Supporting Information

Exploring Synthetic and Therapeutic Prospects of New Thiazoline Derivatives as Aldose Reductase (ALR2) Inhibitors

Muhammad Tariq Shehzad,[a‡] , Aqeel Imran[b‡], Abdul Hameed[c], Mariya al-Rashida[c], Marium Bibi,[d] Maliha Uroos,[e] Asnuzilawati Asari,[f] Shafia Iftikhar,[g] Habsah Mohamad,[h] Muhammad Nawaz Tahir,[i] Zahid Shafiq,[a*] and Jamshed Iqbal,[b*]

[a] Institute of Chemical Sciences, Bahauddin Zakariya University, Multan 60800, Pakistan
[b]Centre for Advanced Drug Research, COMSATS University Islamabad, Abbottabad Campus, Abbottabad-22060, Pakistan
[c]Department of Chemistry, Forman Christian College (A Chartered University), Ferozepur Road, Lahore-54600, Pakistan

[d] Department of Biosciences, 90 and 100 Clifton, Shaheed Zulfikar Ali Bhutto Institute of Science and Technology, Block 5, Clifton, Karachi-75600, Pakistan
[e] Institute of Chemistry, University of The Punjab, Lahore-54590, Pakistan
[f] Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia
[g] Department of Chemistry, University of Sahiwal, Sahiwal 57000, Pakistan
[h] Institute of Marine Biotechnology, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia
[i] Department of Physics, University of Sargodha, Sargodha, Pakistan

‡Both authors contributed equally

*zahidshafiq@bzu.edu.pk (Z. Shafiq)

*drjamshed@ciit.net.pk / jamshediqb@googlemail.com (J. Iqbal).

Molecular Docking Studies.

Protein selection ;

To perform docking analysis , crystalized protein structures were downloaded in PDB format. The crystal structures of porcine ALR1[1] and human ALR2[2] were downloaded from the Protein Data Bank [PDB ids: 3FX4 at 1.99 Å and 1US0 at 0.66 Å respectively]. The porcine and human ALR1 bears identical active site residues and approximately 97% sequence homology. The issues related downloaded crystallographic protein were resolved like removal of undesired co-crystal ligand and water molecules. The addition of hydrogen atoms and correct charges were assigned to protein structures.

Preparation of the ligands:

The structures for newly synthesized derivatives were developed by using builder tool of MOE software (version 2019). Initially, the charges were assigned to each atom and hydrogen atoms were added to all synthesized derivatives. Eventually, the energy minimization for each inhibitor's structure was performed via applying force field named MMFF94x along with RMS gradient of 0.001kcal/mol/A^2.

Docking studies:

Docking studies for ALR1 and ALR2 were executed through automated molecular docking program LeadIT(2.3.2) using default parameters. While using LeadIT software first PDB protein structure is uploaded during new project execution then receptor preparation (3FX4 and 1US0) was carried out. The ligand structure was uploaded and docking study was initiated. LeadIt generated various docked poses. The hyde assessment for these docked pose was done and free binding energy was estimated. Those poses exhibited lowest free binding energy (ΔG), were chosen for further visualization of docked compound at the active site of enzyme. The exploration of putative 2D and 3D binding interaction of inhibitor with residues of active site of the enzyme was carried out by using Discovery studio visualizer (Discovery Studio Visualizer, 4.0).

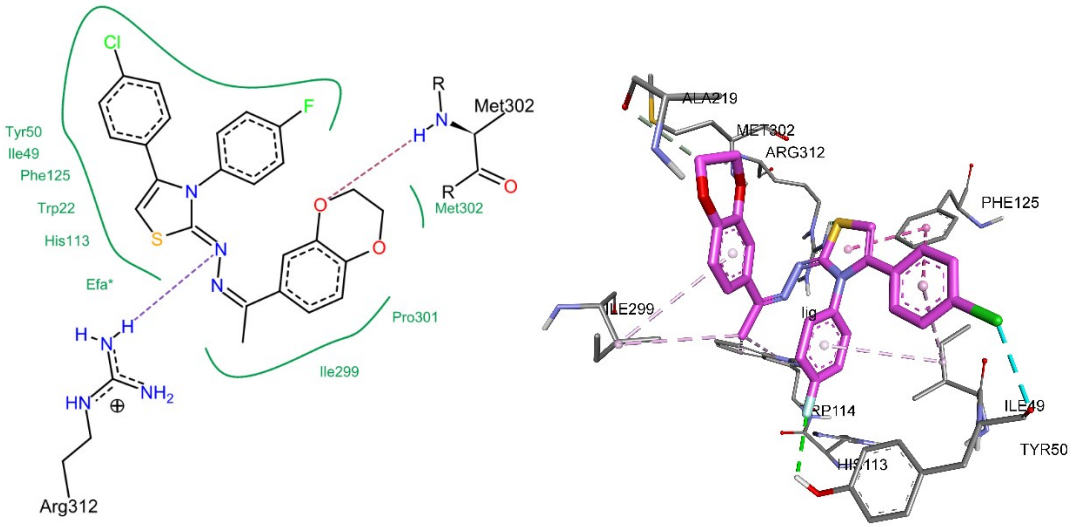


Figure S1: Docked conformation of ALR1 inhibitor **7h**.

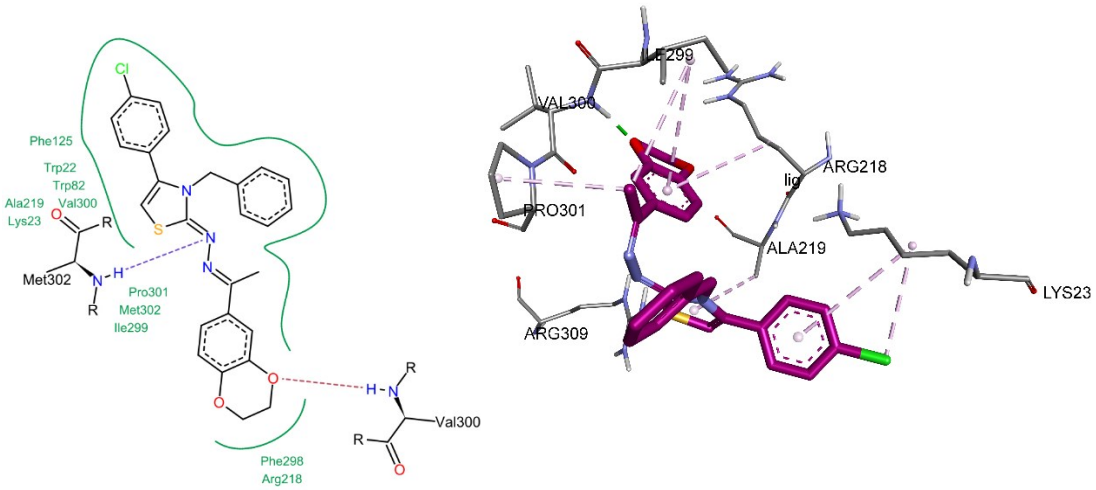


Figure S2: Docked conformation of ALR1 inhibitor **7i**.

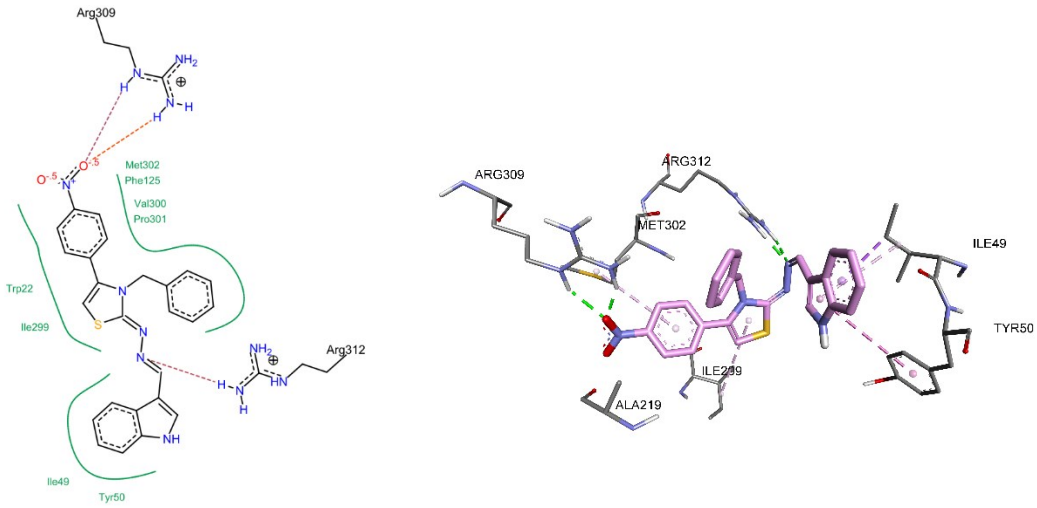


Figure S3: Docked conformation of ALR1 inhibitor **8e**.

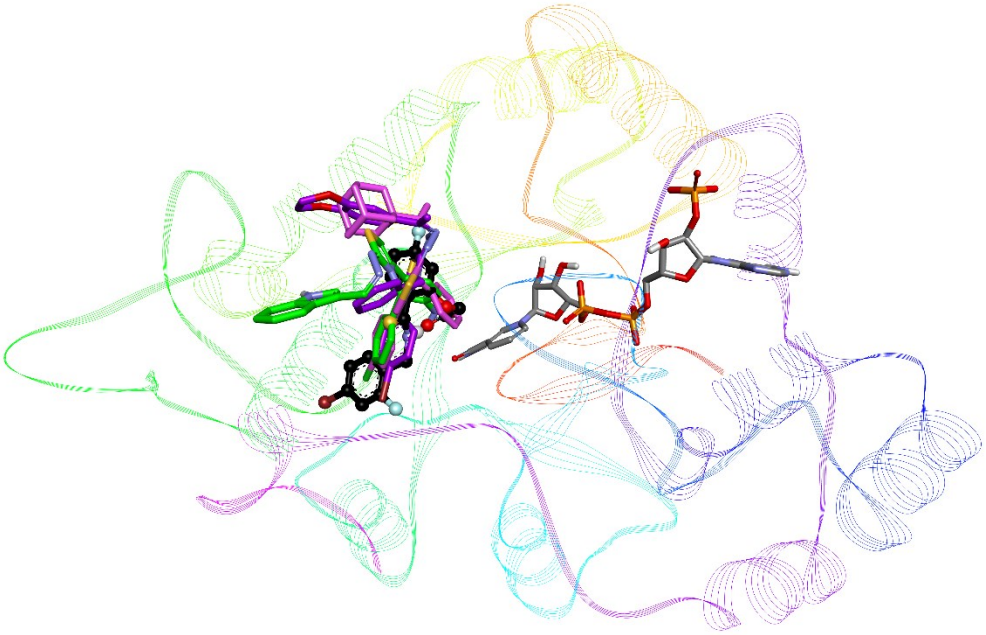


Figure S4: Overlap of ALR2 inhibitors **6e** (pink), **7b** (purple) and **8e** (green) with the co-crystallized inhibitor LDT [2-[(4-bromo-2-fluorobenzyl)carbamothioyl]-5-fluorophenoxy]acetic acid (black), NADPH is shown in grey.

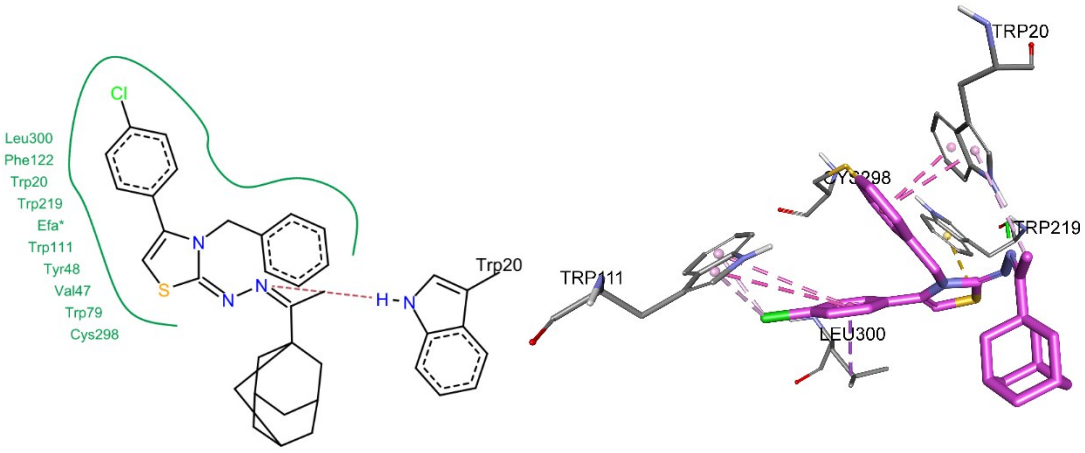


Figure S5: Docked conformation of ALR2 inhibitor **6e**.

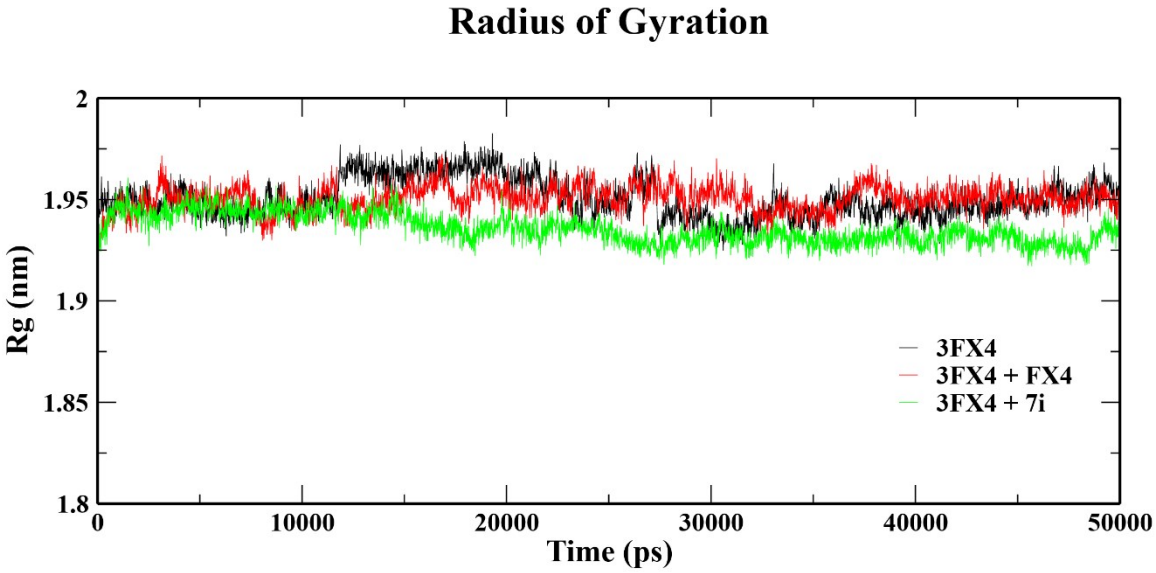


Figure S6: Radius of gyration (Rg) of 3FX4, protein plus cognate ligand (FX4) and protein plus selective compound (**7i**) during 50 ns MD-simulation run.

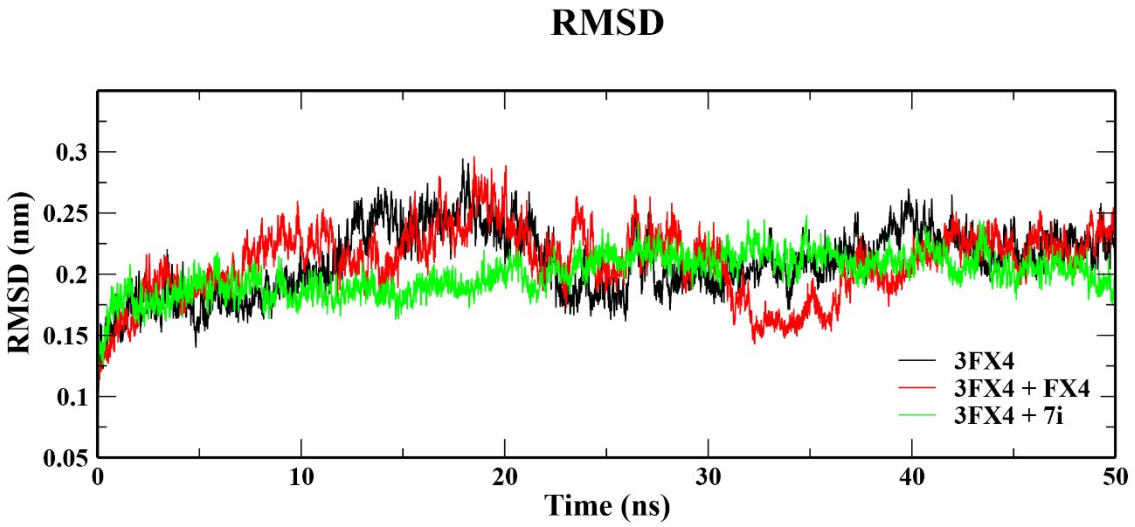


Figure S7: Root Mean Square Deviation (RMSD) of 3FX4, protein plus cognate ligand (FX4) and protein plus selective compound (7i) during 50 ns MD-simulation run.

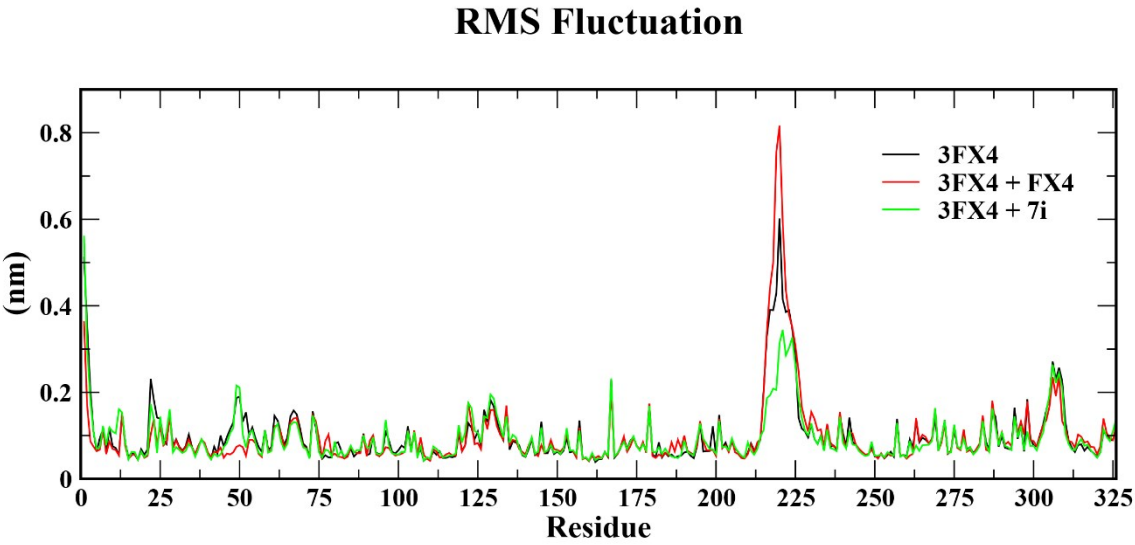


Figure S8: Root Mean Square Fluctuation (RMSF) of 3FX4, protein plus cognate ligand (FX4) and protein plus selective compound (7i) during 50 ns MD-simulation run.

Table S1: Binding free energies and non-bonded interactions of ALR1 (**7h, 7i, 8e**) and ALR2 (**6e, 7b, 8e**) inhibitors with their respective receptors.

Ligand	Binding Free Energy (kJ/mol)	Hydrophobic Interactions	Hydrogen bond interactions	Hydrogen bond distance (Å)	Other interactions and distance (Å)
ALR1 Inhibitors					
7h	-17	Phe125 (pi-pi stacked), Ile299 (alkyl, pi-alkyl), Ile49 (pi-alkyl), Trp114 (pi-alkyl)	Tyr50 (H-Donor towards F), Met302 (H-Donor), Arg312 (H-Donor)	2.56, 2.15, 2.30	Tyr50 (Halogen bond acceptor) (3.02)
7i	-19	Ile299 (alkyl, pi-alkyl), Pro301 (alkyl), Lys23 (alkyl, pi-alkyl), Ala219 (pi-alkyl), Arg218 (pi-alkyl)	Val300 (H-Donor), Arg302 (H-Donor)	1.73, 2.01	_
8e	-18	Ile49 (pi-sigma, pi-alkyl), Tyr50 (pi-pi stacked), Ile299 (pi-alkyl), Met302 (pi-alkyl)	Arg309 (H-Donor), Arg312 (H-Donor)	2.17 and 1.78, 1.89 and 2.66	_
ALR2 Inhibitors					
6e	-15	Leu300 (pi-sigma), Trp20 (pi-pi stacked, pi-alkyl), Trp111 (pi-stacked, pi-alkyl)	Trp20 (H-Donor)	1.89	Trp219 (pi-sulfur) (4.12), Cys298 (pi-sulfur) (4.61)
7b	-16	Trp111 (pi-pi stacked, pi-alkyl), Trp20 (pi-pi T-shaped), Pro218 (alkyl), Leu300 (pi-alkyl), Val47 (pi-alkyl)	Trp20 (H-Donor)	1.99, 2.12	Tyr48 (pi-sulfur) (4.89)
8e	-16	Leu300 (pi-sigma, pi-	Tyr48 (H-Donor),	2.30, 1.56	Lys77 (electrostatic,

		alkyl), Phe122 (pi-pi T-shaped), Trp20 (pi-pi T-shaped), Val47 (pi-alkyl)	Trp111 (H-Donor)		attractive charge) (5.42), Trp20 (electrostatic, pi-anion) (4.89)

Bioactivity Protocol

Enzyme extraction and determination of enzyme activities

Extraction of aldehyde reductase (ALR1):

Kidneys were removed from the calf soon after slaughtering and dissolved in 3 volume of 10 mM sodium phosphate buffer, pH 7.2, containing 0.25M sucrose, 2.0 mM EDTA dipotassium salt and 2.5 mM β-mercaptoethanols. Centrifuged the homogenate at 12,000 x g at 0-4 0C for 30 minutes. The precipitate was discarded as it contains insoluble lipids. Collected supernatant layer was subjected to 40% ammonium sulfate saturation to isolate ALR1. This 40% saturated liquid is centrifuged at 12,000 x g at at 0-4 0C for 30 minutes. Again precipitate was discarded and supernatant was subjected to 50% saturation with ammonium sulphate salt. Then the same procedure was repeated with this and in the last step powdered ammonium sulphate was added to increase the saturation upto 75%. Centrifuged the supernatant at 12,000 x g for 30 min, causing the precipitation of ALR1. Now precipitated material is collected and supernatant was discarded. The precipitated material containing ALR1 was redissolved in 10 mM sodium phosphate buffer, pH 7.2, containing 2.0 mM EDTA dipotassium salt and 2.0 mM β-mercaptoethanol and then dialyzed over night using the same buffer. The dialyzed material containing ALR1 was aliquoted and stored at -80 0C before use[3]

Extraction of Aldose reductase (ALR2):

Isolation of ALR2 was done as described in (Hayman and Kinoshita 1965) by minor modification. Briefly, ALR2 was isolated from calf lenses. The lenses were removed from the eyes immediately after slaughtering and were frozen until use. Lenses (100-200g) were homogenized in 3 volumes of cold distilled water and then homogenate was centrifuged at 10,000 x g for 15 minutes to remove insoluble material. Precipitated material was discarded as it contained lipids. Supernatant layer was separated and ammonium sulphate salt was added to make the saturation upto 40%. It was centrifuged at 10,000 x g for 15 min, again precipitate was discarded. Additional inert protein was removed by increasing the concentration of ammonium sulfate upto 50%. Pure ALR2 was precipitated by addition of powdered ammonium sulfate to 75% saturation. After centrifugation, supernatant was discarded and redissolved the precipitated enzyme in 50 mM NaCl and dialyzed over night against 4 liters 50 mM NaCl. The volume of the suspension was recorded and the sample was dialyzed overnight against 50 mM NaCI (double replacement of dialysis solution). After

dialysis, the volume of the sample was recorded and treated to liquid nitrogen then samples were stored in 1 mL aliquots in eppendorf tubes in deep freezer at -80 ºC for the determination of the total protein, enzyme activity and inhibition studies[4].

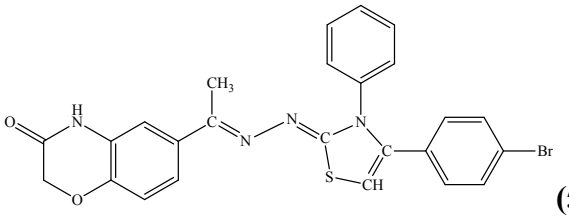
Determination Enzymatic activity for ALR1 and ALR2.

The activity of ALR2 and ALR1 was assayed by using FLUOstar® Omega micro plate reader (BMG LABTECH) by measuring absorbance at 340 nm and decrease in absorbance of NADPH was associated with enzymatic activity. To calculate the inhibitory activity for ALR2, DL-glyceraldehyde was used as substrate whereas inhibitory activity of ALR1 was estimated with sodium -D-glucuronate as a substrate. Newly synthesized compounds were dissolved in DMSO and final concentration of DMSO was kept 0.1% in all incubations. The reaction mixture (total assay volume 100µL) was composed of 20µL of phosphate buffer (100mM), 10µL of test compound (1mM), 30µL of enzyme (partially purified) and 20µL(0.1mM) of substrate. The reaction mixture was pre incubated for 5minutes, then enzymatic reaction was initiated by the addition of cofactor NADPH (0.1mM). Pre-read was taken at 0 minute and again the mixture was incubated at 30ºC for 20 minutes. Then after-read was taken and change in absorbance was noted[5]. In the assay valproic acid and sorbinil was used as standard inhibitor for ALR1 and ALR2, respectively. All enzymatic reactions were performed in triplicate and percent inhibition was calculated and IC_{50} values were calculated through non-linear regression analysis via using GraphPad Prism version 8.

References:

1. V. Carbone and O. El-Kabbani, *RSCB Protein Databank. PDB ID: 3FX4*, 2009.
2. E. I. Howard, R. Sanishvili, R. Cachau, A. Mitschler, B. Chevrier, P. Barth, V. Lamour, M. Van Zandt, E. Sibley and C. Bon, *Proteins: Structure, Function, and Bioinformatics*, 2004, **55**, 792-804.
3. W. H. Ward, C. M. Sennitt, H. Ross, A. Dingle, D. Timms, D. J. Mirrlees and D. P. Tuffin, *Biochemical pharmacology*, 1990, **39**, 337-346.
4. P. F. Kador, J. Kinoshita, D. Brittain, D. Mirrlees, C. Sennitt and D. Stribling, *Biochemical Journal*, 1986, **240**, 233-237.
5. F. Da Settimo, G. Primofiore, A. Da Settimo, C. La Motta, S. Taliani, F. Simorini, E. Novellino, G. Greco, A. Lavecchia and E. Boldrini, *Journal of medicinal chemistry*, 2001, **44**, 4359-4369.

