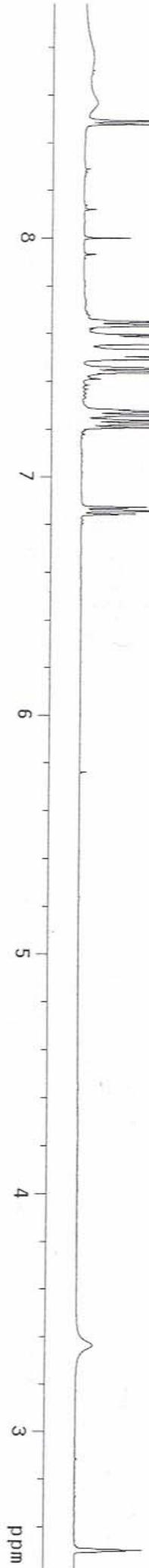
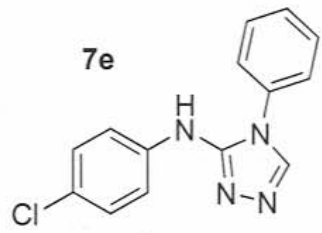
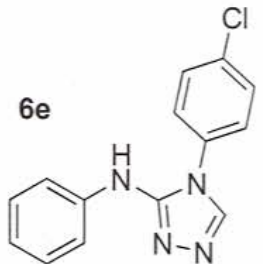


Total ion chromatogram of the reaction mixture and pure 6d and 7d



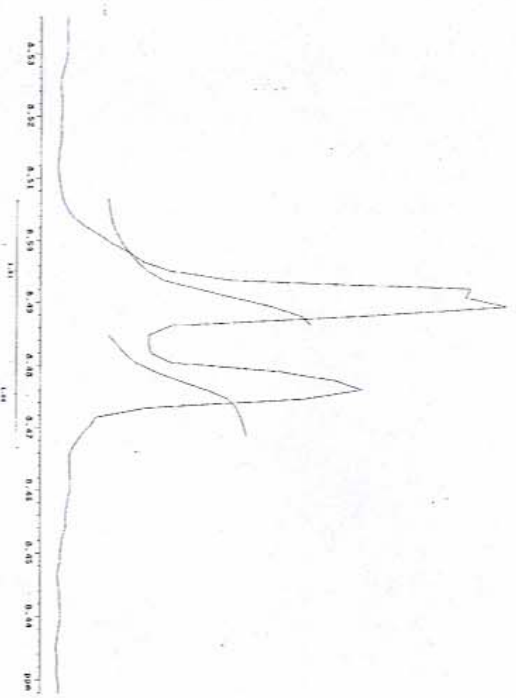
1HNMR of reaction mixture of 6e and 7e

CRUDE MIXTURE



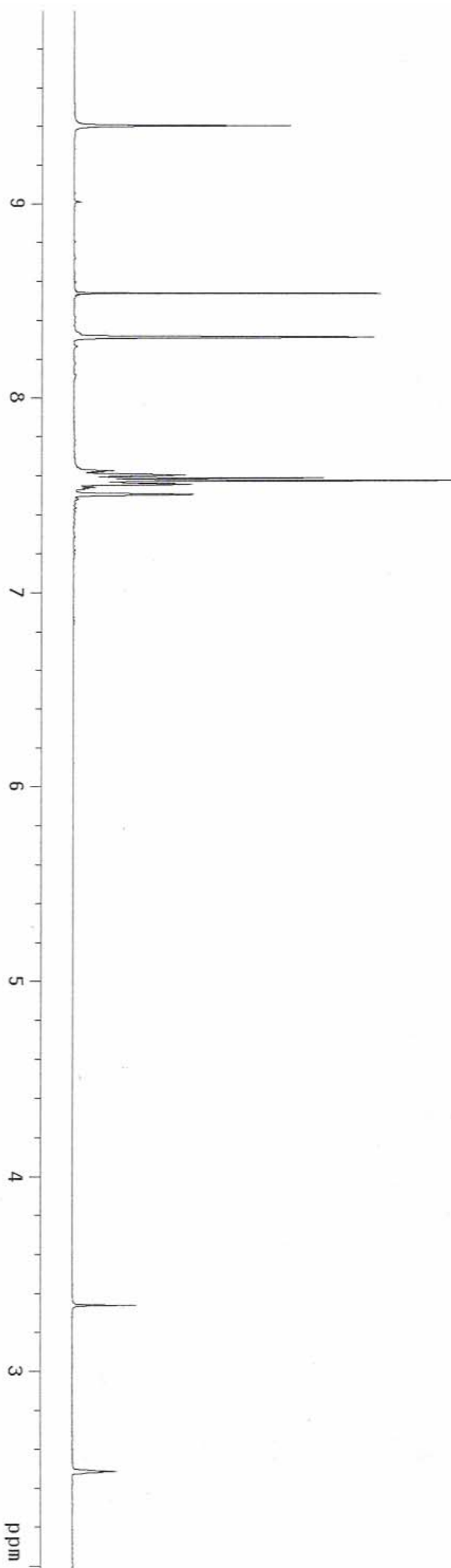
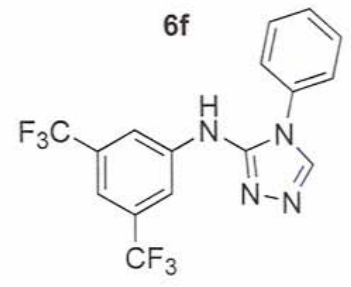
Integration
LC trace

