Electronic supplementary materials *Mendeleev Commun.*, 2019, **29**, 323–325

Highly selective synthesis of tricyclic compounds from semithioglycoluril, formaldehyde and amines

Vladimir V. Baranov, Yana A. Barsegyan, Natalya G. Kolotyrkina and Angelina N. Kravchenko

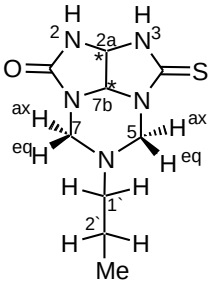
General

^{1}H and ^{13}C NMR spectra were recorded using Bruker AM-300 spectrometers (^{1}H, 300.13 MHz; ^{13}C, 75.5 MHz) in DMSO-d_6. Chemical shifts are reported in the δ scale relative to Me_4Si as internal standard. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II instrument using the electrospray ionization method (ESI). Melting points were determined in a SMP10 instrument (Stuart). Amines and paraformaldehyde were purchased from Acros.

Compounds **4a-i** *(general procedures).* A suspension of semithioglycoluril **1** (0.5 g, 3.2 mmol), parafomaldehyde (0.19 g, >90%) and the corresponding amine (3.2 mmol) in H_2O (10 ml) (for compounds **4a-c,e,f**) or mixture of H_2O (10 ml) and Pr^{i}OH (10 ml) (for compounds **4d,g-i**) was refluxed with stirring for 2 h. The mixture was cooled to room temperature, and the precipitate of products was filtered off and washed with Pr^{i}OH. The filtrate was evaporated at reduced pressure to the solid and recrystallized from MeOH for compounds **4a-c**,**e-g**, H_2O:Pr^{i}OH (3:1) for compounds **4h**,**i**, or acetone for compound **4d**.

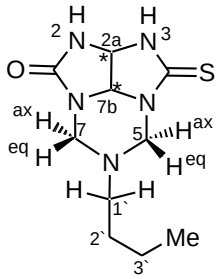
^{1}H NMR and ^{13}C NMR spectra of compounds

6-Propyl-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4c**.



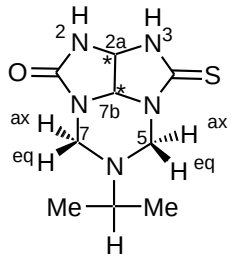
Beige powder, yield 81%, mp 237 – 239 °C (Pr^{i}OH). ^{1}H NMR, δ: 0.79 (t, 3 H, ^{3}J = 7.4 Hz, Me), 1.44 – 1.48 (m, 2 H, C(2')H_2), 2.22 – 2.34 (m, 2 H, C(1')H_2), 4.24 (d, 1 H, ^{2}J = 13.7 Hz, C(7)H^{ax}), 4.43 (d, 1 H, ^{2}J = 13.3 Hz, C(5)H^{ax}), 4.50 (d, 1 H, ^{2}J = 13.7 Hz, C(7)H^{eq}), 5.07 (d, 1 H, ^{2}J = 13.3 Hz, C(5)H^{eq}), 5.44 (d, 1 H, ^{3}J = 7.8 Hz, C(2a)H), 5.56 (d, 1 H, ^{3}J = 7.8 Hz, C(7b)H), 8.06 (s, 1 H, N(2)H), 9.54 (s, 1 H, N(3)H). ^{13}C NMR, δ: 11.65 (Me); 20.35 (C(2`)$H_2$); 50.62 (C(1`)H_2); 59.49 (C(7)H_2); 61.08 (C(5)H_2); 63.71 (C(2a)H); 70.82 (C(7b)H); 159.06 (C=O); 181.80 (C=S). HRMS, m/z: 242.1080 $[M+H]^+$ (calc. for: $C_9H_{15}N_5OS$+H 242.1070).

6-Butyl-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4d.**



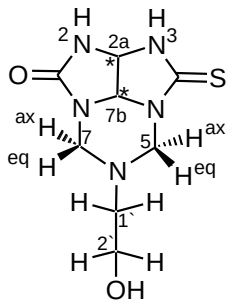
Beige powder, yield 78%, mp 237 – 239 °C (Me_2CO). ^{1}H NMR, δ: 0.83 (t, 3 H, ^3J = 7.2 Hz, Me), 1.17 – 1.27 (m, 2 H, C(3')H_2), 1.39 – 1.45 (m, 2 H, C(2')H_2), 2.21 – 2.30 (m, 1 H, C(1`)H_2), 2.32 – 2.41 (m, 1 H, C(1')H_2), 4.22 (d, 1 H, ^2J = 13.6 Hz, C(7)H^{ax}), 4.41 (d, 1 H, ^2J = 13.3 Hz, C(5)H^{ax}), 4.49 (d, 1 H, ^2J = 13.6 Hz, C(7)H^{eq}), 5.06 (d, 1 H, ^2J = 13.3 Hz, C(5)H^{eq}), 5.43 (d, 1 H, ^3J = 7.7 Hz, C(2a)H), 5.55 (d, 1 H, ^3J = 7.7 Hz, C(7b)H), 8.04 (s, 1 H, N(2)H), 9.52 (s, 1 H, N(3)H). ^{13}C NMR, δ: 13.72 (Me); 19.76 (C(3`)$H_2$); 29.13 (C(2`)H_2); 48.31 (C(1`)H_2); 59.42 (C(7)H_2); 61.08 (C(5)H_2); 63.65 (C(2a)H); 70.75 (C(7b)H); 159.00 (C=O); 181.72 (C=S). HRMS, m/z: 256.1220 $[M+H]^+$ (calc. for: $C_{10}H_{17}N_5OS$+H 256.1227).

6-Isopropyl-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4e.**



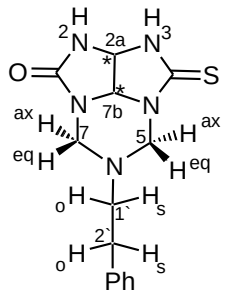
Beige powder, yield 83%, mp 227 – 229 °C (H_2O). ^{1}H NMR, δ: 1.08 (d, 3 H, ^3J = 6.1 Hz, Me), 1.15 (d, 3 H, ^3J = 6.0 Hz, Me), 2.51 – 2.61 (m, 2 H, CH), 4.15 (d, 1 H, ^2J = 13.9 Hz, C(7)H^{ax}), 4.38 (d, 1 H, ^2J = 13.6 Hz, C(5)H^{ax}), 4.75 (d, 1 H, ^2J = 13.9 Hz, C(7)H^{eq}), 5.25 (d, 1 H, ^2J = 13.6 Hz, C(5)H^{eq}), 5.40 (d, 1 H, ^3J = 7.8 Hz, C(2a)H), 5.55 (d, 1 H, ^3J = 7.8 Hz, C(7b)H), 8.00 (c, 1 H, N(2)H), 9.48 (s, 1 H, N(3)H). ^{13}C NMR, δ: 20.86, 21.92 (Me); 45.63 (CH(*i*-Pr)); 56.29 (C(7)H_2); 59.05 (C(5)H_2); 63.66 (C(2a)H); 70.90 (C(7b)H); 158.73 (C=O); 181.09 (C=S). HRMS, m/z: 242.1060 $[M+H]^+$ (calc. for: $C_9H_{15}N_5OS$+H 242.1070).

6-(2-Hydroxyethyl)-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4f.**



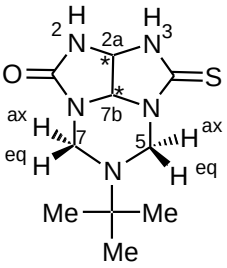
Beige powder, yield 85%, mp 210-212 °C (Pr^iOH). ^{1}H NMR, δ: 2.34 – 2.43 (m, 1 H, C(1')H), 2.48 – 2.55 (m, 1 H, C(1')H), 3.41 – 3.45 (m, 2 H, C(2')H_2), 4.24 (d, 1 H, ^2J = 13.6 Hz, C(7)H^{ax}), 4.41 – 4.51 (m, 3 H, C(5)H^{ax} + C(7)H^{eq} + OH), 5.06 (d, 1 H, ^2J = 13.3 Hz, C(5)H^{eq}), 5.44 (d, 1 H, ^3J = 7.8 Hz, C(2a)H), 5.56 (d, 1 H, ^3J = 7.8 Hz, C(7b)H), 8.08 (s, 1 H, N(2)H), 9.56 (s, 1 H, N(3)H). ^{13}C NMR, δ: 51.36 (C(1`)$H_2$); 58.61(C(2`)H_2); 59.72 (C(7)H_2); 61.70 (C(2a)H_2); 63.71(C(5)H_2); 70.72 (C(7b)H); 159.07 (C=O); 181.68 (C=S). HRMS, m/z: 244.0856 $[M+H]^+$ (calc. for: $C_8H_{13}N_5OS$+H 244.0863).

