Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Selective synthesis and comparative activity of olefinic isomers of 1,2-benzothiazine-1,1-dioxide carboxylates as aldose reductase inhibitors

Shagufta Parveen,[a] Saghir Hussain,[a] Shaojuan Zhu,[a] Xiangyu Qin,[a] Xin Hao,[a] Shuzhen Zhang,[a] Jianglu Lu,[a] and Changjin Zhu (s)[a,b]

Department of Applied Chemistry, Beijing Institute of Technology,

No. 5, Zhongguancun South Street, 100081 Beijing, China

Tel./fax: +86 10 68918506

zcj@bit.edu

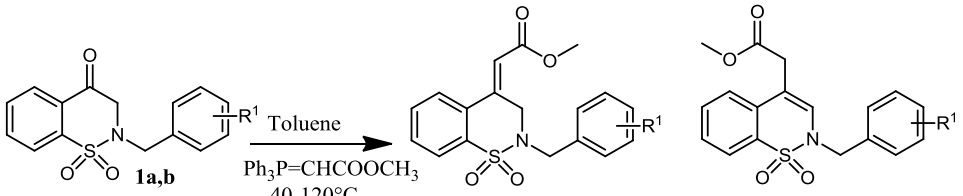
Table of contents

General Experiment:

Melting points were recorded on a XT4A microscopic melting points apparatus and uncorrected. Thin layer chromatography (TLC) was performed on silica gel Merck $60F_{254}$. Nuclear Magnetic Resonance (NMR) spectra were recorded using a 400 MHz spectrometer (1HNMR at 400MHz and 13CNMR at 100MHz) in [d6]-DMSO using TMS as internal reference. 1HNMR data are reported as follow: chemical shifts (δ, ppm), multiplicity (s=singlet, d= doublet, dd= doublet of doublet, t=triplet, q=quartet, m=multiplet, br=broad), integration, coupling constants (Hz). Data for 13C NMR are reported in terms of chemical shifts (δ, ppm). Individual resonances were assigned on the basis of their chemical shifts, signal intensities, multiplicity of resonances and coupling constants. MS was performed on varian 500-ms ion trap mass by the ESI method and FTIR spectra was obtained from PerkinElmer Spectrum One FTIR spectrometer.

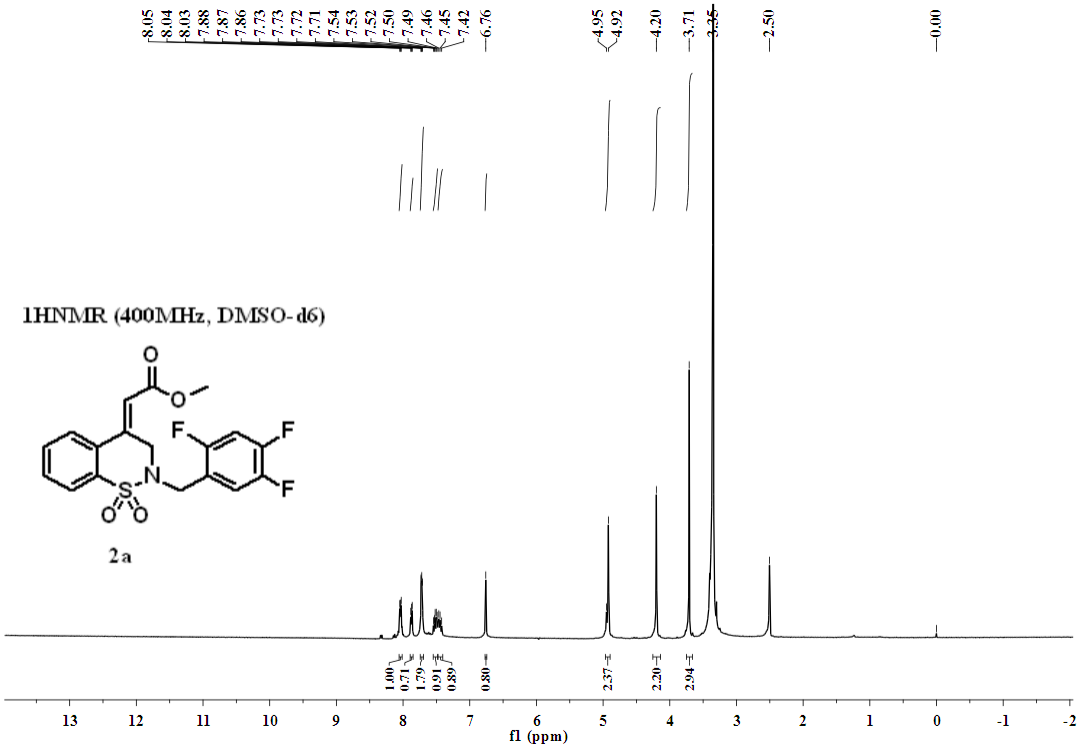
1. Optimizationof Wittig reaction of 1(a,b)

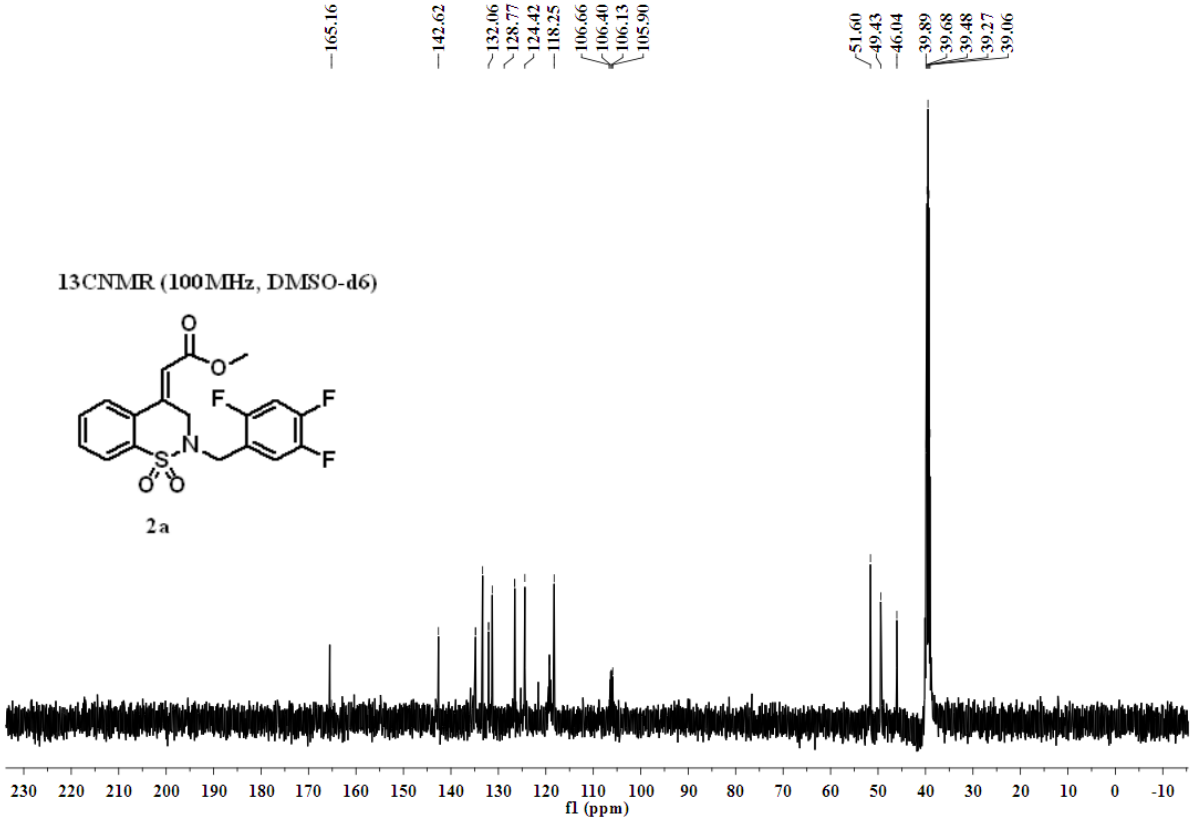
Table S1. Synthesis of E, Z and Endocyclic isomers of N-substituted benzothiazine 1,1-dioxide acetic acid deivatives

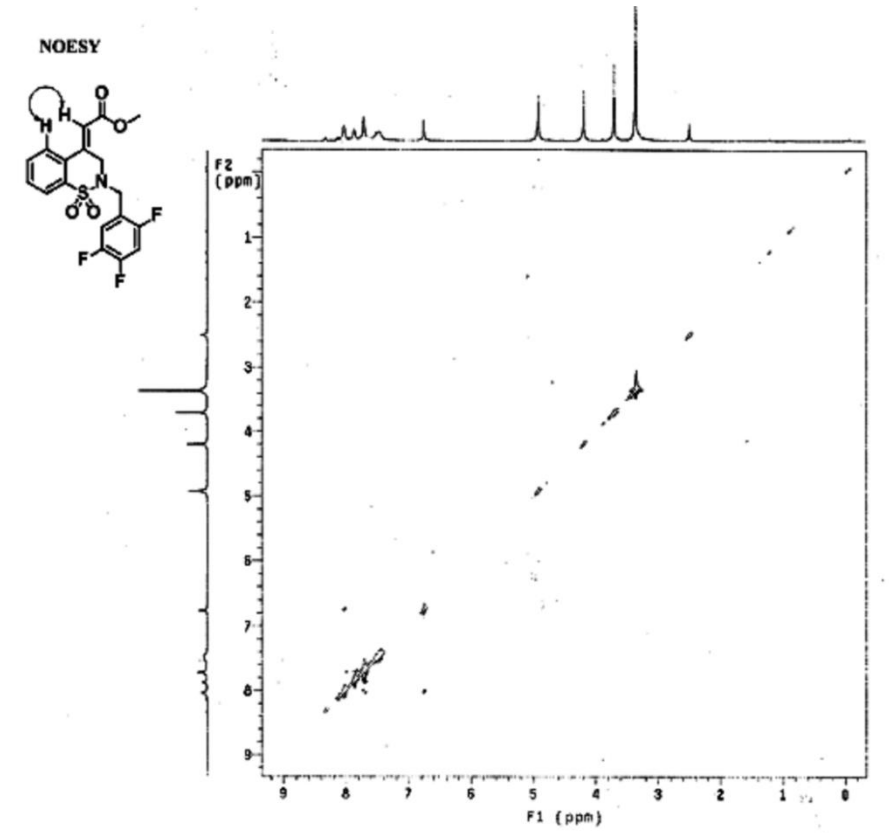


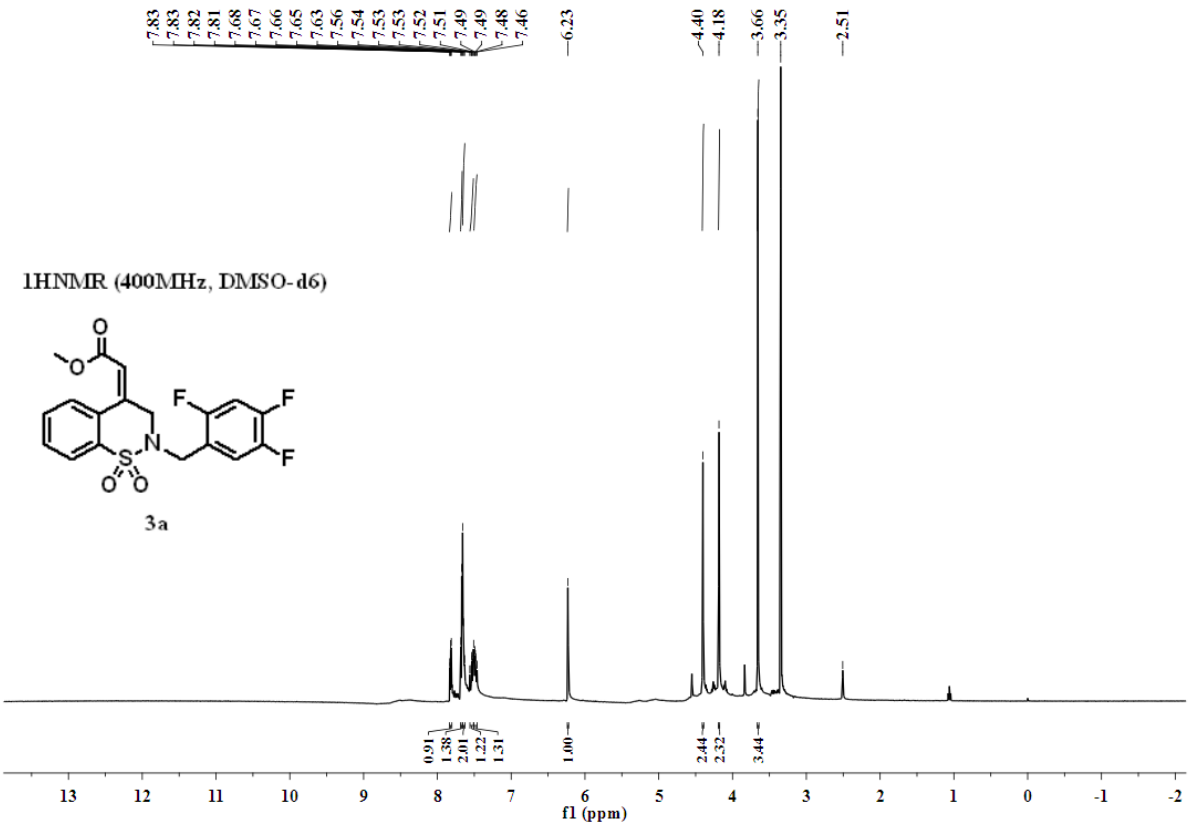
R	Product	% yield at different temperature				
		40 °C	**60°C**	**80°C**	**100°C**	**120°C**
2,4,5-F (**1a**)	**Exocyclic**					
	Z-isomer (**2a**)	66	48	37	15.5	5.6
	E-isomer (**3a**)	10.1	16.1	11.4	5	2
	Endocyclic (4a)	0	18.2	34.5	68.4	30
2-F,4-Br (**1b**)	**Exocyclic**					
	Z-isomer (**2b**)	74	59	32	15.7	2
	E-isomer (**3b**)	15	15.3	9.8	6.2	1.5
	Endocyclic (4b)	0	20.1	38.9	65.1	81

