An Automated Process for a Sequential Heterocycle/Multicomponent Reaction: Multistep Continuous Flow Synthesis of 5-(Thiazol-2-yl)-3,4-Dihydropyrimidin-2(*1H*)-ones

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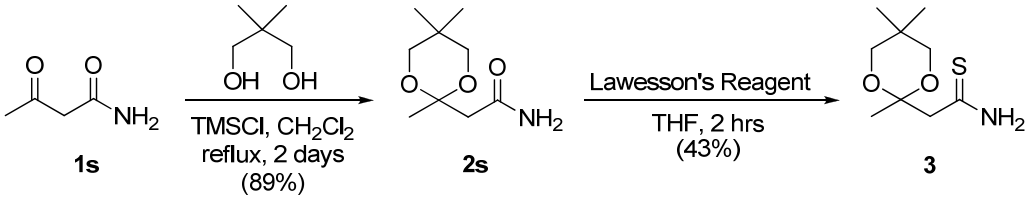
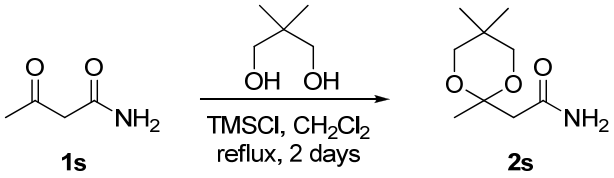
Content

All reactions were carried out using oven-dried glassware and conducted under a positive pressure of nitrogen unless otherwise specified. NMR spectra were recorded on a JEOL JNM-CS400 (400 MHz) spectrometer. With the exception of thioamide **3** ($CDCl_3$), all NMR samples were prepared using DMSO-d_6. High resolution mass spectra were obtained on an Agilent mass spectrometer using ESI-TOF at the Scripps Research Institute Mass Spectrometry Laboratory. LC/MS analyses were carried out on a Shimadzu LC/MS 2010 Series LC System with a Kromasil 100 5 micron C18 column (50 x 2.1 mmID). Silica gel purifications were accomplished using a CombiFlash R_f system from Teledyne Isco using RediSep R_f pre-packed columns. All reagents as solvents were used as received from standard suppliers. Microfluidic experiments were conducted using a Syrris AFRICA® synthesis station.

A) Overview for the synthesis of thioamide 3

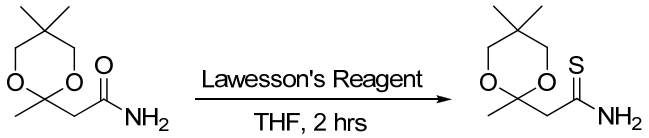


B) Experimental procedures for the synthesis of thioamide 3 including characterization data



Ketal-protected Amide 2s. To a vacuum dried solid mixture of ketone **1s** (5.05 g, 50.0 mmol, 1 equiv) and neopentyl glycol (11.0 g, 110 mmol, 2.2 equiv) was added anhydrous CH_2Cl_2 (200 mL) followed by chlorotrimethylsilane (28.0 mL, 220 mmol, 4.4 equiv). The resulting clear solution was heated to reflux for 2 days. The resulting cloudy reaction mixture was cooled to 0 °C, carefully quenched with portion-wise addition of saturated aqueous $NaHCO_3$, and the

resulting biphasic mixture separated. Then, the organic layer was washed with brine, dried using Na_2SO_4, and concentrated to dryness *in vacuo*. The resulting clear oil was loaded onto a pre-packed silica gel column (120 g) using CH_2Cl_2 and chromatographed using CH_2Cl_2:MeOH (85 mL/min, 100% CH_2Cl_2 for 5 min, then ramping to 20% MeOH over 20 min). Following concentration of product eluents, **2s** (8.35 g, 89%) was isolated as a clear oil which slowly became white crystals over time. ^{1}H NMR consistent with literature reported spectrum.[1]

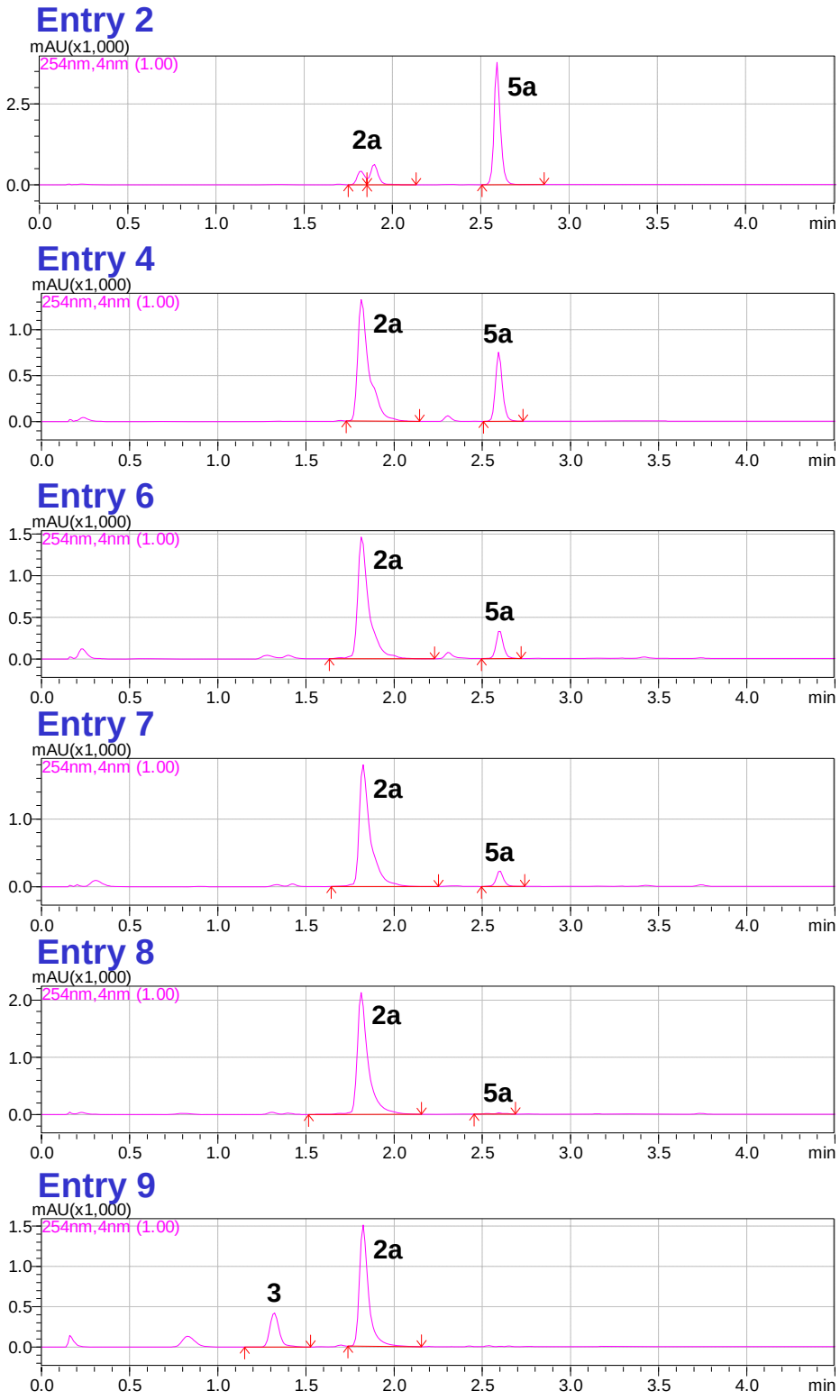


2s **3**

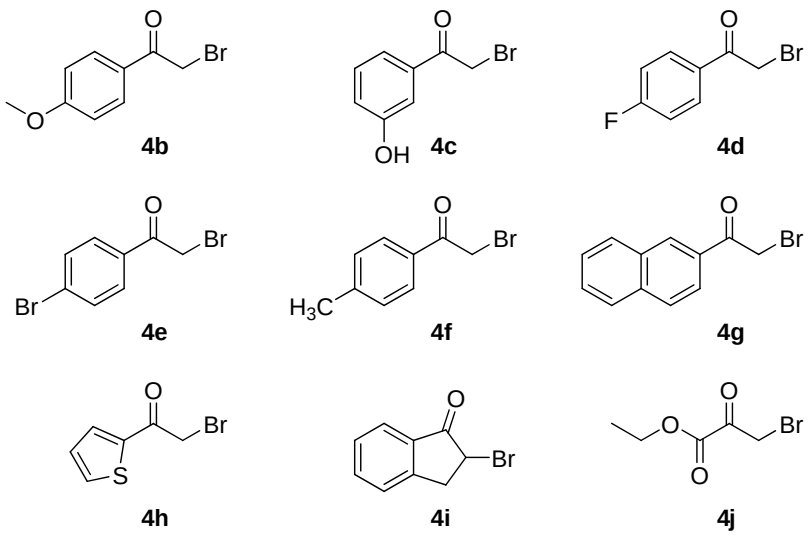
Ketal-protected Thioamide 3. A solution of **2s** (5.81 g, 31.1 mmol, 1 equiv) in anhydrous THF was prepared and cooled to 0 °C. Lawesson's reagent (6.91 g, 17.1 mmol, 0.55 equiv) was then added and the resulting yellow suspension was allowed to naturally warm to room temperature, stirring for a total of 2 hrs. The resulting yellow solution was concentrated *in vacuo* and re-dissolved in EtOAc. Then, the organic phase was washed with saturated aqueous $NaHCO_3$ followed by brine, dried using Na_2SO_4, and concentrated to dryness *in vacuo*. The crude material was adsorbed onto silica gel, loaded onto a pre-packed silica gel column (120 g), and chromatographed using hexanes:EtOAc (85 mL/min, 0% EtOAc to 30% EtOAc over 60 min). Following concentration of product eluents, the resulting white solid still required further purification. Thus, the chromatographed material was treated with toluene (50 mL), cooled to -20 °C, and the resulting white precipitate collected to provide **3** (2.70 g, 43%) as white crystals. Mp 111-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.25 (s, 1H), 7.85 (s, 1H), 3.63 (d, J = 11.0 Hz, 2H), 3.44 (d, J = 11.0 Hz, 2H), 3.16 (s, 2H), 1.46 (s, 3H), 1.06 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 205.0, 98.2, 54.0, 30.1, 23.1, 22.4, 18.8. HRMS (ESI): *m/z* calcd for $C_9H_{18}NO_2S$ $(M + H)^+$ 204.1053, found $(M + H)^+$ 204.1050.

Reference 1: For similar reaction conditions, see: Zamir, L. O.; Nguyen, C. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 1189-1196. For characterization data of **2s**, see: Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492-4501.

C) Selected HLPC data for Table 1 – Separation conditions: Reverse-phase (C18) using an acetonitrile gradient of 10% to 95% over 4 min in water containing 0.05 % formic acid with a flow rate of 1.0 mL/min. Refer to page S2 for column information.



D) Structures of α-bromoketones 4b-4j



E) General experimental procedure for the microfluidic synthesis of β-ketothiazoles 2 and characterization data for 2a-2j

Synthesis of β-ketothiazoles 2: All reactions were conducted in DMF under a positive pressure of nitrogen. Streams of the thioamide **3** (25 μL/min, 0.5 M, DMF, 1 equiv) and a solution of α-bromoketones **4** (25 μL/min, 0.5 M, DMF, 1 equiv) containing 1.0 equiv of H_2O were mixed in a 250 μL glass reactor heated to 150 °C (5 min). After exiting the chip, the reaction flow was then collected (1000 μL) after passing though the back pressure regulator. These reactions were carried out with a back pressure of 6.0 bar. Then, the crude reaction mixture was adsorbed onto silica gel, loaded onto a pre-packed silica gel column (12 g), and chromatographed using hexanes:EtOAc (30 mL/min, 100% hexanes for 5 min, then ramping to 40% EtOAc over 20 min).

Ketothiazole 2a. Title compound was isolated as a brown semi-solid (40 mg, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.03 (s, 1H), 7.94 (m, 2H), 7.43 (m, 2H), 7.33 (m, 1H), 4.36 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.4, 153.5, 134.1, 128.7, 127.9, 125.9, 114.9, 46.6, 29.7. HRMS (ESI): *m/z* calcd for $C_{12}H_{12}NOS$ $(M + H)^+$ 218.0634, found $(M + H)^+$ 218.0645.

Ketothiazole 2b. Title compound was isolated as a brown semi-solid (56 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.86 (s, 3H), 6.99 (d, J = 8.5 Hz, 2H), 4.34 (s, 2H), 3.79 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.2, 159.0, 153.4, 127.2, 126.9, 114.1, 112.8, 55.1, 46.6, 29.7. HRMS (ESI): *m/z* calcd for $C_{13}H_{14}NO_2S$ $(M + H)^+$ 248.0740, found $(M + H)^+$ 248.0743.

Ketothiazole 2c. Title compound was isolated as an orange semi-solid (53 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.50 (s, 1H), 7.94 (s, 1H), 7.36-7.33 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 6.73 (dd, J = 7.9, 1.8 Hz, 1H), 4.34 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.2, 157.7, 153.6, 135.3, 129.7, 116.7, 114.9, 114.7, 112.9, 46.6, 29.7. HRMS (ESI): *m/z* calcd for $C_{12}H_{12}NO_2S$ $(M + H)^+$ 234.0583, found $(M + H)^+$ 234.0588.

Ketothiazole 2d. Title compound was isolated as an orange semi-solid (42 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.02 (s, 1H), 7.97 (m, 2H), 7.26 (m, 2H), 4.36 (m, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.6, 161.8 ($d_{C\text{-}F}$, J = 245.4 Hz), 152.5, 130.7, 127.9 ($d_{C\text{-}F}$, J = 7.7 Hz), 115.6 ($d_{C\text{-}F}$, J = 22.0 Hz), 114.7, 46.5, 29.7. HRMS (ESI): *m/z* calcd for $C_{12}H_{11}FNOS$ $(M + H)^+$ 236.0540, found $(M + H)^+$ 236.0535.

Ketothiazole 2e. Title compound was isolated as a light yellow semi-solid (52 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.12 (s, 1H), 7.89 (m, 2H), 7.63 (m, 2H), 4.36 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.8, 152.2, 133.3, 131.7, 127.9, 121.0, 115.7, 40.1, 29.7. HRMS (ESI): *m/z* calcd for $C_{12}H_{11}BrNOS$ $(M + H)^+$ 295.9739, found $(M + H)^+$ 295.9735.

Ketothiazole 2f. Title compound was isolated as a light yellow semi-solid (47 mg, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.94 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 4.33 (s, 2H), 2.31 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.2, 153.6, 137.2, 131.4, 129.3, 125.8, 114.0, 46.6, 29.7, 20.8. HRMS (ESI): *m/z* calcd for $C_{13}H_{14}NOS$ $(M + H)^+$ 232.0791, found $(M + H)^+$ 232.0793.