^{1}H NMR & ^{13}C Spectra



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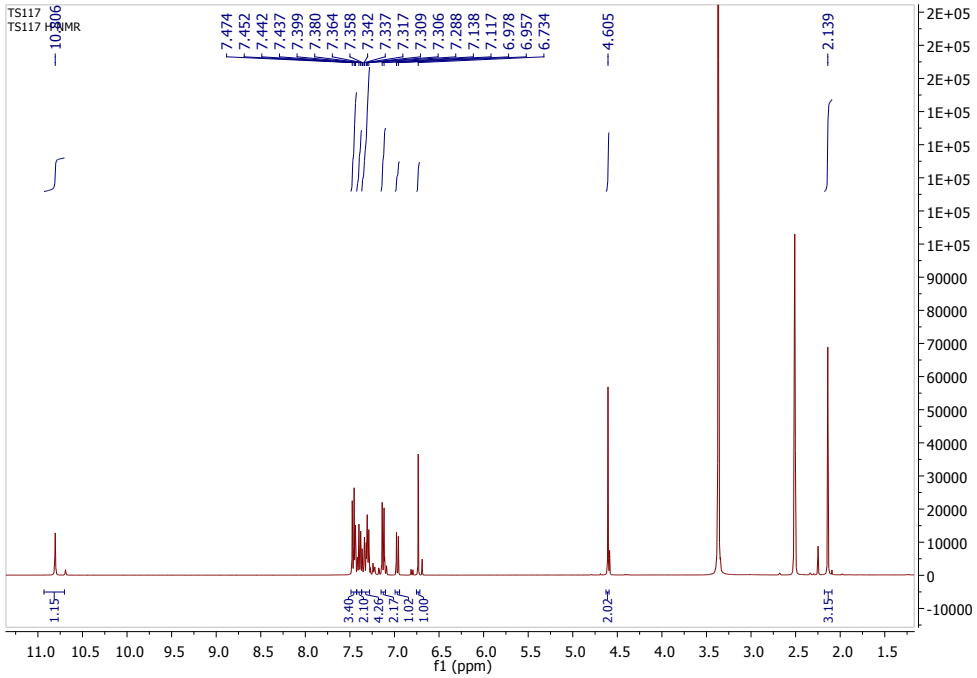

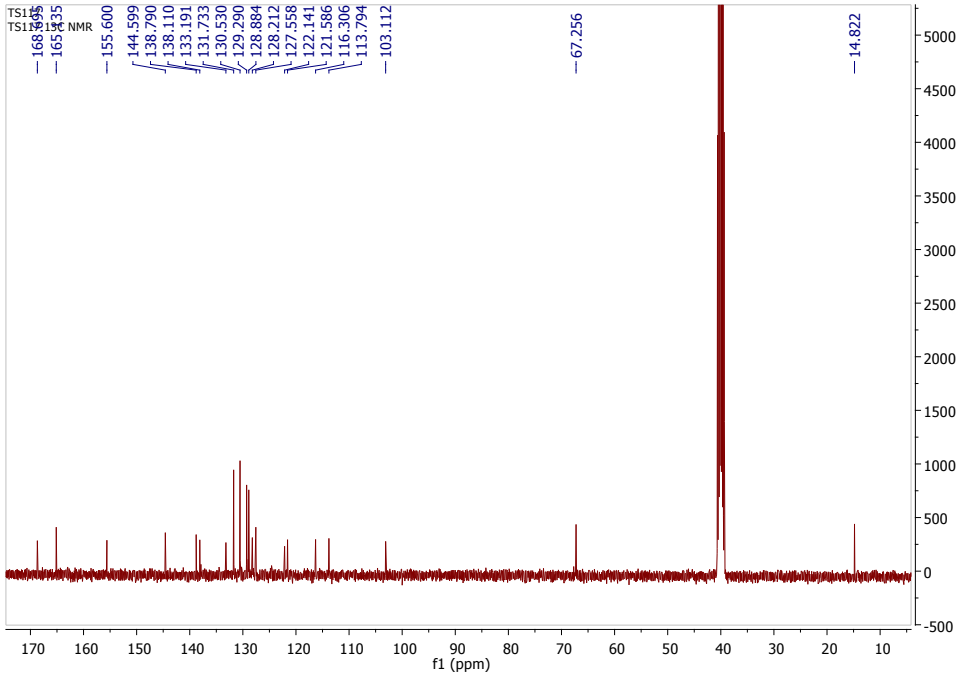

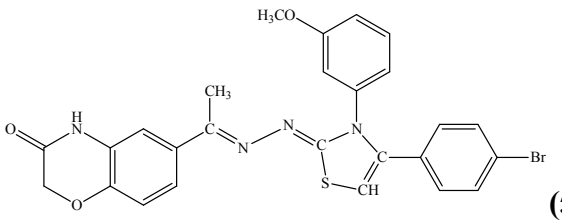
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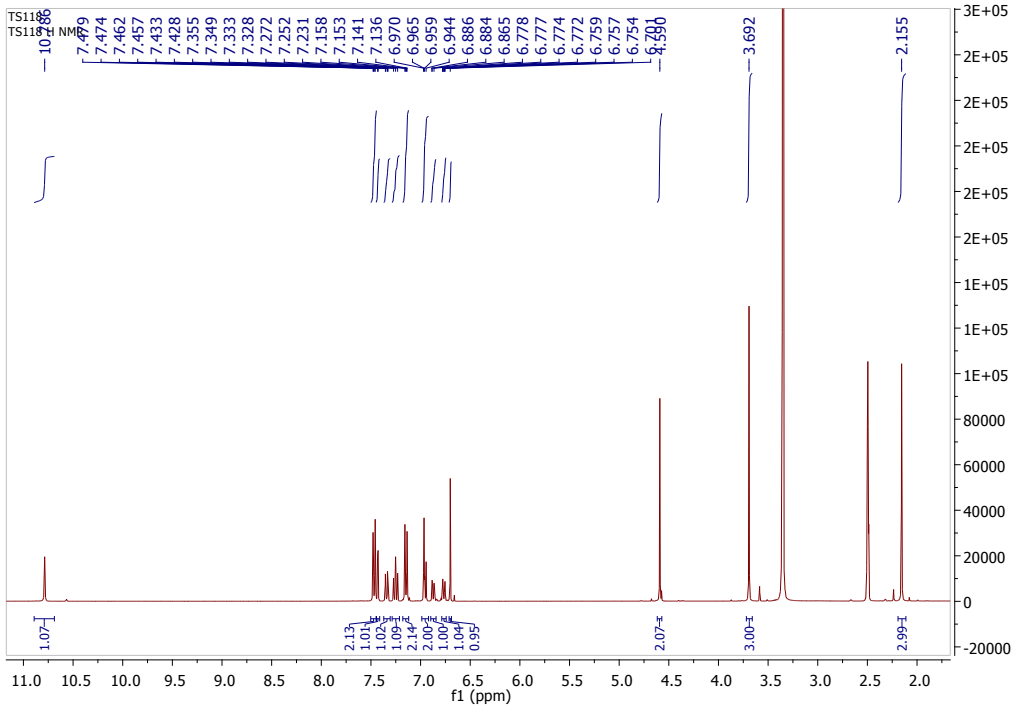
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7.272
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7.231
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7.153
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7.136
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6.778
6.777
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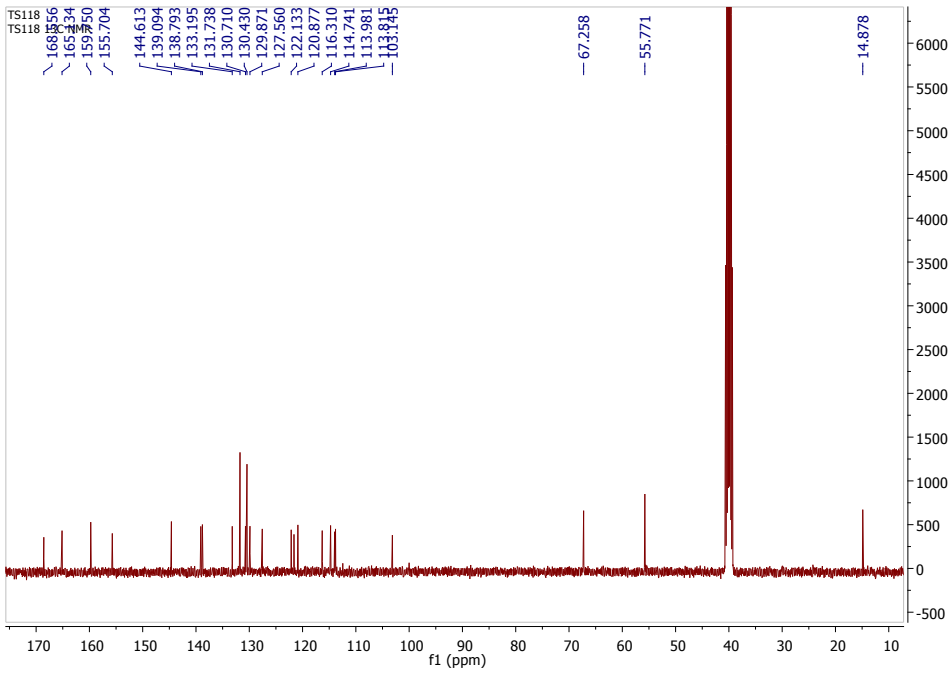
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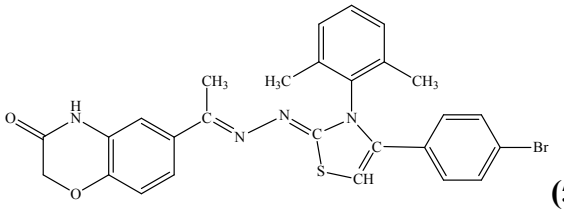

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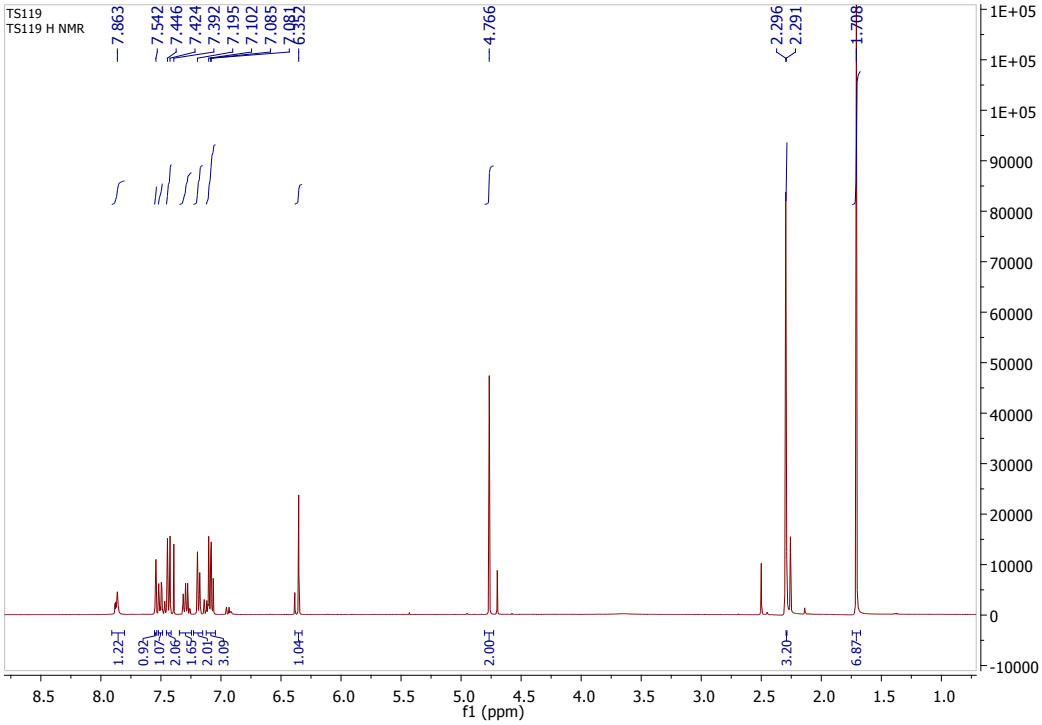
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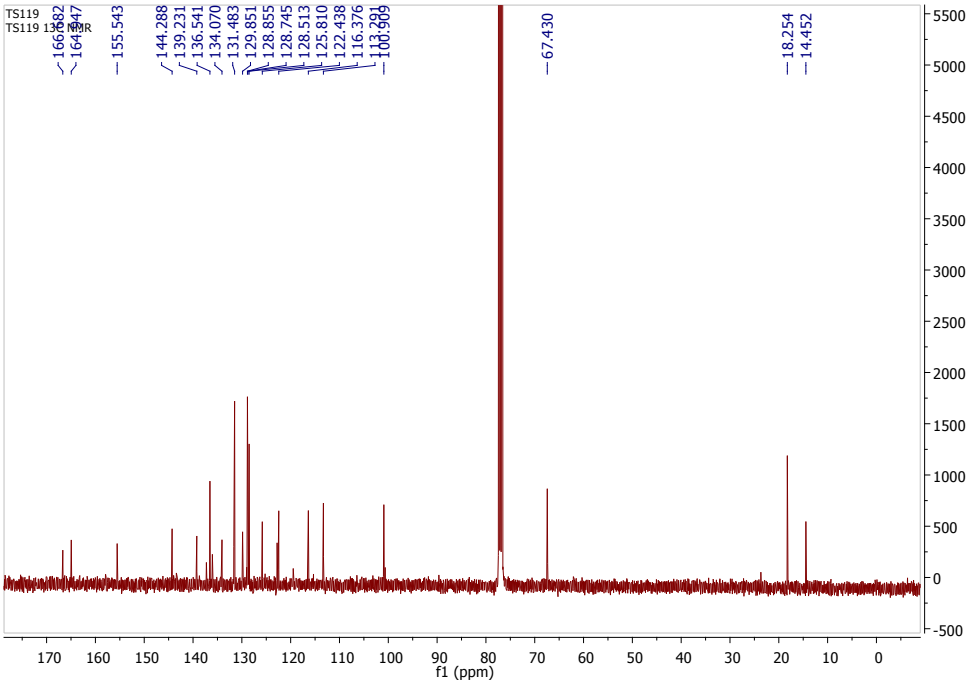
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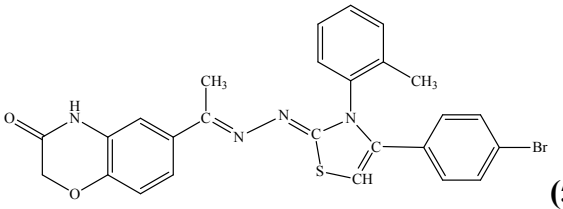
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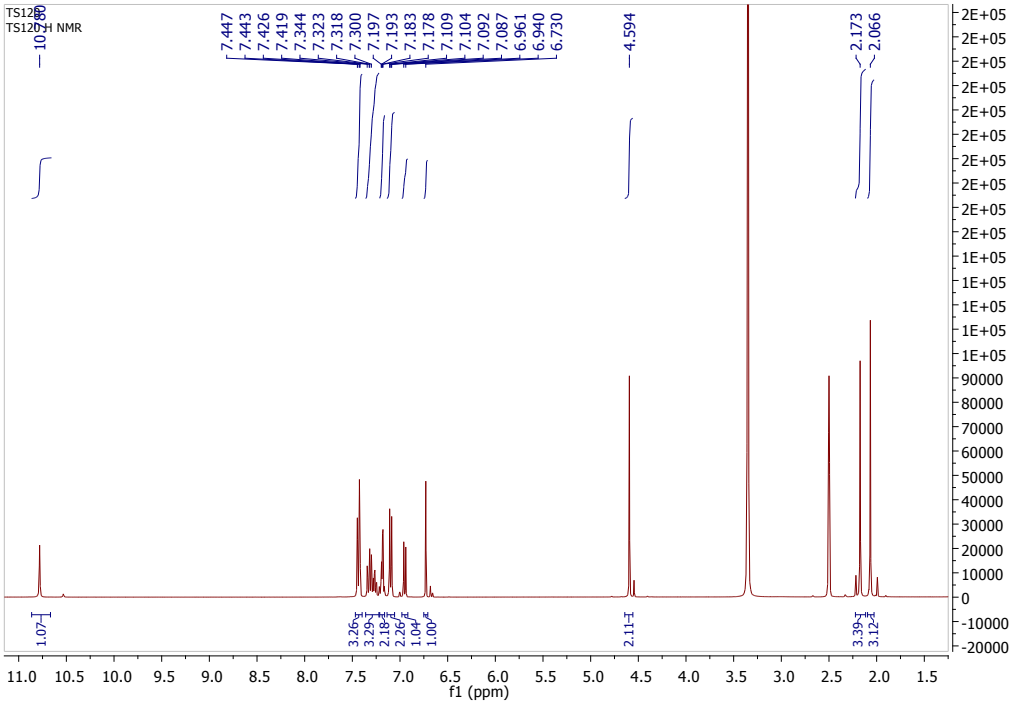
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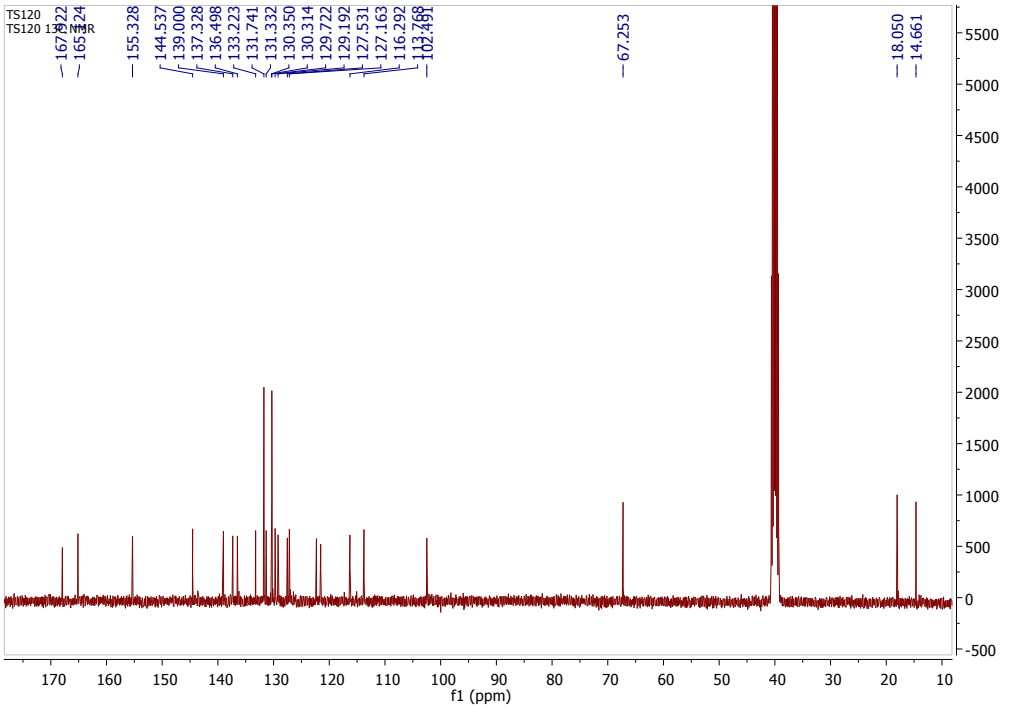
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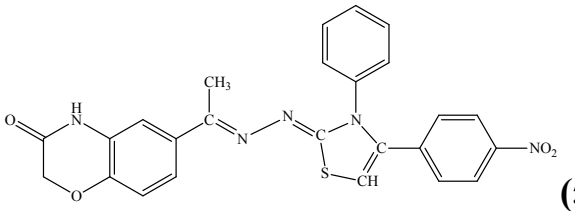

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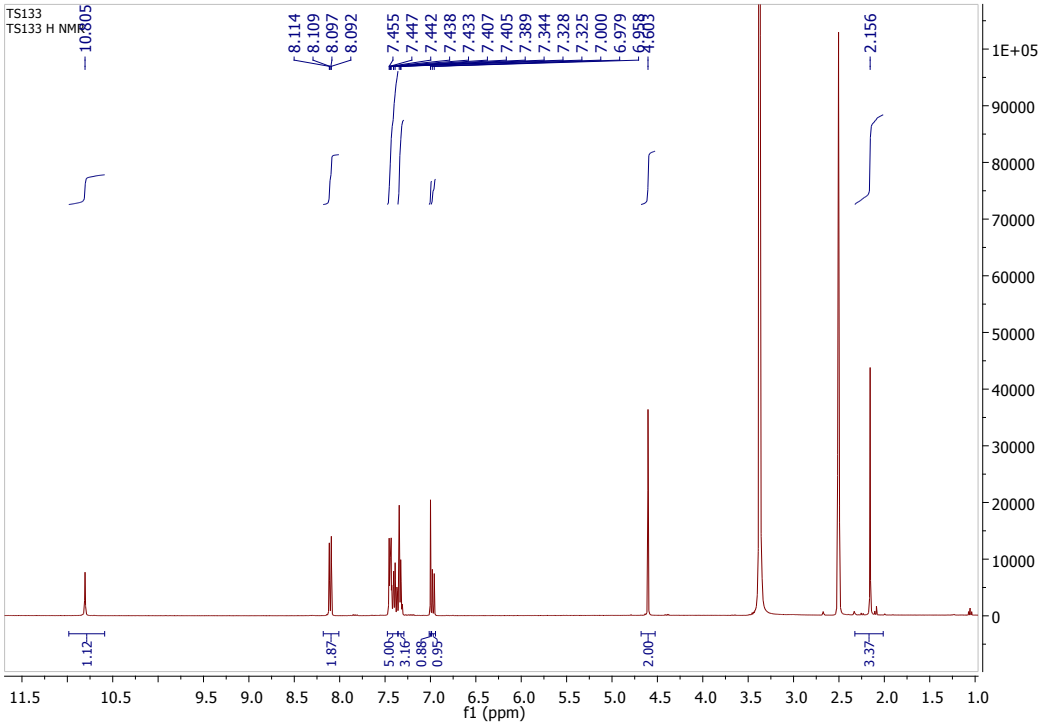
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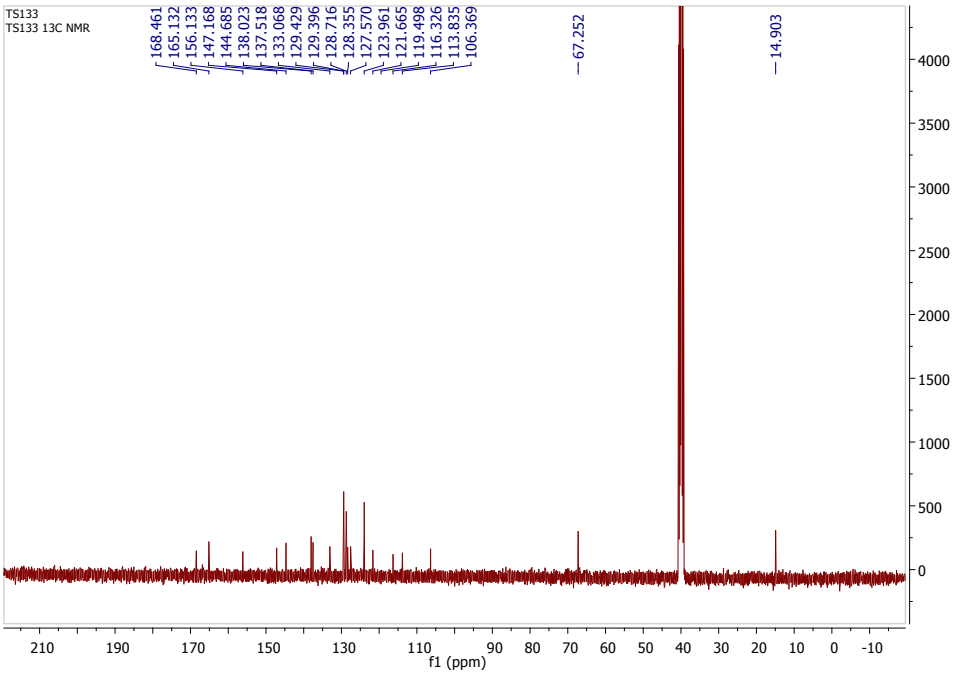
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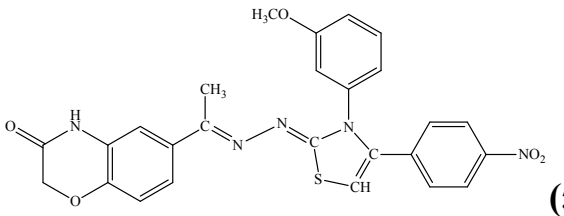
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C
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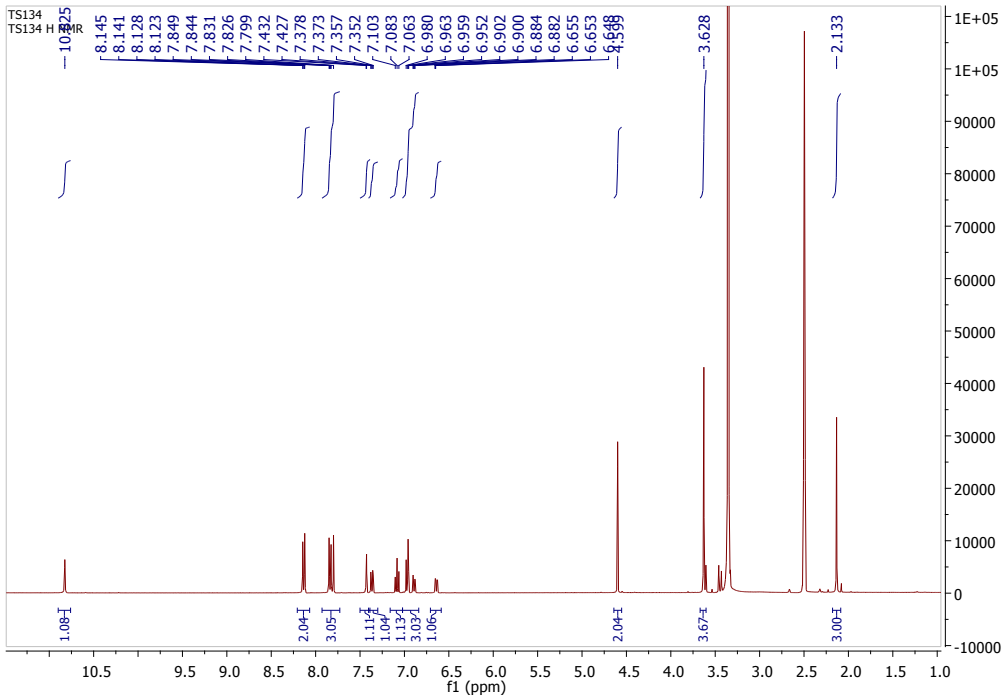
(5f)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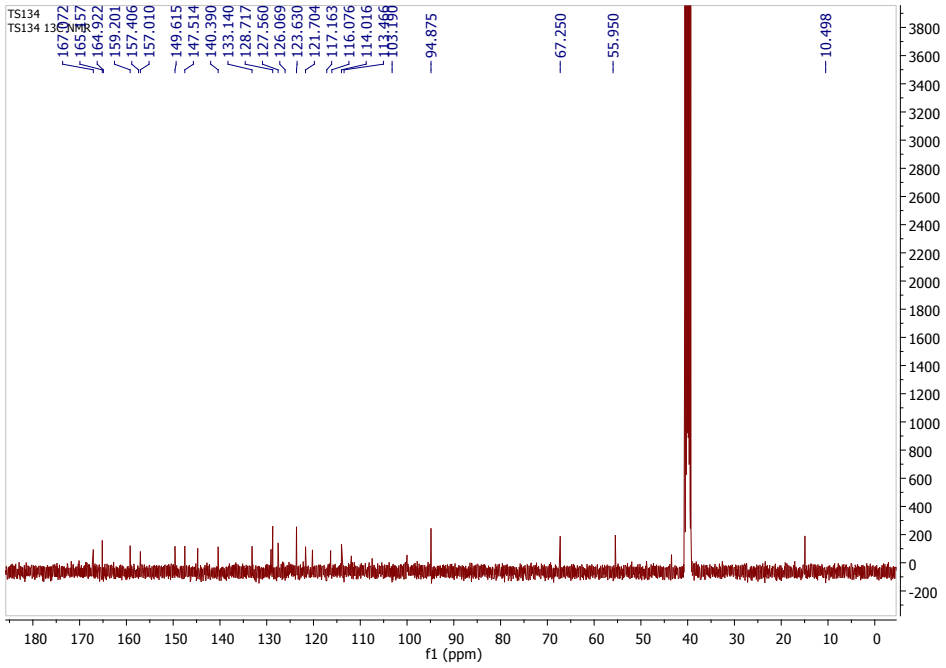
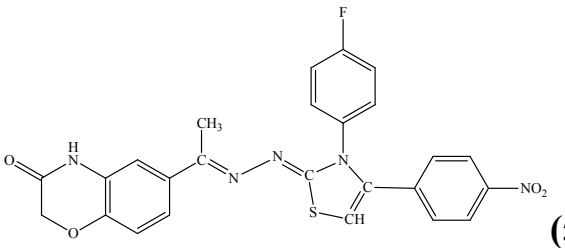
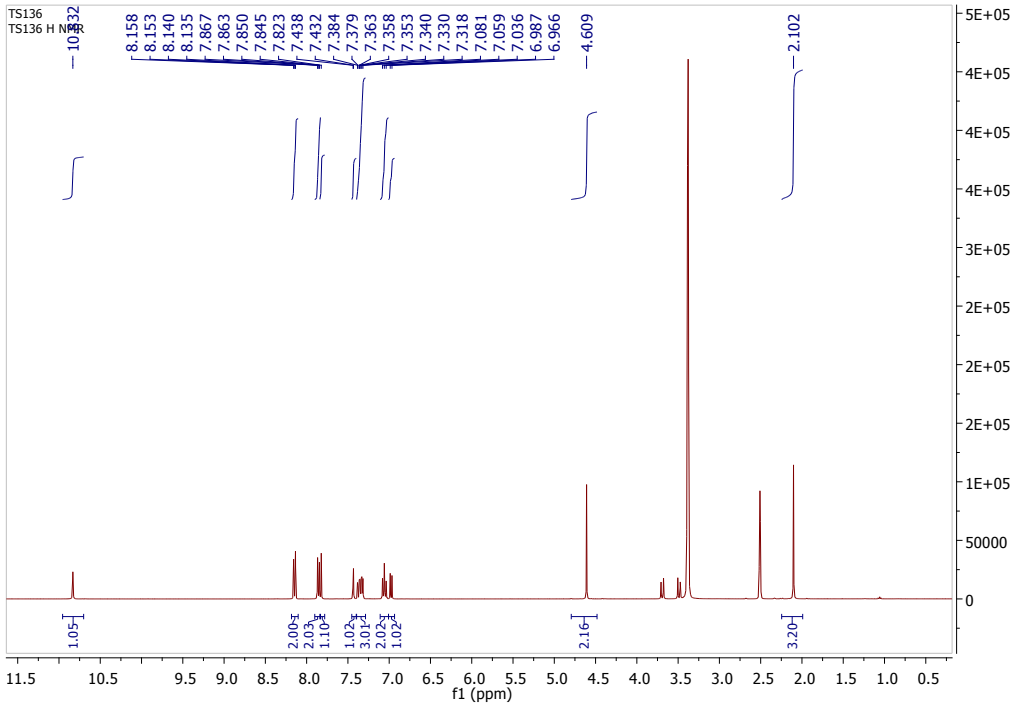
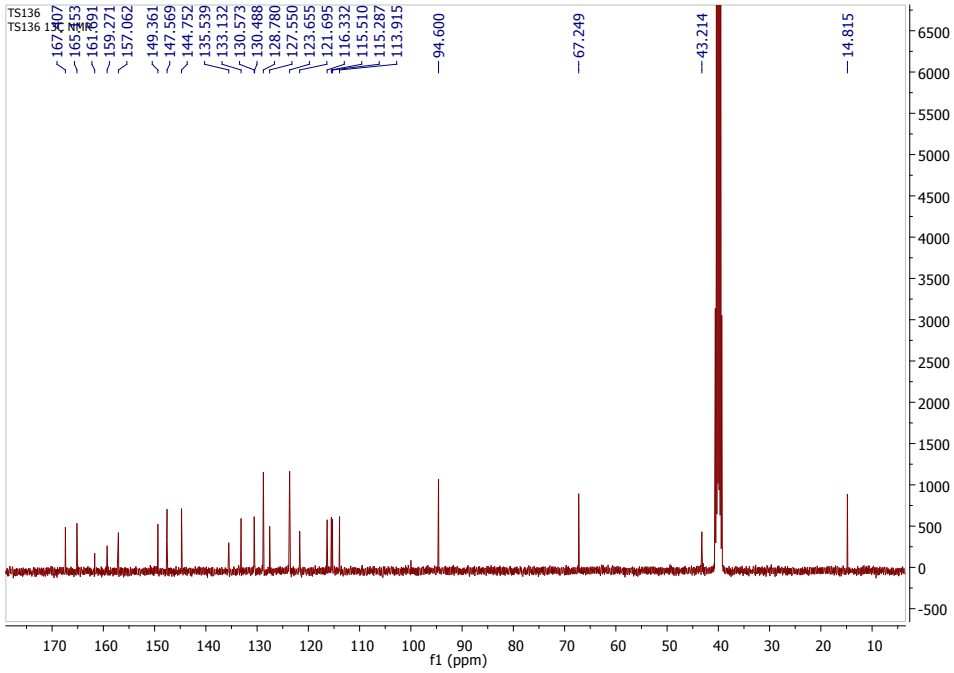
1.08
2.04
3.05
1.11
1.04
1.13
3.03
1.06
2.04
3.67
3.00
f1 (ppm)

