

# Synthesis of Valsartan *via* Decarboxylative Biaryl

## Coupling

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**General:** Reactions were performed under a nitrogen atmosphere in oven-dried glassware containing a teflon-coated stirrer bar and dry septum. Solvents were freshly distilled. GC analyses were carried out using a capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min. at 60 °C, followed by 30 °C/min. ramp to 300 °C, then 3 min. at this temp. Column chromatography was performed using an MPLC system and RediSep packed column (12 g). TLC analyses were performed on commercial Kieselgel 60 F254 silica gel plates. NMR spectra were obtained using CDCl<sub>3</sub> or DMSO-d<sub>6</sub> as solvent, with proton and carbon resonances at 400 MHz or 600 MHz and 100 MHz or 150 MHz, respectively.

### Synthesis of starting materials.

**Synthesis of 2-cyanobenzoic acid (2c) [CAS: 3839-22-3];** The synthesis follows the literature procedure of T. Yoneta, S. Shibahara, S. Fukatsu, S. Seki, *Bulletin of the Chemical Society of Japan* **1978**, *51*, 3296-3297; and N. Miyaara, *Top. Curr. Chem.*, **219**, Springer-Verlag, Berlin Heidelberg, **2002**, 131-209. An oven-dried flask was charged with phthalic anhydride (27.7 g, 187 mmol) and THF (100 mL). Ammonia was bubbled through the reaction solution for 15 min. under vigorous stirring at room temperature. The resulting white solid was filtered off, washed successively with small amounts of water and hot acetone, then dried under high vacuum to yield a white ammonium salt (21.1 g, 62 %). This salt was dissolved in pyridine (400 mL) and stirred at room temperature for 30 min., then acetic anhydride (32.6 g, 319.7 mmol) was added and the reaction mixture was stirred until a clear solution formed. The solvent was removed under reduced pressure, and the remaining solid was redissolved in ethyl acetate (500 mL). The organic phase was washed twice with aqueous HCl solution (1N) and brine, and dried over MgSO<sub>4</sub>. The solvent was removed, and the solid was recrystallized from ethyl acetate to yield **2c** as a white solid (14.6 g, 72 %). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 8.06-8.11 (m, 1H), 7.94-7.99 (m, 1H), 7.76-7.84 (m, 2H) ppm. <sup>13</sup>C-NMR (101 MHz, DMSO-d<sub>6</sub>): δ = 165.7, 135.6, 133.7, 133.5, 131.5, 118.2, 112.1 ppm. Anal. Calcd for C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub>: C, 65.3; H, 3.4; N, 9.5. Found: C, 65.1; H, 3.2; N, 9.5. MS (Ion trap, EI): m/z (%) = 147 [M<sup>+</sup>] (100), 104 (81), 76 (95), 66 (8), 50 (52).

**Synthesis of 2-(4-bromophenyl)-1,3-dioxolane (7c) [CAS: 10602-01-4];** The synthesis follows the literature procedure of G. Drefahl, D. Lorenz, *J. Prakt. Chem.* **1964**, *24*, 106-111. An oven-dried flask, equipped with a dropping funnel filled with molecular sieves, was charged with 4-bromobenzaldehyde (2.8 g, 15.0 mmol), 4-toluenesulfonic acid (6.3 mg, 0.03 mmol), ethan-1,2-diol (1.2 g, 19.0 mmol) and toluene (20 mL). The reaction mixture was refluxed over-night (15h), then cooled, washed successively with saturated aqueous NaHCO<sub>3</sub>, and water, and dried over MgSO<sub>4</sub>. The toluene was distilled off. The crude yellow product was purified by Kugelrohr-distillation to yield compound **3c** as a colorless liquid (3.0 g, 88 %). Anal. Calcd for C<sub>9</sub>H<sub>9</sub>BrO<sub>2</sub>: C, 47.2; H, 3.9. Found: C, 47.2; H, 4.0. MS (Ion trap, EI): m/z (%) = 229 [M<sup>+</sup>] (100), 185 (15), 149 (30), 73 (32), 50 (12).

### Representative procedure for the biaryl synthesis.

**Synthesis of 2-cyano-4'-methylbiphenyl (4a) [CAS: 114772-53-1];** An oven-dried 20 mL crimp top vial was charged with copper(II) oxide (11.9 mg, 0.15 mmol), potassium carbonate (151.1 mg, 1.00 mmol), potassium fluoride (29.1 mg, 0.50 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol), 2-cyanobenzoic acid (176.0 mg, 1.20 mmol), palladium(II) bromide (5.3 mg, 0.02 mmol), triphenylphosphine (5.2 mg, 0.02 mmol) and ground 3Å molecular sieves (250 mg). The reaction vessel was closed with a septum cap, evacuated and flushed with nitrogen three times. Subsequently, a solution of 4-bromotoluene (171.0 mg, 1.00 mmol) and the internal standard *n*-tetradecane (50 µL) in quinoline (1.5 mL) was added *via* syringe. The resulting solution was stirred for 24h at 170 °C, then poured into aqueous HCl (1N, 20 mL). The resulting mixture was extracted repeatedly with ethyl acetate (20 mL portions). The combined organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, ethyl acetate / hexane 1:5), yielding **4a** as a yellow solid (138.3 mg, 71 %). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.77 (d, <sup>3</sup>J = 7.9 Hz, 1H), 7.65 (td, <sup>3</sup>J = 7.6 Hz, 1H), 7.53 (d, <sup>3</sup>J = 7.3 Hz, 1H), 7.42-7.50 (m, 3H), 7.33 (d, <sup>3</sup>J = 7.9 Hz, 2H), 2.45 (s, 3H) ppm. <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ = 145.5, 138.7, 135.3, 133.7, 132.7, 130.0, 129.5, 128.6, 127.3, 118.8, 111.3, 21.2 ppm. Anal. Calcd for C<sub>14</sub>H<sub>11</sub>N: C, 87.0; H, 5.7; N, 7.3. Found: C, 87.1 ; H, 5.7; N, 7.3. MS (Ion trap, EI): m/z (%) = 193 [M<sup>+</sup>] (100), 192 (48), 165 (29), 139 (4), 75 (4). (The data correspond to those reported in the literature: B. Sain, J. S. Sandhu, *J. Org. Chem.* **1990**, *55*, 2545-2546.)

**Synthesis of 2-cyano-4'-formylbiphenyl (4b) [CAS: 135689-93-9] from 4-bromobenzaldehyde (7b).** An oven-dried 20 mL crimp top vial equipped with a septum cap was charged with copper carbonate (45.3 mg, 0.20 mmol), potassium carbonate (165.9 mg, 1.20 mmol), 1,10-phenanthroline (18.0 mg, 0.10 mmol) [these compounds were dried before for 3h at 100 °C under high vacuum], 2-cyanobenzoic acid (176.6 mg, 1.20 mmol), 4-bromobenzaldehyde (185.0 mg, 1.00 mmol), palladium(II) bromide (5.3 mg, 0.02 mmol), triphenylphosphine (73.0 mg, 0.03 mmol) and ground 3Å molecular sieves (250 mg, dried in the microwave and for 3h at 210 °C in high vacuum) and was flushed with nitrogen. Subsequently, dry, degassed quinoline (1.5 ml) was added via syringe. The resulting solution was stirred for 24h at 170 °C and was then poured into an aqueous HCl solution (1N, 20 mL). The resulting mixture was extracted repeatedly ethyl acetate (20 mL portions). The combined organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, ethyl acetate / hexane 1:1), yielding **4b** as a light yellow solid (106.2 mg, 50 %).

**Synthesis of 4b from 2-(4-bromophenyl)-1,3-dioxolane (7c).** An oven-dried 20 mL crimp top vial equipped with a septum cap was charged with copper(II) oxide (11.9 mg, 0.15 mmol), potassium carbonate (138.0 mg, 1.00 mmol), potassium fluoride (32.6 mg, 0.50 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol) [these compounds were dried before for 3h at 100 °C under high vacuum], 2-cyanobenzoic acid (147.1 mg, 1.00 mmol), 2-(4-bromophenyl)-1,3-dioxolane (**7c**) (343.6 mg, 1.50 mmol), palladium(II) bromide (5.3 mg, 0.02 mmol), triphenylphosphine (5.2 mg, 0.02 mmol) and ground 3Å molecular sieves (250 mg, dried in the microwave and for 3h at 210 °C in high vacuum) and was flushed with nitrogen. Subsequently, dry, degassed quinoline (1.5 ml) was added via syringe. The resulting solution was stirred for 24h at 170 °C and was then poured into an aqueous HCl solution (3N, 20 mL) and heated up to 50 °C under stirring for 2h. The resulting mixture was extracted repeatedly with ethyl acetate (20 mL portions). The combined organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, ethyl acetate / hexane 3:2), yielding **4b** as a light yellow solid (167.9 mg, 81 %).