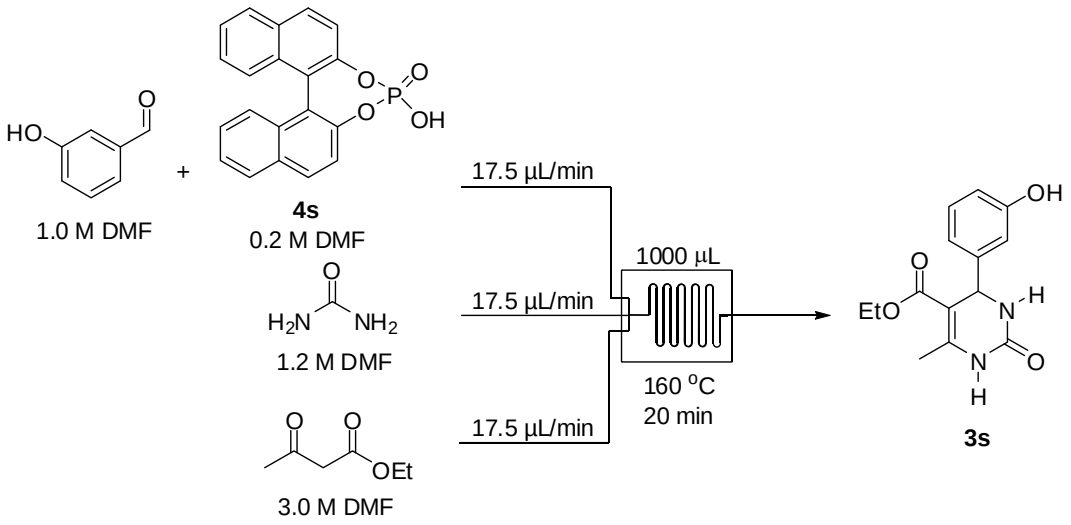
Ketothiazole 2g. Title compound was isolated as a beige semi-solid (56 mg, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.51 (s, 1H), 8.18 (s, 1H), 8.09 (dd, J = 8.2, 1.8 Hz, 1H), 8.00-7.91 (m, 3H), 7.54-7.50 (m, 2H), 4.41 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 162.7, 153.4, 133.2, 132.6, 131.5, 128.3, 128.2, 127.6, 126.5, 126.2, 124.5, 124.2, 115.5, 46.6, 29.7. HRMS (ESI): *m/z* calcd for $C_{16}H_{14}NOS$ $(M + H)^+$ 268.0791, found $(M + H)^+$ 268.0801.

Ketothiazole 2h. Title compound was isolated as a brown semi-solid (42 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.87 (s, 1H), 7.54 (dd, J = 3.7, 0.9 Hz, 1H), 7.50 (dd, J = 5.0, 0.9 Hz, 1H), 7.10 (dd, J = 5.0, 3.7 Hz, 1H), 4.35 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.5, 162.7, 148.2, 138.0, 128.0, 125.7, 124.0, 113.3, 46.3, 29.7. HRMS (ESI): *m/z* calcd for $C_{10}H_{10}NOS_2$ $(M + H)^+$ 224.0198, found $(M + H)^+$ 224.0206.

Ketothiazole 2i. Title compound was isolated as an orange semi-solid (28 mg, 49%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.63 (d, J = 7.3 Hz, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.37 (t, J = 6.7 Hz, 1H), 7.26 (td, J = 7.3, 1.2 Hz, 1H), 4.39 (s, 2H), 3.93 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.6, 166.5, 160.2, 146.0, 137.1, 136.6, 126.9, 125.3, 125.2, 118.2, 47.3, 32.3, 29.6. HRMS (ESI): *m/z* calcd for $C_{13}H_{12}NOS$ $(M + H)^+$ 230.0634, found $(M + H)^+$ 230.0636.

Ketothiazole 2j. Title compound was isolated as a bright yellow semi-solid (27 mg, 51%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.45 (s, 1H), 4.37 (s, 2H), 4.29 (q, J = 7.3 Hz, 2H), 2.24 (s, 3H), 1.29 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 203.5, 163.3, 160.8, 145.2, 129.8, 60.6, 46.2, 29.7, 14.2. HRMS (ESI): *m/z* calcd for $C_9H_{12}NO_3S$ $(M + H)^+$ 214.0532, found $(M + H)^+$ 214.0531.

F) Selected example of one-chip Biginelli flow synthesis



Synthesis of DHPM 3s: Reaction was conducted in DMF under a positive pressure of nitrogen. Streams of 3-hydroxybenzaldehyde (17.5 µL/min, 1.0 M, DMF, 1 equiv) containing 0.2 equiv of acid **4s**,[2] urea (17.5 µL/min, 1.2 M, DMF, 1.2 equiv), and ethyl acetoacetate (17.5 µL/min, 3.0 M, DMF, 3 equiv) were mixed in a 1000 µL glass reactor heated to 160 °C (20 min). After exiting the chip, the reaction flow was then collected (1500 µL) after passing though the back pressure regulator. The reaction was carried out with a back pressure of 6.0 bar. Then, the crude reaction mixture was adsorbed onto silica gel, loaded onto a pre-packed silica gel column (12 g), and chromatographed using hexanes:EtOAc (30 mL/min, 10% EtOAc to 100% EtOAc over 20 min). Following concentration of product eluents, the title compound was isolated as a white solid (89 mg, 64%). ^{1}H NMR is consistent with literature reported spectra.

It is important to note that in the absence of acid **4s**, this reaction and others of its kind remain incomplete.

Reference 2: For the use of phosphoric acids in the Biginelli reaction, see: Chen, X. H.; Xu, X. Y.; Liu, H.; Cun, L. F.; Gong, L. Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802-14803.

G) General experimental procedure for the microfluidic synthesis of DHPMs 1 and characterization data for DHPMs 1b-1i

Synthesis of DHPMs 1: All reactions were conducted in DMF under a positive pressure of nitrogen. Streams of the thioamide **3** (32.5 μL/min, 0.75 M, DMF, 1 equiv) and a solution of α-bromoketones **4** (32.5 μL/min, 0.75 M, DMF, 1 equiv) were mixed in a 250 μL glass reactor heated to 150 °C (3.75 min). After exiting the chip, the combined flow (65.0 μL/min) was introduced to a single steam (32.5 μL/min, 0.9 M, DMF, 1.2 equiv) of 3-hydroxybenzaldehyde **6** and urea **7** in a 1000 μL glass reactor heated to 200 °C (10 min). The reaction flow was then collected (1250 μL) after passing though the back pressure regulator. These reactions were carried out with a back pressure of 6.0 bar. Then, the crude reaction mixtures were adsorbed onto silica gel, loaded onto a pre-packed silica gel column (12 g), and chromatographed using hexanes:EtOAc (30 mL/min, 10% EtOAc to 100% EtOAc over 20 min).

DHPM 1b. Title compound was isolated as a light yellow semi-solid (52 mg, 46%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.36 (s, 1H), 9.02 (d, J = 1.8 Hz, 1H), 7.93-7.91 (m, 3H), 7.69 (m, 1H), 7.43 (m, 2H), 7.32 (m, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.80 (m, 1H), 6.78 (m, 1H), 6.60 (m, 1H), 5.44 (d, J = 3.2 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.5, 157.4, 153.2, 152.5, 145.4, 137.8, 134.2, 129.3, 128.7, 127.9, 126.0, 117.5, 114.4, 113.5, 111.7, 104.0, 56.6, 17.9. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}N_3O_2S$ $(M + H)^+$ 364.1114, found $(M + H)^+$ 364.1128.

DHPM 1c. Title compound was isolated as a light yellow semi-solid (53 mg, 43%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.34 (s, 1H), 8.99 (d, J = 1.8 Hz, 1H), 7.84-7.82 (m, 2H), 7.72 (s, 1H), 7.67 (m, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.97-6.95 (m, 2H), 6.78 (m, 1H), 6.76 (m, 1H), 6.59 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 5.42 (d, J = 3.7 Hz, 1H), 3.76 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.2, 159.1, 157.4, 153.1, 152.5, 145.4, 137.6, 129.3, 127.3, 127.1, 117.5, 114.4, 114.1, 113.5, 109.7, 104.1, 56.6, 55.1, 17.9. HRMS (ESI): *m/z* calcd for $C_{21}H_{20}N_3O_3S$ $(M + H)^+$ 394.1220, found $(M + H)^+$ 394.1228.

DHPM 1d. Title compound was isolated as a yellow semi-solid (54 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.48 (s, 1H), 9.35 (s, 1H), 9.01 (d, J = 1.8 Hz, 1H), 7.81 (s, 1H), 7.70 (m, 1H), 7.35-7.32 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.80 (d, 7.8 Hz, 1H), 6.76 (m, 1H), 6.72 (m, 1H), 6.60 (m, 1H), 5.45 (d, J = 3.2 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.2, 157.6, 157.4, 153.3, 152.5, 145.4, 137.7, 135.4, 129.7, 129.3, 117.5, 116.8, 114.9, 114.3, 113.4, 112.9, 111.6, 104.1, 56.5, 17.9. HRMS (ESI): *m/z* calcd for $C_{20}H_{18}N_3O_3S$ $(M + H)^+$ 380.1063, found $(M + H)^+$ 380.1066.

DHPM 1e. Title compound was isolated as a light yellow semi-solid (46 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.35 (s, 1H), 9.02 (d, J = 1.8 Hz, 1H), 7.96-7.93 (m, 2H), 7.88 (s, 1H), 7.69 (m, 1H), 7.24 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 6.79-6.75 (m, 2H), 6.59 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 5.42 (d, J = 3.2 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.6, 161.8 ($d_{C\text{-}F}$, J = 244.4 Hz), 157.4, 152.4, 152.2, 145.4, 138.0, 130.8, 129.4, 127.9, 117.5, 115.6 ($d_{C\text{-}F}$, J = 22.0 Hz), 114.4, 113.5, 111.4, 103.9, 56.6, 17.9. HRMS (ESI): *m/z* calcd for $C_{20}H_{17}FN_3O_2S$ $(M + H)^+$ 382.1020, found $(M + H)^+$ 382.1022.

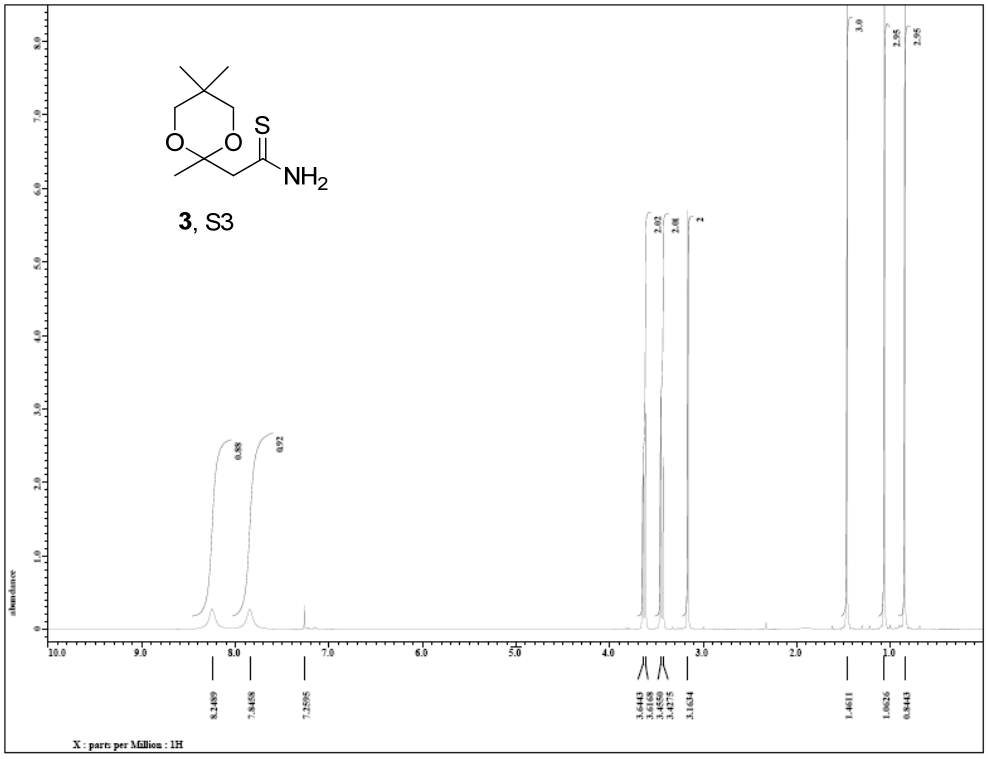
DHPM 1f. Title compound was isolated as a light yellow semi-solid (59 mg, 43%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.36 (s, 1H), 9.04 (d, J = 1.8 Hz, 1H), 7.98 (s, 1H), 7.88 (m, 2H), 7.71 (m, 1H), 7.62 (m, 2H), 7.08 (t, J = 8.0 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.76 (s, 1H), 6.60 (m, 1H), 5.43 (d, J = 3.2 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.7, 157.4, 152.4, 152.0, 145.3, 138.1, 133.4, 131.7, 129.3, 128.0, 121.0, 117.5, 114.4, 113.5, 112.5, 103.9, 56.6, 17.9. HRMS (ESI): *m/z* calcd for $C_{20}H_{17}BrN_3O_2S$ $(M + H)^+$ 442.0219, found $(M + H)^+$ 442.0220.

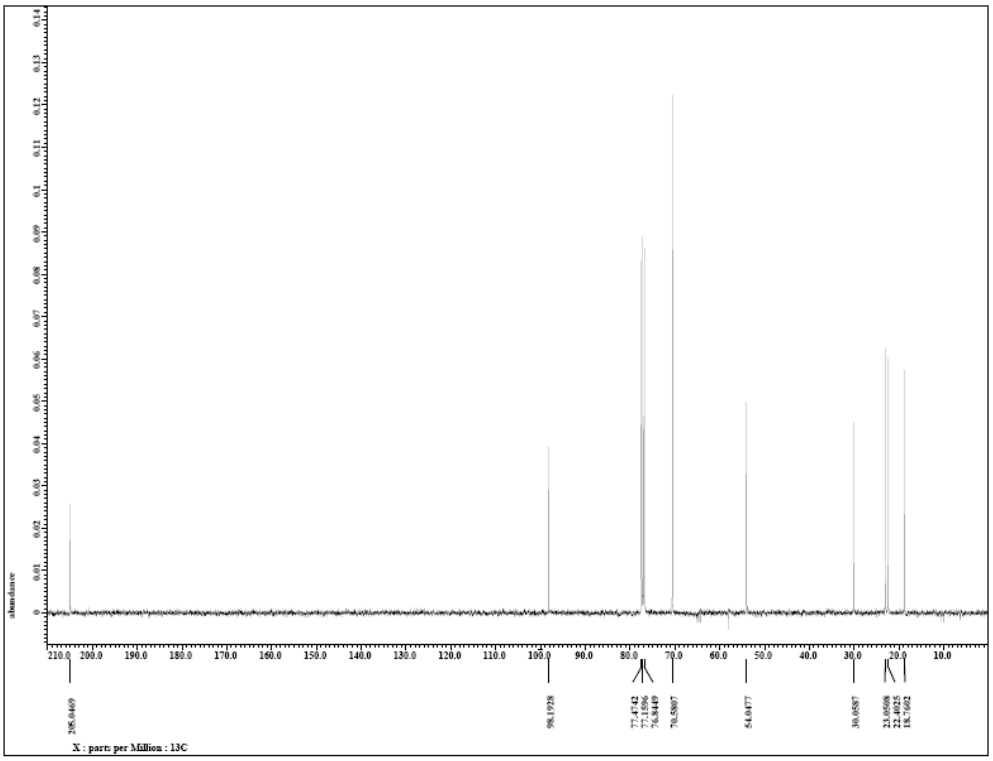
DHPM 1g. Title compound was isolated as a light yellow semi-solid (52 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.35 (s, 1H), 9.00 (d, J = 1.8 Hz, 1H), 7.80 (s, 1H), 7.80-7.78 (m, 2H), 7.67 (m, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.06 (t, J = 7.8 Hz, 1H), 6.79-6.75 (m, 2H), 6.59 (ddd, J = 7.8, 2.3, 0.9 Hz, 1H), 5.42 (d, J = 3.2 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.3, 157.4, 153.3, 152.5, 145.4, 137.7, 137.2, 131.5, 129.3, 129.3, 125.9, 117.5, 114.4, 113.5, 110.8, 104.1, 56.6, 20.8, 17.9. HRMS (ESI): *m/z* calcd for $C_{21}H_{20}N_3O_2S$ $(M + H)^+$ 378.1271, found $(M + H)^+$ 378.1281.