2:3 mixture



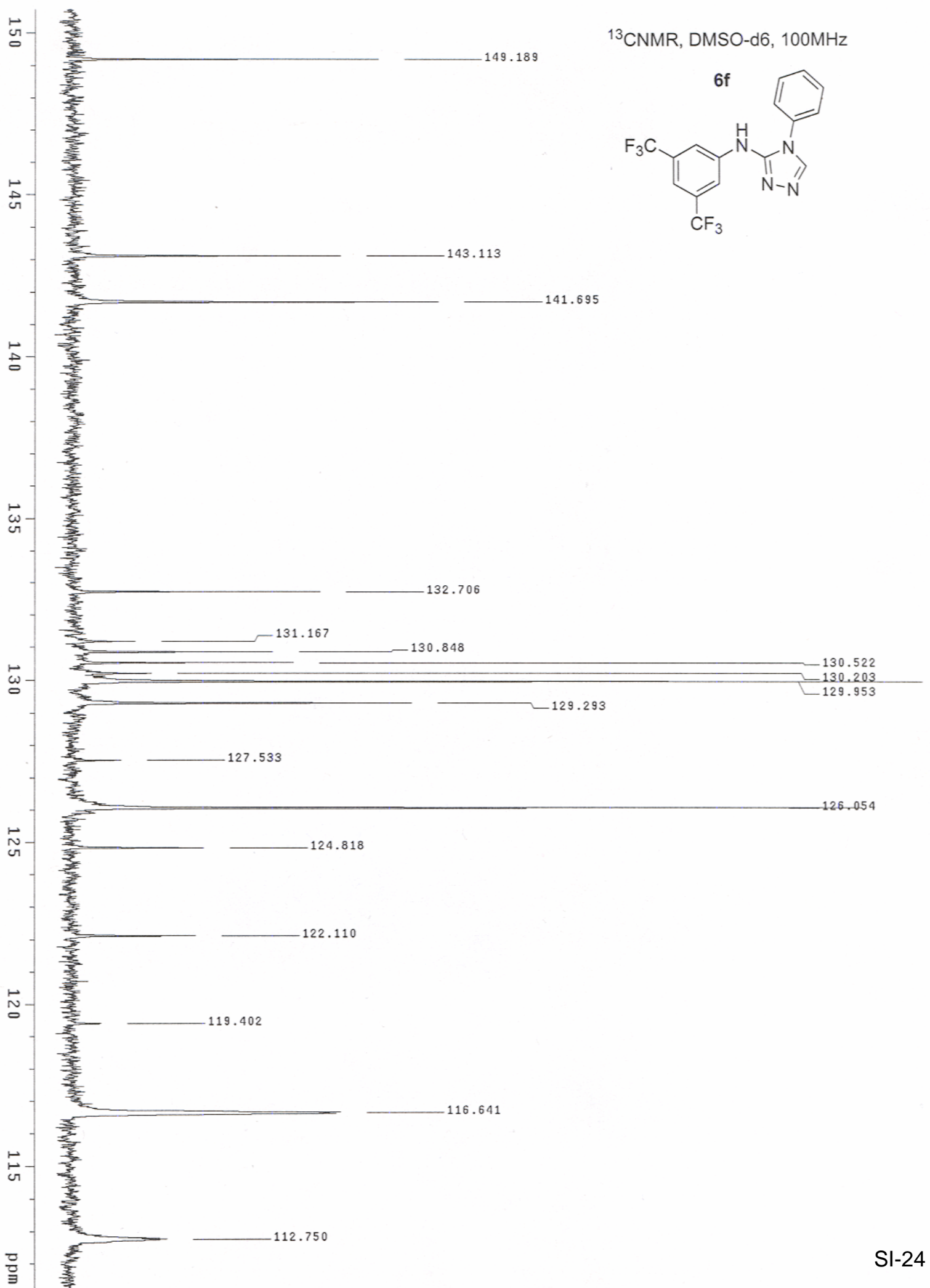
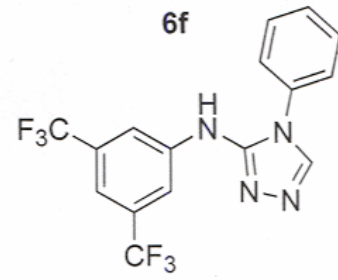
Integration
NMR expanded