**Synthesis of 4b from 1-bromo-(4-dimethoxymethyl)benzene (7d):** An oven-dried 20 mL crimp top vial equipped with a septum cap was charged with copper(II) oxide (11.9 mg, 0.15 mmol), potassium carbonate (138.0 mg, 1.00 mmol), potassium fluoride (32.6 mg, 0.50 mmol), [these compounds were dried before for 3h at 100 °C under high vacuum], 1,10-phenanthroline (27.0 mg, 0.15 mmol), 2-cyanobenzoic acid (147.1 mg, 1.00 mmol), 1-bromo-(4-dimethoxymethyl)benzene (346.6 mg, 1.50 mmol), palladium(II) bromide (5.3 mg, 0.02 mmol), triphenylphosphine (5.2 mg, 0.02 mmol) and ground 3Å molecular sieves (250 mg, dried in the microwave and for 3h at 210 °C in high vacuum) and was flushed with nitrogen. Subsequently, dry, degassed quinoline (1.5 ml) was added via syringe. The resulting solution was stirred for 24h at 170 °C and was then poured into an aqueous HCl solution (3N, 20 mL) and heated up to 50 °C under stirring for 2h. The resulting mixture was extracted repeatedly with ethyl acetate (20 mL portions). The combined organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (SiO<sub>2</sub>, ethyl acetate / hexane 3:2), yielding **4b** as a light yellow solid (165.9 mg, 80 %). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 10.12 (s, 1H), 8.04 (d, <sup>3</sup>J = 6.5 Hz, 2H), 7.83, (d, <sup>3</sup>J = 7.3 Hz, 1H), 7.76 (d, <sup>3</sup>J = 6.7 Hz, 2H), 7.67 – 7.74 (m, 1H), 7.57 (d, <sup>3</sup>J = 7.6 Hz, 1H), 7.54 (s, 1H) ppm. <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>): δ = 191.8, 144.0, 144.0, 136.2, 134.0, 133.1, 130.1, 130.1, 129.6, 128.6, 118.3, 111.3 ppm. Anal. Calcd for C<sub>14</sub>H<sub>9</sub>NO: C, 81.1; H, 4.3; N, 6.7. Found: C, 80.9; H, 4.0; N, 6.4. MS (Ion trap, EI): m/z (%) = 207 [M<sup>+</sup>] (55), 206 (100), 178 (25), 151 (18), 50 (6). (The data correspond to those reported in the literature: J. Kristensen, M. Lysén, P. Vedsø, M. Begtrup, *Org. Lett.* **2001**, 3, 1435-1436.)

**Large scale procedure for the synthesis 2-cyano-4'-methylbiphenyl (4a) [CAS: 114772-53-1].** An oven-dried flask was equipped with an internal thermometer, a dropping funnel filled with molecular sieves, a condenser, and charged with 2-cyanobenzoic acid (809.2 mg, 5.50 mmol), potassium carbonate (855.2 mg, 5.50 mmol), 7.5 mL dry quinoline and 7.5 mL dry toluene. The reaction mixture was stirred for 1h at 80 °C, refluxed for 30 min., then the toluene was removed *in vacuo*. After flushing the vessel with alternating vacuum and nitrogen purge cycles, copper(II) oxide (59.7 mg, 0.75 mmol), potassium fluoride (145.3 mg, 2.50 mmol) [these compounds were dried before for 3h at 120 °C under high vacuum], 1,10-phenanthroline (135.2 mg, 0.75 mmol), 4-bromotoluene (1733.2 mg, 7.50 mmol), palladium(II) bromide (26.6 mg, 0.10 mmol), triphenylphosphine (78.7 mg, 0.30 mmol) were added. The vessel was lowered into an oil bath and heated to 190 °C. The temperature inside remained constant at 160 °C. After stirring the reaction mixture for 24 h, it was allowed to cool to room temperature. The solution was acidified with aqueous HCl solution (1N, 75 mL) and extracted repeatedly with ethyl acetate (40 mL portions). The combined organic layers were washed twice with aqueous HCL (1N, 75 mL), saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub> and filtered. The volatiles were removed *in vacuo*, and the residue was purified by Kugelrohr-distillation, yielding **4a** as a yellow solid (556.4 mg, 58 %).

**Large scale procedure for the synthesis 2-cyano-4'-formylbiphenyl (4b) [CAS: 135689-93-9].** An oven-dried flask was equipped with an internal thermometer, a dropping funnel filled with molecular sieves, a condenser, and charged with 2-cyanobenzoic acid (735.6 mg, 5.00 mmol), potassium carbonate (691.0 mg, 5.00 mmol), 7.5 mL dry quinoline and 7.5 mL dry toluene. The reaction mixture was stirred for 1h at 80 °C, refluxed for 30 min., then the toluene was removed *in vacuo*. After flushing the vessel with alternating vacuum and nitrogen purge cycles, copper(II) oxide (59.7 mg, 0.75 mmol), potassium fluoride (145.3 mg, 2.50 mmol) [these compounds were dried before for 3h at 100 °C under high vacuum], 1,10-phenanthroline (135.2 mg, 0.75 mmol), 1-bromo-(4-dimethoxymethyl)benzene (1733.2 mg, 7.50 mmol), palladium(II) bromide (26.6 mg, 0.10 mmol) and triphenylphosphine (26.2 mg, 0.10 mmol) were added. The vessel was lowered into an oil bath and heated to 190 °C. The temperature inside remained constant at 160 °C. After stirring the reaction mixture for 24 h, it was allowed to cool to room temperature, 50 mL ethyl acetate were added, the solution was acidified with aqueous HCl solution (1N, 75 mL) and heated at 50 °C under stirring for 1h. The organic layer was separated, washed with aqueous HCL solution (1N, 50 mL), saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub> and filtered. The volatiles were removed *in vacuo*, and the residue was purified by column chromatography (SiO<sub>2</sub>, ethyl acetate / hexane 3:2), yielding **4b** as a light yellow solid (992.8 mg, 78 %).

## Representative procedure for the Valsartan synthesis

**4'-Bromomethyl-2-cyanobiphenyl (4c)** [CAS: 114772-54-2]; An oven-dried 20 mL crimp top vial equipped with a septum cap was charged with 2-cyano-4'-methylbiphenyl (138.5 mg, 0.72 mmol), *N*-bromosuccinimide (99.5 mg, 0.56 mmol), AIBN (2.0 mg, 0.01 mmol), dry cyclohexane (1.5 mL) and CCl<sub>4</sub> (3 mL). The reaction mixture was heated for 18h at 75 °C. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO<sub>2</sub>, ethyl acetate / hexane 3:7). The resulting solid was recrystallized with 4 drops ethyl acetate and hexane to yield compound **4c** as white crystals (88.6 mg, 45 %). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.80 (d, <sup>3</sup>*J* = 7.8 Hz, 1H), 7.65 – 7.71 (m, 1H), 7.52 – 7.59 (m, 5H), 7.48 (d, <sup>3</sup>*J* = 7.6 Hz, 1H), 4.58 (s, 2H) ppm. <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>): δ = 144.8, 138.4, 133.8, 132.8, 130.0, 129.4, 129.2, 127.7, 118.5, 118.4, 111.5, 32.6 ppm. Anal. Calcd for C<sub>14</sub>H<sub>10</sub>BrN: C, 61.8; H, 3.7; N, 5.1. Found: C, 61.8; H, 3.7; N, 5.1. (The data correspond to those reported in the literature: D. Carini, J. Duncia, P. Aldrich, A. Chiu, A. Johnson, M. Pierce, W. Price, J. Santella, G. Wells, R. Wexler, P. Wong, SE. Yoo, P. Timmermans, *J. Med. Chem.* **1991**, 34, 2525-2547.)

***N*-[(2'-Cyanobiphenyl-4-yl)-methyl]-(*L*)-valine methyl ester (6)** [CAS: 137863-89-9]; was prepared according to the literature [P. Bühlmayer, F. Ostermayer, T. Schmidlin, *Eur. Pat. Appl.*, EP443983, **1991**]. An oven-dried flask was charged with 2-cyano-4'-formylbiphenyl **4b** (1.99 g, 9.64 mmol), *L*-valine methyl ester hydrochloride (3.02 g, 18.00 mmol), ground 3 Å molecular sieves (2.50 g, dried in the microwave) and dry THF (100 mL). The reaction mixture was stirred at room temperature for 60h. Afterwards, the solution was cooled to 0 °C and sodium cyanoborohydride (628.4 mg, 10.00 mmol) dissolved in 4 mL EtOH was added. The mixture was again stirred at 23 °C for 24h, then the molecular sieves were filtered off over Celite® and the solution was washed with saturated aqueous NaHCO<sub>3</sub> (ethyl acetate was added for a better separation) and dried over MgSO<sub>4</sub>. The organic layer was restricted and purified by column chromatography (SiO<sub>2</sub>, DCM, 1 % MeOH), to yield compound **5** as a yellowish oil (2.8 g, 90 %). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.73 – 7.80 (m, 1H), 7.65 (dd, <sup>3</sup>*J* = 7.6, 1.5 Hz, 1H), 7.45 – 7.55 (m, 6H), 3.92 (d, <sup>3</sup>*J* = 13.5 Hz, 1H), 3.76 (s, 3H), 3.67 (d, <sup>3</sup>*J* = 13.2 Hz, 1H), 3.08 (d, <sup>3</sup>*J* = 6.2 Hz, 1H), 1.97 (s, 1H), 1.83 (s, 1H), 0.99 (t, <sup>3</sup>*J* = 6.5 Hz, 6H) ppm. <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>): δ = 175.5, 145.5, 141.0, 136.9, 133.7, 132.6, 130.0, 128.7, 128.5, 127.3, 118.6, 111.5, 77.2, 66.9, 52.3, 31.7, 19.3, 18.6, ppm. Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 74.5; H, 6.9; N, 8.7. Found: C, 74.1; H, 6.9; N, 8.6.

