Supporting Information

Synthesis of functionalized tetrahydro-1,3-diazepin-2-ones and 1-carbamoyl-1*H*-pyrroles via ring expansion and ring expansion/ring contraction of tetrahydropyrimidines

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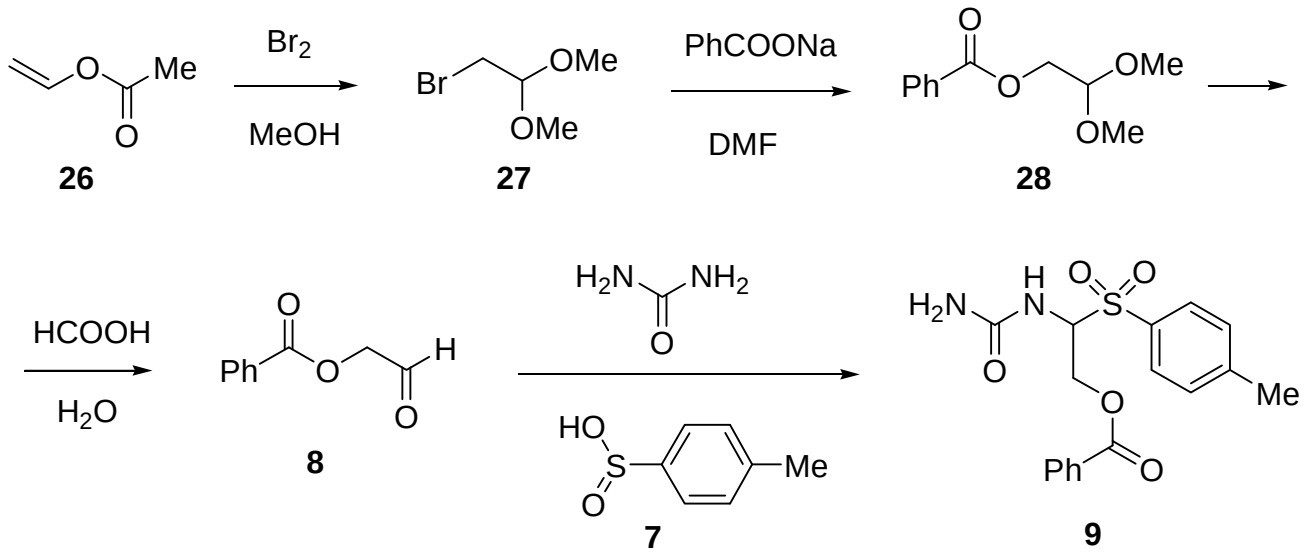
Synthesis of *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea (9)



General: Our experience shows that both yield and purity of the products (*Note 1*) formed in the reaction of enolates of α-functionalized ketones with α-tosyl-substituted *N*-alkylureas and *N*-alkythioureas strongly depend on purity of starting electrophilic reagents. When aldehyde (*Note 2*) and *p*-toluenesulfinic acid (*Note 3*) are appropriate, the three-component condensation of aldehyde, *p*-toluenesulfinic acid and urea or thiourea proceeds smoothly and gives the high yield of pure product. The problem which arose when we tried to use the procedure described in ref.[1] was that the diethylacetal of 2-benzoyloxyethanal could not be distilled at 0.1 mm Hg. When we tried (5 times) to distill this compound it decomposed each time at the beginning of distillation. Use of crude material as reported in ref.[1] for hydrolysis led to formation of 2-benzoyloxyethanal (**8**) with inappropriate purity for the following condensation *even* after distillation. This was the reason why we used dimethylacetal of 2-chloroethanal as a starting material in the reaction with sodium benzoate (DMF, reflux, 61 h).[2] The product formed, dimethylacetal of 2-benzoyloxyethanal (**28**), could be successfully distilled at 0.1 mm Hg. Hydrolysis of **28** gave aldehyde **8**, which after distillation was successfully used for the preparation of *N*-[(2-benzoyloxy-1-tosyl)ethyl]urea (**9**) in high yield and purity. But the prolonged time of reaction of dimethylacetal of 2-chloroethanal with sodium benzoate and the low yield of the product (40%) initiated our further efforts to improve the preparation of dimethylacetal of 2-benzoyloxyethanal (**28**). This was achieved by using dimethylacetal of 2-bromoethanal (**27**) in reaction with sodium benzoate.

D**imethylacetal of 2-bromoethanal (27)**: MeOH (140 mL) (*Note 4*) was charged to a 500 mL three-neck round-bottom flask equipped with a magnetic stirring bar, two dropping funnels and a thermometer. The flask was cooled in an ice-cold bath or NaCl/ace bath (*Note 5*) and the reagents, Br_2

(102.98 g, 0.64 mol) and vinyl acetate (55.52 g, 0.64 mol) (*Note 6*), were simultaneously added under vigorous stirring dropwise at the rate when the internal temperature was not higher than 5 ^{o}C. The resulting colorless solution (*Note 7*) was left overnight at room temperature. The flask was cooled (–10 ^{o}C) and the reaction mixture was poured into a 1 L glass cooled in an ice-cold bath and charged with ice-cold H_2O (80 mL) and $NaHCO_3$ (56.10 g, 0.67 mol) under vigorous stirring using a magnetic stirrer. Then CH_2Cl_2 (80 mL) was added and the liquids were stirred under cooling in an ice-bath for 30 min until the foam had disappeared. The organic layer was separated, the water layer was extracted with CH_2Cl_2 (10 and 30 mL), the combined organic phase was washed with brine (20 mL), dried over Na_2SO_4 for 30 min, filtered, CH_2Cl_2 was removed under reduced pressure and the fraction collected at 70–82 ^{o}C/80 mm Hg (84.06 g, 77%) was immediately used in the reaction with sodium benzoate.

Dimethylacetal of 2-benzoyloxyethanal (28): A two-necked 2 L round-bottom flask equipped with a mechanical stirrer and reflux condenser was charged with dimethylacetal of 2-bromoethanal (**27**) (64.41 g, 0.38 mol), sodium benzoate (60.92 g, 0.42 mol) and DMF (440 mL) (*Note 8*). The reaction mixture was refluxed for 5 h under vigorous stirring (*Note 9*), cooled, diluted with H_2O (440 mL) and extracted with AcOEt (5 × 150 mL) (*Note 10*). The combined extracts were washed with H_2O (4 × 75 mL) and dried with Na_2SO_4 (*Note 11*). The solvent was removed under reduced pressure and the residue was distilled at 86–102 ^{o}C/0.1 mm Hg to give 55.79 g (70%) of dimethylacetal of 2-benzoyloxyethanal (**28**) as a slightly yellow liquid.

2-Benzoyloxyethanal (8): To dimethylacetal of 2-benzoyloxyethanal (**28**) (55.79 g, 0.27 mol) was added 80% aqueous HCOOH (500 mL) and the obtained solution was stirred at room temperature for 4 h. The solvent was removed under vacuum, the residue was dissolved in $CHCl_3$ (300 mL), the solution was washed with satd. aqueous $NaHCO_3$, water, brine, dried over Na_2SO_4 (*Note 12*), filtered, the solvent was removed under vacuum, and the residue was distilled at 95–98 ^{o}C/0.1 mm Hg to give 2-benzoyloxyethanal (**8**) (32.91 g, 76%) as an almost uncolored liquid (*Note 13*), which was immediately used in the next stage (*Note 14*).

***N*-[(2-Benzoyloxy-1-tosyl)ethyl]urea (9)**: To a fine emulsion of 2-benzoyloxyethanal (**8**) (16.73 g, 0.1 mol) (*Note 15*) in H_2O (100 mL) at room temperature under vigorous stirring using a magnetic stirrer was added *p*-toluenesulfinic acid (16.02 g, 0.1 mol) and H_2O (30 mL) (*Note 16*). To the obtained suspension was added urea (30.61 g, 0.51 mol) and H_2O (30 mL). The reaction mixture was stirred at room temperature for 20 h (*Note 17*), cooled to 0 ^{o}C, the precipitate was filtered off, carefully washed with ice-cold water, petroleum ether (*Note 18*), and dried over P_2O_5 (*Note 19*) to give 34.6 g (97%) (*Note 20*) of **9**, which was used without further purification.

Notes

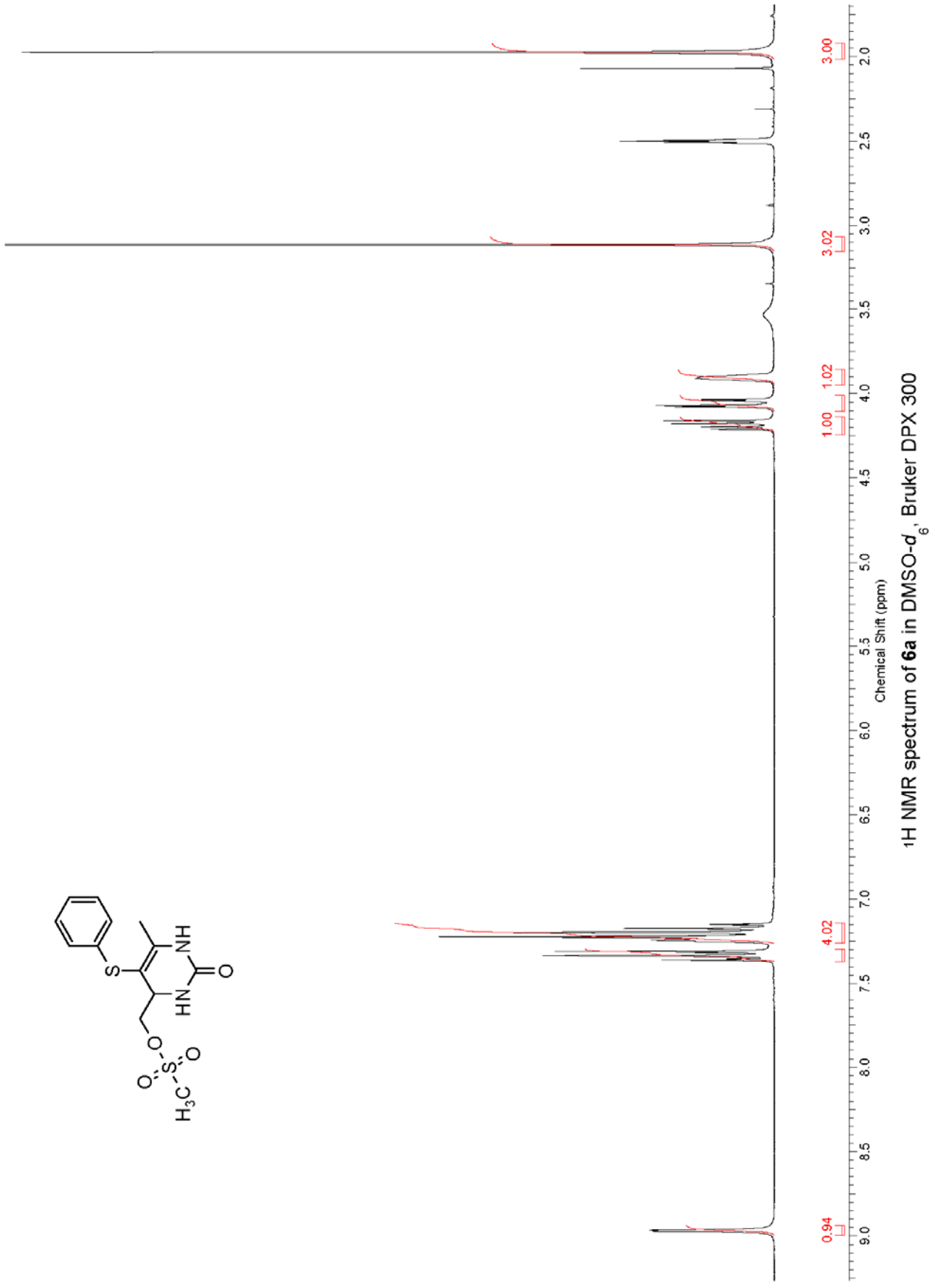
1. In most cases, high yield means good purity.
2. Aldehyde should be purified by distillation or otherwise.
3. M.p. about 81 ^{o}C (clear melt).
4. We used distilled MeOH (99.5%).
5. Upon cooling in a NaCl/salt bath the addition of the reagents could be faster (compared with ice-bath). After addition of both reagents the internal temperature of reaction mixture should be monitored, because it may rise if the bath was removed immediately after addition of the reagents.
6. Purchased from Aldrich (99 %+) without distillation.
7. The resulting solution could be slightly yellowish due to impurities in bromine. It is necessary to put attention on coloring, because no excess of Br_2 could be allowed to remain in the reaction mixture. Extra quantity of vinyl acetate should be added to react with residual Br_2.
8. DMF was dried over KOH pellets and distilled.
9. After about 1 h from the beginning of the reaction the precipitate becomes very fine and can accumulate in the bottom of the flask. It can cause bumping of the reaction mixture.
10. The first portion of AcOEt significantly dissolves in the solution formed, but at the end of extraction about 600 mL of extract was collected. The extraction was always complicated to a greater or lesser extent by the formation of an dark insoluble material during the reaction, and sometimes it was difficult to determine the interface of phases (in especially difficult cases use of the bright lamp helped). Each time after separation, the organic layer was filtered through a cotton wool plug, thus the dark material was partially separated. When the filtration became very slow the cotton wool plug was changed and the filtration repeated. The filtration through a cotton wool plug was also made after each washing of the combined extract with H_2O. All this makes the extraction very laborious, it takes about 3 h. The final combined extract was brown clear liquid.
11. Silica gel (0.1–0.4 mm), previously activated by heating at 100 °C for 1 h, was also added. It additionally removed some dark coloring.
12. The extract may stay not quite clear after drying. Silica gel (0.1–0.4 mm), previously activated by heating at 100 °C for 1 h, was also added.
13. At the end of distillation some amount of yellow colored product may come. It is not so essential for further reaction but should be avoided if possible.
14. The aldehyde was distilled into two 250 mL round-bottom flasks in roughly equal amounts. After the mass of each portion of aldehyde was measured, H_2O (50 mL) was immediately added to aldehyde to prevent oxidation. Thus the final stage proceeded in two flasks.

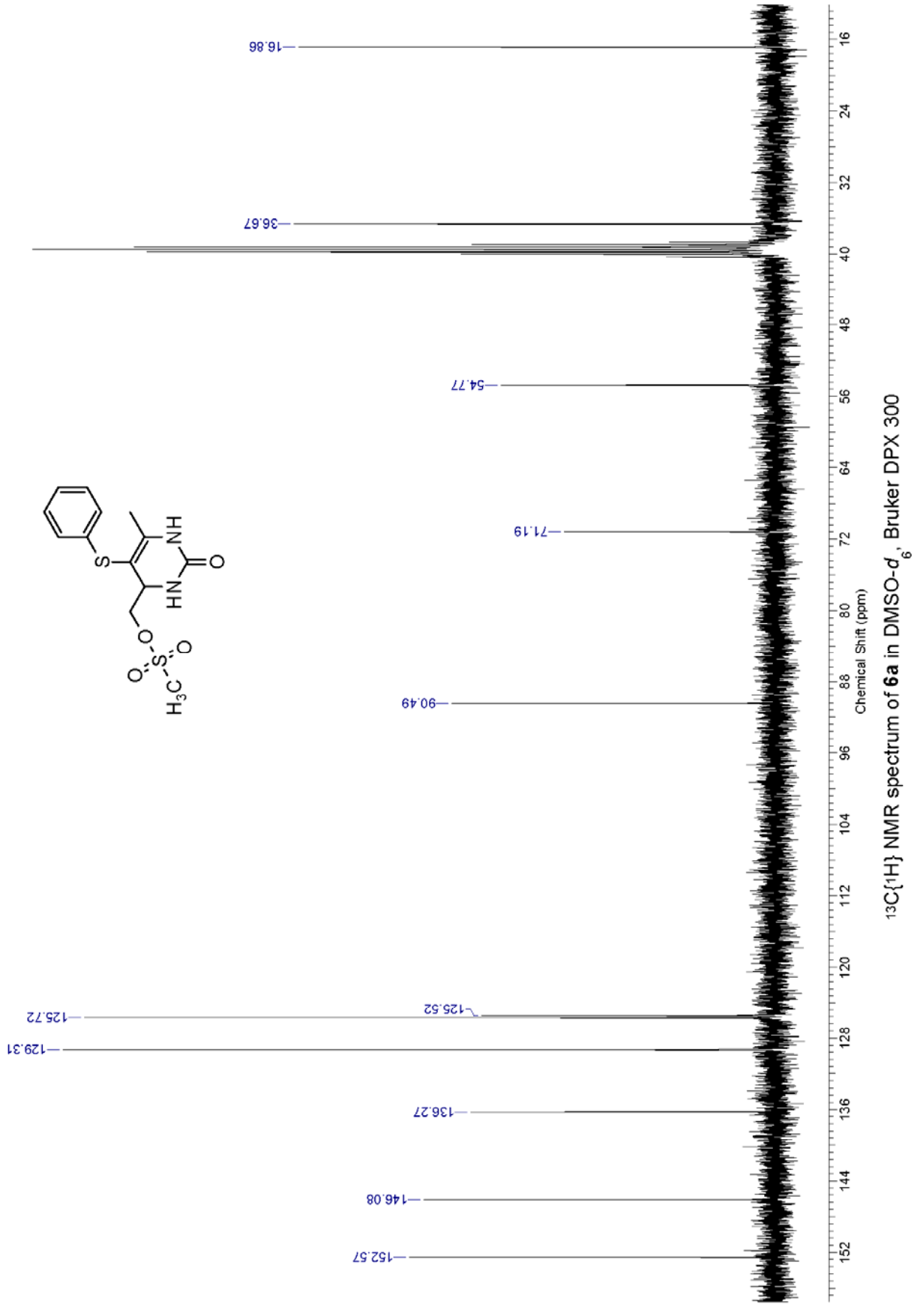
15. The maximal amount of the aldehyde was about 25 g. This amount should not be exceeded, because in this case the synthesis becomes *very* laborious.
16. After addition of *p*-toluenesulfinic acid, the oily solid formed and starting from this moment it must be triturated with spatula. After about 5–7 min it becomes solid and it is very important that no big pieces of solid formed. It is very hard to crush big pieces, but if all was done as described their formation was prevented. The practically fine suspension formed after trituration and it could be effectively stirred to remove the rest of the small pieces. Only after formation of the fine suspension urea should be added.
17. The mixture may become very dense after about 6–7 h from the beginning of the reaction. In this case it should be shaken periodically, once it becomes fluid again it can be stirred by the stirrer and it did not become dense again.
18. The precipitate was washed 4 times. After each washing the cake was formed on a filter to remove the water more completely, the next portion of water was the same high as the cake; the cake was carefully crushed and washed to remove the excess of urea. After the last washing with water some amount of petroleum ether (about 20–30 mL) was passed through the cake without crushing, then the cake was washed twice with petroleum ether and after the second time no cake was formed. After petroleum ether was removed by passing air through the filter, the product became a white solid.
19. The solid holds a lot of water, drying must be performed as fast as possible (in a big vacuum desiccator) and P_2O_5 must be changed every hour (for 5–6 times) until most part of water was removed from product. Attention should be paid on that the internal temperature of desiccator did not rise because of intensive absorption of water by P_2O_5, the product may decompose because of this heat. Complete drying of the product takes 2–3 days.
20. It is the best yield; the average yields are about 92–94%.

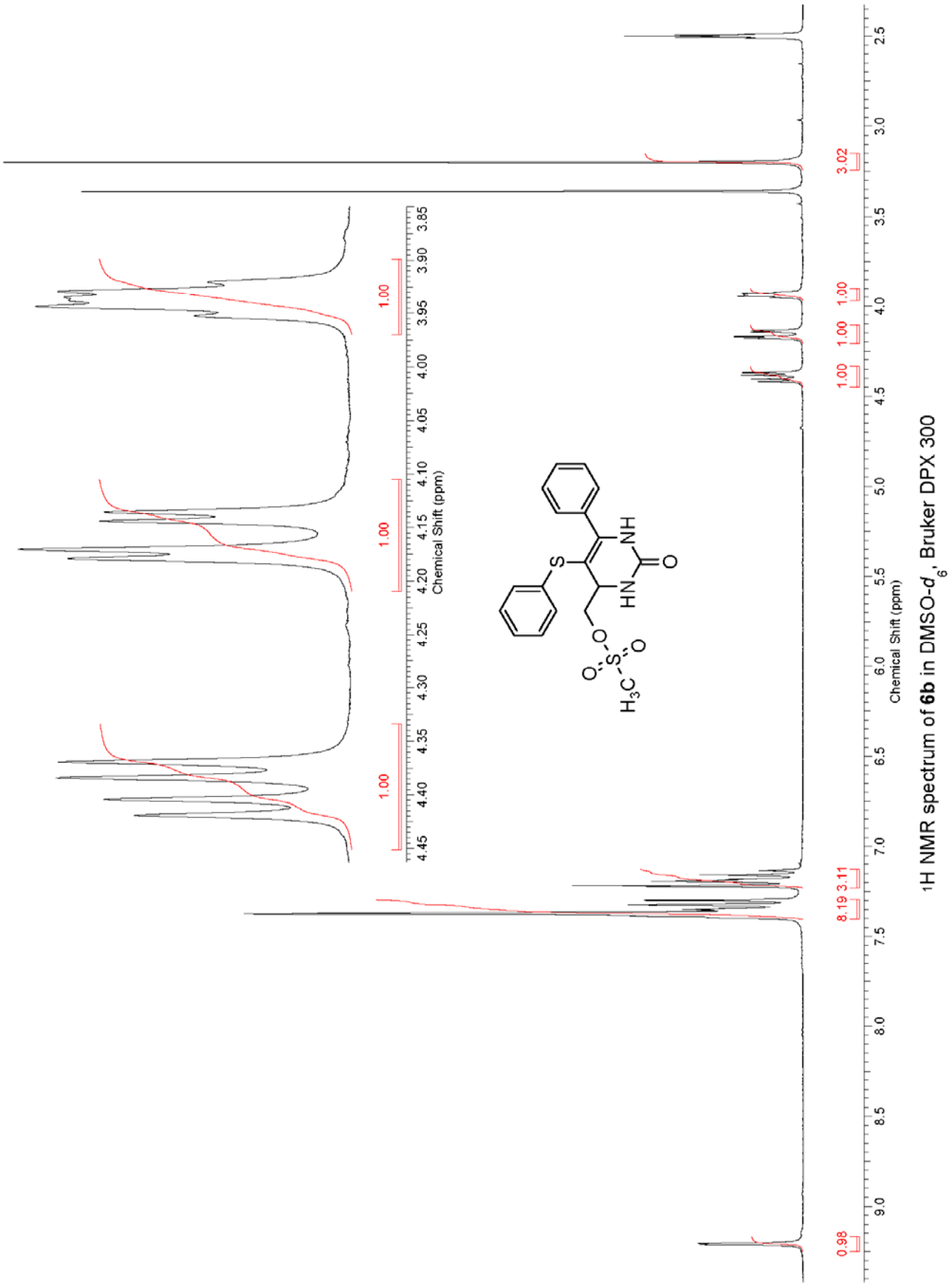
References

1 J. Du, K. A. Watanabe, *Synth. Commun.*, 2004, **34**, 1925–1930.

2 A. A. Fesenko, M. L. Tullberg, A. D. Shutalev, *Tetrahedron*, 2009, **65**, 2344–2350.







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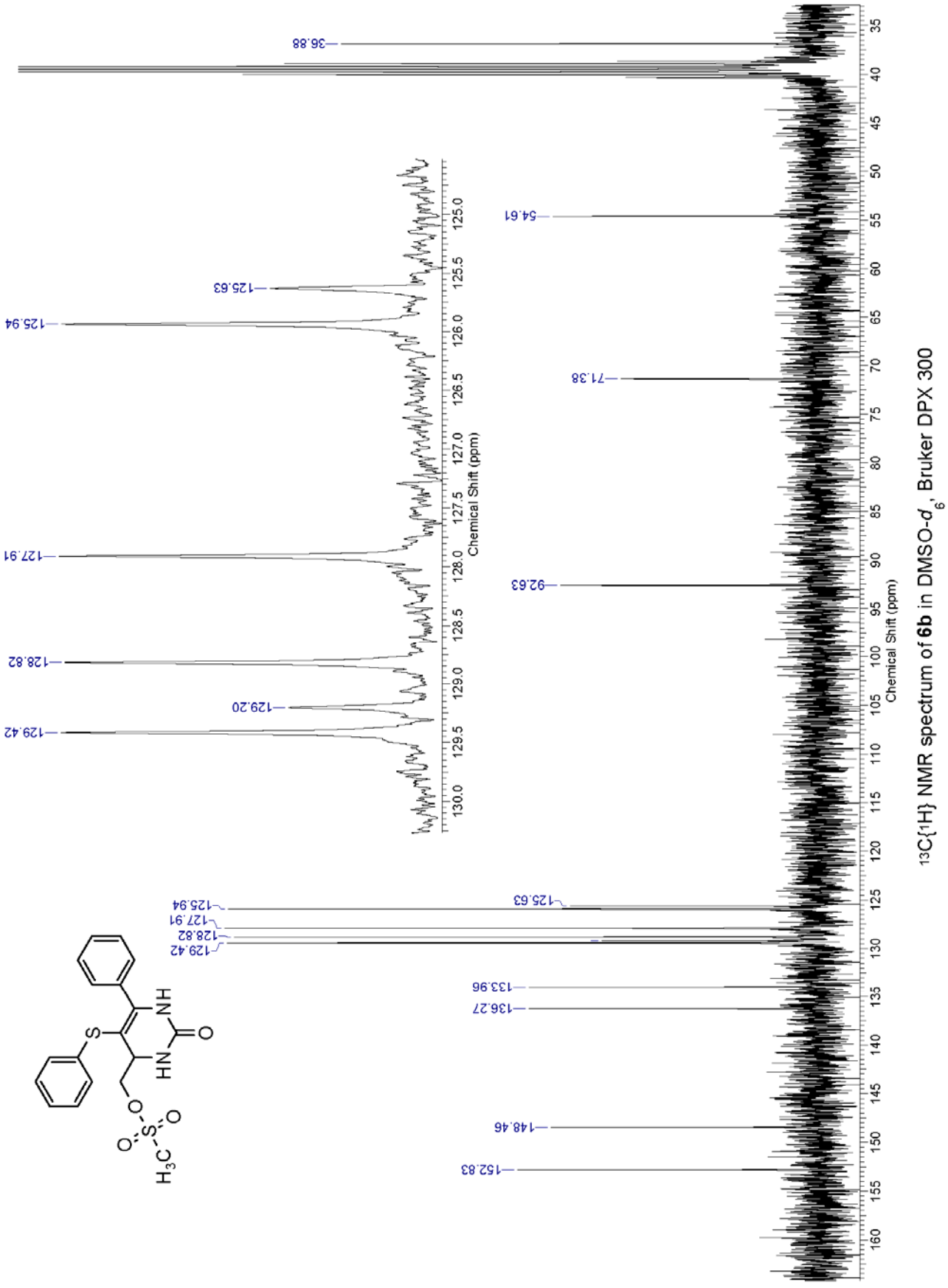

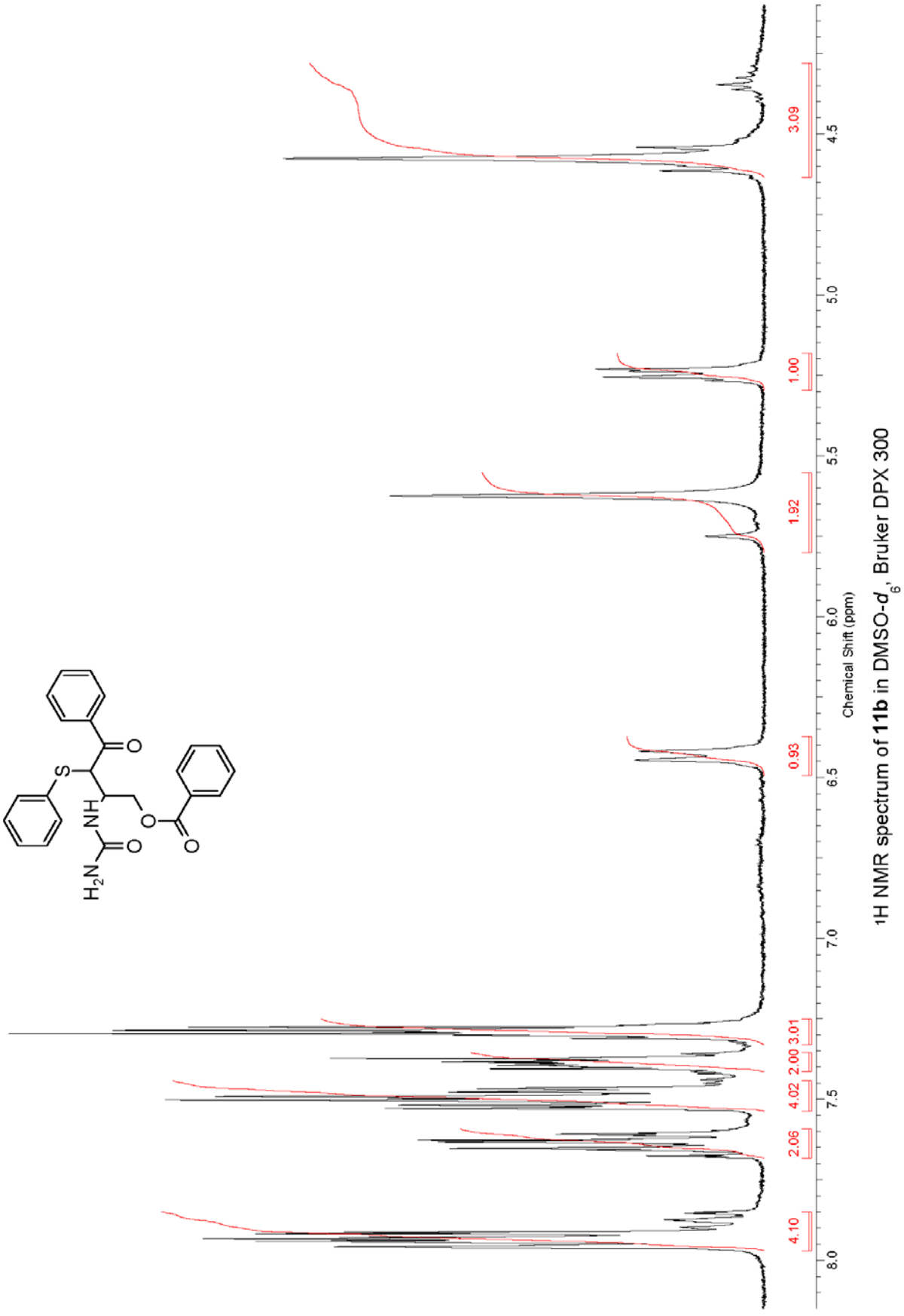

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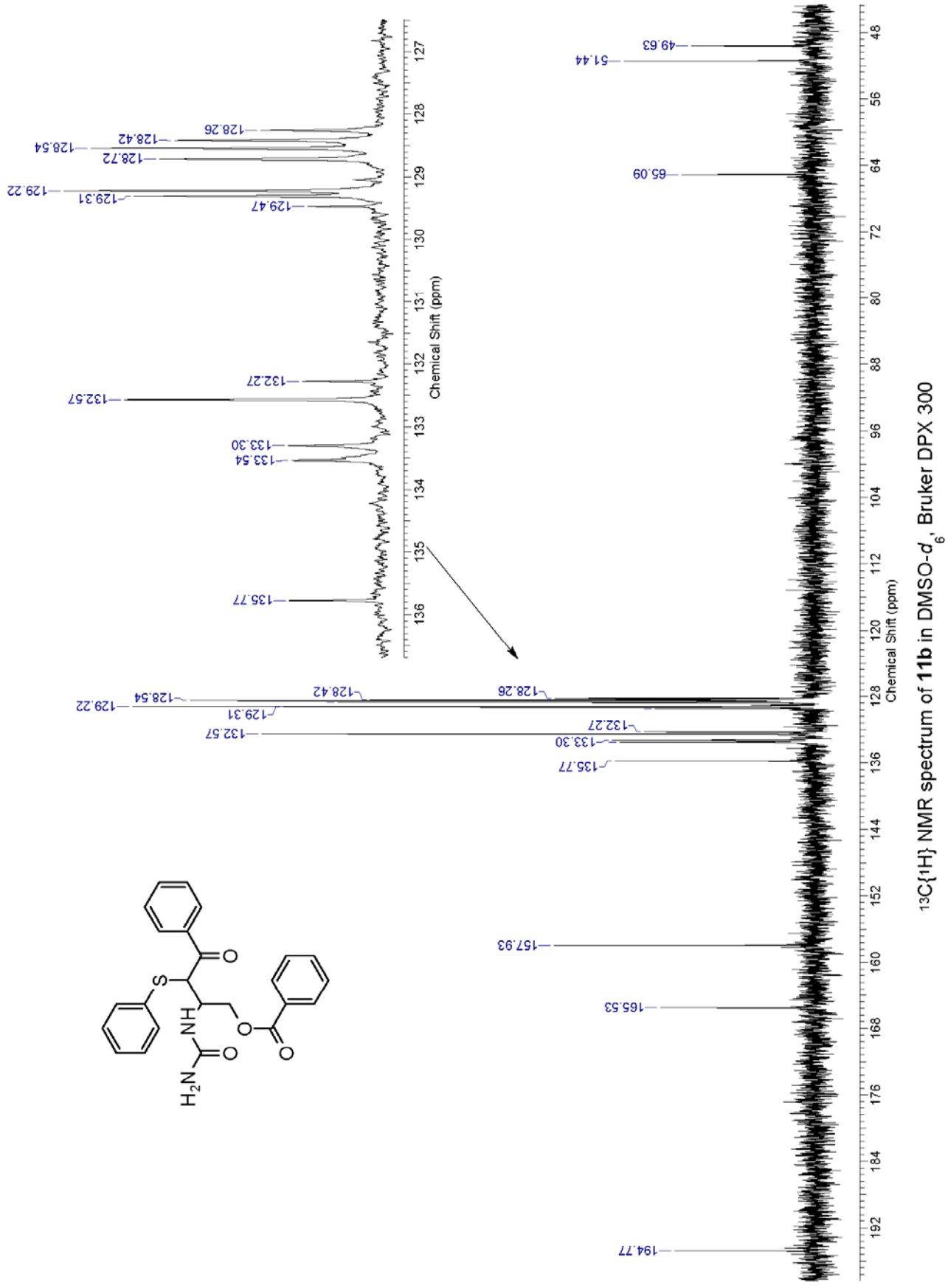
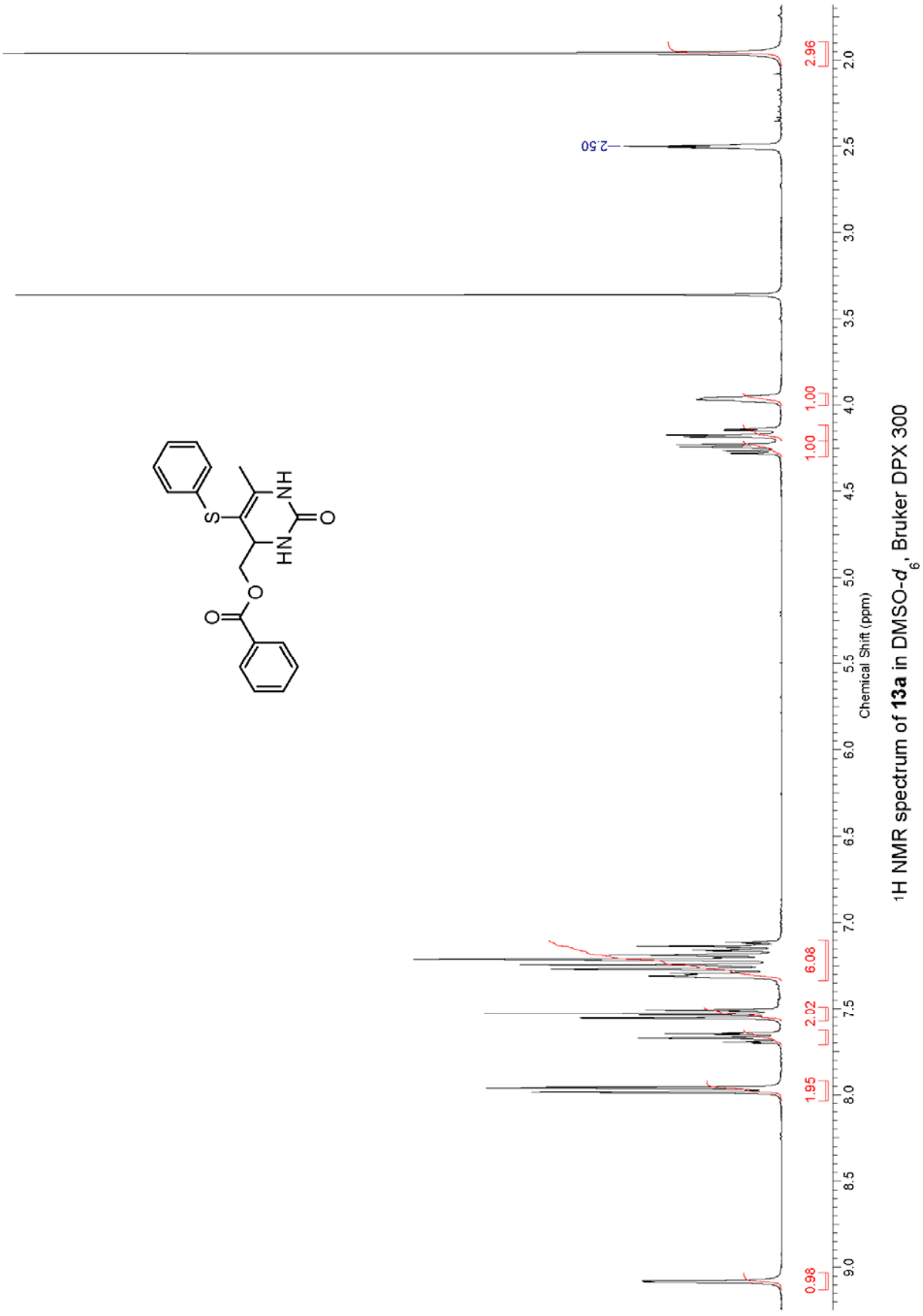


