

## A new uncatalyzed aldol reaction of thiazolidinediones

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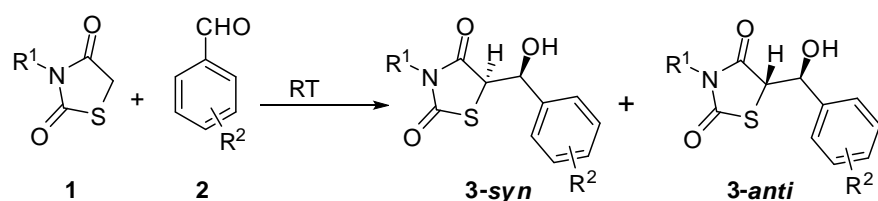
## 1.0 General Information:

All experiments were carried out under an inert atmosphere of argon in flame-dried microwave vials. Solvents were dried using standard procedures reported in Perrin, D. D.; Armarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988. All starting materials were obtained from commercial suppliers and used as received. Products were purified by flash chromatography on silica gel (100-200 mesh, Merck). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were recorded in CDCl<sub>3</sub>. <sup>1</sup>H NMR spectra were recorded at 500 MHz using Bruker ADVANCE 500 MHz and JEOL 400 MHz instruments at 278K. Signals are quoted as  $\delta$  values in ppm using residual protonated solvent signals as internal standard (CDCl<sub>3</sub>:  $\delta$  7.26 ppm). Data is reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). <sup>13</sup>C NMR spectra were recorded on either a JEOL-400 (100 MHz), or a Bruker ADVANCE 500 MHz (125 MHz) with complete proton decoupling. Chemical shifts ( $\delta$ ) are reported in ppm downfield from tetramethylsilane with the solvent as the internal reference (CDCl<sub>3</sub>:  $\delta$  77.23 ppm). Infrared (FTIR) spectra were recorded on a Perkin Elmer spectrophotometer with the KBr disk and KBr plate techniques for solid and liquid samples,  $\nu_{\max}$  cm<sup>-1</sup>. Single crystal X-ray analysis of **3aa-syn** and **12-syn** was recorded on a Bruker high resolution X-ray diffractometer instrument.

## 2.0 General procedure:

**Preparation of Tert-butyl-2,4-dioxothiazolidine-3-carboxylate 1c:** Boc anhydride (3.9 mL, 17.1 mmol, 2 equiv.) was added to a solution of 2,4-thiazolidinedione **1** (1 g, 8.53 mmol, 1 equiv.) and Et<sub>3</sub>N (3.0 mL, 21.3 mmol, 2.5 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.7 M) at 0 °C and stirred for 7 h while warming to ambient temperature. The reaction mixture was quenched with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography on silica gel with EtOAc–hexane (05/95) to provide compounds tert-butyl-2,4-dioxothiazolidine-3-carboxylate **1c** (899 mg, 52%) as a colorless liquid. <sup>1</sup>H NMR (500 MHz): 3.78 (2H, s), 1.59 (9H, s); <sup>13</sup>C NMR (125 MHz): 172.7, 172.3, 146.7, 85.1, 33.1, 28.3; FT-IR (neat): 3395, 2981, 2859, 2433, 2374, 1751, 1657, 1584, 1436, 1356, 1043, 942; (ESI) calcd for C<sub>8</sub>H<sub>12</sub>NO<sub>4</sub>S [M+H]<sup>+</sup>: 219.0560; found, 219.0591.

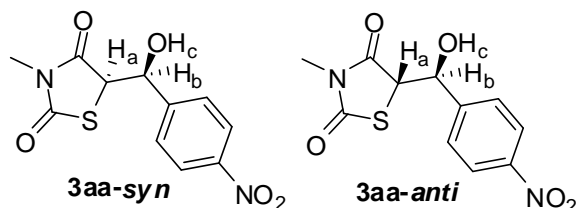
**General Procedure for Aldol reactions:** A mixture of a thiazolidinedione **1** (0.14 mmol, 1.1 equiv.) and aldehyde **2** (0.13 mmol, 1 equiv.) was stirred in the presence of water or DMSO (0.04 M). The suspension was stirred for the specified time (Tables 2 and 3, 10 min to 14 days) following TLC and crude NMR analysis. The reaction mixture was extracted with ethyl acetate (3 times). The combined organic phases were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum. The crude residue was then purified by column chromatography on 100-200 mesh silica gel using ethyl acetate–hexane (10/90 to 20/80) to provide compounds **3**.



**3.0 Aldol reaction with 4-nitrobenzaldehyde:** A mixture of *N*-methyl 2,4-thiazolidinedione **1a** (18.2 mg, 0.14 mmol, 1.1 equiv.) and 4-nitrobenzaldehyde **2a** (20 mg, 0.13 mmol, 1 equiv.) was stirred on water (0.04 M) at room temperature. The precipitated solid after 5 h was filtered and dried under vacuum to afford aldol product **3aa** as a white solid (37.2 mg, 99%). This material was > 99% pure by <sup>1</sup>H NMR analysis.

**5-(hydroxy(4-nitrophenyl)methyl)-3-methylthiazolidine-2,4-dione 3aa:** obtained as colorless crystals (ethyl acetate/hexanes), m.p. 143-146 °C; HRMS (ESI) calcd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>SK [M+K]<sup>+</sup>: 320.9947;

found, 320.9963; FT-IR (neat): 3436, 2919, 2851, 2364, 2344, 1667, 1515, 1364, 1347, 1273, 1078, 1016, 837, 773  $\text{cm}^{-1}$ .



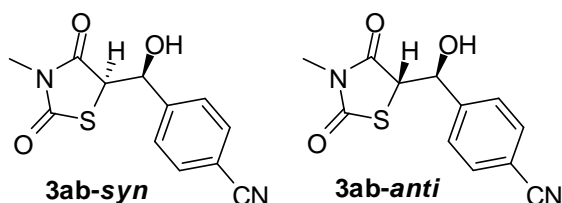
**Compound 3aa-syn:**  $^1\text{H}$  NMR (400 MHz): 8.27 (2H, d,  $J = 10.9$  Hz), 7.60 (2H, d,  $J = 10.1$  Hz), 5.73 (1H<sub>b</sub>, dd,  $J = 7.8, 3.2$  Hz), 4.55 (1H<sub>a</sub>, d,  $J = 3.5$  Hz), 3.15 (3H, s), OH could not be detected;  $^{13}\text{C}$  NMR (125 MHz): 172.4, 170.5, 148.1, 146.7, 126.7, 124.1, 71.0, 57.4, 28.1.

**Compound 3aa-anti:**  $^1\text{H}$  NMR (400 MHz): 8.24 (2H, d,  $J = 10.9$  Hz), 7.61 (2H, d,  $J = 10.1$  Hz), 5.30 (1H<sub>b</sub>, d,  $J = 9.4$  Hz), 4.55 (1H<sub>a</sub>, d,  $J = 9.7$  Hz), 4.04 (1H<sub>c</sub>, br), 3.07 (3H, s);  $^{13}\text{C}$  NMR (100 MHz): 173.4, 169.8, 148.4, 145.1, 128.0, 123.7, 73.9, 55.0, 28.0.

#### 4.0 Characterization data of aldol products:



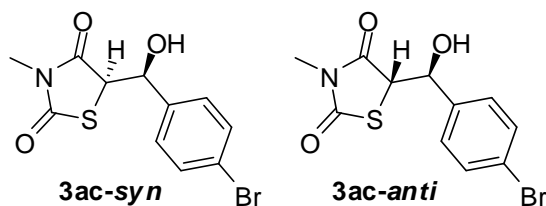
**4-(hydroxy(3-methyl-2,4-dioxothiazolidin-5-yl)methyl)benzotrile, 3ab:** Yield 31.0 mg, 91%; obtained as colorless solid; m.p. 120-125 °C; HRMS (ESI) calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3\text{SK}$   $[\text{M}+\text{K}]^+$ : 301.0049; found, 301.0077; FT-IR (neat): 3410, 2921, 2851, 2361, 2340, 2228, 1674, 1424, 1368, 1279, 1073, 1049, 1015, 862, 831  $\text{cm}^{-1}$ .



**Compound 3ab-syn:**  $^1\text{H}$  NMR (400 MHz): 7.70 (2H, d,  $J = 10.4$  Hz), 7.53 (2H, d,  $J = 10.1$  Hz), 5.66 (1H<sub>b</sub>, s<sub>br</sub>), 4.53 (1H<sub>a</sub>, d,  $J = 3.5$  Hz), 3.14 (3H, s), 2.80 (1H<sub>c</sub>, s<sub>br</sub>);  $^{13}\text{C}$  NMR (100 MHz): 172.5, 170.6, 144.9, 132.7, 126.5, 118.2, 112.7, 71.1, 57.4, 28.1.

**Compound 3ab-anti:**  $^1\text{H}$  NMR (400 MHz): 7.68 (2H, d,  $J = 10.4$  Hz), 7.55 (2H, d,  $J = 10.2$  Hz), 5.23 (1H<sub>b</sub>, d,  $J = 9.5$  Hz), 4.52 (1H<sub>a</sub>, d,  $J = 9.4$  Hz), 3.07 (3H, s), OH could not be detected;  $^{13}\text{C}$  NMR (100 MHz): 173.5, 169.9, 143.3, 132.3, 127.8, 118.2, 113.1, 74.1, 55.0, 28.0.

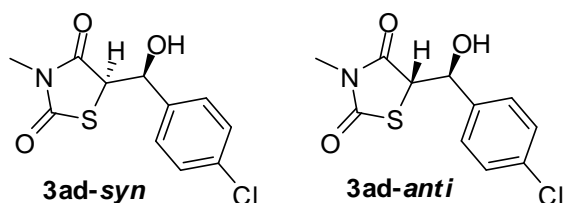
**5-((4-bromophenyl)(hydroxy)methyl)-3-methylthiazolidine-2,4-dione, 3ac:** Yield 33.3 mg, 81%; obtained as colorless liquid; HRMS (ESI) calcd for C<sub>11</sub>H<sub>10</sub>NO<sub>3</sub>SBrK [M+K]<sup>+</sup>: 353.9202; found, 353.9230; FT-IR (neat): 3400, 2925, 2851, 2364, 2340, 1672, 1366, 1275, 1216, 1072, 1008, 858, 821, 769.



**Compound 3ac-syn:**  $^1\text{H}$  NMR (400 MHz): 7.53 (2H, d,  $J = 10.6$  Hz), 7.27 (2H, d,  $J = 10.7$  Hz), 5.58 (1H<sub>b</sub>, d,  $J = 3.2$  Hz), 4.50 (1H<sub>a</sub>, d,  $J = 3.1$  Hz), 3.13 (3H, s), OH could not be detected;  $^{13}\text{C}$  NMR (100 MHz): 172.7, 171.0, 138.8, 132.0, 127.2, 122.8, 71.2, 57.8, 28.0.

**Compound 3ac-anti:**  $^1\text{H}$  NMR (400 MHz): 7.50 (2H, d,  $J = 10.5$  Hz), 7.29 (2H, d,  $J = 10.5$  Hz), 5.13 (1H<sub>b</sub>, d,  $J = 9.8$  Hz), 4.51 (1H<sub>a</sub>, d,  $J = 9.8$  Hz), 3.90 (1H<sub>c</sub>, s<sub>br</sub>), 3.06 (3H, s);  $^{13}\text{C}$  NMR (100 MHz): 173.9, 170.4, 137.3, 131.8, 128.6, 123.3, 74.2, 55.2, 27.9.

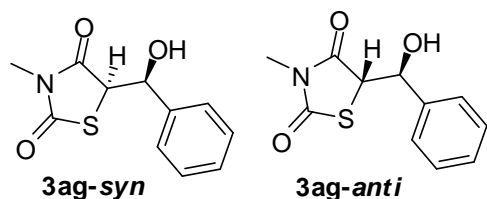
**5-((4-chlorophenyl)(hydroxy)methyl)-3-methylthiazolidine-2,4-dione, 3ad:** Yield 25.8 mg, 73%; obtained as colorless liquid; HRMS (ESI) calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>3</sub>SCl [M+H]<sup>+</sup>: 272.0148; found, 272.0119; FT-IR (neat): 3420, 2925, 2847, 2361, 2343, 1653, 1542, 1269, 1155, 1095, 1051, 769, 718, 668.



**Compound 3ad-syn:**  $^1\text{H}$  NMR (400 MHz): 7.39-7.32 (4H, m), 5.59 (1H<sub>b</sub>, s), 4.50 (1H<sub>a</sub>, d,  $J = 3.5$  Hz), 3.13 (3H, s), 2.54 (1H<sub>c</sub>, s);  $^{13}\text{C}$  NMR (100 MHz): 172.7, 170.9, 138.3, 134.7, 129.1, 126.9, 71.2, 57.8, 28.0.

**Compound 3ad-anti:**  $^1\text{H}$  NMR (400 MHz): 7.35 (4H, s), 5.14 (1H<sub>b</sub>, d,  $J = 9.9$  Hz), 4.52 (1H<sub>a</sub>, d,  $J = 9.9$  Hz), 3.86 (1H<sub>c</sub>, s), 3.06 (3H, s);  $^{13}\text{C}$  NMR (100 MHz): 173.9, 170.4, 136.8, 135.1, 128.8, 128.4, 74.2, 55.3, 27.8.

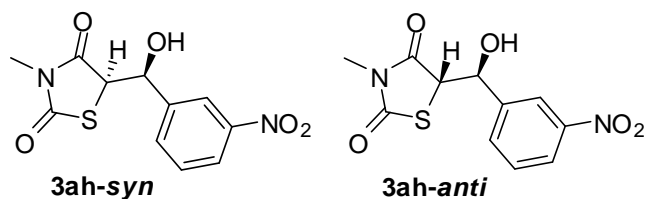
**5-(hydroxy(phenyl)methyl)-3-methylthiazolidine-2,4-dione, 3ag:** Yield 29.9 mg, 97%; obtained as colorless liquid; HRMS (ESI) calcd for C<sub>11</sub>H<sub>12</sub>NO<sub>3</sub>S [M+H]<sup>+</sup>: 238.0521; found, 238.0503; FT-IR (neat): 3468, 2924, 2853, 2364, 2344, 1743, 1670, 1429, 1370, 1279, 1088, 1062, 1013, 909, 735, 702, 651 cm<sup>-1</sup>.



**Compound 3ag-syn:**  $^1\text{H}$  NMR (400 MHz): 7.40-7.36 (5H, m), 5.62 (1H<sub>b</sub>, s), 4.54 (1H<sub>a</sub>, d,  $J = 3.2$  Hz), 3.13 (3H, s), 2.52 (1H<sub>c</sub>, s);  $^{13}\text{C}$  NMR (100 MHz): 173.0, 171.2, 139.8, 128.9, 128.8, 125.4, 71.8, 58.1, 27.9.

**Compound 3ag-anti:**  $^1\text{H}$  NMR (400 MHz): 7.40-7.35 (5H, m), 5.14 (1H<sub>b</sub>, d,  $J = 9.9$  Hz), 4.55 (1H<sub>a</sub>, d,  $J = 9.9$  Hz), 3.86 (1H<sub>c</sub>, s), 3.05 (3H, s);  $^{13}\text{C}$  NMR (100 MHz): 174.2, 170.6, 138.3, 129.3, 128.6, 127.0, 75.0, 55.4, 27.8.

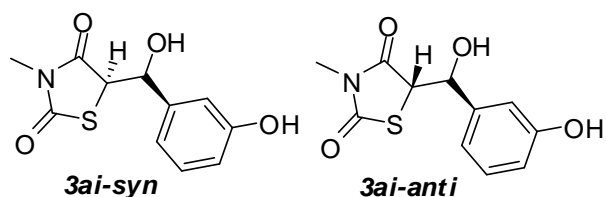
**5-(hydroxy(3-nitrophenyl)methyl)-3-methylthiazolidine-2,4-dione, 3ah:** Yield 34.9 mg, 95%; obtained as colorless liquid; HRMS (ESI) calcd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>SK [M+K]<sup>+</sup>: 320.9942; found, 320.9921; FT-IR (neat): 3400, 2925, 2859, 2363, 2340, 1668, 1525, 1359, 1270, 1158, 1052, 930, 904, 775, 684.



**Compound 3ah-syn:**  $^1\text{H}$  NMR (400 MHz): 8.29 (1H, t,  $J = 2.2$  Hz), 8.24-8.22 (1H, m), 7.77-7.75 (1H, m), 7.61 (1H, t,  $J = 9.9$  Hz), 5.72 (1H<sub>b</sub>, dd,  $J = 8.1, 3.5$  Hz), 4.58 (1H<sub>a</sub>, d,  $J = 3.7$  Hz), 3.15 (3H, s), OH could not be detected;  $^{13}\text{C}$  NMR (100 MHz): 172.4, 170.5, 148.5, 141.9, 131.6, 130.0, 123.7, 120.8, 70.8, 57.4, 28.1.

**Compound 3ah-anti:**  $^1\text{H}$  NMR (400 MHz): 8.33 (1H, t,  $J = 2.5$  Hz), 8.25-8.22 (1H, m), 7.75 (1H, d,  $J = 9.8$  Hz), 7.58 (1H, t,  $J = 9.9$  Hz), 5.28 (1H<sub>b</sub>, d,  $J = 9.9$  Hz), 4.55 (1H<sub>a</sub>, d,  $J = 9.8$  Hz), 4.07 (1H<sub>c</sub>, s), 3.09 (3H, s);  $^{13}\text{C}$  NMR (100 MHz): 173.6, 169.8, 148.3, 140.5, 133.0, 129.6, 124.1, 122.1, 74.0, 55.0, 28.0.

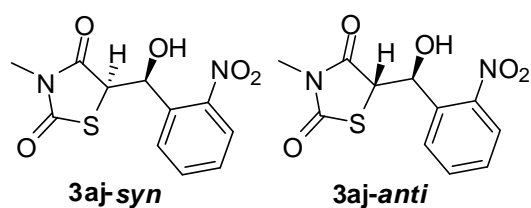
**5-Hydroxy(3-hydroxyphenyl)methyl-3-methylthiazolidine-2,4-dione, 3ai:** Yield 24.0 mg, 73%; obtained as colorless liquid; HRMS (ESI) calcd for  $C_{11}H_{12}NO_4S$   $[M+H]^+$ : 254.0482; found, 254.0457; FT-IR (neat): 3441, 2933, 2862, 2314, 2324, 1664, 1525, 1371, 1332, 1285, 1085, 1063, 825  $cm^{-1}$ .



**Compound 3ai-syn:**  $^1H$  NMR (from 67:33 *syn/anti* mixture, 400 MHz): 7.24-7.19 (1H, merged with *anti* isomer), 6.92-6.88 (2H, merged with *anti* isomer), 6.83-6.89 (1H, merged with *anti* isomer), 5.56 (1H<sub>b</sub>, d,  $J = 3.1$  Hz), 4.51 (1H<sub>a</sub>, d,  $J = 3.2$  Hz), 3.11 (3H, s), OH could not be detected;  $^{13}C$  NMR (from 83:17 *syn/anti* mixture, 100 MHz): 173.2, 171.7, 156.2, 141.7, 130.3, 117.5, 115.8, 112.5, 71.4, 58.1, 28.0.

**Compound 3ai-anti:**  $^1H$  NMR (from 67:33 *syn/anti* mixture, 400 MHz): 7.24-7.19 (1H, merged with *syn* isomer), 6.92-6.88 (2H, merged with *syn* isomer), 6.83-6.89 (1H, merged with *syn* isomer), 5.10 (1H<sub>b</sub>, t,  $J = 9.8$  Hz), 4.53 (1H<sub>a</sub>, d,  $J = 9.5$  Hz), 3.07 (3H, s), OH could not be detected;  $^{13}C$  NMR (from 83:17 *syn/anti* mixture, 100 MHz): 174.1, 170.9, 155.9, 139.9, 129.9, 119.3, 116.4, 113.8, 74.5, 64.7, 27.8.

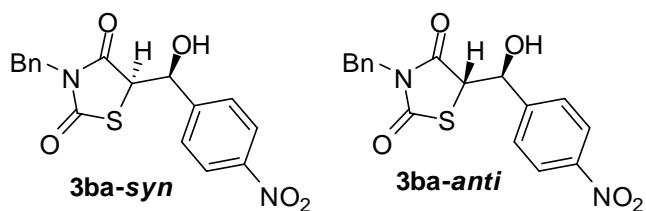
**5-(hydroxy(2-nitrophenyl)methyl)-3-methylthiazolidine-2,4-dione 3aj** (from 75:25 *syn/anti* mixture): Yield 22.0 mg, 60%; obtained as colorless solid; m.p. 84-88 °C; HRMS (ESI) calcd for  $C_{11}H_{11}N_2O_5S$   $[M+H]^+$ : 283.0328; found, 283.0357; FT-IR (neat): 3462, 2926, 2840, 2312, 2284, 1656, 1535, 1382, 1323, 1291, 1011, 1096, 935  $cm^{-1}$ .



**Compound 3aj-syn:**  $^1H$  NMR (500 MHz): 8.07-8.04 (1H, m, merged with *anti* isomer), 7.60 (1H, dd,  $J = 7.9, 1.2$  Hz), 7.74 (1H, dt,  $J = 7.7, 1.2$  Hz), 7.55-7.51 (1H, m, merged with *anti* isomer), 6.17 (1H<sub>b</sub>, d,  $J = 2.9$  Hz), 4.91 (1H<sub>a</sub>, d,  $J = 2.9$  Hz), 3.11 (3H<sub>c</sub>, s), OH could not be detected;  $^{13}C$  NMR (125 MHz): 172.7, 171.3, 146.9, 135.9, 134.1, 129.5, 129.1, 124.9, 67.5, 56.2, 28.0.

**Compound 3aj-anti:**  $^1H$  NMR (500 MHz): 8.07-8.04 (1H, merged with *syn* isomer), 7.89 (1H, m), 7.74 (1H, dd,  $J = 7.7, 1.2$  Hz), 7.55-7.51 (1H, merged with *syn* isomer), 5.74 (1H<sub>b</sub>, d,  $J = 4.1$  Hz), 4.69 (1H<sub>a</sub>, d,  $J = 4.1$  Hz), 3.08 (3H, s), OH could not be detected;  $^{13}C$  NMR (125 MHz): 172.4, 170.8, 147.2, 134.7, 133.6, 129.6, 129.1 (merged with *syn* isomer), 124.8, 70.4, 54.6, 27.9.

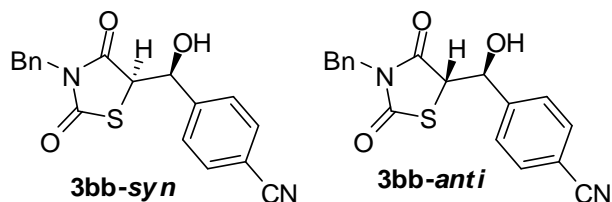
**3-benzyl-5-(hydroxy(4-nitrophenyl)methyl)thiazolidine-2,4-dione, 3ba:** Yield 39.6 mg, 85%; obtained as colorless liquid; HRMS (ESI) calcd for  $C_{17}H_{14}N_2O_5SNa$   $[M+Na]^+$ : 381.0521; found, 381.0549; FT-IR (neat): 3432, 2925, 2855, 1676, 1521, 1384, 1348, 1158, 1078, 856, 701  $cm^{-1}$ .



**Compound 3ba-syn:**  $^1H$  NMR (400 MHz): 8.21-8.19 (2H, m), 7.56-7.53 (2H, m), 7.34-7.30 (5H, m), 5.65 (1H<sub>b</sub>, d,  $J = 2.8$  Hz), 4.77 (2H, s), 4.55 (1H<sub>a</sub>, d,  $J = 3.7$  Hz), 2.96 (1H<sub>c</sub>, s<sub>br</sub>);  $^{13}C$  NMR (100 MHz): 172.3, 170.3, 148.0, 146.4, 134.7, 128.7, 128.5, 128.3, 126.7, 124.0, 71.2, 56.9, 45.5.

**Compound 3ba-anti:**  $^1H$  NMR (400 MHz): 7.95-7.93 (2H, m), 7.40-7.38 (2H, m), 7.23-7.16 (3H, m), 7.13-7.11 (2H, m), 5.33 (1H<sub>b</sub>, d,  $J = 8.1$  Hz), 4.62-4.52 (3H, benzyl proton and the C-H<sub>a</sub> proton merged together), 3.49 (1H<sub>c</sub>, s<sub>br</sub>);  $^{13}C$  NMR (100 MHz): 172.4, 170.0, 148.1, 144.2, 134.4, 128.8, 128.6, 128.5, 128.0, 123.4, 73.3, 55.4, 45.2.

**4-((3-benzyl-2,4-dioxothiazolidin-5-yl)(hydroxy)methyl)benzotrile, 3bb:** Yield 40.0 mg, 91%; obtained as a colorless liquid; HRMS (ESI) calcd for  $C_{18}H_{14}N_2O_3SNa$   $[M+Na]^+$ : 361.0623; found, 361.0602; FT-IR (neat): 3402, 2925, 2855, 2364, 2348, 2228, 1648, 1594, 1384, 1148, 1119, 1045, 857, 775  $cm^{-1}$ .



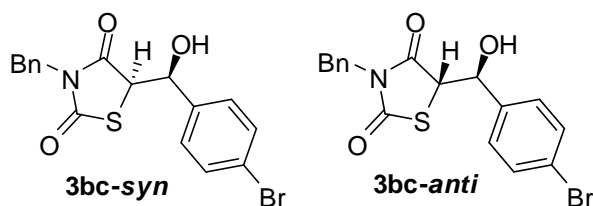
**Compound 3bb-syn:**  $^1H$  NMR (400 MHz): 7.66-7.63 (2H, m), 7.50-7.48 (2H, m), 7.35-7.31 (5H, m), 5.61 (1H<sub>b</sub>, s), 4.77 (2H, s), 4.53 (1H<sub>a</sub>, d,  $J = 3.3$  Hz), OH could not be detected;  $^{13}C$  NMR (100 MHz): 172.3, 170.3, 144.5, 134.7, 132.6, 128.7, 128.5, 128.3, 126.5, 118.1, 112.6, 71.3, 57.0, 45.4.