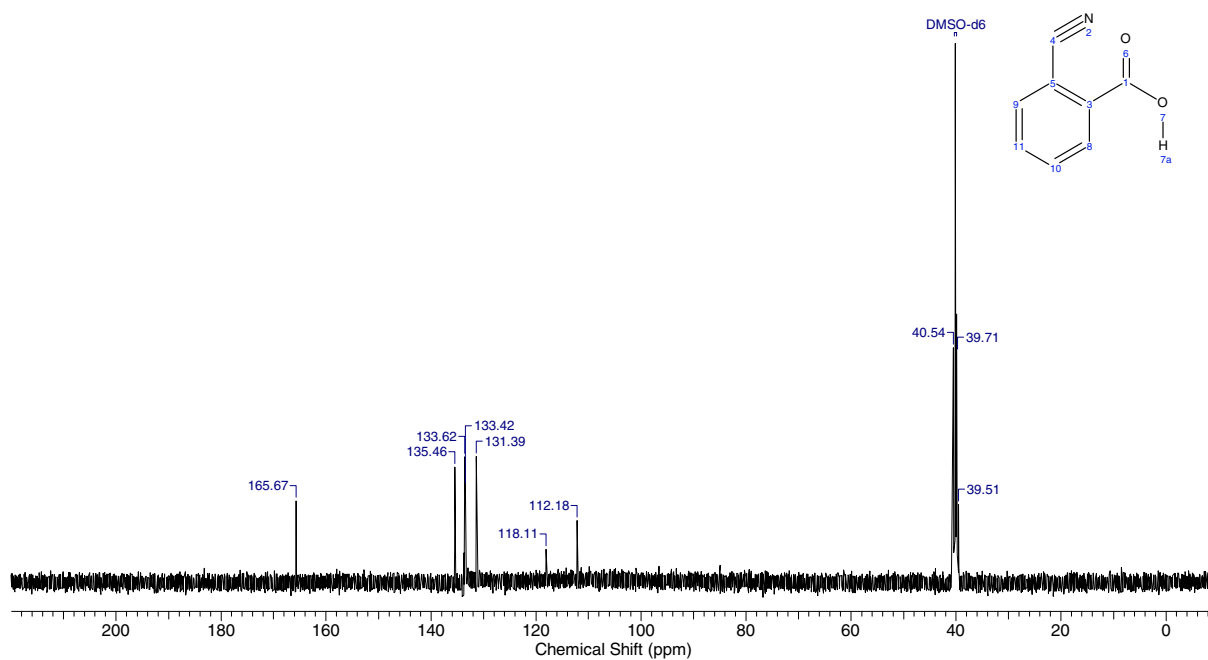
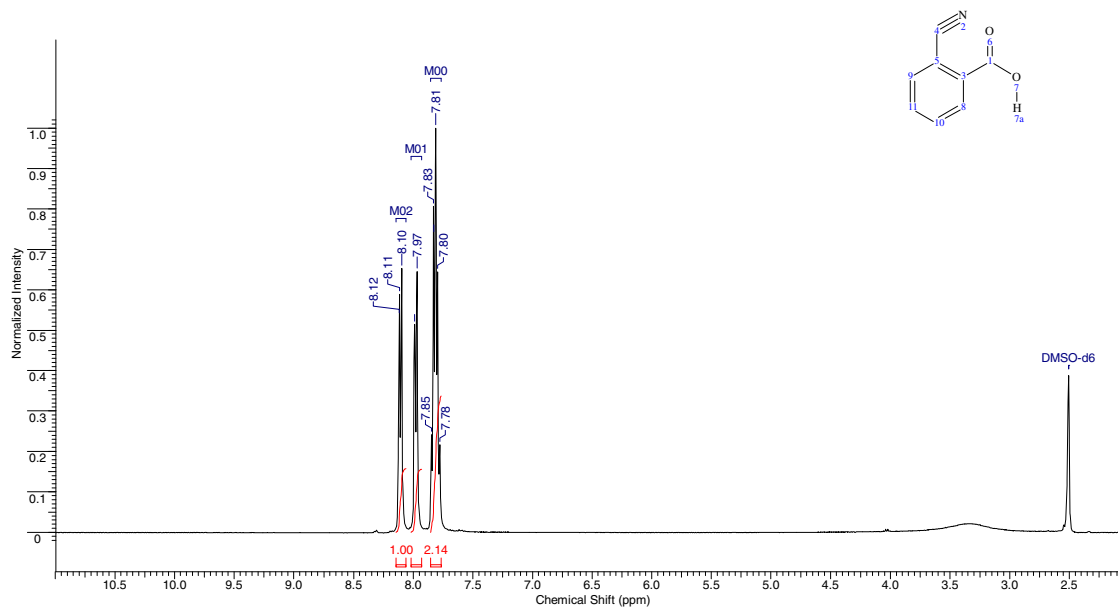
***N*-Pentanoyl-*N*-[(2'-cyanobiphenyl-4-yl)-methyl]-(*L*)-valine methyl ester (8)** [CAS: 137863-90-2]; An oven-dried flask was filled with *N*-[(2'-cyanobiphenyl-4-yl)-methyl]-(*L*)-valine methyl ester **6** (1.0 g, 3.1 mmol) dissolved in dichloromethane (30 mL) and pyridine (474.6 mg, 6.0 mmol) and then cooled to 0 °C. Afterwards valeroyl chloride (723.5 mg, 6 mmol) in dichloromethane was added slowly drop by drop under stirring and the reaction mixture was stirred over-night and later heated by 40 °C for 2h. The solvent was removed and the crude product was taken up with diethyl ether, washed with saturated aqueous NaHCO<sub>3</sub> and brine, the organic layer was restricted and the created solid was purified by column chromatography (SiO<sub>2</sub>, DCM / *i*PrOH = 9.5 / 0.5), to yield compound **6** as a yellow oil (1.2 g, 98 %). <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>) mixture of rotamers: δ = 7.72 – 7.76 (m, 1H), 7.59 – 7.65 (m, 1H), 7.39 – 7.53 (m, 4H), 7.27 – 7.30 (m, 2H), 5.07 and 4.25 (2 d, <sup>3</sup>*J* = 15.45 Hz, 1H), 4.96 and 4.05 (2 d, <sup>3</sup>*J* = 10.40 Hz, 1H), 4.64 – 4.71 (m, 1H), 3.44 (s, 2H), 3.35 (s, 1H), 2.58 – 2.60 and 2.36 – 2.47 (2 m, 1H), 2.26 – 2.35 (m, 2H), 1.73 – 1.74 (m, 1H), 1.60 – 1.64 (m, 1H), 1.35 – 1.40 (m, 1H), 1.27 – 1.30 (m, 1H), 0.95 – 0.98 (m, 4H), 0.84 – 0.90 (m, 5H) ppm. <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ = 174.6, 174.3, 171.1, 170.3, 145.3, 144.8, 138.7, 138.0, 137.1, 136.6, 133.8, 133.7, 132.9, 132.8, 130.1, 129.1, 128.5, 127.9, 127.7, 127.5, 126.3, 118.5, 111.3, 65.8, 61.7, 52.1, 51.7, 48.1, 45.3, 33.4, 27.8, 27.6, 27.5, 22.6, 22.5, 19.9, 18.7, 13.9 ppm. Anal. Calcd for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>: C, 73.8; H, 7.4; N, 7.0. Found: C, 73.7; H, 7.4; N, 6.9.