2. [1]HNMR, [13]CNMR & NOE spectra

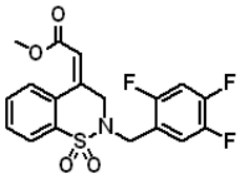





NOESY
F2 (ppm)
F1 (ppm)

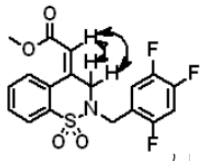

7.83
7.83
7.82
7.81
7.68
7.67
7.66
7.65
7.63
7.56
7.54
7.53
7.53
7.52
7.51
7.49
7.49
7.48
7.46
6.23
4.40
4.18
3.66
3.35
2.51
1HNMR (400MHz, DMSO-d6)
3a
0.91
1.38
2.01
1.22
1.31
1.00
2.44
2.32
3.44
f1 (ppm)

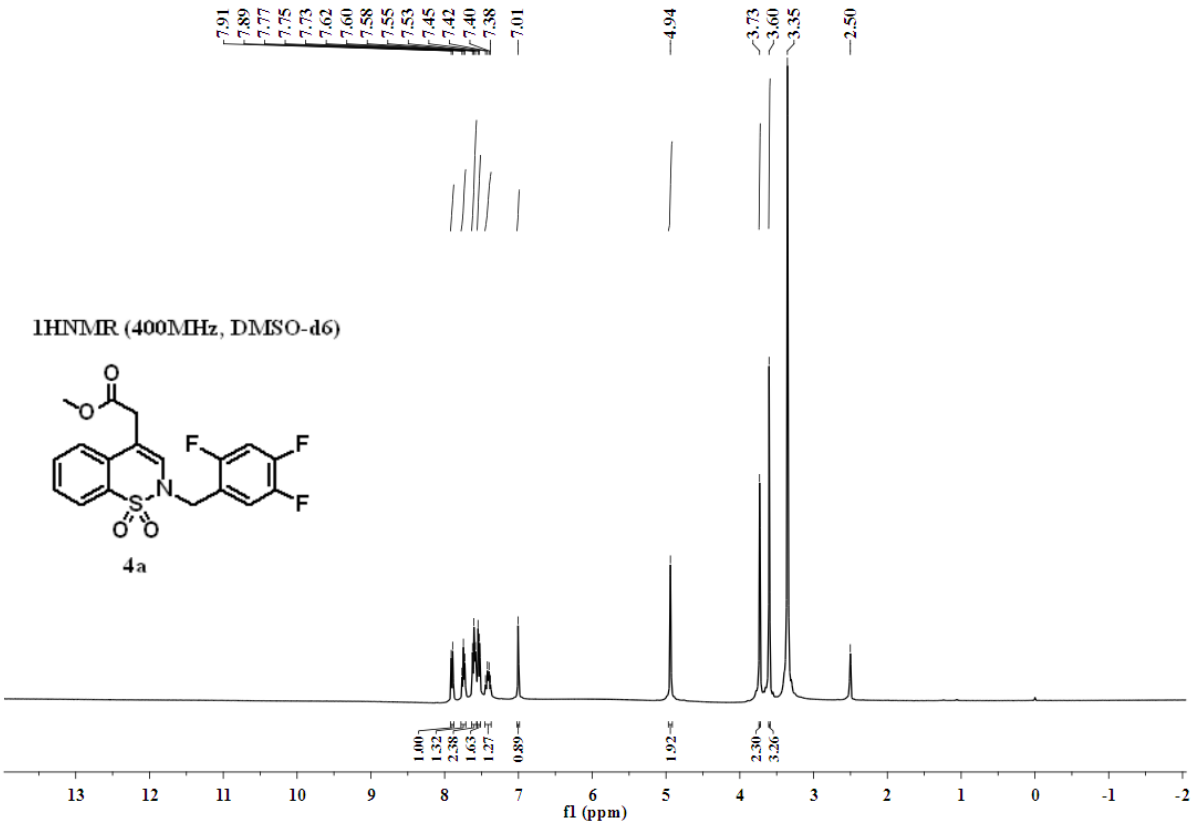
13CNMR (100MHz, DMSO-d6)