¹HNMR, DMSO-d₆, 400MHz

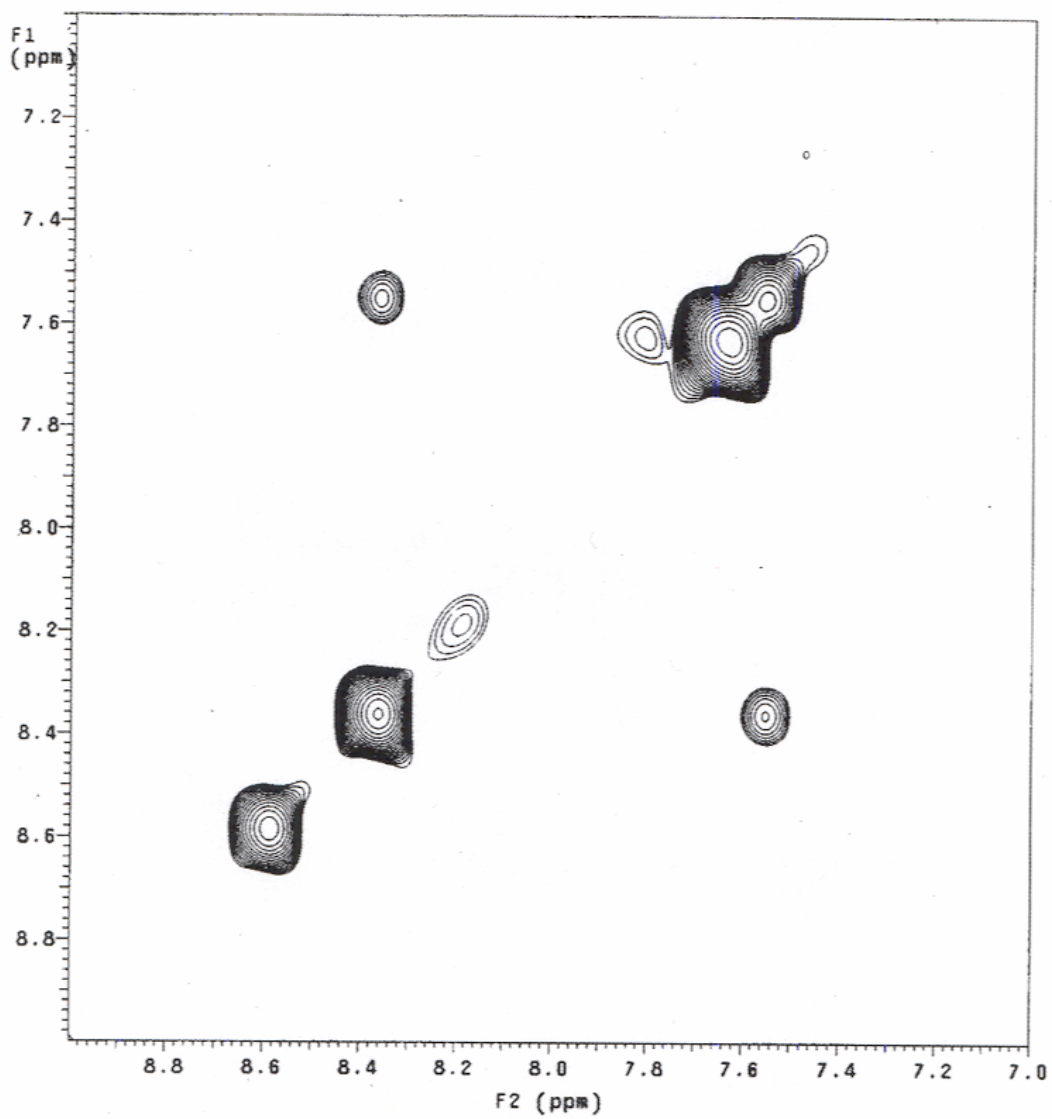
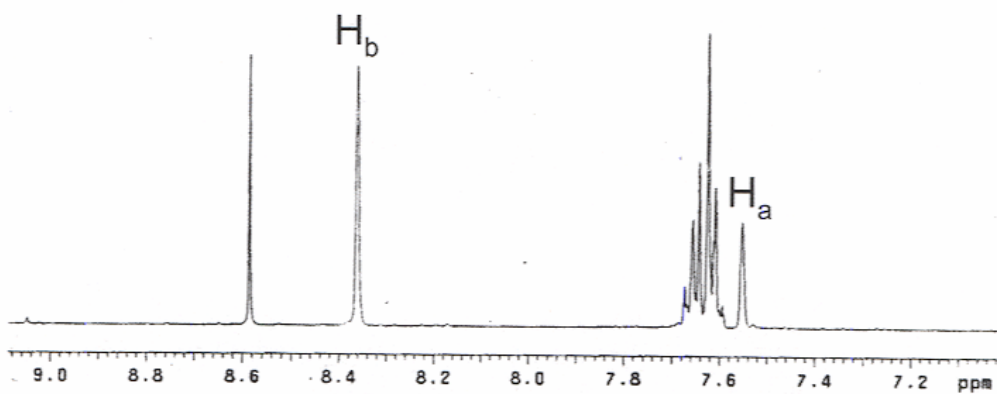
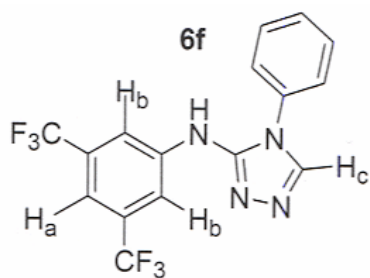