$^{13}C\{^1H\}$ NMR spectrum of **11b** in DMSO-d_6, Bruker DPX 300



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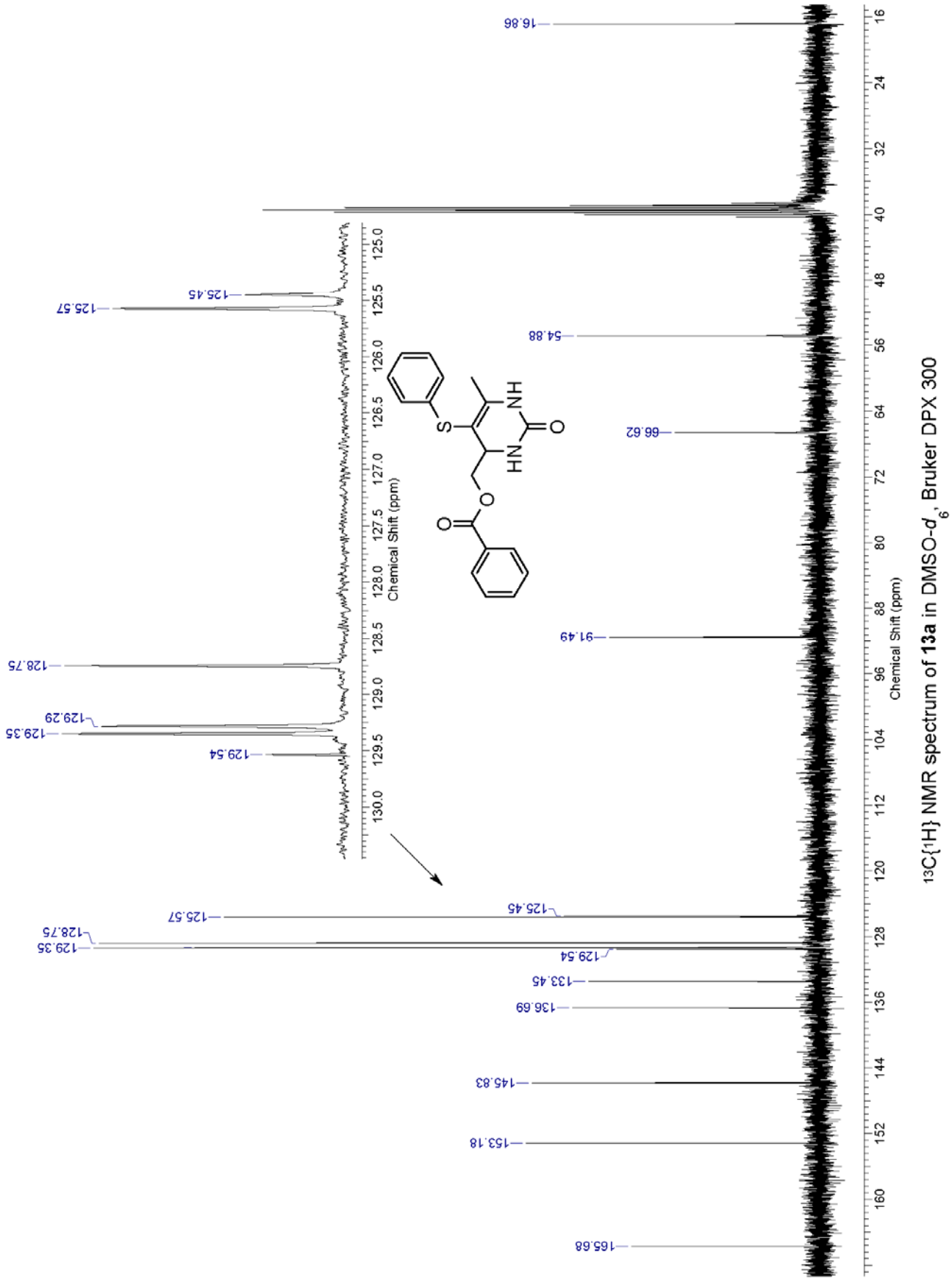
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125.45
125.57
128.75
129.29
129.35
129.54
133.45
136.69
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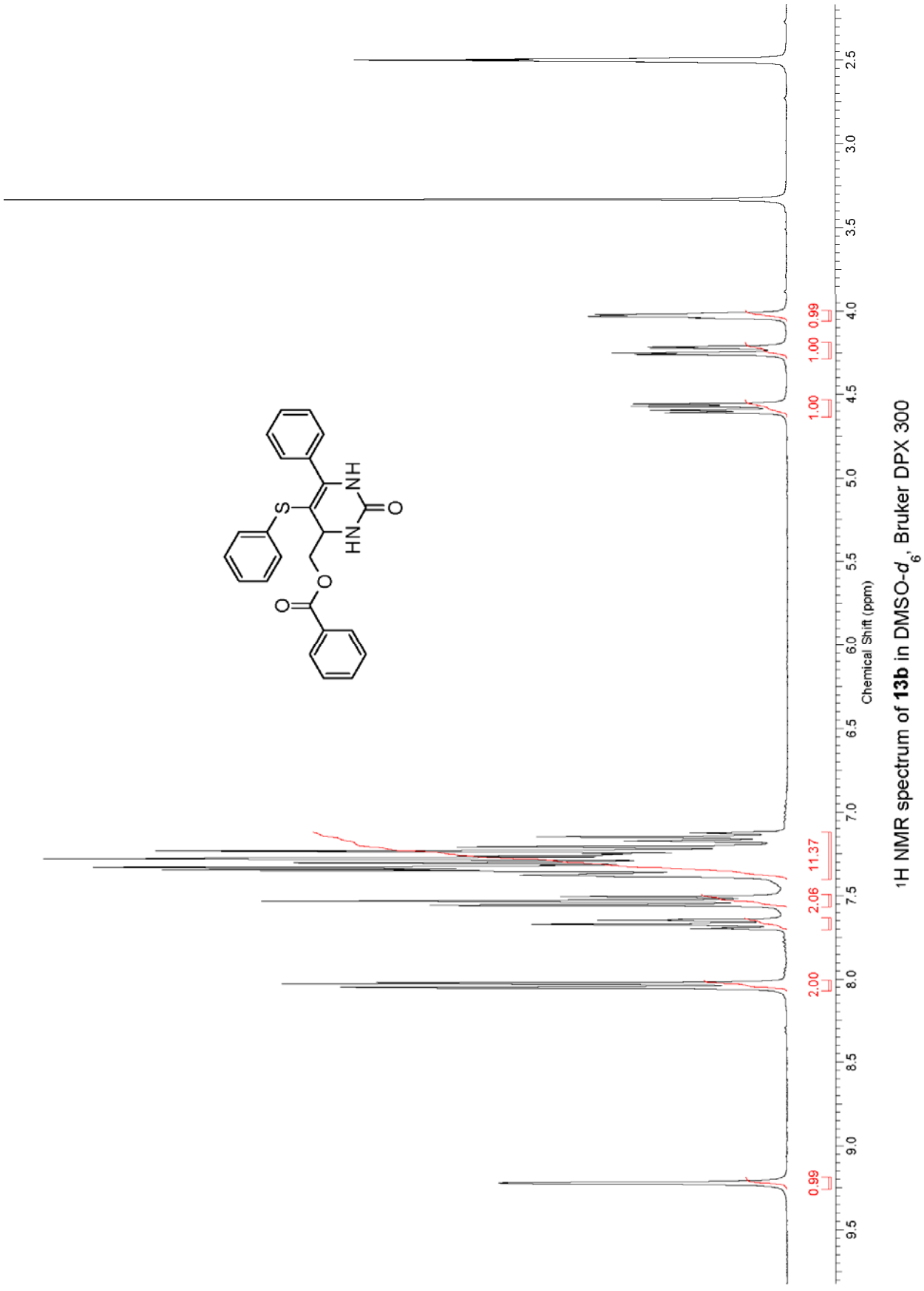
153.18
165.68
Chemical Shift (ppm)
Chemical Shift (ppm)
13C{1H} NMR spectrum of 13a in DMSO-d6, Bruker DPX 300



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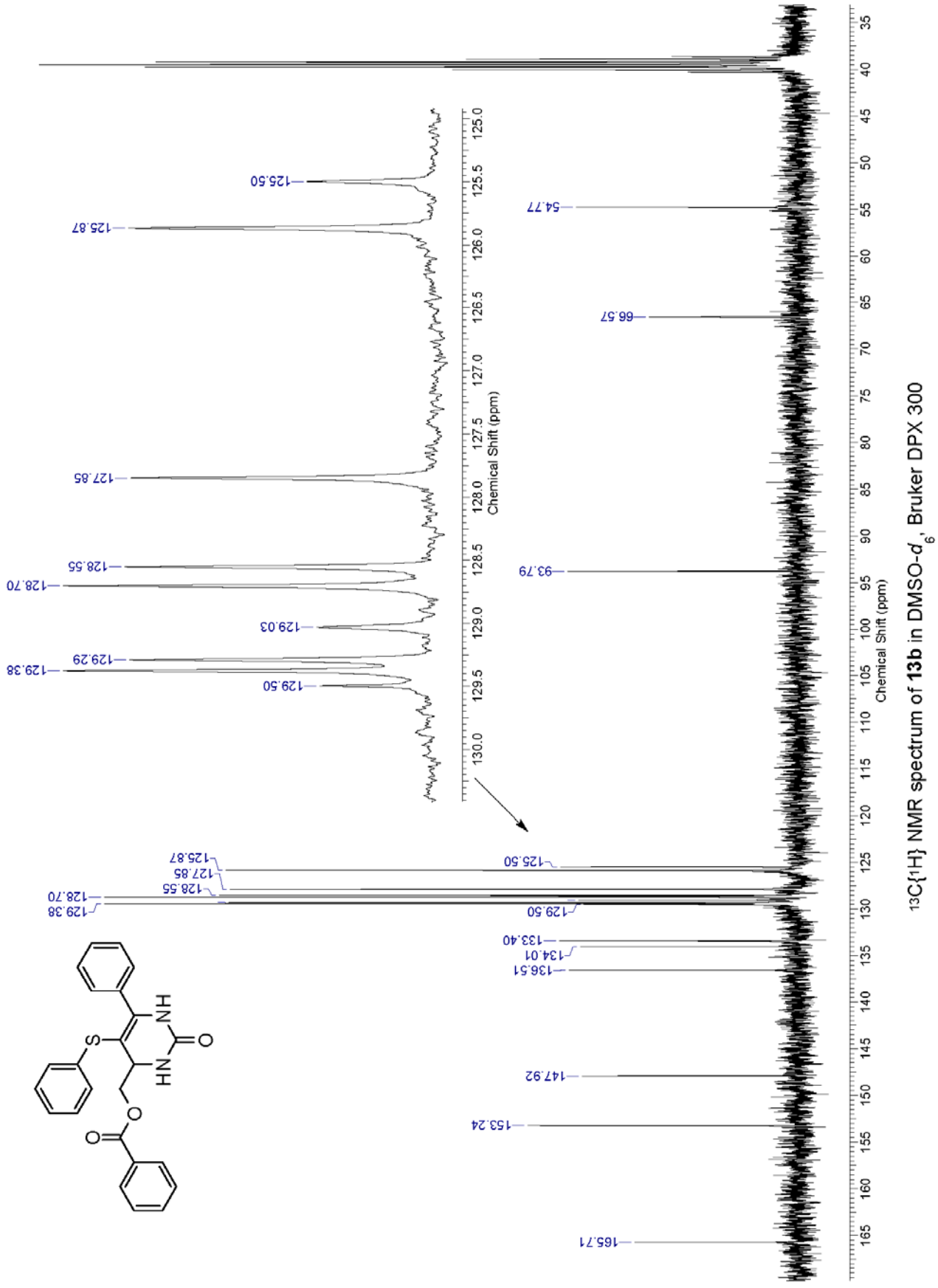

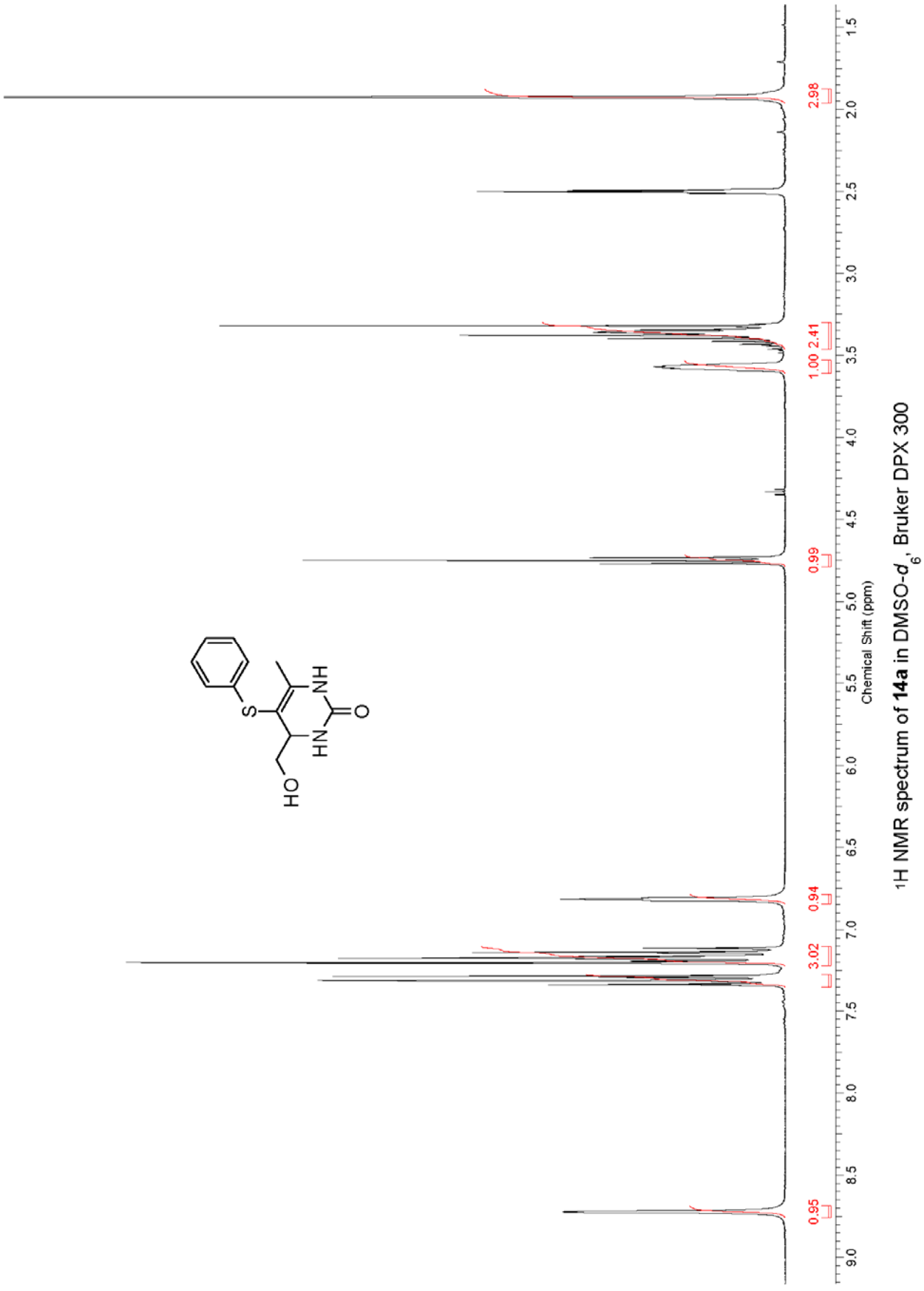

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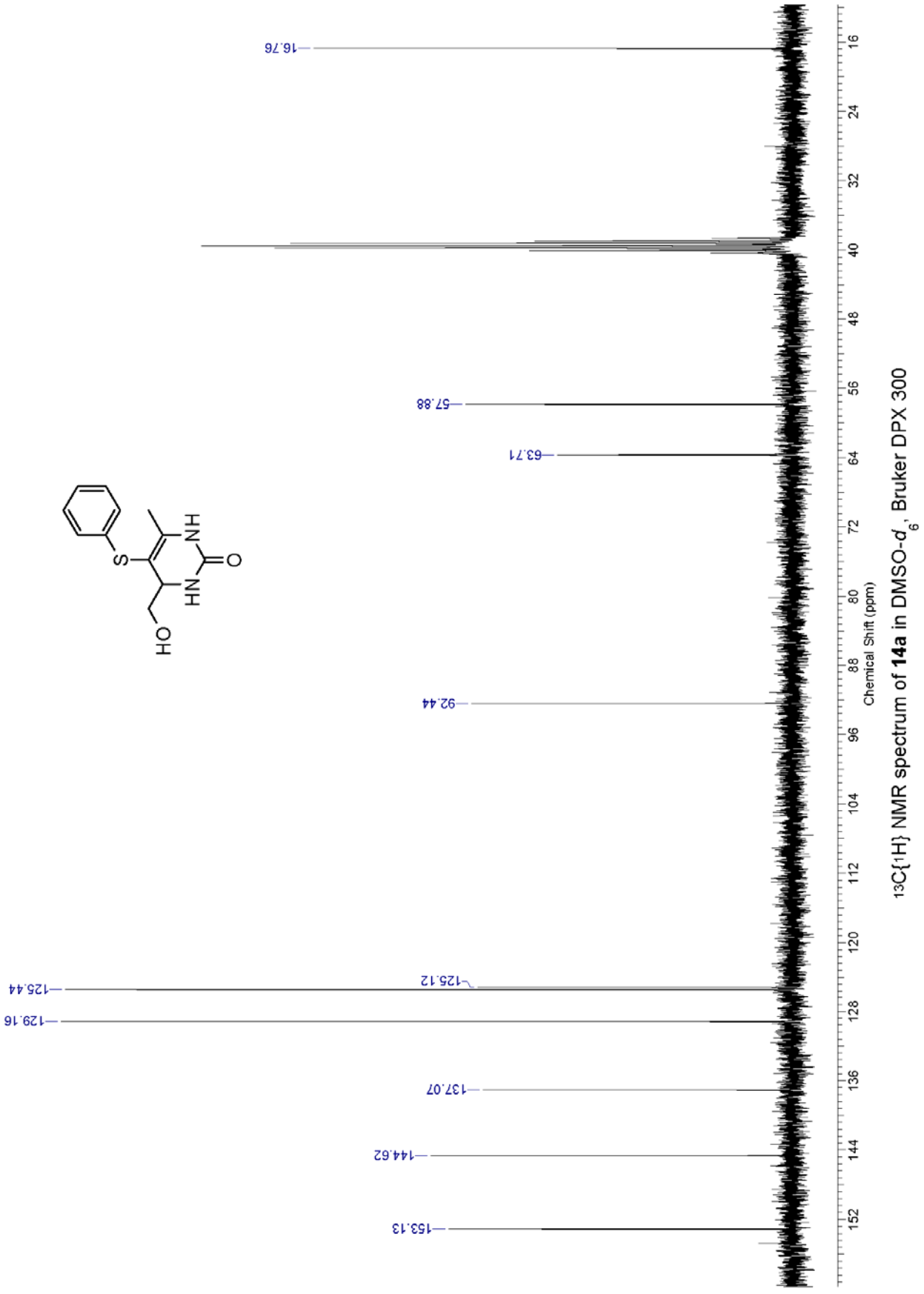
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92.44
125.12
125.44
129.16
137.07
144.62
153.13
Chemical Shift (ppm)
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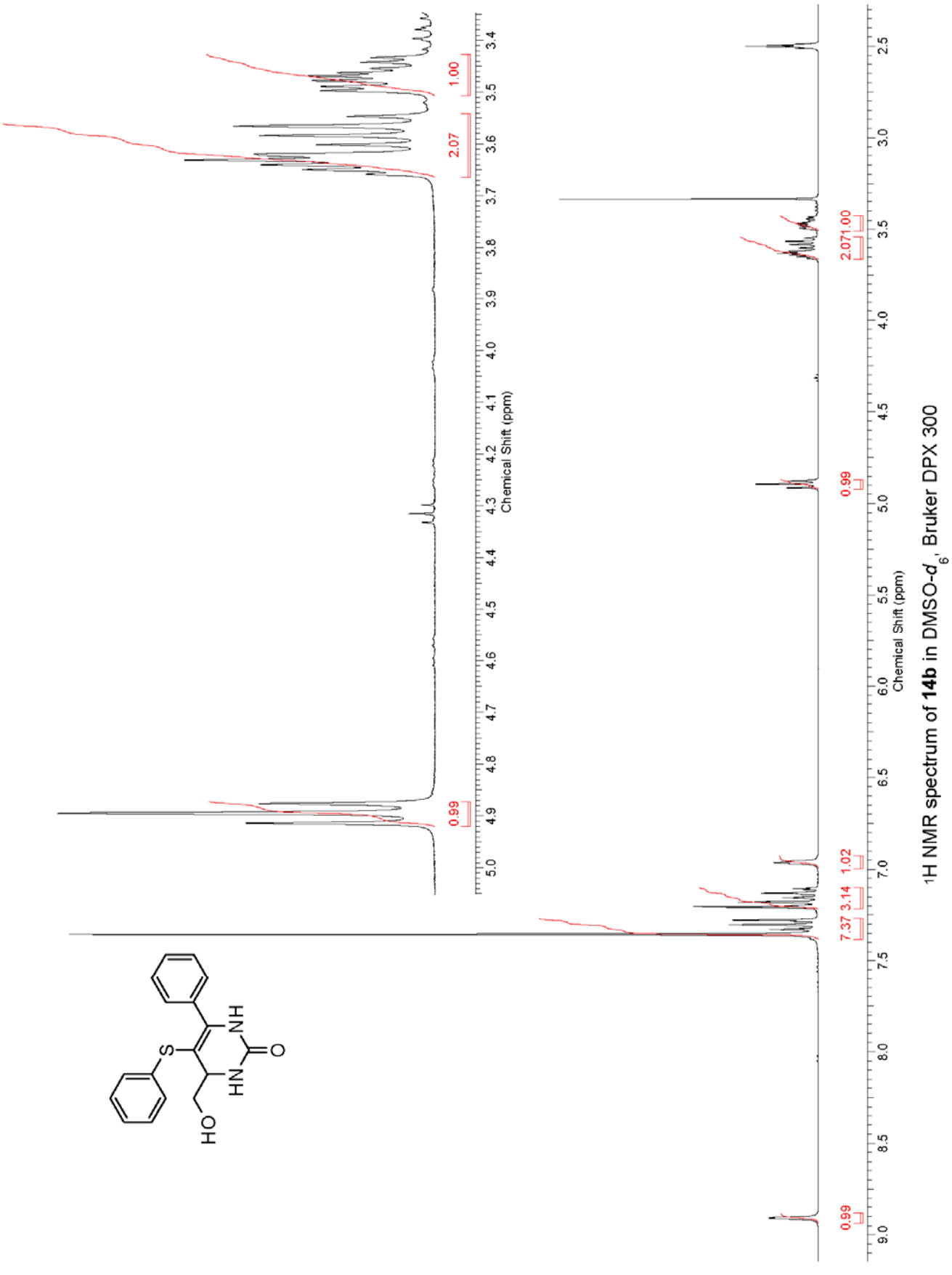

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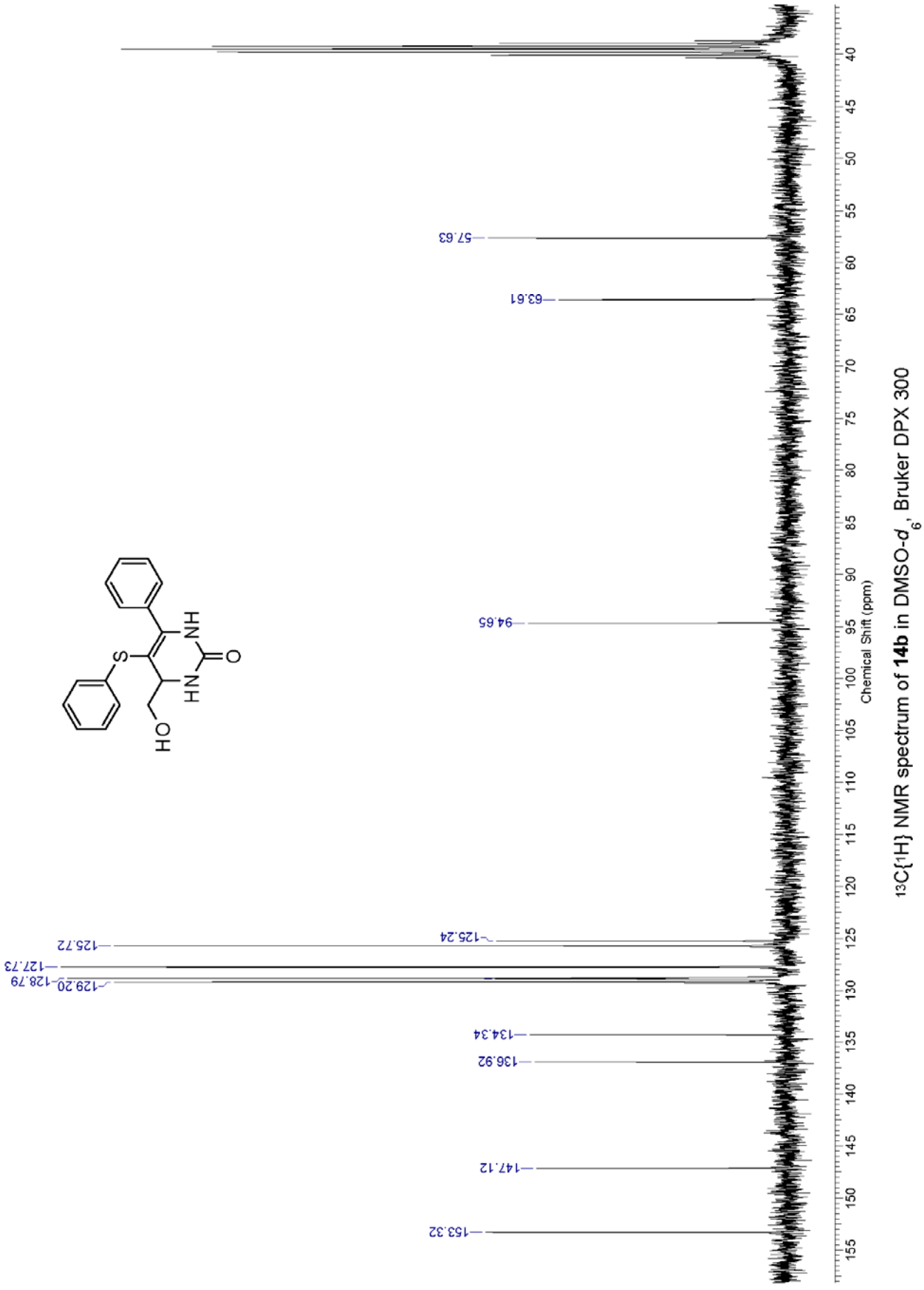

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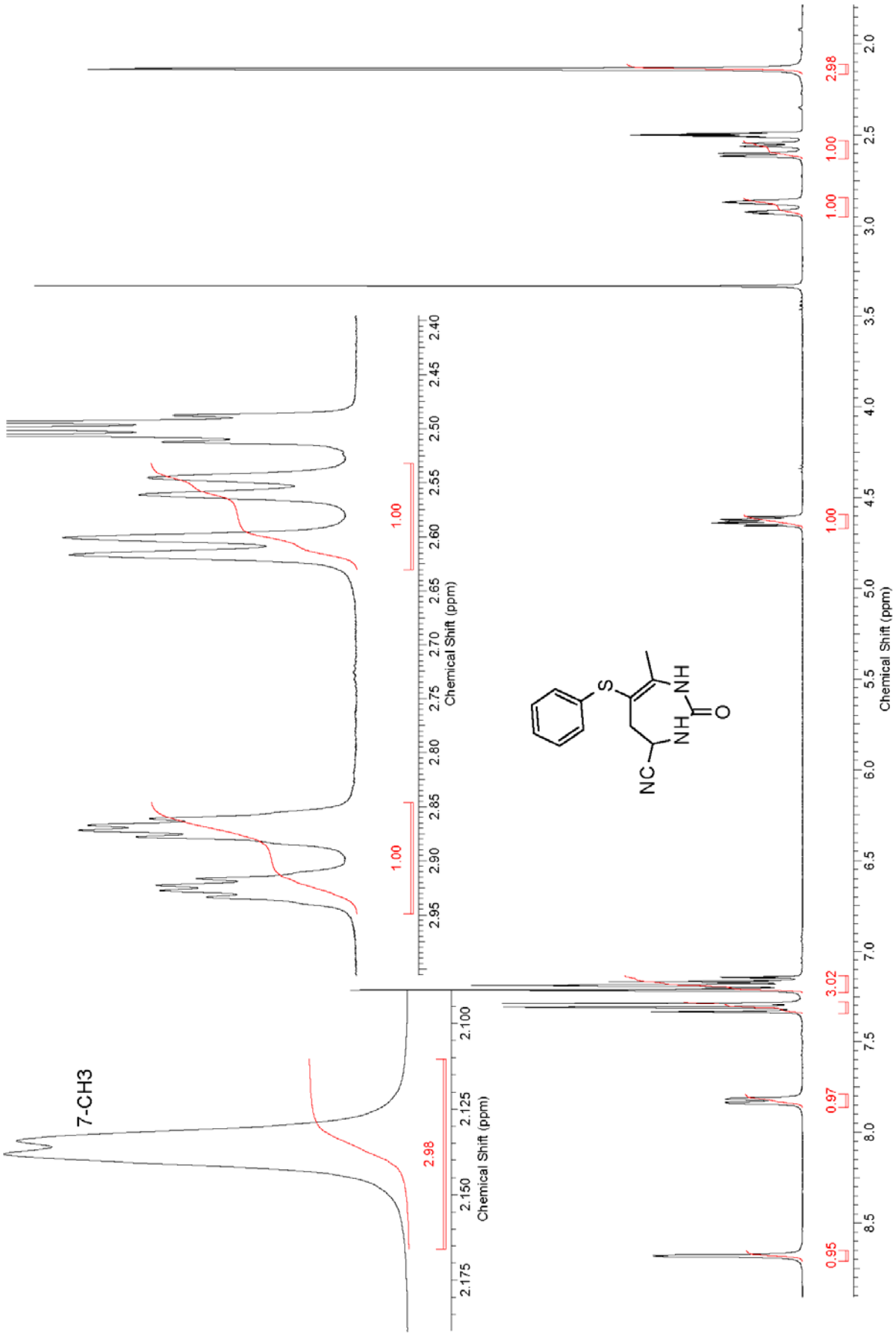

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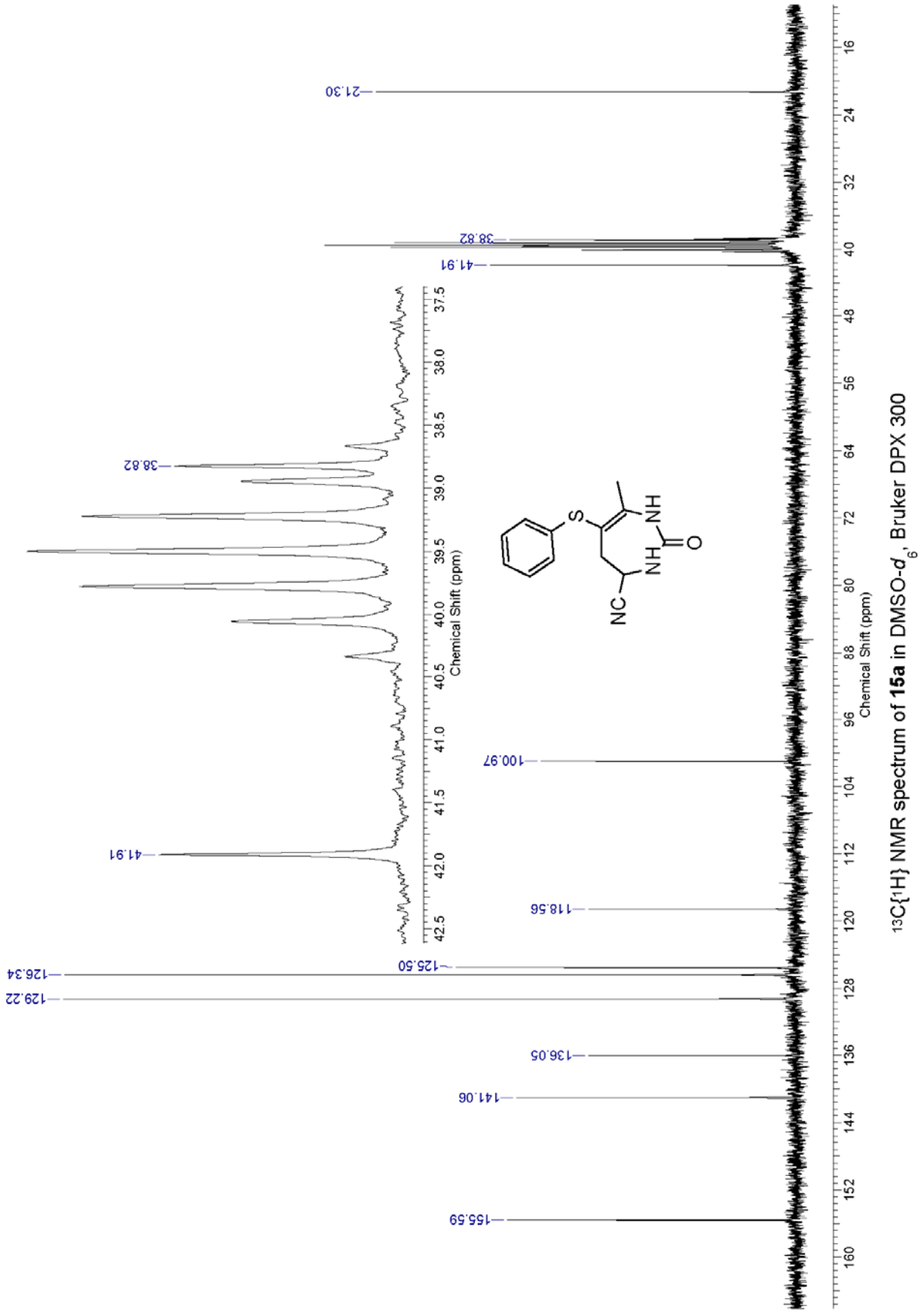

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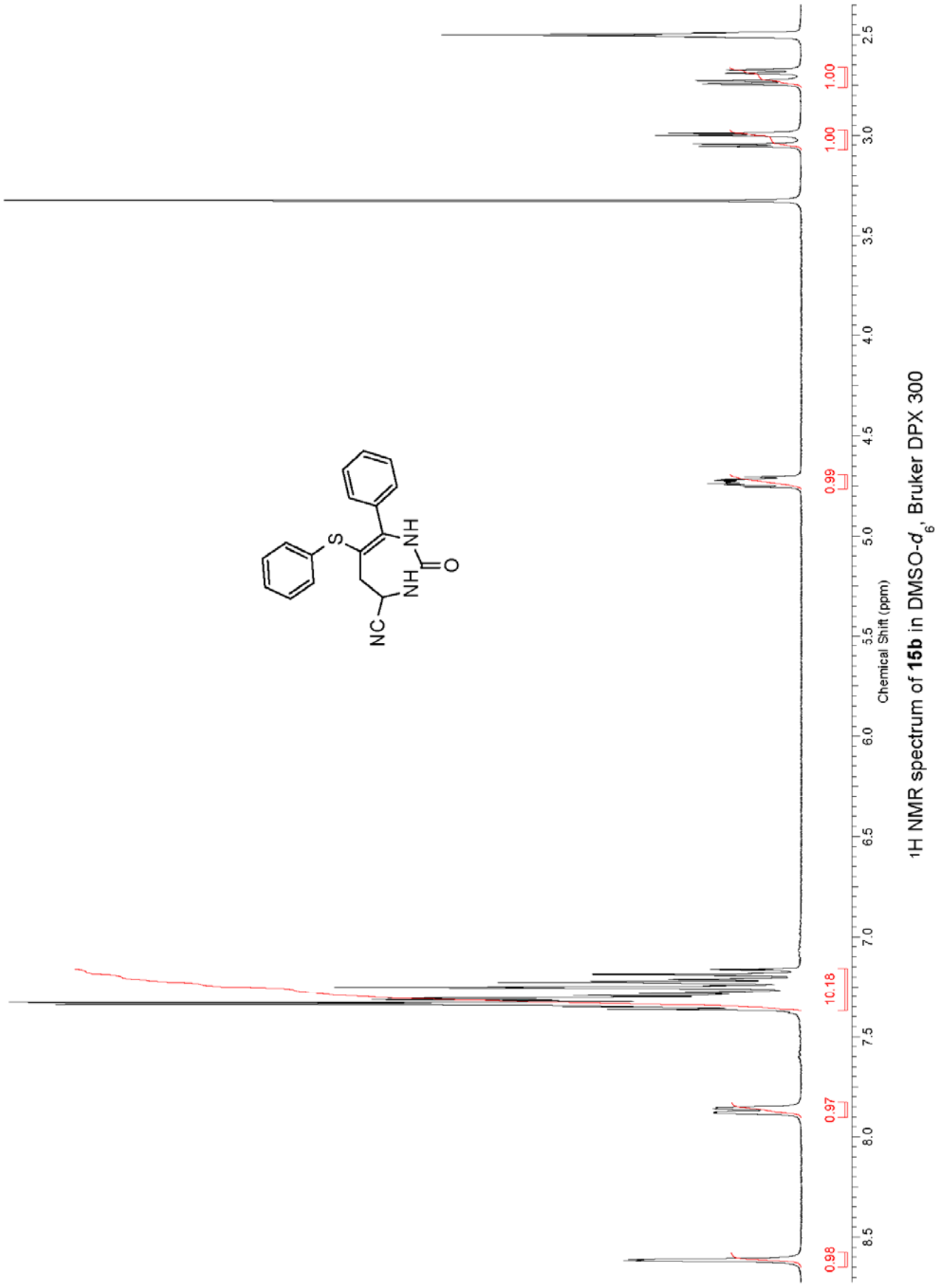

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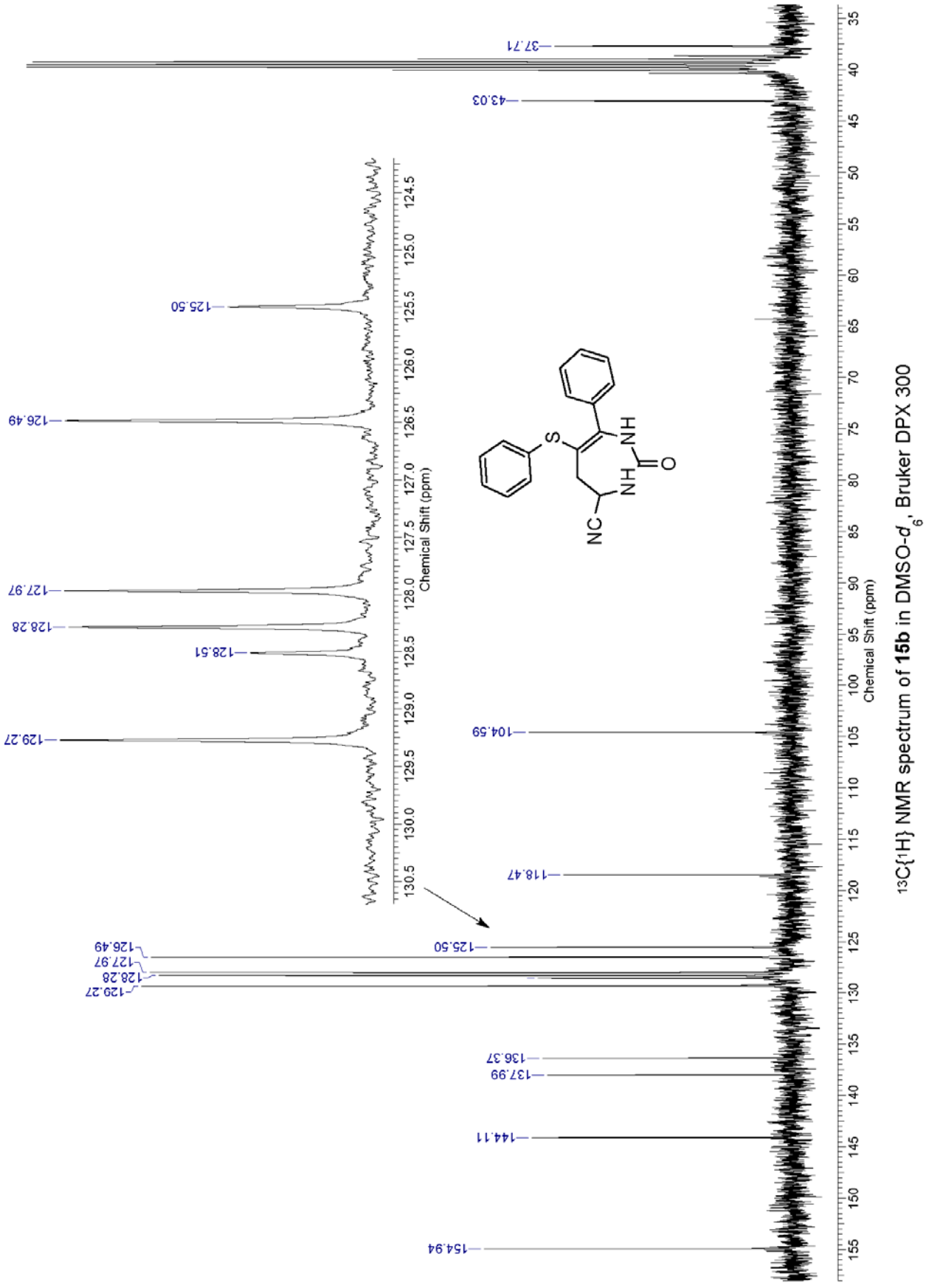
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144.11
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Chemical Shift (ppm)
Chemical Shift (ppm)
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NH
O
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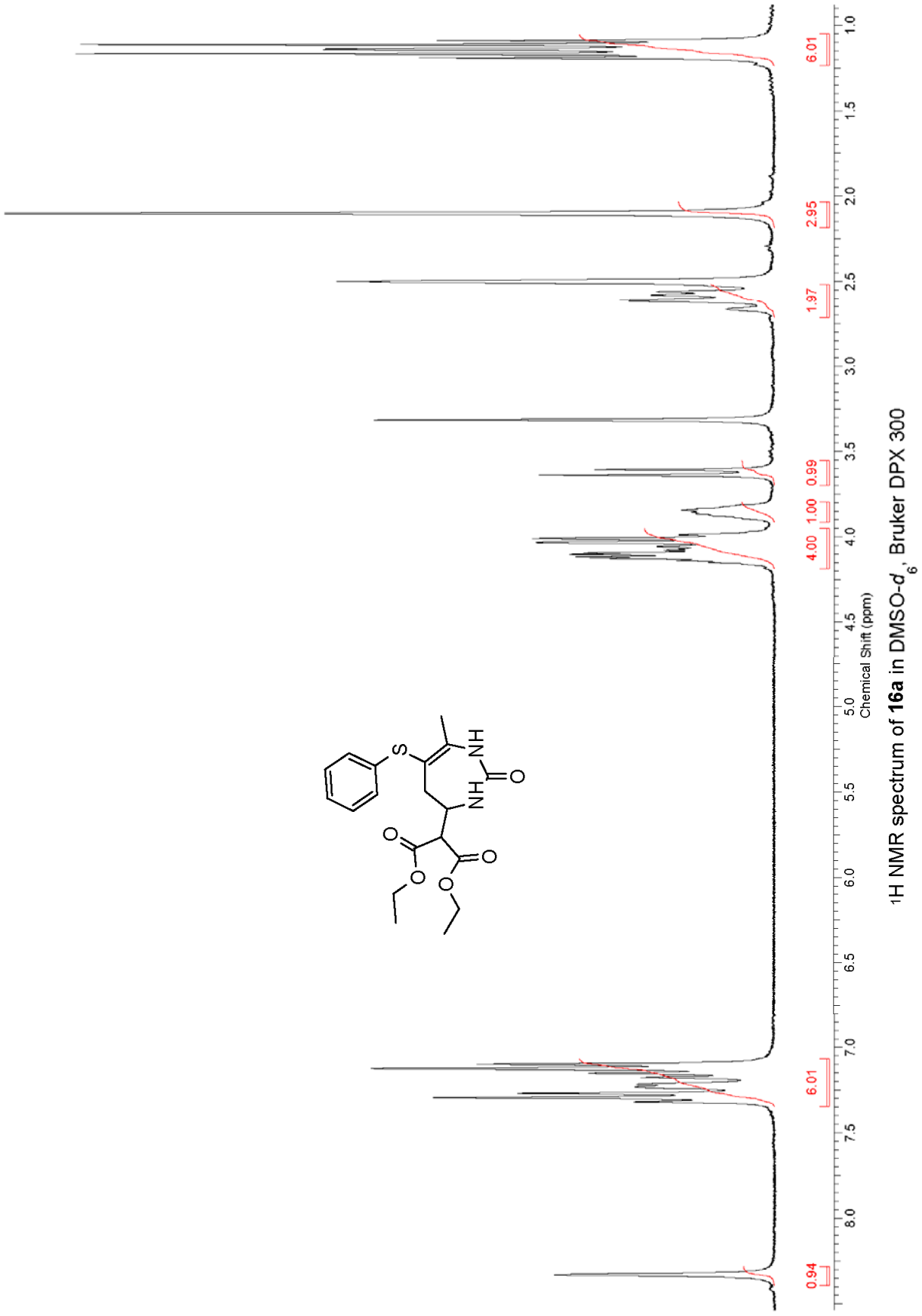

