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Graphical Abstract

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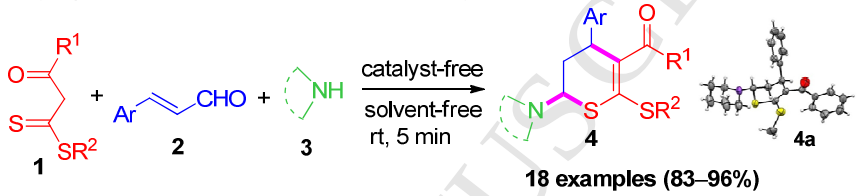

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ABSTRACT

Highly convergent and regioselective approach to hitherto unreported and synthetically demanding 6-cycloamino-2-(methyl/benzyl)sulfanyl-3-(aroyl/hetaroyl/alkanoyl)-4-aryl-5,6-dihydro-4*H*-thiopyrans has been developed via one-pot three-component domino coupling of *β*-oxodithioesters, *α*,*β*-unsaturated aldehydes, and cyclic aliphatic secondary amines at room temperature under catalyst-free and solvent-free conditions. The attractive features of this strategy include mild conditions, short reaction time, high atom-economy, excellent yields, and efficacy of forming three new bonds (C─C, C─N and C─S) and one ring in a single stroke.

1. Introduction

Design and development of practical cascades that provide maximum structural miscellany and intricacy with a minimum number of straightforward synthetic steps for the rapid generation of function-oriented molecules is a key goal in modern organic synthesis. A pressing challenge for synthetic chemists is to advance new protocols that are not only efficient, selective, and high yielding but also rapid and eco-compatible. One approach to address this challenge involves the development of eco-friendly multicomponent procedures. Multicomponent reactions[1,2] (MCRs) have experienced exponential growth over the past two decades and have become important tools for the rapid generation of molecular complexity and diversity with predefined functionality in chemical biology and drug discovery.[3,4] In the pursuit of a more efficient and greener process, performing the reactions without any solvent has appeared promising.[5]

Thiopyran is a well-known privileged structural motif, as many of its derivatives possess useful pharmacological activities.[6] They have been frequently utilized in the construction of analogues of natural products such as tetrahydrodicranenone B,[7] serricornin,[8] thromoboxanes,[9] and cyclopentanoids[10] with promising biological activities. Given their high importance, many classical methods such as Diels−Alder reaction,[11a,b] Michael addition, Pummerer-type thioglycosylation reaction, and rearrangement of sulfonium ylides[12] have been developed.

Masson and co-workers[13] have revealed the synthesis of phosphono-substituted dihydrothiopyrans using *α*-phosphono-*α*,*β*-unsaturated dithioesters. However, one-pot multicomponent approach to construct this privileged scaffold is still surprisingly rare.[14]

Albeit the reported approaches are useful tools for the synthesis of thiopyrans, most of them suffer from significant limitations such as harsh reaction conditions, long reaction time, poor yields, production of wastes, and difficult workup procedure. Therefore, more general, efficient, rapid, and viable routes are in high demand, and would be of great relevance to both synthetic and medicinal chemists. Prompted by the awe-inspiring chemistry of *β*-oxodithioesters, on the basis of retrosynthetic analysis, we envisioned that the scaffold of dihydro-4*H*-thiopyran could be constructed via three-component

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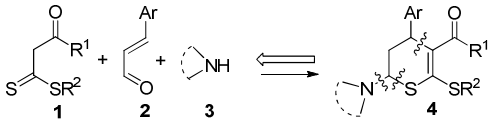
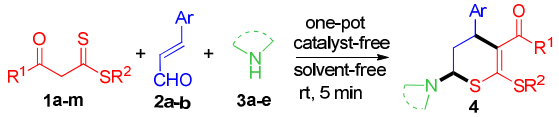
domino coupling of *β*-oxodithioesters **1**, *α,β*-unsaturated aldehydes **2**, and amines **3** (Scheme 1).



Scheme 1. A proposed three-component approach to 5,6-dihydro-4*H*-thiopyrans **4**.

2. Results and discussion

β-Oxodithioesters have received much attention as versatile building blocks in organic synthesis.[15] Our recent efforts in the development of a novel synthetic strategy to construct heterocyclic scaffolds[16] utilizing *β*-oxodithioesters as a key substrate prompted us to investigate the present coupling reaction with the aim to devise more general synthetic route for bioactive heterocycles. Thus, as a part of our recent research program to develop solvent-free new MCRs,[17] herein, we report an easy access to 5,6-dihydro-4*H*-thiopyrans via one-pot three-component domino coupling of *β*-oxodithioesters, *α,β*-unsaturated aldehydes, and cyclic aliphatic secondary amines at room temperature under solvent-free conditions (Scheme 2).

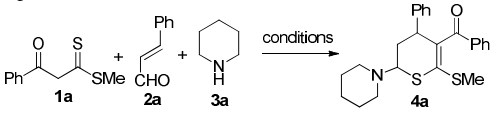


1a: R^1=Ph, R^2=Me; **1b**: R^1=2-BrC$_6$H$_4$, R^2=Me; **1c**: R^1=1-naphthyl, R^2=Me;
1d: R^1=2-thienyl, R^2=Me; **1e**: R^1=3-pyridyl, R^2=Me; **1f**: R^1=3-MeOC$_6$H$_4$, R^2=Me;
1g: R^1=Ph, R^2=PhCH$_2$; **1h**: R^1=2-furyl, R^2=Me; **1i**: R^1=4-MeOC$_6$H$_4$, R^2=Me;
1j: R^1=3-(N-methylpyrrole), R^2=Me; **1k**: R^1=isopropyl, R^2=Me;
1l: R^1=4-CF$_3$C$_6$H$_4$, R^2=Me; **1m**: R^1=ferrocenyl, R^2=Me;
2a: Ar=Ph; **2b**: Ar=4-MeOC$_6$H$_4$;
3a=piperidine; **3b**=morpholine; **3c**=1-phenyl piperazine;
3d=ethyl-1-piperazine carboxylate; **3e**=pyrrolidine

Scheme 2. Synthesis of 5,6-dihydro-4*H*-thiopyrans **4**.

β-Oxodithioesters are not commercially sourced, and were synthesized by literature methods.[15] Initially, the three-component model reaction of methyl 3-oxo-3-phenyl-propanedithioate (**1a**), cinnamaldehyde (**2a**), and piperidine (**3a**) was investigated without any catalyst under varying conditions to optimize the reaction conditions, and the results are listed in Table 1. Interestingly, DCM and EtOH provided the desired product at 25 °C (Table 1, entries 1 and 3). Increasing the temperature decreased the yields drastically (Table 1, entries 2 and 4). The reaction became sluggish in DMSO and yield of the product decreased considerably (Table 1, entry 5). No reaction occurred in H_2O at 25 °C as well as at 100 °C even after 24 h (Table 1, entries 6 and 7). This might be due to insolubility of *β*-oxodithioesters in water.

Table 1
Optimization of reaction conditions[a]

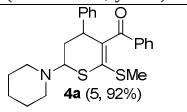
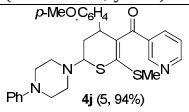
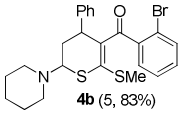
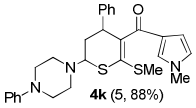
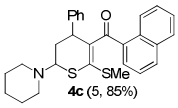
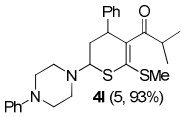
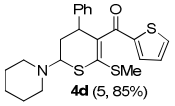
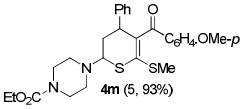
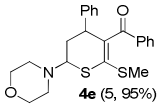
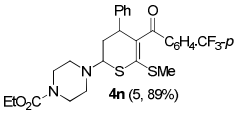
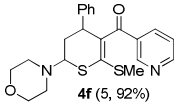
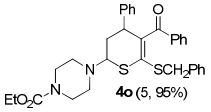
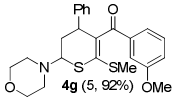
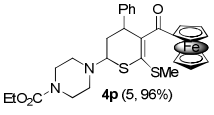


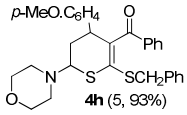
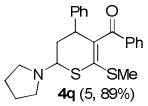
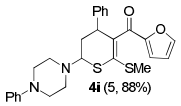
Entry	Solvent	Temp (°C)	Time	Yield[b] (%)
1	DCM	25	30 min	82
2	DCM	40	30 min	40
3	EtOH	25	30 min	80
4	EtOH	80	30 min	32
5	DMSO	25	60 min	65
6	H_2O	25	24 h	nr[c]
7	H_2O	100	24 h	nr[c]
8	none	25	5 min	92
9	none	40	15 min	45
10	None	15	60 min	76

[a] Reaction conditions: 1.0 mmol of each **1a**, **2a** and **3a**; and 2 ml of each solvent was used. [b]Isolated yield. [c]nr = no reaction.

Motivated by the above results, we investigated the model reaction under solvent-free conditions. To our pleasure, a breakthrough result was achieved that is the desired thiopyran **4a** was obtained in 92% yield at 25 °C in 5 min (Table 1, entry 8). Next the effect of reaction temperature was also examined, and the results showed that increasing or decreasing the temperature did not bring any improvement (Table 1, entries 9 and 10). It was observed that at elevated temperature (> 40 °C), the lower yield of the desired product is due to a competitive formation of thioamide.[16a] Hence, the optimal conditions were equimolar amounts of **1a**, **2a**, and **3a** at 25 °C under solvent-free conditions (Table 1, entry 8).With optimal conditions established, we then investigated the scope and limitations of the reaction using various *β*-oxodithioesters **1a-m**, *α,β*-unsaturated aldehydes **2a-b**, and secondary cyclic amines **3a-e**. The results are presented in Table 2.

Table 2
Synthesis of dihydrothiopyrans **4**

Entry	Product **4** (time in min, yield[a])	Entry	Product **4** (time in min, yield[a])
1	 **4a** (5, 92%)	10	 **4j** (5, 94%)
2	 **4b** (5, 83%)	11	 **4k** (5, 88%)
3	 **4c** (5, 85%)	12	 **4l** (5, 93%)
4	 **4d** (5, 85%)	13	 **4m** (5, 93%)
5	 **4e** (5, 95%)	14	 **4n** (5, 89%)
6	 **4f** (5, 92%)	15	 **4o** (5, 95%)
7	 **4g** (5, 92%)	16	 **4p** (5, 96%)

8	 **4h** (5, 93%)	17	 **4q** (5, 89%)
9	 **4i** (5, 88%)	18	 **4r** (5, 91%)

[a] Isolated pure yields.

In general, all reactions were completed within 5 minutes providing a range of valuable 5,6-dihydro-4*H*-thiopyrans **4a-r** in 83-96% yields. Both electron-rich and electron-poor aryl groups at the R^1 position were well tolerated and showed very good chemical yields of thiopyrans **4**. The reaction with extended aromatic group **1c** also proceeded smoothly providing the desired thiopyran **4c** in 85% yield (Table 2, entry 3). In addition, good results were also obtained by using R^1 as hetaryl substituents such as 2-thienyl, 3-pyridyl, 2-furyl, and 3-(N-methylpyrrole) (Table 2, entries 4, 6, 9 and 11). Furthermore, aliphatic dithioester **1k** containing R^1 as isopropyl group was also successful affording the product **4l** in 93% yield (Table 2, entry 12). Importantly, ferrocenoyl dithioester **1m** was also a viable substrate for this approach affording the desired thiopyran **4p** in 96% yield (Table 2, entry 16). A limited variation has also been made at the 2- and 4-position of thiopyran ring providing the desired thiopyran derivatives in excellent yields (Table 2, entries 8, 10, 15, and 18). The results showed the good scope and generality of the various starting substrates.

Furthermore, to expand the scope of this reaction and to gain a greater insight into the reaction, various primary amines, tertiary amines, and acyclic secondary amines were also investigated but unfortunately, primary and tertiary amines could not trigger the reaction in the desired direction even after 24 h, while acyclic secondary amines showed a complex TLC pattern of several very close spots, which could not be isolated. This result limits the scope of the reaction to some extent. The structural characterization of **4a-r** was achieved by spectroscopic data (^{1}H and ^{13}C NMR, IR, and HRMS) and unequivocally established by the X-ray single crystal diffraction analysis[18] of one of the representative compound 3-benzoyl-2-methylsulfanyl-4-phenyl-6-piperidino-5,6-dihydro-4*H*-thiopyran **4a** (Figure 1).

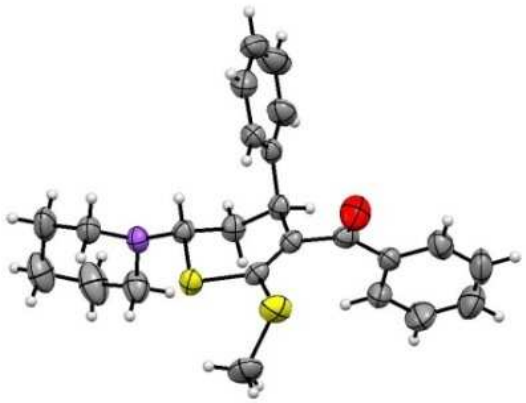
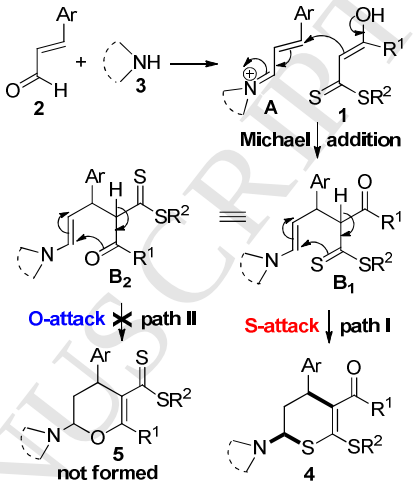


Fig. 1. ORTEP diagram of **4a**.

On the basis of results obtained, a plausible mechanism is outlined in Scheme 3. We conceived that initially a reaction between aldehyde **2** and secondary amine **3** would occur to give iminium ion intermediate **A**. Subsequently, Michael-type attack of enolic form of *β*-oxodithioester **1** to iminium ion **A** generated open-chain intermediate $\mathbf{B_1}$, which could probably cyclize via its two possible rotamers $\mathbf{B_1}$ and $\mathbf{B_2}$ through pathways **I** and **II** to furnish dihydrothiopyran **4** and dihydropyran **5**, respectively. The intermediate $\mathbf{B_1}$ undergoes regioselective cyclization by attack through sulfur via route **I** to give the desired dihydrothiopyran **4** exclusively in accordance with our previous results.[17b] The alternative O-cyclization of $\mathbf{B_2}$ via route **II** could lead to pyran **5**, which was not observed even in trace during our investigations.



Scheme 3. Plausible mechanism for the formation of **4**.

3. Conclusion

In summary, a rapid and highly efficient regioselective approach to densely functionalized 5,6-dihydro-4*H*-thiopyrans has been developed for the first time via one-pot three-component domino coupling of *β*-oxodithioesters, *α,β*-unsaturated aldehydes, and cyclic aliphatic secondary amines at room temperature under catalyst-free and solvent-free conditions in excellent yields. Importantly, for the first time cyclic aliphatic secondary amine has been incorporated in the core nucleus of thiopyran at position 6. The simplicity of execution, mild conditions, short reaction time (5 min) flexible substitution patterns, and easy purification make the protocol eye-catching for academic research and realistic applications.

4. Experimental section

4.1. General

The starting materials were commercially available and used as received without any further purification. All reagents were weighed and handled in air at room temperature. *β*-Oxodithioesters **1** were prepared following the known procedures.[15] Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates. Infrared (IR) spectra are measured in KBr, and wavelengths (ν) are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on NMR spectrometer operating at 500/300 and 125/75 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) using the residue solvent peaks as reference relative to tetramethylsilane (TMS). Coupling constant (J) values are given in hertz (Hz). Mass spectra were recorded using electrospray ionization (ESI) mass spectrometry. The melting points are uncorrected.

*4.2. General procedure for the synthesis of dihydro-4H-thiopyran (**4a-r**)*

To a mixture of *β*-ketodithioesters **1** (1.0 mmol) and cinnamaldehydes **2** (1.0 mmol), secondary cyclic amines **3** (1.0 mmol) was added and the reaction mixture was stirred for the stipulated period of time at room temperature. After completion of the reaction (monitored by TLC), water (20 mL) was added to the reaction mixture followed by extraction with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated under vacuo. The crude residue thus obtained was purified by column chromatography over silica gel using ethyl acetate/hexane mixture as eluent to afford pure dihydrothiopyran.

*4.2.1. 3-Benzoyl-2-methylsulfanyl-4-phenyl-6-piperidino-5,6-dihydro-4H-thiopyran (**4a**).*

Pale yellow solid, mp 111-113 °C; FT IR (KBr, cm^{-1}): 3053, 2929, 1654, 1575, 1254, 1179; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 6.9 Hz, 2H), 7.45-7.25 (m, 8H), 4.53 (dd, J_1 = 1.5 Hz, J_2 = 12.0 Hz, 1H), 4.32 (t, J = 3.6 Hz, 1H), 2.78 (t, J = 5.2 Hz, 2H), 2.61 (t, J = 5.1 Hz, 2H), 2.36-2.23 (m, 5H), 1.55-1.45 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.58, 141.16, 138.24, 132.08, 130.05, 129.07, 128.74, 128.52, 128.32, 128.22, 126.90, 70.38, 49.77, 44.14, 34.72, 25.68, 24.13, 17.81; HRMS $[M+H]^+$ calcd for $C_{24}H_{28}NOS_2$ 410.1607, found 410.1616.

*4.2.2. 3-(2-Bromobenzoyl)-2-methylsulfanyl-4-phenyl-6-piperidino-5,6-dihydro-4H-thiopyran (**4b**).*

Pale yellow solid, mp 142-144 °C; FT IR (KBr, cm^{-1}): 3037, 2946, 1610, 1491, 1251, 1176; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 8.0 Hz, 1H), 7.21-7.16 (m, 3H), 7.10 (t, J = 8.25 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.91-6.90 (m, 2H), 6.58 (d, J = 7.0 Hz, 1H), 4.38 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 1H), 4.05 (br, 1H), 2.83-2.79 (m, 2H), 2.66-2.65 (m, 2H), 2.54 (s, 3H), 2.46-2.40 (m, 2H), 1.58-1.56 (m, 4H), 1.47-1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.62, 142.30, 141.89, 132.05, 129.68, 128.39, 128.01, 127.86, 126.75, 126.67, 124.23, 118.79, 72.16, 49.54, 43.64, 34.32, 25.79, 24.21, 16.35; HRMS $[M+H]^+$ calcd for $C_{24}H_{27}BrNOS_2$ 488.0712, found 488.0717.

*4.2.3. 2-Methylsulfanyl-3-(1-naphthoyl)-4-phenyl-6-piperidino-5,6-dihydro-4H-thiopyran (**4c**).*

Pale yellow solid, mp 161-162 °C; FT IR (KBr, cm^{-1}): 3016, 2939, 1645, 1562, 1256, 1183; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.0 Hz, 1H), 7.79 (dd, J_1 = 8.0 Hz, J_2 = 11.0 Hz, 2H), 7.47-7.41 (m, 2H), 7.23-7.14 (m, 4H), 7.03-6.96 (m, 3H), 4.43 (dd, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 4.15 (t, J = 3.5 Hz, 1H), 2.83-2.82 (m, 2H), 2.70-2.68 (m, 2H), 2.47 (s, 3H), 2.43-2.25 (m, 2H), 1.60 (br, 4H), 1.48-1.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.05, 133.38, 130.16, 129.80, 128.51, 128.21, 128.03, 126.87, 126.79, 126.08, 125.22, 125.07, 124.50, 71.11, 49.81, 43.40, 33.81, 25.38, 23.93, 16.82; HRMS $[M+H]^+$ calcd for $C_{28}H_{30}NOS_2$ 460.1763, found 460.1767.

*4.2.4. 2-Methylsulfanyl-4-phenyl-6-piperidino-3-(2-thienoyl)-5,6-dihydro-4H-thiopyran (**4d**).*

Pale yellow solid, mp 111-112 °C; FT IR (KBr, cm^{-1}): 3028, 2932, 1661, 1567, 1251, 1172; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (br, 2H), 7.25-7.13 (m, 5H), 7.02 (br, 1H), 4.52 (dd, J_1 = 1.5 Hz, J_2 = 11.1 Hz, 1H), 4.36 (t, J = 3.1 Hz, 1H), 2.75 (t, J = 2.5 Hz, 2H), 2.62 (t, J = 7.9 Hz, 2H), 2.47-2.23 (m, 5H), 1.54-1.45 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.03, 144.88, 141.13, 139.68, 137.03, 134.37, 133.40, 132.74, 128.44, 127.72, 126.96, 70.54, 49.74, 44.38, 35.10, 25.90, 24.27, 18.14; HRMS $[M+Na]^+$ calcd for $C_{22}H_{25}NOS_3Na$ 438.0990, found 438.0996.

*4.2.5. 3-Benzoyl-2-methylsulfanyl-6-morpholino-4-phenyl-5,6-dihydro-4H-thiopyran (**4e**).*

Pale yellow solid, mp 117-118 °C; FT IR (KBr, cm^{-1}): 2956, 2843 1648, 1594 1247, 1171; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 7.51 Hz, 2H), 7.49-7.44 (m, 2H), 7.39-7.23 (m, 6H), 4.48 (dd, J_1 = 2.4 Hz, J_2 = 11.1 Hz, 1H), 4.31 (t, J = 3.4 Hz, 1H), 3.67 (br, 4H), 2.84-2.67 (m, 4H), 2.45-2.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.47,141.16, 138.16, 133.67, 132.16, 128.73, 128.58, 128.27, 128.24, 128.05, 126.97, 69.20, 66.73, 48.73, 44.00, 34.55, 17.78; HRMS $[M+H]^+$ calcd for $C_{23}H_{26}NO_2S_2$ 412.1399, found 412.1403.

*4.2.6. 2-Methylsulfanyl-6-morpholino-4-phenyl-3-(3-pyridoyl)-5,6-dihydro-4H-thiopyran (**4f**).*

Pale yellow solid, mp 122-123 °C; FT IR (KBr, cm^{-1}): 3028, 2937, 1639, 1574, 1253, 1183; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.63 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.25-7.18 (m, 5H), 7.09-7.01 (m, 1H), 4.51 (dd, J_1 = 2.7 Hz, J_2 = 11.7 Hz, 1H), 4.39 (t, J = 3.4 Hz, 1H), 3.68 (br, 4H), 2.80-2.70 (m, 4H), 2.43-2.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.32, 167.88, 153.87, 151.70, 147.02, 136.12, 135.66, 133.99, 128.73, 128.06, 127.10, 123.30, 69.92, 66.35, 48.67, 43.82, 34.49, 17.28; HRMS $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_2S_2$ 413.1352, found 413.1360.

*4.2.7. 3-(2-Methoxybenzoyl)-2-methylsulfanyl-6-morpholino-4-phenyl-5,6-dihydro-4H-thiopyran(**4g**).*

Pale yellow solid, mp 128-129 °C; FT IR (KBr, cm^{-1}): 3045, 2952, 1624, 1587, 1286, 1176; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.20 (m, 7H), 7.08-6.99 (m, 2H), 4.47 (dd, J_1 = 2.7 Hz, J_2 = 11.7 Hz, 1H), 4.29 (t, J = 3.6 Hz, 1H), 3.74-3.67 (m, 7H), 2.80-2.69 (m, 4H), 2.43-2.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.22, 159.53, 141.15, 139.60, 133.44, 129.20, 128.61, 128.34, 128.30, 127.00, 121.42, 118.78, 112.64, 69.31, 66.73, 55.25, 48.72, 43.99, 34.49, 17.79; HRMS $[M]^+$ calcd for $C_{24}H_{27}NO_3S_2$ 441.1432, found 441.1431.

*4.2.8. 3-Benzoyl-2-benzylsulfanyl-4-(4-methoxyphenyl)-6-morpholino-5,6-dihydro-4H-thiopyran (**4h**).*

Pale yellow solid, mp 69-70 °C; FT IR (KBr, cm^{-1}): 3039, 2946, 1624, 1566, 1282, 1179; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 7.2 Hz, 2H), 7.47-7.20 (m, 8H), 7.05 (d, J = 8.4 Hz, 2H), 6.89-6.76 (m, 2H), 4.43 (dd, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 4.18-4.09 (m, 2H), 3.99-3.90 (m, 1H), 3.73-3.65 (m, 7H), 2.77-2.68 (m, 4H), 2.34-2.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.47, 158.43, 137.72, 137.07, 136.65, 135.44, 132.64, 132.26, 129.23, 128.84, 128.27, 128.24, 127.17, 113.87, 113.65, 69.01, 66.69, 55.10, 48.72, 43.23, 38.99, 34.49. HRMS $[M+H]^+$ calcd for $C_{30}H_{32}NO_3S_2$ 518.1818, found 518.1822.