6-(2-Phenylethyl)-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4g.**



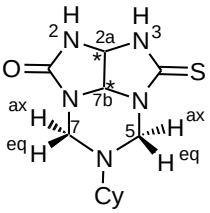
Beige powder, yield 69%, mp 248-250 °C (Pr^iOH). ^{1}H NMR, δ: 2.4 – 2.61 (m, 2 H, C(2')H_2), 2.66 – 2.75 (m, 1 H, C(1')H), 2.80 – 2.89 (m, 1 H, C(1')H), 4.29 (d, 1 H, ^2J = 13.8 Hz, C(7)H^{ax}), 4.50 (d, 1 H, ^2J = 13.4 Hz, C(5)H^{ax}), 4.60 (d, 1 H, ^2J = 13.8 Hz, C(5)H^{eq}), 5.21 (d, 1 H, ^2J = 13.4 Hz, C(7)H^{eq}), 5.46 (d, 1 H, ^3J = 7.7 Hz, C(2a)H), 5.59 (d, 1 H, ^3J = 7.7 Hz, C(7b)H), 7.18 – 7.29 (m, 5 H, Ph), 8.09 (s, 1 H, N(2)H), 9.58 (s, 1 H, N(3)H). ^{13}C NMR, δ: 33.63 (C(2`)$H_2$); 51.08 (C(1`)H_2); 59.56 (C(7)H_2); 60.82 (C(5)H_2); 63.69 (C(2a)H); 70.72 (C(7b)H); 125.95, 128.19, 128.67, 139.64 (Ph); 159.01 (C=O); 181.63 (C=S). HRMS, m/z: 304.1234 $[M+H]^+$ (calc. for: $C_{14}H_{17}N_5OS$+H 304.1227).

6-(tert-Butyl)-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4h.**

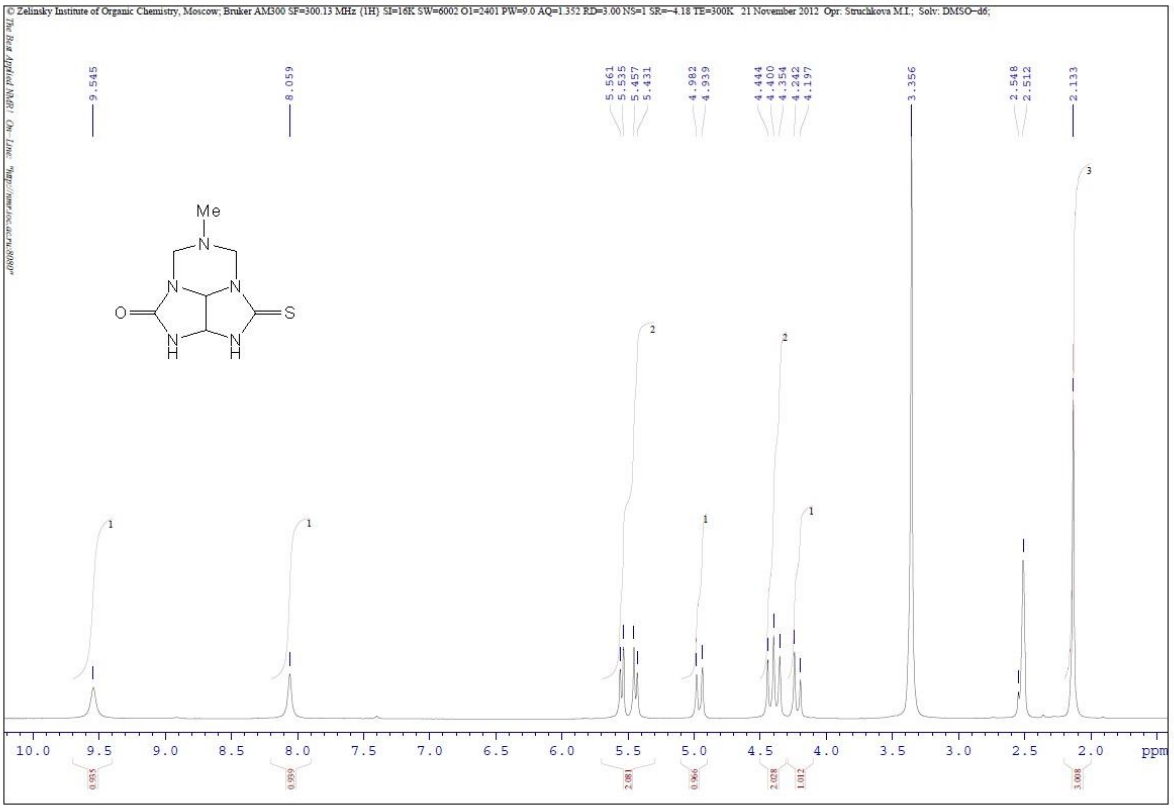


Beige powder, yield 80%, mp 227 – 229 °C (H_2O/ Pr^iOH). ^{1}H NMR, δ: 1.07 (s, 9 H, Me (*t*-Bu)), 3.94 (d, 1 H, ^2J = 13.0 Hz, C(7)H^{ax}), 4.12 (d, 1 H, ^2J = 12.5 Hz, C(5)H^{ax}), 4.77 (d, 1 H, ^2J = 12.5 Hz, C(5)H^{eq}), 4.75 (d, 1 H, ^2J = 13.0 Hz, C(7)H^{eq}), 5.37 (d, 1 H, ^3J = 7.0 Hz, C(2a)H), 5.50 (d, 1 H, ^3J = 7.0 Hz, C(7b)H), 7.97 (s, 1 H, N(2)H), 9.41 (s, 1 H, N(3)H). ^{13}C NMR, δ: 27.42 (Me), 52.26 (C(*t*-Bu)); 54.82 (C(7)H_2); 57.69 (C(5)H_2); 63.60 (C(2a)H); 70.68 (C(7b)H); 158.83 (C=O); 181.10 (C=S). HRMS, m/z: 242.1060 $[M+H]^+$ (calc. for: $C_9H_{15}N_5OS$+H 242.1070).

6-Cyclohexyl-4-thioxohexahydro-5H-2,3,4a,6,7a-pentaazacyclopenta[cd]inden-1(2H)-one **4i.**