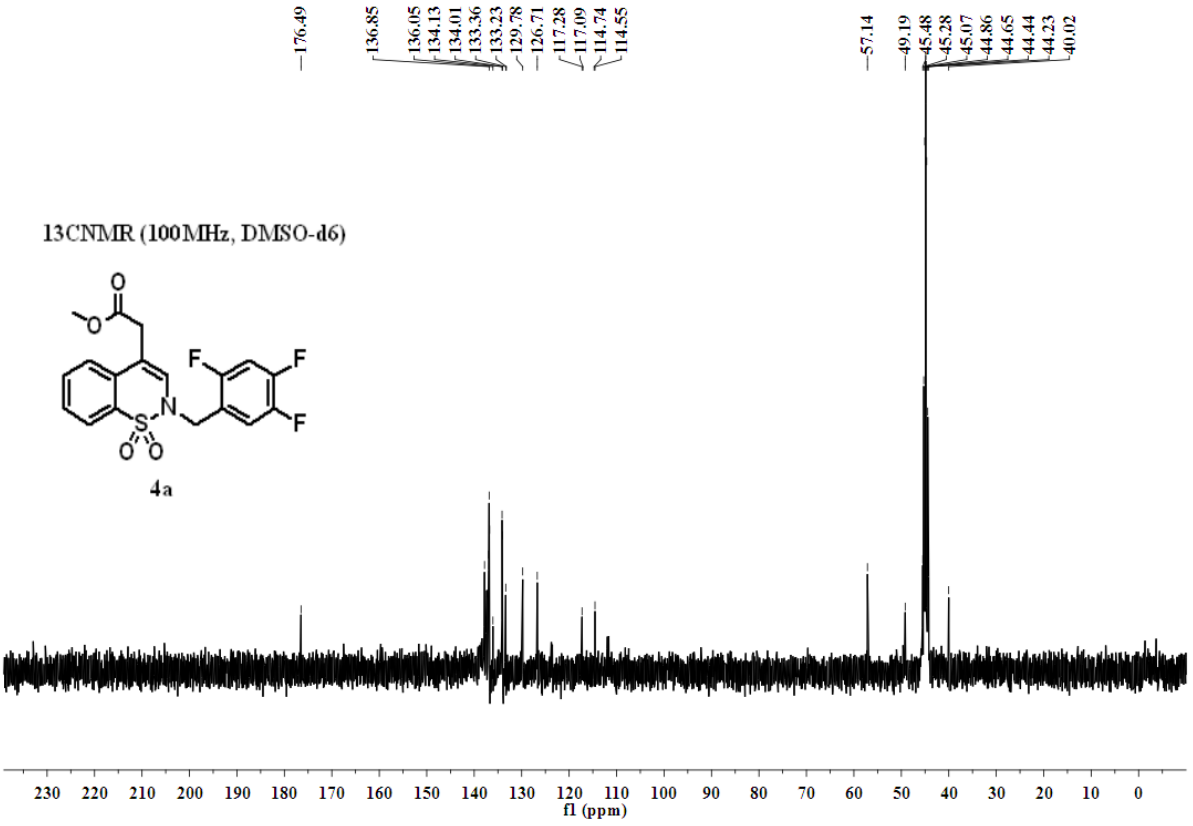


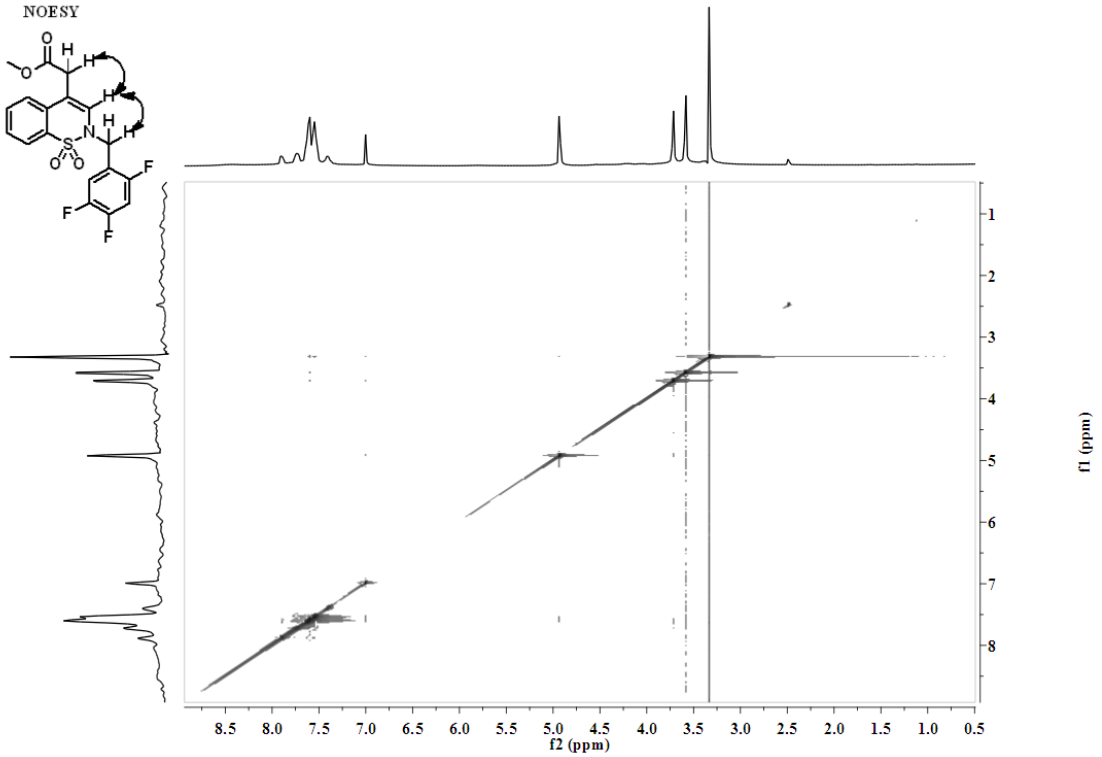
3a

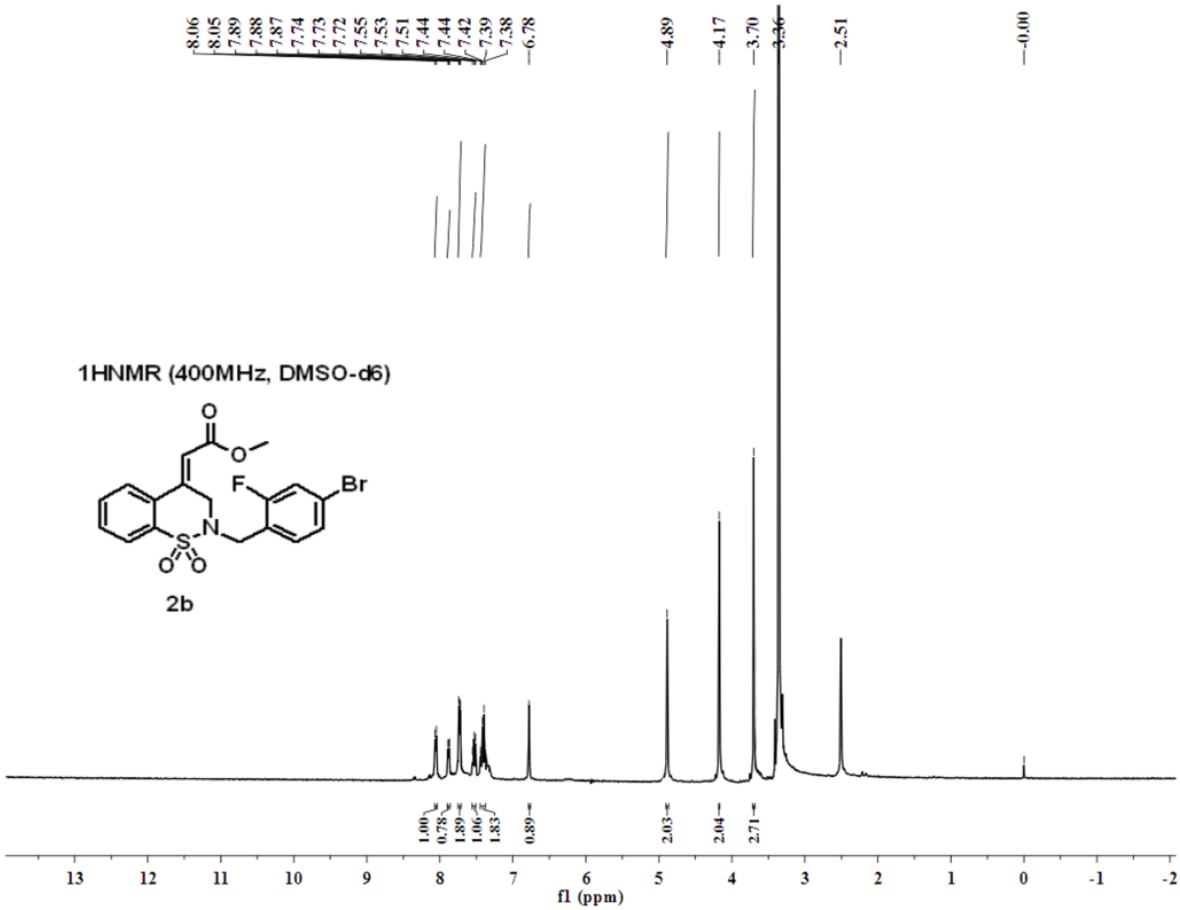
NOESY

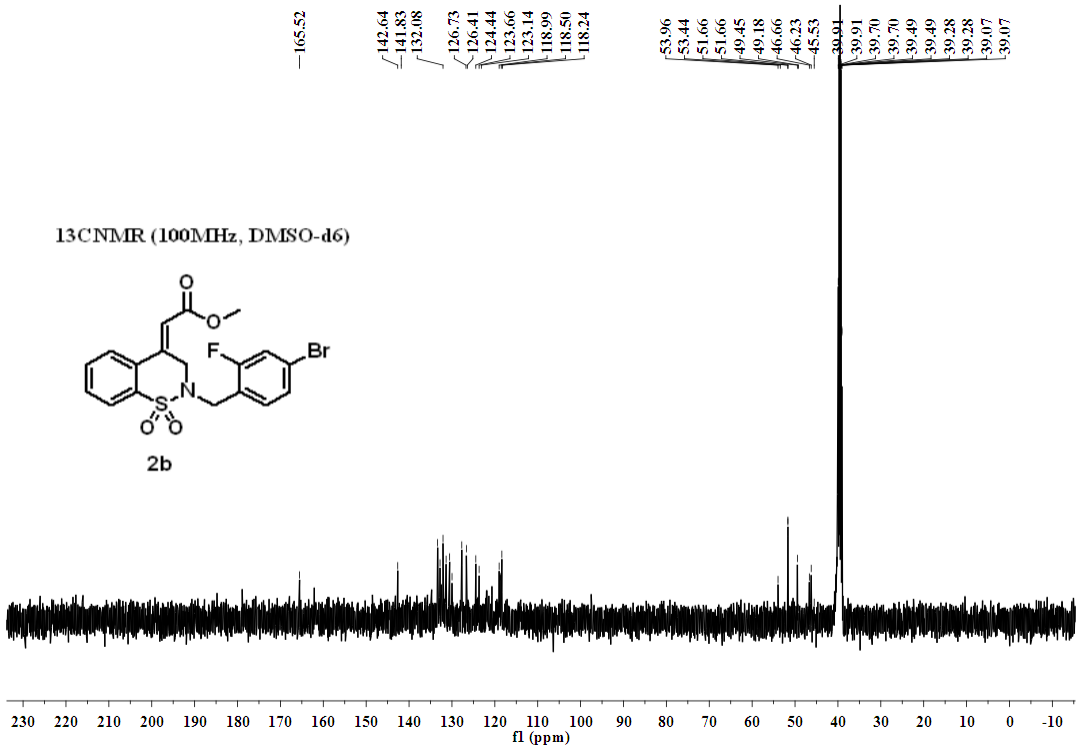


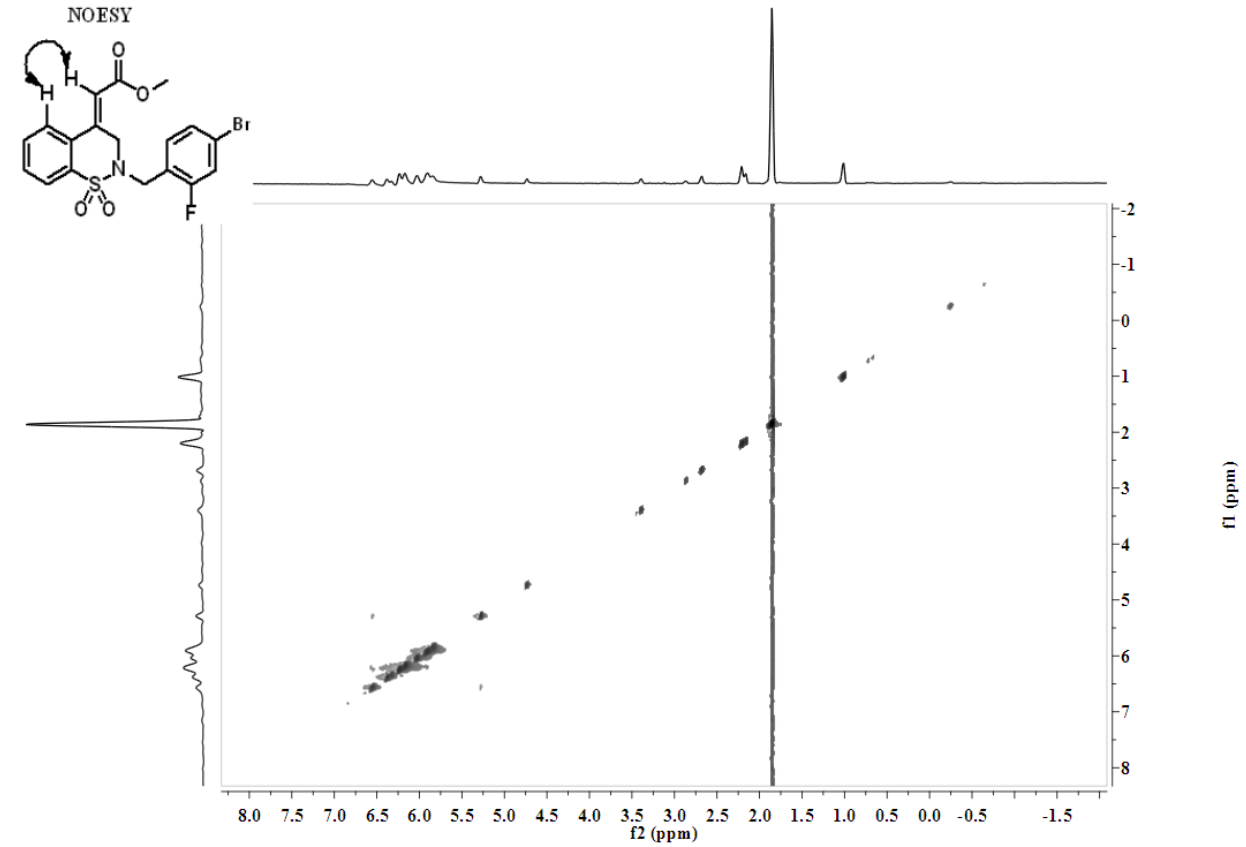

7.91
7.89
7.77
7.75
7.73
7.62
7.60
7.58
7.55
7.53
7.45
7.42
7.40
7.38
7.01
4.94
3.73
3.60
3.35
2.50
1HNMR (400MHz, DMSO-d6)
4a
1.00
1.32
2.38
1.63
1.27
0.89
1.92
2.30
3.26
fl (ppm)

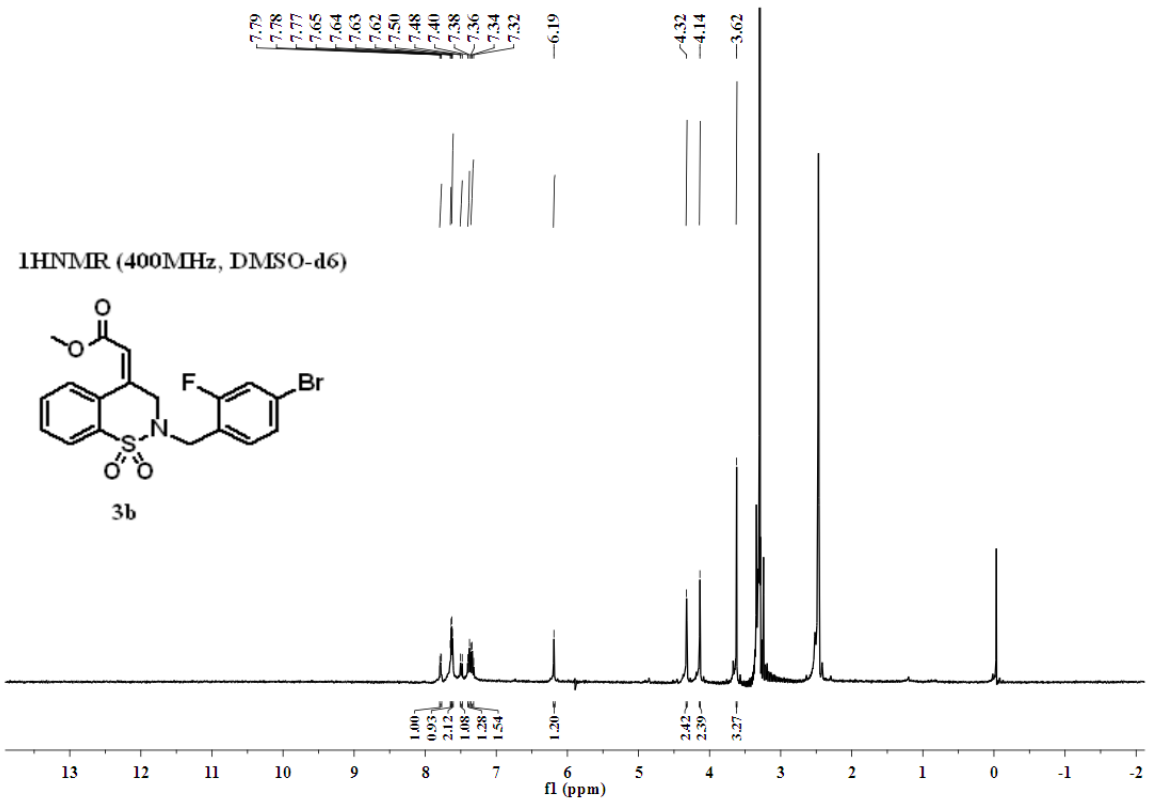

176.49
136.85
136.05
134.13
134.01
133.36
133.23
129.78
126.71
117.28
117.09
114.74
114.55
57.14
49.19
45.48
45.28
45.07
44.86
44.65
44.44
44.23
40.02
13CNMR (100MHz, DMSO-d6)
4a
fl (ppm)

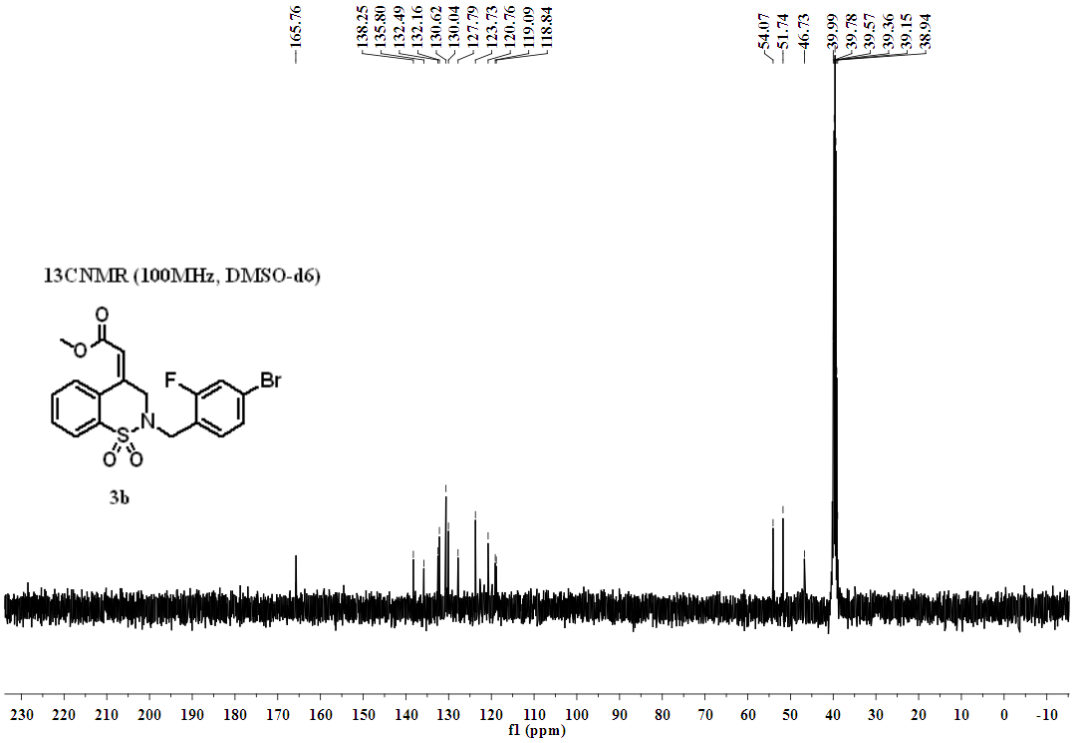

NOESY
f2 (ppm)
f1 (ppm)