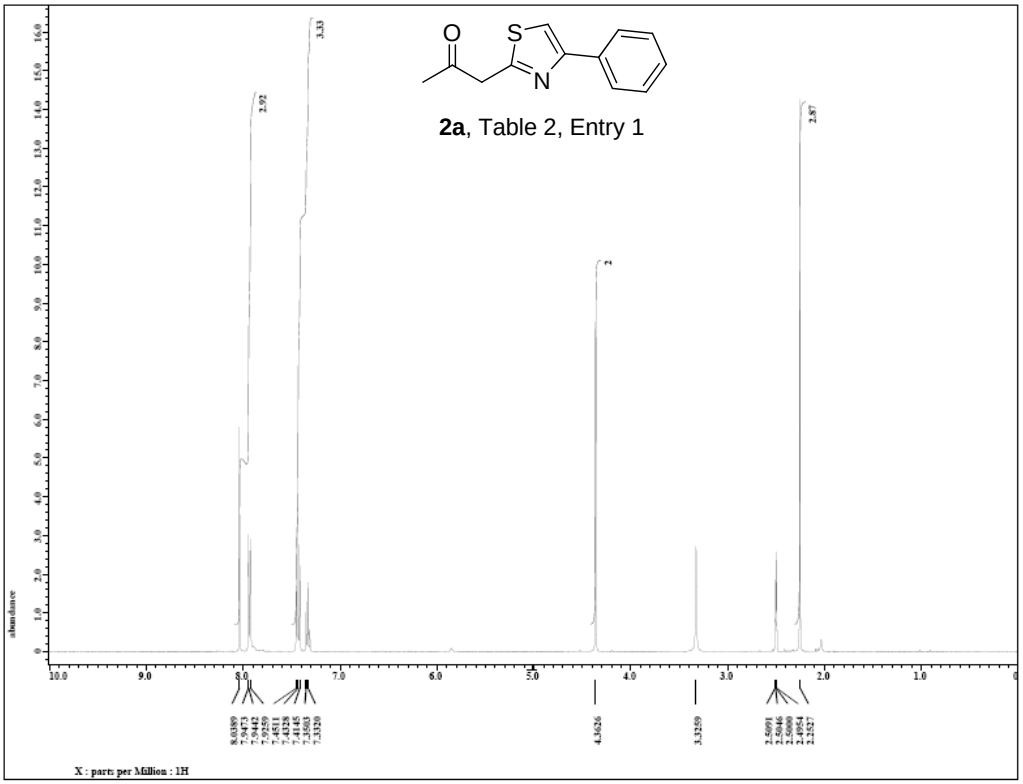
DHPM 1h. Title compound was isolated as a light yellow semi-solid (56 mg, 43%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.38 (s, 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.46 (s, 1H), 8.08-8.06 (m, 2H), 7.99-7.90 (m, 3H), 7.72 (m, 1H), 7.52 (m, 2H), 7.10 (t, J = 7.8 Hz, 2H), 6.85 (d, J = 7.8 Hz, 1H), 6.82 (m, 1H), 6.61 (m, 1H), 5.50 (d, J = 3.2 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.6, 157.4, 153.1, 152.4, 145.5, 137.9, 133.1, 132.6, 131.7, 129.4, 128.3, 128.2, 127.6, 126.5, 126.1, 124.6, 124.2, 117.5, 114.4, 113.6, 112.4, 104.1, 56.7, 18.0. HRMS (ESI): *m/z* calcd for $C_{24}H_{20}N_3O_2S$ $(M + H)^+$ 414.1271, found $(M + H)^+$ 414.1290.

DHPM 1i. Title compound was isolated as a brown semi-solid (52 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.35 (s, 1H), 9.05 (d, J = 1.8 Hz, 1H), 7.74 (s, 1H), 7.69 (m, 1H), 7.52-7.49 (m, 2H), 7.09 (dd, J = 5.3, 3.4 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.77 (m, 1H), 6.60 (m, 1H), 5.41 (d, J = 3.7 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 164.4, 157.4, 152.4, 147.9, 145.4, 138.2, 138.1, 129.3, 128.0, 125.8, 123.9, 117.6, 114.4, 113.5, 110.0, 103.8, 56.5, 17.9. HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N_3O_2S_2$ $(M + H)^+$ 370.0678, found $(M + H)^+$ 370.0689.