**Compound 3bb-anti:**  $^1H$  NMR (400 MHz): 7.47-7.44 (2H, m), 7.41-7.39 (2H, m), 7.34-7.28 (3H, m), 7.20-7.18 (2H, m), 5.33 (1H<sub>b</sub>, d,  $J = 8.2$  Hz), 4.65-4.62 (3H, benzyl proton and the C-H<sub>a</sub> proton merged together), 3.59 (1H<sub>c</sub>, s<sub>br</sub>);  $^{13}C$  NMR (100 MHz): 172.5, 170.1, 142.5, 134.5, 132.1, 128.8, 128.7, 128.5, 127.8, 118.2, 112.8, 73.5, 55.3, 45.2.

**3-benzyl-5-((4-bromophenyl)(hydroxy)methyl)thiazolidine-2,4-dione, 3bc:** Yield 34.7 mg, 68%; obtained as a colorless liquid; HRMS (ESI) calcd for  $C_{17}H_{14}NO_3SBrNa$   $[M+Na]^+$ : 413.9776; found,



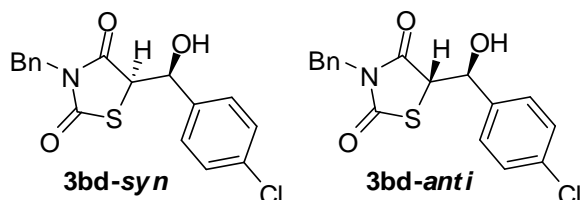
413.9781; FT-IR (neat): 3408, 2925, 2855, 2360, 2344, 1676, 1594, 1387, 1341, 1121, 1072, 912, 823, 744, 701  $\text{cm}^{-1}$ .



**Compound 3bc-syn:**  $^1\text{H}$  NMR (400 MHz): 7.50-7.48 (2H, m), 7.35-7.29 (5H, m), 7.26-7.23 (2H, m), 5.53 (1H<sub>b</sub>, s), 4.77 (2H, d,  $J = 7.2$  Hz), 4.50 (1H<sub>a</sub>, d,  $J = 3.5$  Hz), OH could not be detected;  $^{13}\text{C}$  NMR (100 MHz): 172.6, 170.8, 138.6, 134.8, 132.0, 128.7, 128.4, 128.2, 127.2, 122.7, 71.3, 57.5, 45.3.

**Compound 3bc-anti:**  $^1\text{H}$  NMR (400 MHz): 7.37-7.35 (2H, m), 7.31-7.28 (3H, m), 7.20-7.16 (4H, m), 5.21 (1H<sub>b</sub>, d,  $J = 8.7$  Hz), 4.65 (2H, s), 4.59 (1H<sub>a</sub>, d,  $J = 8.5$  Hz), OH could not be detected;  $^{13}\text{C}$  NMR(100 MHz): 173.0, 170.4, 136.6, 134.5, 131.6, 128.7, 128.7, 128.6, 128.3, 123.2, 73.8, 55.4, 45.1.

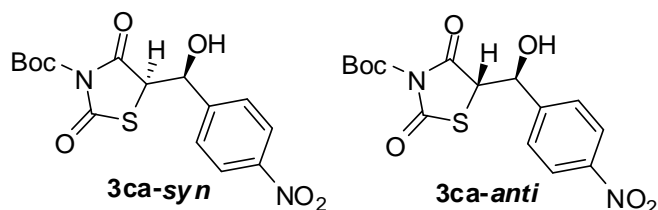
**3-benzyl-5-((4-chlorophenyl)(hydroxy)methyl)thiazolidine-2,4-dione, 3bd:** Yield 44.3 mg, 98%; obtained as a colorless liquid; HRMS (ESI) calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{SCl}$  [ $\text{M}+\text{NH}_4$ ] $^+$ : 365.0721; found, 365.0750; FT-IR (neat): 3405, 2921, 2855, 2356, 2337, 1672, 1384, 1337, 1156, 1171, 1044, 852, 825, 758, 700  $\text{cm}^{-1}$ .



**Compound 3bd-syn:**  $^1\text{H}$  NMR (400 MHz): 7.35-7.28 (9H, m), 5.55 (1H<sub>b</sub>, d,  $J = 2.6$  Hz), 4.76 (2H, d,  $J = 7.7$  Hz), 4.50 (1H<sub>a</sub>, d,  $J = 3.7$  Hz), 2.72(1H<sub>c</sub>, s<sub>br</sub>);  $^{13}\text{C}$  NMR (100 MHz): 172.6, 170.8, 138.1, 134.8, 134.6, 129.0, 128.7, 128.4, 128.2, 127.0, 71.3, 57.6, 45.3.

**Compound 3bd-anti:**  $^1\text{H}$  NMR (400 MHz): 7.32-7.25 (5H, m), 7.22-7.16 (4H, m), 5.22 (1H<sub>b</sub>, d,  $J = 8.8$  Hz), 4.65 (2H, s), 4.60 (1H<sub>a</sub>, d,  $J = 8.6$  Hz), 3.52 (1H<sub>c</sub>, s<sub>br</sub>);  $^{13}\text{C}$  NMR (100 MHz): 173.0, 170.4, 136.2, 135.0, 134.5, 128.7, 128.7, 128.5, 128.4, 128.3, 73.8, 55.5, 45.1.

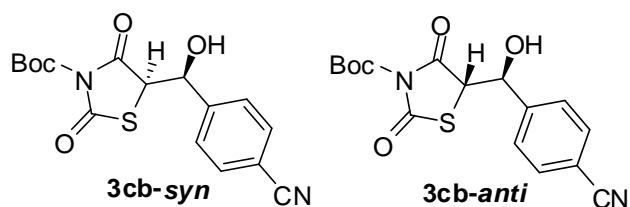
**tert-butyl 5-(hydroxy(4-nitrophenyl)methyl)-2,4-dioxothiazolidine-3-carboxylate 3ca:** Yield 41.2 mg, 86%; obtained as colorless solid; m.p. 155-159 °C; HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_7\text{S}$  [ $\text{M}+\text{H}$ ] $^+$ : 369.0751; found, 369.0739; FT-IR (neat): 3334, 2835, 2653, 2544, 2250, 1681, 1547, 1333, 1254, 1086, 1024, 963, 841  $\text{cm}^{-1}$ .



**Compound 3ca-syn:**  $^1\text{H}$  NMR (500 MHz): 8.25 (2H, d,  $J = 8.7$  Hz), 7.57 (2H, d,  $J = 8.7$  Hz), 5.62 (1H<sub>b</sub>, d,  $J = 3.7$  Hz), 4.36 (1H<sub>a</sub>, d,  $J = 2.9$  Hz), 1.60 (9H, s), OH could not be detected;  $^{13}\text{C}$  NMR: (125 MHz): 173.8, 170.9, 148.0, 146.9, 126.7, 123.9, 71.5, 62.8, 55.7, 28.4, one carbon could not be detected.

**Compound 3ca-anti** (from a 33:67 (*syn/anti*) mixture):  $^1\text{H}$  NMR (500 MHz): 8.24-8.20 (2H, merged with *syn* isomer), 7.62-7.56 (2H, merged with *syn* isomer), 5.26 (1H<sub>b</sub>, d,  $J = 7.3$  Hz), 4.37 (1H<sub>a</sub>, d,  $J = 7.3$  Hz), 1.52 (9H, s), OH could not be detected;  $^{13}\text{C}$  NMR (125 MHz): 174.8, 170.4, 148.2, 145.3, 128.2, 123.6, 74.0, 62.8, 53.7, 28.3, one carbon could not be detected.

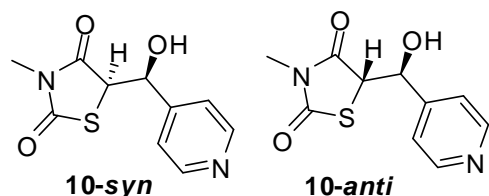
**tert-butyl 5-((4-cyanophenyl)(hydroxy)methyl)-2,4-dioxothiazolidine-3-carboxylate 3cb** (from a 60:40 (*syn/anti*) mixture): Yield 27.2 mg, 60%; obtained as colorless liquid; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{NaO}_5\text{S}$   $[\text{M}+\text{Na}]^+$ : 371.0672; found, 371.0691; FT-IR (neat): 3358, 2911, 2697, 2513, 2350, 2201, 1672, 1563, 1489, 1232, 1178, 1022, 961, 843  $\text{cm}^{-1}$ .



**Compound 3cb-syn:**  $^1\text{H}$  NMR (500 MHz): 7.69-7.66 (2H, merged with *anti* isomer), 7.55-7.50 (1H, merged with *anti* isomer), 5.55 (1H<sub>b</sub>, d,  $J = 2.6$  Hz), 4.33 (1H<sub>a</sub>, d,  $J = 2.9$  Hz), 1.60 (9H, s), OH could not be detected;  $^{13}\text{C}$  NMR (125 MHz): 173.9, 171.0, 145.0, 132.5, 126.5, 118.3, 112.4, 71.6, 62.7, 55.7, 28.3, one carbon could not be detected.

**Compound 3cb-anti:**  $^1\text{H}$  NMR (500 MHz): 7.69-7.66 (2H, merged with *syn* isomer), 7.55-7.50 (1H, merged with *syn* isomer), 5.19 (1H<sub>b</sub>, d,  $J = 7.5$  Hz), 4.35 (1H<sub>a</sub>, d,  $J = 7.4$  Hz), 1.52 (9H, s), OH could not be detected;  $^{13}\text{C}$  NMR (125 MHz): 174.9, 170.5, 143.4, 132.2, 128.0, 118.3, 112.9, 74.2, 62.8, 53.7, 28.4, one carbon could not be detected.

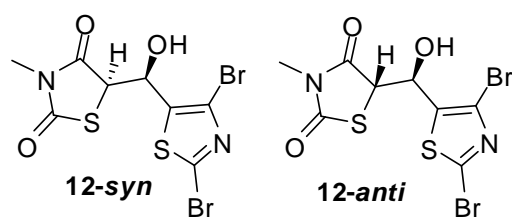
**5-(hydroxy(pyridin-4-yl)methyl)-3-methylthiazolidine-2,4-dione 10:** Yield 30.7 mg, 99%; obtained as colorless solid; m.p. 137-141 °C; HRMS (ESI) calcd for C<sub>10</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 239.0485; found, 239.0501; FT-IR (neat): 3455, 2954, 2748, 2354, 2243, 1675, 1535, 1279, 1095, 1042, 783, 742, 656.



**Compound 10-syn:** <sup>1</sup>H NMR (400 MHz): 8.58 (2H, d, *J* = 7.5 Hz), 7.34 (2H, d, *J* = 7.3 Hz), 5.61 (1H<sub>b</sub>, d, *J* = 2.9 Hz), 4.54 (1H<sub>a</sub>, d, *J* = 3.2 Hz), 3.13 (3H, s), OH could not be detected; <sup>13</sup>C NMR (100 MHz): 172.6, 170.7, 149.9, 149.4, 120.7, 70.3, 57.3, 57.1, 28.1

**Compound 10-anti** (from 55:45 *syn/anti* mixture): <sup>1</sup>H NMR (500 MHz): 8.49 (2H, d, *J* = 7.4 Hz), 7.34 (2H, d, *J* = 7.4 Hz), 5.31 (1H<sub>b</sub>, d, *J* = 7.7 Hz), 4.63 (1H<sub>a</sub>, d, *J* = 7.7 Hz), 2.99 (3H, s), OH could not be detected; <sup>13</sup>C NMR (125 MHz): 172.7, 170.3, 150.0, 147.8, 122.1, 72.7, 55.4, 27.8

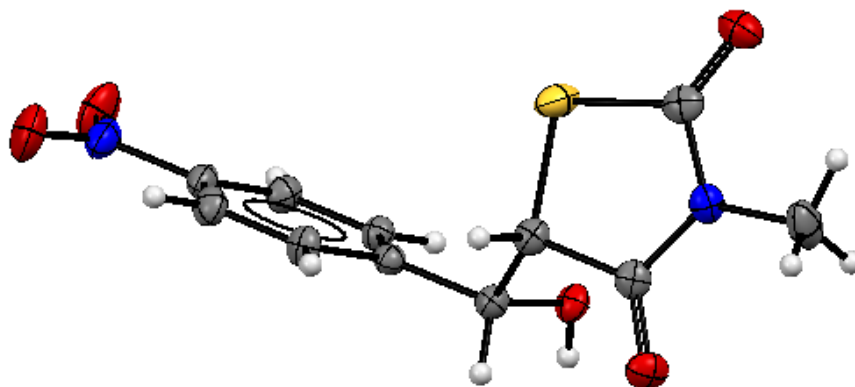
**5-((2,4-dibromothiazol-5-yl)(hydroxy)methyl)-3-methylthiazolidine-2,4-dione 12:** Yield 51.7 mg, 99%; obtained as colorless crystals (CDCl<sub>3</sub>-H<sub>2</sub>O); m.p. 94-96 °C; HRMS (ESI) calcd for C<sub>8</sub>H<sub>6</sub>Br<sub>2</sub>N<sub>2</sub>NaO<sub>3</sub>S<sub>2</sub> [M+Na]<sup>+</sup>: 422.8084; found, 422.8099; FT-IR (neat): 3420, 2922, 2781, 2389, 2343, 2231, 1626, 1554, 1256, 1165, 1072, 1014, 765, 721, 692.



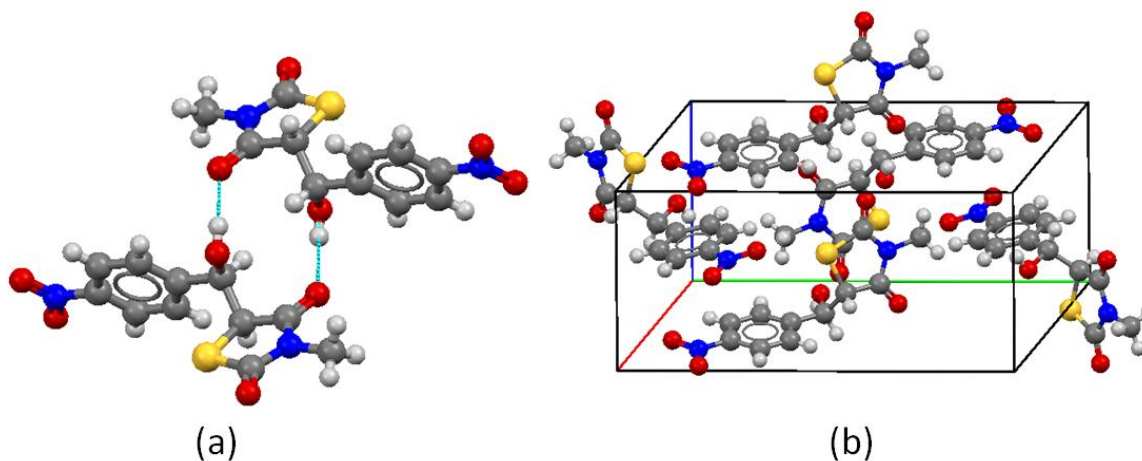
**Compound 12-syn:** <sup>1</sup>H NMR (400 MHz): 5.79 (1H<sub>b</sub>, dd, *J* = 6.6, 3.5 Hz), 4.69 (1H<sub>a</sub>, d, *J* = 3.7 Hz), 3.12 (3H, s), OH could not be detected; <sup>13</sup>C NMR (100 MHz): 171.9, 170.5, 138.3, 137.0, 120.4, 67.4, 55.1, 28.2.

**Compound 12-anti** (from 71:29 *syn/anti* mixture): <sup>1</sup>H NMR (500 MHz): 5.55 (1H<sub>b</sub>, t, *J* = 6.6 Hz), 4.50 (1H<sub>a</sub>, merged with *syn* isomer), 4.45 (1H<sub>c</sub>, b), 3.07 (3H, s); <sup>13</sup>C NMR (125 MHz): 171.8, 170.1, 138.2, 136.0, 123.3, 69.2, 54.6, 28.1.

**5.0 X-Ray Crystallography of 3aa and 11:** Intensity data were collected on a Bruker's Kappa Apex II CCD Duo diffractometer with graphite monochromated  $\text{MoK}\alpha$  radiation ( $0.71073 \text{ \AA}$ ) at the temperature of 296 K. Scaling and multi-scan absorption correction were employed using SADABS.<sup>1</sup> The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically while the hydrogen atoms fixed in the predetermined positions by Shelxs-97 and Shelxl-97 packages respectively.<sup>2</sup>



**Figure S1.** The ORTEP diagram of *syn* aldol **3aa**. Ellipsoids are drawn at the 50% probability level.



**Figure S2.** (a) X-ray crystal structure showing H-bonded dimer of **3aa** and (b) the packing diagram of **3aa**.

<sup>1</sup> Bruker. SADABS V2008-1, Bruker AXS: Madison, WI, USA (2008).

<sup>2</sup> G. M. Sheldrick, SHELX93, Program for Crystal Structure Determination, University of Göttingen (1997).

### Crystal Data and Details of the Structure Determination for *syn* aldol 3aa:

Formula	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>5</sub> S
Formula weight	282.27
Crystal system	Monoclinic
Crystal size	0.16 x 0.18 x 0.38 mm
Space group	P21/c
a, b, c [Å]	10.7880(5), 16.5308(8), 7.1104(3)
α, β, γ [°]	90, 106.861, 90
V [Å <sup>3</sup> ]	1213.52
Z	4
dm [Mgm <sup>-3</sup> ]	1.545

### Data Collection

Temperature (K)	100
MoKα (Å)	0.71073
θ Min, Max [°]	2.0, 27.0
Tot., Uniq. Data	12149, 2639
Observed data [I > 2σ(I)]	2392

### Refinement

R, wR2	0.0290, 0.0787
Min., Max. resd. dens. [e/Å <sup>-3</sup> ]	-0.23, 0.31

**Table 1. Bond Distances (Å)**

S1-C1	1.7594(14)	C5-C10	1.3885(17)
S1-C3	1.8169(13)	C5-C6	1.3985(18)
O1-C1	1.2067(16)	C6-C7	1.3837(19)
O2-C2	1.2136(15)	C7-C8	1.3801(19)
O3-C4	1.4134(15)	C8-C9	1.3840(19)
O4-N2	1.2253(17)	C9-C10	1.3891(18)
O5-N2	1.2265(17)	C3-H4	0.9800
O3-H10	0.8200	C4-H5	0.9800
N1-C2	1.3662(16)	C6-H9	0.9300
N1-C11	1.4579(19)	C7-H8	0.9300
N1-C1	1.3867(17)	C9-H7	0.9300
N2-C8	1.4688(18)	C10-H10A	0.9300
C2-C3	1.5149(18)	C11-H11A	0.9600
C3-C4	1.5309(17)	C11-H11B	0.9600
C4-C5	1.5211(17)	C11-H11C	0.9600

**Table 2. Bond Angles (°)**

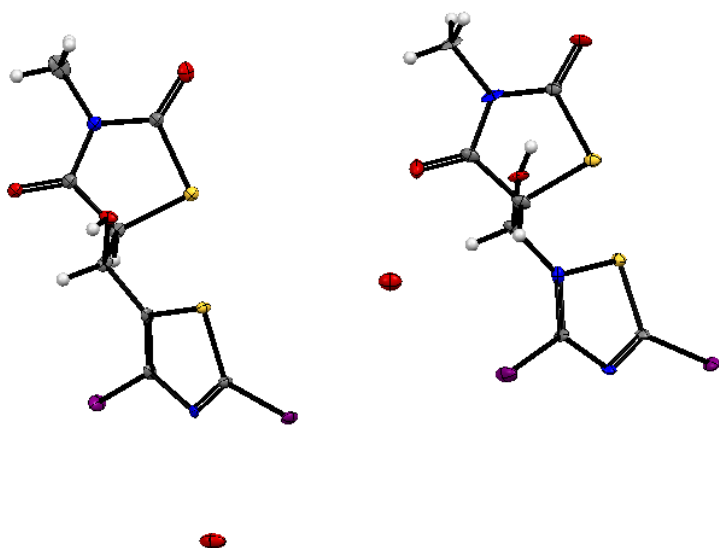
C1-S1-C3	92.61(6)	N2-C8-C7	118.84(12)
C4-O3-H10	109.00	N2-C8-C9	118.49(12)
C1-N1-C11	121.21(11)	C7-C8-C9	122.67(12)
C2-N1-C11	121.67(11)	C8-C9-C10	118.08(12)
C1-N1-C2	117.10(11)	C5-C10-C9	120.93(12)
O4-N2-C8	118.13(12)	S1-C3-H4	108.00
O5-N2-C8	118.47(11)	C2-C3-H4	108.00
O4-N2-O5	123.40(13)	C4-C3-H4	108.00
S1-C1-N1	110.95(9)	O3-C4-H5	108.00
O1-C1-N1	124.63(12)	C3-C4-H5	109.00
S1-C1-O1	124.42(11)	C5-C4-H5	108.00
O2-C2-N1	123.25(12)	C5-C6-H9	120.00
N1-C2-C3	112.45(10)	C7-C6-H9	120.00
O2-C2-C3	124.26(11)	C6-C7-H8	121.00
S1-C3-C2	106.32(8)	C8-C7-H8	121.00
C2-C3-C4	111.85(10)	C8-C9-H7	121.00
S1-C3-C4	113.43(8)	C10-C9-H7	121.00
O3-C4-C5	112.98(9)	C5-C10-H10A	119.00
C3-C4-C5	110.96(10)	C9-C10-H10A	120.00
O3-C4-C3	107.28(10)	N1-C11-H11A	109.00
C4-C5-C10	120.86(11)	N1-C11-H11B	109.00
C6-C5-C10	119.18(11)	N1-C11-H11C	109.00
C4-C5-C6	119.95(11)	H11A-C11-H11B	110.00
C5-C6-C7	120.77(12)	H11A-C11-H11C	109.00
C6-C7-C8	118.34(12)	H11B-C11-H11C	109.00

**Table 3. Torsion Angles (°)**

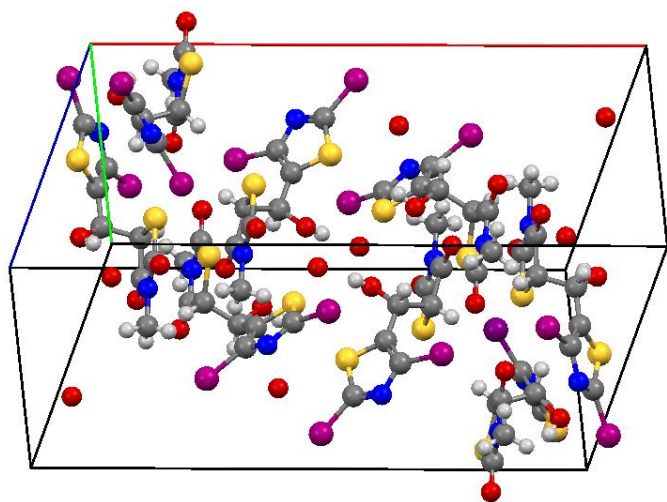
C3-S1-C1-O1	176.04(13)	O2-C2-C3-S1	174.01(11)
C3-S1-C1-N	-3.00(10)	S1-C3-C4-O3	-62.85(11)
C1-S1-C3-C2	6.01(9)	S1-C3-C4-C5	61.00(12)
C1-S1-C3-C4	129.34(10)	C2-C3-C4-O3	57.40(12)
C2-N1-C1-O1	179.49(13)	C2-C3-C4-C5	-178.75(10)
C11-N1-C1-S1	176.80(11)	O3-C4-C5-C10	-5.01(16)
C2-N1-C1-S1	-1.48(15)	C3-C4-C5-C6	55.28(15)
C11-N1-C2-C3	-171.87(12)	O3-C4-C5-C6	175.80(11)
C11-N1-C2-O2	6.2(2)	C3-C4-C5-C10	-125.53(12)
C11-N1-C1-O1	-2.2(2)	C10-C5-C6-C7	1.50(19)
C1-N1-C2-O2	-175.55(12)	C4-C5-C6-C7	-179.30(12)
C1-N1-C2-C3	6.40(16)	C6-C5-C10-C9	-0.69(18)
O4-N2-C8-C9	4.19(18)	C4-C5-C10-C9	-179.89(11)
O5-N2-C8-C7	3.56(18)	C5-C6-C7-C8	-0.83(19)
O5-N2-C8-C9	-175.36(12)	C6-C7-C8-C9	-0.7(2)
O4-N2-C8-C7	-176.90(13)	C6-C7-C8-N2	-179.53(12)
N1-C2-C3-S1	-7.95(13)	N2-C8-C9-C10	-179.69(11)
N1-C2-C3-C4	-132.27(11)	C7-C8-C9-C10	1.44(19)
N1-C2-C3-S1	-7.95(13)	C8-C9-C10-C5	-0.74(18)
O2-C2-C3-C4	49.70(17)		

**Table 4: Intermolecular Hydrogen Bonding Parameters**

D-H-A	H---A (Å)	D---A (Å)	D-H
O3--H10..O2	0.8200	2.0000	159.00
C3--H4..O4	0.9800	2.3900	149.00
C4--H5..O1	0.9800	2.5200	137.00
C7--H8..O1	0.9300	2.4600	153.00
C10--H10A..O3	0.9300	2.4300	103.00
C11--H11B..O1	0.9600	2.4600	103.00



