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Synthesis of *N*-benzoyl Amino Esters and *N*-benzoyl Amino Acids and their Antifungal Activity

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Supplementary Information

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Materials and Methods

Reagents were used as received from Sigma-Aldrich without further purification. NMR spectra were recorded on a Varian Mercury spectrometer (400 MHz for ^{1}H, 100.6 MHz for ^{13}C). Chemical shifts are quoted in ppm (δ) and spectra were referenced to the residual solvent signals (7.27 and 77.2 ppm for $CDCl_3$). Coupling constants (*J*) are expressed in Hertz (Hz). Multiplicities are recorded as follows: s= singlet, d= doublet, t= triplet, dd= doublet of doublets, td= triplet of doublets, dh= doublet of heptuplet, brs= broad singlet, q= quartet, and m= multiplet. IR spectra were acquired on FTIR Perkin Elmer Spectrum 100 (range: 4000-600 cm^{-1}). High-resolution mass spectra (HRMS) were recorded on a JEOL JMStation-JM 700 mass spectrometer at 70 eV in a matrix of glycerol or in a Synapt G2-Si (Waters) spectrometer equipped with electrospray ion source (ESI), single quadrupole mass filter and time of flight mass analyzer (Q-TOF). Melting points were measured in a Mel-Temp apparatus and were not corrected. Analytical TLC was performed using pre-coated silica gel plates 60 F_{254}, and chromatographic columns were carried out on Davisil™ grade 633 silica gel (200–425 mesh).

General Procedure for the synthesis of α-aminoesters

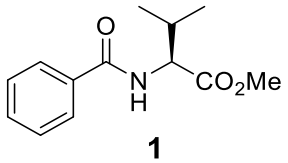
Trimethylsilane chloride (2 mmol) was added to a solution of the corresponding aminoacid (1 mmol) in MeOH (5 mL). The solution was stirred for 12 h at room temperature. Then, the solvent was evaporated under reduced pressure. The residue was characterized and used without further purification in the following reaction.

General Procedure for the synthesis of *N*-benzoylamino acid methyl esters (1-7, 9-17 and 19)

A solution of the corresponding α-aminoester (1 mmol), the carboxylic acid (1 mmol), DMAP (0.1 mmol), *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.5 mmol) and triethylamine (2 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature overnight. Then, CH_2Cl_2 (20 mL) and NH_4Cl sat. aqueous solution (10 mL) were added to the mixture. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtrated and the filtrate was evaporated under reduced pressure; the residue was purified as indicated below.

Characterization data of compounds 1-7, 9-17 and 19

N-Benzoyl-L-valine methyl ester (1)



1

Purification by column chromatography (hexane–EtOAc, 80:20) gave 1 as a white solid (200 mg, 85% yield); mp 110.9–111.4 ºC; Characterization of 1 has been previously reported in the literature [1,2]; IR (cm^{-1}): 3333 (NH), 2977, 2300, 1755 (COOR), 1500, 1560; NMR ^{1}H (400 MHz, $CDCl_3$) δ: 7.76–7.72 (2H, dd, *J*= 7.0, 1.6 Hz, H_{Ar}), 7.47–7.43 (1H, m, H_{Ar}), 7.40–7.36 (2H, m, H_{Ar}), 6.55 (1H, d, *J*= 8.7 Hz, NH), 4.72 (1H, dd, *J*= 8.7, 4.9 Hz, $H_α$), 3.71 (3H, s, CH_3O), 2.22 (1H, dh, *J*= 6.9, 4.9 Hz, $H_β$), 0.95 (3H, d, *J*= 6.9 Hz, $H_γ$), 0.92 (3H, d, *J*= 6.9 Hz, $H_{γ'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 172.8 (COOR), 167.4 (CON), 134.4 (C_{Ar}), 131.9 (C_{Ar}), 128.8 (C_{Ar}), 127.2 (C_{Ar}), 57.6 (CH_3O), 52.5 ($C_α$), 31.9 ($C_β$), 19.2 ($C_γ$), 18.2 ($C_{γ'}$). ESI-HRMS calcd. for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1287, found: 236.1269.

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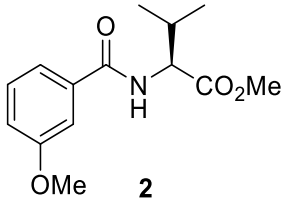
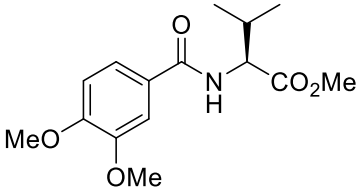
_N_-(3-methoxybenzoyl)-L-valine methyl ester (2)



2

Purification by column chromatography (hexane–EtOAc, 80:20) gave 2 as a white solid (199 mg, 75% yield); mp 80.9–81.5 ºC; IR (cm^{-1}): 3224 (NH), 1719 (CO_2R), 1620 (CONH), 1522; NMR ^1H (400 MHz, $CDCl_3$) δ: 7.40–7.27 (3H, m, H_{Ar}), 7.01 (1H, ddd, *J*= 8.0, 2.6, 1.1 Hz, H_{Ar}), 6.95 (1H, d, *J*= 8.7 Hz, NH), 4.74 (1H, dd, *J*= 8.7, 5.4 Hz, H_α), 3.80 (3H, s, CH_3OAr), 3.75 (3H, s, CH_3O), 2.27 (1H, dh, *J*= 6.8, 5.4 Hz, H_β), 1.00 (3H, d, *J*= 6.8 Hz, H_γ), 0.98 (3H, d, *J*= 6.8 Hz, $H_{\gamma'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 172.5 (COOR), 167.2 (CON), 199.5 (C_{Ar}), 136.4 (C_{Ar}), 129.4 (C_{Ar}), 118.8 (C_{Ar}), 117.7 (C_{Ar}), 112.5 (C_{Ar}), 57.6 (CH_3OAr), 55.3 (CH_3O), 52.1 (C_α), 31.3 (C_β), 18.9 (C_γ), 18.0 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{14}H_{20}NO_4$ $[M+H]^+$: 266.1392, found: 266.1378.

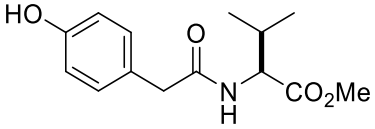
_N_-(3,4-dimethoxybenzoyl)-L-valine methyl ester (3)



3

Purification by column chromatography (hexane–EtOAc, 60:40) gave 3 as a white solid (221 g, 75% yield); mp 90.5-91.0 ºC; IR (cm^{-1}): 3270 (NH), 1732 (CO_2R), 1620 (CONH); NMR ^1H (400 MHz, $CDCl_3$) δ: 7.44 (1H, d, *J*= 2.0 Hz, H_{Ar}), 7.34 (1H, dd, *J*= 8.4, 2.0 Hz, H_{Ar}), 6.88 (1H, d, *J*= 8.4 Hz, H_{Ar}), 6.57 (1H, d, *J*= 8.6 Hz, NH), 4.77 (1H, dd, *J*= 8.6, 5.0 Hz, H_α), 3.94 (3H, s, 3-CH_3O), 3.93 (3H, s, 4-CH_3O), 3.78 (3H, s, CH_3O), 2.28 (1H, dh, *J*= 6.9, 5.0 Hz, H_β), 1.02 (3H, d, *J*= 6.9 Hz, H_γ), 0.99 (3H, d, *J*= 6.9 Hz, $H_{\gamma'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 173.0 (COOR), 167.0 (CON), 152.2 (C_{Ar}), 149.3 (C_{Ar}), 127.0 (C_{Ar}), 119.6 (C_{Ar}), 111.0 (C_{Ar}), 110.5 (C_{Ar}), 57.6 (3-CH_3O), 56.3 (4-CH_3O), 56.2 (CH_3O), 52.4 (C_α), 31.9 (C_β), 19.2 (C_γ), 18.2 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{15}H_{22}NO_5$ $[M+H]^+$: 296.1498, found: 296.1501.

_N_-[2-(4-hydroxyphenyl)acetyl]-L-valine methyl ester (4)



4

Purification by column chromatography (hexane-EtOAc, 50:50) gave 4 as a yellow solid (216 mg, 86% yield), mp 111.1-112.7 ºC. IR (cm^{-1}): 3290 (OH), 1752 (CO_2R), 1600 (CONH). NMR ^1H (400 MHz, $CDCl_3$) δ: 8.14 (1H, brs, OH), 7.05 (2H, d, *J*= 8.5 Hz, H_{Ar}), 6.78 (2H, dd, *J*= 8.5, 2.4 Hz, H_{Ar}), 6.29 (1H, d, *J* = 8.8 Hz, NH), 4.51 (1H, dd, *J*= 8.8, 5.2 Hz, H_α), 3.67 (3H, s, CH_3O), 3.52 (2H, s, CH_2Ph), 2.07 (1H, dh, *J*= 6.8, 5.2 Hz, H_β), 0.84 (3H, d, *J*= 6.8 Hz, H_γ), 0.76 (3H, d, *J* = 6.8 Hz, $H_{\gamma'}$). NMR ^{13}C (101 MHz, $CDCl_3$) δ: 172.8 (COOR), 172.5 (CON), 156.2 (C_{Ar}), 130.5 (C_{Ar}), 125.2 (C_{Ar}), 116.1 (C_{Ar}), 57.3 (CH_3O), 52.4 (C_α), 42.6 (CH_2Ph), 31.1 (C_β), 19.0 (C_γ), 17.7 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{14}H_{20}NO_4$ $[M+H]^+$: 266.1392 found: 266.1381.

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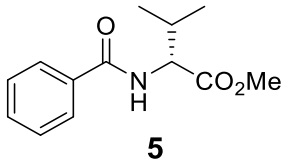
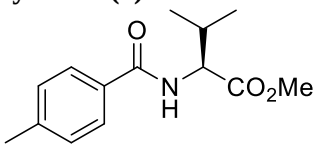
_N_-Benzoyl-D-valine methyl ester (5)



5

Purification by column chromatography (hexane–EtOAc, 80:20) gave 5 as a white solid (200 mg, 85% yield); mp 110.9–111.4 ºC; Characterization of 5 has been previously reported in the literature [6]; IR (cm^{-1}): 3333 (NH), 2977, 2300, 1755 (COOR), 1500, 1560; NMR ^{1}H (400 MHz, $CDCl_3$) δ: 7.86–7.76 (2H, m, H_{Ar}), 7.56–7.49 (1H, m, H_{Ar}), 7.48–7.42 (2H, m, H_{Ar}), 6.63 (1H, d, *J*= 8.7 Hz, NH), 4.79 (1H, dd, *J*= 8.7, 4.9 Hz, H_α), 3.78 (3H, s, CH_3O), 2.28 (1H, dh, *J*= 6.9, 4.9 Hz, H_β), 1.02 (3H, d, *J*= 6.9 Hz, H_γ), 0.99 (3H, d, *J*= 6.9 Hz, $H_{\gamma'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 172.8 (COOR), 167.4 (CON), 134.4 (C_{Ar}), 131.9 (C_{Ar}), 128.8 (C_{Ar}), 127.2 (C_{Ar}), 57.6 (CH_3O), 52.5 (C_α), 31.9 (C_β), 19.2 (C_γ), 18.2 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{13}H_{15}NNaO_2$ [M-H_2O+Na]$^+$: 240.1000 found: 240.1421

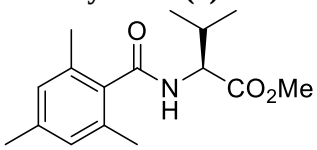
_N_-(4-methylbenzoyl)-L-valine methyl ester (6)



6

Purification by column chromatography (hexane–EtOAc, 50:50) gave 6 as a white solid (246 mg, 99% yield); mp 93-96 ºC; IR (cm^{-1}): 3326 (NH), 1741 (CO_2R), 1634 (CONH); NMR ^{1}H ($CDCl_3$) δ: 7.72 (2H, dd, *J*= 8.4, 0.6 Hz, H_{Ar}), 7.24 (2H, dd, *J*= 8.4, 0.6 Hz, H_{Ar}), 6.66 (1H, d, *J*= 8.7 Hz, NH), 4.78 (1H, dd, *J*= 8.7, 5.0 Hz, H_α), 3.77 (3H, s, CH_3O), 2.40 (3H, s, CH_3-Ar), 2.27 (1H, dh, *J*= 6.9, 5.0 Hz, H_β), 1.01 (3H, d, *J*= 6.9 Hz, H_γ), 0.99 (3H, d, *J*= 6.9 Hz, $H_{\gamma'}$); NMR ^{13}C ($CDCl_3$) δ: 172.9 (COOR), 167.4 (CON), 142.3 (C_{Ar}), 131.4 (C_{Ar}), 129.4 (C_{Ar}), 127.2 (C_{Ar}), 57.5 (C_α), 52.4 (CH_3O), 31.8 (C_β), 21.6 (CH_3-Ar), 19.1 (C_γ), 18.1 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{14}H_{20}NO_3$ [M+H]$^+$: 250.1443, found: 250.1442.

_N_-(2,4,6-trimethylbenzoyl)-L-valine methyl ester (7)



7

Purification by column chromatography (hexane–EtOAc, 60:40) gave 7 as a white solid (100 mg, 36% yield); mp 78-79 ºC; IR (cm^{-1}): 1709 (CO_2R), 1660 (CONH); NMR ^{1}H ($CDCl_3$) δ: 6.86 (2H, s, H_{Ar}), 6.11 (1H, d, *J*= 8.8 Hz, NH), 4.80 (1H, dd, *J*= 8.8, 4.6 Hz, H_α), 3.77 (3H, s, CH_3O), 2.36–2.23 (1H, m, H_β), 2.31 (6H, s, *o*-CH_3-Ar) 2.28 (3H, s, *p*-CH_3-Ar), 1.05 (3H, d, *J*= 6.9 Hz, H_γ), 0.93 (3H, d, *J*= 6.9 Hz, $H_{\gamma'}$); NMR^{13}C ($CDCl_3$) δ: 172.5 (COOR), 170.7 (CON), 138.8 (C_{Ar}), 134.7 (C_{Ar}), 134.5 (C_{Ar}), 128.4 (C_{Ar}), 57.1 (C_α), 52.4 (CH_3O), 31.2 (C_β), 21.3 (*p*-CH_3-Ar), 19.4 (C_γ), 19.4 (*o*-CH_3-Ar), 17.9 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{16}H_{23}NNaO_3$ [M+Na]$^+$: 300.1576, found: 300.1574.

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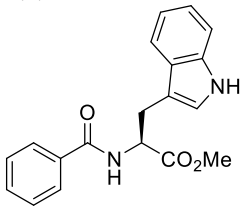
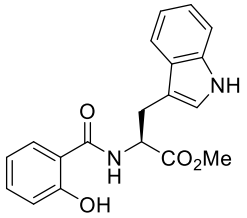
N-Benzoyl-L-tryptophan methyl ester (9)



9

Purification by column chromatography (hexane–EtOAc, 70:30) gave 9 as a yellow solid (145 mg, 45% yield); mp 107-109 °C; Characterization of 9 has been previously reported in the literature [3]; IR (cm^{-1}): 3360 (NH), 1733 (CO_2R), 1636 (CONH); NMR ^1H ($CDCl_3$) δ: 8.36 (1H, s, NH_{Indol}), 7.67 (2H, dd, *J*= 8.3, 1.2 Hz, H_{Ar}), 7.54 (2H, d, *J*= 7.9 Hz, H_{Ar}), 7.49–7.44 (1H, m, H_{Ar}), 7.38–7.32 (2H, m, H_{Ar}), 7.20-7.15 (1H, m, H_{Ar}), 7.09-7.05 (1H, m, H_{Ar}), 6.97 (1H, d, *J*= 2.4 Hz, H_{Ar}), 6.71 (1H, d, *J*= 7.6 Hz, NH), 5.15 (1H, dt, *J*= 7.6, 5.2 Hz, $H_α$), 3.71 (3H, s, CH_3O), 3.47 (1H, dd, *J*= 14.8, 5.2 Hz, $H_β$), 3.42 (1H, dd, *J*= 14.8, 5.2 Hz, $H_{β'}$); NMR ^{13}C ($CDCl_3$) δ: 172.6 (COOR), 167.2 (CON), 136.3 (C_{Ar}), 134.0 (C_{Ar}), 131.9 (C_{Ar}), 128.7 (C_{Ar}), 127.8 (C_{Ar}), 127.2 (C_{Ar}), 123.0 (C_{Ar}), 122.4 (C_{Ar}), 119.9 (C_{Ar}), 118.8 (C_{Ar}), 111.5 (C_{Ar}), 110.1 (C_{Ar}), 53.7 ($C_α$), 52.6 (CH_3O), 27.8 ($C_β$). HRMS-FAB calcd. for $C_{19}H_{19}N_2O_3$ $[M+H]^+$: 323.1396, found: 323.1416.

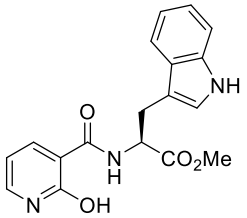
N-(2-hydroxybenzoyl)-L-tryptophan methyl ester (10)



10

Purification by column chromatography (hexane–EtOAc, 80:20) gave 10 as a yellow oil (196 mg, 58% yield); IR (cm^{-1}): 3406 (NH), 1731 (CO_2R), 1638 (CONH); NMR ^1H ($CDCl_3$) δ: 12.15 (1H, s, OH), 8.18 (1H, brs, NH_{indol}), 7.53 (1H, dd, *J*= 8.0, 0.8 Hz, H_{Ar}), 7.39–7.35 (2H, m, H_{Ar}), 7.24–7.07 (3H, m, H_{Ar}), 7.00 (1H, d, *J*= 2.4 Hz, H_{Ar}), 6.97 (1H, dd, *J*= 8.4, 1.2 Hz, H_{Ar}), 6.85 (1H, d, *J*= 7.4 Hz, NH), 6.75 (1H, ddd, *J*= 8.2, 7.3, 1.2 Hz, H_{Ar}), 5.10 (1H, dt, *J*= 7.4, 5.2 Hz, $H_α$), 3.74 (3H, s, CH_3O), 3.47 (1H, dd, *J*= 20.0, 5.2 Hz, $H_β$), 3.42 (1H, dd, *J*= 20.0, 5.2 Hz, $H_{β'}$); NMR ^{13}C ($CDCl_3$) δ: 172.2 (COOR), 169.7 (CON), 161.6 (C_{Ar}-OH), 136.3 (C_{Ar}), 134.6 (C_{Ar}), 127.6 (C_{Ar}), 126.0 (C_{Ar}), 123.1 (C_{Ar}), 122.5 (C_{Ar}), 119.9 (C_{Ar}), 118.9 (C_{Ar}), 118.5 (C_{Ar}), 113.9 (C_{Ar}), 111.6 (C_{Ar}), 109.6 (C_{Ar}), 53.2 ($C_α$), 52.7 (CH_3O), 27.6 ($C_β$). HRMS- FAB calcd. for $C_{19}H_{19}N_2O_4$ $[M+H]^+$: 339.1345, found: 339.1351.

N-(2-hydroxynicotinoyl)-L-tryptophan methyl ester (11)



11

Purification by column chromatography (EtOAc) gave 11 as white solid (146 g, 43% yield); mp 113-117 °C; IR (cm^{-1}): 3242 (NH), 1737 (CO_2R), 1661 (CONH); NMR ^1H ($CDCl_3$) δ: 11.97 (1H, brs, OH), 10.13 (1H, d, *J*= 7.2 Hz, NH), 8.47 (1H, dd, *J*= 7.2, 2.0 Hz, H_{Ar}), 8.38 (1H, brs, NH), 7.56 (1H, d, *J*= 8.2 Hz, H_{Ar}),

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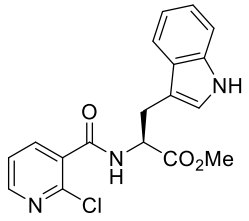
7.26–7.23 (1H, m, H_{Ar}), 7.14–7.03 (4H, m, H_{Ar}), 6.30 (1H, dd, *J*= 7.2, 6.4 Hz, H_{Ar}), 5.11–5.05 (1H, m, H_{α}), 3.70 (3H, s, CH_3O), 3.42 (1H, dd, *J*= 14.8, 6.2 Hz, H_{β}), 3.38 (1H, dd, *J*= 14.8, 5.3 Hz, $H_{\beta'}$); NMR ^{13}C ($CDCl_3$) δ: 172.9 (COOR), 163.8 (C_{Ar}-OH), 163.4 (CO-NH), 145.4 (C_{Ar}), 138.4 (C_{Ar}), 136.2 (C_{Ar}), 127.5 (C_{Ar}), 123.5 (C_{Ar}), 122.2 (C_{Ar}), 120.7 (C_{Ar}), 119.6 (C_{Ar}), 118.7 (C_{Ar}), 111.5 (C_{Ar}), 110.0 (C_{Ar}), 107.8 (C_{Ar}), 53.4 (C_{α}), 52.6 (CH_3O), 27.8 (C_{β}). HRMS-FAB calcd. for $C_{18}H_{18}N_3O_4$ $[M+H]^+$: 340.1297, found: 340.1315.

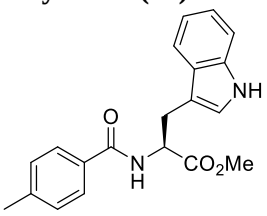
N-(2-chloronicotinoyl)-L-tryptophan methyl ester (12)



12

Purification by column chromatography (hexane–EtOAc, 60:40) gave 12 as brown oil (100 mg, 28% yield); mp 113–117 °C; IR (cm^{-1}): 3303 (NH), 1738 (CO_2R), 1650 (CONH); NMR ^1H ($CDCl_3$) δ: 8.46 (1H, brs, NH_{Indol}), 8.37 (1H, d, *J*= 2.2 Hz, H_{Ar}), 7.91 (1H, d, *J*= 7.5 Hz, H_{Ar}), 7.54 (1H, d, *J*= 8.0 Hz, H_{Ar}), 7.31 (1H, d, *J*= 8.0 Hz, H_{Ar}), 7.25–7.20 (1H, m, H_{Ar}), 7.18–7.13 (1H, m, H_{Ar}), 7.11–7.02 (3H, m, H_{Ar}), 5.11 (1H, dt, *J*= 12.9, 5.6 Hz, H_{α}), 3.73 (3H, s, CH_3O), 3.49 (1H, dd, *J*= 14.8, 5.6 Hz, H_{β}), 3.41 (1H, dd, *J*= 14.8, 5.6 Hz, $H_{\beta'}$); NMR ^{13}C ($CDCl_3$) δ: 172.1 (COOR), 164.5 (CON), 151.1 (C_{Ar}), 147.5 (C_{Ar}), 139.8 (C_{Ar}), 136.3 (C_{Ar}), 130.8 (C_{Ar}), 127.6 (C_{Ar}), 123.2 (C_{Ar}), 122.8 (C_{Ar}), 122.4 (C_{Ar}), 119.8 (C_{Ar}), 118.6 (C_{Ar}), 111.5 (C_{Ar}), 109.6 (C_{Ar}), 54.0 (C_{α}), 52.8 (CH_3O), 27.6 (C_{β}). HRMS-FAB calcd. for $C_{18}H_{17}ClN_3O_3$ $[M+H]^+$: 358.0958, found: 358.0945.

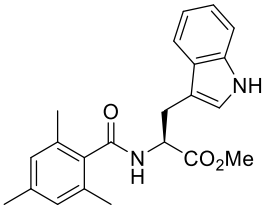
N-(4-methylbenzoyl)-l-tryptophan methyl ester (13)



13

Purification by column chromatography (hexane–EtOAc, 80:20) gave 13 as a yellow solid (255 mg, 76% yield); mp 117–119 °C; IR (cm^{-1}): 3360 (NH), 1731 (CO_2R), 1633 (CONH); NMR ^1H ($CDCl_3$) δ: 8.81 (1H, s, NH_{Indol}), 7.54 (2H, d, *J*= 8.2 Hz, H_{Ar}), 7.50 (1H, d, *J*= 7.7 Hz, H_{Ar}), 7.26 (1H, dd, *J*= 8.9, 0.7 Hz, H_{Ar}), 7.15–7.02 (3H, m, H_{Ar}) 6.90 (1H, d, *J*= 2.4 Hz, H_{Ar}), 6.80 (1H, d, *J*= 7.6 Hz, NH), 5.11 (1H, dt, *J*= 7.6, 5.2, Hz, H_{α}), 3.64 (3H, s, CH_3O), 3.41 (1H, dd, *J*= 16.4, 5.2 Hz, H_{β}), 3.38 (1H, dd, *J*= 16.4, 5.2 Hz, $H_{\beta'}$), 2.30 (3H, s, CH_3); NMR ^{13}C ($CDCl_3$) δ: 172.6 (COOR), 167.3 (CON), 142.3 (C_{Ar}), 136.3 (C_{Ar}), 130.9 (C_{Ar}), 129.3 (C_{Ar}), 127.7 (C_{Ar}), 127.2 (C_{Ar}), 123.2 (C_{Ar}), 122.1 (C_{Ar}), 119.6 (C_{Ar}), 118.5 (C_{Ar}), 111.6 (C_{Ar}), 109.6 (C_{Ar}), 53.7 (C_{α}), 52.5 (CH_3O), 27.7 (C_{β}), 21.5 (CH_3-Ar). HRMS-FAB calcd. for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1552, found: 337.1535.