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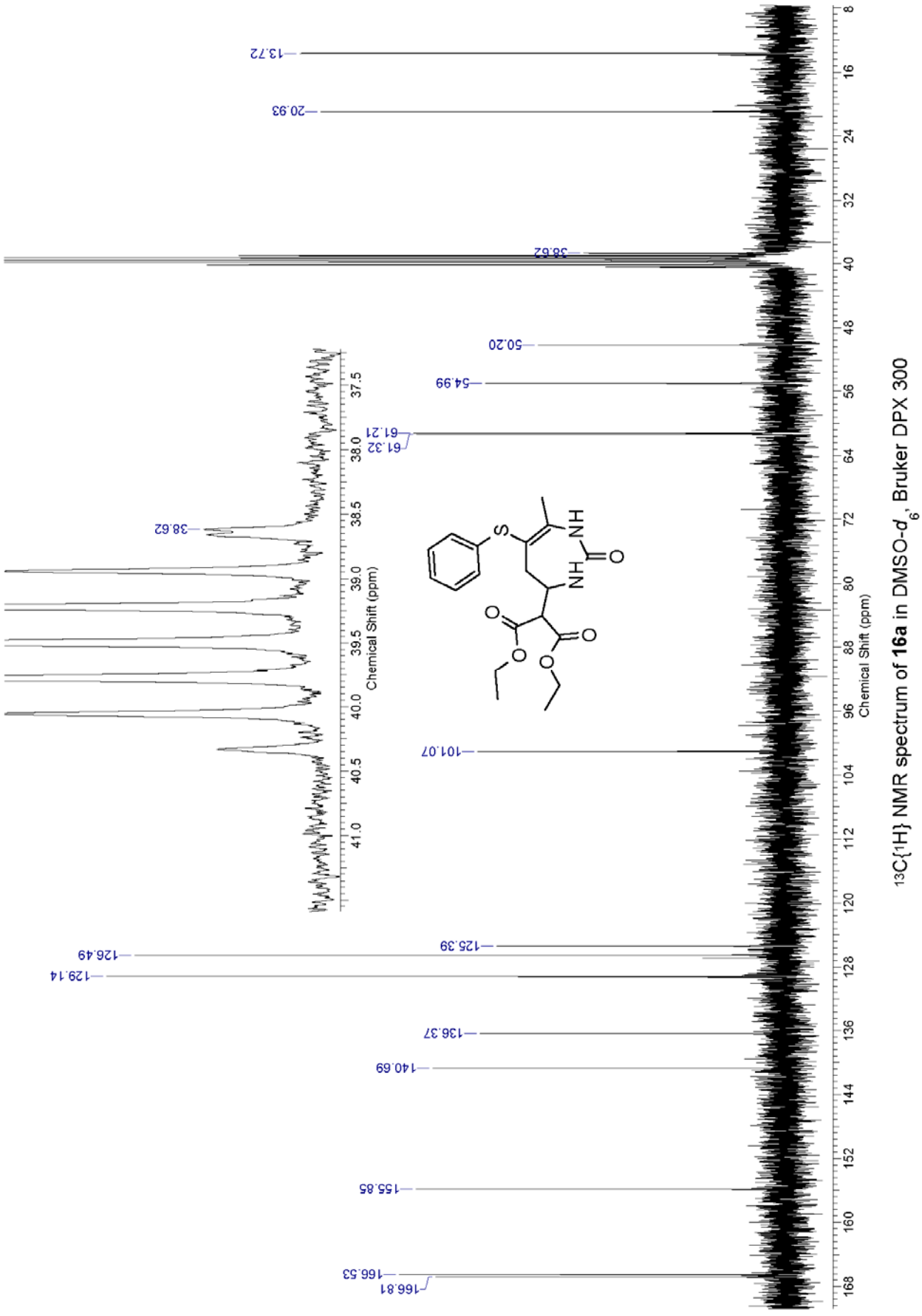

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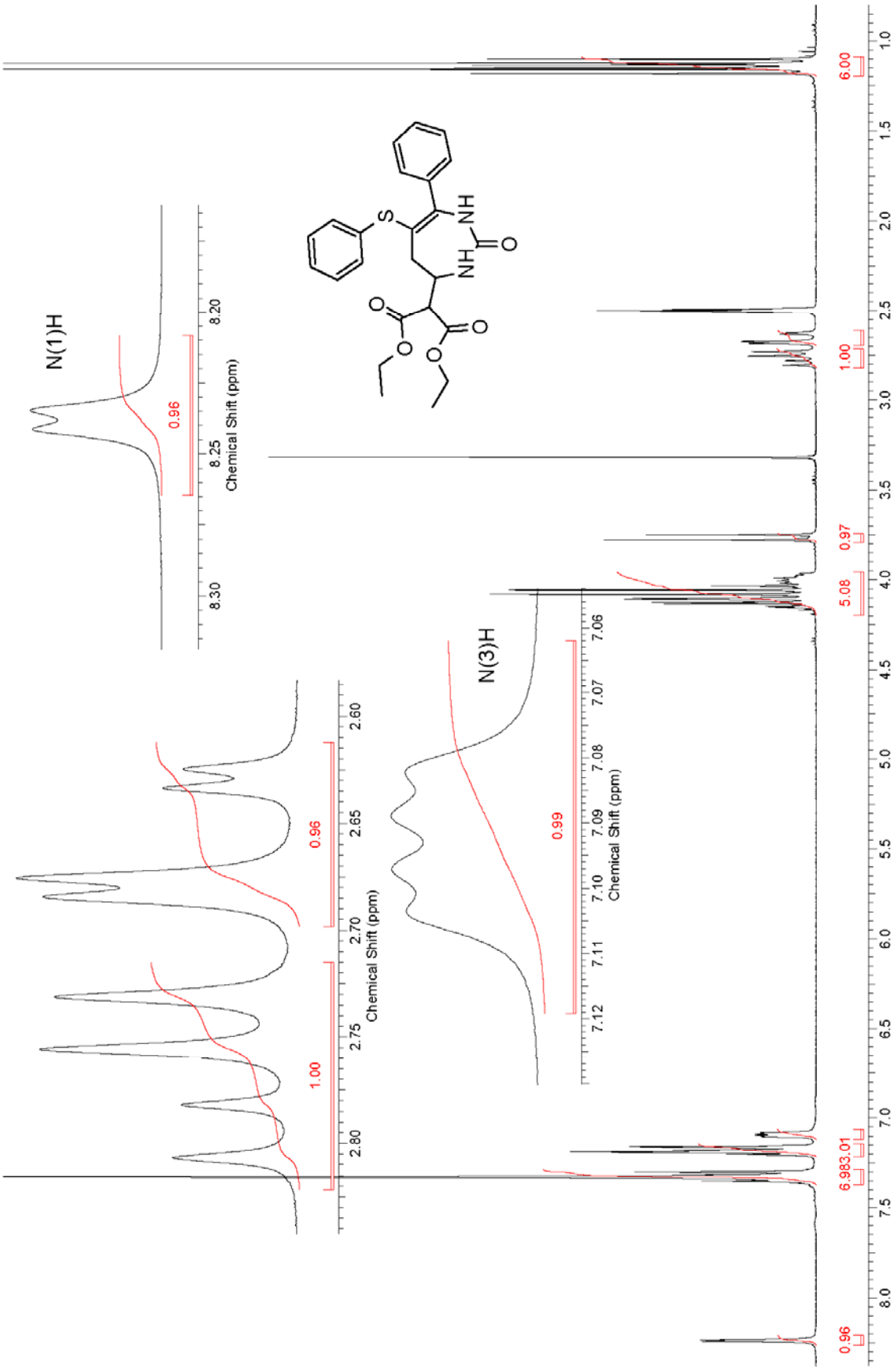

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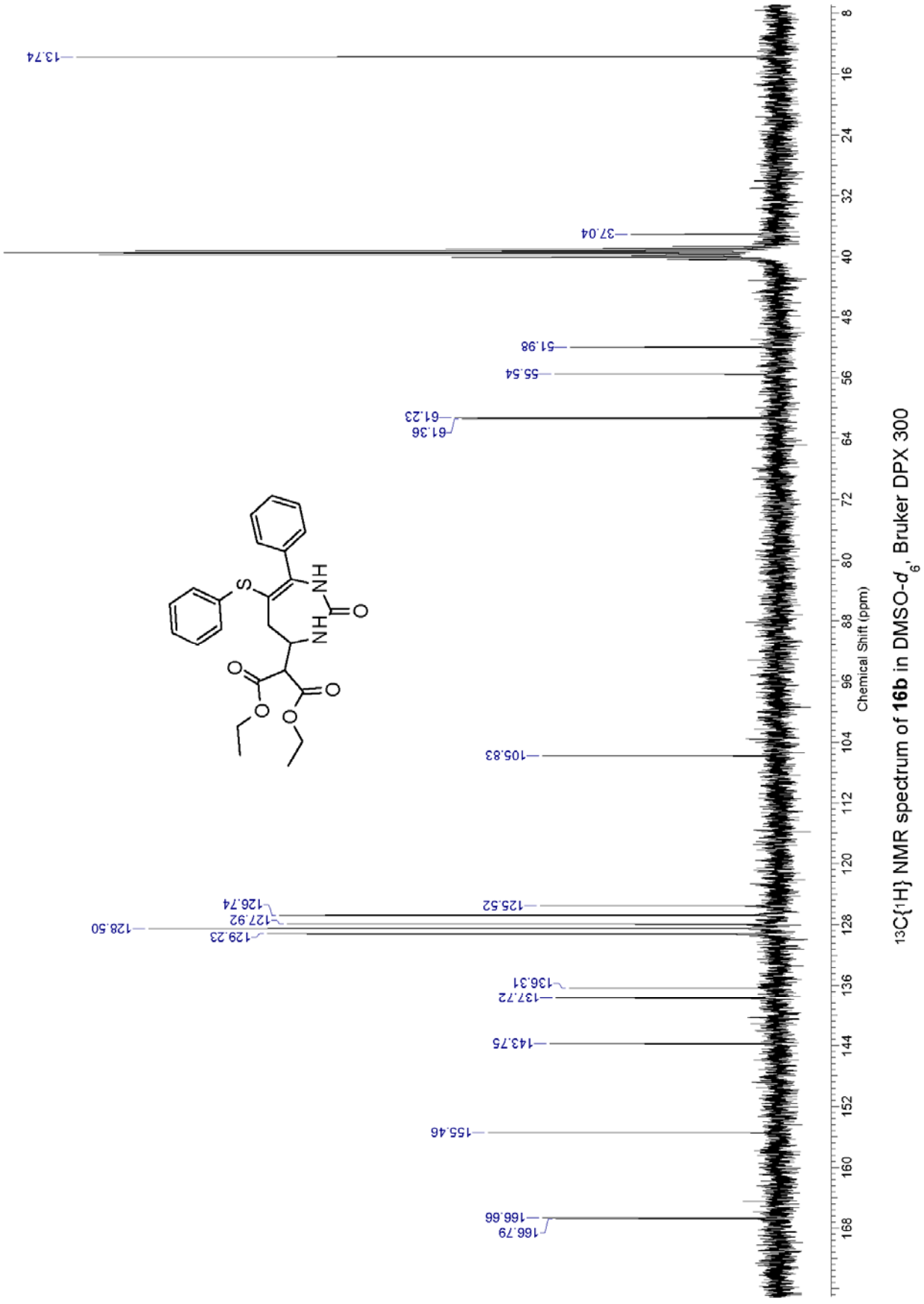
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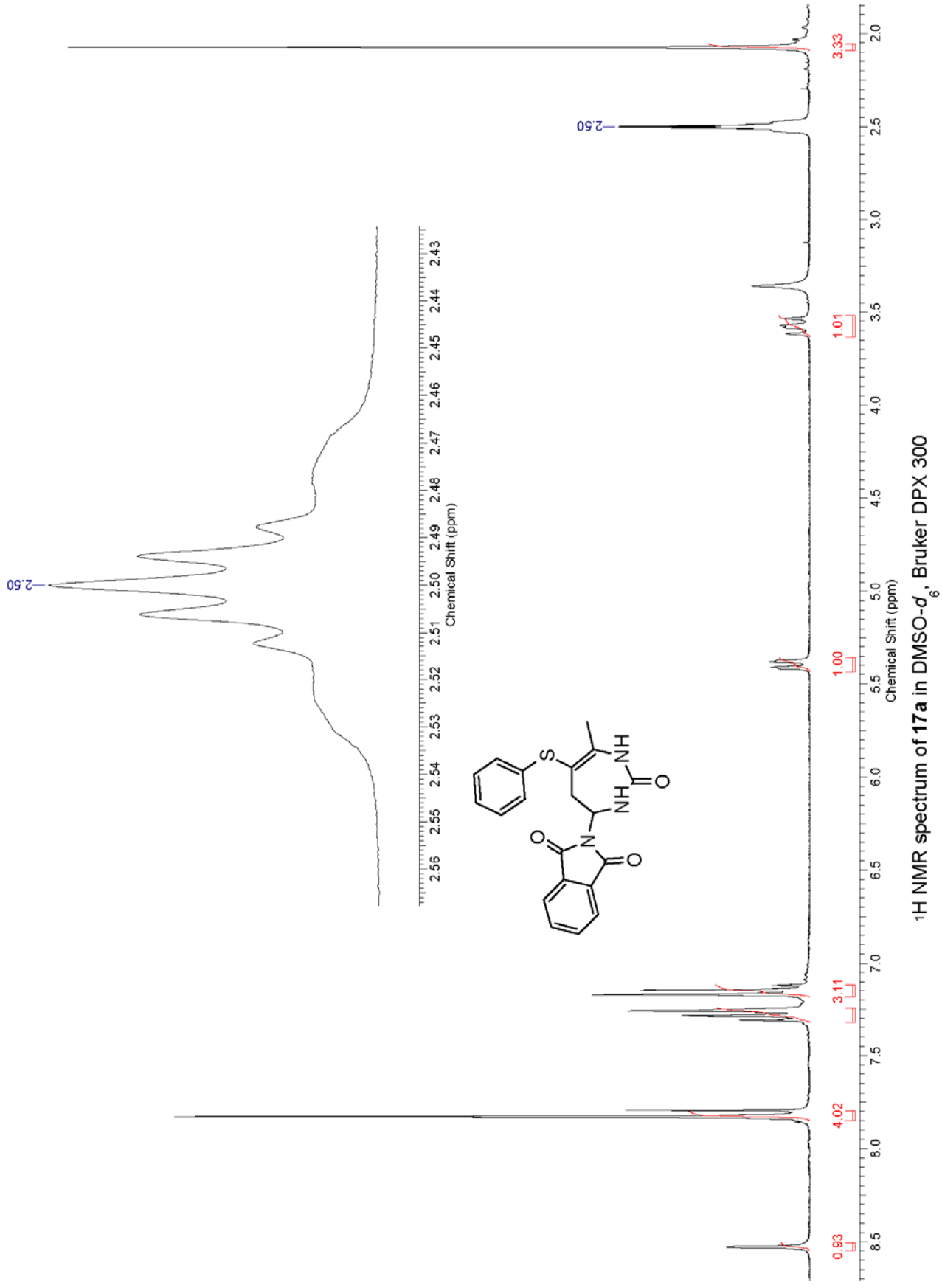
Chemical Shift (ppm)
13C{1H} NMR spectrum of 16b in DMSO-d6, Bruker DPX 300



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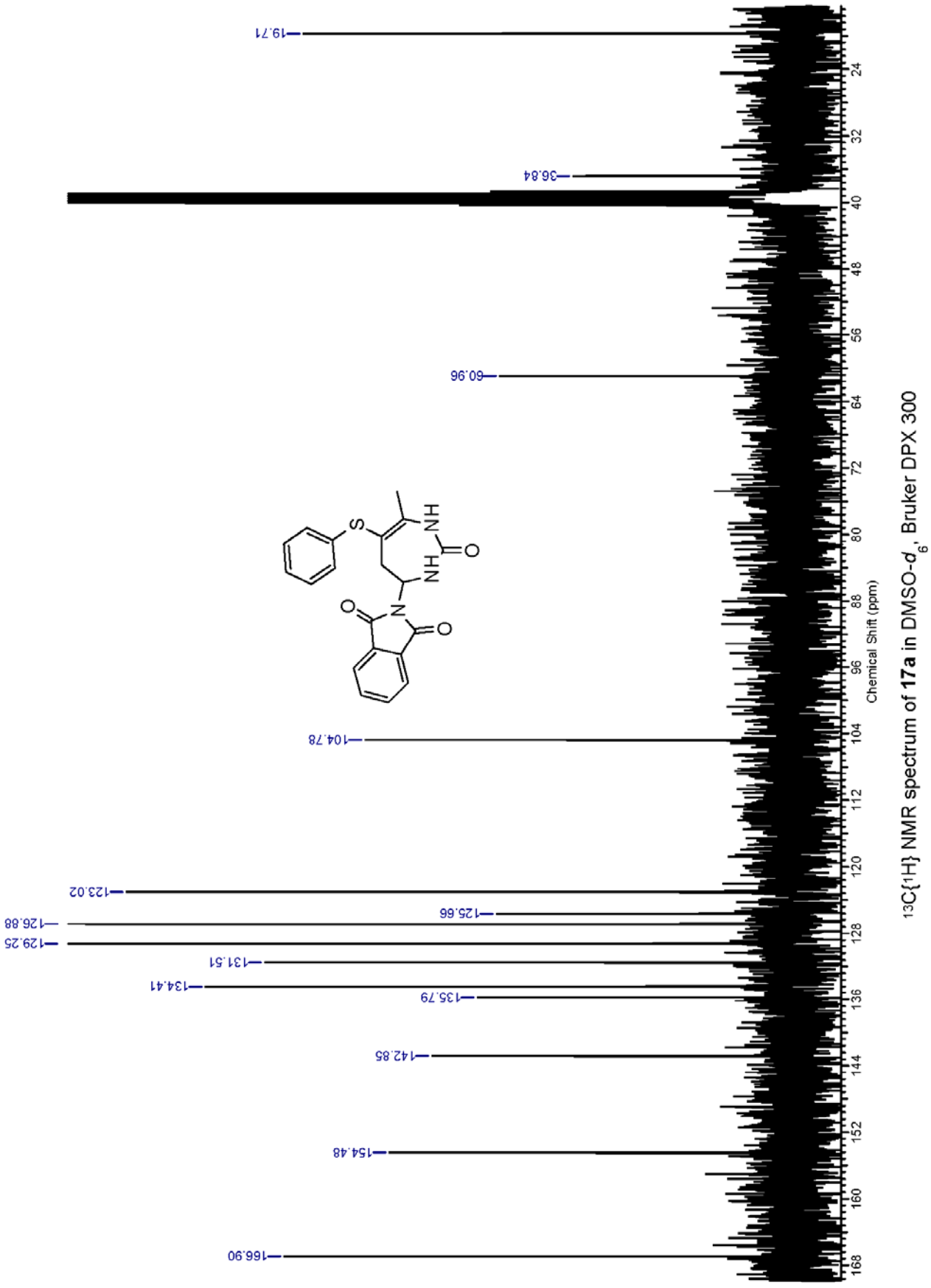
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129.25
131.51
134.41
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Chemical Shift (ppm)
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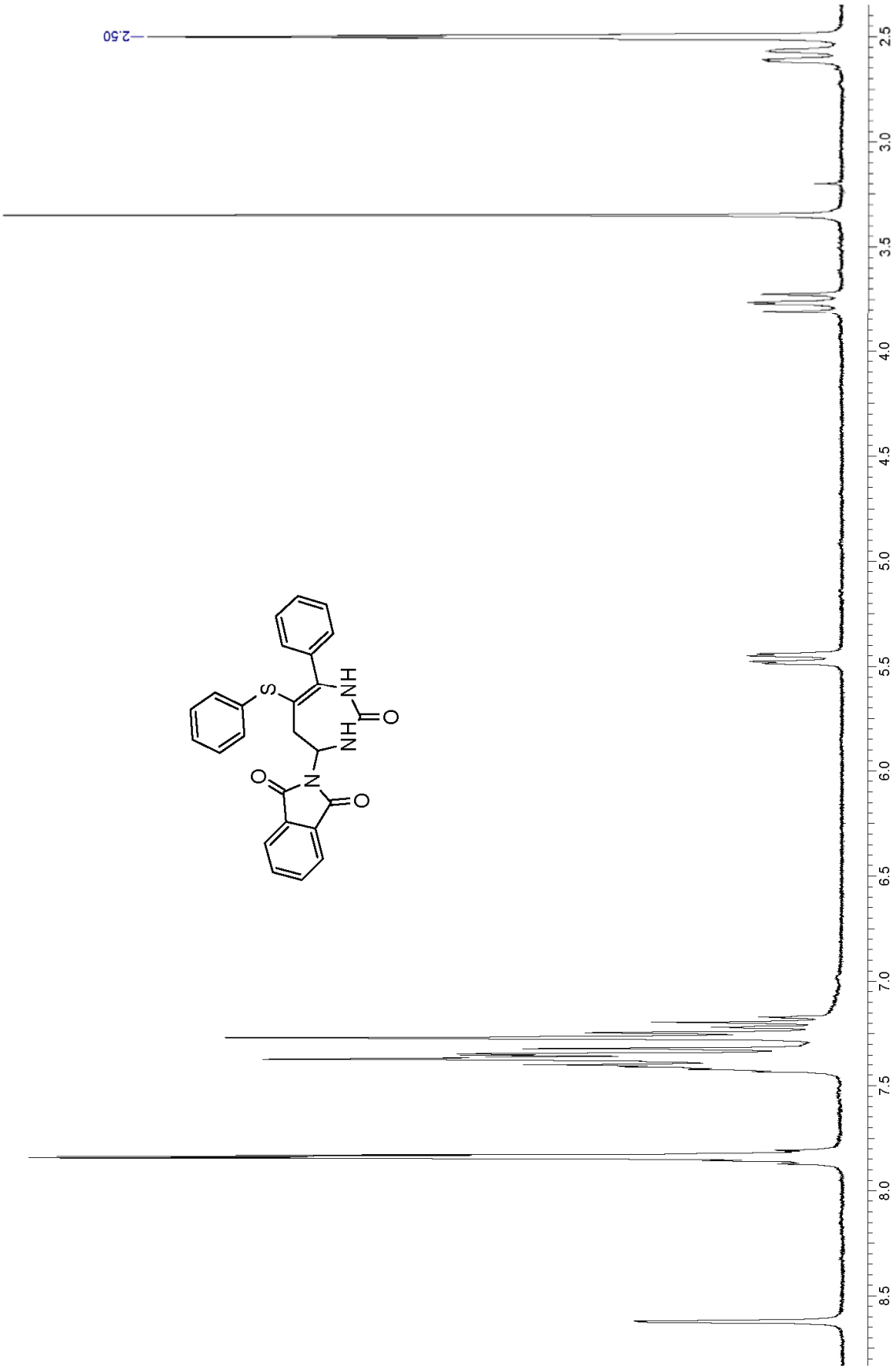

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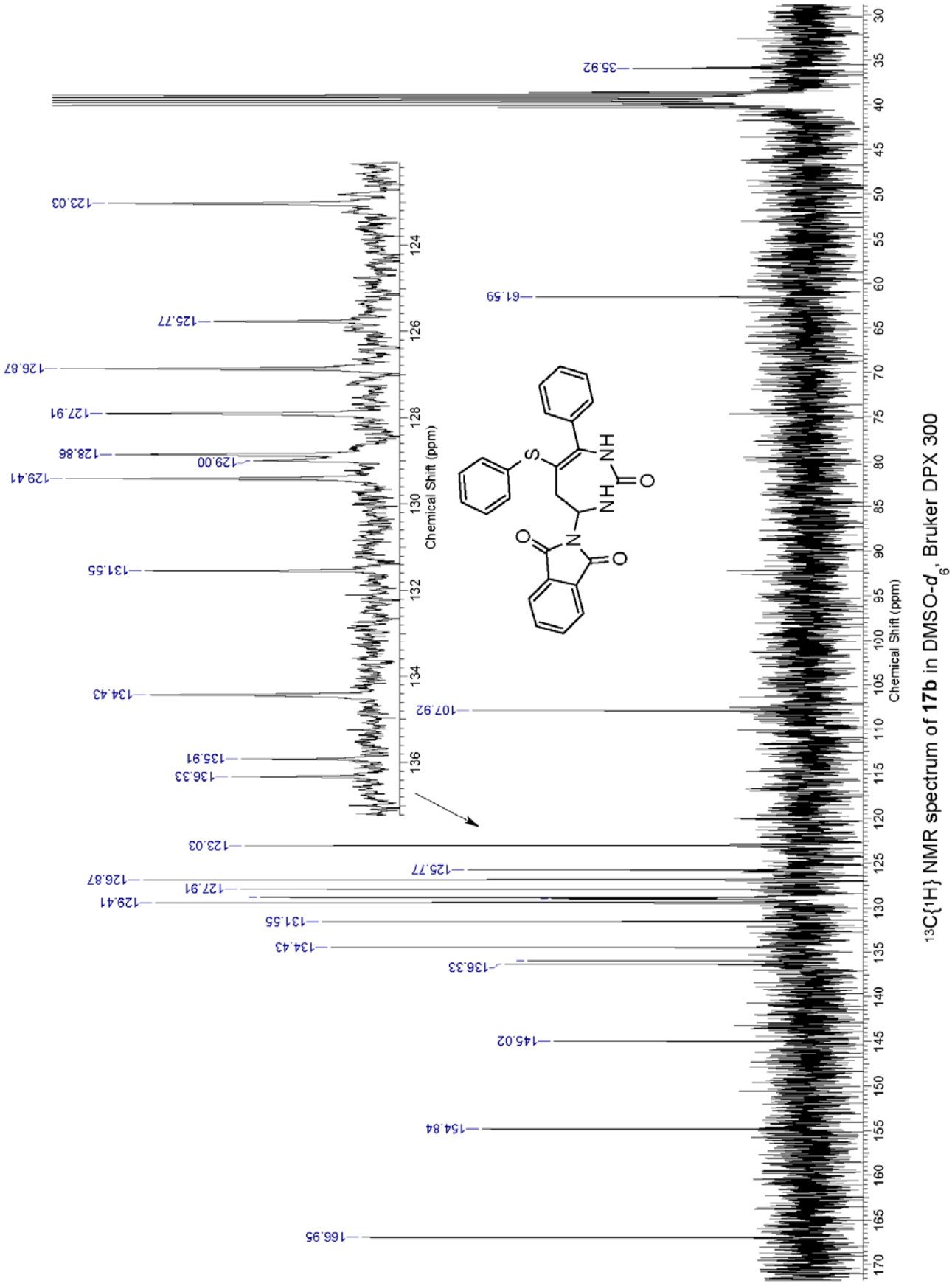
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154.84
166.95
Chemical Shift (ppm)
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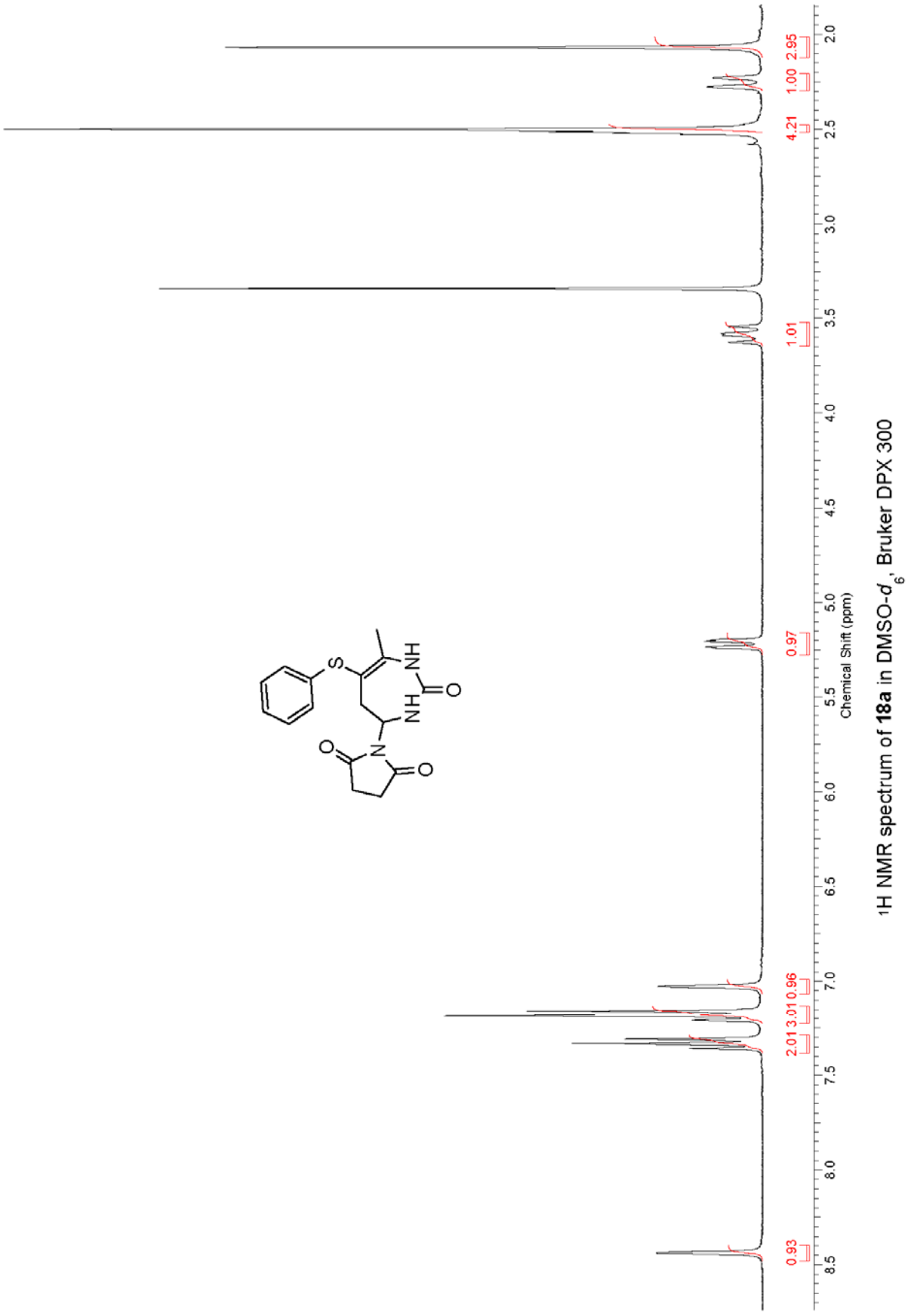

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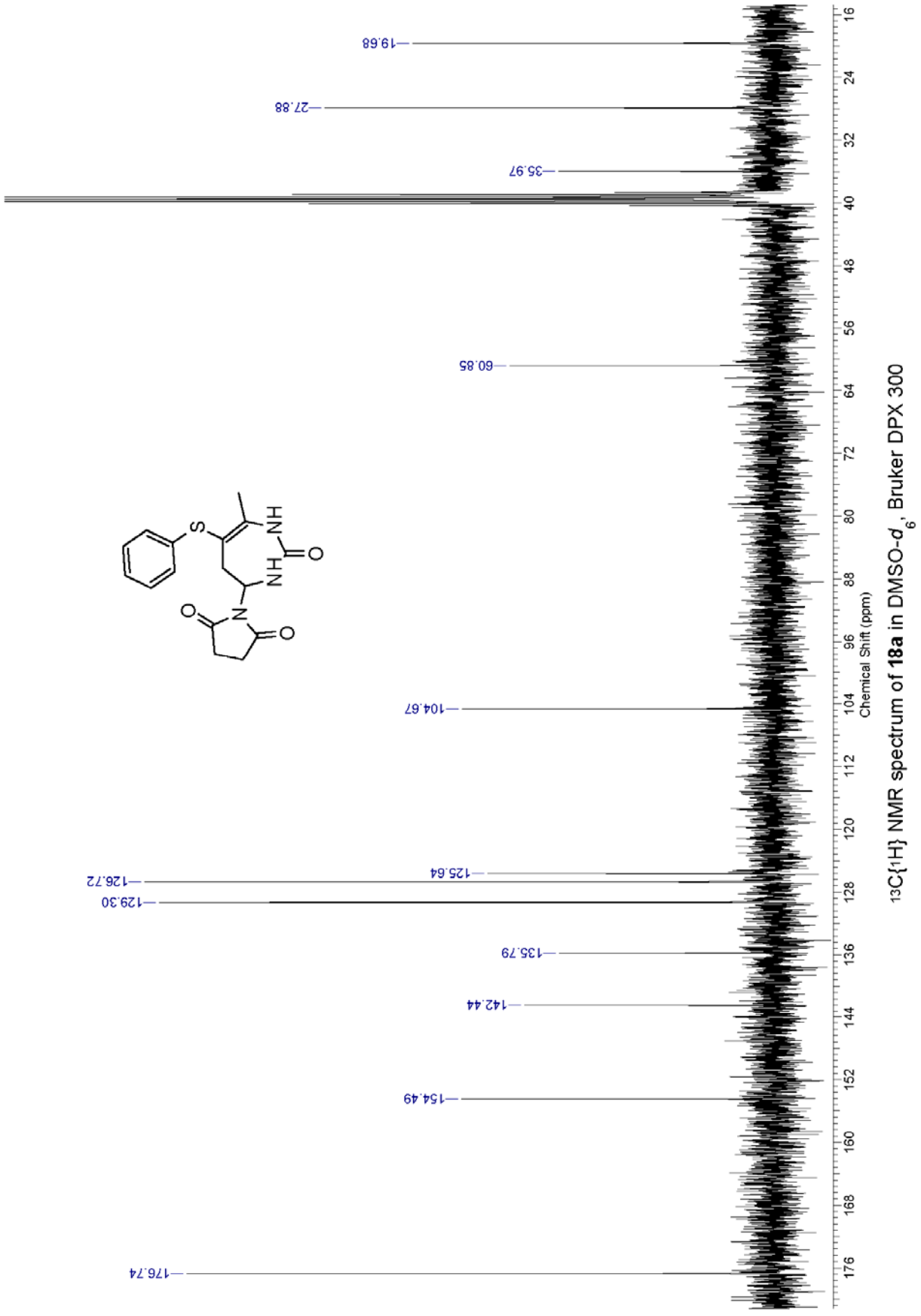
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Chemical Shift (ppm)
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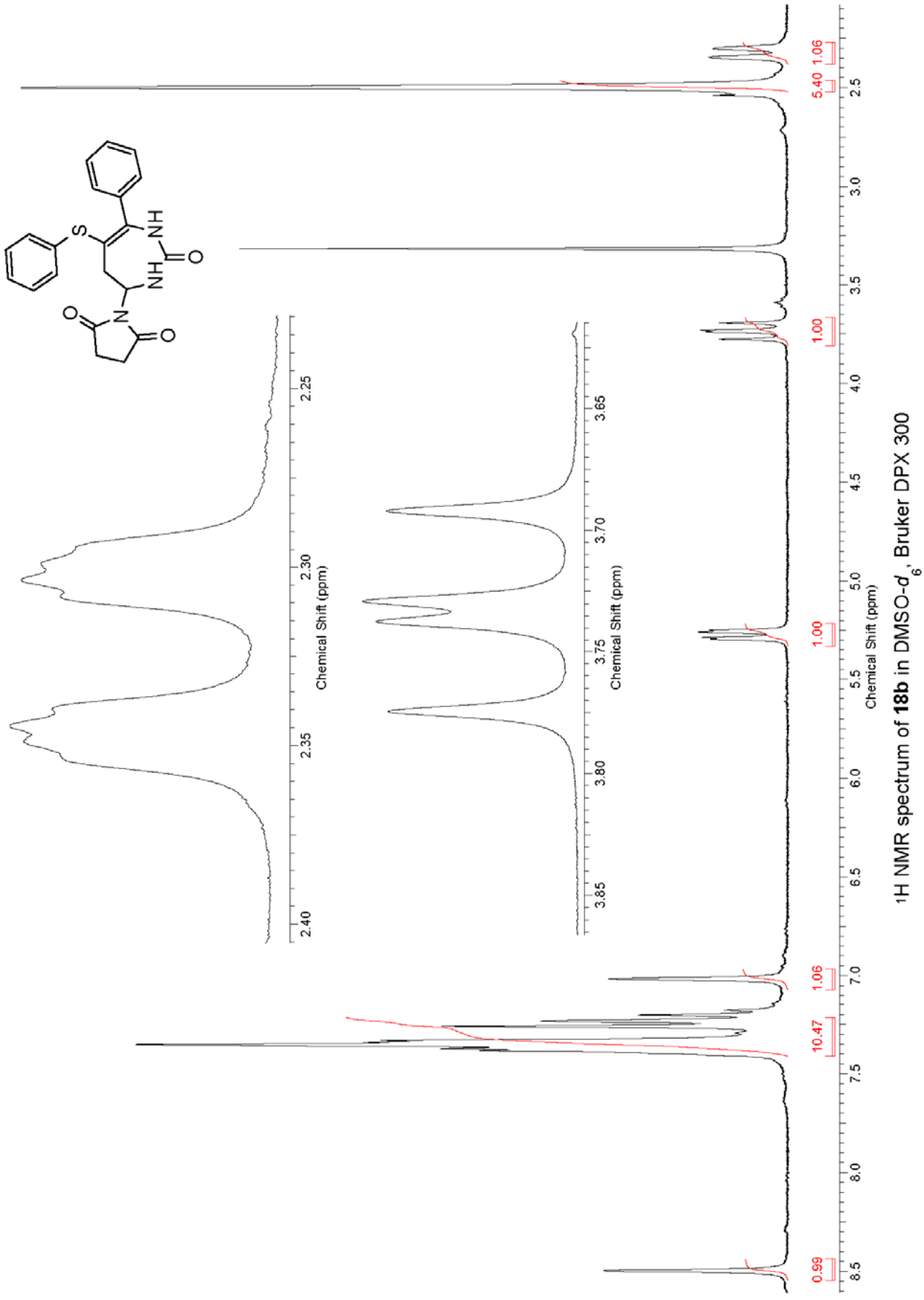