*4.2.9. 3-(2-Furoyl)-2-methylsulfanyl-4-phenyl-6-(4-phenylpiperazino)-5,6-dihydro-4H-thiopyran (**4i**).*

Pale yellow solid, mp 101-103 °C; FT IR (KBr, cm^{-1}): 3042, 2944, 1654, 1589, 1248, 1181; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.36 (m, 2H), 7.20-7.05 (m, 5H), 6.94-6.75 (m,5H), 6.47-6.28 (m, 1H), 4.45-4.43 (m, 2H), 3.11-3.05 (m, 4H), 2.87-2.74 (m, 4H), 2.39-2.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.96, 153.22, 151.02, 145.87, 142.18, 141.29, 132.76, 129.07, 128.51, 128.28, 126.88, 120.01, 117.79, 116.28, 112.24, 69.01, 49.20, 48.38, 43.47, 35.22, 18.05; HRMS $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_2S_2$ 477.1665, found 477.1671.

*4.2.10.4-(4-Methoxyphenyl)-2-methylsulfanyl-6-(4-phenylpiperazino)-3-(3-pyridoyl)-5,6-dihydro-4H-thiopyran (**4j**).*

Pale yellow solid, mp 93-95 °C; FT IR (KBr, cm^{-1}): 3051, 2926, 1641, 1579, 1278, 1152; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.64 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.25 (br, 2H), 7.13-7.10 (m, 2H), 6.94-6.81 (m, 6H), 4.59 (dd, J_1 = 2.4 Hz, J_2 = 11.4 Hz, 1H), 4.34 (t, J = 3.9 Hz, 1H), 3.76 (s, 3H), 3.16 (br, 4H), 3.00-2.85 (m, 4H), 2.71-2.63 (m, 4H), 2.45-2.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.44, 158.58, 151.86, 151.03, 149.64, 145.99, 135.58, 134.57, 133.14, 131.73, 129.15, 129.09, 123.27, 120.07, 116.31, 114.12, 69.82, 55.16, 49.22, 48.44, 43.16, 34.96, 17.28; HRMS $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_2S_2$ 518.1930, found 518.1938.

*4.2.11. 3-(N-Methyl-2-pyrroloyl)-2-methylsulfanyl-4-phenyl-6-(4-phenylpiperazino)-5,6-dihydro-4H-thiopyran (**4k**).*

Pale yellow solid, mp 154-155 °C; FT IR (KBr, cm^{-1}): 3048, 2916, 1638, 1584, 1228, 1172; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.26 (m, 6H), 7.21-7.09 (m, 2H), 6.97-6.94 (m, 2H), 6.90 (t, J = 7.2 Hz, 1H), 4.54 (dd, J_1 = 2.5 Hz, J_2 = 11.5 Hz, 1H), 4.36 (t, J = 4.0 Hz, 1H), 3.62 (s, 3H), 3.24-3.17 (m, 4H), 3.03-3.01 (m, 2H), 2.93-2.89 (m, 2H), 2.41 (s, 3H), 2.33-2.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.40, 141.27, 136.94, 133.79, 129.20, 128.50, 128.48, 128.23, 128.06, 126.90, 125.74, 123.18, 120.52, 116.56, 110.28, 68.23, 49.48, 48.37, 44.18, 36.62, 34.84, 18.43; HRMS $[M+H]^+$ calcd for $C_{28}H_{32}N_3OS_2$ 490.1981, found 490.1983.

*4.2.12. 3-Isopropanoyl-2-methylsulfanyl-4-phenyl-6-(4-phenylpiperazino)-5,6-dihydro-4H-thiopyran (**4l**).*

Pale yellow solid, mp 94-95 °C; FT IR (KBr, cm^{-1}): 3017, 2944, 1636, 1572, 1284, 1163; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.16 (m, 7H), 6.91-6.86 (m, 3H), 4.38-4.32 (m, 2H), 3.15-3.11 (m, 4H), 2.95-2.80 (m, 5H), 2.47-2.37 (m, 5H), 0.99 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.10, 153.38, 151.06, 141.67, 129.10, 128.78, 127.94, 126.99, 126.69, 120.11, 116.35, 69.17, 49.25, 48.15, 42.61, 35.88, 34.31, 19.86, 18.87, 16.75; HRMS $[M+H]^+$ calcd for $C_{26}H_{33}N_2OS_2$ 453.2029, found 453.2028.

*4.2.13. 6-(1-Carboethoxyl)piperazino-3-(4-methoxybenzoyl)-2-methylsulfanyl-4-phenyl-5,6-dihydro-4H-thiopyran (**4m**).*

Pale yellow solid, mp 140-141°C; FT IR (KBr, cm^{-1}): 3015, 2925, 1642, 1572, 1282, 1167; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.5 Hz, 2H), 7.30-7.09 (m, 5H), 6.88 (d, J = 8.5 Hz, 2H), 4.52 (dd, J_1 = 2.0 Hz, J_2 = 12.0 Hz, 1H), 4.28 (t, J = 3.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.48-3.41 (m, 4H), 2.77 (br, 2H), 2.65 (t, J = 4.7 Hz, 2H), 2.35 (s, 3H), 2.29-2.25 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.55, 163.28, 155.35, 141.18, 136.27, 131.49, 130.46, 128.60, 128.39, 127.03, 113.65, 113.40, 68.62, 61.47, 55.43, 48.52, 48.34, 44.33, 34.97, 18.04, 14.67; HRMS $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_4S_2$ 513.1876, found 513.1901.

*4.2.14.6-(1-Carboethoxyl)piperazino-2-methylsulfanyl-4-phenyl-3-(4-trifluoromethylbenzoyl)-5,6-dihydro-4H-thiopyran (**4n**).*

Pale yellow solid, mp 130-131 °C; FT IR (KBr, cm^{-1}): 3034, 2943, 1629, 1578, 1251, 1162; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.38-7.17 (m, 5H), 4.52 (dd, J_1 = 2.5 Hz, J_2 = 11.5 Hz, 1H), 4.33 (t, J = 3.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.49-3.41 (m, 4H), 2.77-2.65 (m, 4H), 2.37 (s, 3H), 2.32-2.27 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.95, 155.33, 141.21, 131.43, 128.80, 128.73, 128.51, 128.18, 127.22, 127.11, 125.23, 125.20, 69.71, 61.52, 48.33, 48.04, 43.93, 43.51, 34.74, 17.46, 14.66; HRMS $[M+H]^+$ calcd for $C_{27}H_{30}F_3N_2O_3S_2$ 551.1644, found 551.1652.

*4.2.15.3-Benzoyl-2-benzylsulfanyl-6-(1-carboethoxyl)piperazino-4-phenyl-5,6-dihydro-4H-thiopyran (**4o**).*

Pale yellow solid, mp 67-68 °C; FT IR (KBr, cm^{-1}): 3036, 2951, 1662, 1583, 1271, 1161; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 7.2 Hz, 2H), 7.43-6.97 (m, 13H),4.56 (dd, J_1 = 3.3 Hz, J_2 = 14.1 Hz, 1H), 4.19-3.85 (m, 5H), 3.43 (br, 4H), 2.71-2.63 (m, 4H), 2.30-2.21 (m, 2H), 1.25 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.31, 155.15, 140.55, 137.67, 136.62, 136.51, 135.97, 132.24, 129.16, 128.78, 128.46, 128.22, 127.94,127.16, 127.00, 126.91, 68.70, 61.34, 48.43, 48.17, 43.94, 43.38, 38.92, 34.47, 14.56; HRMS $[M+H]^+$ calcd for $C_{32}H_{35}N_3O_3S_2$ 559.2084, found 559.2087.

*4.2.16.6-(1-Carboethoxyl)piperazino-3-ferrocenoyl-2-methyl-sulfanyl-4-phenyl-5,6-dihydro-4H-thiopyran (**4p**).*

Pale yellow solid, mp 147-149 °C; FT IR (KBr, cm^{-1}): 3041, 2922, 1632, 1561, 1245, 1168; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.25 (m, 5H), 4.87 (br, 1H), 4.59 (br, 1H), 4.49 (br, 3H), 4.37 (br, 1H), 3.71 (br, 5H), 3.43 (br, 4H), 2.74-2.64 (m, 4H), 2.38-2.22 (m, 5H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.91, 155.33, 141.48, 137.64, 136.33, 128.95, 128.44, 127.35, 81.10, 71.86, 71.21, 70.60, 70.27, 69.82, 69.02, 61.46, 48.20, 43.90, 34.73, 18.15, 14.65; HRMS $[M]^+$ calcd for $C_{30}H_{34}FeN_2O_3S_2$ 590.1360, found 590.1360.

*4.2.17. 3-Benzoyl-2-methylsulfanyl-4-phenyl-6-pyrrolidino-5,6-dihydro-4H-thiopyran (**4q**).*

Pale yellow solid, mp 103-105 °C; FT IR (KBr, cm^{-1}): 3015, 2921, 1641, 1587, 1259, 1185; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 6.6 Hz, 2H), 7.66-7.25 (m, 8H), 4.83 (t, J = 5.8 Hz, 1H), 4.27 (br, 1H), 2.87 (t, J = 6.1 Hz, 4H), 2.36 (br, 5H), 1.78 (br, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.52, 140.93, 138.29, 133.69, 132.05, 129.00, 128.67, 128.50, 128.19, 127.38, 126.85, 67.49, 48.32, 44.18, 36.53, 24.18, 17.74; HRMS $[M+H]^+$ calcd for $C_{23}H_{26}NOS_2$ 396.1450, found 396.1454.

*4.2.18. 4-(4-Methoxyphenyl)-3-(4-methylbenzoyl)-2-methyl-sulfanyl-6-pyrrolidino-5,6-dihydro-4H-thiopyran (**4r**).*

Pale yellow solid, mp 88-90 °C; FT IR (KBr, cm^{-1}): 3047, 2942, 1649, 1585, 1273, 1165; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 6.6 Hz, 2H), 7.25-7.15 (m, 4H), 6.80 (d, J = 6.9 Hz, 2H), 4.83 (br, 1H), 4.19 (br, 1H), 3.75 (s, 3H), 2.87 (br, 4H), 2.36 (br, 5H), 1.78 (br, 7H); ^{13}C NMR (75 MHz, CDCl3): δ 195.55, 158.35, 142.99, 135.39, 133.13, 129.42, 129.25, 129.16, 129.04, 128.96, 113.83, 64.44, 55.13, 48.18, 43.66, 37.02, 24.55, 24.20, 21.60, 17.85; HRMS $[M+H]^+$ calcd for $C_{25}H_{30}NO_2S_2$ 440.1712, found 440.1711.

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Supplementary Material

Supplementary data associated with this article can be found in the online version at http://

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18. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 885756 (**4a**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

Diversity oriented catalyst-free and solvent-freeone-pot MCR at room temperature: rapid and regioselective convergent approach to highlyfunctionalized dihydro-4*H*-thiopyrans

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Supporting information

(45 pages including the cover pages)

1. Experimental section

General methods

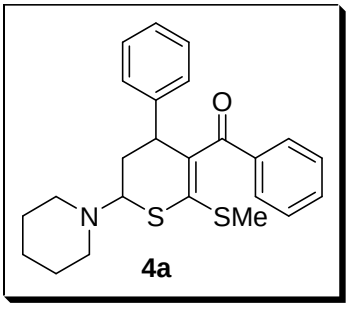
The starting materials were commercially available and used as received without further purification. *β*-Oxodithioesters **1** were prepared following the known procedure. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates. Infrared (IR) spectra are measured in KBr, and wavelengths (*v*) are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on NMR spectrometer operating at 500, 300, and 125 or 75 MHz, respectively. Chemical shifts (*δ*) are given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. *J* values are given in Hertz (Hz). Mass spectra were recorded using electrospray ionization (ESI) mass spectrometry. The melting points are uncorrected.

General procedure for the synthesis of the dihydro-4*H*-thiopyran (**4a-r**)

To a mixture of *β*-ketodithioester (1.0 mmol) and cinnamaldehyde (1.0 mmol), secondary cyclic amine (1.0 mmol) was added and the reaction mixture was stirred for the stipulated period of time at room temperature (Table-1 of main manuscript). After completion of the reaction (monitored by TLC), water (20 mL) was added to the reaction mixture followed by extraction with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated under vacuo. The crude residue was purified by column chromatography over silica gel (100-200 mesh) using ethyl acetate/hexane mixture as eluent to afford pure dihydrothiopyran.

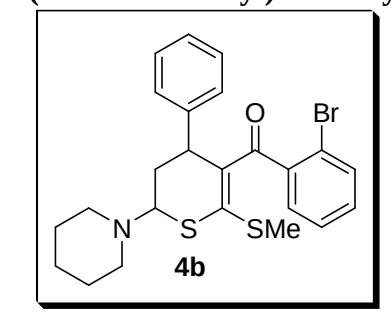
2. Characterization data of the compounds

3-Benzoyl-2-methylsulfanyl-4-phenyl-6-piperidino-5,6-dihydro-4*H*-thiopyran(4a): Pale yellow solid, mp111-113 °C; FT IR (KBr, cm^{-1}): 3053, 2929, 1654, 1575, 1254, 1179; ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 6.9 Hz, 2H), 7.45-7.25 (m, 8H), 4.53 (dd, J_1 = 1.5 Hz, J_2 = 12.0 Hz, 1H), 4.32 (t, J = 3.6 Hz, 1H), 2.78(t, J = 5.2 Hz, 2H), 2.61 (t, J = 5.1 Hz, 2H), 2.36-2.23 (m, 5H), 1.55-1.45 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.58, 141.16, 138.24, 132.08, 130.05, 129.07, 128.74, 128.52, 128.32, 128.22, 126.90, 70.38, 49.77, 44.14, 34.72, 25.68, 24.13, 17.81; HRMS $[M+H]^+$ calcd. For $C_{24}H_{28}NOS_2$ 410.1607, found 410.1616.



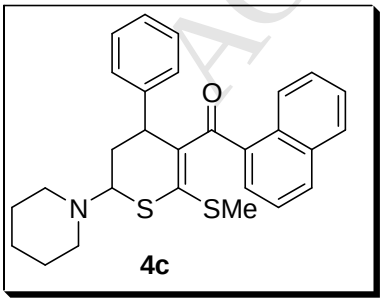
4a

3-(2-Bromobenzoyl)-2-methylsulfanyl-4-phenyl-6-piperidino-5,6-dihydro-4*H*-thiopyran (4b): Pale yellow solid, mp 142-144 °C; FT IR (KBr, cm^{-1}): 3037, 2946, 1610, 1491, 1251, 1176; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 8.0 Hz, 1H), 7.21-7.16 (m, 3H), 7.10 (t, J = 8.25 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.91-6.90 (m, 2H), 6.58 (d, J = 7.0 Hz, 1H), 4.38 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 1H), 4.05 (br, 1H), 2.83-2.79 (m, 2H), 2.66-2.65 (m, 2H), 2.54 (s, 3H), 2.46-2.40 (m, 2H), 1.58-1.56 (m, 4H), 1.47-1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.62, 142.30, 141.89, 132.05, 129.68, 128.39, 128.01, 127.86, 126.75, 126.67, 124.23, 118.79, 72.16, 49.54, 43.64, 34.32, 25.79, 24.21, 16.35; HRMS $[M+H]^+$ calcd. For $C_{24}H_{27}BrNOS_2$ 488.0712, found 488.0717.



4b

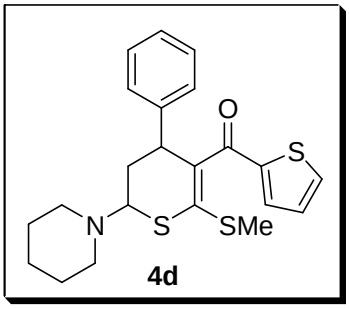
2-Methylsulfanyl-3-(1-naphthoyl)-4-phenyl-6-piperidino-5,6-dihydro-4*H*-thiopyran (4c): Pale yellow solid, mp 161-162 °C; FT IR (KBr, cm^{-1}): 3016, 2939, 1645, 1562, 1256, 1183; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.0 Hz, 1H), 7.79 (dd, J_1 = 8.0 Hz, J_2 = 11.0 Hz, 2H), 7.47-7.41 (m, 2H), 7.23-7.14 (m, 4H), 7.03-6.96 (m, 3H), 4.43 (dd, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 4.15 (t, J = 3.5 Hz, 1H), 2.83-2.82 (m, 2H), 2.70-2.68 (m, 2H), 2.47 (s, 3H), 2.43-2.25 (m, 2H),



4c

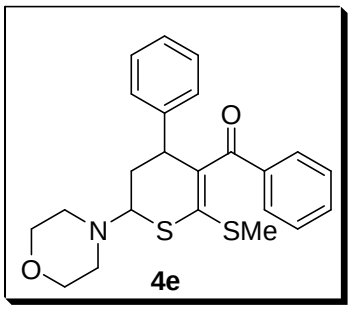
1.60 (br, 4H), 1.48-1.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.05, 133.38, 130.16, 129.80, 128.51, 128.21, 128.03, 126.87, 126.79, 126.08, 125.22, 125.07, 124.50, 71.11, 49.81, 43.40, 33.81, 25.38, 23.93, 16.82; HRMS $[M+H]^+$ calcd. For $C_{28}H_{30}NOS_2$ 460.1763, found 460.1767.

2-Methylsulfanyl-4-phenyl-6-piperidino-3-(2-thienoyl)-5,6-dihydro-4*H*-thiopyran (4d): Pale yellow solid, mp 111-112 °C; FT IR (KBr, cm^{-1}): 3028, 2932, 1661, 1567, 1251, 1172; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (br, 2H), 7.25-7.13 (m, 5H), 7.02 (br, 1H), 4.52 (dd, J_1 = 1.5 Hz, J_2 = 11.1 Hz, 1H), 4.36 (t, J = 3.1 Hz, 1H), 2.75 (t, J = 2.5 Hz, 2H), 2.62 (t, J = 7.9 Hz, 2H), 2.47-2.23 (m, 5H), 1.54-1.45 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 1 88.03, 144.88, 141.13, 139.68, 137.03, 134.37, 133.40, 132.74, 128.44, 127.72, 126.96, 70.54, 49.74, 44.38, 35.10, 25.90, 24.27, 18.14; HRMS $[M+Na]^+$ calcd. For $C_{22}H_{25}NOS_3Na$ 438.0990, found 438.0996.



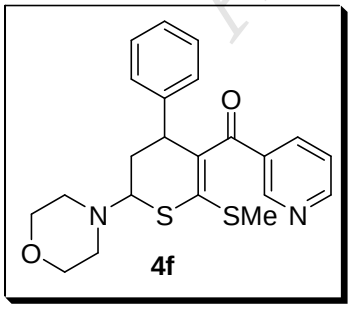
4d

3-Benzoyl-2-methylsulfanyl-6-morpholino-4-phenyl-5,6-dihydro-4*H*-thiopyran (4e): Pale yellow solid, mp 117-118 °C; FT IR (KBr, cm^{-1}): 2956, 2843 1648, 1594, 1247, 1171; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 7.51 Hz, 2H), 7.49-7.44 (m, 2H), 7.39-7.23 (m, 6H), 4.48 (dd, J_1 = 2.4 Hz, J_2 = 11.1 Hz, 1H), 4.31 (t, J = 3.4 Hz, 1H), 3.67 (br, 4H), 2.84-2.67 (m, 4H), 2.45-2.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.47, 141.16, 138.16, 133.67, 132.16, 128.73, 128.58, 128.27, 128.24, 128.05, 126.97, 69.20, 66.73, 48.73, 44.00, 34.55, 17.78; HRMS $[M+H]^+$ calcd. For $C_{23}H_{26}NO_2S_2$ 412.1399, found 412.1403.



4e

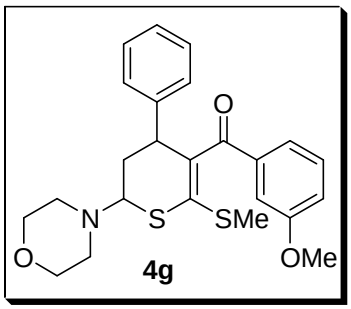
2-Methylsulfanyl-6-morpholino-4-phenyl-3-(3-pyridoyl)-5,6-dihydro-4*H*-thiopyran (4f): Pale yellow solid, mp 122-123 °C; FT IR (KBr, cm^{-1}): 3028, 2937, 1639, 1574, 1253, 1183; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.63 (d, J = 4.5 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.25-7.18 (m, 5H), 7.09-7.01 (m, 1H), 4.51 (dd, J_1 = 2.7 Hz, J_2 = 11.7 Hz, 1H), 4.39 (t, J = 3.4 Hz, 1H), 3.68 (br, 4H), 2.80-2.70 (m, 4H), 2.43-2.27 (m, 5H);



4f

^{13}C NMR (75 MHz, $CDCl_3$): δ 189.32, 167.88, 153.87, 151.70, 147.02, 136.12, 135.66, 133.99, 128.73, 128.06, 127.10, 123.30, 69.92, 66.35, 48.67, 43.82, 34.49, 17.28; HRMS $[M+H]^+$ calcd. For $C_{22}H_{25}N_2O_2S_2$ 413.1352, found 413.1360.

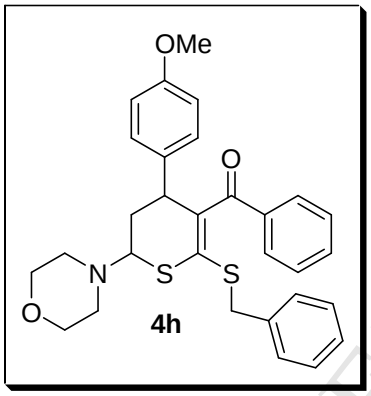
3-(2-Methoxybenzoyl)-2-methylsulfanyl-6-morpholino-4-phenyl-5,6-dihydro-4*H*-thiopyran



4g

(4g): Pale yellow solid, mp 128-129 °C; FT IR (KBr, cm^{-1}): 3045, 2952, 1624, 1587, 1286, 1176; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.20 (m, 7H), 7.08-6.99 (m, 2H), 4.47 (dd, J_1 = 2.7 Hz, J_2 = 11.7 Hz, 1H), 4.29 (t, J = 3.6 Hz, 1H), 3.74-3.67 (m, 7H), 2.80-2.69 (m, 4H), 2.43-2.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.22, 159.53, 141.15, 139.60, 133.44, 129.20, 128.61, 128.34, 128.30, 127.00, 121.42, 118.78, 112.64, 69.31, 66.73, 55.25, 48.72, 43.99, 34.49, 17.79; HRMS $[M]^+$ calcd. For $C_{24}H_{27}NO_3S_2$ 441.1432, found 441.1431.

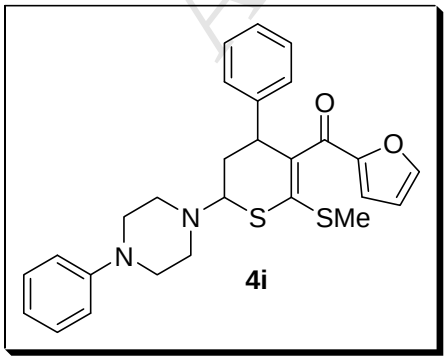
3-Benzoyl-2-benzylsulfanyl-4-(4-methoxyphenyl)-6-morpholino-5,6-dihydro-4*H*-thiopyran



4h

(4h): Pale yellow solid, mp 69-70 °C; FT IR (KBr, cm^{-1}): 3039, 2946, 1624, 1566, 1282, 1179; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 7.2 Hz, 2H), 7.47-7.20 (m, 8H), 7.05 (d, J = 8.4 Hz, 2H), 6.89-6.76 (m, 2H), 4.43 (dd, J_1 = 3.0 Hz, J_2 = 12.0 Hz, 1H), 4.18-4.09 (m, 2H), 3.99-3.90 (m, 1H), 3.73-3.65 (m, 7H), 2.77-2.68 (m, 4H), 2.34-2.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.47, 158.43, 137.72, 137.07, 136.65, 135.44, 132.64, 132.26, 129.23, 128.84, 128.27, 128.24, 127.17, 113.87, 113.65, 69.01, 66.69, 55.10, 48.72, 43.23, 38.99, 34.49; HRMS $[M+H]^+$ calcd. For $C_{30}H_{32}NO_3S_2$ 518.1818, found 518.1822.