N-(2,4,6-trimethylbenzoyl)-L-tryptophan methyl ester (14)



14

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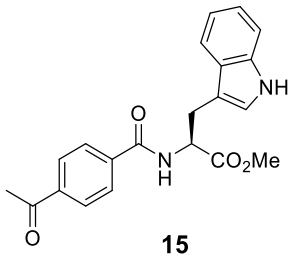
Purification by column chromatography (hexane–EtOAc, 80:20) gave 14 as a yellow oil (109 mg, 30% yield); IR (cm^{-1}): 3279 (NH), 1738 (CO_2R), 1640 (CONH); NMR ^1H ($CDCl_3$) δ: 8.57 (1H, brs, NH_{indol}), 7.53 (1H, d, *J*= 8.0 Hz, H_{Ar}), 7.24 (1H, d, *J*= 8.0 Hz, H_{Ar}), 7.16-7.03 (2H, m, H_{Ar}), 6.91 (1H, d, *J*= 2.4 Hz, H_{Ar}), 6.75 (2H, s, H_{Ar}), 6.13 (1H, d, *J*= 8.0 Hz, NH), 5.18 (1H, ddd *J*= 8.0, 6.8, 5.7 Hz, $H_α$), 3.69 (3H, s, CH_3O), 3.36 (1H, dd, *J*= 14.8, 5.7 Hz, $H_β$), 3.31 (1H, dd, *J*= 14.8, 6.8 Hz, $H_{β'}$), 2.22 (3H, s, *p*-CH_3Ar), 2.11 (6H, s, *o*-CH_3Ar); NMR ^{13}C ($CDCl_3$) δ: 172.6 (COOR), 170.6 (CON), 138.7 (C_{Ar}), 136.4 (C_{Ar}), 134.5 (C_{Ar}), 134.2 (C_{Ar}), 128.3 (C_{Ar}), 127.4 (C_{Ar}), 123.0 (C_{Ar}), 122.2 (C_{Ar}), 119.6 (C_{Ar}), 118.5 (C_{Ar}), 111.5 (C_{Ar}), 109.7 (C_{Ar}), 52.6 ($C_α$$CH_3O$), 28.0 ($C_β$(*p*-$CH_3$-Ar), 19.0 (*o*-$CH_3$-Ar). HRMS-FAB calcd. for $C_{22}H_{25}N_2O_3$ $[M+H]^+$: 365.1865, found: 365.1839.

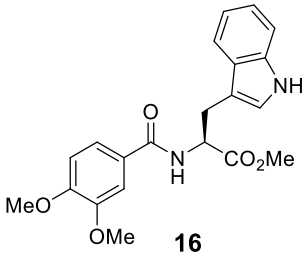
N-(4-acetylbenzoyl)-L-tryptophan methyl ester (15)



15

Purification by column chromatography (hexane–EtOAc, 60:40) gave 15 as a yellow solid (1.2 g, 48% yield); mp 126-129 °C; IR (cm^{-1}): 3355 (NH), 1727 (CO_2R), 1682 (CONH); NMR ^1H ($CDCl_3$) δ: 8.28 (1H, brs, NH_{indol}), 7.93 (2H, d, *J*= 8.6 Hz, H_{Ar}), 7.74 (2H, d, *J*= 8.6 Hz, H_{Ar}), 7.54 (1H, dd, *J*= 8.0, 0.8 Hz, H_{Ar}), 7.36 (1H, dt, *J*= 8.2, 0.8 Hz, H_{Ar}), 7.19 (1H, ddd, *J*= 8.0, 7.2, 0.8 Hz, H_{Ar}), 7.08 (1H, ddd, *J*= 8.0, 7.2, 0.8 Hz, H_{Ar}), 7.00 (1H, d, 2.4 Hz, H_{Ar}), 6.74 (1H, d, *J*= 7.6 Hz, NH), 5.15 (1H, dt, *J*= 7.6, 5.2 Hz, $H_α$), 3.75 (3H, s, CH_3O), 3.49 (1H, dd, *J*= 15.2, 5.2 Hz, $H_β$), 3.44 (1H, dd, *J*= 15.2, 5.2 Hz, $H_{β'}$), 2.61 (3H, s, CH_3CO); NMR ^{13}C ($CDCl_3$) δ: 197.7 (CO), 172.4 (COOR), 166.1 (CON), 139.4 (C_{Ar}), 137.8 (C_{Ar}), 136.3 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (C_{Ar}), 127.6 (C_{Ar}), 123.0 (C_{Ar}), 122.6 (C_{Ar}), 120.0 (C_{Ar}), 118.7 (C_{Ar}), 111.6 (C_{Ar}), 110.0 (C_{Ar}), 53.8 ($C_α$), 52.7 (CH_3O), 27.7 ($C_β$), 27.0 (CH_3CO). HRMS-FAB calcd. for $C_{21}H_{21}N_2O_4$ $[M+H]^+$: 365.1501, found: 365.1491.

N-(3,4-dimethoxybenzoyl)-L-tryptophan methyl ester (16)



16

Purification by column chromatography (hexane–EtOAc, 60:40) gave 16 as a white solid (1.2 g, 84% yield); mp 118–123 °C; IR (cm^{-1}): 3387 (NH), 1741 (CO_2R), 1627 (CONH); NMR ^1H ($CDCl_3$) δ: 8.45 (1H, brs, NH_{indol}), 7.55 (1H, d, *J*= 8.0 Hz, H_{Ar}), 7.33 (1H, dd, *J*= 8.4, 0.8 Hz, H_{Ar}), 7.27 (1H, *d*, *J*= 2.0 Hz, H_{Ar}), 7.19-7.15 (2H, m, H_{Ar}), 7.08 (1H, ddd, *J*= 7.6, 6.8, 1.2 Hz, H_{Ar}), 6.97 (1H, d, *J*= 2.4 Hz, H_{Ar}), 6.75 (1H, d, *J*= 8.4 Hz, H_{Ar}), 6.63 (1H, d, *J*= 8.0 Hz, NH), 5.13 (1H, dt, *J*= 8.0, 5.2 Hz, $H_α$), 3.87 (3H, s, CH_3OAr), 3.80 (3H, s, CH_3OAr), 3.72 (3H, s, CH_3O), 3.46 (1H, dd, *J*= 14.8, 5.2 Hz, $H_β$), 3.41 (1H, dd, *J*= 14.8, 5.2 Hz, $H_{β'}$); NMR ^{13}C ($CDCl_3$) δ: 172.7 (COOR), 167.7 (CON), 152.0 (C_{Ar}), 149.0 (C_{Ar}), 136.3 (C_{Ar}), 127.8 (C_{Ar}), 126.4 (C_{Ar}), 123.1 (C_{Ar}), 122.3 (C_{Ar}), 120.0 (C_{Ar}), 119.8 (C_{Ar}), 118.7 (C_{Ar}), 111.5 (C_{Ar}), 110.5 (C_{Ar}), 110.3 (C_{Ar}), 110.0 (C_{Ar}), 56.1 (CH_3OAr), 56.0 (CH_3OAr), 53.7 ($C_α$), 52.6 (CH_3O), 27.7 ($C_β$). HRMS-FAB calcd. for $C_{21}H_{23}N_2O_5$ $[M+H]^+$: 383.1607, found: 383.1643.

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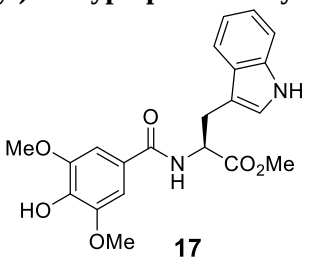
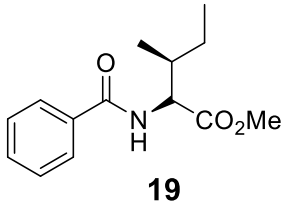
_N_-(4-hydroxy-3,5-dimethoxybenzoyl)-L-tryptophan methyl ester (17)



17

Purification by column chromatography (EtOAc–hexane, 60:40) gave 17 as a yellow solid (203 mg, 51% yield); mp 98-102 °C; IR (cm^{-1}): 3377 (NH), 1731 (CO_2R), 1642 (CONH); NMR ^1H ($CDCl_3$) δ: 8.83 (1H, brs, NH_{indol}), 7.55 (1H, d, *J*= 8.0 Hz, H_{Ar}), 7.30 (1H, d, *J*= 8.4 Hz, H_{Ar}), 7.17-6.99 (2H, m, H_{Ar}), 6.95 (1H, d, *J*= 1.6 Hz, H_{Ar}), 6.83 (2H, s, H_{Ar}), 6.67 (1H, d, *J*= 8.0 Hz, NH), 6.11 (1H, sa, OH), 5.10 (1H, dt, *J*= 8.0, 5.2 Hz, $H_α$), 3.71 (3H, s, CH_3OAr), 3.67 (6H, s, CH_3OAr, CH_3O), 3.43 (1H, dd, *J*= 14.8, 5.2 Hz, $H_β$), 3.38 (1H, dd, *J*= 14.8, 5.2 Hz, $H_{β'}$; NMR ^{13}C ($CDCl_3$) δ: 172.8 (COOR), 167.1 (CON), 146.8 (C_{Ar}), 136.2 (C_{Ar}), 136.3 (C_{Ar}), 127.8 (C_{Ar}), 124.7 (C_{Ar}), 123.2 (C_{Ar}), 122.1 (C_{Ar}), 119.7 (C_{Ar}), 118.4 (C_{Ar}), 111.6 (C_{Ar}), 109.6 (C_{Ar}), 104.4 (C_{Ar}), 56.3 (CH_3OAr), 53.9 ($C_α$), 52.5 (CH_3O), 27.4 ($C_β$). HRMS-FAB calcd. for $C_{21}H_{23}N_2O_6$ $[M+H]^+$: 399.1556, found: 399.1577.

_N_-Benzoyl-L-isoleucine methyl ester (19)



19

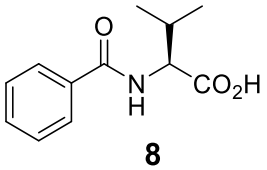
Purification by column chromatography (hexane–EtOAc, 80:20) gave 19 as a white solid (72 mg, 29% yield); mp 90.4-91.5 °C; Characterization of 19 has been previously reported in the literature [4]; IR (cm^{-1}): 3330 (NH), 1719 (CO_2R), 1633 (CONH); NMR ^1H (400 MHz, $CDCl_3$) δ: 7.82–7.79 (2H, m, H_{Ar}), 7.54–7.43 (3H, m, H_{Ar}), 6.65 (1H, d, *J*= 8.4 Hz, NH), 4.83 (1H, dd, *J*= 8.4, 5.2 Hz, $H_α$), 3.78 (3H, s, CH_3O), 2.07-1.97 (1H, m, $H_β$), 1.59-1.48 (1H, m, $H_δ$), 1.32-1.21 (1H, m, $H_{δ'}$), 0.97 (1H, d, *J*= 6.9 Hz, $H_γ$), 0.95 (3H, t, *J*= 7.4 Hz, $H_ε$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 172.8 (COOR), 167.3 (CON), 134.3 (C_{Ar}), 131.9 (C_{Ar}), 128.8 (C_{Ar}), 127.2 (C_{Ar}), 57.0 (CH_3O), 52.4 ($C_α$), 38.5 ($C_β$), 25.6 ($C_δ$), 15.7 ($C_γ$), 11.8 ($C_ε$). ESI-HRMS calcd. for $C_{13}H_{18}NO_3$ $[M+H]^+$: 250.1443, found: 250.1449.

General Procedure for the synthesis of *N*-benzoylaminoacids (8, 18, 20-23)

A solution of the corresponding α-aminoester (1 mmol), benzoic anhydride (1 mmol) and AcOH (25 mL) was refluxed for 2 h. After cooling the solution, the solvent was evaporated under reduced pressure and the residue was purified as indicated in each case.

Characterization data of compounds 8, 18, 20-23

_N_-Benzoyl-L-valine (8)



8

Purification by column chromatography (hexane-EtOAc, 70:30) gave 8 as a solid (155 mg, 70% yield); mp 127.0–127.7 °C; Characterization of 8 has been previously reported in the literature [5]. IR (cm^{-1}):

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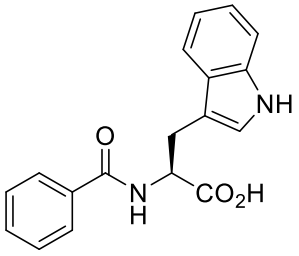
3297 (OH), 2952, 1649 (CO_2H), 1633 (CONH), 1520; NMR ^1H (400 MHz, $CDCl_3$) δ: 8.57 (1H, s, COOH), 7.82-7.76 (2H, m, H_{Ar}), 7.54-7.42 (3H, m, H_{Ar}), 6.74 (1H, d, *J*= 8.4 Hz, NH), 4.79 (1H, dd, *J*= 8.4, 4.8 Hz, H_α), 2.42-2.27 (1H, m, H_β), 1.04 (3H, d, *J*= 6.9 Hz, H_γ), 1.03 (3H, d, *J*= 6.9 Hz, $H_{\gamma'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 176.0 (COOH), 168.2 (CON), 134.0 (C_{Ar}), 132.1 (C_{Ar}), 128.9 (C_{Ar}), 127.3 (C_{Ar}), 57.7 (C_α), 31.5 (C_β), 19.2 (C_γ), 18.0 ($C_{\gamma'}$). ESI-HRMS calcd. for $C_{12}H_{14}NO_3$ $[M-H]^-$: 220.0974, found: 220.0965.

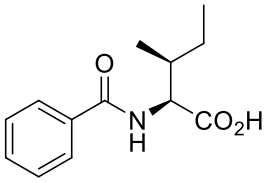
_N_-Benzoyl-L-tryptophan (18)



18

Purification by column chromatography (hexane–AcOEt, 70:30) gave 18 as oil (231 mg, 75% yield); Characterization of 18 has been previously reported in the literature [5]; IR (cm^{-1}): 3493 (OH), 3045, 2926, 1726 (CO_2H), 1626 (CONH); NMR ^1H (400 MHz, $CDCl_3$) δ: 8.47 (1H, s, NH), 7.95 (1H, brs, COOH), 7.54-7.45 (3H, m, H_{Ar}), 7.34-7.28 (1H, m, H_{Ar}), 7.22-7.14 (3H, m, H_{Ar}, NH), 7.06 (1H, m, H_{Ar}), 6.96 (1H, m, H_{Ar}), 6.86 (2H, d, *J*= 7.2 Hz, H_{Ar}), 5.13–4.97 (1H, m, H_α), 3.39 (1H, dd, *J*= 15.2, 5.4 Hz, H_β), 3.33 (1H, dd, *J*= 15.2, 5.4 Hz, $H_{\beta'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 175.3 (COOH), 168.3 (CON), 136.3 (C_{Ar}), 133.2 (C_{Ar}), 132.1 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (C_{Ar}), 127.3 (C_{Ar}), 123.6 (C_{Ar}), 122.2 (C_{Ar}), 119.7 (C_{Ar}), 118.6 (C_{Ar}), 111.6 (C_{Ar}), 109.4 (C_{Ar}), 54.1 (C_α), 27.2 (C_β). ESI-HRMS calcd. for $C_{18}H_{15}N_2O_3$ $[M-H]^-$: 307.1083, found: 307.1078.

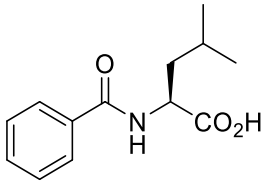
_N_-Benzoyl-L-isoleucine (20)



20

Purification by column chromatography (hexane–AcOEt, 50:50) gave 20 as a white solid (73 mg, 31% yield); mp 119.0–120.0 °C; Characterization of 20 has been previously reported in the literature [5]; IR (cm^{-1}): 3393 (OH), 1733 (CO_2H), 1620 (CONH); NMR ^1H (400 MHz, $CDCl_3$) δ: 9.70 (1H, brs, COOH), 7.79 (2H, dd, *J*= 7.8, 1.4 Hz, H_{Ar}), 7.56–7.36 (3H, m, H_{Ar}), 6.86 (1H, d, *J*= 8.7 Hz, NH), 6.77 (1H, d, *J*= 8.7 Hz, NH), 4.93 (1H, dd, *J*= 8.7, 4.8 Hz, H_α), 4.83 (1H, dd, *J*= 8.8, 4.8 Hz, H_α), 2.14–2.01 (1H, m, H_β), 1.62–1.46 (1H, m, H_δ), 1.33–1.20 (1H, m, $H_{\delta'}$), 1.00–0.94 (6H, m, H_γ, H_ε); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 176.4 (COOH), 175.9 (COOH), 168.3 (CON), 168.1 (CON), 134.0 (C_{Ar}), 133.9 (C_{Ar}), 132.1 (C_{Ar}), 128.8 (C_{Ar}), 127.3 (C_{Ar}), 57.1 (C_α), 56.0 (C_α), 38.1 (C_β), 38.0 (C_β), 26.5 (C_δ), 25.4 (C_δ), 15.6 (C_γ), 14.8 (C_γ), 11.9 (C_ε), 11.8 (C_ε). ESI-HRMS calcd. for $C_{13}H_{16}NO_3$ $[M-H]^-$: 234.1130, found: 234.1073.

_N_-Benzoyl-L-leucine (21)



21

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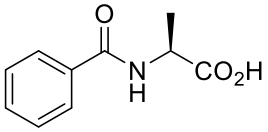
Purification by column chromatography (hexane–AcOEt, 70:30) gave 21 as oil (68 mg. 29% yield); Characterization of 21 has been previously reported in the literature [5]; IR (cm^{-1}): 3323 (OH), 1713 (CO_2H), 1620 (CONH); NMR ^1H (400 MHz, $CDCl_3$) δ: 7.76 (2H, dd, *J*= 8.4, 1.4 Hz, H_{Ar}), 7.48–7.34 (3H, m, H_{Ar}), 7.24 (1H, brs, COOH), 7.07 (1H, d, *J*= 8.2 Hz, NH), 4.80 (1H, m, H_α), 1.78–1.67 (3H, m, H_β, H_γ), 0.94 (3H, d, *J*= 5.9 Hz, H_δ), 0.93 (3H, d, *J*= 5.9 Hz, $H_{\delta'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 176.4 (COOH), 168.4 (CON), 133.6 (C_{Ar}), 132.0 (C_{Ar}), 128.7 (C_{Ar}), 127.3 (C_{Ar}), 51.6 (C_α), 41.2 (C_β), 25.1 (C_γ), 23.0 (C_δ), 22.0 ($C_{\delta'}$). ESI-HRMS calcd. for $C_{13}H_{16}NO_3$ $[M-H]^-$: 234.1130, found: 234.1138.

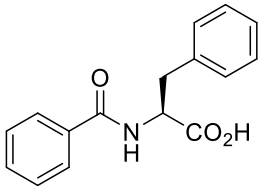
N-Benzoyl-L-alanine (22)



22

Purification by column chromatography (hexane–AcOEt, 50:50) gave 22 as a solid (137 mg. 71% yield); mp 121.2–122.7 ºC; Characterization of 22 has been previously reported in the literature [5]. IR (cm^{-1}): 3376 (OH), 1726 (CO_2H), 1593, 1540; NMR ^1H (400 MHz, $CDCl_3$) δ: 7.83–7.78 (2H, m, H_{Ar}), 7.54–7.38 (3H, m, H_{Ar}), 4.82 (1H, brs, NH) 4.72 (1H, q, *J*= 7.2 Hz, H_α), 1.53 (3H, d, *J*= 7.2 Hz, H_β); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 175.1 (COOH), 167.8 (CON), 133.6 (C_{Ar}), 131.8 (C_{Ar}), 128.5 (C_{Ar}), 127.1 (C_{Ar}), 127.0 (C_{Ar}), 48.5 (C_α), 17.9 (C_β). ESI-HRMS calcd. for $C_{10}H_{10}NO_3$ $[M-H]^-$: 192.0661, found: 192.0664.

N-Benzoyl-L-phenylalanine (23)



23

Purification by column chromatography (hexane–AcOEt, 70:30) gave 23 as a white solid (126 mg, 47% yield); mp 141-141.5 °C; Characterization of 23 has been previously reported in the literature [5]; IR (cm^{-1}): 3337 (OH), 1713 (CO_2H), 1633 (CONH), 1527; NMR ^1H (400 MHz, $CDCl_3$) δ: 8.69 (1H, s, COOH), 7.70–7.66 (2H, m, H_{Ar}), 7.53–7.37 (3H, m, H_{Ar}), 7.31–7.18 (5H, m, H_{Ar}), 6.64 (1H, d, *J*= 7.4 Hz, NH), 5.10 (1H, dt, *J*= 7.4, 5.8 Hz, H_α), 3.35 (1H, dd, *J*= 14.0, 5.8 Hz, H_β), 3.26 (1H, dd, *J*= 14.0, 5.8 Hz, $H_{\beta'}$); NMR ^{13}C (101 MHz, $CDCl_3$) δ: 175.3 (COOH), 167.9 (CON), 135.8 (C_{Ar}), 133.6 (C_{Ar}), 132.3 (C_{Ar}), 129.6 (C_{Ar}), 128.9 (C_{Ar}), 127.5 (C_{Ar}), 127.3 (C_{Ar}), 53.8 (C_α), 37.5 (C_β). ESI-HRMS calcd. for $C_{16}H_{14}NO_3$ $[M-H]^-$: 268.0974, found: 268.0974.

Active Site Validation

The active site of chitinase (PDB ID: 5WV9) was validated with the co-crystallized native ligand 2-acetamido-2-deoxy-β-d-glucopyranose. Comparison of the poses obtained by the AutoDock Vina program with those of the crystallized protein yielded root mean square deviation (RMSD) = 2.094 Å, indicating an appropriate optimization score. These values are small and support binding at the simulation site with the original orientation of the co-crystallized molecule (Fig. S1).

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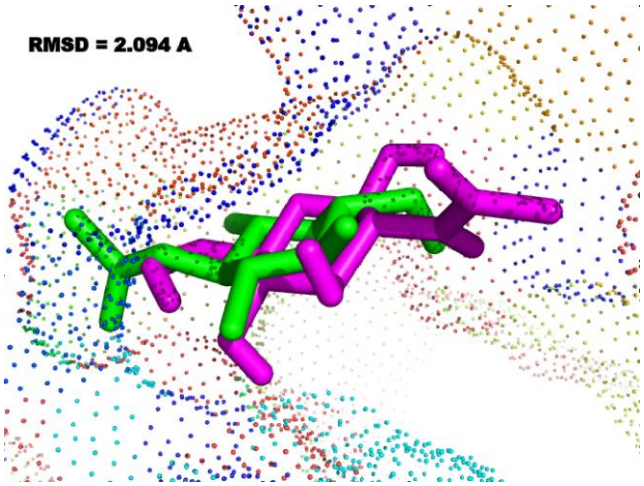

Fig. S1. Ligand-binding site of chitinase protein with co-crystalized native 2-acetamido-2-deoxy-β-d-glucopyranose (green) and 2-acetamido-2-deoxy-β-d-glucopyranose as posed calculated by the Autodock Vina program (pink).

Table 1. Binding affinity for the interaction of glucose and tested the N-benzoyl amino derivatives with chitinase.

Compound	**No. of H-Bonds**	**Residue Receptor H-Bonds**	**Bond Length (Å)**	**Docking Score (kcal/mol)**	***K_i* (μM) [a]**
2-acetamido-2-deoxy-β-d-glucopyranose	4	A/ARG`342/NH1 A/ASP`286/OD2 A/TYR`285/OH A/TRP`176/N`B	2.4 2.3 2.3 3.4	-6.5	16.52
1	1	A:TYR340:OH	3.09	-7.90	1.54
2	3	A:TYR285:OH A:ASP286:OD2 A:ASP215:OD2	3.21 2.65 3.42	-7.80	1.83
3	3	A:GLY175:CA A:TRP176:CD1:B A:ASP215:OD2	3.66 3.38 3.47	-7.73	2.06
4	6	A:TRP176:N A:TRP176:N:B A:TYR285:OH A:ARG342:NH1 A:MET283:SD A:ASP286:OD2 A:TRP433	2.96 2.97 3.04 3.34 3.18 2.40	-7.9	1.62
5	1	A:TRP176:N:B	4.17	-7.87	1.62
6	3	A:TYR218:OH A:GLY175:CA A:ARG342:NH1	3.34 2.80 3.61	-8.51	0.55
7	2	A:ARG342:NH1 A:TRP433:NE1	3.33 3.22	-8.51	0.55
8	1	A:TRP176:N:B	2.19	-8.24	0.87
9	1	A:GLU217:OE1	3.35	-10.20	0.03
10	4	A:TRP176:N A:TRP176:N:B	3.33 3.34	-9.90	0.05

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		A:TRP176:N:B A:GLY175:CA	2.04 3.48		
11	2	A:TRP176:N A:TRP176:N	2.53 2.54	-9.80	0.05
12	2	A:TYR218:OH A:ASP215:OD2	2.63 3.54	-10.1	0.03
13	3	A:TRP176:N:B LIG1:O A:GLU370:OE1	2.78 3.63 3.56	-10.50	0.02
14	2	A:ASP286:OD2 A:TRP176:CD1:B	2.75 3.56	-10.40	0.02
15	4	A:TRP433:NE1 A:GLY175:CA A:TYR218:OH A:ASP286:OD2	3.34 3.70 3.55 3.43	-9.81	0.06
16	1	A:TRP176:N:B	2.50	-9.79	0.06
17	1	A:TRP176:N:B	2.61	-9.69	0.07
18	3	A:TRP176:N:B A:ASP286:OD2 A:TYR340:OH	2.49 2.44 2.07	-10.40	0.02
19	---	---	---	-10.40	0.02
20	1	A:TRP176:N:B	2.21	-8.03	1.24
21	1	A:GLU217:OE2	3.70	-8.03	1.24
22	1	A:TRP176:N:B	2.72	-7.32	4.12
23	1	A:TYR340:OH	3.09	-9.40	0.12

[a] $Ki = e^{-\Delta G/RT}$ ΔG = Gibbs free energy; R = 1.9872 cal/mol.K; T = 298.15 °K.