***N*-Pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-(*L*)-valine methyl ester (**1c**) [CAS: 137863-17-3]; An oven-dried flask was filled with *N*-pentanoyl-*N*-[(2'-cyanobiphenyl-4-yl)-methyl]-(*L*)-valine methyl ester **8** (745.0 mg, 1.8 mmol), sodium azide (234 mg, 3.6 mmol), tributyltin chloride (1.2 g, 3.6 mmol), tetrabutylammonium boronide (12.9 mg, 0.04 mmol) and toluene (20 mL). The reaction mixture was refluxed for 72h. After cooling to room temperature the solution was charged with 1.8 mL acetic acid (1 mL acid, 2 mL water) and stirred over-night. The organic phase was separated, concentrated and purified by column chromatography (SiO<sub>2</sub>, DCM / (DCM, 10% MeOH) = 1 / 1). A light yellow solid was obtained (453 mg, 55 %). <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>) mixture of rotamers: δ = 7.96 – 8.04 (m, 1H), 7.58 – 7.62 (m, 1H), 7.52 – 7.54 (m, 1H), 7.41 – 7.45 (m, 1H), 7.07 – 7.19 (m, 4H), 4.97 and 4.25 (2 d, <sup>3</sup>*J* = 15.45 Hz, 1H), 4.87 and 4.05 (2 d, <sup>3</sup>*J* = 10.63 Hz, 1H), 4.67 and 4.62 (2 d, <sup>3</sup>*J* = 17.59, 1H), 3.46 (s, 1.5H), 3.41 (s, 1.4H), 2.55 – 2.60 and 2.39 – 2.46 (2 m, 1H), 2.27 – 2.38 and 2.19 – 2.24 (2 m, 2H), 1.55 – 1.68 (m, 2H), 1.35 – 1.40 (m, 1H), 1.25 – 1.32 (m, 1H), 0.85 – 1.01 (m, 9H) ppm. <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ = 174.9, 174.9, 171.3, 170.3, 140.9, 138.6, 138.1, 137.8, 137.2, 131.3, 130.8, 130.7, 130.7, 129.3, 128.9, 128.2, 128.1, 127.9, 126.5, 122.6, 66.0, 61.8, 52.2, 51.9, 48.2, 45.6, 33.5, 27.6, 27.6, 27.3, 22.5, 19.9, 18.8, 18.7, 13.9 ppm. Anal. Calcd for C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O<sub>3</sub>: C, 66.8; H, 6.9; N, 15.6. Found: C, 66.5; H, 6.9; N, 15.2.**

***N*-Pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-(*L*)-valine (Valsartan) (**1b**) [CAS: 137862-53-4]; An oven-dried flask was charged with *N*-pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-(*L*)-valine methyl ester **1c** (400.0 mg, 0.88 mmol) dissolved in diethyl ether, dist. water (7 mL) and aqueous NaOH (1N, 3 mL) and stirred over-night at room temperature. The organic phase was separated and the aqueous layer was acidified with aqueous HCl solution (3N) until a pH of 3 was reached. Extraction was carried out with diethyl ether followed by drying and evaporating to dryness, recrystallized from ethyl acetate and pentane to furnish the desired product as a white solid (380.2 mg, 99 %). <sup>1</sup>H-NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) mixture of rotamers: *major rotamer*: δ = 8.03 – 8.05 (m, 1H), 7.64 – 7.66 (m, 1H), 7.59 – 7.62 (m, 1H), 7.52 – 7.55 (m, 1H), 7.23 – 7.27 (m, 4H), 5.03 (d, <sup>3</sup>*J* = 15.31 Hz, 1H), 4.25 (d, <sup>3</sup>*J* = 15.32 Hz, 1H), 3.41 – 3.44 (m, 1H), 2.71 – 2.77 (m, 1H), 2.61 – 2.65 (m, 2H), 1.70 – 1.78 (m, 2H), 1.41 – 1.50 (m, 2H), 0.96 – 1.01 (m, 9H). *minor rotamer*: δ = 7.92 – 7.94 (m), 7.62 – 7.67 (m), 7.54 – 7.56 (m), 7.47 – 7.49 (m), 7.11 – 7.19 (m), 6.98 – 7.00 (m), 5.17 (d, <sup>3</sup>*J* = 15.58), 4.09 – 4.15 (m), 3.47 – 3.50 (m), 2.51 (m), 1.66 – 1.68 (m), 1.36 – 1.40 (m), 1.30 (bs, 1H), 0.86 – 1.07 (m) ppm. <sup>13</sup>C-NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ = 177.4, 172.5, 170.9, 154.6, 140.5, 139.3, 135.4, 131.2, 130.9, 130.5, 129.8, 128.7, 128.4, 128.3, 123.2, 60.3, 34.3, 33.4, 27.3, 26.8, 22.5, 22.4, 20.8, 19.6, 19.2, 19.0, 18.4, 14.0, 13.7, 13.6 ppm. ESI-MS: [M+H]<sup>+</sup> 436, [M+Na]<sup>+</sup> 459, [M+K]<sup>+</sup> 475. (The data correspond to those reported in the literature: J. L. Rafecas, A. Escale Riera, M. Queralto Ecija, A. Moyano, A. Comely, I. Casalprim, *Int. Patent*, WO200606721, 2006.)**

## 2-Cyanobenzoic acid (2c) [CAS: 3839-22-3]:

<sup>1</sup>H NMR (400 MHz, DMSO-D<sub>6</sub>) δ ppm 7.76 - 7.86 (m, 3 H) 7.93 - 8.02 (m, 1 H) 8.06 - 8.14 (m, 1 H)

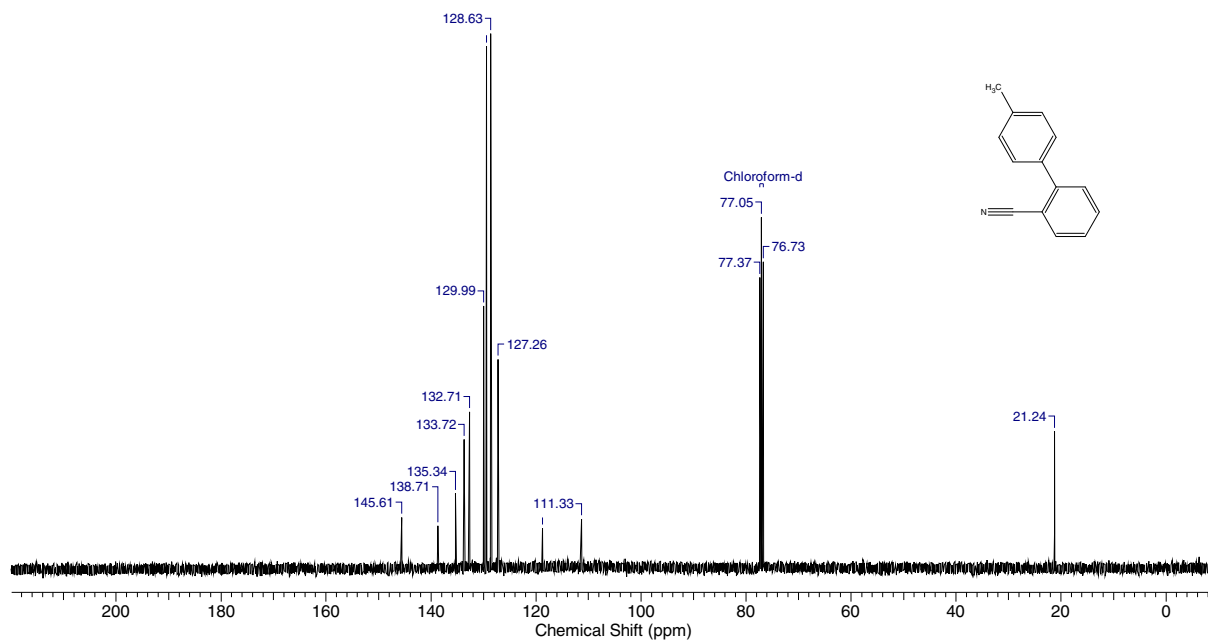
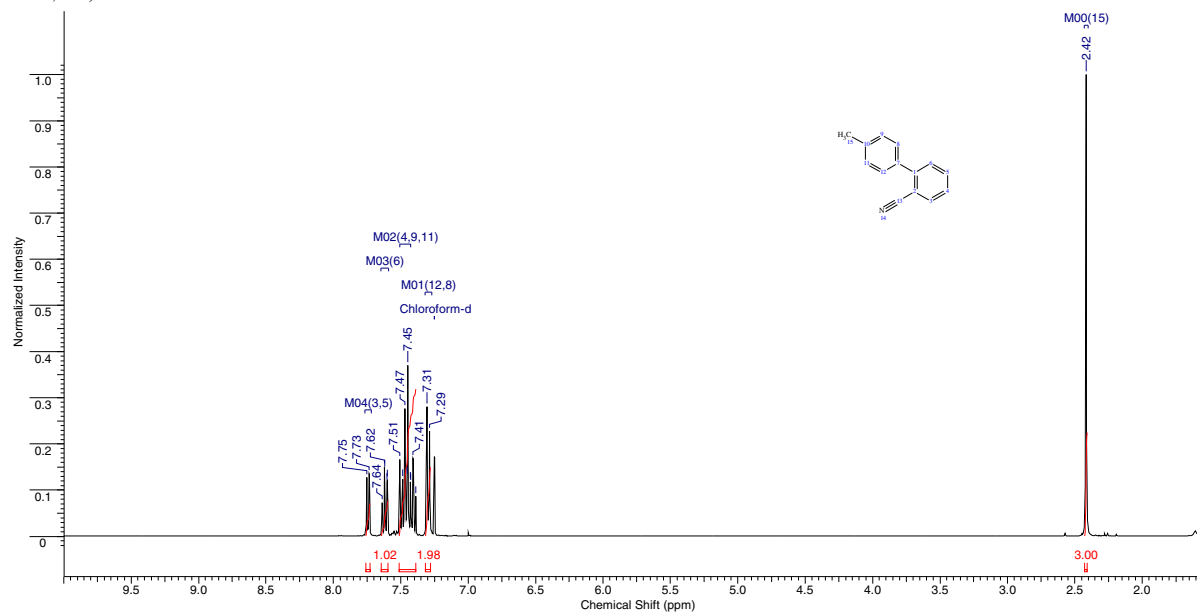


%	C	H	N
Theory	65.3	3.4	9.5
Analysis	65.1	3.2	9.5

MS (Ion trap, EI): m/z (%) = 147 (100 [M<sup>+</sup>]), 104 (81), 76 (95), 66 (8), 50 (52).