¹³CNMR, DMSO-d₆, 100MHz

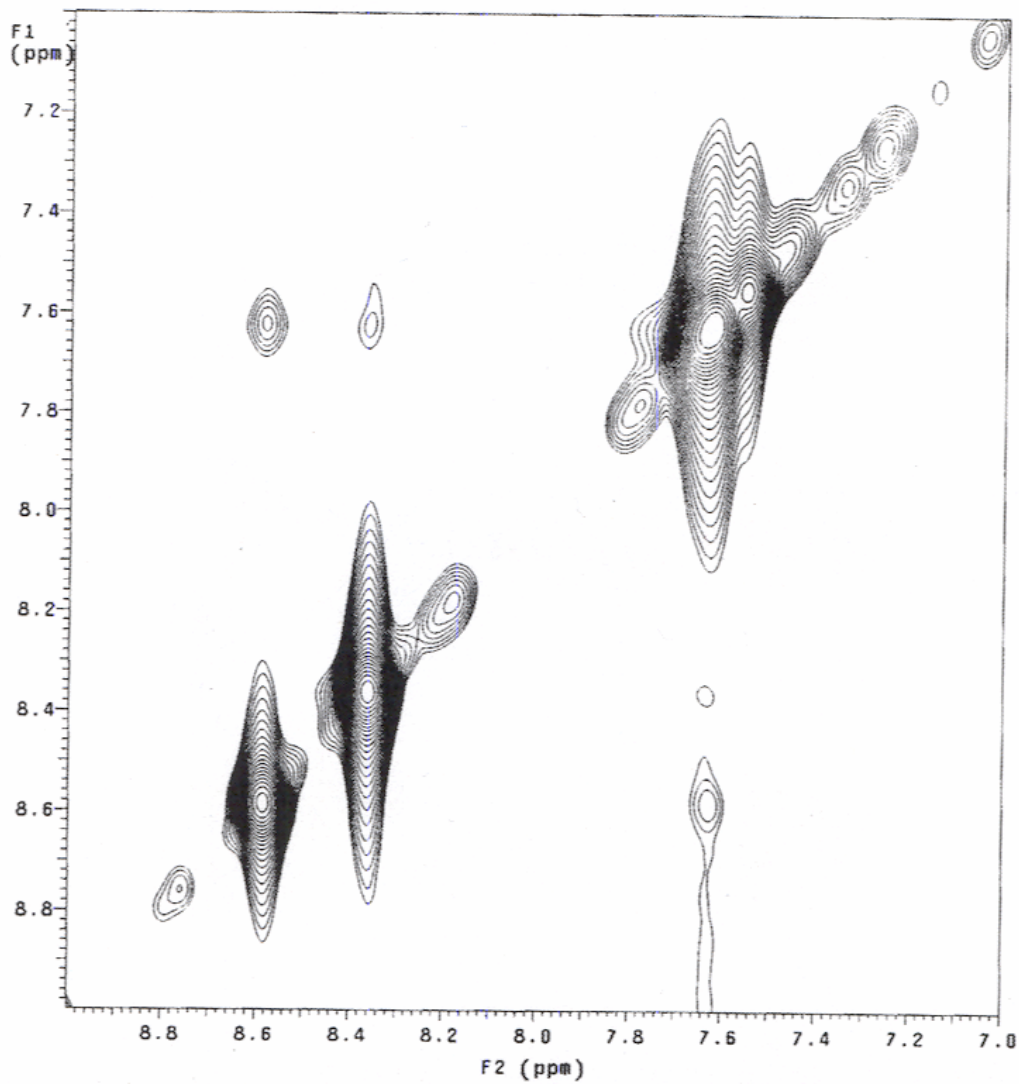
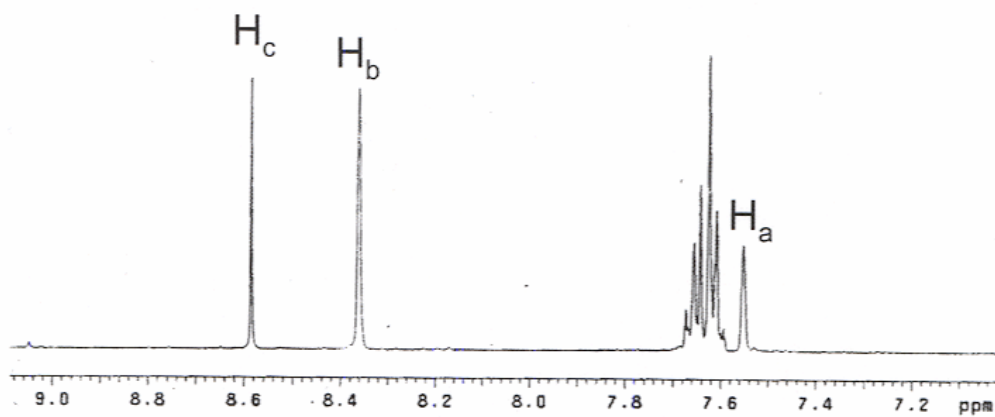
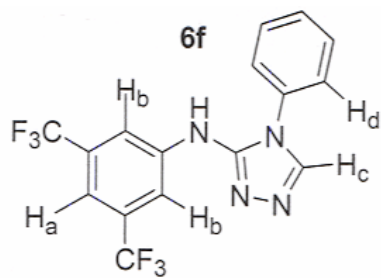
6f



