Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Organocatalytic Asymmetric Tandem Condensation-Intramolecular Rearrangement-Protonation: An Approach to Optically Active α-Amino Thioester Derivatives

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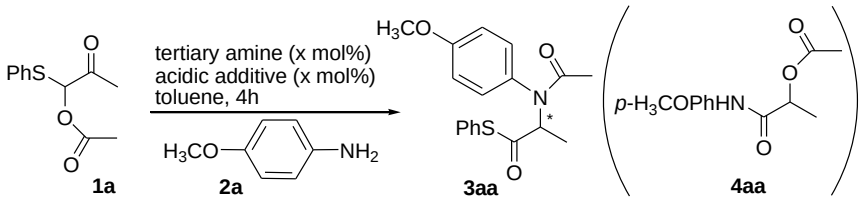
1. Experimental section:

General methods

^{1}H NMR spectra were recorded on 300, 400 and 500 MHz spectrometer at ambient temperature with $CDCl_3$ as solvent. ^{13}C NMR were recorded at 75, 100 and 125 MHz at ambient temperature with $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Infrared spectra were recorded on a FT-IR spectrophotometer and are reported in wavenumbers. Mass spectra analysis were conducted on a GC-MS using electron spray ionization (E.I. 70eV).
The enantiomeric excesses of the products were determined by HPLC using Chiralcel OJ, OD-H and Chiralpak AD-H, AS-H analytical columns with *i*-PrOH/hexane as eluent in comparison to the corresponding racemic samples (prepared by using DMAP/(R)-BDHP (20 mol%) or PTSA (20 mol%) as catalysts). The optical rotation values were measured at 21-32°C. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 70-200 mesh silica gel. Yields refer to chromatography and spectroscopically pure materials.

Screening results.



entry	catalyst		solvent	T/°C	ratio 3:4[b]	yield (%) of 3[c]	yield (%) of 4[c]	ee (%) of 3[d]
	tertiary amine (mol%)	acidic additive (mol%)						
1	**Quinidine** (20)	TsOH (20)	$CHCl_3$	62	8.7:1.0	65	7	53
2	**Quinidine** (20)	TsOH (20)	CH_2Cl_2	40	-	No reaction	No reaction	-
3	**Quinidine** (20)	TsOH (20)	THF	66	>20:1.0	25	-	33
4	**Quinidine** (20)	TsOH (20)	MeOH	65	1.0:>20	-	11	-
5	**Quinidine** (20)	TsOH (20)	DMF	60	1.0:>20	-	29	-
6	**Quinidine** (20)	TsOH (20)	CH_3CN	81	1.0:2.0	4	9	ND
7	**Quinidine** (20)	TsOH (20)	Toluene	30	>20:1.0	10	-	50
8	**Quinidine** (20)	TsOH (20)	Toluene	90	>20:1.0	65	-	60
9	**Quinidine** (10)	(S)-BDHP (10)	Toluene	60	>20:1.0	27	-	72
10[e]	**Quinidine** (20)	(S)-BDHP (20)	Toluene	60	>20:1.0	79	-	63
11[f]	**Quinidine** (20)	(S)-BDHP (20)	Toluene	60	12.9:1.0	61	5	62
12[g]	**Quinidine** (20)	(S)-BDHP (40)	Toluene	60	>20:1.0	67	-	18
13[g]	**Quinidine** (20)	(R)-BDHP (40)	Toluene	60	>20:1.0	73	-	42
14[g]	**(DHQD)$_2$PHAL** (20)	(S)-BDHP (20)	Toluene	60	4.9:1.0	55	11	-80
15[g]	**(DHQ)$_2$PHAL** (20)	(R)-BDHP (20)	Toluene	60	9.6:1.0	67	7	69
16[g]	**(DHQD)$_2$PHAL** (20)	(R)-BDHP (30)	Toluene	60	5.0:1.0	60	12	-75
17[g]	**(DHQD)$_2$PHAL** (20)	(R)-BDHP (40)	Toluene	60	11.7:1.0	67	5	-68
18[g,h]	**(DHQD)$_2$PHAL** (20)	(S)-BDHP (20)	Toluene	60	5.3:1.0	42	8	-66
19[i,j]	**(DHQD)$_2$PHAL** (20)	(S)-BDHP (20)	Toluene	60	2.2:1.0	52	23	-76
20[g]	**(DHQD)$_2$AQN** (20)	(R)-BDHP (20)	Toluene	60	1.0:>20	traces	64	-28
21[g]	**(DHQ)$_2$AQN** (20)	(R)-BDHP (20)	Toluene	60	1.0:2.8	11	33	4
22[g]	**(DHQ)$_2$PYR** (20)	(R)-BDHP (20)	Toluene	60	1.0:1.4	29	40	48
23	**DBU** (20)	(R)-BDHP (20)	Toluene	60	1.0:>20	-	47	-

[a]Conditions: 0.22 mmol of 1a, 0.27 mmol of 2a, 0.044 mmol of amine and 0.044 mmol of acid, 0.5 mL solvent. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c]Isolated yield after chromatography. [d]Determined by HPLC analysis using a chiral stationary column. [e] 3eq. of $MgSO_4$ was used. [f] 1vol% of H_2O was used. [g] Reaction carried out over 24h. [h] In 0.25 mL of Toluene. [i] In 1mL of Toluene. [j] Reaction carried out over 48h.

General procedure for the Synthesis of α-acyloxy-β-ketosulfides 1a-f:

β-Keto sulfoxide (0.252 mmol) was dissolved in a mixture of dichloromethane (2 mL), pyridine (0.2 mL), and acetic anhydride (0.2 mL); then 4-dimethylamino pyridine (3 mg) was added to the solution. The resulting mixture was stirred for 24h at room temperature. HCl (1 M, 10 mL) and ethyl acetate (10 mL) was added to the mixture and extracted. The organic layer was separated and washed with water (6 mL), saturated $NaHCO_3$ aqueous solution (7 mL), and saturated NaCl aqueous solution (7 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through a flash column chromatography on silica gel (mixture of hexane/ether) to give the corresponding α-acyloxy-β-ketosulfide **1a-f** (85-90% yield). α-acyloxy-β-ketosulfides **1a-e** are known compounds, and were reported in literature.[1]

1-(*p*-tolylthio)-2-oxopropyl acetate (1f): Colorless oil. IR (neat): 1754, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.18 (s, 3H), 2.22 (s, 3H), 2.35 (s, 3H), 6.14 (s, 1H), 7.12 (d, 2H, *J* = 4.8 Hz), 7.37 (d, 2H, *J* = 5.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.8, 21.2, 26.3, 81.9, 125.9, 130.0, 134.0, 139.6, 169.8, 197.1. MS m/z: 238 (M^+ (24)), 195 (50), 153 (77), 124 (100), 91 (47), 77 (12).

Representative general procedure for the Synthesis of α-amino thioesters 3.

In an ordinary vial equipped with a magnetic stir bar, quinidine (0.044 mmol) and (S)-BDHP (0.044 mmol) were suspended in toluene (0.5 mL). After stirring at room temperature for 15 min, the primary amine **2** (0.27 mmol) was added, followed by the addition of the α-acyloxy-β-ketosulfide **1** (0.22 mmol). The mixture was allowed to stir at 60°C for 4-48 h. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of hexane/ether).

2. Characterization data:

S-phenyl-2-(N-(4-methoxyphenyl)acetamido)propanethioate (3aa): Orange oil. Yield 66%. IR (neat): 1719, 1668 cm^{-1}. $[\alpha]_D^{32}$= -29.8 (*c* 2.01, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.28 (d, 3H, *J* = 7.2 Hz), 1.84 (s, 3H), 3.80 (s, 3H), 5.21 (q, 1H, *J* = 7.5 Hz), 6.88 (d, 2H, *J* = 7.8 Hz), 7.24-7.26 (m, 2H), 7.37-7.44 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.7, 23.0, 55.4, 61.4, 114.5, 127.3, 129.1, 129.3, 130.6, 132.7, 134.7, 159.4, 171.4, 197.9. MS m/z: 220 (M^+-109 (57)), 192 (23), 150 (100), 134 (11), 109 (11), 43 (23). The *ee* was determined to be 76% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 26.82 min, t_R(minor) = 41.53 min, or (Chiralpak AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 15.50 min, t_R(minor) = 16.94 min. Anal. Calcd. for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.57; H, 5.83; N, 4.20; S, 9.65.

S-phenyl-2-(N-(4-methoxyphenyl)acetamido)butanethioate (3ba): Orange oil. Yield 75%. $[\alpha]_D^{23}$= +5.7 (*c* 0.69, $CHCl_3$). IR (neat): 1708, 1662 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.98 (t, 3H, *J* = 7.5 Hz), 1.59-1.69 (m, 2H), 1.88 (s, 3H), 3.81 (s, 3H), 5.18 (dd, 1H, *J* = 6.3 Hz, *J* = 8.25 Hz), 6.89 (d, 2H, *J* = 9 Hz), 7.26 (d, 2H, *J* = 8.7 Hz), 7.35-7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.1, 22.5, 23.0, 55.3, 67.0, 114.4, 127.4, 129.1, 129.2, 130.3, 132.6, 134.5, 159.3, 171.6, 196.9. MS m/z: 234 (M^+-109 (62)), 206 (30), 164 (100), 134 (12), 109 (12). The *ee* was determined to be 22% *ee* by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 16.84 min, t_R(minor) = 18.37 min. Anal. Calcd. for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 66.40; H, 6.21; N, 4.01; S, 9.29.

S-phenyl-2-(N-(4-methoxyphenyl)acetamido)-4-phenylbutanethioate (3ca): Orange oil. Yield 62%. $[\alpha]_D^{22}$= +11.5 (*c* 2.59, $CHCl_3$). IR (neat): 1704, 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.90 (s, 3H), 2.15-2.25 (m, 2H), 2.65-2.72 (m, 2H), 3.82 (s, 3H), 5.31 (t, 1H, *J* = 6.6 Hz), 6.90 (d, 2H, *J* = 9 Hz), 7.06 (d, 2H, *J* = 9.3 Hz), 7.10-7.29 (m, 5H), 7.39-7.49 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.1, 31.3, 32.7, 55.4, 65.2, 114.6, 126.1, 127.3, 128.3, 128.4, 129.1, 129.4, 130.3, 132.6,

[1]Capitta, F.; Frongia, A.; Piras, P. P.; Pitzanti, P.; Secci, F. *Adv. Synth. Catal.* **2010**, *352*, 2955-2960.

134.6, 140.7, 159.4, 171.6, 196.9. MS m/z: 310 (M^+-109 (54)), 282 (25), 240 (100), 166 (17), 149 (35), 109 (25), 91 (51), 43 (54). The *ee* was determined to be 22% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 47.09 min, t_R(minor) = 53.17 min. Anal. Calcd. for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34; S, 7.64. Found: C, 71.62; H, 6.13; N, 3.30; S, 7.69.

S-phenyl-2-(N-(4-methoxyphenyl)acetamido)-2-phenylethanethioate (3da): Pale yellow solid; mp = 145-150°C. Yield 10%. IR (KBr): 1711, 1657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.81 (s, 3H), 3.69 (s, 3H), 6.44 (s, 1H), 7.00 (d, 2H, *J* = 8.1 Hz), 7.13-7.36 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.0, 55.3, 69.9, 113.9, 125.4, 128.4, 128.7, 129.1, 129.4, 130.9, 131.5, 132.5, 133.0, 134.8, 159.0, 171.5, 196.4. MS m/z: 282 (M^+-109 (50)), 254 (25), 212 (100), 196 (13), 109 (10). Anal. Calcd. for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.41; H, 5.48; N, 3.49; S, 8.30; **(4da)**: Gray solid; mp = 151-157 °C. Yield 67%. IR (KBr): 1743, 1682 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 3.77 (s, 3H), 6.18 (s, 1H), 6.83 (d, 2H, *J* = 9 Hz), 7.36-7.50 (m, 7H), 7.69 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0, 55.4, 114.3, 121.6, 127.2, 127.5, 129.0, 129.8, 135.2, 156.7, 166.0, 169.0. MS m/z: 299 (M^+(57)), 211 (100), 196 (22), 149 (22), 123 (47), 108 (100), 90 (13). The *ee* was determined to be 26% *ee* by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 33.20 min, t_R(minor) = 62.48 min. Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.15; H, 5.80; N, 4.55.

S-4-bromophenyl 2-(N-(4-methoxyphenyl)acetamido)propanethioate (3ea): Orange oil. Yield 47%. $[\alpha]_D^{21}$= -21 (*c* 1.7, $CHCl_3$). IR (neat): 1715, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.28 (d, 3H, *J* = 4.5 Hz), 1.84 (s, 3H), 3.81 (s, 3H), 5.14 (q, 1H, *J* = 4.2 Hz), 6.89 (d, 2H, *J* = 5.4 Hz), 7.23-7.24 (m, 2H), 7.52 (d, 2H, *J* = 4.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.7, 23.0, 55.4, 61.7, 114.6, 124.0, 126.5, 130.5, 132.3, 136.2, 159.4, 171.4, 197.3. MS m/z: 220 (M^+-187 (35)), 192 (26), 150 (100), 108 (21), 43 (48). The *ee* was determined to be 54% *ee* by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 22.91 min, t_R(minor) = 27.37 min. Anal. Calcd. for $C_{18}H_{18}BrNO_3S$: C, 52.95; H, 4.44; N, 3.43; S, 7.85. Found: C, 51.40; H, 4.47; N, 3.31; S, 7.80.