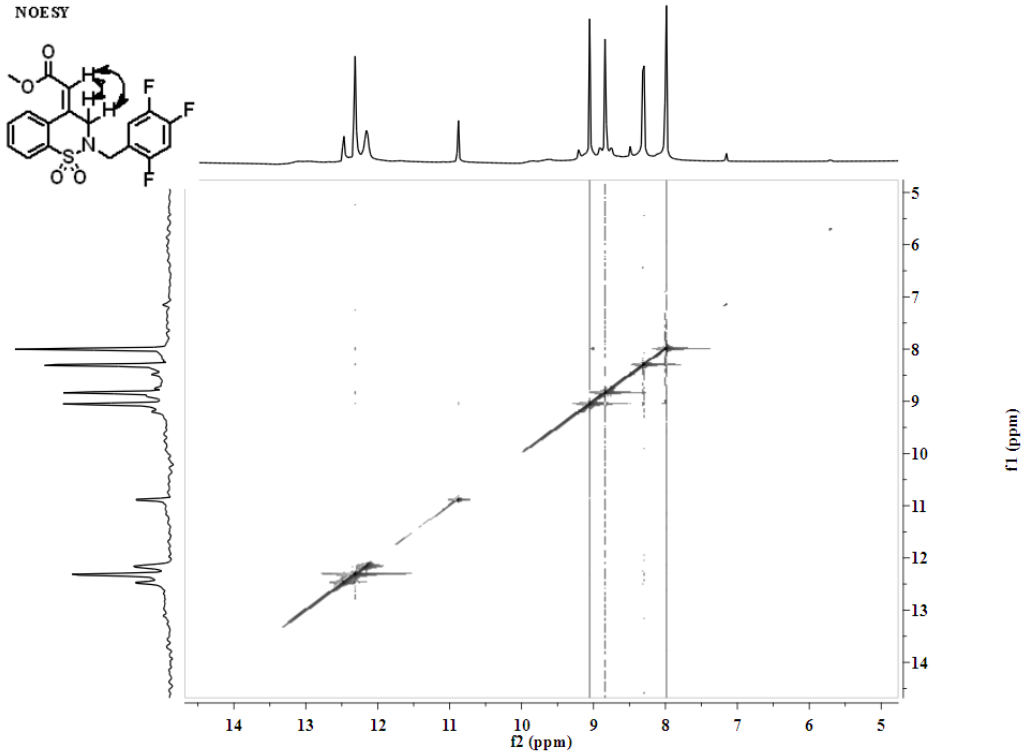

1HNMR (400MHz, DMSO-d6)
2b
f1 (ppm)

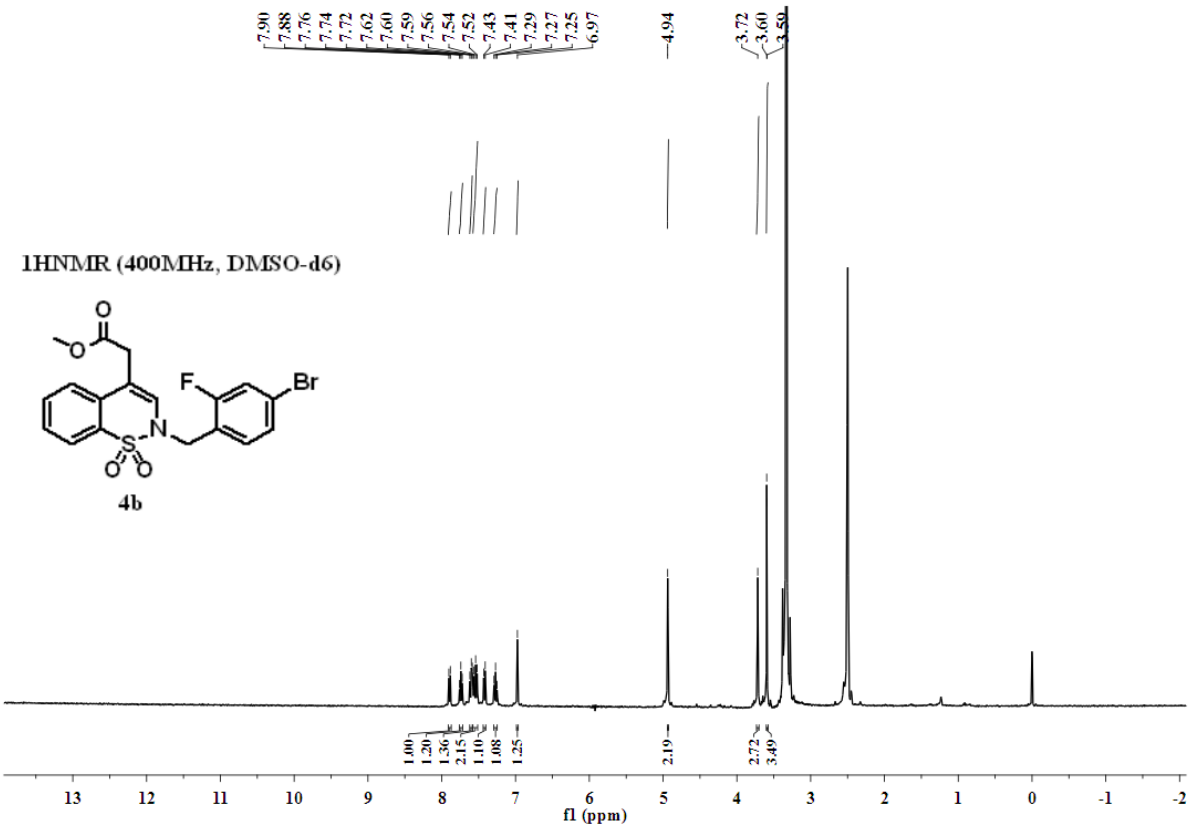

165.52
142.64
141.83
132.08
126.73
126.41
124.44
123.66
123.14
118.99
118.50
118.24
53.96
53.44
51.66
51.66
49.45
49.18
46.66
46.23
45.53
39.91
39.91
39.70
39.70
39.49
39.49
39.28
39.28
39.07
39.07
13CNMR (100MHz, DMSO-d6)
O
O
F
Br
N
S
O
O
2b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


NOESY
O
O
H
H
Br
N
S
O
O
F
-2
-1
0
1
2
3
4
5
6
7
8
f1 (ppm)
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 -1.5
f2 (ppm)

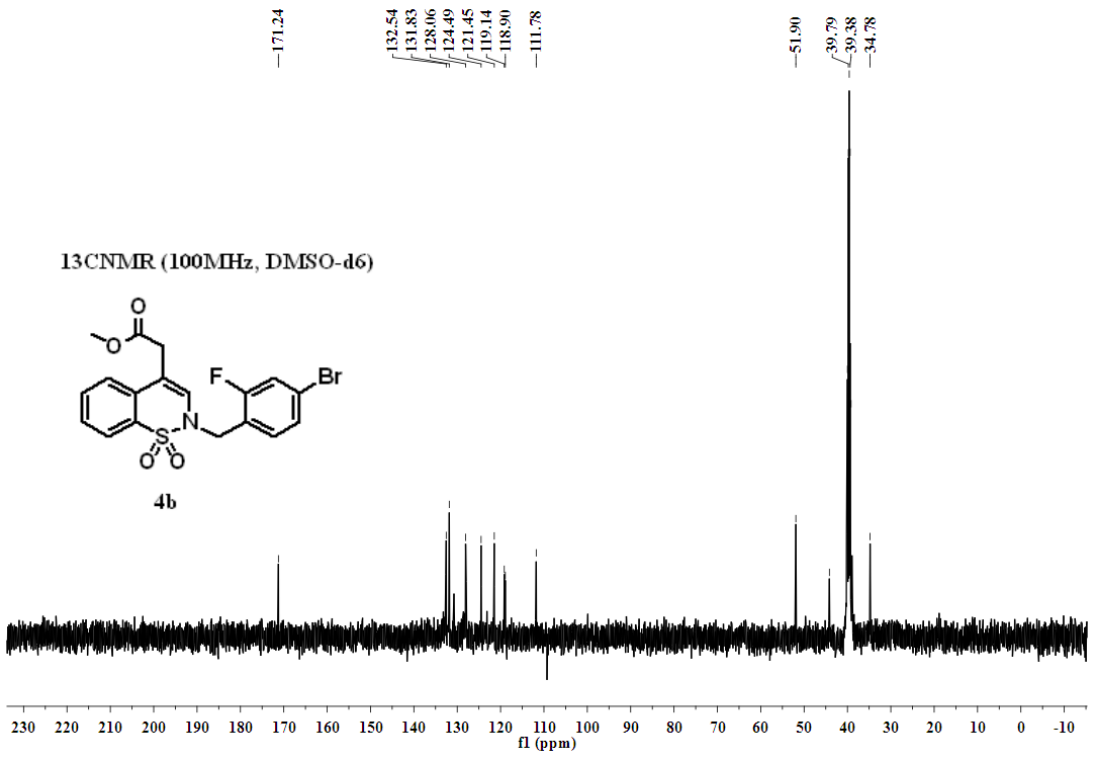

1HNMR (400MHz, DMSO-d6)
3b
7.79
7.78
7.77
7.65
7.64
7.63
7.62
7.50
7.48
7.40
7.38
7.36
7.34
7.32
6.19
4.32
4.14
3.62
1.00
0.93
2.12
1.08
1.28
1.54
1.20
2.42
2.39
3.27
fl (ppm)

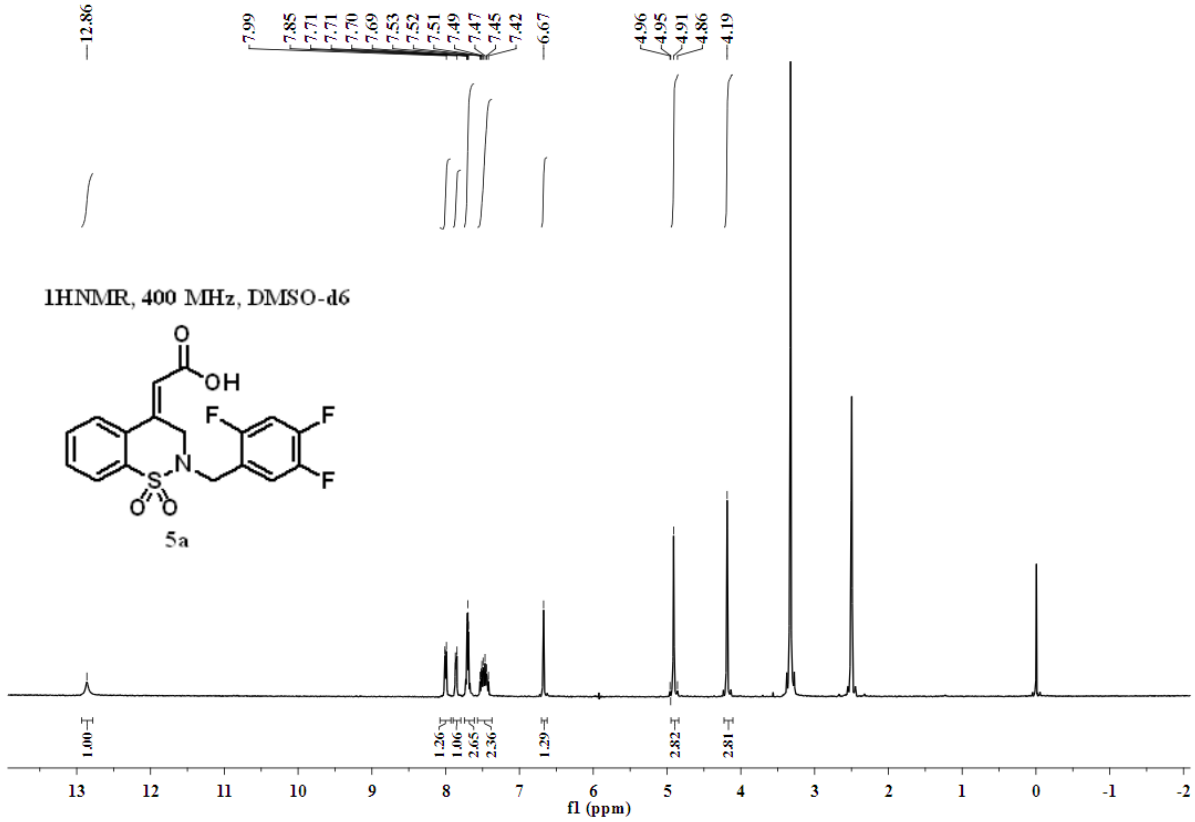

13CNMR (100MHz, DMSO-d6)
3b
165.76
138.25
135.80
132.49
132.16
130.62
130.04
127.79
123.73
120.76
119.09
118.84
54.07
51.74
46.73
39.99
39.78
39.57
39.36
39.15
38.94
fl (ppm)

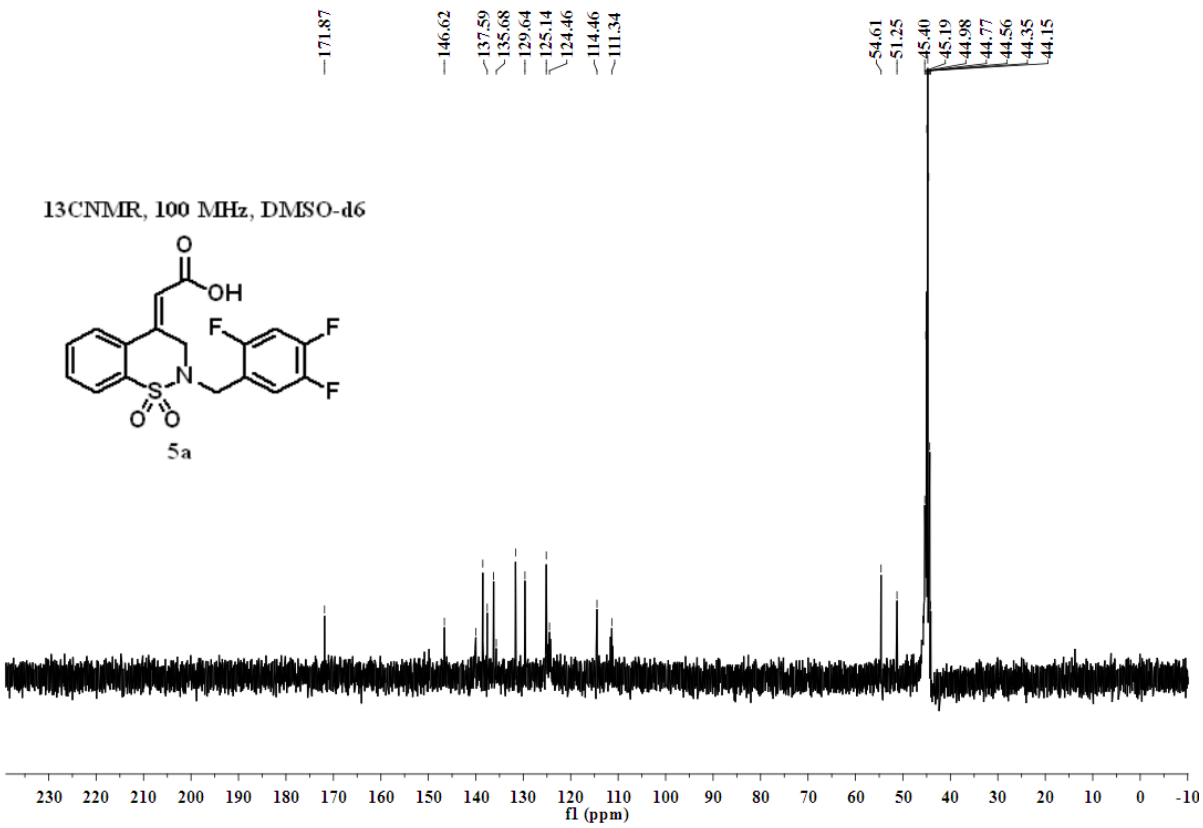

NOESY
f2 (ppm)
f1 (ppm)