3-(2-Furoyl)-2-methylsulfanyl-4-phenyl-6-(4-phenylpiperazino)-5,6-dihydro-4*H*-thiopyran

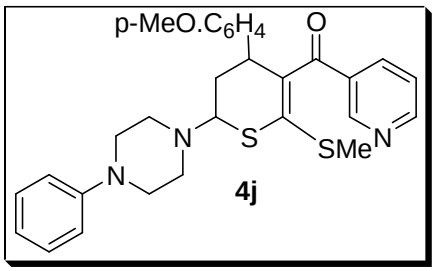


4i

(4i): Pale yellow solid, mp 101-103 °C; FT IR (KBr, cm^{-1}): 3042, 2944, 1654, 1589, 1248, 1181; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.36 (m, 2H), 7.20-7.05 (m, 5H), 6.94-6.75 (m, 5H), 6.47-6.28 (m, 1H), 4.45-4.43 (m, 2H), 3.11-3.05 (m, 4H), 2.87-2.74 (m, 4H), 2.39-2.24 (m, 5H); ^{13}C NMR

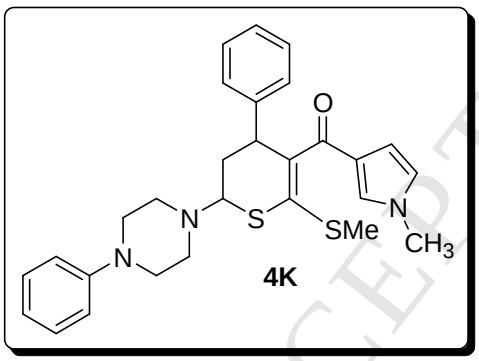
(75 MHz, $CDCl_3$): δ 182.96, 153.22, 151.02, 145.87, 142.18, 141.29, 132.76, 129.07, 128.51, 128.28, 126.88, 120.01, 117.79, 116.28, 112.24, 69.01, 49.20, 48.38, 43.47, 35.22, 18.05; HRMS $[M+H]^+$ calcd. For $C_{27}H_{29}N_2O_2S_2$ 477.1665, found 477.1671.

4-(4-Methoxyphenyl)-2-methylsulfanyl-6-(4-phenylpiperazino)-3-(3-pyridoyl)-5,6-dihydro-



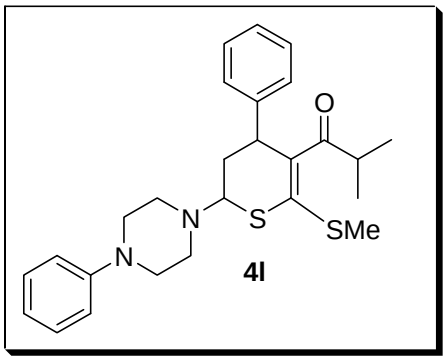
4*H*-thiopyran (4j): Pale yellow solid, mp 93-95 °C; FT IR (KBr, cm^{-1}): 3051, 2926, 1641, 1579, 1278, 1152; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.64 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.25 (br, 2H),7.13-7.10 (m, 2H), 6.94-6.81 (m, 6H), 4.59 (dd, J_1 = 2.4 Hz, J_2 = 11.4 Hz, 1H), 4.34 (t, J = 3.9 Hz, 1H), 3.76 (s, 3H), 3.16 (br, 4H), 3.00-2.85 (m, 4H), 2.71-2.63 (m, 4H), 2.45-2.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.44, 158.58, 151.86, 151.03, 149.64, 145.99, 135.58, 134.57, 133.14, 131.73, 129.15, 129.09, 123.27, 120.07, 116.31, 114.12, 69.82, 55.16, 49.22, 48.44, 43.16, 34.96, 17.28; HRMS $[M+H]^+$ calcd. For $C_{29}H_{32}N_3O_2S_2$518.1930, found 518.1938.

3-(*N*-Methyl-2-pyrroloyl)-2-methylsulfanyl-4-phenyl-6-(4-phenylpiperazino)-5,6-dihydro-



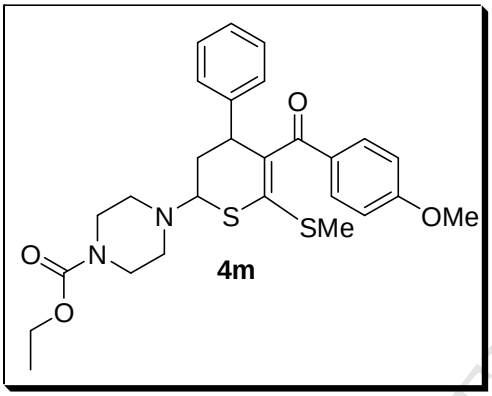
4*H*-thiopyran (4k): Pale yellow solid, mp 154-155 °C; FT IR (KBr, cm^{-1}): 3048, 2916, 1638, 1584, 1228, 1172; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.26 (m, 6H), 7.21-7.09 (m, 2H), 6.97-6.94 (m, 2H), 6.90 (t, J = 7.2 Hz, 1H), 4.54 (dd, J_1 = 2.5 Hz, J_2 = 11.5 Hz, 1H), 4.36 (t, J = 4.0 Hz, 1H), 3.62 (s, 3H), 3.24-3.17 (m, 4H), 3.03-3.01 (m, 2H), 2.93-2.89 (m, 2H), 2.41 (s, 3H), 2.33-2.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.40, 141.27, 136.94, 133.79, 129.20, 128.50, 128.48, 128.23, 128.06, 126.90, 125.74, 123.18, 120.52, 116.56, 110.28, 68.23, 49.48, 48.37, 44.18, 36.62, 34.84, 18.43; HRMS $[M+H]^+$ calcd. For $C_{28}H_{32}N_3OS_2$ 490.1981, found 490.1983.

3-Isopropanoyl-2-methylsulfanyl-4-phenyl-6-(4-phenylpiperazino)-5,6-dihydro-4*H*-



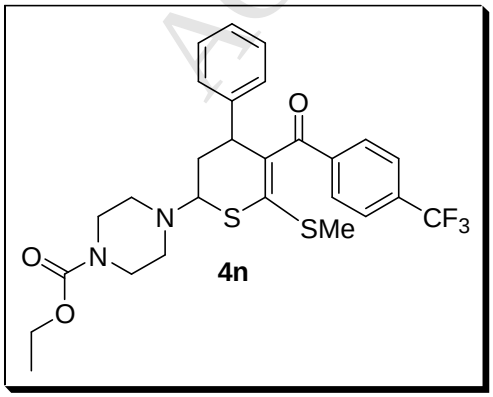
thiopyran (4l): Pale yellow solid, mp 94-95 °C; FT IR (KBr, cm^{-1}): 3017, 2944, 1636, 1572, 1284, 1163; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.16 (m, 7H), 6.91-6.86 (m, 3H), 4.38-4.32 (m, 2H), 3.15-3.11 (m, 4H), 2.95-2.80 (m, 5H), 2.47-2.37 (m, 5H), 0.99 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.10, 153.38, 151.06, 141.67, 129.10, 128.78, 127.94, 126.99, 126.69, 120.11, 116.35, 69.17, 49.25, 48.15, 42.61, 35.88, 34.31, 19.86, 18.87, 16.75; HRMS $[M+H]^+$ calcd. For $C_{26}H_{33}N_2OS_2$ 453.2029, found 453.2028.

6-(1-Carboethoxyl)piperazino-3-(4-methoxybenzoyl)-2-methylsulfanyl-4-phenyl-5,6-



dihydro-4*H*-thiopyran (4m): Pale yellow solid, mp 140-141°C; FT IR (KBr, cm^{-1}): 3015, 2925, 1642, 1572, 1282, 1167; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 8.5 Hz, 2H), 7.30-7.09 (m, 5H), 6.88 (d, J = 8.5 Hz, 2H), 4.52 (dd, J_1 = 2.0 Hz, J_2 = 12.0 Hz, 1H), 4.28 (t, J = 3.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.48-3.41 (m, 4H), 2.77 (br, 2H), 2.65 (t, J = 4.7 Hz, 2H), 2.35 (s, 3H), 2.29-2.25 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.55, 163.28, 155.35, 141.18, 136.27, 131.49, 130.46, 128.60, 128.39, 127.03, 113.65, 113.40, 68.62, 61.47, 55.43, 48.52, 48.34, 44.33, 34.97, 18.04, 14.67; HRMS $[M+H]^+$ calcd. For $C_{27}H_{33}N_2O_4S_2$ 513.1876, found 513.1901.

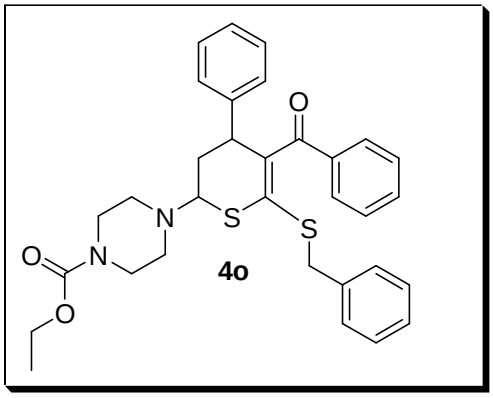
6-(1-Carboethoxyl)piperazino-2-methylsulfanyl-4-phenyl-3-(4-trifluoromethylbenzoyl)-5,6-



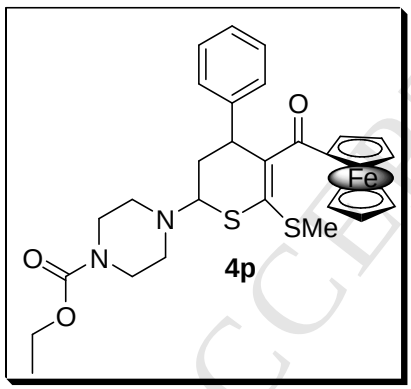
dihydro-4*H*-thiopyran (4n): Pale yellow solid, mp 130-131 °C; FT IR (KBr, cm^{-1}): 3034, 2943, 1629, 1578, 1251, 1162; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.38-7.17 (m, 5H), 4.52 (dd, J_1 = 2.5 Hz, J_2= 11.5 Hz, 1H), 4.33 (t, J = 3.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.49-3.41 (m,

4H), 2.77-2.65 (m, 4H), 2.37 (s, 3H), 2.32-2.27 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.95, 155.33, 141.21, 131.43, 128.80, 128.73, 128.51, 128.18, 127.22, 127.11, 125.23, 125.20, 69.71, 61.52, 48.33, 48.04, 43.93, 43.51, 34.74, 17.46, 14.66; HRMS $[M+H]^+$ calcd. For $C_{27}H_{30}F_3N_2O_3S_2$ 551.1644, found 551.1652.

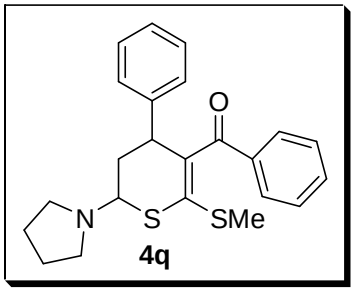
3-Benzoyl-2-benzylsulfanyl-6-(1-carboethoxyl)piperazino-4-phenyl-5,6-dihydro-4*H*-thiopyran (4o): Pale yellow solid, mp 67-68 °C; FT IR (KBr, cm^{-1}): 3036, 2951, 1662, 1583, 1271, 1161; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 7.2 Hz, 2H), 7.43-6.97 (m, 13H), 4.56 (dd, J_1 = 3.3 Hz, J_2 = 14.1 Hz, 1H), 4.19-3.85 (m, 5H), 3.43 (br, 4H), 2.71-2.63 (m, 4H), 2.30-2.21 (m, 2H), 1.25 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.31, 155.15, 140.55, 137.67, 136.62, 136.51, 135.97, 132.24, 129.16, 128.78, 128.46, 128.22, 127.94, 127.16, 127.00, 126.91, 68.70, 61.34, 48.43, 48.17, 43.94, 43.38, 38.92, 34.47, 14.56; HRMS $[M+H]^+$ calcd. For $C_{32}H_{35}N_3O_3S_2$ 559.2084, found 559.2087.



6-(1-Carboethoxyl)piperazino-3-ferrocenoyl-2-methylsulfanyl-4-phenyl-5,6-dihydro-4*H*-thiopyran (4p): Pale yellow solid, mp 147-149 °C; FT IR (KBr, cm^{-1}): 3041, 2922, 1632, 1561, 1245, 1168; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.25 (m, 5H), 4.87 (br, 1H), 4.59 (br, 1H), 4.49 (br, 3H), 4.37 (br, 1H), 3.71 (br, 5H), 3.43 (br, 4H), 2.74-2.64 (m, 4H),2.38-2.22 (m, 5H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.91, 155.33, 141.48, 137.64, 136.33, 128.95, 128.44, 127.35, 81.10, 71.86, 71.21, 70.60, 70.27, 69.82, 69.02, 61.46, 48.20, 43.90, 34.73, 18.15, 14.65; HRMS $[M]^+$ calcd. For $C_{30}H_{34}FeN_2O_3S_2$ 590.1360, found 590.1360.

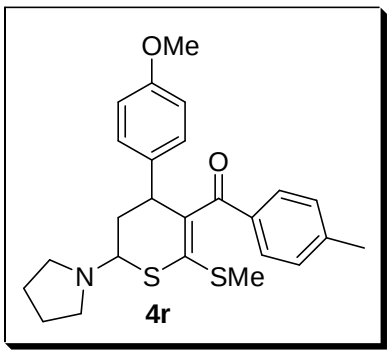


3-Benzoyl-2-methylsulfanyl-4-phenyl-6-pyroldino-5,6-dihydro-4*H*-thiopyran (4q): Pale yellow solid, mp 103-105°C; FT IR (KBr, cm^{-1}): 3015, 2921, 1641, 1587, 1259, 1185; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 6.6 Hz, 2H), 7.66-7.25 (m, 8H), 4.83 (t, J = 5.8 Hz, 1H), 4.27 (br, 1H), 2.87 (t, J=6.1 Hz, 4H), 2.36 (br, 5H),1.78 (br, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.52, 140.93, 138.29, 133.69, 132.05, 129.00, 128.67, 128.50, 128.19, 127.38, 126.85, 67.49, 48.32, 44.18, 36.53, 24.18, 17.74; HRMS $[M+H]^+$ calcd. For $C_{23}H_{26}NOS_2$ 396.1450, found 396.1454.



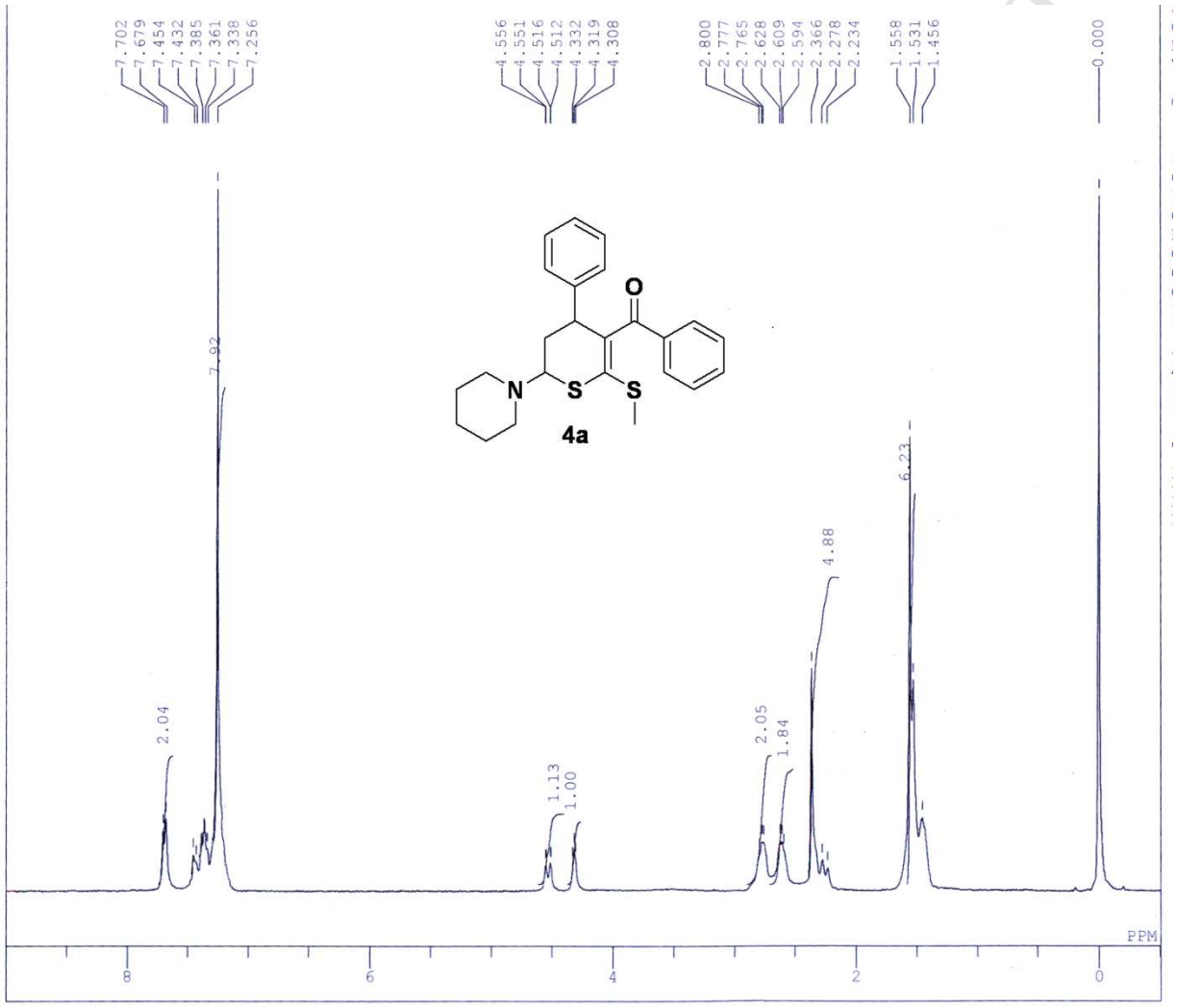
4q

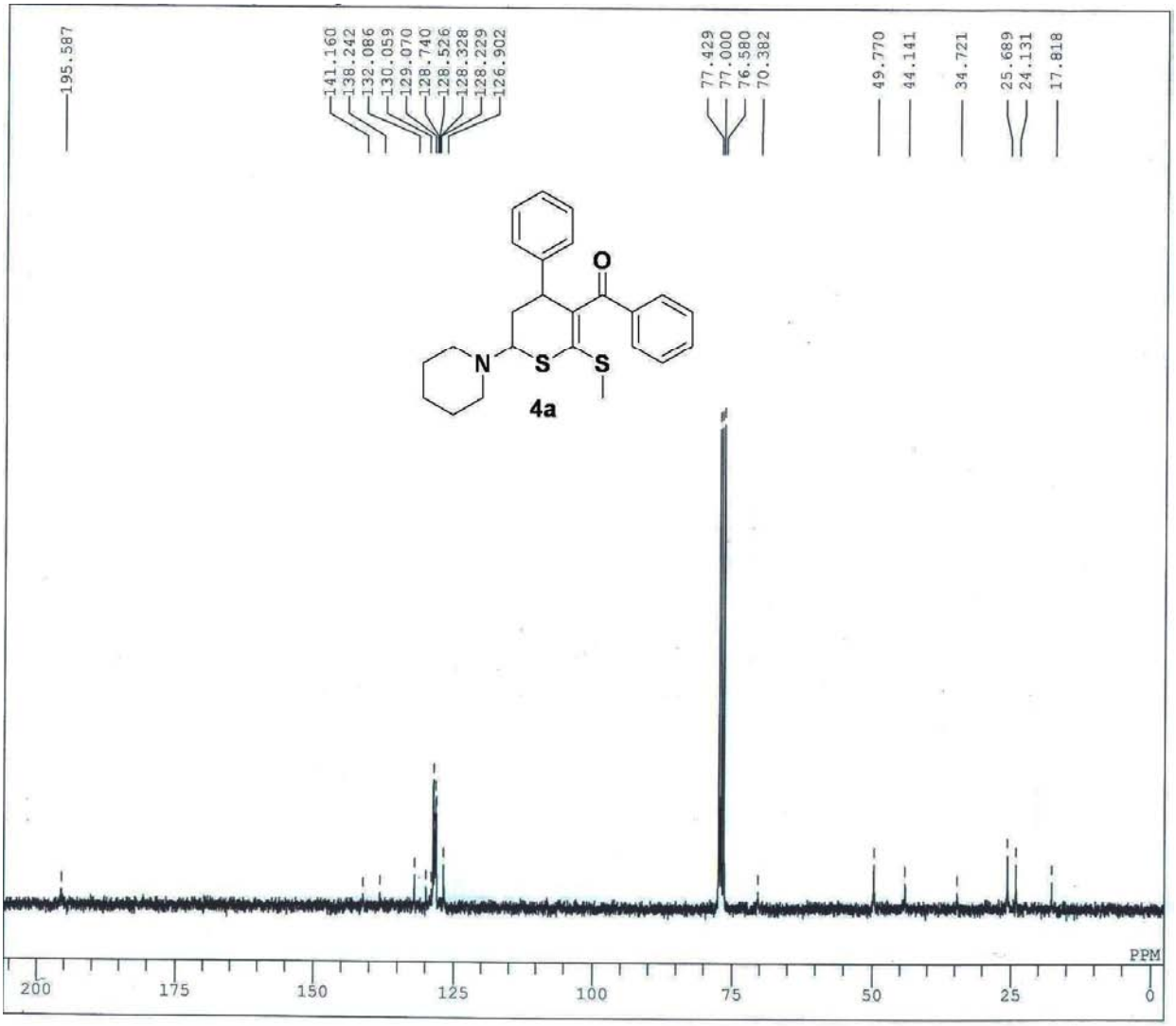
4-(4-Methoxyphenyl)-3-(4-methylbenzoyl)-2-methylsulfanyl-6-pyroldino-5,6-dihydro-4*H*-thiopyran(4r): Pale yellow solid, mp 88-90 °C; FT IR (KBr, cm^{-1}): 3047, 2942, 1649, 1585, 1273, 1165; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 6.6 Hz, 2H), 7.25-7.15 (m, 4H), 6.80 (d, J = 6.9 Hz, 2H), 4.83 (br, 1H), 4.19 (br, 1H), 3.75 (s, 3H), 2.87 (br, 4H), 2.36 (br, 5H), 1.78 (br, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.55, 158.35, 142.99, 135.39, 133.13, 129.42, 129.25, 129.16, 129.04, 128.96, 113.83, 64.44, 55.13, 48.18, 43.66, 37.02, 24.55, 24.20, 21.60, 17.85; HRMS $[M+H]^+$ calcd. For $C_{25}H_{30}NO_2S_2$ 440.1712, found 440.1711.