S-*p*-tolyl 2-(N-(4-methoxyphenyl)acetamido)propanethioate (3fa): Orange oil. Yield 62%. $[\alpha]_D^{25}$= -29.2 (*c* 1.99, $CHCl_3$). IR (neat): 1711, 1669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (d, 3H, *J* = 7.2 Hz), 1.82 (s, 3H), 2.33 (s, 3H), 3.78 (s, 3H), 5.20 (q, 1H, *J* = 7.2 Hz), 6.86 (d, 2H, *J* = 9.2 Hz), 7.17-7.30 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 21.3, 23.0, 55.4, 61.3, 114.5, 123.7, 130.0, 130.6, 132.7, 134.7, 139.6, 159.4, 171.4, 198.3. MS m/z: MS m/z: 220 (M^+-123 (45)), 192 (21), 150 (100), 134 (13), 43 (26). The *ee* was determined to be 62% *ee* by HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 36.06 min, t_R(minor) = 42.57 min. Anal. Calcd. for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 66.49; H, 6.10; N, 3.92; S, 9.28.

S-phenyl-2-(N-phenylacetamido)propanethioate (3ab): Orange oil. Yield 60%. IR (neat): 1715, 1668 cm^{-1}. $[\alpha]_D^{30}$= -22.5 (*c* 0.62, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, 3H, *J* = 7.2 Hz), 1.86 (s, 3H), 5.21 (q, 1H, *J* = 7.5 Hz), 7.37-7.46 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.7, 23.1, 61.7, 127.2, 128.6, 129.3, 129.5, 132.8, 134.7, 140.2, 170.9, 197.8. MS m/z: 190 (M^+-109 (26)), 162 (24), 120 (100), 104 (6). The *ee* was determined to be 70% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 16.33 min, t_R(minor) = 19.32 min. Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.70. Found: C, 68.24; H, 5.80; N, 4.60; S, 10.60.

S-phenyl-2-(N-*p*-tolylacetamido)propanethioate (3ac): Orange oil. Yield 60%. IR (neat): 1715, 1668 cm^{-1}. $[\alpha]_D^{32}$= -19.2 (*c* 2.39, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30 (d, 3H, *J* = 7.2 Hz), 1.85 (s, 3H), 2.36 (s, 3H), 5.19 (q, 1H, *J* = 7.5 Hz), 7.17-7.24 (m, 4H), 7.37-7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.9, 21.3, 23.2, 61.8, 127.6, 129.40, 129.47, 129.59, 130.4, 135.0, 137.7, 138.8, 171.5, 198.1. MS m/z: 204 (M^+-109 (50)), 176 (18), 134 (100), 91 (13). The *ee* was

determined to be 64% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 14.56 min, t_R(minor) = 19.78 min. Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47; S, 10.23. Found: C, 68.90; H, 6.14; N, 4.50; S, 10.51; **(4ac)**: Yellow oil. Yield 18%. IR (neat): 3249, 1741, 1666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.54 (d, 3H, *J* = 7 Hz), 2.19 (s, 3H), 2.31 (s, 3H), 5.31 (q, 1H, *J* = 6.5 Hz), 7.12 (d, 2H, *J* = 8.5 Hz), 7.4 (d, 2H, *J* = 8 Hz), 7.76 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 20.8, 70.9, 120.1, 129.5, 134.3, 134.5, 168.1, 169.4. MS m/z: 221 (M^+(31)), 134 (11), 107 (100), 87 (14). Anal. Calcd. For $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.99; H, 7.00; N, 6.29.

S-phenyl-2-(N-(4-ethylphenyl)acetamido)propanethioate (3ad): Orange oil. Yield 70%. IR (neat): 1719, 1668 cm^{-1}. $[\alpha]_D^{27}$= -18.2 (*c* 3.19, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, 3H, *J* = 7.5 Hz), 1.31 (d, 3H, *J* = 7.2 Hz), 1.86 (s, 3H), 2.66 (q, 2H, *J* = 7.5 Hz), 5.18 (q, 1H, *J* = 7.5 Hz), 7.2-7.26 (m, 4H), 7.38-7.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.2, 15.6, 23.0, 28.3, 61.6, 127.3, 128.8, 129.1, 129.23, 129.28, 134.7, 137.6, 144.7, 171.1, 197.7. MS m/z: 218 (M^+-109 (46)), 190 (20), 148 (100), 132 (8). The *ee* was determined to be 56% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95:5, flow rate 0.8 mL/min, λ = 254 nm) t_R(major) = 19.97 min, t_R(minor) = 28.69 min. Anal. Calcd. for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.61; H, 6.39; N, 4.30; S, 9.71; **(4ad)**: Orange oil. Yield 7%. IR (neat): 1704, 1657 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.20 (t, 3H, *J* = 7.5 Hz), 1.54 (d, 3H, *J* = 7 Hz), 2.19 (s, 3H), 2.60 (q, 2H, *J* = 8 Hz), 5.32 (q, 1H, *J* = 7 Hz), 7.15 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 2H, *J* = 8.5 Hz), 7.76 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.7, 17.8, 21.1, 28.4, 70.9, 120.2, 128.3, 134.5, 140.9, 169.4, 168.0. MS m/z: 235 (M^+(46)), 148 (13), 121 (100), 106 (68) 87 (21).

S-phenyl-2-(N-(4-butylphenyl)acetamido)propanethioate (3ae): Yellow oil. Yield 53%. $[\alpha]_D^{27}$= -14.4 (*c* 2.6, $CHCl_3$). IR (neat): 1713, 1666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, 3H, *J* = 7.2 Hz), 1.21-1.42 (m, 2H), 1.31 (d, 3H, *J* = 7.2 Hz), 1.55-1.65 (m, 2H), 1.86 (s, 3H), 2.62 (t, 2H, *J* = 7.8 Hz), 5.18 (q, 1H, *J* = 7.2 Hz), 7.18-7.25 (m, 4H), 7.38-7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 15.6, 22.3, 23.0, 33.3, 35.1, 61.7, 127.4, 129.15, 129.19, 129.3, 132.8, 134.7, 137.7, 143.5, 171.2, 197.8. MS m/z: 246 (M^+-109 (52)), 218 (22), 176 (100), 132 (22), 109 (12), 43 (22). The *ee* was determined to be 58% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 14.42 min, t_R(minor) = 20.63 min. Anal. Calcd. for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; S, 9.02. Found: C, 70.89; H, 7.11; N, 3.99; S, 9.08; **(4ae)**: Yellow oil. Yield 34%. IR (neat): 3315, 1680, 1540 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, 3H), 1.27-1.31 (m, 2H), 1.50-1.54 (m, 5H), 2.15 (s, 3H), 2.53 (t, 2H), 5.27 (q, 1H, *J* = 6.5 Hz), 7.1 (d, 2H, *J* = 8 Hz), 7.38 (d, 2H, *J* = 8.5 Hz), 7.78 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 17.7, 21.1, 22.2, 33.5, 35.0, 70.9, 120.1, 128.8, 134.5, 139.5, 168.1, 169.4. MS m/z: 263 (M^+(48)), 220 (8), 149 (77), 132 (19), 106 (100), 87 (22). Anal. Calcd. For $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 69.59; H, 7.20; N, 5.43.

S-phenyl-2-(N-(4-fluorophenyl)acetamido)propanethioate (3af): Yellow oil. Yield 77%. $[\alpha]_D^{26}$= -22.5 (*c* 3.93, $CHCl_3$). IR (neat): 1712, 1667 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.29 (d, 3H, *J* = 7.5 Hz), 1.84 (s, 3H), 5.22 (q, 1H, *J* = 7.0 Hz), 7.07-7.10 (m, 2H), 7.34-7.43 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.8, 23.0, 61.3, 116.5, 127.0, 129.1, 131.4, 134.7, 135.9, 161.2, 163.2, 170.9, 197.7. MS m/z: 208 (M^+-109 (49)), 180 (26), 138 (100), 109 (14). The *ee* was determined to be 62% *ee* by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 26.99 min, t_R(minor) = 29.86 min. Anal. Calcd. for $C_{17}H_{16}FNO_2S$: C, 64.33; H, 5.08; N, 4.41; S, 10.10. Found: C, 64.30; H, 5.13; N, 4.50; S, 9.98; **(4af)**: White solid; mp = 95°C. Yield 6%. IR (neat): 3257, 1741, 1667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.53 (d, 3H, *J* = 6.6 Hz), 2.18 (s, 3H), 5.29 (q, 1H, *J* = 6.9 Hz), 7.00 (t, 2H), 7.39-7.49 (m, 2H), 7.88 (brs, 1H). MS m/z: 225 (M^+(41)), 138 (13), 111 (100), 87 (29).

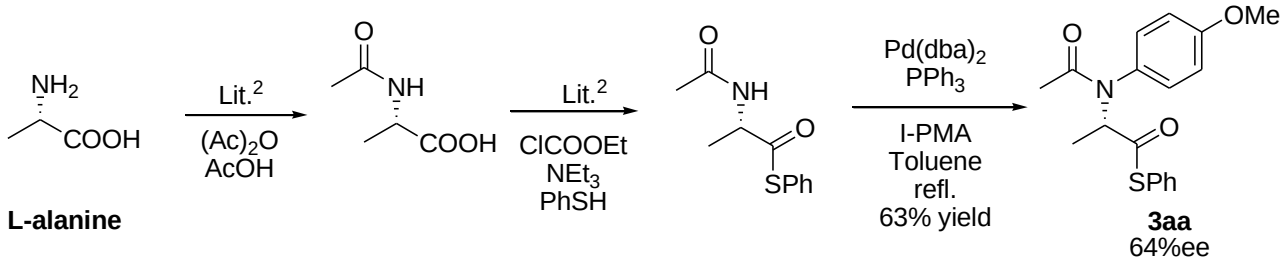
S-phenyl-2-(N-(4-chlorophenyl)acetamido)propanethioate (3ag): Orange oil. Yield 52%. IR (neat): 1711, 1672 cm^{-1}. $[\alpha]_D^{27}$= - 38.3 (*c* 1.99, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.30 (d, 3H, *J* = 7.2 Hz), 1.85 (s, 3H), 5.22 (q, 1H, *J* = 7.5 Hz), 7.29-7.43 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$)

δ: 15.8, 23.0, 61.3, 127.0, 129.2, 129.4, 129.7, 131.0, 134.6, 134.7, 138.6, 170.6, 197.8. MS m/z: 224 (M^+-109 (46)), 196 (16), 154 (100), 111 (11). The *ee* was determined to be 54% *ee* by HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 96:4, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 21.43 min, t_R(minor) = 25.38 min. Anal. Calcd. for $C_{17}H_{16}ClNO_2S$: C, 61.16; H, 4.83; N, 4.20; S, 9.61. Found: C, 61.20; H, 4.78; N, 4.85; S, 9.57; **(4ag)**: Yellow solid. Yield 9%. IR (neat): 1742, 1667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54 (d, 3H, *J* = 6.9 Hz), 2.19 (s, 3H), 5.31 (q, 1H, *J* = 6.9 Hz), 7.29 (d, 2H, *J* = 8.7 Hz), 7.48 (d, 2H, *J* = 9 Hz), 7.84 (brs, 1H). MS m/z: 241 (M^+(29)), 153 (9), 127 (100), 87 (46), 63 (6).

1-(4-methoxyphenylcarbamoyl)ethyl acetate (4aa): (Table 1, entry 17) The reaction was performed in toluene at 60°C in the presence of quinidine free base. White solid; mp = 120-124°C. Yield 50%. IR (KBr): 1742, 1668 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54 (d, 3H, *J* = 6.9 Hz), 2.18 (s, 3H), 3.78 (s, 3H), 5.31 (q, 1H, 6.9 Hz), 9.35 (d, 2H, *J* = 9 Hz), 7.42 (d, 2H, *J* = 9 Hz), 7.73 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 21.1, 55.4, 70.8, 114.1, 121.9, 129.9, 156.7, 168.1, 169.4. MS m/z: 237 (M^+(61)), 149 (20), 123 (100), 108 (40), 87 (11). The *ee* was determined to be 78% *ee* by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) t_R(major) = 19.64 min, t_R(minor) = 27.63 min. Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.69; H, 6.33; N, 5.82.

3. Absolute configuration determination of 3aa

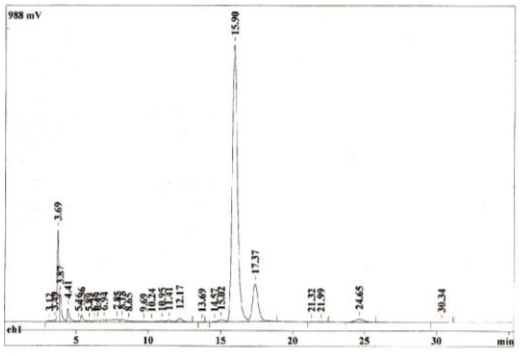
Comparison of HPLC chromatograms (see below) and $[\alpha]_D$ value obtained for compound **3aa** ($[\alpha]_D^{32}$= -29.8 (*c* 2.01, $CHCl_3$, ee 76%)), synthesized by enantioselective tandem condensation-intramolecular rearrangement-protonation, to that obtained for **3aa** ($[\alpha]_D^{27}$= -10.2 (c 4.13, $CHCl_3$, ee 64%) prepared by an independent synthesis[2] from enantiopure (*S*)-alanine allowed us to assign a *S* configuration at the 2 position.