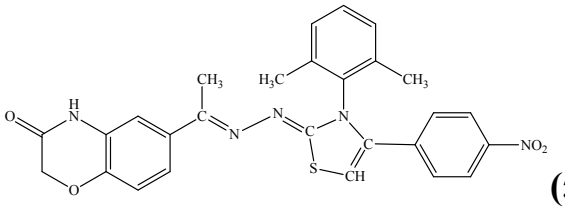

TS134
TS134 13C NMR
167.372
165.357
164.922
159.201
157.406
157.010
149.615
147.514
140.390
133.140
128.717
127.560
126.069
123.630
121.704
117.163
116.076
114.016
94.875
67.250
55.950
10.498
f1 (ppm)


F
CH3
H
N
O
N
C
N
N
C
N
C
S
CH
NO2
O

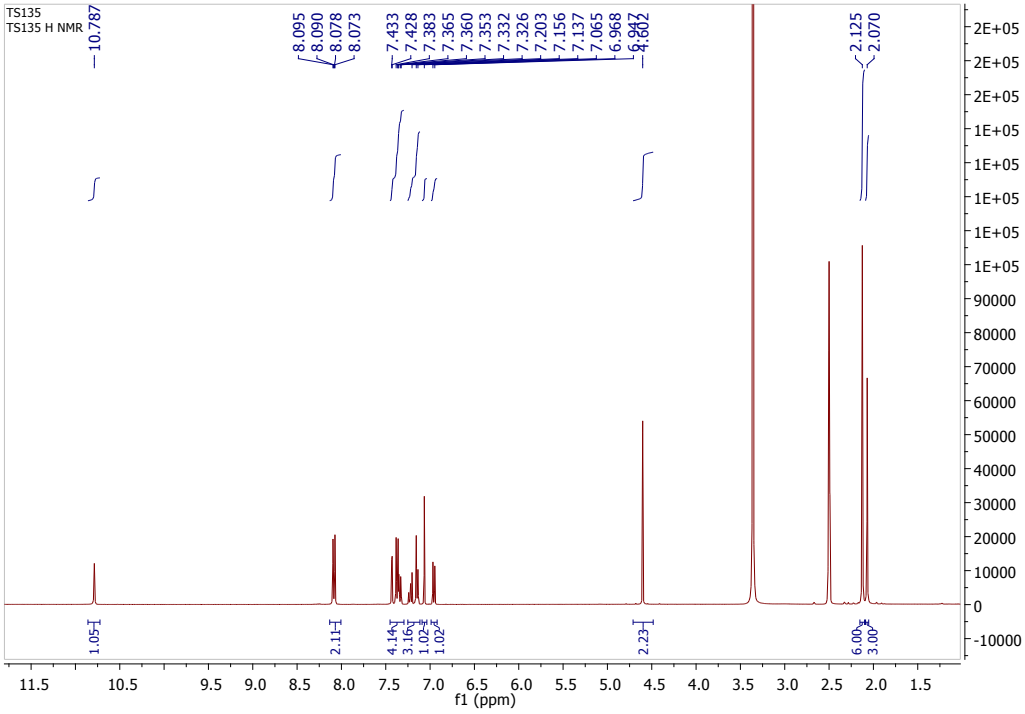
(5g)

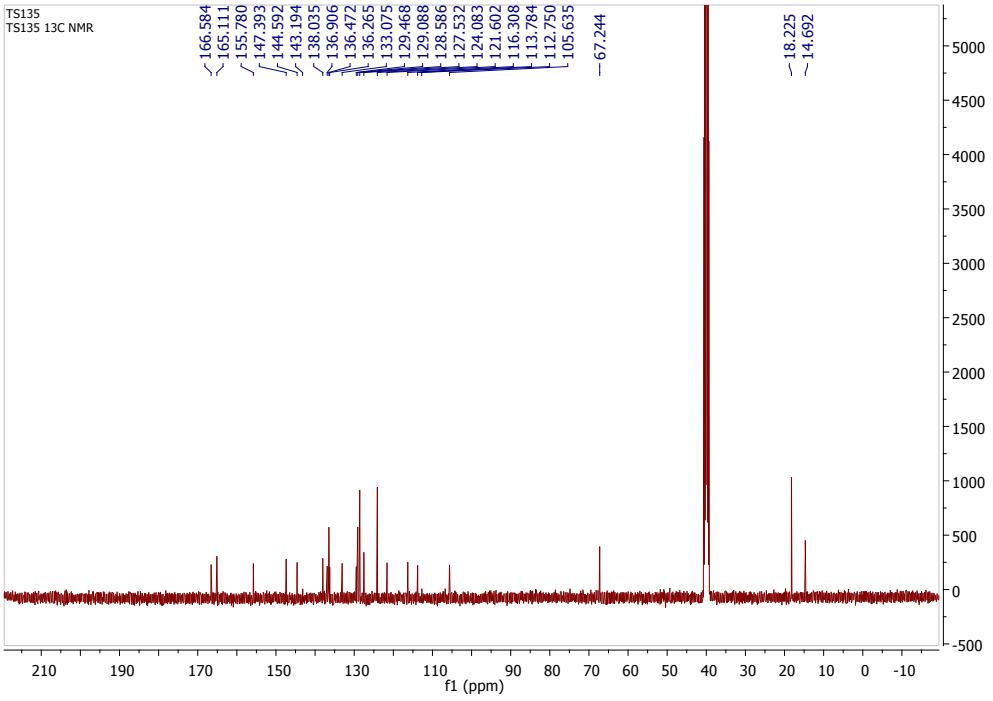

TS136
TS136 H NMR
10.332
8.158
8.153
8.140
8.135
7.867
7.863
7.850
7.845
7.823
7.438
7.432
7.384
7.379
7.363
7.358
7.353
7.340
7.330
7.318
7.081
7.059
7.036
6.987
6.966
4.609
2.102
1.05
2.00
2.03
1.10
1.02
3.01
2.02
1.02
2.16
3.20
f1 (ppm)

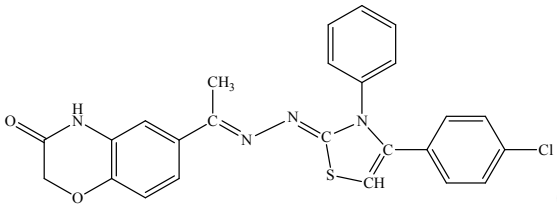

TS136
TS136 13C NMR
167.807
165.453
161.891
159.271
157.062
149.361
147.569
144.752
135.539
133.132
130.573
130.488
128.780
127.550
123.655
121.695
116.332
115.510
115.287
113.915
94.600
67.249
43.214
14.815
f1 (ppm)



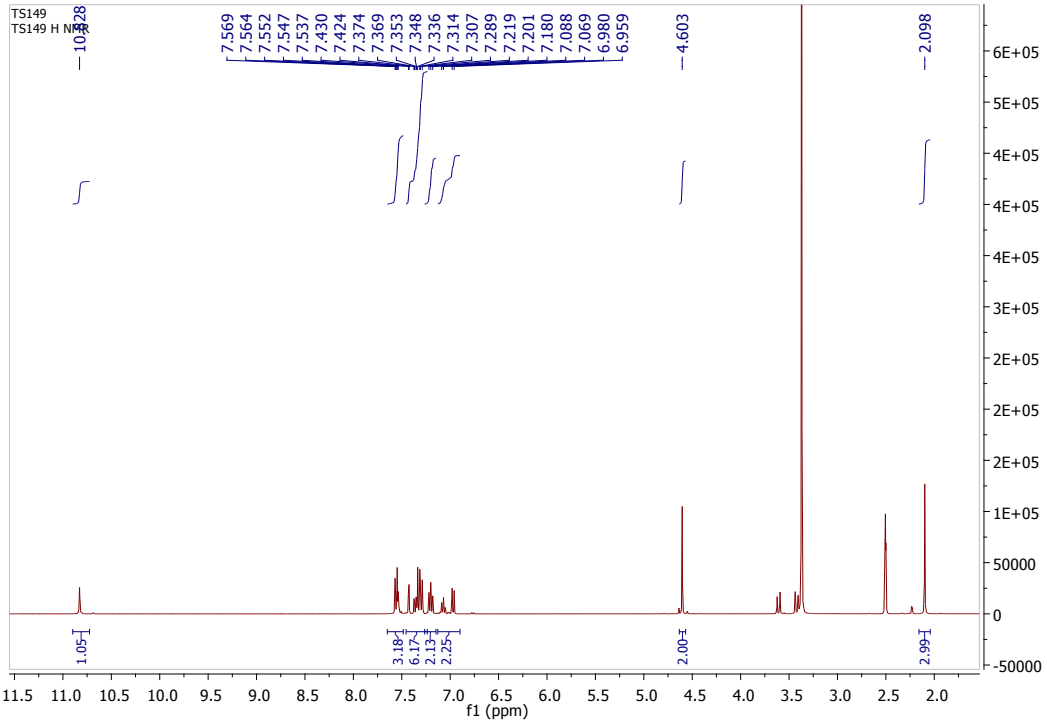
(5h)

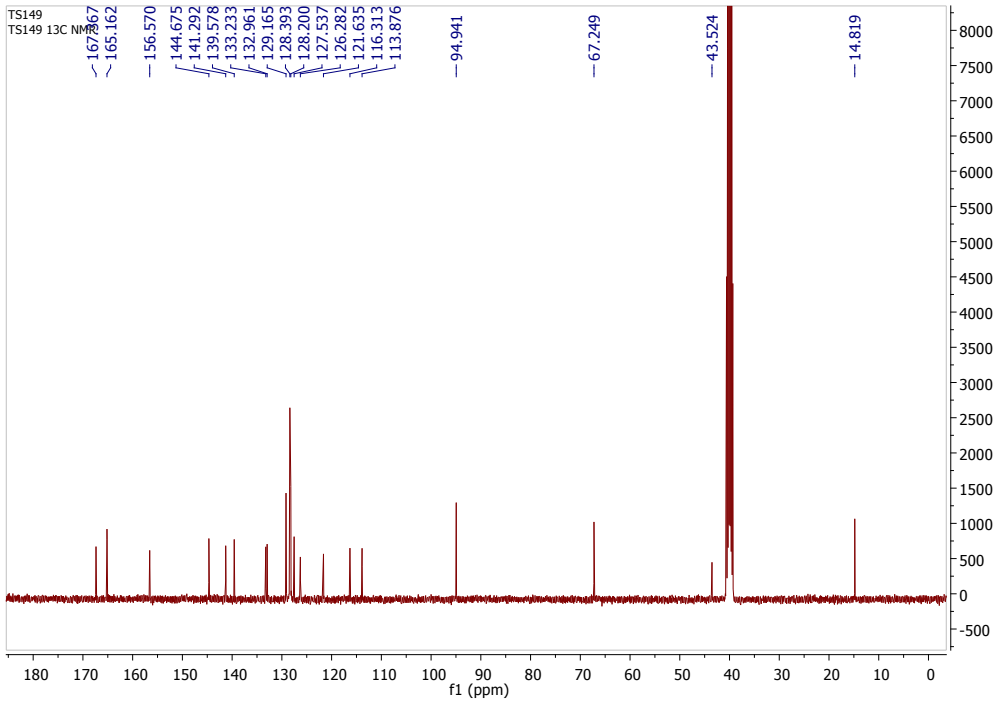

TS135
TS135 H NMR
10.787
8.095
8.090
8.078
8.073
7.433
7.428
7.383
7.365
7.360
7.353
7.332
7.326
7.203
7.156
7.137
7.065
6.968
6.947
6.602
2.125
2.070
1.05
2.11
4.14
3.16
1.02
1.02
2.23
6.00
3.00
f1 (ppm)

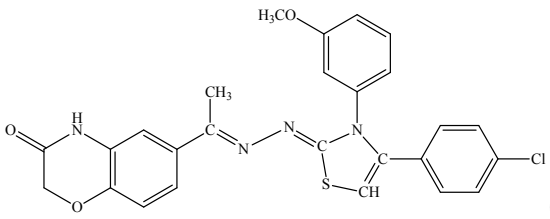

TS135
TS135 13C NMR
166.584
165.111
155.780
147.393
144.592
143.194
138.035
136.906
136.472
136.265
133.075
129.468
129.088
128.586
127.532
124.083
121.602
116.308
113.784
112.750
105.635
67.244
18.225
14.692
f1 (ppm)



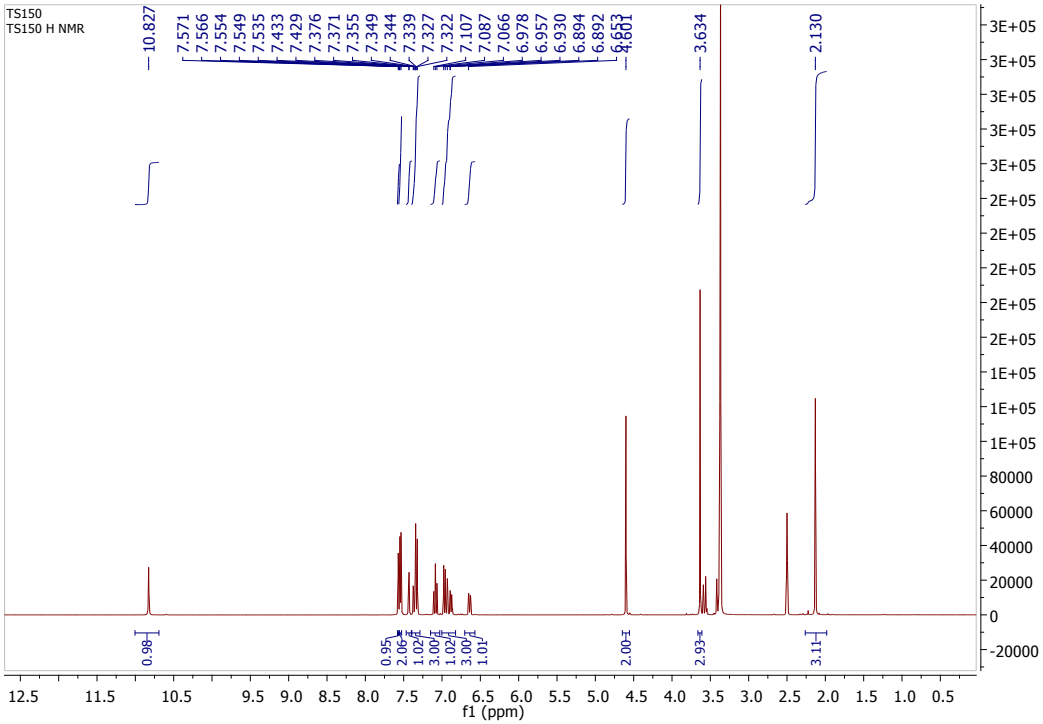
(5i)

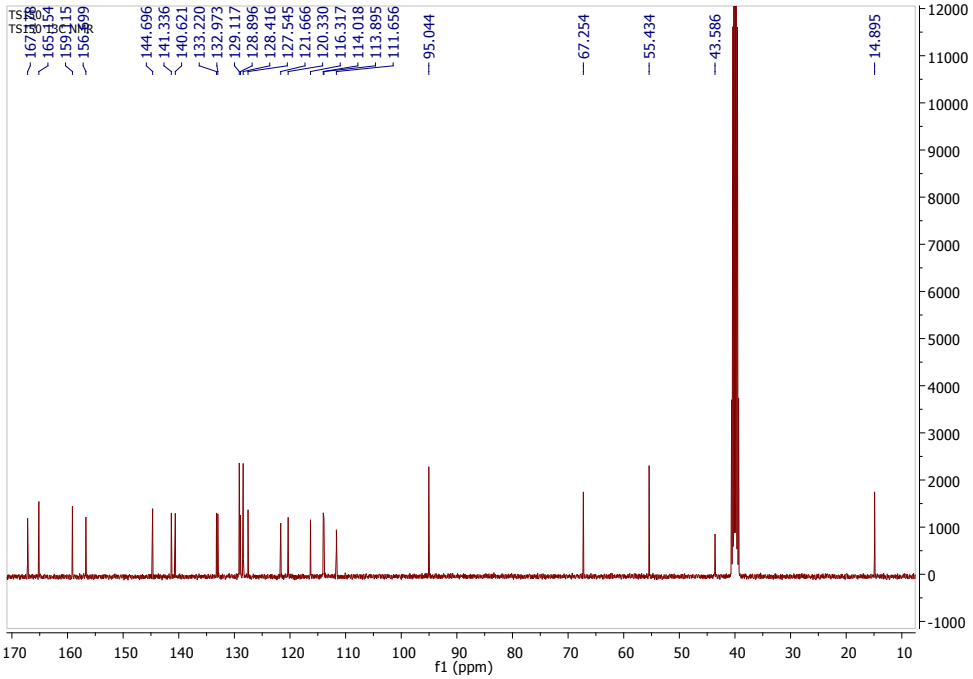

TS149
TS149 H NMR
10.328
7.569
7.564
7.552
7.547
7.537
7.430
7.424
7.374
7.369
7.353
7.348
7.336
7.314
7.307
7.289
7.219
7.201
7.180
7.088
7.069
6.980
6.959
4.603
2.098
1.05
3.18
6.17
2.13
2.25
2.00
2.99
f1 (ppm)

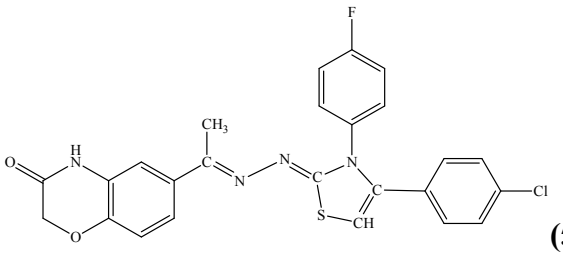

TS149
TS149 13C NMR
167.867
165.162
156.570
144.675
141.292
139.578
133.233
132.961
129.165
128.393
128.200
127.537
126.282
121.635
116.313
113.876
94.941
67.249
43.524
14.819
f1 (ppm)


H3CO
CH3
H
N
O
O
C
N
N
C
N
C
S
CH
Cl

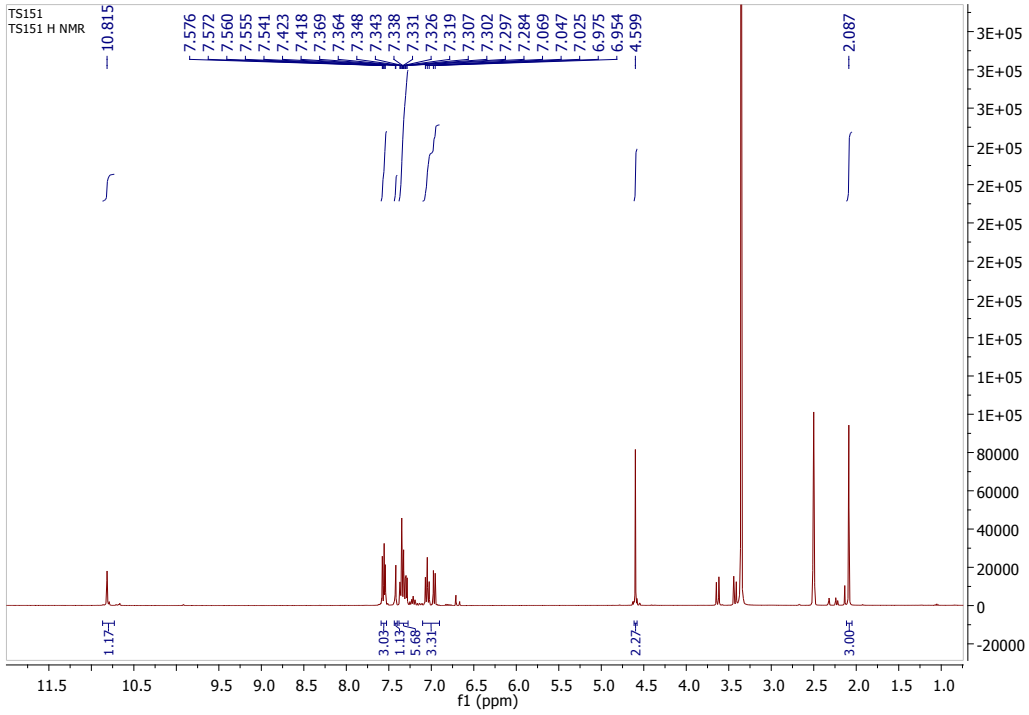
(5j)

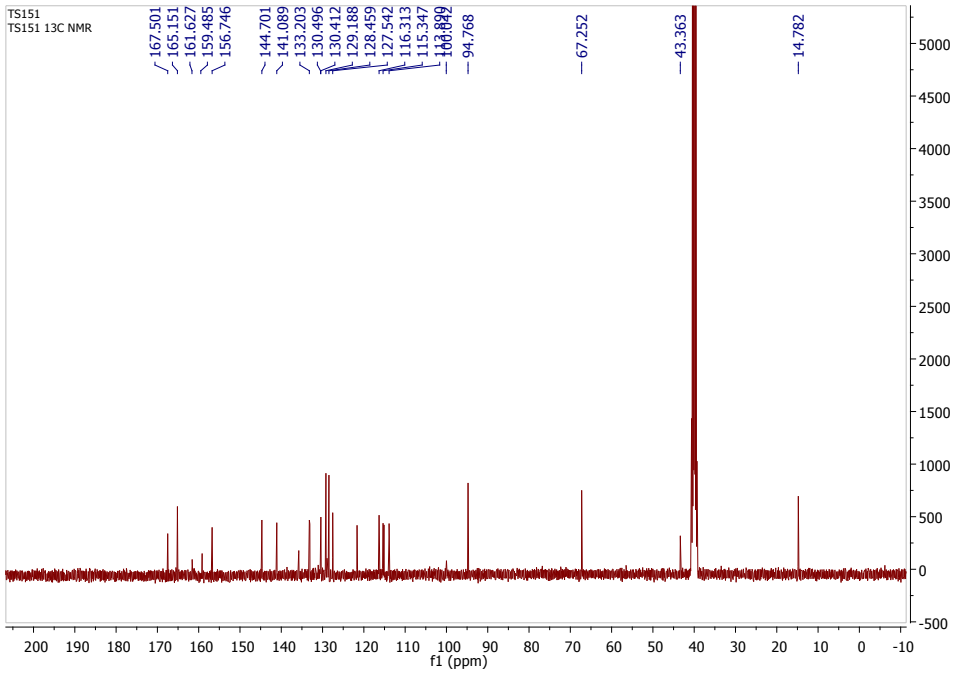

TS150
TS150 H NMR
10.827
7.571
7.566
7.554
7.549
7.535
7.433
7.429
7.376
7.371
7.355
7.349
7.344
7.339
7.327
7.322
7.107
7.087
7.066
6.978
6.957
6.930
6.894
6.892
4.601
3.634
2.130
0.98
0.95
2.06
1.02
3.00
1.02
3.00
1.01
2.00
2.93
3.11
f1 (ppm)