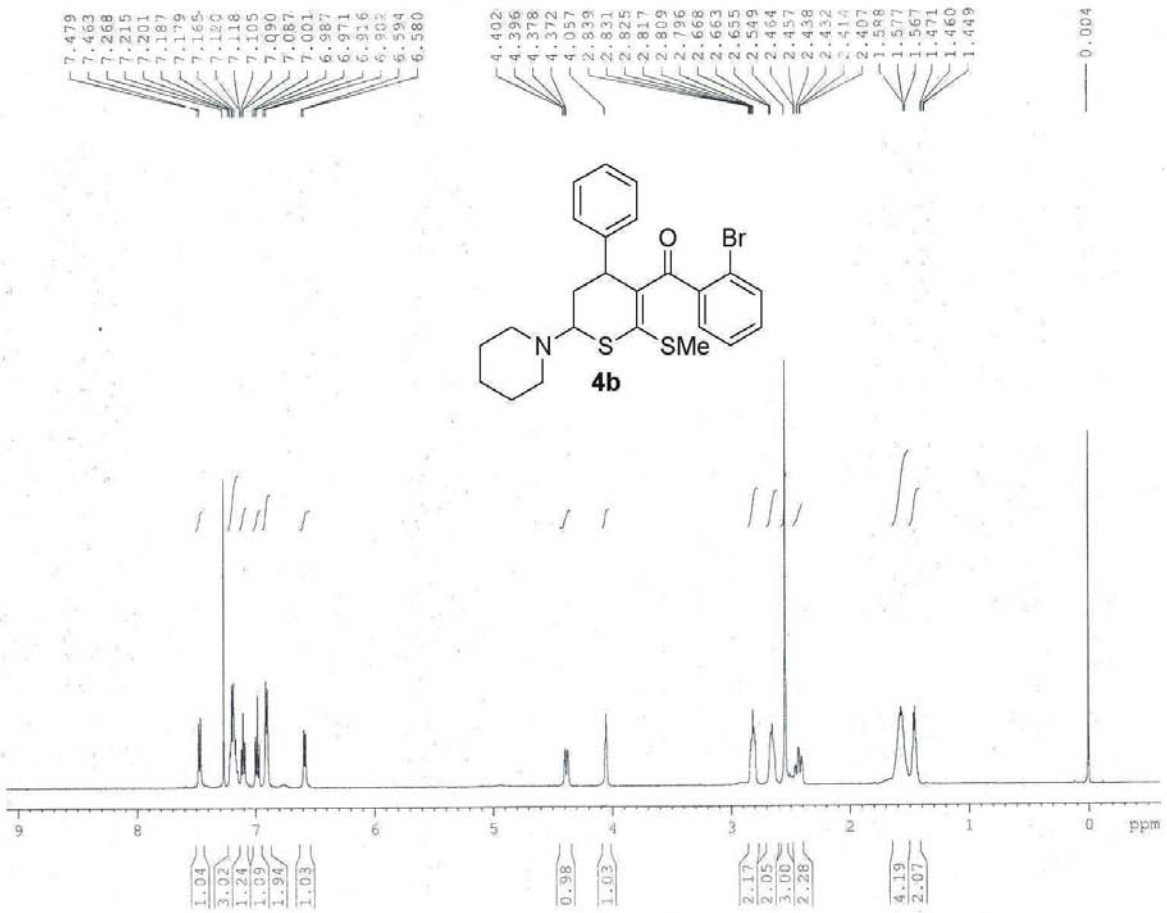


4r

3. Copies of the ^{1}H and ^{13}C NMR spectra of all the new compounds



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7.087
7.001
6.987
6.971
6.916
6.903
6.594
6.580
4.402
4.396
4.378
4.372
4.057
2.839
2.831
2.825
2.817
2.809
2.796
2.668
2.663
2.655
2.549
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2.457
2.438
2.432
2.407
1.588
1.577
1.567
1.471
1.460
1.449
0.004
O
Br
N
S
SMe
4b
9
8
7
6
5
4
3
2
1
0
ppm
1.04
3.02
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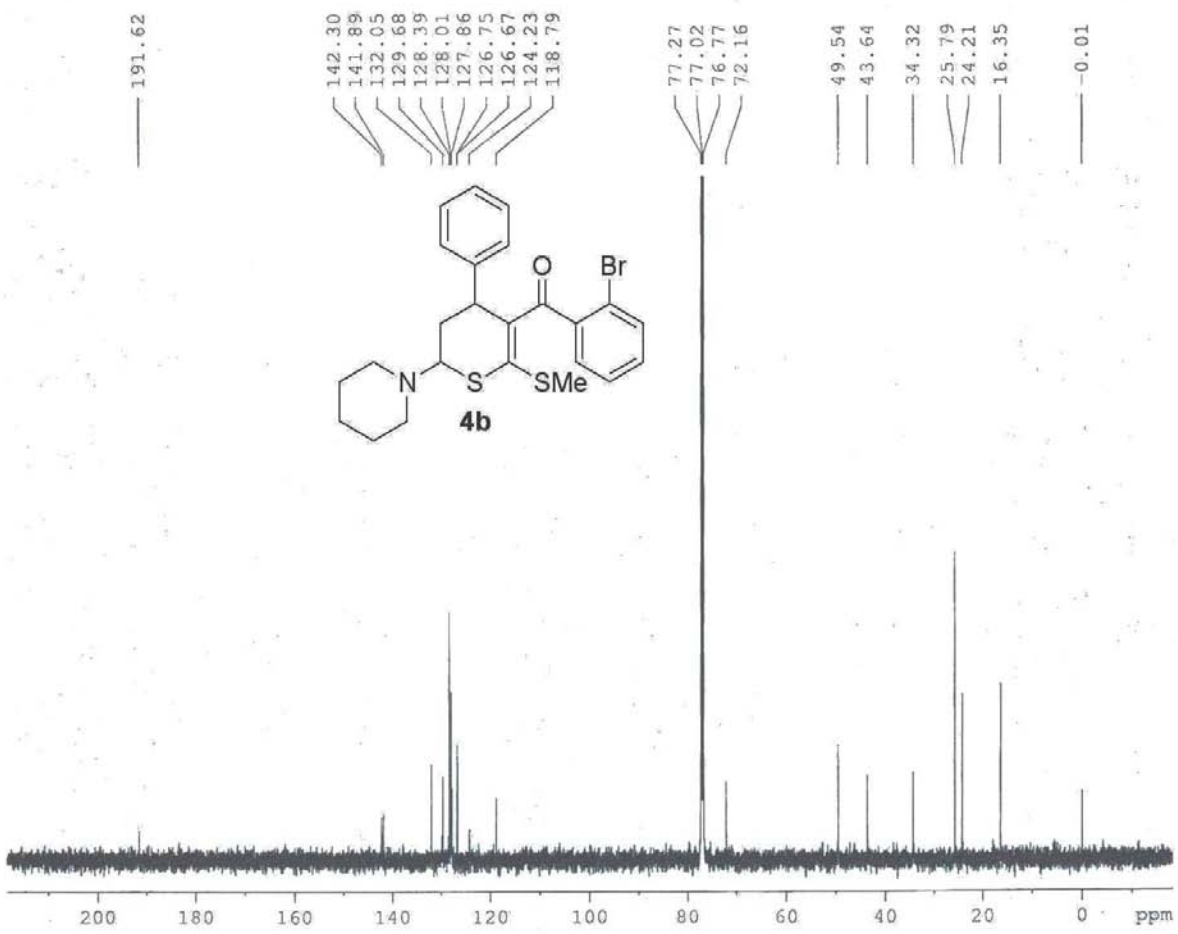
2.07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124.23
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77.02
76.77
72.16
49.54
43.64
34.32
25.79
24.21
16.35
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S
SMe
4b
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40
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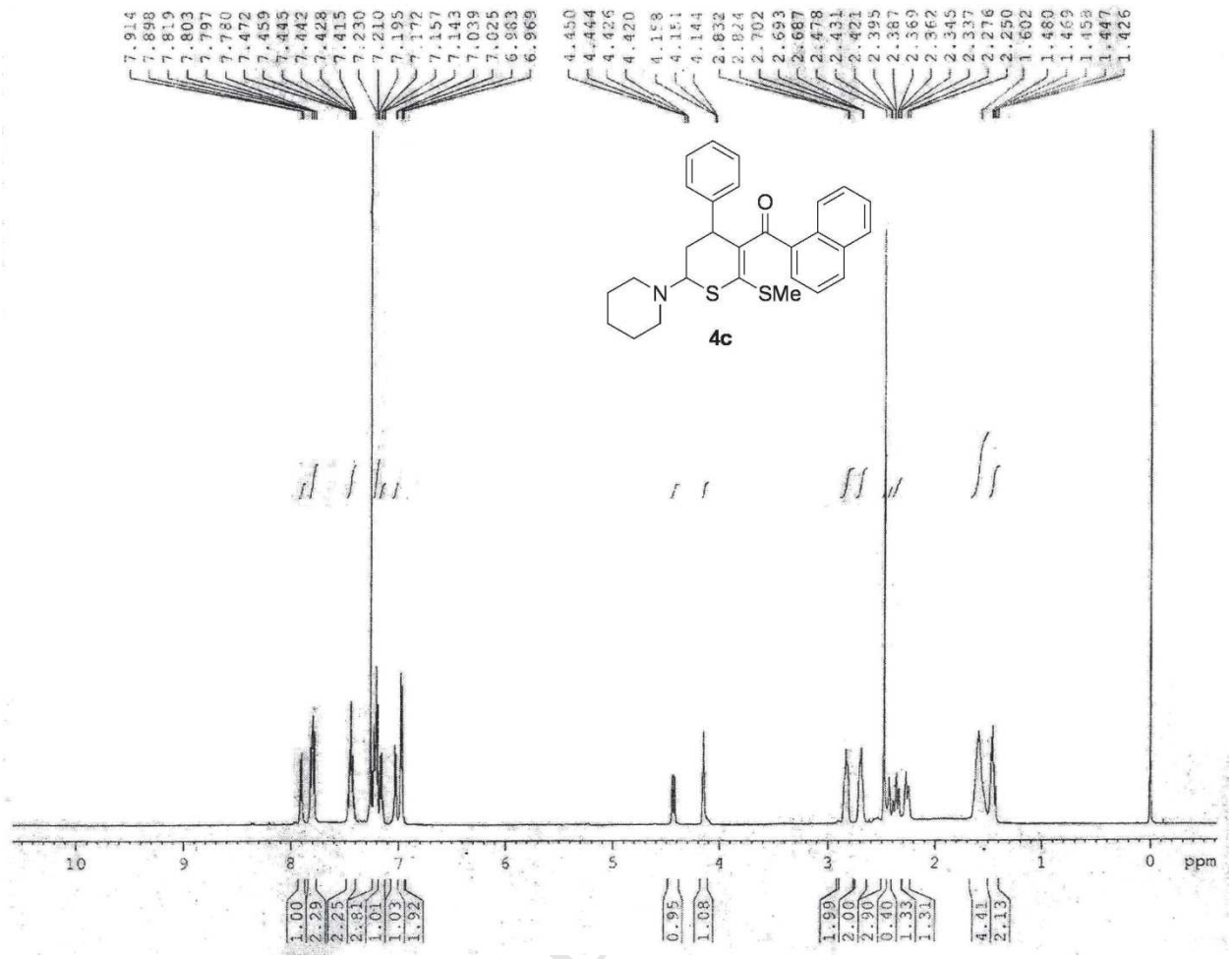
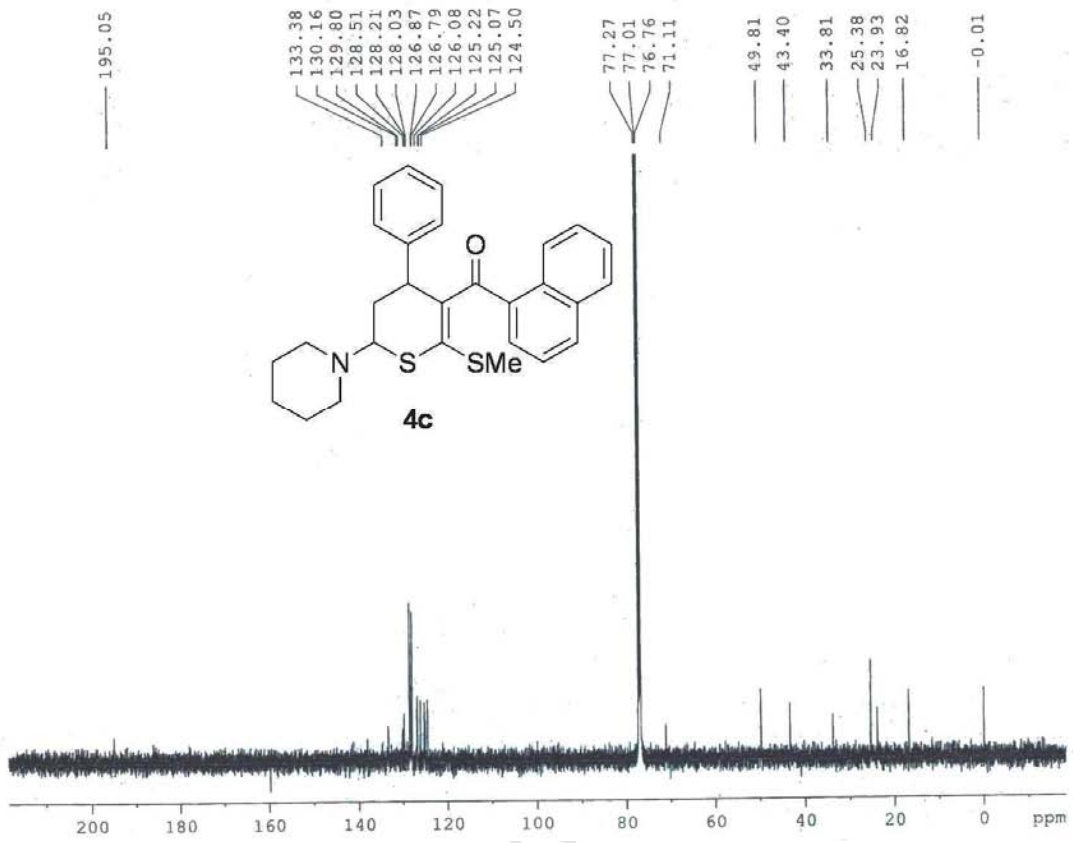
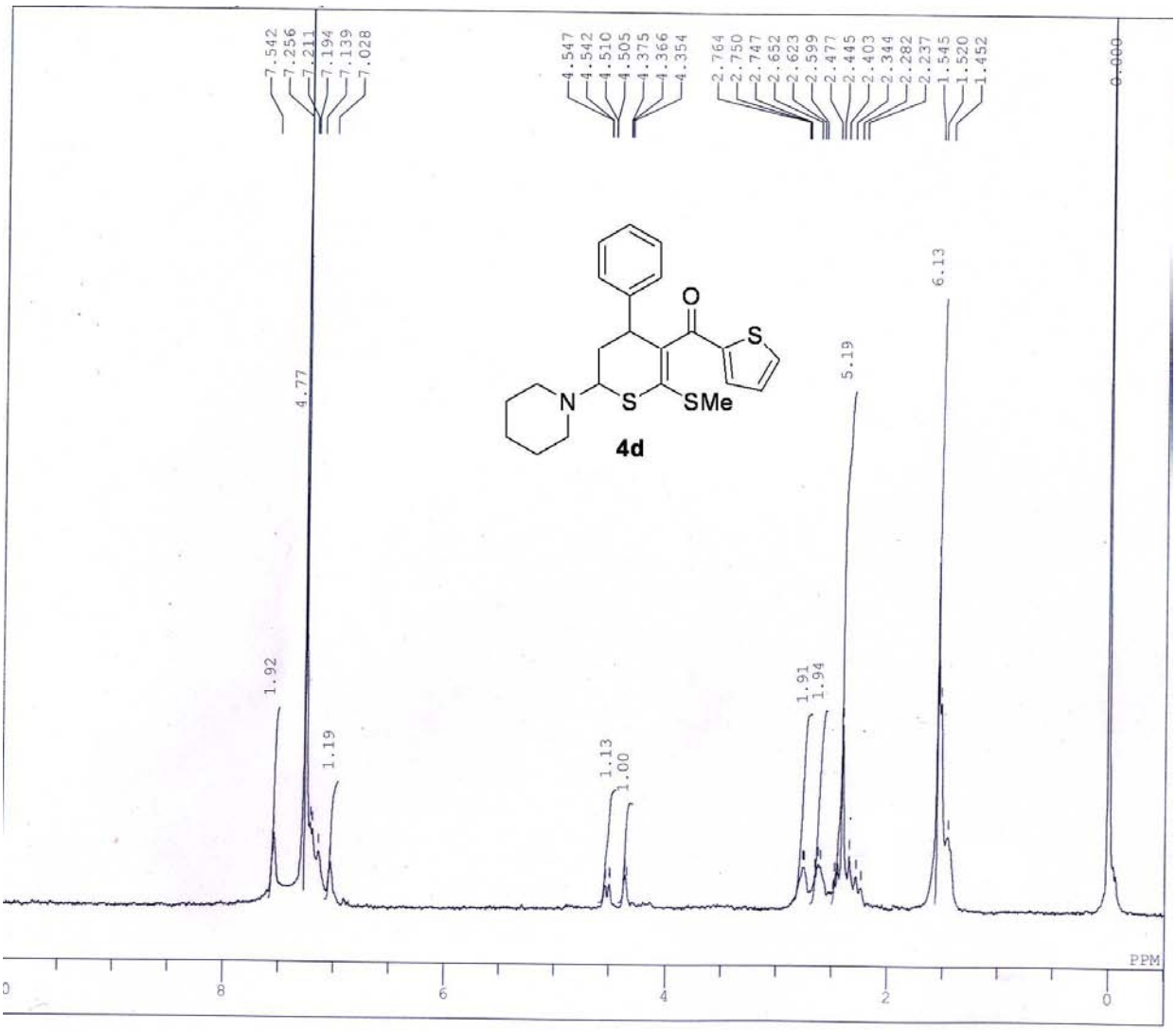
ppm



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2.652
2.623
2.599
2.477
2.445
2.403
2.344
2.282
2.237
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1.520
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0.000
4.77
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1.19
1.13
1.00
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6.13
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S
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SMe
4d
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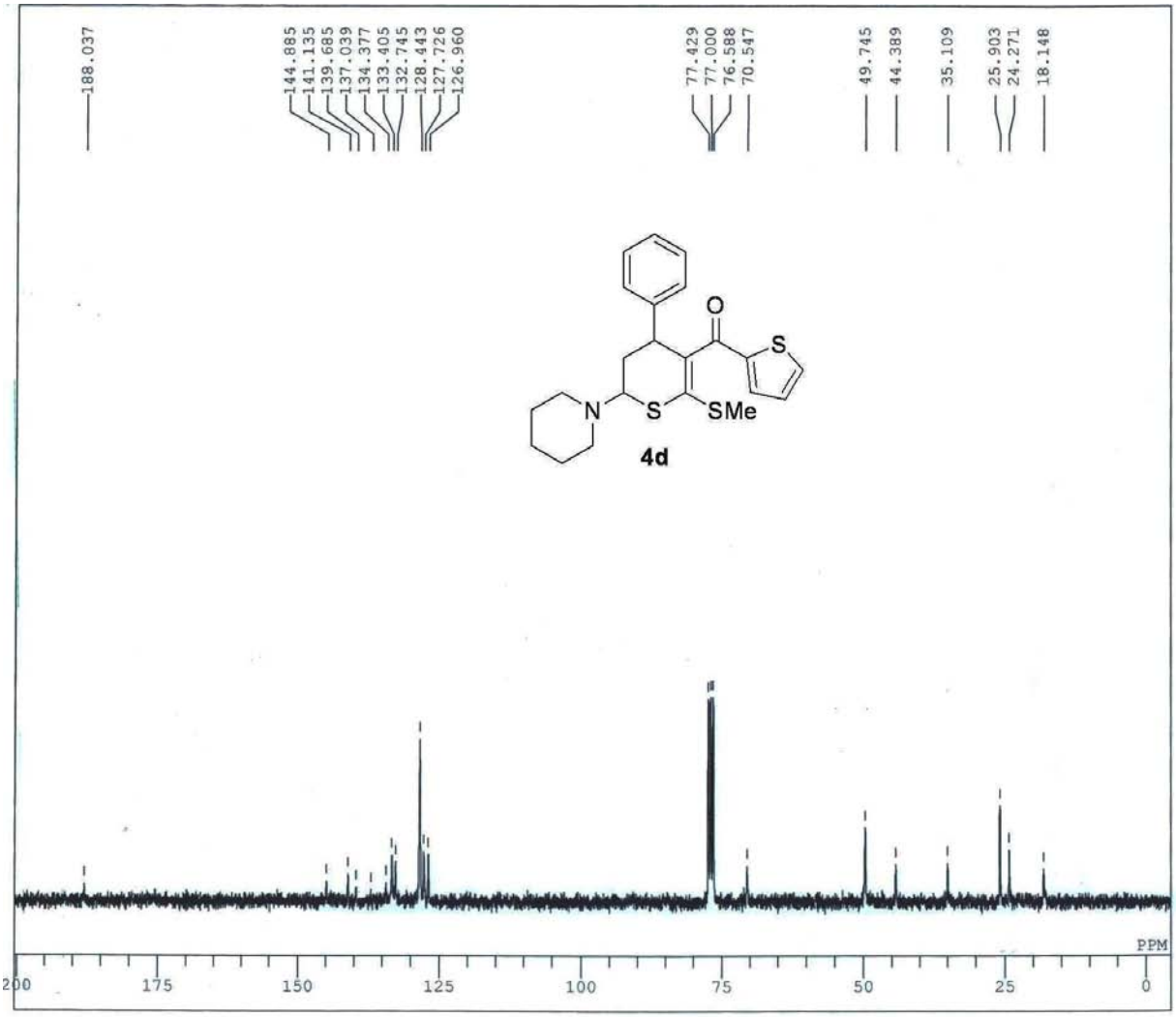
2
0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76.588
70.547
49.745
44.389
35.109
25.903
24.271
18.148
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S
N
S
SMe
4d
PPM
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175
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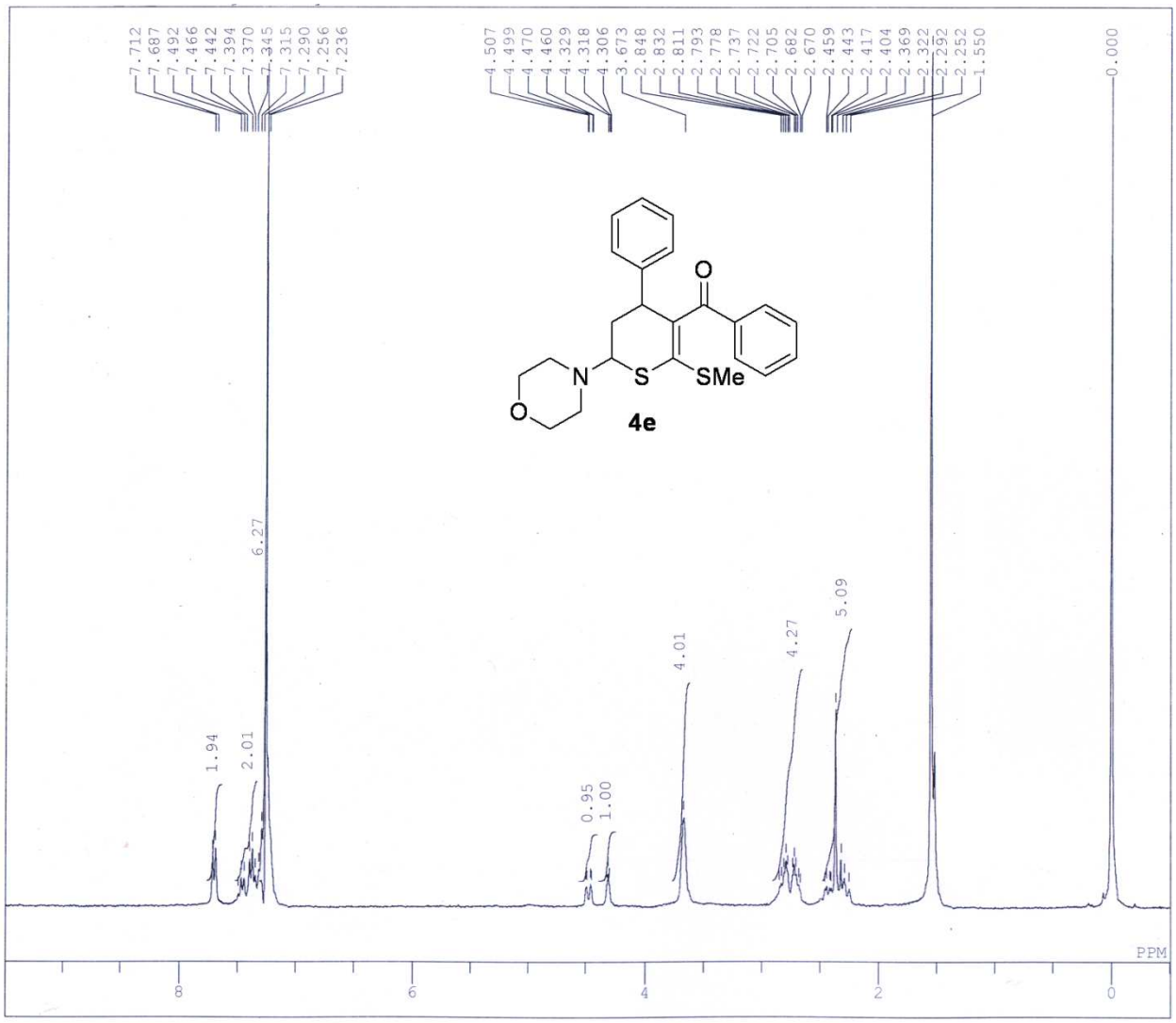
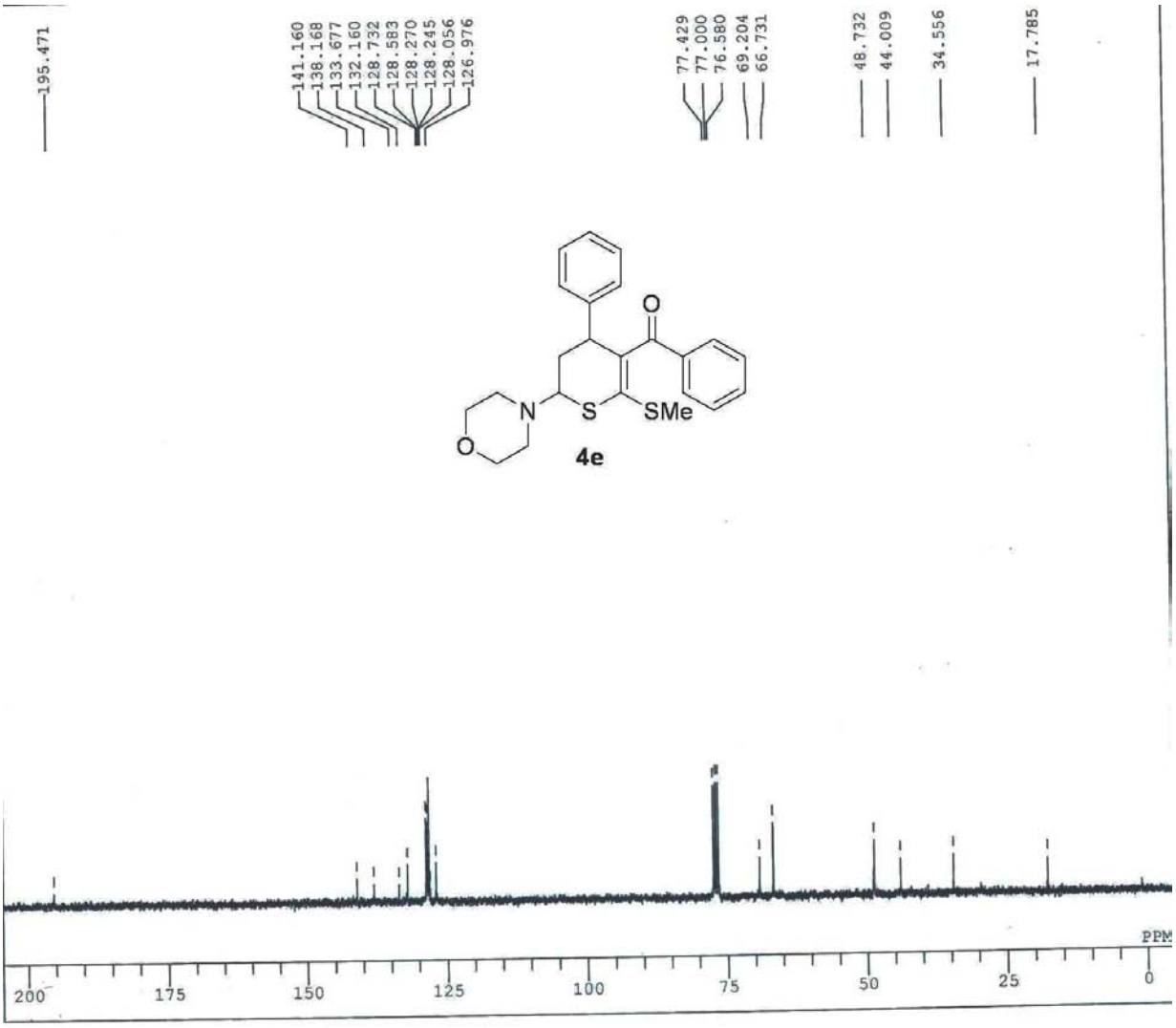
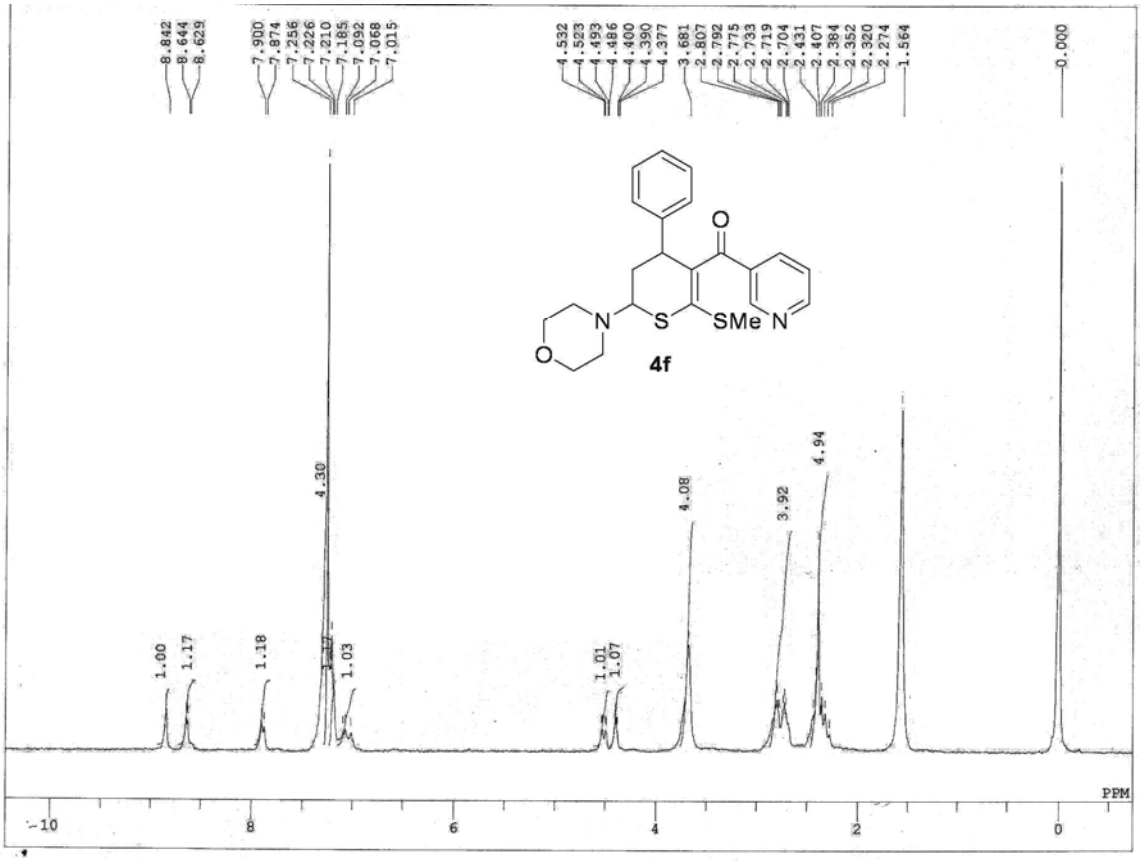
100
75
50
25
0