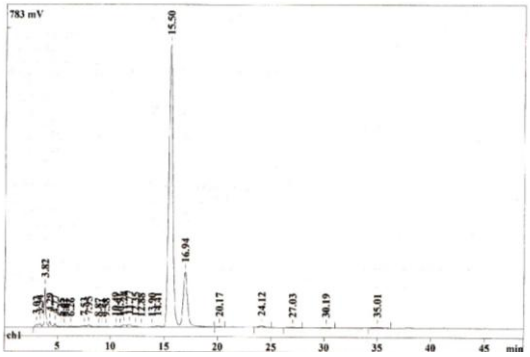
(*S*)-S-phenyl-2-(N-(4-methoxyphenyl)acetamido)propanethioate (3aa). To a mixture of I-PMA (250 mg, 1.068 mmol), potassium carbonate (368 mg, 2.67 mmol), CuI (17 mg, 0.089 mmol), PPh_3 (35 mg, 0.13 mmol) and $Pd(dba)_2$ (51 mg, 0.089 mmol) in 15 mL of DMF, (*S*)-S-phenyl 2-acetamidopropanethioate (200 mg, 0.89 mmol) as a solution of toluene (10 ml) was added and the resulting suspension was heated under argon at 110°C for 16h. After cooling to room temperature, water (10 ml) was added to the reaction mixture. After addition of ethyl acetate (20 ml), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL, three times). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was chromatographed (silica gel, ethyl acetate:petroleum ether=1:5–1:1 as eluent) to afford the coupled product **3aa** (63% yield; 64% ee).

HPLC of 3aa (Chiralpak AD-H column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm)

A:



B:

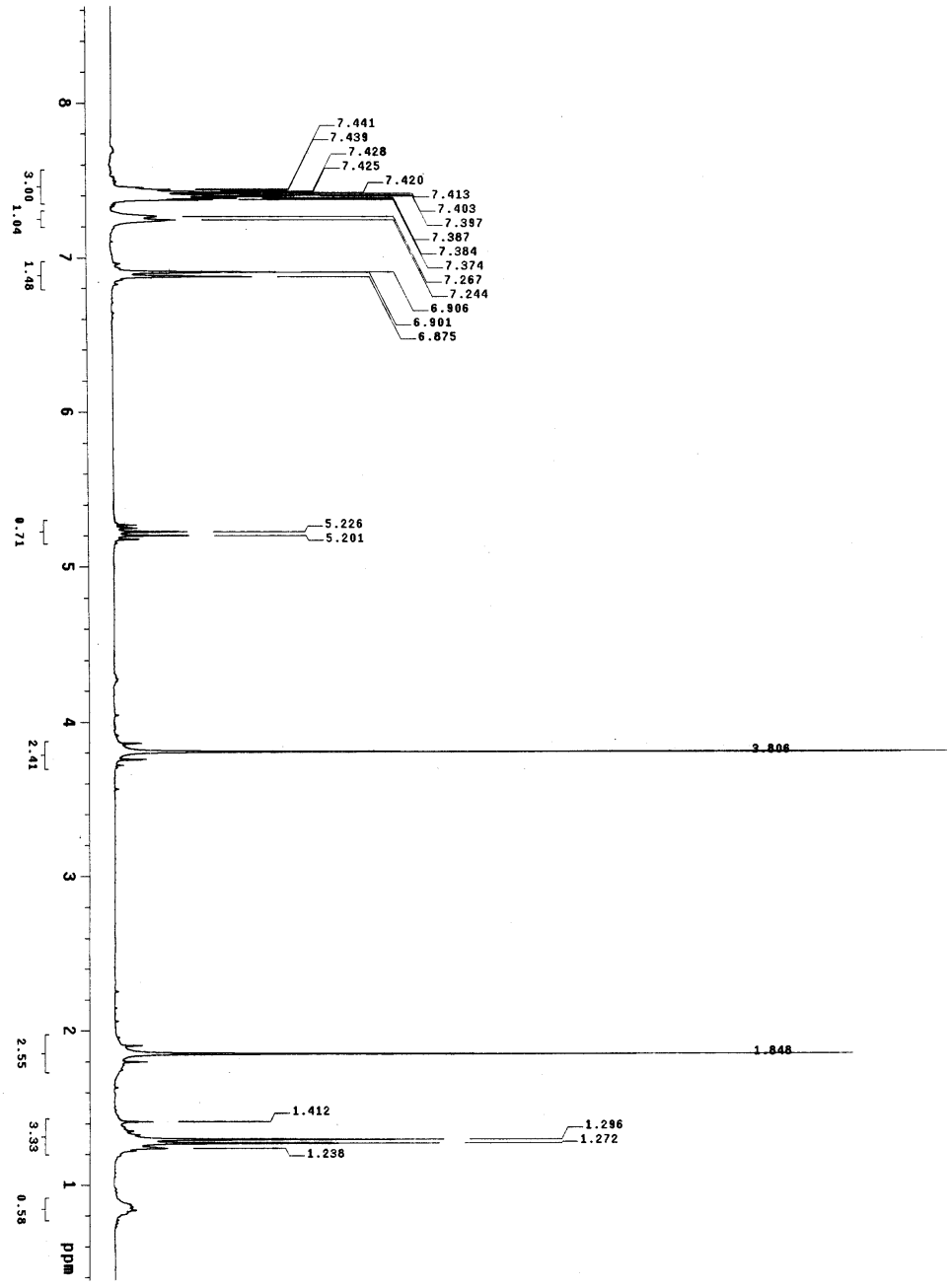


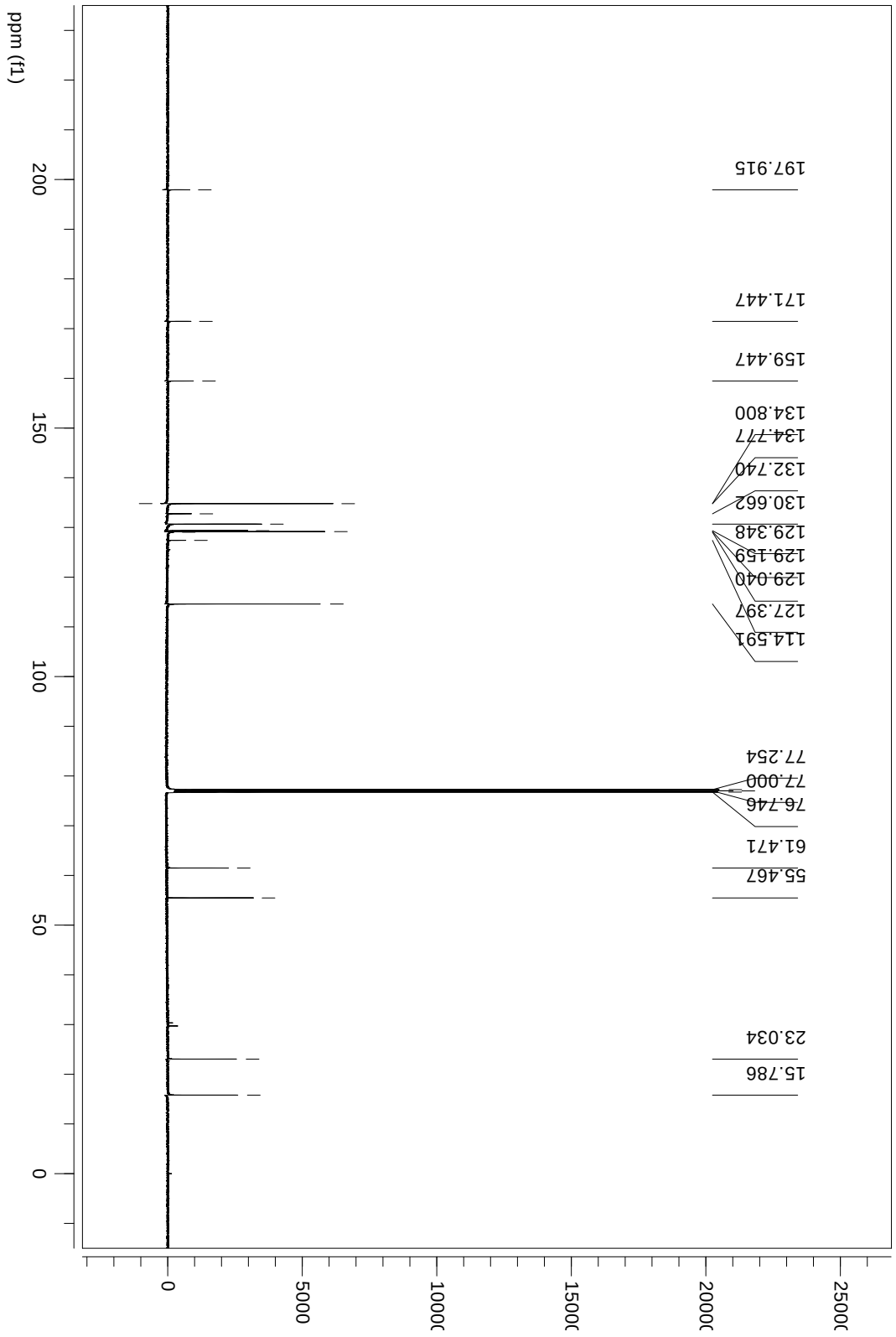
A:Synthesized by enantioselective tandem condensation-intramolecular rearrangement-protonation.
B:Prepared by an independent synthesis from enantiopure (*S*)-Alanine.

[2] J. W. Sims, E. W. Schmidt, *J. Am. Chem. Soc.*, **2008**, *130*, 11149–11155

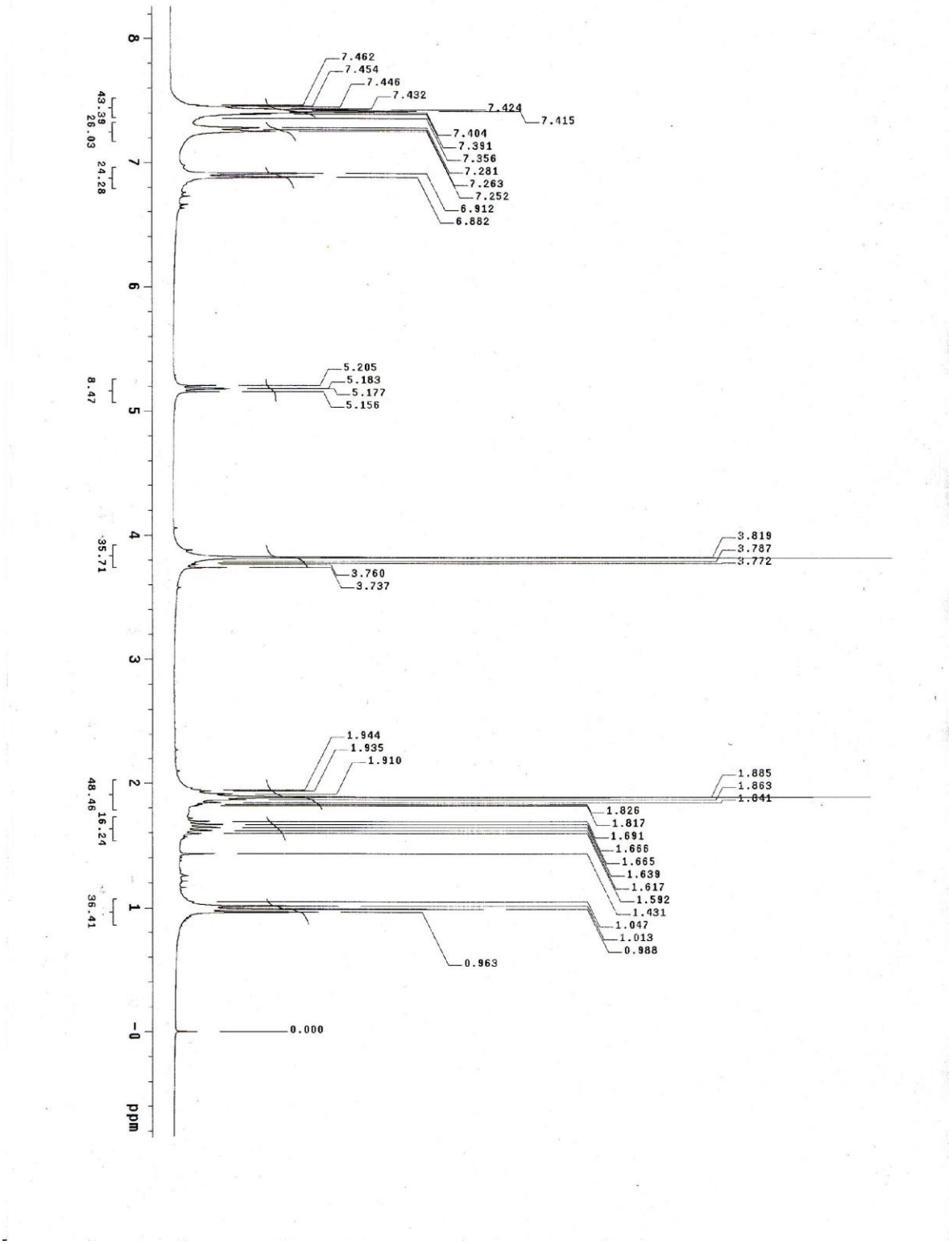
4. ^{1}H and ^{13}C NMR charts of the new compounds:

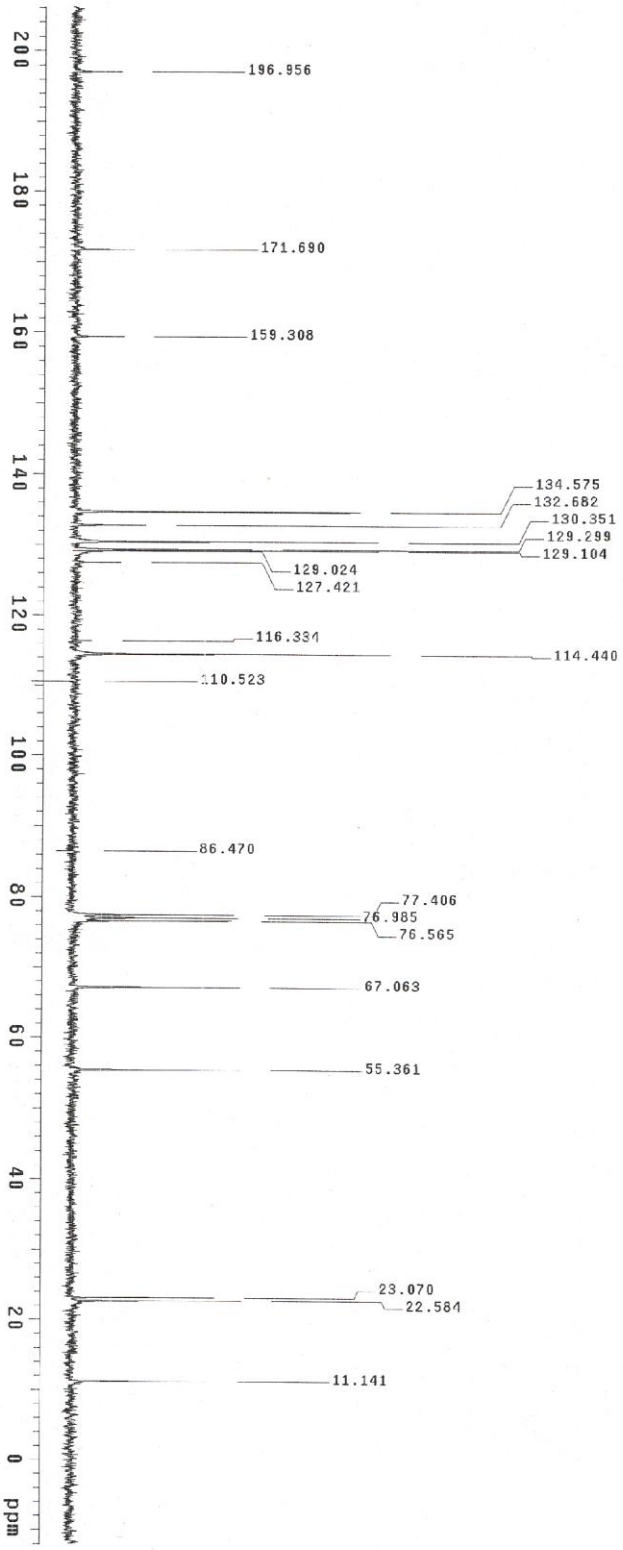
S-phenyl-2-(N-(4-methoxyphenyl)acetamido)propanethioate (3aa):



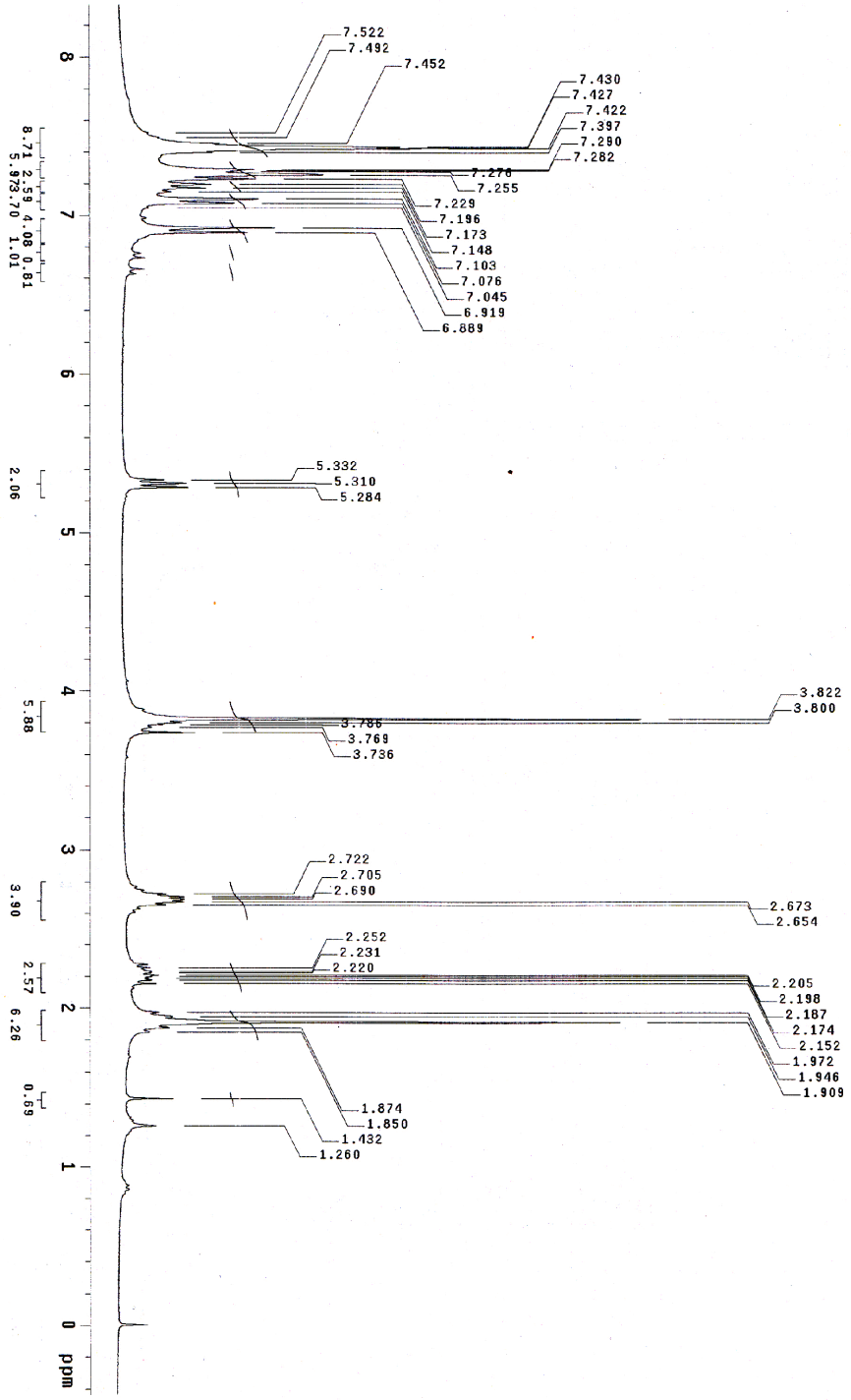


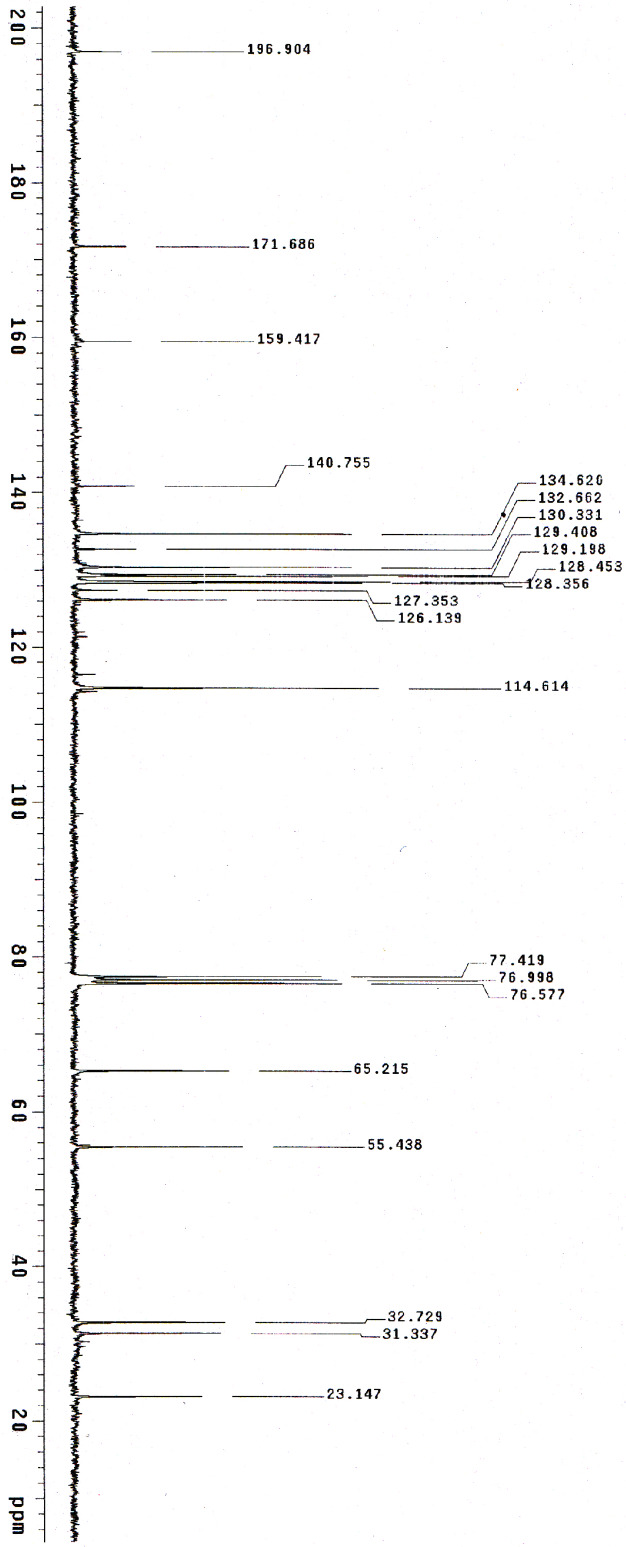
S-phenyl-2-(N-(4-methoxyphenyl)acetamido)butanethioate (3ba):