White powder, yield 89%, mp 232-234 °C (H_2O/Pr^iOH). ^{1}H NMR, δ: 1.07 (s, 5 H, Cy), 1.50 (s, 1 H, Cy), 1.65 (s, 2 H, Cy), 1.34 – 1.29 (m, 3 H, Cy), 4.15 (d, 1 H, ^2J = 13.9 Hz, C(7)H^{ax}), 4.37 (d, 1 H, ^2J = 13.6 Hz, C(5)H^{ax}), 4.39 (d, 1 H, ^2J = 13.9 Hz, C(7)H^{eq}), 4.37 (d, 1 H, ^2J = 13.6 Hz, C(5)H^{eq}), 5.40 (d, 1 H, ^3J = 7.8 Hz, C(2a)H), 5.45 (d, 1 H, ^3J = 7.8 Hz, C(7b)H), 7.99 (s, 1 H, N(2)H), 9.46 (s, 1 H, N(3)H). ^{13}C NMR, δ: 24.41, 24.54, 25.50, 29.68, 30.77 (CH_2(Cy)); 53.27 (CH(Cy)); 55.70 (C(7)H_2); 58.67 (C(5)H_2); 63.83 (C(2a)H); 71.18 (C(7b)H); 158.69 (C=O); 181.29 (C=S). HRMS, m/z: 282.1392 $[M+H]^+$ (calc. for: $C_{12}H_{19}N_5OS$+H 282.1383).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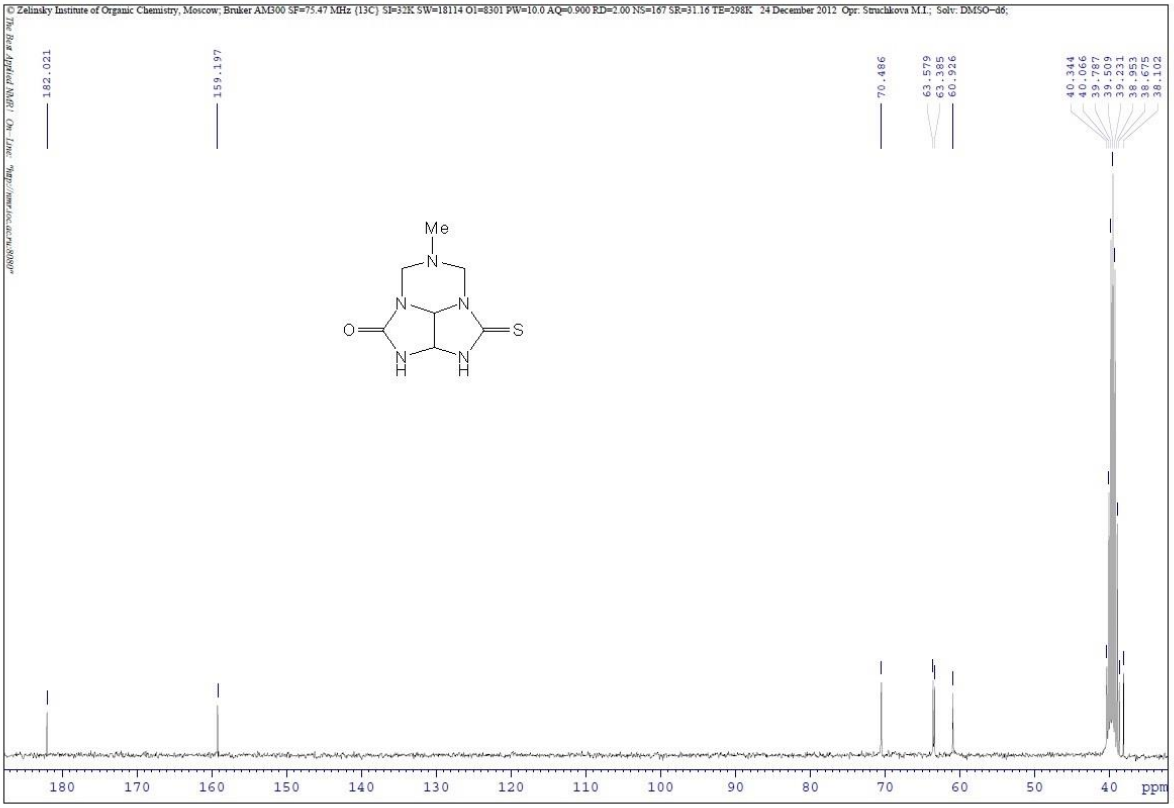