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4.523
4.493
4.486
4.400
4.390
4.377
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2.807
2.792
2.775
2.733
2.719
2.704
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2.407
2.384
2.352
2.320
2.274
1.564
0.000
O
N
S
SMe
N
O
4f
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1.01
1.07
4.08
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2
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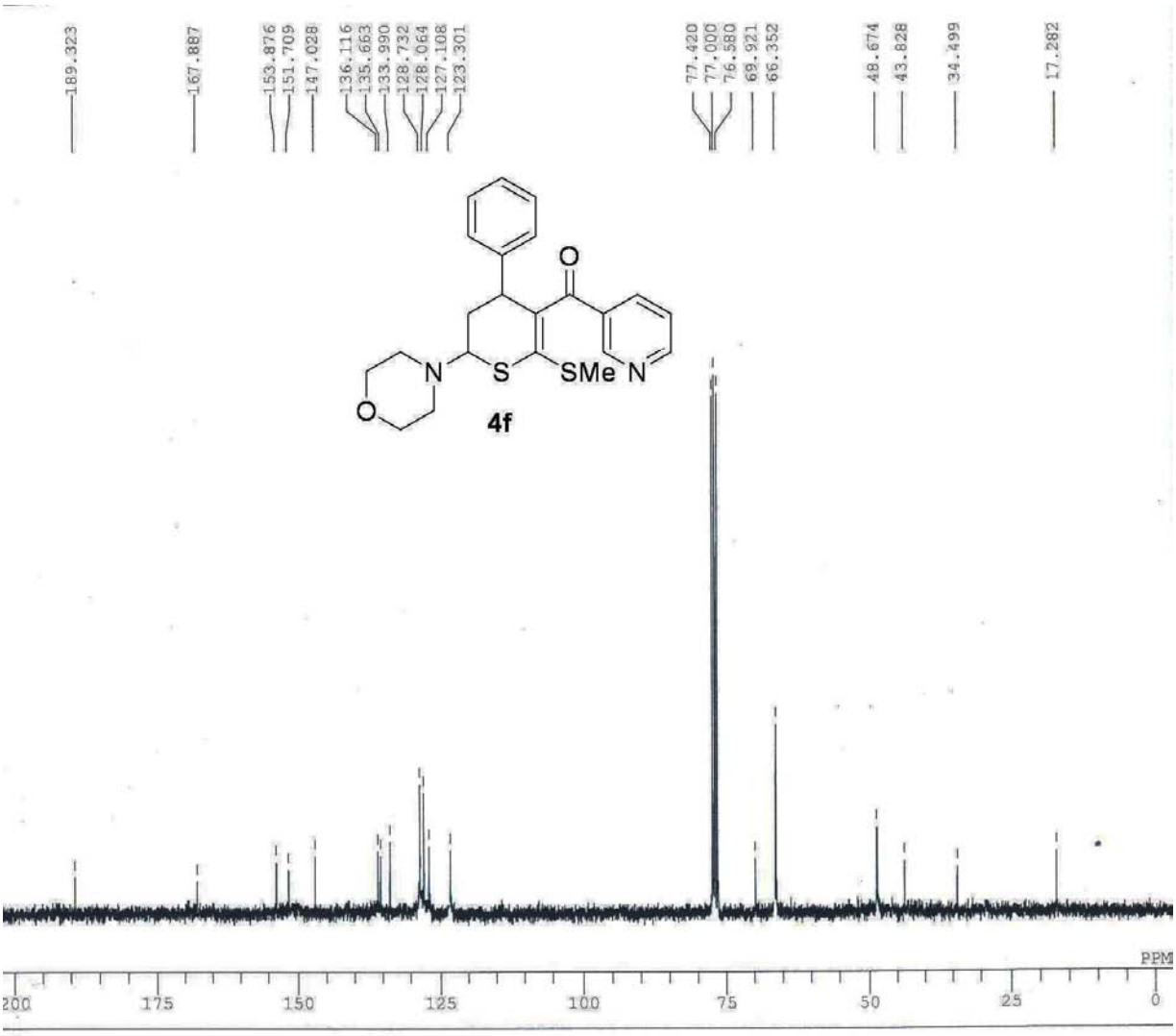