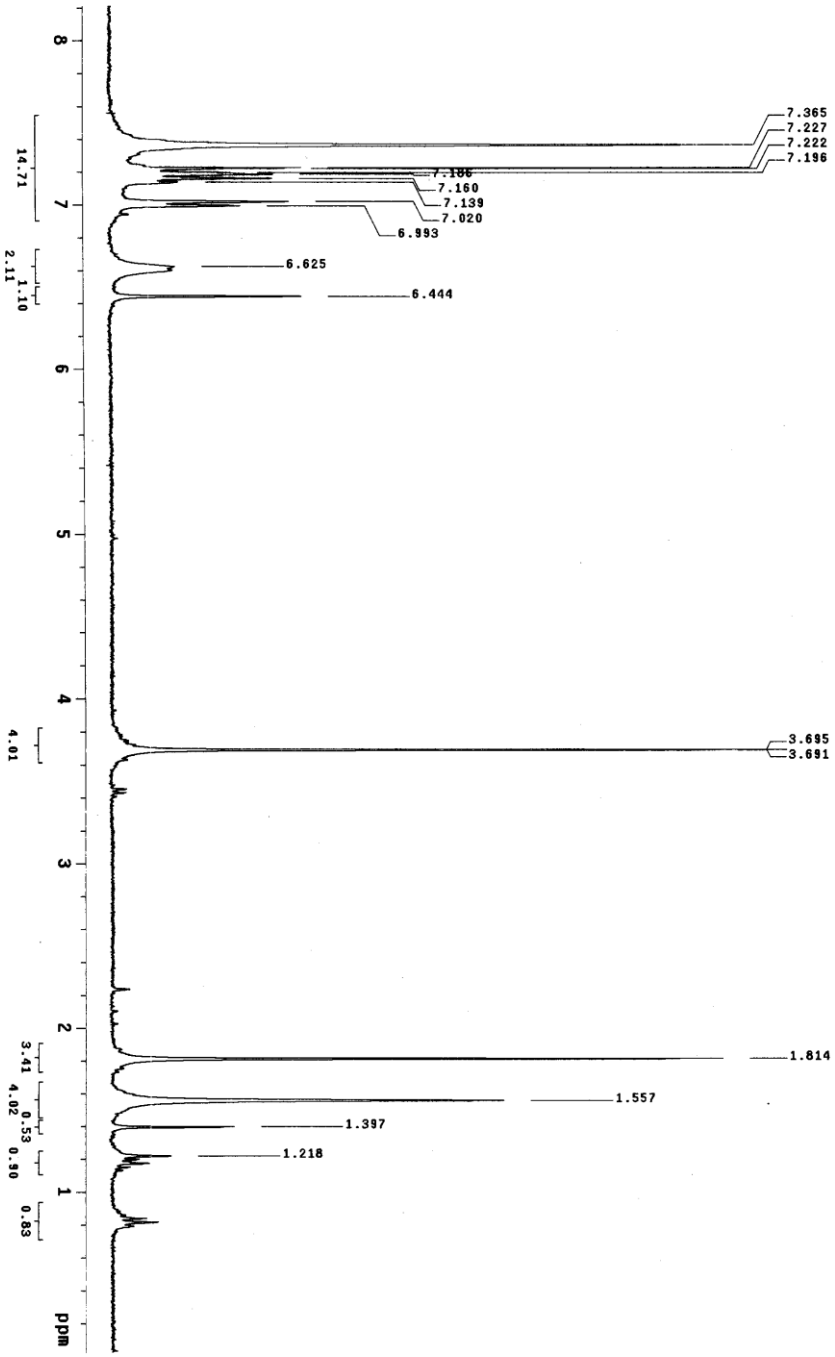


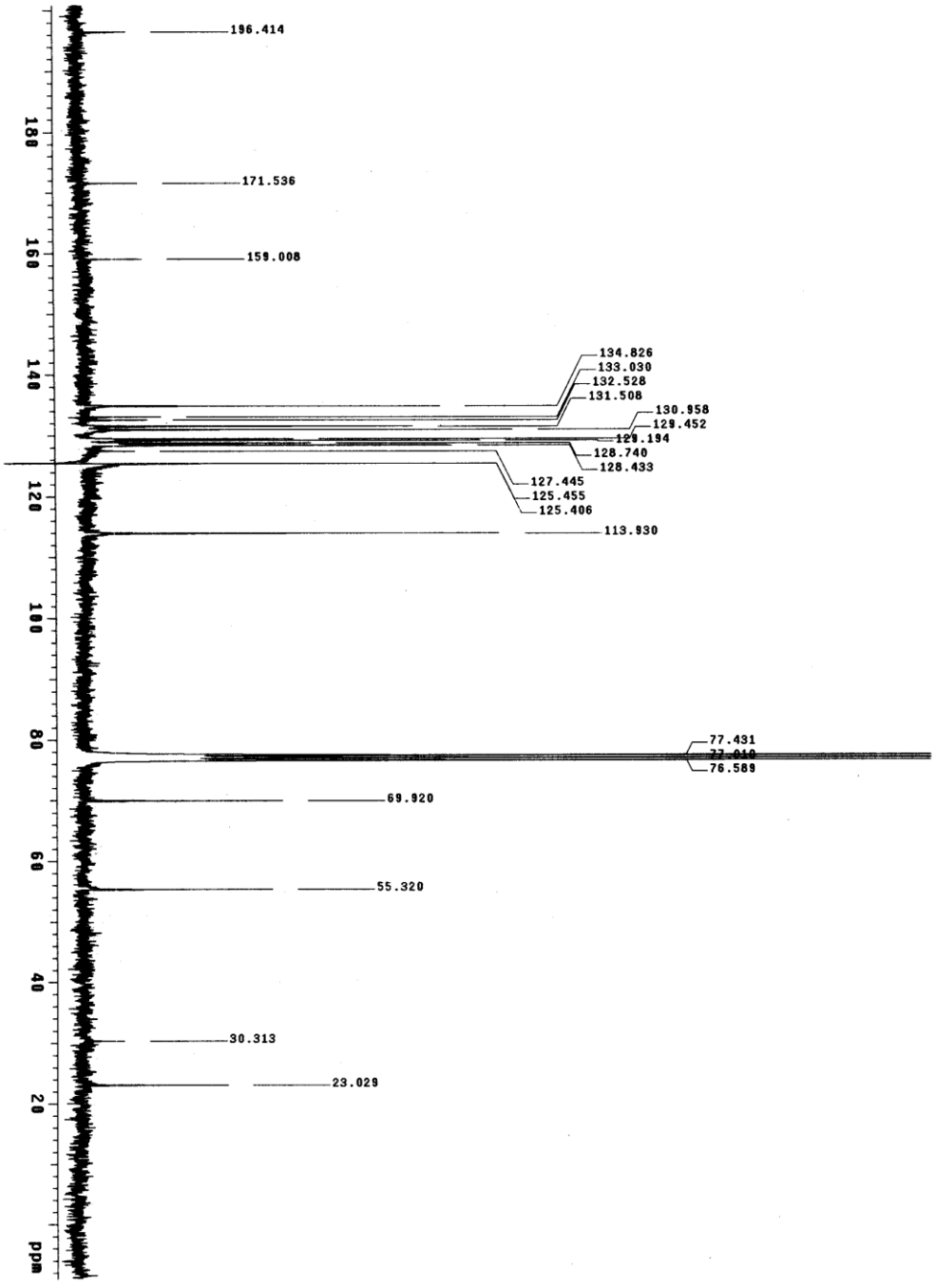
S-phenyl-2-(N-(4-methoxyphenyl)acetamido)-4-phenylbutanethioate (3ca):



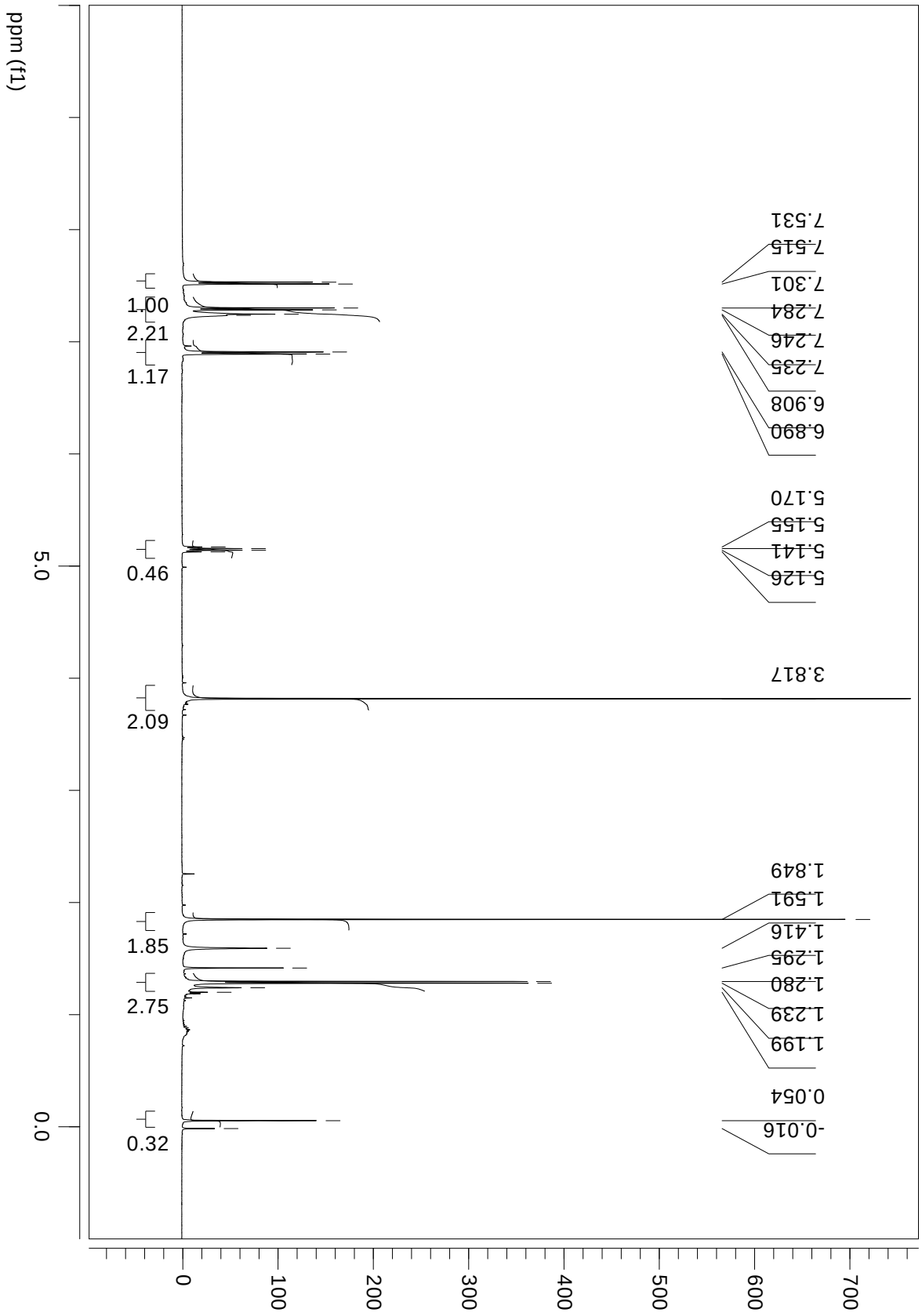


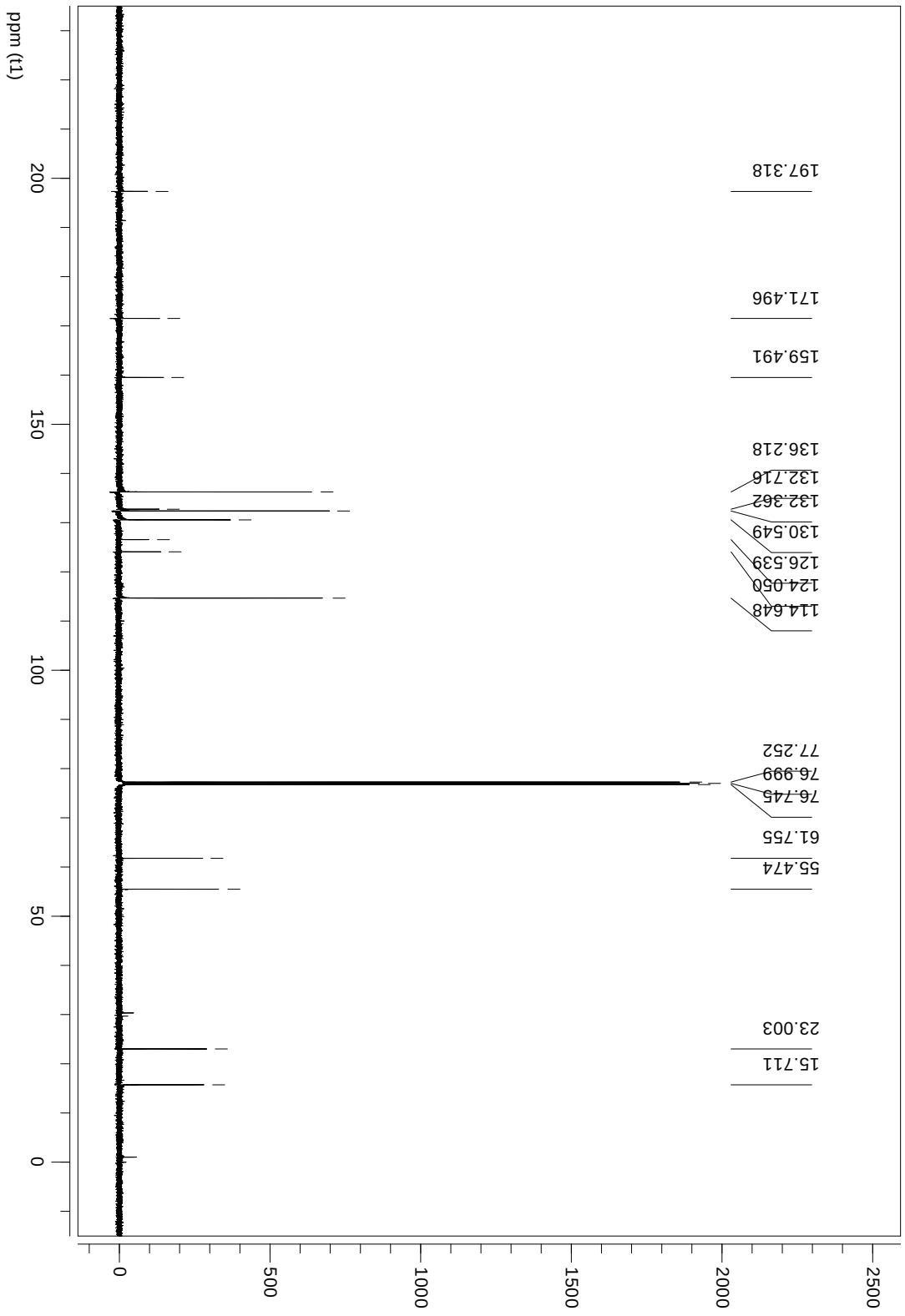
S-phenyl-2-(N-(4-methoxyphenyl)acetamido)-2-phenylethanethioate (3da):