## 2-Cyano-4'-methylbiphenyl (4a) [CAS: 114772-53-1]:

<sup>1</sup>H NMR (400 MHz, CHLOROFORM-D)  $\delta$  ppm 2.42 (s, 3 H) 7.30 (d,  $J=7.95$  Hz, 2 H) 7.42 - 7.51 (m, 3 H) 7.62 (td,  $J=7.71, 1.43$  Hz, 1 H) 7.74 (d,  $J=6.36$  Hz, 1 H)

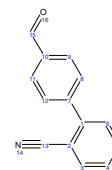
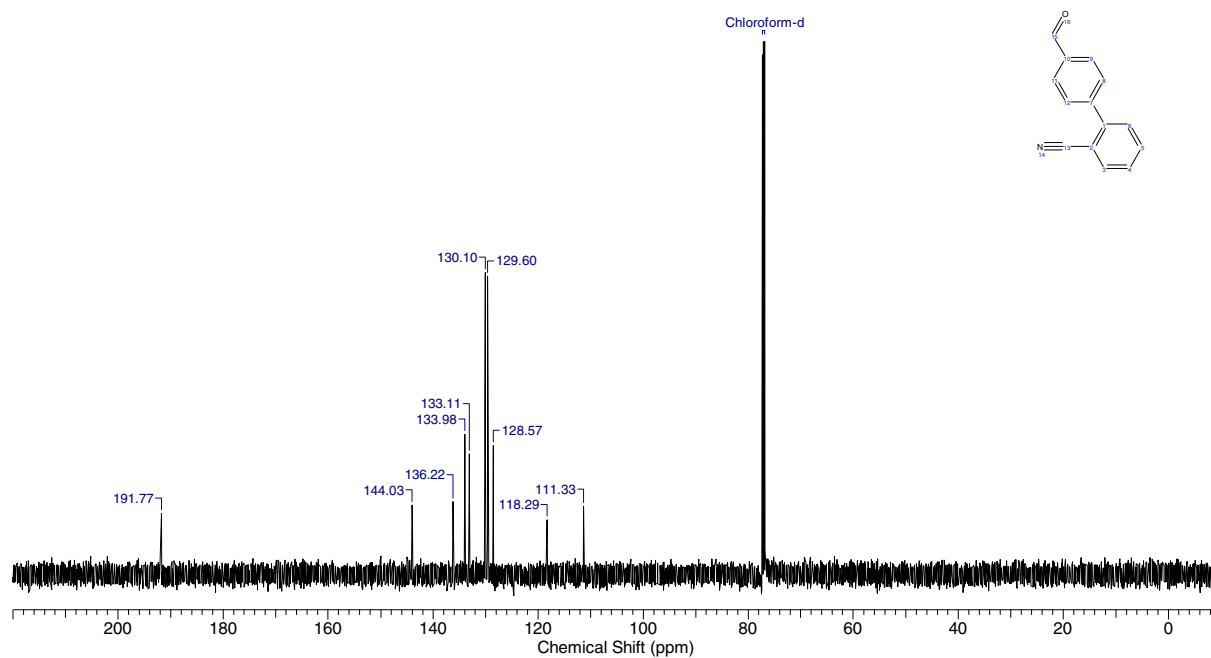
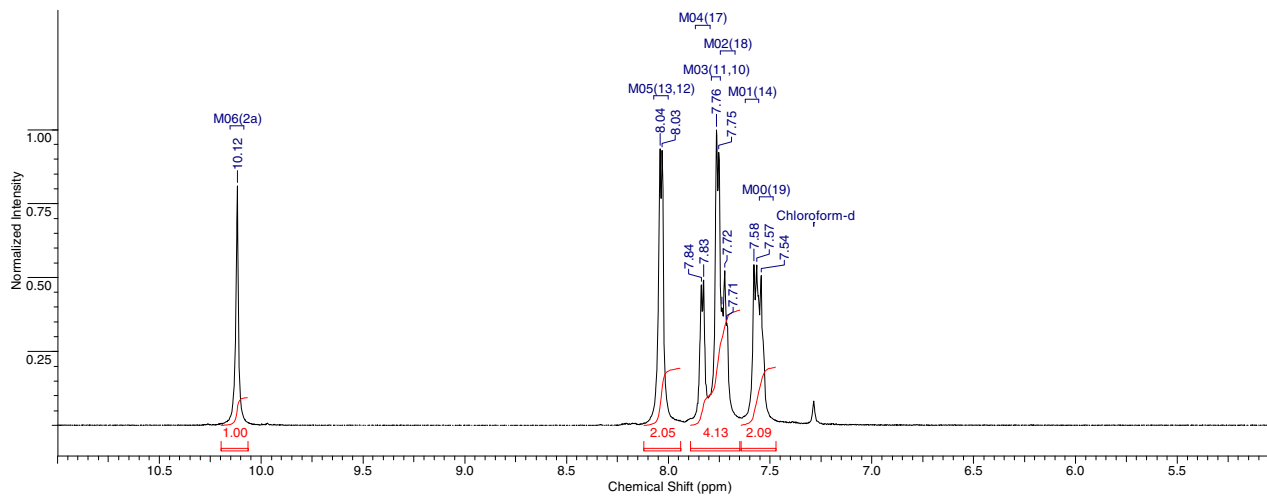
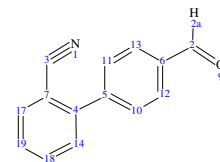


%	C	H	N
<b>Theory</b>	87.0	5.7	7.3
<b>Analysis</b>	87.1	5.7	7.3

MS (Ion trap, EI):  $m/z$  (%) = 193 (100 [ $M^+$ ]), 192 (48), 165 (29), 139 (4), 91 (4), 75 (4), 50 (4).

## 2-Cyano-4'formylbiphenyl (4b) [CAS: 135689-93-9] :

<sup>1</sup>H NMR (600 MHz, CHLOROFORM-D)  $\delta$  ppm 7.54 (s, 1 H) 7.57 (d,  $J=7.63$  Hz, 1 H) 7.67 - 7.74 (m, 1 H) 7.76 (d,  $J=6.75$  Hz, 2 H) 7.83 (d,  $J=7.34$  Hz, 1 H) 8.04 (d,  $J=6.46$  Hz, 2 H) 10.12 (s, 1 H)