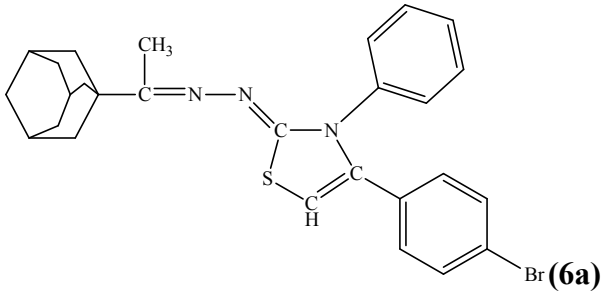

TS150
TS150 13C NMR
167.554
165.154
159.115
156.199
144.696
141.336
140.621
133.220
132.973
129.117
128.896
128.416
127.545
121.666
120.330
116.317
114.018
113.895
111.656
95.044
67.254
55.434
43.586
14.895
f1 (ppm)


F
CH3
H
N
O
N
C
N
N
C
C
Cl
S
CH
O

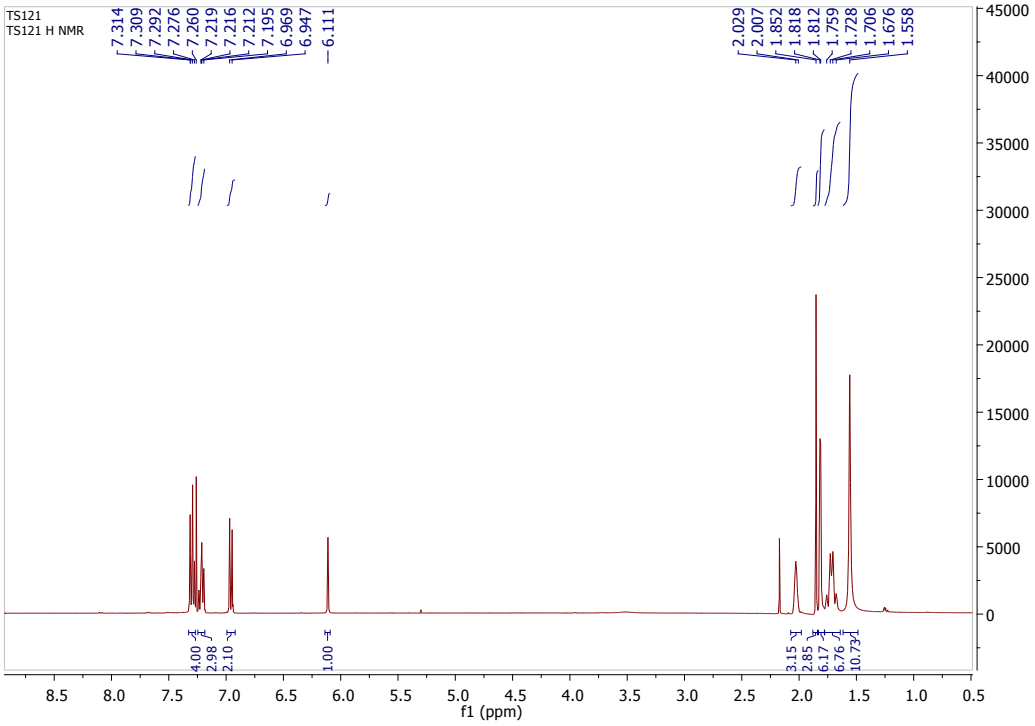
(5k)

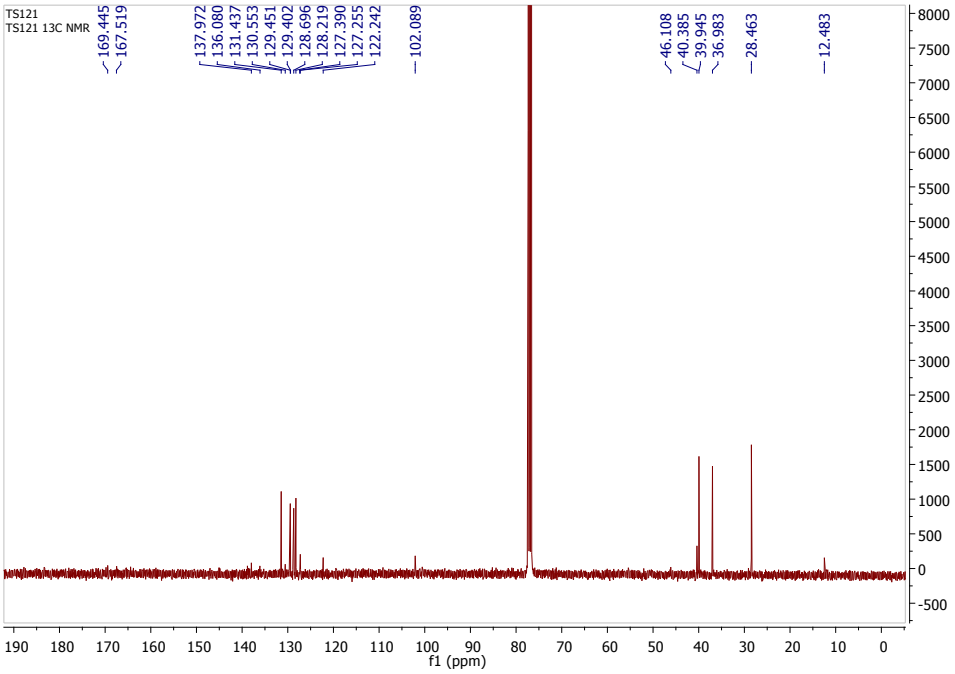

TS151
TS151 H NMR
10.815
7.576
7.572
7.560
7.555
7.541
7.423
7.418
7.369
7.364
7.348
7.343
7.338
7.331
7.326
7.319
7.307
7.302
7.297
7.284
7.069
7.047
7.025
6.975
6.954
4.599
2.087
1.17
3.03
1.13
5.68
3.31
2.27
3.00
f1 (ppm)

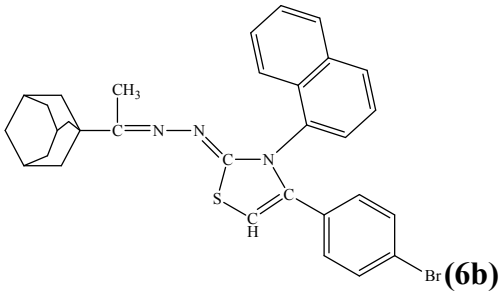

TS151
TS151 13C NMR
167.501
165.151
161.627
159.485
156.746
144.701
141.089
133.203
130.496
130.412
129.188
128.459
127.542
116.313
115.347
94.768
67.252
43.363
14.782
f1 (ppm)


CH3
C
N
N
C
N
S
C
C
H
Br

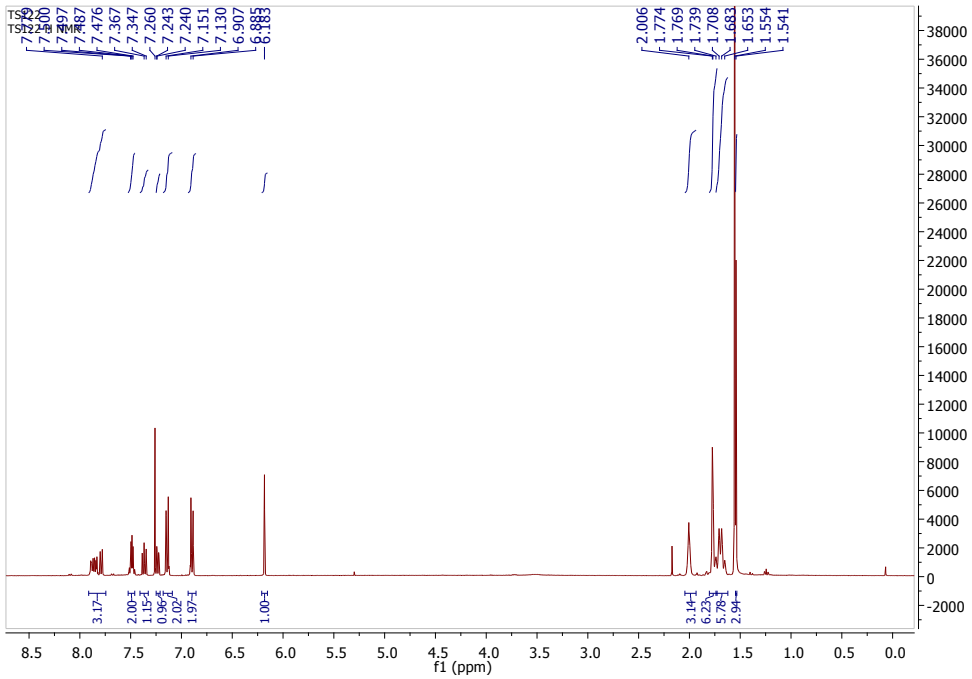
(6a)

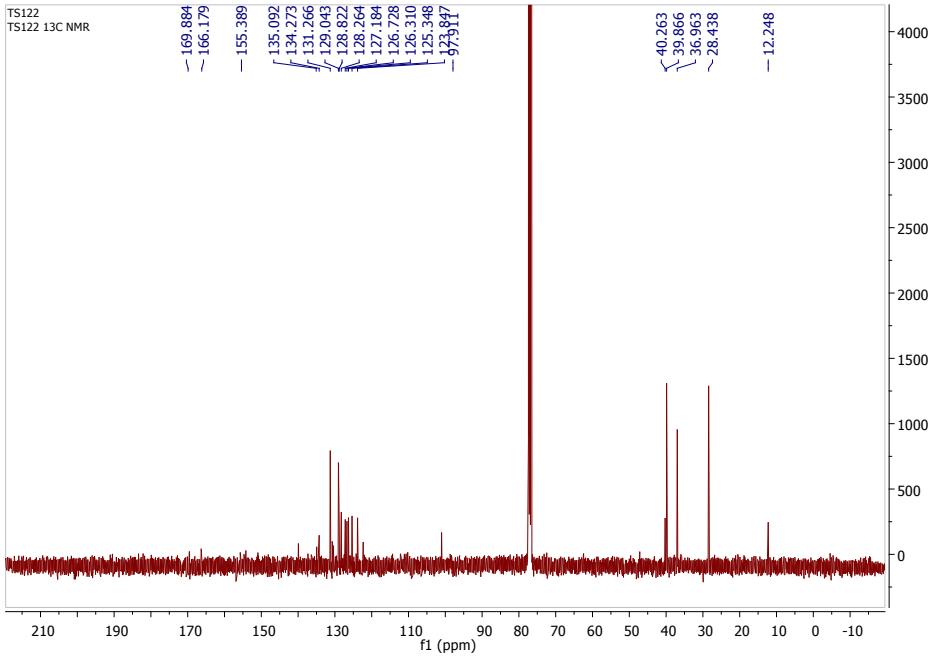

TS121
TS121 H NMR
7.314
7.309
7.292
7.276
7.260
7.219
7.216
7.212
7.195
6.969
6.947
6.111
2.029
2.007
1.852
1.818
1.812
1.759
1.728
1.706
1.676
1.558
4.00
2.98
2.10
1.00
3.15
2.85
6.17
6.76
10.731
f1 (ppm)

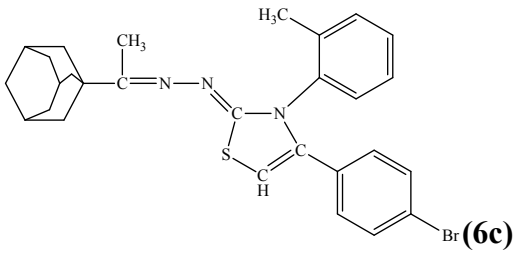

TS121
TS121 13C NMR
169.445
167.519
137.972
136.080
131.437
130.553
129.451
129.402
128.696
128.219
127.390
127.255
122.242
102.089
46.108
40.385
39.945
36.983
28.463
12.483
f1 (ppm)


CH3
C
N
N
C
N
S
C
C
H
Br

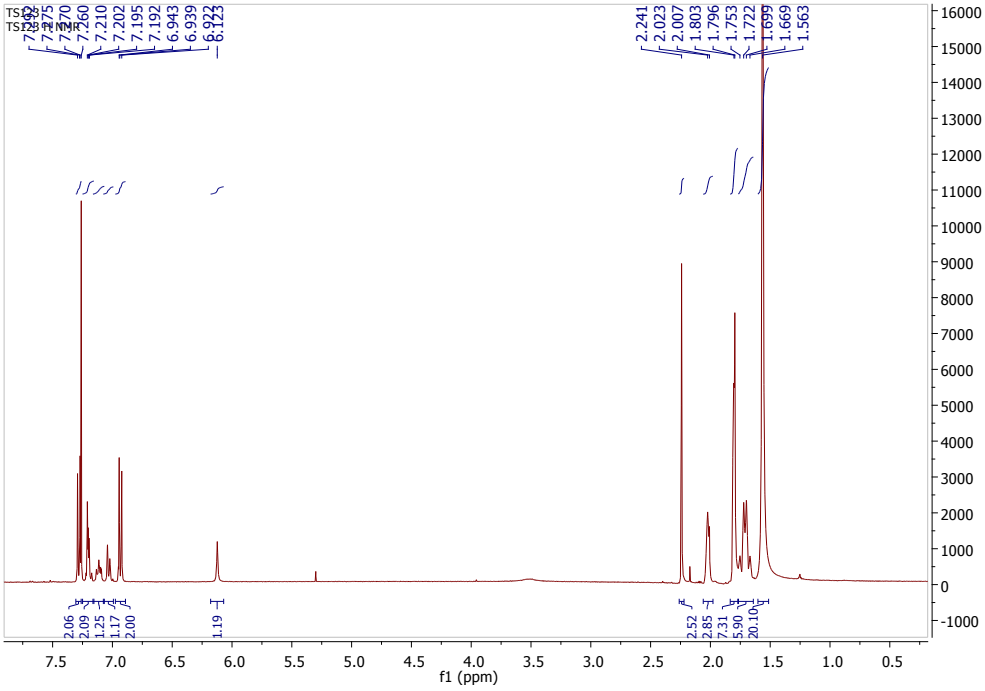
(6b)

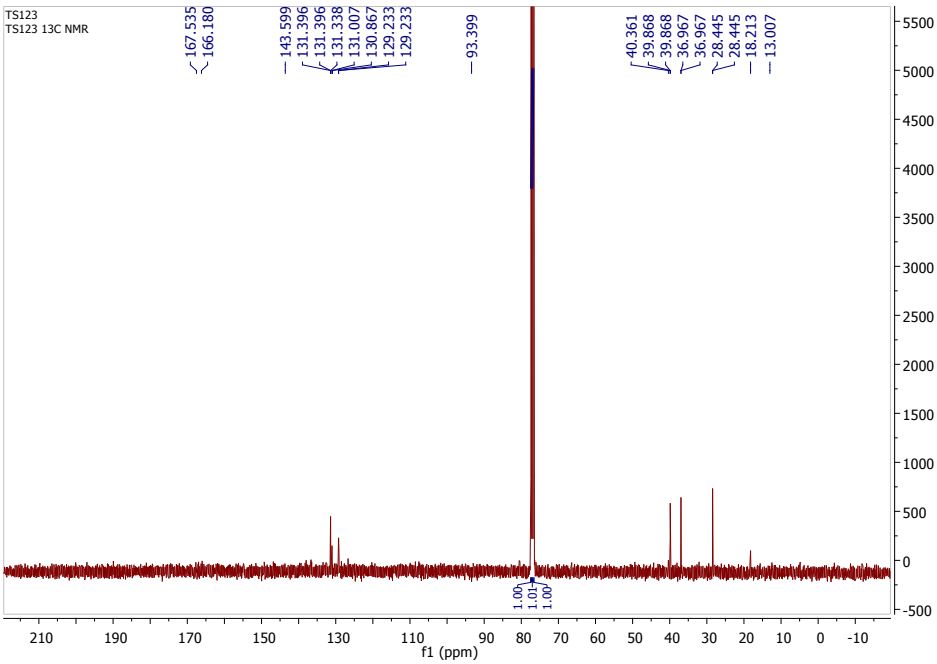

TS122
TS122 1H NMR
7.500
7.497
7.487
7.476
7.367
7.347
7.260
7.243
7.240
7.151
7.130
6.907
6.885
6.883
2.006
1.774
1.769
1.739
1.708
1.683
1.653
1.554
1.541
3.17
2.00
1.15
0.96
2.02
1.97
1.00
3.14
6.23
5.78
2.94
f1 (ppm)

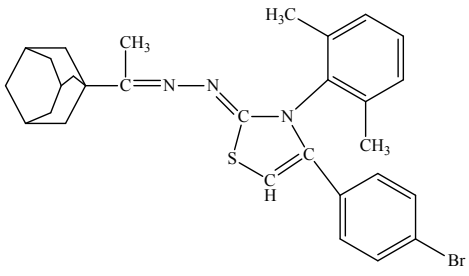

TS122
TS122 13C NMR
169.884
166.179
155.389
135.092
134.273
131.266
129.043
128.822
128.264
127.184
126.728
126.310
125.348
123.847
97.911
40.263
39.866
36.963
28.438
12.248
f1 (ppm)


H3C
CH3
C
N
N
C
N
S
C
C
H
Br

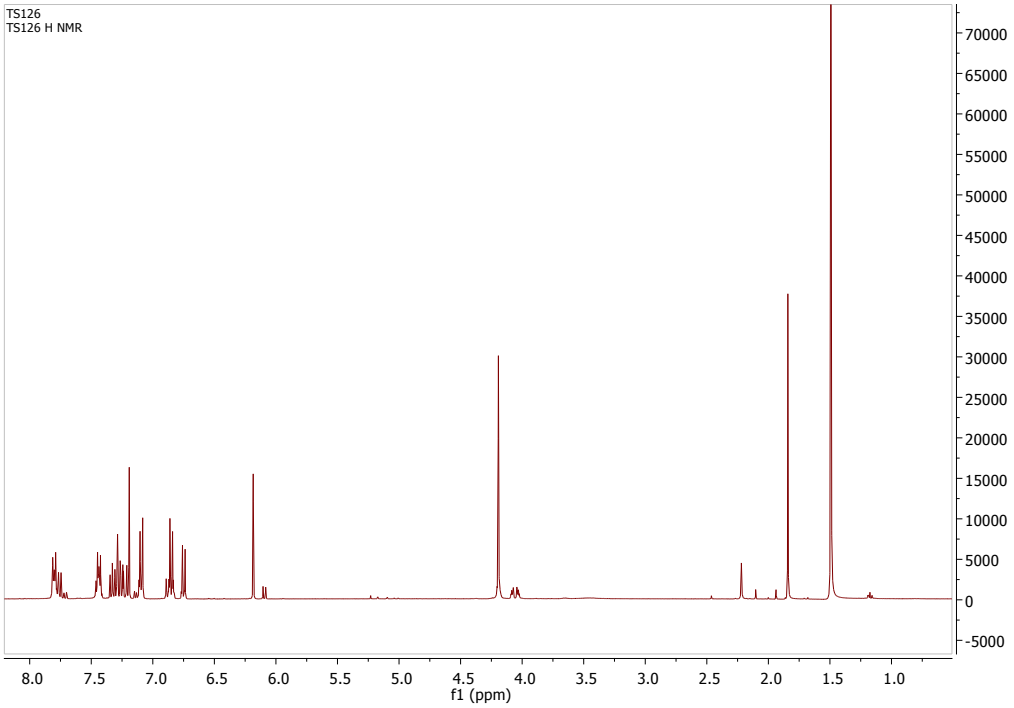
(6c)

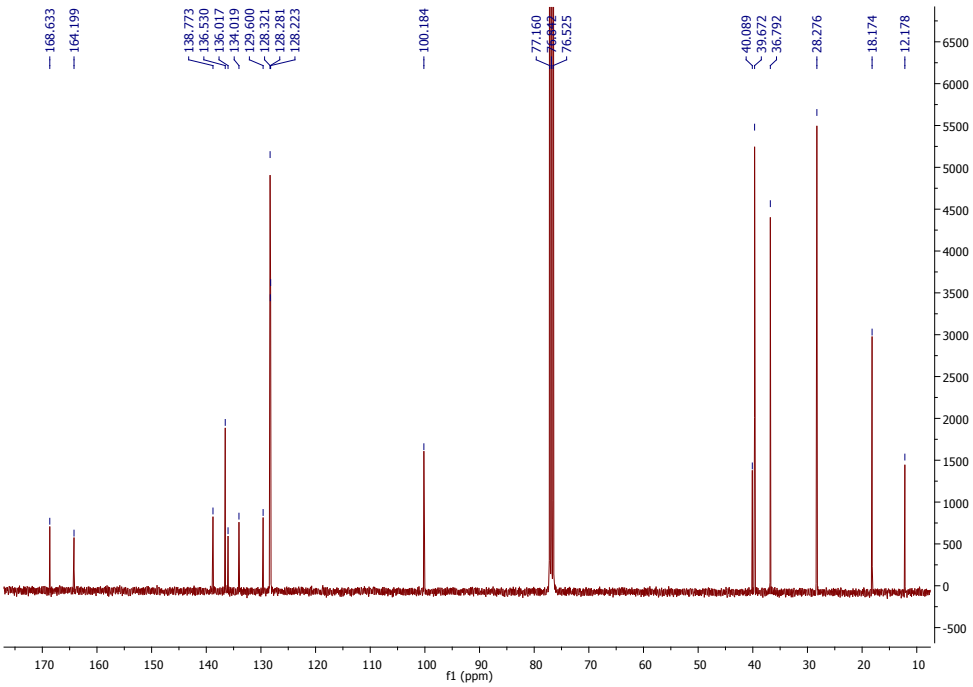

TS123
TS123 1H NMR
7.775
7.770
7.260
7.210
7.202
7.195
7.192
6.943
6.939
6.922
6.123
2.241
2.023
2.007
1.803
1.796
1.753
1.722
1.699
1.669
1.563
2.06
2.09
1.25
1.17
2.00
1.19
2.52
2.85
7.31
5.90
20.10
f1 (ppm)

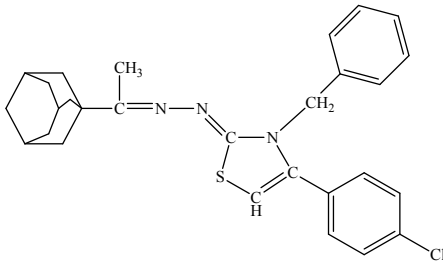

TS123
TS123 13C NMR
167.535
166.180
143.599
131.396
131.396
131.338
131.007
130.867
129.233
129.233
93.399
40.361
39.868
39.868
36.967
36.967
28.445
28.445
18.213
13.007
1.00
1.01
1.00
f1 (ppm)


H3C
CH3
C
N
N
C
N
S
C
C
H
CH3
Br

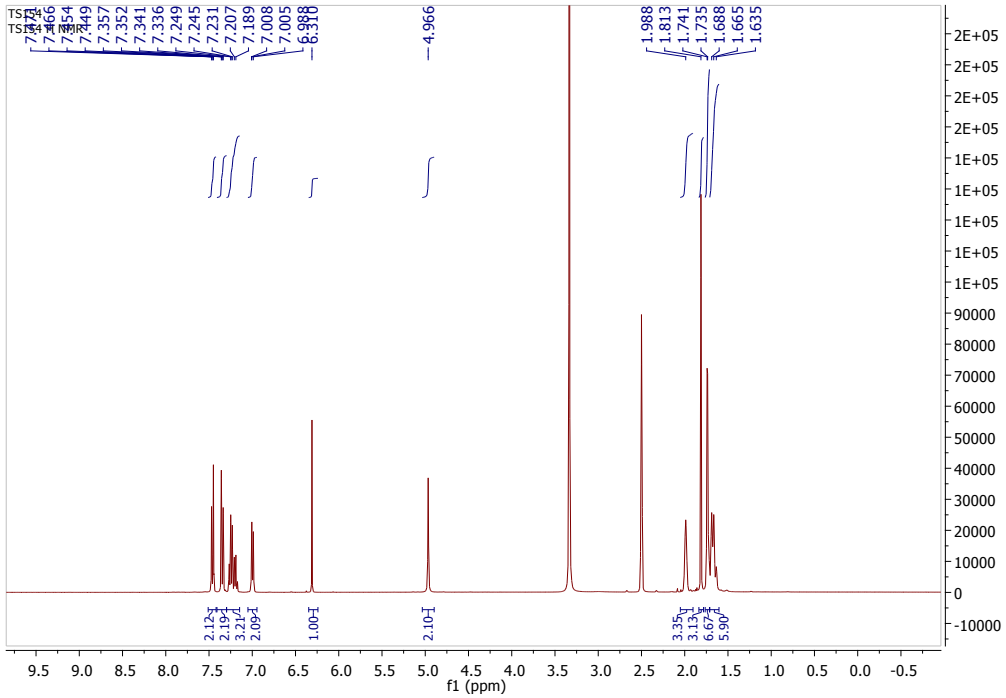
(6d)

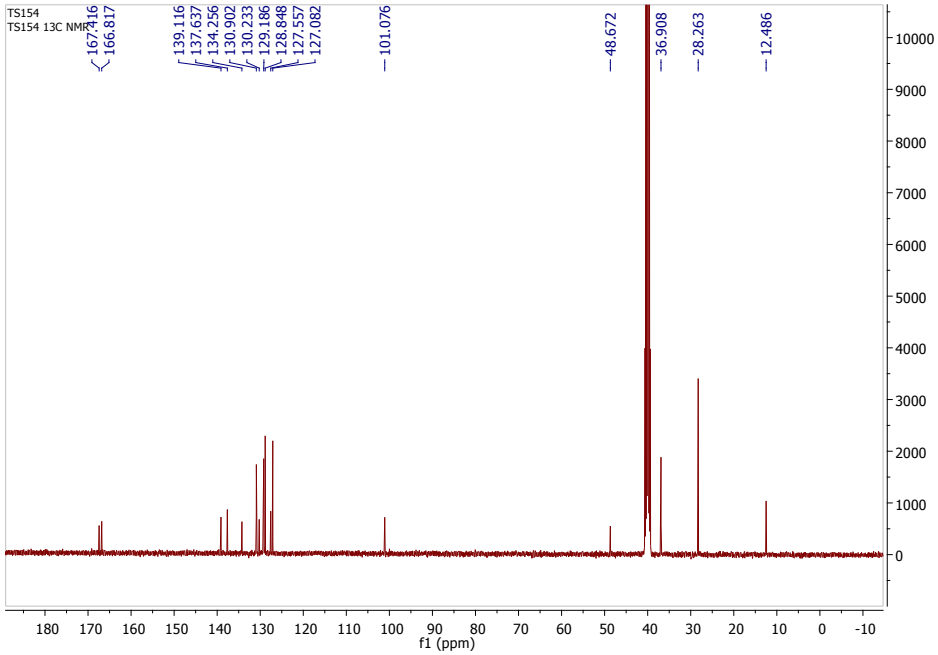

TS126
TS126 H NMR
f1 (ppm)

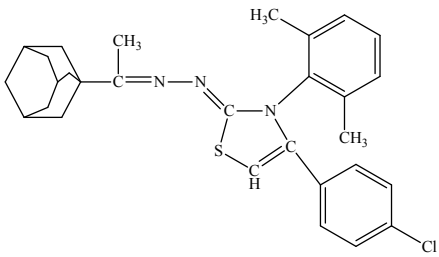

168.633
164.199
138.773
136.530
136.017
134.019
129.600
128.321
128.281
128.223
100.184
77.160
76.842
76.525
40.089
39.672
36.792
28.276
18.174
12.178
f1 (ppm)