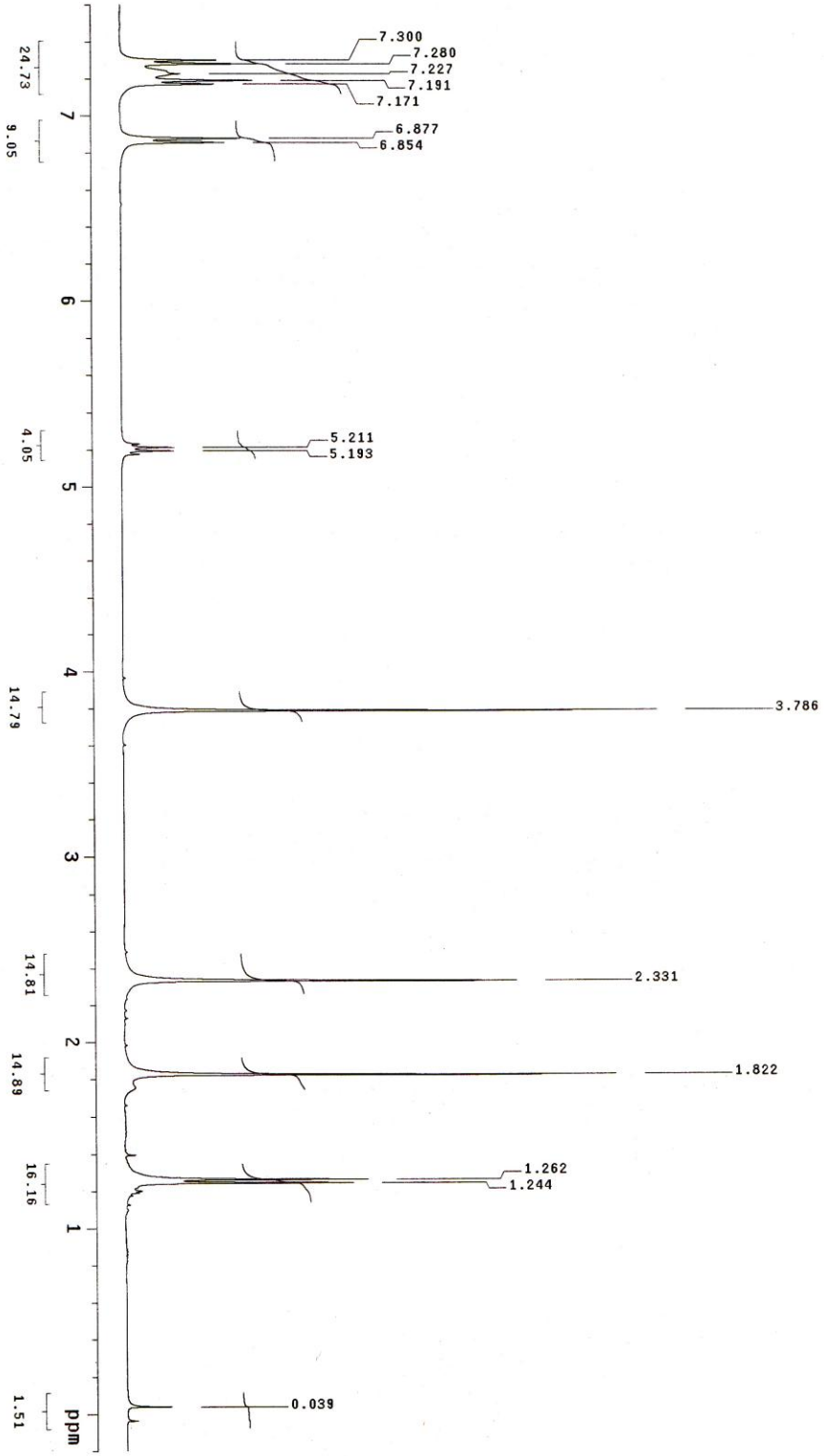


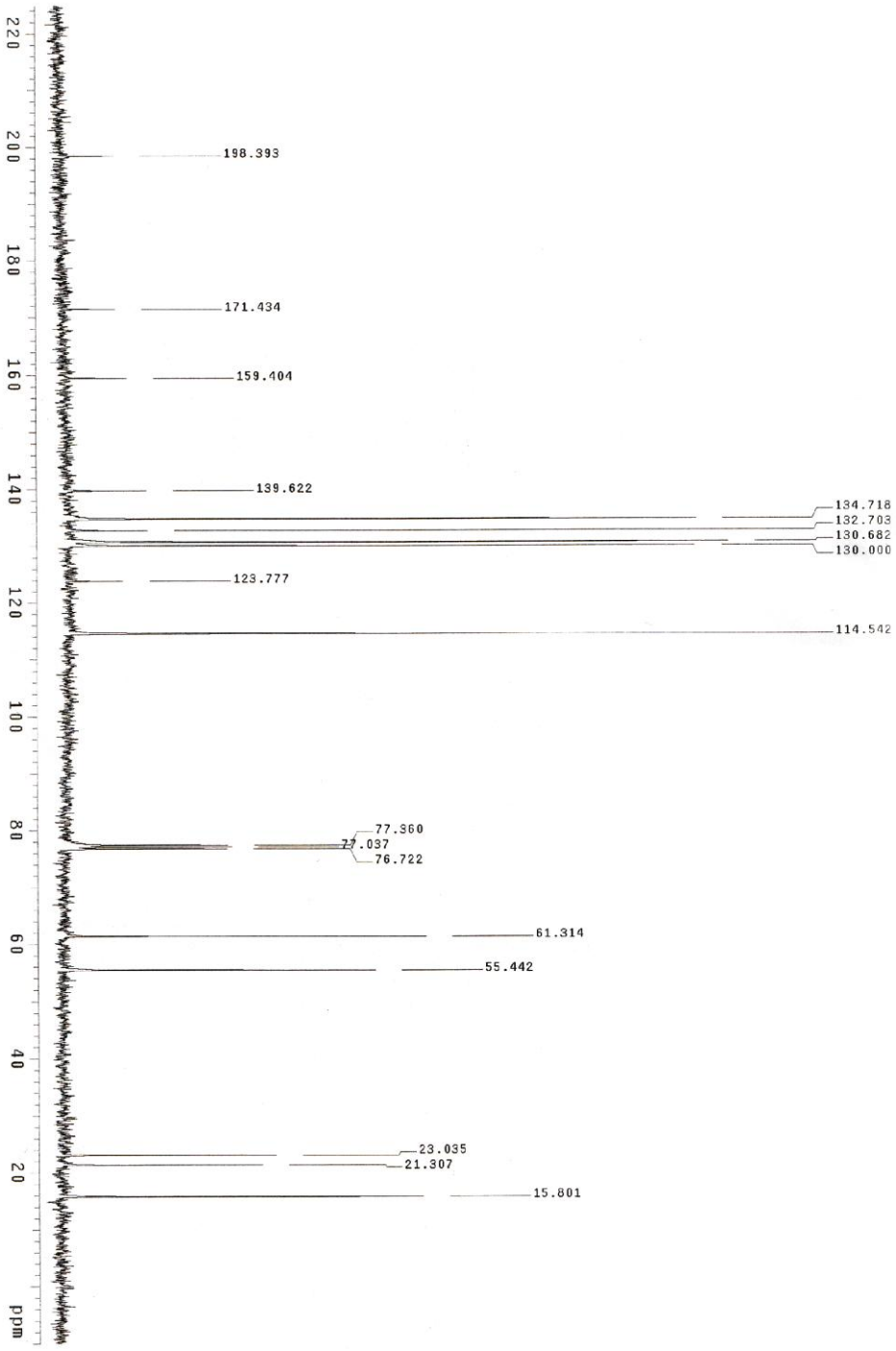
S-4-bromophenyl 2-(N-(4-methoxyphenyl)acetamido)propanethioate (3ea):



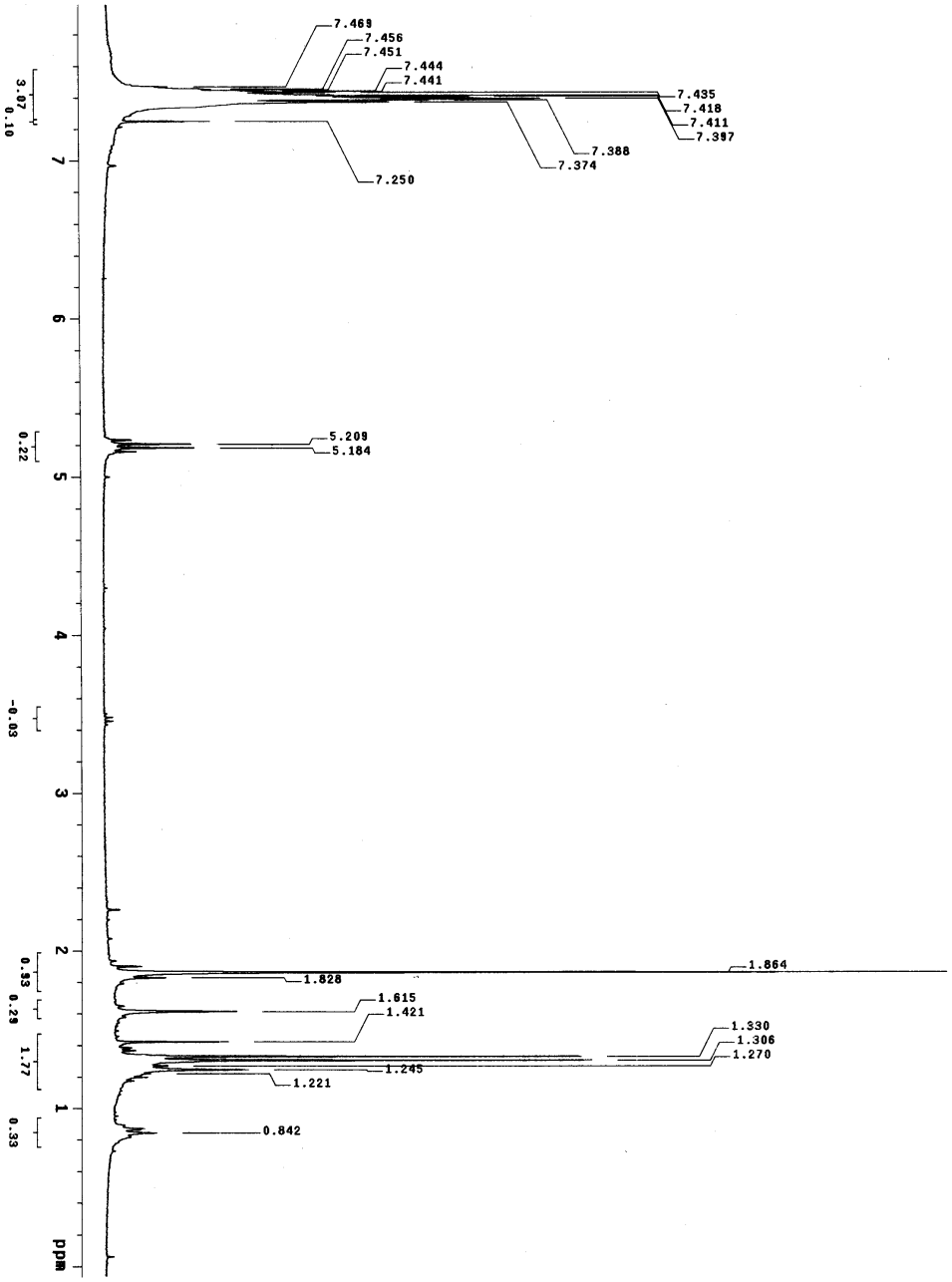


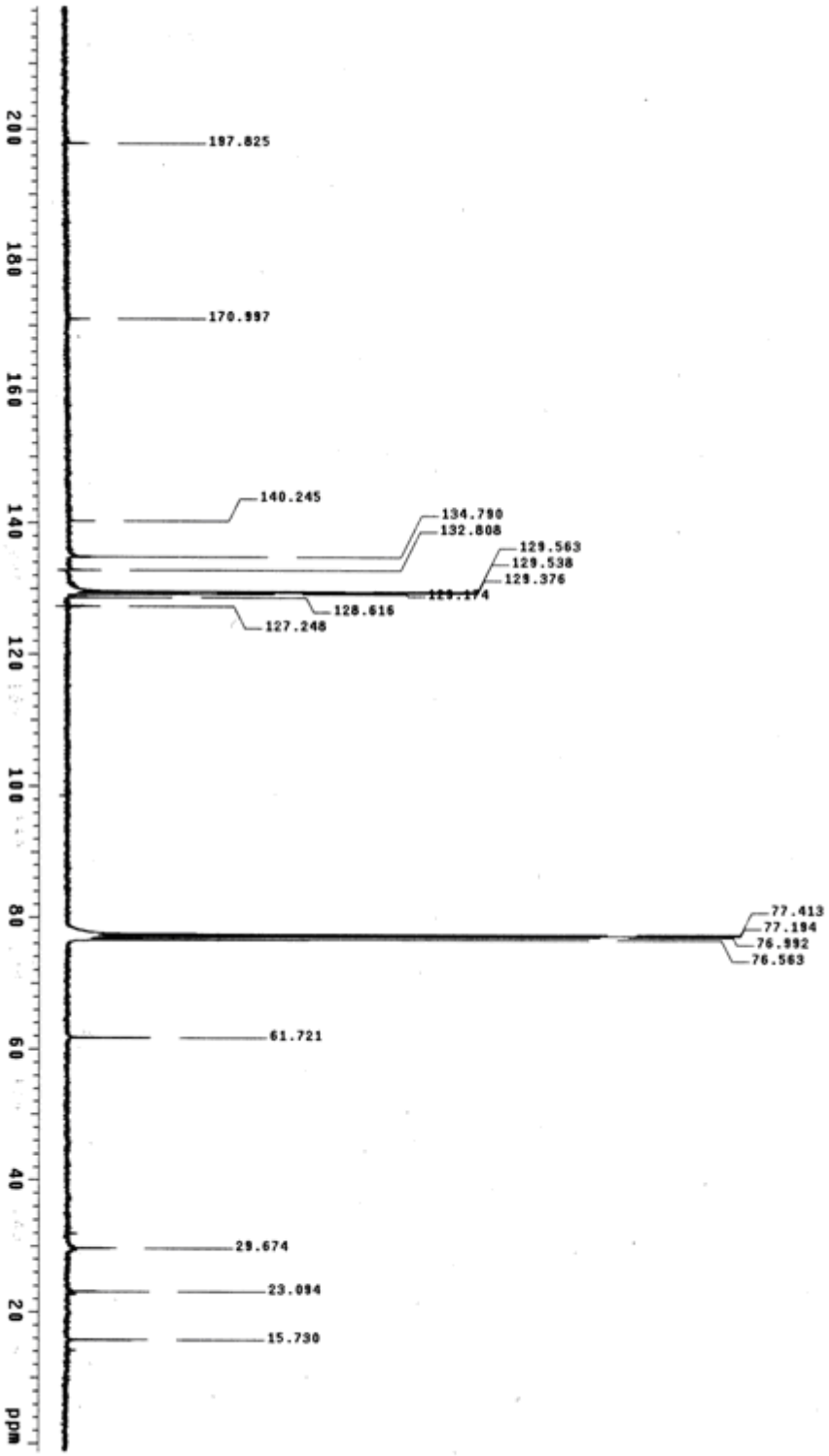
S-*p*-tolyl 2-(N-(4-methoxyphenyl)acetamido)propanethioate (3fa):