Methodology

Validation of Active Site

The active site on chitinase was validated using glucose as the native ligand (PDB: 5WV9). RMSD was set to less than 2.094 Å to determine the best docking position between chitinase and the ligands using Autodock Vina [7]. The validation was performed with 1000 poses, ten replicates for each, selecting the lowest energy value. Protein visualization and overlap were carried out using Pymol 3.1 (Schrödinger, San Diego; http://www.pymol.org/ was used for the protein visualization and overlap).

Molecular Docking

The docking of with each ligand (*N*-benzoyl amino derivatives) was simulated using the program AutoDock Vina, which has been used to estimate the conformation of protein–ligand complexes.

All calculations for protein-fixed ligand-flexible docking were analyzed using the Lamarckian Genetic Algorithm (LGA) method. The docking site on chitinase was defined by establishing a grid box using Pymol 3.1. The grid box size for the coordinates *x*, *y*, and *z* was 60 Å, with a grid spacing of 0.375 Å, centered on x = -19.693, y = 18.902, and z = 25.671 Å. The best conformation was chosen based on the lowest binding energy after the docking search was completed. In the AutoDock Vina configuration files, the parameter number modes were set to 1000 modes and exhaustiveness to 1000. And for each run, the best pose was saved. The average binding energy for the best poses was used as the final binding energy value. This process was repeated ten times.

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Table 2. Validation table.

RMSD	**ARG342NH1**				
repetition	**60**	**50**	**40**	**30**	**20**
1	-6.5	-6.5	-6.6	-6.5	-6.4
	2.368	2.306	2.376	2.426	2.17
2	-6.5	-6.5	-6.6	-6.5	-6.3
	2.465	2.254	2.311	2.493	2.334
3	-6.5	-6.5	-6.6	-6.6	-6.3
	2.284	2.329	2.288	2.36	2.346
4	-6.5	-6.5	-6.6	-6.5	-6.2
	2.356	2.348	2.381	2.233	2.21
5	-6.5	-6.5	-6.6	-6.5	-6.3
	2.385	2.33	2.37	2.334	2.493
6	-6.5	-6.5	-6.6	-6.5	-6.3
	2.453	2.396	2.157	2.342	2.362
7	-6.6	-6.5	-6.6	-6.5	-6.3
	2.331	2.427	2.417	2.327	2.41
8	-6.5	-6.5	-6.5	-6.5	-6.3
	2.319	2.404	2.434	2.286	2.248
9	-6.5	-6.5	-6.6	-6.5	-6.3
	2.474	2.244	2.561	2.363	2.389
10	-6.5	-6.5	-6.6	-6.5	-6.3
	2.499	2.33	2.11	2.367	2.389
	2.393	**2.337**	**2.341**	**2.353**	**2.335**

Table 3. Validation table.

RMSD	**ASP215OD2**				
repetition	**60**	**50**	**40**	**30**	**20**
1	-6.5	-6.5	-6.6	-6.5	-6.5
	2.128	2.319	2.555	2.051	1.98
2	-6.6	-6.5	-6.6	-6.5	-6.5
	2.094	2.34	2.492	2.052	2.021
3	-6.6	-6.5	-6.5	-6.5	-6.5
	2.502	2.103	2.608	2.317	2.228
4	-6.5	-6.5	-6.5	-6.5	-6.5
	2.405	2.249	2.56	2.04	2.032
5	-6.5	-6.5	-6.6	-6.5	-6.5
	2.39	2.269	2.6	2.142	2.366
6	-6.5	-6.5	-6.5	-6.5	-6.5
	2.114	2.073	2.295	2.099	2.26
7	-6.5	-6.5	-6.5	-6.5	-6.5
	2.187	2.357	2.597	2.231	2.209
8	-6.5	-6.5	-6.5	-6.5	-6.5
	2.136	2.116	2.351	2.258	2.221
9	-6.5	-6.5	-6.5	-6.5	-6.5
	2.304	2.134	2.635	2.098	2.098
10	-6.5	-6.5	-6.5	-6.5	-6.5
	2.286	2.272	2.457	2.113	2.038
	2.255	**2.223**	**2.515**	**2.140**	**2.145**

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Table 4. Validation table.

RMSD	**ASP286OD2**				
repetition	**60**	**50**	**40**	**30**	**20**
1	-6.6	-6.6	-6.5	-6.6	-6.6
	2.297	2.271	2.401	2.241	2.319
2	-6.6	-6.6	-6.5	-6.6	-6.6
	2.404	2.25	2.449	2.315	2.284
3	-6.6	-6.6	-6.5	-6.6	-6.6
	2.307	2.168	2.67	2.19	2.464
4	-6.6	-6.6	-6.5	-6.5	-6.6
	2.167	2.413	2.342	2.16	2.211
5	-6.6	-6.6	-6.5	-6.6	-6.6
	2.367	2.019	2.402	2.225	2.269
6	-6.5	-6.6	-6.5	-6.6	-6.6
	2.367	2.372	2.283	2.417	2.32
7	-6.6	-6.5	-6.5	-6.6	-6.6
	2.481	2.397	2.438	2.341	2.363
8	-6.6	-6.6	-6.5	-6.6	-6.6
	2.34	2.158	2.512	2.38	2.251
9	-6.6	-6.6	-6.5	-6.6	-6.6
	2.134	2.28	2.524	2.393	2.311
10	-6.6	-6.6	-6.5	-6.6	-6.6
	2.356	2.455	2.762	2.243	2.252
	2.322	**2.278**	**2.478**	**2.291**	**2.304**

Table 5. Validation table.

RMSD	**GLU217OE2**				
repetition	**60**	**50**	**40**	**30**	**20**
1	-6.5	-6.5	-6.5	-6.5	-6.5
	2.356	2.449	2.581	2.342	2.191
2	-6.5	-6.5	-6.5	-6.5	-6.5
	2.215	2.428	2.095	2.206	2.194
3	-6.5	-6.5	-6.5	-6.5	-6.5
	2.321	2.329	2.334	2.34	2.187
4	-6.5	-6.5	-6.5	-6.5	-6.5
	2.482	2.203	2.375	2.298	2.177
5	-6.5	-6.5	-6.5	-6.5	-6.5
	2.237	2.331	2.516	2.343	2.35
6	-6.5	-6.5	-6.5	-6.5	-6.5
	2.338	2.432	2.407	2.309	2.342
7	-6.5	-6.5	-6.5	-6.5	-6.5
	2.385	2.311	2.365	2.162	2.452
8	-6.5	-6.5	-6.5	-6.5	-6.5
	2.38	2.517	2.509	2.326	2.378
9	-6.5	-6.5	-6.5	-6.5	-6.5
	2.342	2.428	2.35	2.155	2.312
10	-6.5	-6.5	-6.5	-6.5	-6.5
	2.256	2.175	2.109	2.247	2.434
	2.331	**2.360**	**2.364**	**2.273**	**2.302**

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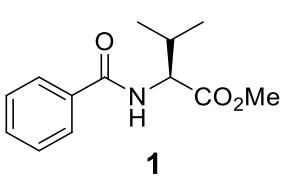
Table 6. Means energy free Gibbs for all N-benzoyl amino derivatives.

No.	ΔG1	ΔG2	ΔG3	ΔG4	ΔG5	ΔG6	ΔG7	ΔG8	ΔG9	ΔG10	mean ΔG	Ki µg/mol
1	-7.9	-7.9	-7.9	-7.9	-7.9	-7.9	-7.9	-7.9	-7.9	-7.9	-7.90	1.54
2	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.8	-7.80	1.83
3	-7.7	-7.8	-7.8	-7.8	-7.7	-7.7	-7.7	-7.7	-7.7	-7.7	-7.73	2.06
4	-7.8	-7.8	-7.8	-7.9	-7.8	-7.9	-7.9	-7.9	-7.9	-7.9	-7.87	1.62
5	-7.9	-7.8	-7.9	-7.8	-7.8	-7.9	-7.9	-7.9	-7.9	-7.9	-7.87	1.62
6	-8.5	-8.5	-8.5	-8.6	-8.5	-8.5	-8.5	-8.5	-8.5	-8.5	-8.51	0.55
7	-8.5	-8.5	-8.5	-8.6	-8.5	-8.5	-8.5	-8.5	-8.5	-8.5	-8.51	0.55
8	-8.2	-8.2	-8.2	-8.3	-8.3	-8.3	-8.3	-8.2	-8.2	-8.2	-8.24	0.87
9	-10.2	-10.2	-10.2	-10.2	-10.2	-10.2	-10.2	-10.2	-10.2	-10.2	-10.20	0.03
10	-9.9	-9.9	-9.9	-9.9	-9.9	-9.9	-9.9	-9.9	-9.9	-9.9	-9.90	0.05
11	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	-9.8	0.05
12	-10.1	-10.1	-10.1	-10.1	-10.1	-10.1	-10.1	-10.1	-10.1	-10.1	-10.1	0.03
13	-10.5	-10.5	-10.5	-10.5	-10.5	-10.5	-10.5	-10.5	-10.5	-10.5	-10.50	0.02
14	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.40	0.02
15	-10.6	-9.6	-9.6	-10.6	-9.7	-9.6	-9.6	-9.6	-9.6	-9.6	-9.81	0.06
16	-9.8	-9.9	-9.6	-9.8	-9.8	-9.8	-9.6	-9.9	-9.8	-9.9	-9.79	0.06
17	-9.7	-9.6	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.7	-9.69	0.07
18	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.40	0.02
19	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.4	-10.40	0.02
20	-8.0	-8.1	-8.1	-8.0	-8.0	-8.1	-8.0	-8.0	-8.0	-8.0	-8.03	1.24
21	-8.0	-8.1	-8.1	-8.0	-8.0	-8.1	-8.0	-8.0	-8.0	-8.0	-8.03	1.24
22	-7.3	-7.3	-7.3	-7.3	-7.4	-7.3	-7.3	-7.3	-7.4	-7.3	-7.32	4.12
23	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.4	-9.40	0.12

Tabla 7. Figure Supplementary Material.



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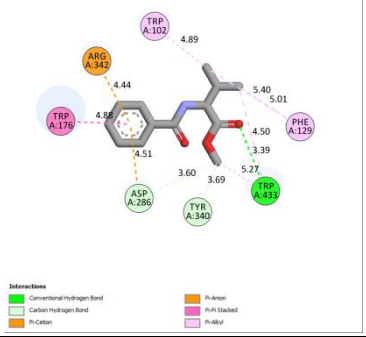

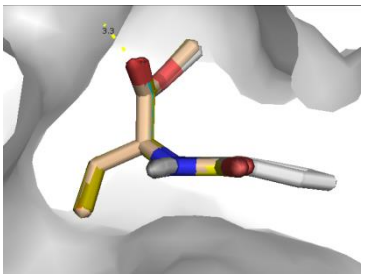

syn

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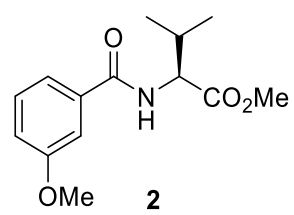
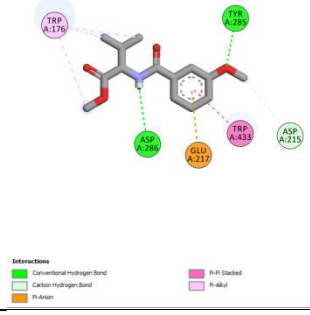
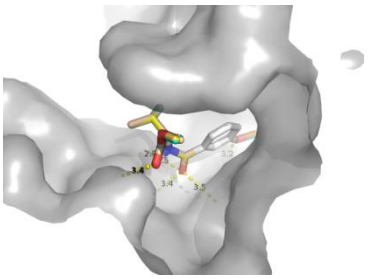
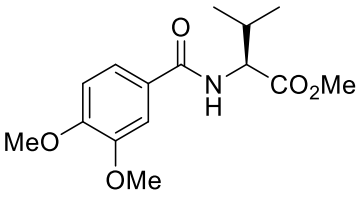
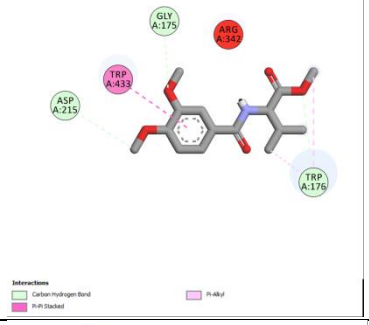
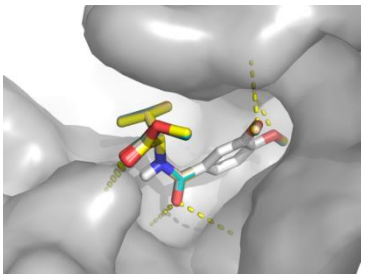
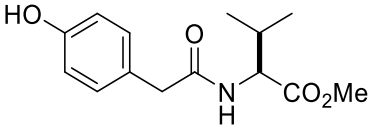
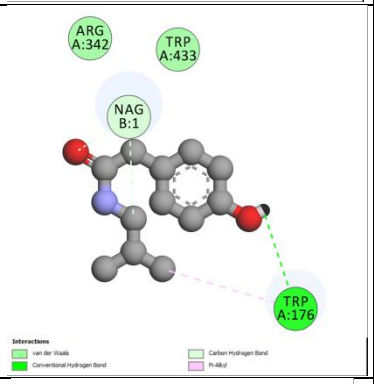
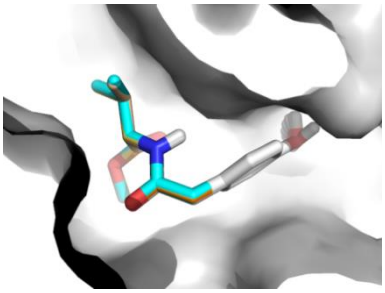
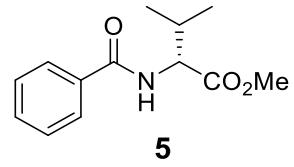
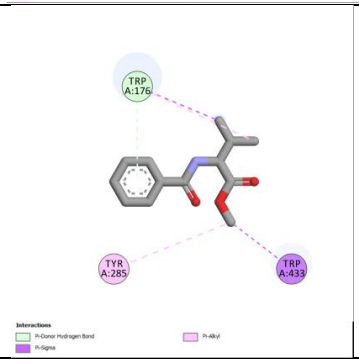
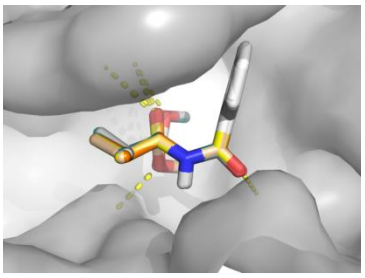
 **2**		 syn
 **3**		 syn
 **4**		 anti
 **5**		 syn

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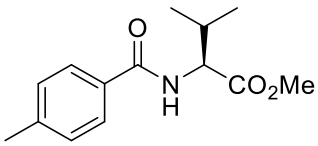
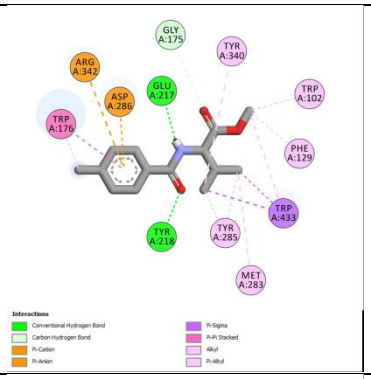
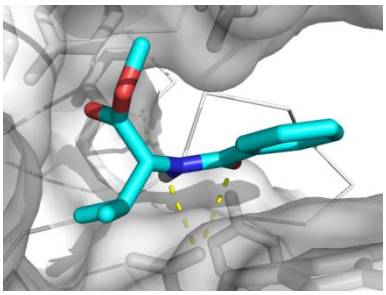
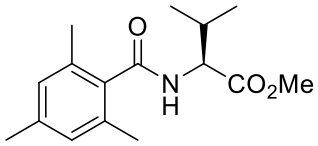
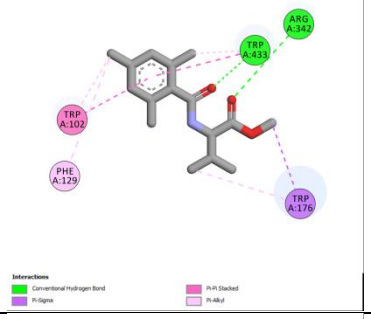
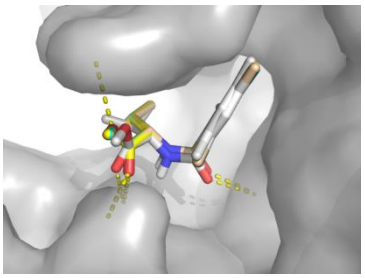
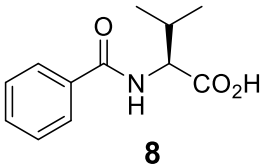
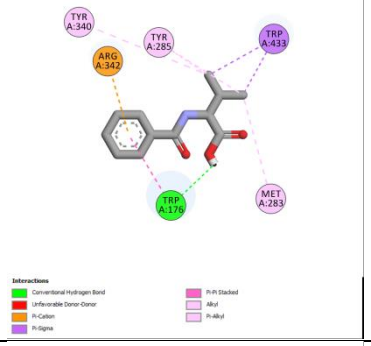
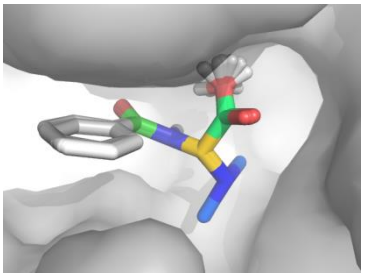
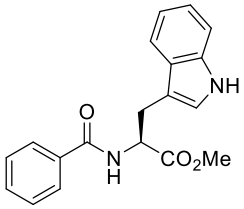
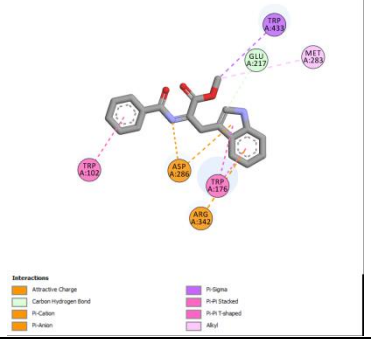
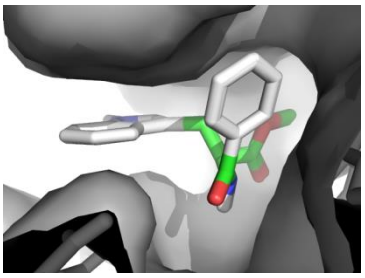
 **6**		 syn
 **7**		 syn
 **8**		 syn
 **9**		 syn

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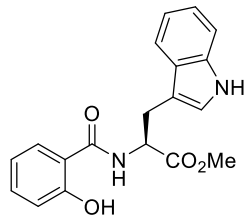
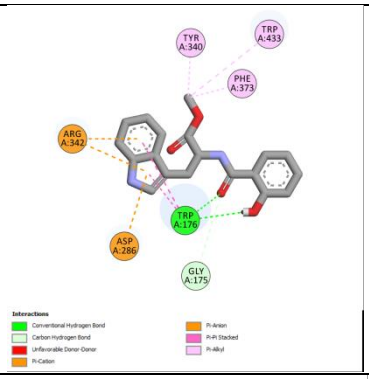
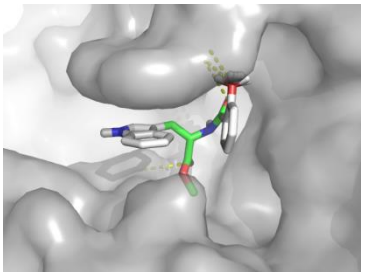
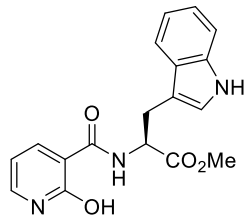
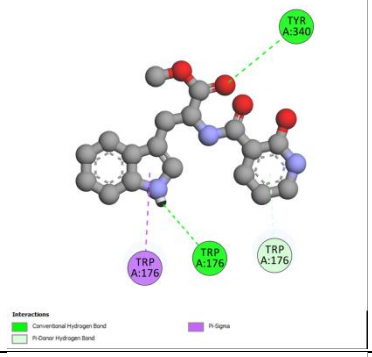
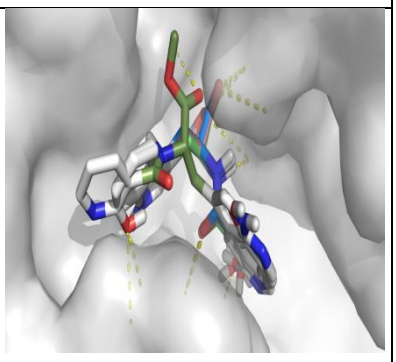
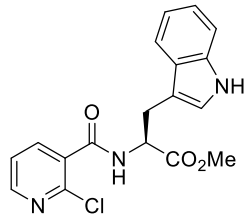
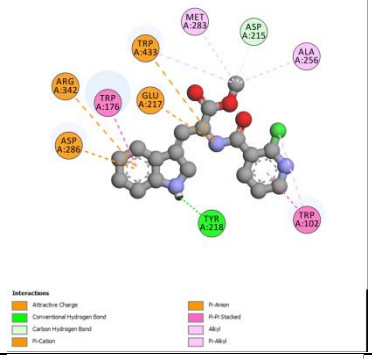
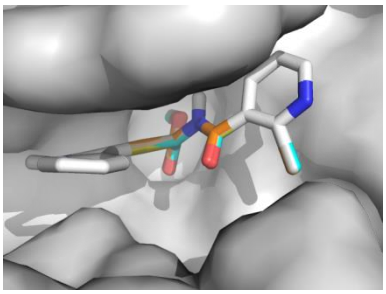
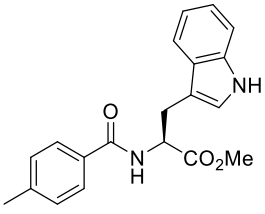
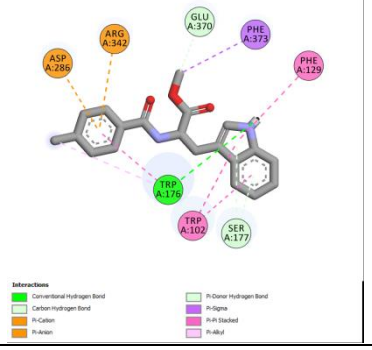
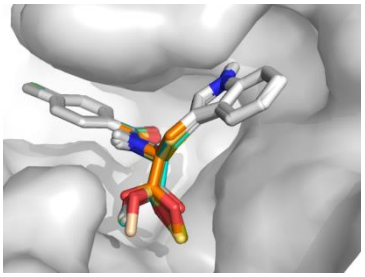
 **10**		 syn
 **11**		 syn
 **12**		 syn
 **13**		 anti