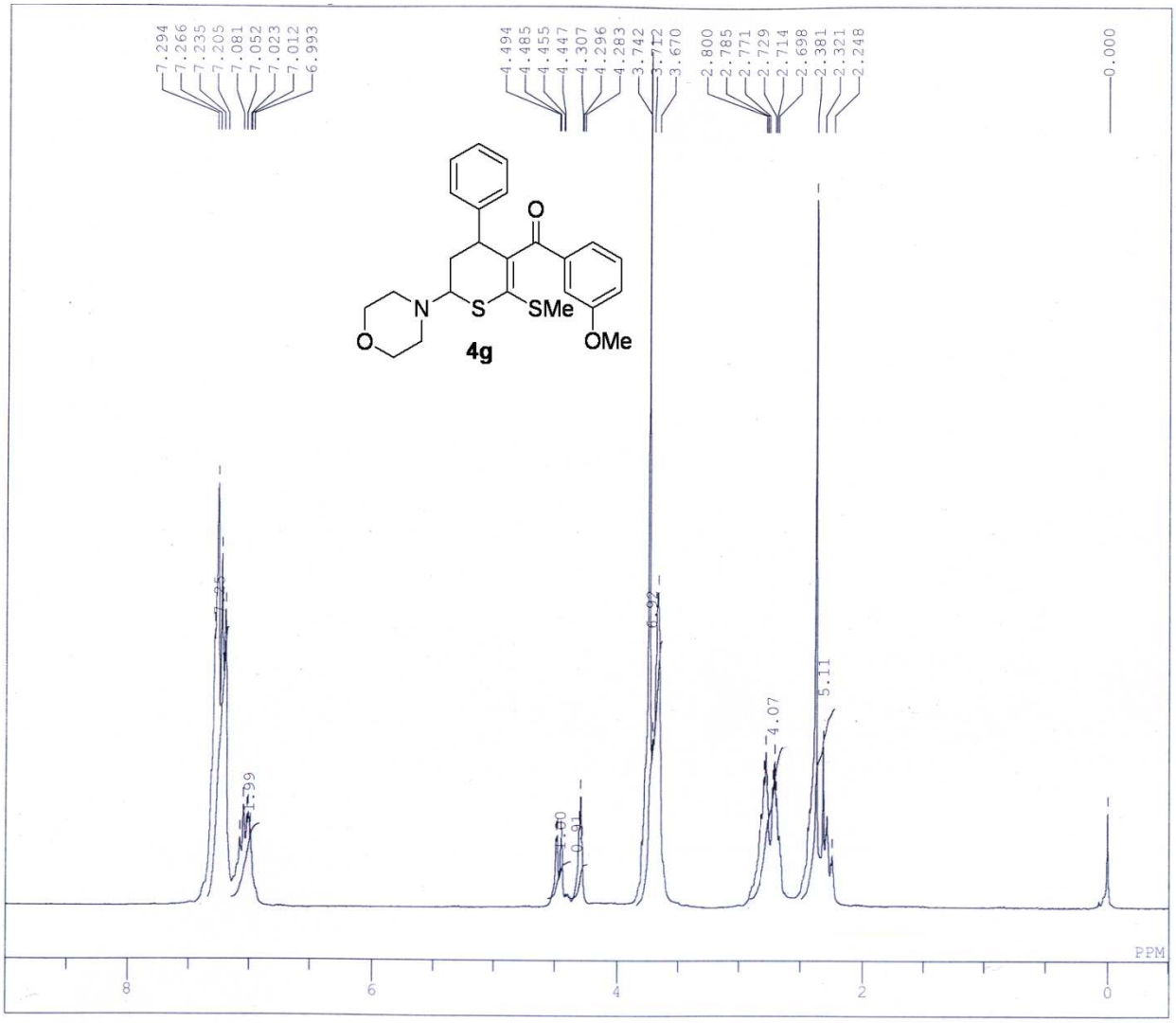

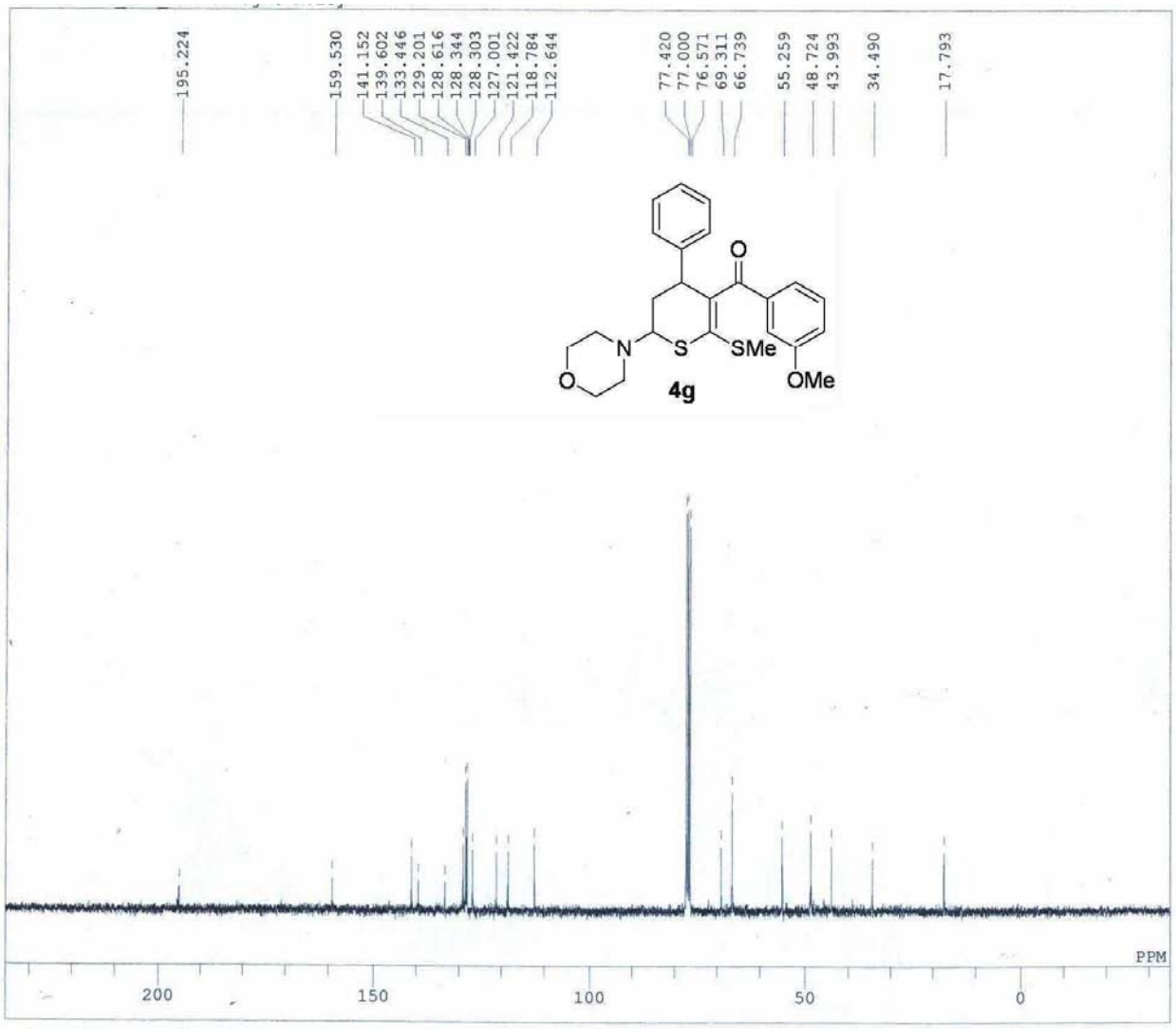

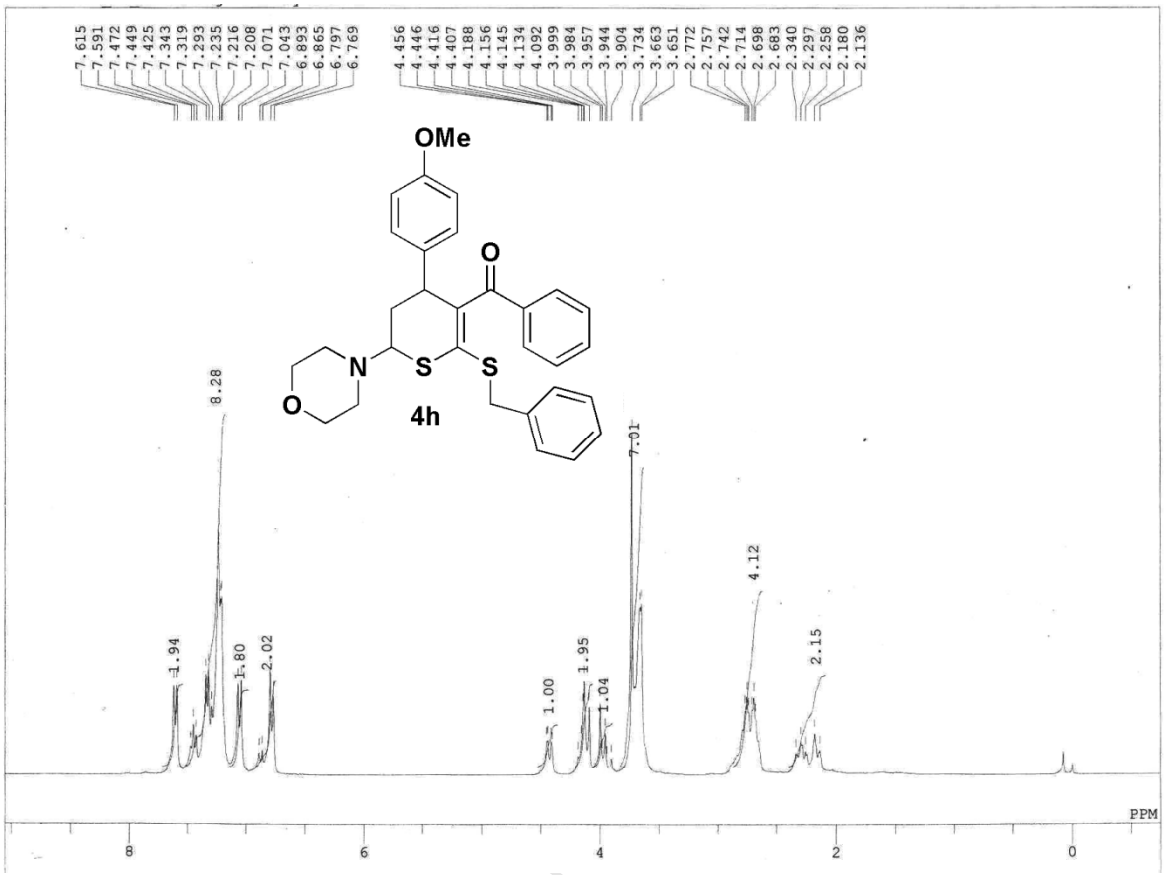

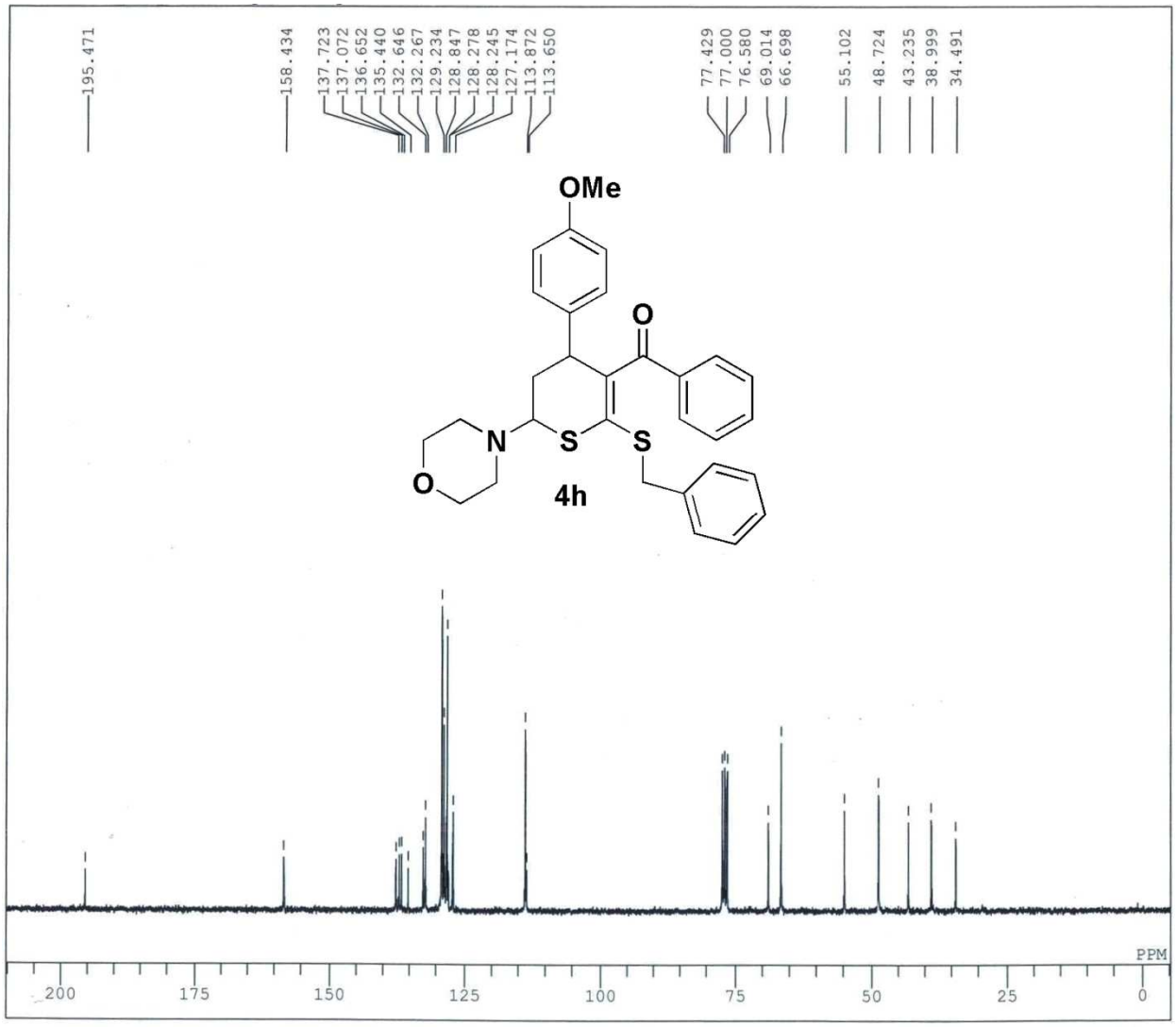

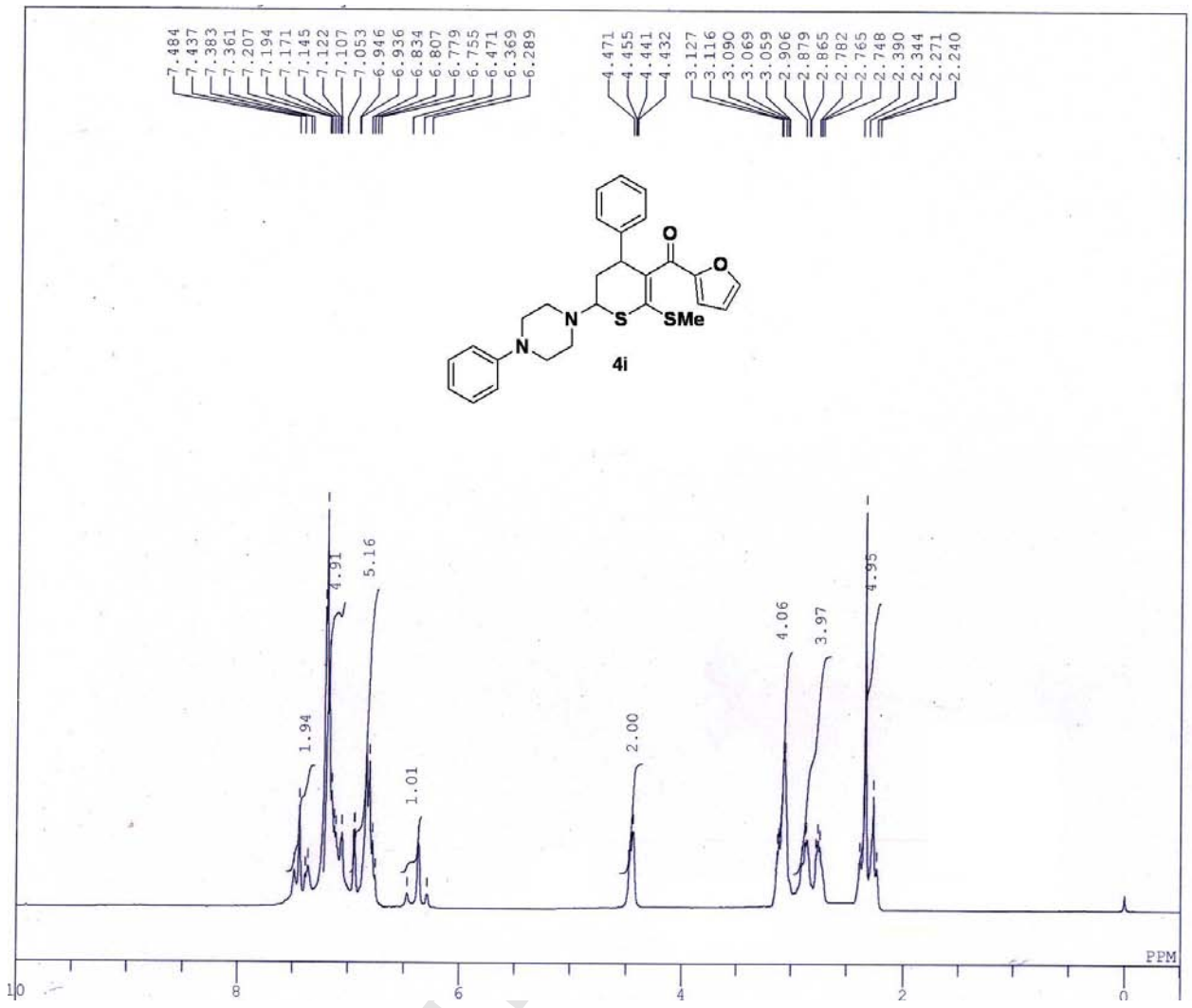

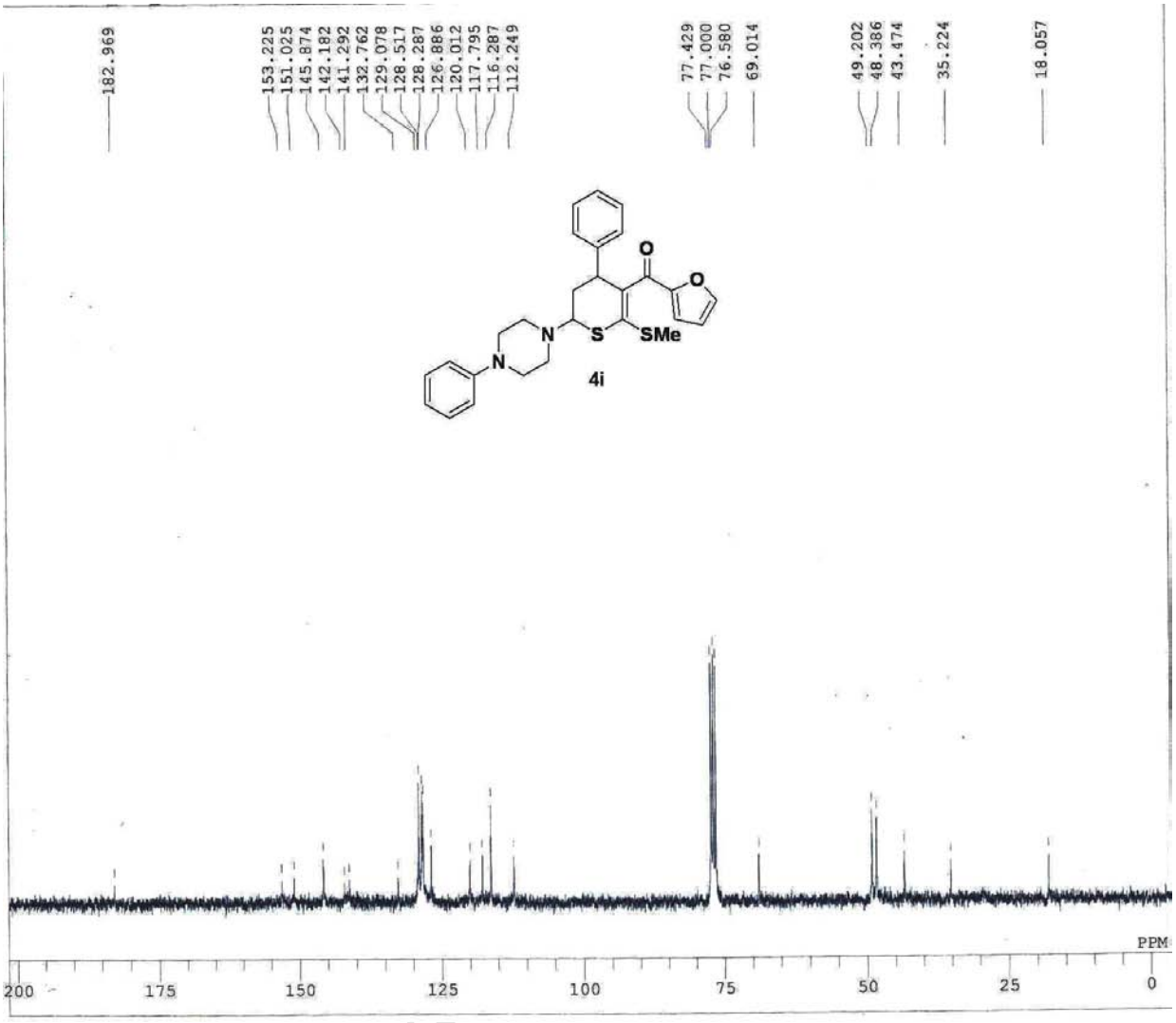

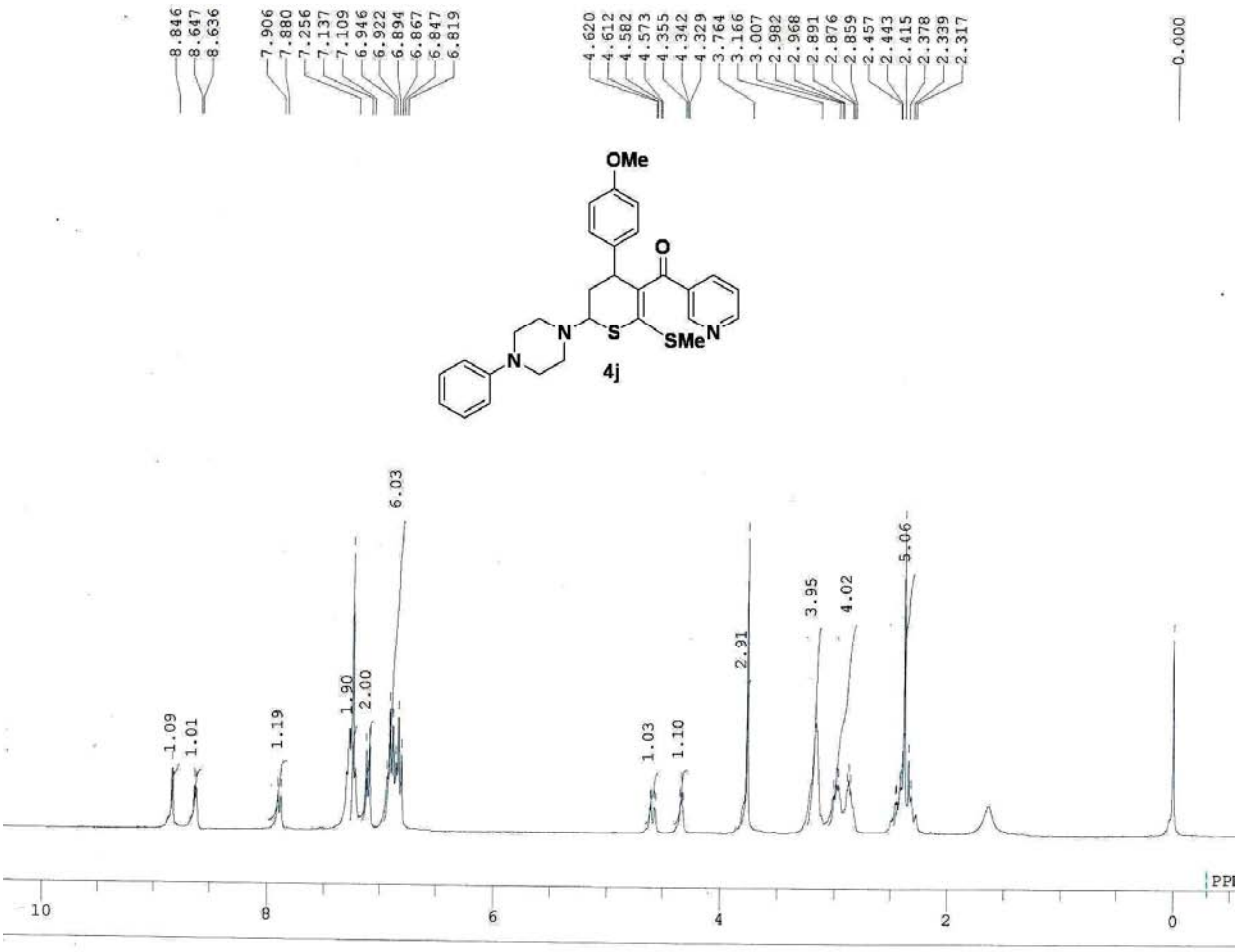
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4.342
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3.007
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S
SMe
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4j
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1.90
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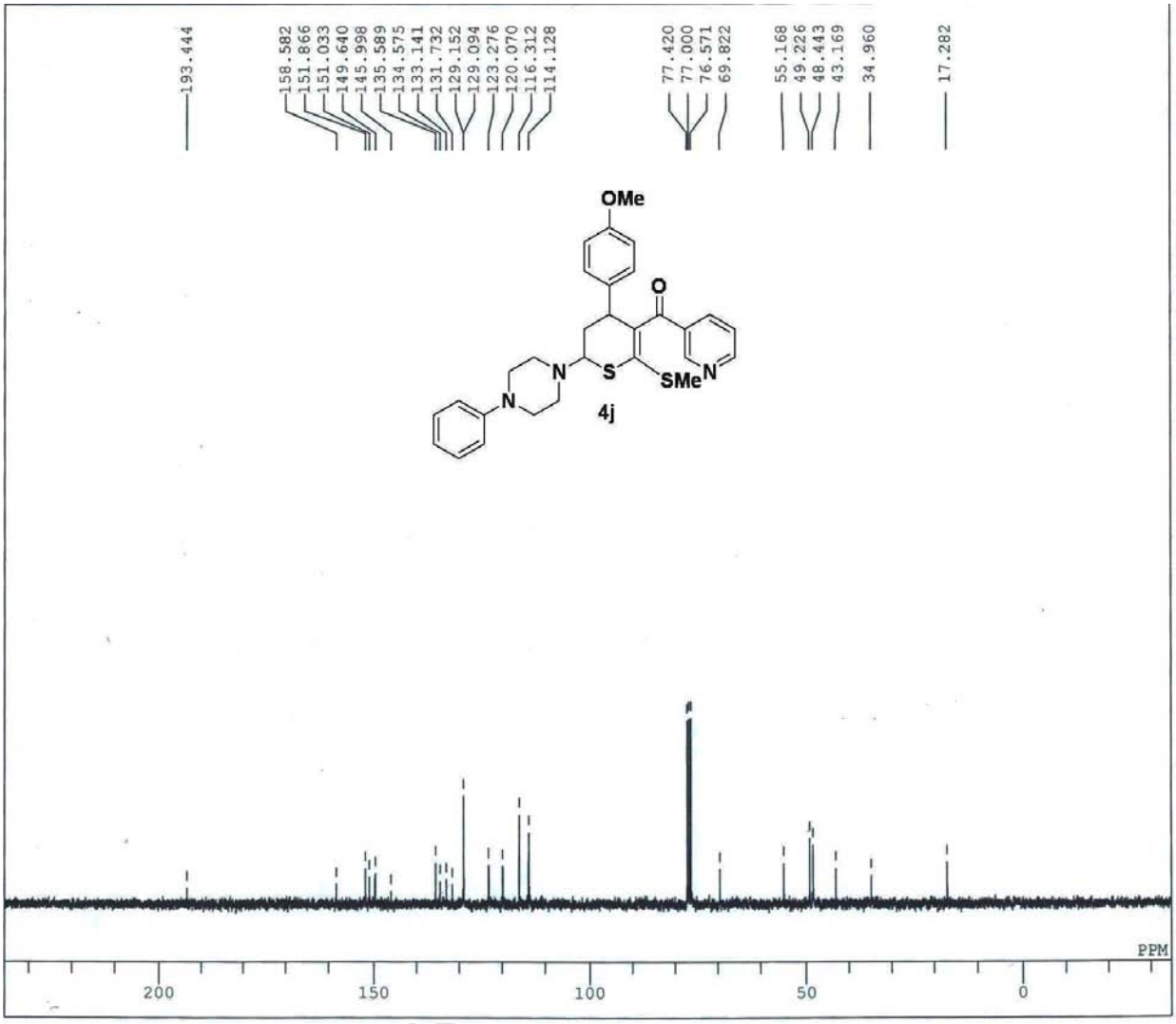

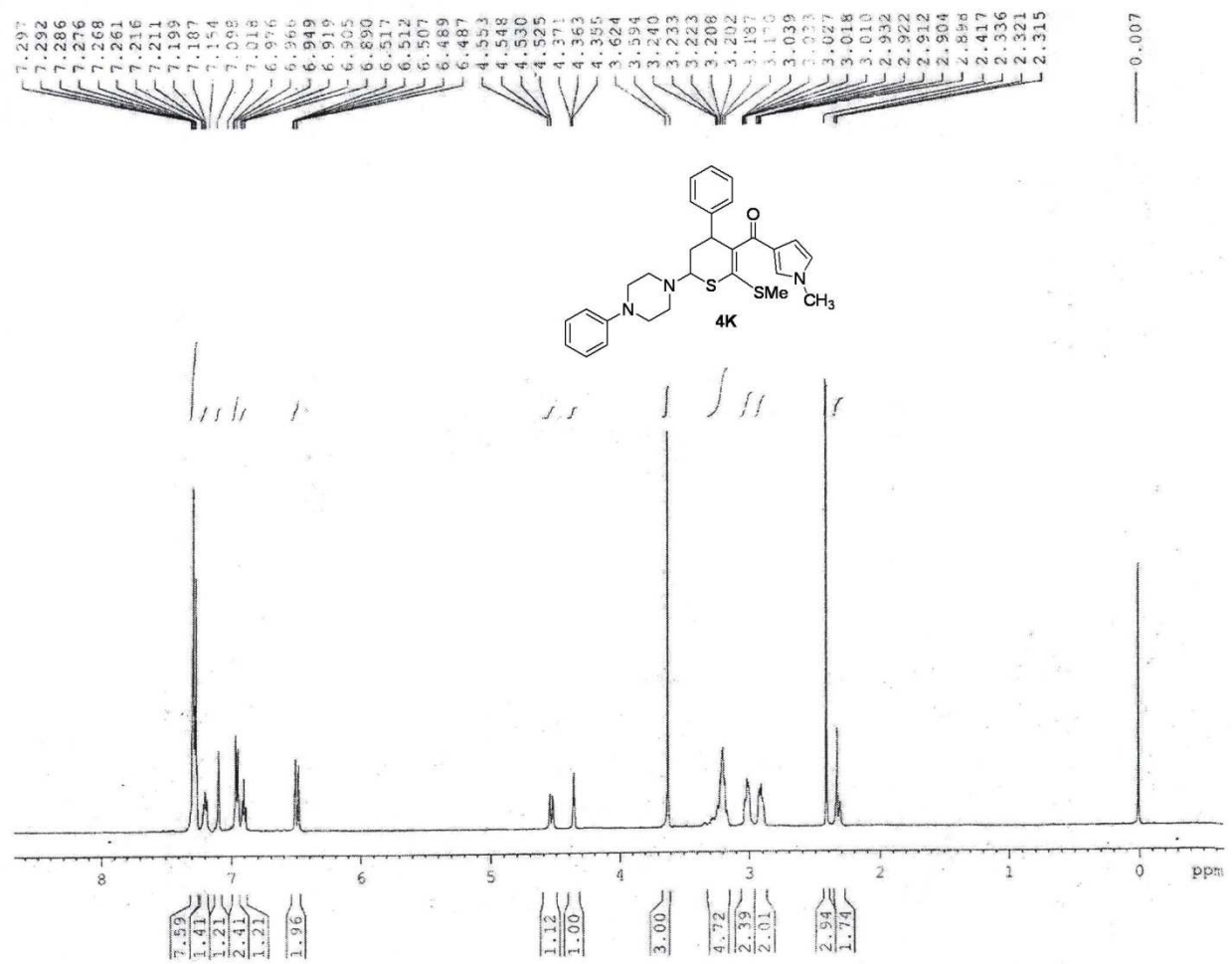

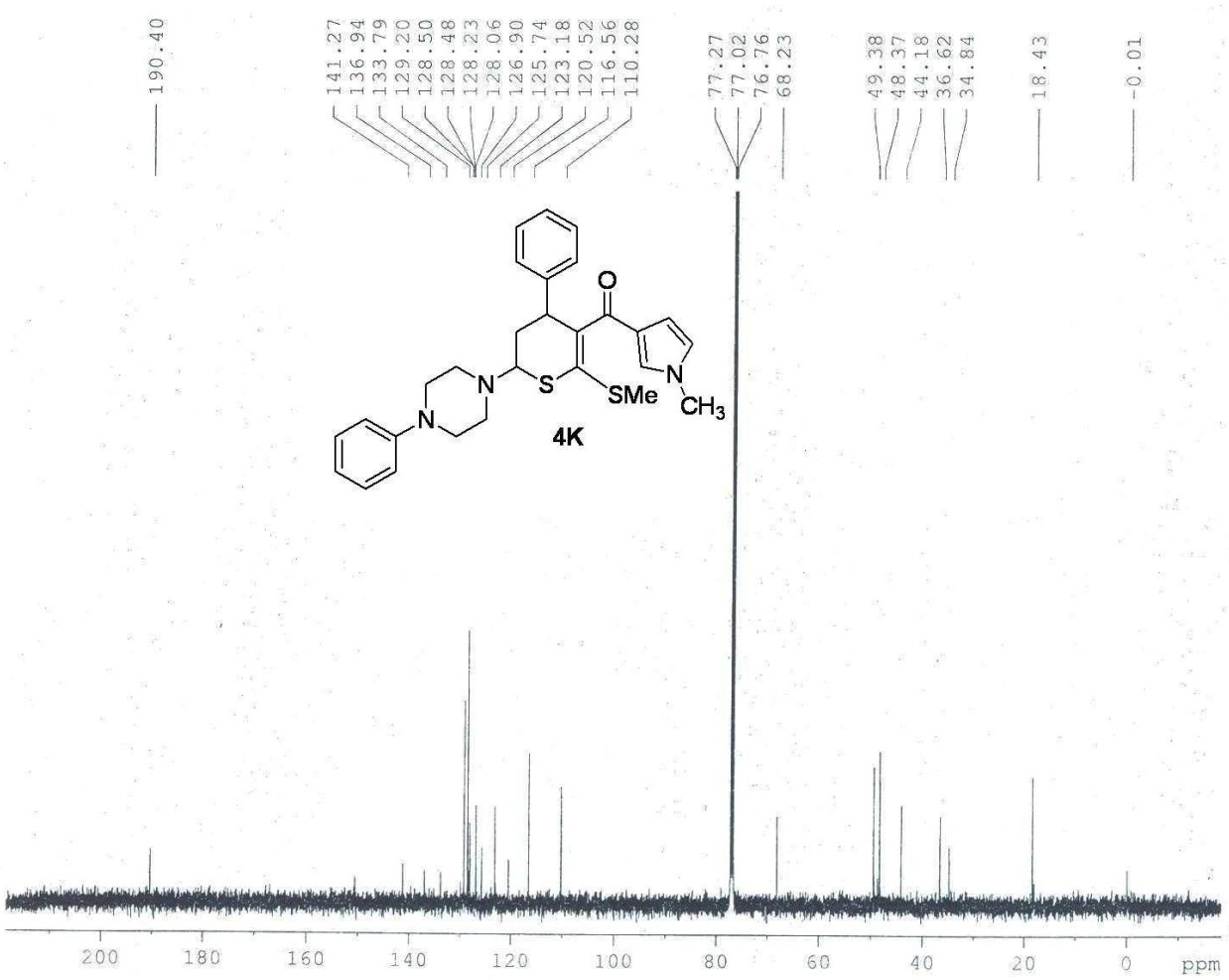
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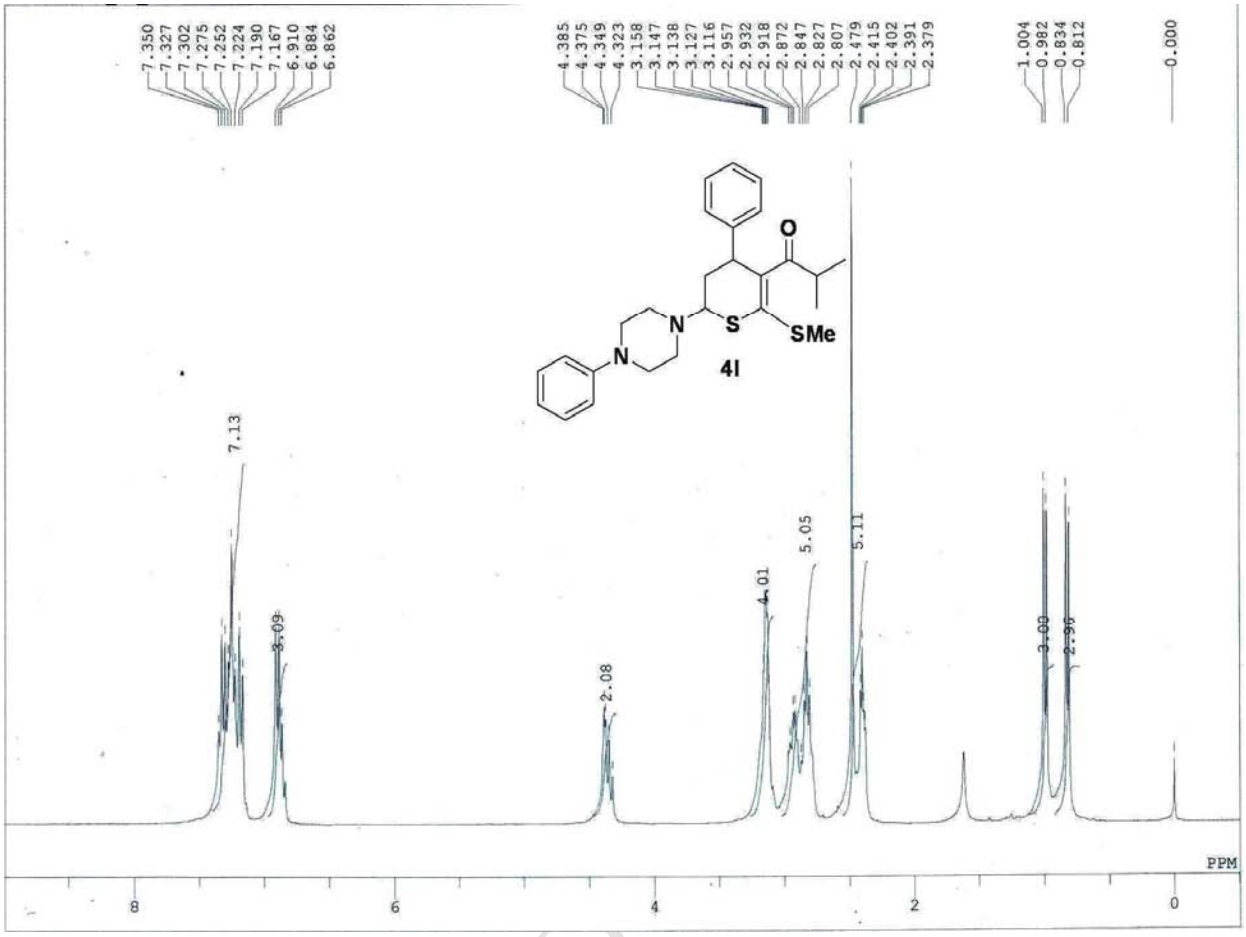
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N
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3.09
2.08
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5.05
5.11
3.00
2.96
PPM
8
6
4
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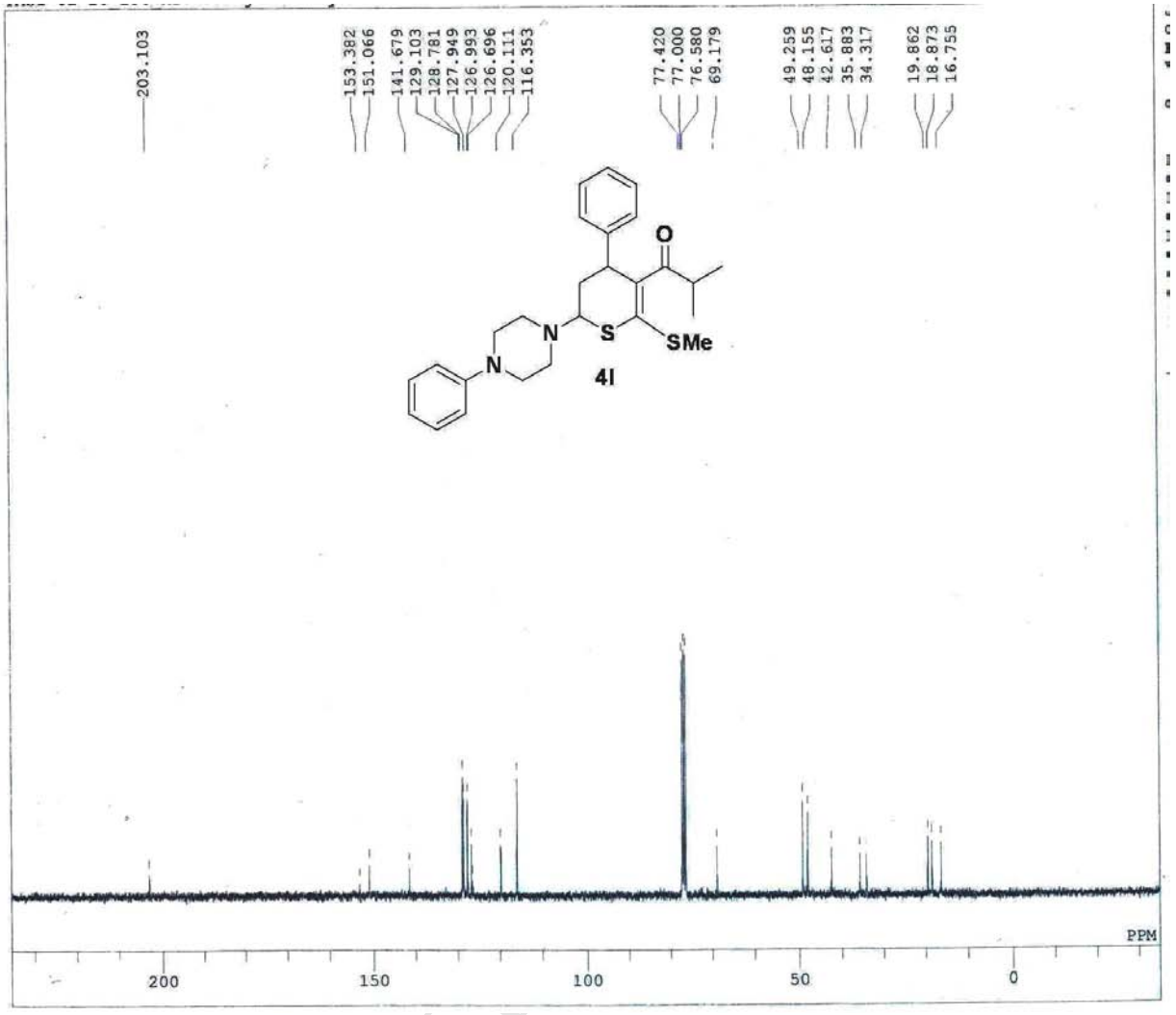