CH3
C
N
N
CH2
C
N
S
C
C
H
Cl

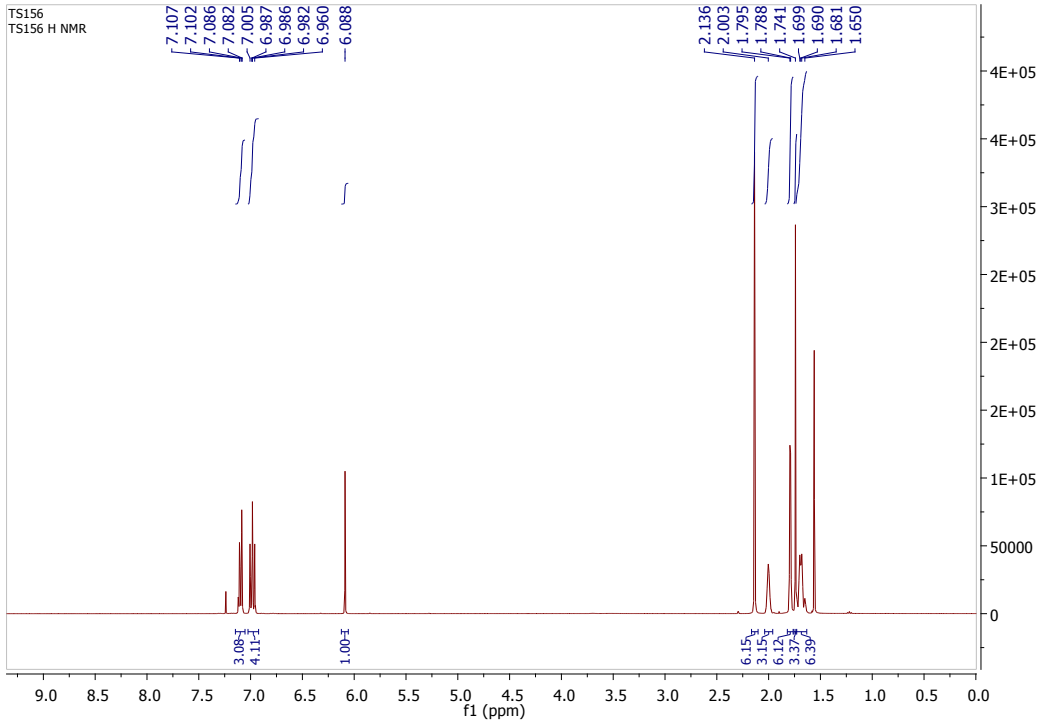
(6e)

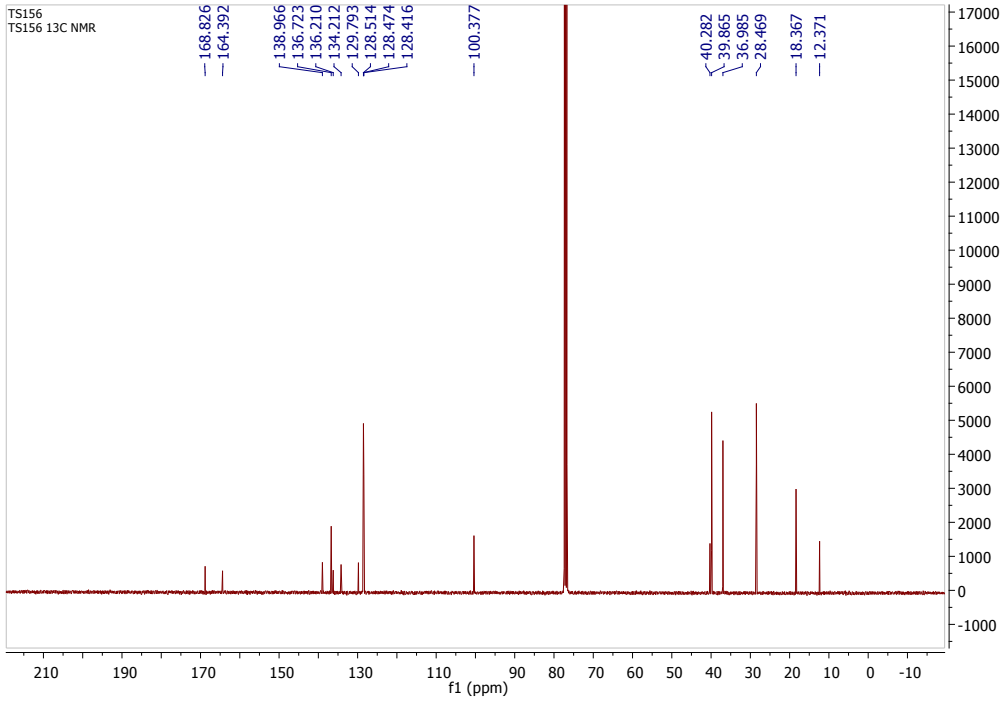

TS154
TS154 1H NMR
7.474
7.466
7.454
7.449
7.357
7.352
7.341
7.336
7.249
7.245
7.231
7.207
7.189
7.008
7.005
6.988
6.310
4.966
1.988
1.813
1.741
1.735
1.688
1.665
1.635
2.12
2.19
3.21
2.09
1.00
2.10
3.35
3.13
6.67
5.90
f1 (ppm)

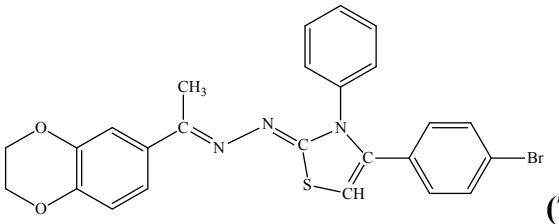

TS154
TS154 13C NMR
167.416
166.817
139.116
137.637
134.256
130.902
130.233
129.186
128.848
127.557
127.082
101.076
48.672
36.908
28.263
12.486
f1 (ppm)


H3C
CH3
C
N
N
C
N
CH3
S
C
C
H
Cl

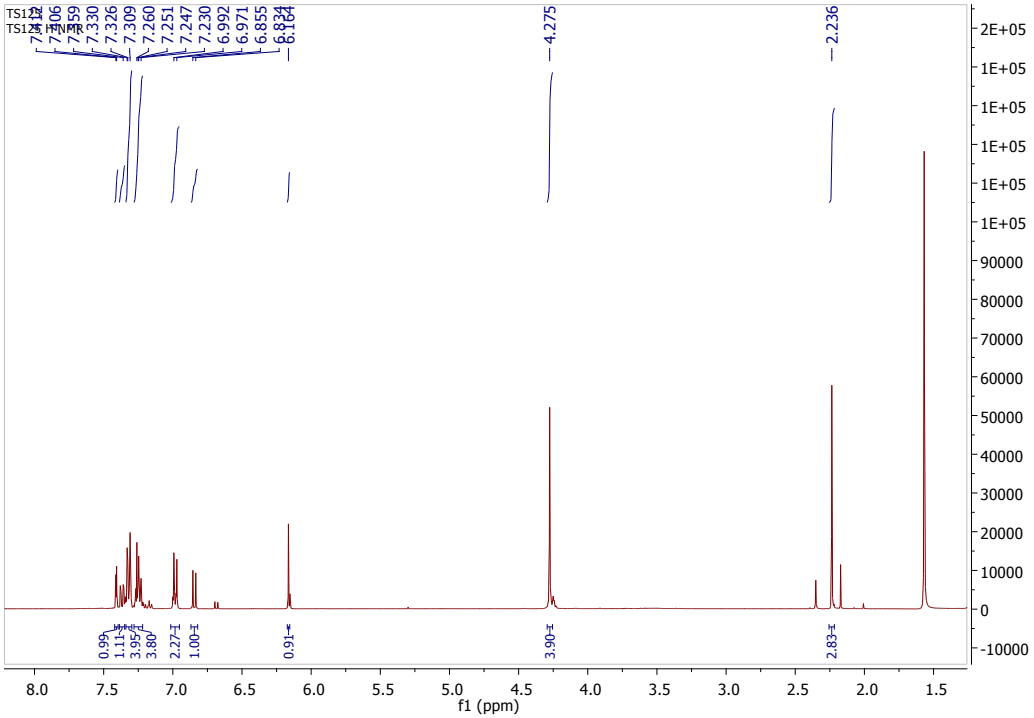
(6f)

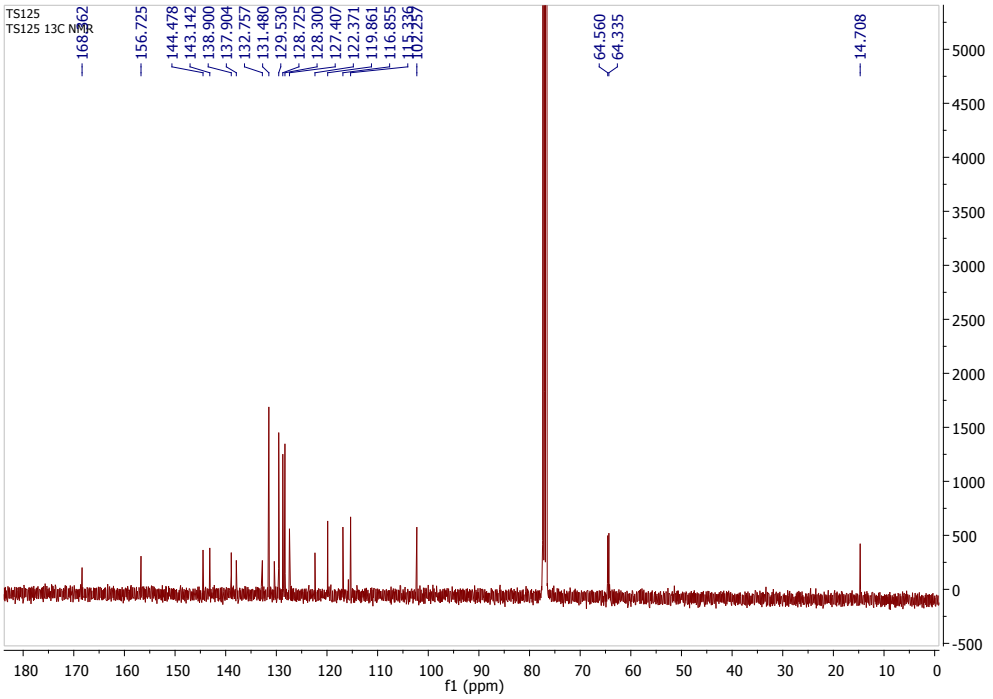

TS156
TS156 H NMR
7.107
7.102
7.086
7.082
7.005
6.987
6.986
6.982
6.960
6.088
2.136
2.003
1.795
1.788
1.741
1.699
1.690
1.681
1.650
3.08
4.11
1.00
6.15
3.15
6.12
3.37
6.39
f1 (ppm)

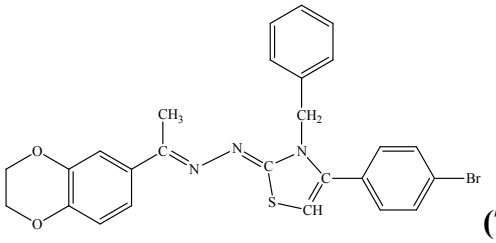

TS156
TS156 13C NMR
168.826
164.392
138.966
136.723
136.210
134.212
129.793
128.514
128.474
128.416
100.377
40.282
39.865
36.985
28.469
18.367
12.371
f1 (ppm)


CH3
O
O
C
N
N
C
N
C
S
CH
Br

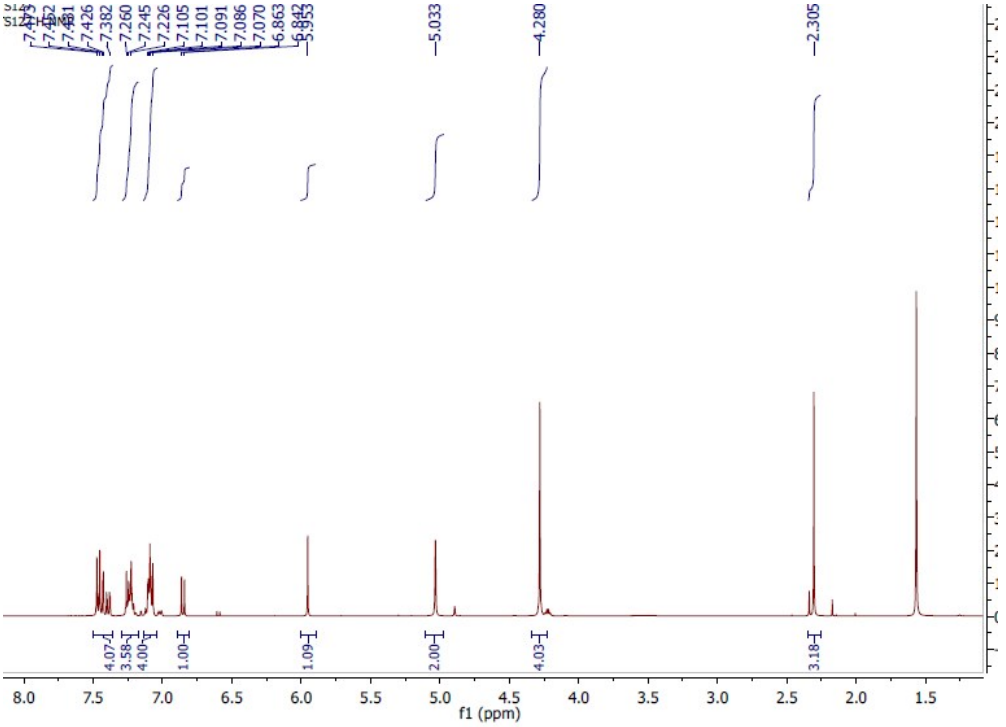
(7a)

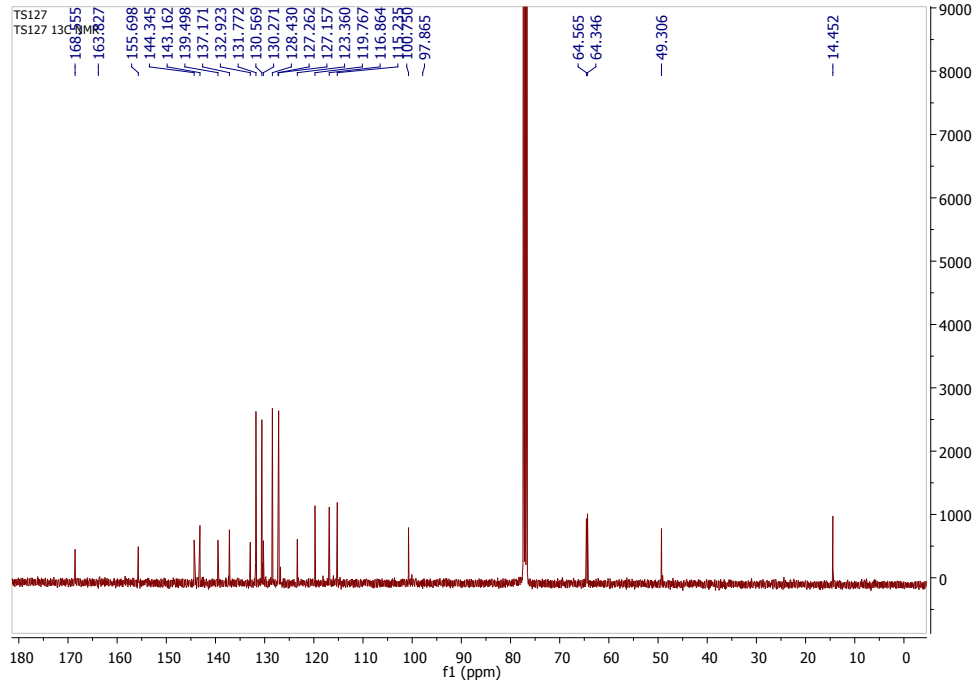

TS125
TS125 1H NMR
7.326
7.309
7.260
7.251
7.247
7.230
6.992
6.971
6.855
6.834
6.184
4.275
2.236
0.99
1.11
3.95
3.80
2.27
1.00
0.91
3.90
2.83
f1 (ppm)

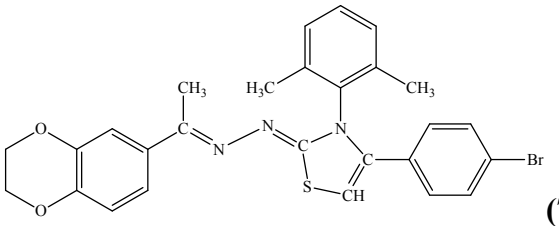

TS125
TS125 13C NMR
168.162
156.725
144.478
143.142
138.900
137.904
132.757
131.480
129.530
128.725
128.300
127.407
122.371
119.861
116.855
102.257
64.560
64.335
14.708
f1 (ppm)



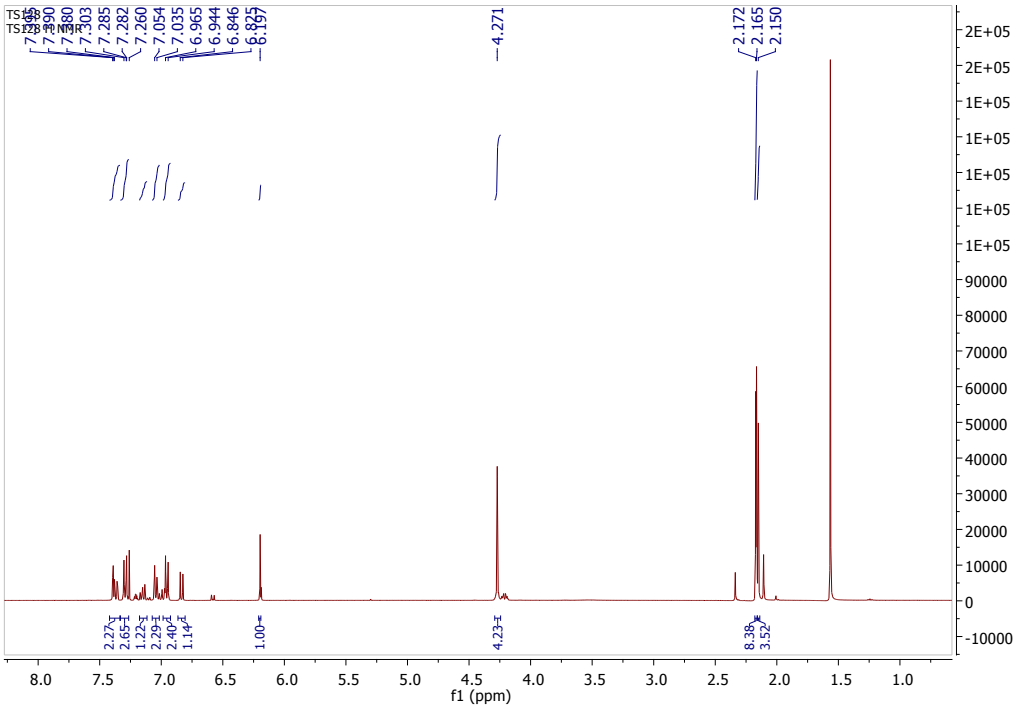
(7b)

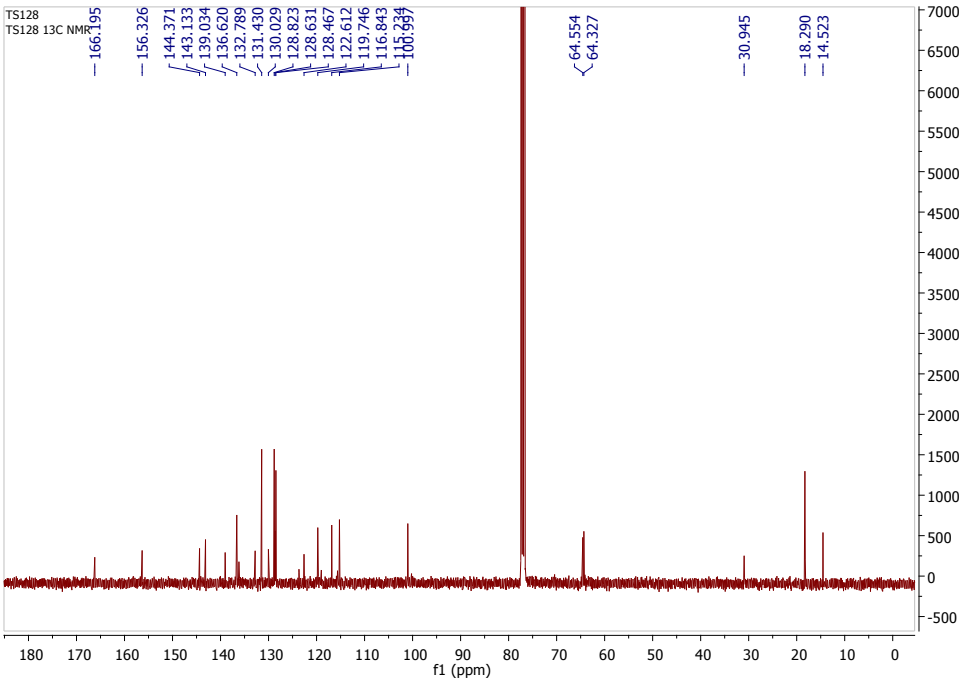

7.426
7.382
7.260
7.245
7.226
7.105
7.101
7.091
7.086
7.070
6.863
6.842
5.953
5.033
4.280
2.305
4.07
3.58
4.00
1.00
1.09
2.00
4.03
3.18
f1 (ppm)

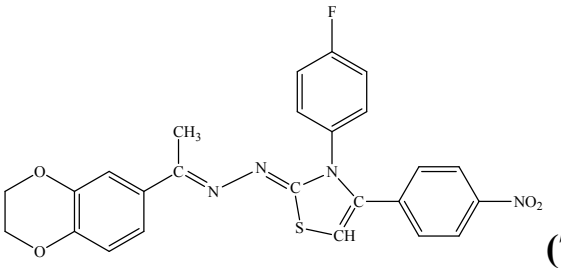

TS127
TS127 13C NMR
168.555
163.827
155.698
144.345
143.162
139.498
137.171
132.923
131.772
130.569
130.271
128.430
127.262
127.157
123.360
119.767
116.864
115.235
100.750
97.865
64.565
64.346
49.306
14.452
f1 (ppm)


CH3
H3C
CH3
O
O
C
N
N
C
N
C
S
CH
Br

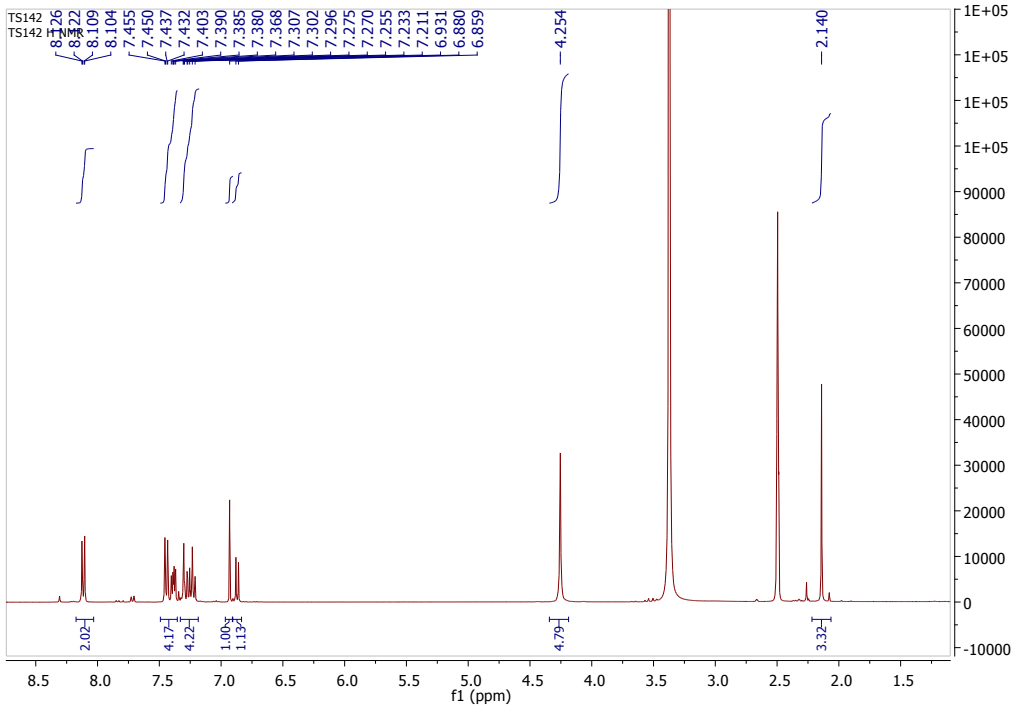
(7c)

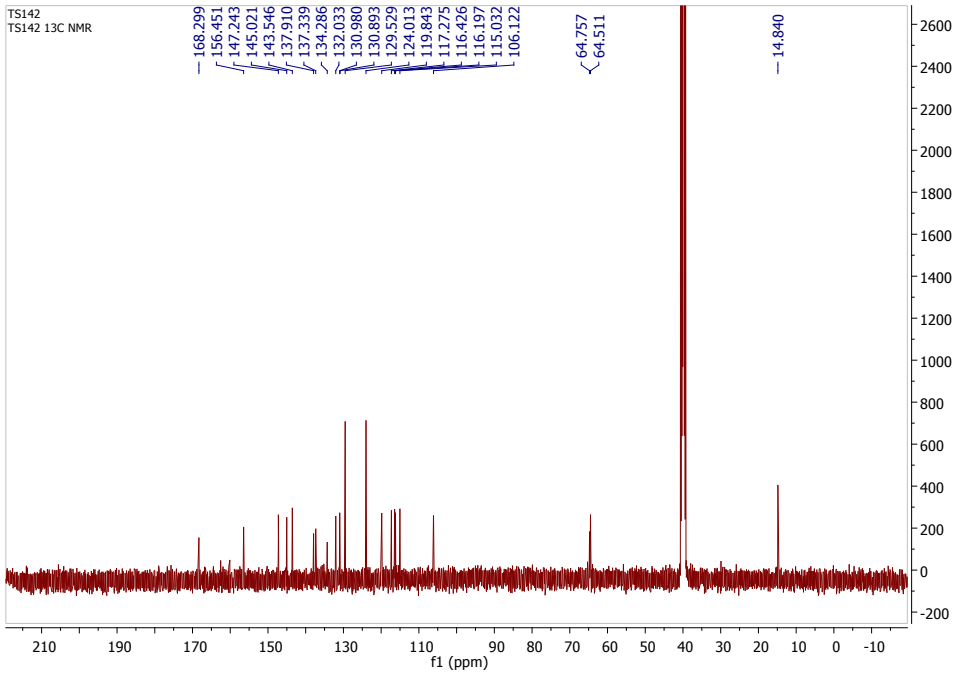

7.490
7.480
7.303
7.285
7.282
7.260
7.054
7.035
6.965
6.944
6.846
6.825
6.197
4.271
2.172
2.165
2.150
2.27
2.65
1.22
2.29
2.40
1.14
1.00
4.23
8.38
3.52
f1 (ppm)

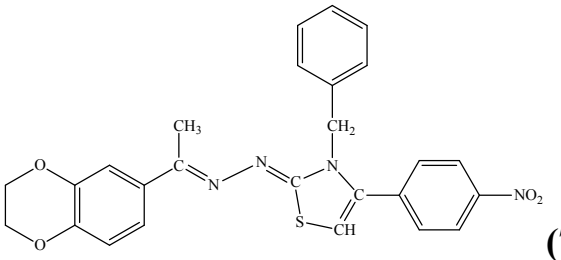

TS128
TS128 13C NMR
166.195
156.326
144.371
143.133
139.034
136.620
132.789
131.430
130.029
128.823
128.631
128.467
122.612
119.746
116.843
115.234
100.997
64.554
64.327
30.945
18.290
14.523
f1 (ppm)