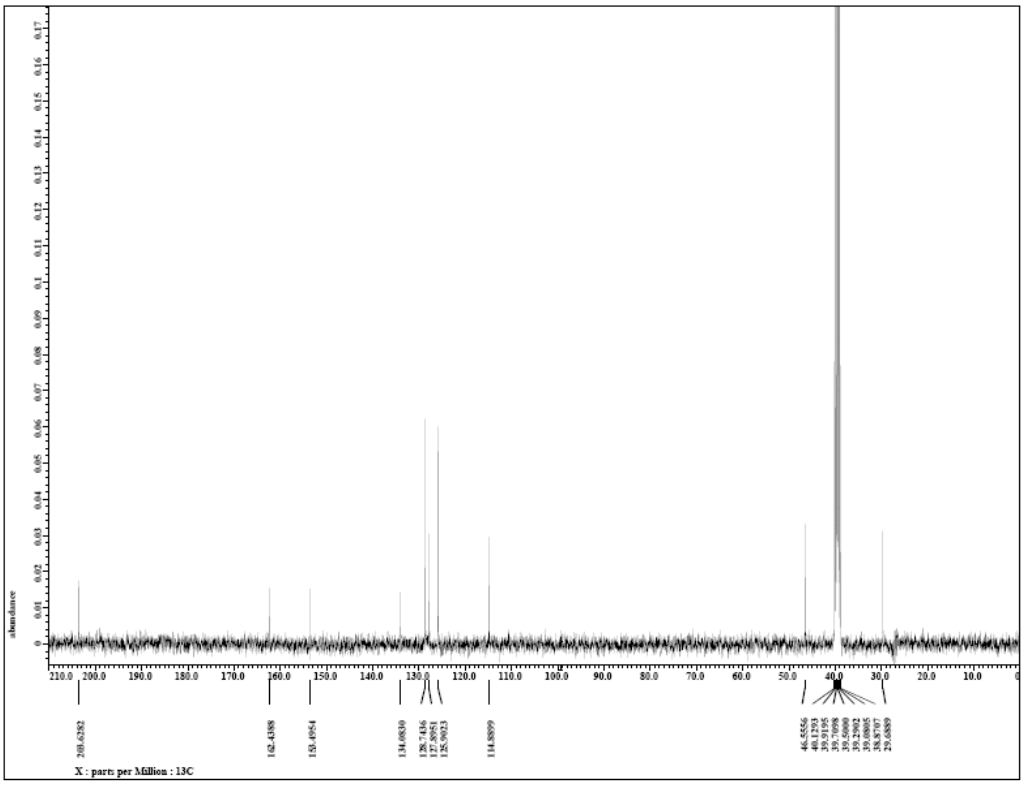
H) NMR Spectra

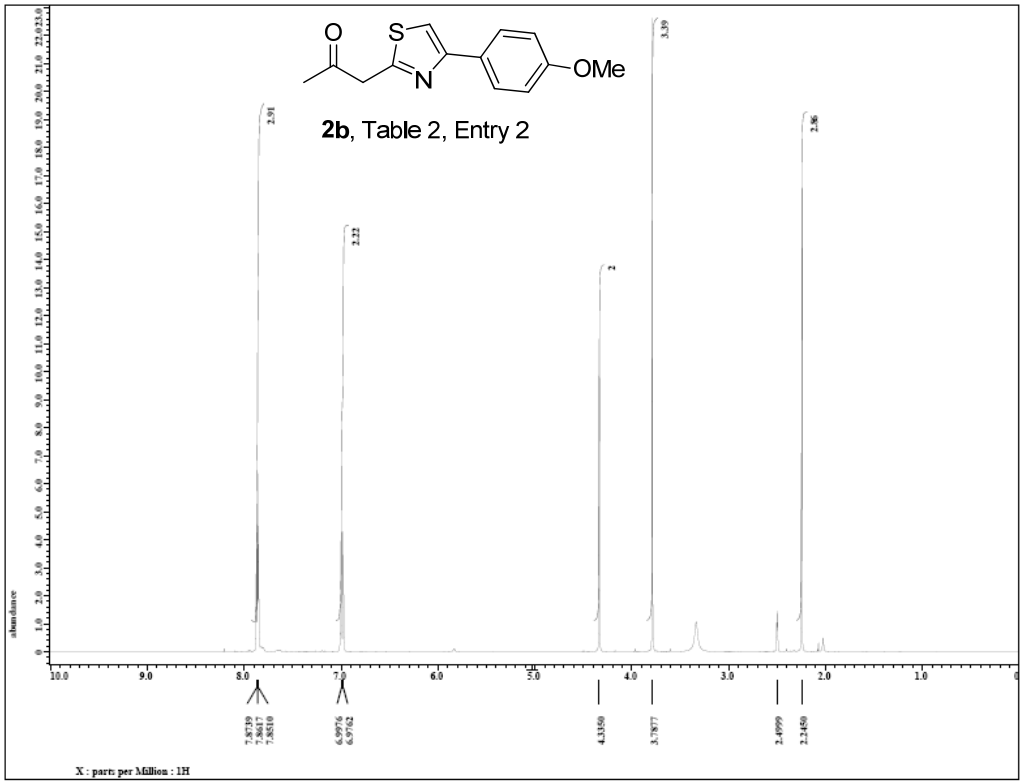


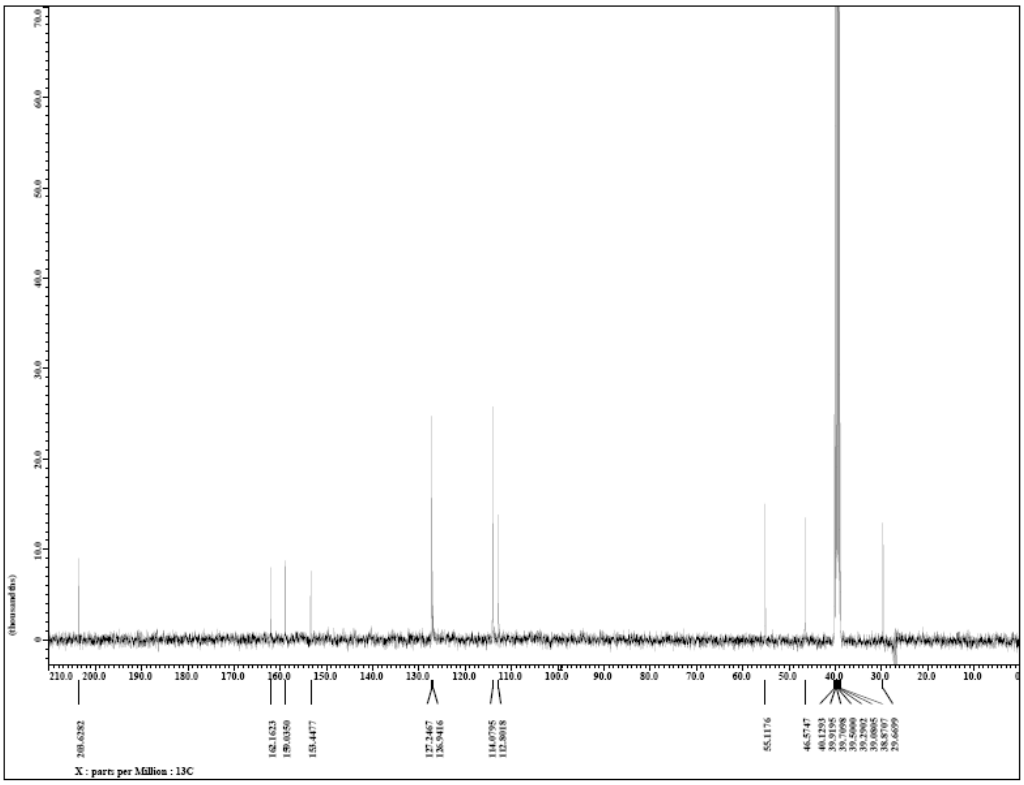


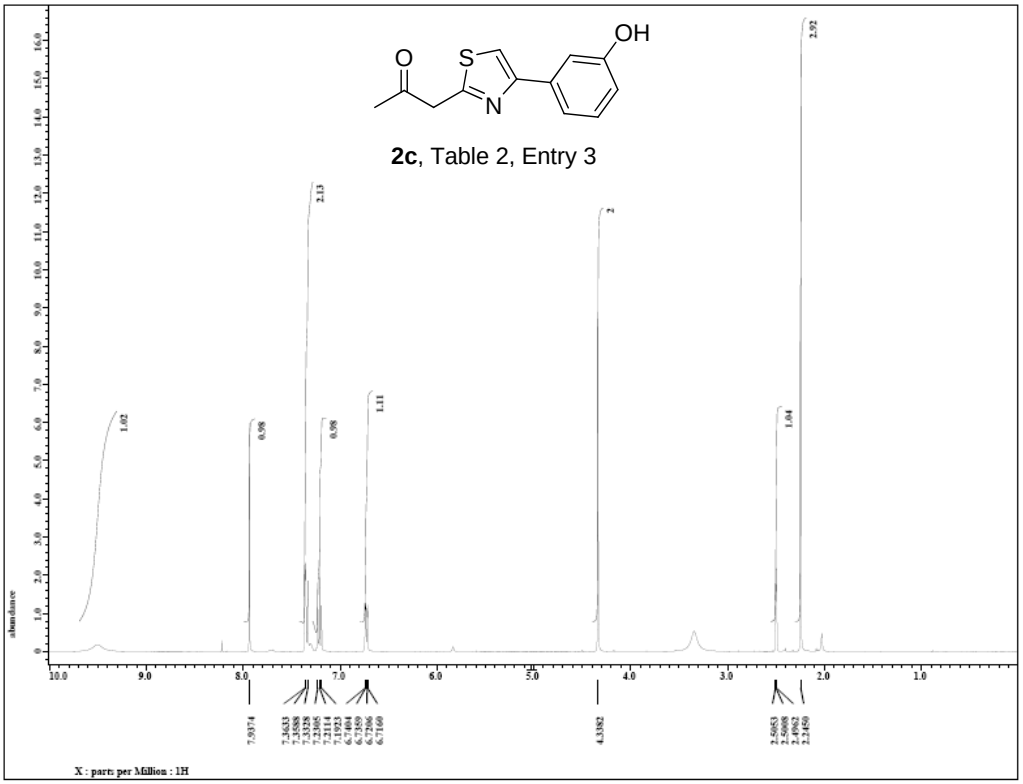


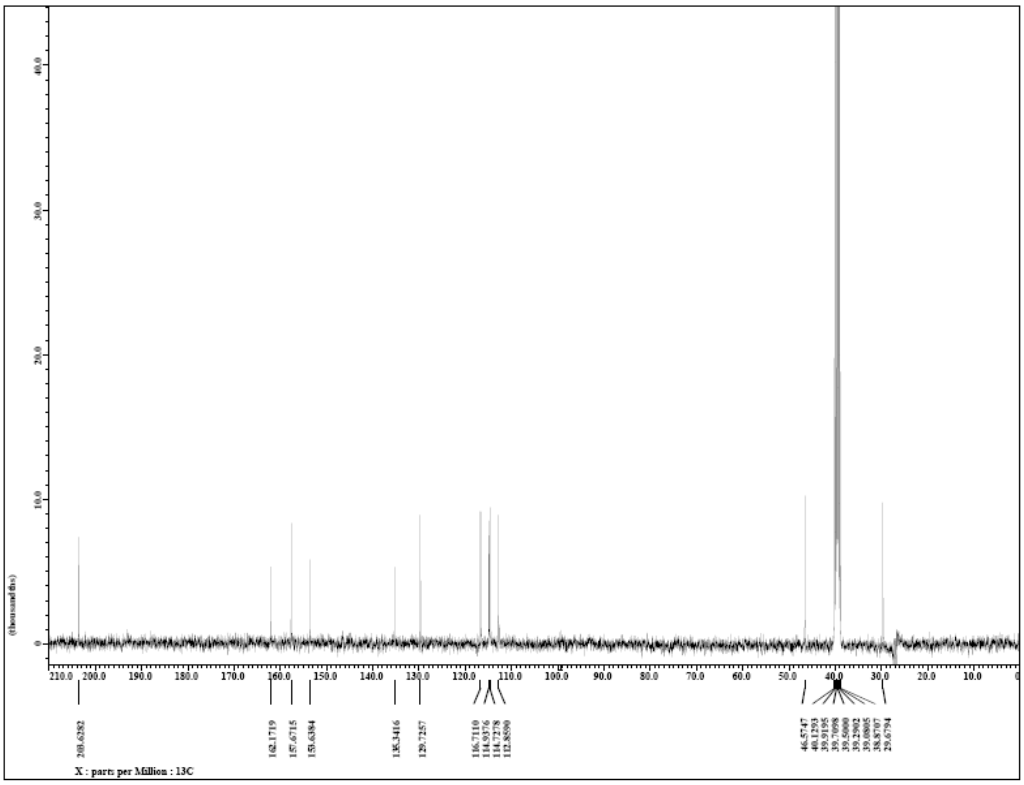
2a, Table 2, Entry 1

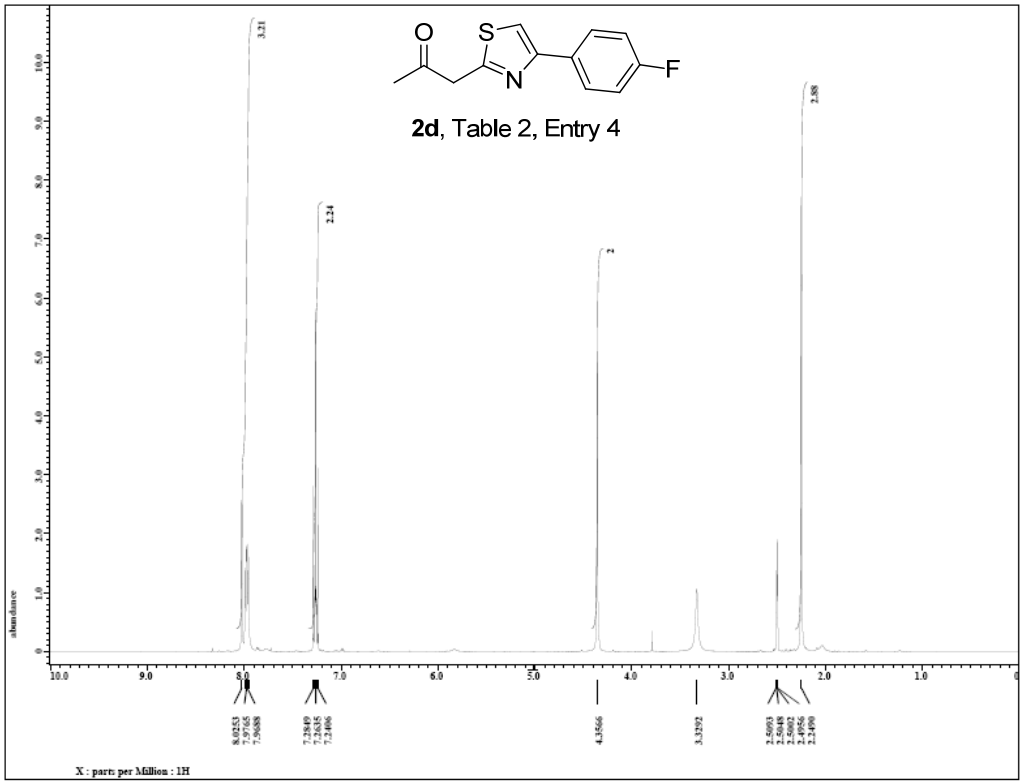


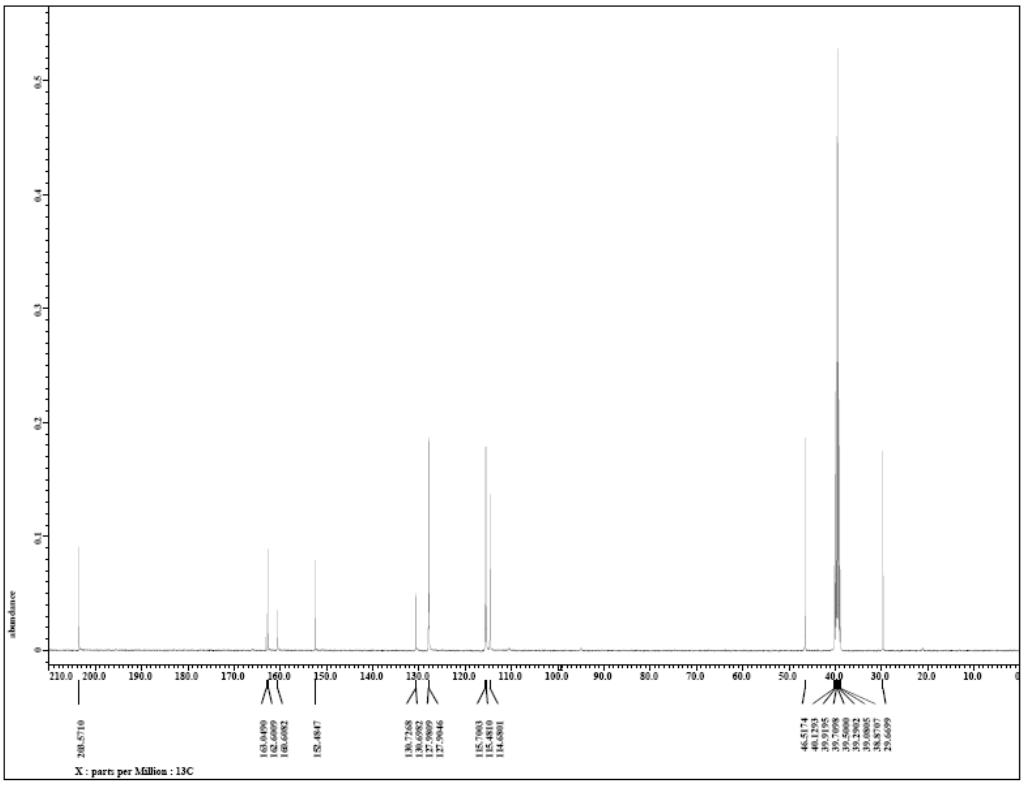

O
S
N
OMe
2b, Table 2, Entry 2
2.91
2.22
2
3.39
2.86
abundance
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.8739
7.8617
7.8510
6.9976
6.9762
4.3350
3.7877
2.4999
2.2450
X : parts per Million : 1H

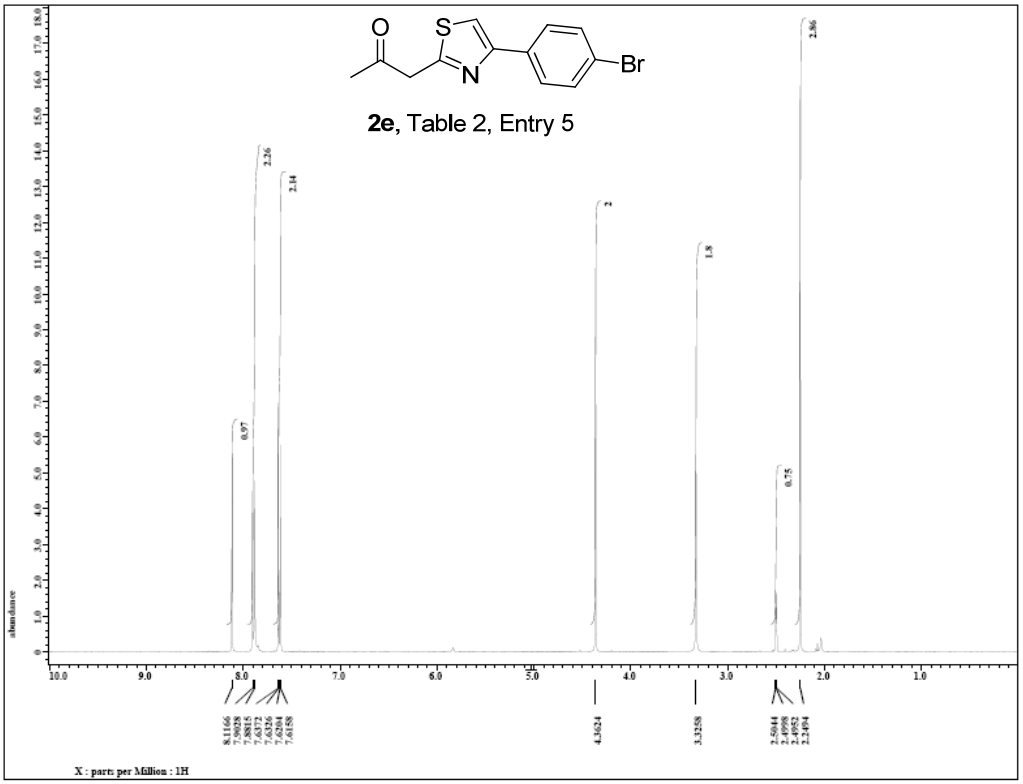

(thousand/hz)
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
208.6282
162.1623
159.0350
153.4477
137.2467
126.9416
114.0795
112.8918
55.1176
46.5747
40.1293
39.9178
39.7098
39.5060
39.2892
39.0805
38.8707
29.6699
X : parts per Million : 13C

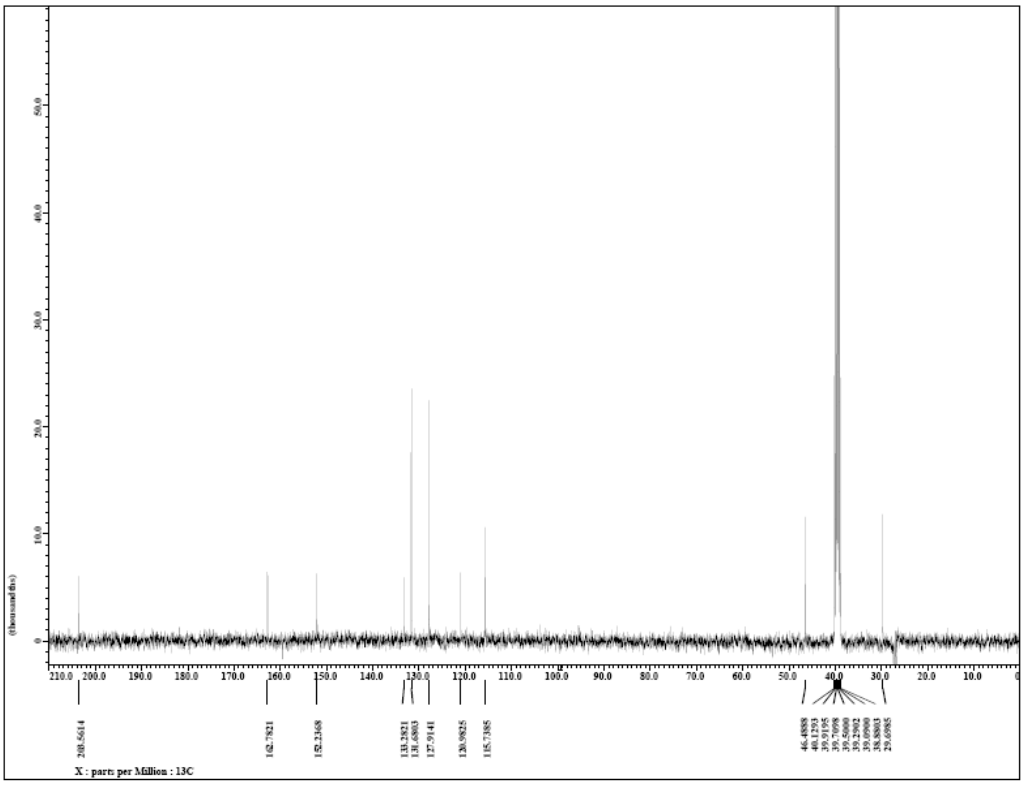

OH
O
S
N
2c, Table 2, Entry 3
X : parts per Million : 1H

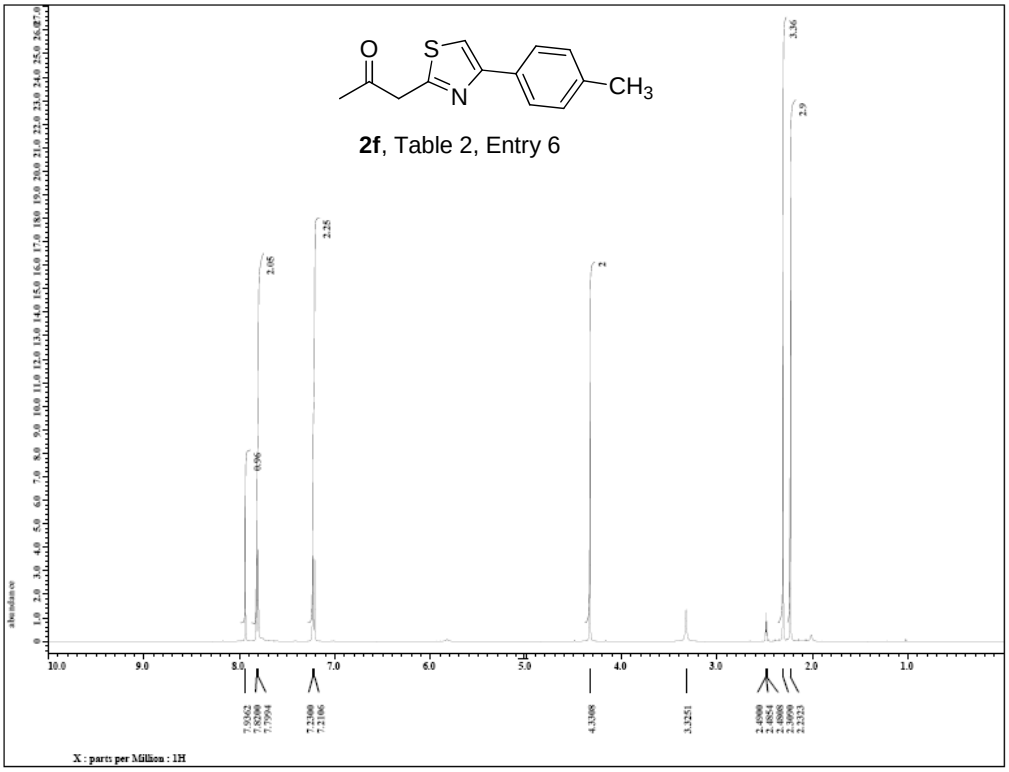

X : parts per Million : 13C

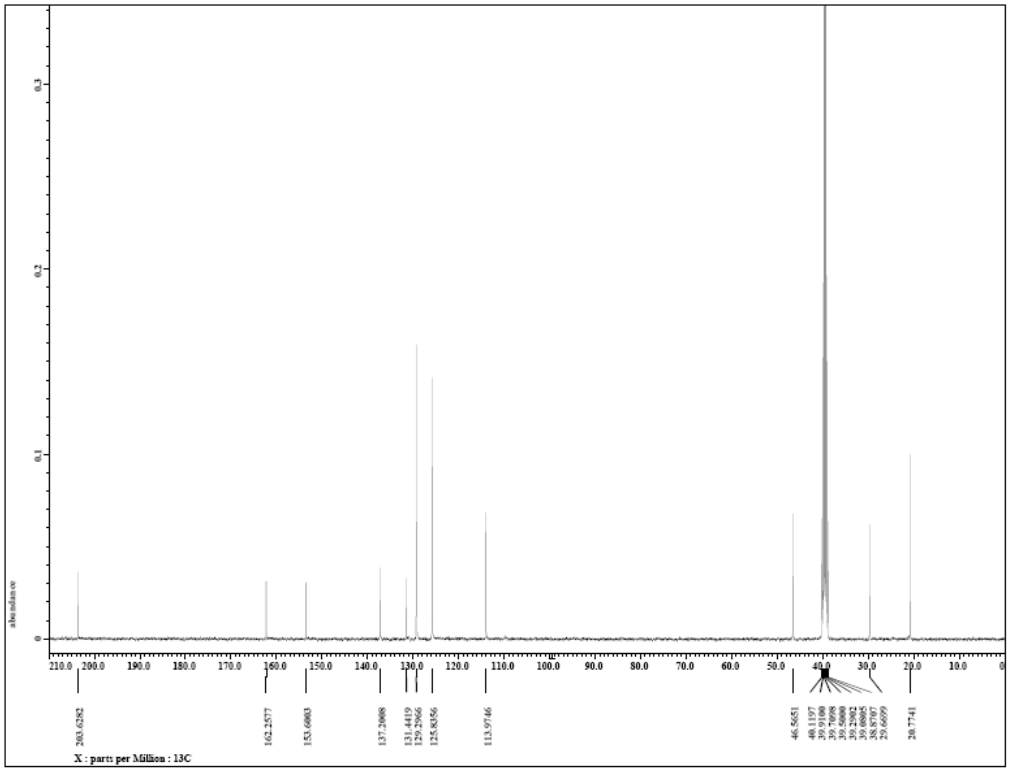

O
S
N
F
2d, Table 2, Entry 4
3.21
2.24
2
2.88
abundance
X : parts per Million : 1H