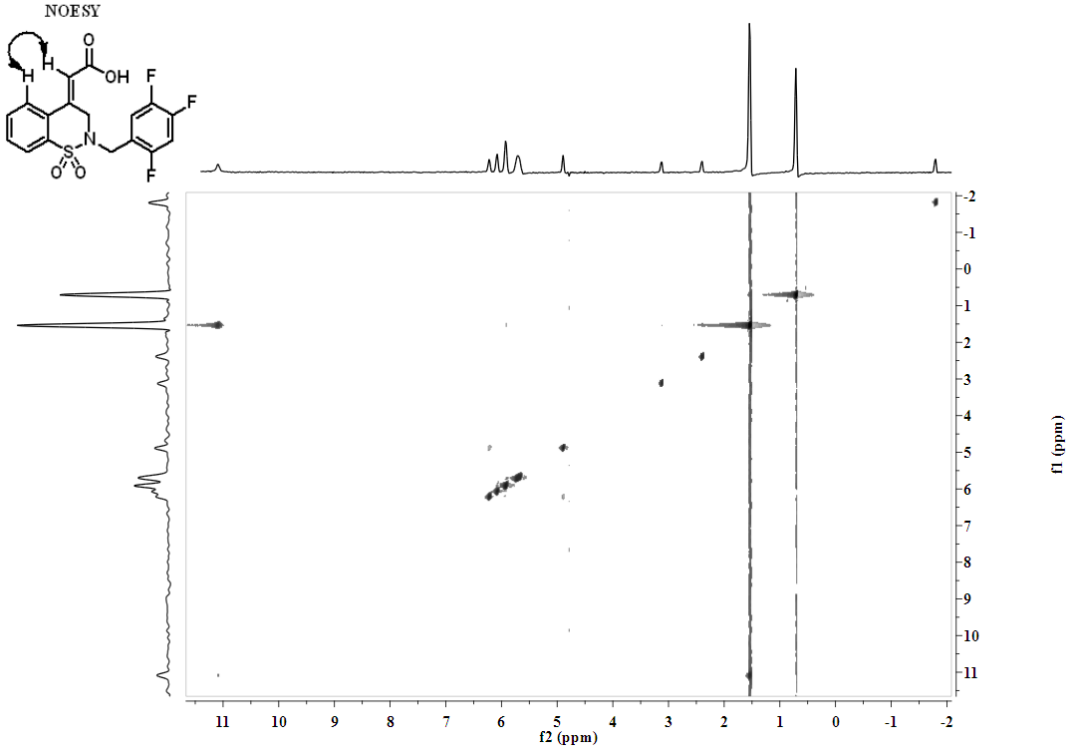

1HNMR (400MHz, DMSO-d6)
7.90
7.88
7.76
7.74
7.72
7.62
7.60
7.59
7.56
7.54
7.52
7.43
7.41
7.29
7.27
7.25
6.97
4.94
3.72
3.60
3.59
1.00
1.20
1.36
2.15
1.10
1.08
1.25
2.19
2.72
3.49
f1 (ppm)

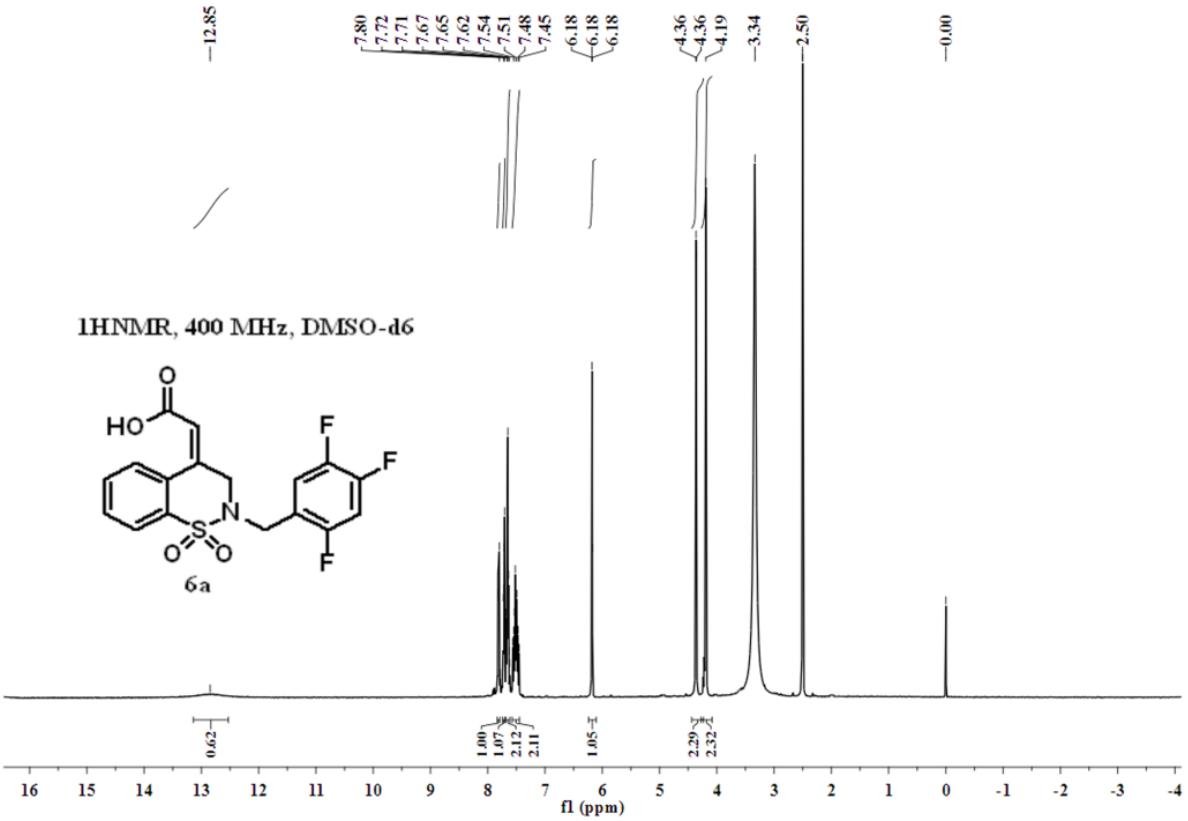
4b

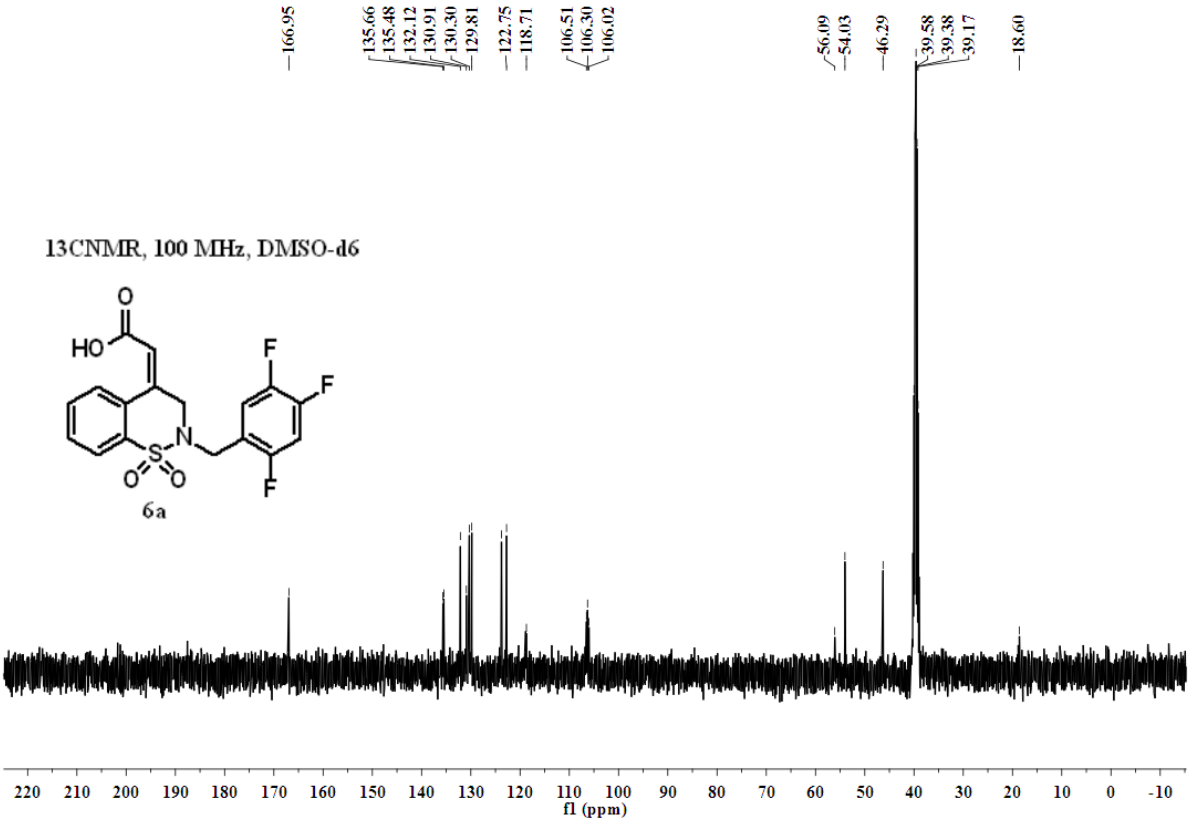

171.24
132.54
131.83
128.06
124.49
121.45
119.14
118.90
111.78
51.90
39.79
39.38
34.78
13CNMR (100MHz, DMSO-d6)
O
O
F
Br
N
S
O
O
4b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

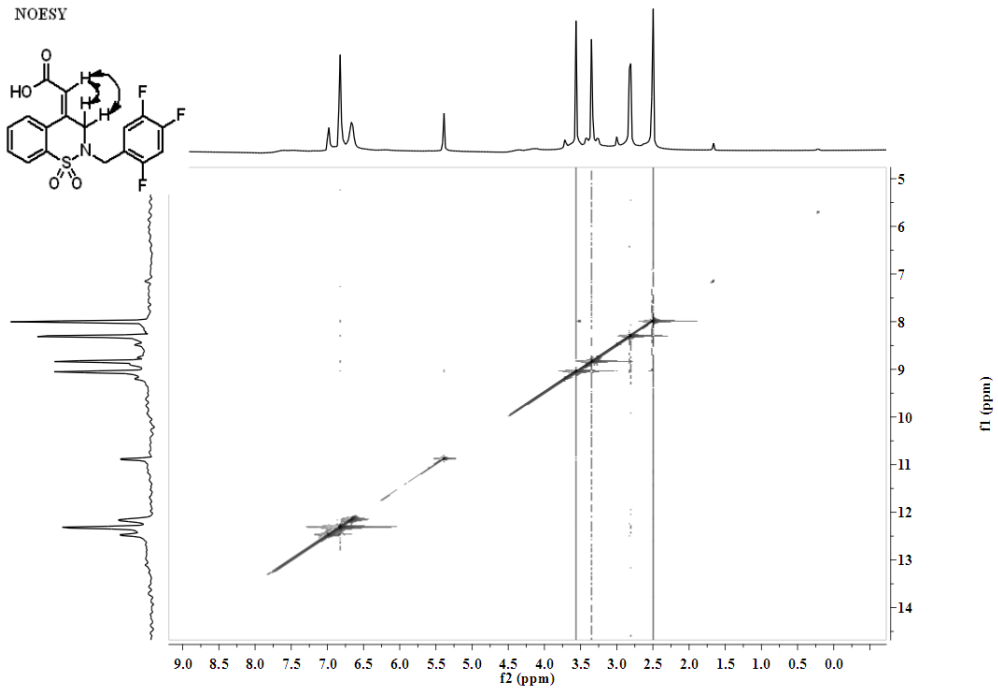

12.86
7.99
7.85
7.71
7.71
7.70
7.69
7.53
7.52
7.51
7.49
7.47
7.45
7.42
6.67
4.96
4.95
4.91
4.86
4.19
1HNMR, 400 MHz, DMSO-d6
O
OH
F
F
F
N
S
O
O
5a
1.00
1.26
1.06
2.65
2.36
1.29
2.82
2.81
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