F
CH3
O
O
C
N
N
C
N
C
S
CH
NO2

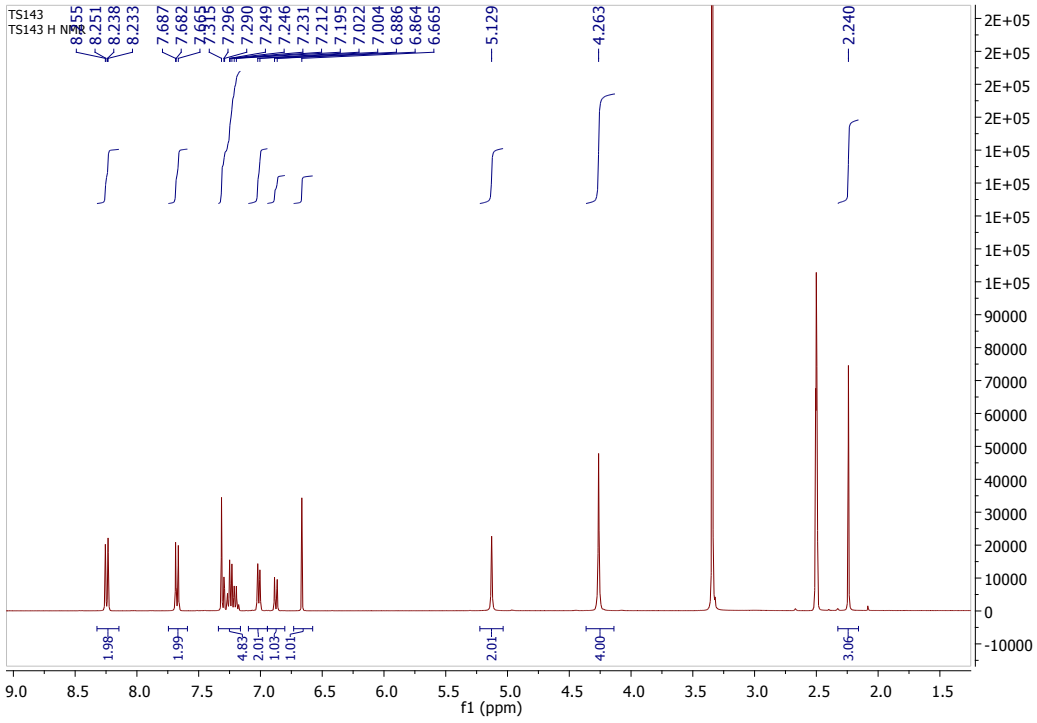
(7d)

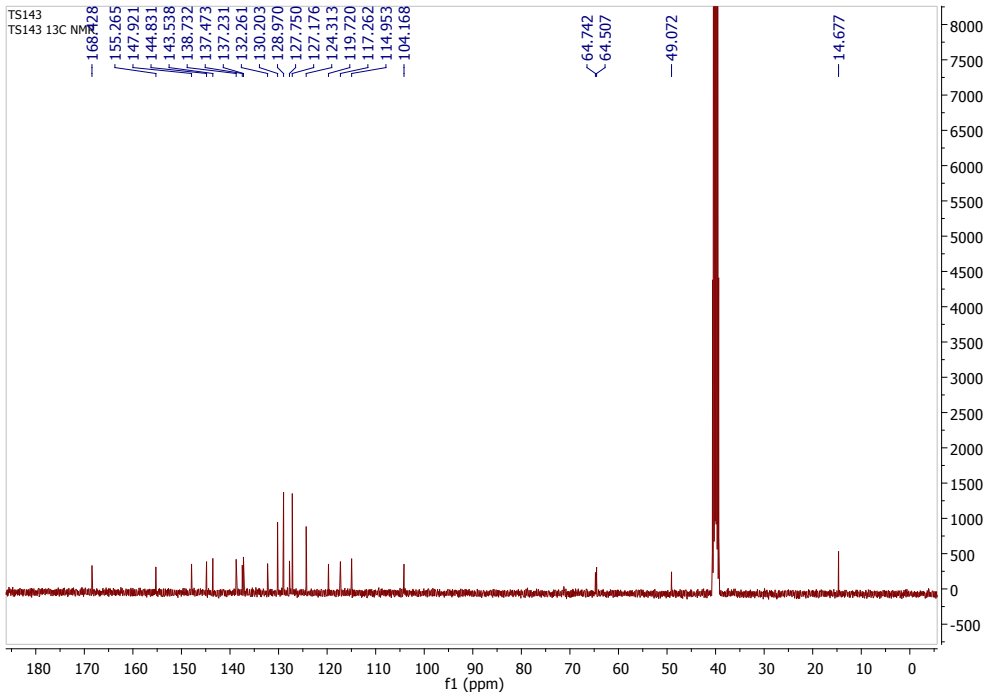

TS142
TS142 1H NMR
8.126
8.122
8.109
8.104
7.455
7.450
7.437
7.432
7.403
7.390
7.385
7.380
7.368
7.307
7.302
7.296
7.275
7.270
7.255
7.233
7.211
6.931
6.880
6.859
4.254
2.140
2.02
4.17
4.22
1.00
1.13
4.79
3.32
f1 (ppm)

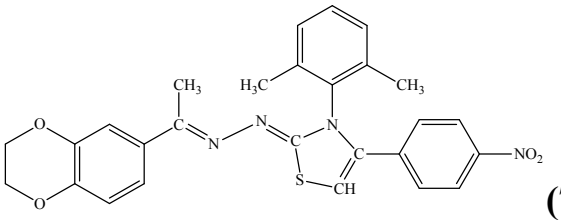

TS142
TS142 13C NMR
168.299
156.451
147.243
145.021
143.546
137.910
137.339
134.286
132.033
130.980
130.893
129.529
124.013
119.843
117.275
116.426
116.197
115.032
106.122
64.757
64.511
14.840
f1 (ppm)



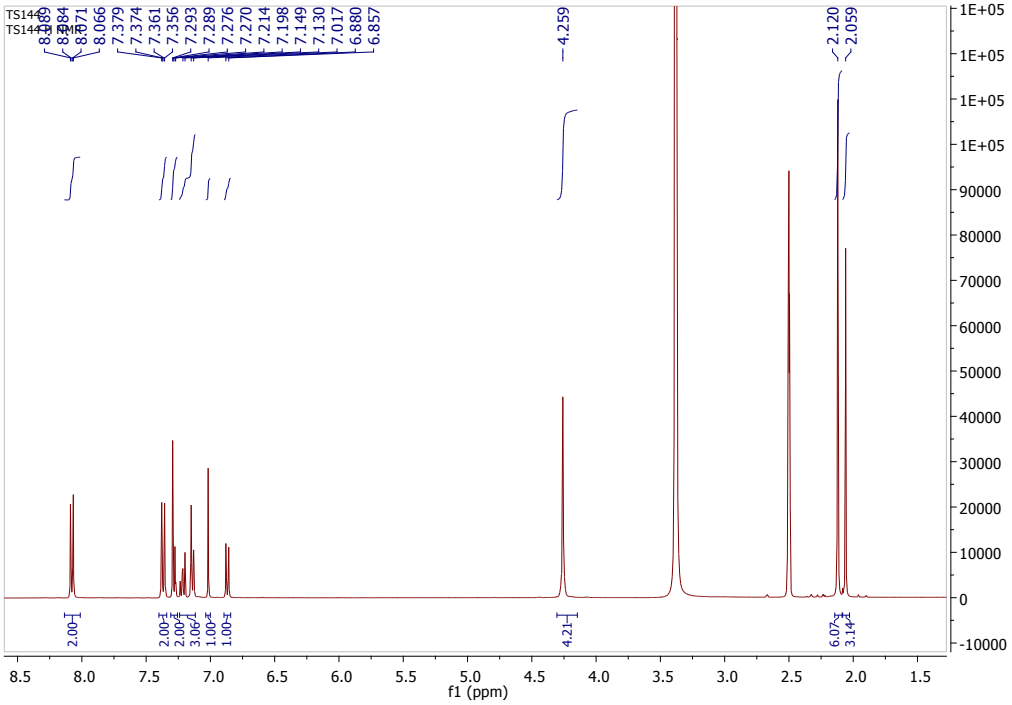
(7e)

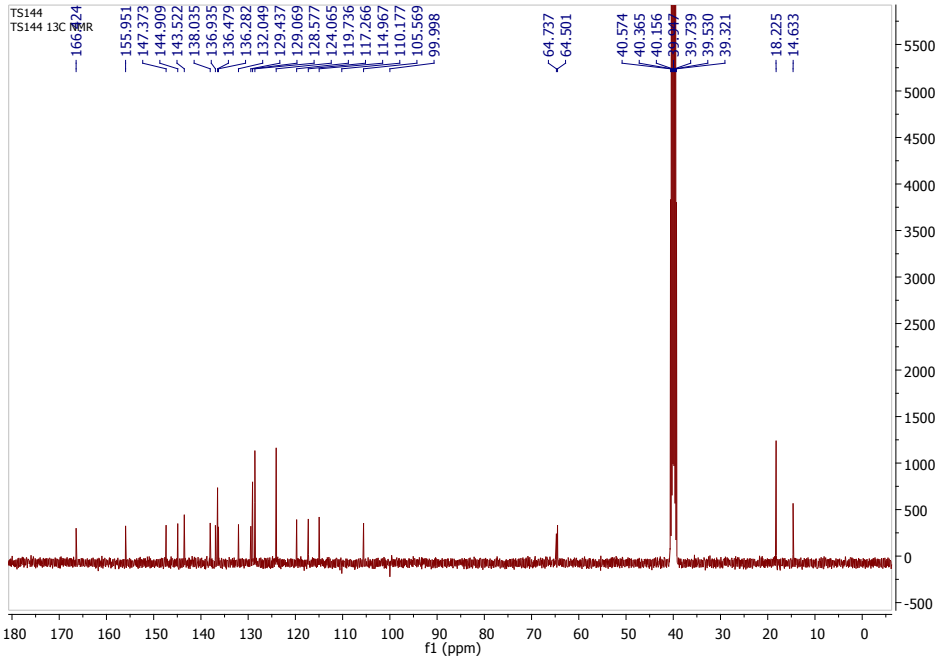

TS143
TS143 H NMR
8.855
8.251
8.238
8.233
7.687
7.682
7.665
7.515
7.296
7.290
7.249
7.246
7.231
7.212
7.195
7.022
7.004
6.886
6.864
6.665
5.129
4.263
2.240
1.98
1.99
4.83
2.01
1.03
1.01
2.01
4.00
3.06
f1 (ppm)

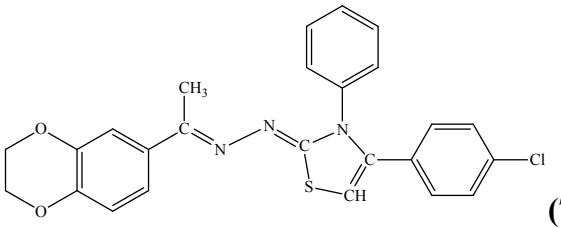

TS143
TS143 13C NMR
168.428
155.265
147.921
144.831
143.538
138.732
137.473
137.231
132.261
130.203
128.970
127.750
127.176
124.313
119.720
117.262
114.953
104.168
64.742
64.507
49.072
14.677
f1 (ppm)


CH3
H3C
CH3
O
O
C
N
N
C
N
C
S
CH
NO2

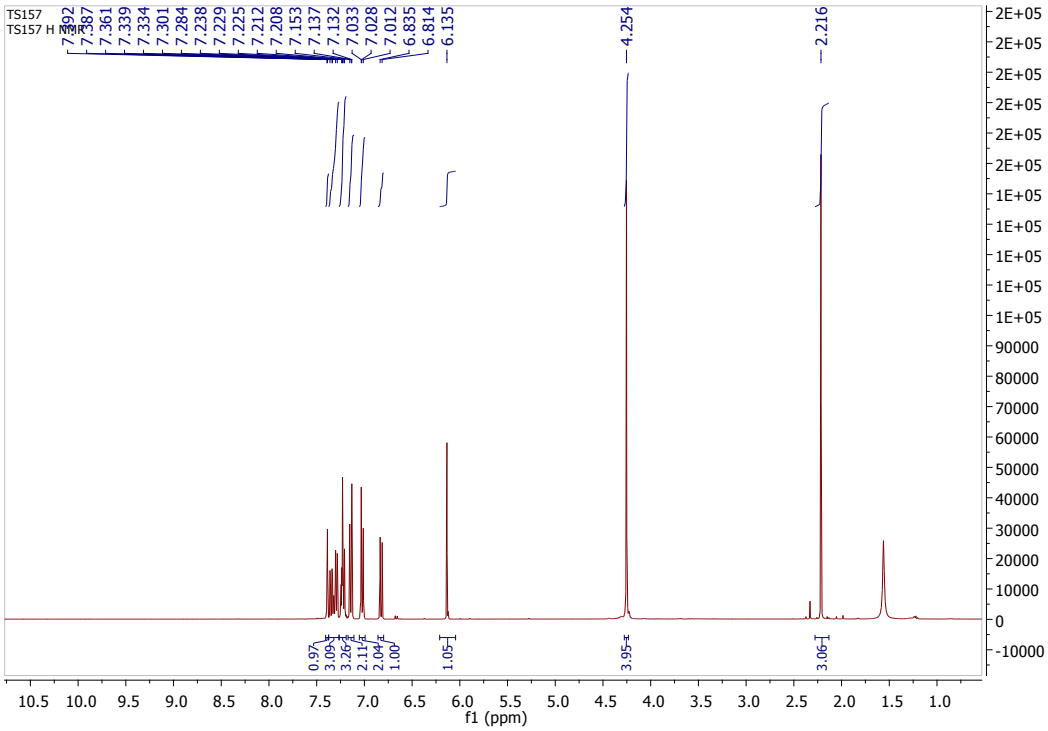
(7f)

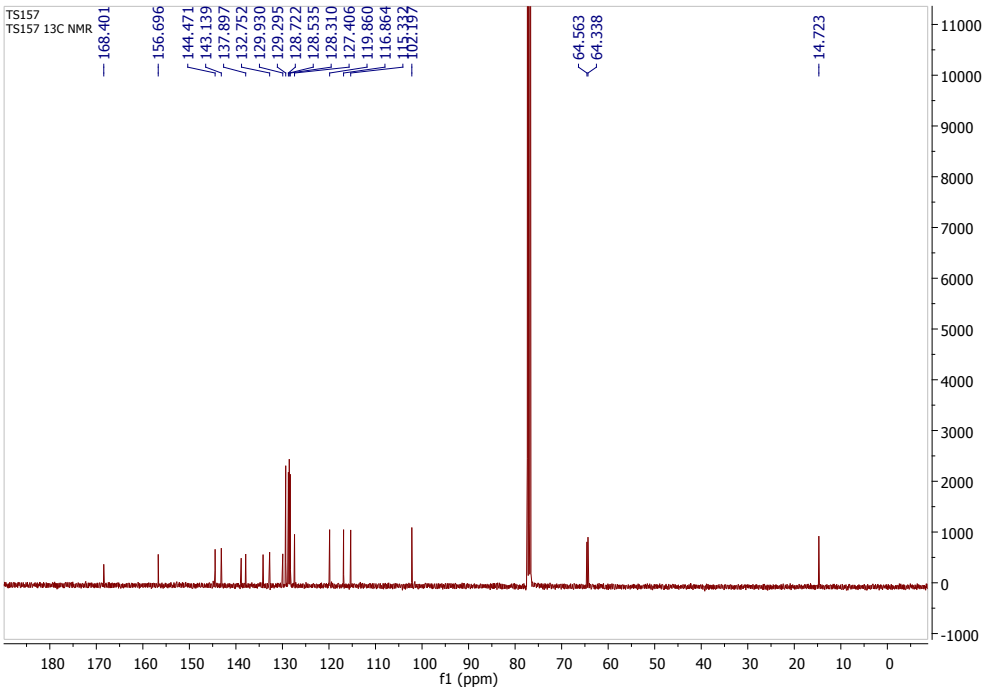

TS144
TS144 1H NMR
8.085
8.084
8.071
8.066
7.379
7.374
7.361
7.356
7.293
7.289
7.276
7.270
7.214
7.198
7.149
7.130
7.017
6.880
6.857
4.259
2.120
2.059
2.00
2.00
2.00
3.06
1.00
1.00
4.21
6.07
3.14
f1 (ppm)

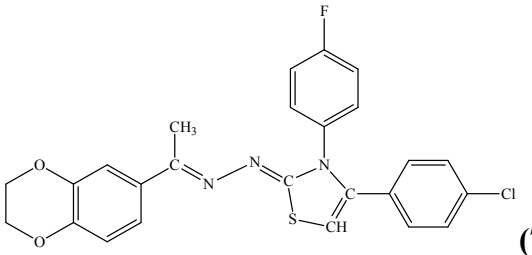

TS144
TS144 13C NMR
166.424
155.951
147.373
144.909
143.522
138.035
136.935
136.479
136.282
132.049
129.437
129.069
128.577
124.065
119.736
117.266
114.967
110.177
105.569
99.998
64.737
64.501
40.574
40.365
40.156
39.739
39.530
39.321
18.225
14.633
f1 (ppm)


CH3
O
O
C
N
N
C
N
C
S
CH
Cl

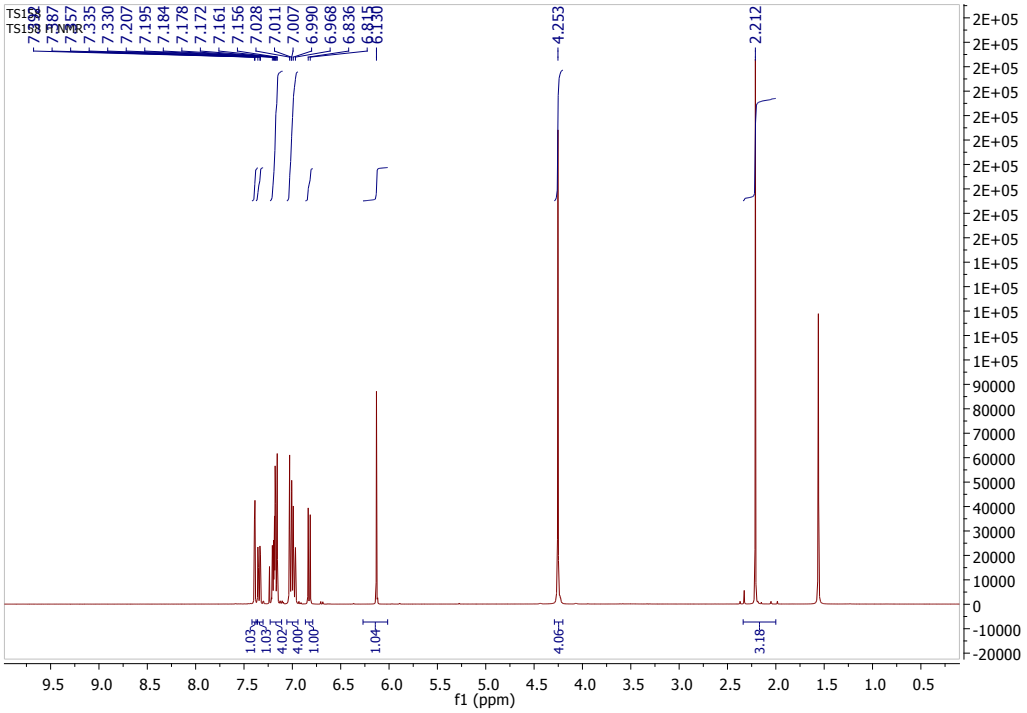
(7g)

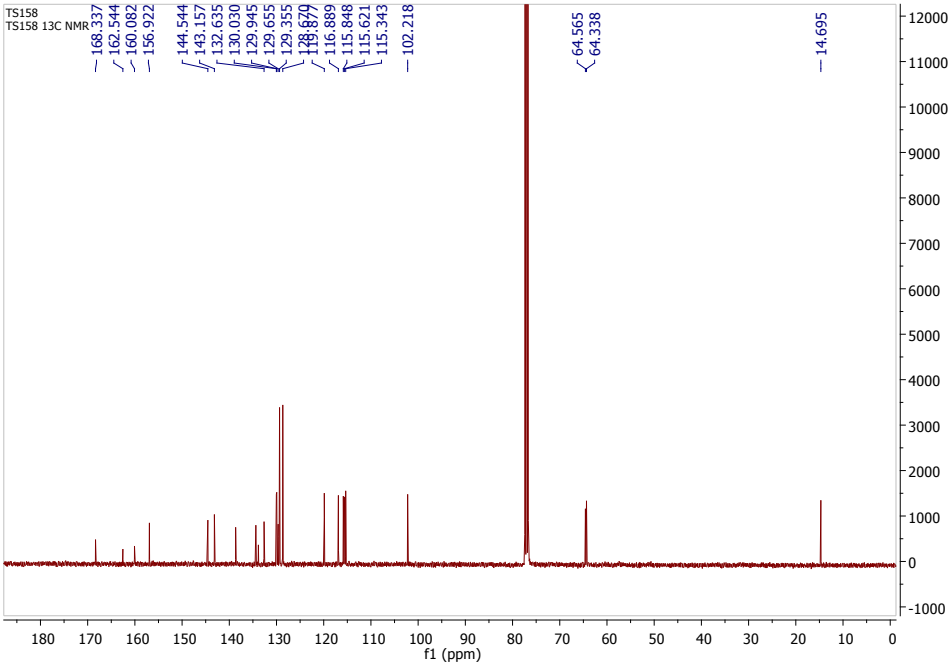

TS157
TS157 H NMR
7.392
7.387
7.361
7.339
7.334
7.301
7.284
7.238
7.229
7.225
7.212
7.208
7.153
7.137
7.132
7.033
7.028
7.012
6.835
6.814
6.135
4.254
2.216
0.97
3.09
3.26
2.11
2.04
1.00
1.05
3.95
3.06
f1 (ppm)

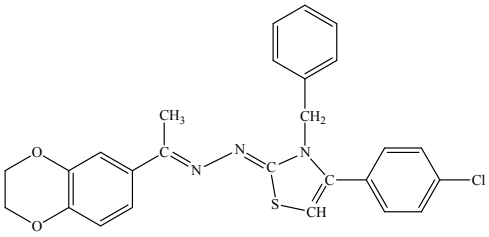

TS157
TS157 13C NMR
168.401
156.696
144.471
143.139
137.897
132.752
129.930
129.295
128.722
128.535
128.310
127.406
119.860
116.864
115.332
102.197
64.563
64.338
14.723
f1 (ppm)


F
CH3
O
O
C
N
N
C
N
C
S
CH
Cl

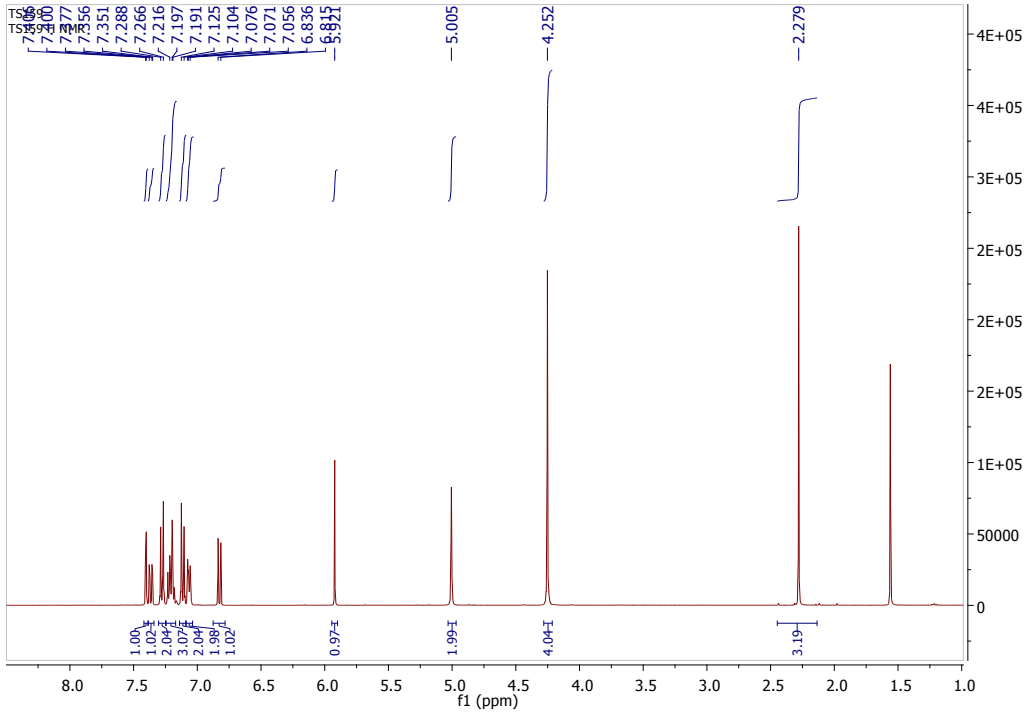
(7h)

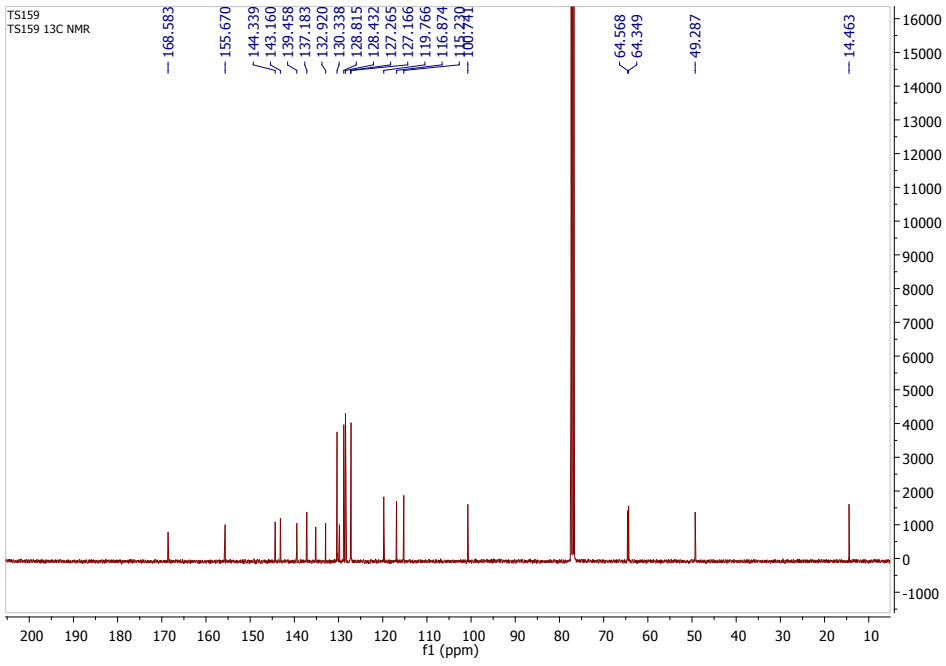

TS158
TS158 1HNMR
7.387
7.357
7.335
7.330
7.207
7.195
7.184
7.178
7.172
7.161
7.156
7.028
7.011
7.007
6.990
6.968
6.836
6.815
6.130
4.253
2.212
1.03
1.03
4.02
4.00
1.00
1.04
4.06
3.18
f1 (ppm)

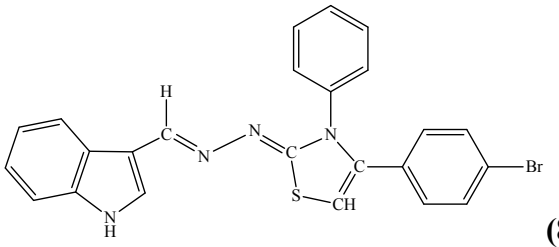

TS158
TS158 13C NMR
168.337
162.544
160.082
156.922
144.544
143.157
132.635
130.030
129.945
129.655
129.355
116.889
115.848
115.621
115.343
102.218
64.565
64.338
14.695
f1 (ppm)