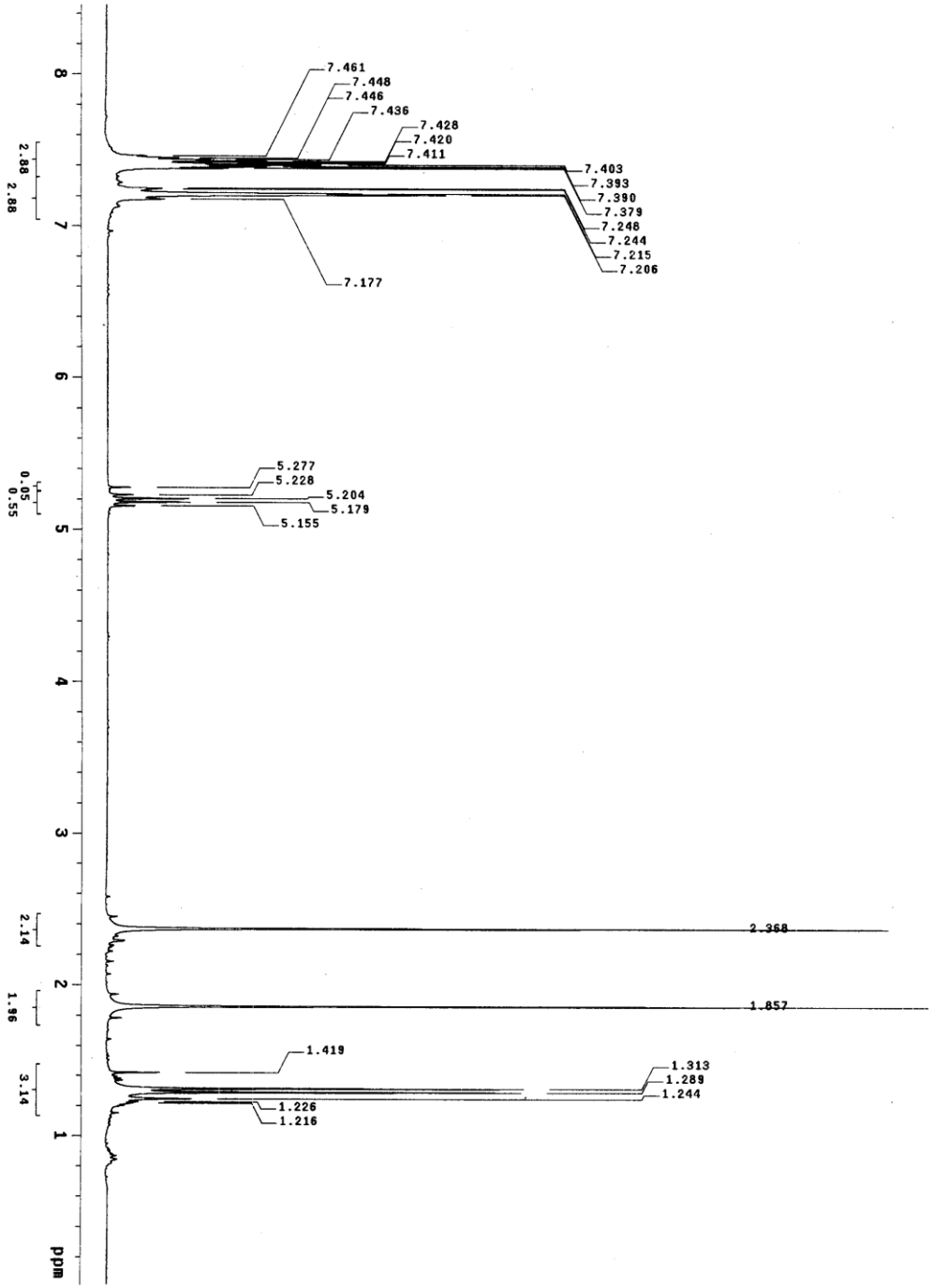


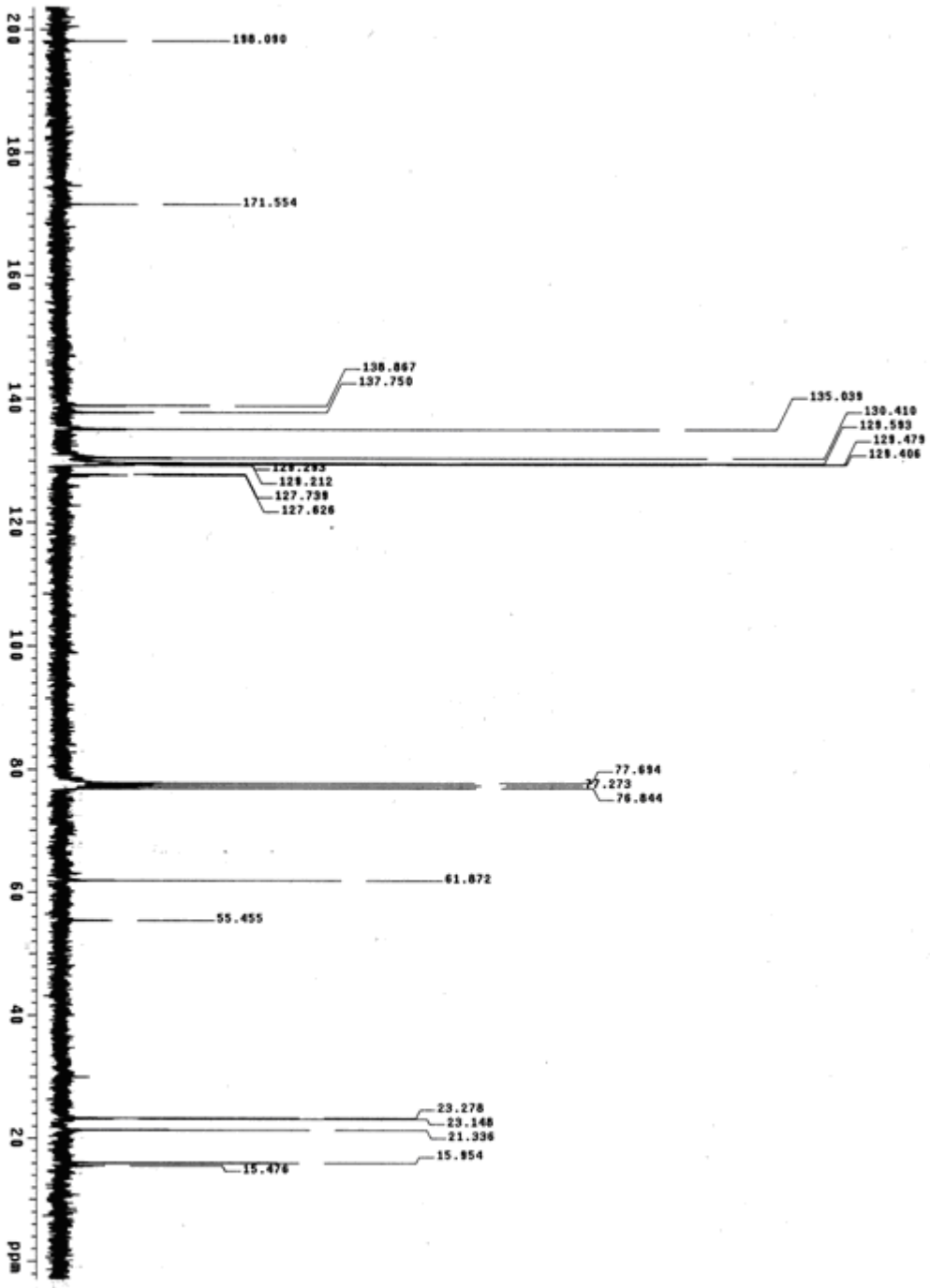
S-phenyl-2-(N-phenylacetamido)propanethioate (3ab):



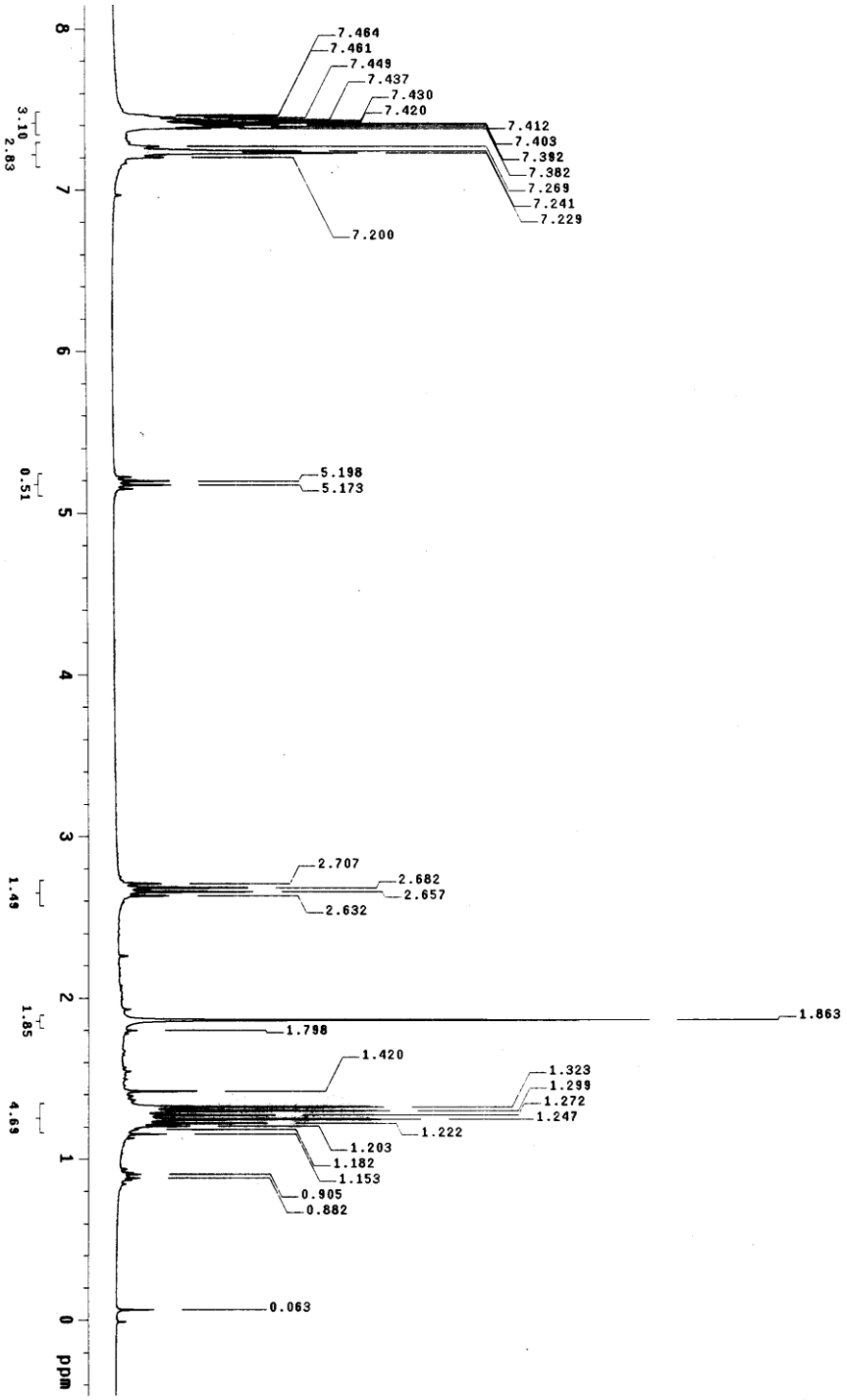


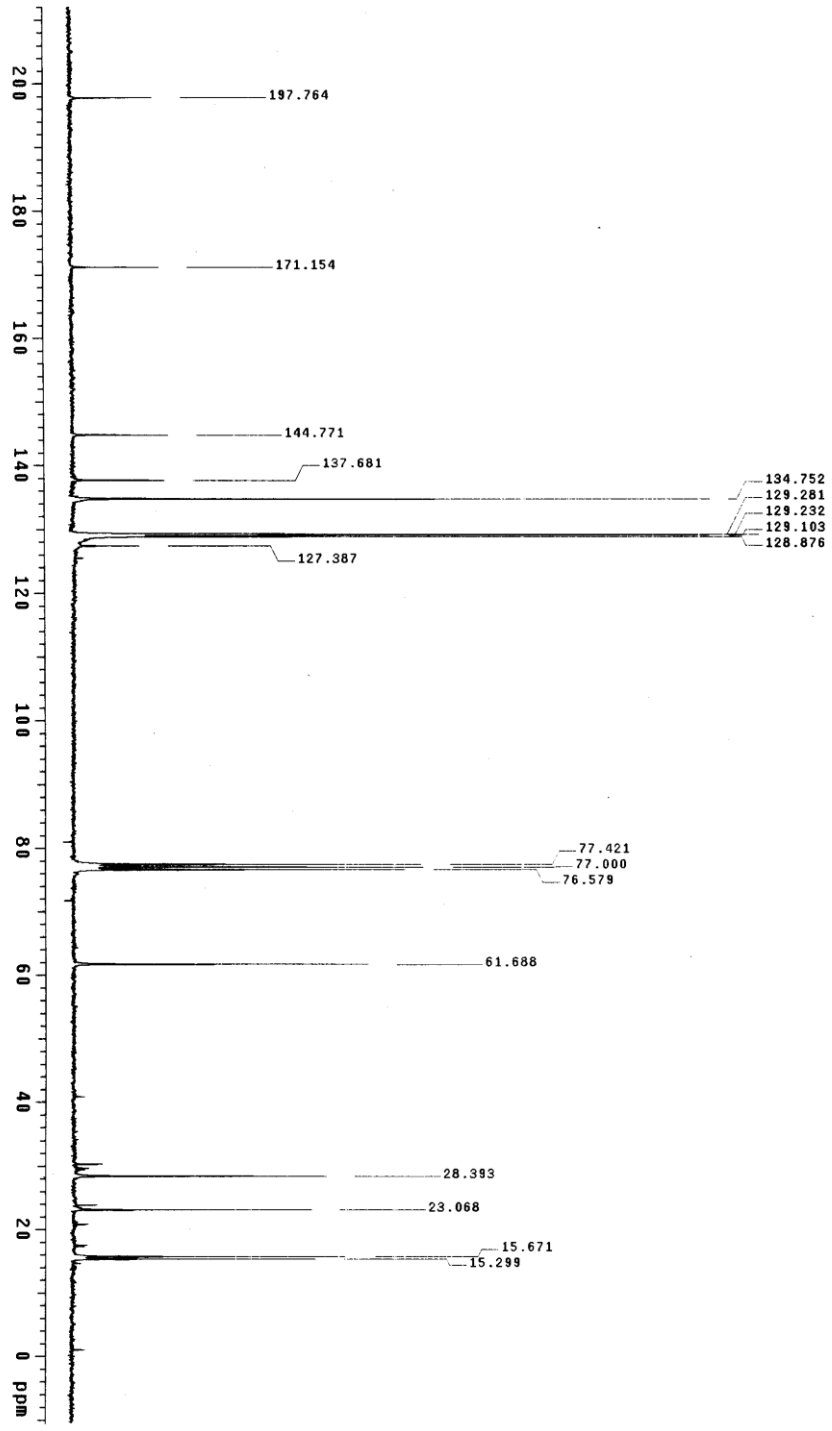
S-phenyl-2-(N-p-tolylacetamido)propanethioate (3ac):