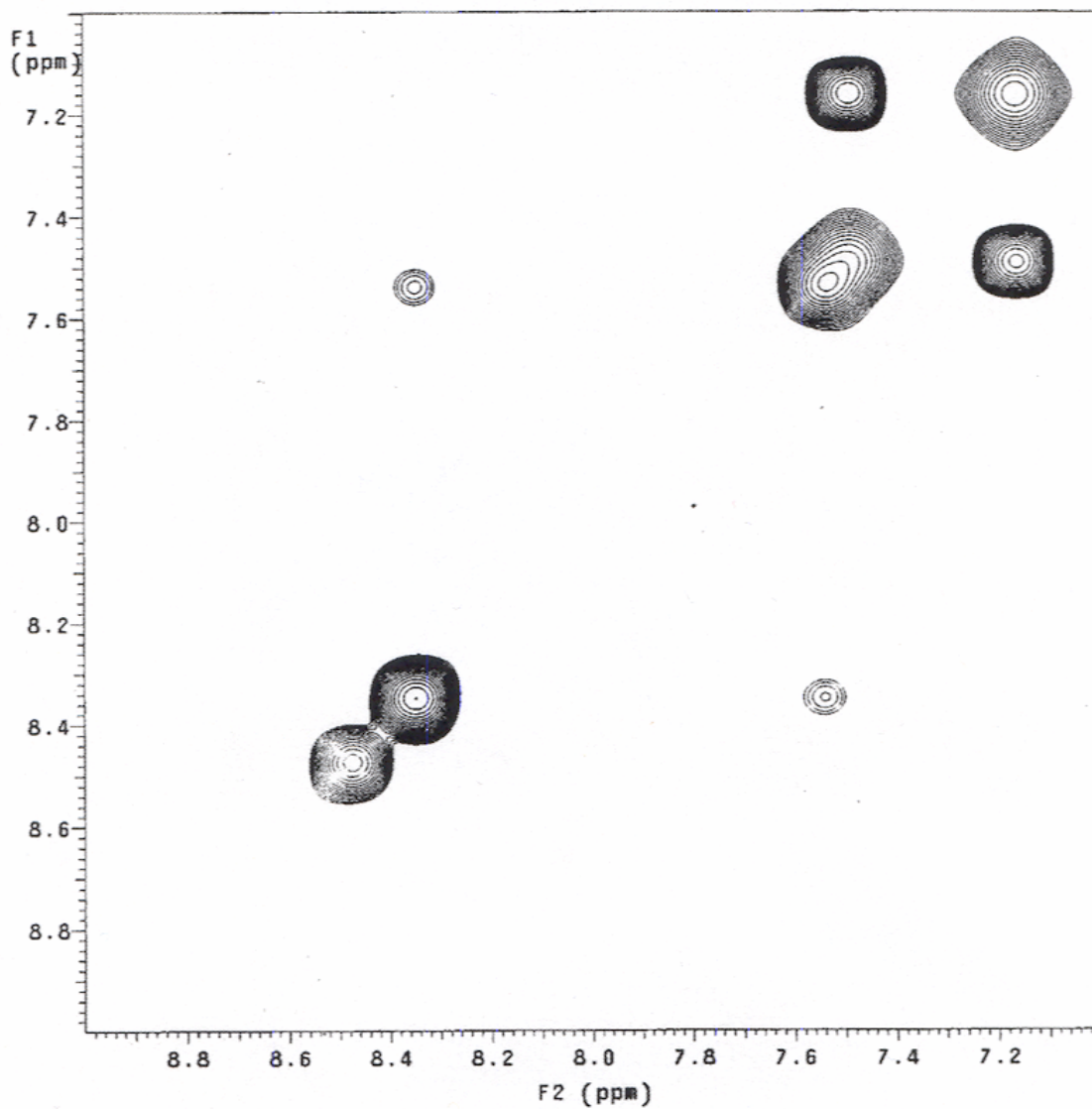
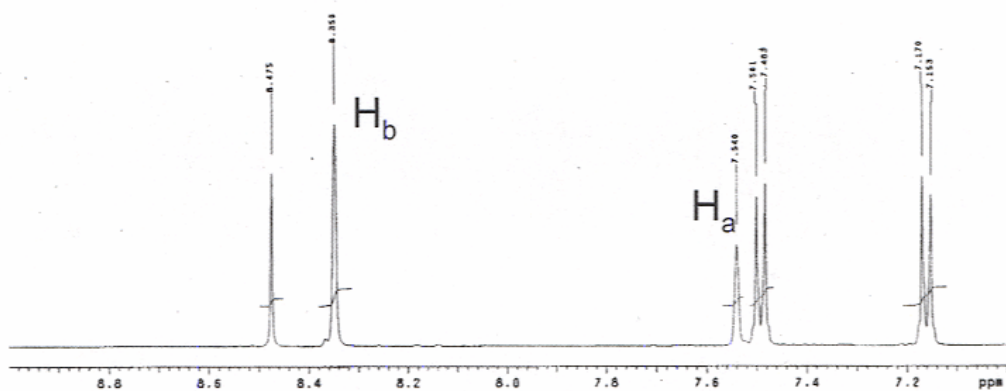
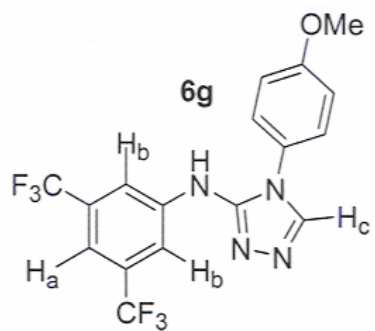
TOCSY