**Figure S3.** The ORTEP diagram of *syn* aldol **12**. Ellipsoids are drawn at the 50% probability level.



**Figure S4.** X-ray crystal structure showing the packing diagram of **12**.

**Crystal Data and Details of the Structure Determination for *syn*-aldol **12**:**

Formula	C <sub>8</sub> H <sub>6</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub> , O
Formula weight	418.09
Crystal system	Monoclinic
Crystal size	0.15 X 0.21 X 0.25 mm
Space group	P21/c
a, b, c [Å]	20.804(2), 11.9934(14), 10.9684(11)
α, β, γ [°]	90, 102.666(2), 90
V [Å <sup>3</sup> ]	2670.1(5)
Z	8
dm [Mgm <sup>-3</sup> ]	2.080



## Data Collection

Temperature (K)	100
MoK $\alpha$ (Å)	0.71073
$\theta$ Min, Max [°]	1.0, 25.1
Tot., Uniq. Data	19654, 4717, 0.049
Observed data [ $I > 2\sigma(I)$ ]	4166

## Refinement

R, wR2	0.0840, 0.2132, 1.15
Min., Max. resd. dens. [ $e/\text{Å}^{-3}$ ]	-1.58, 2.63

**Table 1. Bond Distances (Å)**

Br1-C1	1.866(13)	N2-C6	1.374(17)
Br2-C2	1.875(13)	N3-C10	1.375(16)
Br3-C9	1.872(12)	N3-C9	1.294(16)
Br4-C10	1.878(13)	N4-C15	1.353(17)
S1-C3	1.718(13)	N4-C16	1.472(18)
S1-C1	1.719(13)	N4-C14	1.392(17)
S2-C7	1.795(14)	C2-C3	1.347(19)
S2-C5	1.809(13)	C3-C4	1.503(18)
S3-C9	1.717(13)	C4-C5	1.549(18)
S3-C11	1.728(13)	C5-C6	1.516(18)
S4-C15	1.775(14)	C4-H4A	0.9800
S4-C13	1.821(13)	C5-H5	0.9800
O1-C4	1.417(15)	C8-H8C	0.9600
O2-C6	1.214(15)	C8-H8B	0.9600
O3-C7	1.219(16)	C8-H8A	0.9600
O1-H1	0.8200	C10-C11	1.368(18)
O4-C12	1.417(16)	C11-C12	1.485(19)
O5-C14	1.205(16)	C12-C13	1.549(18)
O6-C15	1.219(16)	C13-C14	1.535(18)
O4-H4	0.8200	C12-H12	0.9800
N1-C1	1.308(16)	C13-H13	0.9800
N1-C2	1.387(17)	C16-H16A	0.9600
N2-C7	1.357(17)	C16-H16B	0.9600
N2-C8	1.465(18)	C16-H16C	0.9600

**Table 2. Bond Angles (°)**

C1-S1-C3	89.0(6)	S2-C5-C6	106.8(8)
C5-S2-C7	91.5(6)	N2-C6-C5	111.9(11)
C9-S3-C11	89.3(6)	O2-C6-N2	123.4(12)
C13-S4-C15	91.9(6)	O2-C6-C5	124.7(12)
C4-O1-H1	109.00	O3-C7-N2	125.8(12)
C12-O4-H4	110.00	S2-C7-O3	123.1(10)
C1-N1-C2	108.6(11)	S2-C7-N2	111.1(9)
C6-N2-C7	117.5(11)	C5-C4-H4A	109.00
C6-N2-C8	124.7(11)	C3-C4-H4A	109.00
C7-N2-C8	117.8(11)	O1-C4-H4A	109.00
C9-N3-C10	108.9(10)	C4-C5-H5	109.00
C15-N4-C16	122.1(11)	S2-C5-H5	109.00
C14-N4-C15	116.5(11)	C6-C5-H5	109.00
C14-N4-C16	121.4(11)	H8B-C8-H8C	109.00
S1-C1-N1	116.1(10)	N2-C8-H8A	109.00
Br1-C1-S1	121.3(7)	N2-C8-H8B	109.00
Br1-C1-N1	122.7(9)	H8A-C8-H8B	109.00
Br2-C2-C3	125.6(10)	H8A-C8-H8C	110.00
Br2-C2-N1	117.7(9)	N2-C8-H8C	109.00
N1-C2-C3	116.6(12)	Br3-C9-N3	121.8(9)
S1-C3-C2	109.8(10)	S3-C9-N3	116.4(9)
C2-C3-C4	129.9(12)	Br3-C9-S3	121.7(7)
S1-C3-C4	120.4(10)	Br4-C10-C11	124.7(10)
C3-C4-C5	114.2(10)	N3-C10-C11	117.2(11)
O1-C4-C5	105.0(9)	Br4-C10-N3	118.1(9)
O1-C4-C3	111.7(10)	S3-C11-C12	121.1(10)
C4-C5-C6	107.9(10)	C10-C11-C12	130.8(12)
S2-C5-C4	113.6(9)	S3-C11-C10	108.1(10)
O4-C12-C11	110.5(11)	O4-C12-H12	109.00
O4-C12-C13	106.3(10)	C11-C12-H12	109.00
C11-C12-C13	113.3(11)	C13-C12-H12	109.00
S4-C13-C12	112.1(9)	S4-C13-H13	110.00

S4-C13-C14	106.0(9)	C12-C13-H13	110.00
C12-C13-C14	108.4(10)	C14-C13-H13	110.00
O5-C14-C13	124.0(12)	N4-C16-H16A	109.00
N4-C14-C13	112.1(11)	N4-C16-H16B	109.00
O5-C14-N4	123.9(12)	N4-C16-H16C	109.00
S4-C15-N4	112.6(9)	H16A-C16-H16B	110.00
O6-C15-N4	125.6(12)	H16A-C16-H16C	110.00
S4-C15-O6	121.8(10)	H16B-C16-H16C	109.00

**Table 3. Torsion Angles (°)**

C3-S1-C1-Br1	-179.7(8)	C14-N4-C15-S4	-1.1(14)
C3-S1-C1-N1	-0.7(11)	C16-N4-C14-C13	175.4(11)
C1-S1-C3-C2	-0.2(10)	C15-N4-C14-O5	177.0(13)
C1-S1-C3-C4	178.7(11)	C15-N4-C14-C13	-5.8(16)
C7-S2-C5-C4	-110.0(9)	Br2-C2-C3-S1	178.0(7)
C7-S2-C5-C6	8.9(9)	N1-C2-C3-C4	-177.7(12)
C5-S2-C7-O3	178.1(12)	N1-C2-C3-S1	1.0(15)
C5-S2-C7-N2	-4.4(10)	Br2-C2-C3-C4	-1(2)
C5-S2-C7-N2	-4.4(10)	S1-C3-C4-O1	-12.1(15)
C11-S3-C9-Br3	178.3(8)	S1-C3-C4-C5	106.8(12)
C11-S3-C9-N3	1.8(11)	C2-C3-C4-C5	-74.5(17)
C9-S3-C11-C10	-0.6(10)	C2-C3-C4-O1	166.6(13)
C9-S3-C11-C12	179.9(11)	O1-C4-C5-C6	-58.9(12)
C15-S4-C13-C12	109.7(10)	O1-C4-C5-S2	59.4(11)
C13-S4-C15-O6	-174.1(11)	C3-C4-C5-C6	178.5(10)
C15-S4-C13-C14	-8.4(9)	C3-C4-C5-S2	-63.2(12)
C13-S4-C15-N4	6.0(10)	C4-C5-C6-O2	-65.7(16)
C1-N1-C2-C3	-1.6(16)	S2-C5-C6-N2	-11.9(13)
C2-N1-C1-Br1	-179.7(9)	C4-C5-C6-N2	110.6(12)
C1-N1-C2-Br2	-178.8(9)	S2-C5-C6-O2	171.7(11)
C2-N1-C1-S1	1.4(14)	Br4-C10-C11-S3	179.4(7)
C8-N2-C7-O3	-4.0(19)	N3-C10-C11-C12	178.9(12)

C6-N2-C7-O3	175.1(12)	Br4-C10-C11-C12	-1(2)
C7-N2-C6-C5	9.6(16)	N3-C10-C11-S3	-0.5(15)
C8-N2-C6-O2	5(2)	S3-C11-C12-C13	-104.9(12)
C8-N2-C7-S2	178.6(9)	S3-C11-C12-O4	14.4(15)
C8-N2-C6-C5	-171.4(11)	C10-C11-C12-O4	-165.0(13)
C7-N2-C6-O2	-174.0(12)	C10-C11-C12-C13	75.8(18)
C6-N2-C7-S2	-2.3(14)	C11-C12-C13-C14	-176.9(11)
C9-N3-C10-C11	1.8(16)	C11-C12-C13-S4	66.5(13)
C10-N3-C9-S3	-2.3(14)	O4-C12-C13-S4	-55.2(12)
C10-N3-C9-Br3	-178.8(9)	O4-C12-C13-C14	61.4(13)
C9-N3-C10-Br4	-178.1(9)	C12-C13-C14-N4	-111.0(12)
C16-N4-C14-O5	-2(2)	S4-C13-C14-O5	-173.3(11)
C14-N4-C15-O6	178.9(12)	C12-C13-C14-O5	66.2(16)
C16-N4-C15-S4	177.7(9)	S4-C13-C14-N4	9.5(13)
C16-N4-C15-O6	-2(2)		

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**Table 4. Intermolecular Hydrogen Bonding Parameters**

D-H-A	H---A (Å)	D---A (Å)	D-H
O1--H1..O8	0.8200	1.8700	178.00
O4--H4..S4	0.8200	2.5000	121.00
O4--H4..Br3	0.8200	2.8500	114.00
C8--H8B..O2	0.9600	2.5100	103.00
C8--H8C..O6	0.9600	2.5200	131.00
C16--16B..O5	0.9600	2.4500	104.00

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**6.0 Computational methods:** All structures were fully optimized through the Gaussian03 program,<sup>[3]</sup> using density functional theory (B3LYP)<sup>[4]</sup> and 6-311+G\* basis sets. The relative energies for the compounds were evaluated from gas-phase optimized geometries.

Compound	Total energy (hartree/mol)	Total energy (kJ/mol)	Relative Total energy (kJ/mol) with respect to <b>1a</b>
<b>1a</b>	-758.98509889	-1994018.56	0
<b>4a</b>	-758.94341087	-1993909.03	109.53
<b>2a</b>	-550.22027936	-1445548.09	-
<b>3H<sub>2</sub>O<sup>a</sup></b>	-229.35748157	-602571.88	-
<b>3aa-anti</b>	-1538.58371997	-4042193.29	-54.76 <sup>b</sup>
<b>3aa-syn</b>	-1538.59003110	-4042209.87	-71.34 <sup>b</sup>
<b>H<sub>2</sub>O</b>	-76.44359591	-200833.93	-
<b>2b</b>	-437.92440654	-1150522.47	-
<b>3ab-anti</b>	-1273.36446877	-3345404.76	-29.80 <sup>c</sup>
<b>3ab-syn</b>	-1273.36130797	-3345396.47	-21.51 <sup>c</sup>
<b>4H<sub>2</sub>O<sup>a</sup></b>	-305.80683726	-803420.92	-
<b>9</b>	-361.69760094	-950258.07	-
<b>10-anti</b>	-1426.52939088	-3747802.26	-104.71 <sup>d</sup>
<b>10-syn</b>	-1426.53834938	-3747825.78	-128.23 <sup>d</sup>
<b>11</b>	-5829.55342040	-15315501.84	-
<b>12-anti</b>	-6817.91113665	-17912132.05	-39.77 <sup>e</sup>
<b>12-syn</b>	-6817.91942462	-17912153.82	-61.54 <sup>e</sup>

<sup>a</sup> Optimisation was done by 3H<sub>2</sub>O or 4H<sub>2</sub>O molecule linearly H-bonded to each other.

<sup>b</sup> Relative energy determined:  $E_{\text{rel}} = [E_{3\text{aa}(\text{syn or anti})} - (E_{1\text{a}} + E_{2\text{a}} + E_{3\text{H}_2\text{O}})]$ .

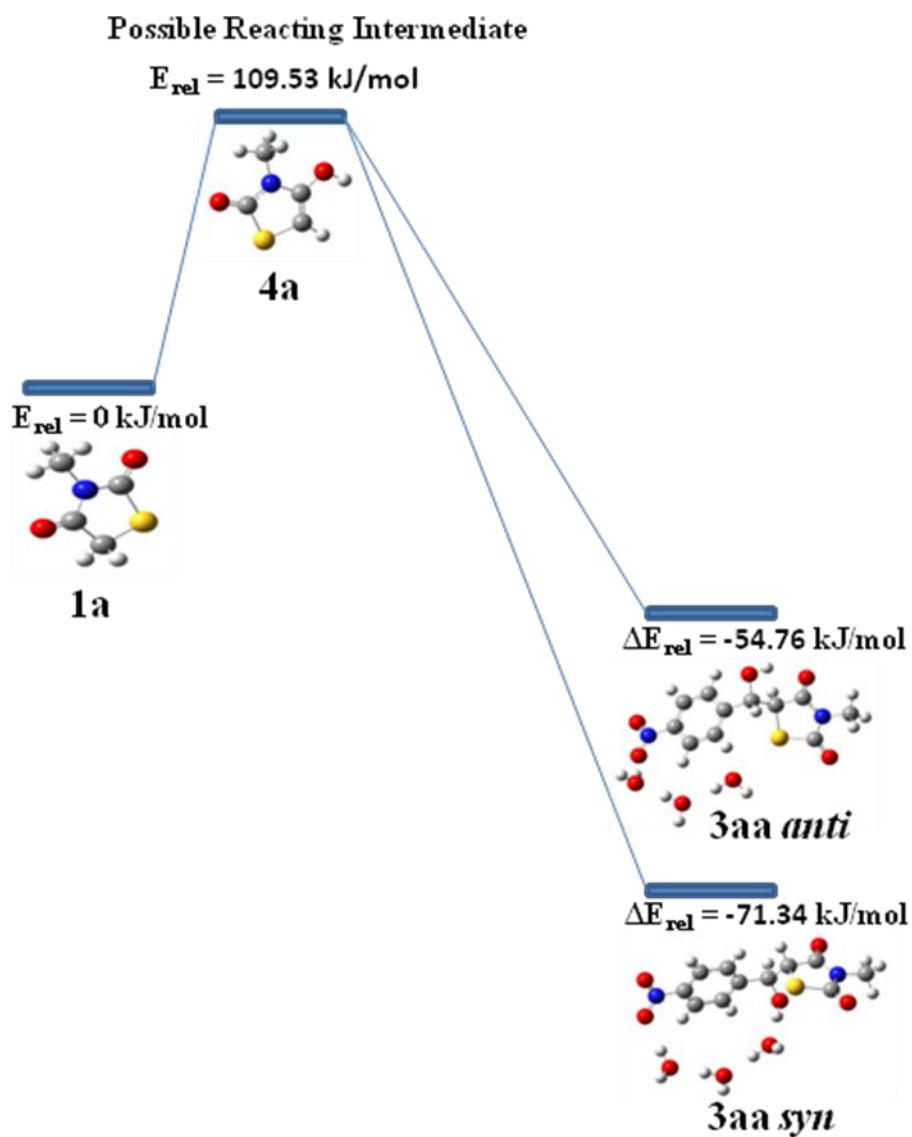
<sup>c</sup> Relative energy determined:  $E_{\text{rel}} = [E_{3\text{ab}(\text{syn or anti})} - (E_{1\text{a}} + E_{2\text{b}} + E_{\text{H}_2\text{O}})]$

<sup>d</sup> Relative energy determined:  $E_{\text{rel}} = [E_{10(\text{syn or anti})} - (E_{1\text{a}} + E_{9} + E_{4\text{H}_2\text{O}})]$

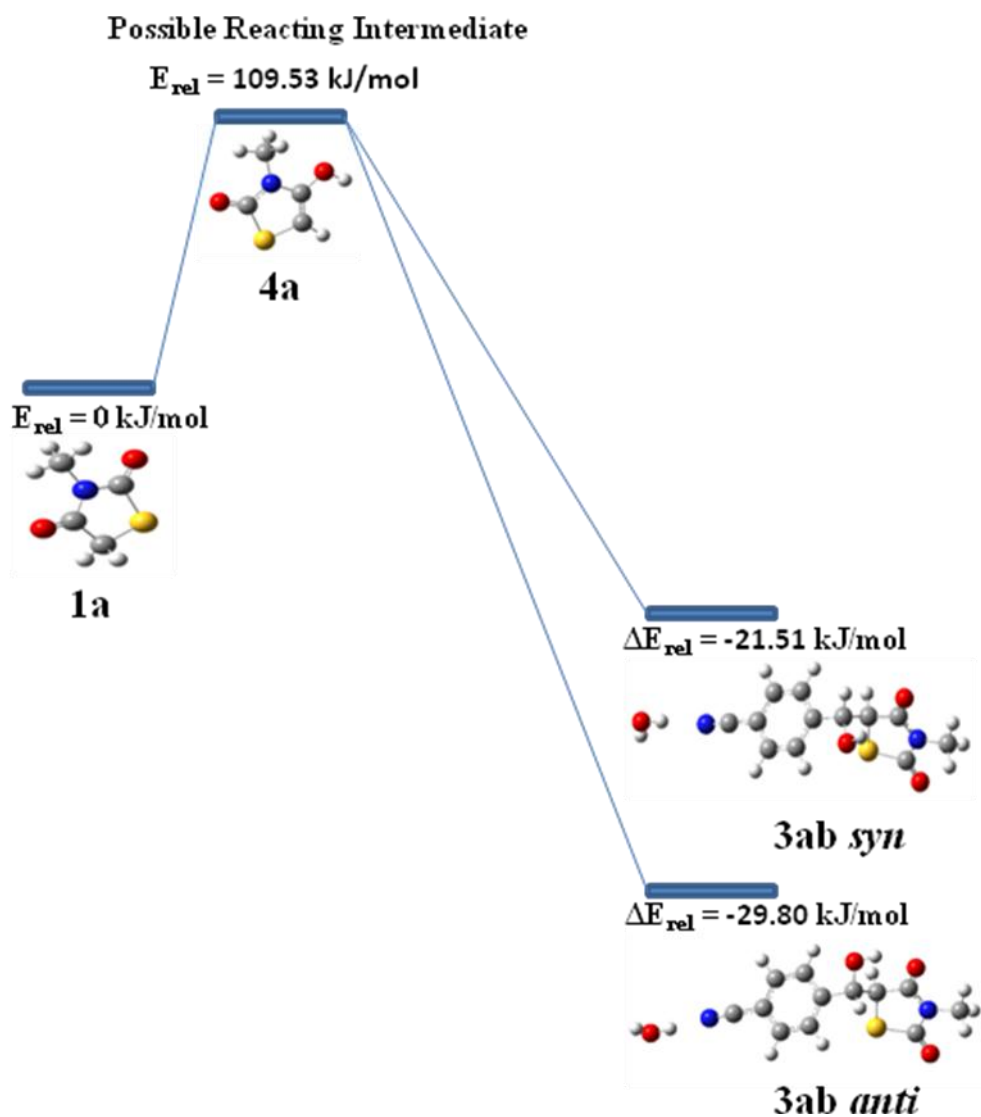
<sup>e</sup> Relative energy determined:  $E_{\text{rel}} = [E_{12(\text{syn or anti})} - (E_{1\text{a}} + E_{11} + E_{3\text{H}_2\text{O}})]$

<sup>3</sup> Gaussian03 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.

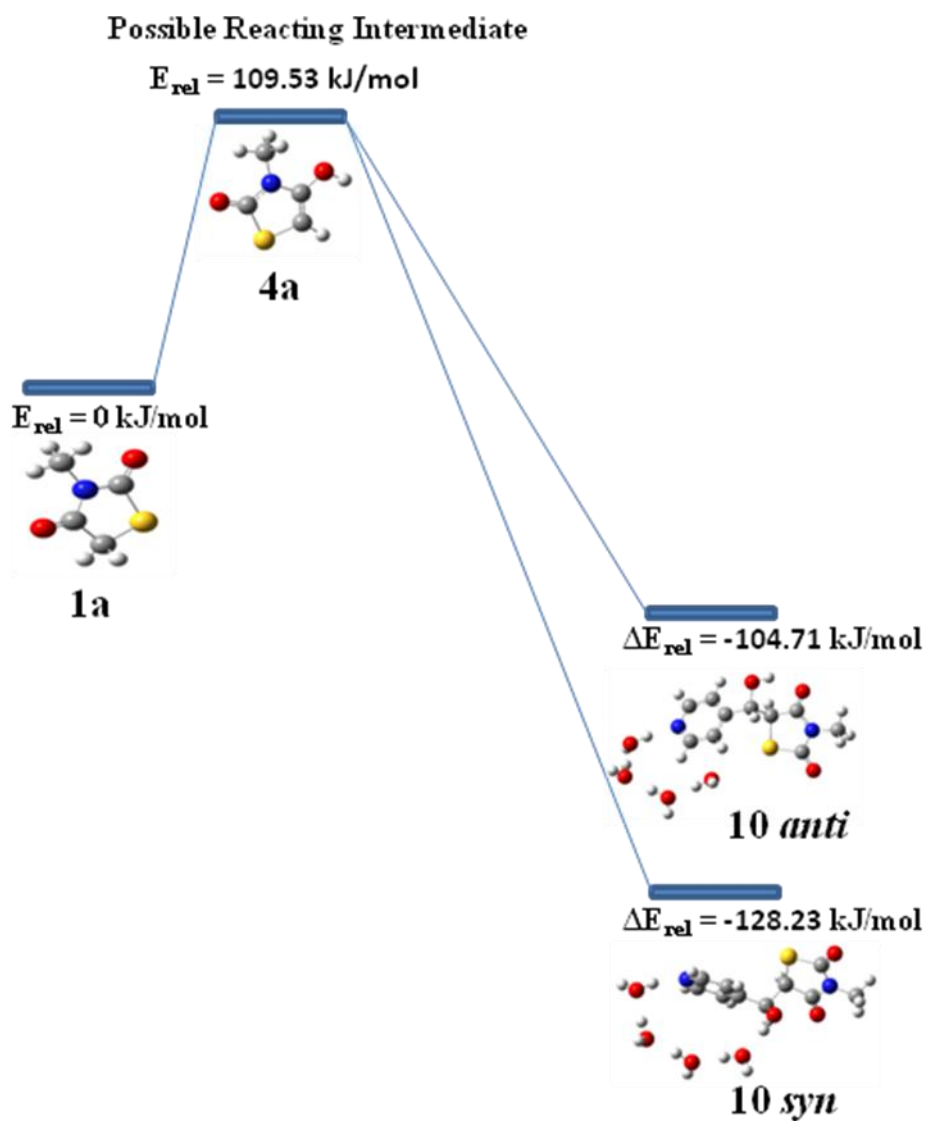
<sup>4</sup> B3LYP hybrid functional: (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.



**Figure S5.** Optimized energy for the two competitive product formation (**3aa-syn** and **3aa-anti**), using B3LYP/6-311+G\* (Not in Scale).

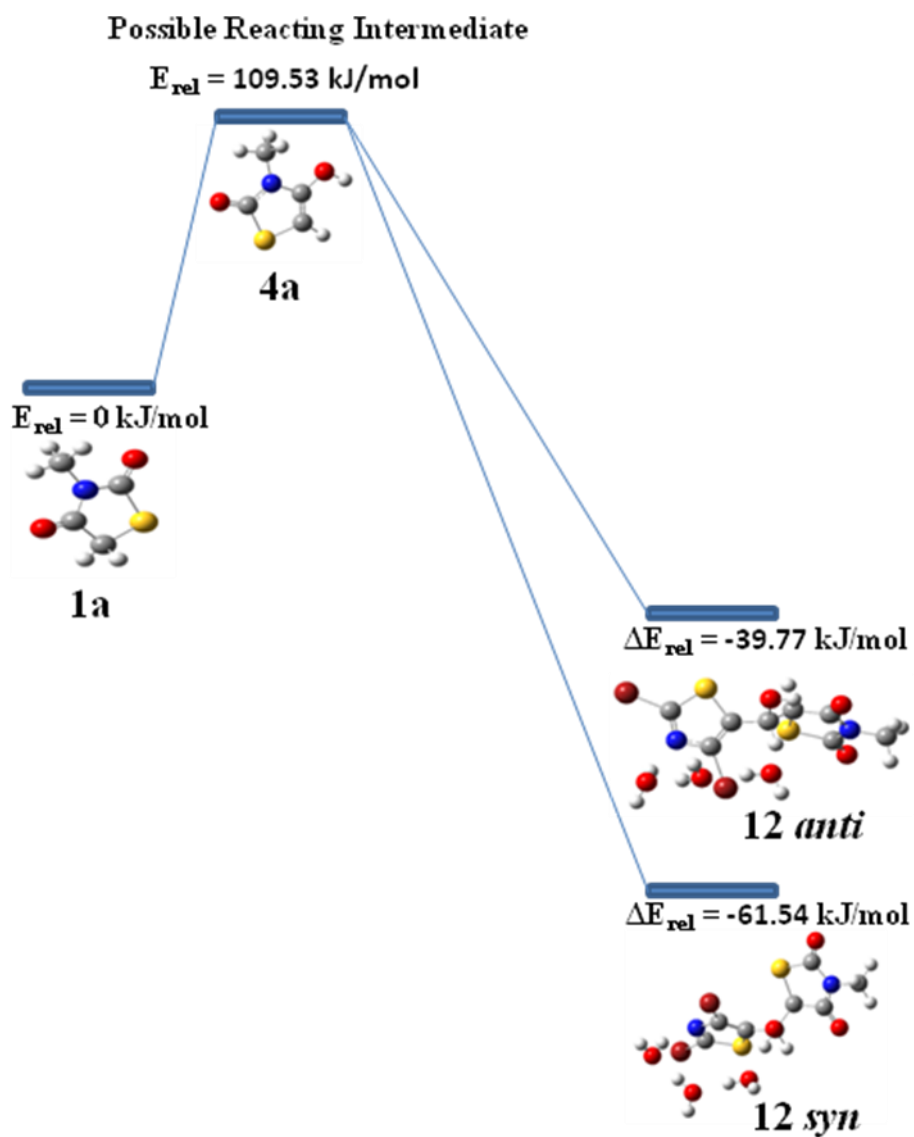


**Figure S6.** Optimized energy for the two competitive product formation (**3ab-syn** and **3ab-anti**), using B3LYP/6-311+G\* (Not in Scale).