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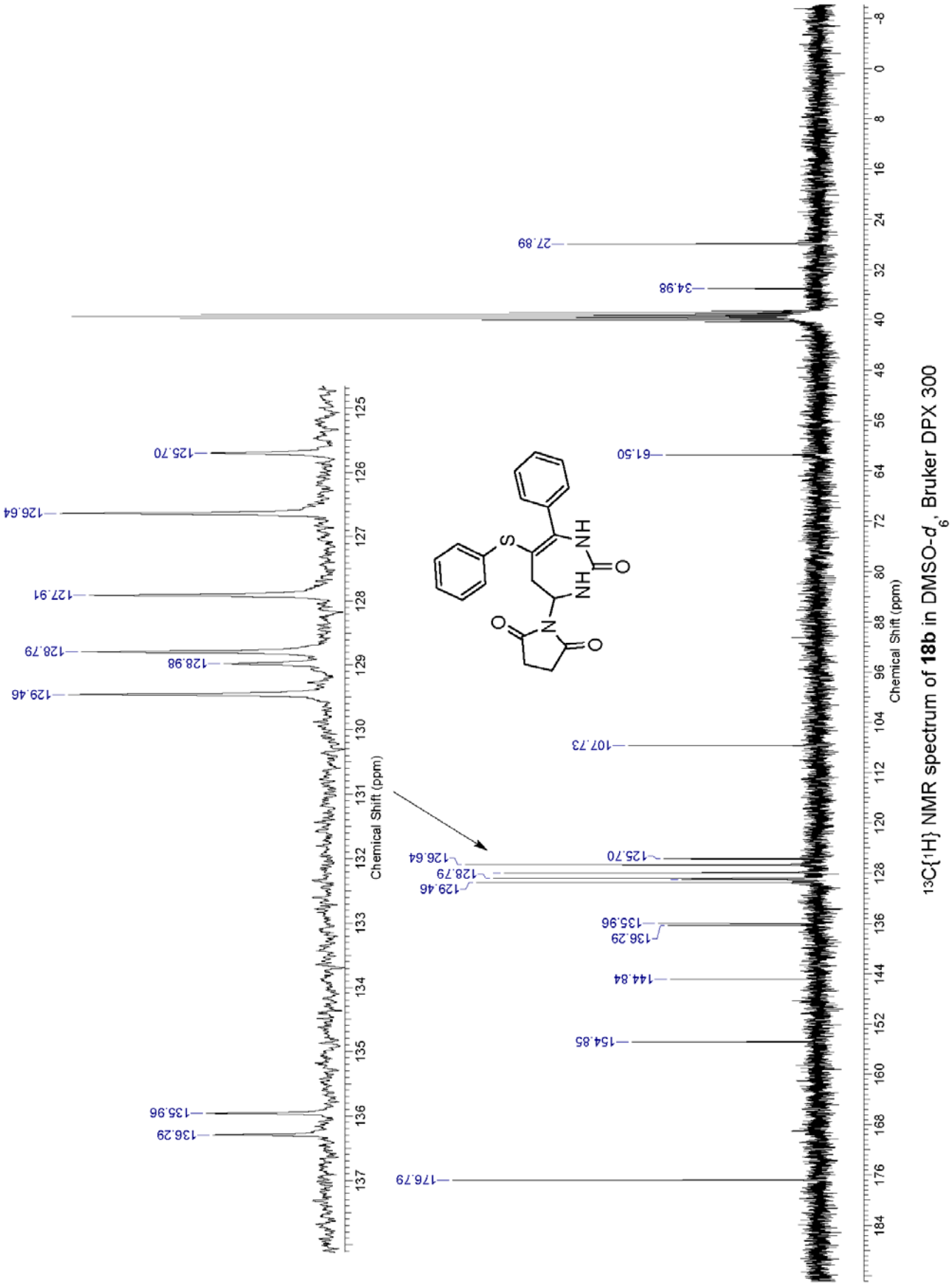
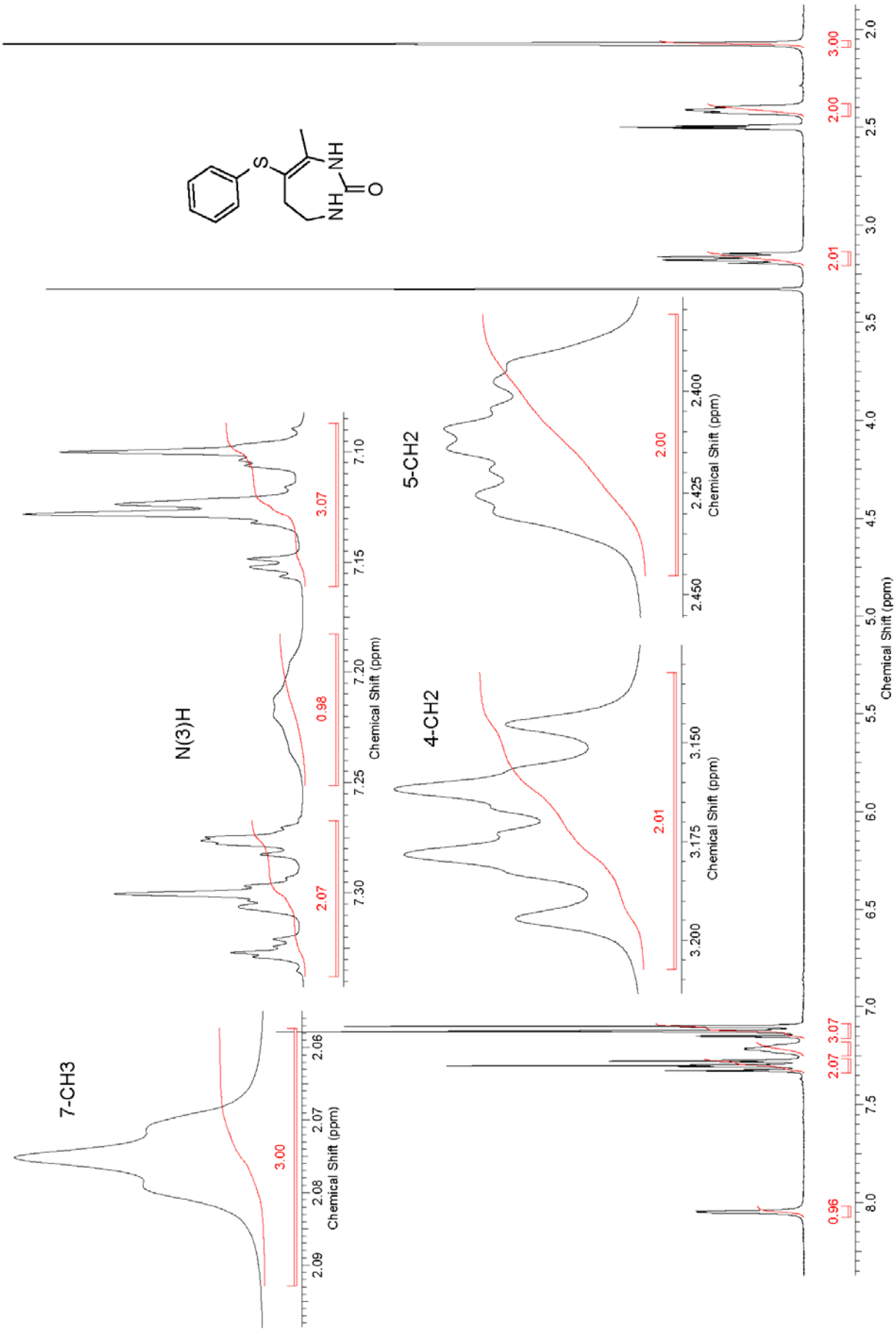
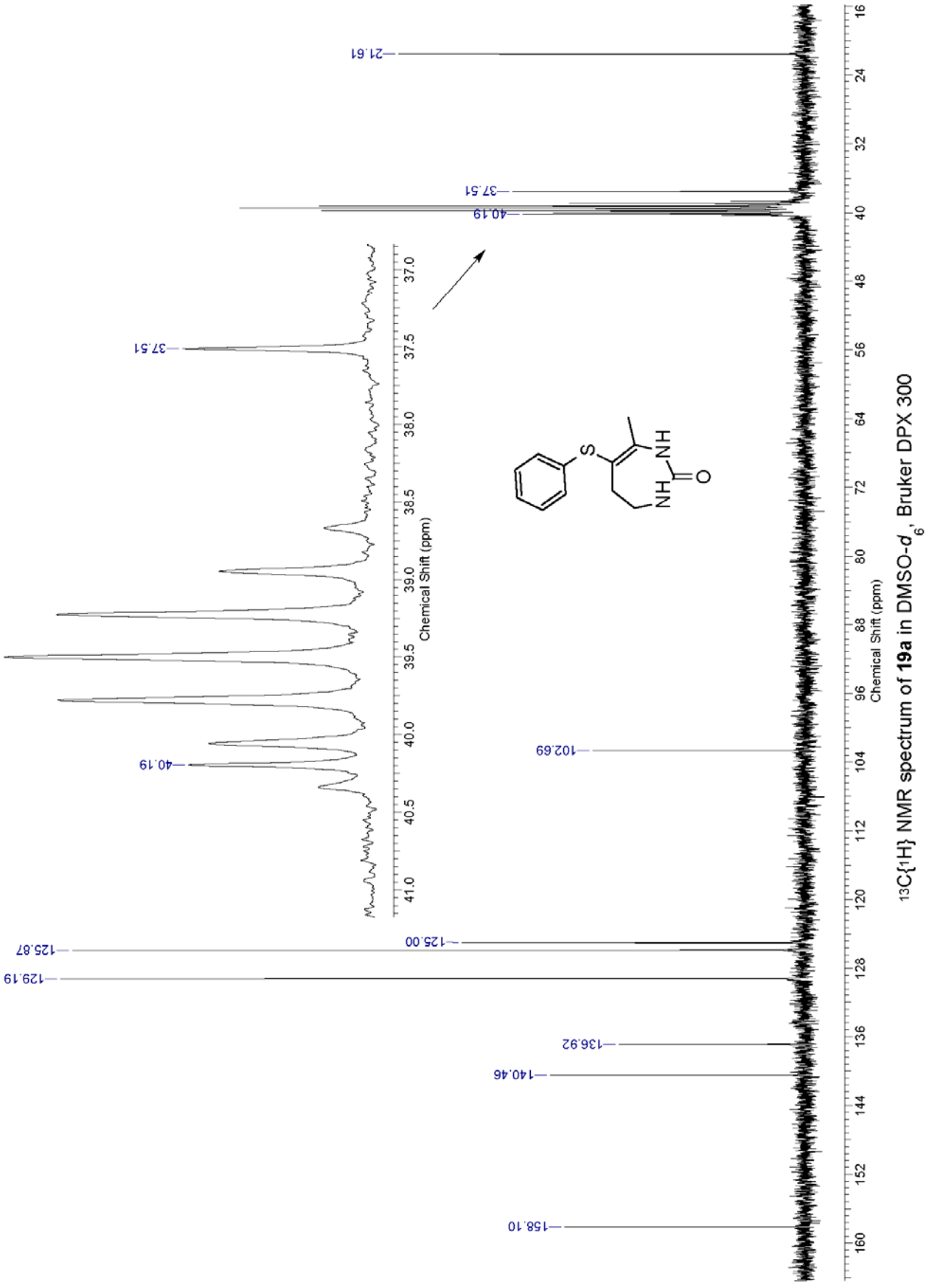
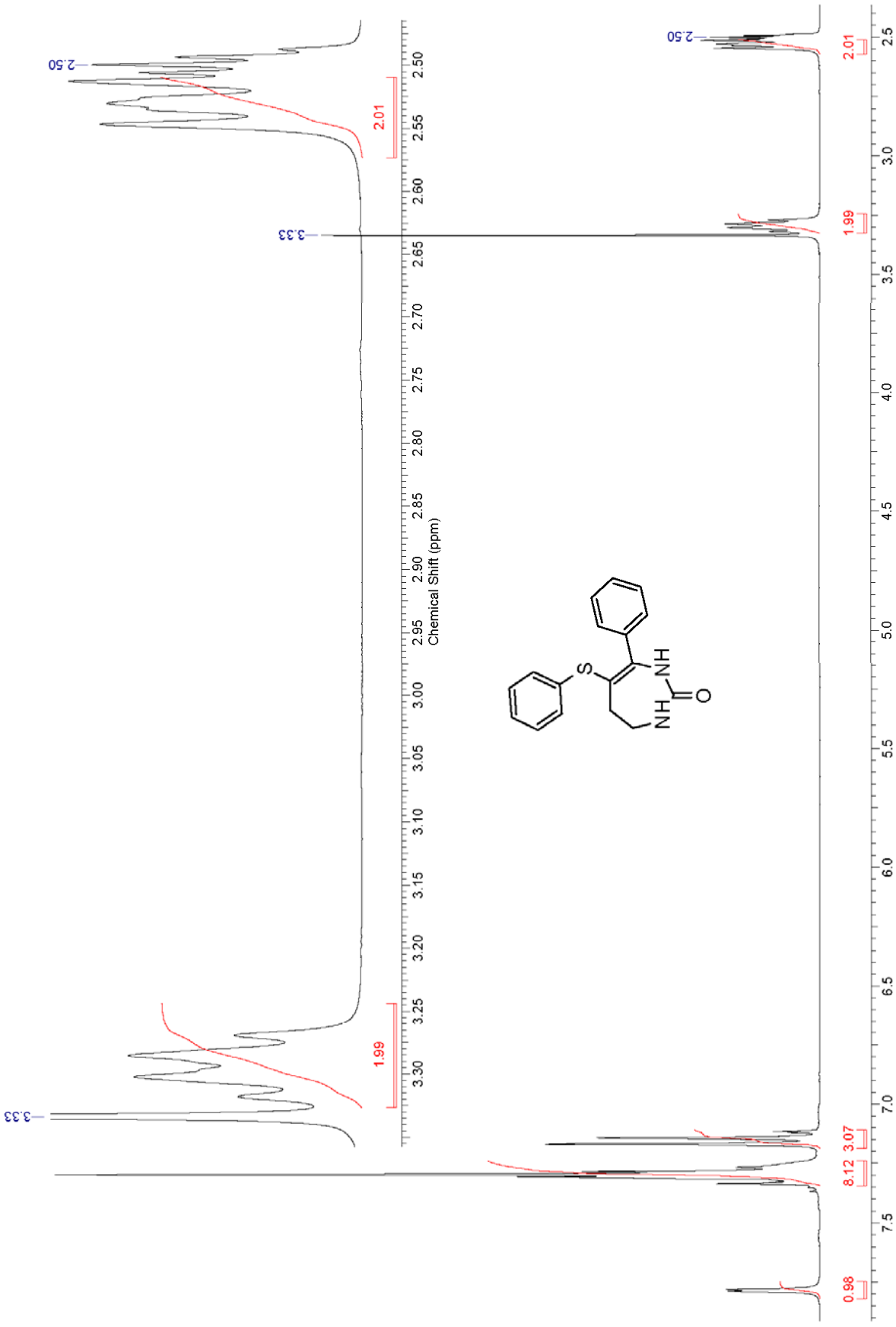

27.89
34.98
61.50
107.73
125.70
126.64
128.79
129.46
135.96
136.29
144.84
154.85
176.79
Chemical Shift (ppm)
Chemical Shift (ppm)
NH
NH
O
O
O
N
S
13C{1H} NMR spectrum of 18b in DMSO-d6, Bruker DPX 300

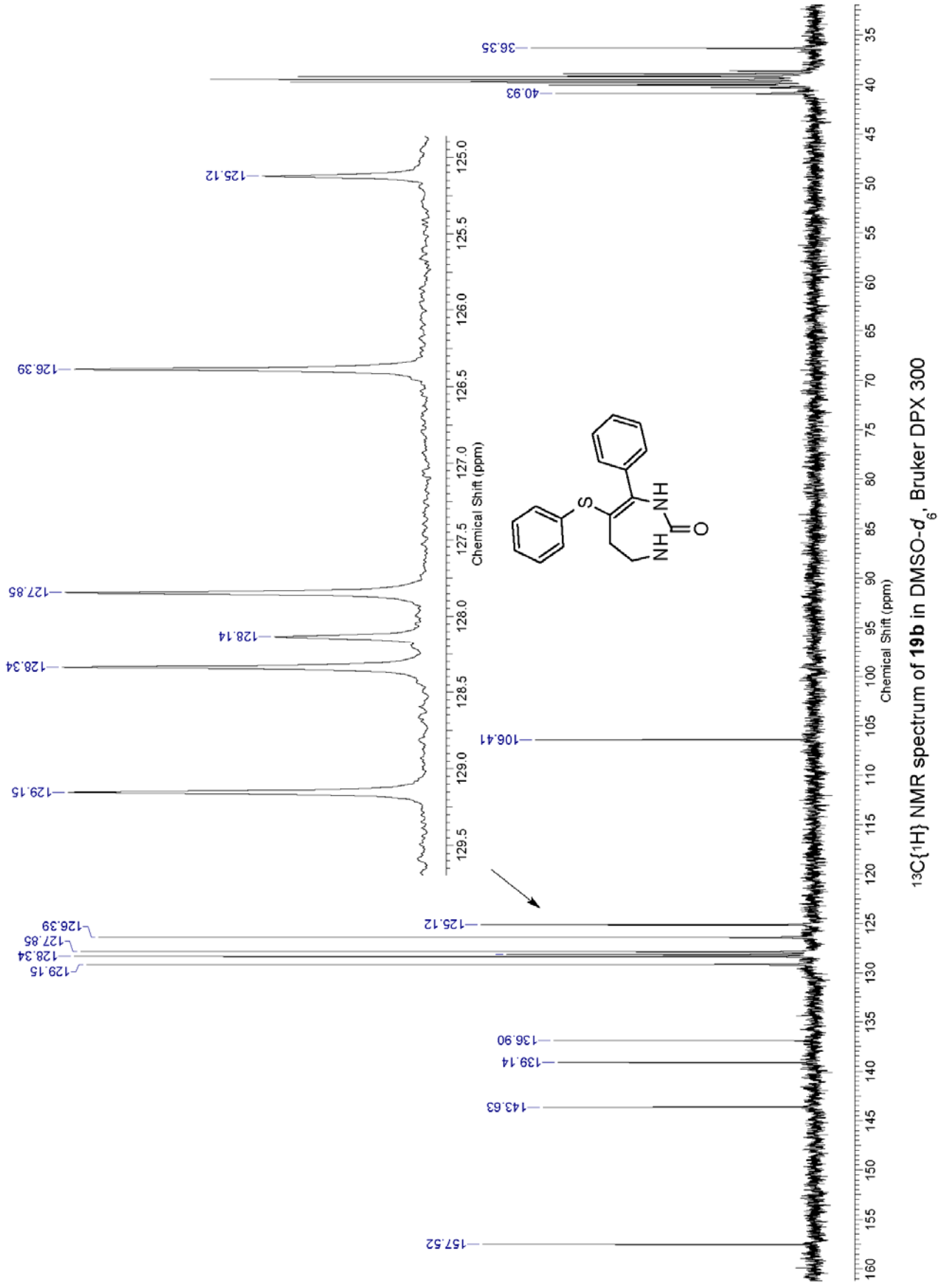


^{1}H NMR spectrum of **19a** in DMSO-d_6, Bruker DPX 300

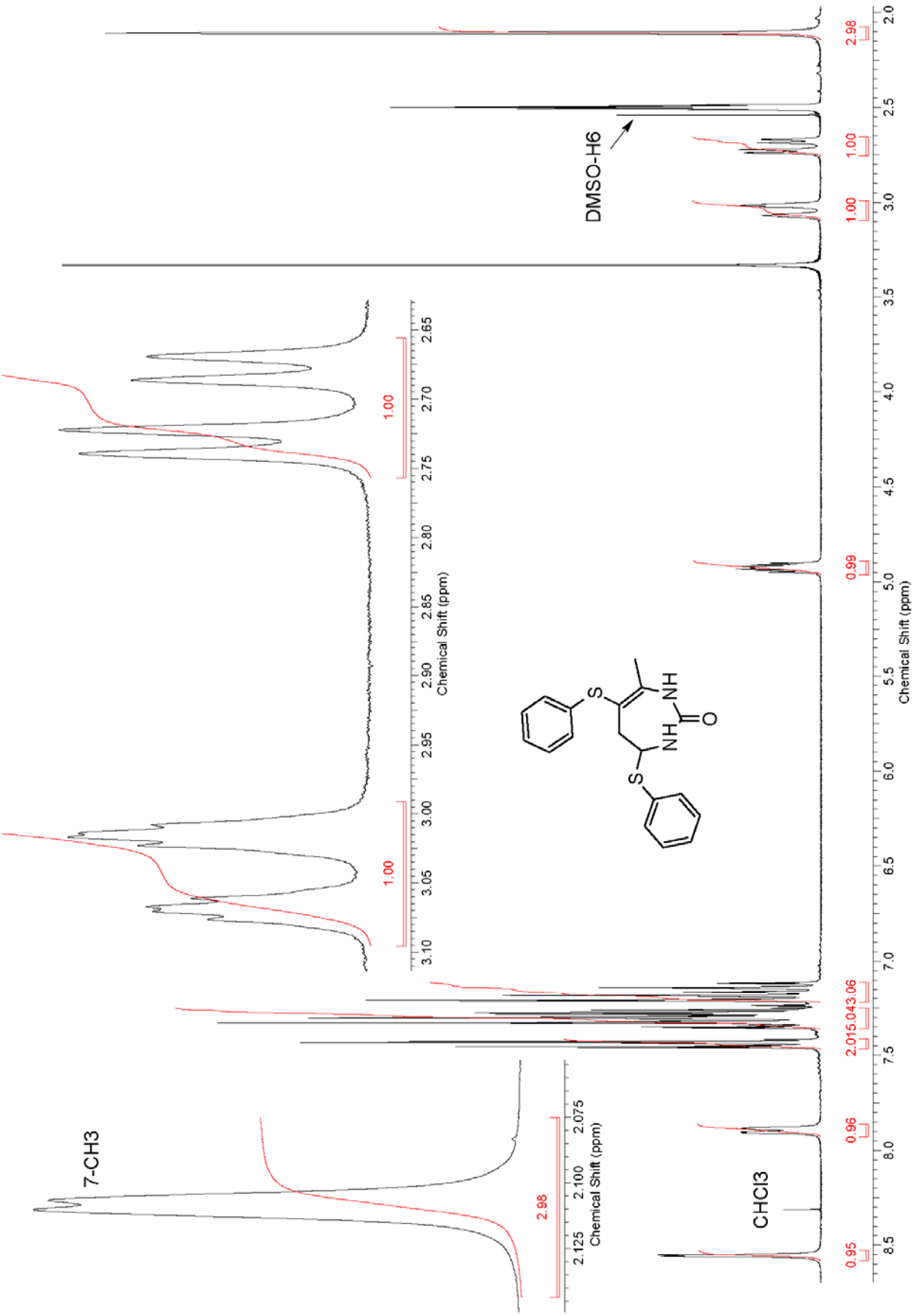

21.61
37.51
40.19
125.00
125.87
129.19
136.92
140.46
158.10
102.69
Chemical Shift (ppm)
$^{13}C\{^1H\}$ NMR spectrum of **19a** in DMSO-d_6, Bruker DPX 300



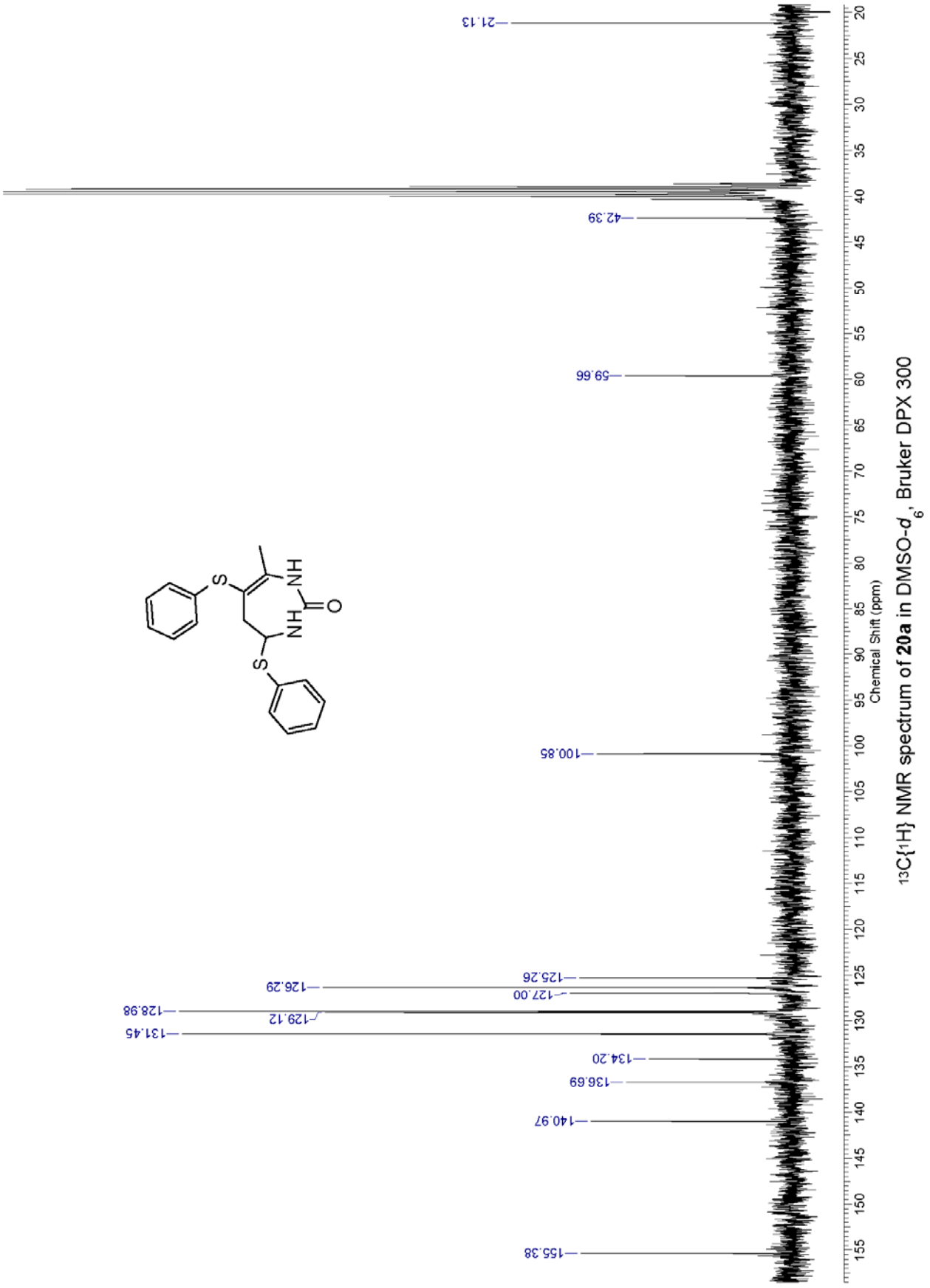
^{1}H NMR spectrum of **19b** in DMSO-d_6, Bruker DPX 300

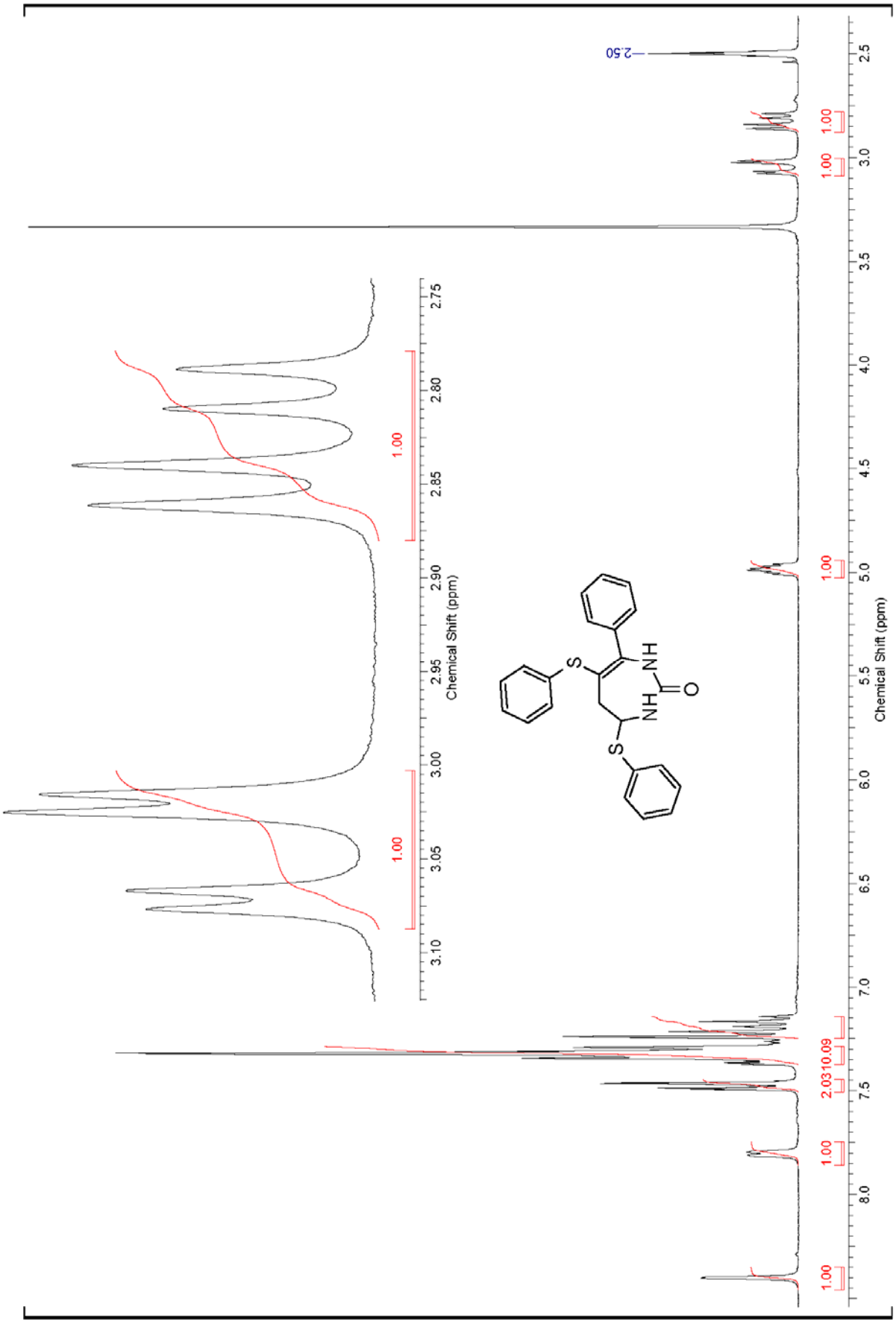


$^{13}C\{^1H\}$ NMR spectrum of **19b** in DMSO-d_6, Bruker DPX 300

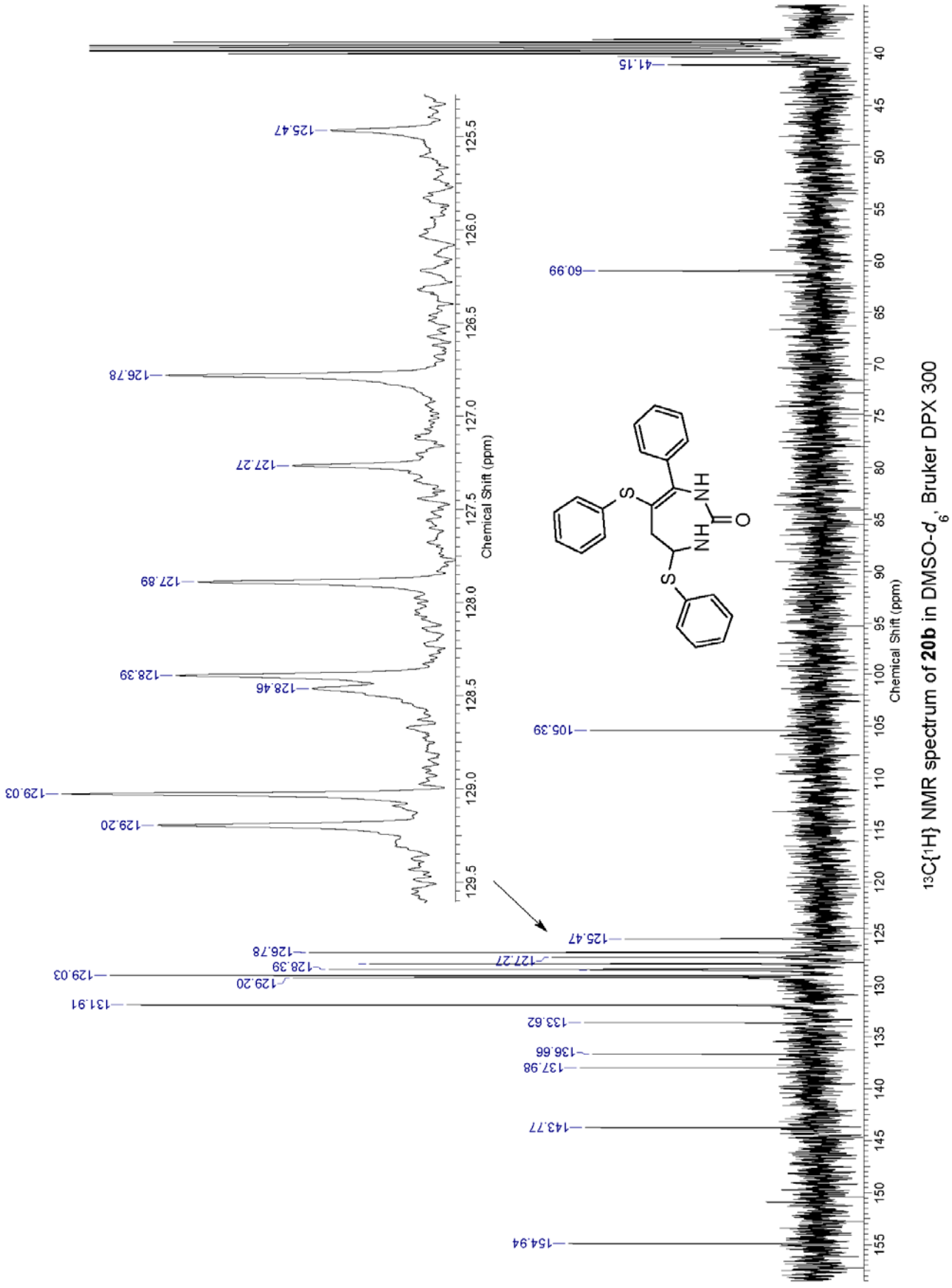


1H NMR spectrum of **20a** in DMSO-d_6, Bruker DPX 300

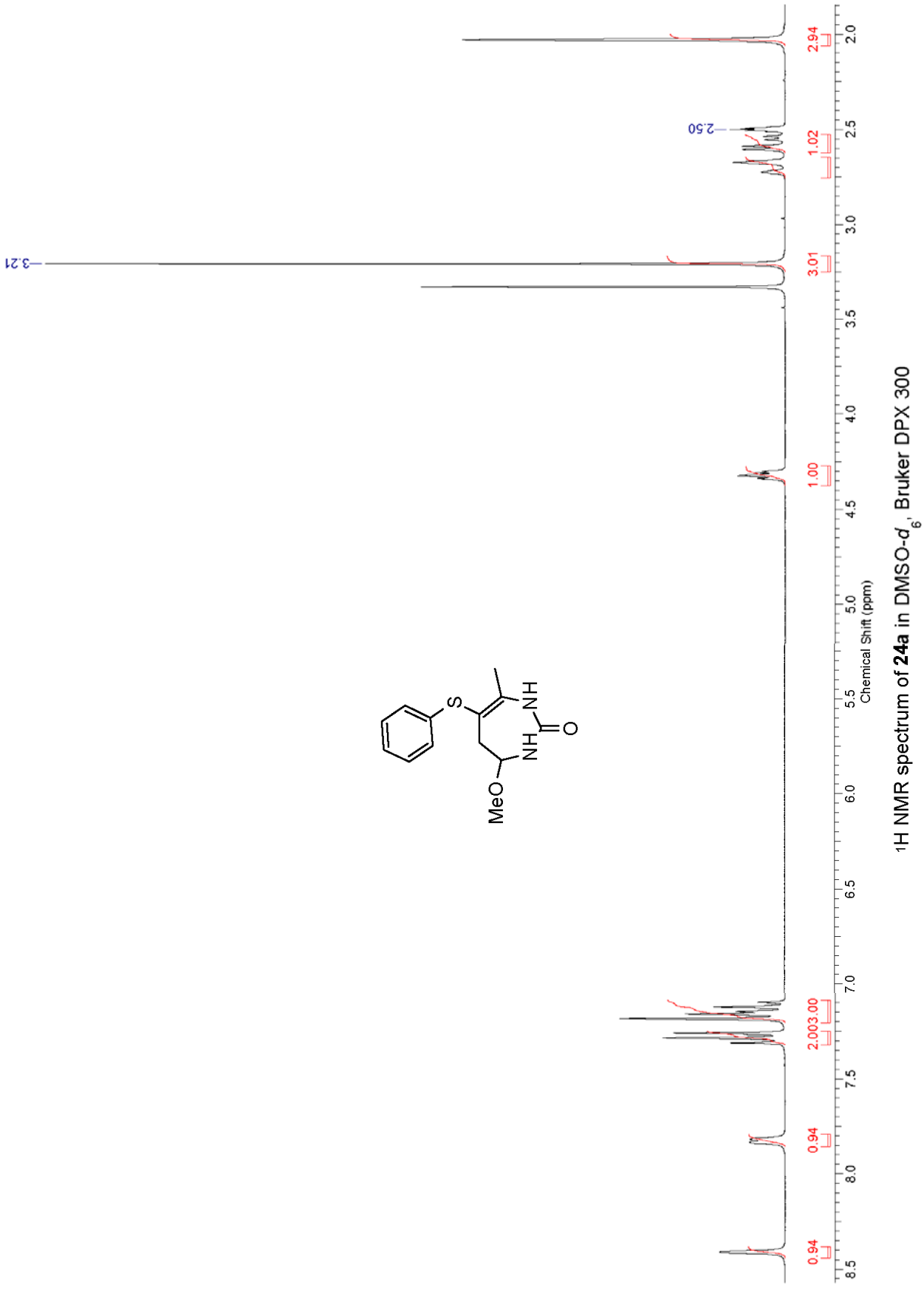

21.13
42.39
59.66
100.85
125.26
126.29
127.00
128.98
129.12
131.45
134.20
136.69
140.97
155.38
Chemical Shift (ppm)
13C{1H} NMR spectrum of 20a in DMSO-d6, Bruker DPX 300