NOESY



TOCSY



General Procedure (I) for 1,3-diarylthioureas: To 1 mmol of substituted phenylisothiocyanate in 2 mL dichloromethane, 1.05 mmol of the substituted aniline in 3 mL dichloromethane was added dropwise. The resulting mixture was allowed to stir at room temperature overnight. The product precipitates out and was filtered and washed with cold dichloromethane and was carried on to the next step without any purification. The following 1,3-disubstituted thioureas are known compounds or commercially available: **3b**,²⁵ **3d**, **3e**, **3f** and **5e**

General Procedure (II) for studying the substituent effect on the synthesis of *N*-aryl-(4-aryl-4*H*-[1,2,4]triazole-3-yl)-amines: To 1 mmol of 1,3-disubstituted thiourea a solution of 1.20 mmol of the hydrazide in 10 mL DMF/acetonitrile (1:1) was added and stirred to dissolve the thiourea. To this solution 0.95 mmol of mercury(II)acetate was added and allowed to stir at RT for 2h. A black precipitate (HgS) was formed over time. The precipitate was filtered and washed with acetonitrile. The filtrate was concentrated to yield a solid that was purified by either silica gel column chromatography (ethyl acetate/hexane and 1% methanol, 1:1) or by recrystallization dichloromethane-ethylacetate-hexanes to obtain the desired [1,2,4]triazole in good yields.

General Procedure (III) for the synthesis of *N*-aryl-(4-aryl-4*H*-[1,2,4]triazole-3-yl)-amines: To 1 mmol of 1,3-disubstituted thiourea 5 mmol of the hydrazide in 25 mL acetonitrile was added and stirred to dissolve. To this solution 1.5 mmol of mercury(II)acetate was added and allowed to stir at RT for 2-16 h. A black precipitate (HgS) was formed over time. The precipitate was filtered and washed with acetonitrile. The filtrate was concentrated to yield a solid that was purified by either silica gel column chromatography (ethyl acetate/hexane and 1% methanol, 1:1) or by recrystallization dichloromethane-ethylacetate-hexanes to obtain the desired [1,2,4]triazole in good yields.

General Procedure for Pd/C debenylation: To 1mmol of the 1-benzyl-1,3-diaryl-[1,2,4]triazole in 5 mL ethyl acetate/acetic acid (5:1), 10% Pd/C (25 mg) was added. The reaction was purged with nitrogen and stirred at RT at 40 psi H₂ overnight. The reaction mixture was filtered through a celite bed, the filtrate was concentrated under reduced pressure. The resulting material was purified by column chromatography (ethyl acetate/hexane and 1% methanol, 1:1).