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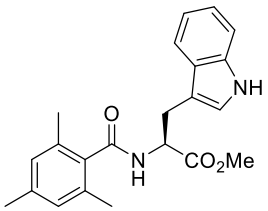
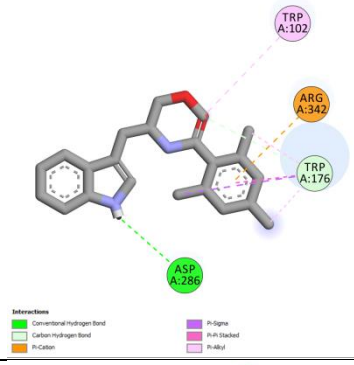
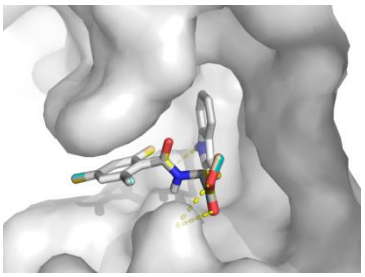
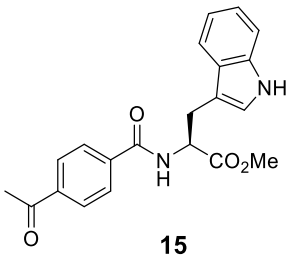
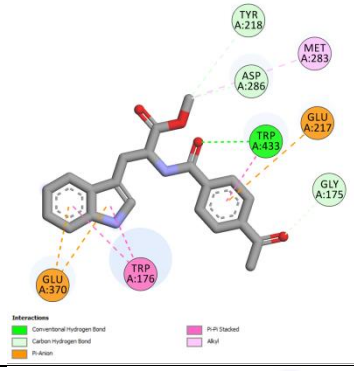
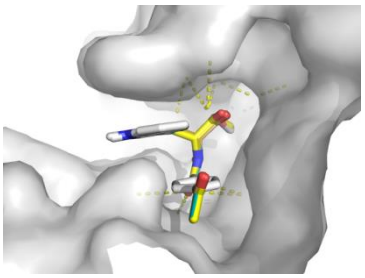
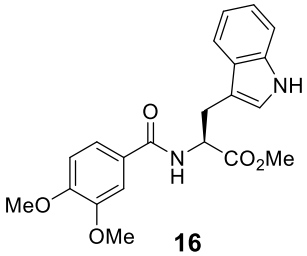
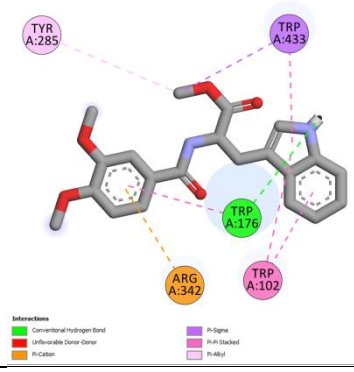
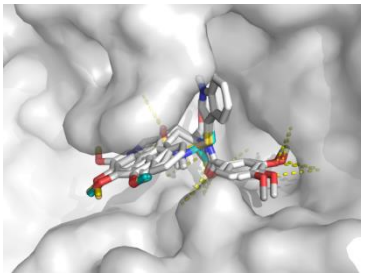
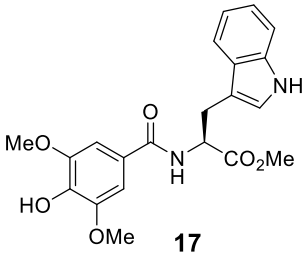
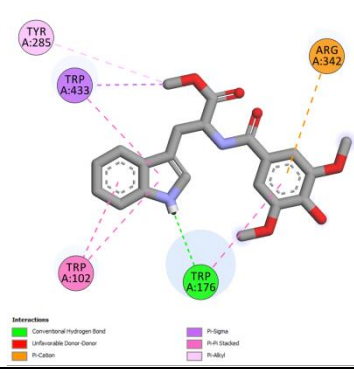
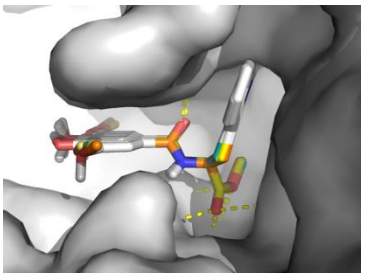
 **14**		 anti
 **15**		 syn
 **16**		 anti
 **17**		 anti

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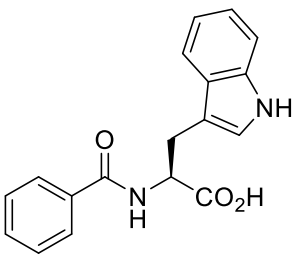
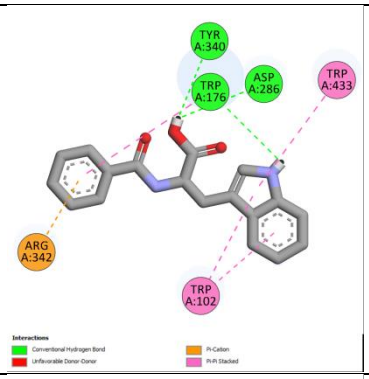
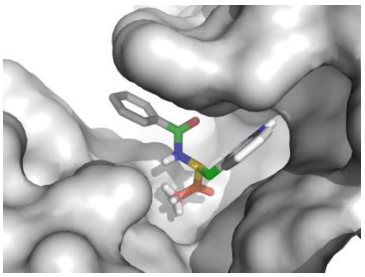
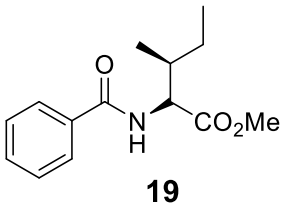
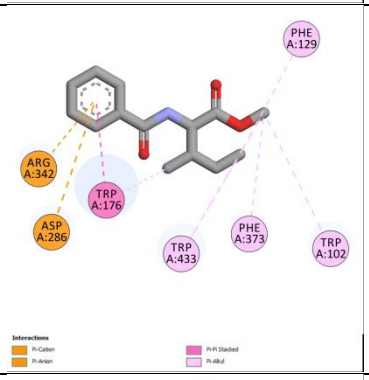
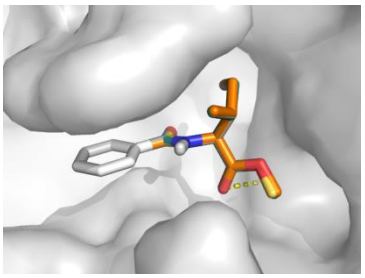
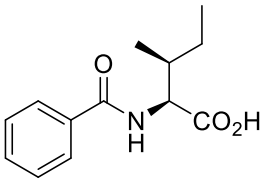
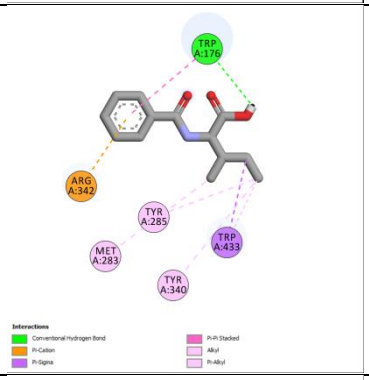
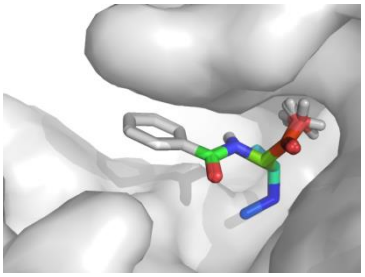
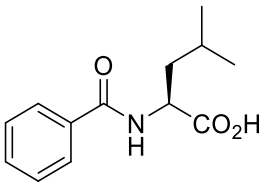
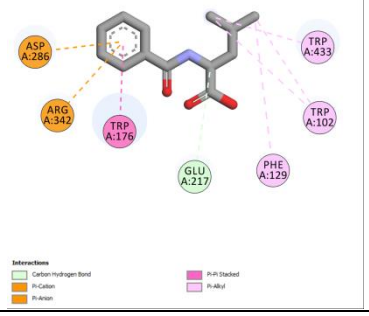
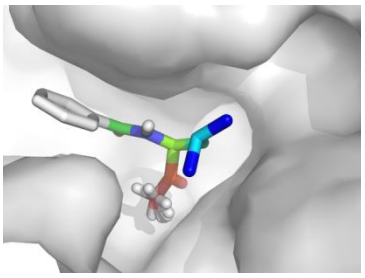
 **18**		 anti
 **19**		 anti
 **20**		 anti
 **21**		 anti

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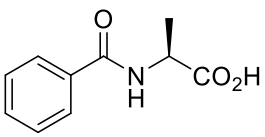

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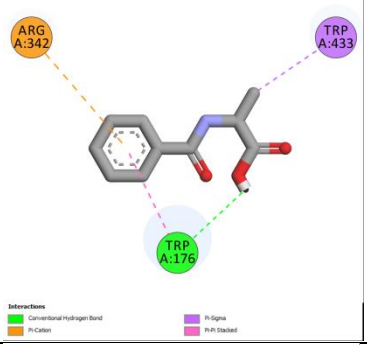

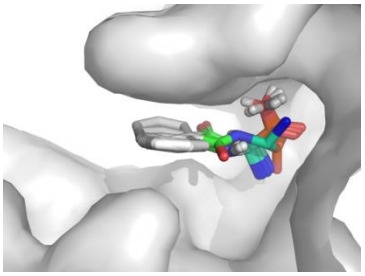

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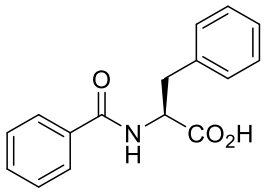

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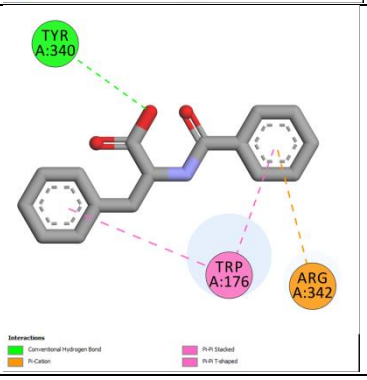

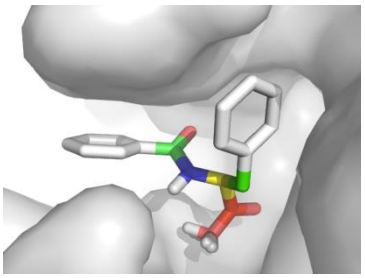

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NMR ^{1}H and ^{13}C Spectra

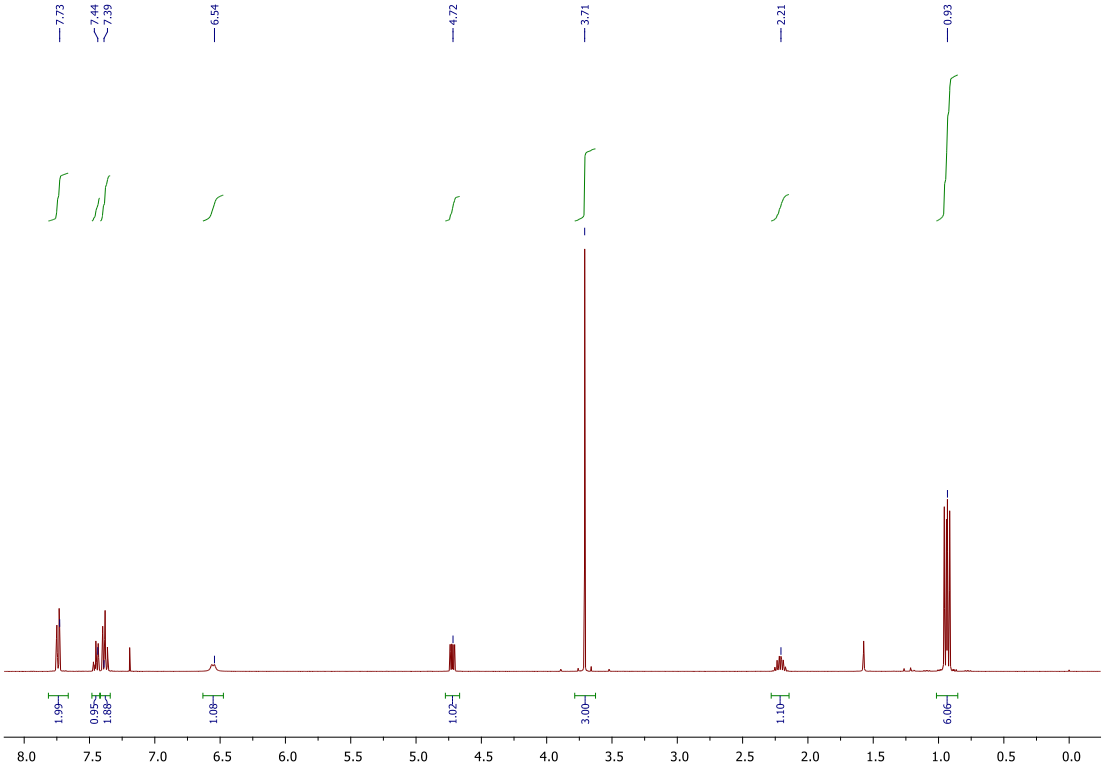

Fig. S2. ^{1}H NMR of *N*-Benzoyl-L-valine methyl ester (1).

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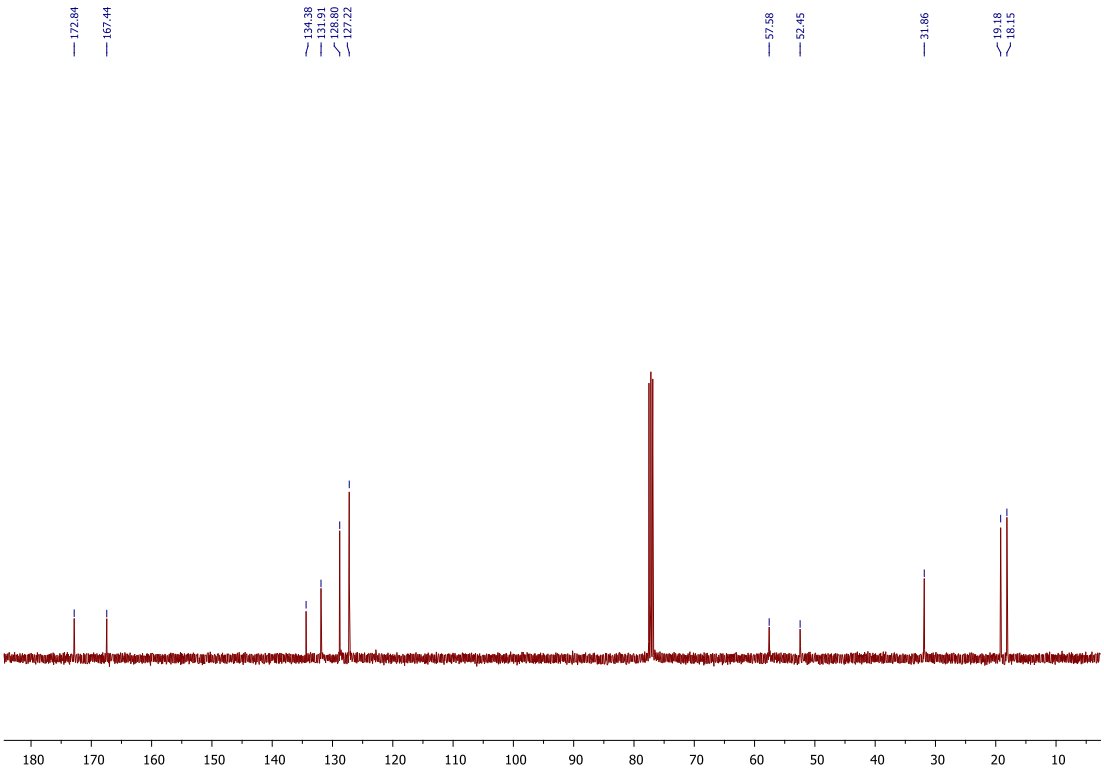

Fig. S3. ^{13}C NMR of *N*-Benzoyl-L-valine methyl ester (1).

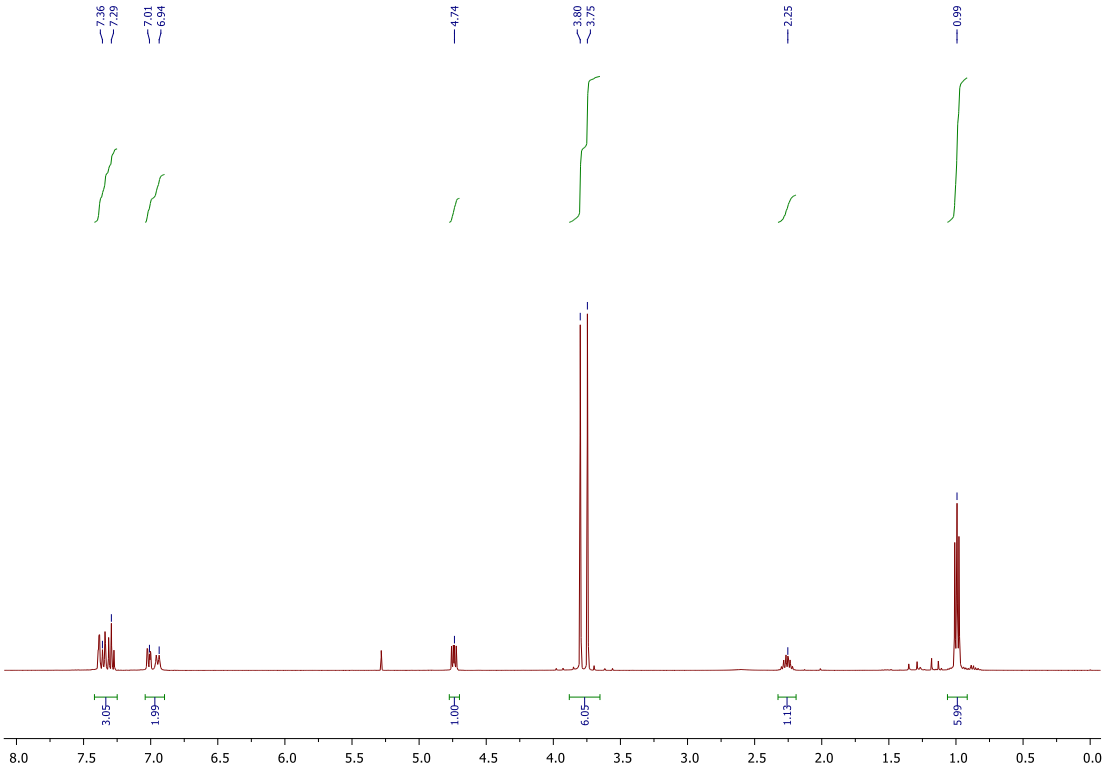

Fig. S4. ^{1}H NMR de *N*-(3-methoxybenzoyl)-L-valine methyl ester (2).

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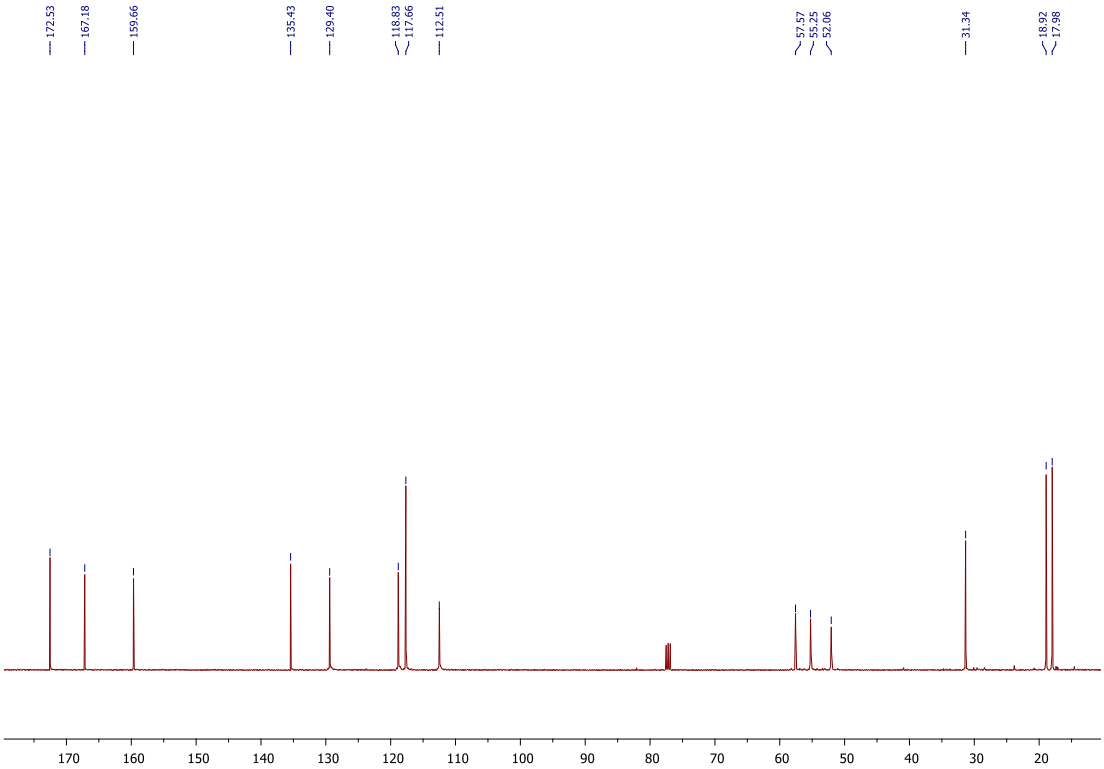

Fig. S4. ^{13}C NMR of de *N*-(3-methoxybenzoyl)-L-valine methyl ester (2).

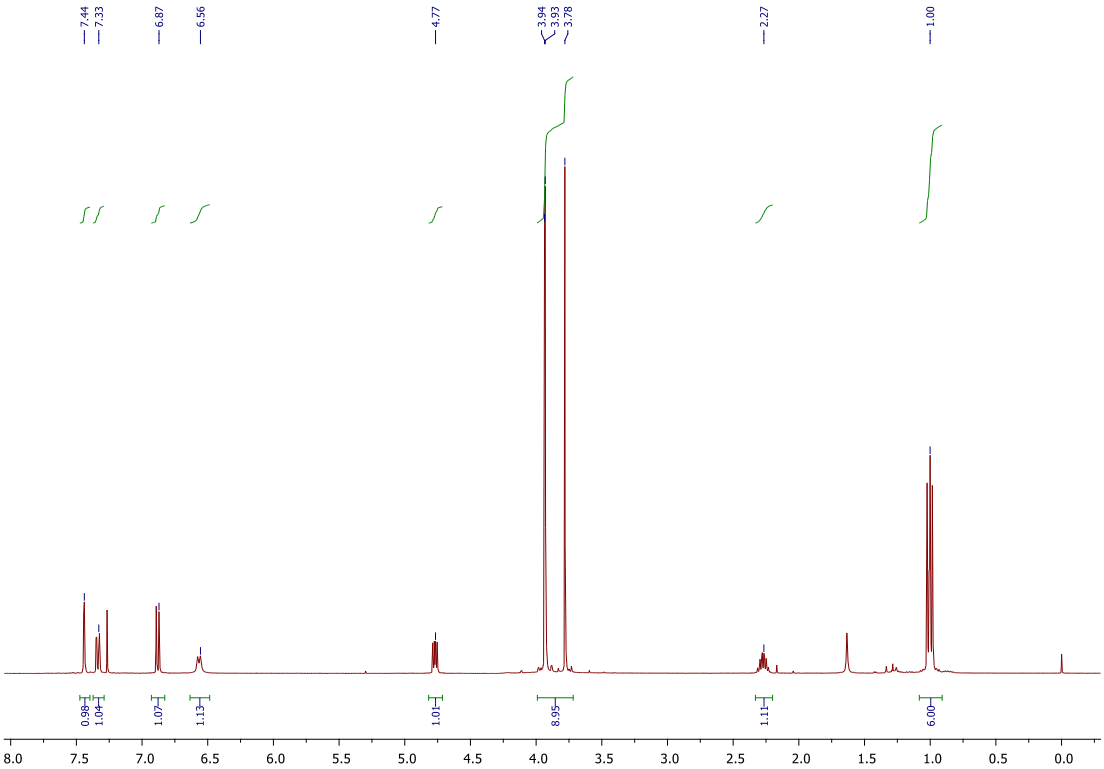

Fig. S5. ^{1}H NMR of *N*-(3,4-dimethoxybenzoyl)-L-valine methyl ester (3).

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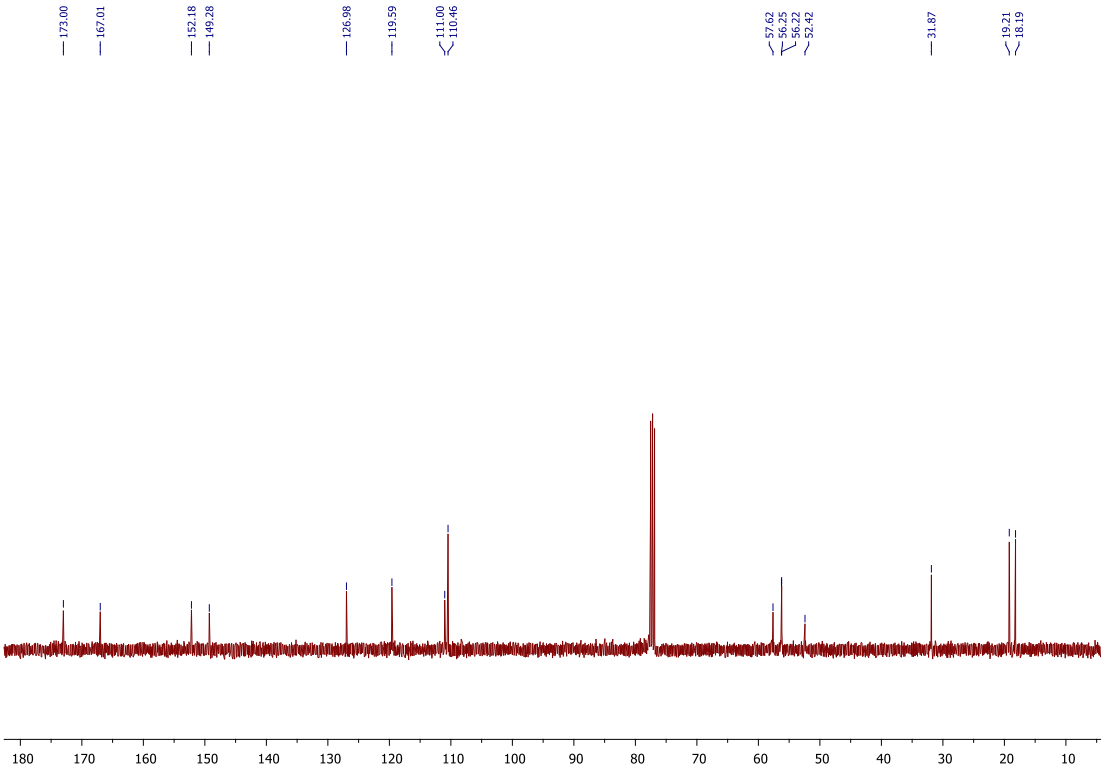

Fig. S6. ^{13}C NMR of *N*-(3,4-dimethoxybenzoyl)-L-valine methyl ester (3).