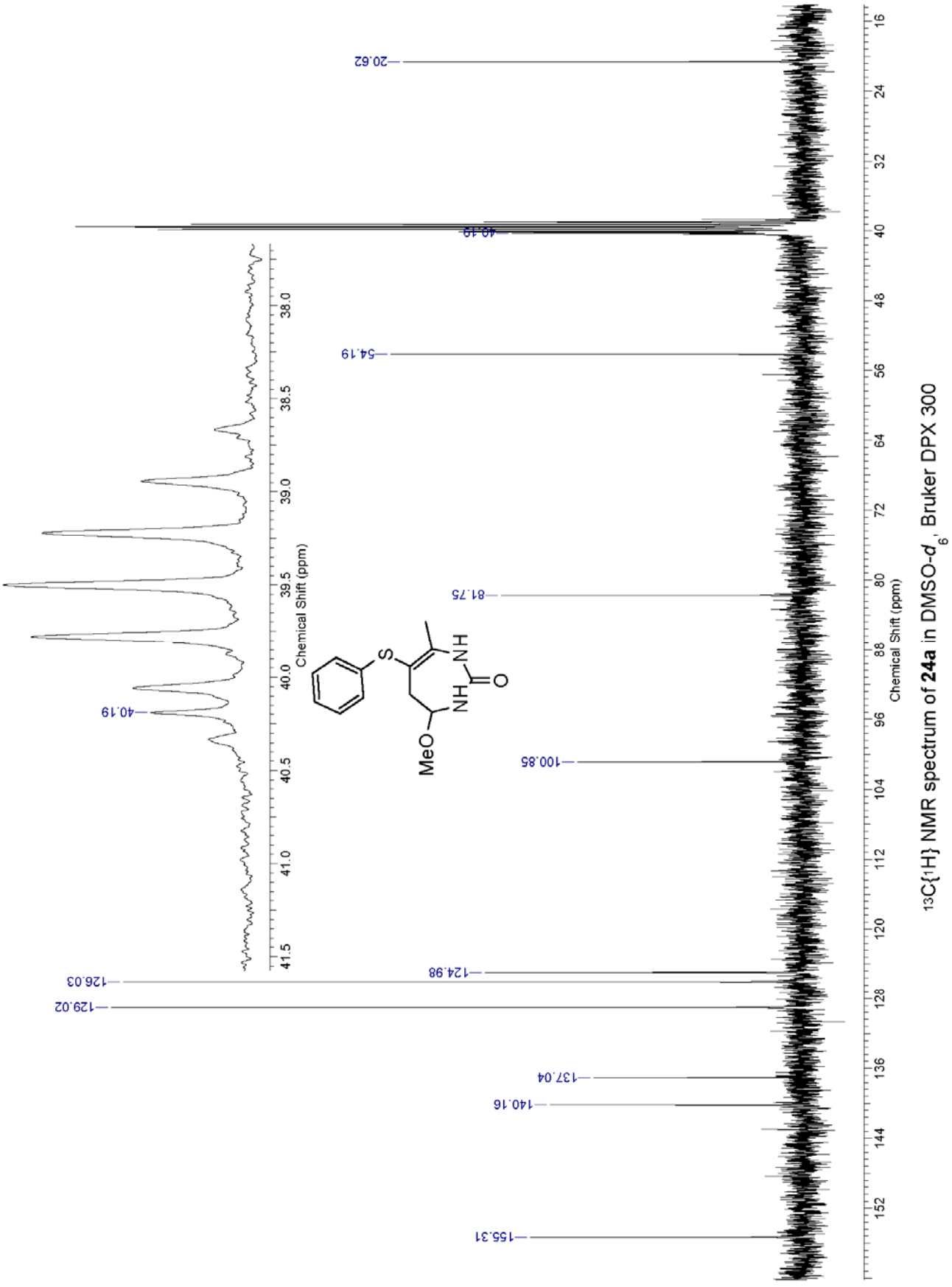
^{1}H NMR spectrum of **20b** in DMSO-d_6, Bruker DPX 300



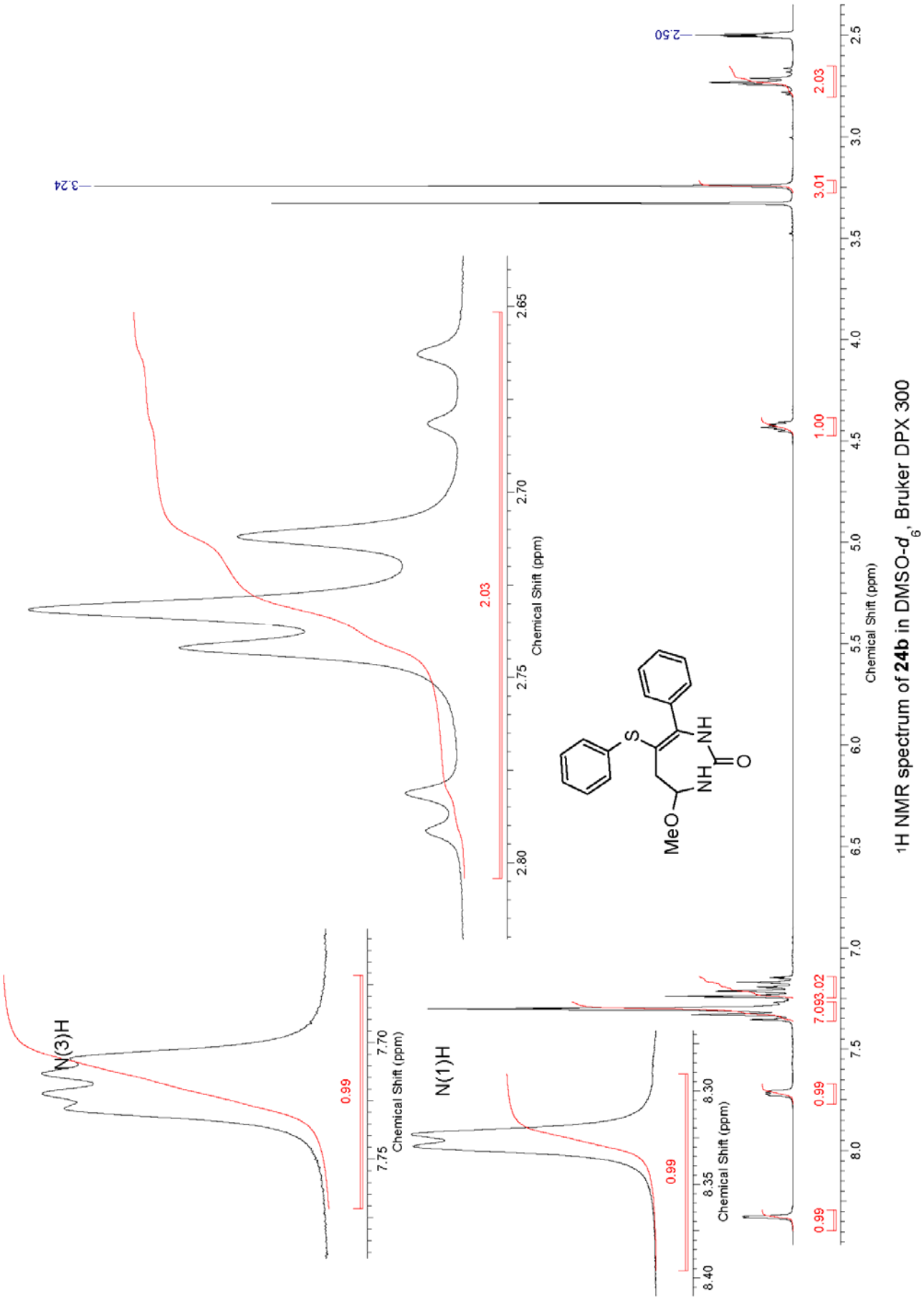
$^{13}C\{^{1}H\}$ NMR spectrum of **20b** in DMSO-d_6, Bruker DPX 300



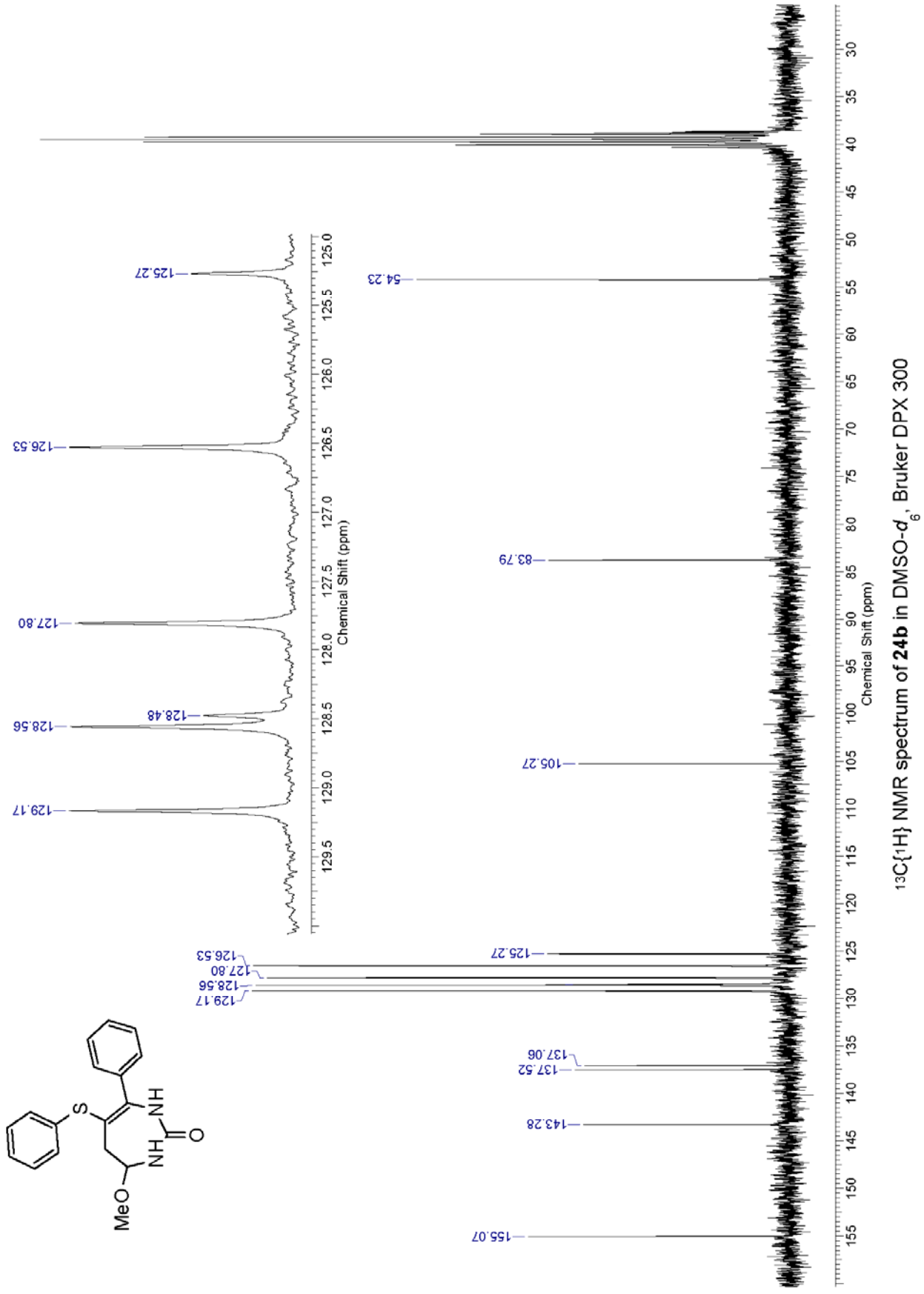
^{1}H NMR spectrum of **24a** in DMSO-d_6, Bruker DPX 300

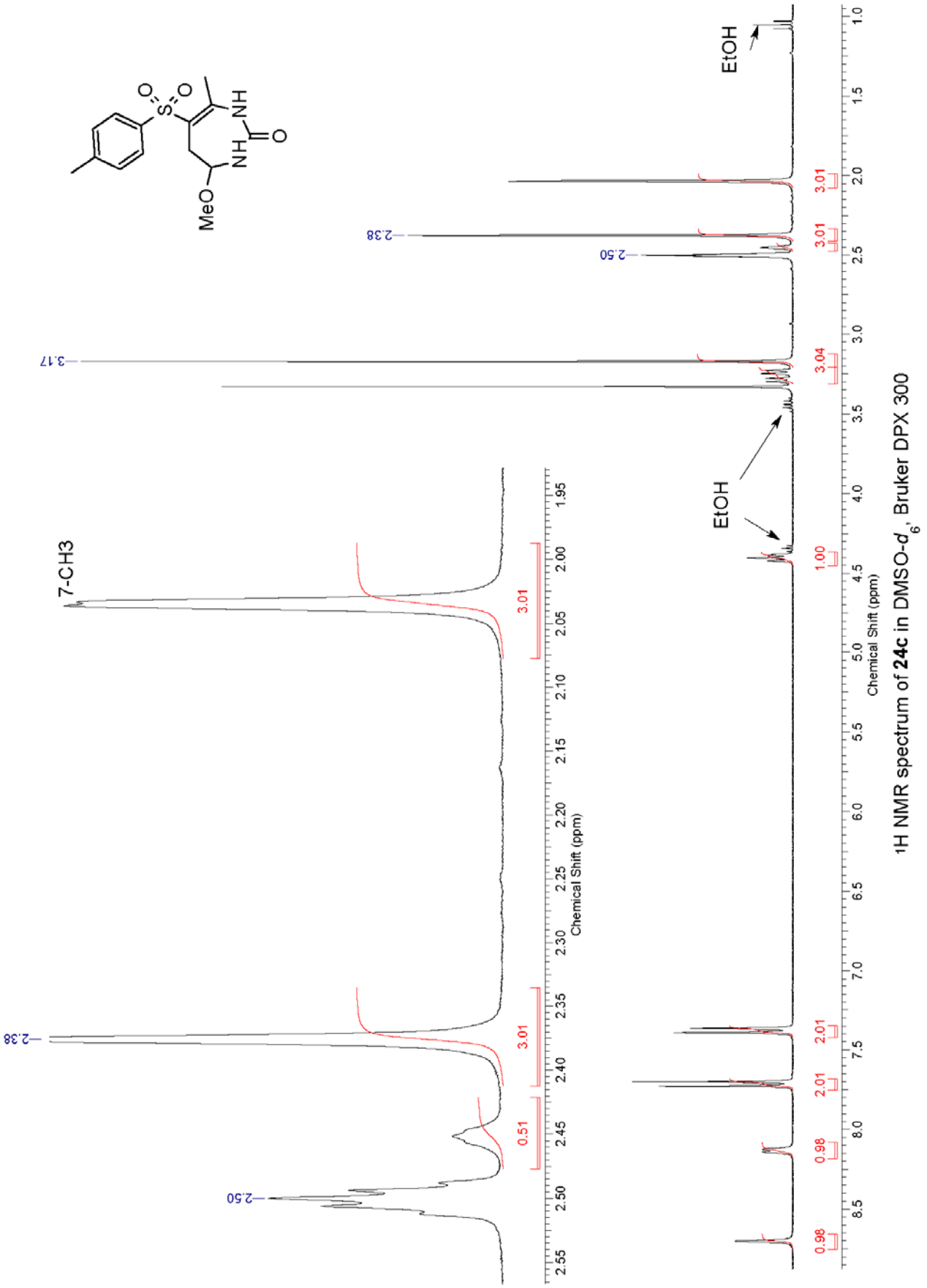


$^{13}C\{^{1}H\}$ NMR spectrum of **24a** in DMSO-d_6, Bruker DPX 300

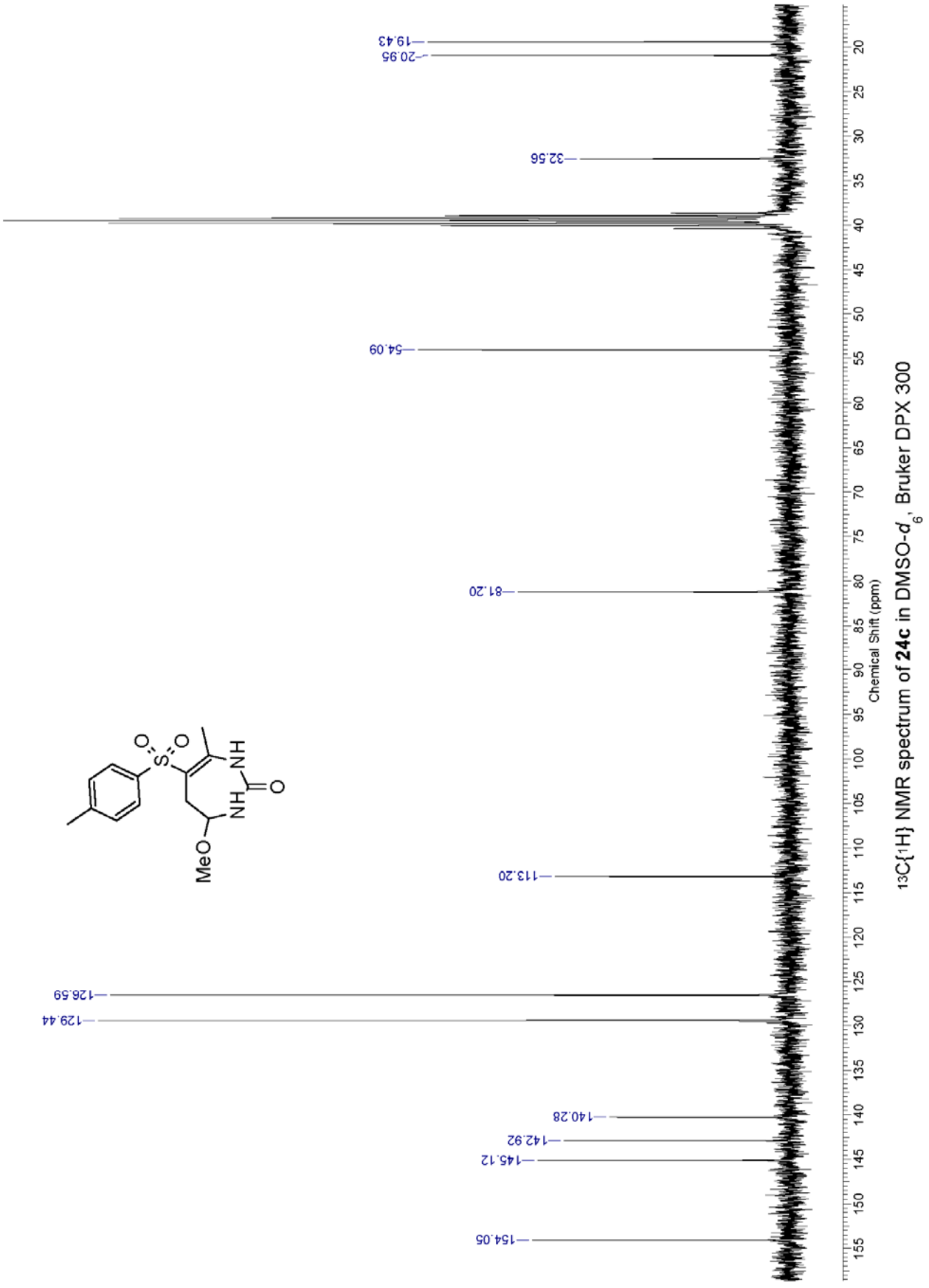


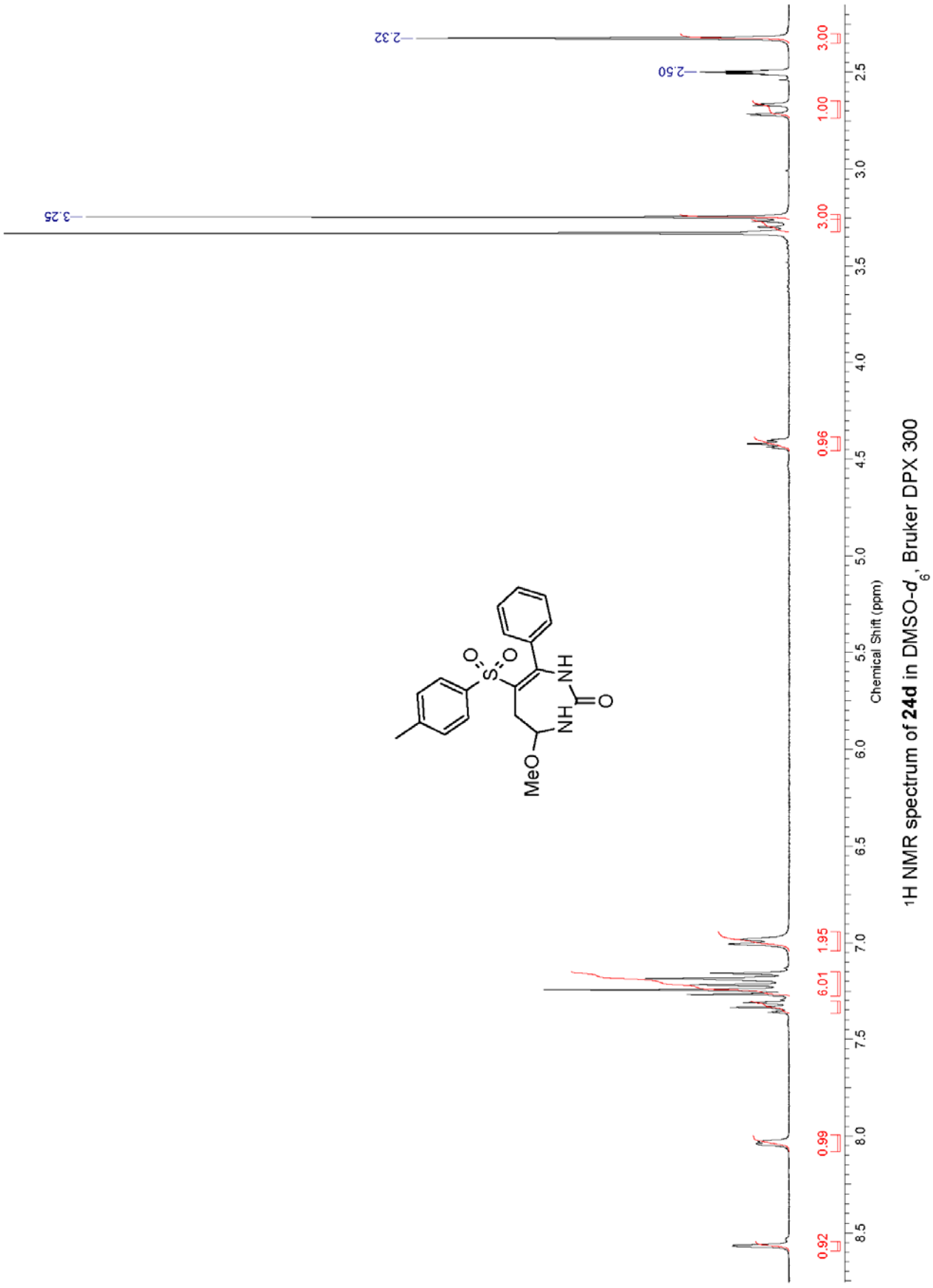
^{1}H NMR spectrum of **24b** in DMSO-d_6, Bruker DPX 300



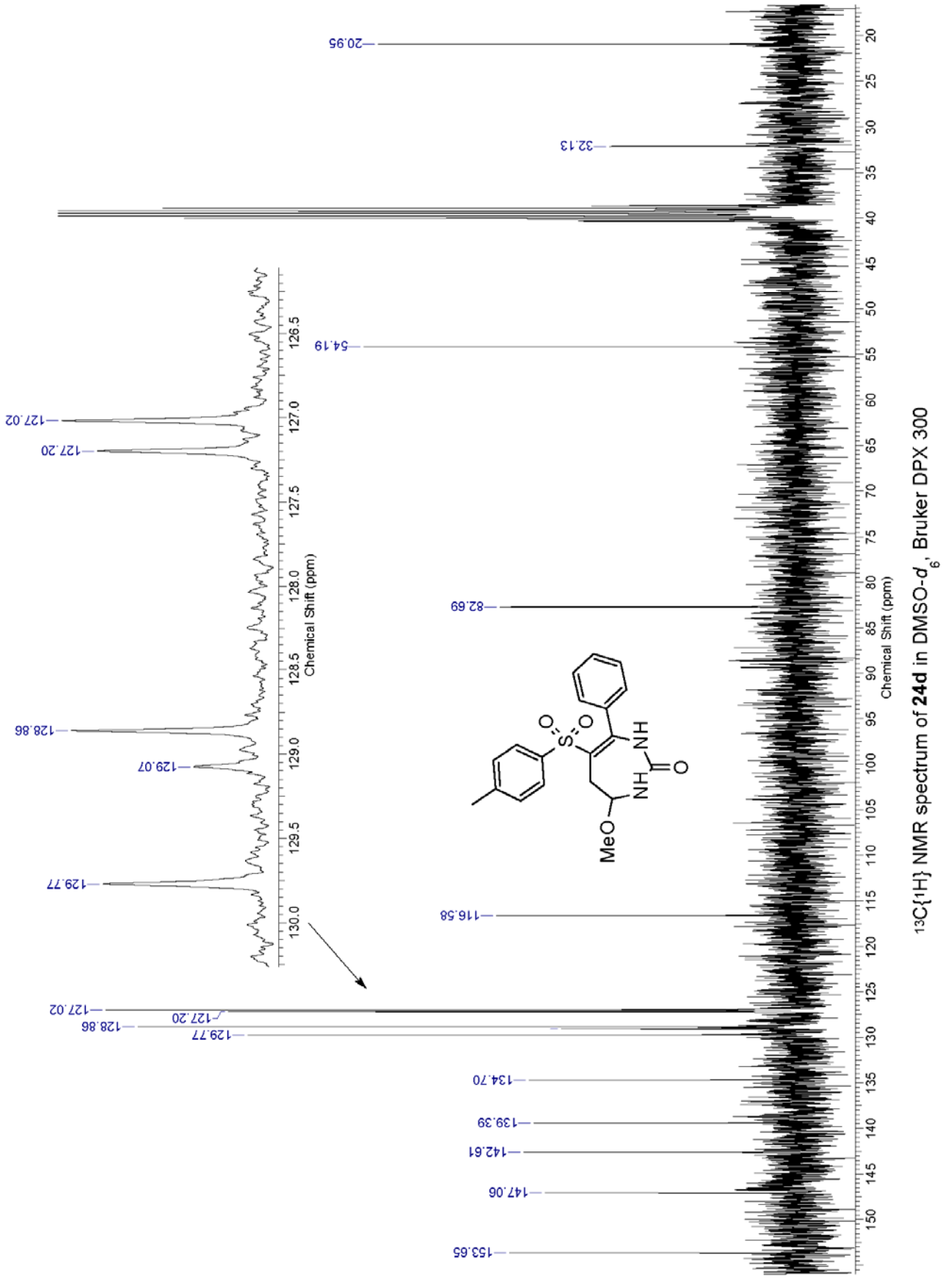


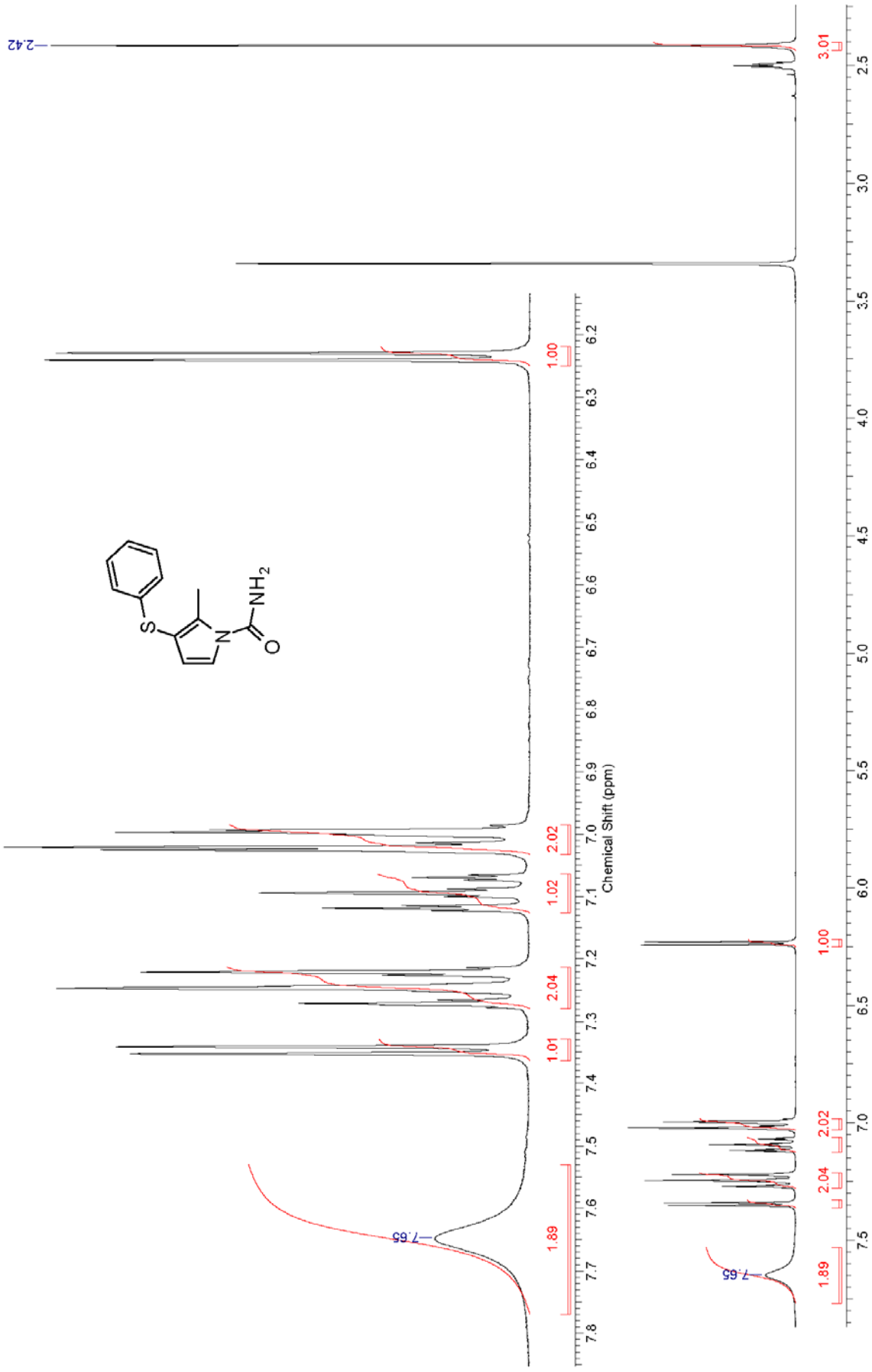
^{1}H NMR spectrum of **24c** in DMSO-d_6, Bruker DPX 300


19.43
20.95
32.56
54.09
81.20
113.20
126.59
129.44
140.28
142.92
145.12
154.05
Chemical Shift (ppm)
$^{13}C\{^{1}H\}$ NMR spectrum of **24c** in DMSO-d_6, Bruker DPX 300
MeO
NH
NH
O
O
O
S

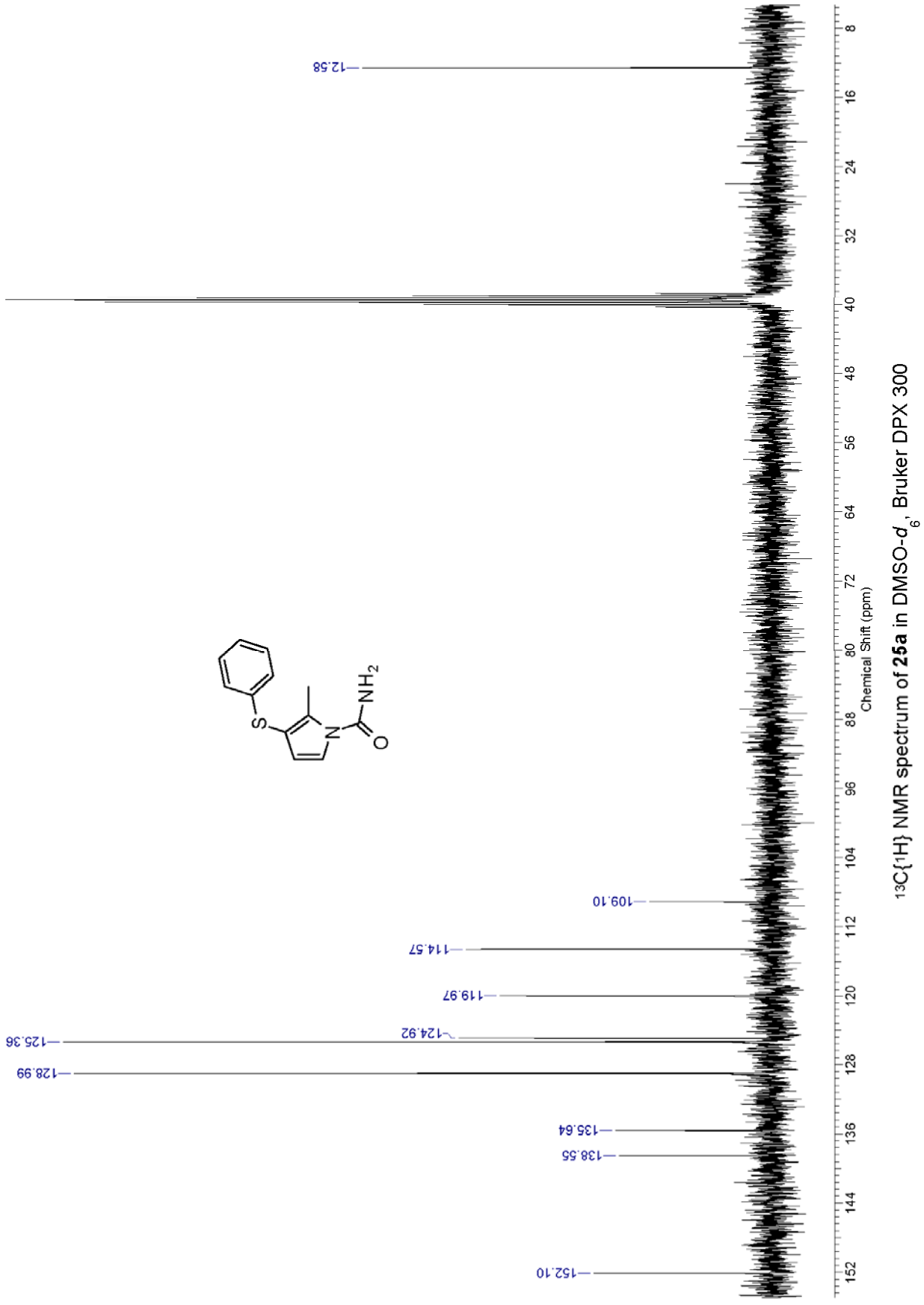


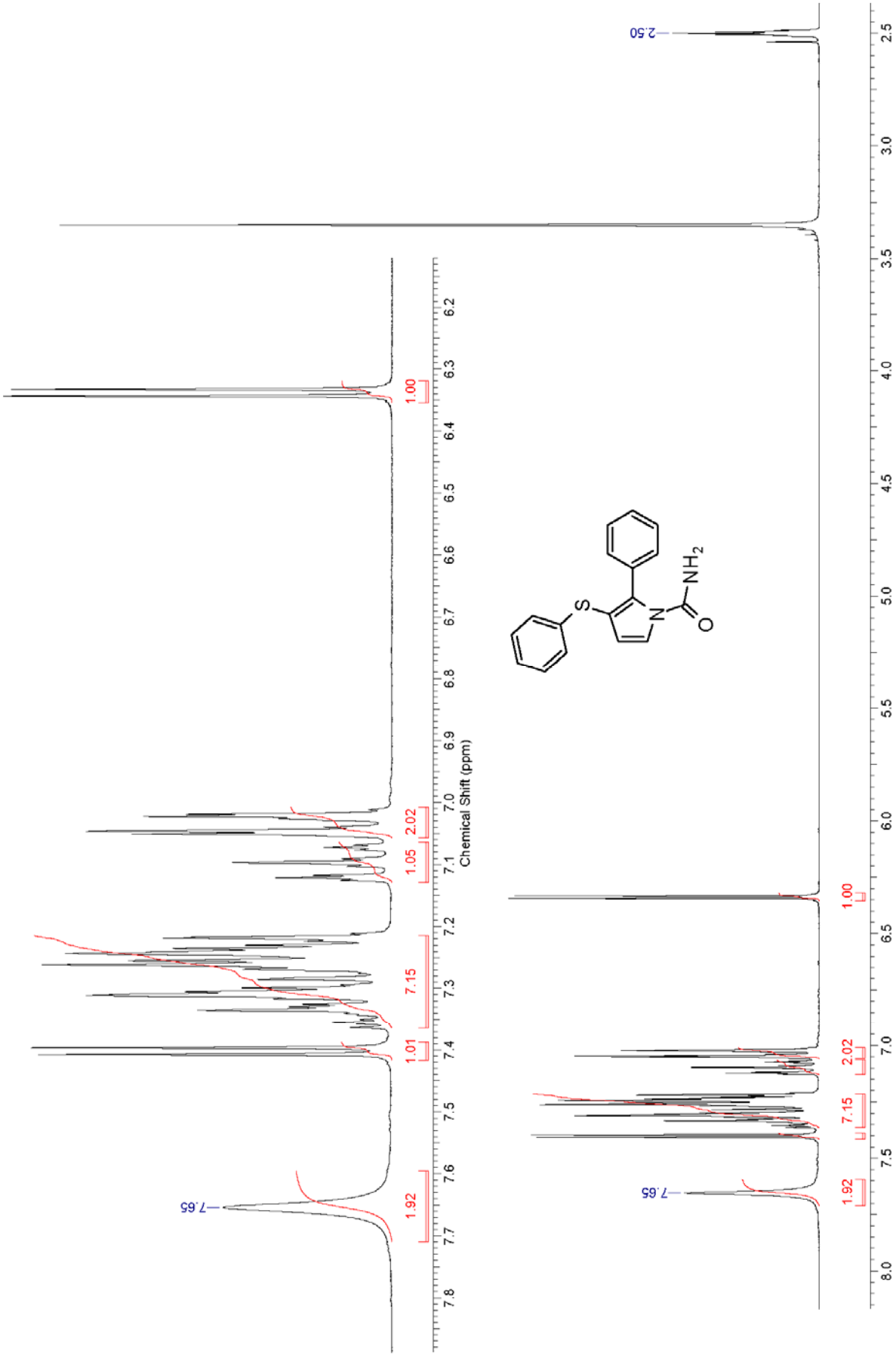
^{1}H NMR spectrum of **24d** in DMSO-d_6, Bruker DPX 300


20.95
32.13
54.19
82.69
116.58
127.02
127.20
128.86
129.07
129.77
134.70
139.39
142.61
147.06
153.65
Chemical Shift (ppm)
MeO
NH
NH
O
O
S
O
$^{13}C\{^1H\}$ NMR spectrum of **24d** in DMSO-d_6, Bruker DPX 300