CH3
CH2
O
O
N
N
C
N
C
S
CH
C
Cl

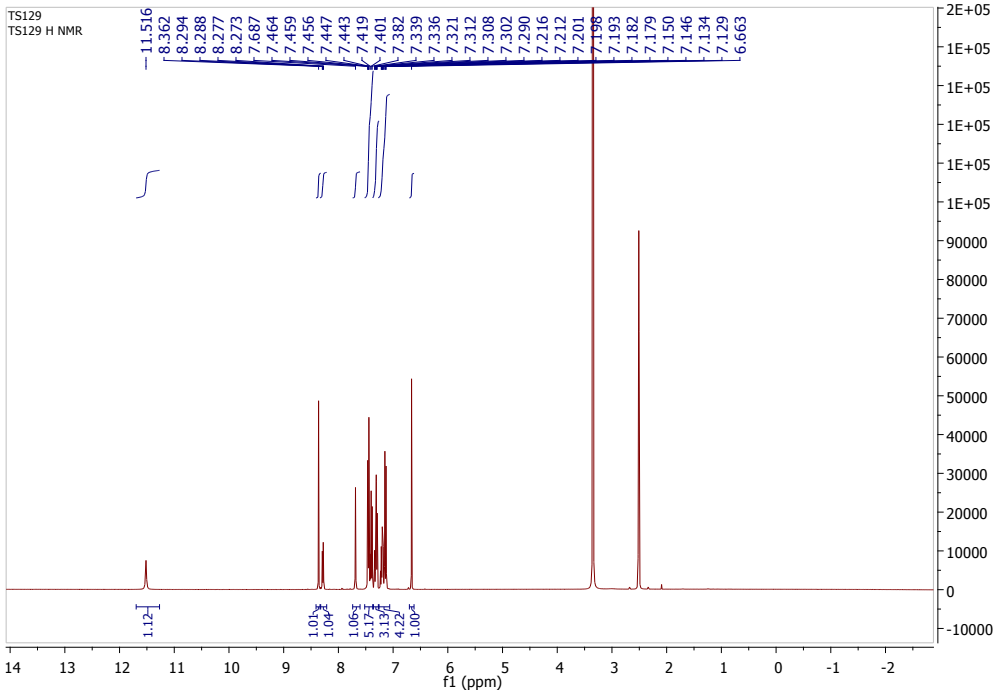
(7i)

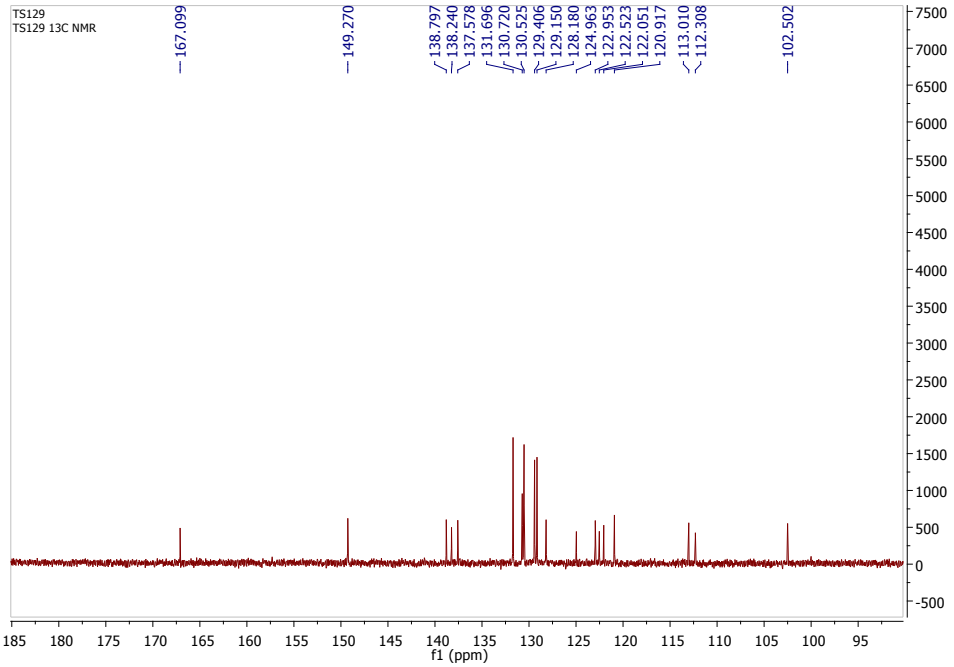

TS159
TS159 1H NMR
7.400
7.377
7.356
7.351
7.288
7.266
7.216
7.197
7.191
7.125
7.104
7.076
7.071
7.056
6.836
6.815
6.811
5.921
5.005
4.252
2.279
1.00
1.02
2.04
3.07
2.04
1.98
1.02
0.97
1.99
4.04
3.19
f1 (ppm)

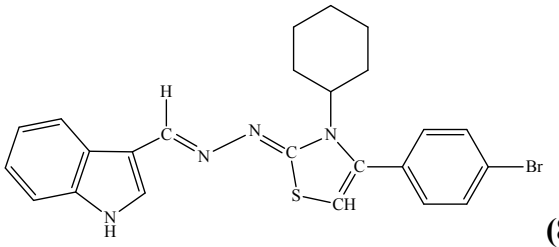

TS159
TS159 13C NMR
168.583
155.670
144.339
143.160
139.458
137.183
132.920
130.338
128.815
128.432
127.265
127.166
119.766
116.874
115.230
100.741
64.568
64.349
49.287
14.463
f1 (ppm)


H
C
N
N
C
N
C
Br
S
CH
N
H

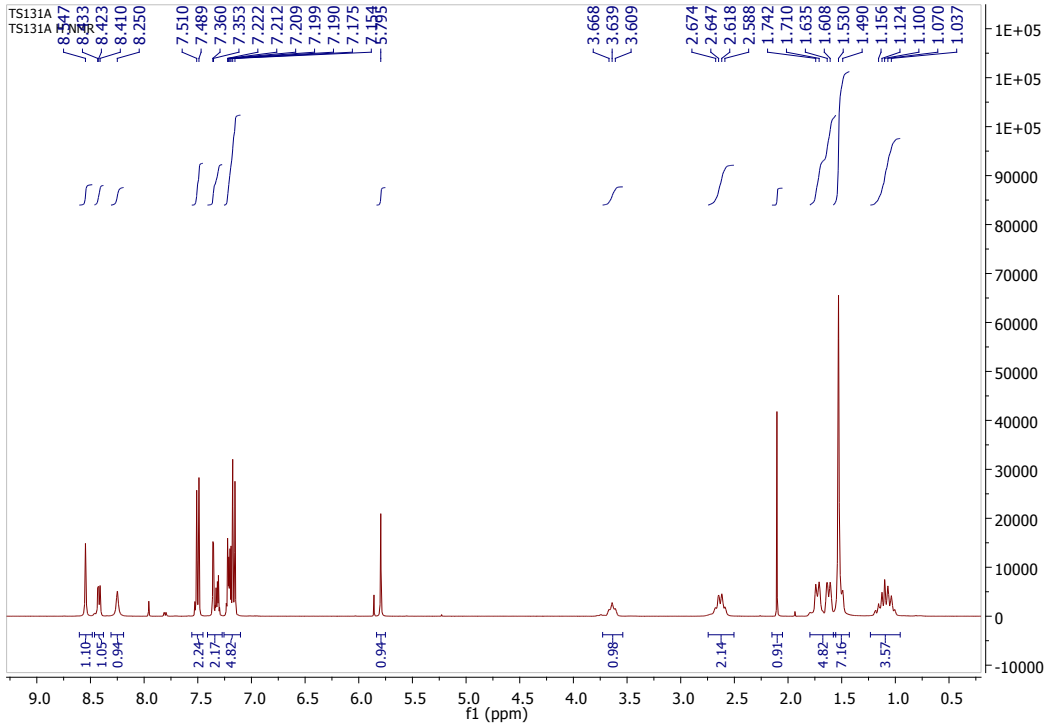
(8a)

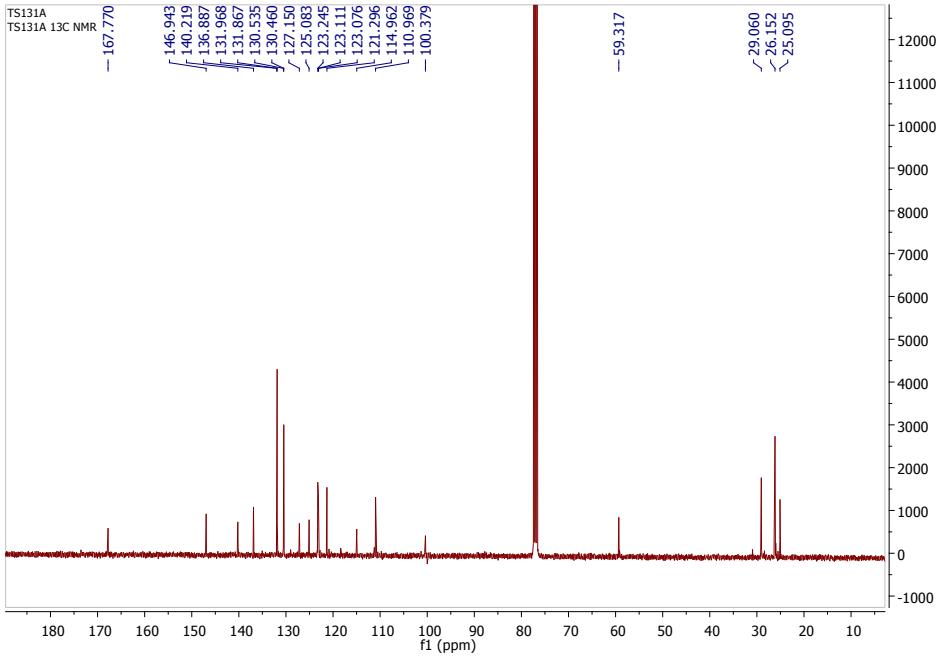

TS129
TS129 H NMR
11.516
8.362
8.294
8.288
8.277
8.273
7.687
7.464
7.459
7.456
7.447
7.443
7.419
7.401
7.382
7.339
7.336
7.321
7.312
7.308
7.302
7.290
7.216
7.212
7.201
7.198
7.193
7.182
7.179
7.150
7.146
7.134
7.129
6.663
1.12
1.01
1.04
1.06
5.17
3.13
4.22
1.00
f1 (ppm)

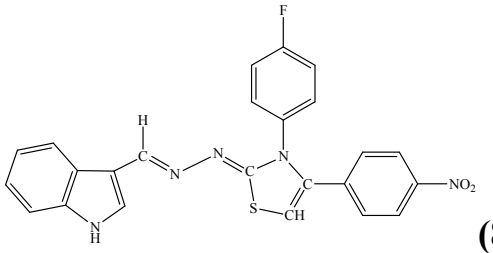

TS129
TS129 13C NMR
167.099
149.270
138.797
138.240
137.578
131.696
130.720
130.525
129.406
129.150
128.180
124.963
122.953
122.523
122.051
120.917
113.010
112.308
102.502
f1 (ppm)


H
C
N
N
C
N
C
Br
S
CH
N
H

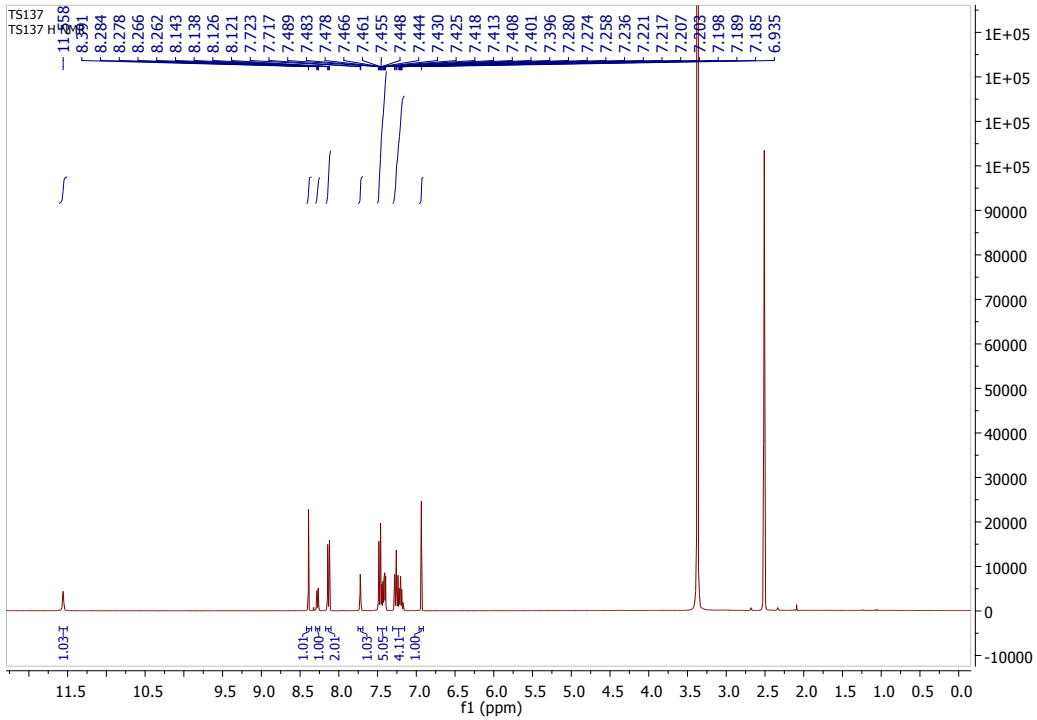
(8b)

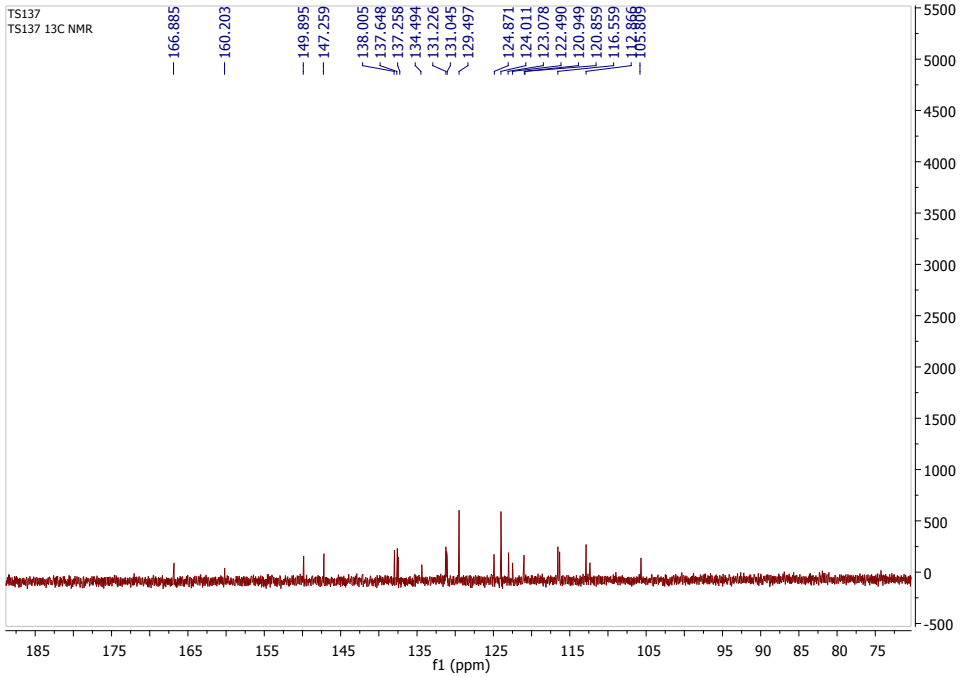

TS131A
TS131A H NMR
8.447
8.433
8.423
8.410
8.250
7.510
7.489
7.360
7.353
7.222
7.212
7.209
7.199
7.190
7.175
7.154
5.795
3.668
3.639
3.609
2.674
2.647
2.618
2.588
1.742
1.710
1.635
1.608
1.530
1.490
1.156
1.124
1.100
1.070
1.037
1.10
1.05
0.94
2.24
2.17
4.82
0.94
0.98
2.14
0.91
4.82
7.16
3.57
f1 (ppm)

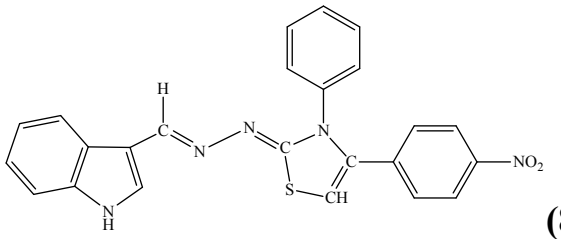

TS131A
TS131A 13C NMR
167.770
146.943
140.219
136.887
131.968
131.867
130.535
130.460
127.150
125.083
123.245
123.111
123.076
121.296
114.962
110.969
100.379
59.317
29.060
26.152
25.095
f1 (ppm)


F
H
C
N
N
C
N
C
C
NO2
S
CH
N
H

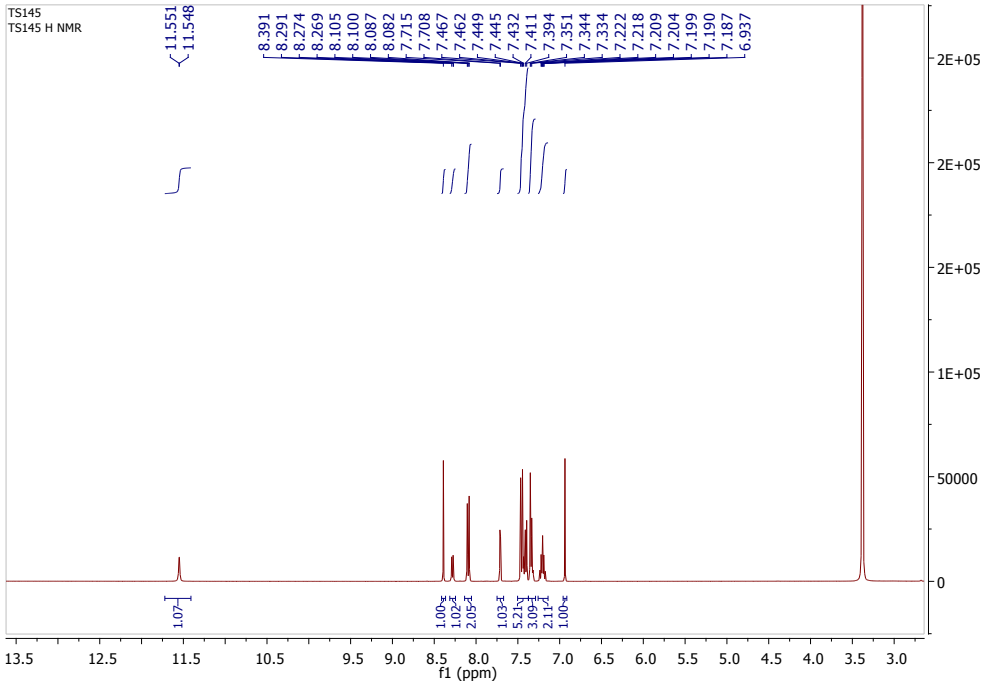
(8c)

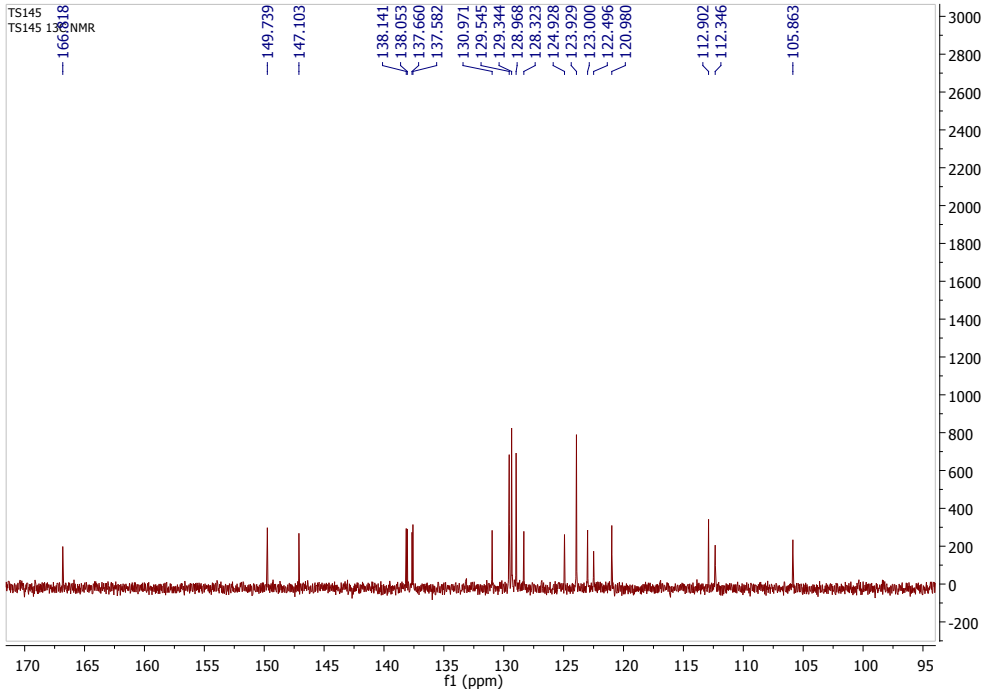

TS137
TS137 H NMR
11.558
8.331
8.284
8.278
8.266
8.262
8.143
8.138
8.126
8.121
7.723
7.717
7.489
7.483
7.478
7.466
7.461
7.455
7.448
7.444
7.430
7.425
7.418
7.413
7.408
7.401
7.396
7.280
7.274
7.258
7.236
7.221
7.217
7.207
7.203
7.198
7.189
7.185
6.935
1.03
1.01
1.00
2.01
1.03
5.05
4.11
1.00
f1 (ppm)

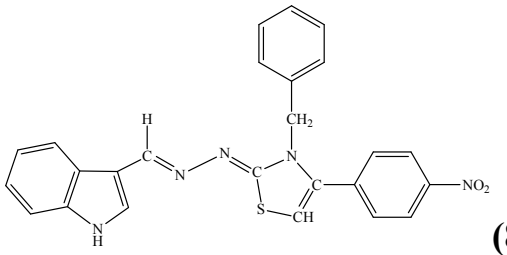

TS137
TS137 13C NMR
166.885
160.203
149.895
147.259
138.005
137.648
137.258
134.494
131.226
131.045
129.497
124.871
124.011
123.078
122.490
120.949
120.859
116.559
112.866
105.888
f1 (ppm)



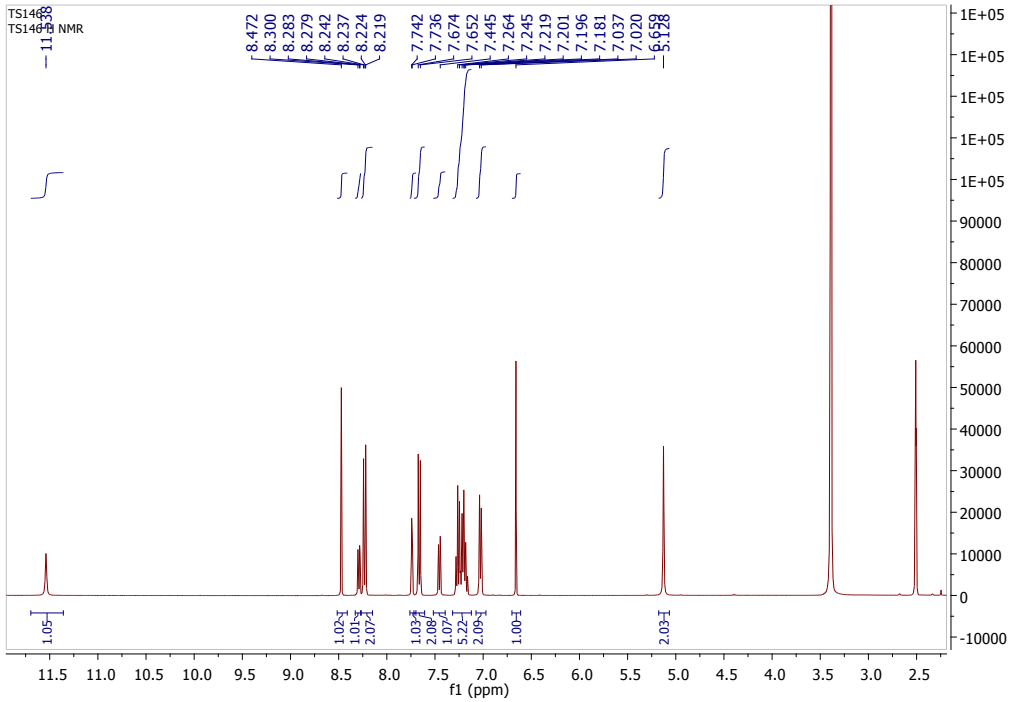
(8d)

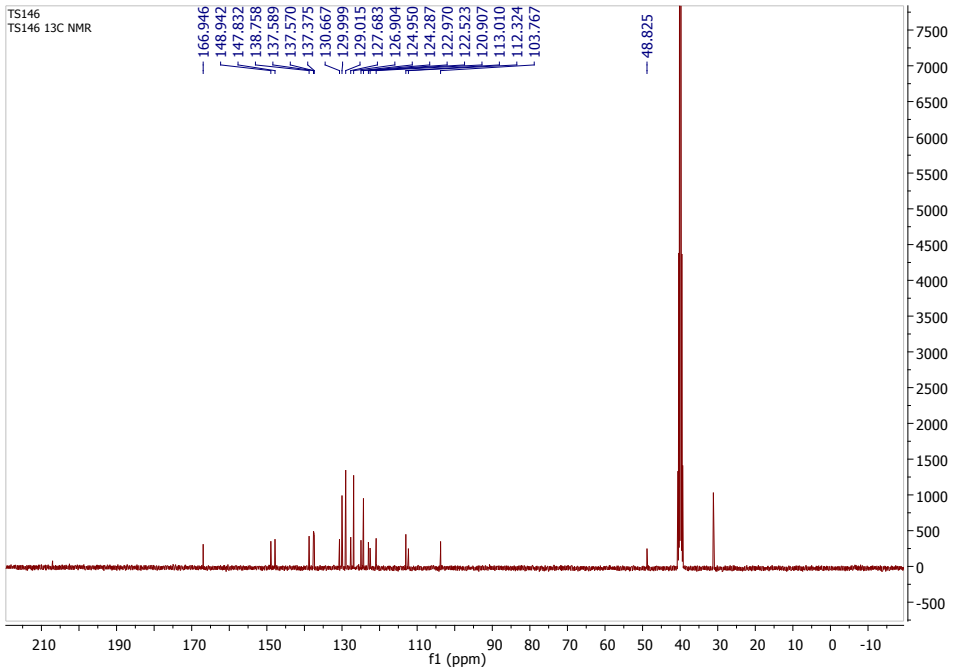

TS145
TS145 H NMR
11.551
11.548
8.391
8.291
8.274
8.269
8.105
8.100
8.087
8.082
7.715
7.708
7.467
7.462
7.449
7.445
7.432
7.411
7.394
7.351
7.344
7.334
7.222
7.218
7.209
7.204
7.199
7.190
7.187
6.937
2E+05
2E+05
2E+05
1E+05
50000
0
1.07
1.00
1.02
2.05
1.03
5.21
3.09
2.11
1.00
13.5
12.5
11.5
10.5
9.5
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
f1 (ppm)

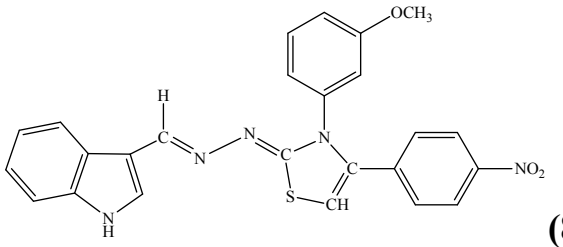

TS145
TS145 13C NMR
166.818
149.739
147.103
138.141
138.053
137.660
137.582
130.971
129.545
129.344
128.968
128.323
124.928
123.929
123.000
122.496
120.980
112.902
112.346
105.863
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
f1 (ppm)