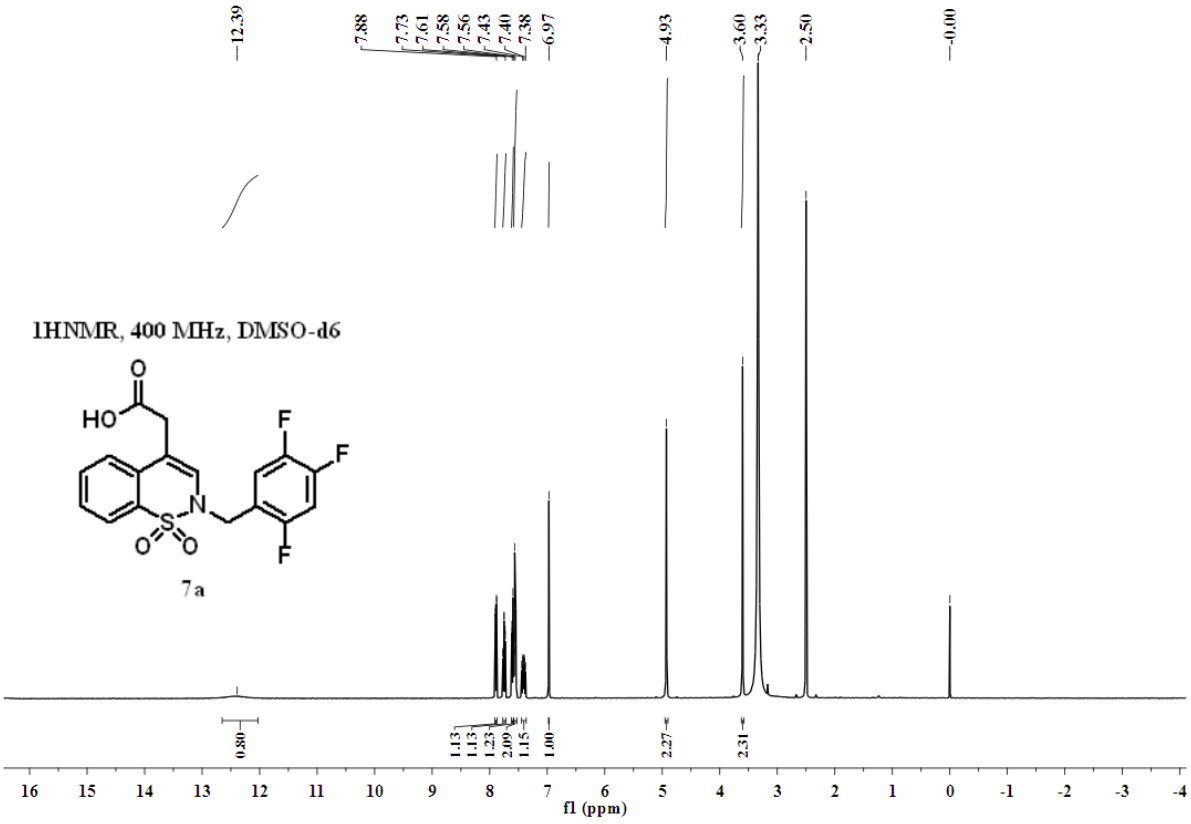

171.87
146.62
137.59
135.68
129.64
125.14
124.46
114.46
111.34
54.61
51.25
45.40
45.19
44.98
44.77
44.56
44.35
44.15
13CNMR, 100 MHz, DMSO-d6
O
OH
F
F
F
N
S
O
O
5a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

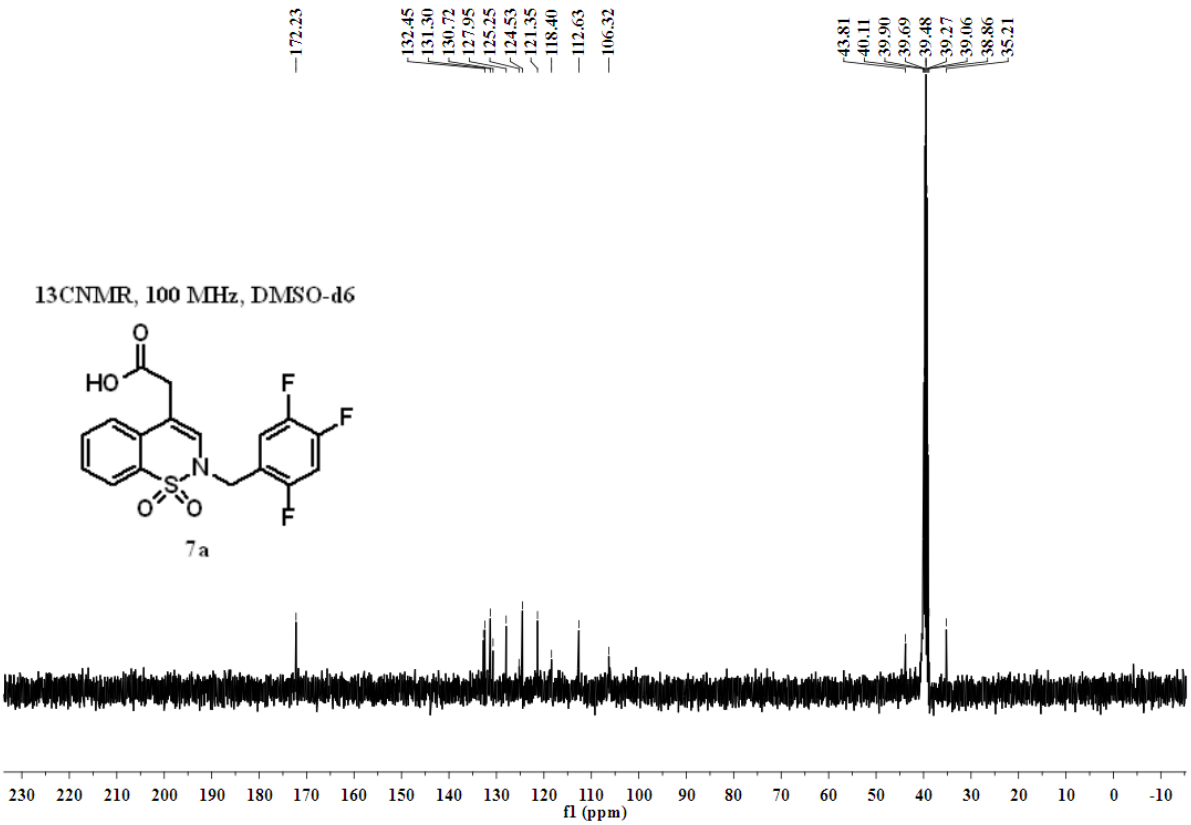

NOESY
H
H
O
OH
F
F
F
N
S
O
O
-2 -1 0 1 2 3 4 5 6 7 8 9 10 11
f1 (ppm)
11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f2 (ppm)

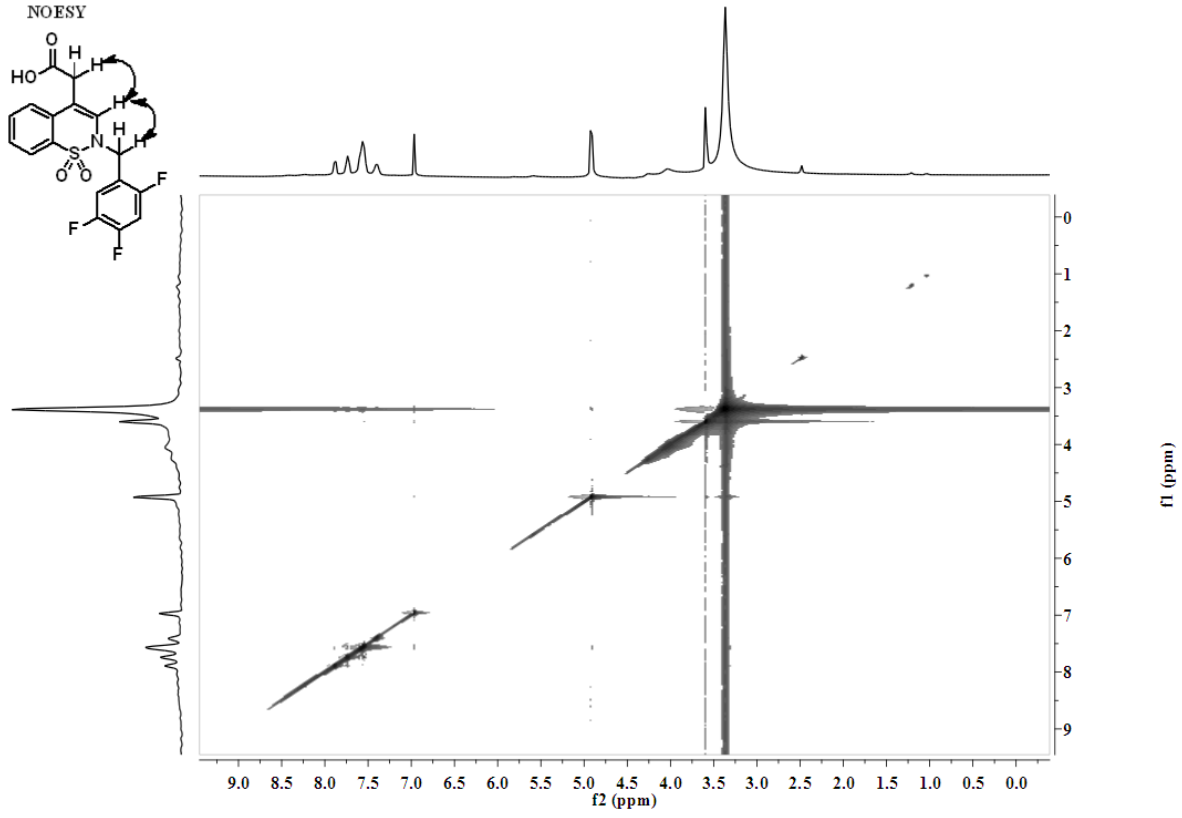

1HNMR, 400 MHz, DMSO-d6
6a
fl (ppm)

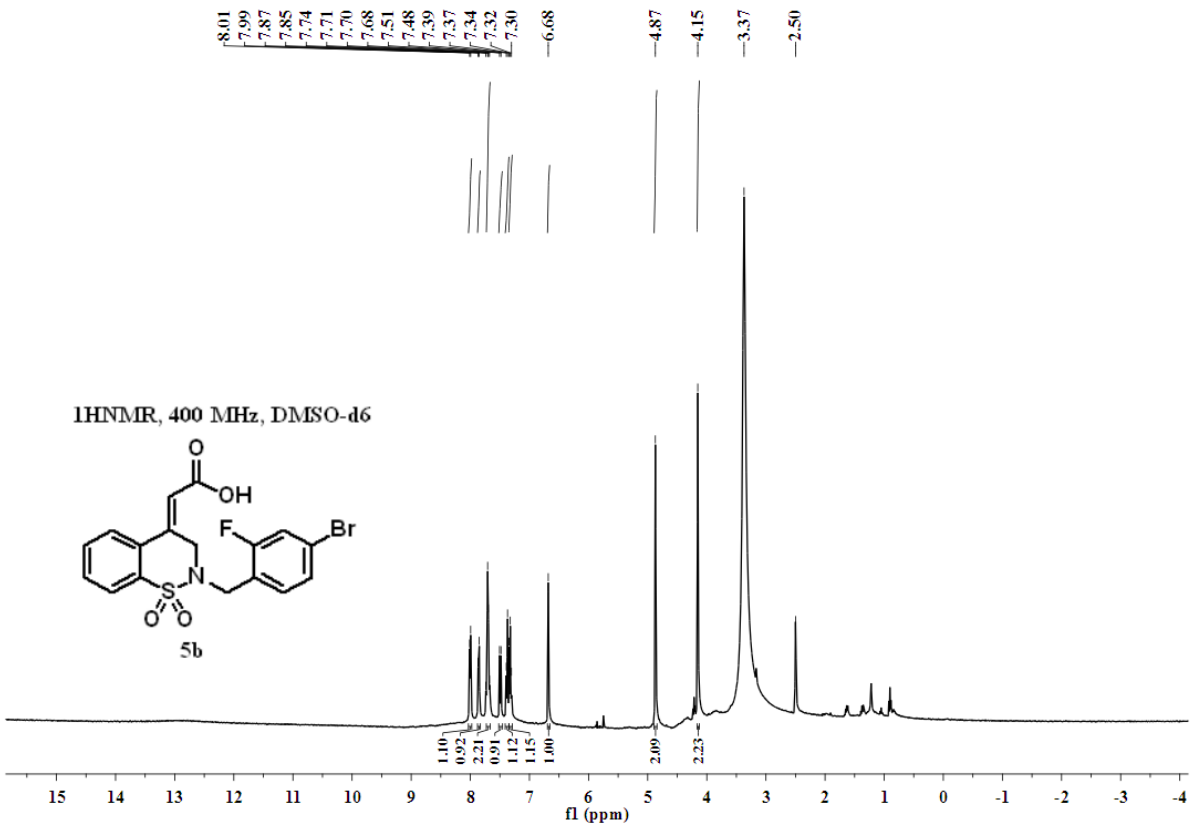

13CNMR, 100 MHz, DMSO-d6
6a
fl (ppm)