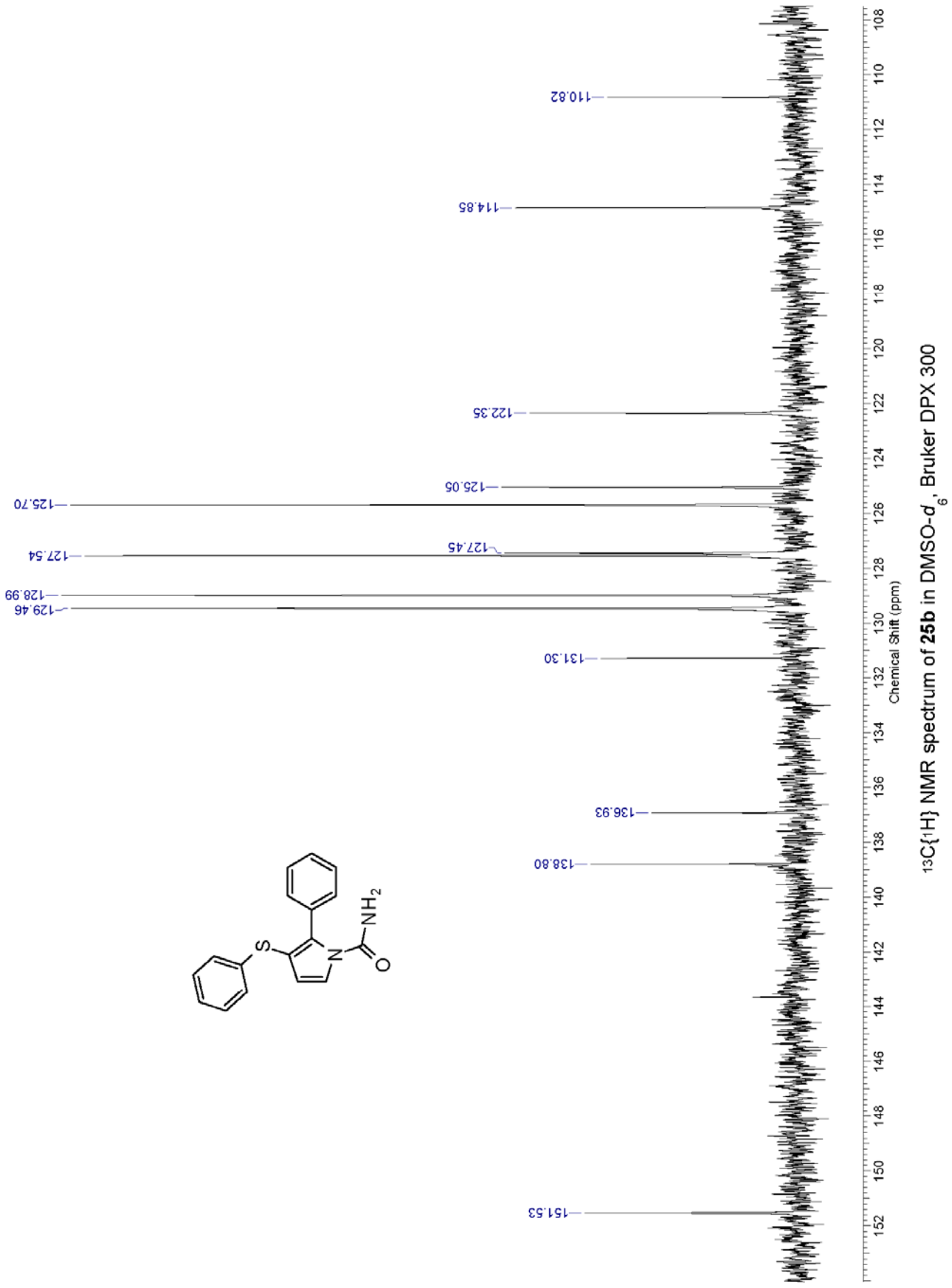


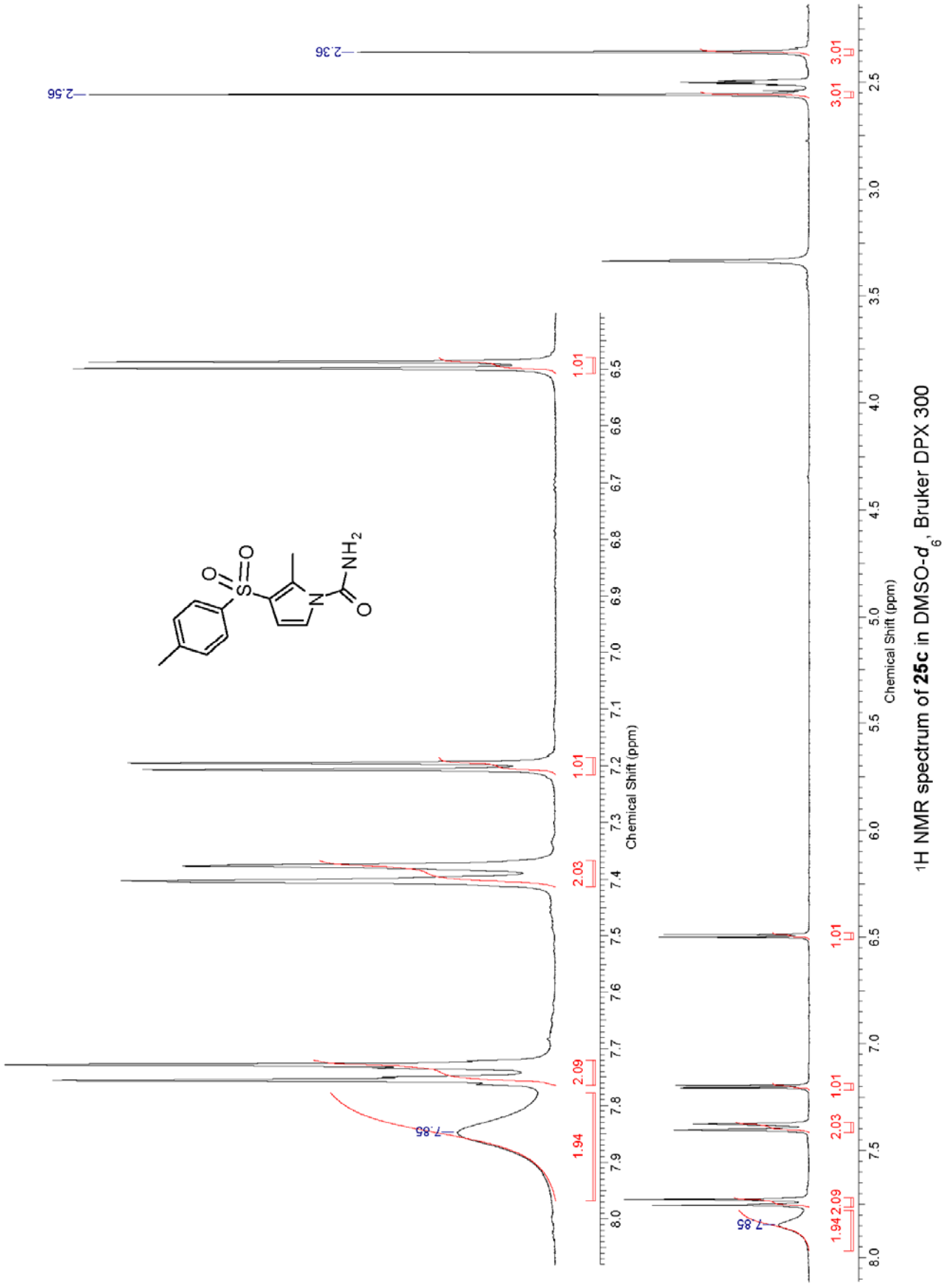
^{1}H NMR spectrum of **25a** in DMSO-d_6, Bruker DPX 300


12.58
109.10
114.57
119.97
124.92
125.36
128.99
135.64
138.55
152.10
S
N
O
NH2
Chemical Shift (ppm)
13C{1H} NMR spectrum of 25a in DMSO-d6, Bruker DPX 300

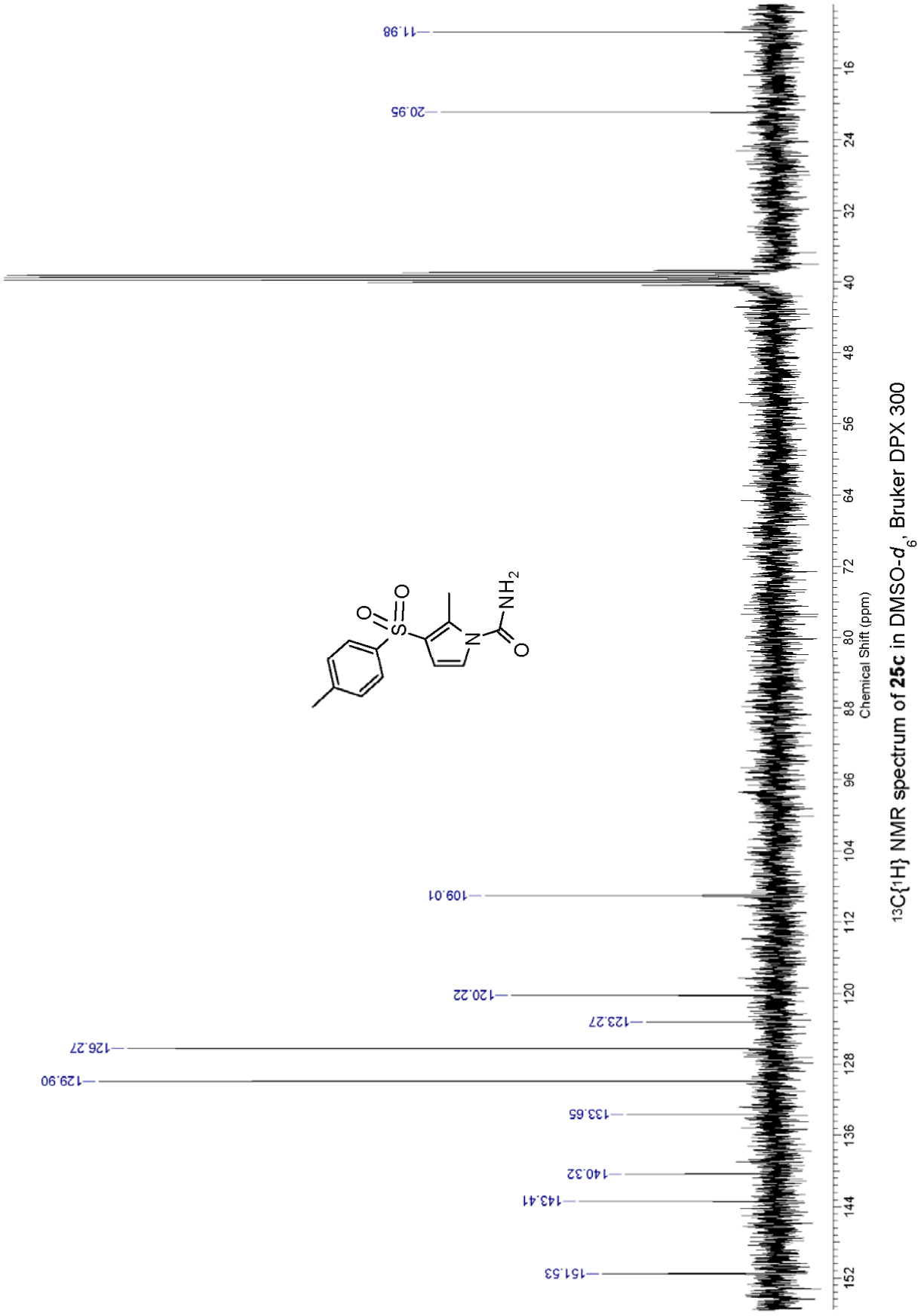


^{1}H NMR spectrum of **25b** in DMSO-d_6, Bruker DPX 300

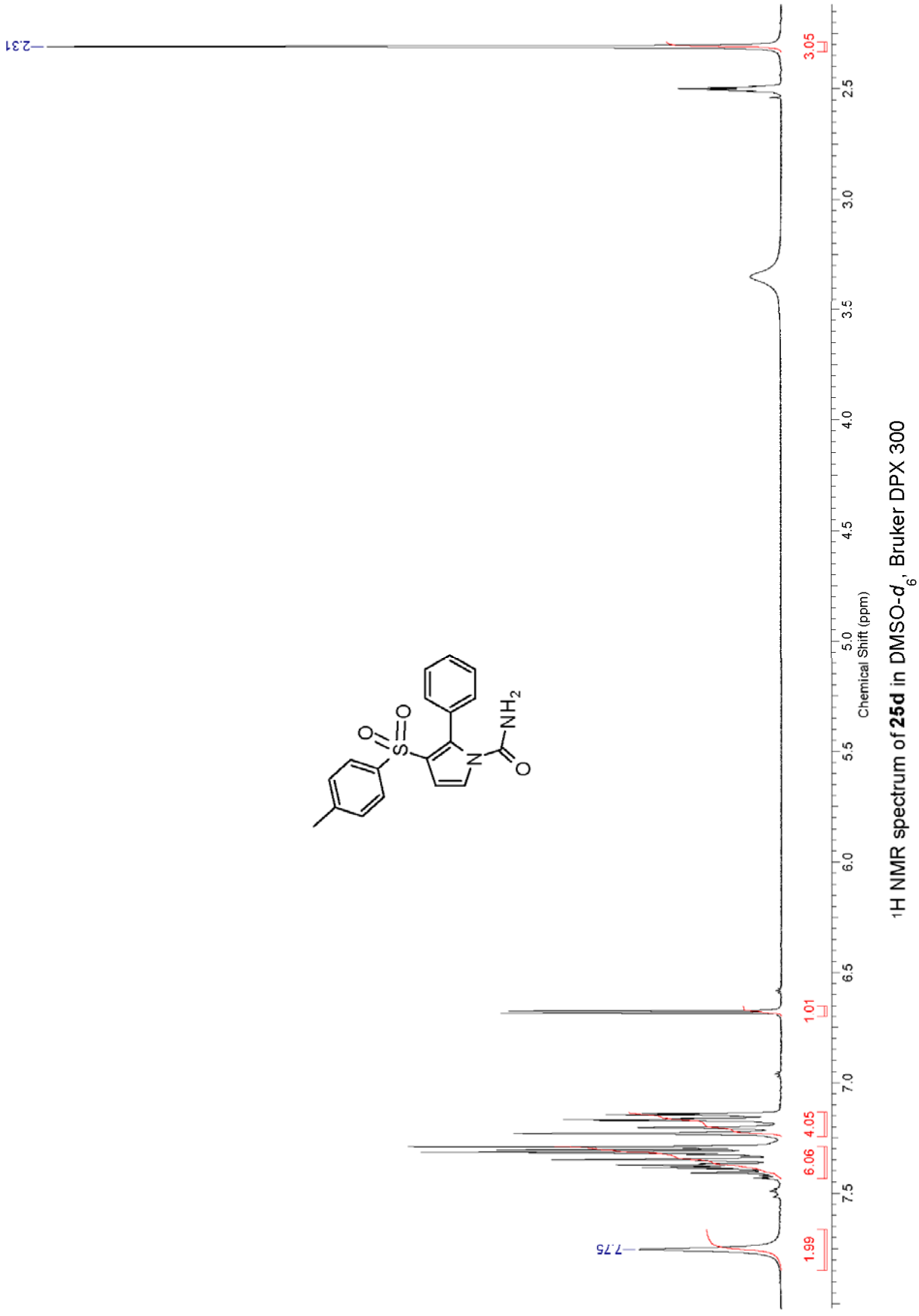

110.82
114.85
122.35
125.05
125.70
127.45
127.54
128.99
129.46
131.30
136.93
138.80
151.53
Chemical Shift (ppm)
$^{13}C\{^{1}H\}$ NMR spectrum of **25b** in DMSO-d_6, Bruker DPX 300
S
N
O
NH2



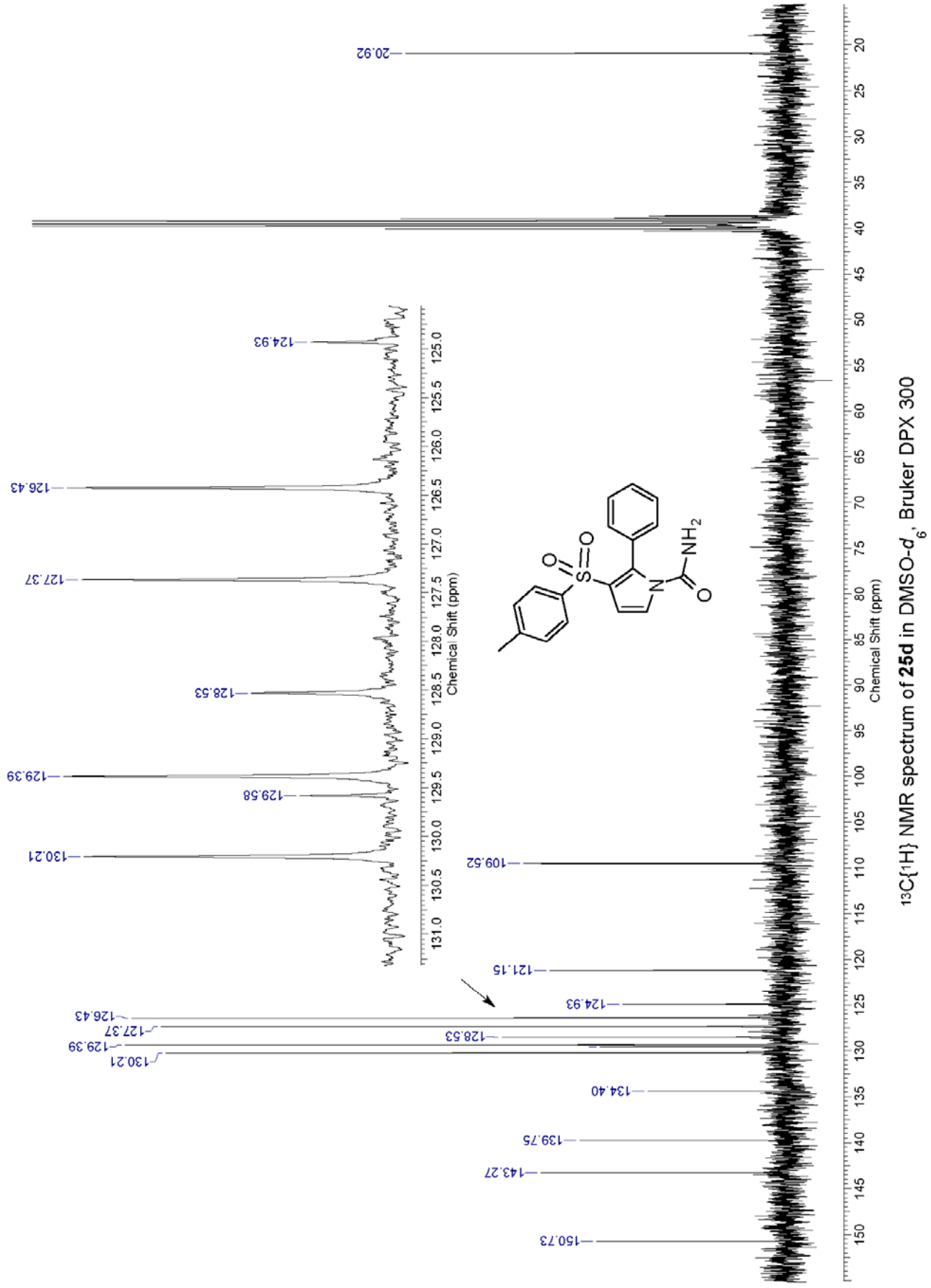
^{1}H NMR spectrum of **25c** in DMSO-d_6, Bruker DPX 300



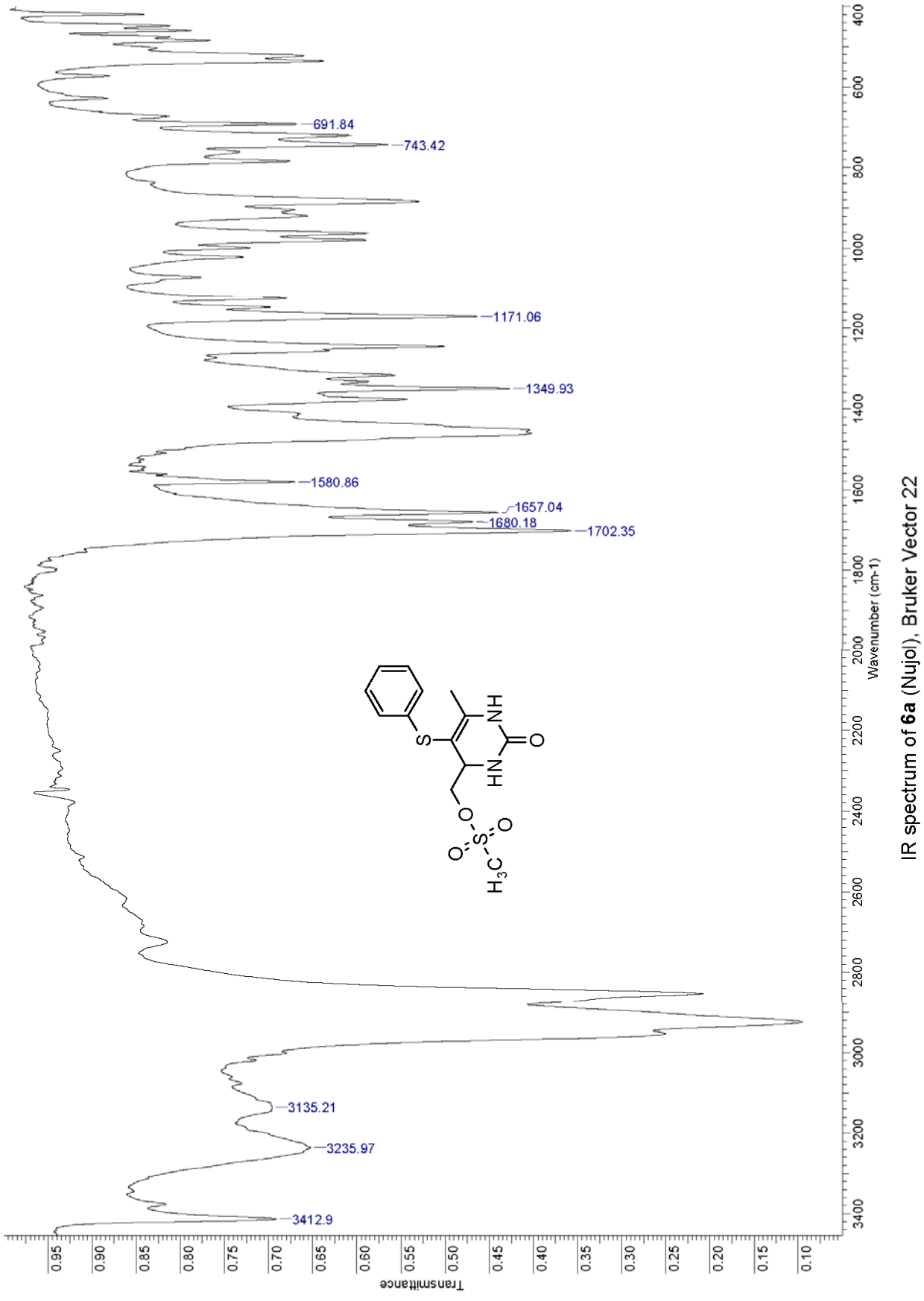
$^{13}C\{^{1}H\}$ NMR spectrum of **25c** in DMSO-d_6, Bruker DPX 300

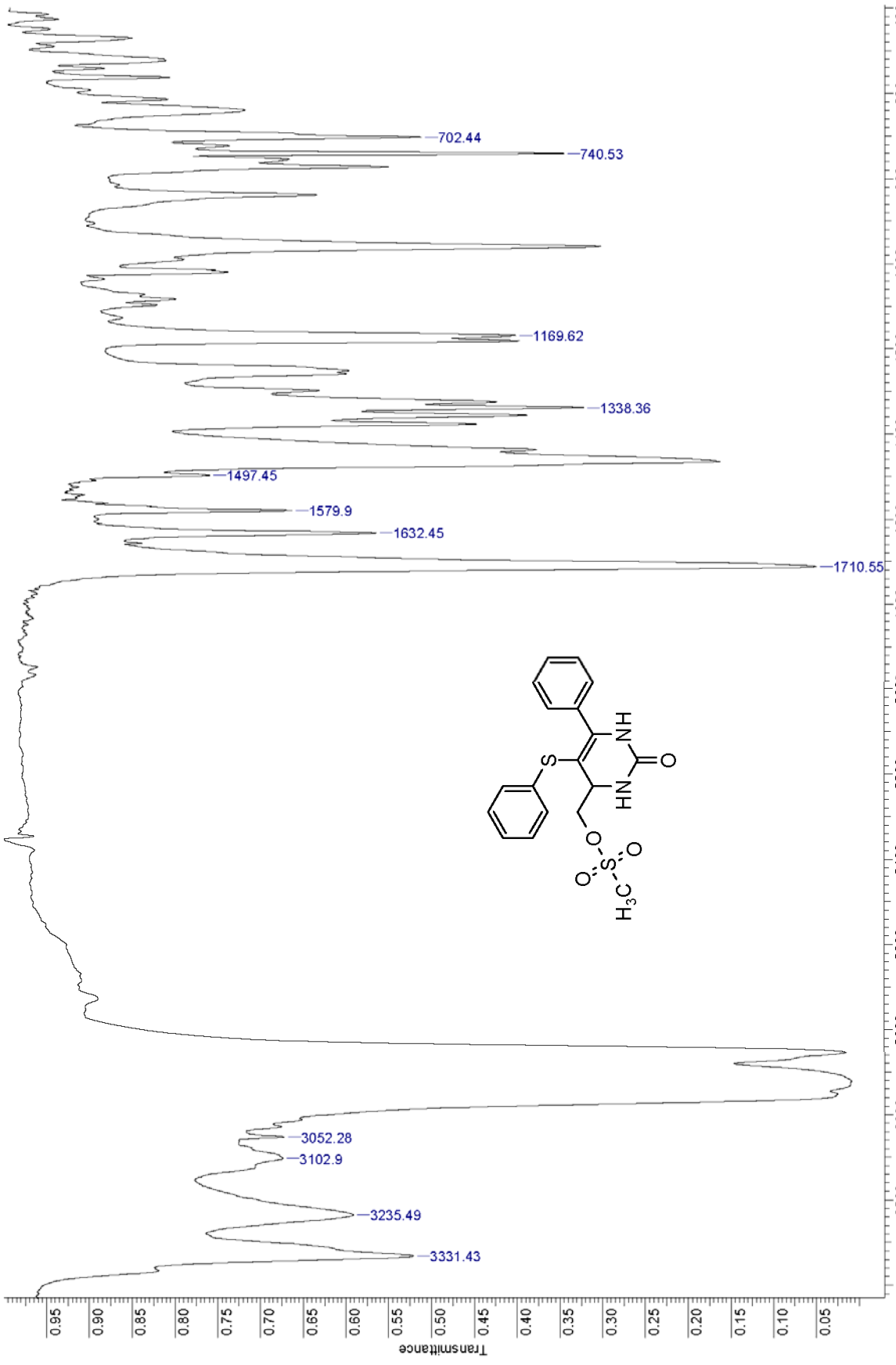


^{1}H NMR spectrum of **25d** in DMSO-d_6, Bruker DPX 300

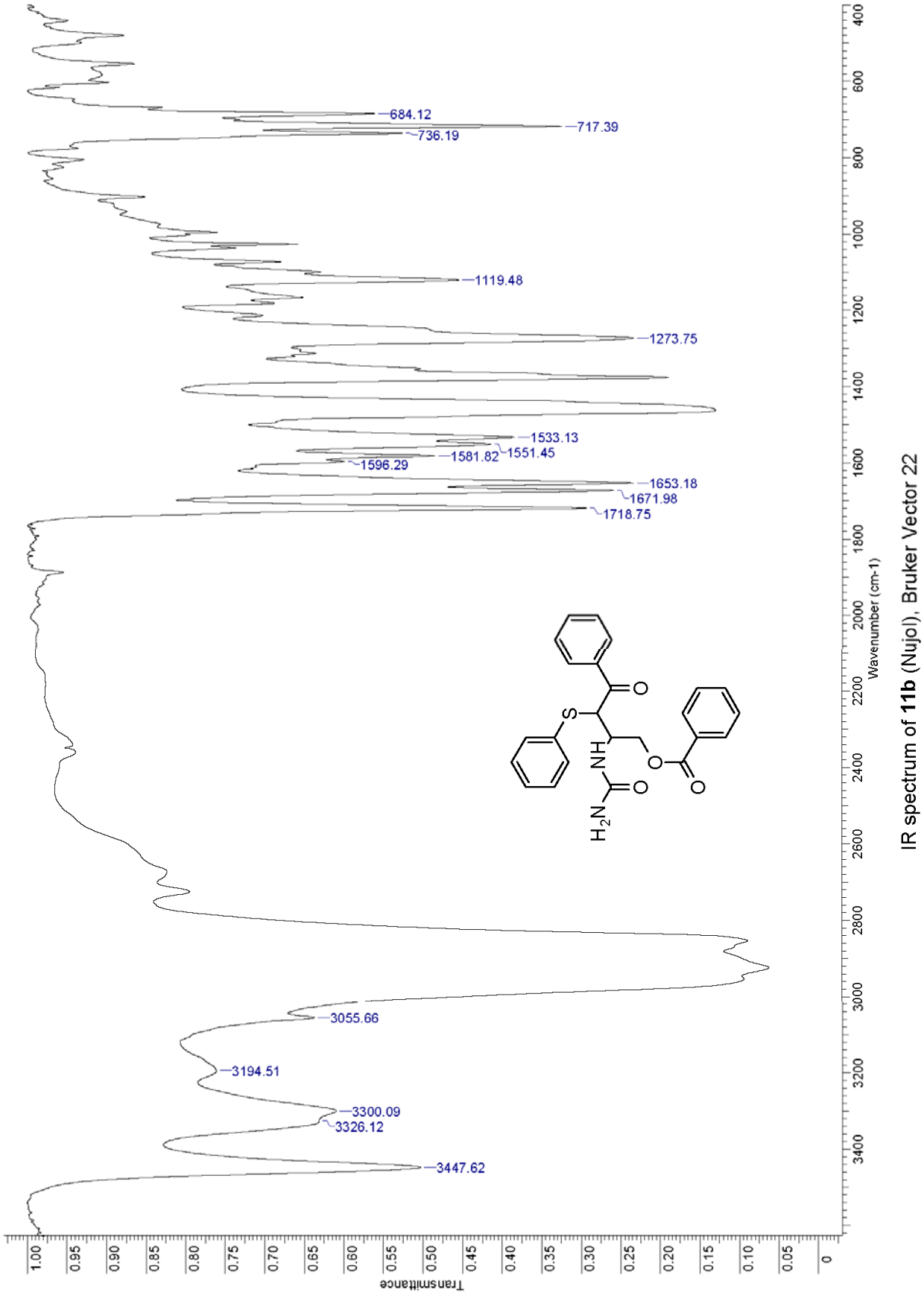


$^{13}C\{^1H\}$ NMR spectrum of **25d** in DMSO-d_6, Bruker DPX 300

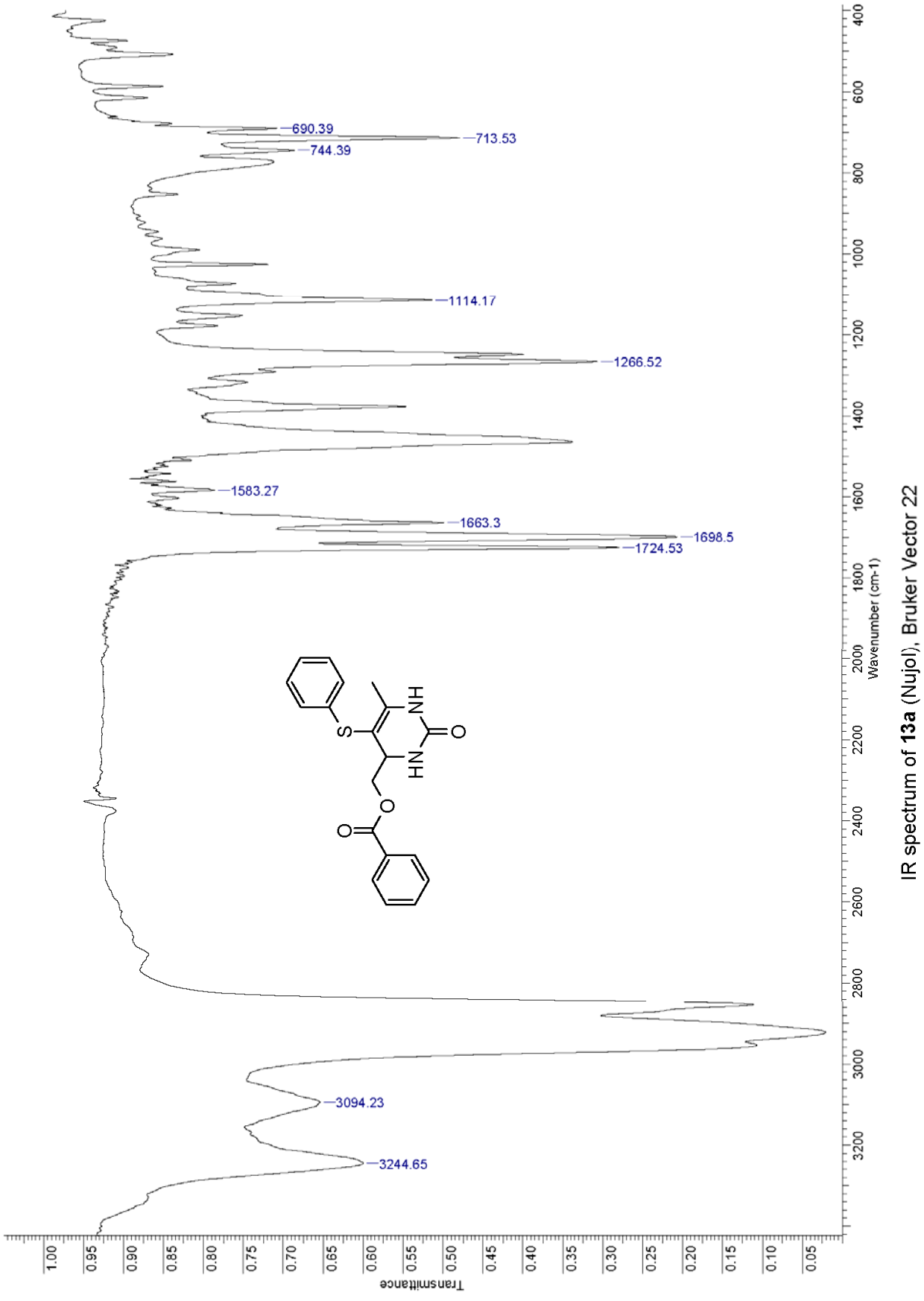

691.84
743.42
1171.06
1349.93
1580.86
1657.04
1680.18
1702.35
3135.21
3235.97
3412.9
Transmittance
Wavenumber (cm-1)
IR spectrum of 6a (Nujol), Bruker Vector 22

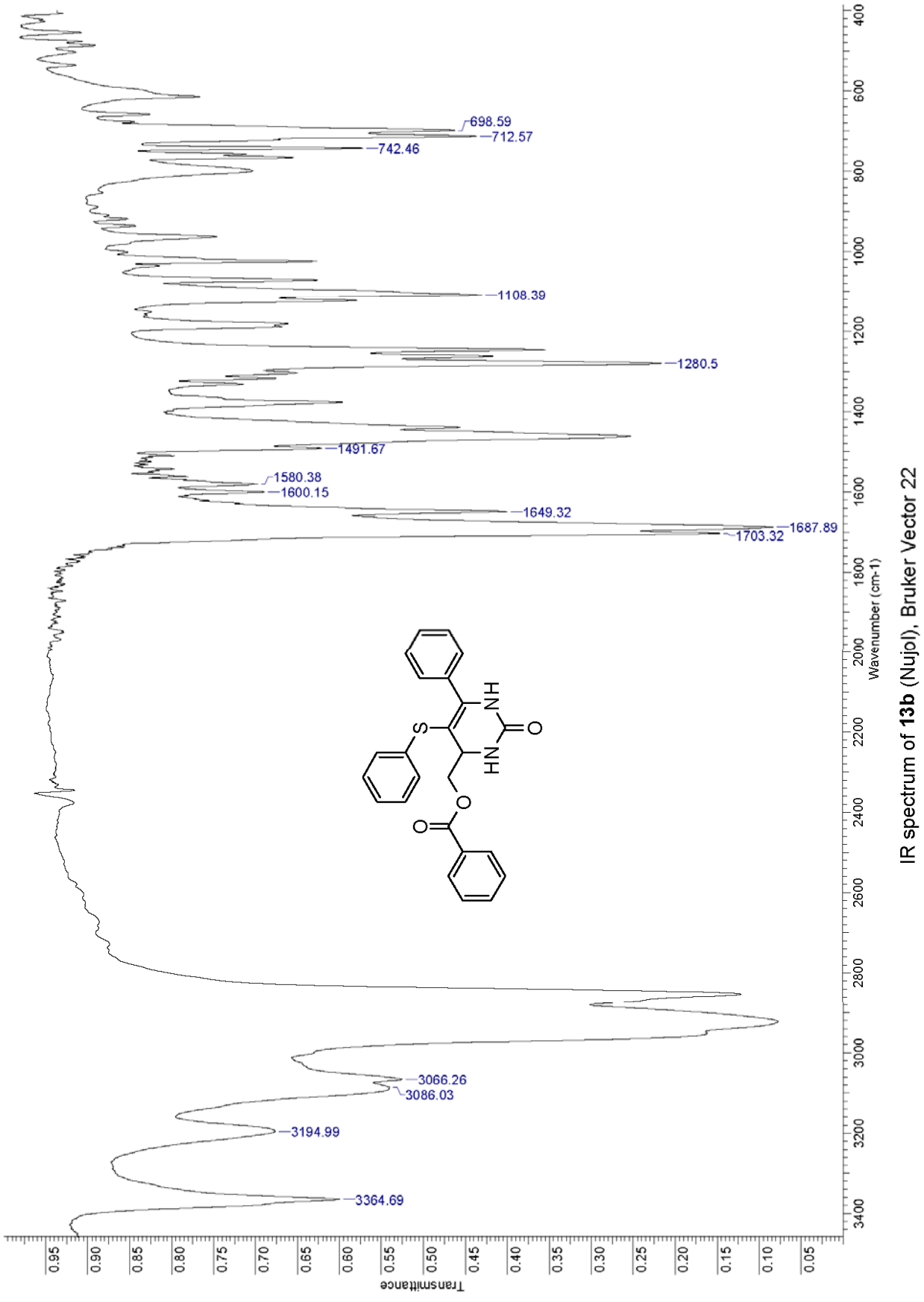


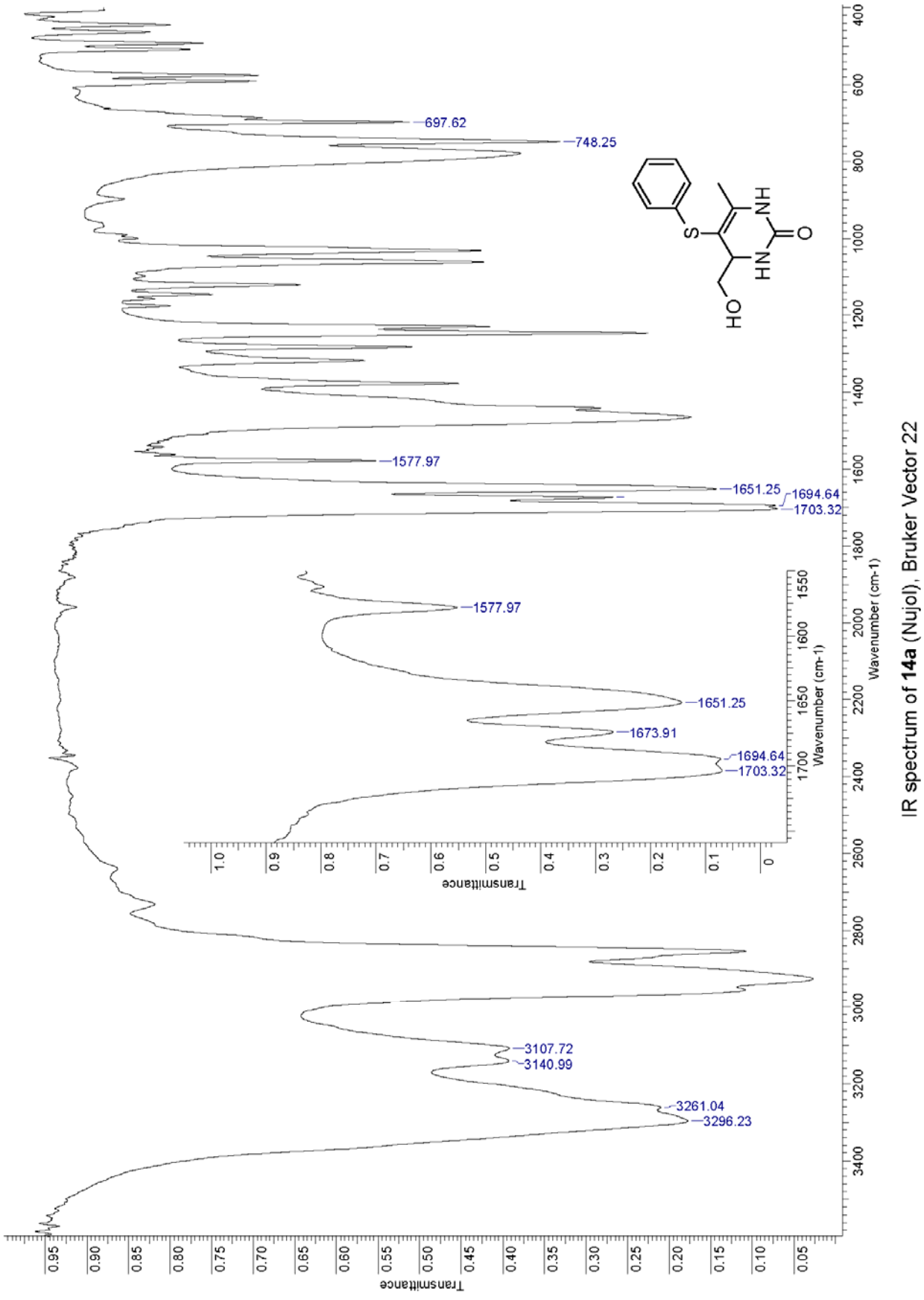
IR spectrum of **6b** (Nujol), Bruker Vector 22