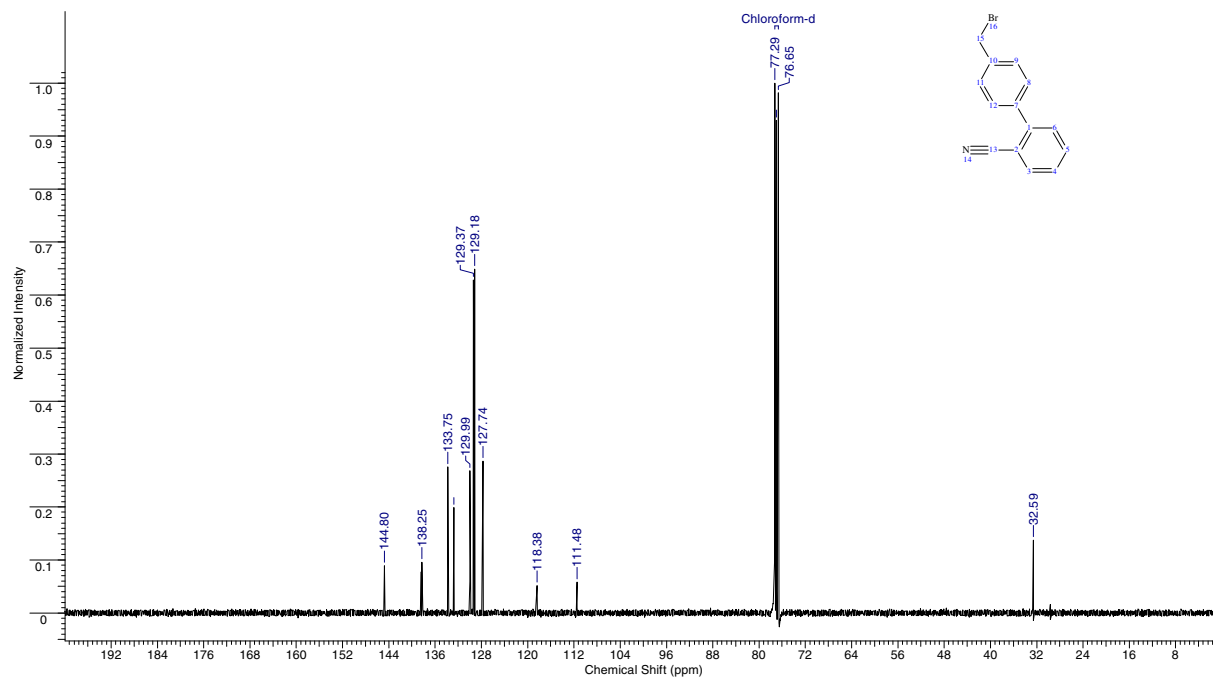
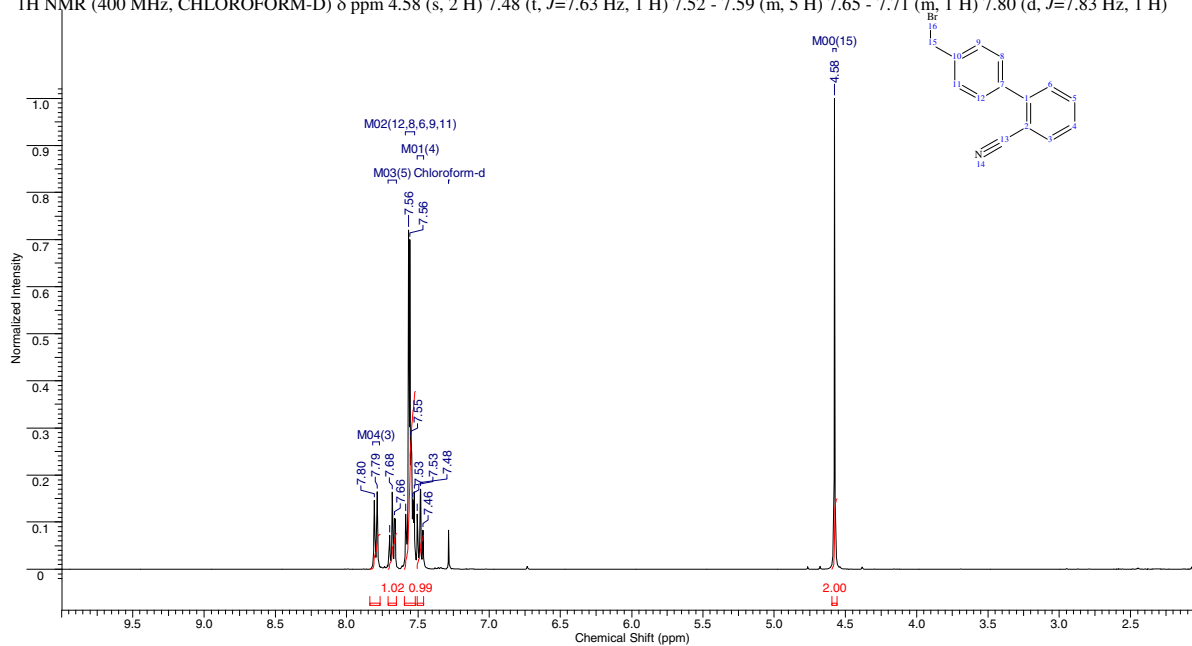


%	C	H	N
<b>Theory</b>	81.1	4.3	6.7
<b>Analysis</b>	80.9	4.0	6.4

MS (Ion trap, EI):  $m/z$  (%) = 207 (55 [ $M^+$ ]), 206 (100), 178 (25), 151 (18), 125 (4), 75 (7), 50 (6).

# 4'-Bromomethyl-2-cyanobiphenyl (4c) [CAS: 114772-54-2]:

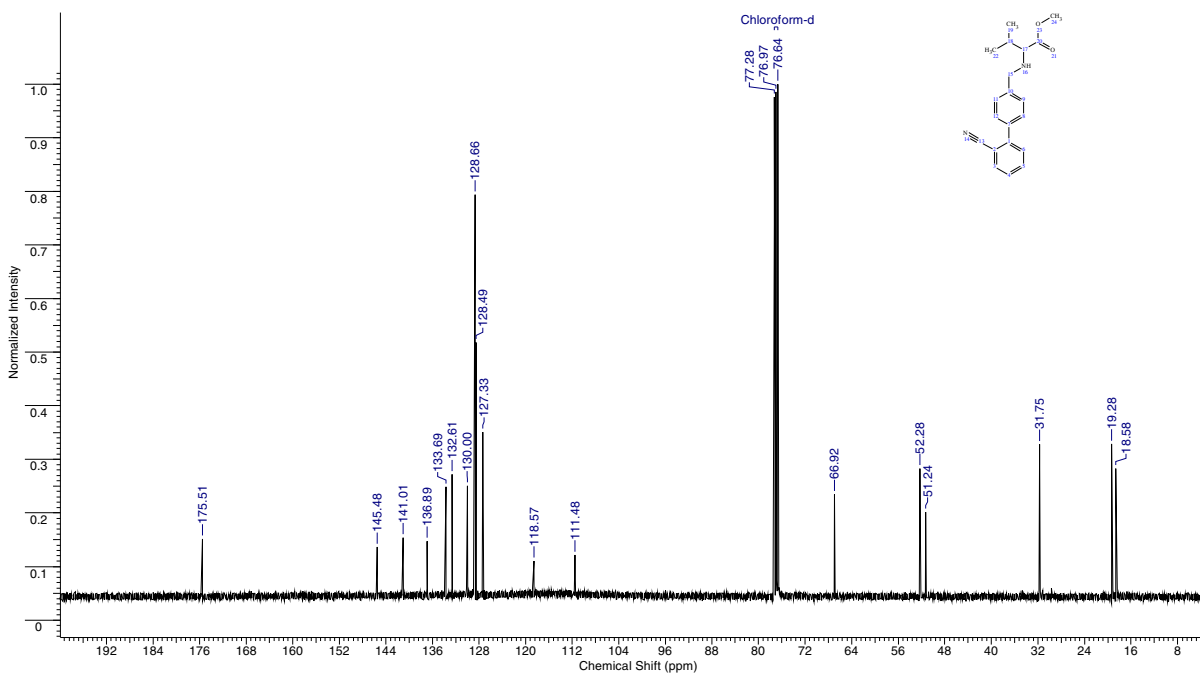
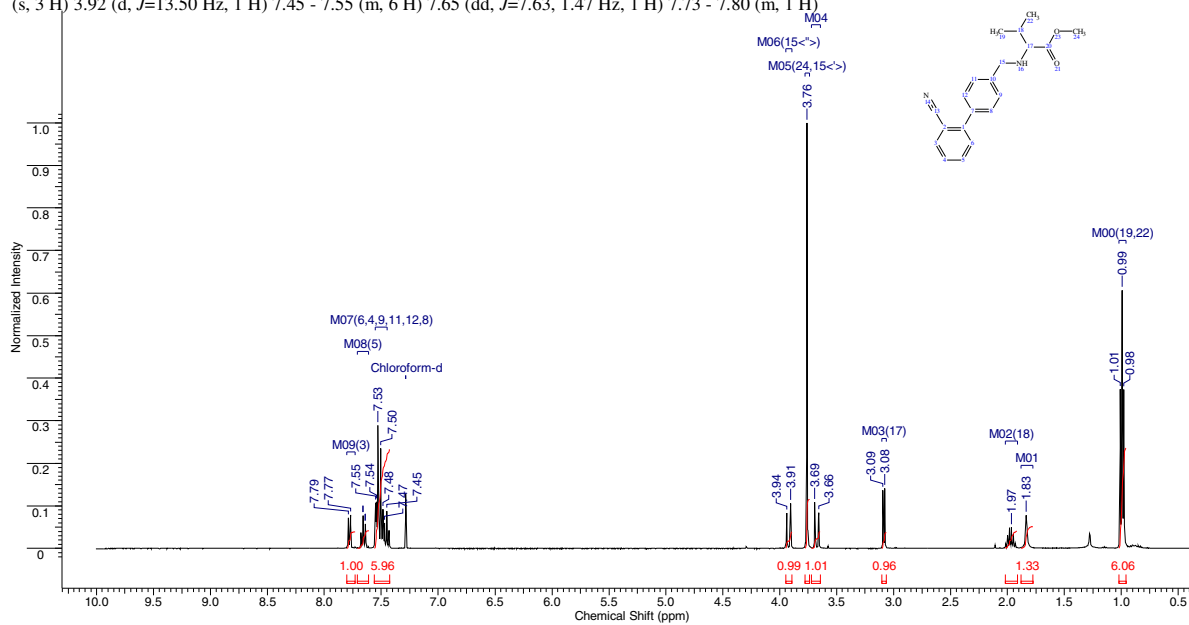
<sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ ppm 4.58 (s, 2 H) 7.48 (t, *J*=7.63 Hz, 1 H) 7.52 - 7.59 (m, 5 H) 7.65 - 7.71 (m, 1 H) 7.80 (d, *J*=7.83 Hz, 1 H)