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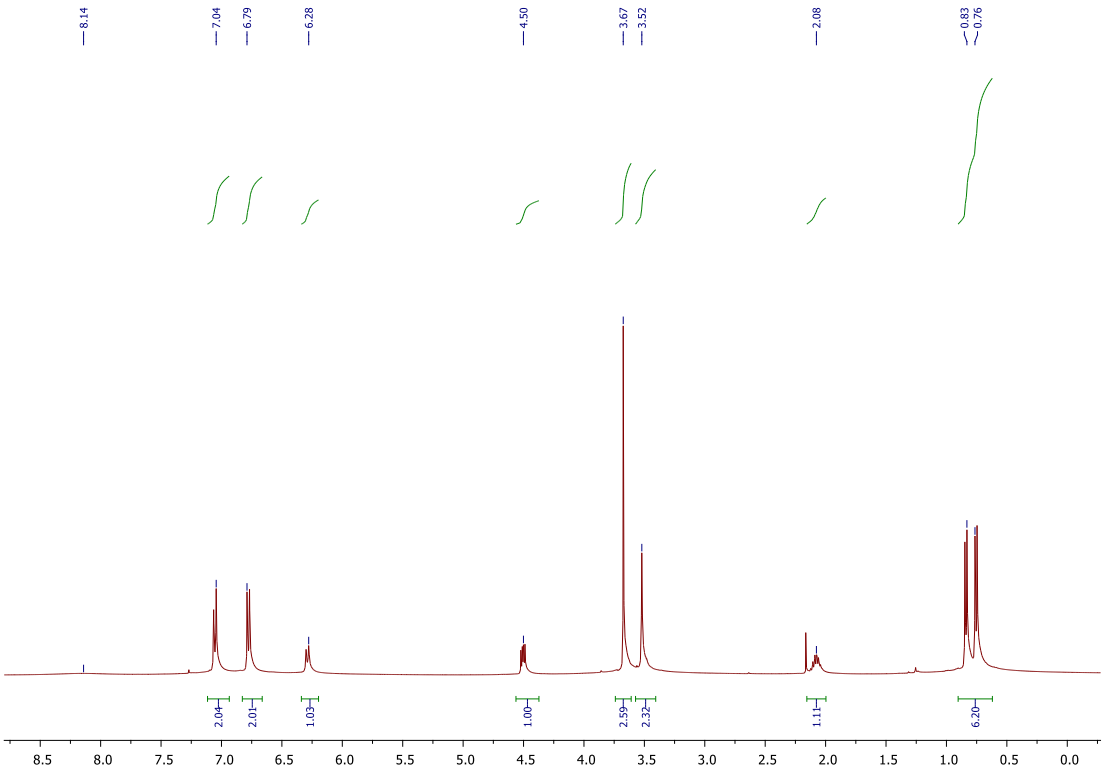

Fig. S7. ^{1}H NMR of *N*-[2-(4-hydroxyphenyl)acetyl]-L-valine methyl ester (4).

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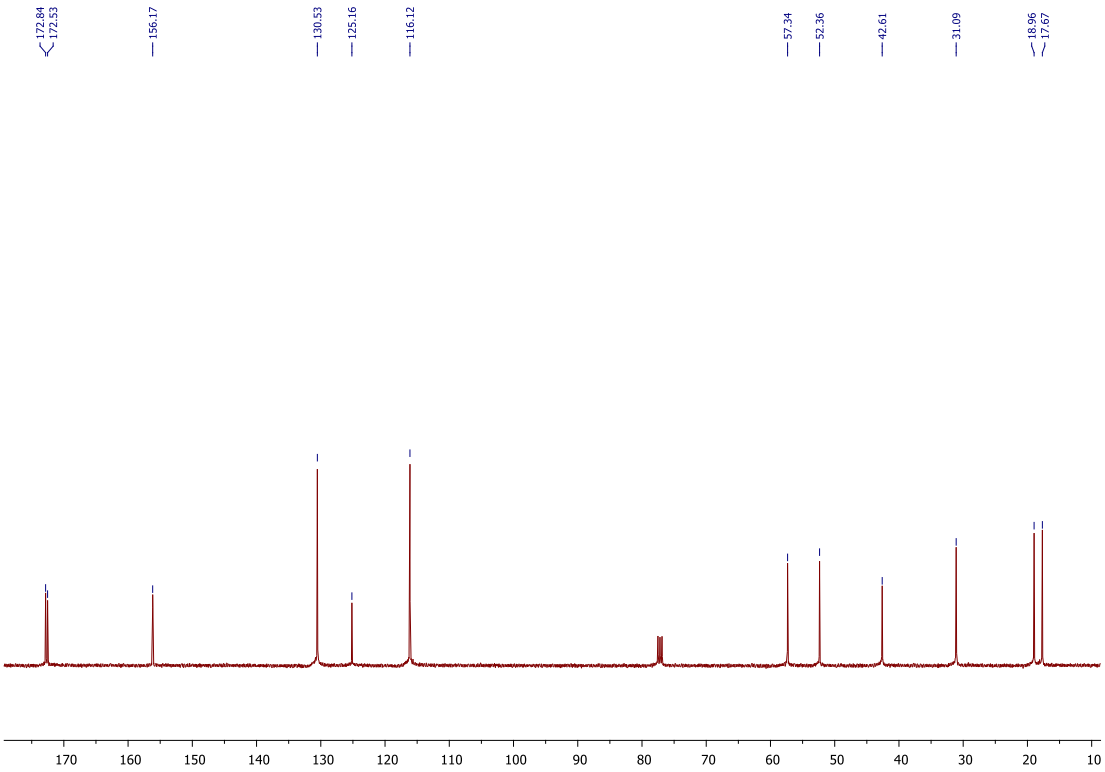

Fig. S8. ^{13}C NMR of *N*-[2-(4-hydroxyphenyl)acetyl]-L-valine methyl ester (4).

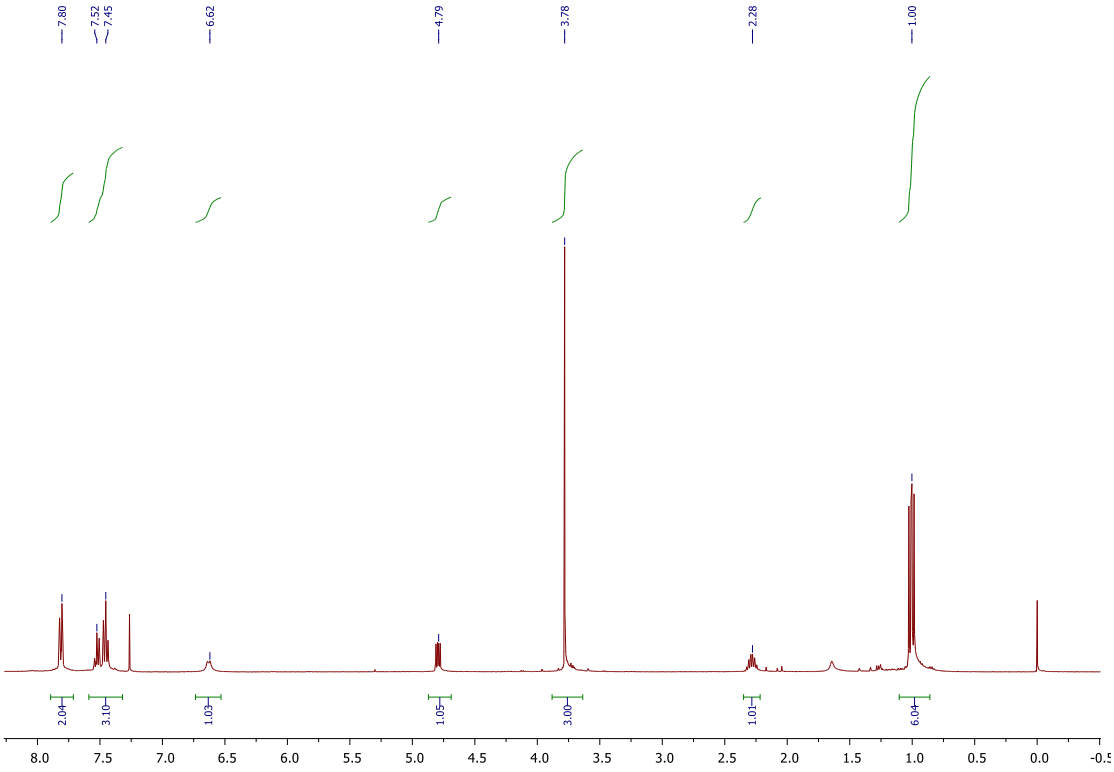

Fig. S9. ^{1}H NMR of *N*-Benzoyl-D-valine methyl ester (5).

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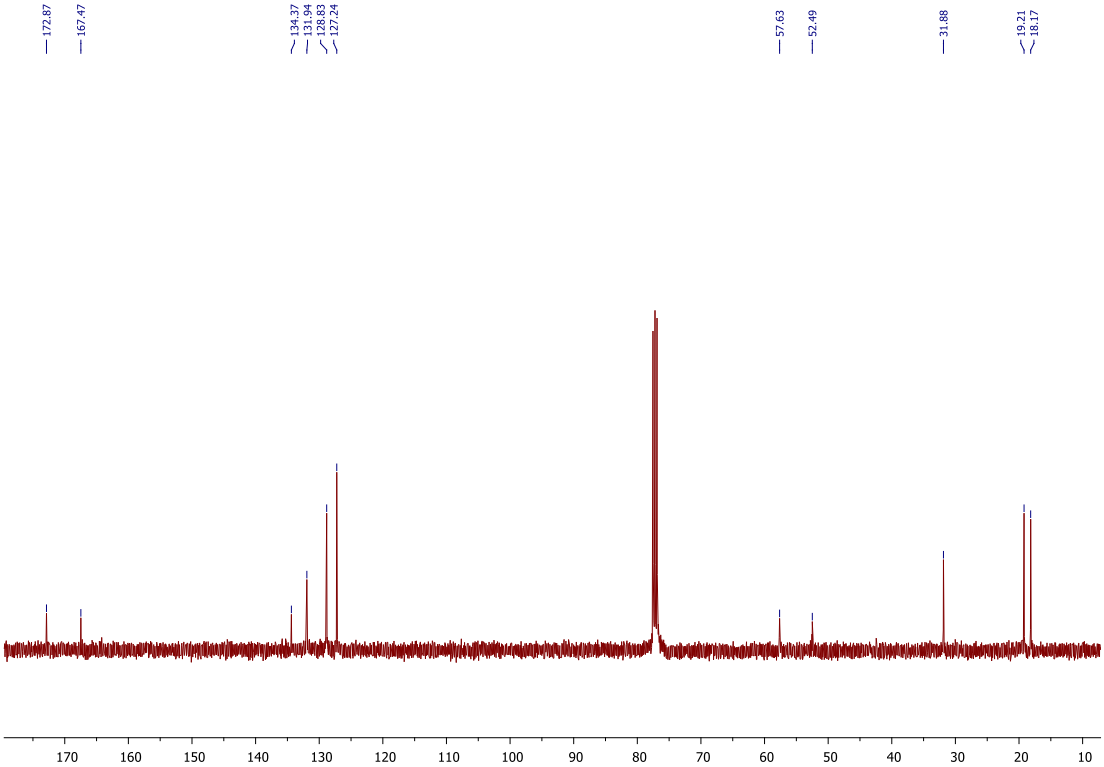

Fig. S10. ^{13}C NMR of *N*-Benzoyl-D-valine methyl ester (5).

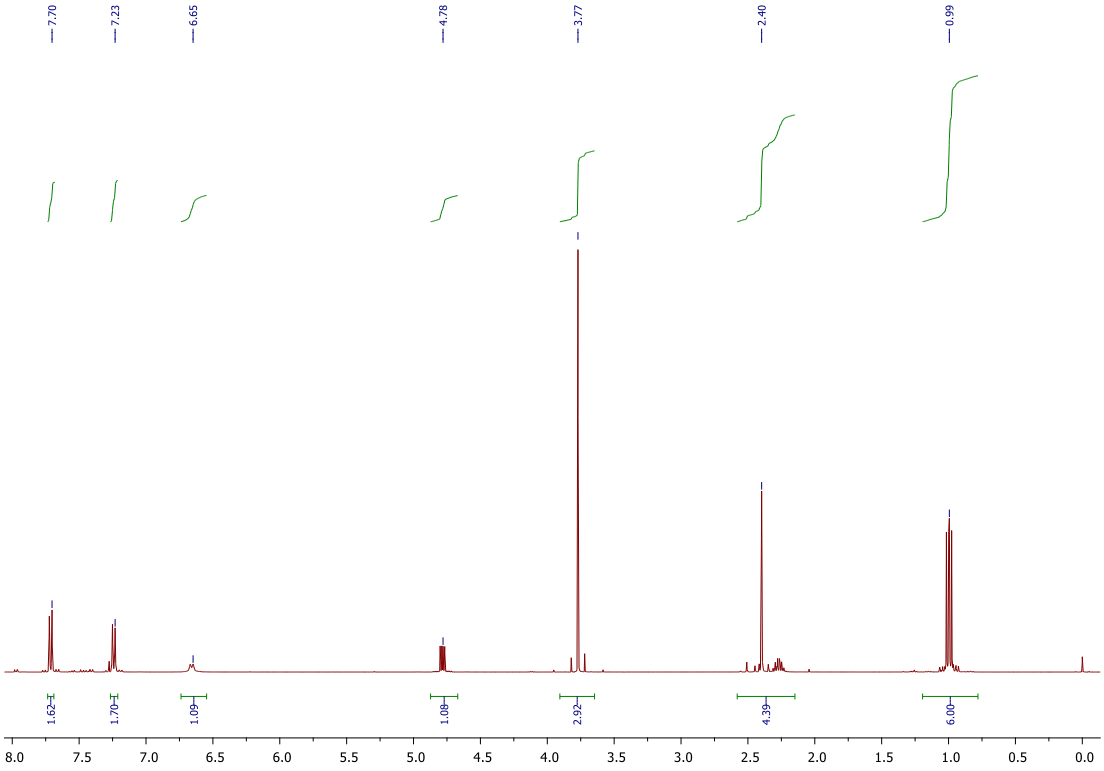

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Fig. S11. ^{1}H NMR of *N*-(4-methylbenzoyl)-L-valine methyl ester (6).

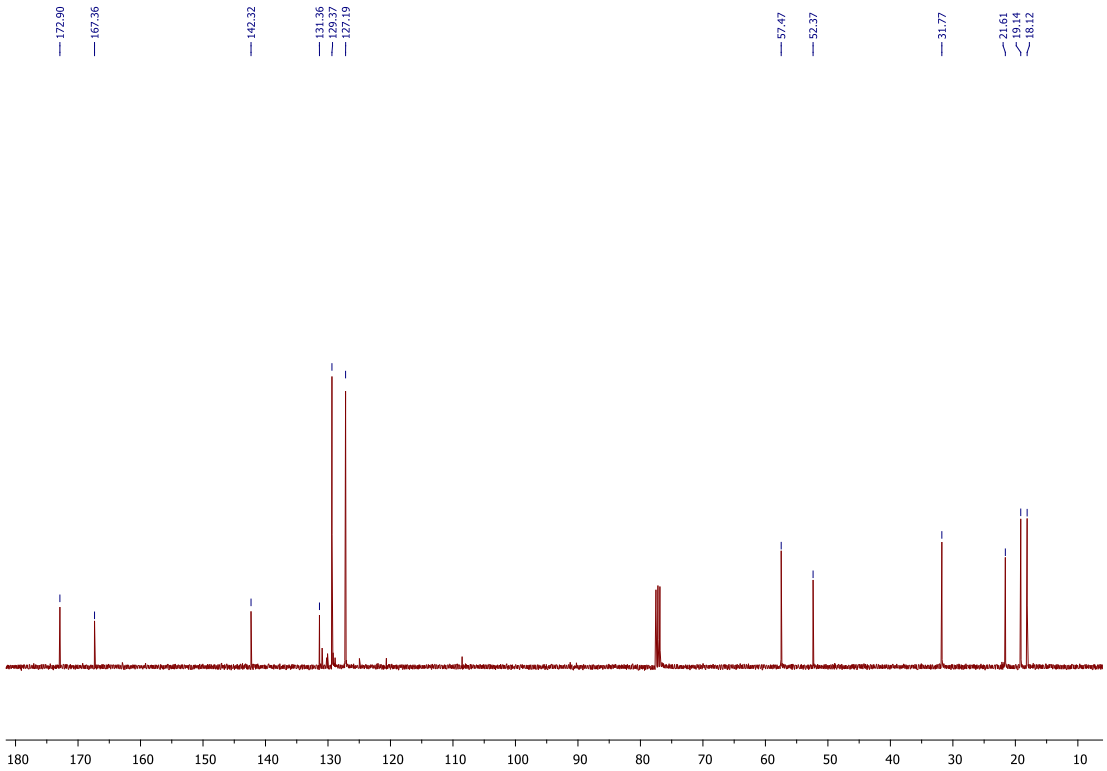

Fig. S11. ^{13}C NMR of *N*-(4-methylbenzoyl)-L-valine methyl ester (6).

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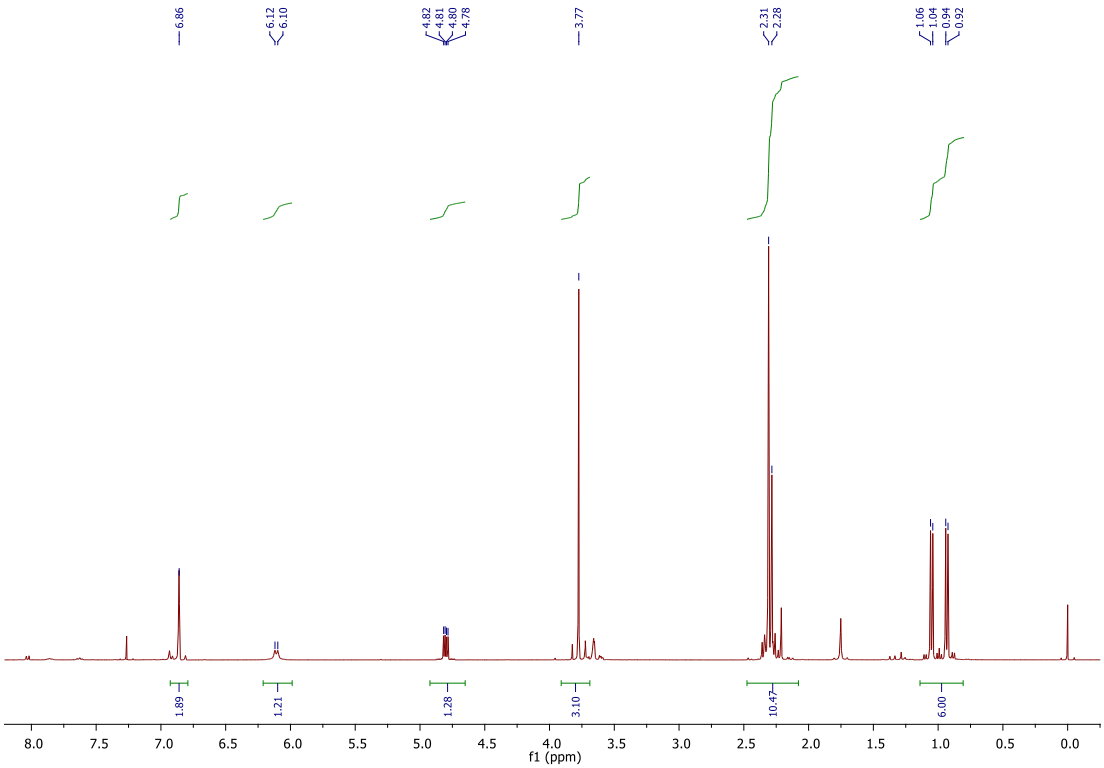

Fig. S12. ^{1}H NMR of *N*-(2,4,6-trimethylbenzoyl)-L-valine methyl ester (7).

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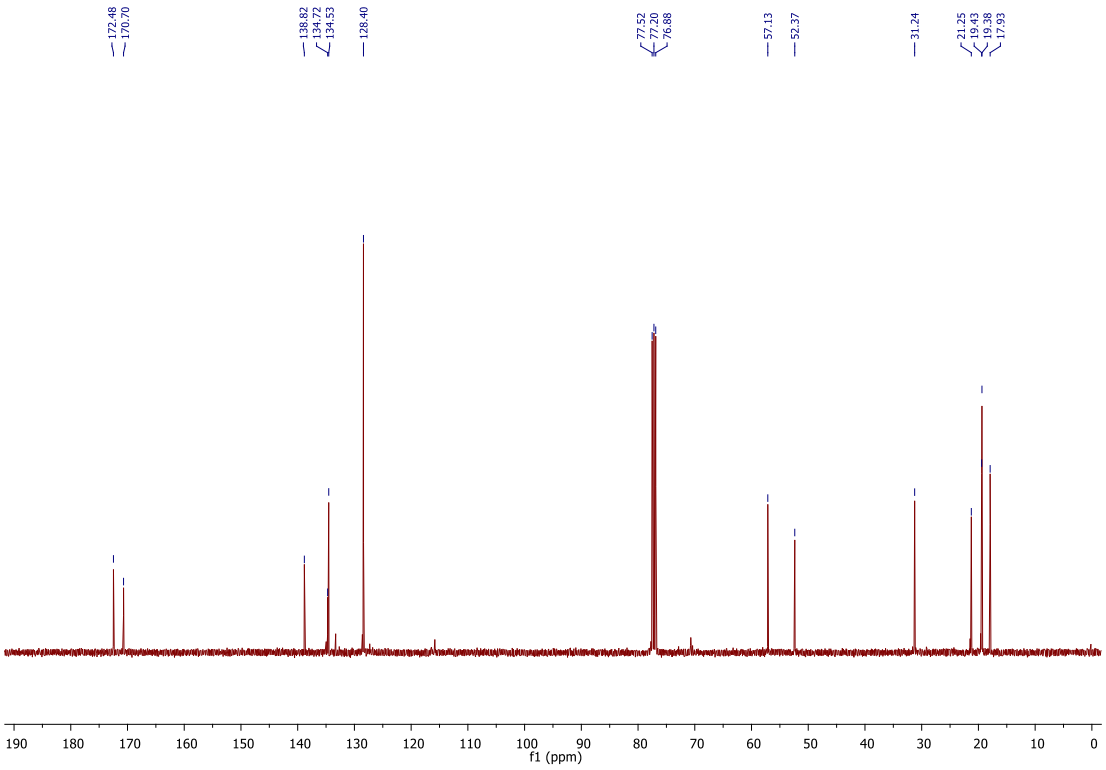

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Fig. S13. ^{13}C NMR of *N*-(2,4,6-trimethylbenzoyl)-L-valine methyl ester (7).