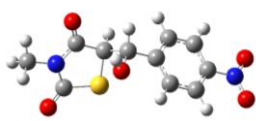
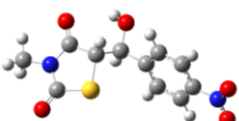
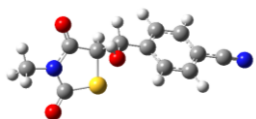

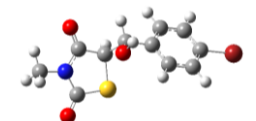
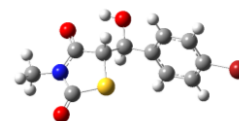
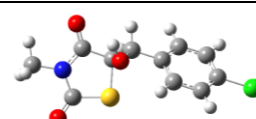
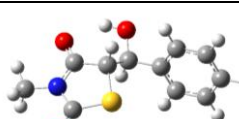

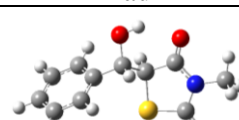
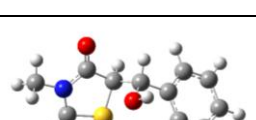
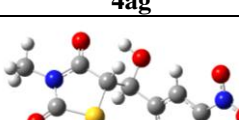
**Figure S7.** Optimized energy for the two competitive product formation (**10-syn** and **10-anti**), using B3LYP/6-311+G\* (Not in Scale).





**Figure S8.** Optimized energy for the two competitive product formation (**12-syn** and **12-anti**), using B3LYP/6-311+G\* (Not in Scale).

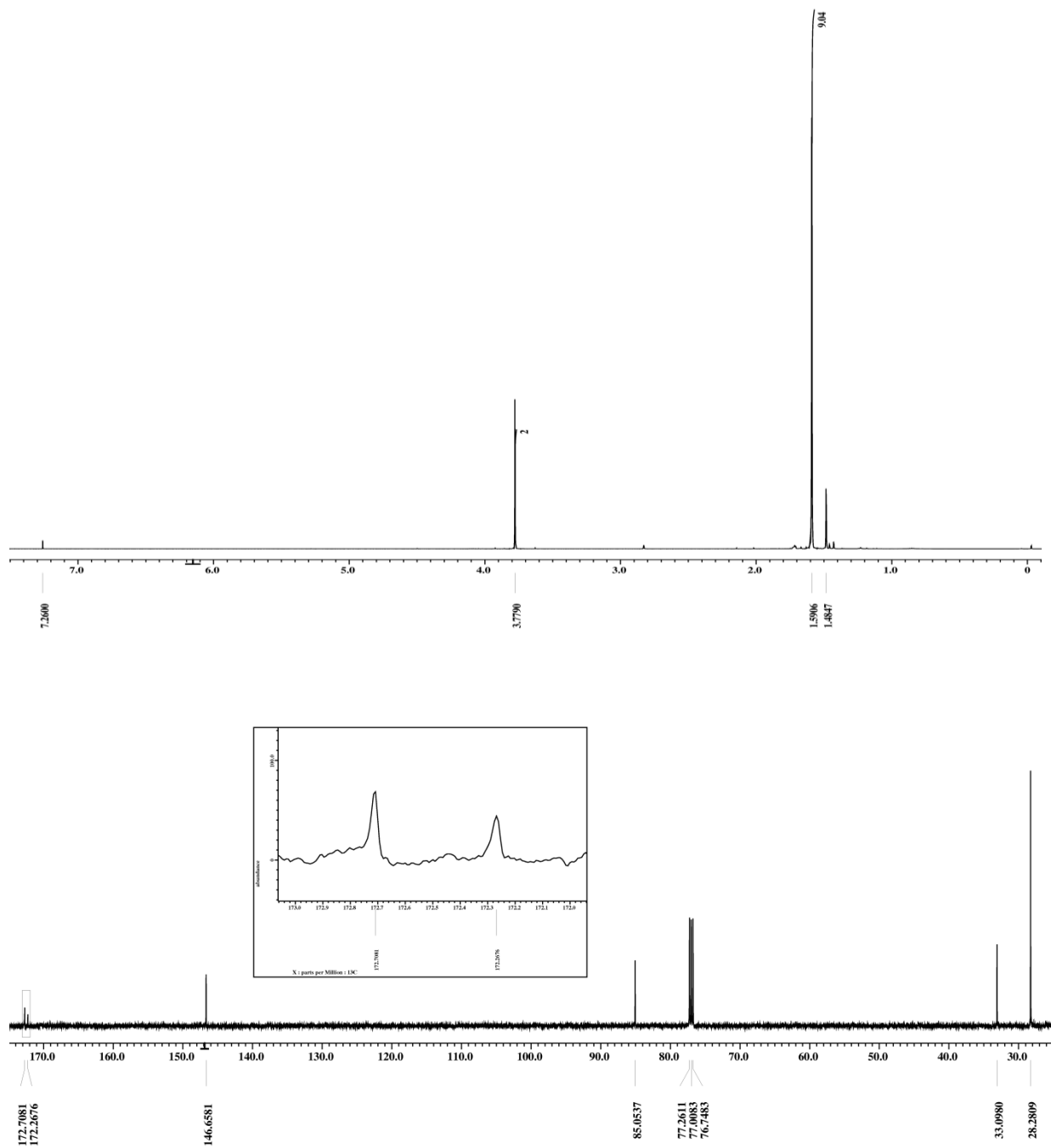
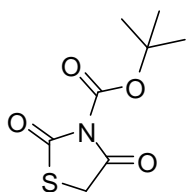
**Stability comparisons of aldol products in DMSO using PCM Model:** All structures were fully optimized through the Gaussian03 program,<sup>[3]</sup> using density functional theory (B3LYP)<sup>[4]</sup> and 6-311++G\*\* basis sets (PCM Model<sup>[5]</sup>, DMSO as a solvent). The relative energies for the compounds were evaluated from gas-phase optimized geometries. In all cases, the *syn* isomer was found to be lower in energy than the *anti* isomer using DMSO as the solvent.

entry	<i>syn</i> aldol product	energy (kJ/mol)	<i>anti</i> aldol product	energy (kJ/mol)	relative stability of <i>syn</i> isomer (kJ/mol)
1	 3aa	-3439722.73	 4aa	-3439713.60	9.13
2	 3ab	-3144677.97	 4ab	-3144669.85	8.12
3	 3ac	-9663516.53	 4ac	-9663505.60	10.93
4	 3ad	-4109787.16	 4ad	-4109780.38	6.78
5	 3ag	-2902261.25	 4ag	-2902250.61	10.63
6	 3ah	-3439708.20	 4ah	-3439697.40	10.80

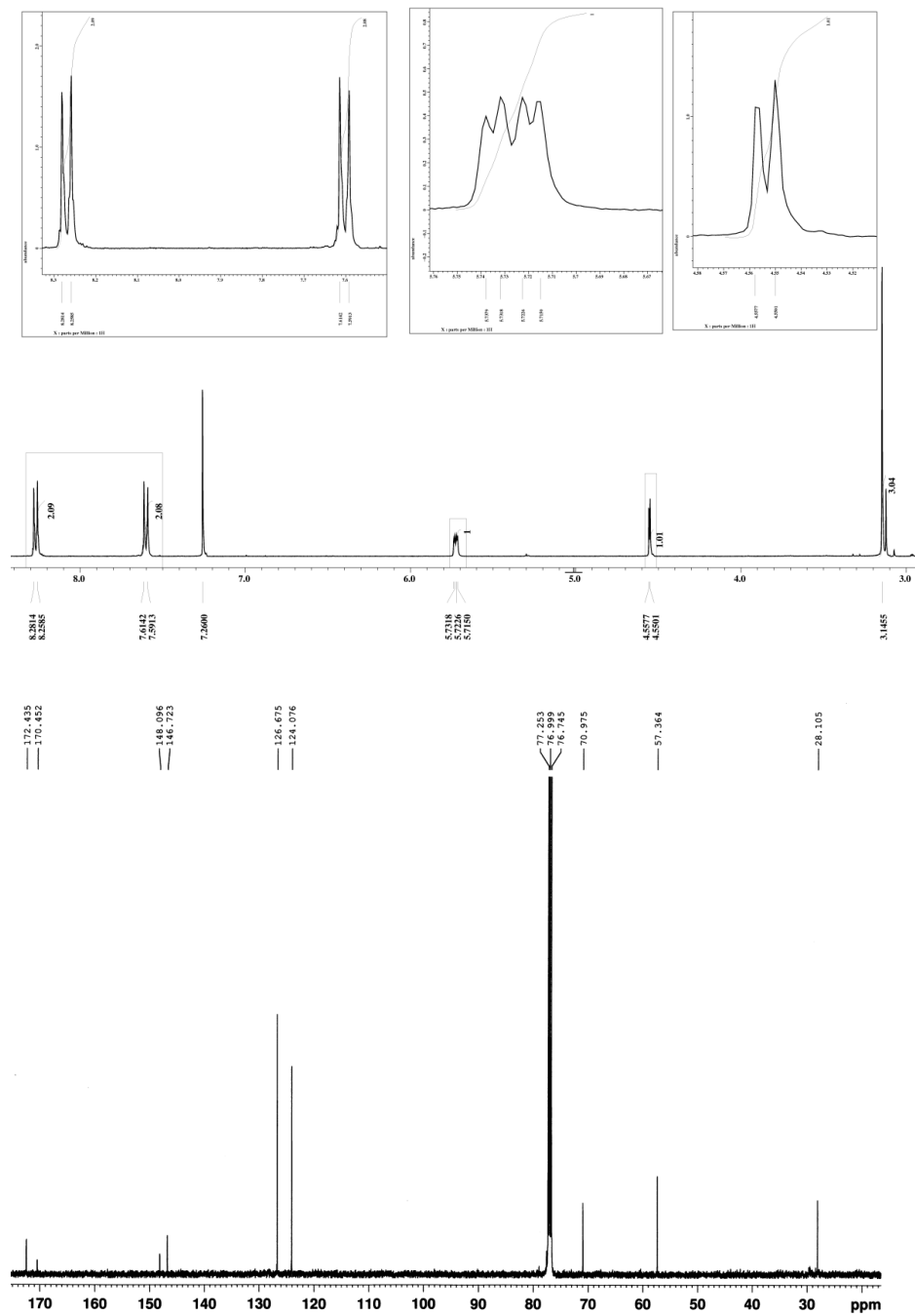
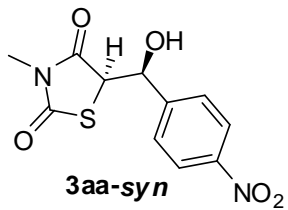
[<sup>3</sup>] a) Cammi, R.; Tomasi, J. *J. Comput. Chem.* **1995**, *16*, 1449; b) S. Miertus, E. Scrocco and J. Tomasi. *Chem. Phys.*, **55** (1981), p. 117.

## 7.0 NMR spectra of compounds:

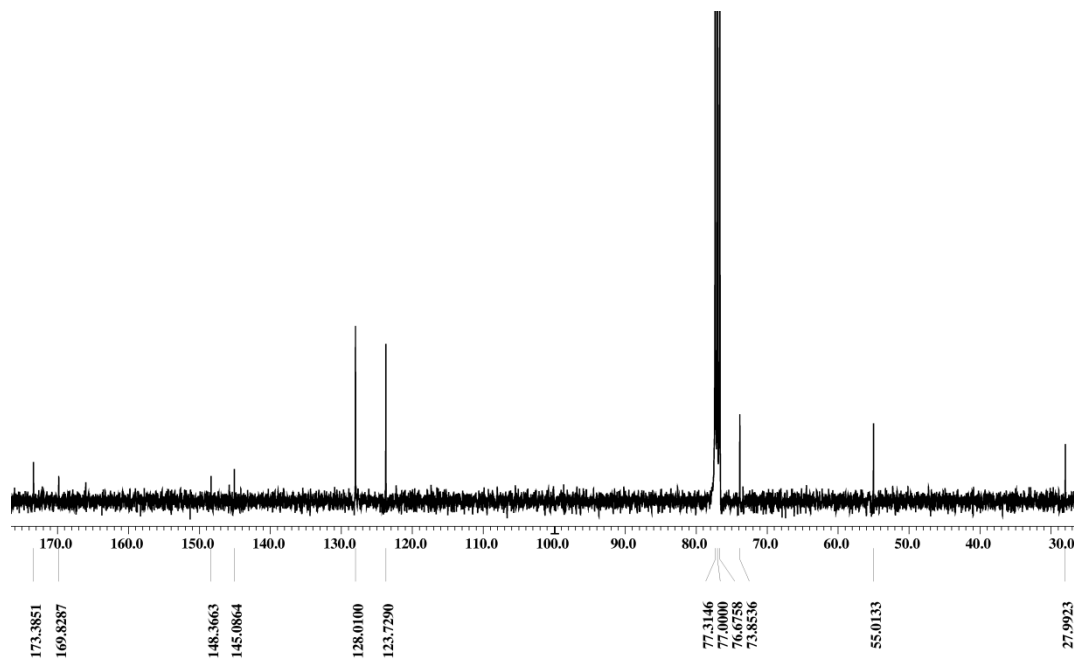
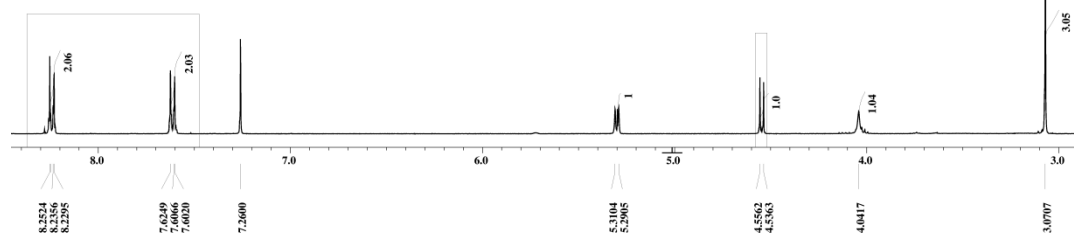
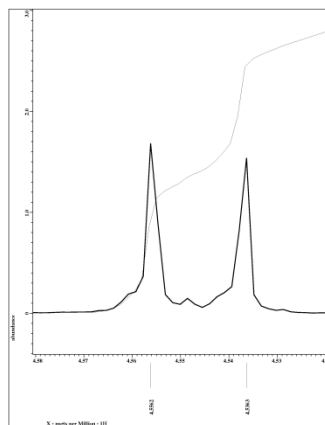
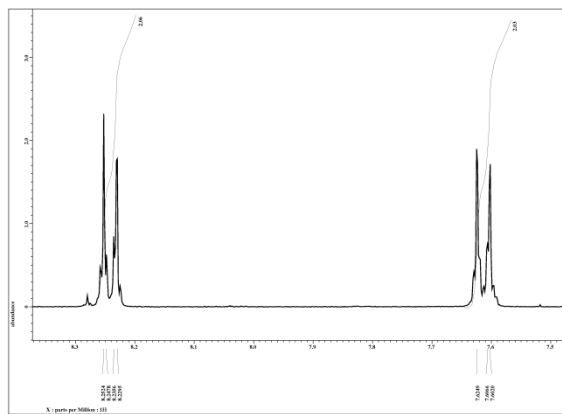
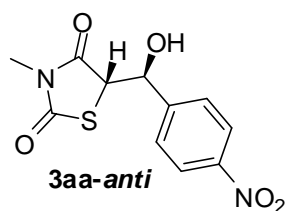
### $^1\text{H}$ and $^{13}\text{C}$ NMR of compound 1c:



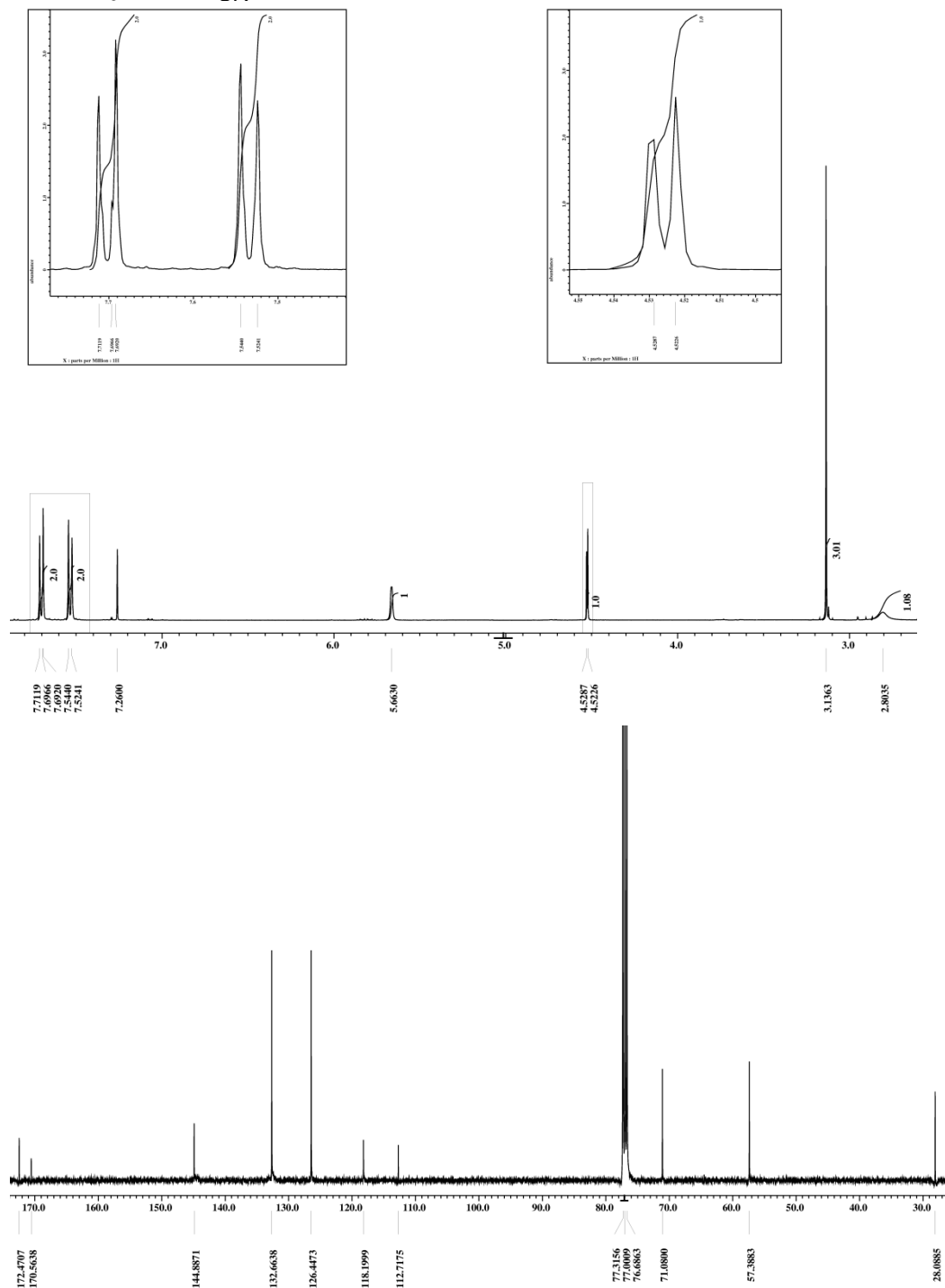
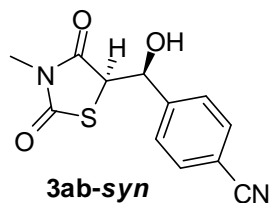
### $^1\text{H}$ and $^{13}\text{C}$ NMR of compound **3aa-syn**:



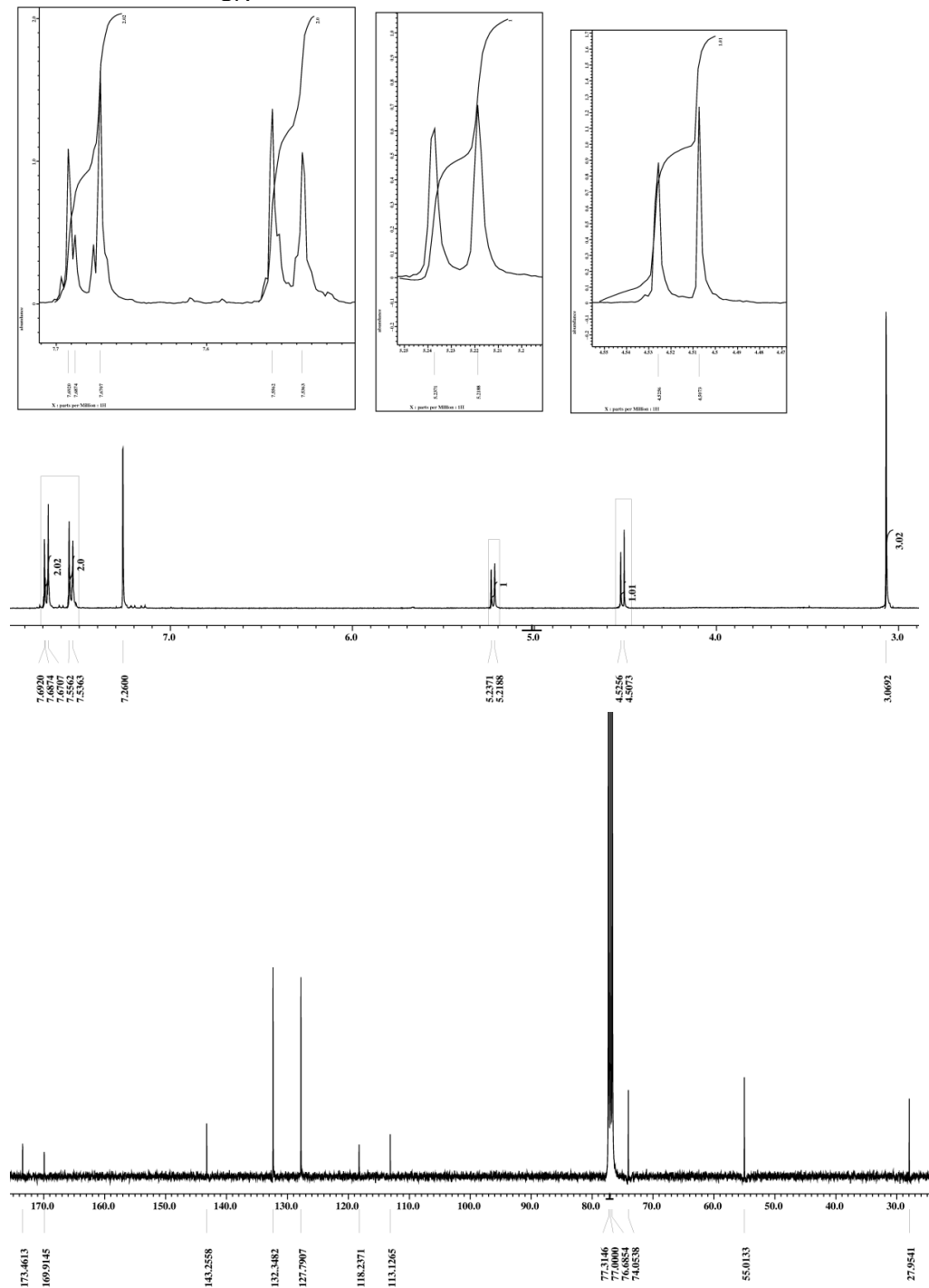
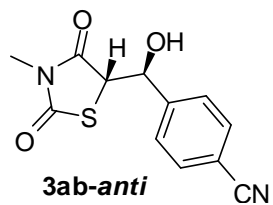
### $^1\text{H}$ and $^{13}\text{C}$ NMR of compound **3aa-anti**:



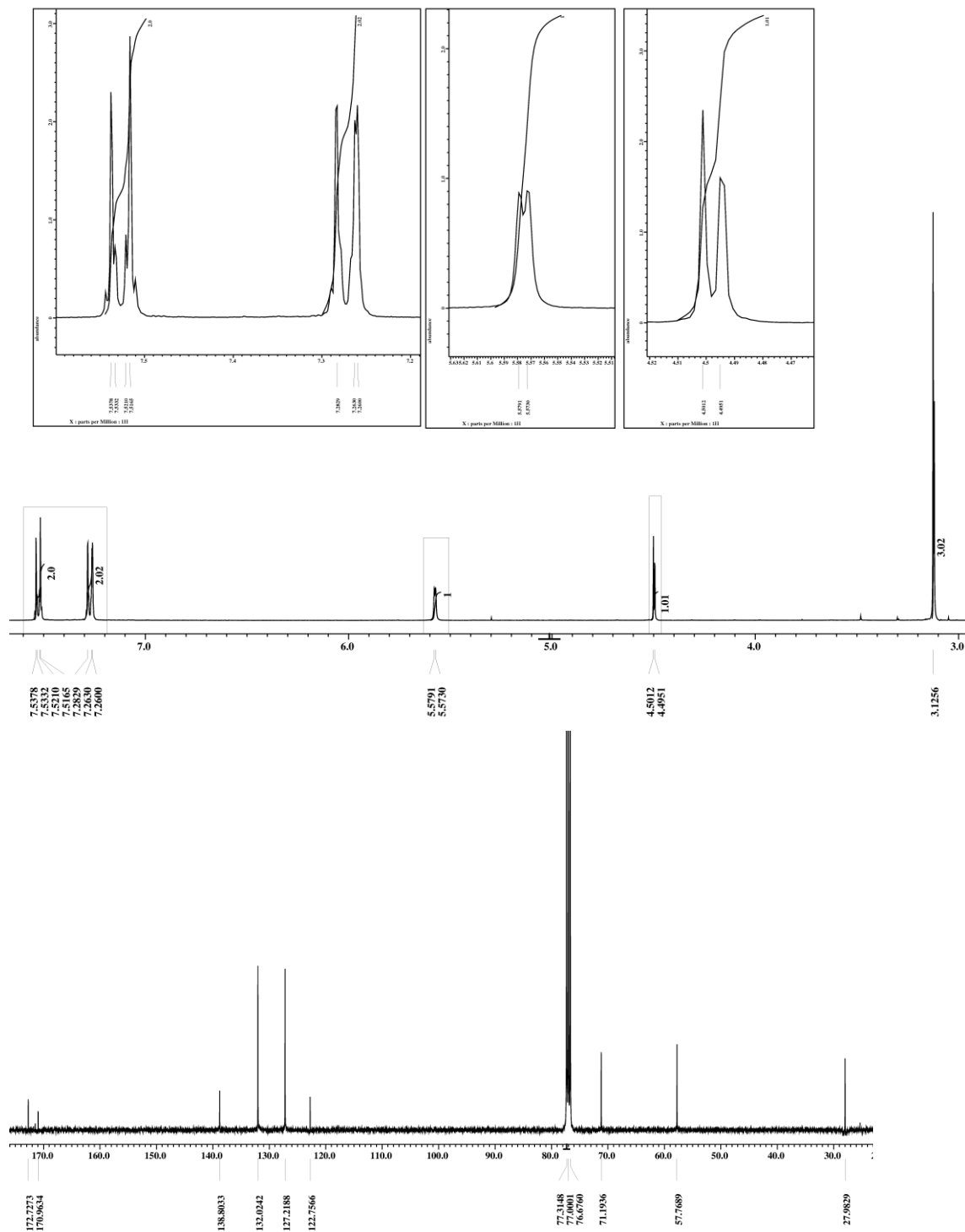
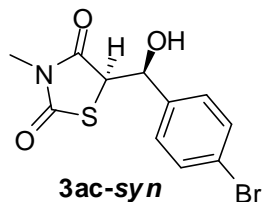
$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ab-syn**:



$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ab-anti**:

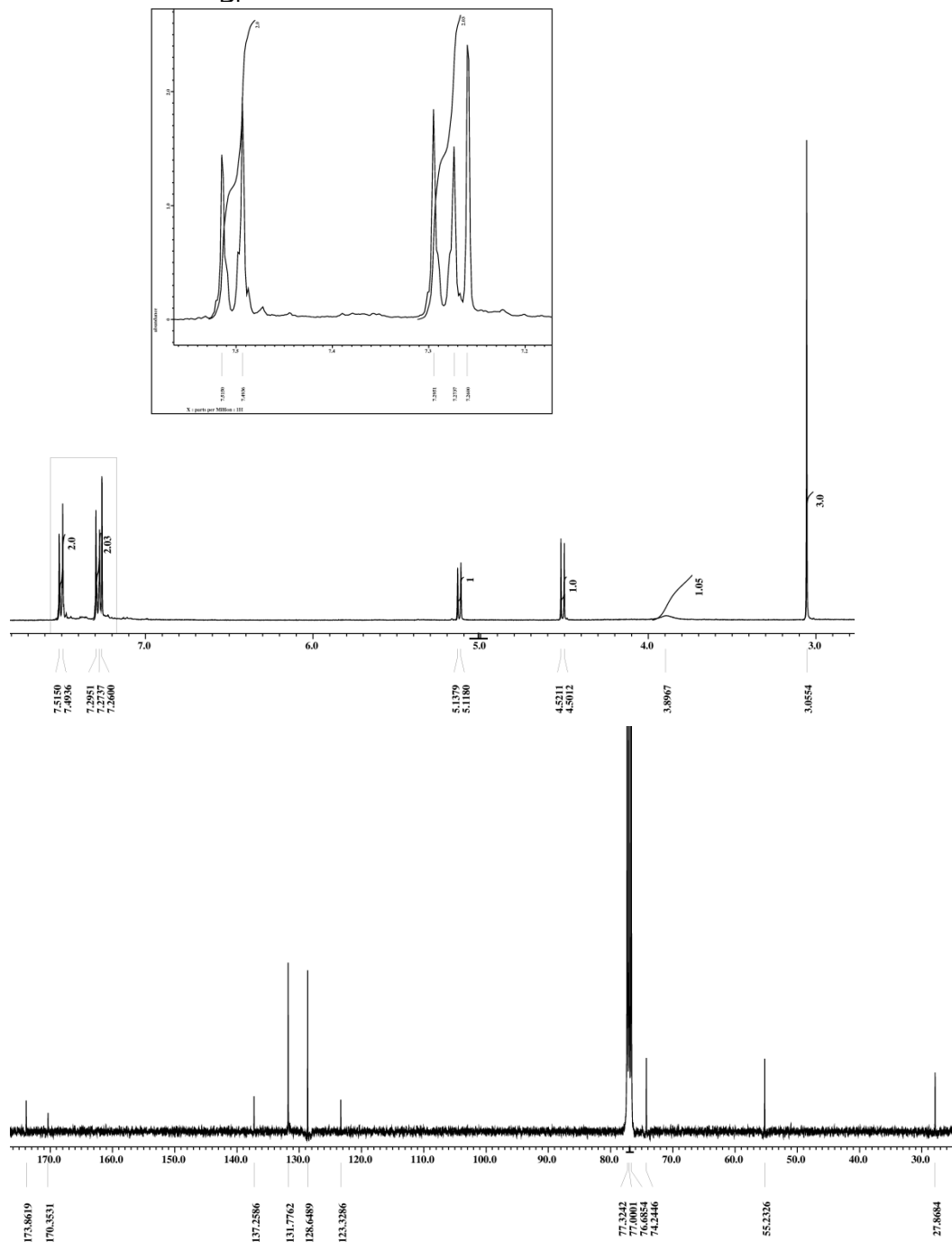
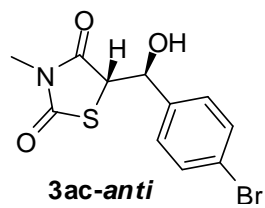


$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ac-syn**:

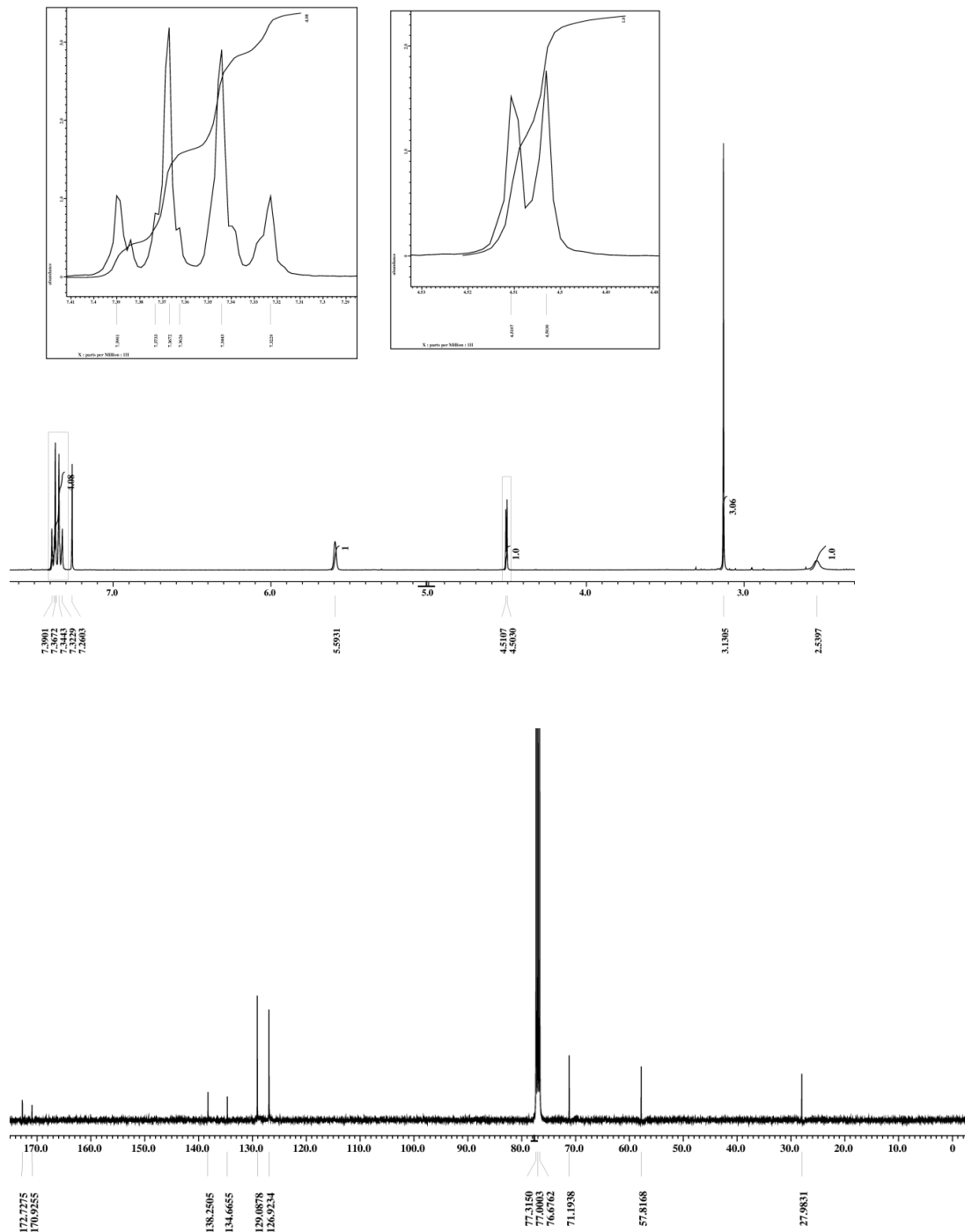
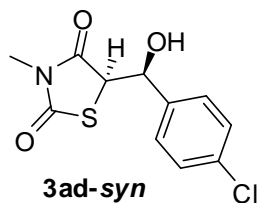




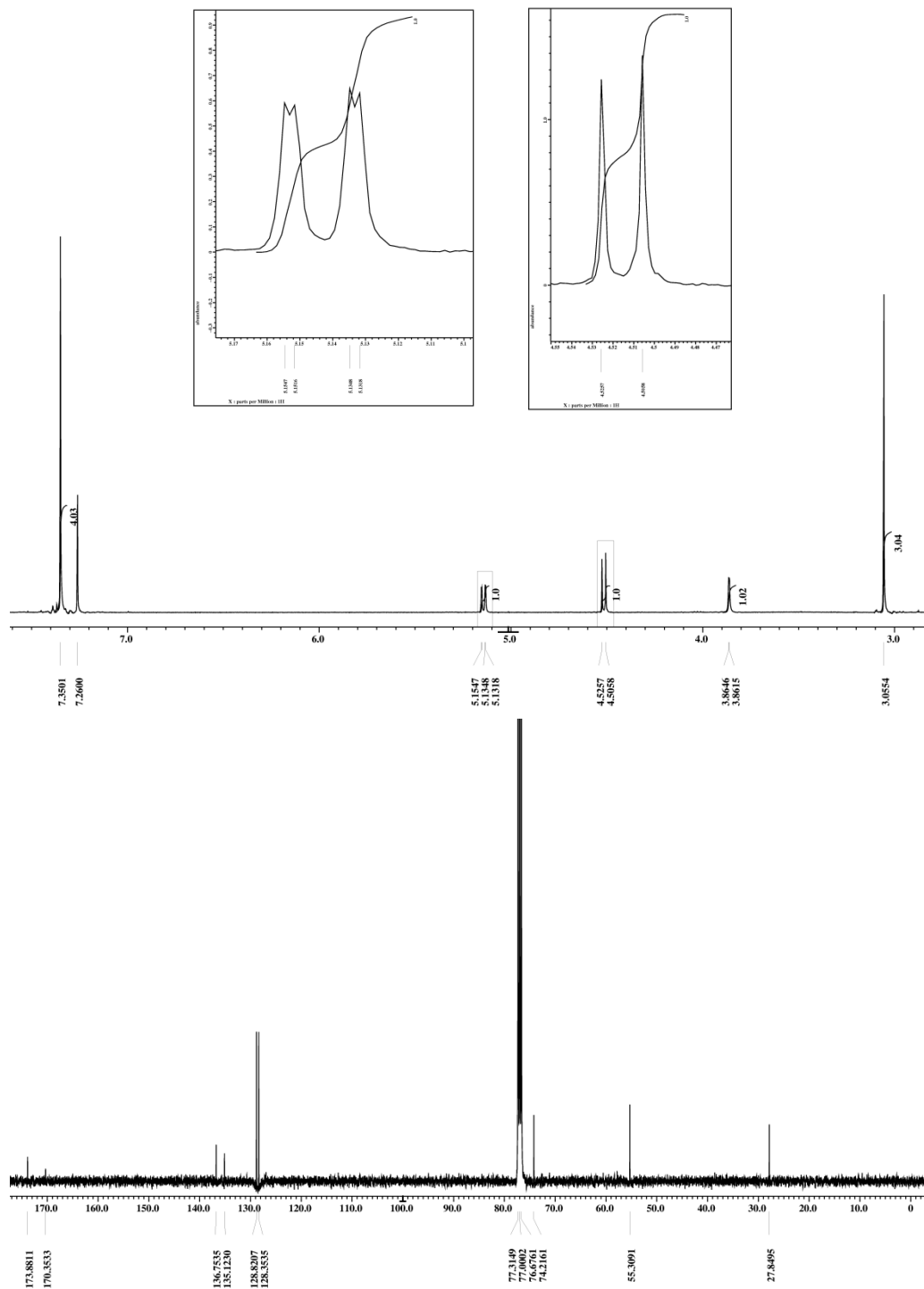
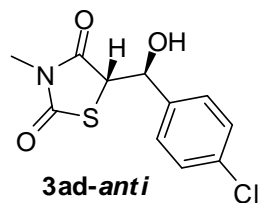
$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ac-anti**:



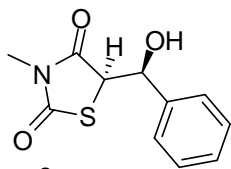
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3ad-syn**:



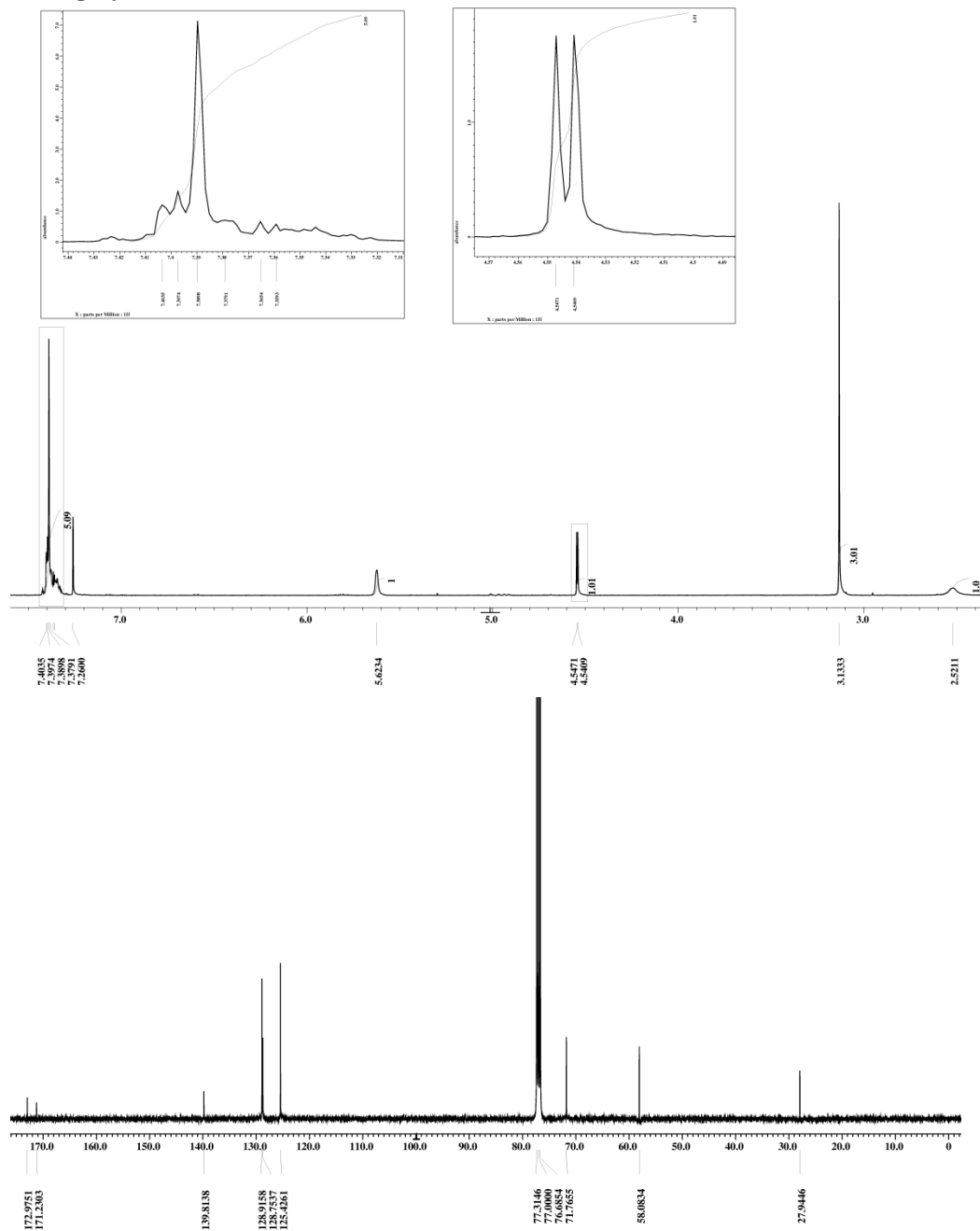
$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ad-anti**:



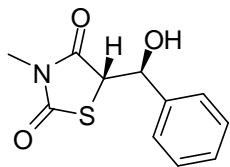
### $^1\text{H}$ and $^{13}\text{C}$ of compound 3ag-syn:



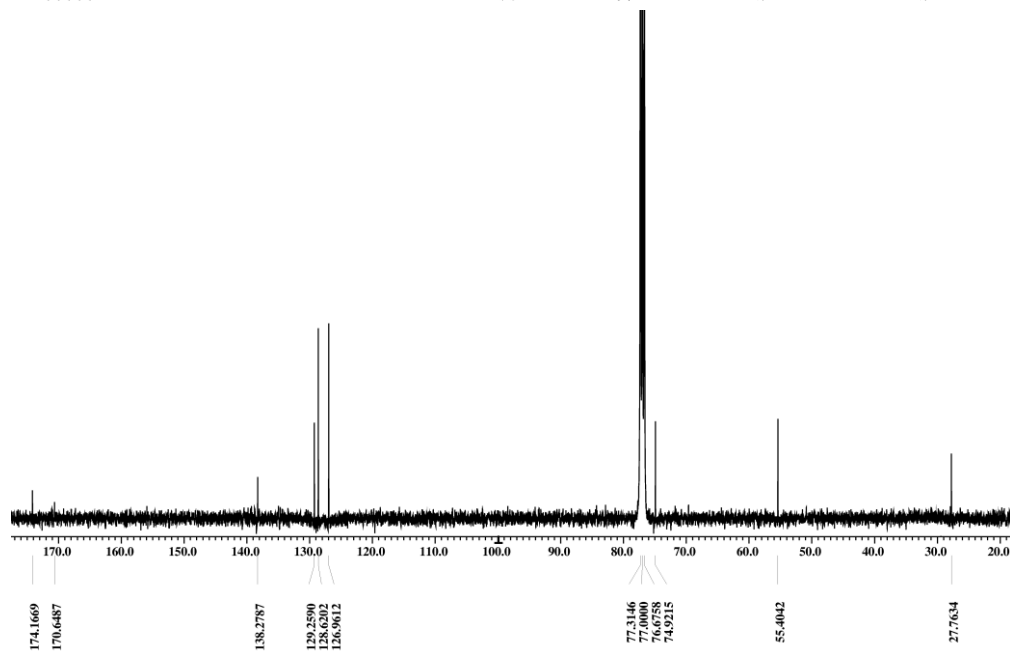
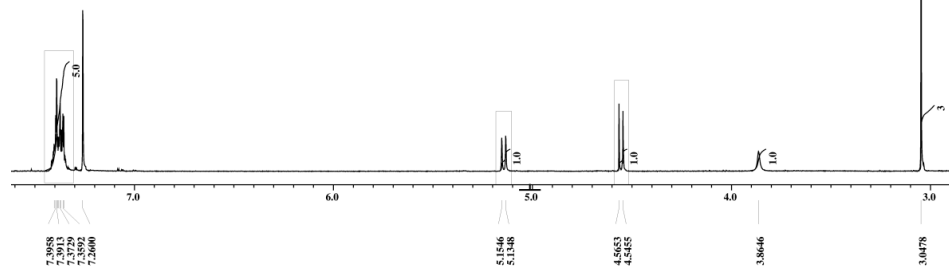
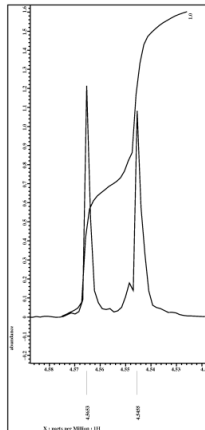
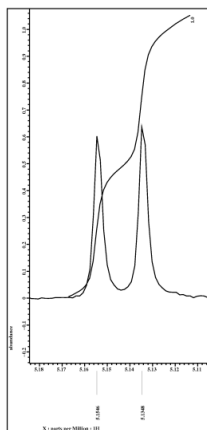
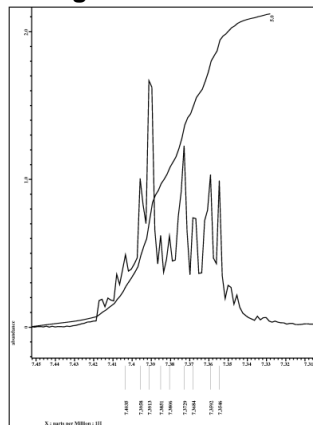
3ag-syn



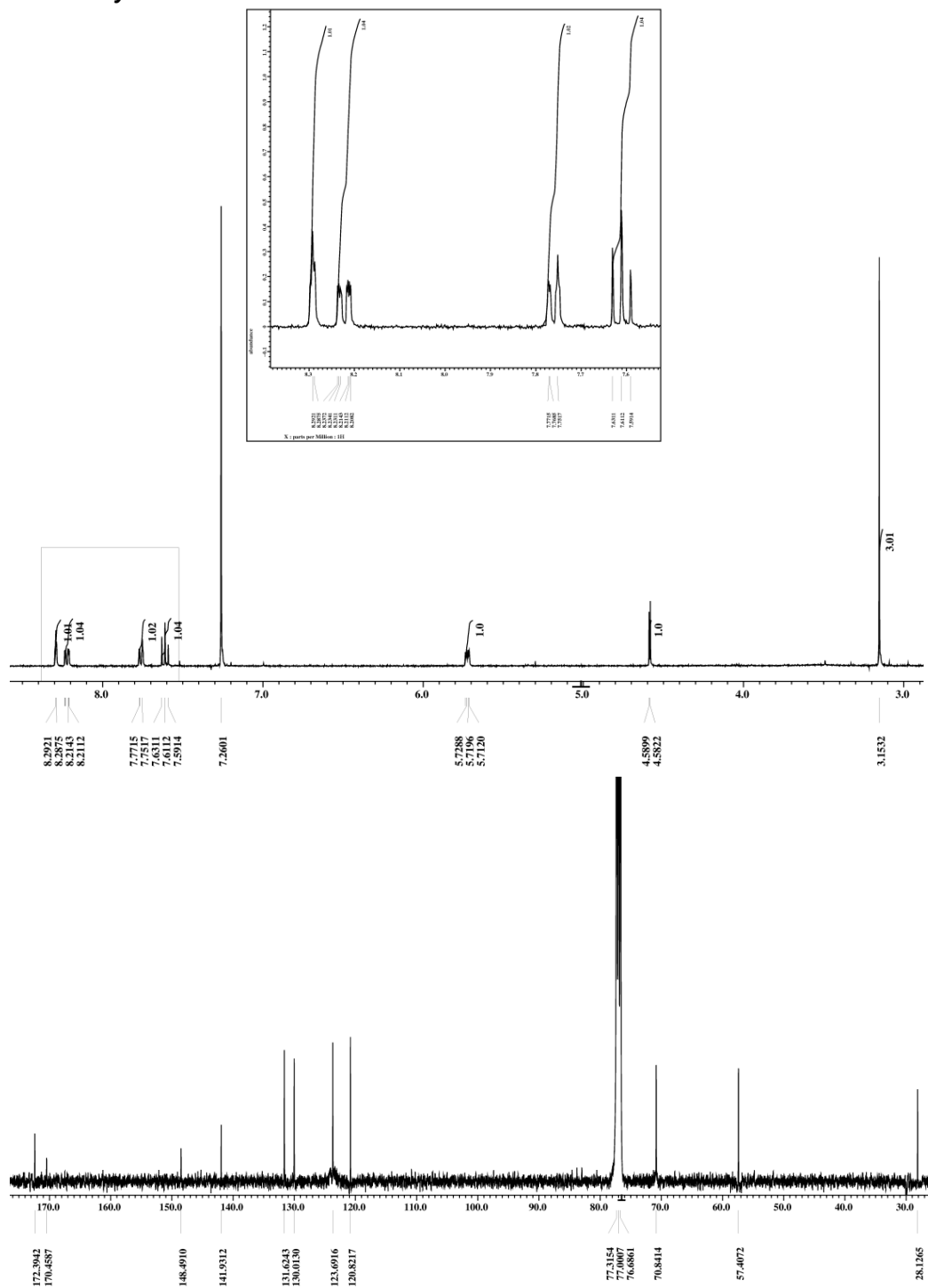
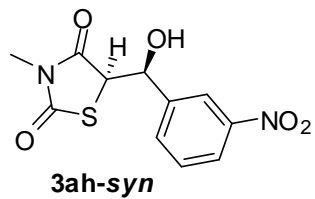
$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ag-anti**:



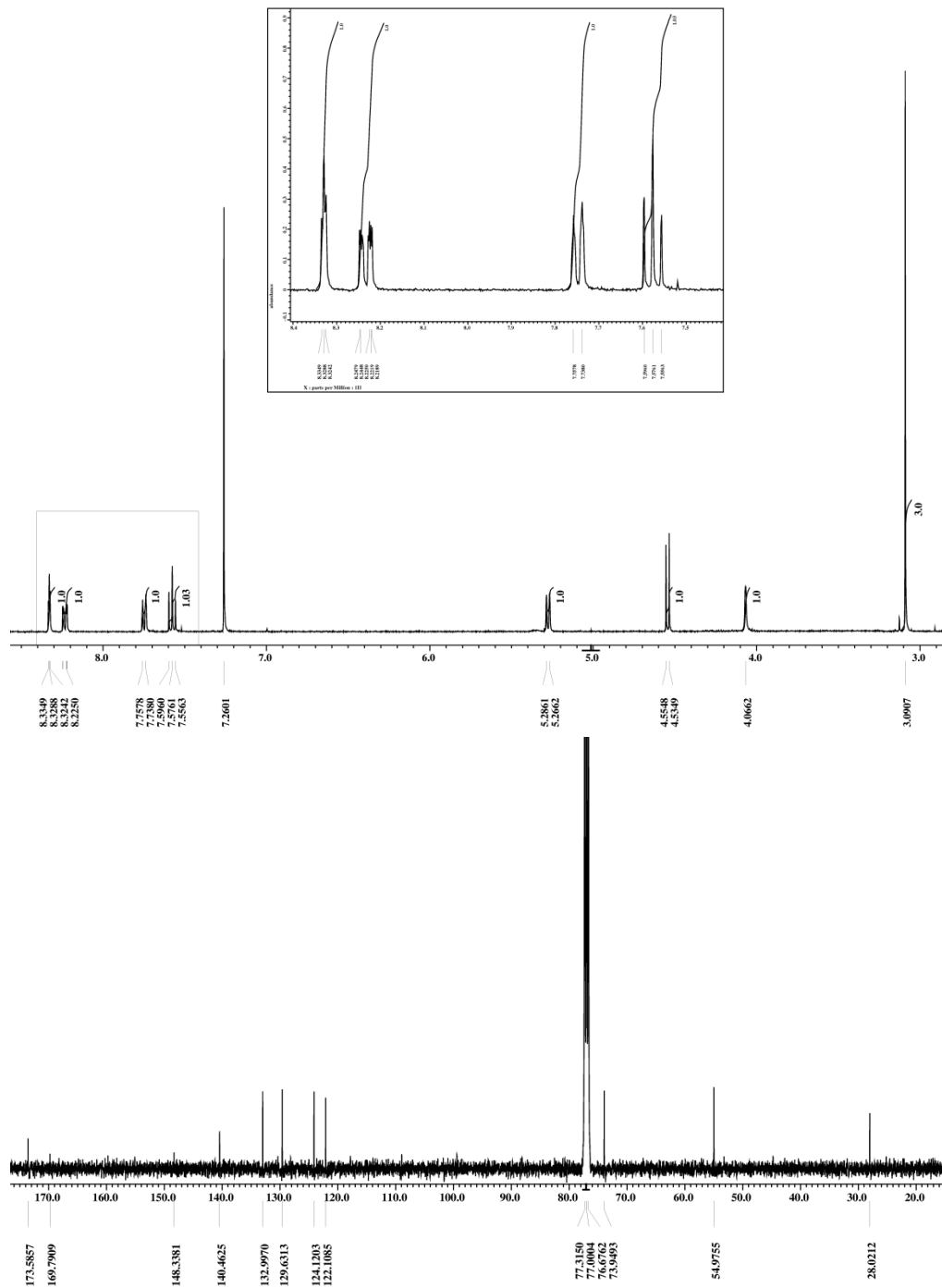
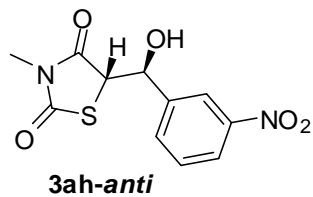
**3ag-anti**



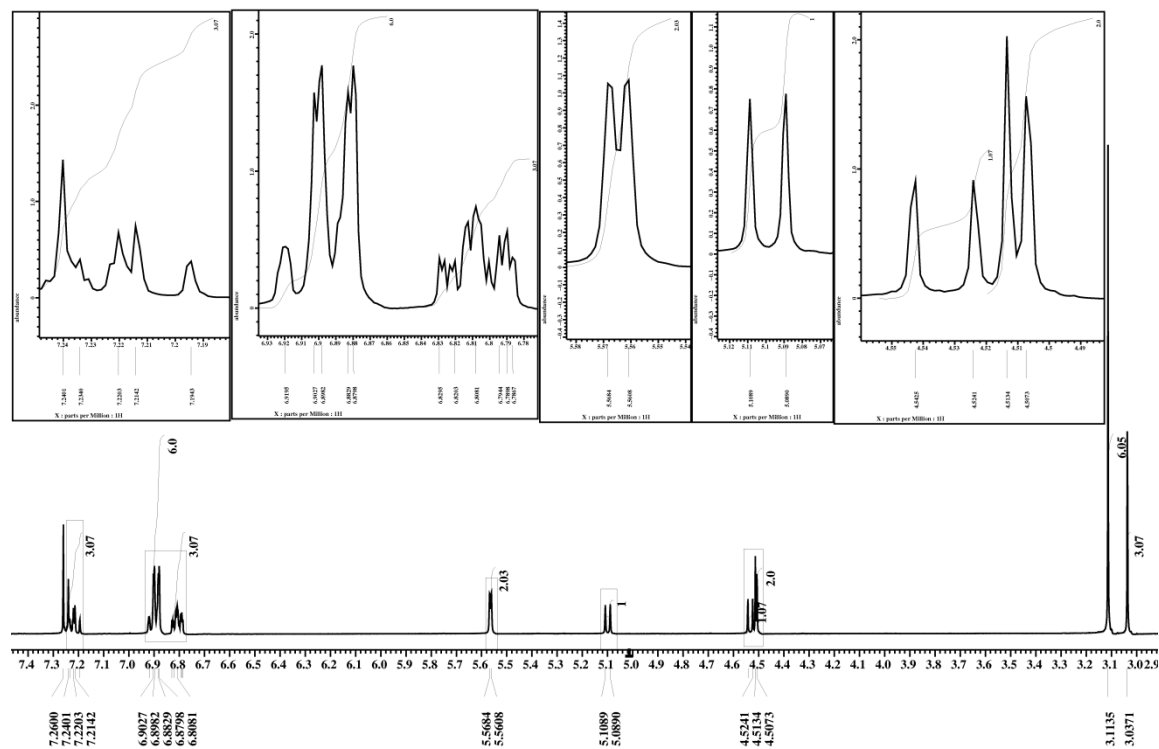
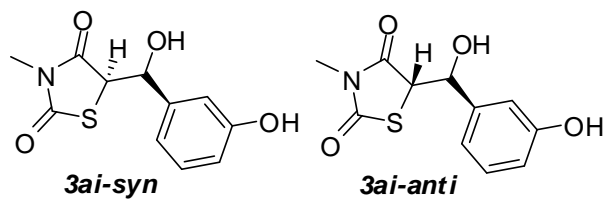
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3ah-syn**:



$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ah-anti**:

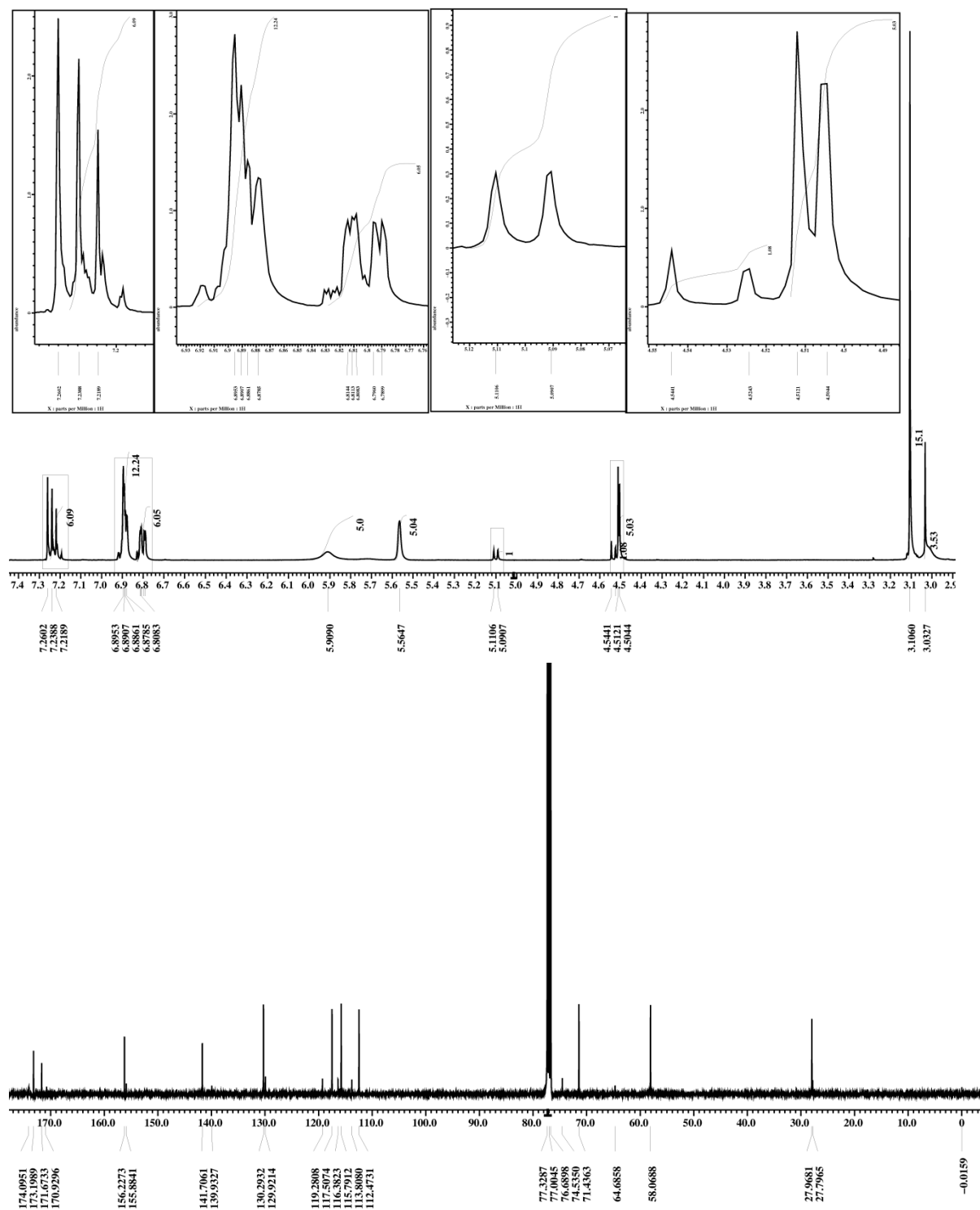
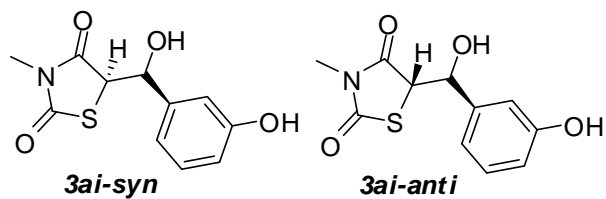


<sup>1</sup>H compound 3ai (from a 67:33 *syn/anti* mixture):

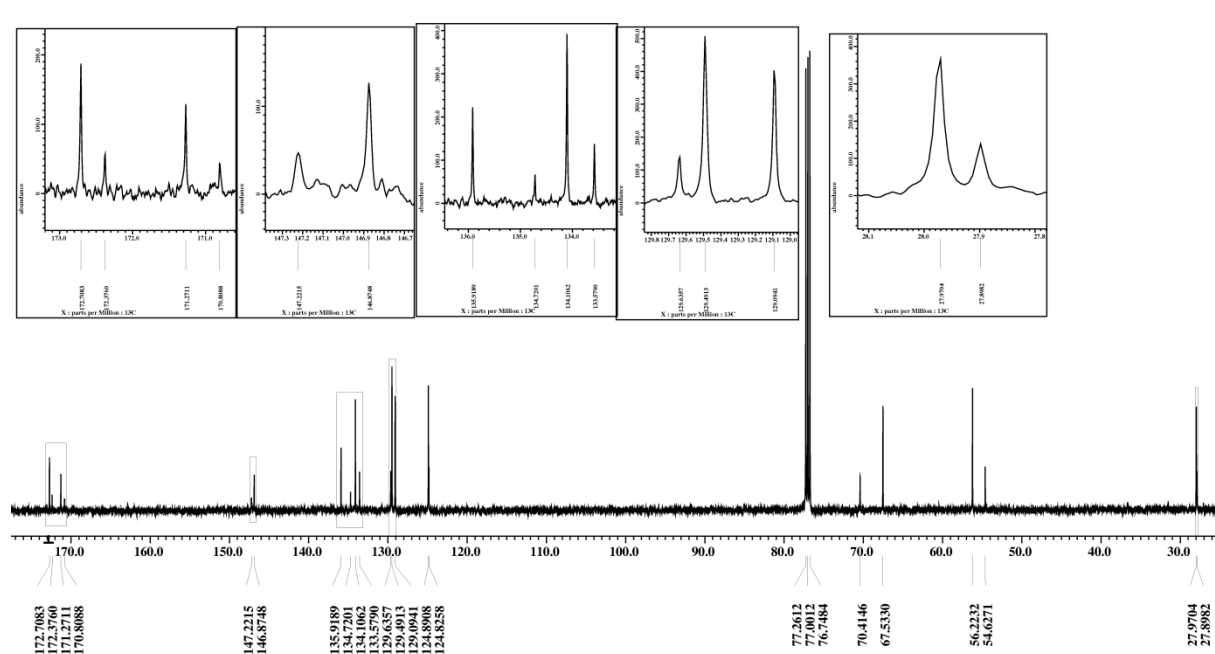
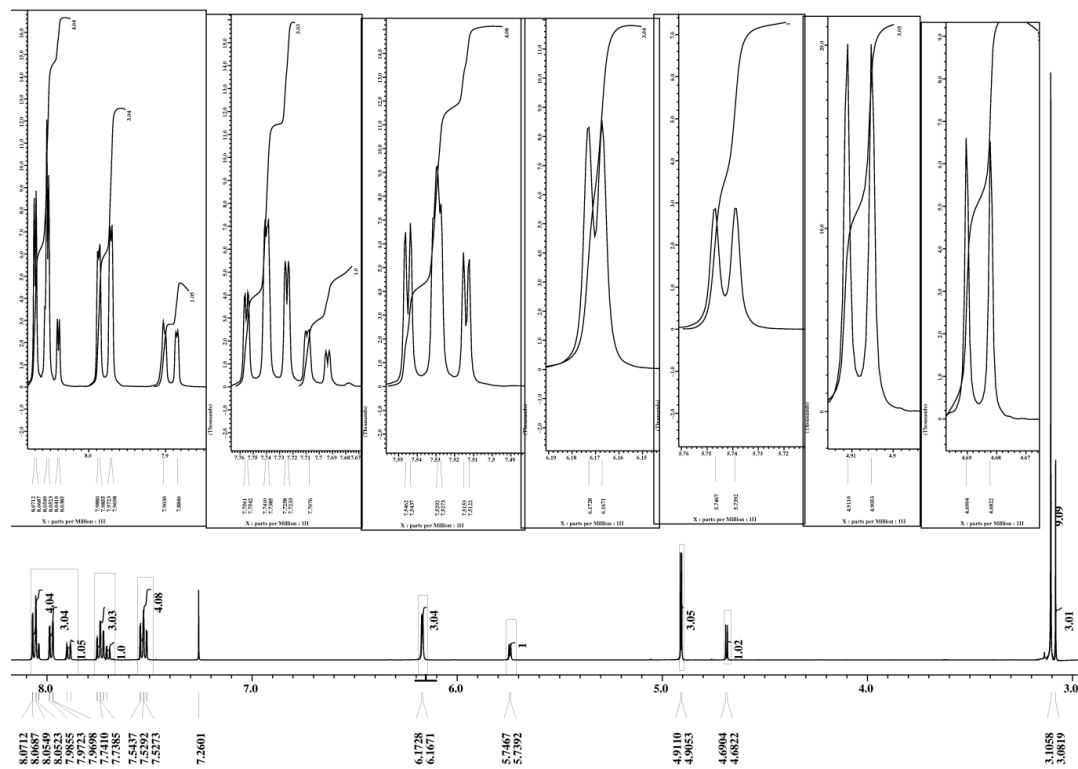
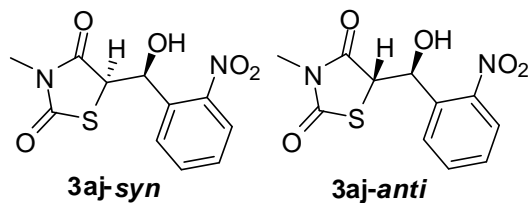




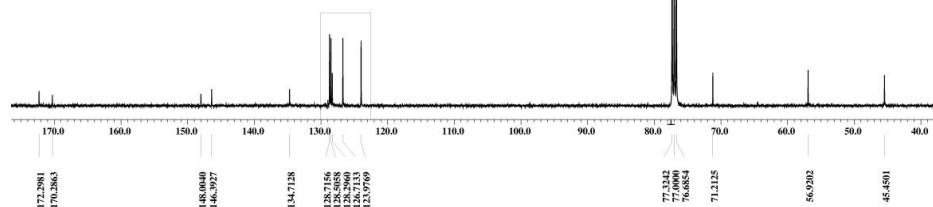
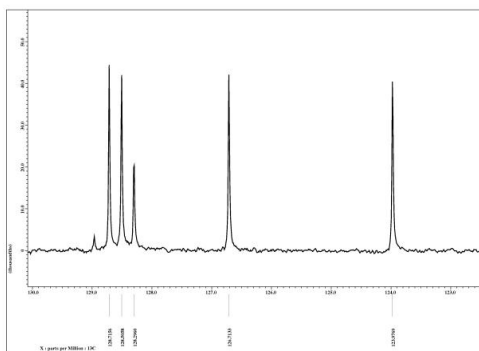
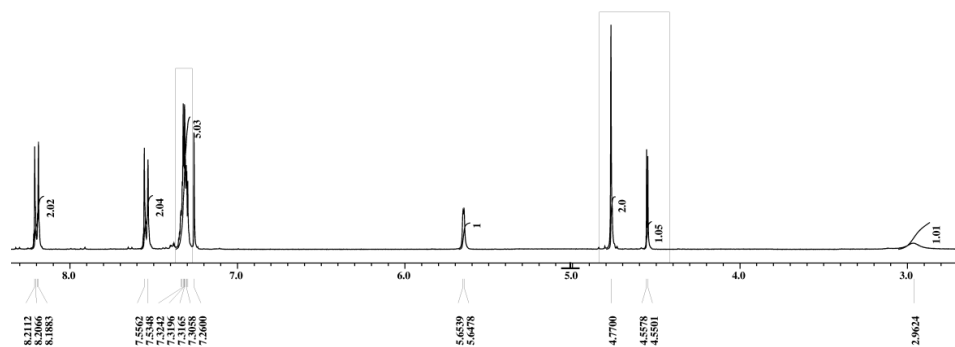
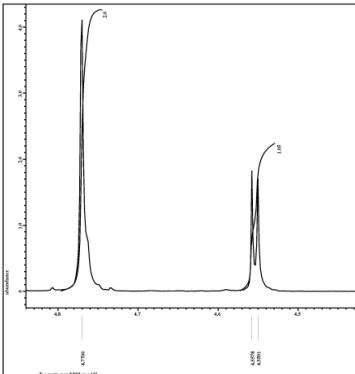
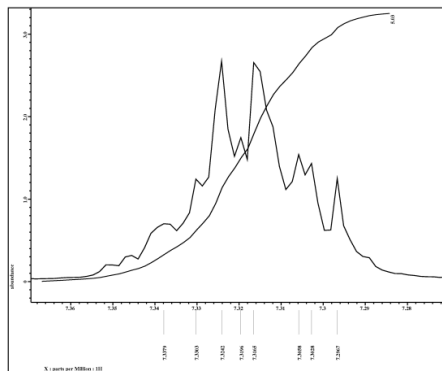
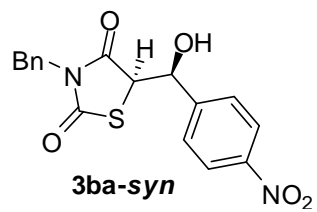
$^1\text{H}$  and  $^{13}\text{C}$  of compound 3ai (from a 83:17 *syn/anti* mixture):



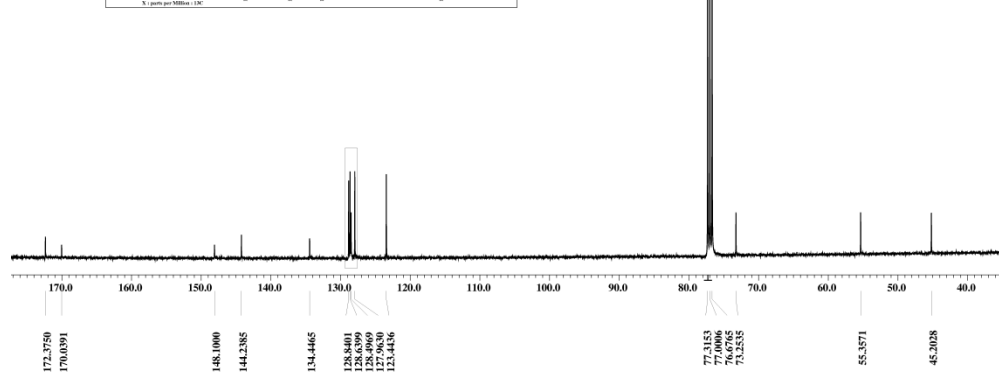
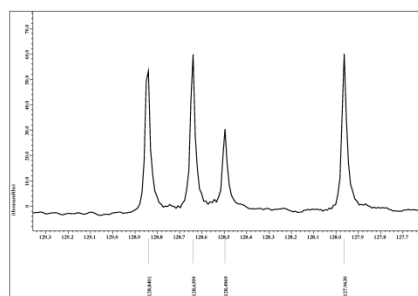
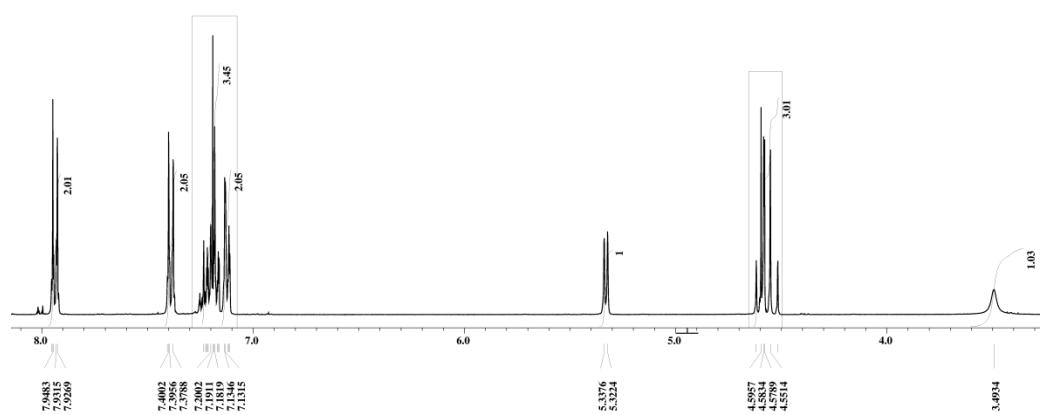
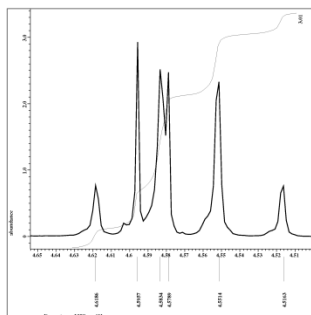
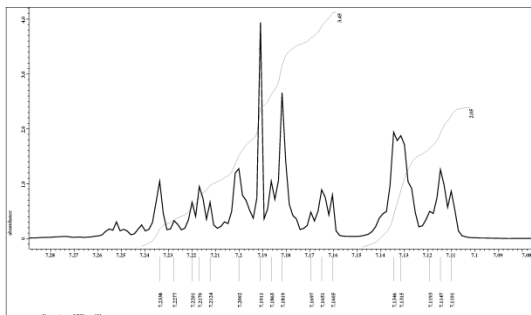
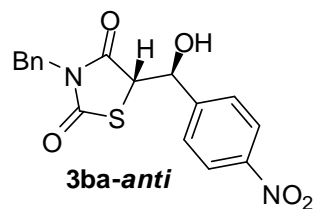
$^1\text{H}$  and  $^{13}\text{C}$  of compound 3aj (from a 75:25 *syn/anti* mixture):