%	C	H	N
Theory	61.8	3.7	5.1
Analysis	61.8	3.7	5.1

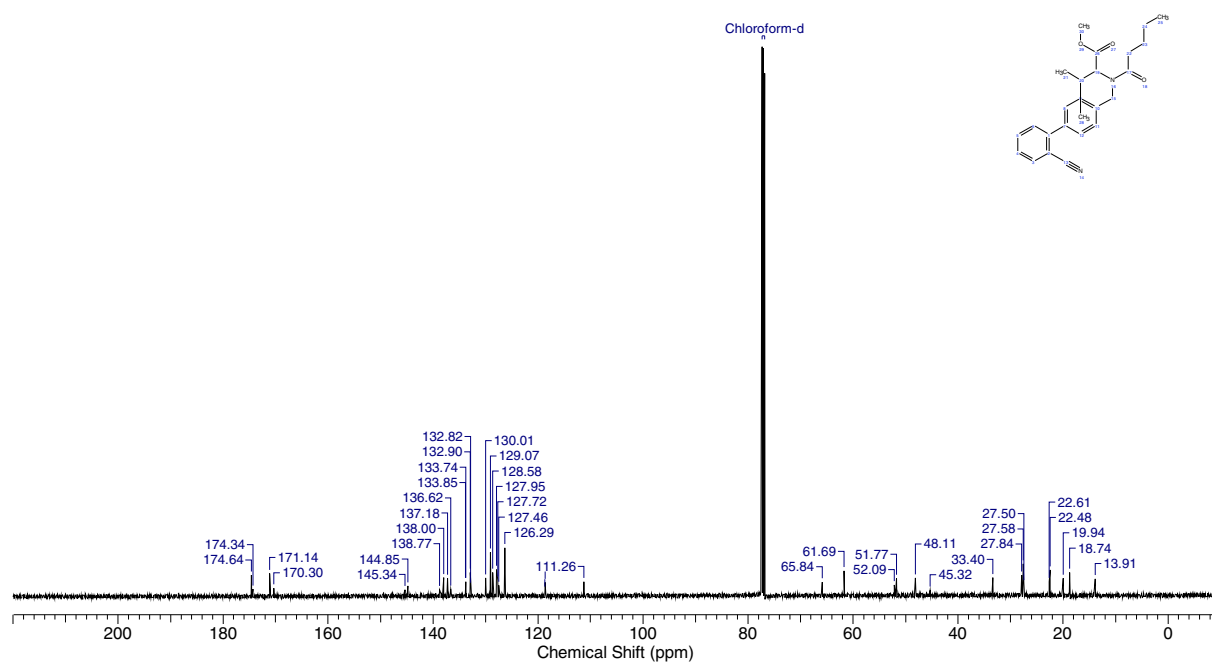
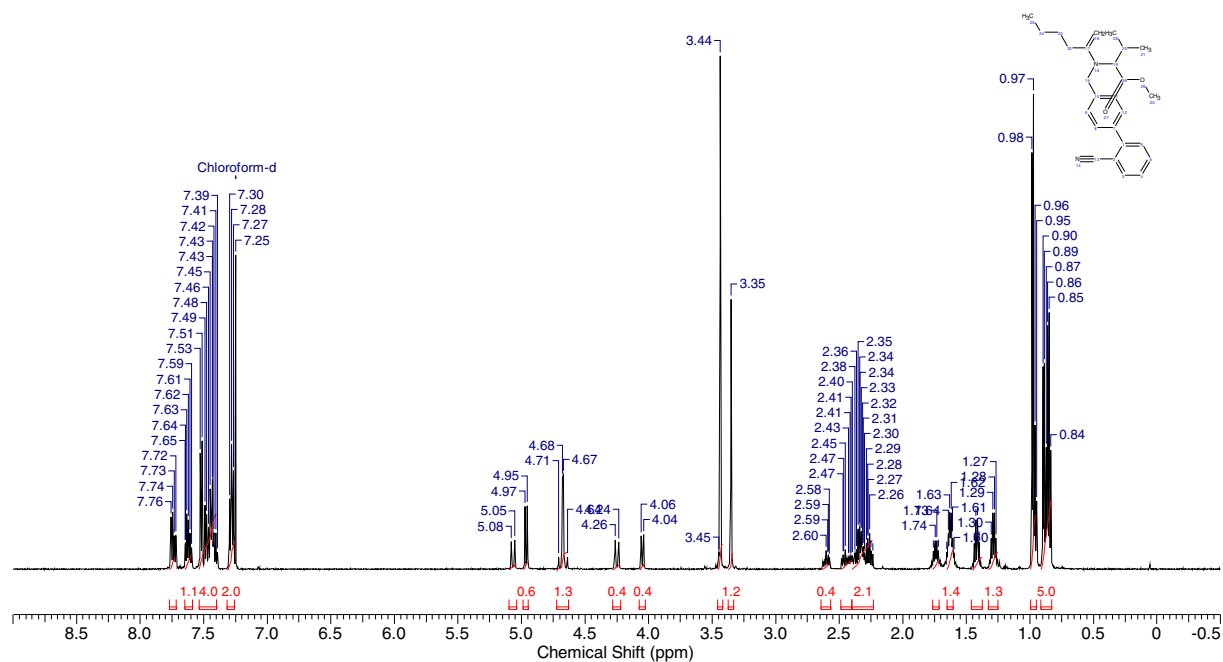
***N*-[(2'-Cyanobiphenyl-4-yl)-methyl]-(*L*)-valine methyl ester (6) [CAS: 137863-89-9] :**

<sup>1</sup>H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.99 (t, *J*=6.46 Hz, 6 H) 1.83 (s, 1 H) 1.97 (s, 1 H) 3.08 (d, *J*=6.16 Hz, 1 H) 3.67 (d, *J*=13.20 Hz, 1 H) 3.76 (s, 3 H) 3.92 (d, *J*=13.50 Hz, 1 H) 7.45 - 7.55 (m, 6 H) 7.65 (dd, *J*=7.63, 1.47 Hz, 1 H) 7.73 - 7.80 (m, 1 H)