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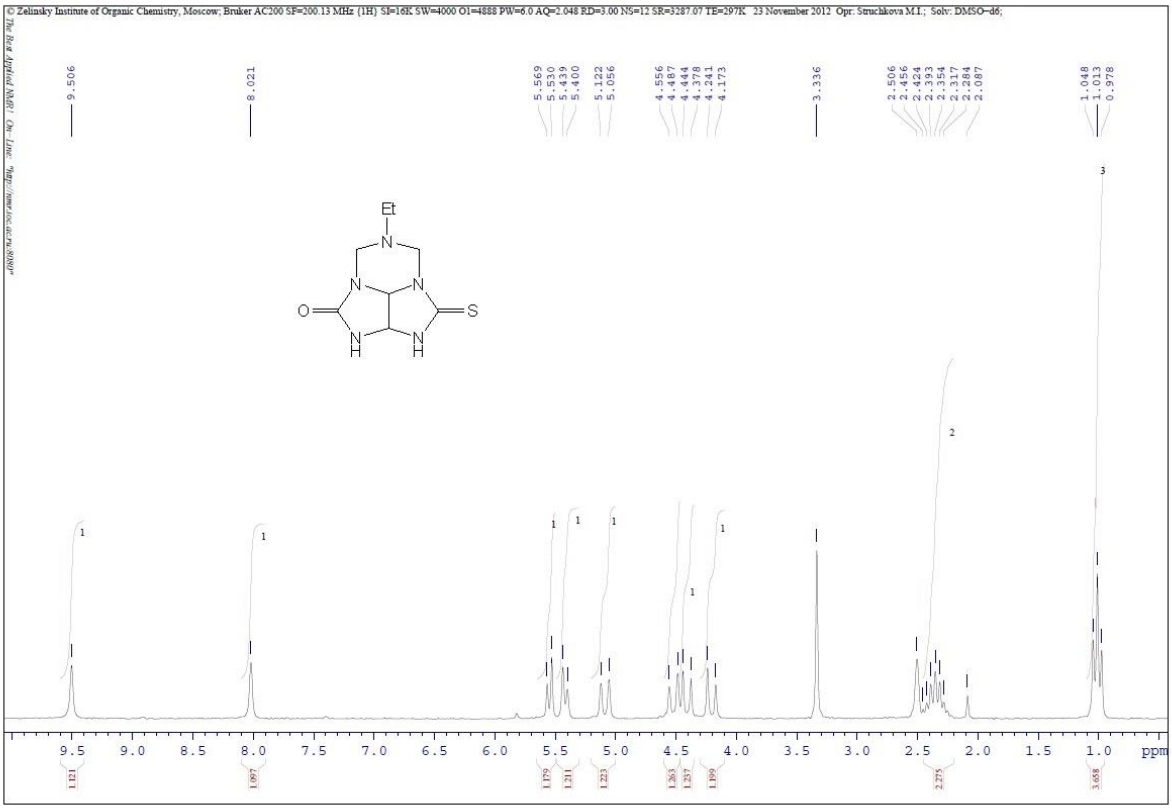
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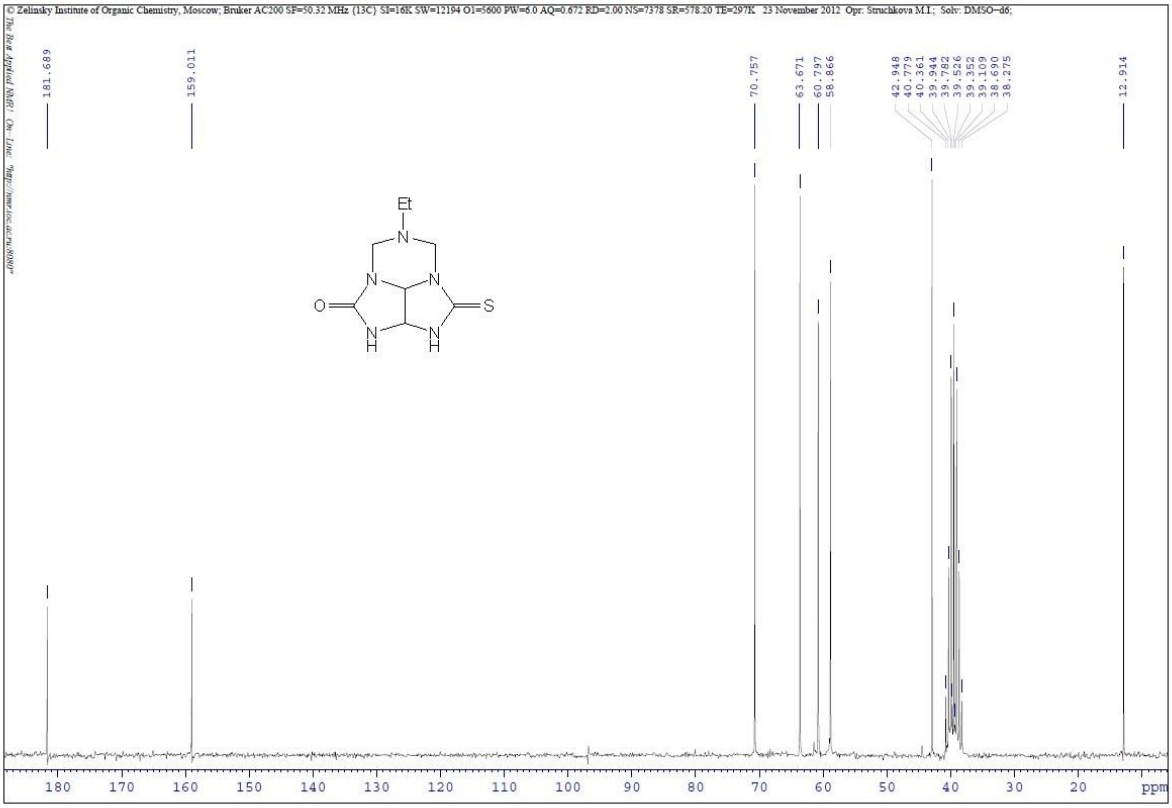
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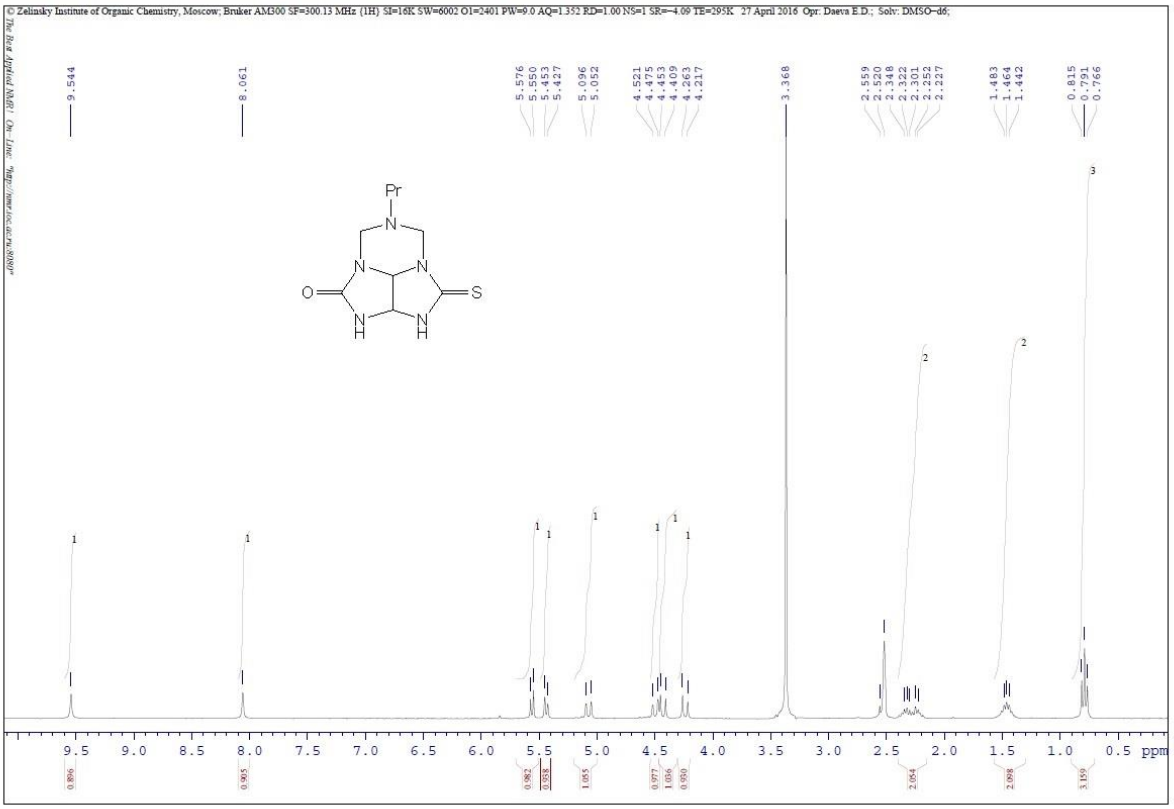
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3.368
2.559
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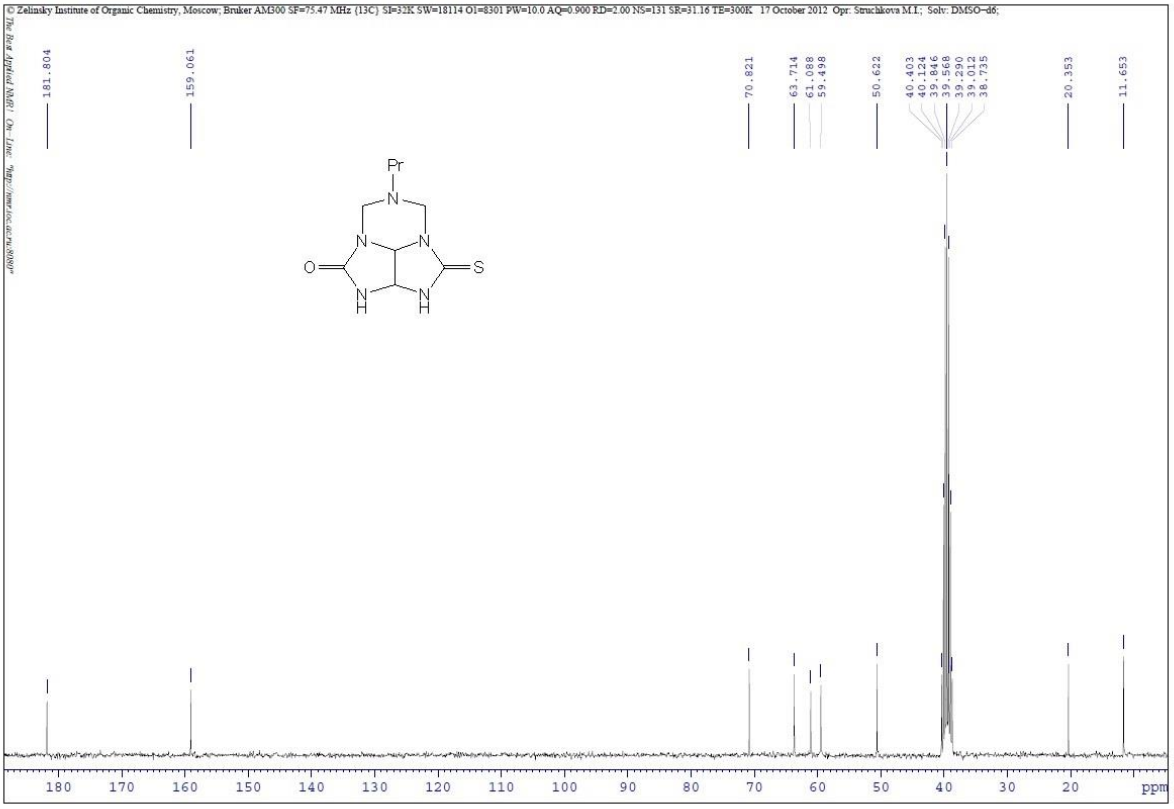