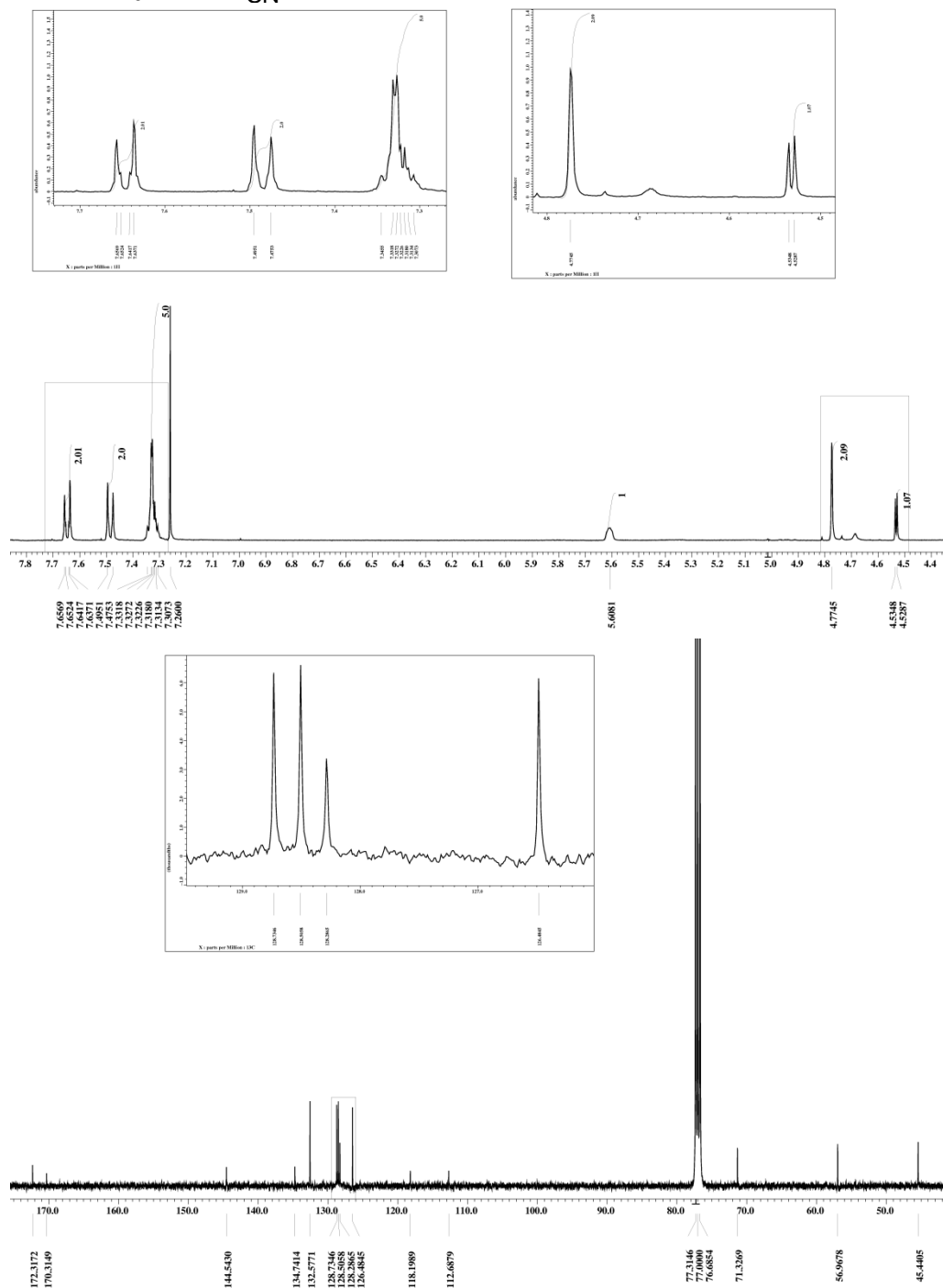
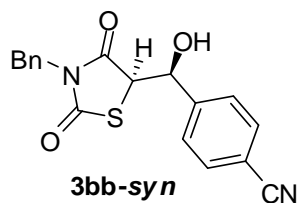
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3ba-syn**:



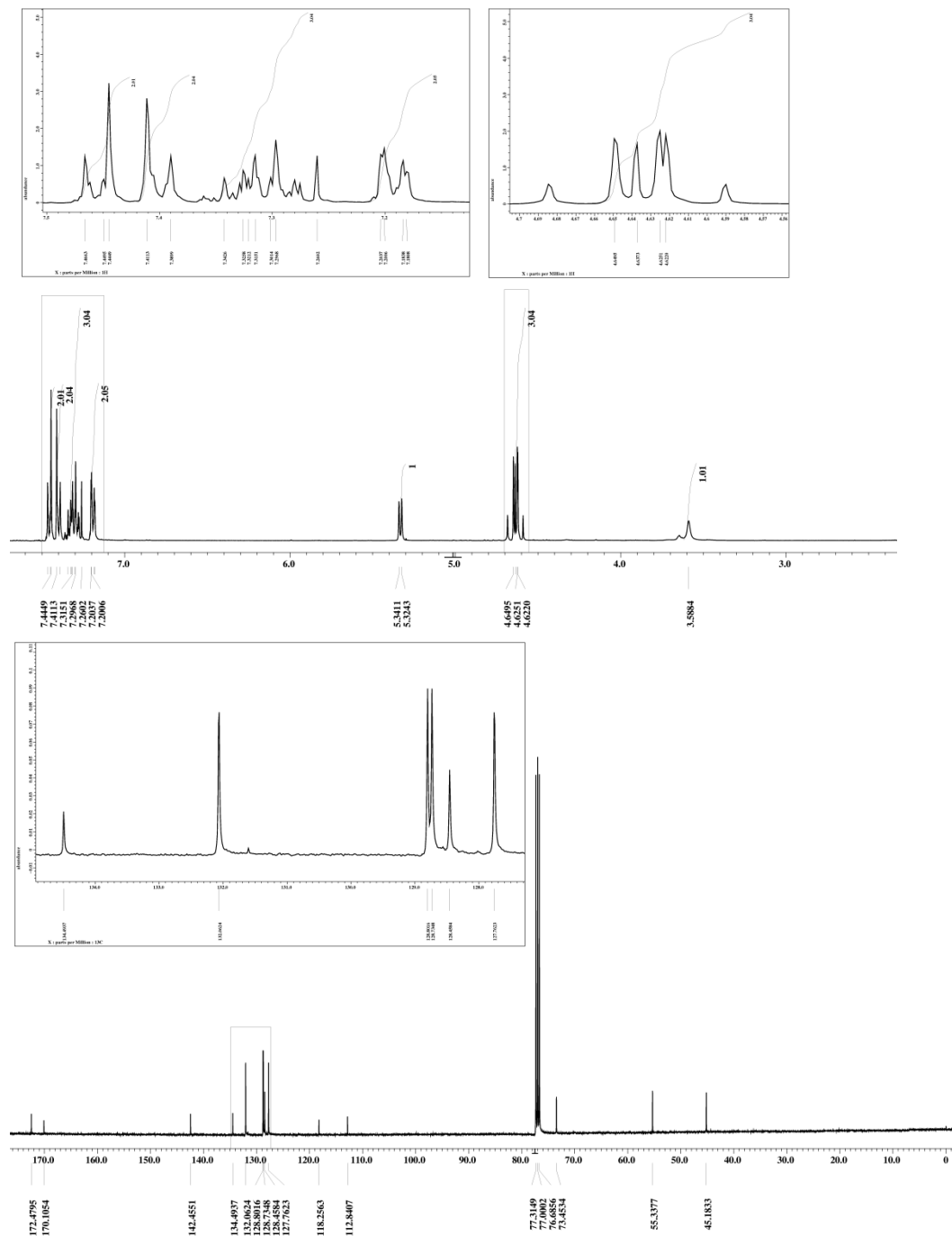
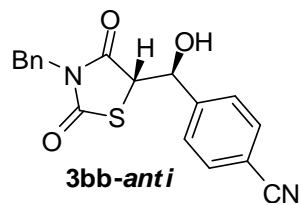
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3ba-anti**:



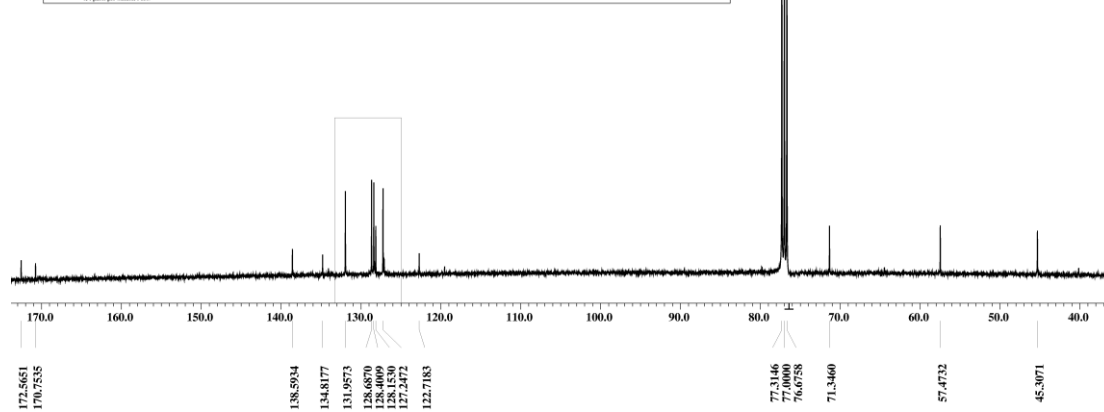
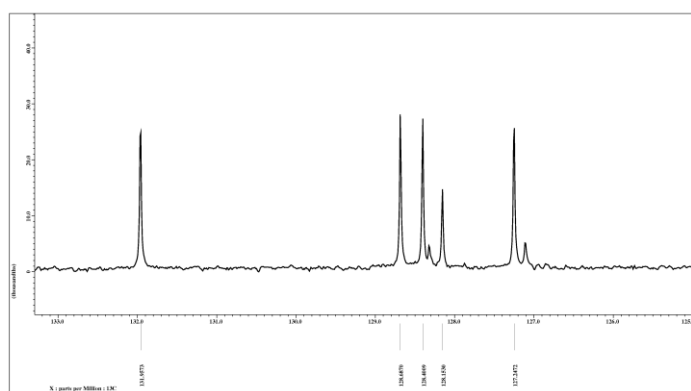
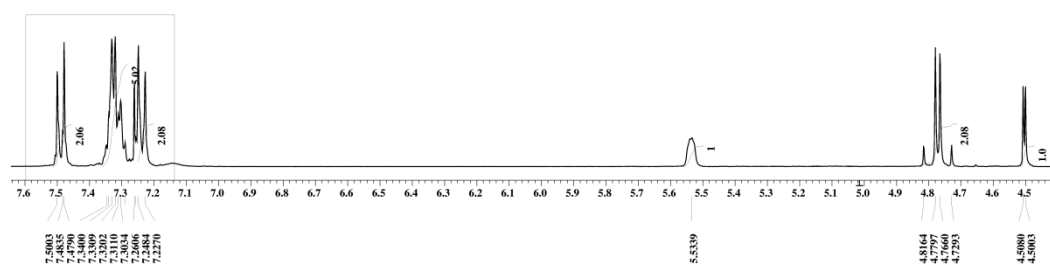
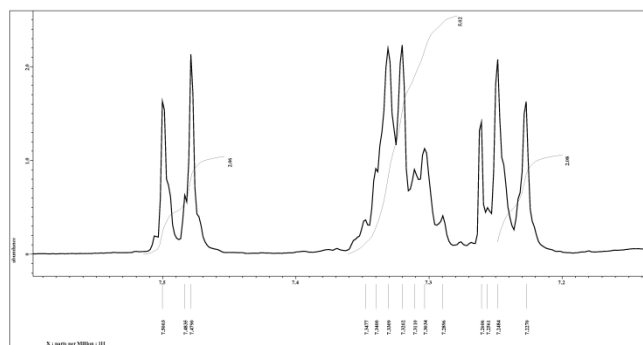
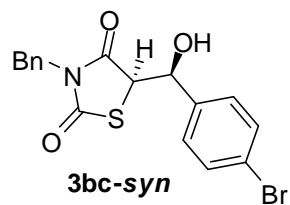
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3bb-syn**:



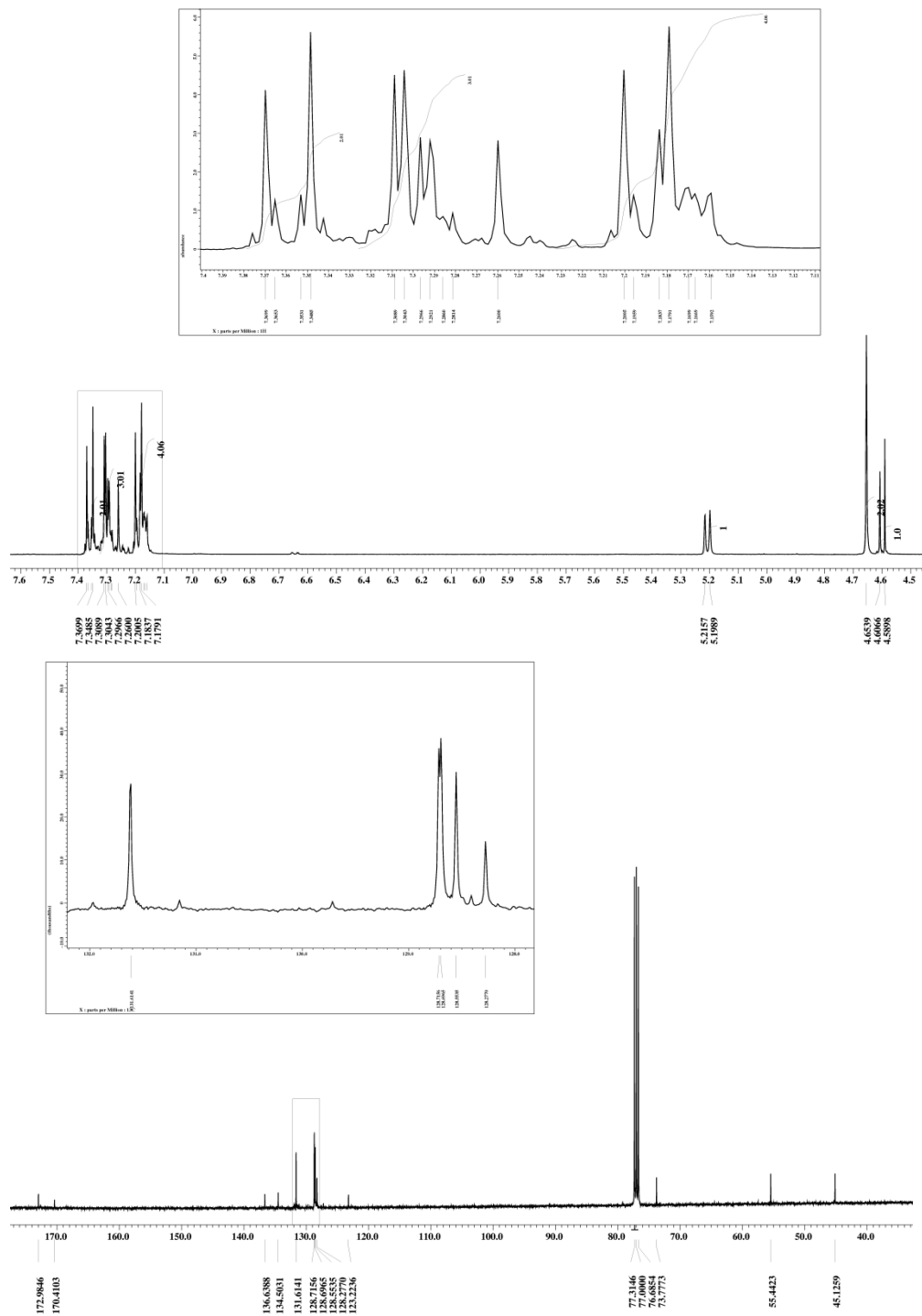
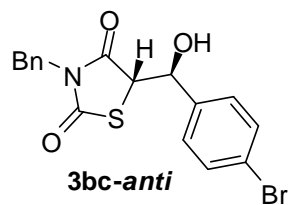
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3bb-anti**:



### $^1\text{H}$ and $^{13}\text{C}$ of compound **3bc-syn**:

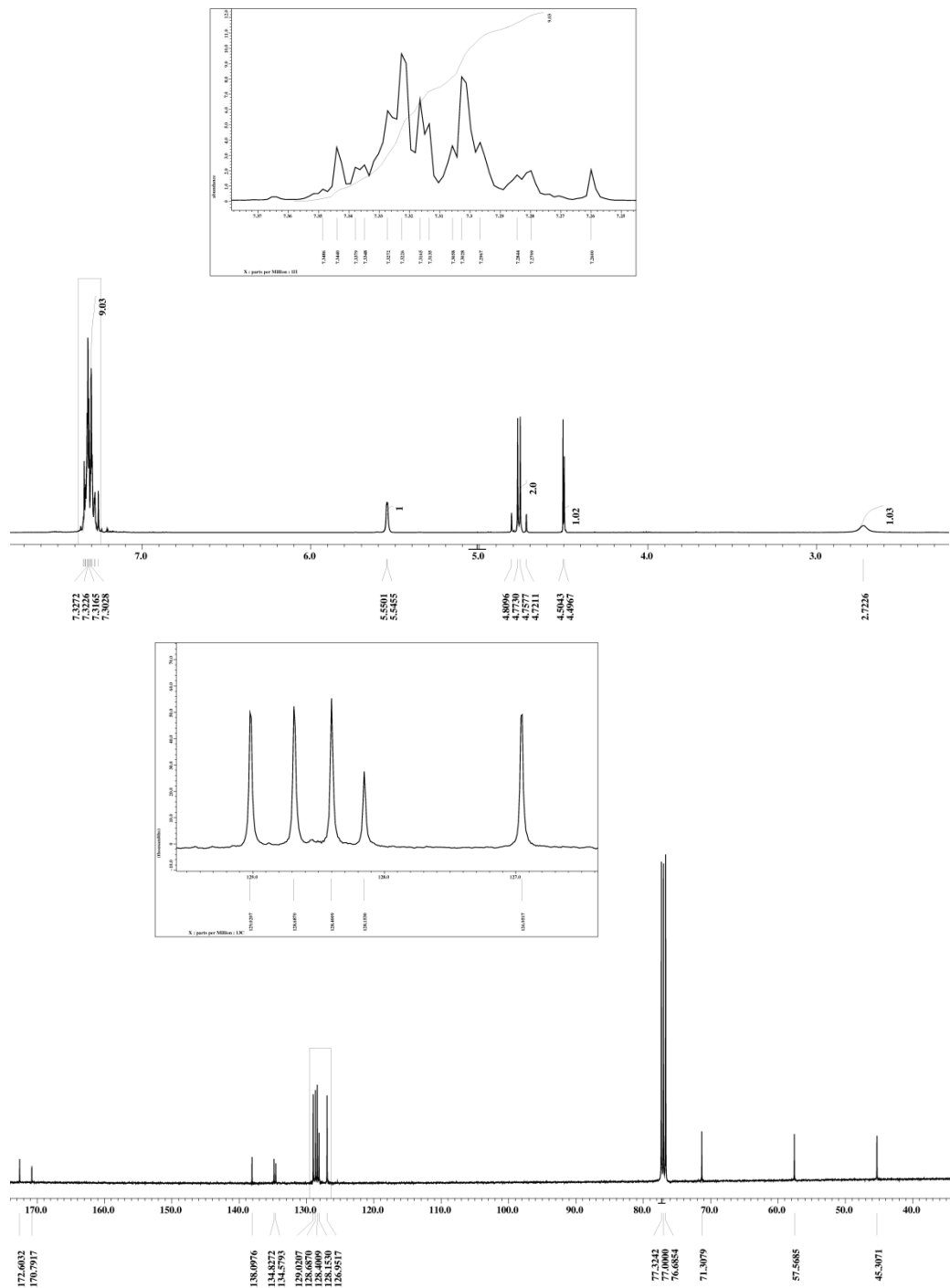
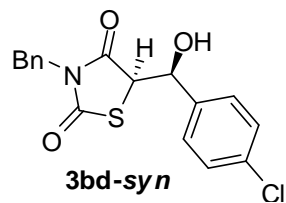


### $^1\text{H}$ and $^{13}\text{C}$ of compound **3bc-anti**:

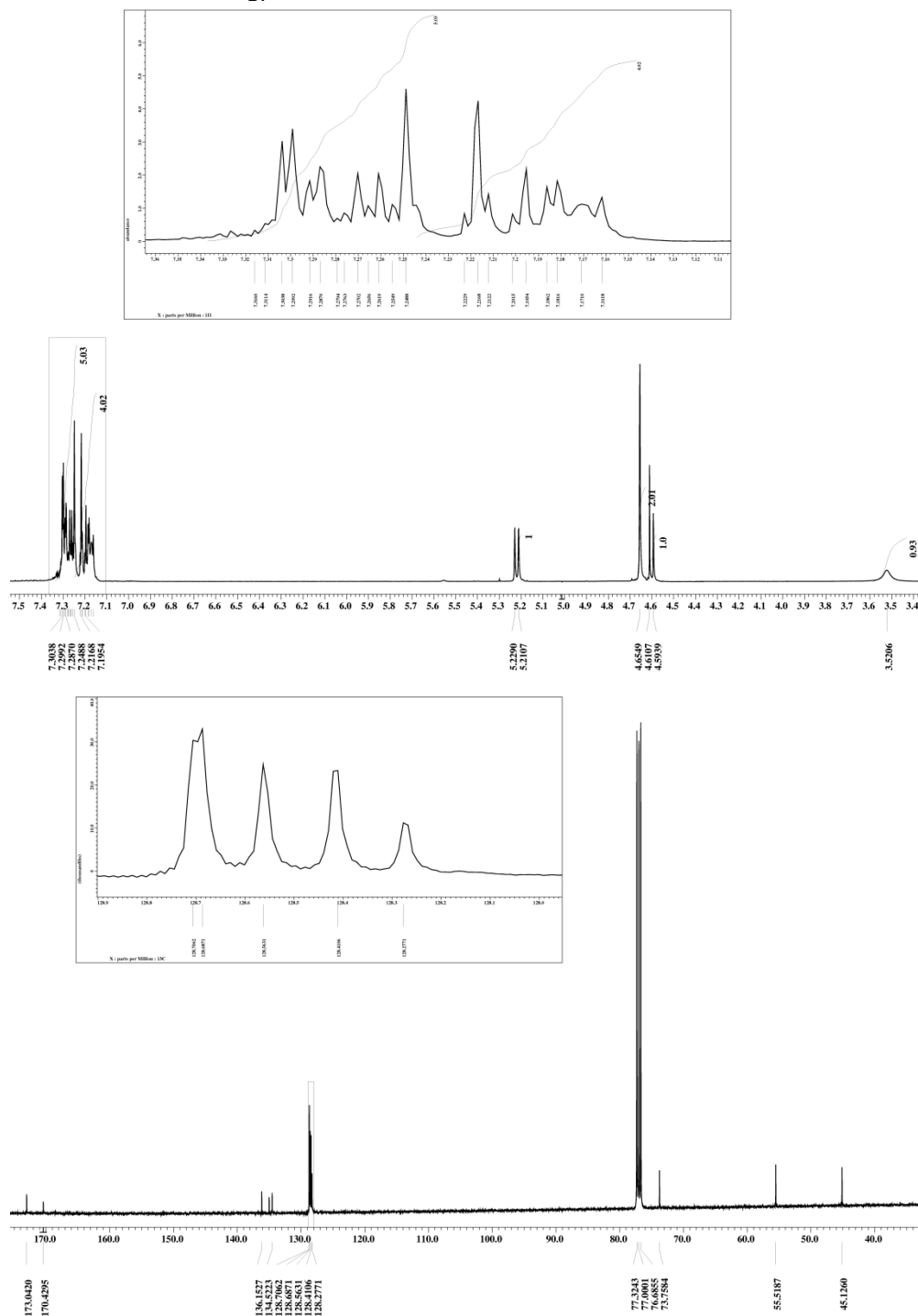
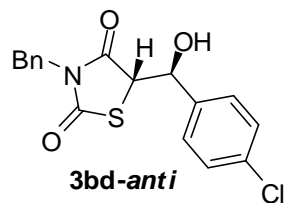