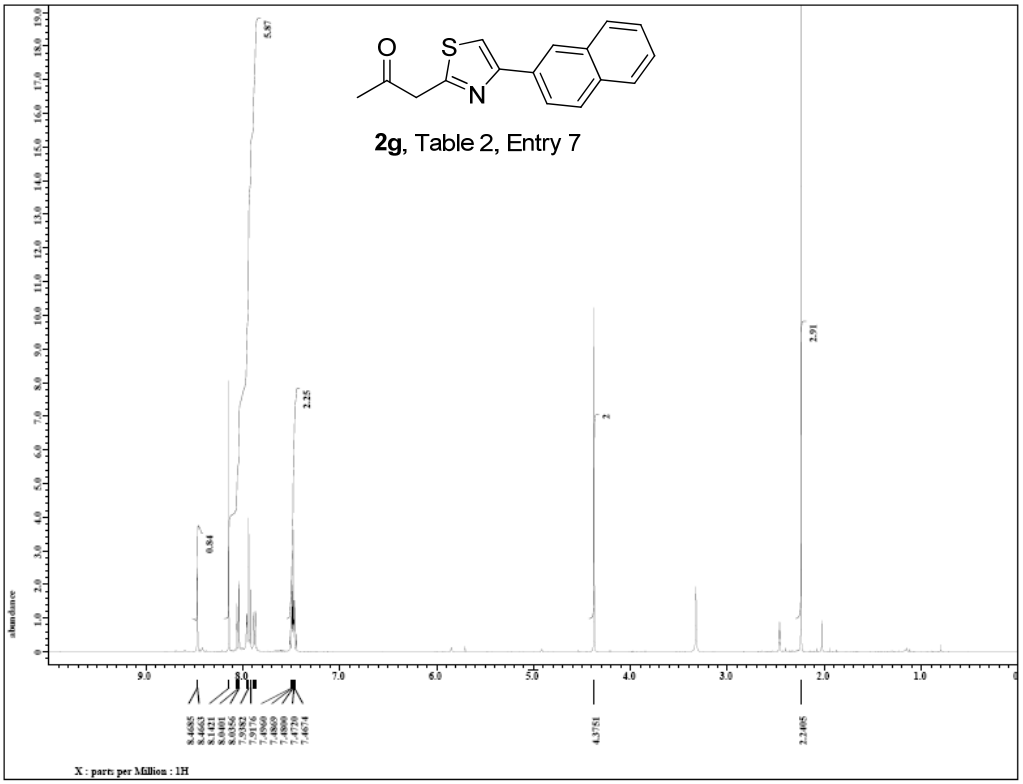

abundance
X : parts per Million : 13C

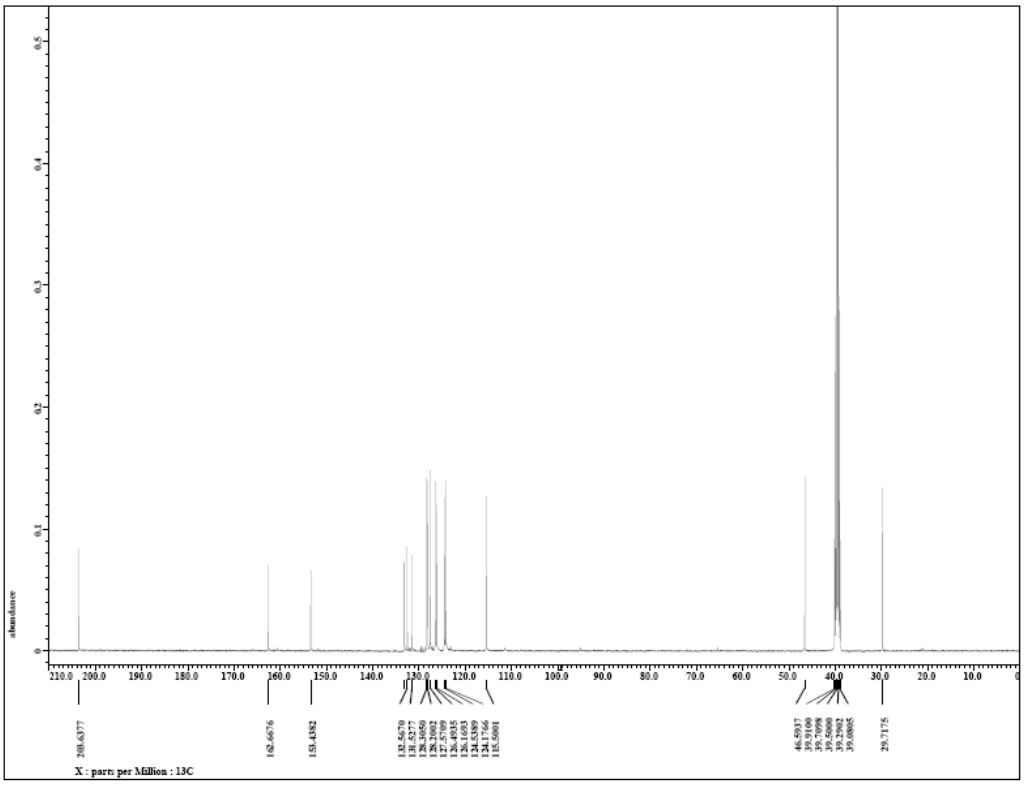

O
S
N
Br
2e, Table 2, Entry 5
abundance
X : parts per Million : 1H

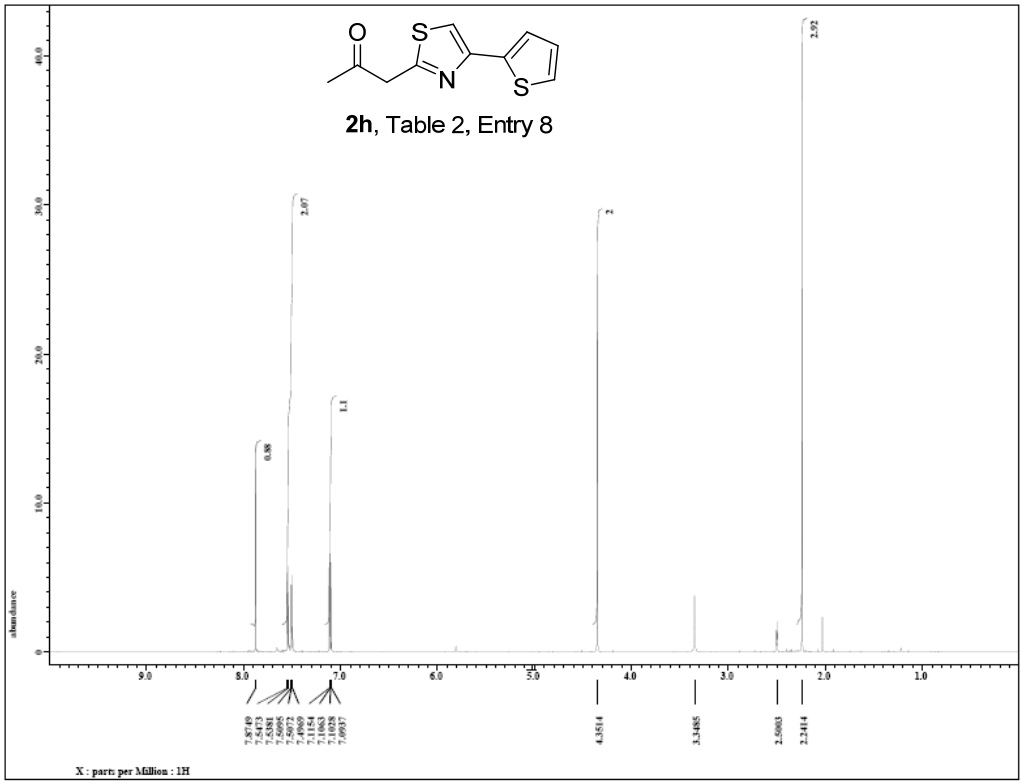

(thousandths)
X : parts per Million : 13C

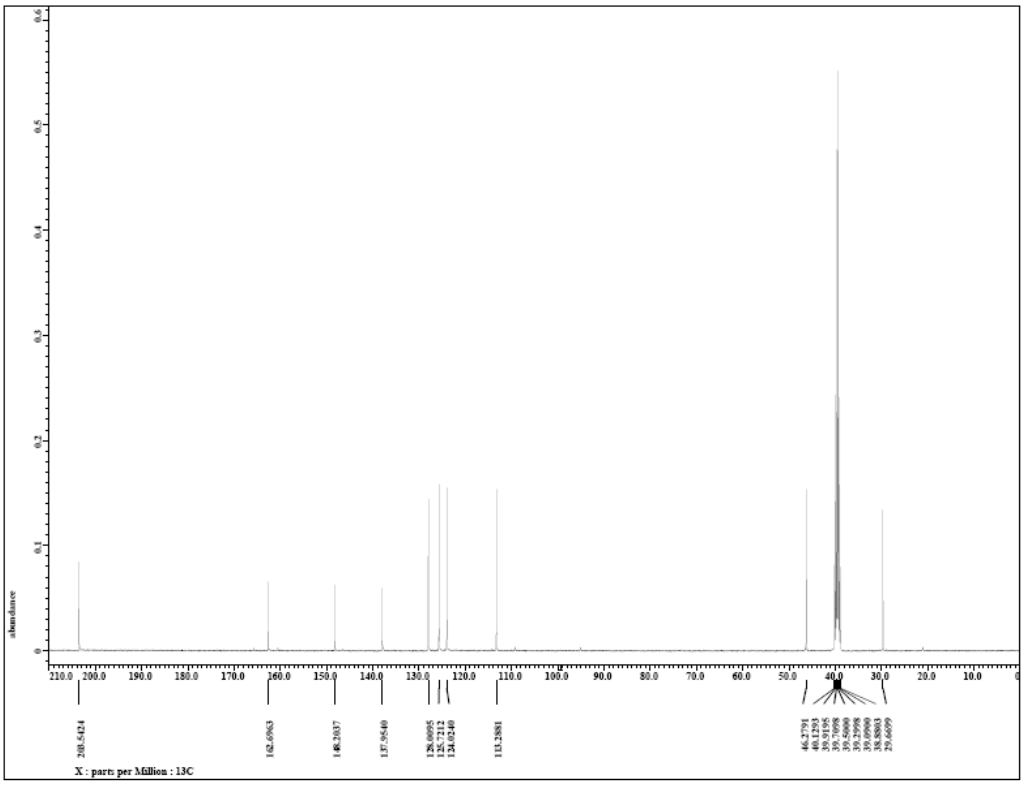

O
S
N
CH3
2f, Table 2, Entry 6
X : parts per Million : 1H

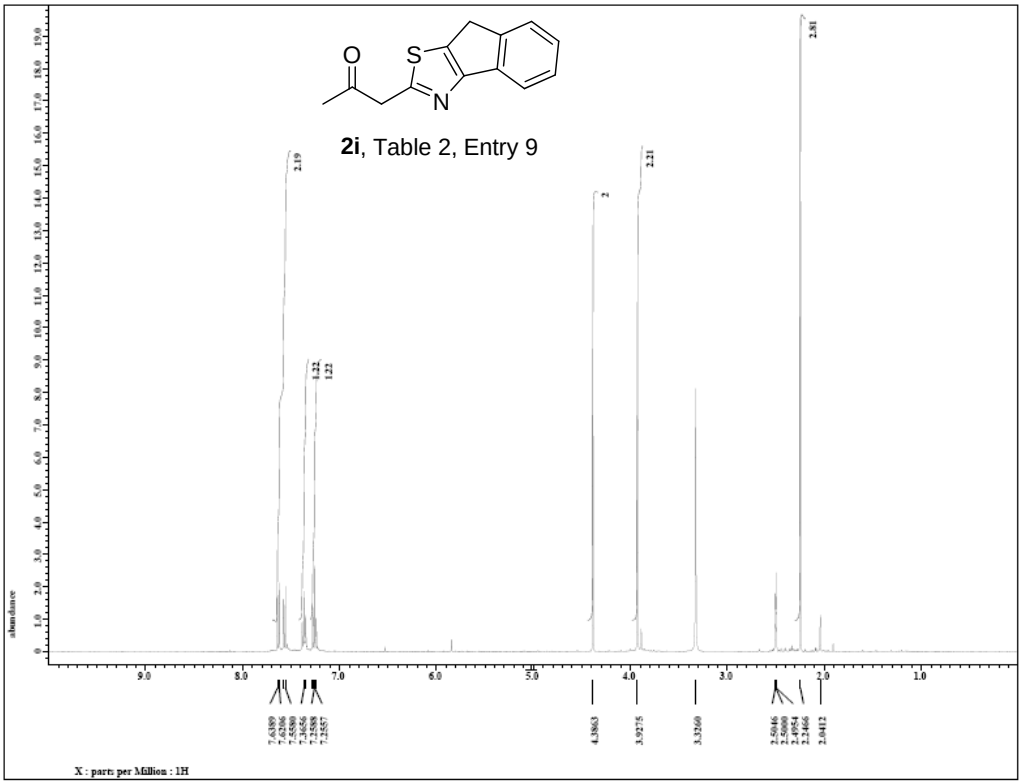

X : parts per Million : 13C

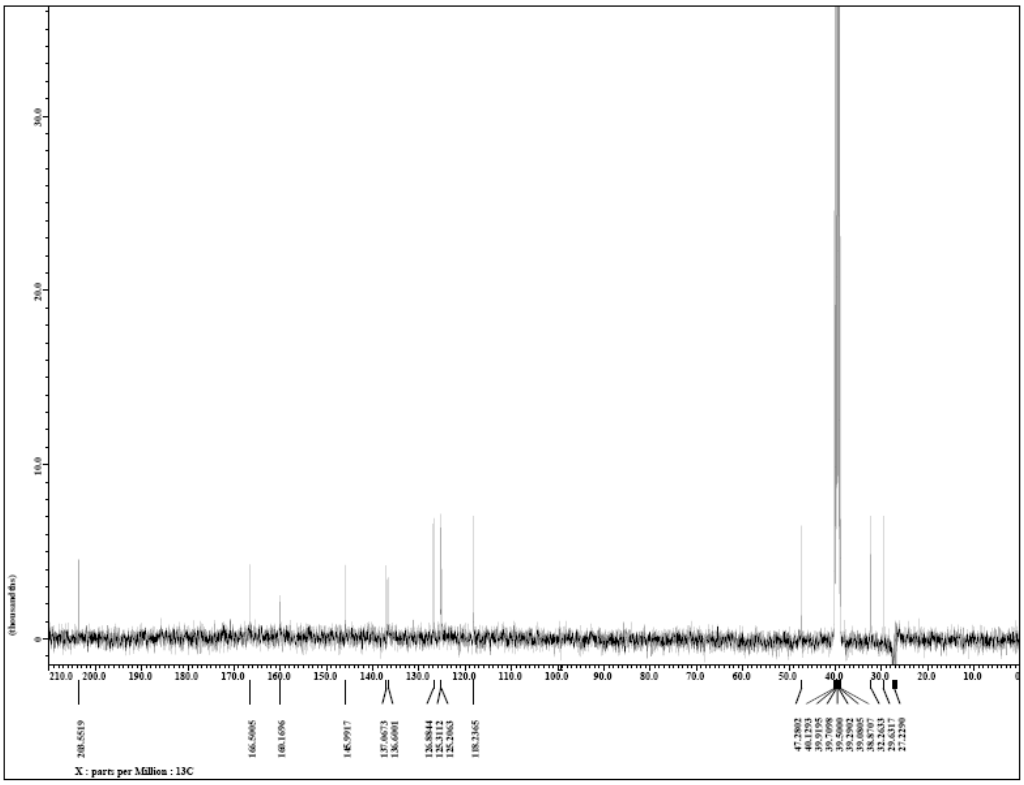

O
S
N
2g, Table 2, Entry 7
abundance
X : parts per Million : 1H