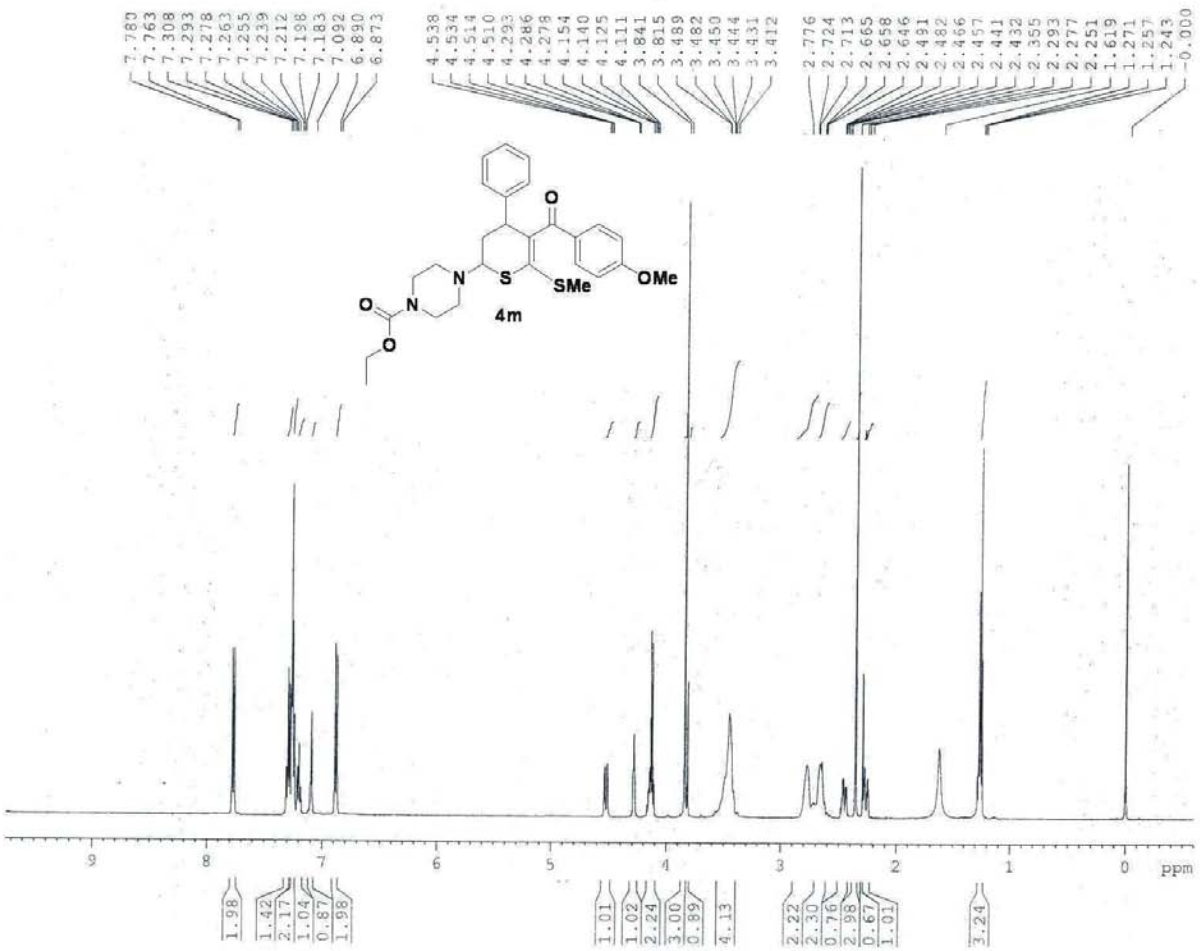
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4.534
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4.125
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2.432
2.355
2.293
2.277
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OMe
O
N
O
4m
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8
7
6
5
4
3
2
1
0
ppm
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2.17
1.04
0.87
1.98
1.01
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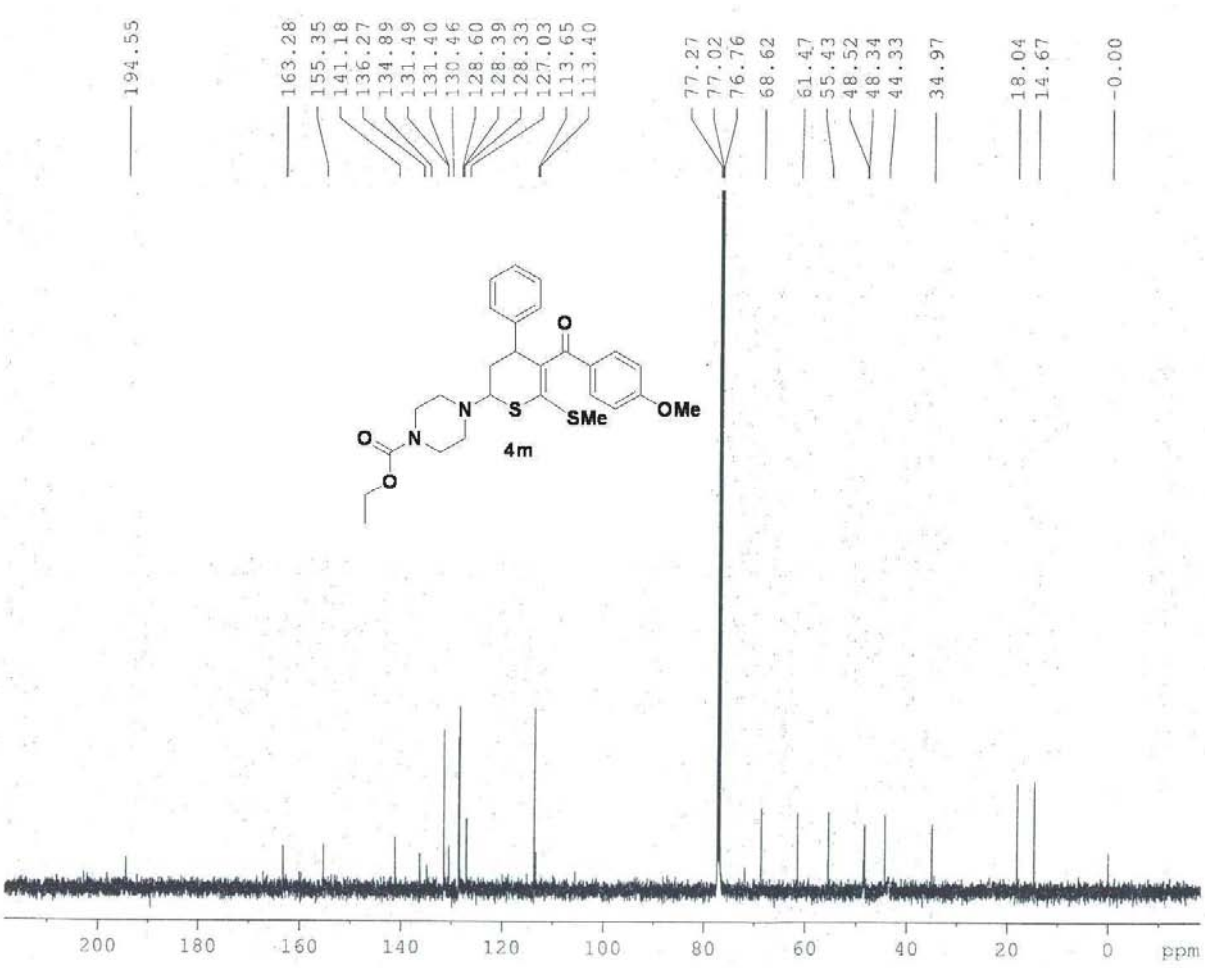
3.24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113.40
77.27
77.02
76.76
68.62
61.47
55.43
48.52
48.34
44.33
34.97
18.04
14.67
-0.00
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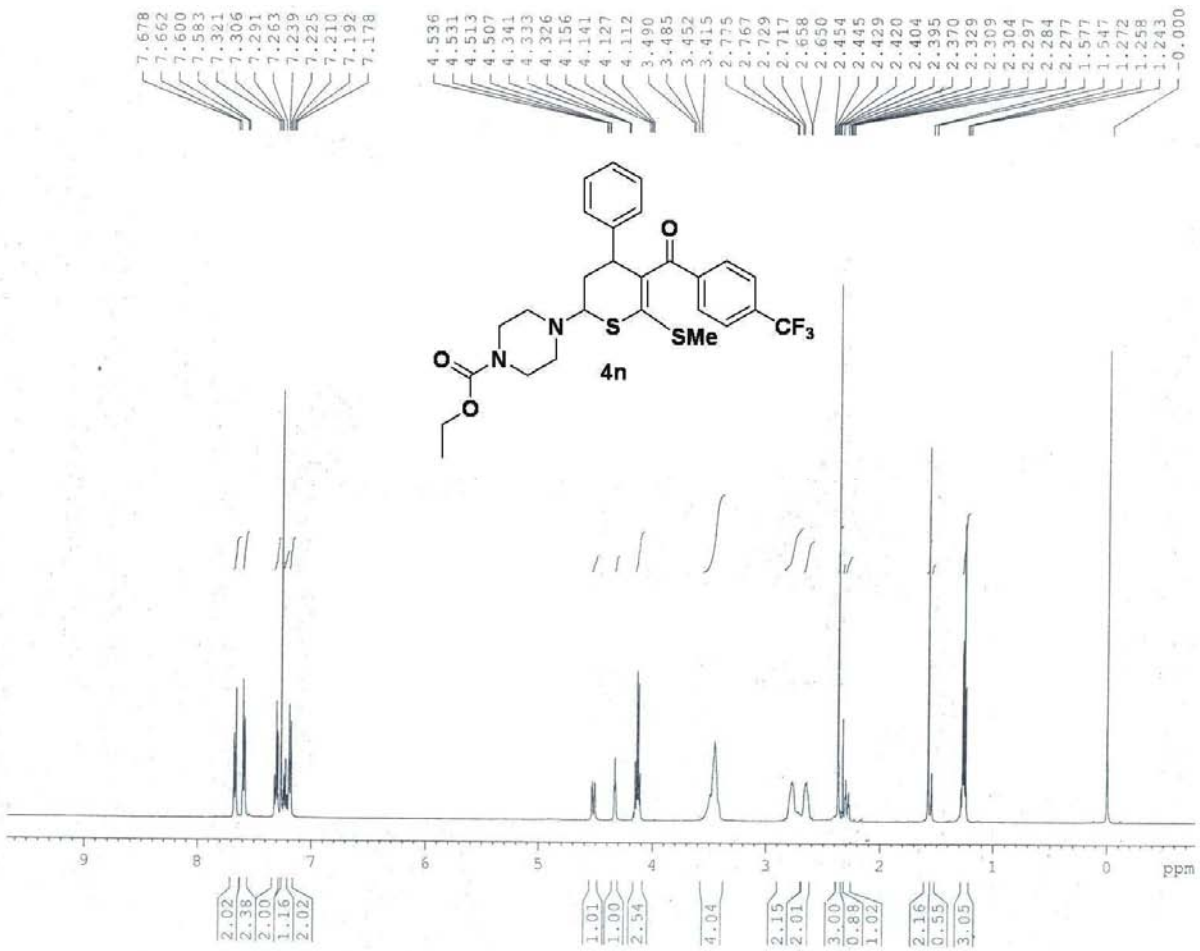
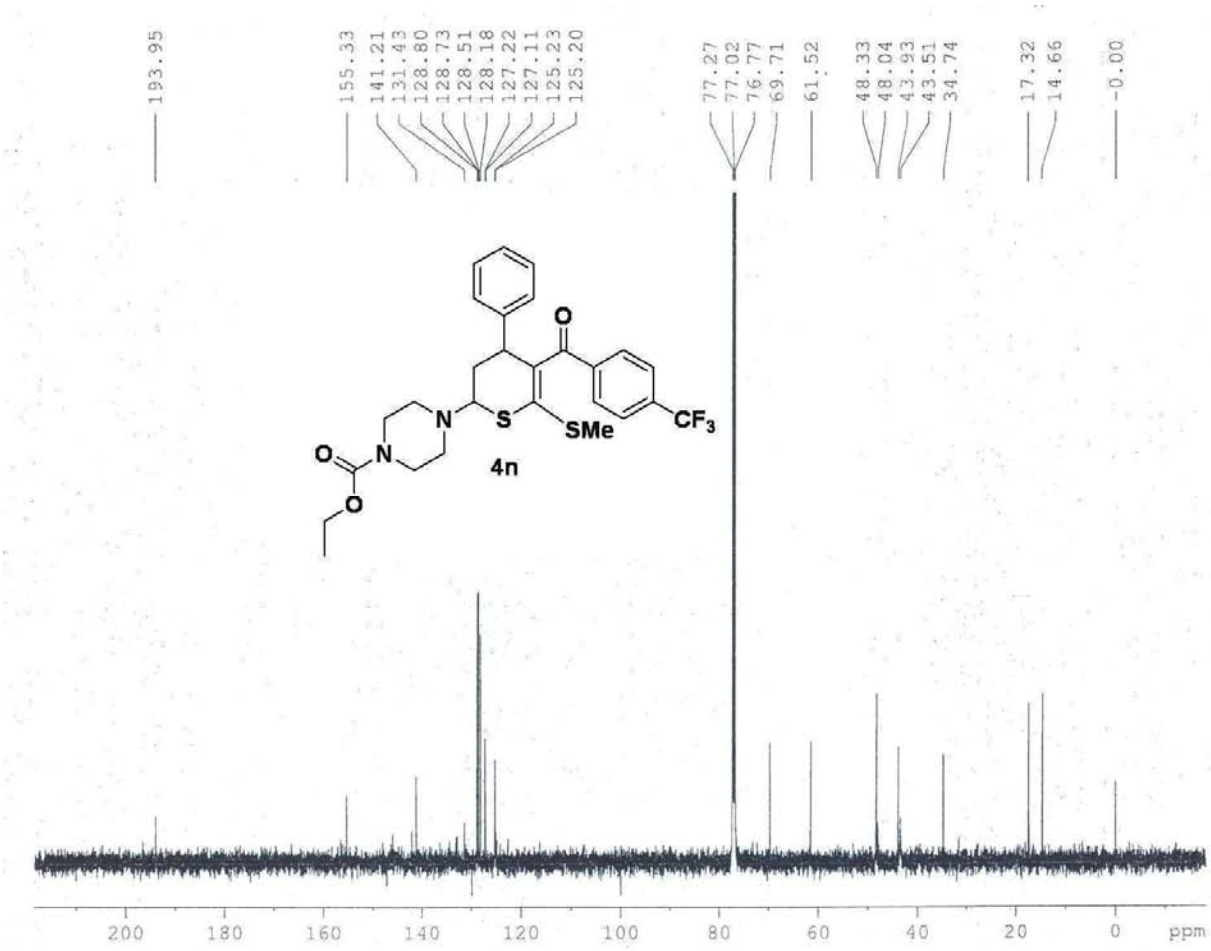
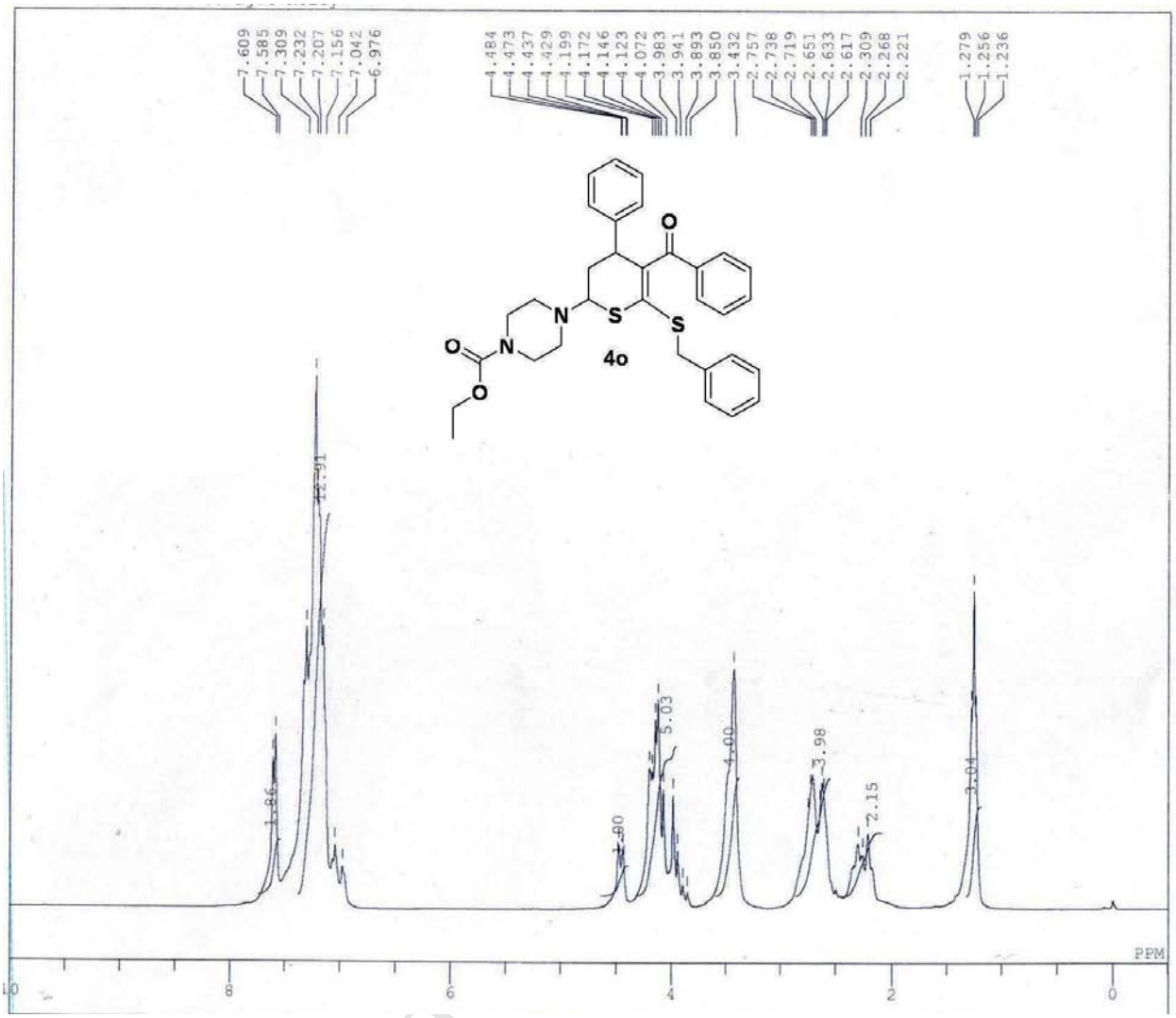
ppm



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4.146
4.123
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3.893
3.850
3.432
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2.738
2.719
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2.633
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N
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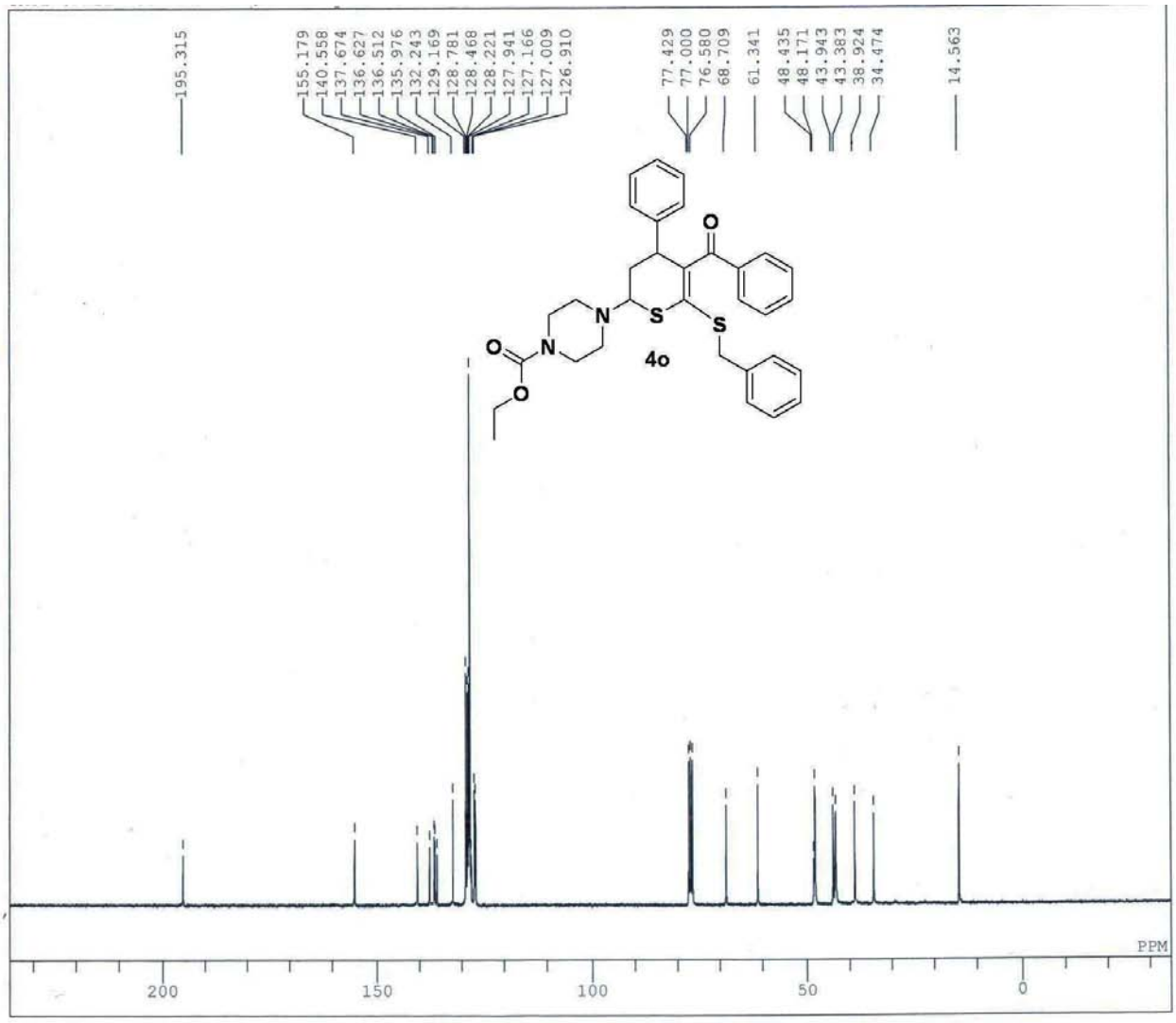