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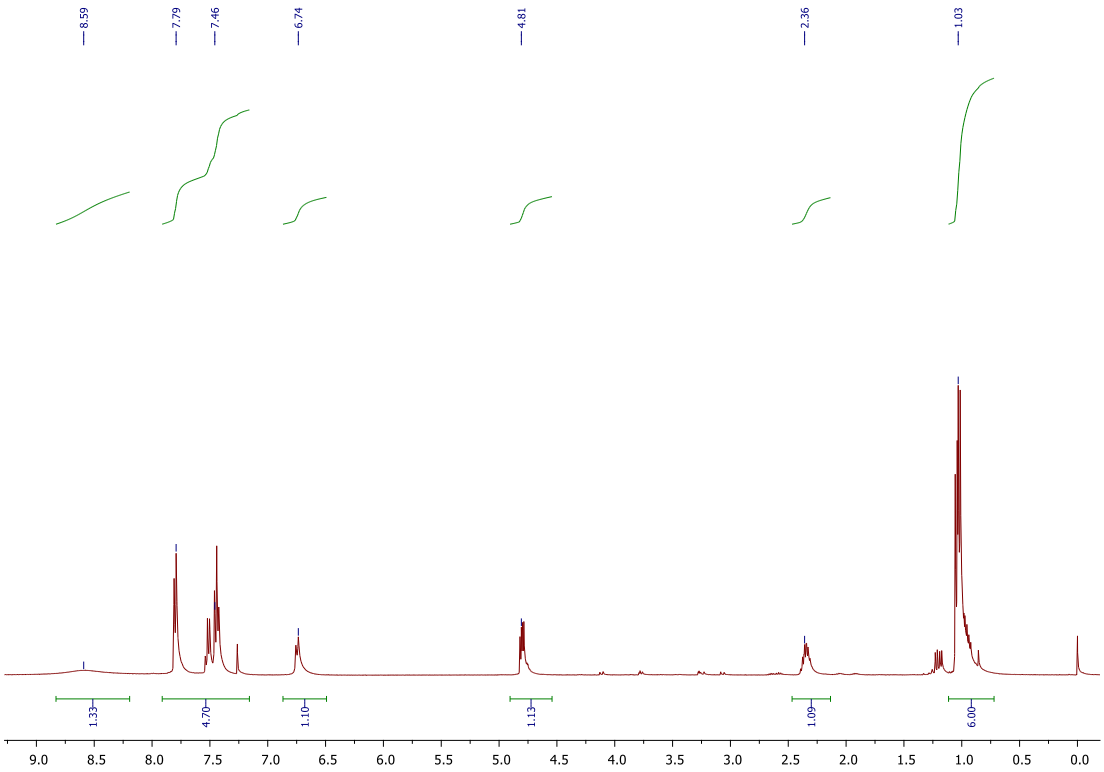

Fig. S14. ^{1}H NMR of *N*-Benzoyl-L-valine (8).

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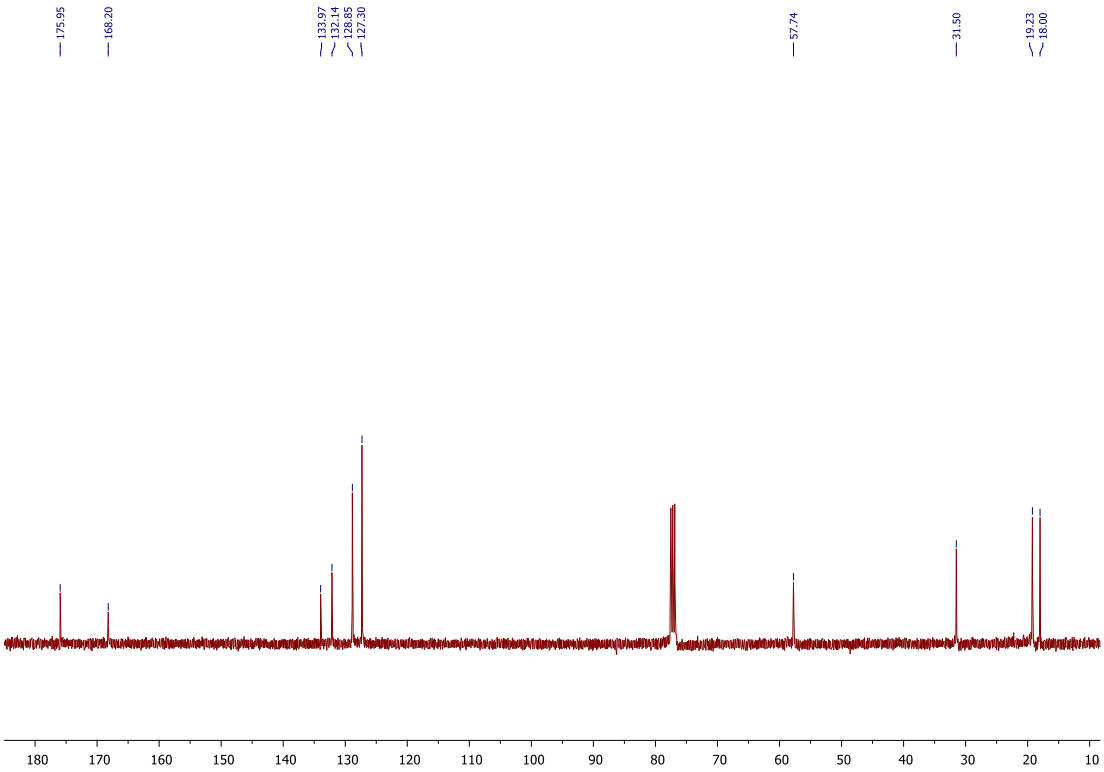

Fig. S15. ^{13}C NMR of *N*-Benzoyl-L-valine (8).

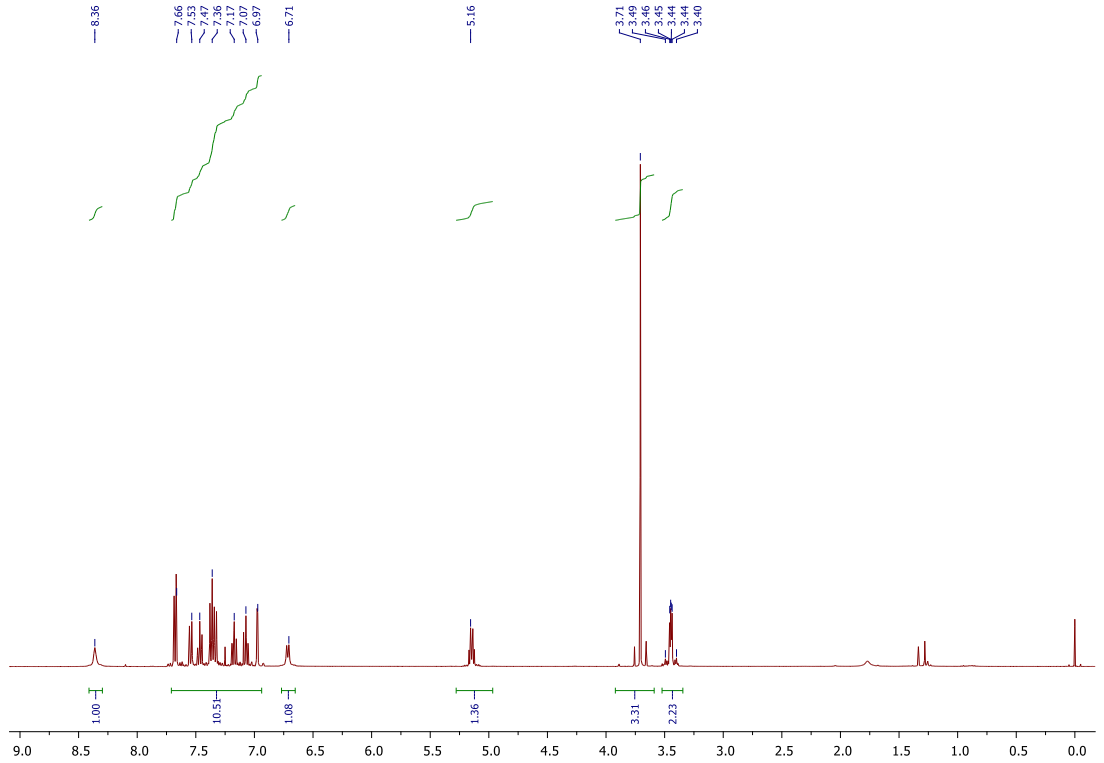

Fig. S16. ^{1}H NMR of *N*-Benzoyl-L-tryptophan methyl ester (9).

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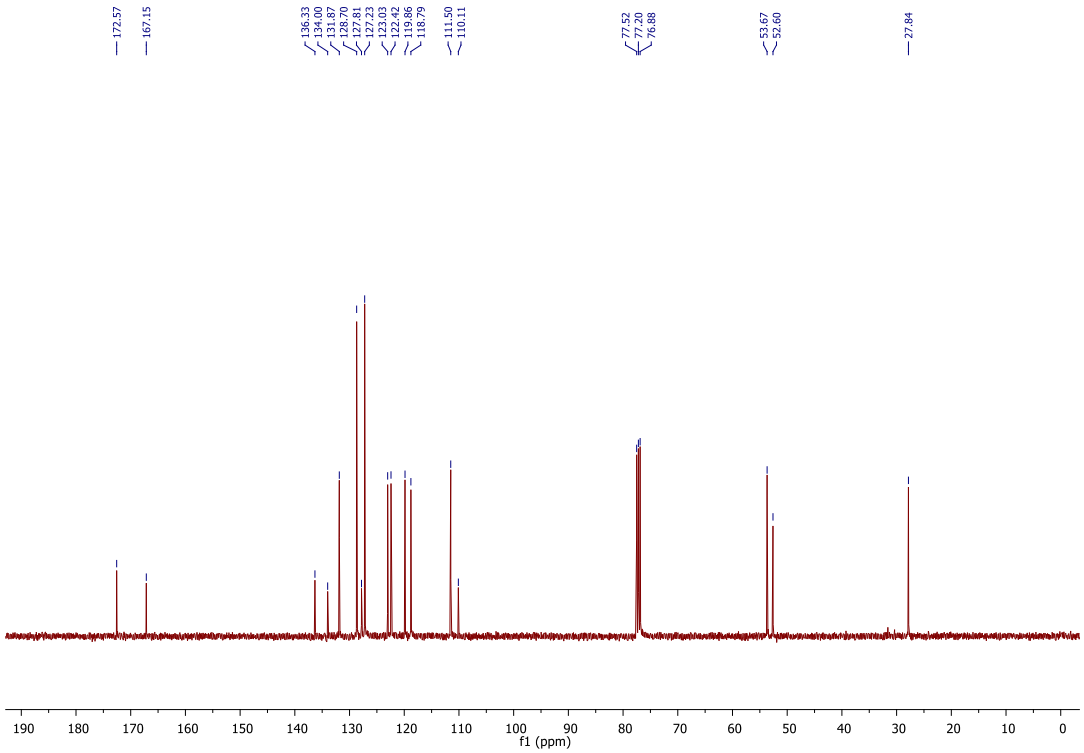

Fig. S17. ^{13}C NMR of *N*-Benzoyl-L-tryptophan methyl ester (9).

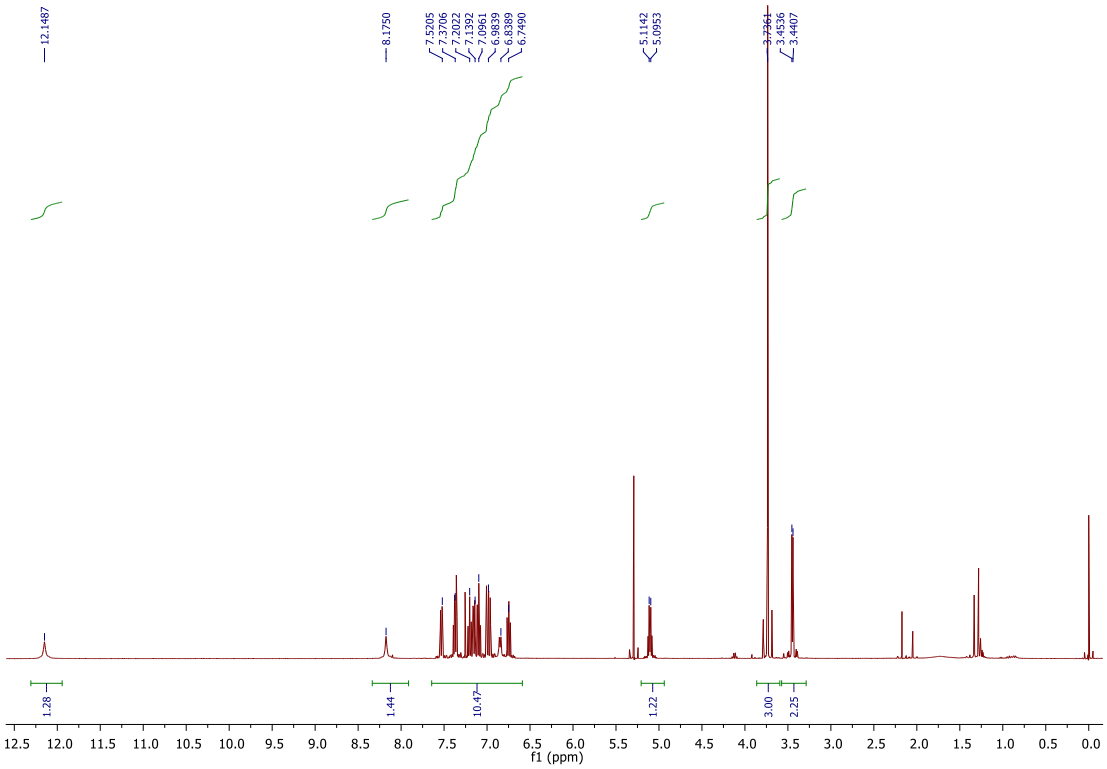

Fig. S18. ^{1}H NMR of *N*-(2-hydroxybenzoyl)-L-tryptophan methyl ester (10).

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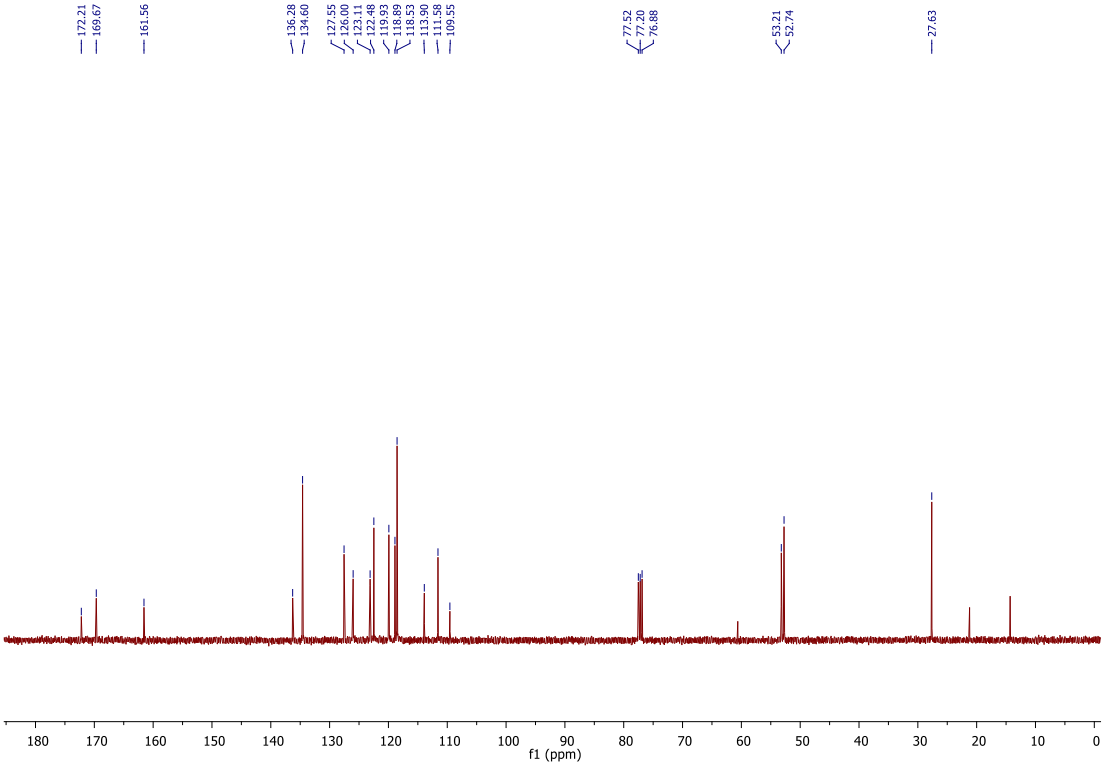

Fig. S19. ^{13}C NMR of *N*-(2-hydroxybenzoyl)-L-tryptophan methyl ester (10).

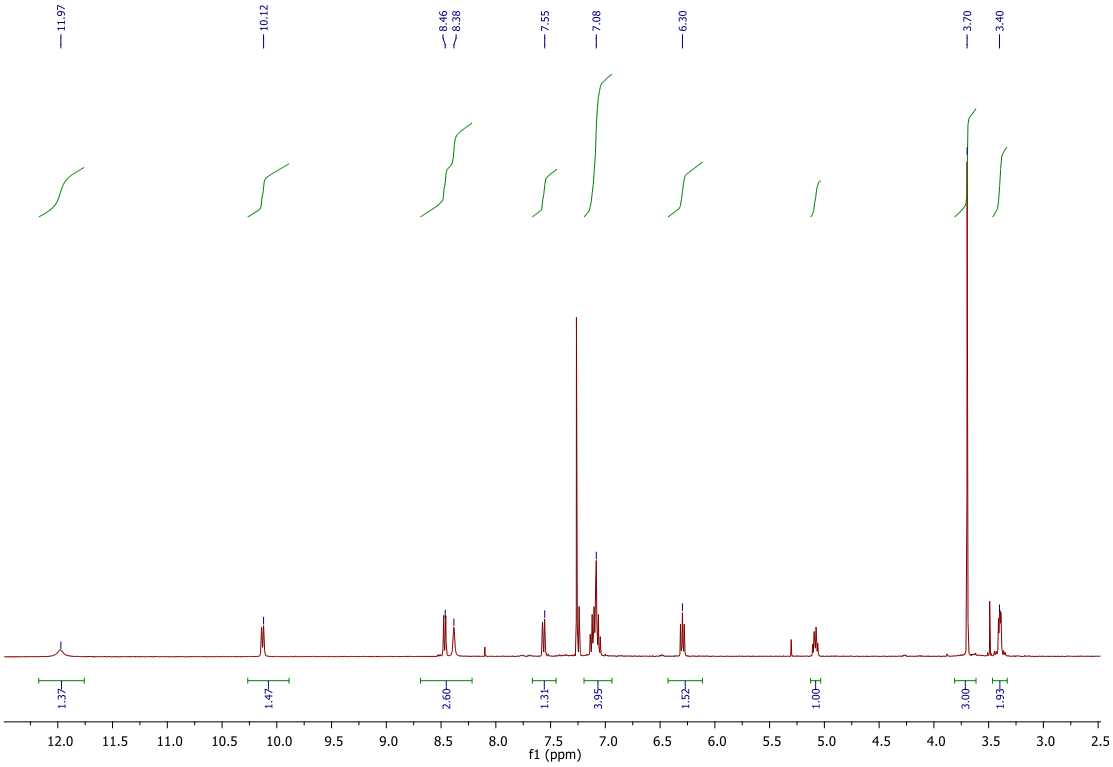

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Fig. S20. ^{1}H NMR of *N*-(2-hydroxynicotinoyl)-L-tryptophan methyl ester (11).

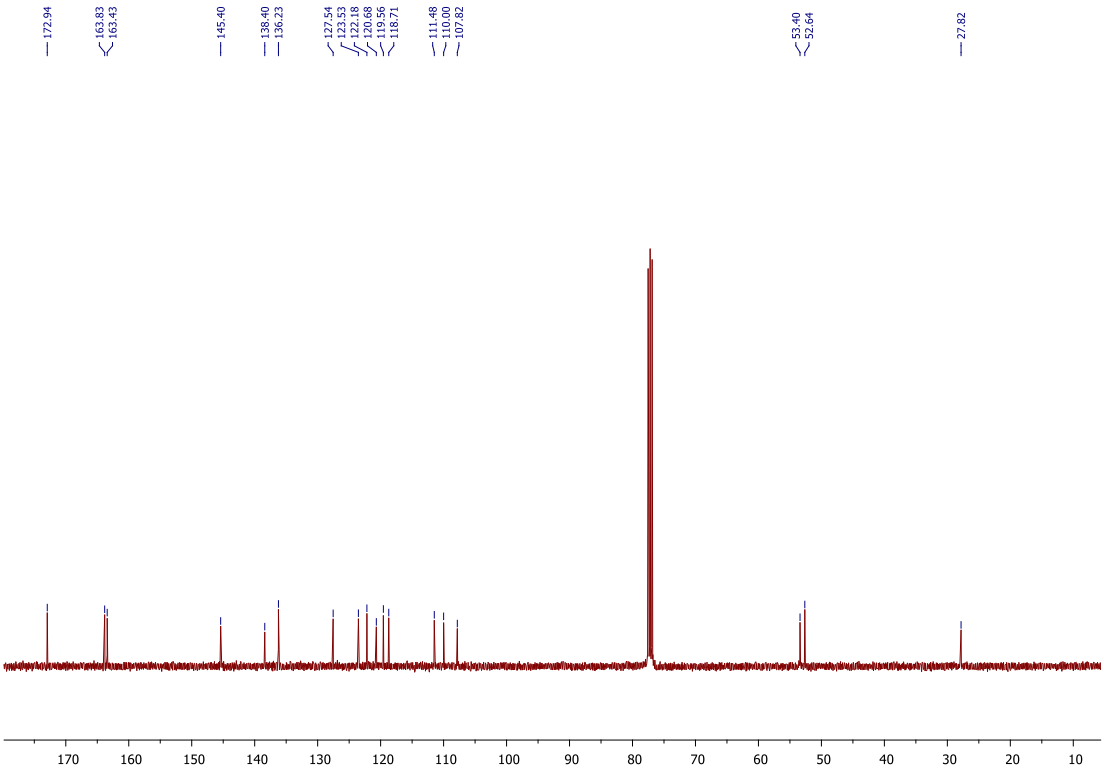

Fig. S21. ^{13}C NMR of *N*-(2-hydroxynicotinoyl)-L-tryptophan methyl ester (11).

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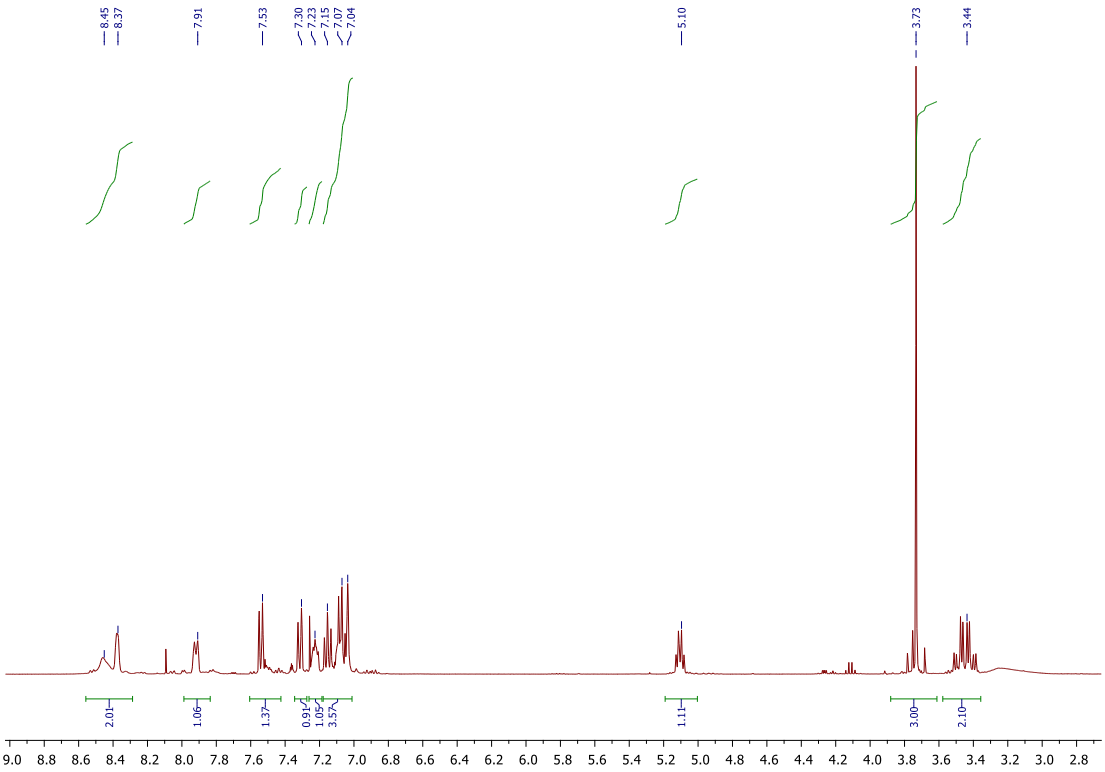

Fig. S22. ^{1}H NMR of *N*-(2-chloronicotinoyl)-L-tryptophan methyl ester (12).