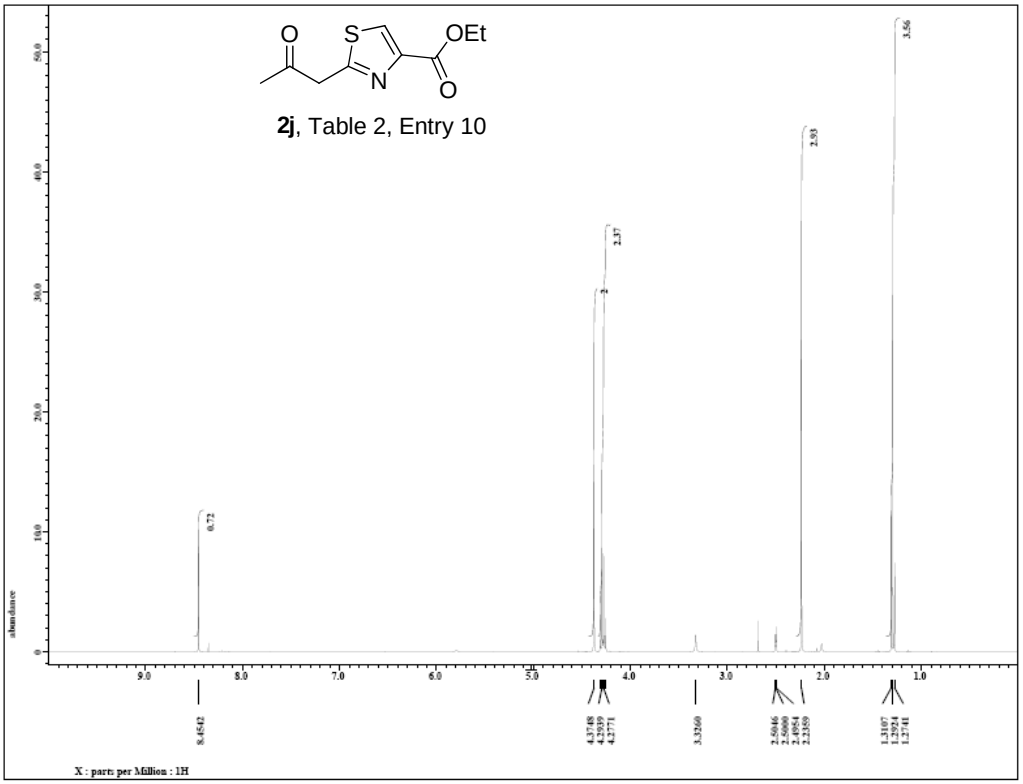

abundance
X : parts per Million : 13C

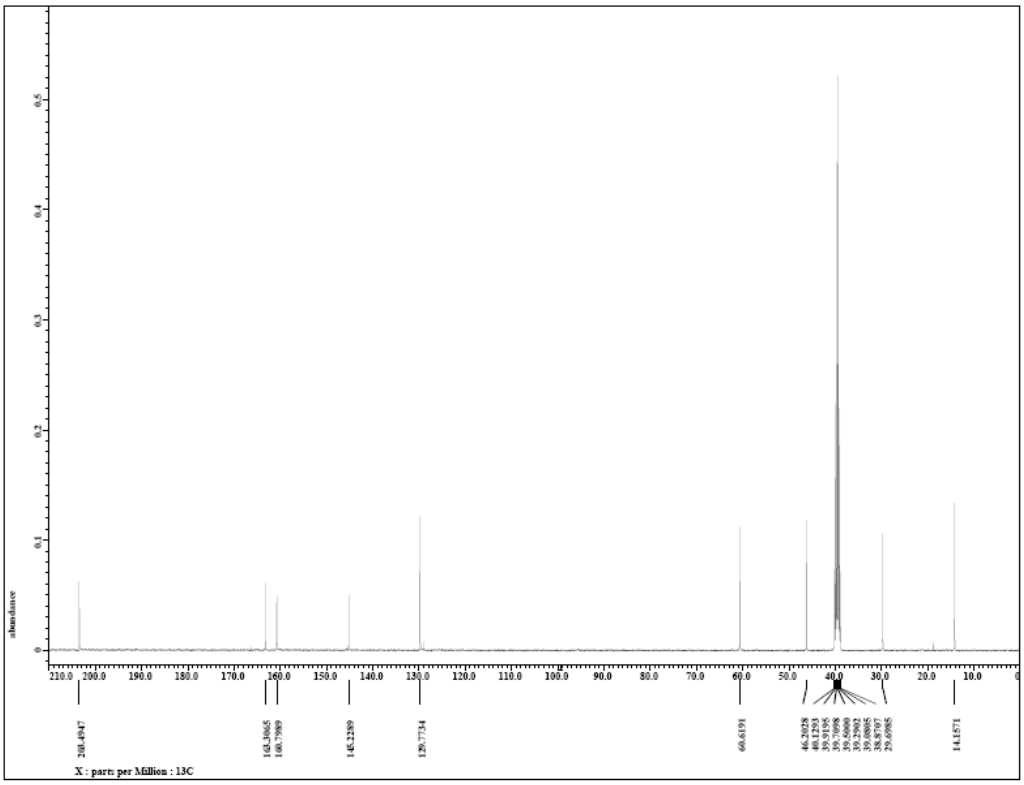

O
S
N
S
2h, Table 2, Entry 8
abundance
X : parts per Million : 1H

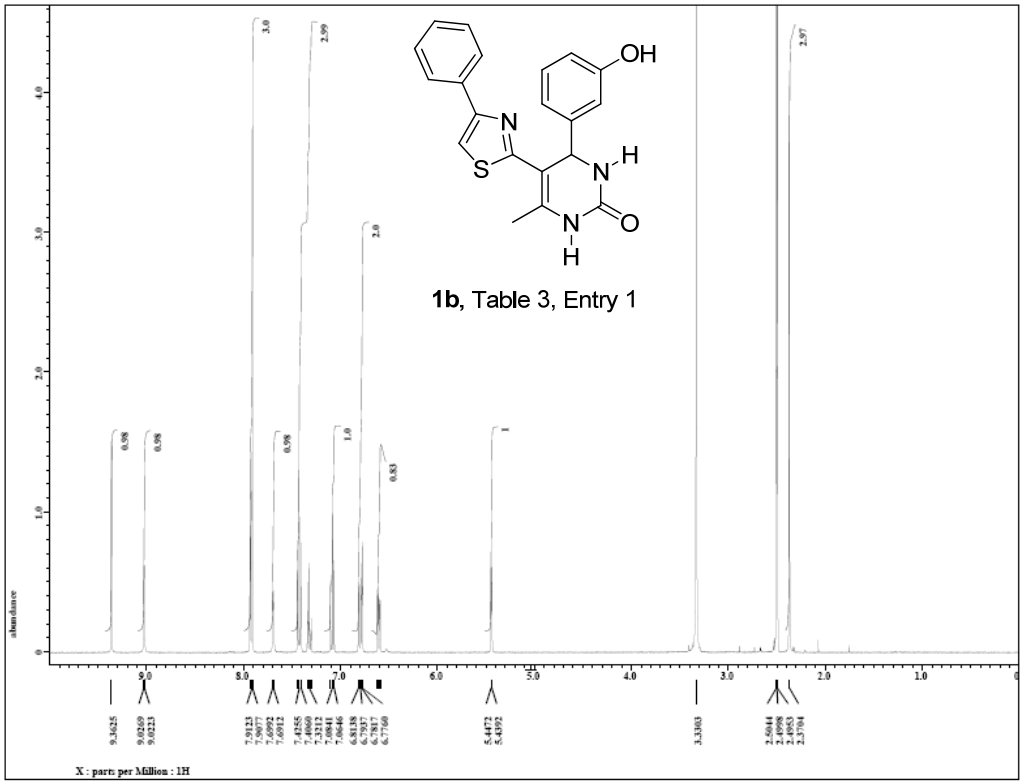

abundance
X : parts per Million : 13C

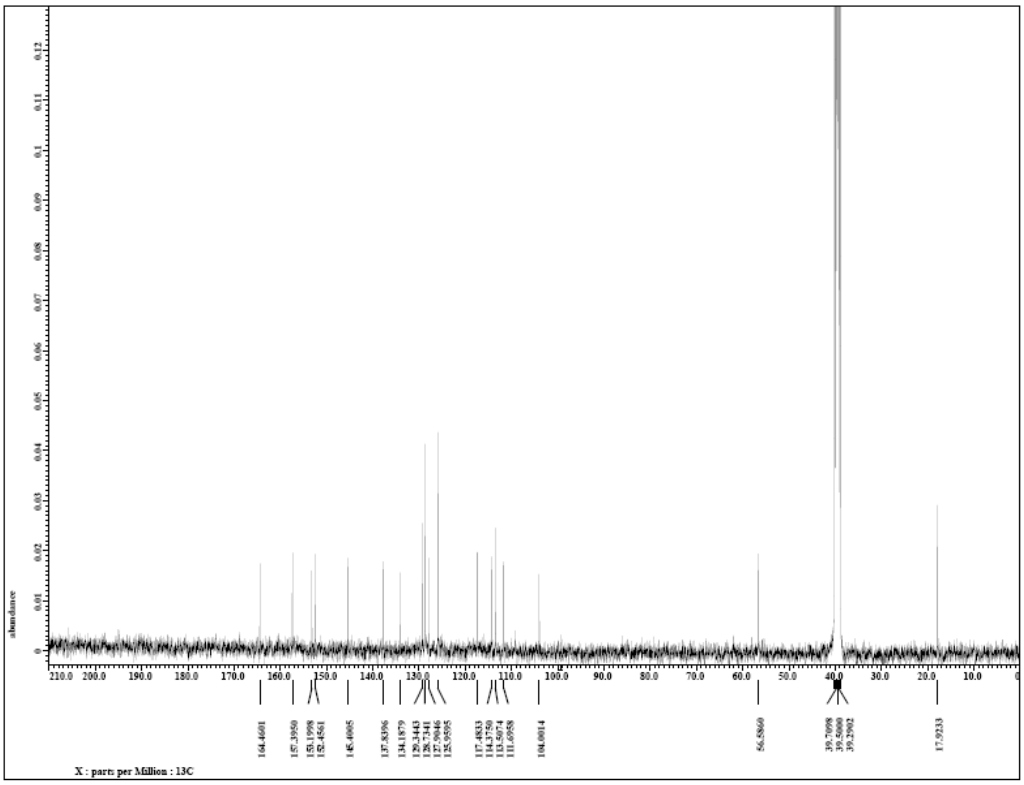

O
S
N
2i, Table 2, Entry 9
X : parts per Million : 1H

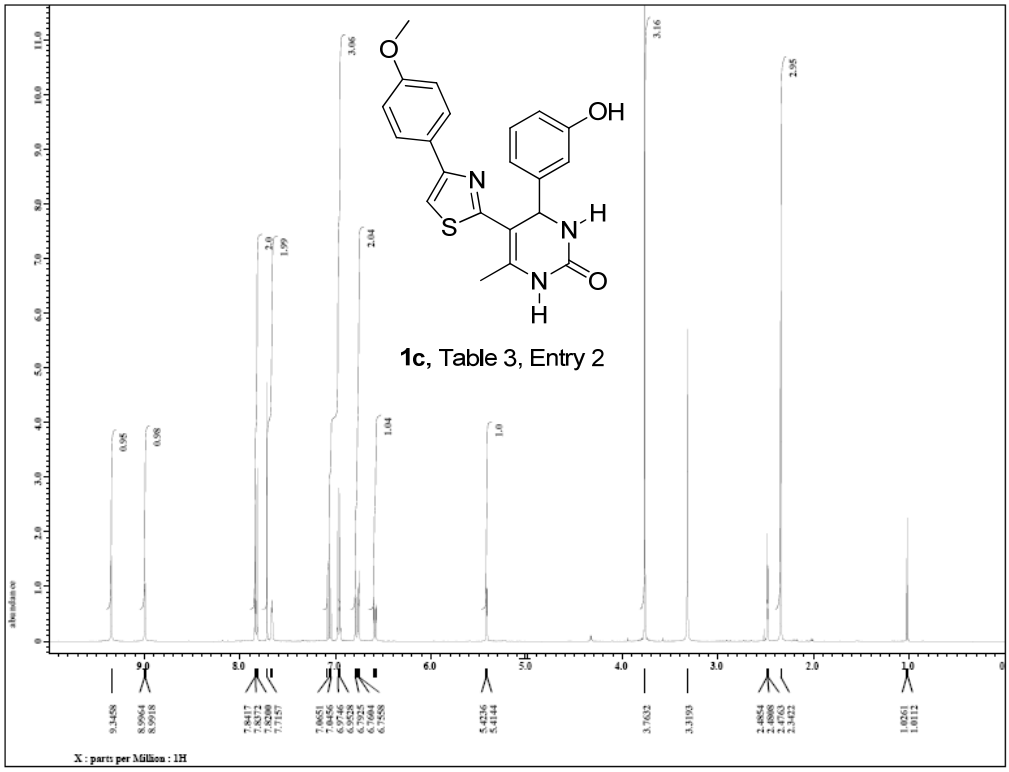

X : parts per Million : 13C

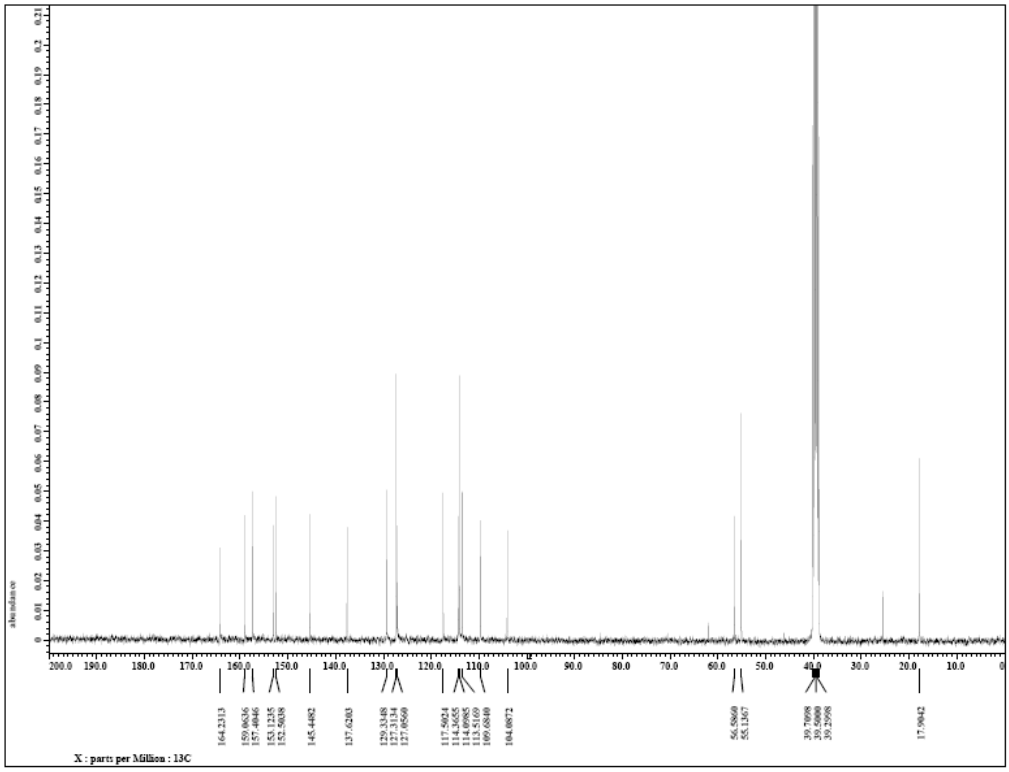

O
S
OEt
N
O
2j, Table 2, Entry 10
abundance
X : parts per Million : 1H