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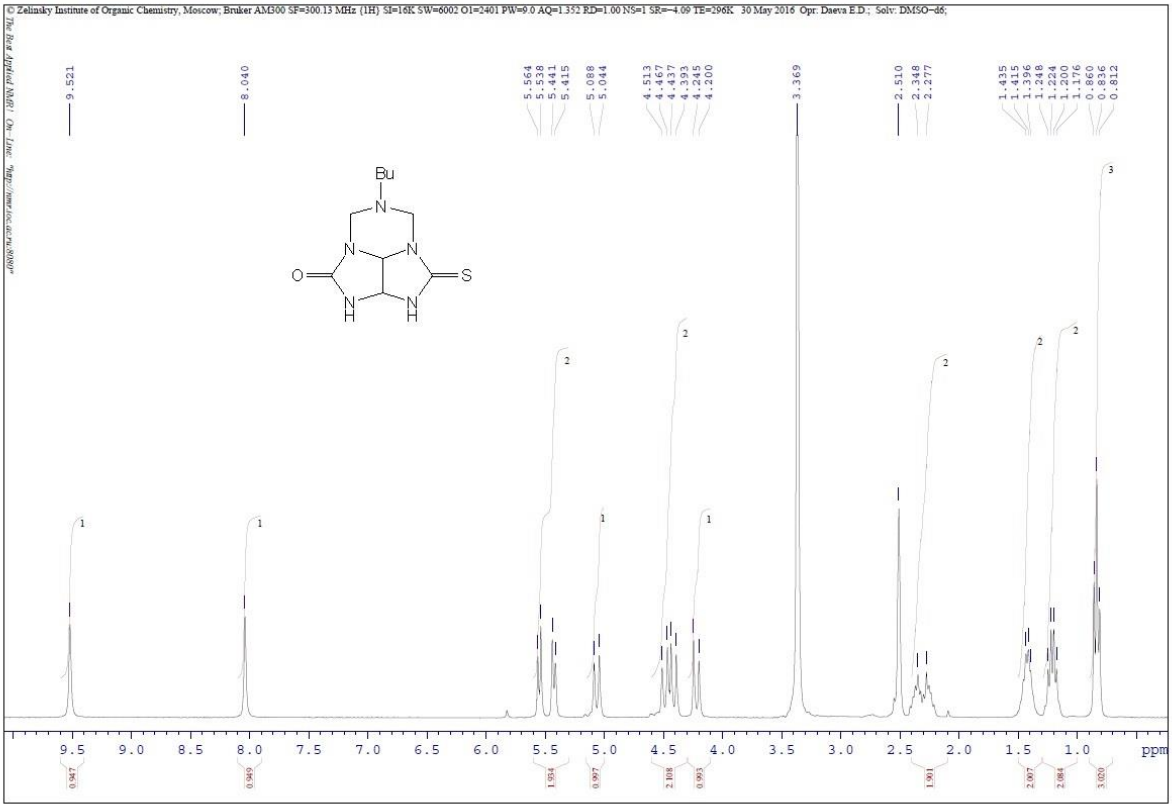
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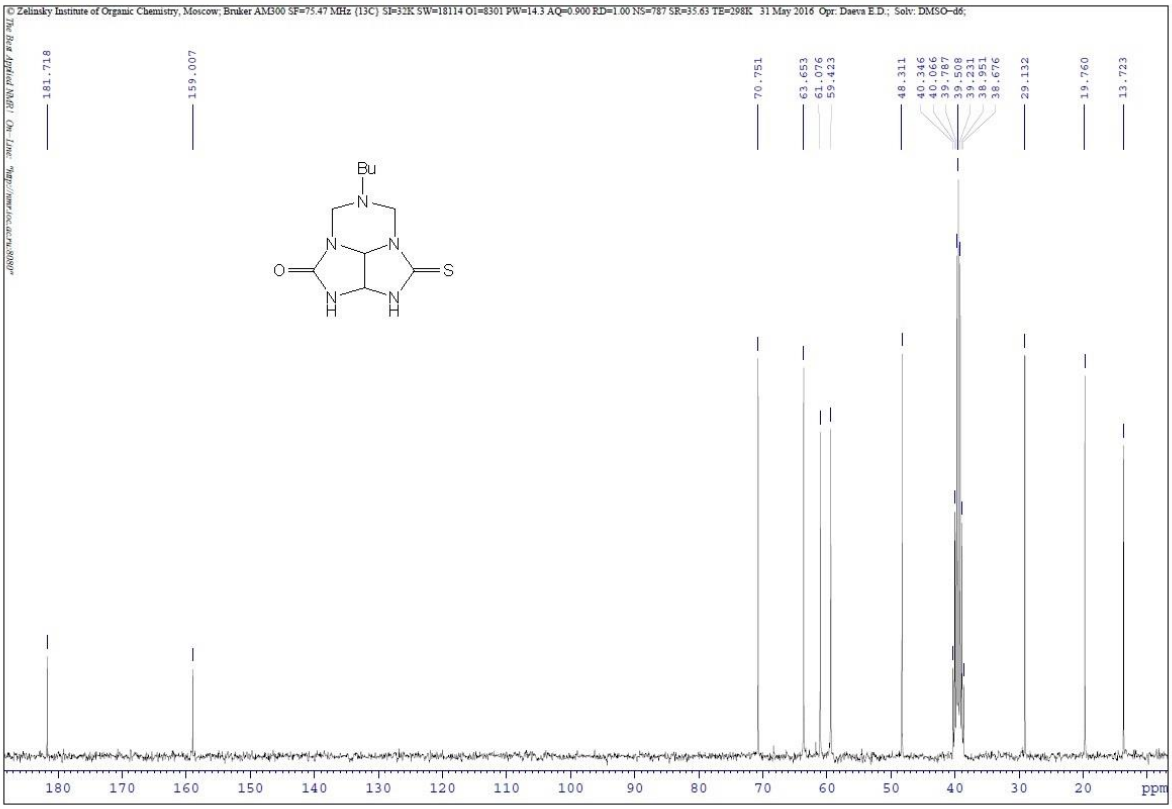
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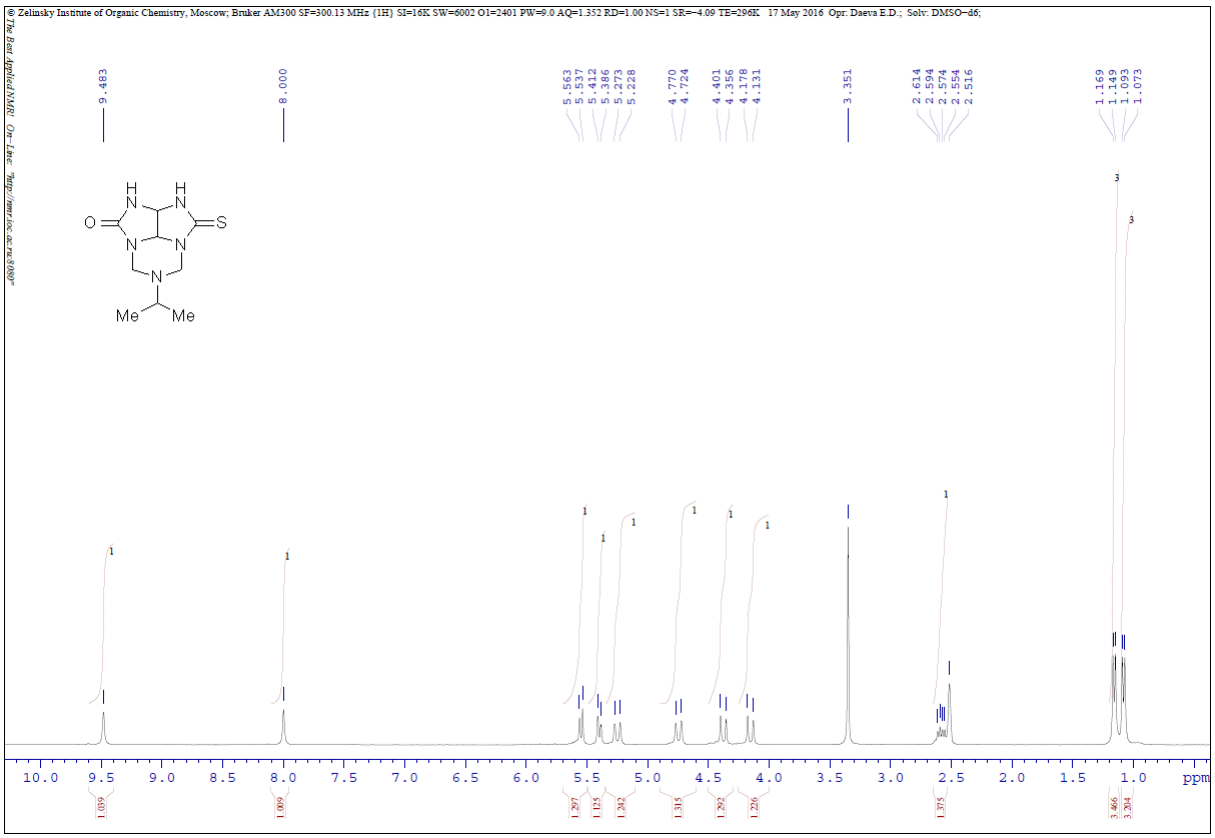
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4.131
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Me