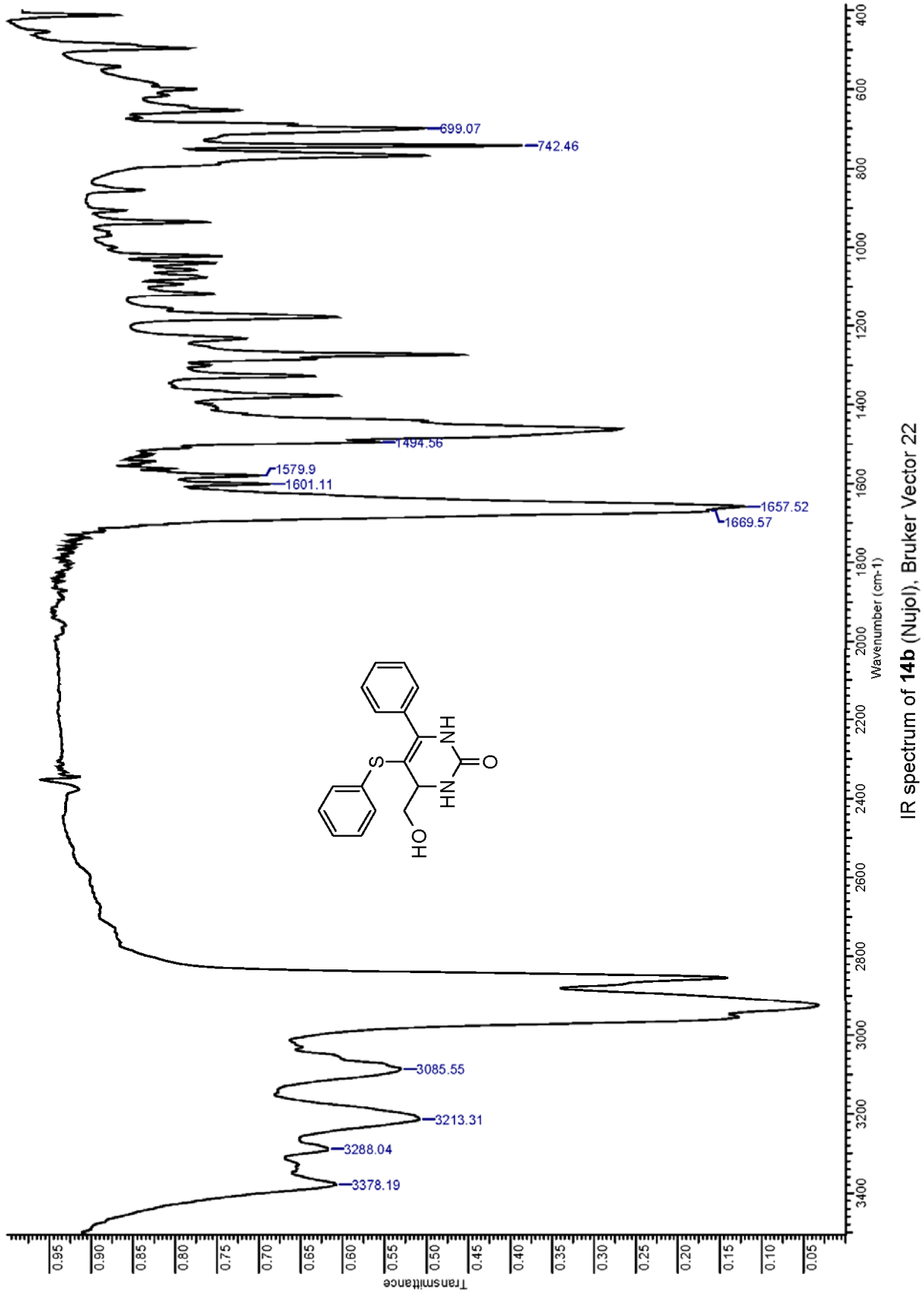
IR spectrum of **11b** (Nujol), Bruker Vector 22

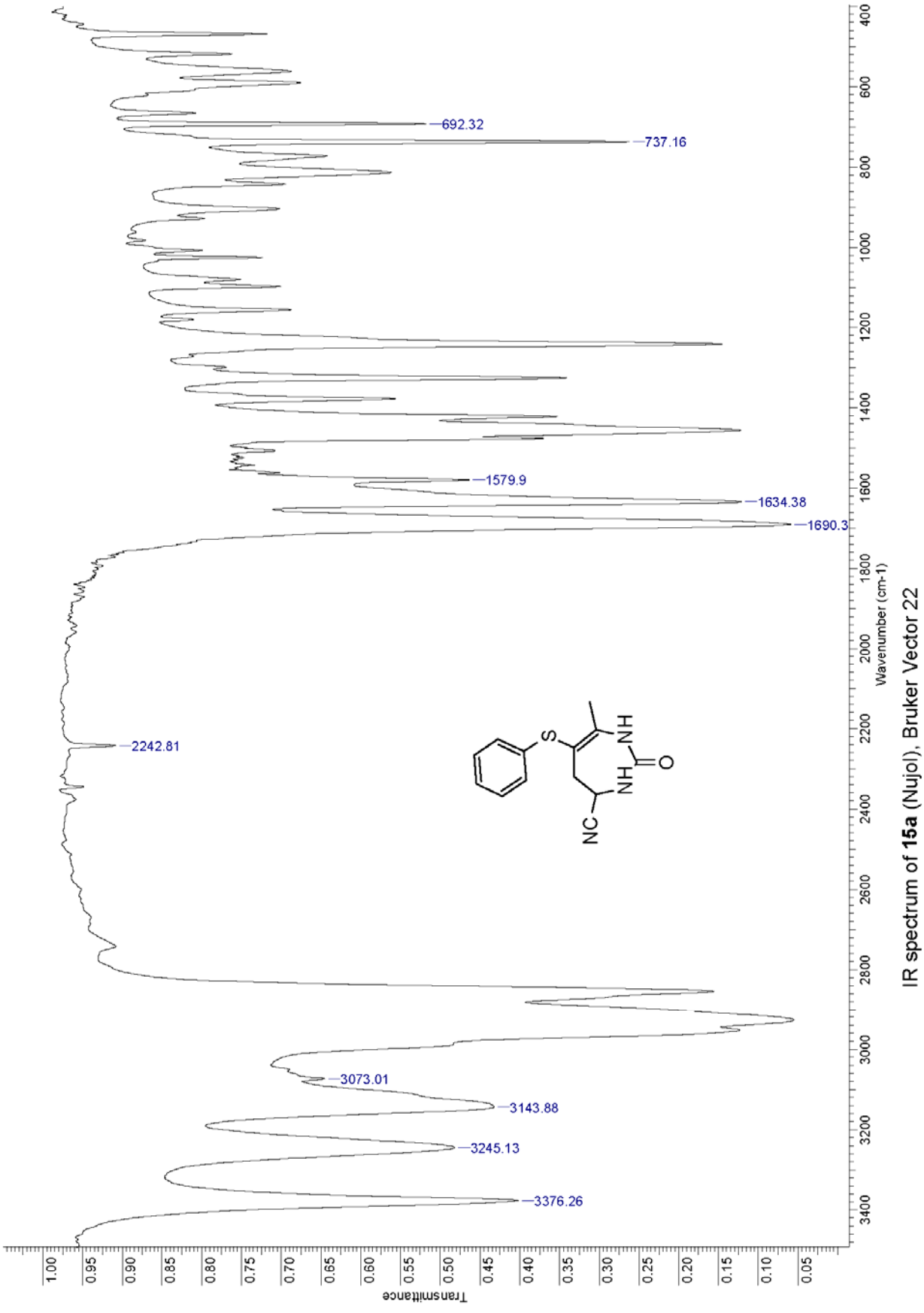

690.39
713.53
744.39
1114.17
1266.52
1583.27
1663.3
1698.5
1724.53
3094.23
3244.65
Wavenumber (cm-1)
Transmittance
IR spectrum of 13a (Nujol), Bruker Vector 22


698.59
712.57
742.46
1108.39
1280.5
1491.67
1580.38
1600.15
1649.32
1687.89
1703.32
3066.26
3086.03
3194.99
3364.69
Transmittance
Wavenumber (cm-1)
IR spectrum of 13b (Nujol), Bruker Vector 22

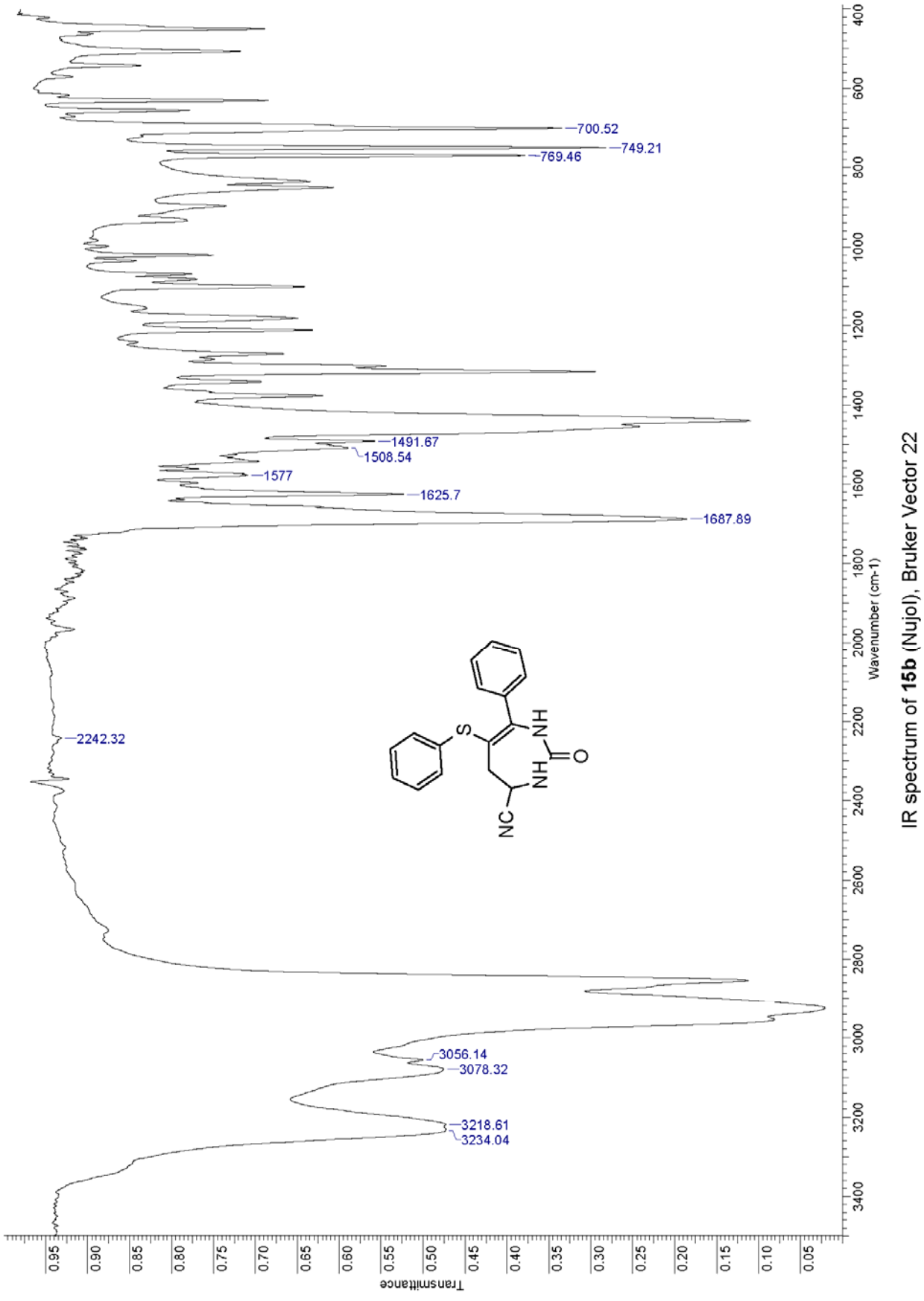


IR spectrum of **14a** (Nujol), Bruker Vector 22

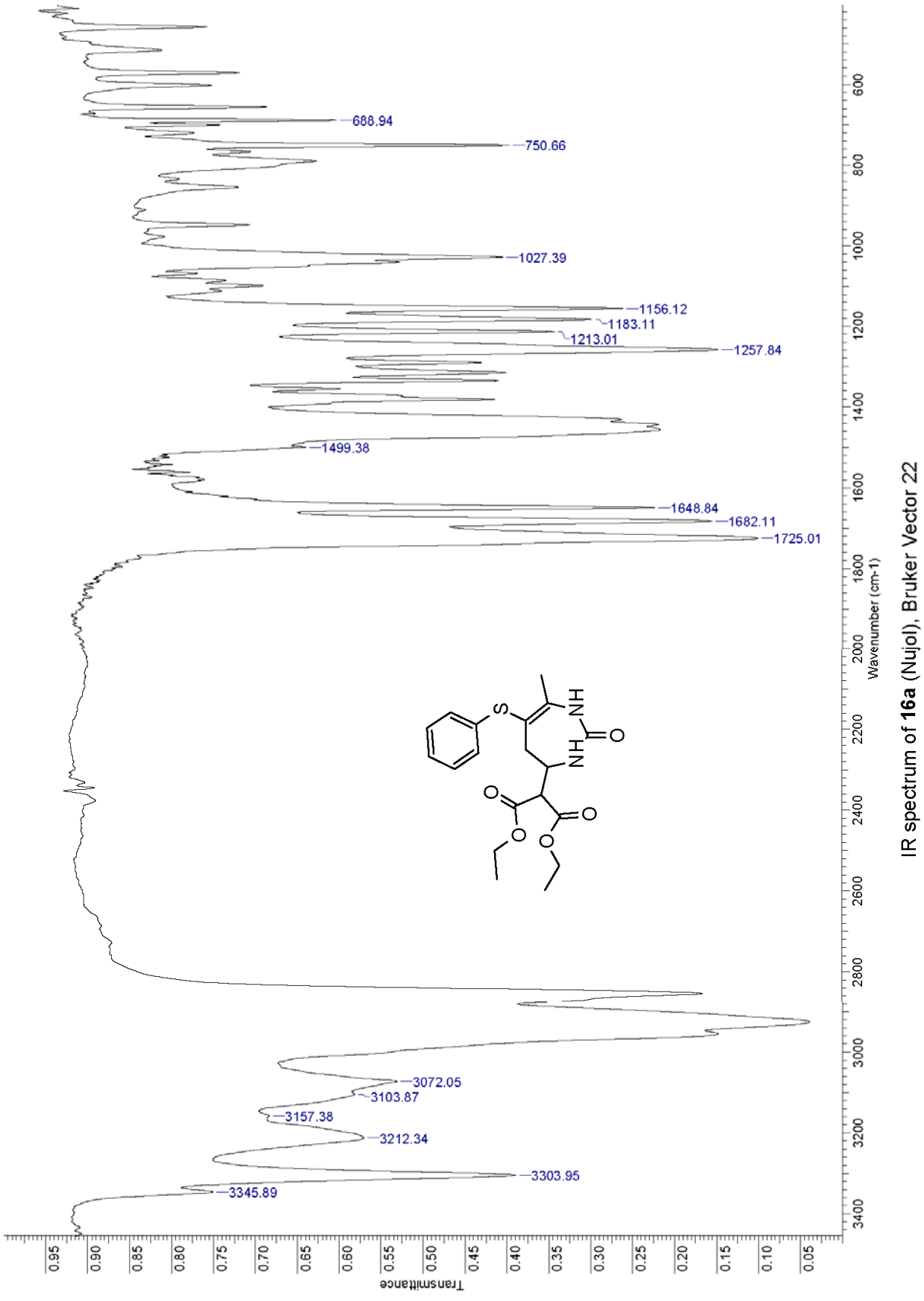


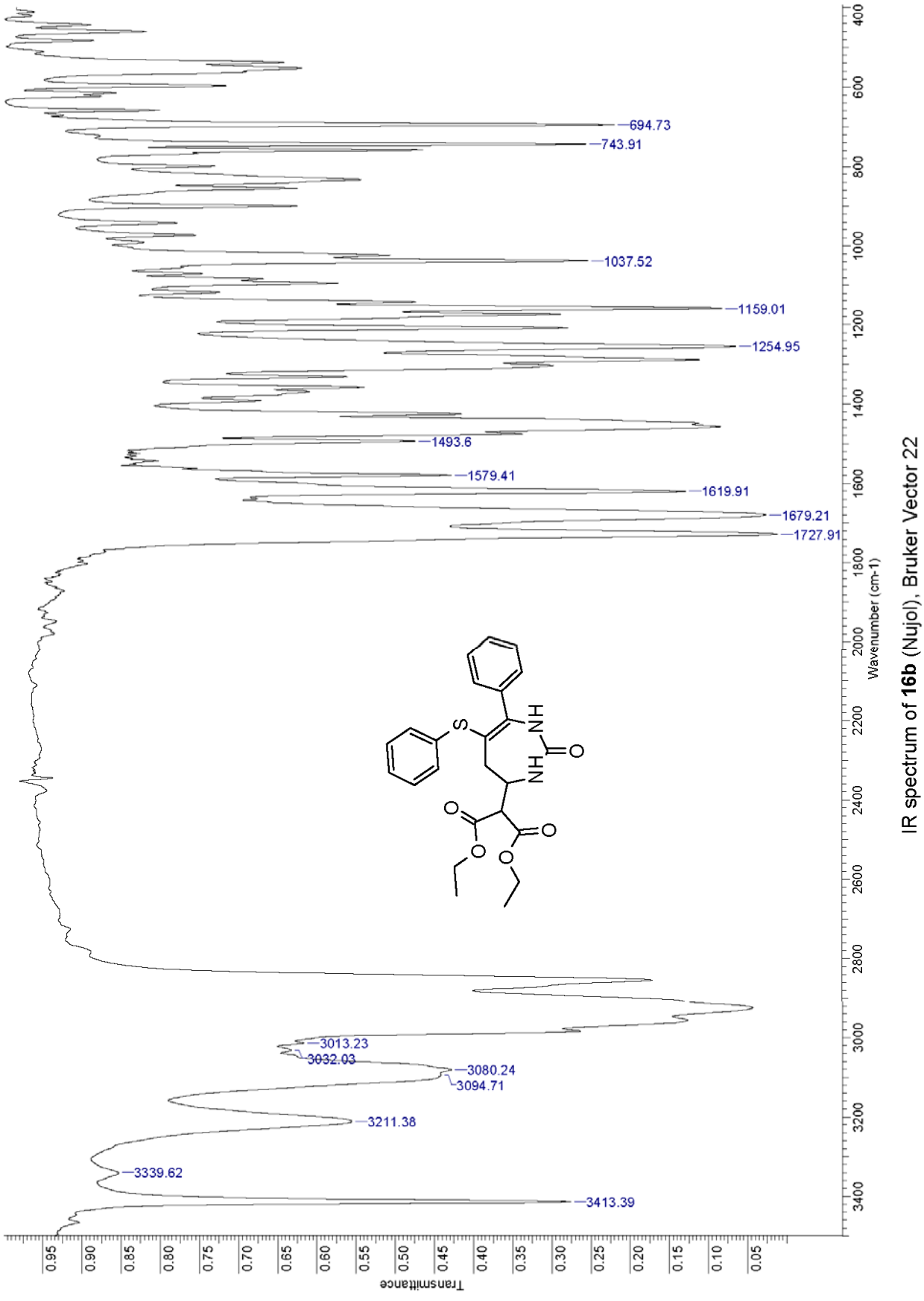


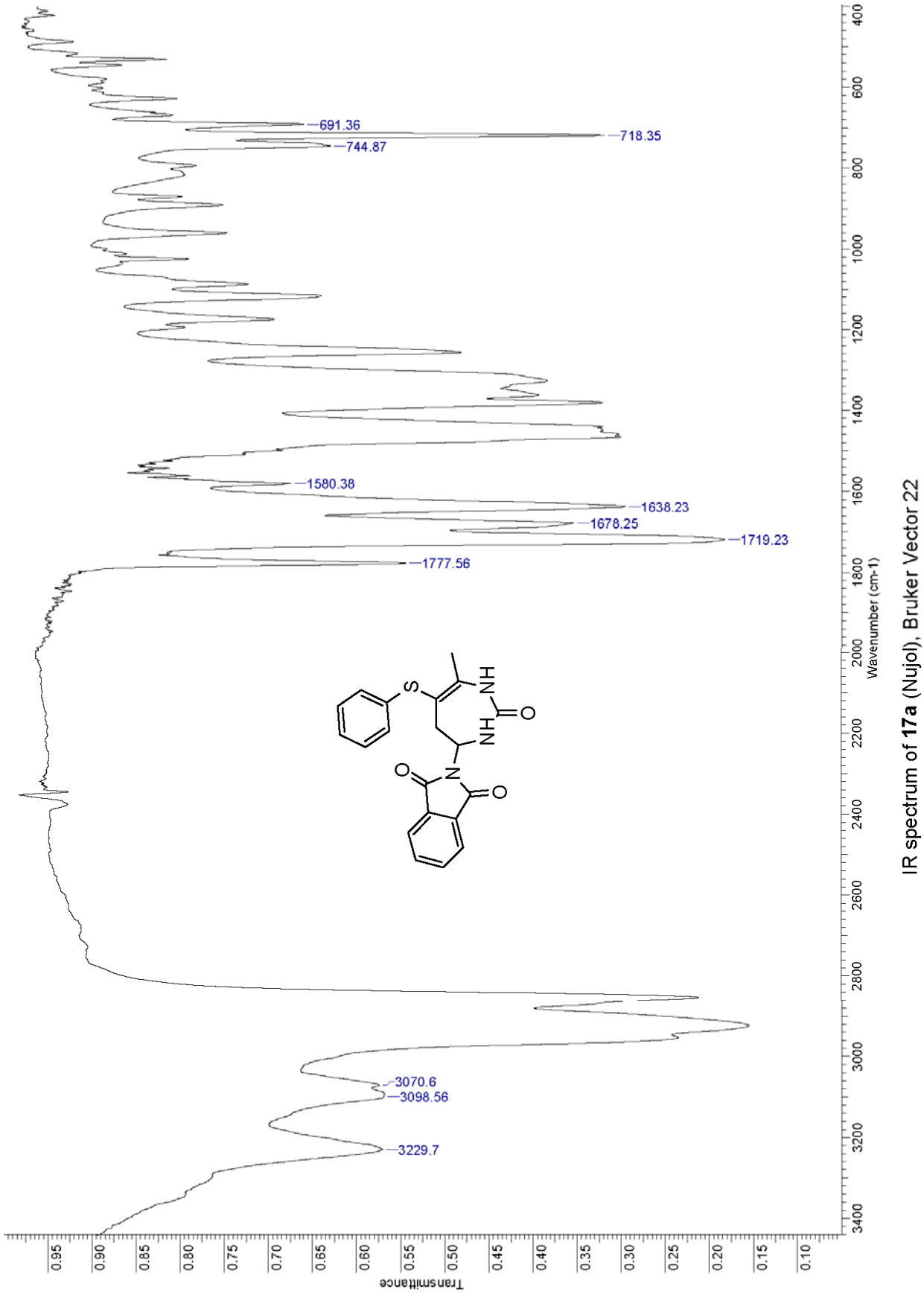
IR spectrum of **15a** (Nujol), Bruker Vector 22



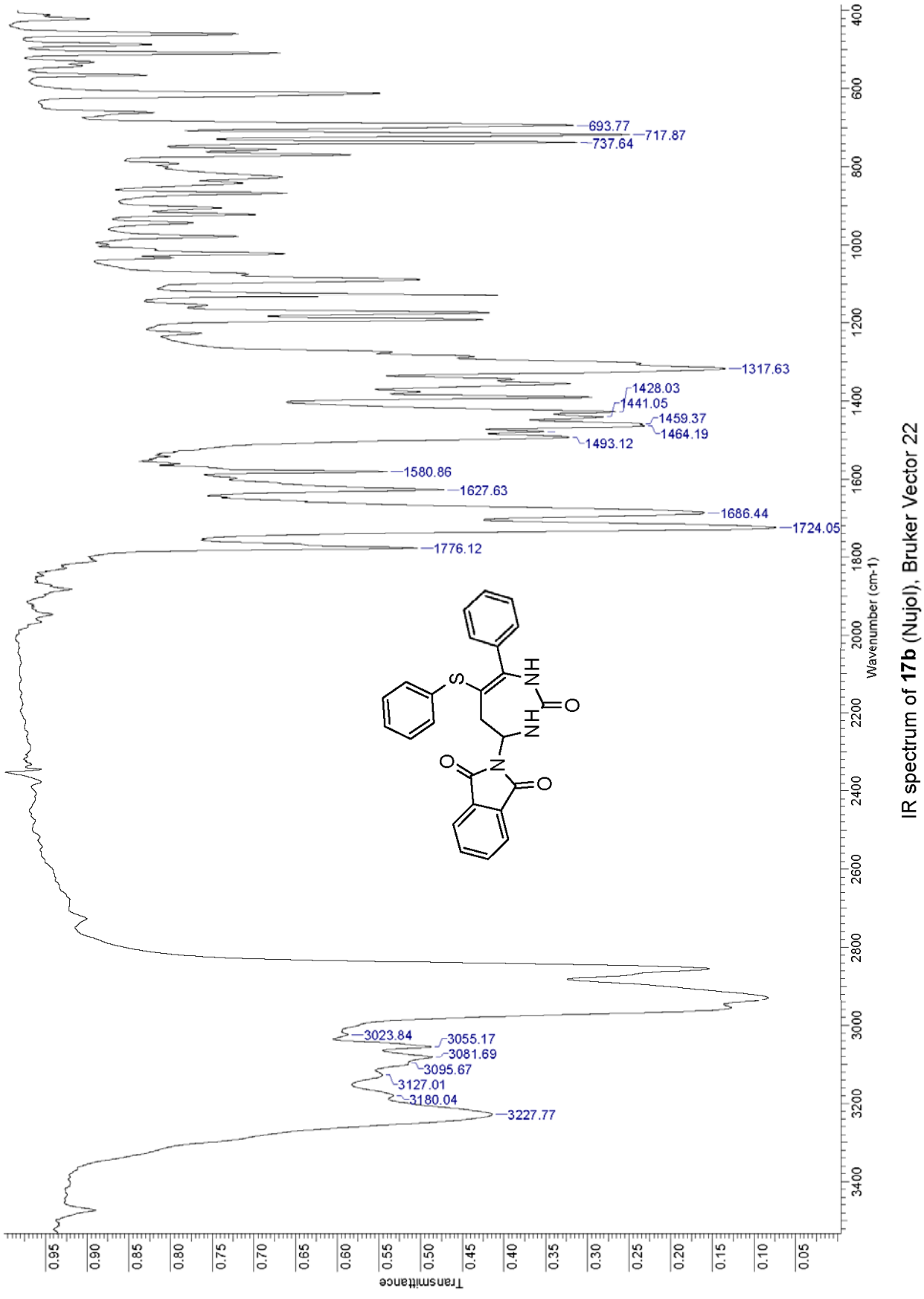
IR spectrum of **15b** (Nujol), Bruker Vector 22

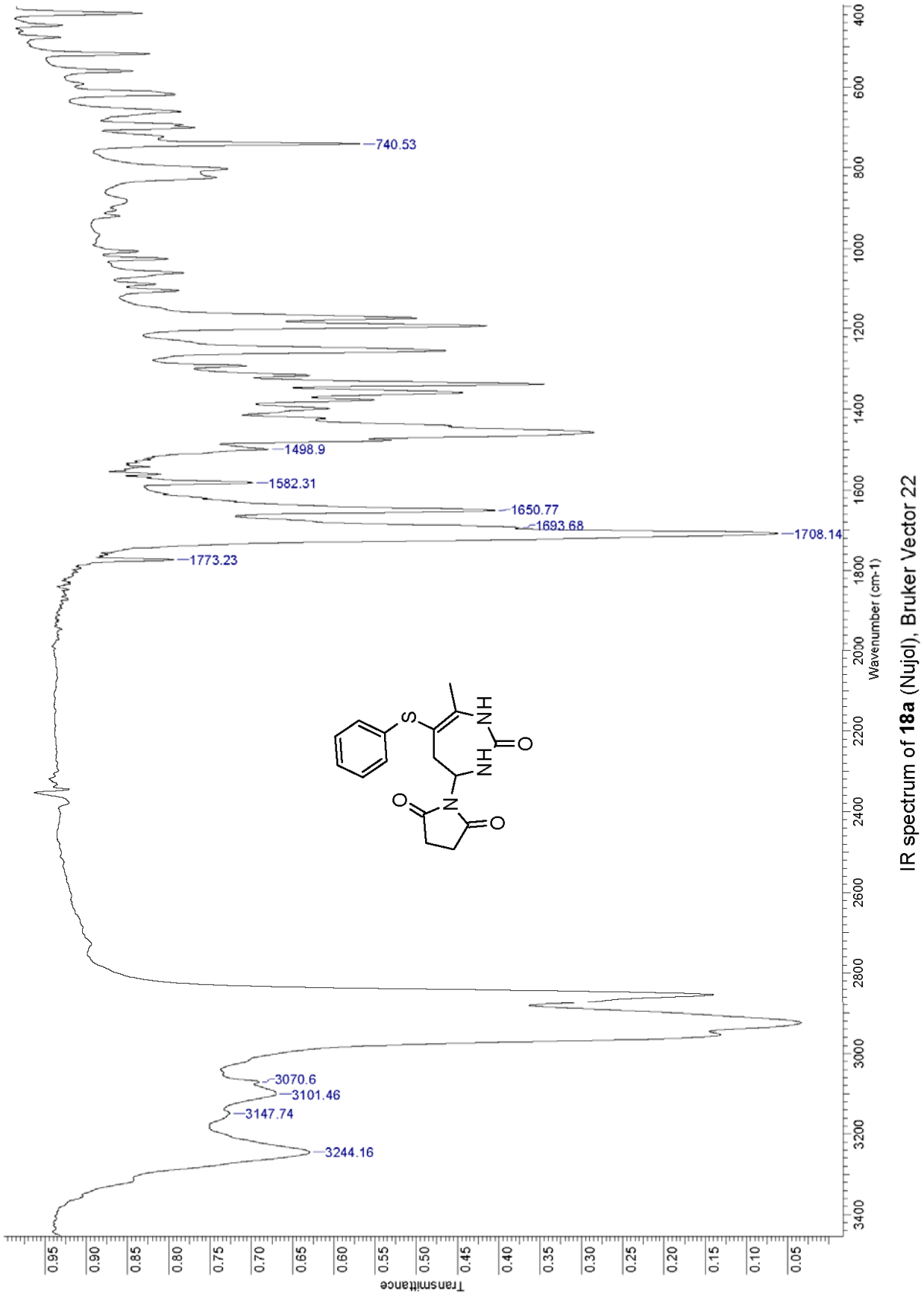

688.94
750.66
1027.39
1156.12
1183.11
1213.01
1257.84
1499.38
1648.84
1682.11
1725.01
3072.05
3103.87
3157.38
3212.34
3303.95
3345.89
Transmittance
Wavenumber (cm-1)
IR spectrum of 16a (Nujol), Bruker Vector 22

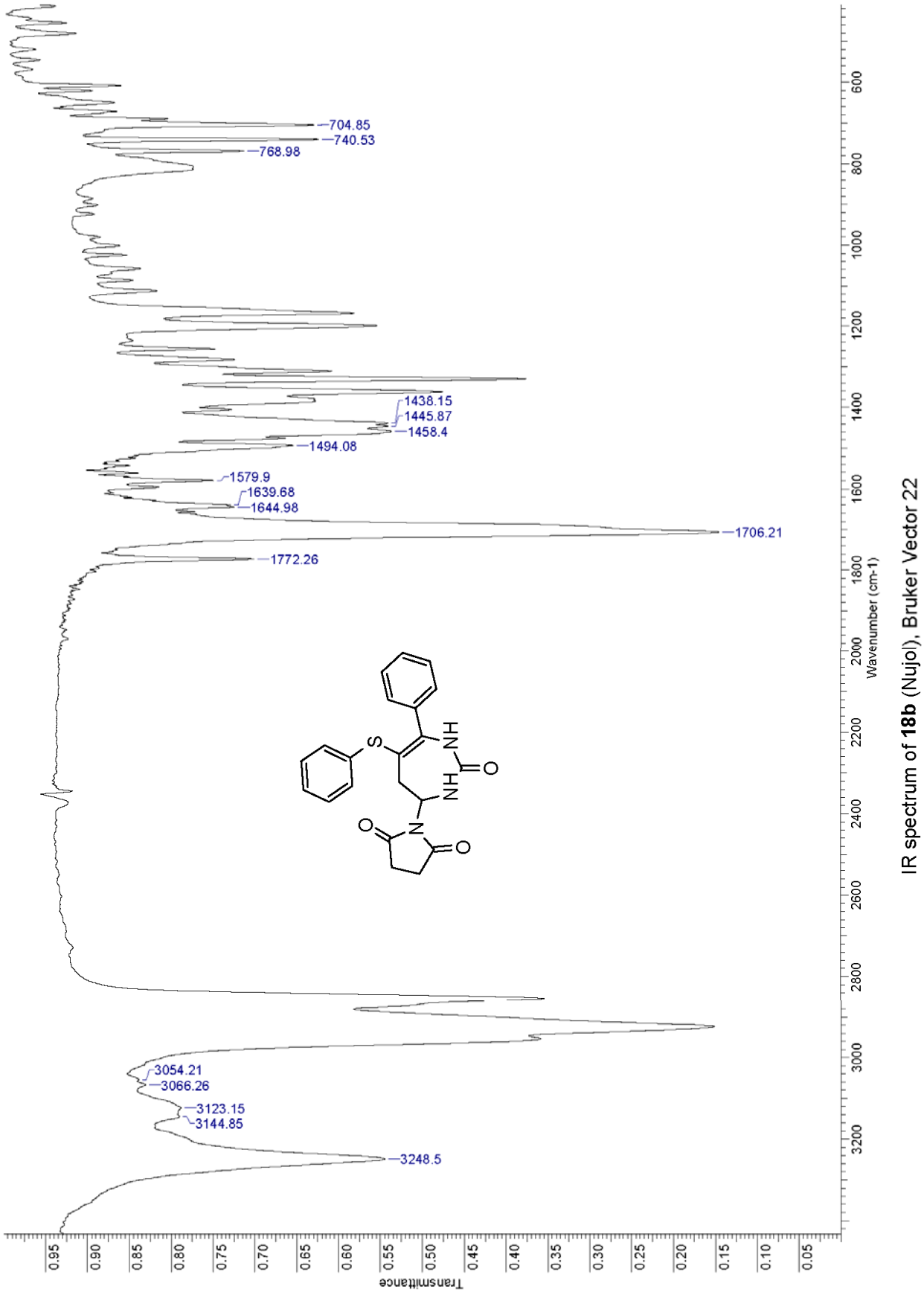


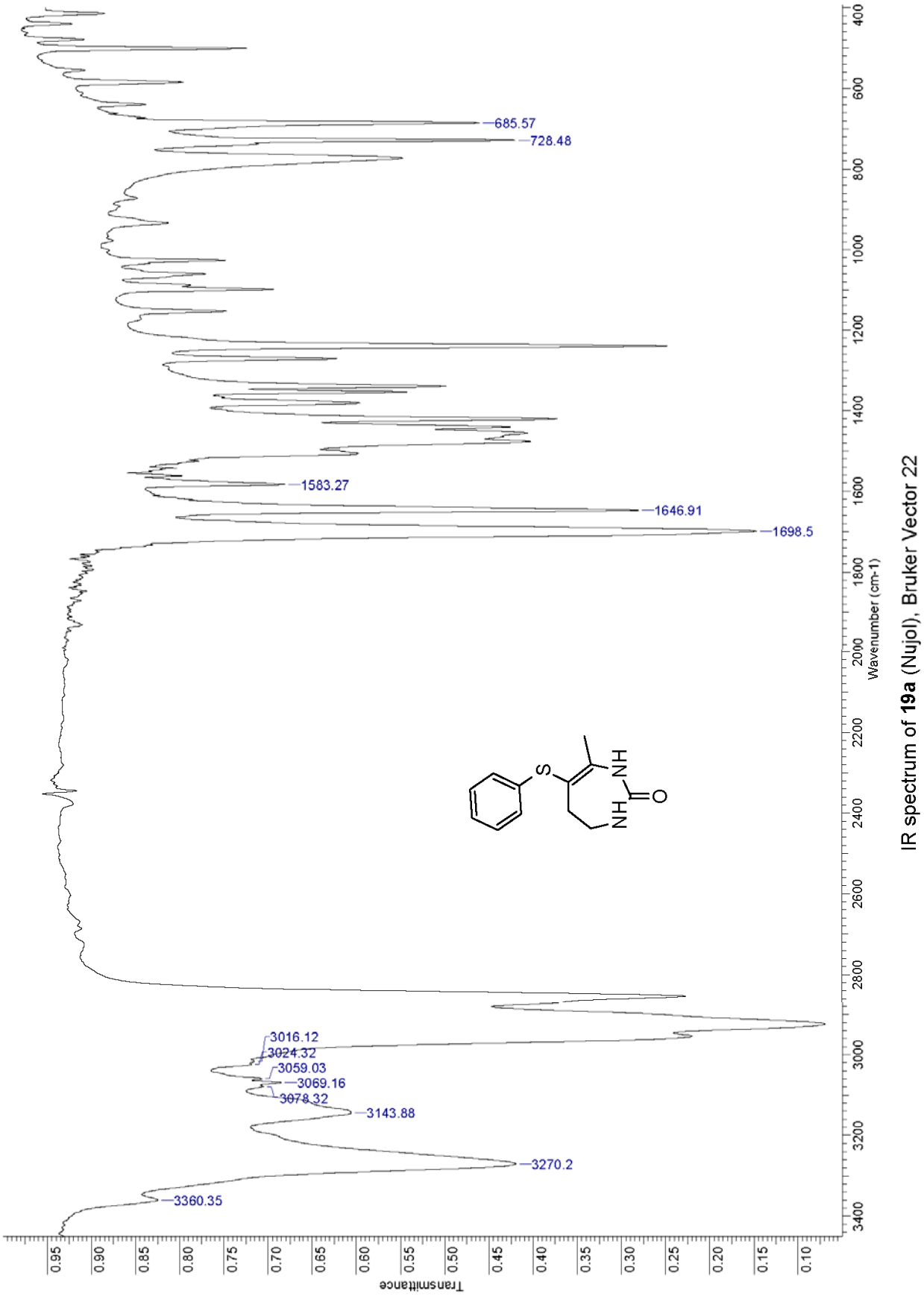


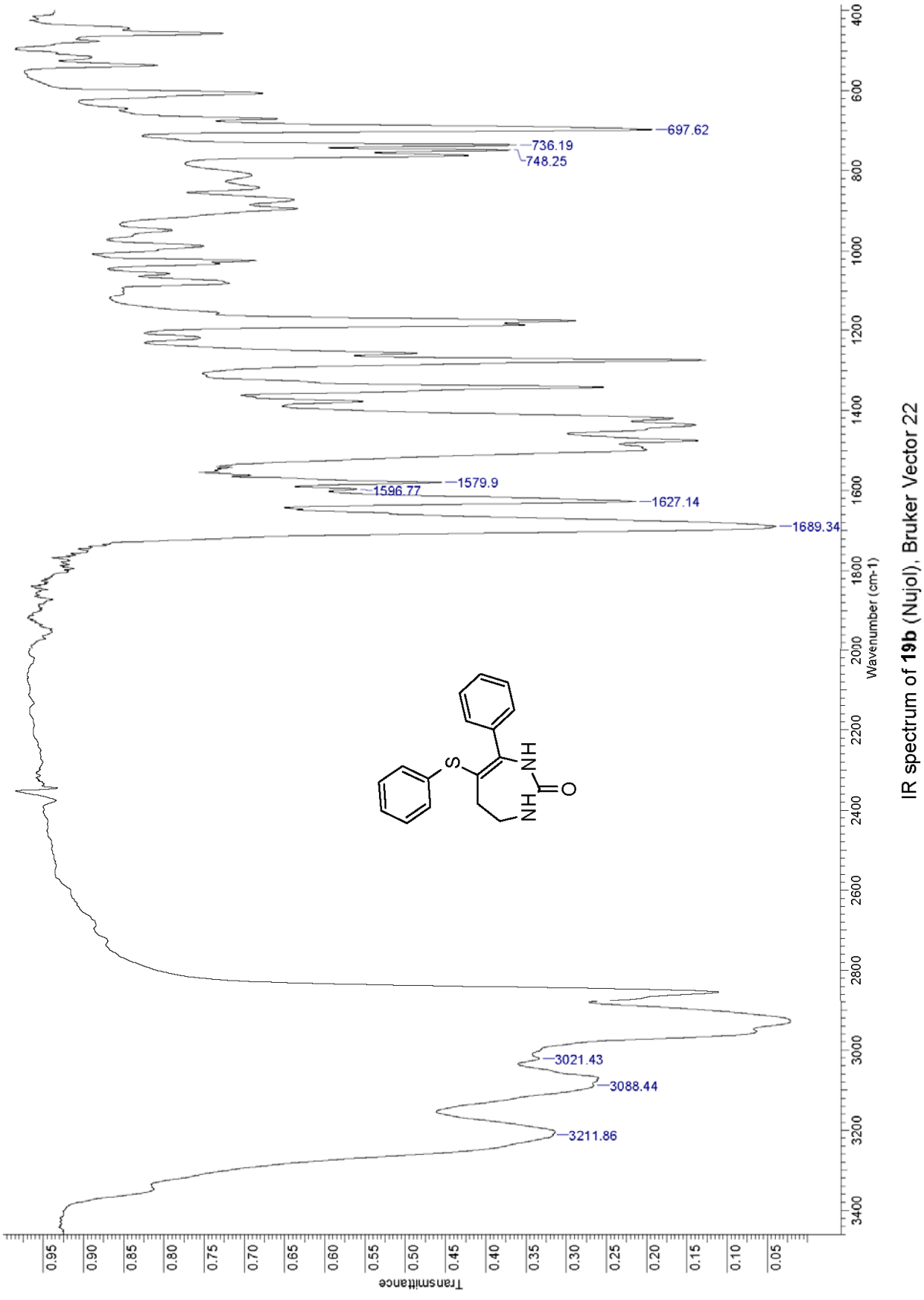
IR spectrum of **17a** (Nujol), Bruker Vector 22