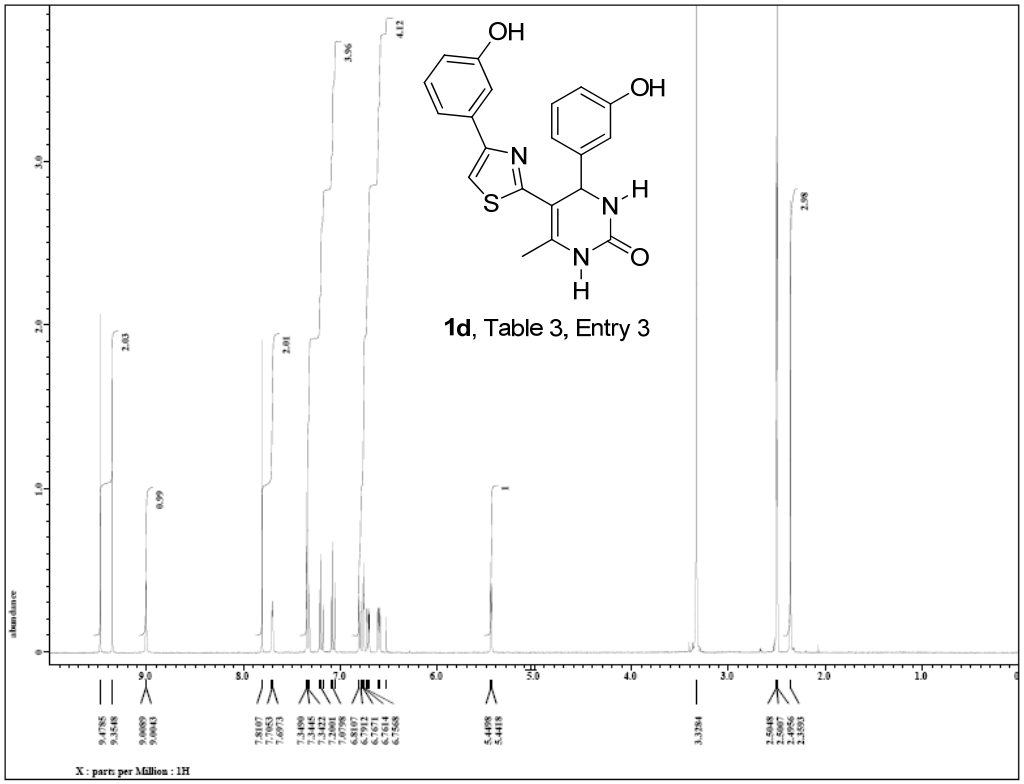

abundance
X : parts per Million : 13C

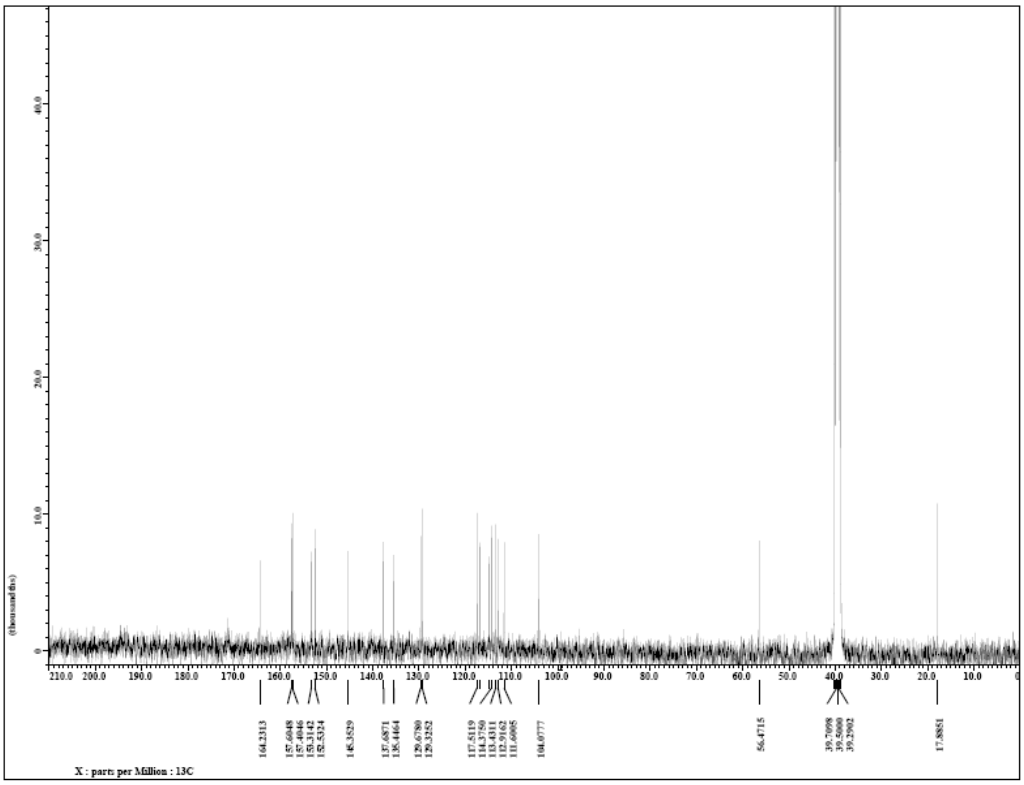

OH
N
S
N
H
N
O
H
1b, Table 3, Entry 1
X : parts per Million : 1H

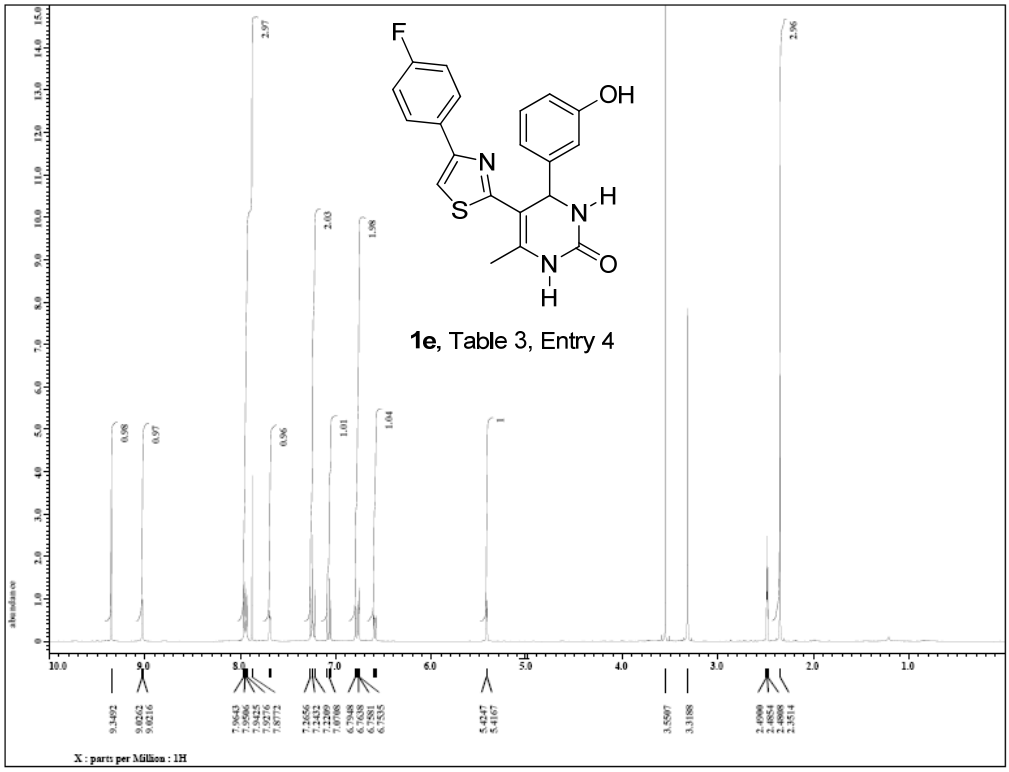

X : parts per Million : 13C

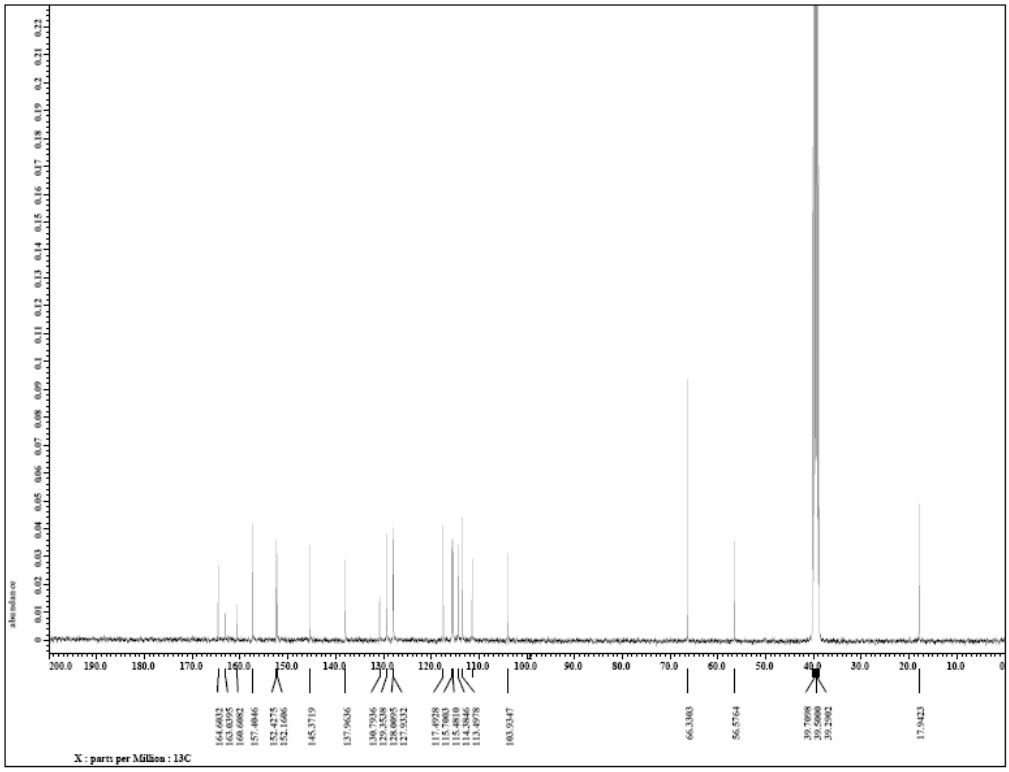

O
OH
N
S
N
H
N
O
H
1c, Table 3, Entry 2
X : parts per Million : 1H

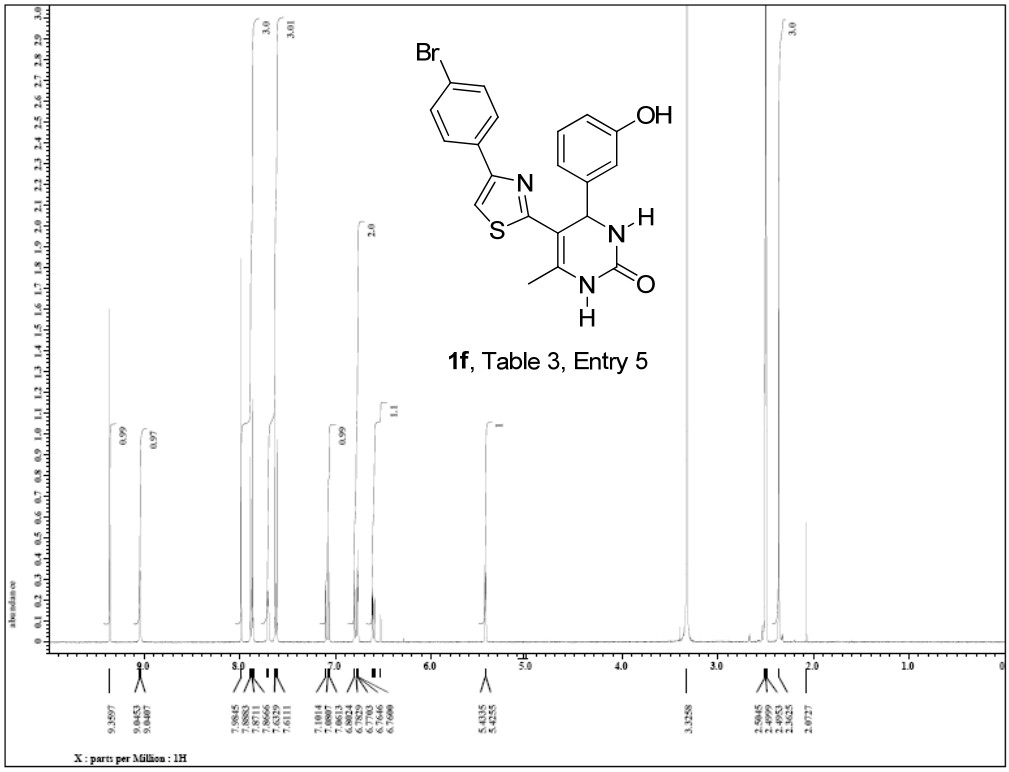

X : parts per Million : 13C

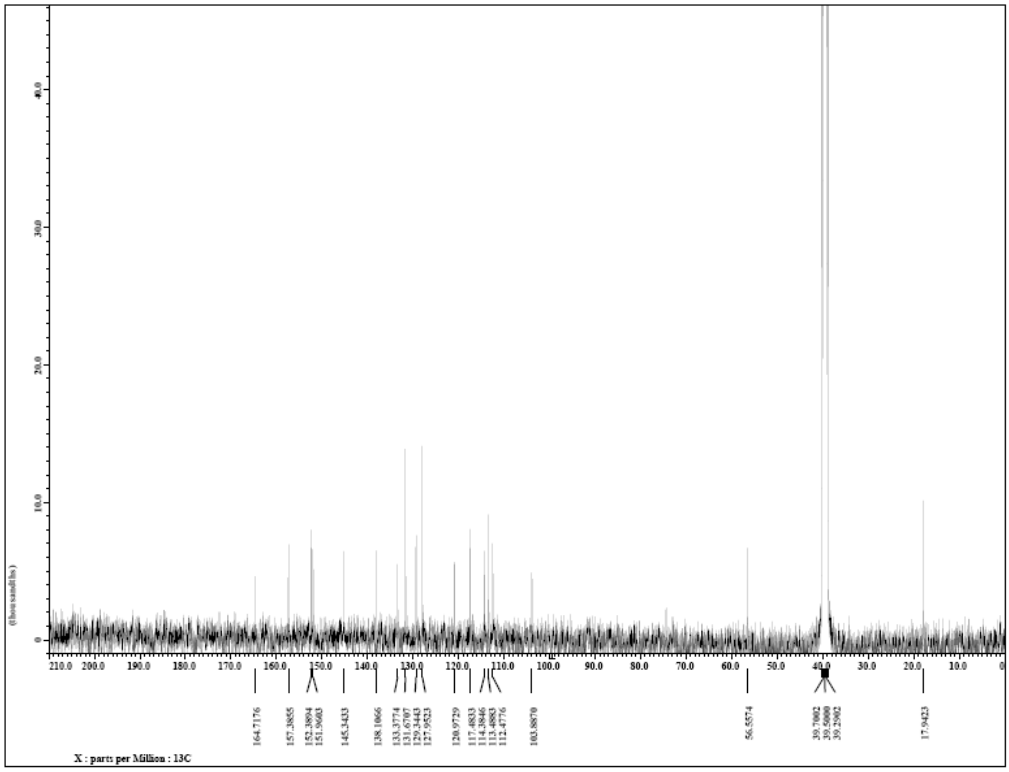

OH
OH
N
S
N
H
N
O
H
1d, Table 3, Entry 3
X : parts per Million : 1H

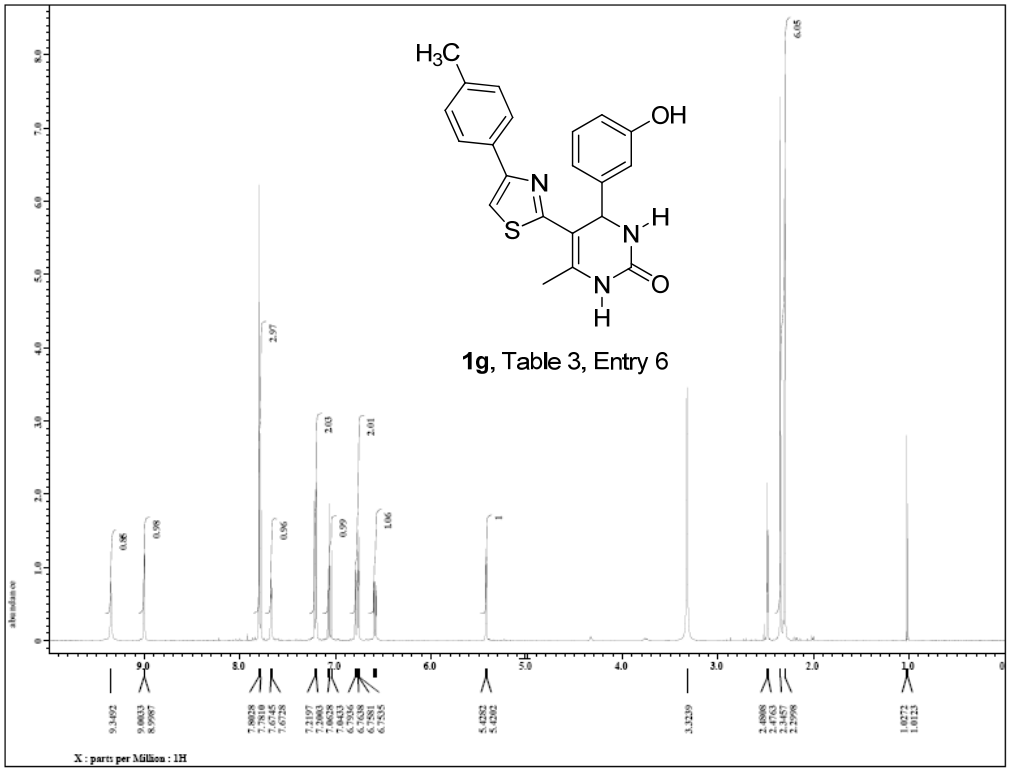