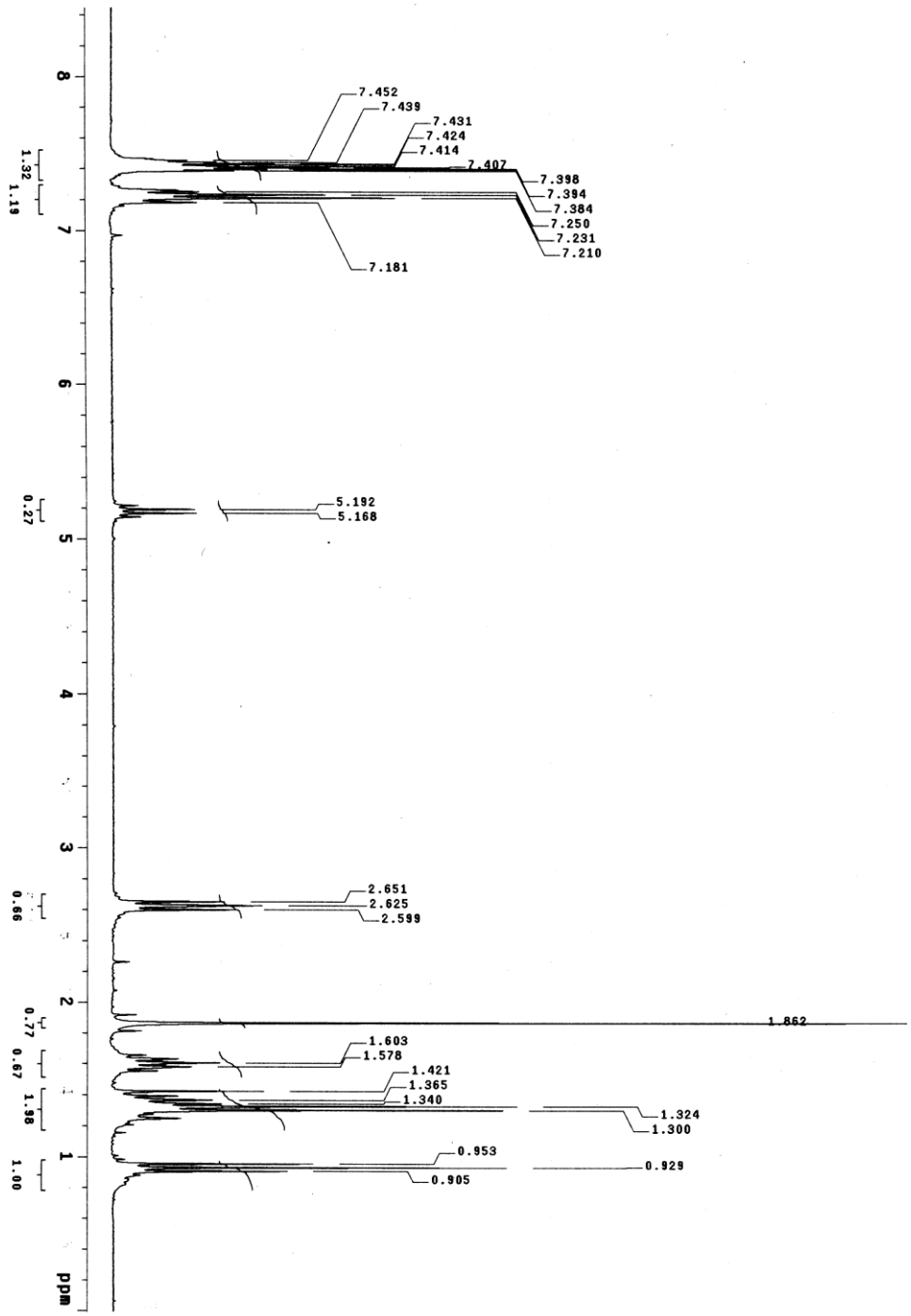


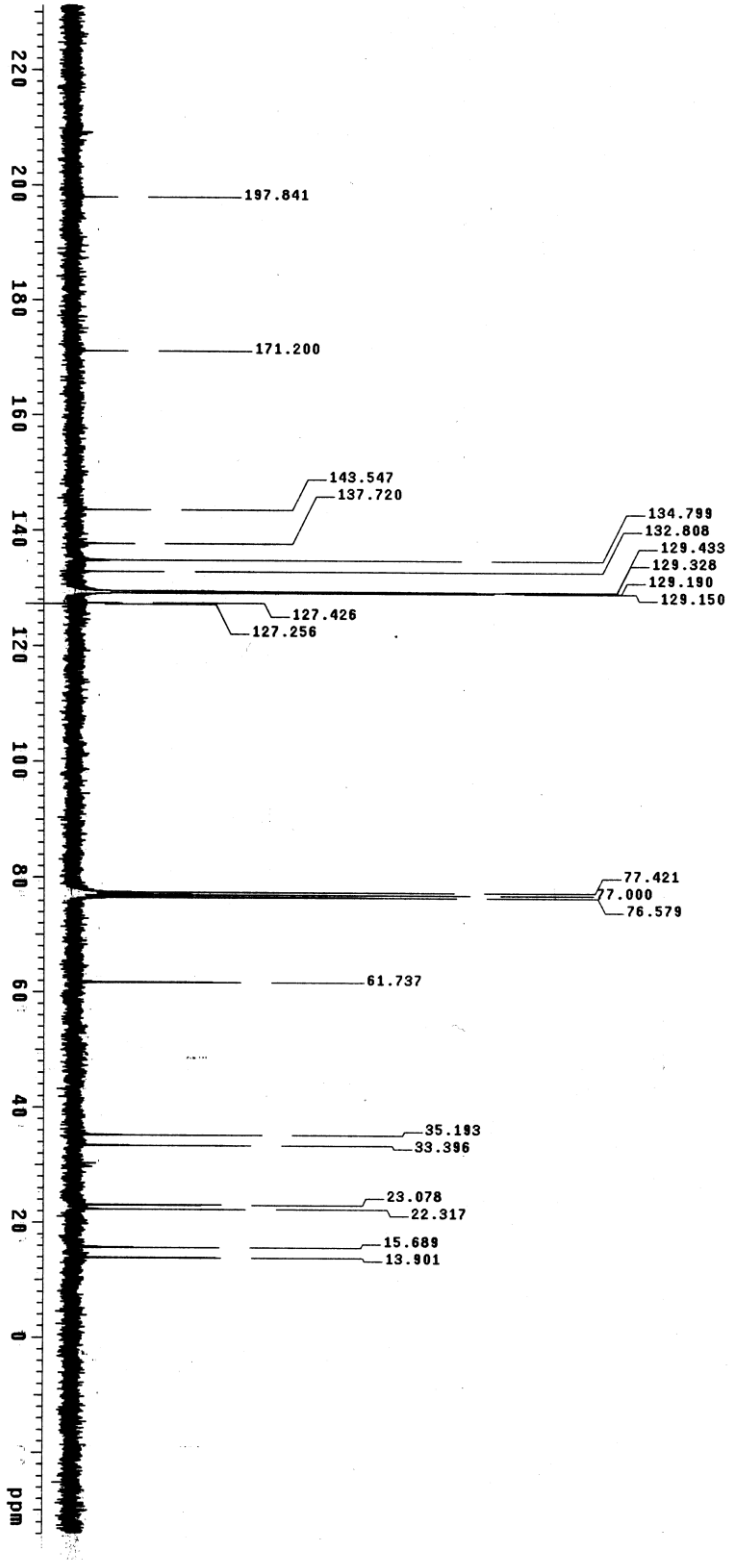
S-phenyl-2-(N-(4-ethylphenyl)acetamido)propanethioate (3ad):



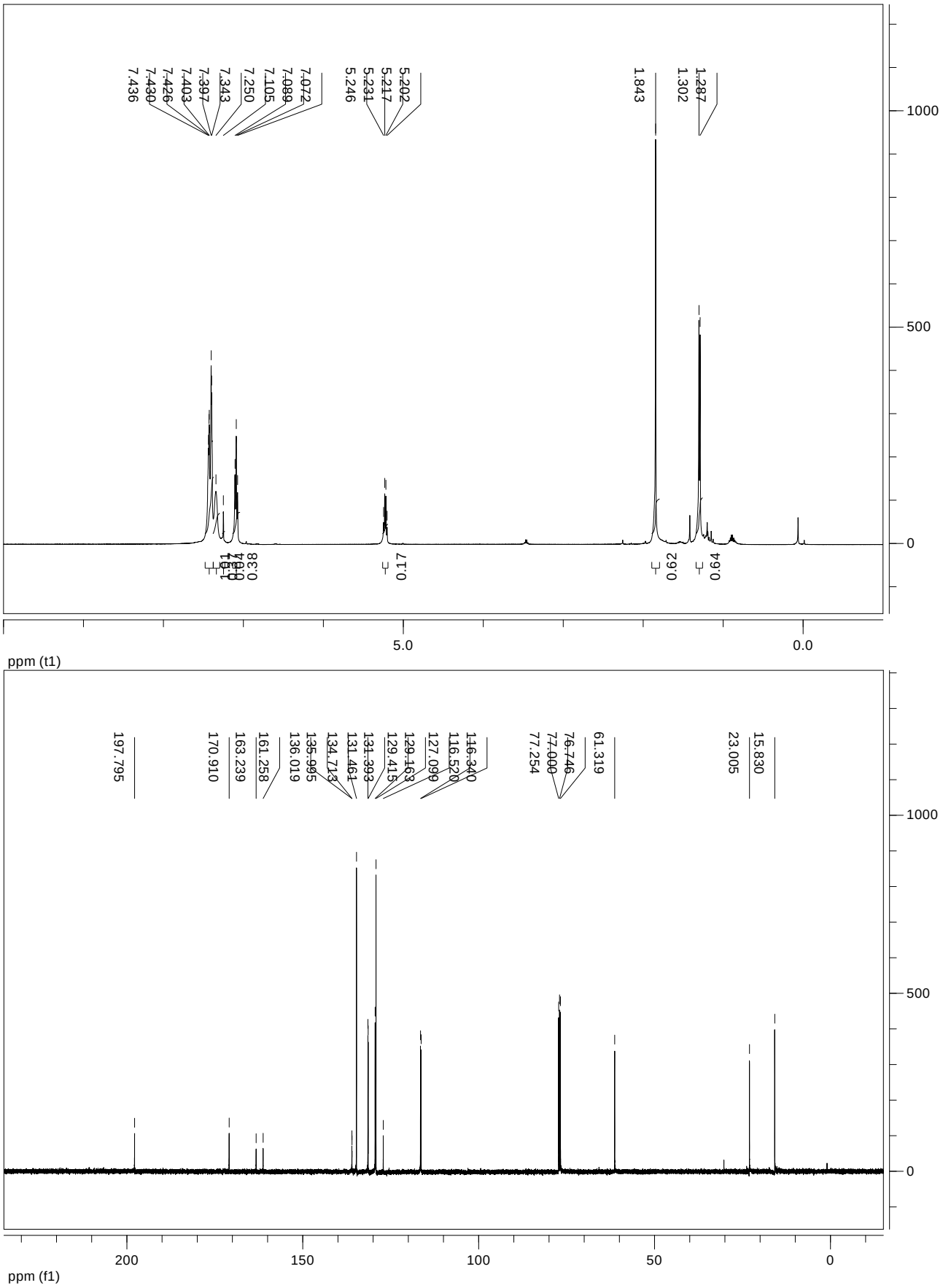


S-phenyl-2-(N-(4-butylphenyl)acetamido)propanethioate (3ae):





S-phenyl-2-(N-(4-fluorophenyl)acetamido)propanethioate (3af):



S-phenyl-2-(N-(4-chlorophenyl)acetamido)propanethioate (3ag):