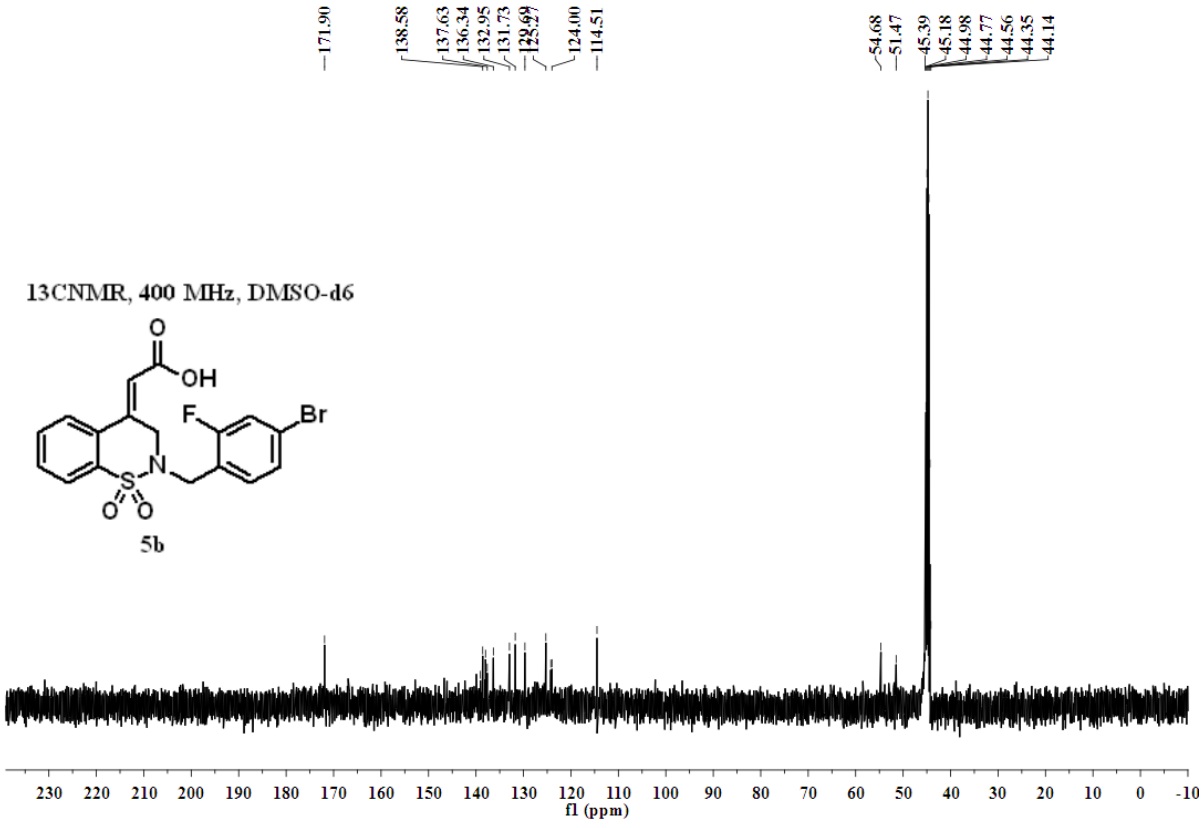

NOESY
f2 (ppm)
f1 (ppm)

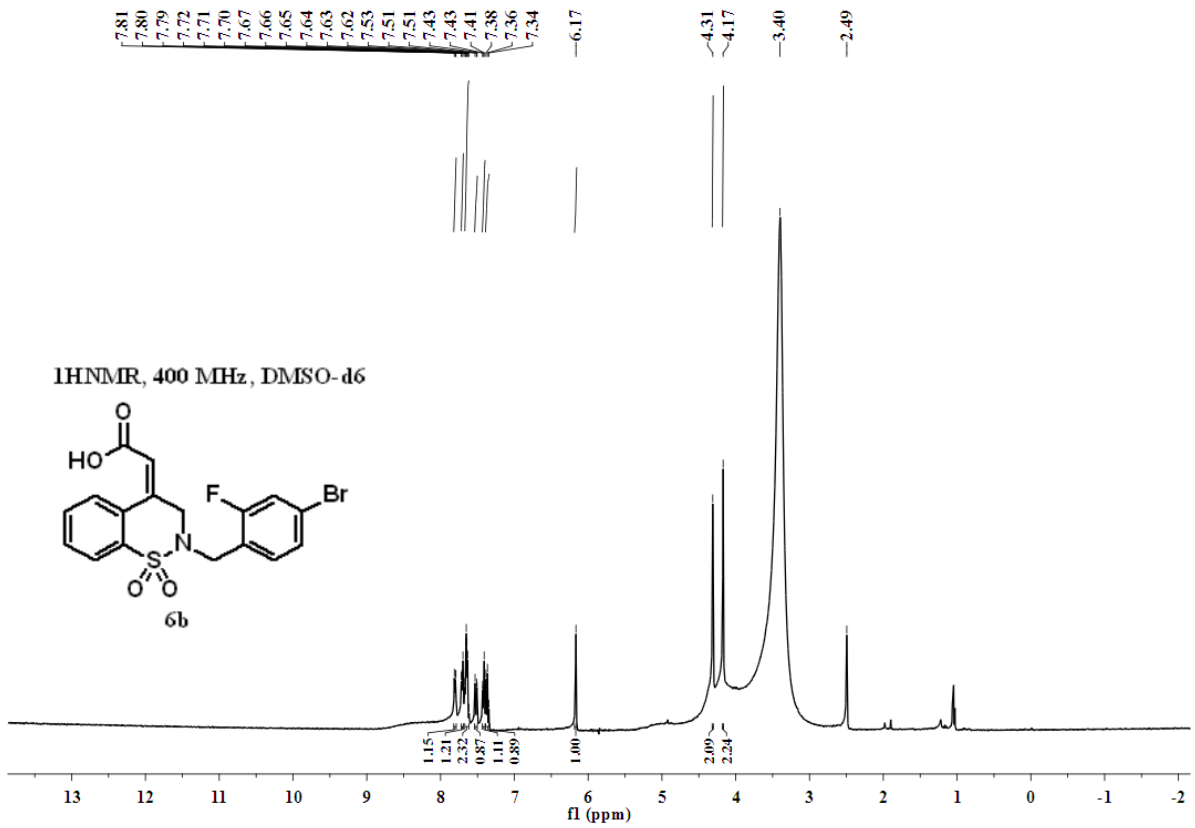

1HNMR, 400 MHz, DMSO-d6
7a
f1 (ppm)

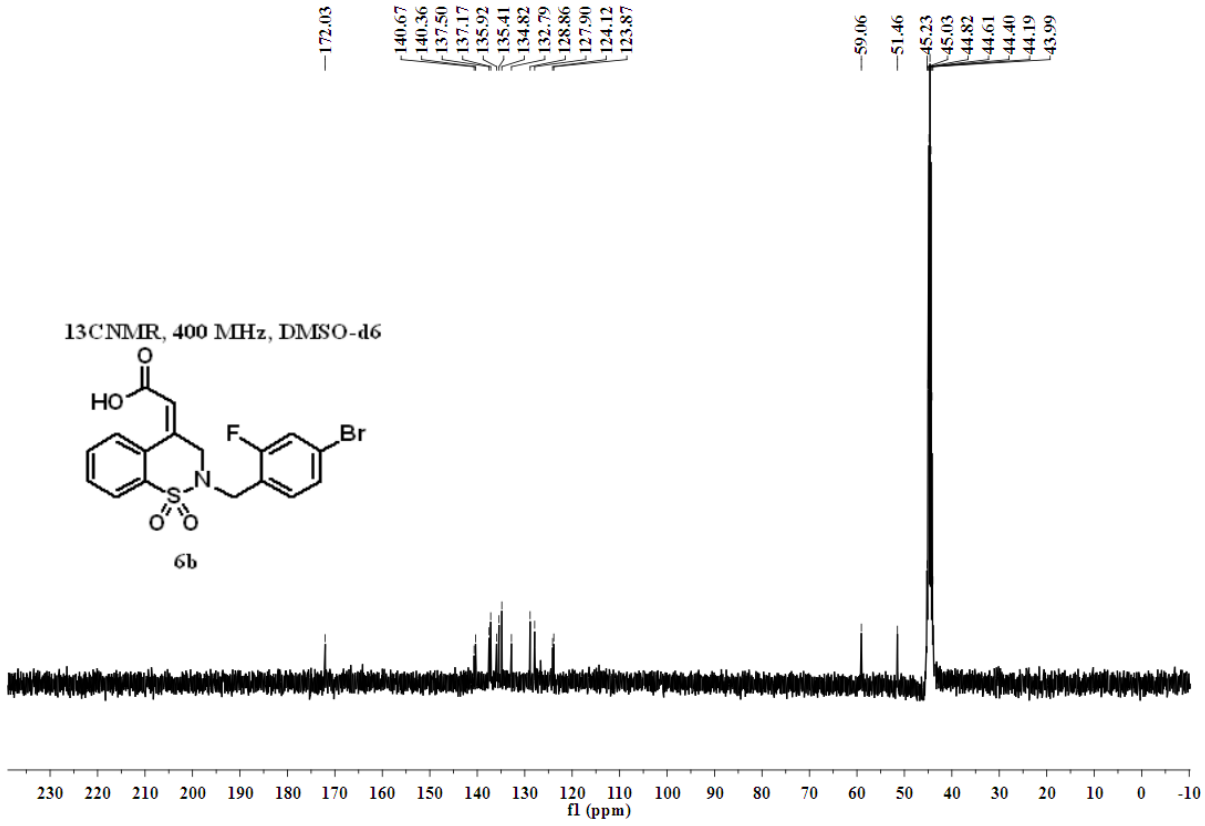

172.23
132.45
131.30
130.72
127.95
125.25
124.53
121.35
118.40
112.63
106.32
43.81
40.11
39.90
39.69
39.48
39.27
39.06
38.86
35.21
13CNMR, 100 MHz, DMSO-d6
HO
O
F
F
F
N
S
O
O
7a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

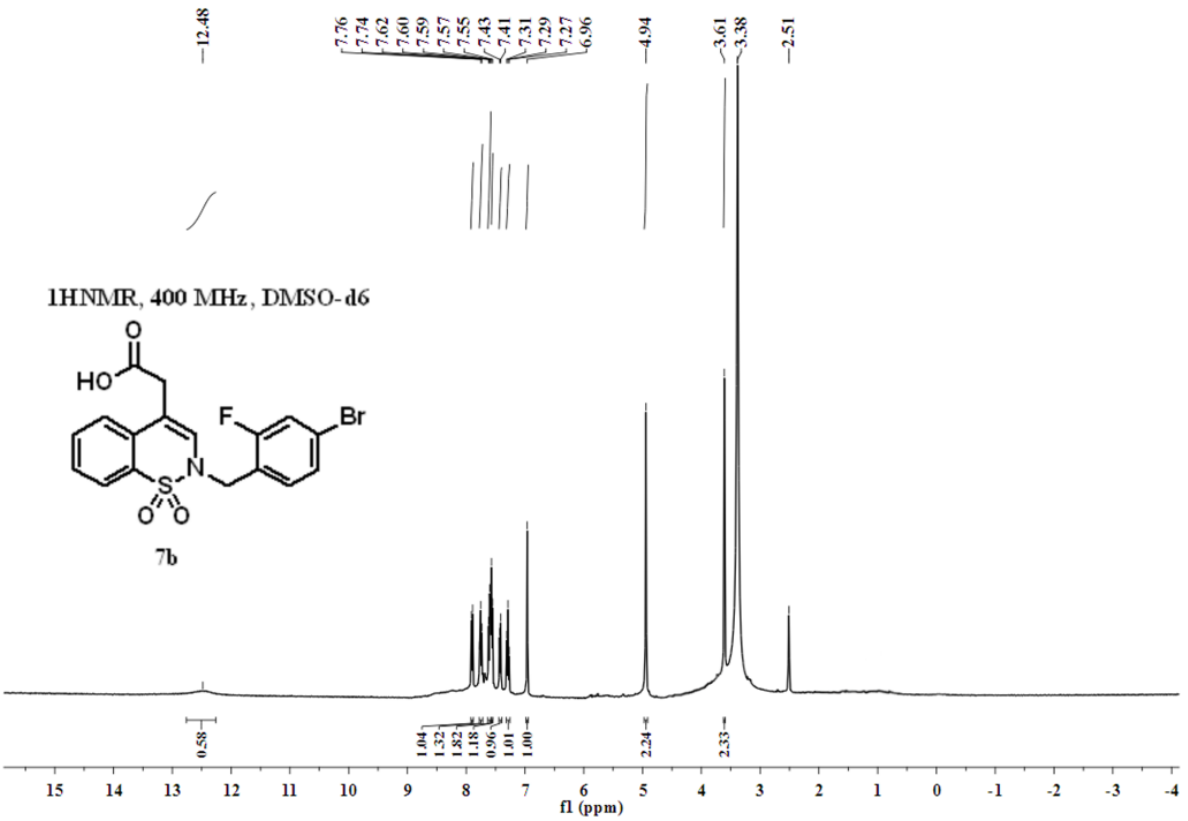

NOESY
HO
O
H
F
F
F
N
S
O
O
0 1 2 3 4 5 6 7 8 9
f1 (ppm)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)