693.77
717.87
737.64
1317.63
1428.03
1441.05
1459.37
1464.19
1493.12
1580.86
1627.63
1686.44
1724.05
1776.12
3023.84
3055.17
3081.69
3095.67
3127.01
3180.04
3227.77
Wavenumber (cm-1)
Transmittance
IR spectrum of 17b (Nujol), Bruker Vector 22

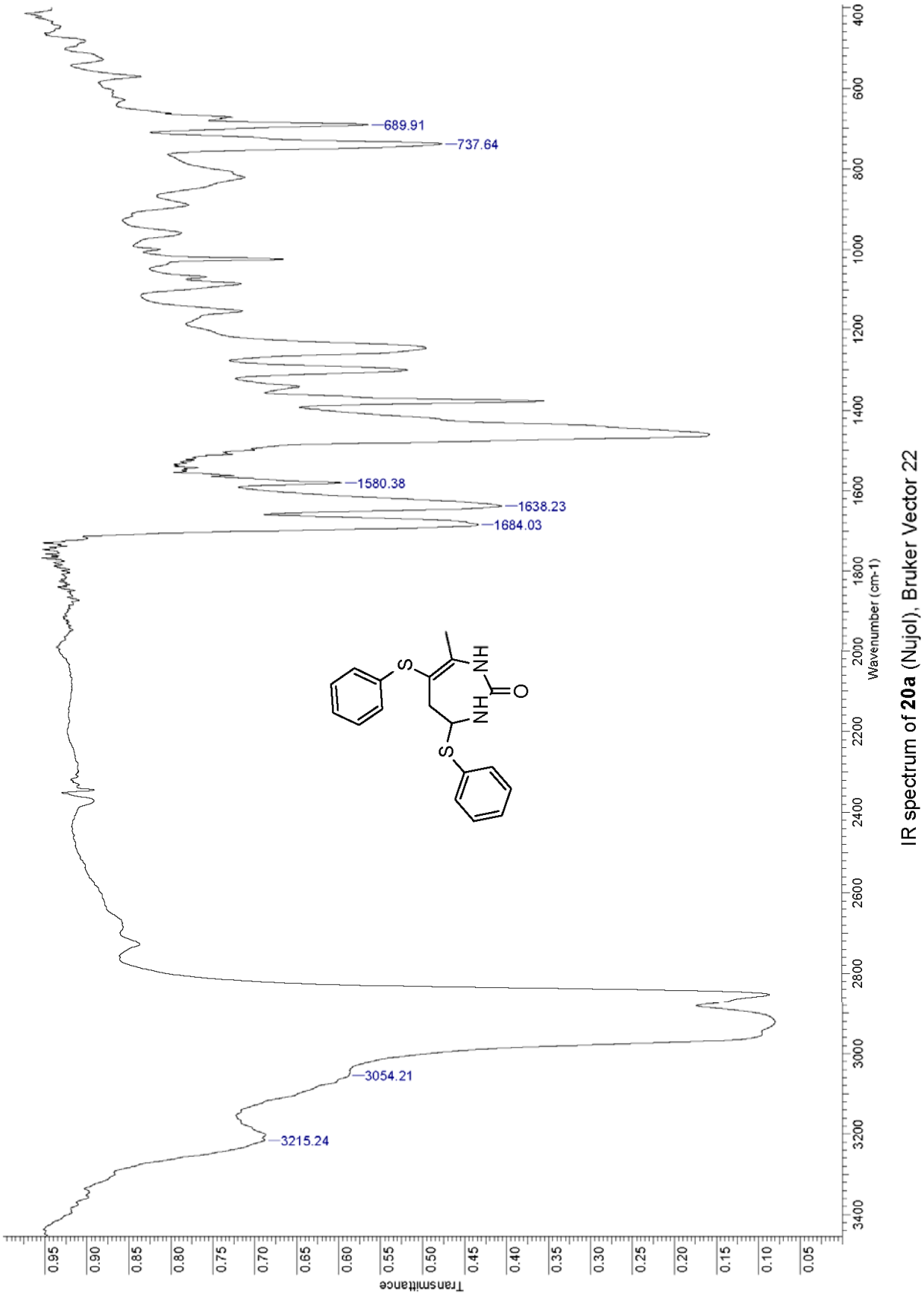

740.53
1498.9
1582.31
1650.77
1693.68
1708.14
1773.23
3070.6
3101.46
3147.74
3244.16
Transmittance
Wavenumber (cm-1)
IR spectrum of 18a (Nujol), Bruker Vector 22

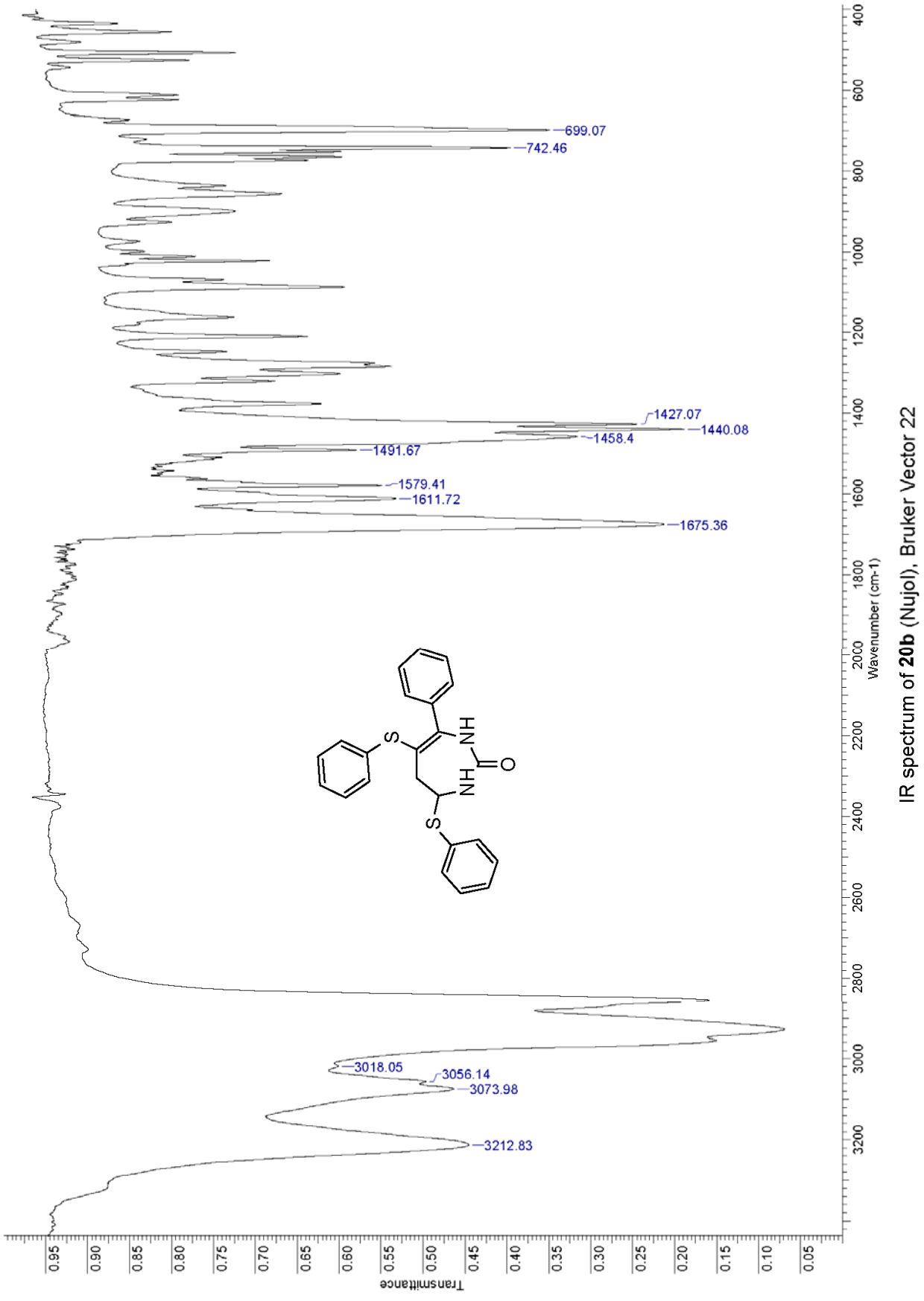


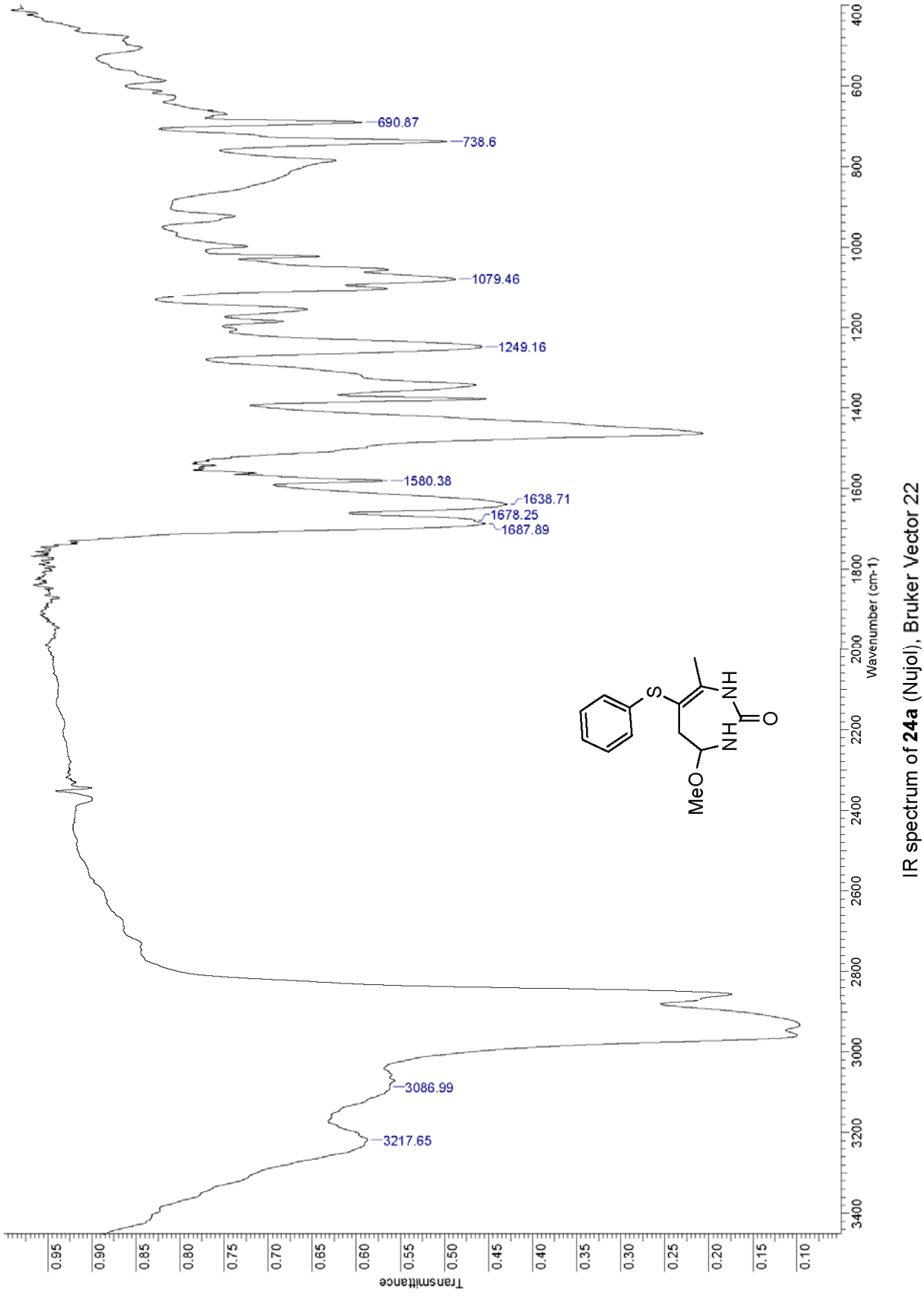




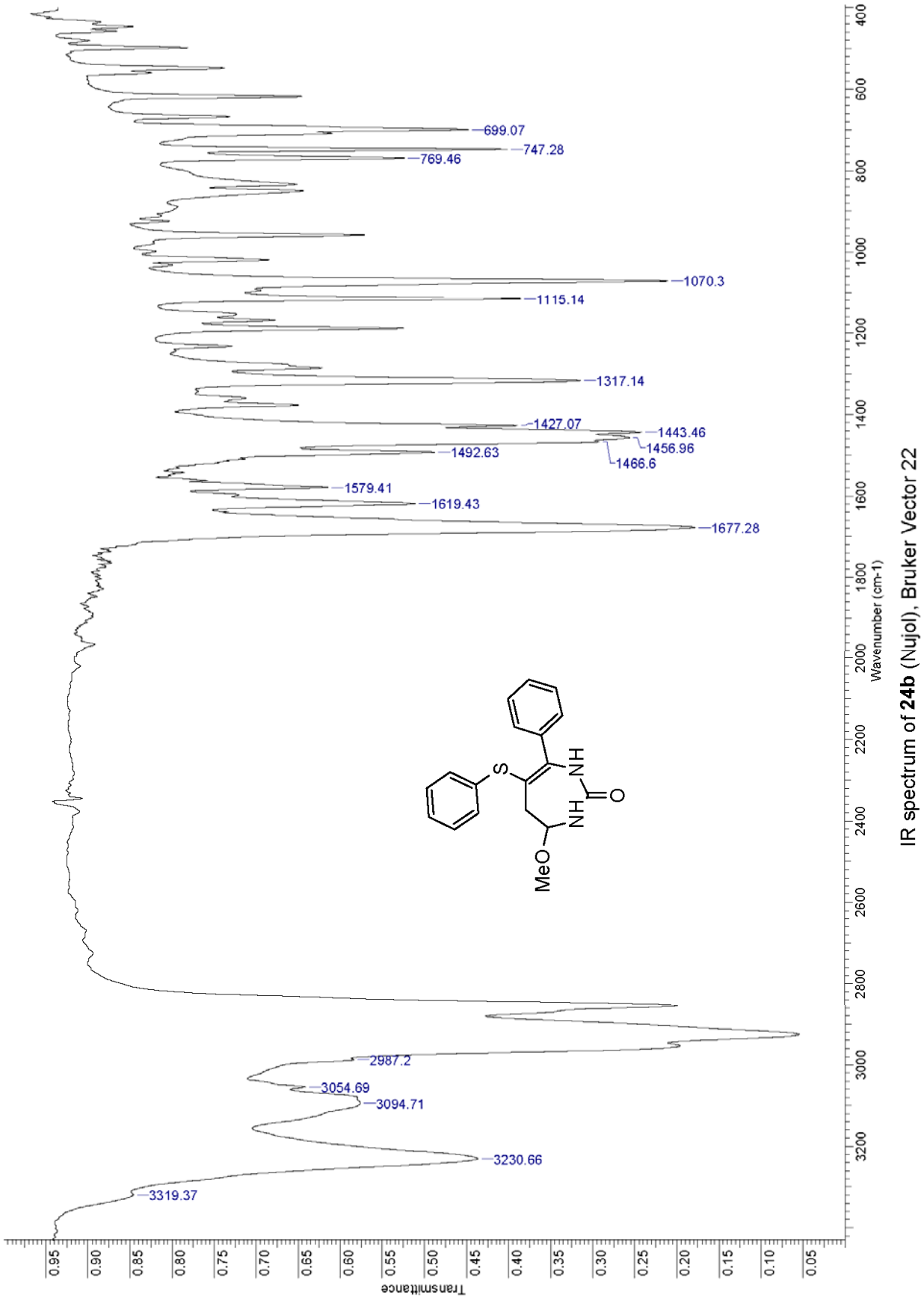
IR spectrum of **19b** (Nujol), Bruker Vector 22

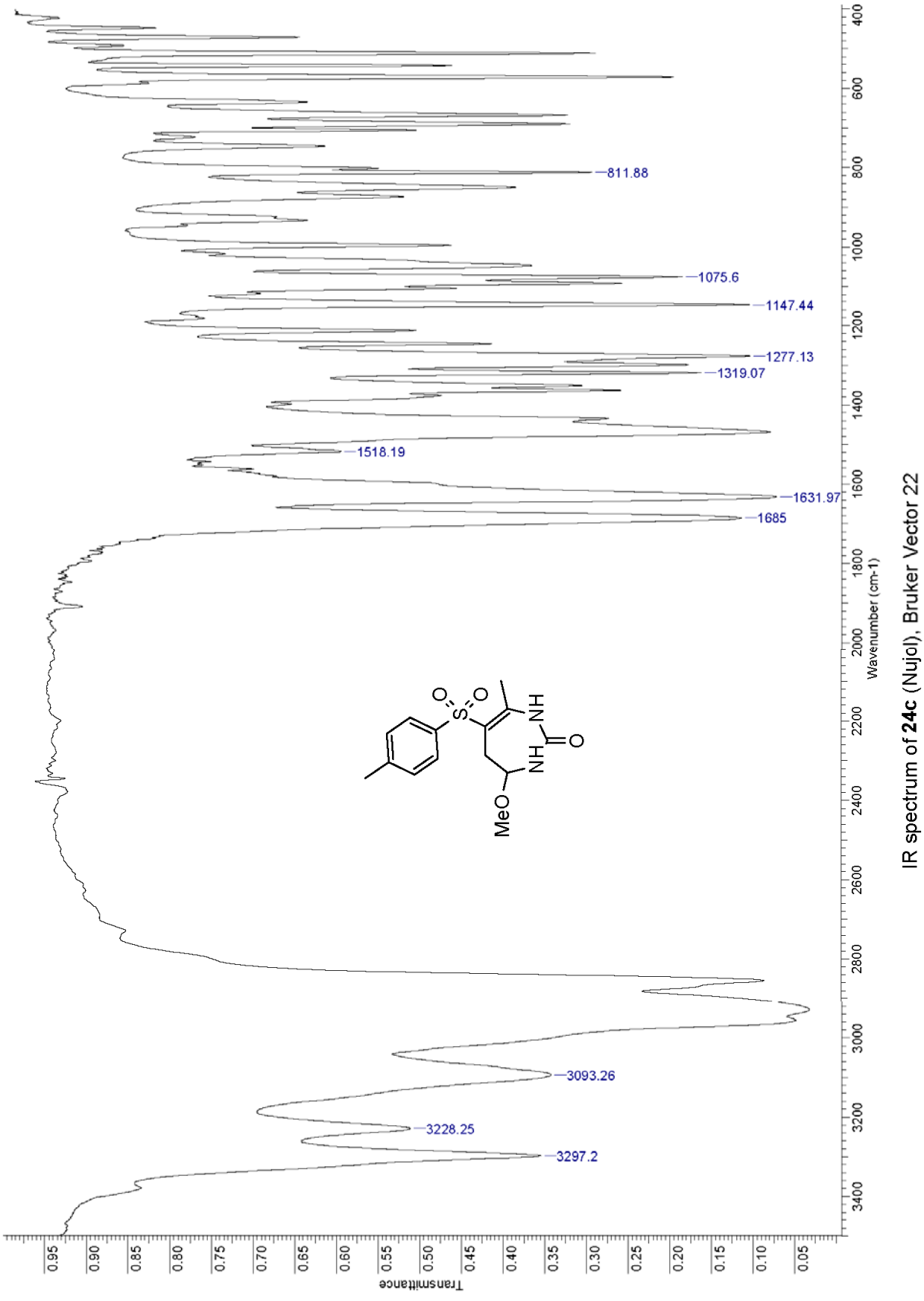

689.91
737.64
1580.38
1638.23
1684.03
3054.21
3215.24
Transmittance
Wavenumber (cm-1)
IR spectrum of 20a (Nujol), Bruker Vector 22



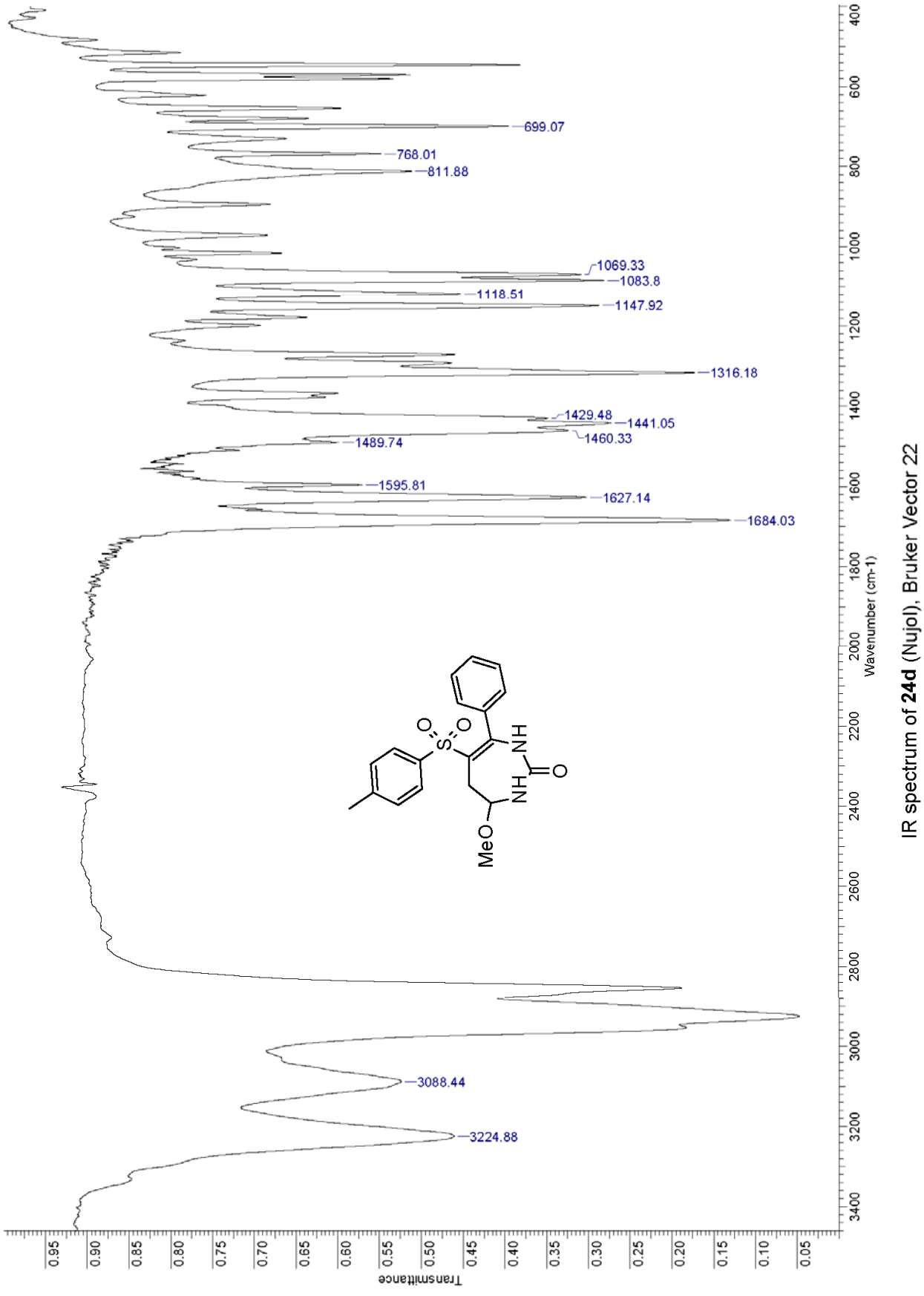


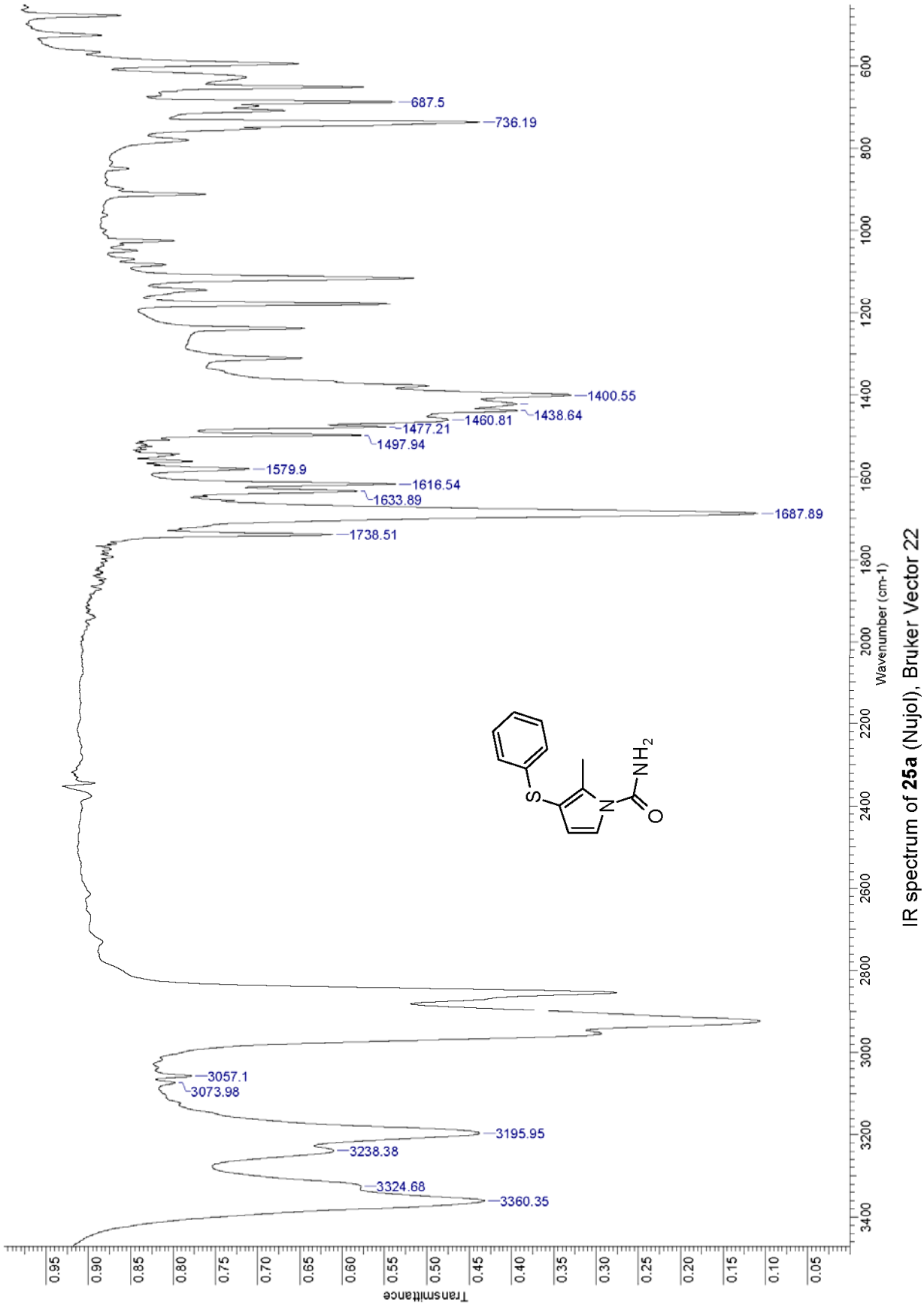
IR spectrum of **24a** (Nujol), Bruker Vector 22


699.07
747.28
769.46
1070.3
1115.14
1317.14
1427.07
1443.46
1456.96
1466.6
1492.63
1579.41
1619.43
1677.28
2987.2
3054.69
3094.71
3230.66
3319.37
Transmittance
Wavenumber (cm-1)
IR spectrum of 24b (Nujol), Bruker Vector 22
S
NH
NH
O
MeO

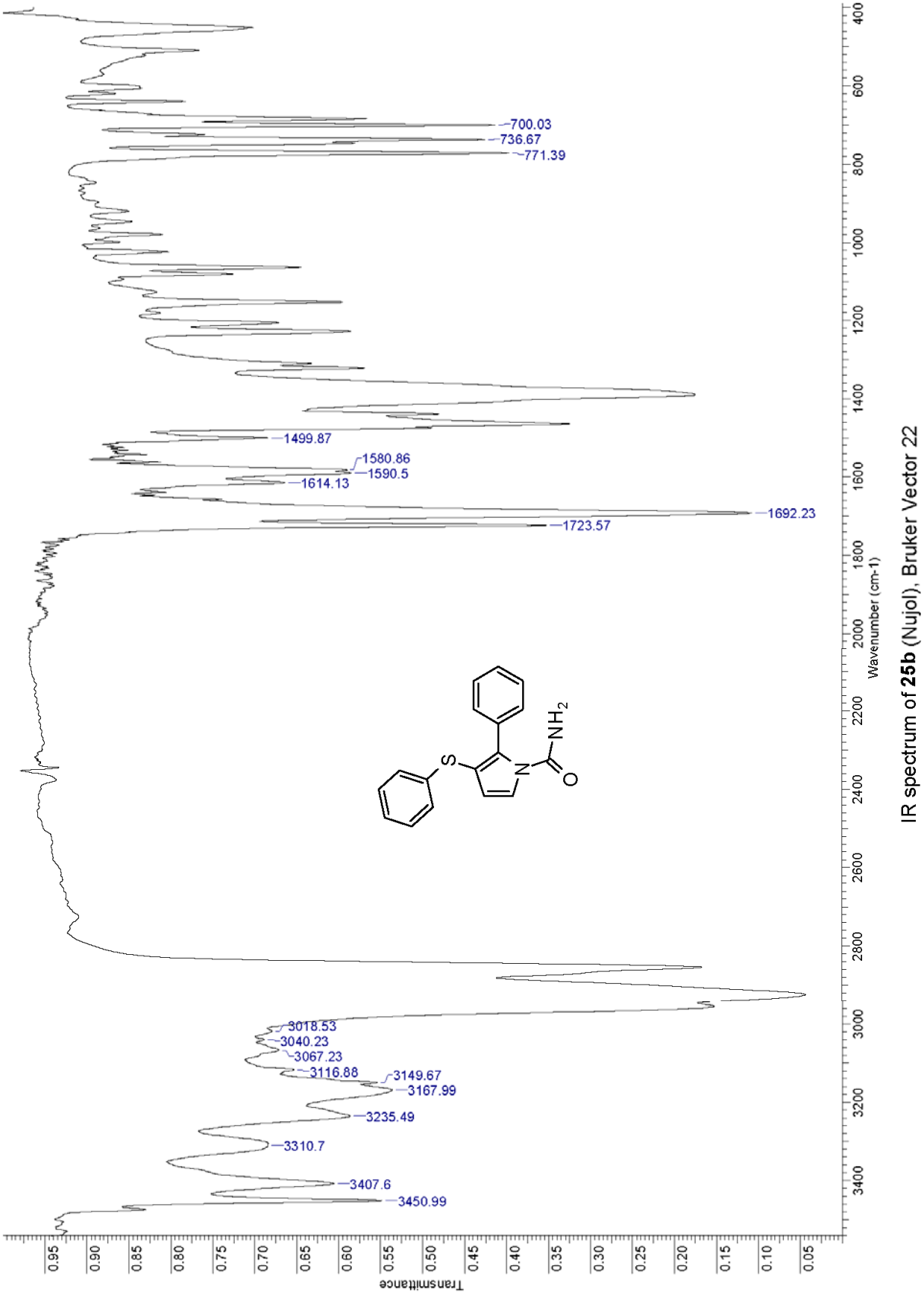


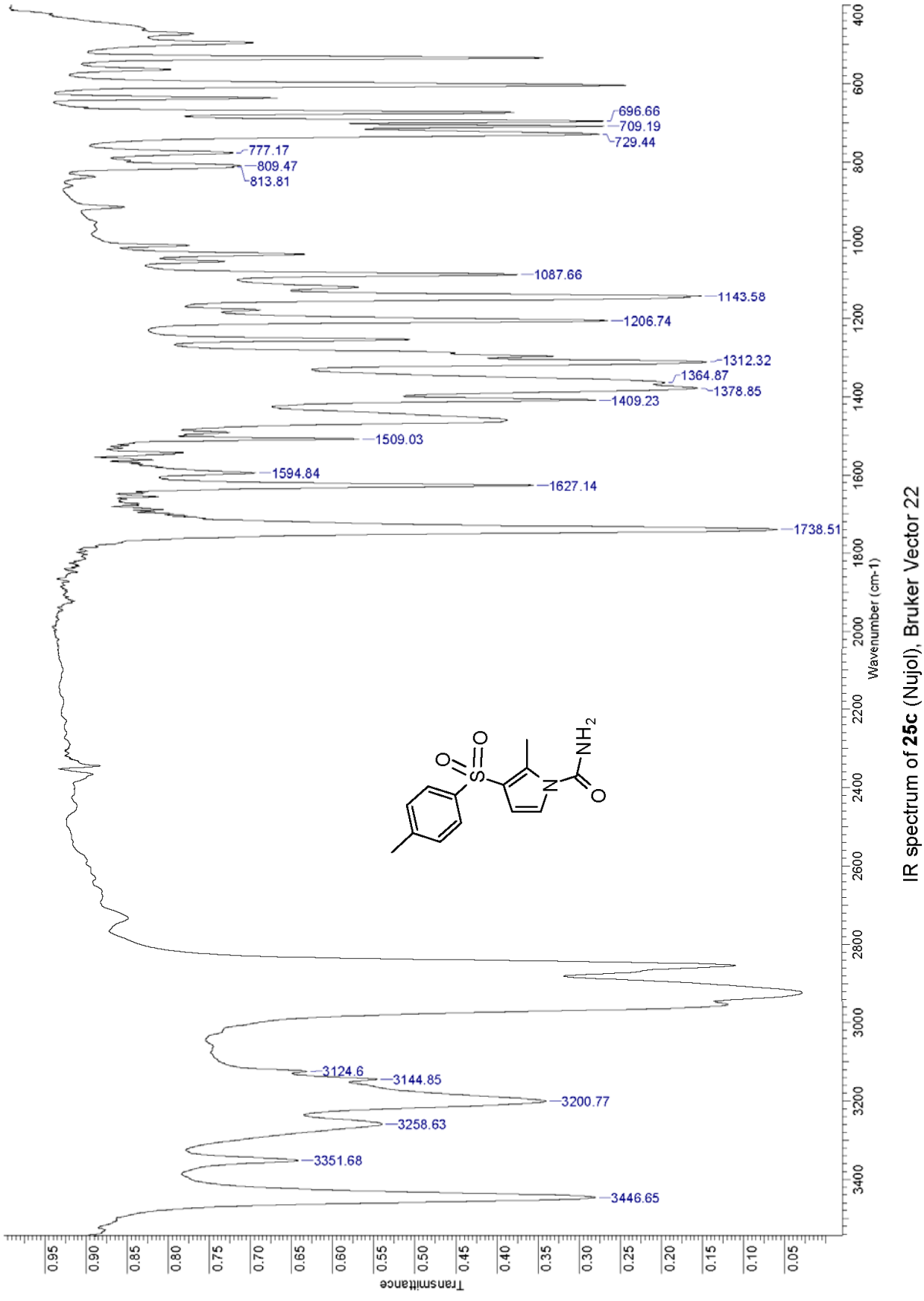
IR spectrum of **24c** (Nujol), Bruker Vector 22

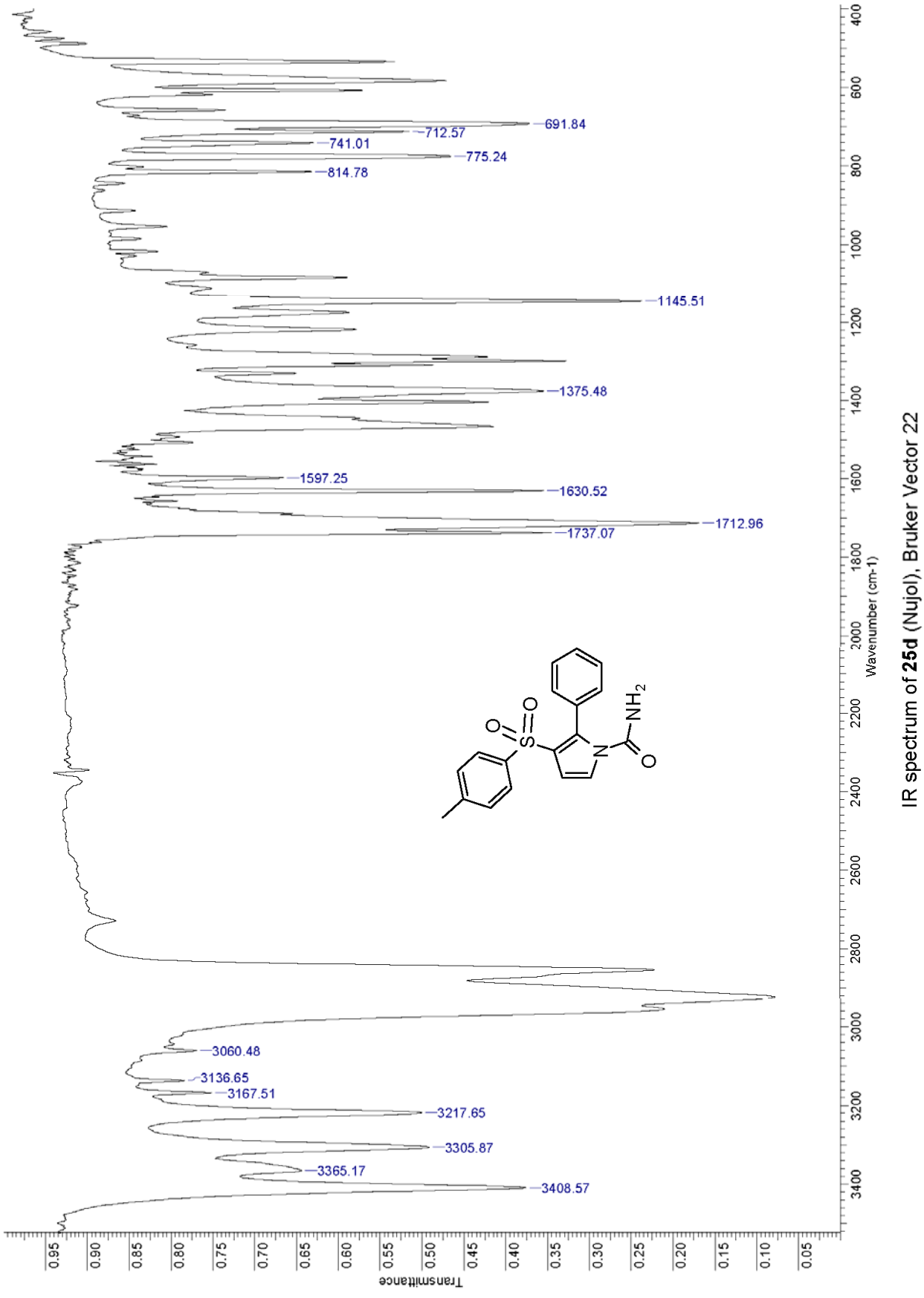

699.07
768.01
811.88
1069.33
1083.8
1118.51
1147.92
1316.18
1429.48
1441.05
1460.33
1489.74
1595.81
1627.14
1684.03
3088.44
3224.88
MeO
NH
NH
O
O
S
O
Transmittance
Wavenumber (cm-1)
IR spectrum of 24d (Nujol), Bruker Vector 22



IR spectrum of **25a** (Nujol), Bruker Vector 22






691.84
712.57
741.01
775.24
814.78
1145.51
1375.48
1597.25
1630.52
1712.96
1737.07
3060.48
3136.65
3167.51
3217.65
3305.87
3365.17
3408.57
Wavenumber (cm-1)
Transmittance
IR spectrum of 25d (Nujol), Bruker Vector 22