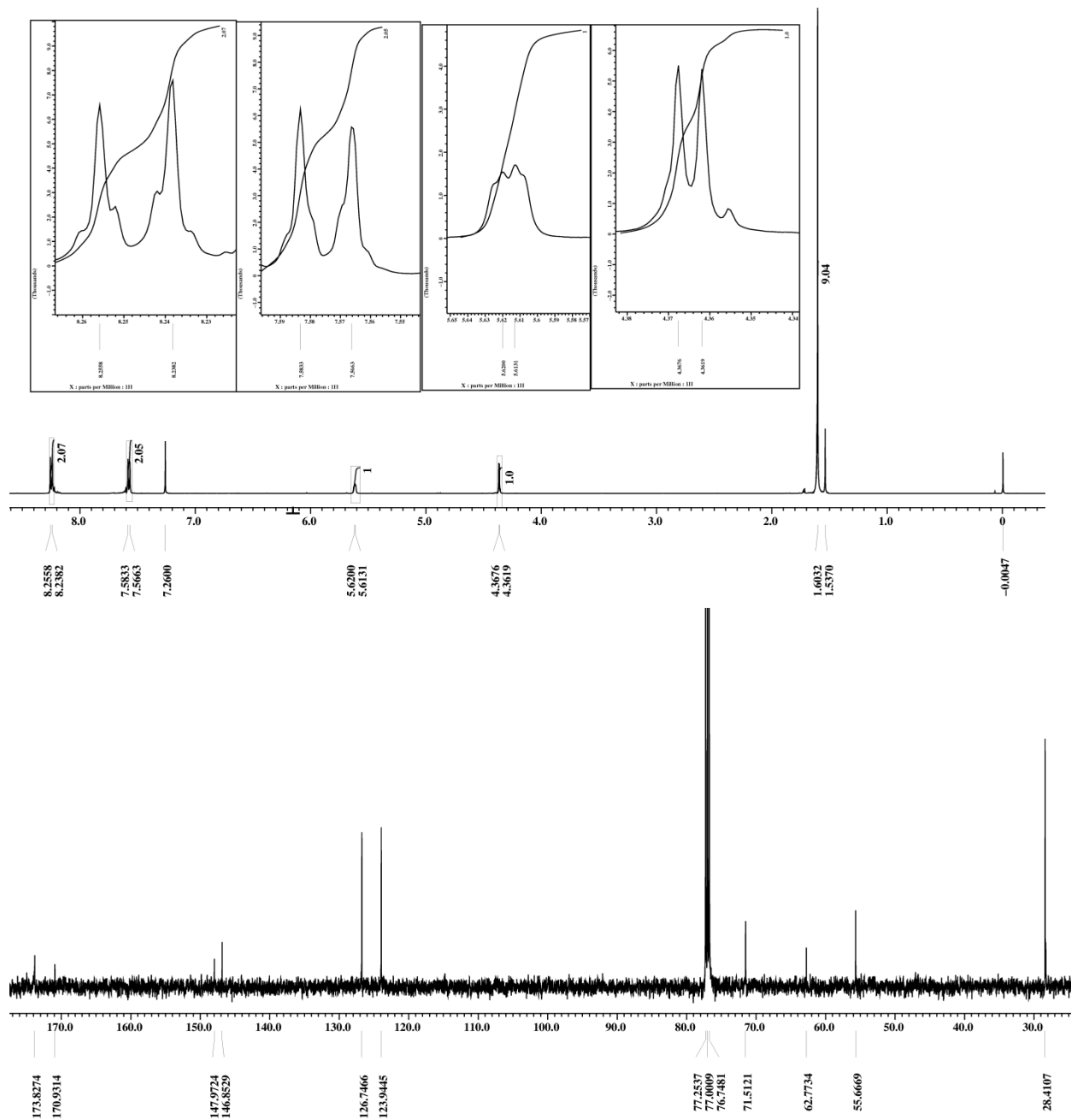
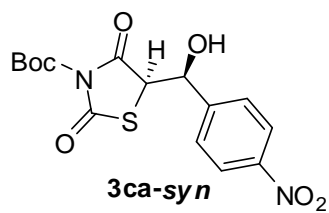
### $^1\text{H}$ and $^{13}\text{C}$ of compound 3bd-syn:



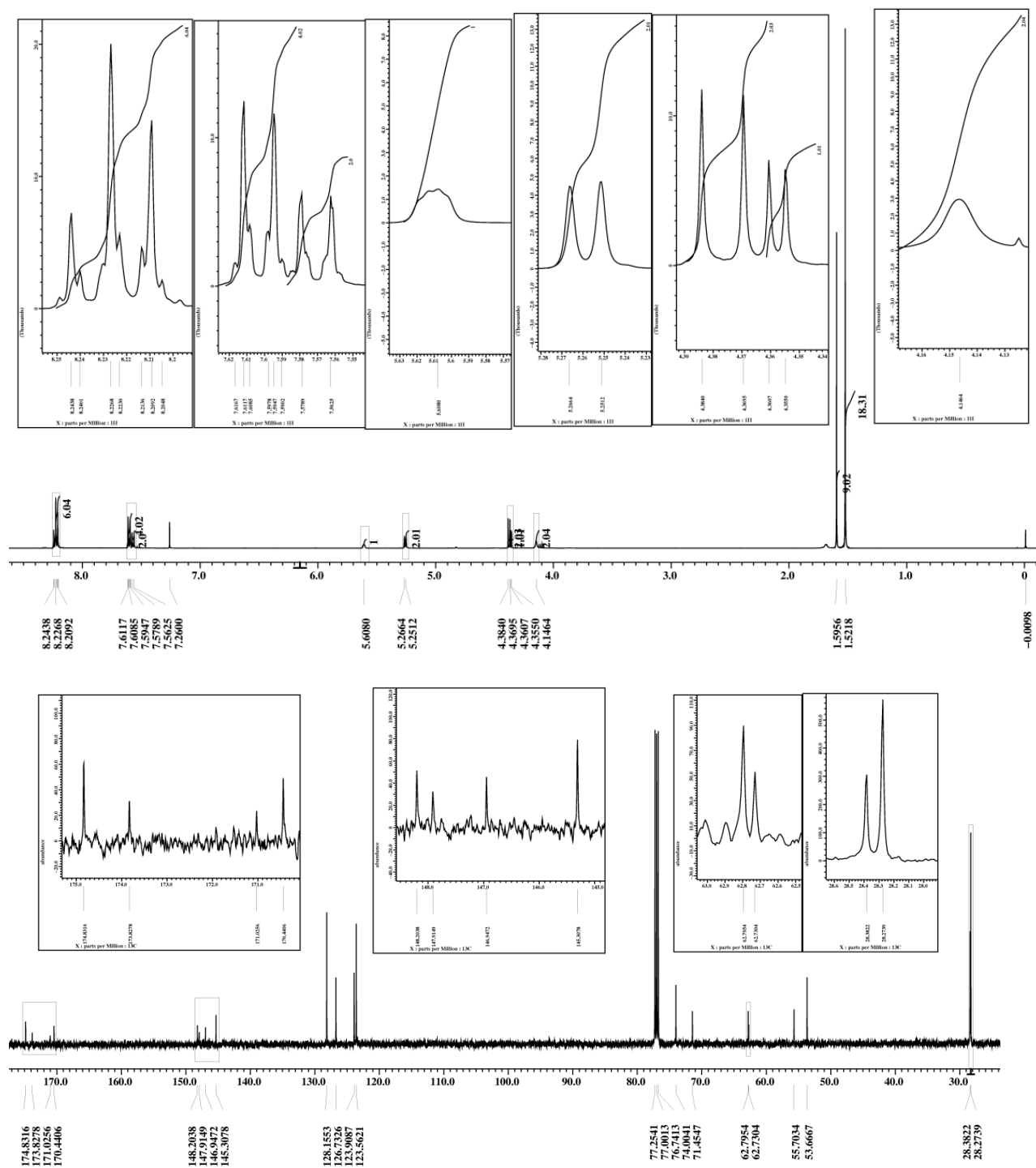
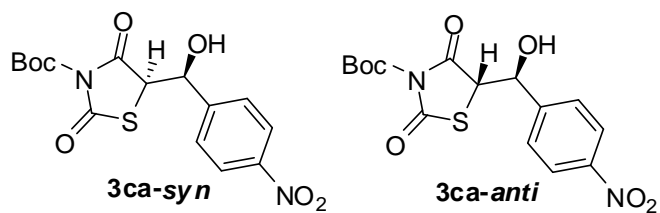
### $^1\text{H}$ and $^{13}\text{C}$ of compound **3bd-anti**:



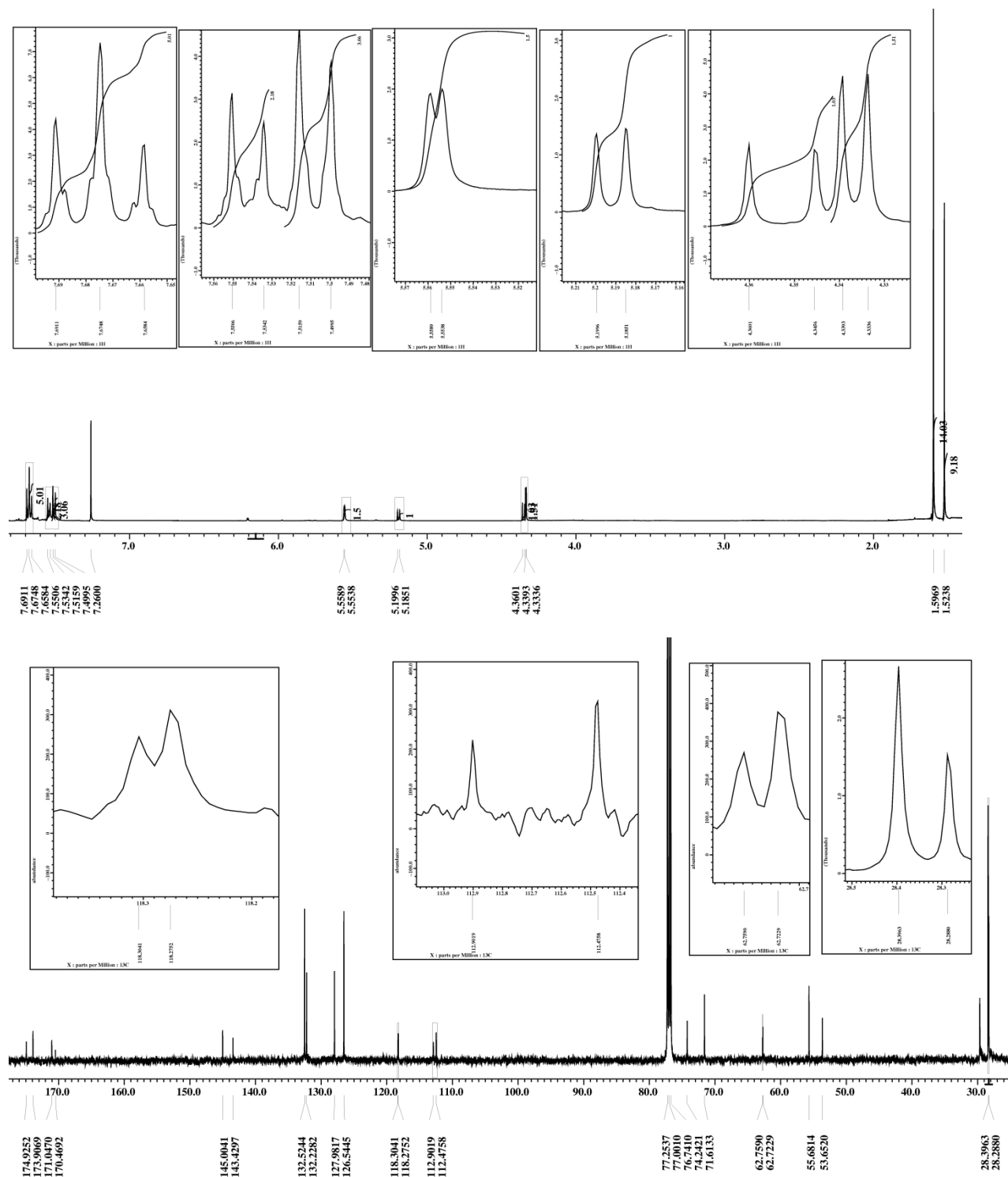
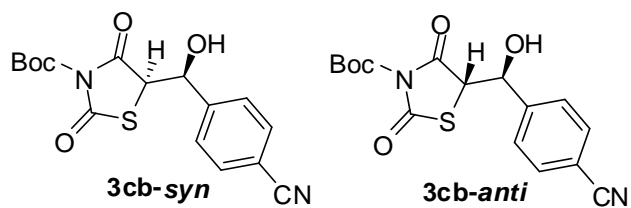
$^1\text{H}$  and  $^{13}\text{C}$  of compound **3ca** (*syn*):



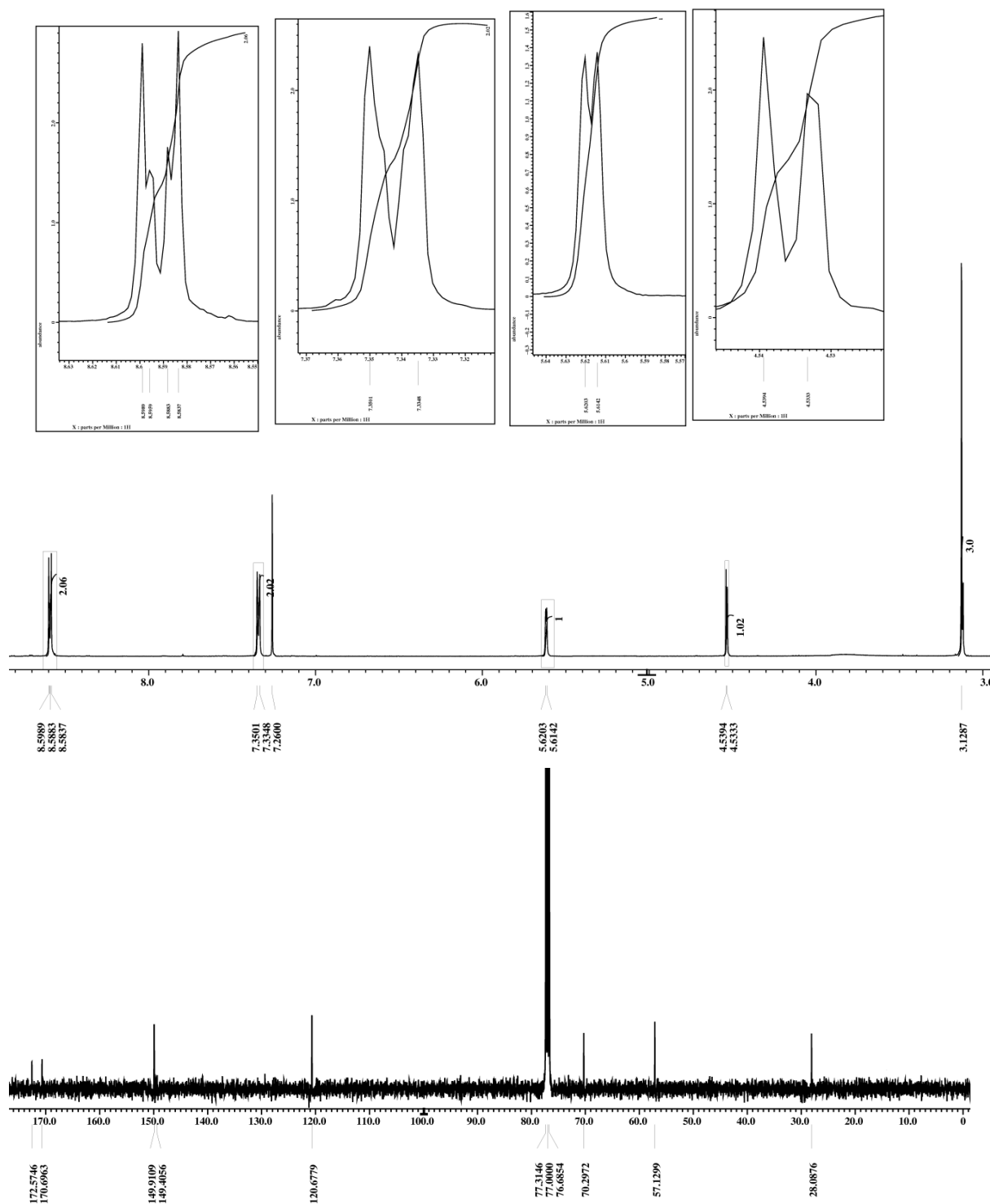
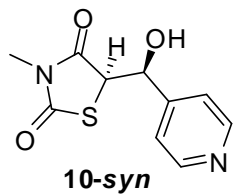
$^1\text{H}$  and  $^{13}\text{C}$  of compound 3ca (from a 33:67 *syn/anti* mixture):



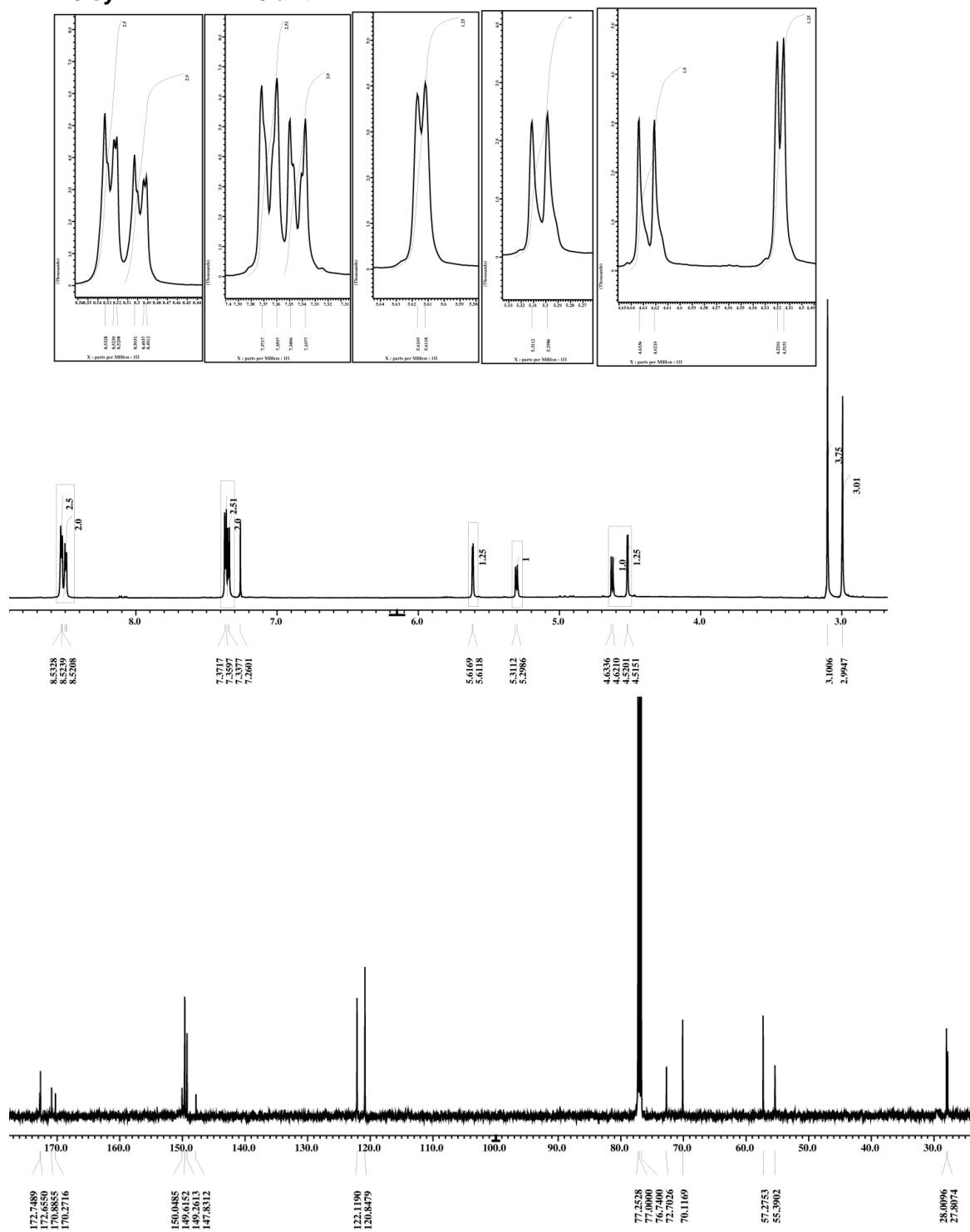
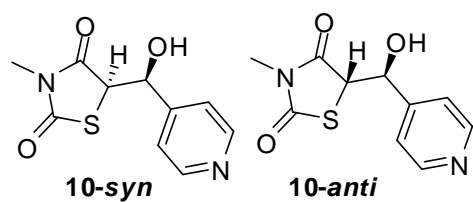
$^1\text{H}$  and  $^{13}\text{C}$  of compound 3cb (from a 60:40 *syn/anti* mixture):



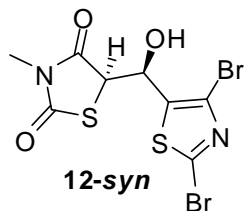
$^1\text{H}$  and  $^{13}\text{C}$  of compound **10-syn**:



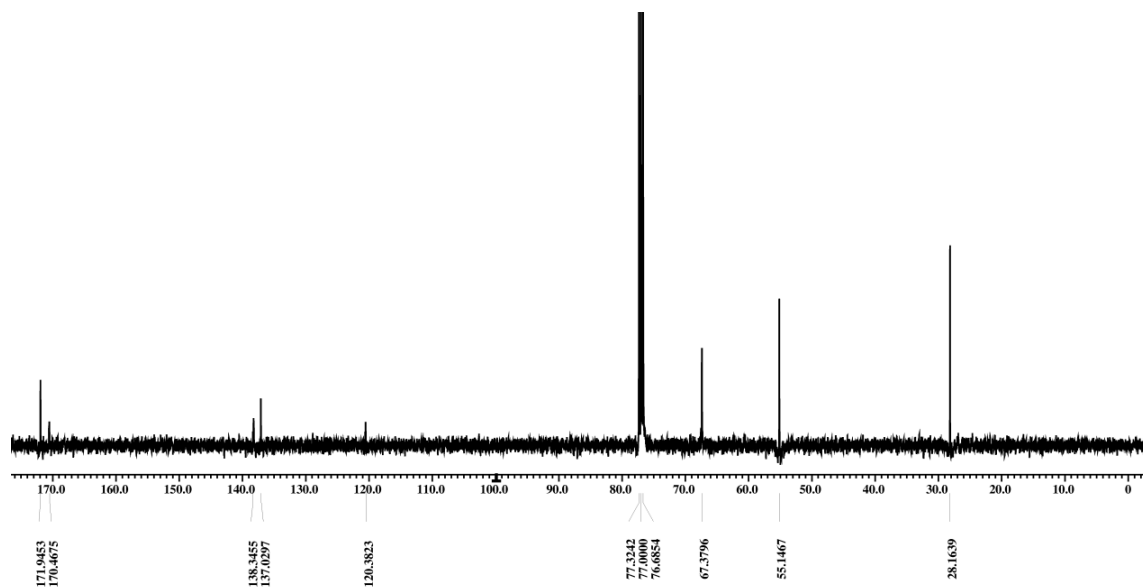
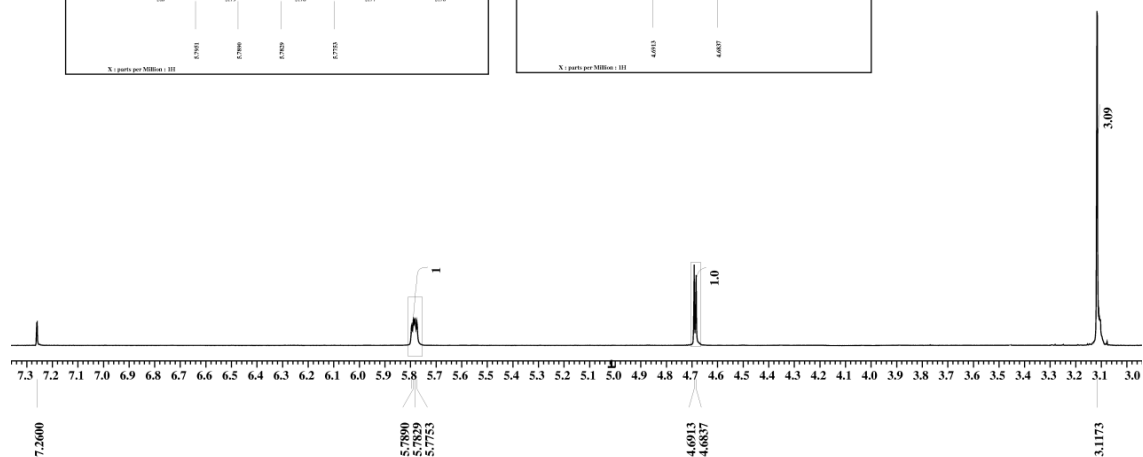
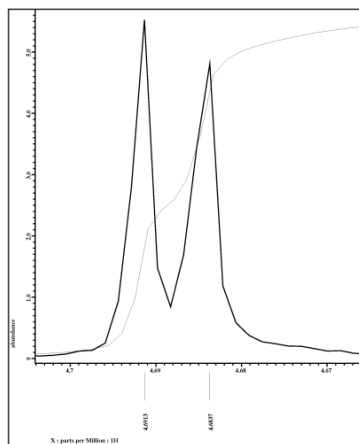
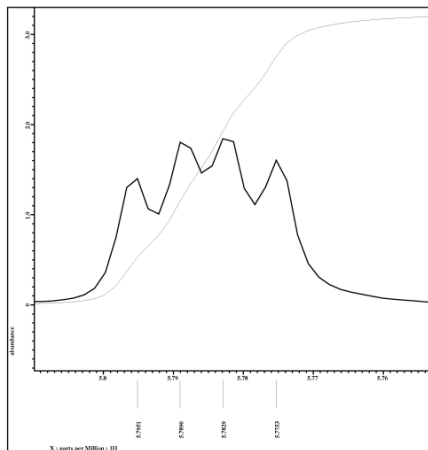
$^1\text{H}$  and  $^{13}\text{C}$  of compound 10 (from a 71:29 *syn/anti* mixture):



$^1\text{H}$  and  $^{13}\text{C}$  of compound **12-syn**:



**12-syn**





$^1\text{H}$  and  $^{13}\text{C}$  of compound 12 (from a 71:29 *syn/anti* mixture):