Me
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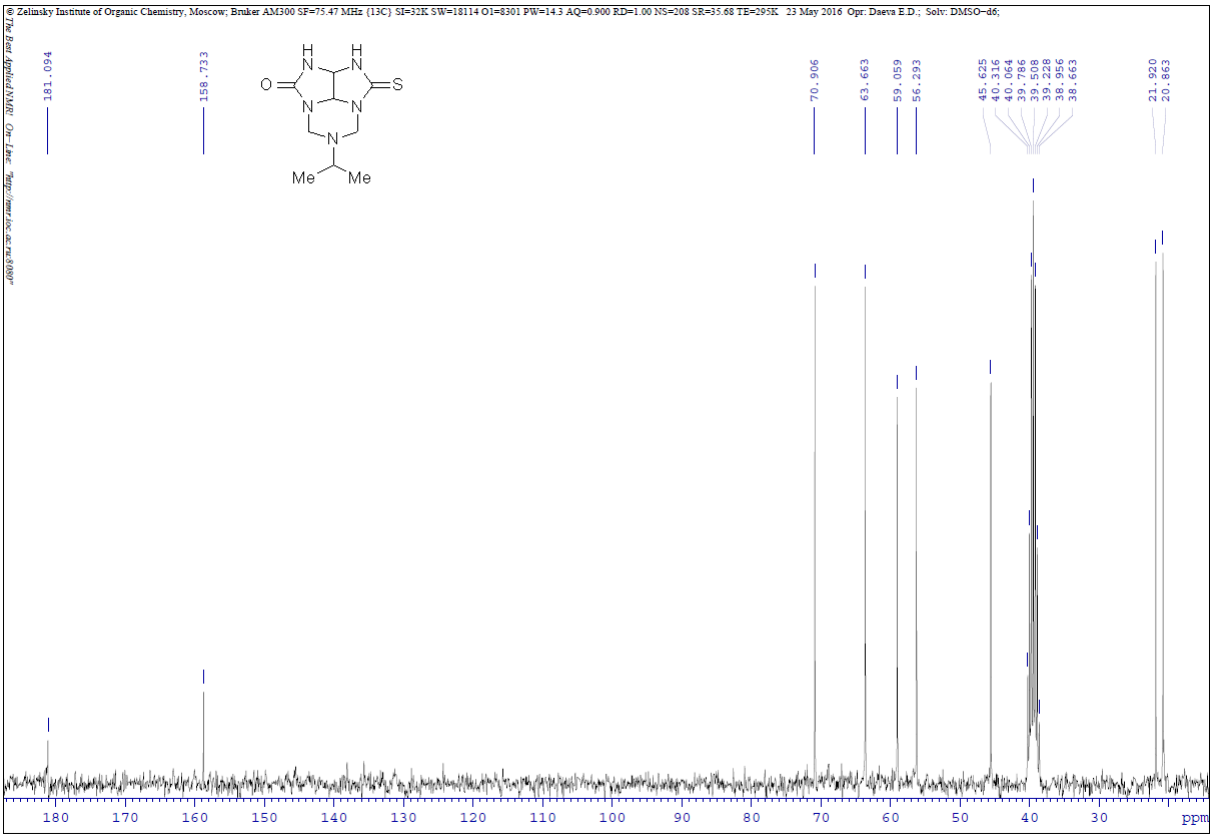
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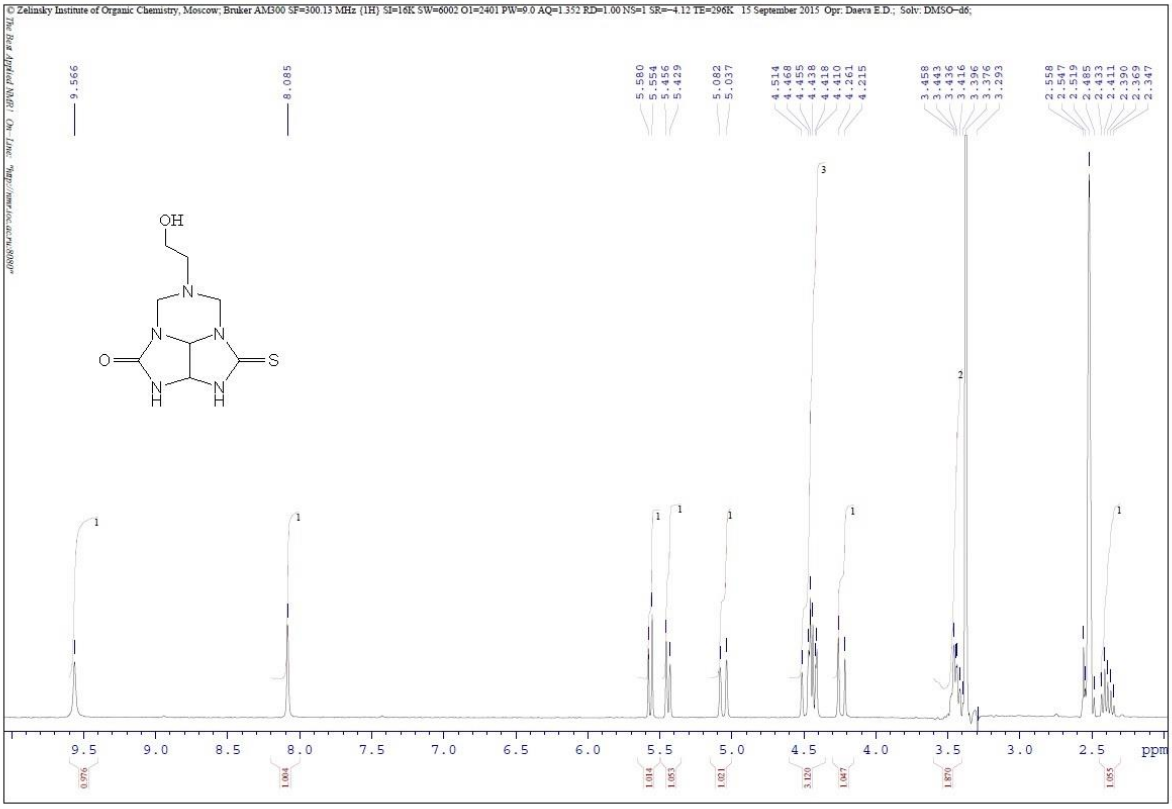
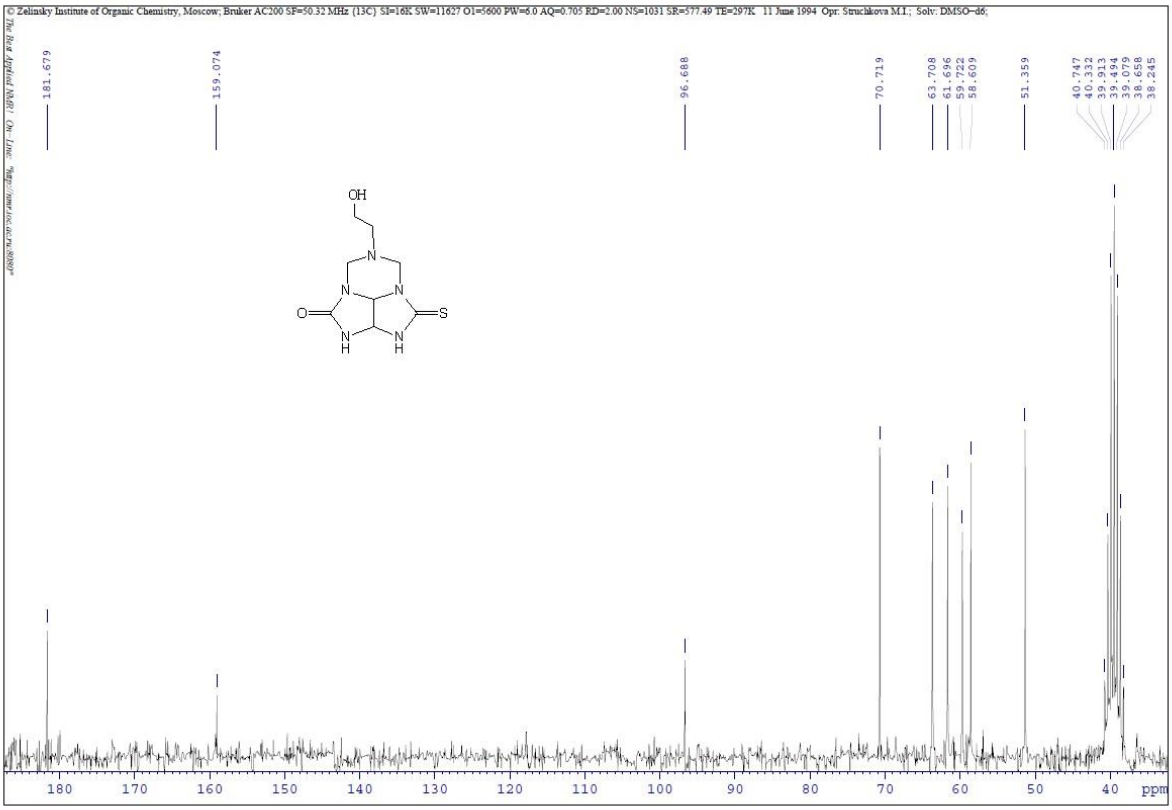
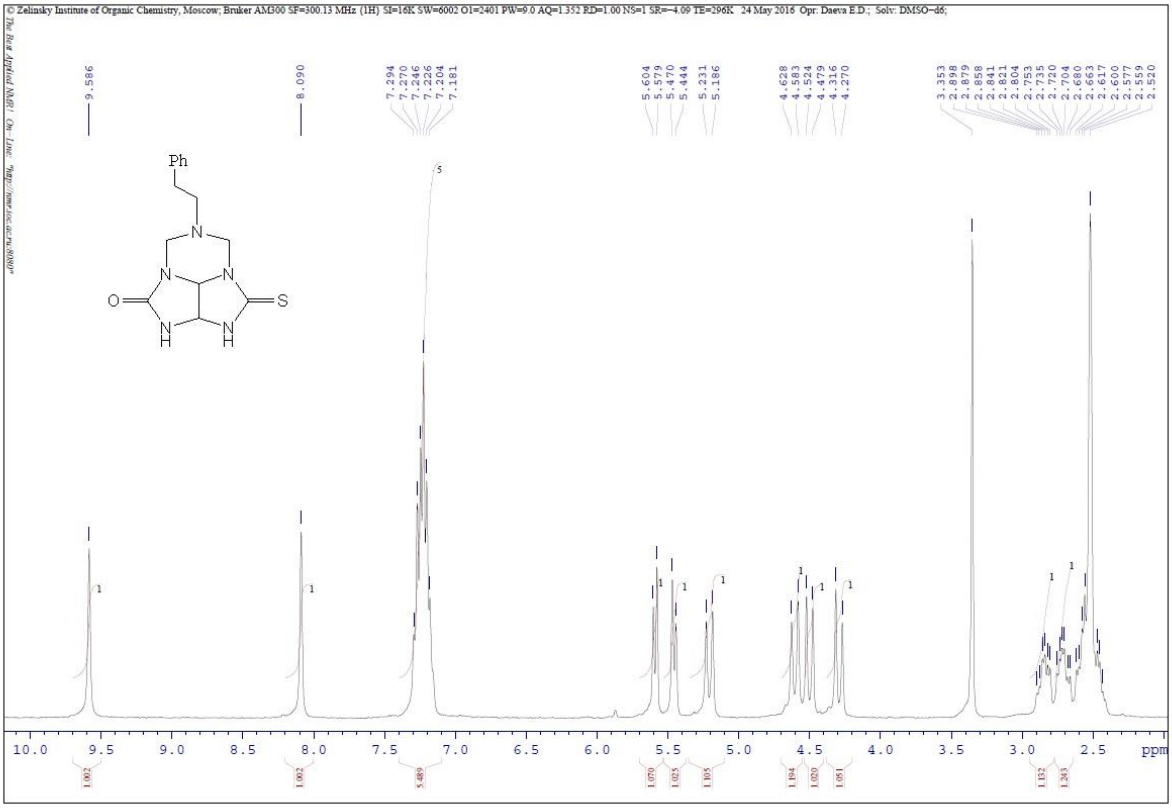
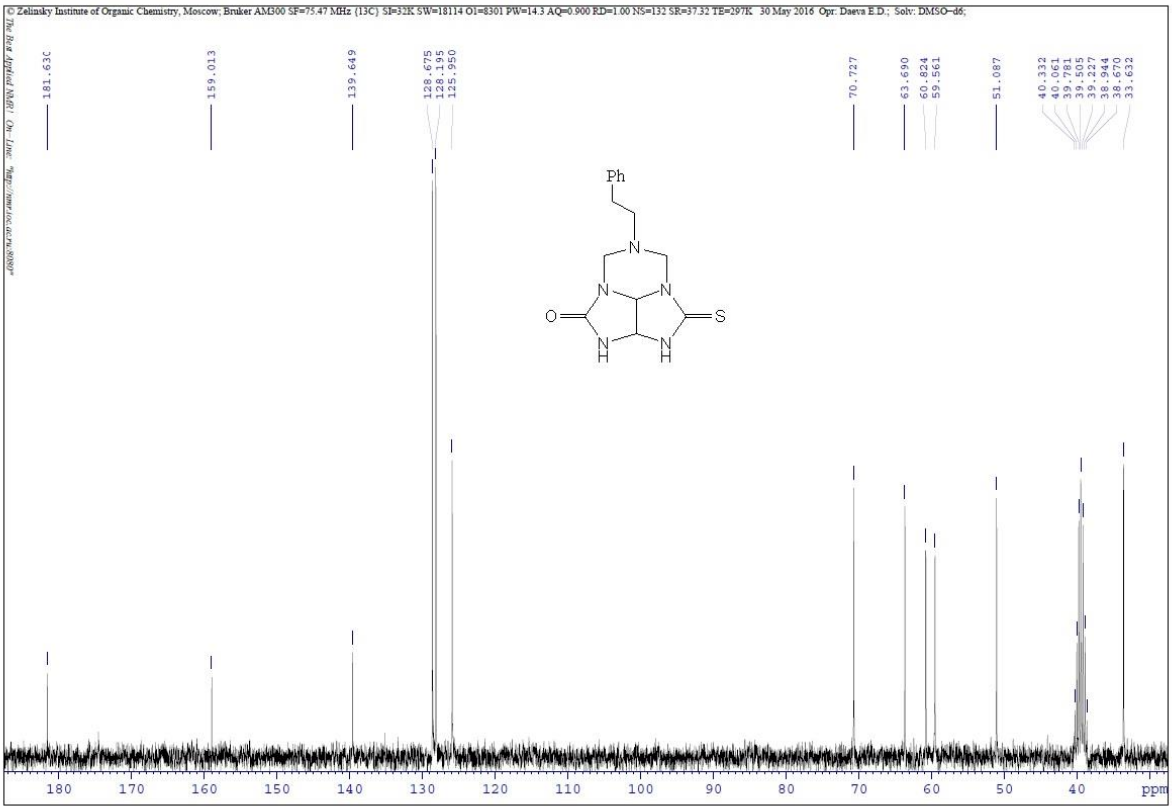
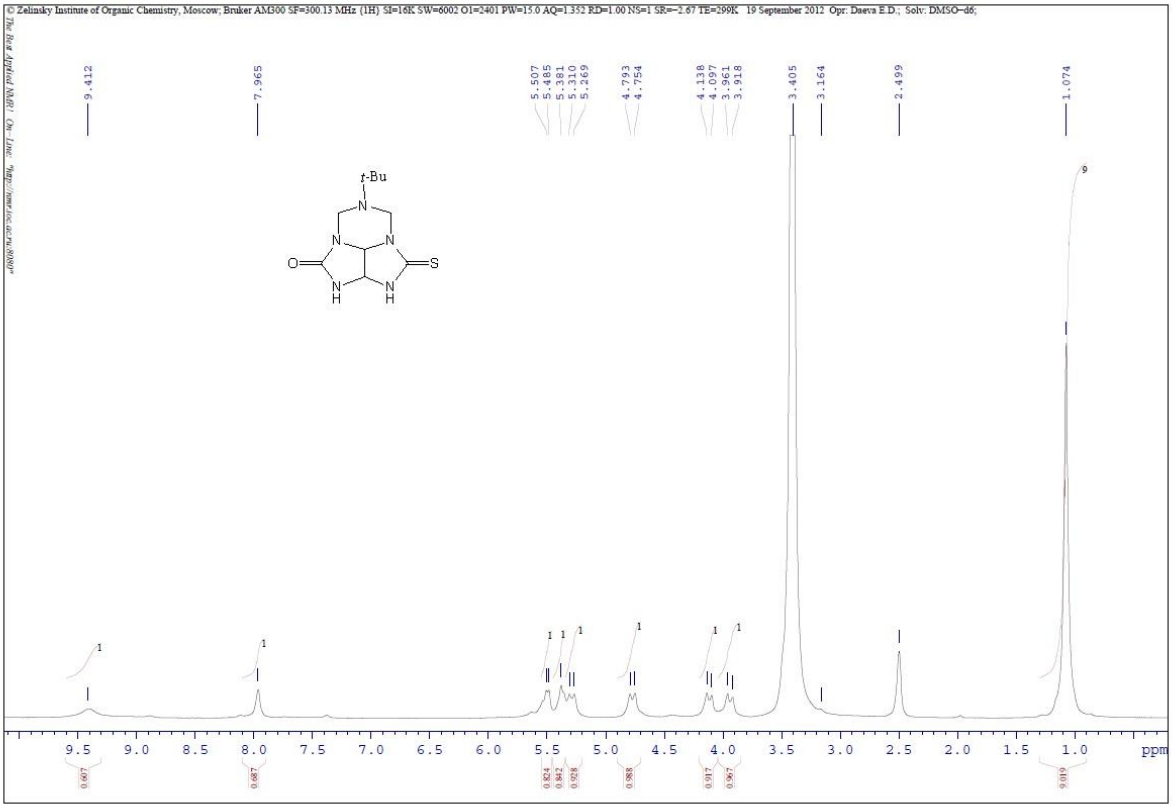
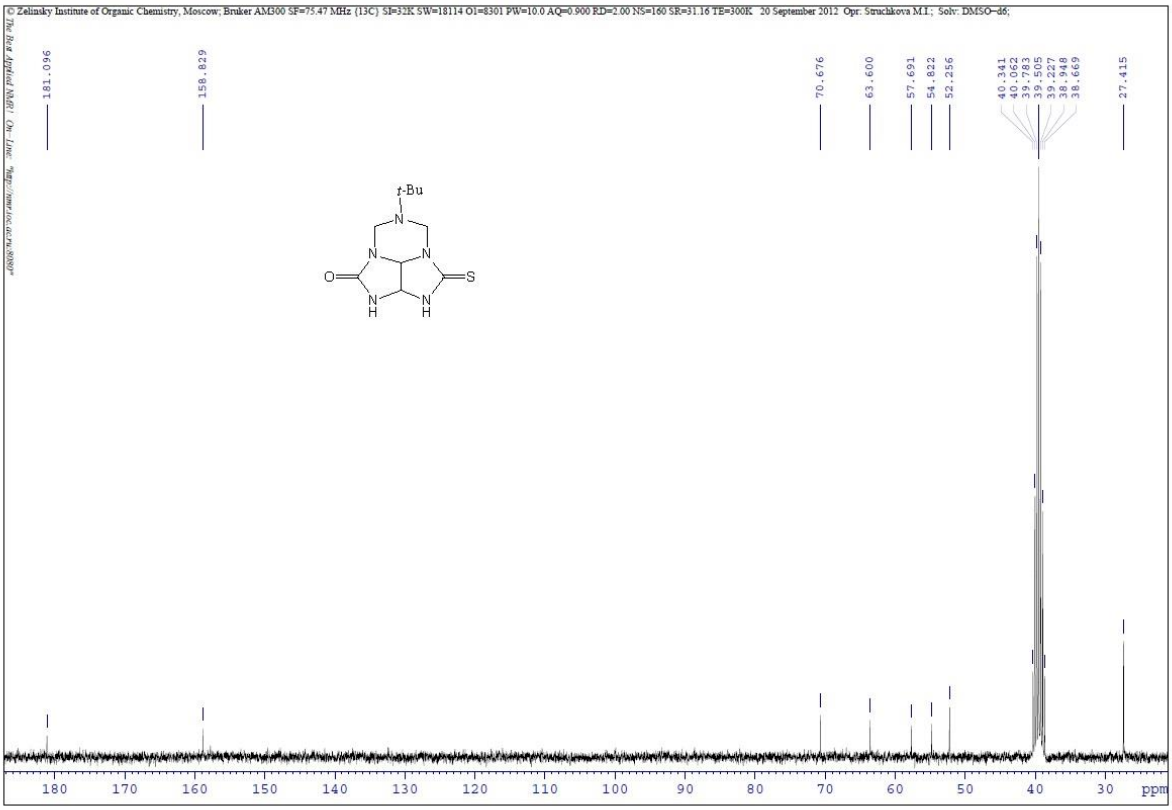

© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=300.13 MHz (1H) SI=16K SW=6002 O1=2401 PW=9.0 AQ=1.352 RD=1.00 NS=1 SR=-4.12 TE=296K 15 September 2015 Opr: Daeva E.D.; Solv: DMSO-d6;
9.566
8.085
5.580
5.554
5.456
5.429
5.082
5.037
4.514
4.468
4.455
4.438
4.418
4.410
4.261
4.215
3.458
3.443
3.436
3.416
3.396
3.376
3.293
2.558
2.547
2.519
2.485
2.433
2.411
2.390
2.369
2.347
OH
N
N
N
O
S
N
H
H
ppm

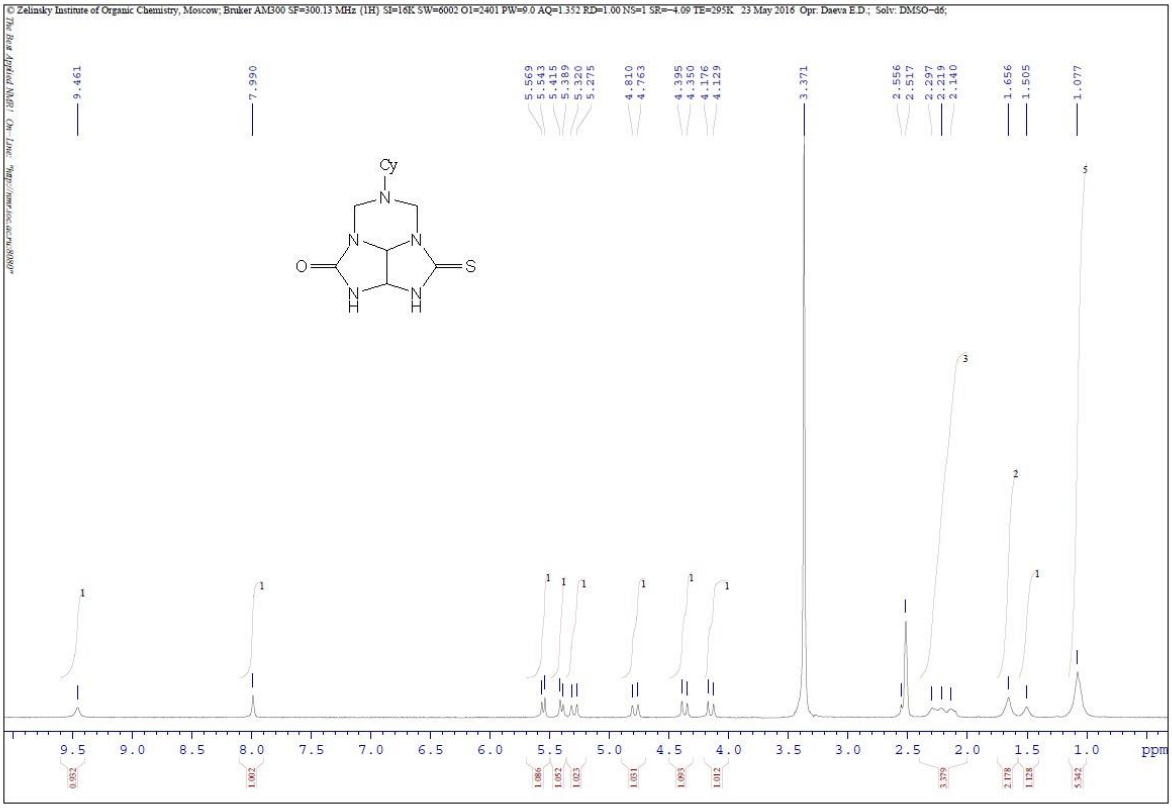

© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AC200 SF=50.32 MHz (13C) SI=16K SW=11627 O1=5600 PW=6.0 AQ=0.705 RD=2.00 NS=1031 SR=577.49 TE=297K 11 June 1994 Opr: Struchkova M.I.; Solv: DMSO-d6;
181.679
159.074
96.688
70.719
63.708
61.696
59.722
58.609
51.359
40.747
40.332
39.913
39.494
39.079
38.658
38.245
OH
N
N
N
O
S
N
H
H
ppm

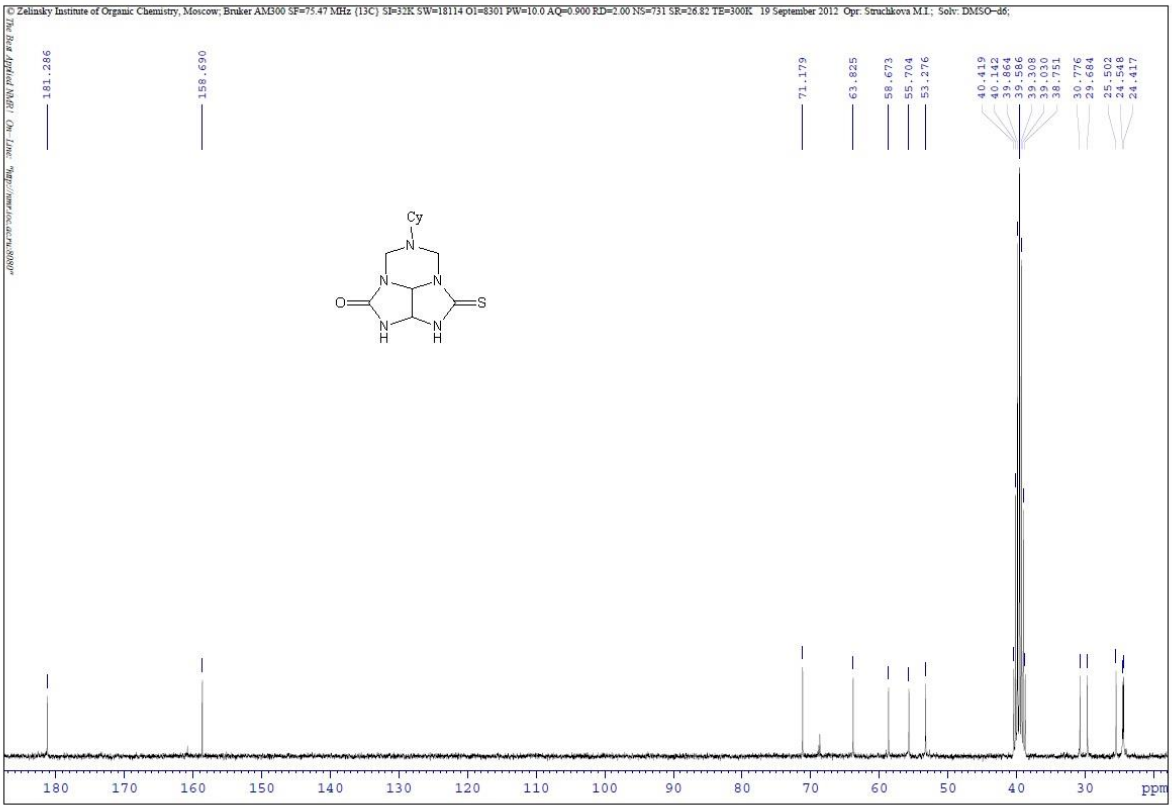

© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=300.13 MHz (1H) SI=16K SW=6002 O1=2401 PW=9.0 AQ=1.352 RD=1.00 NS=1 SR=-4.09 TE=296K 24 May 2016 Opr: Daeva E.D.; Solv: DMSO-d6;
9.586
8.090
7.294
7.270
7.246
7.226
7.204
7.181
5.604
5.579
5.470
5.444
5.231
5.186
4.628
4.583
4.524
4.479
4.316
4.270
3.353
2.879
2.858
2.841
2.821
2.804
2.753
2.735
2.720
2.704
2.680
2.663
2.617
2.600
2.577
2.559
2.520
Ph
N
N
N
O
S
N
H
N
H
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm


© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=75.47 MHz (13C) SI=32K SW=18114 O1=8301 PW=14.3 AQ=0.900 RD=1.00 NS=132 SR=37.32 TE=297K 30 May 2016 Opr: Daeva E.D.; Solv: DMSO-d6;
181.63
159.013
139.649
128.675
128.195
125.950
70.727
63.690
60.824
59.561
51.087
40.332
40.061
39.781
39.515
39.237
38.944
38.670
33.632
Ph
N
N
N
O
S
N
H
N
H
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=300.13 MHz (1H) SI=16K SW=6002 O1=2401 PW=15.0 AQ=1.352 RD=1.00 NS=1 SR=-2.67 TE=299K 19 September 2012 Opr: Daeva E.D.; Solv: DMSO-d6;
9.412
7.965
5.507
5.485
5.481
5.310
5.269
4.793
4.754
4.138
4.097
3.961
3.918
3.405
3.164
2.499
1.074
t-Bu
ppm


© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=75.47 MHz (13C) SI=32K SW=18114 O1=8301 PW=10.0 AQ=0.900 RD=2.00 NS=160 SR=31.16 TE=300K 20 September 2012 Opr: Struchkova M.I.; Solv: DMSO-d6;
181.096
158.829
70.676
63.600
57.691
54.822
52.256
40.341
40.062
39.783
39.505
39.227
38.948
38.669
27.415
t-Bu
ppm


© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=300.13 MHz (1H) SI=16K SW=6002 O1=2401 PW=9.0 AQ=1.352 RD=1.00 NS=1 SR=-4.09 TE=295K 23 May 2016 Opr: Daeva E.D.; Solv: DMSO-d6;
9.461
7.990
5.569
5.543
5.415
5.389
5.320
5.275
4.810
4.763
4.395
4.350
4.176
4.129
3.371
2.556
2.517
2.297
2.219
2.140
1.656
1.505
1.077
Cy
N
O
S
H
ppm


© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=75.47 MHz (13C) SI=32K SW=18114 O1=8301 PW=10.0 AQ=0.900 RD=2.00 NS=731 SR=26.82 TE=300K 19 September 2012 Opr: Struchkova M.I.; Solv: DMSO-d6;
181.286
158.690
71.179
63.825
58.673
55.704
53.276
40.419
40.142
39.864
39.586
39.308
39.030
38.751
30.776
29.684
25.502
24.548
24.417
Cy
N
O
S
H
ppm