X : parts per Million : 13C

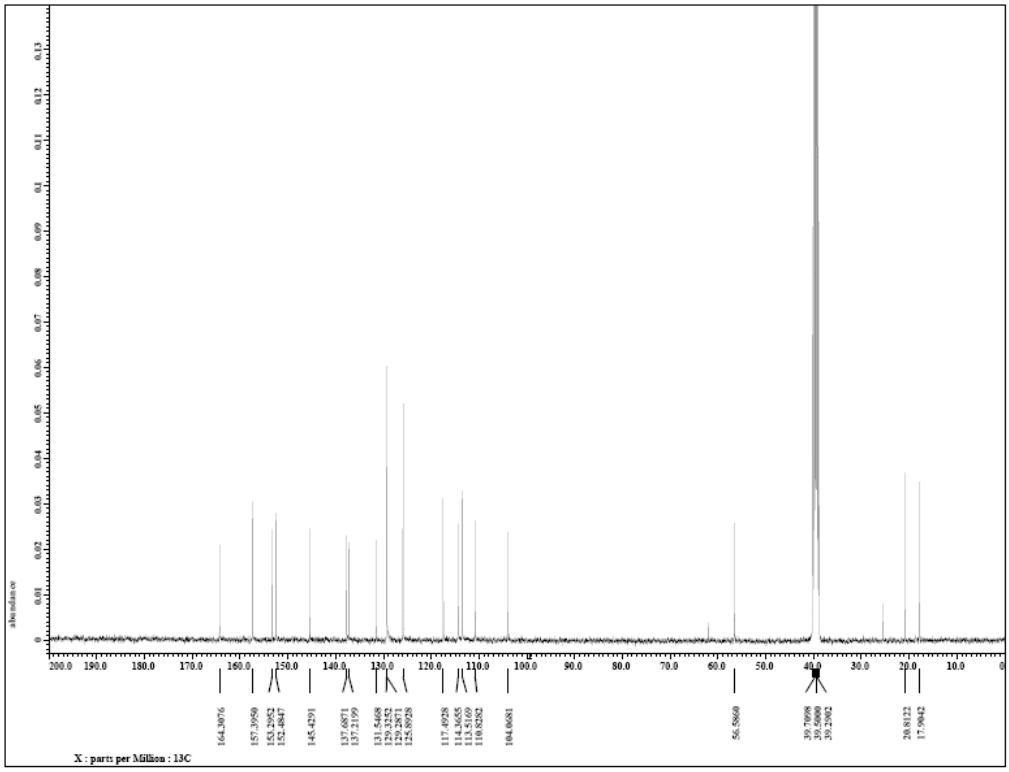

F
OH
N
S
N
H
N
O
H
1e, Table 3, Entry 4
X : parts per Million : 1H

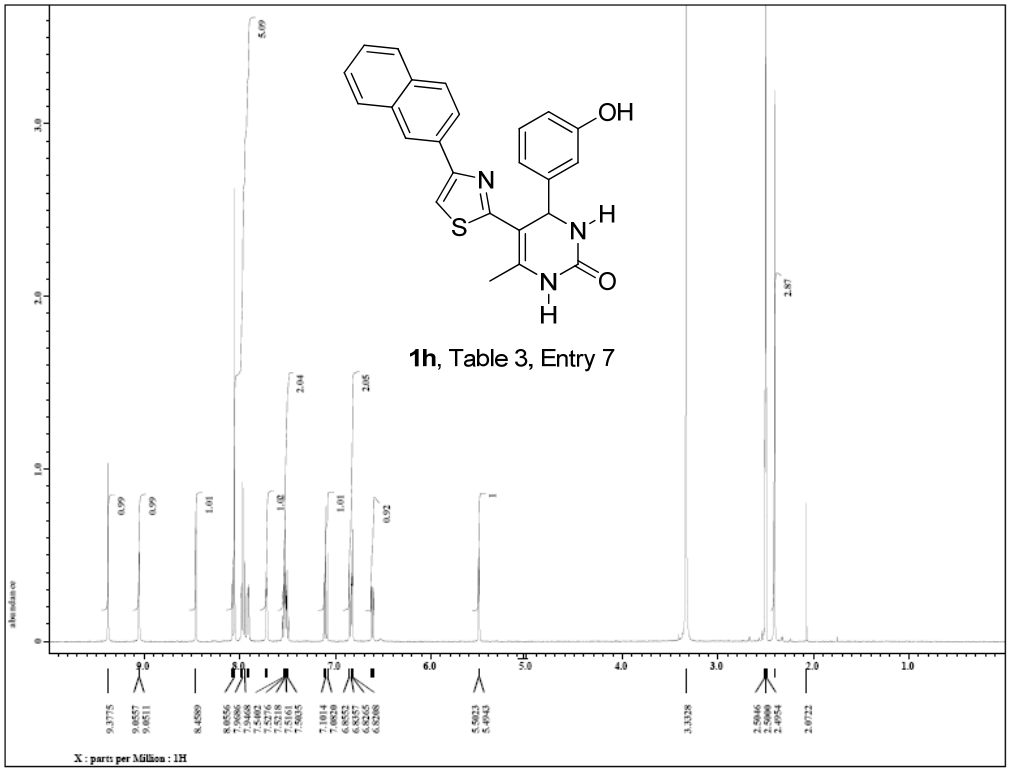

X : parts per Million : 13C


Br
OH
N
S
N
H
N
H
O
1f, Table 3, Entry 5
X : parts per Million : 1H

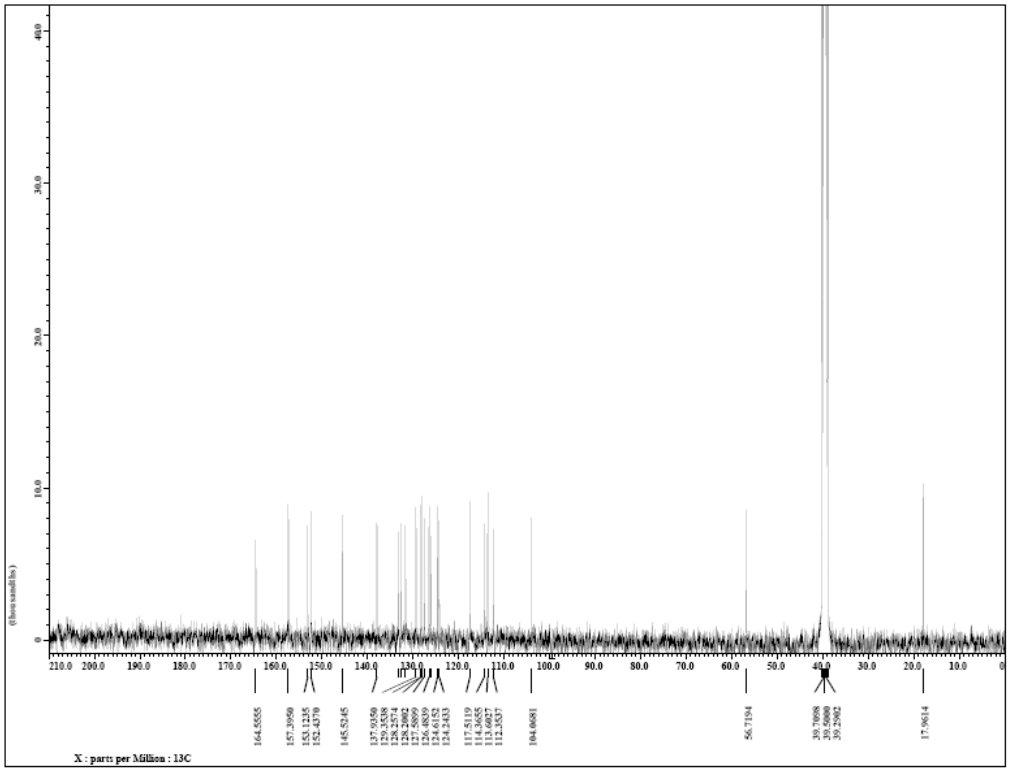

X : parts per Million : 13C

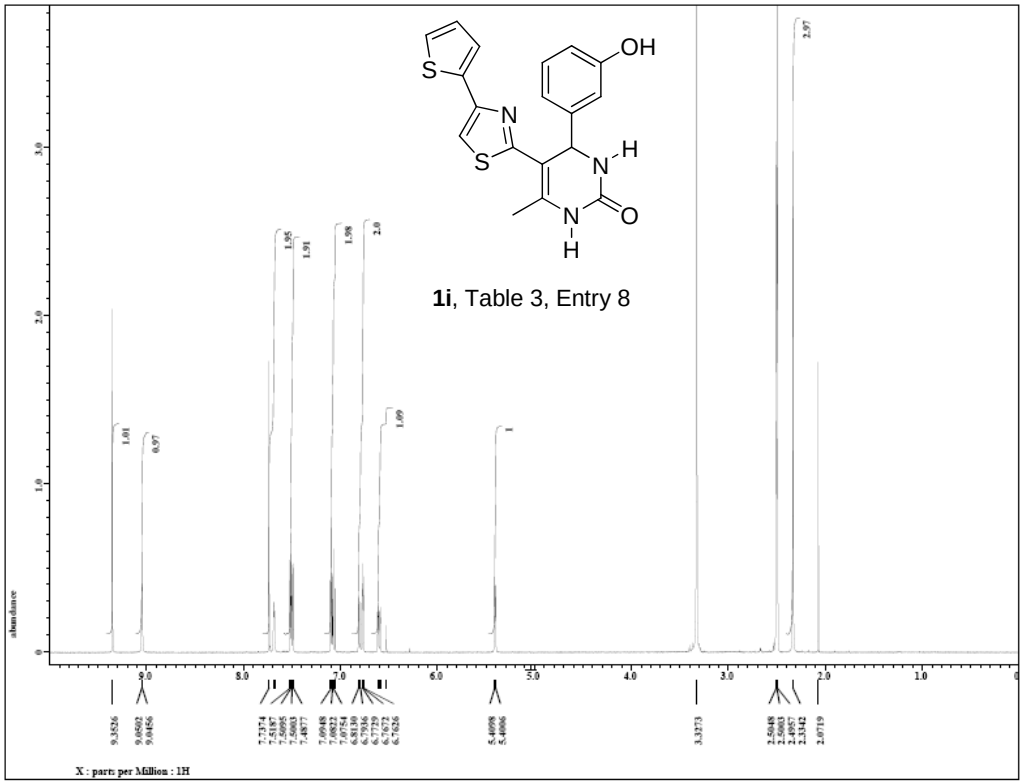

H3C
OH
N
S
N
H
N
H
O
1g, Table 3, Entry 6
X : parts per Million : 1H


X : parts per Million : 13C



1h, Table 3, Entry 7





1i, Table 3, Entry 8