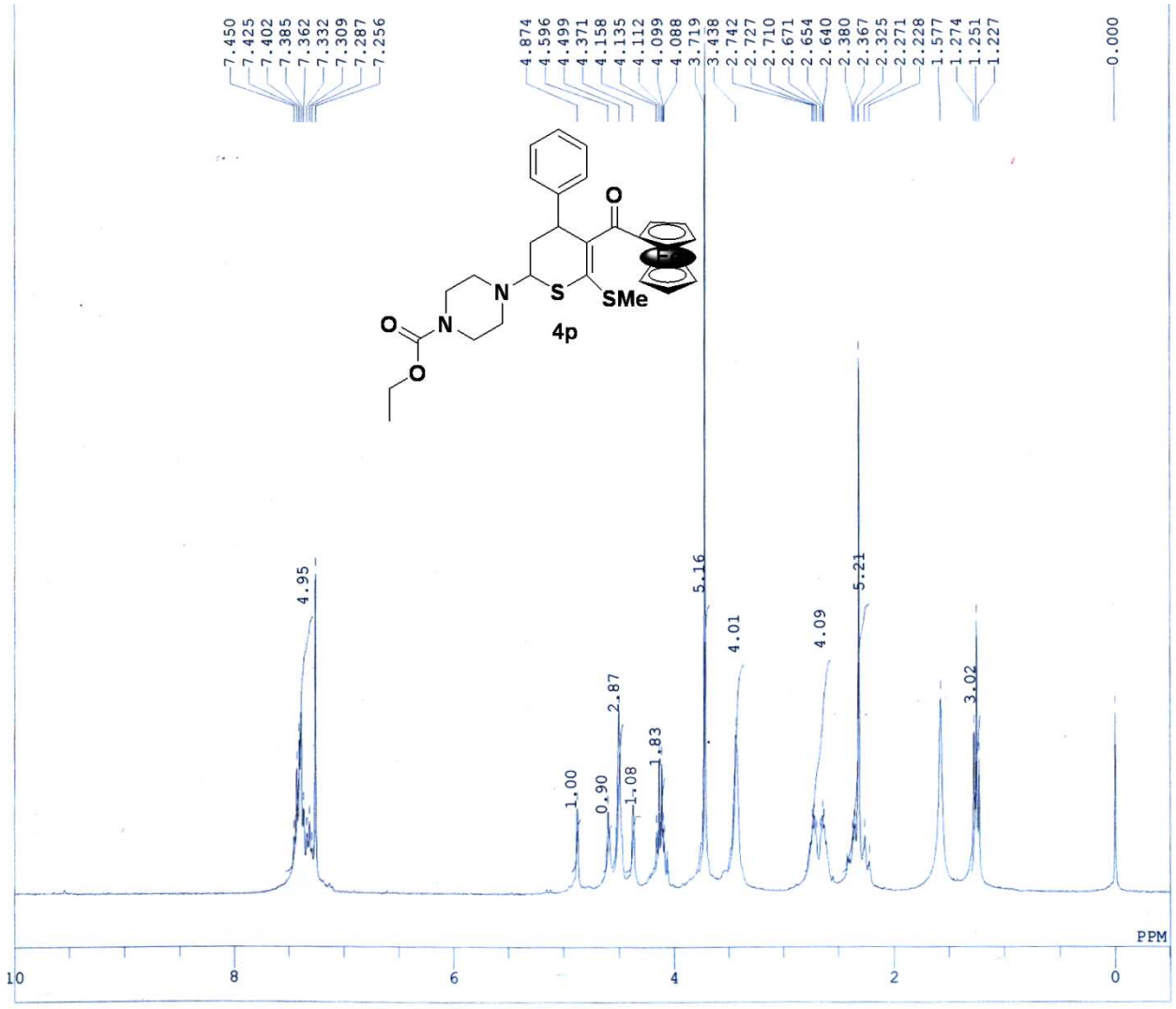

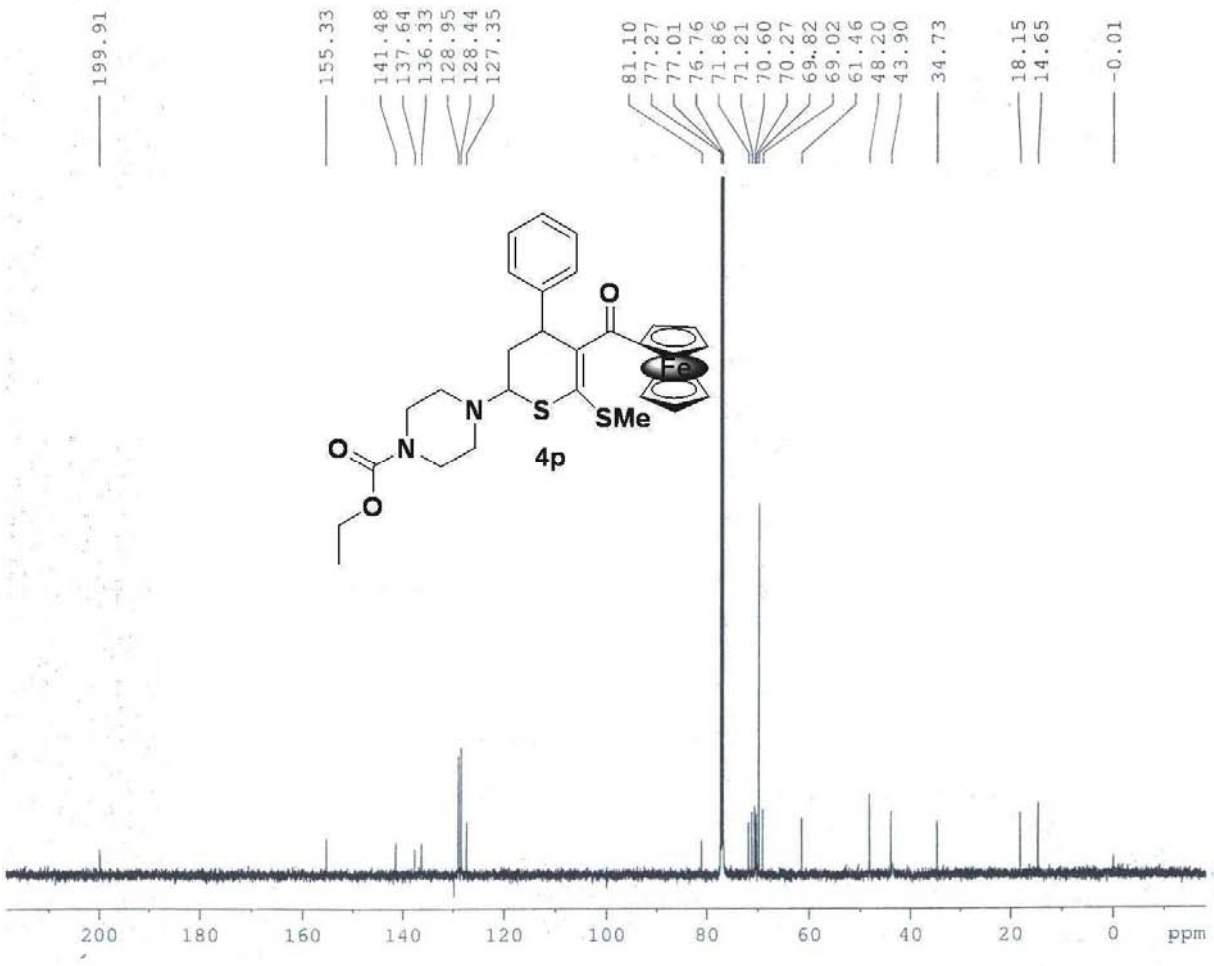
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127.35
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77.27
77.01
76.76
71.86
71.21
70.60
70.27
69.82
69.02
61.46
48.20
43.90
34.73
18.15
14.65
-0.01
O
Fe
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S
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O
N
O
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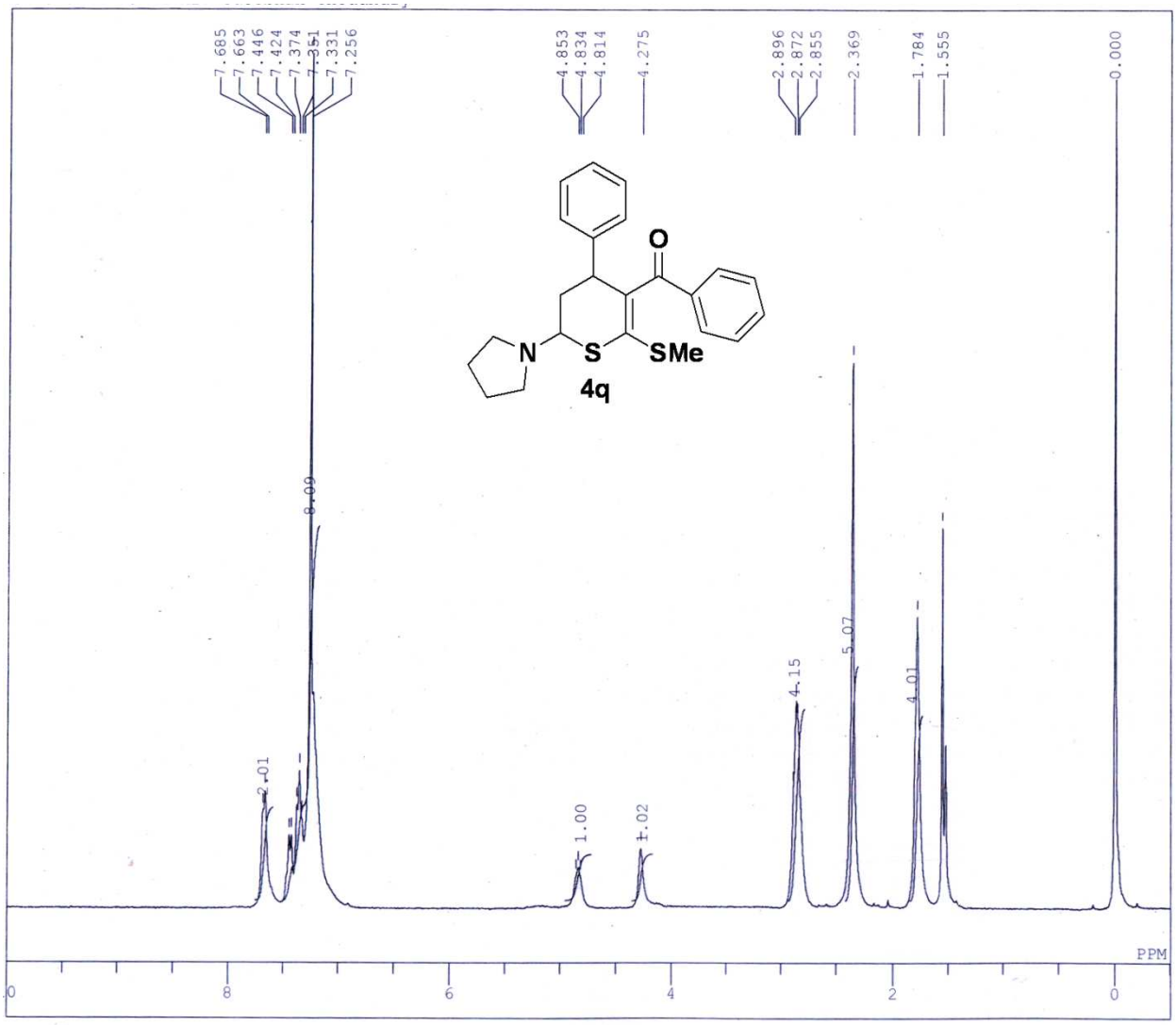
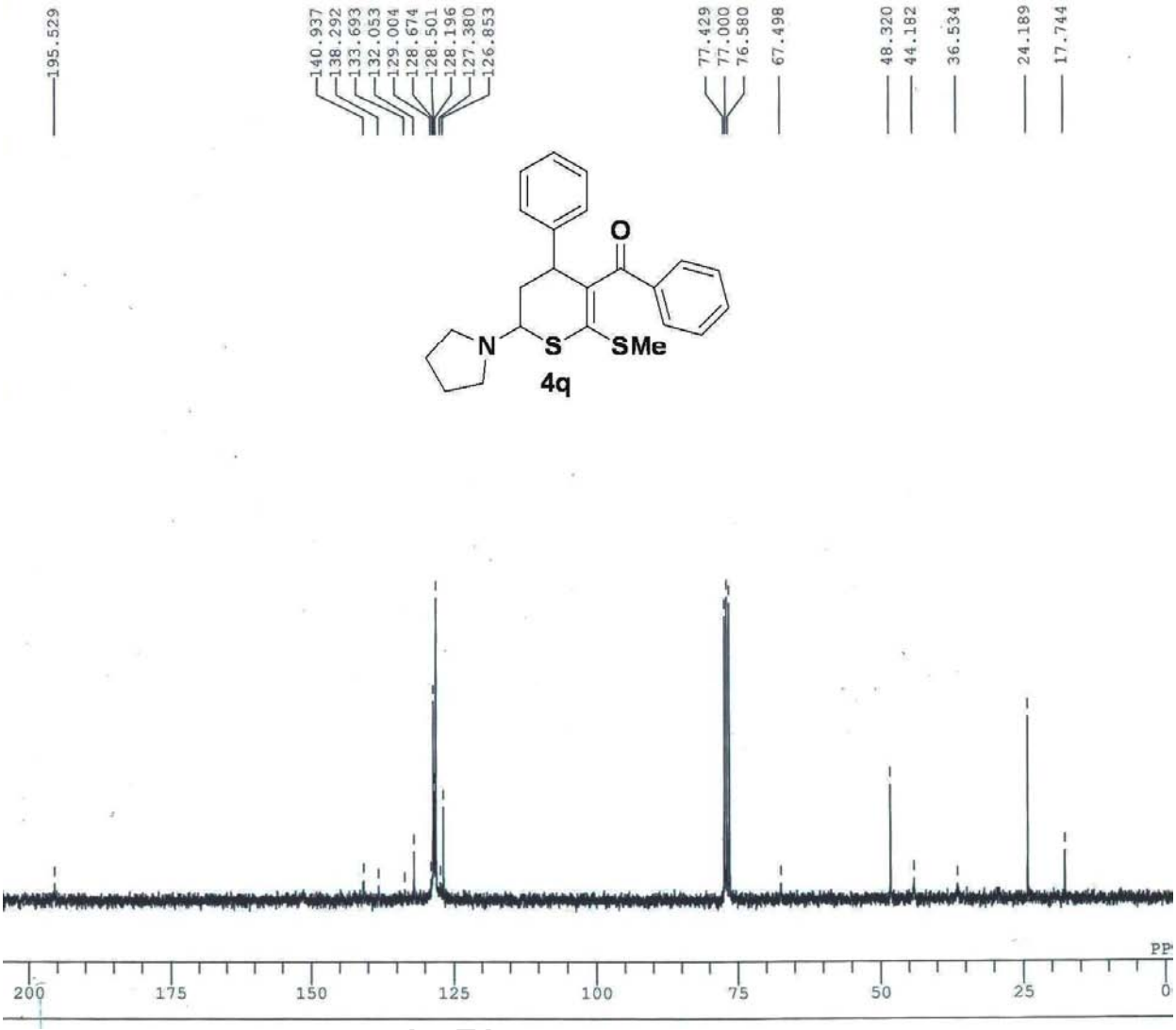
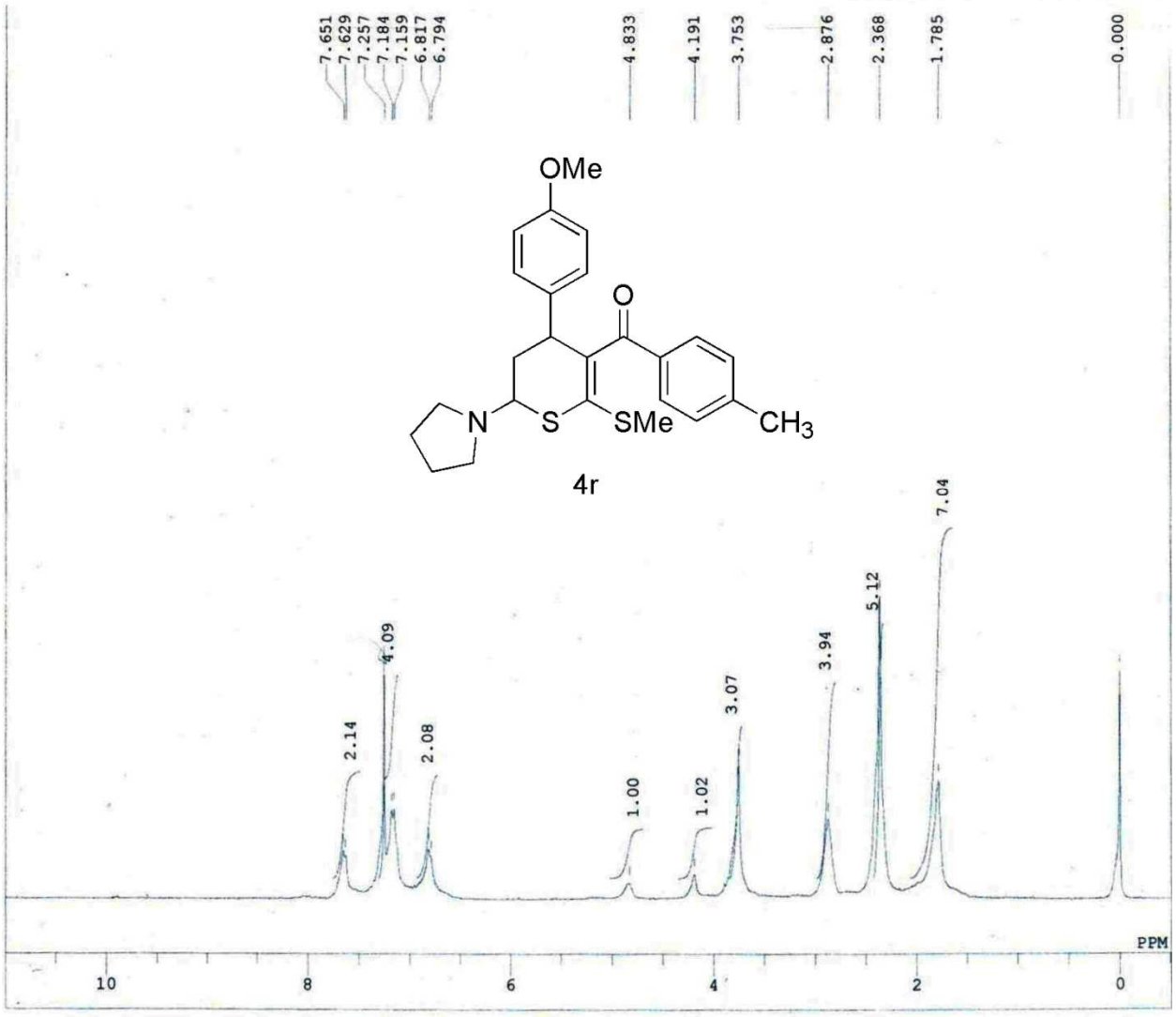
40
20
0
ppm



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2.368
1.785
0.000
OMe
O
N
S
SMe
CH3
4r
2.14
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1.02
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5.12
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PPM
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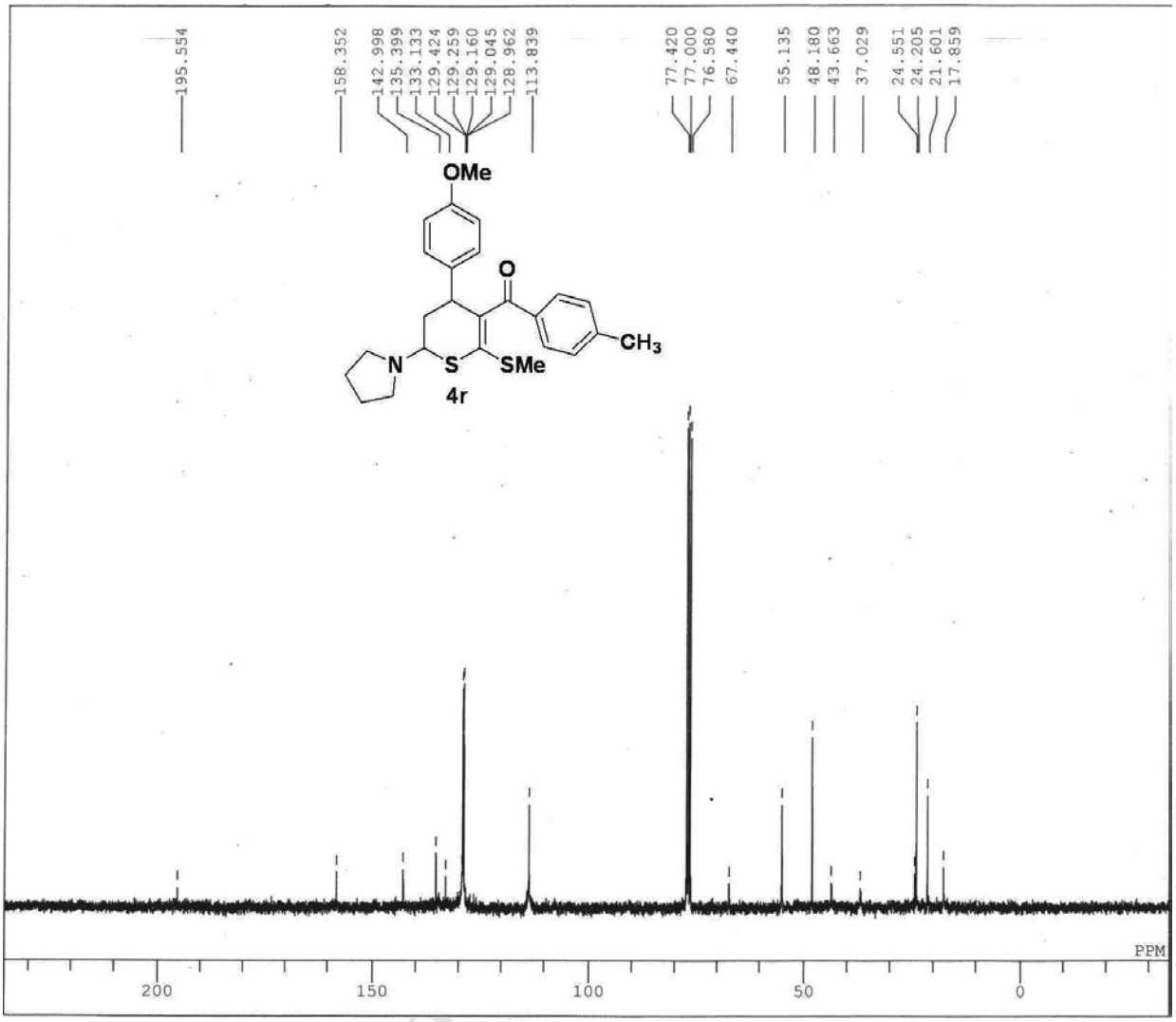
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67.440
55.135
48.180
43.663
37.029
24.551
24.205
21.601
17.859
OMe
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CH3
N
S
SMe
4r
PPM
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100
50
0