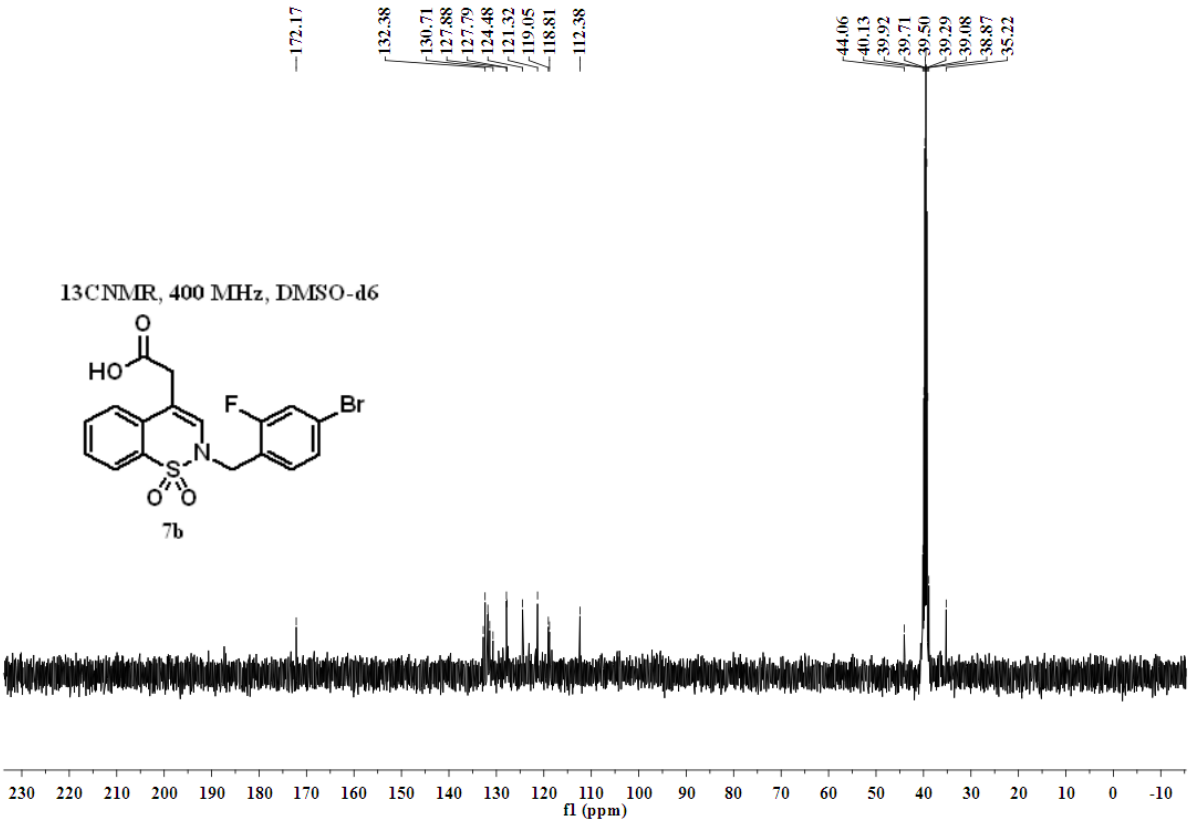

8.01
7.99
7.87
7.85
7.74
7.71
7.70
7.68
7.51
7.48
7.39
7.37
7.34
7.32
7.30
6.68
4.87
4.15
3.37
2.50
1HNMR, 400 MHz, DMSO-d6
O
OH
F
Br
N
S
O
O
5b
1.10
0.92
2.21
0.91
1.12
1.15
1.00
2.09
2.23
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)


171.90
138.58
137.63
136.34
132.95
131.73
129.69
125.27
124.00
114.51
54.68
51.47
45.39
45.18
44.98
44.77
44.56
44.35
44.14
13CNMR, 400 MHz, DMSO-d6
O
OH
F
Br
N
S
O
O
5b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


1HNMR, 400 MHz, DMSO-d6
HO
O
F
Br
N
S
O
O
6b
7.81
7.80
7.79
7.72
7.71
7.70
7.67
7.66
7.65
7.64
7.63
7.62
7.53
7.51
7.51
7.43
7.43
7.41
7.38
7.36
7.34
6.17
4.31
4.17
3.40
2.49
1.15
1.21
2.32
0.87
1.11
0.89
1.00
2.09
2.24
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

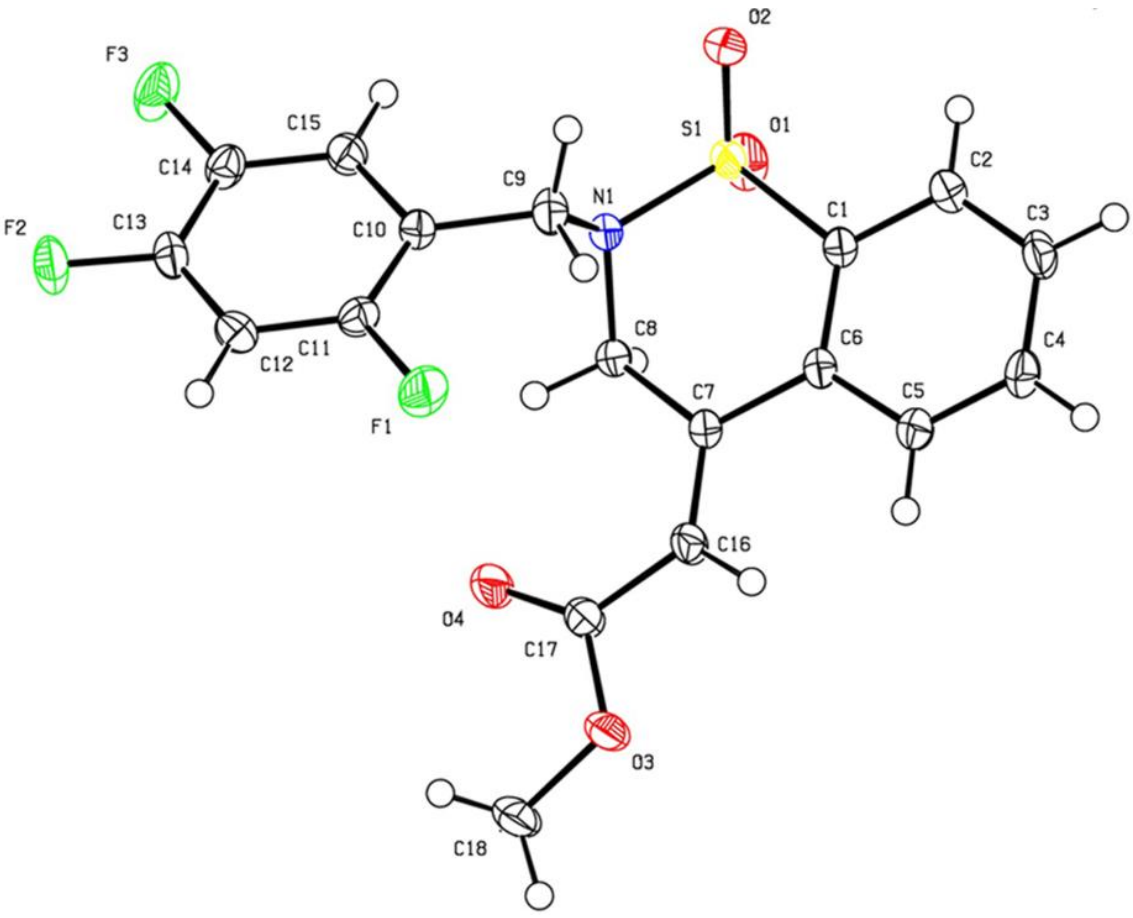

13CNMR, 400 MHz, DMSO-d6
HO
O
F
Br
N
S
O
O
6b
172.03
140.67
140.36
137.50
137.17
135.92
135.41
134.82
132.79
128.86
127.90
124.12
123.87
59.06
51.46
45.23
45.03
44.82
44.61
44.40
44.19
43.99
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


12.48
7.76
7.74
7.62
7.60
7.59
7.57
7.55
7.43
7.41
7.31
7.29
7.27
6.96
4.94
3.61
3.38
2.51
1HNMR, 400 MHz, DMSO-d6
HO
O
F
Br
N
S
O
O
7b
0.58
1.04
1.32
1.82
1.18
0.96
1.01
1.00
2.24
2.33
fl (ppm)


172.17
132.38
130.71
127.88
127.79
124.48
121.32
119.05
118.81
112.38
44.06
40.13
39.92
39.71
39.50
39.29
39.08
38.87
35.22
13CNMR, 400 MHz, DMSO-d6
HO
O
F
Br
N
S
O
O
7b
fl (ppm)

3: X-Ray Crystallography Data

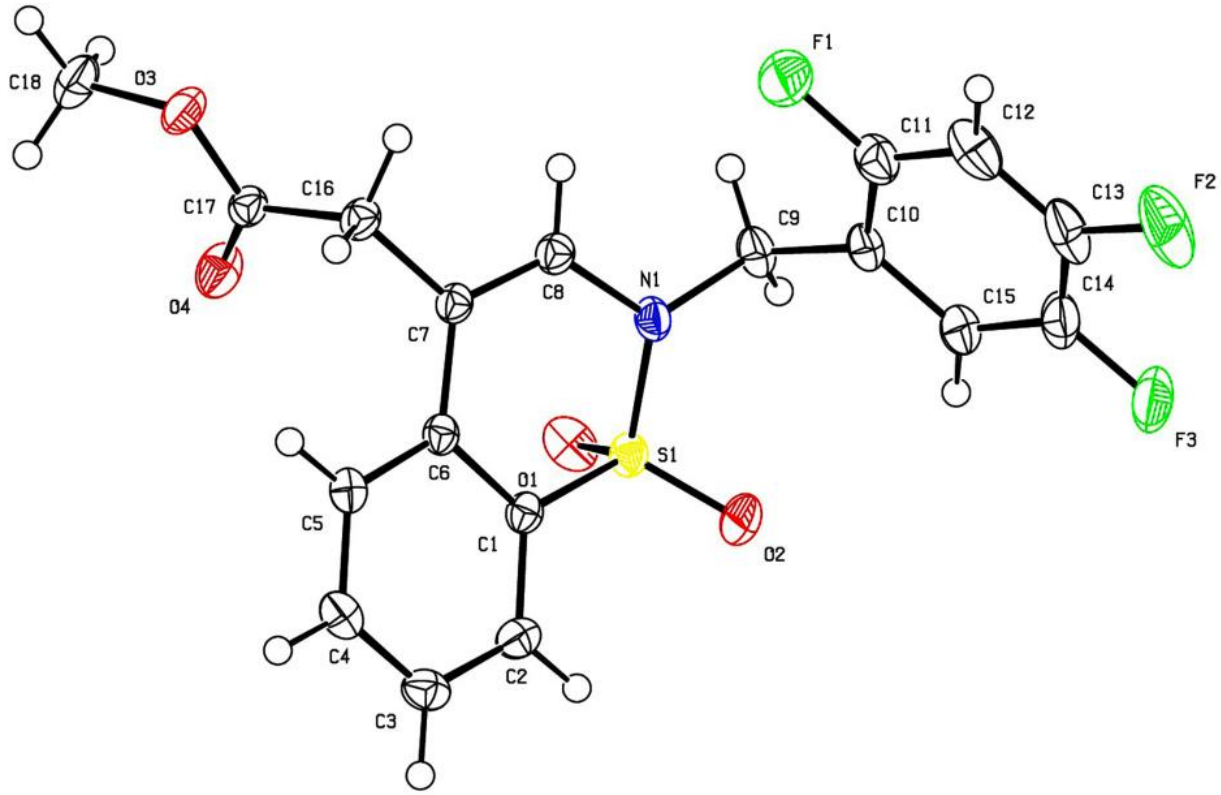
3.1: X-Ray Single Crystal analysis of 2a



Empirical formula	$C_{18}\ H_{14}\ F_3\ N\ O_4\ S$
Formula weight	397.36
Temperature	153(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 18.947(5) A alpha = 90 deg.
	b = 8.529(2) A beta = 110.800(3) deg.

	c = 22.067(6) A gamma = 90 deg.
Volume	3333.8(15) A^3
Z, Calculated density	8, 1.583 Mg/m^3
Absorption coefficient	0.252 mm^-1
F(000)	1632
Crystal size	0.60 x 0.40 x 0.34 mm
Theta range for data collection	2.65 to 29.13 deg.
Limiting indices	-25<=h<=25, -11<=k<=11, -25<=l<=30
Reflections collected / unique	17852 / 4476 [R(int) = 0.0295]
Completeness to theta = 29.13	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9202 and 0.8633
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4476 / 0 / 246
Goodness-of-fit on F^2	1.000
Final R indices [I>2sigma(I)]	R1 = 0.0425, wR2 = 0.1141
R indices (all data)	R1 = 0.0485, wR2 = 0.1201
Extinction coefficient	0.0008(3)
Largest diff. peak and hole	0.272 and -0.387 e.A^-3

3.2: X-Ray Single Crystal analysis of 4a



Empirical formula	$C_{18}\ H_{14}\ F_3\ N\ O_4\ S$
Formula weight	397.36
Temperature	153(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.1171(13) A alpha = 98.125(13) deg.
	b = 9.6587(18) A beta = 103.944(10) deg.
	c = 11.5594(18) A gamma = 117.147(8) deg.
Volume	841.1(2) A^3
Z, Calculated density	2, 1.569 Mg/m^3
Absorption coefficient	0.250 mm^-1
F(000)	408

Crystal size	0.52 x 0.47 x 0.45 mm
Theta range for data collection	2.48 to 29.14 deg.
Limiting indices	-12<=h<=11, -13<=k<=13, -15<=l<=15
Reflections collected / unique	10513 / 4426 [R(int) = 0.0279]
Completeness to theta = 29.14	97.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8958 and 0.8809
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4426 / 0 / 246
Goodness-of-fit on F^2	1.004
Final R indices [I>2sigma(I)]	R1 = 0.0383, wR2 = 0.1007
R indices (all data)	R1 = 0.0472, wR2 = 0.1063
Extinction coefficient	0.005(4)
Largest diff. peak and hole	0.370 and -0.420 e.A^-3