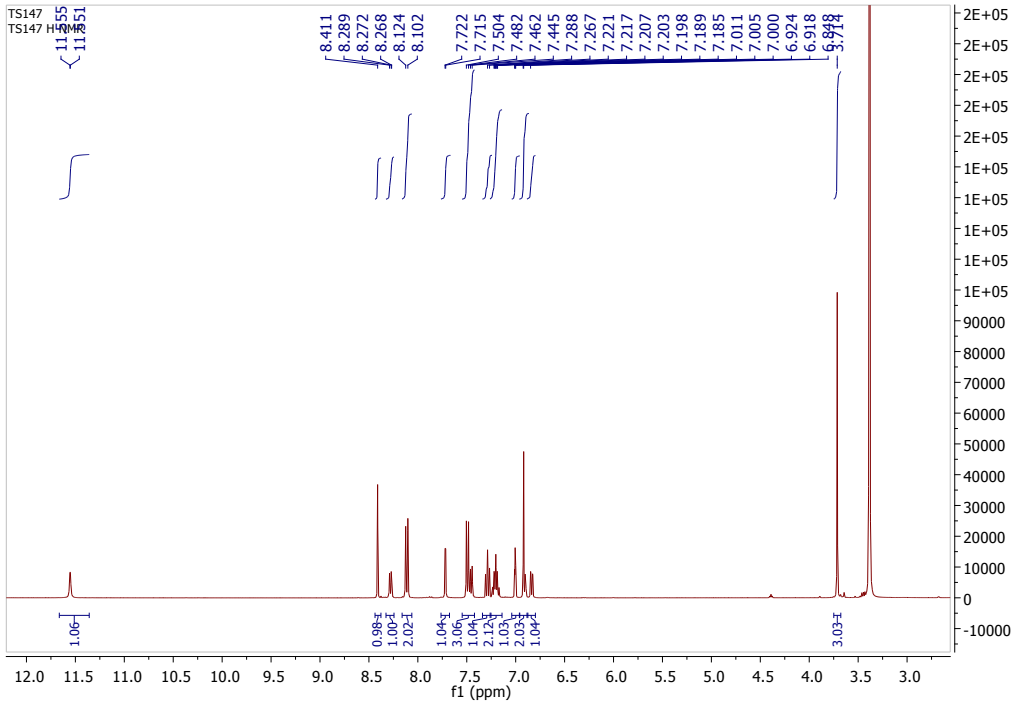
(8e)

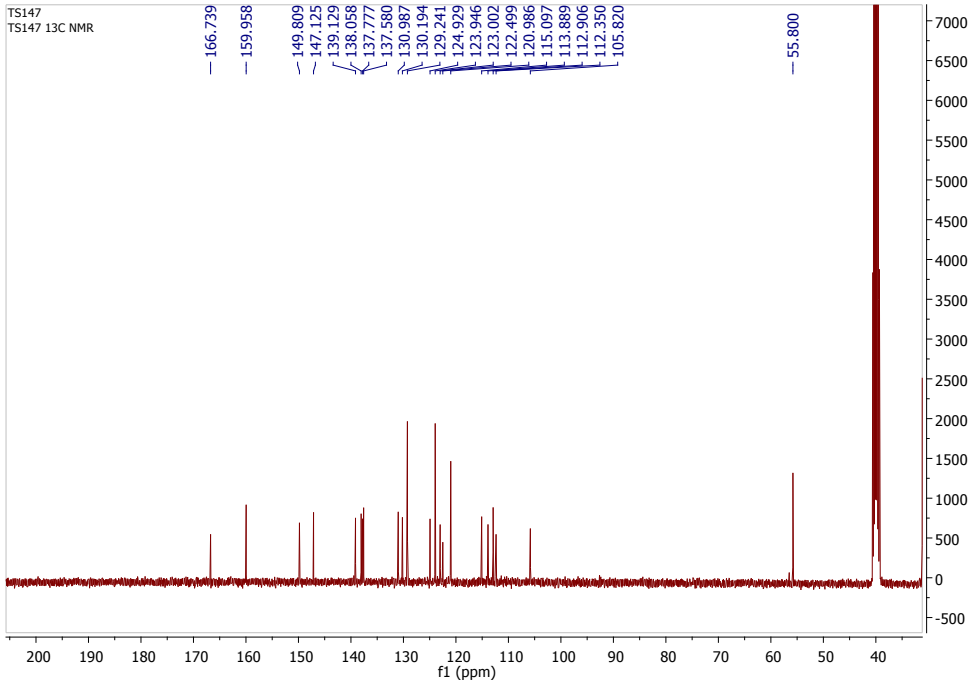

TS146
TS146 1H NMR
11.538
8.472
8.300
8.283
8.279
8.242
8.237
8.224
8.219
7.742
7.736
7.674
7.652
7.445
7.264
7.245
7.219
7.201
7.196
7.181
7.037
7.020
6.659
5.128
1.05
1.02
1.01
2.07
1.03
2.08
1.07
5.22
2.09
1.00
2.03
f1 (ppm)

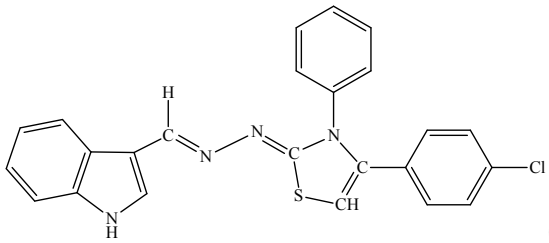

TS146
TS146 13C NMR
166.946
148.942
147.832
138.758
137.589
137.570
137.375
130.667
129.999
129.015
127.683
126.904
124.950
124.287
122.970
122.523
120.907
113.010
112.324
103.767
48.825
f1 (ppm)


OCH3
H
C
N
N
C
N
C
S
CH
NO2
N
H

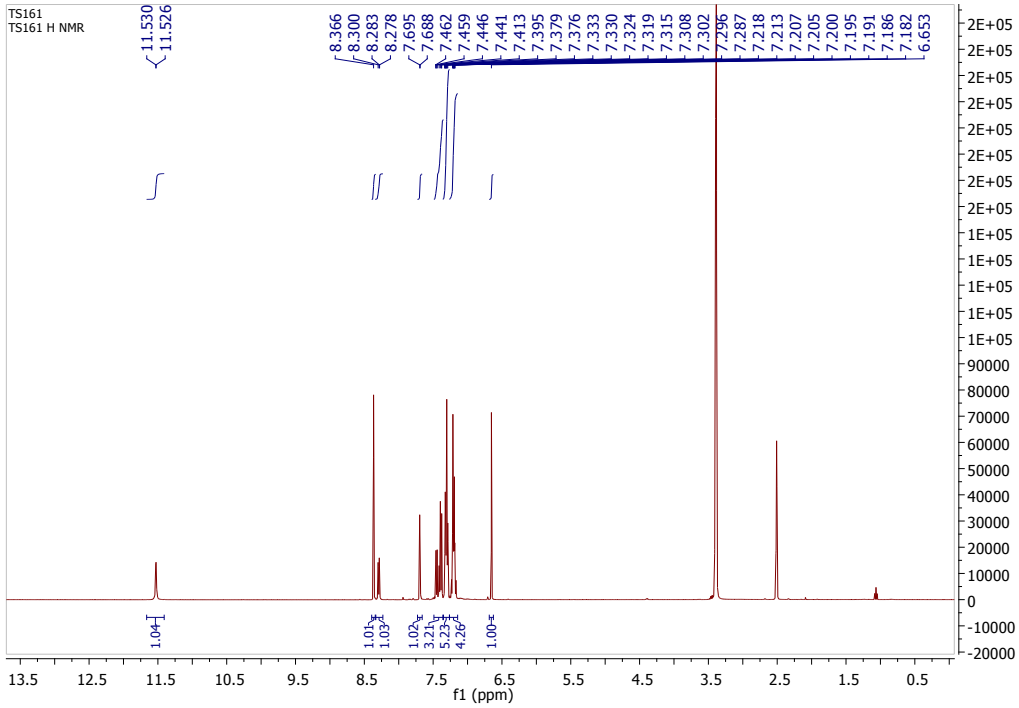
(8f)

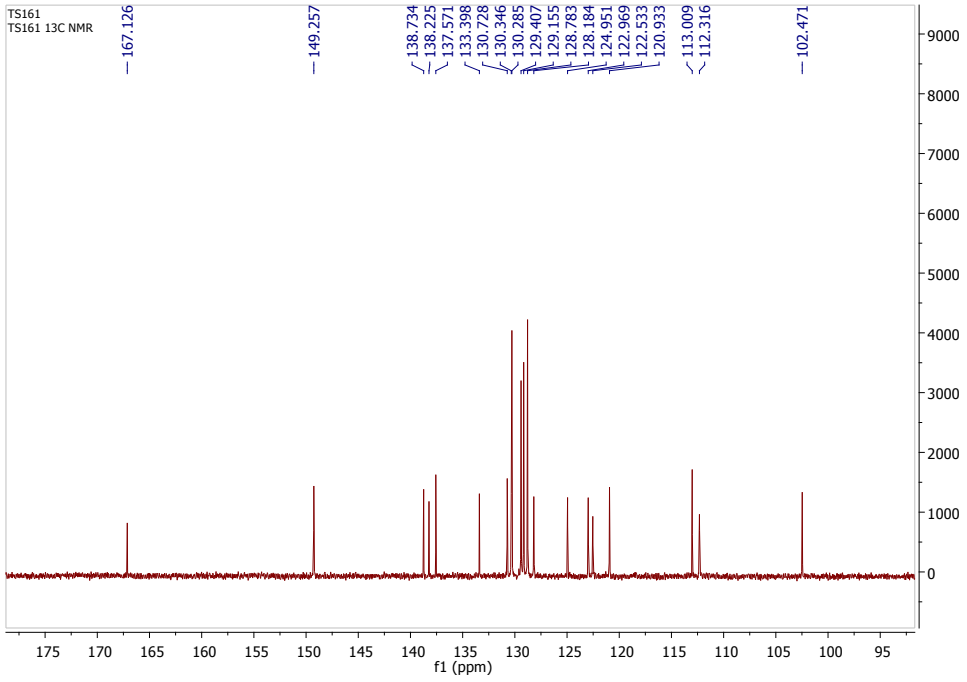

TS147
TS147 HNMR
11.555
11.551
8.411
8.289
8.272
8.268
8.124
8.102
7.722
7.715
7.504
7.482
7.462
7.445
7.288
7.267
7.221
7.217
7.207
7.203
7.198
7.189
7.185
7.011
7.005
7.000
6.924
6.918
6.848
3.714
1.06
0.98
1.00
2.02
1.04
3.06
1.04
2.12
1.03
2.03
1.04
3.03
f1 (ppm)

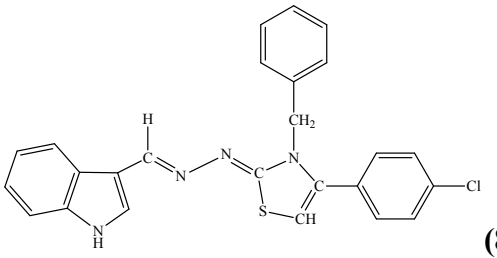

TS147
TS147 13C NMR
166.739
159.958
149.809
147.125
139.129
138.058
137.777
137.580
130.987
130.194
129.241
124.929
123.946
123.002
122.499
120.986
115.097
113.889
112.906
112.350
105.820
55.800
f1 (ppm)


H
C
N
N
C
N
C
Cl
S
CH
N
H

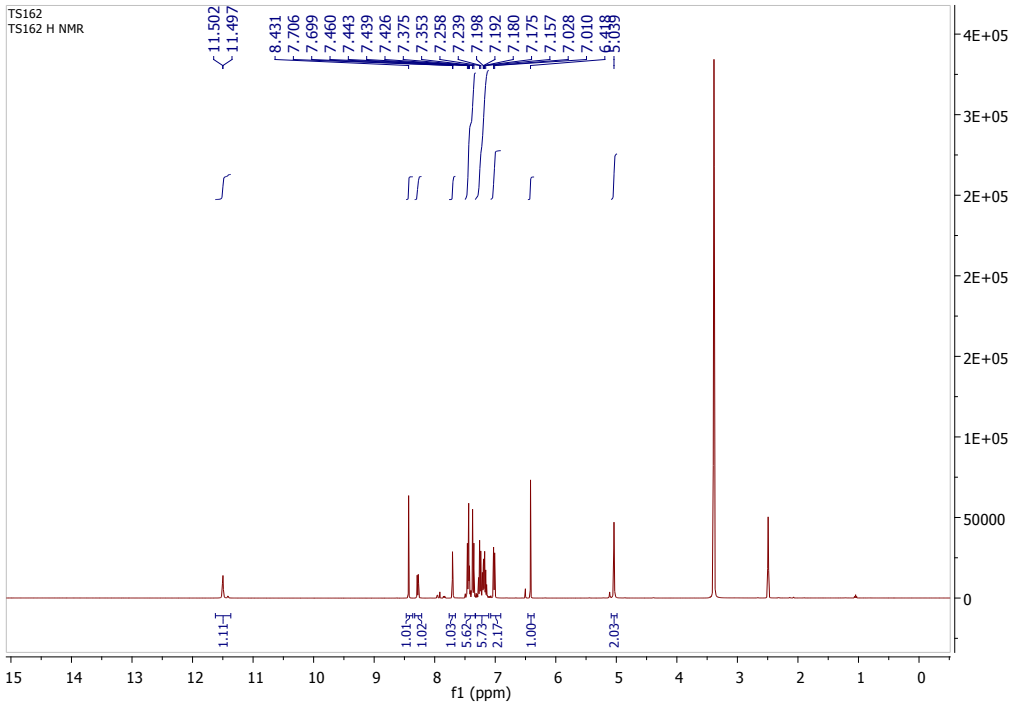
(8g)

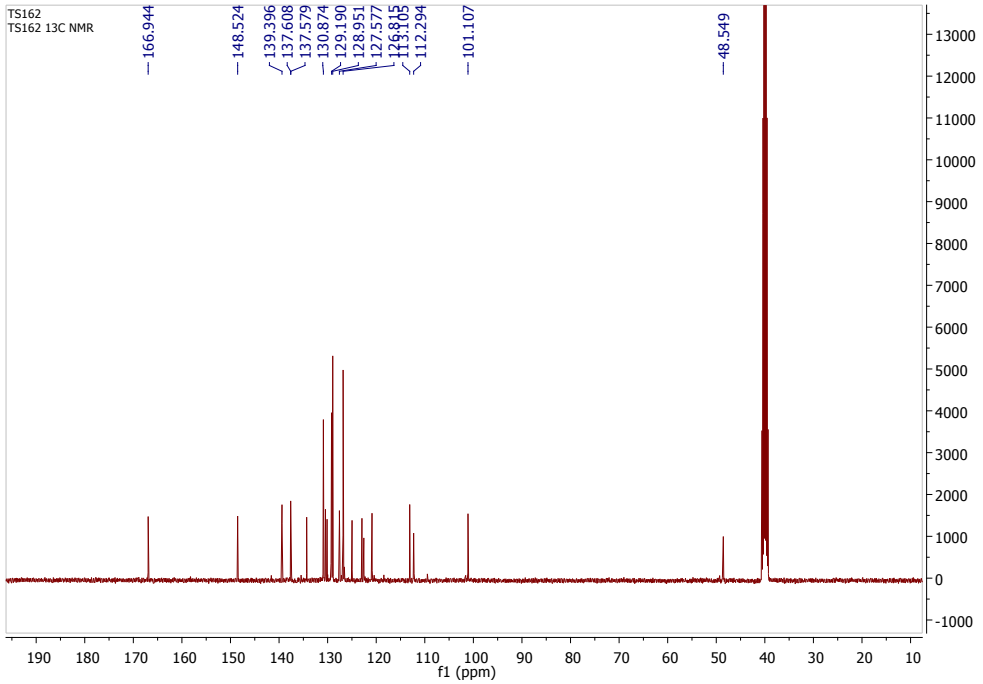

TS161
TS161 H NMR
11.530
11.526
8.366
8.300
8.283
8.278
7.695
7.688
7.462
7.459
7.446
7.441
7.413
7.395
7.379
7.376
7.333
7.330
7.324
7.319
7.315
7.308
7.302
7.296
7.287
7.218
7.213
7.207
7.205
7.200
7.195
7.191
7.186
7.182
6.653
1.04
1.01
1.03
1.02
3.21
5.23
4.26
1.00
f1 (ppm)

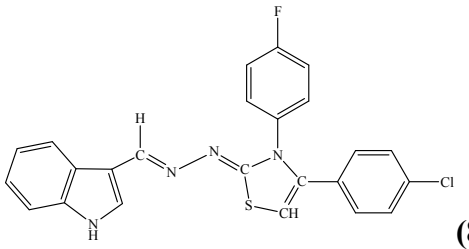

TS161
TS161 13C NMR
167.126
149.257
138.734
138.225
137.571
133.398
130.728
130.346
130.285
129.407
129.155
128.783
128.184
124.951
122.969
122.533
120.933
113.009
112.316
102.471
f1 (ppm)



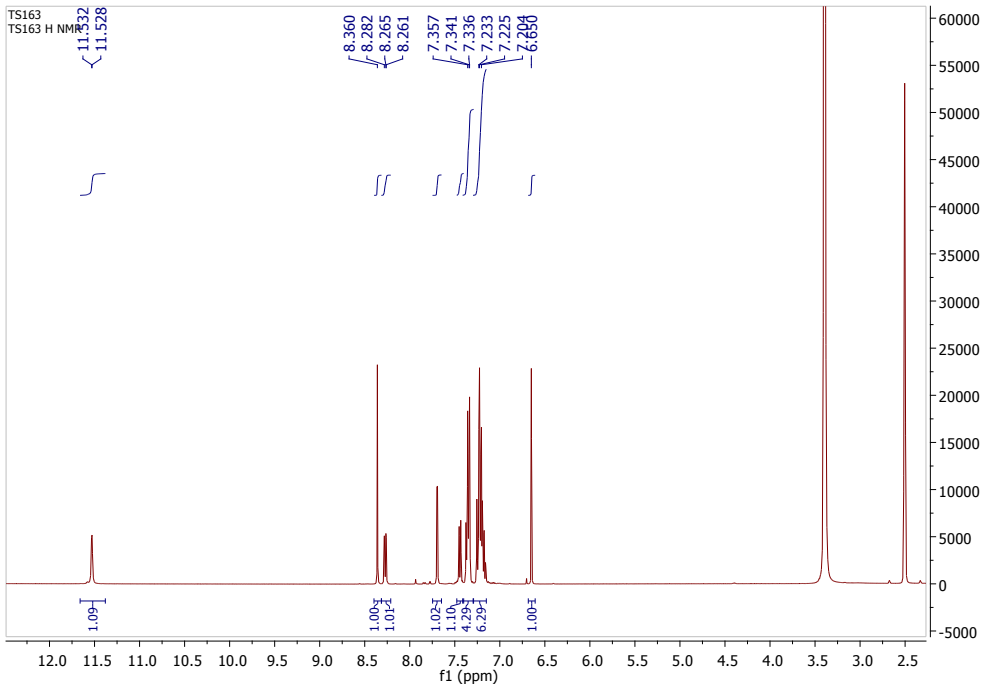
(8h)

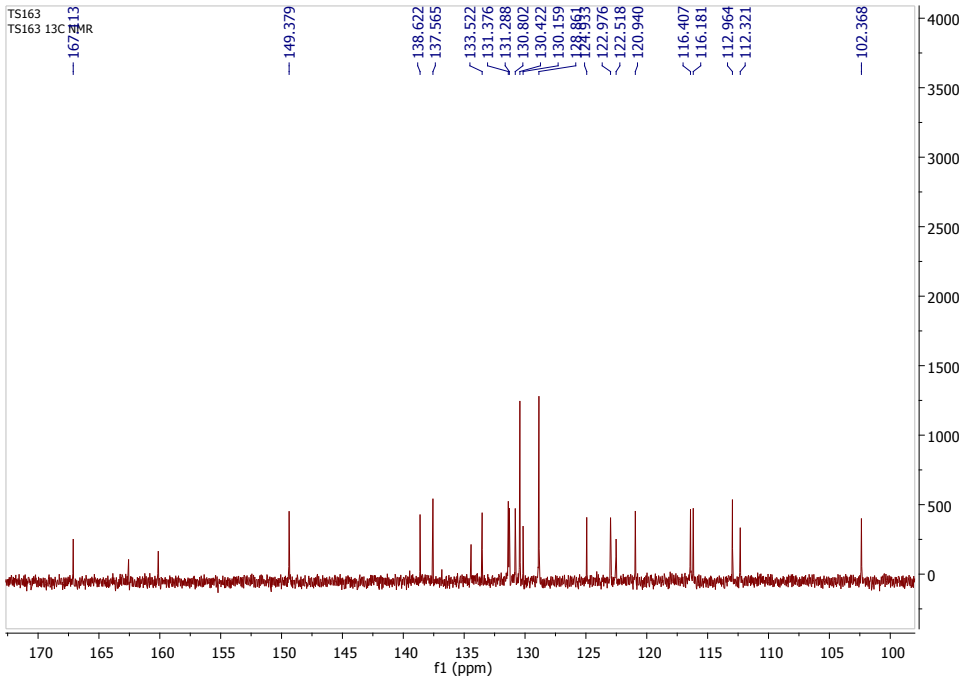

TS162
TS162 H NMR
11.502
11.497
8.431
7.706
7.699
7.460
7.443
7.439
7.426
7.375
7.353
7.258
7.239
7.198
7.192
7.180
7.175
7.157
7.028
7.010
5.039
1.11
1.01
1.02
1.03
5.62
5.73
2.17
1.00
2.03
f1 (ppm)

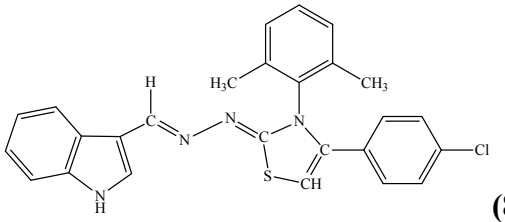

TS162
TS162 13C NMR
166.944
148.524
139.396
137.608
137.579
130.874
129.190
128.951
127.577
112.294
101.107
48.549
f1 (ppm)


F
H
C
N
N
C
N
C
Cl
S
CH
N
H

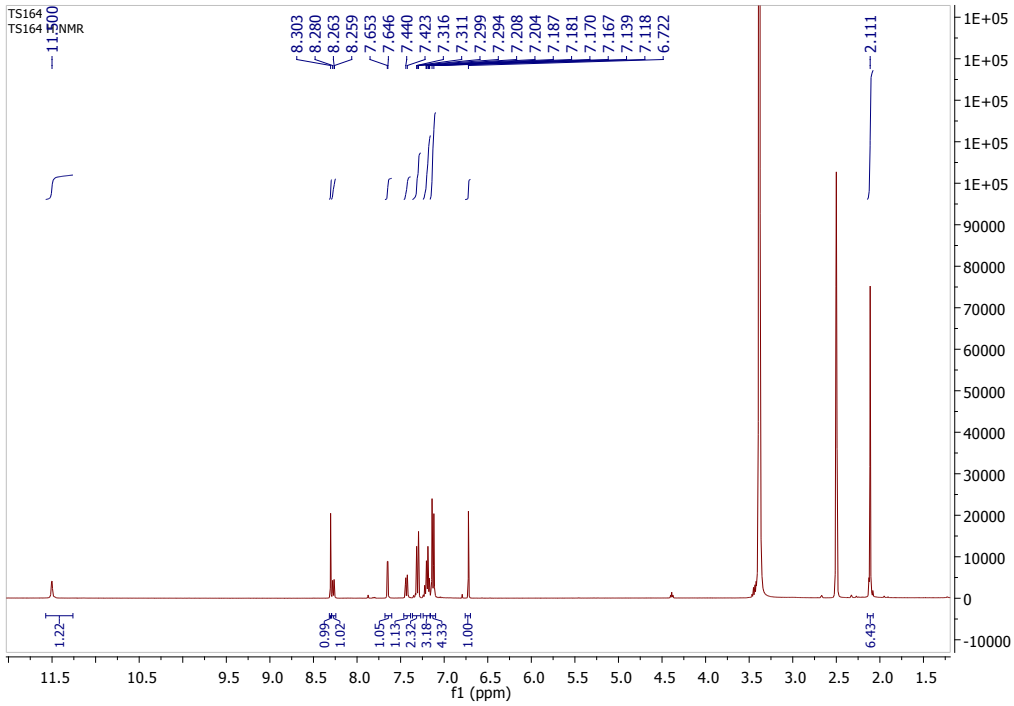
(8i)

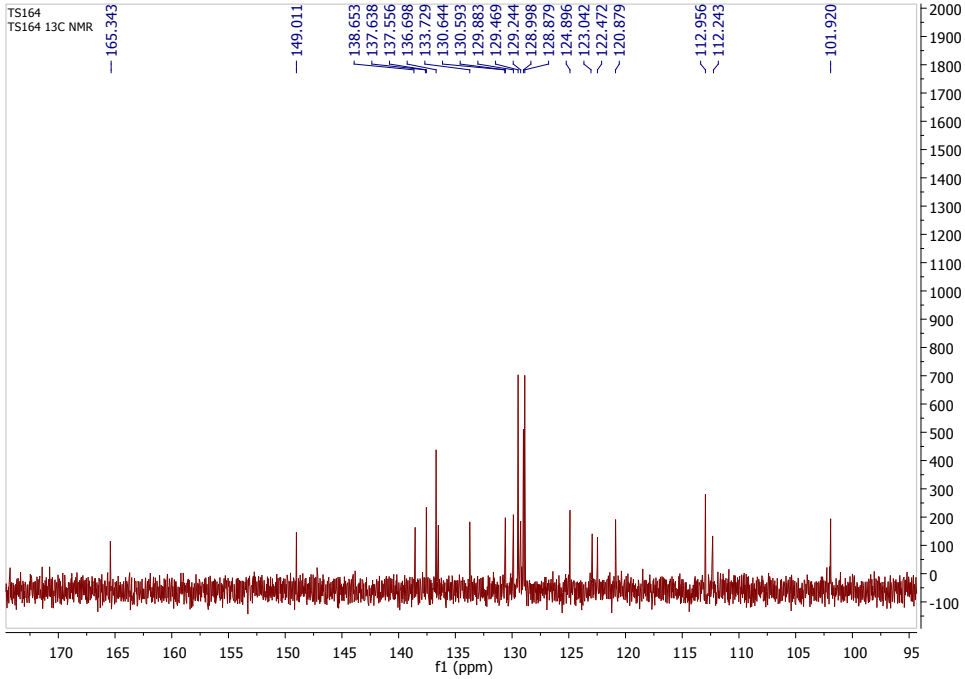

TS163
TS163 H NMR
11.532
11.528
8.360
8.282
8.265
8.261
7.357
7.341
7.336
7.233
7.225
7.204
6.650
1.09
1.00
1.01
1.02
1.10
4.29
6.29
1.00
f1 (ppm)


TS163
TS163 13C NMR
167.113
149.379
138.622
137.565
133.522
131.376
131.288
130.802
130.422
130.159
122.976
122.518
120.940
116.407
116.181
112.964
112.321
102.368
f1 (ppm)



(8j)


TS164
TS164 1H NMR
11.500
8.303
8.280
8.263
8.259
7.653
7.646
7.440
7.423
7.316
7.311
7.299
7.294
7.208
7.204
7.187
7.181
7.170
7.167
7.139
7.118
6.722
2.111
1.22
0.99
1.02
1.05
1.13
2.32
3.18
4.33
1.00
6.43
f1 (ppm)


TS164
TS164 13C NMR
165.343
149.011
138.653
137.638
137.556
136.698
133.729
130.644
130.593
129.883
129.469
129.244
128.998
128.879
124.896
123.042
122.472
120.879
112.956
112.243
101.920
f1 (ppm)