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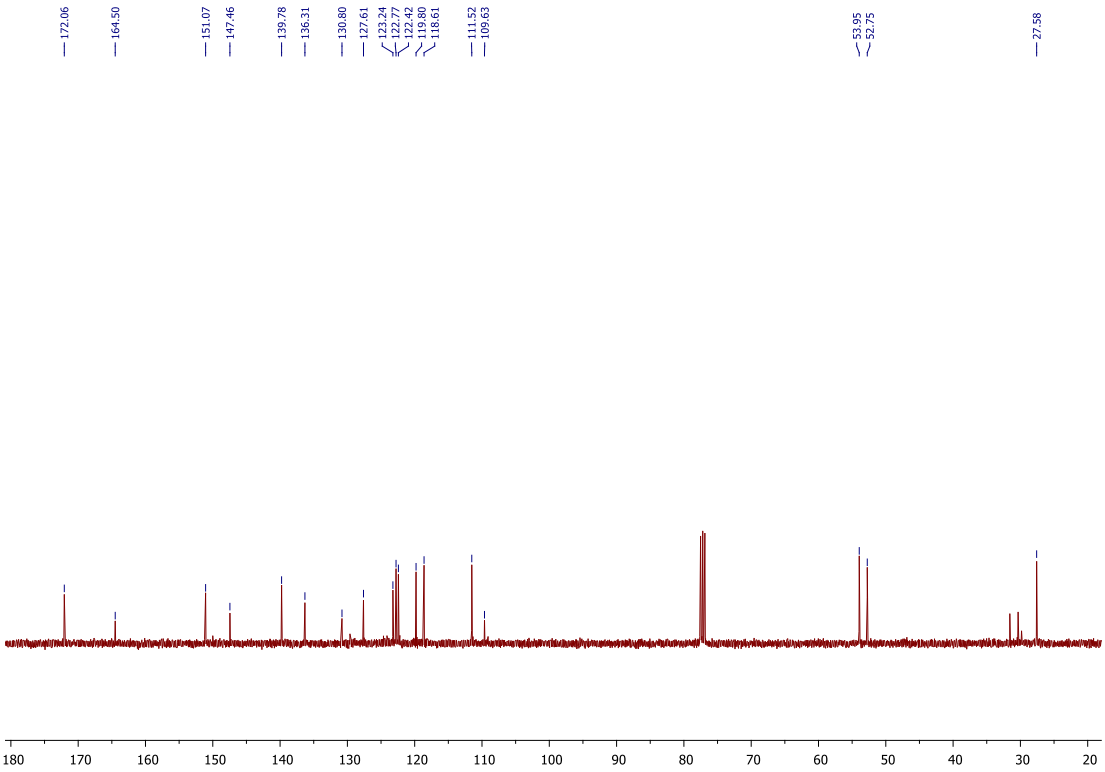

Fig. S23. ^{13}C NMR of *N*-(2-chloronicotinoyl)-L-tryptophan methyl ester (12).

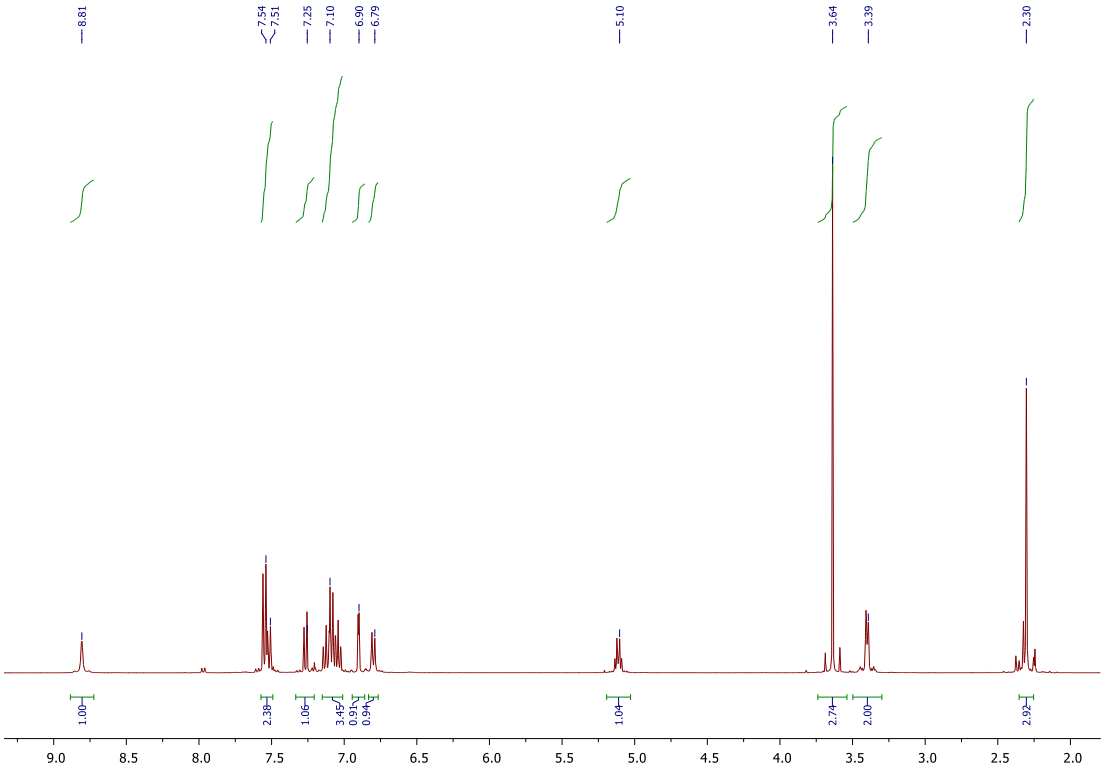

Fig. S24. ^{1}H NMR of *N*-(4-methylbenzoyl)-L-tryptophan methyl ester (13).

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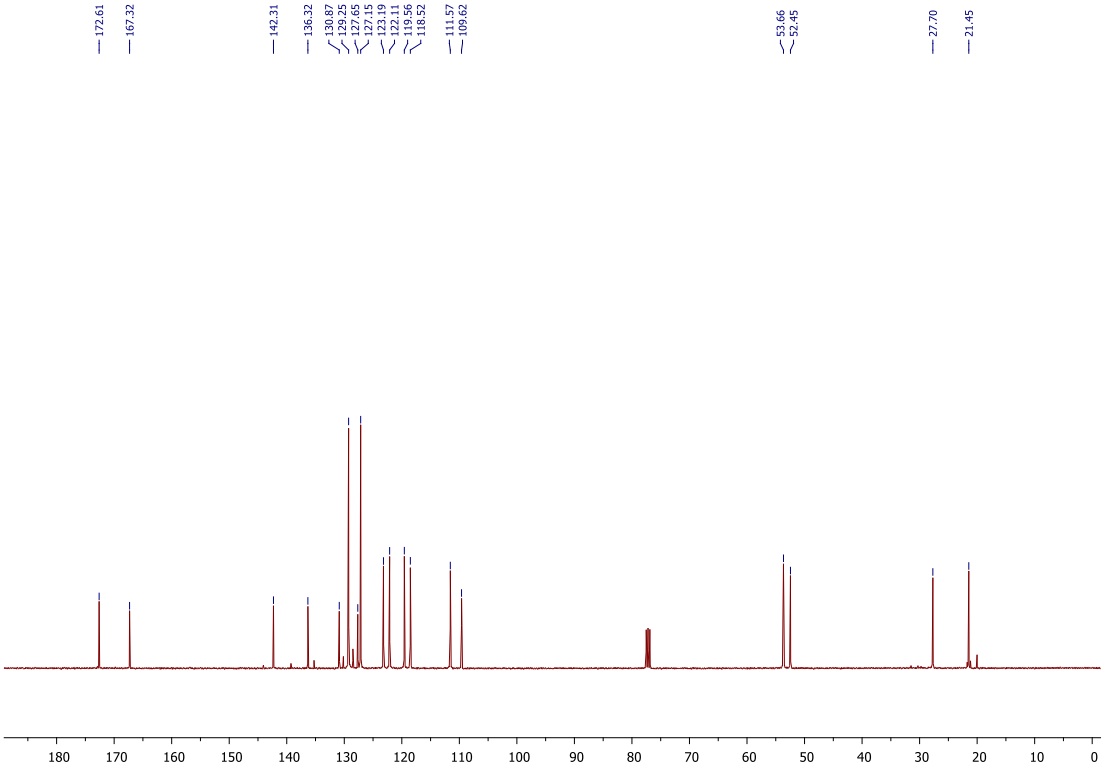

Fig. S24. ^{13}C NMR of *N*-(4-methylbenzoyl)-L-tryptophan methyl ester (13).

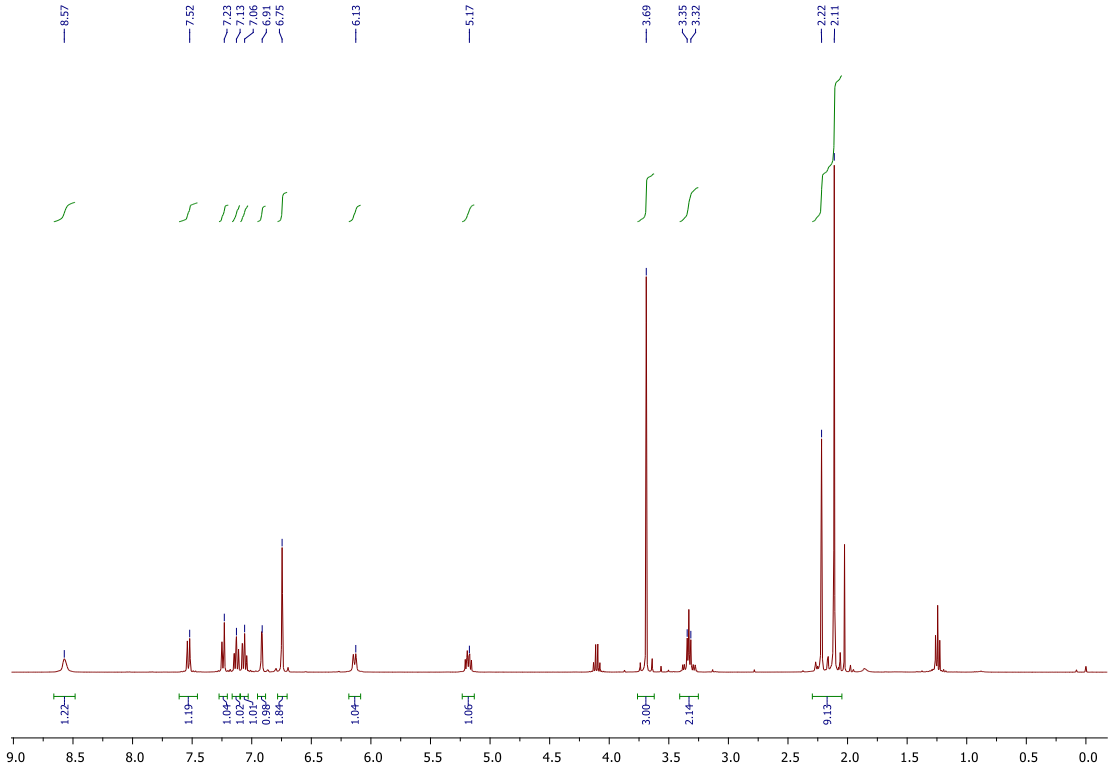

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Fig. S25. ^{1}H NMR of *N*-(2,4,6-trimethylbenzoyl)-L-tryptophan methyl ester (14).

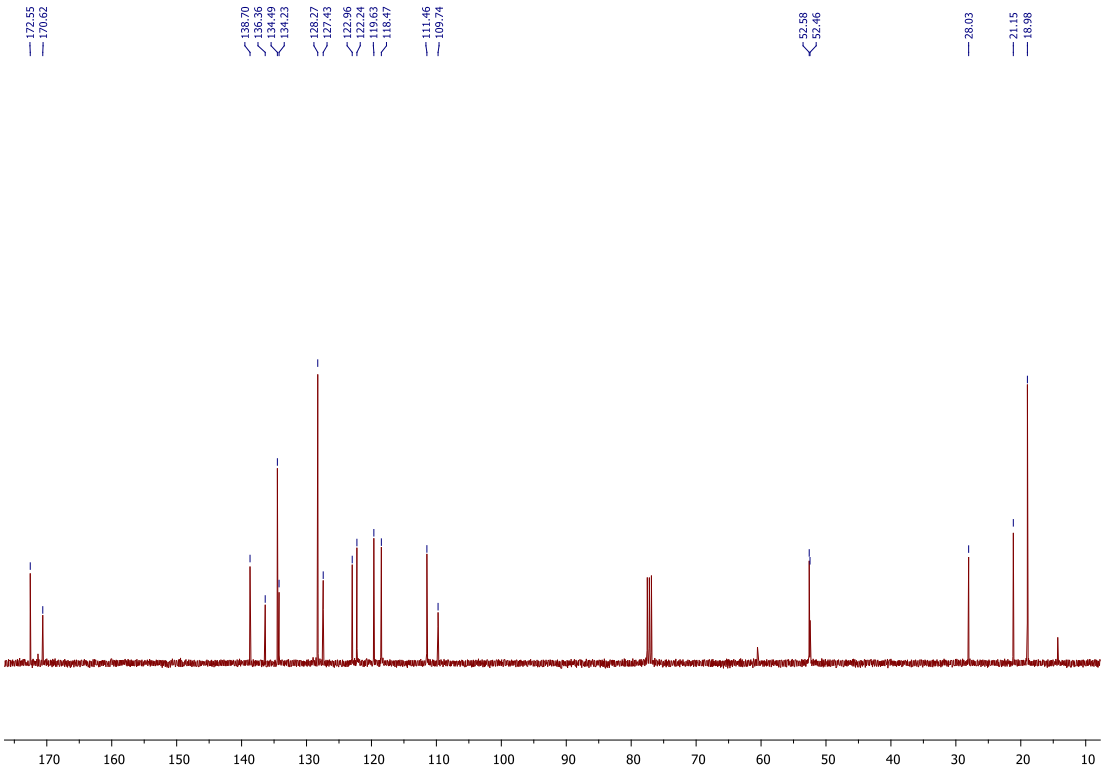

Fig. S26. ^{13}C NMR of *N*-(2,4,6-trimethylbenzoyl)-L-tryptophan methyl ester (14).

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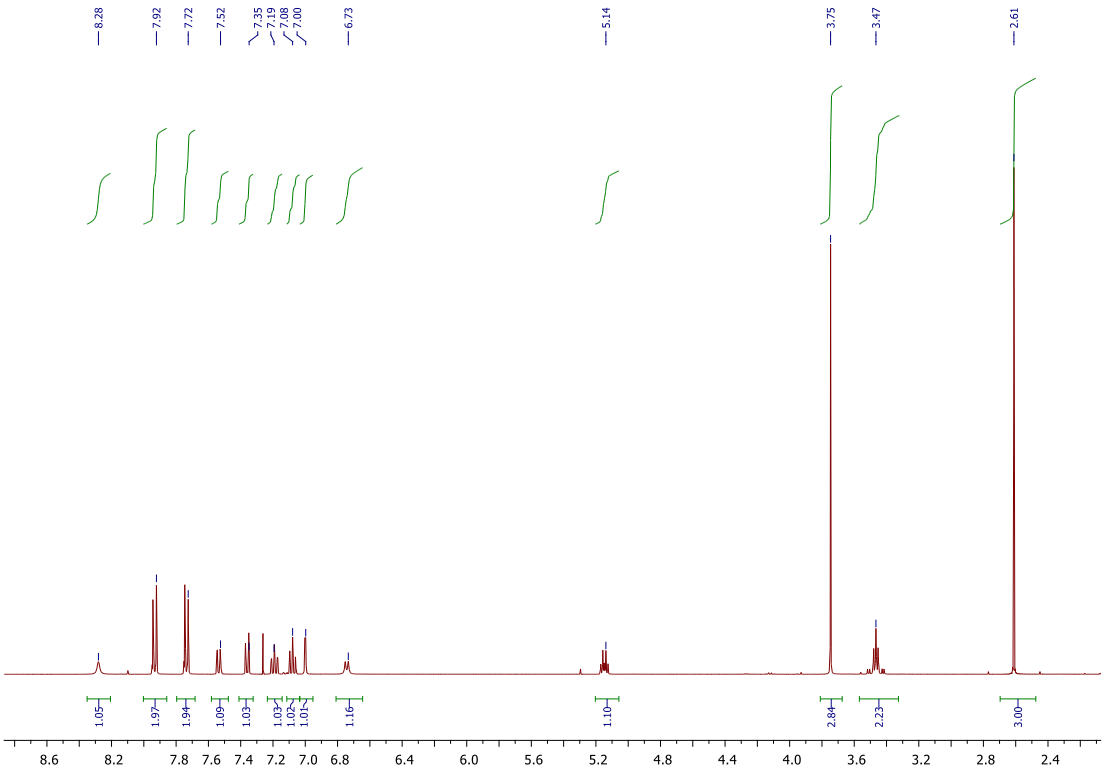

Fig. S27. ^{1}H NMR of *N*-(4-acetylbenzoyl)-L-tryptophan methyl ester (15).

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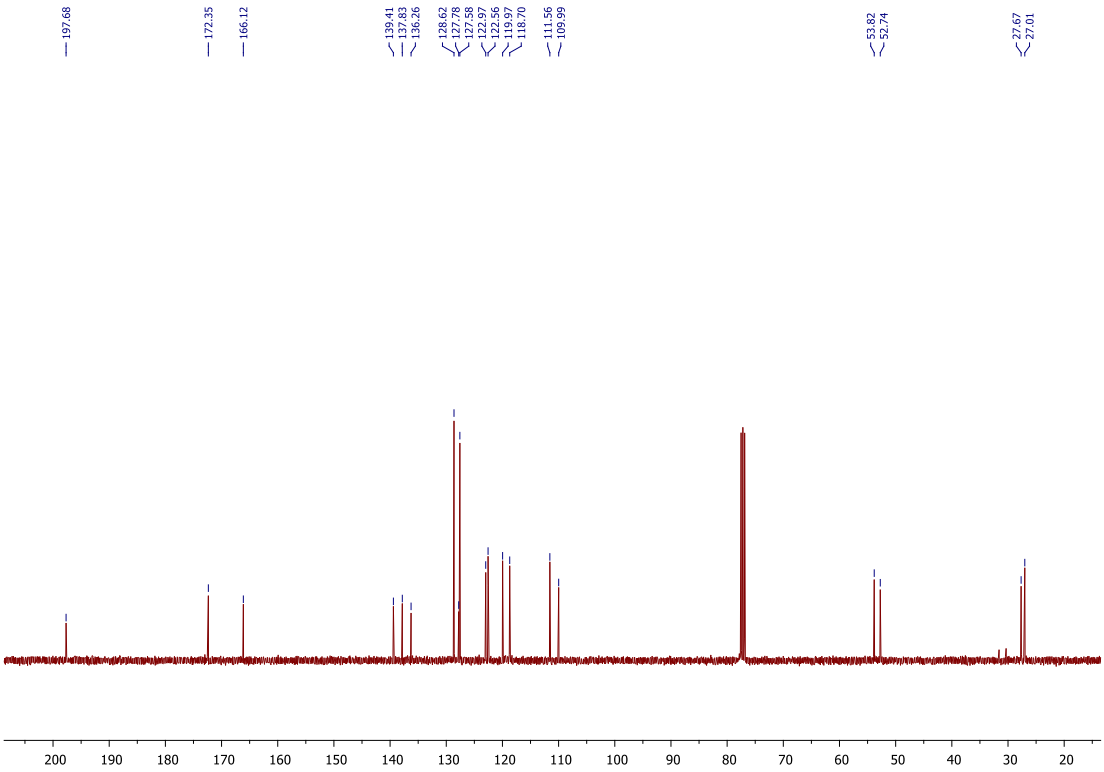

Fig. S28. ^{13}C NMR of *N*-(4-acetylbenzoyl)-L-tryptophan methyl ester (15).

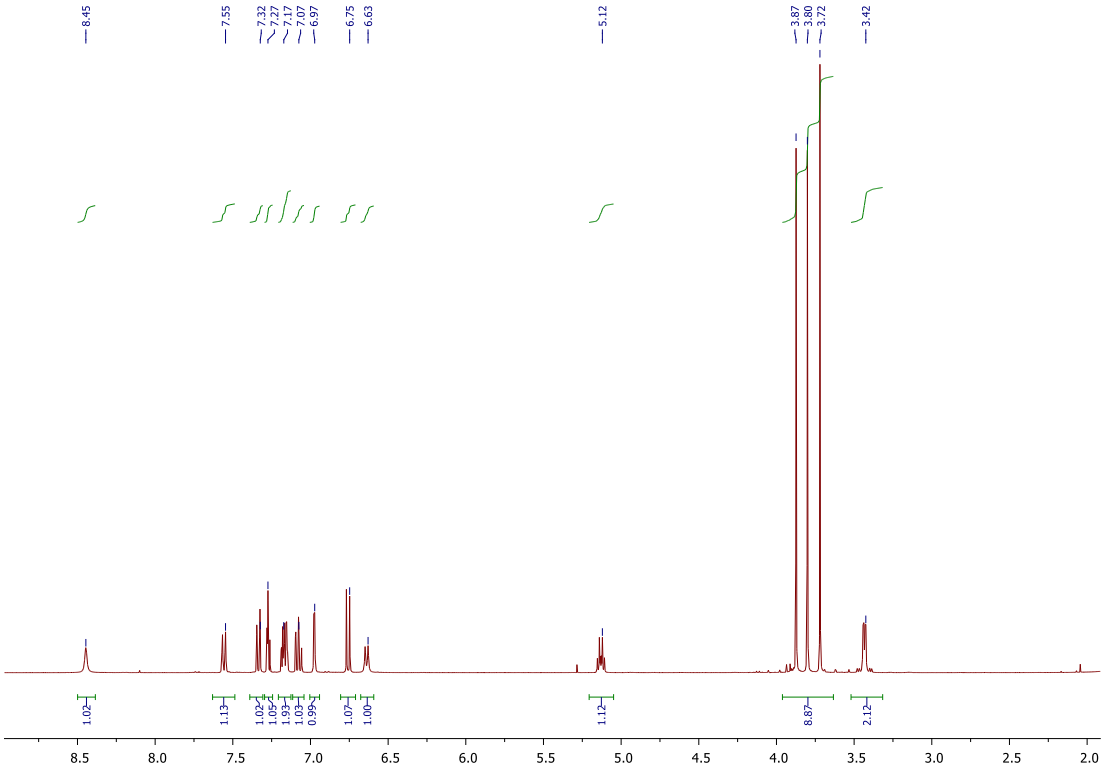

Fig. S29. ^{1}H NMR of *N*-(3,4-dimethoxybenzoyl)-L-tryptophan methyl ester (16).

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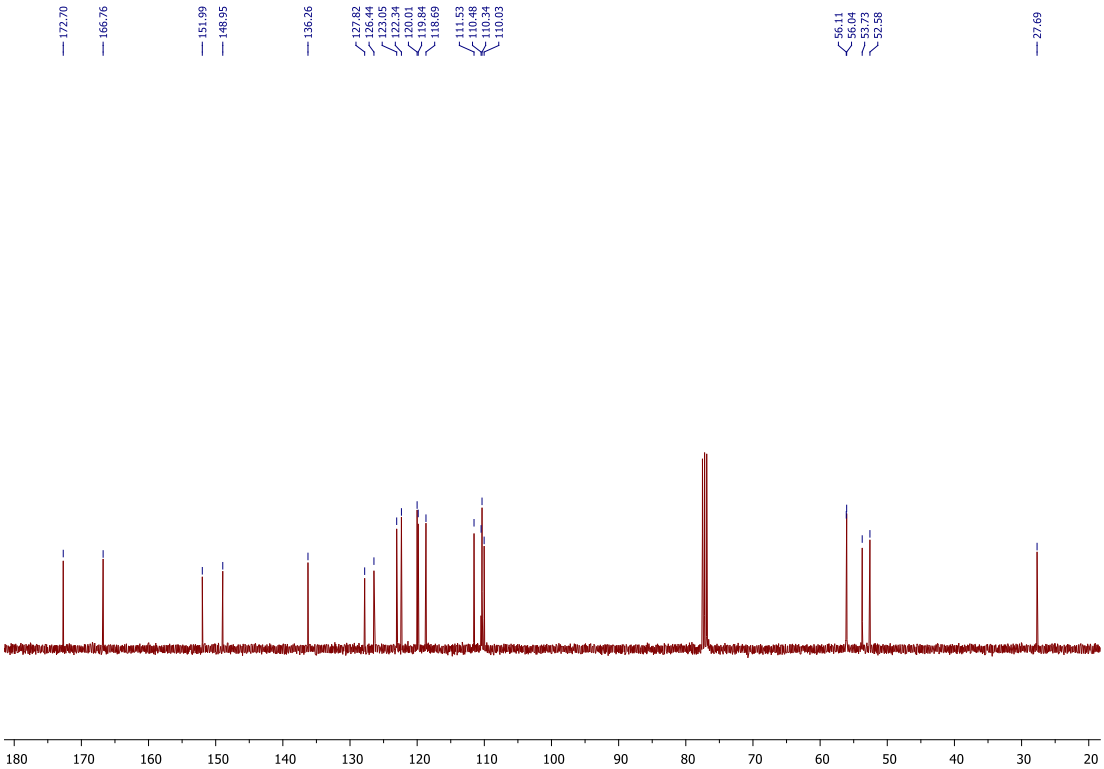

Fig. S30. ^{13}C NMR of *N*-(3,4-dimethoxybenzoyl)-L-tryptophan methyl ester (16).