%	C	H	N
Theory	74.5	6.9	8.7
Analysis	74.1	6.9	8.6

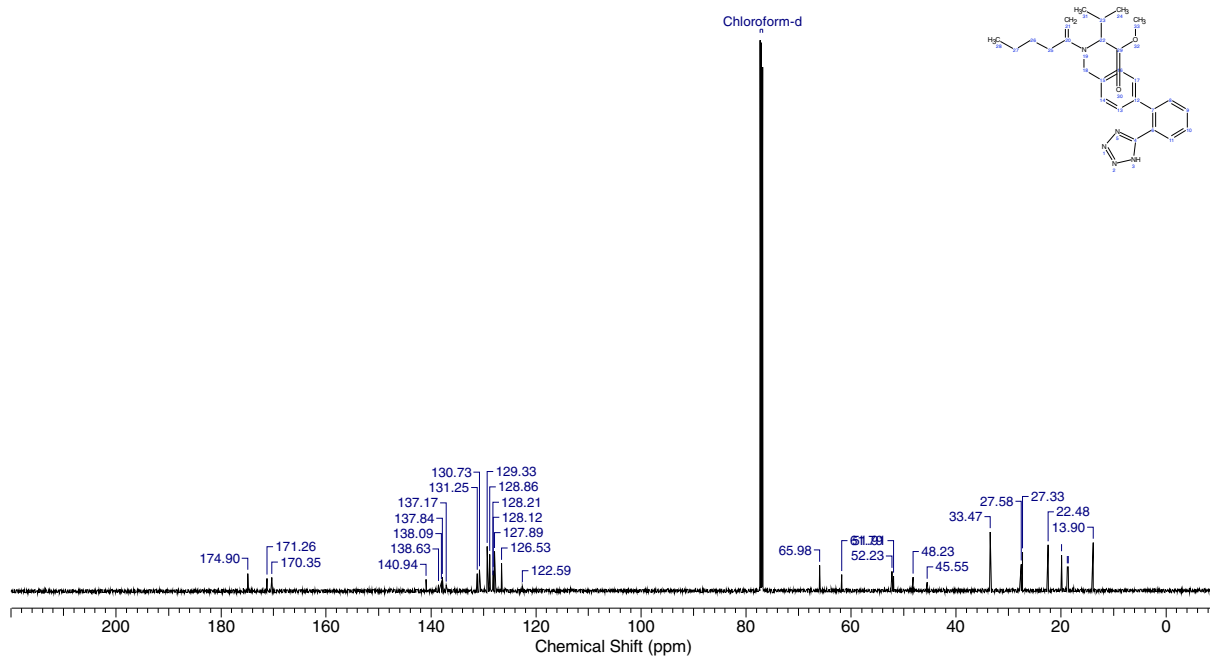
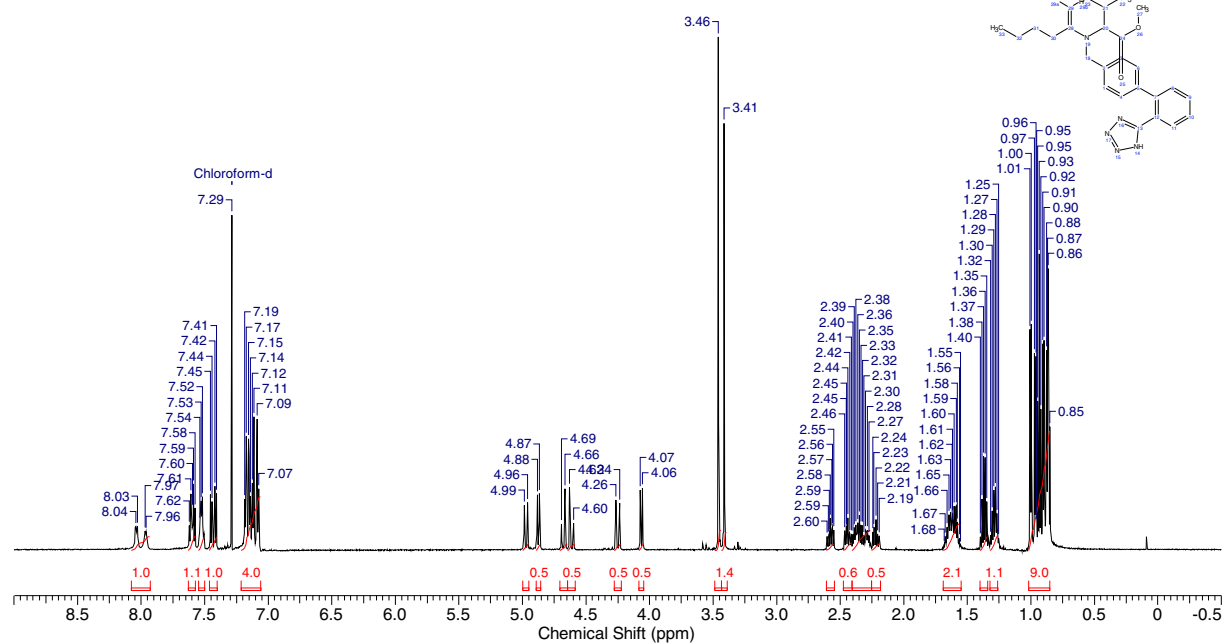
***N*-Pentanoyl-*N*-[(2'-cyanobiphenyl-4-yl)-methyl]-(*L*)-valine methyl ester (8) [CAS: 137863-90-2] :**



%	C	H	N
Theory	73.8	7.4	7.0
Analysis	73.7	7.4	6.9

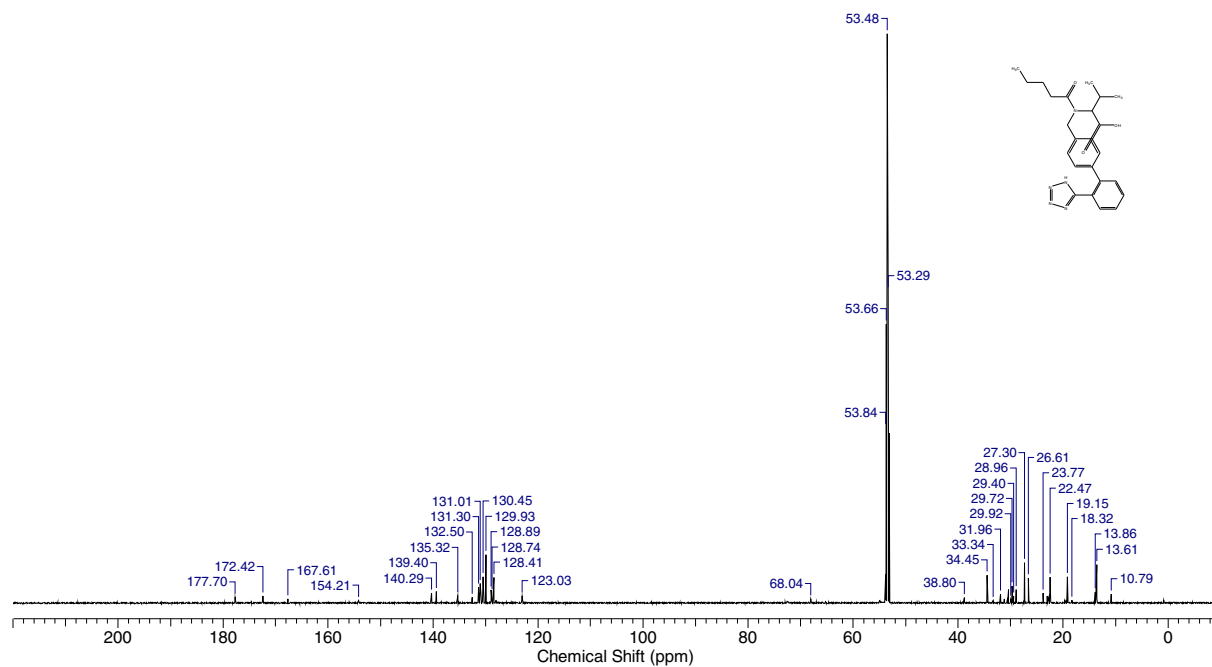
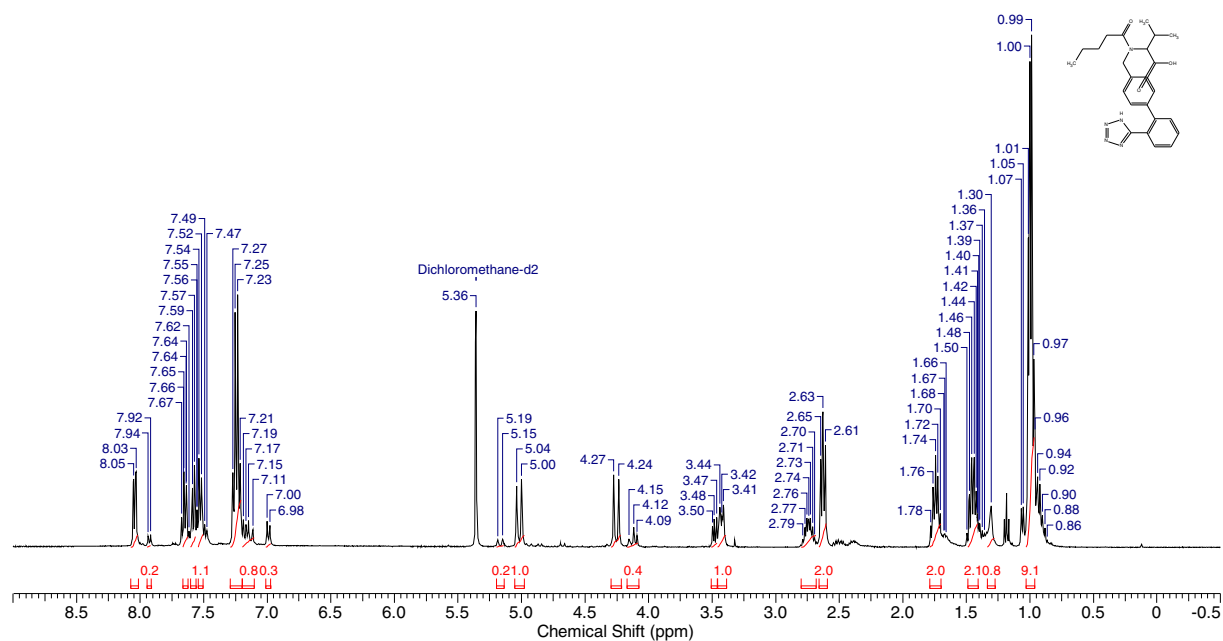
***N*-Pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)-[1, 1'-biphenyl]-4-yl]-methyl]-(*L*)-valine methyl ester (**1c**)**

[CAS: 137863-17-3]:



%	C	H	N
Theory	66.8	6.9	15.6
Analysis	66.5	6.9	15.2

***N*-Pentanoyl-*N*-[[2'-(1*H*-tetrazole-5-yl)-[1,1'-biphenyl]-4-yl]-methyl]-(*L*)-valine (Valsartan) (1b) [CAS: 137862-53-4]:**



%	C	H	N
Theory	66.2	6.7	16.1
Analysis	66.2	6.8	15.8