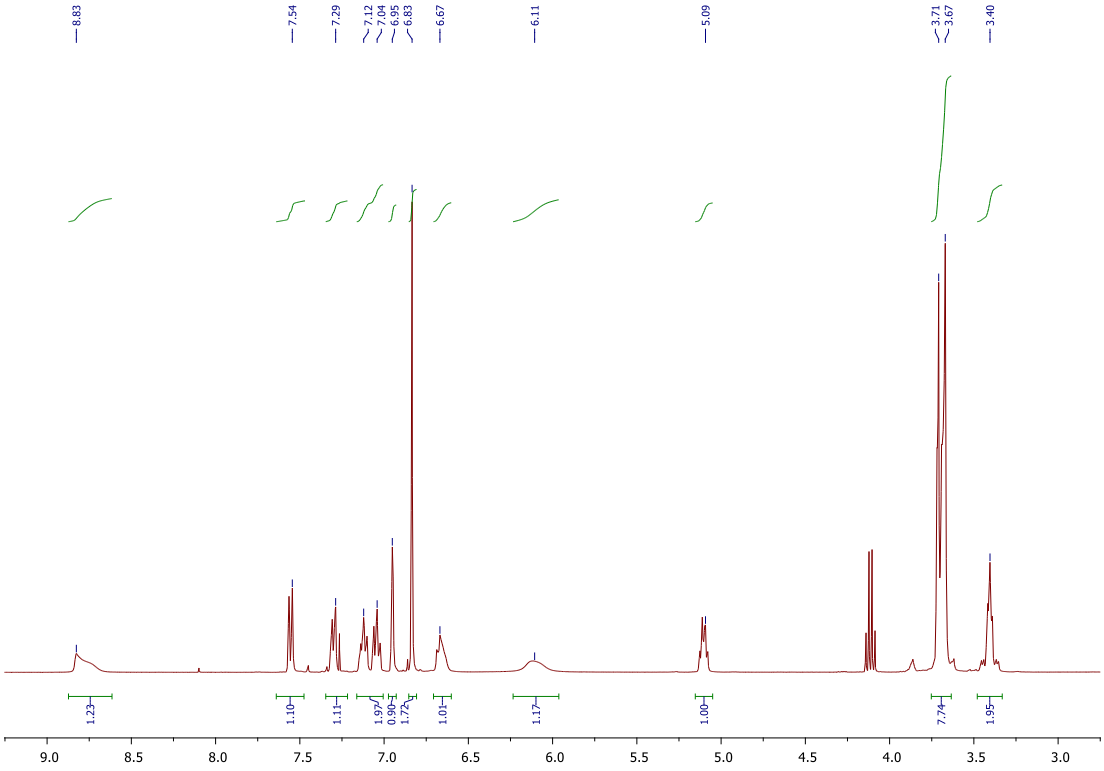

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Fig. S31. ^{1}H NMR of *N*-(4-hydroxy-3,5-dimethoxybenzoyl)-L-tryptophan methyl ester (17).

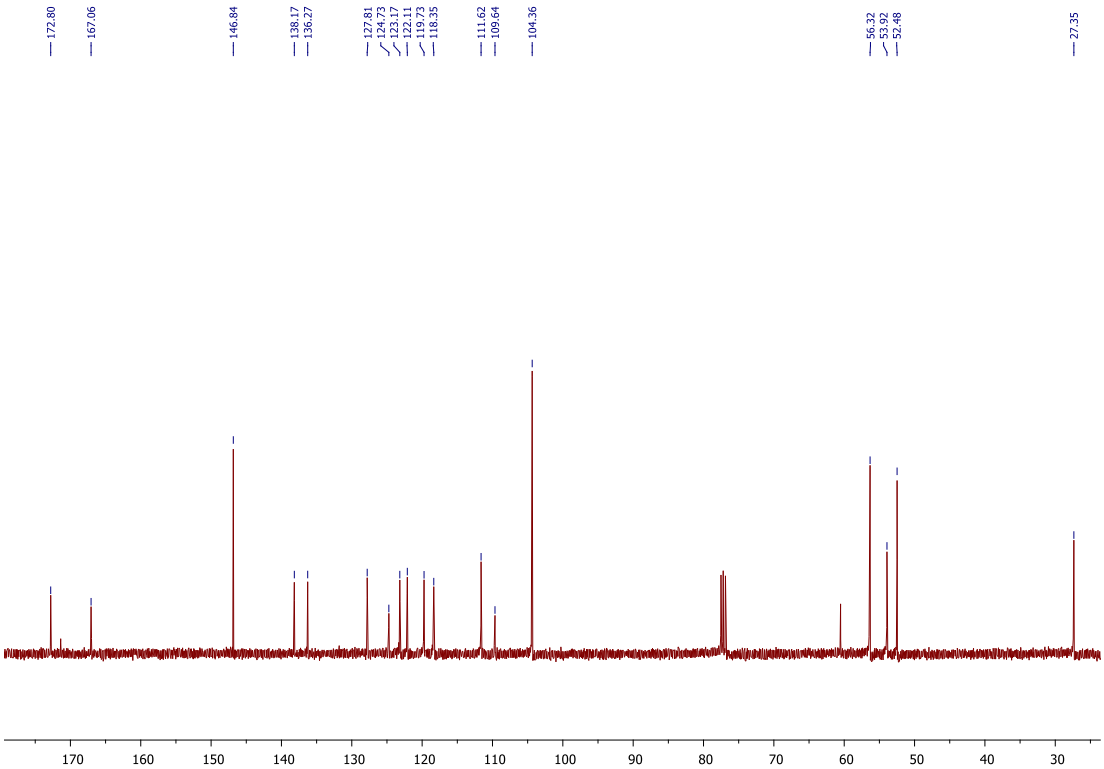

Fig. S32. ^{13}C NMR of *N*-(4-hydroxy-3,5-dimethoxybenzoyl)-L-tryptophan methyl ester (17).

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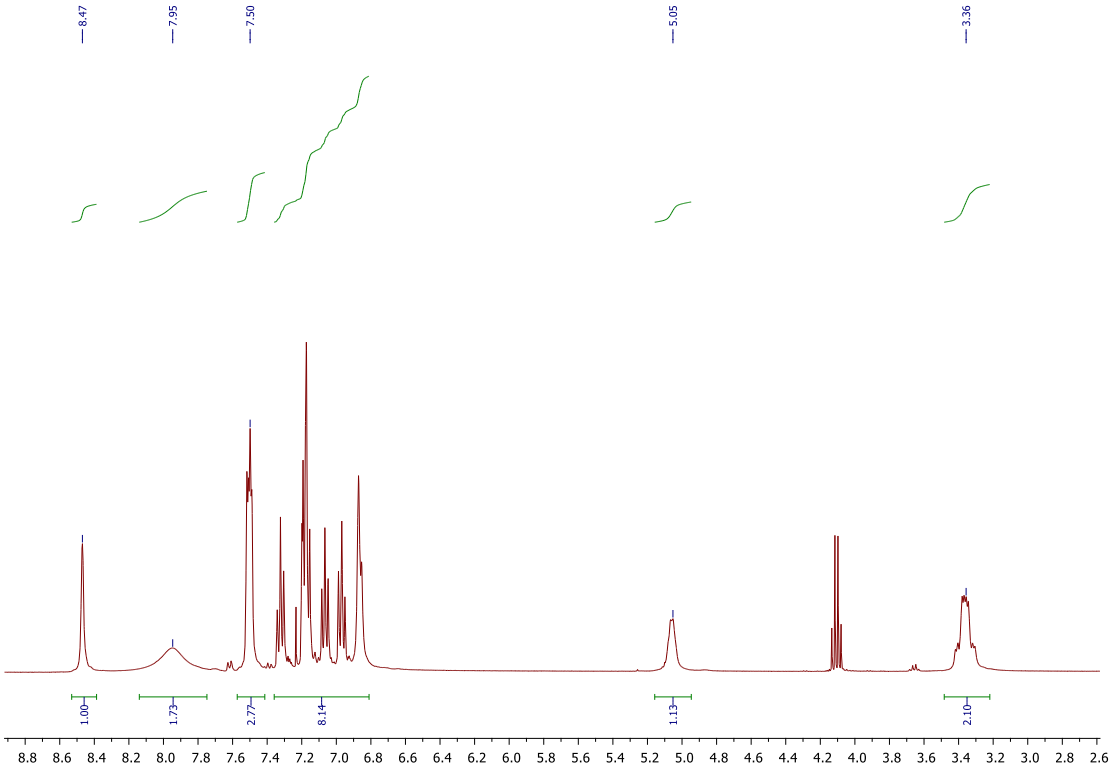

Fig. S33. ^{1}H NMR of *N*-Benzoyl-L-tryptophan (18).

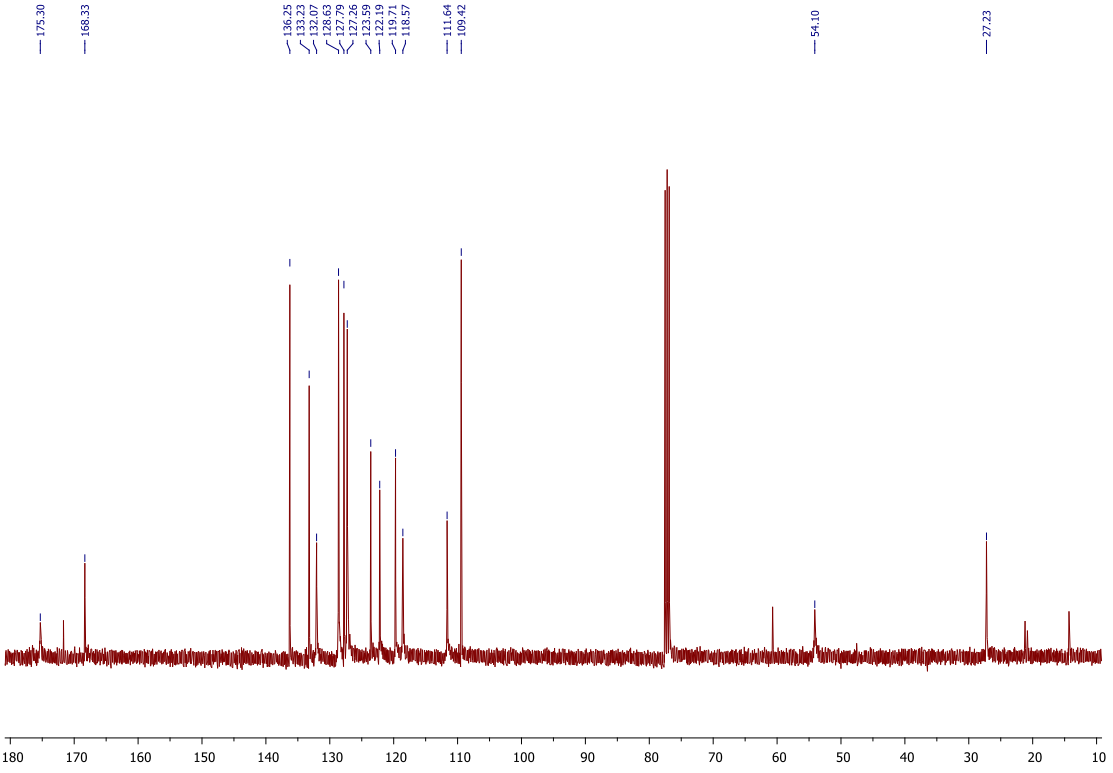

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Fig. S34. ^{13}C NMR of *N*-Benzoyl-L-tryptophan (18).

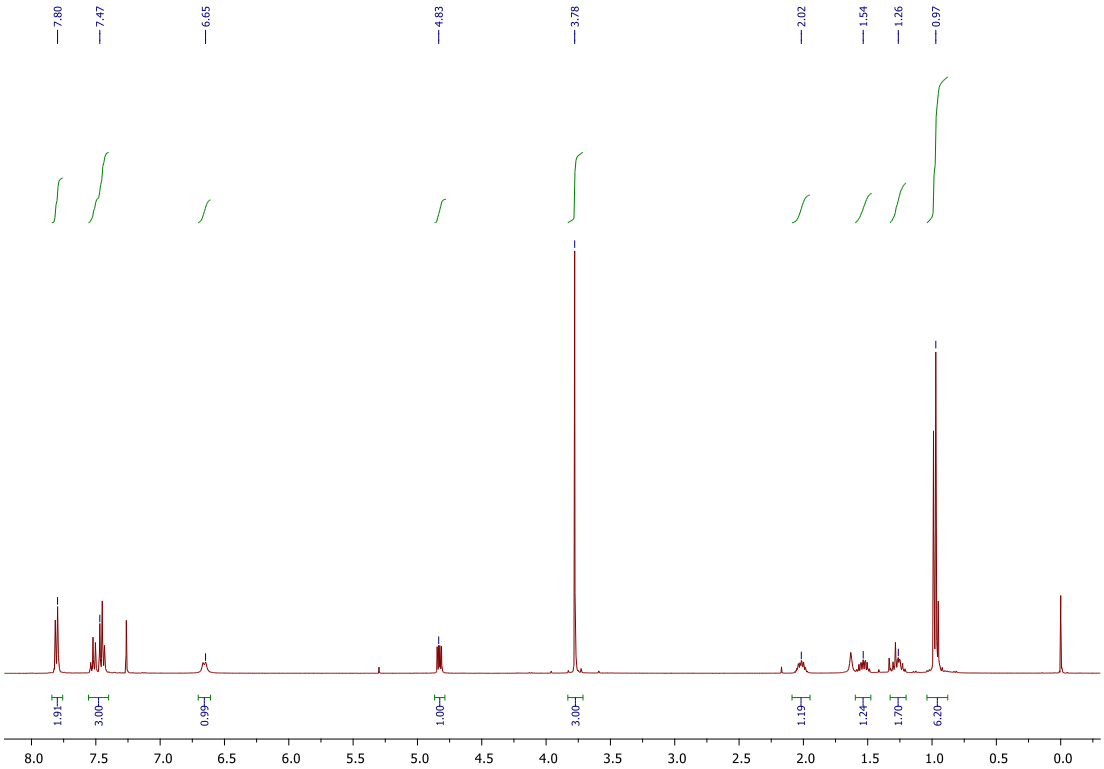

Fig. S35. ^{1}H NMR of *N*-Benzoyl-L-isoleucine methyl ester (19).

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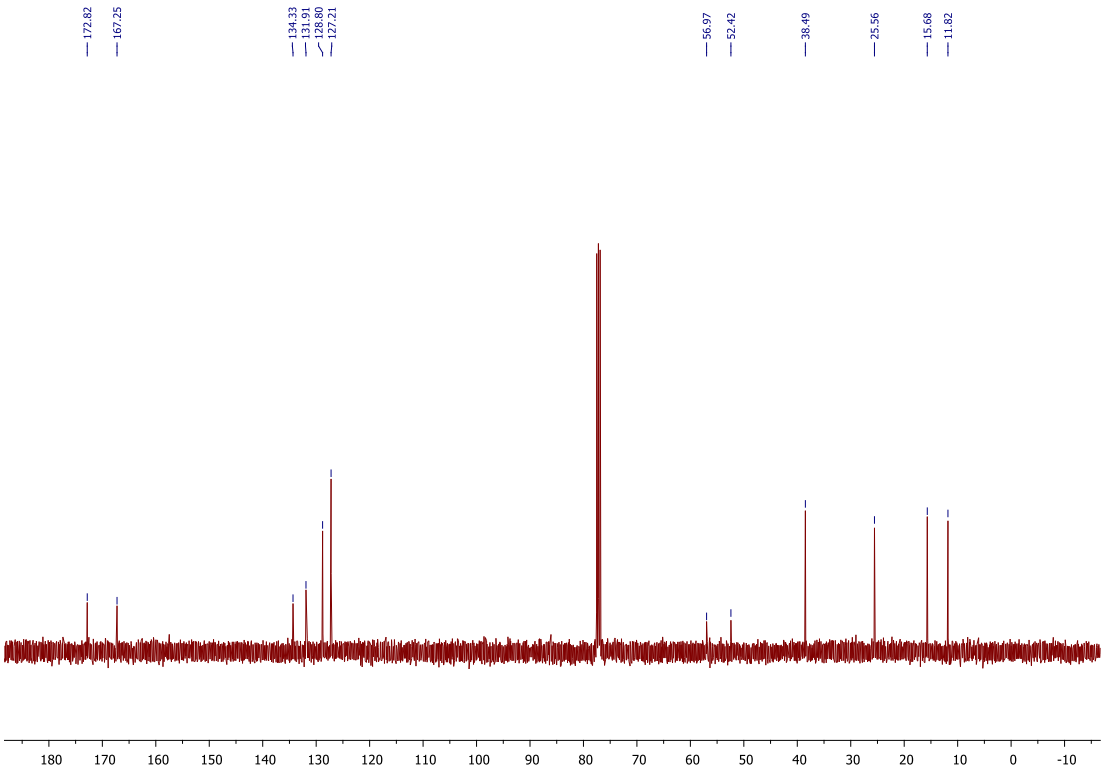

Fig. S36. ^{13}C NMR of *N*-Benzoyl-L-isoleucine methyl ester (19).

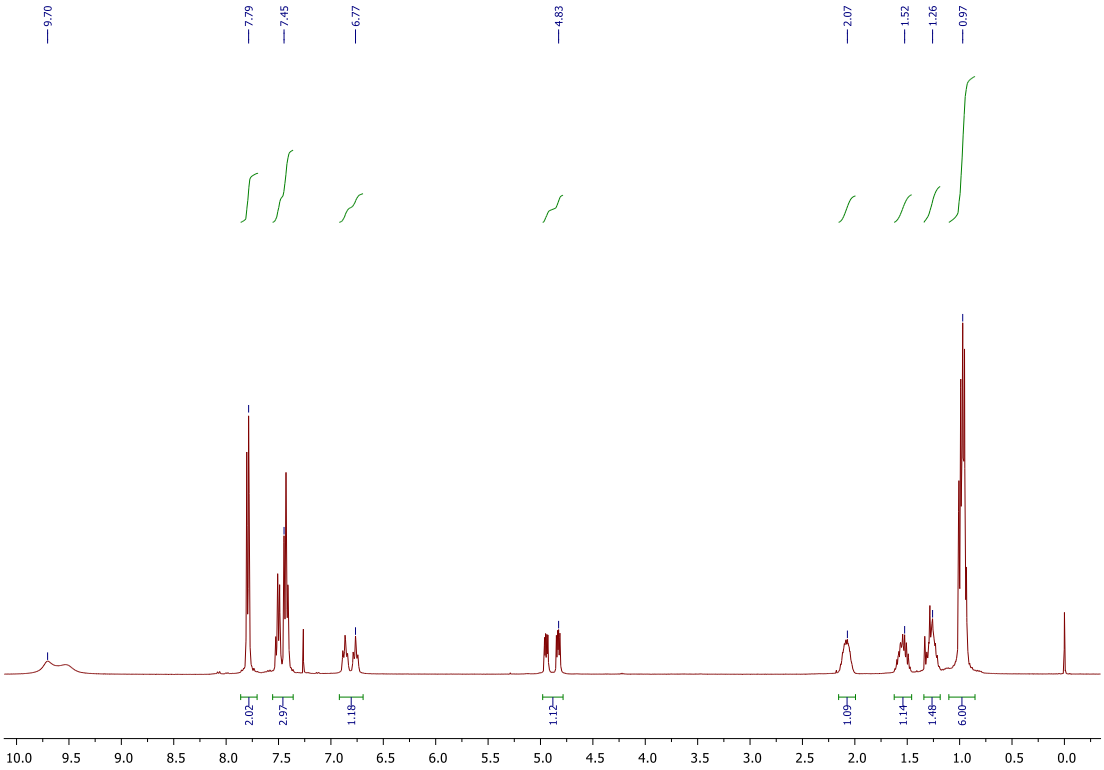

Fig. S37. ^{1}H NMR of *N*-Benzoyl-L-isoleucine (20).

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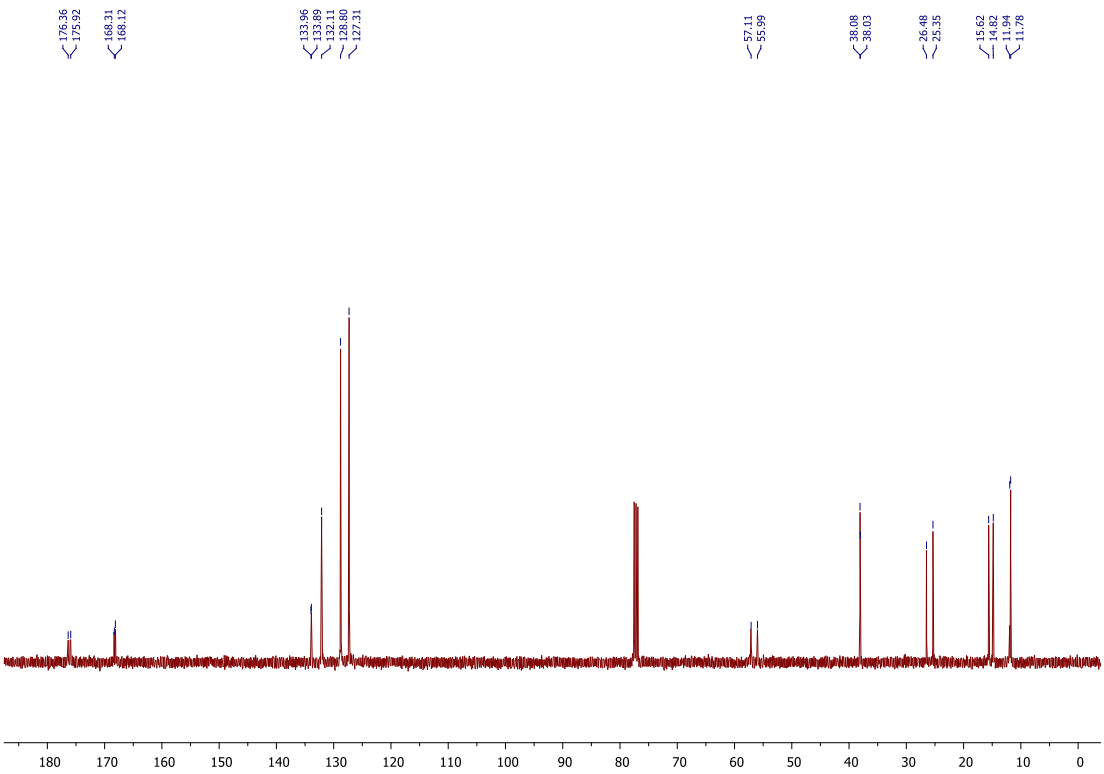

Fig. S38. ^{13}C NMR of *N*-Benzoyl-L-isoleucine (20).

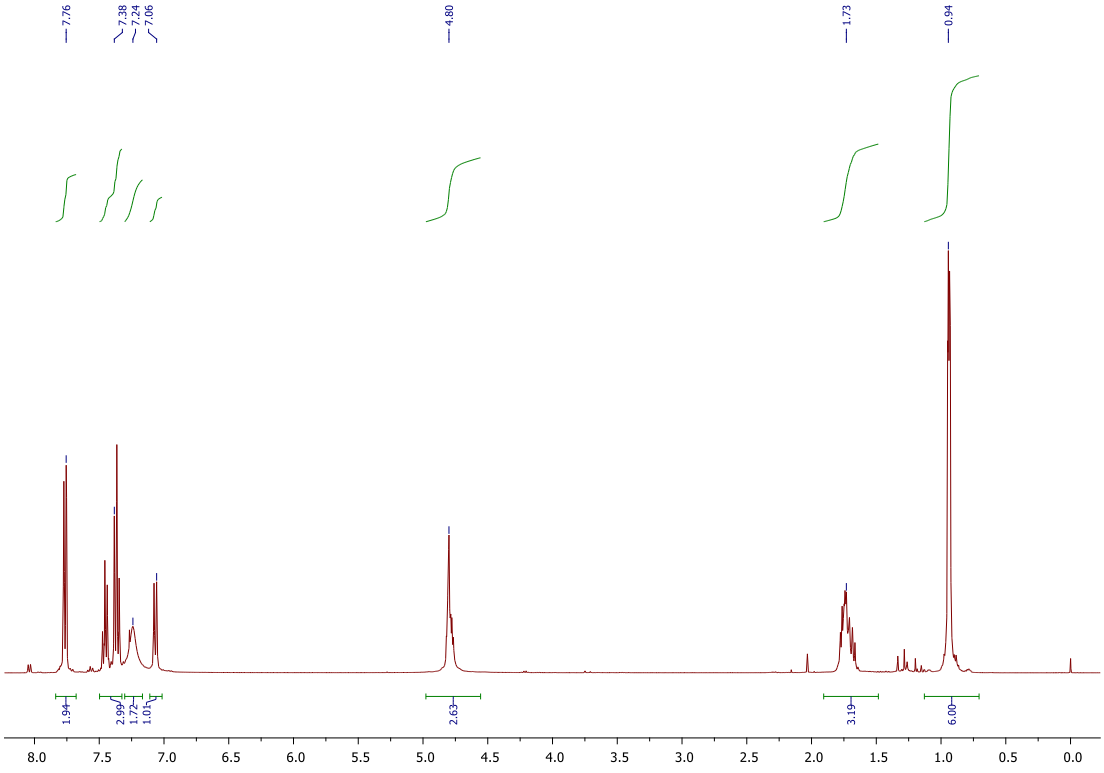

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Fig. S39. ^{1}H NMR of *N*-Benzoyl-L-leucine (21).

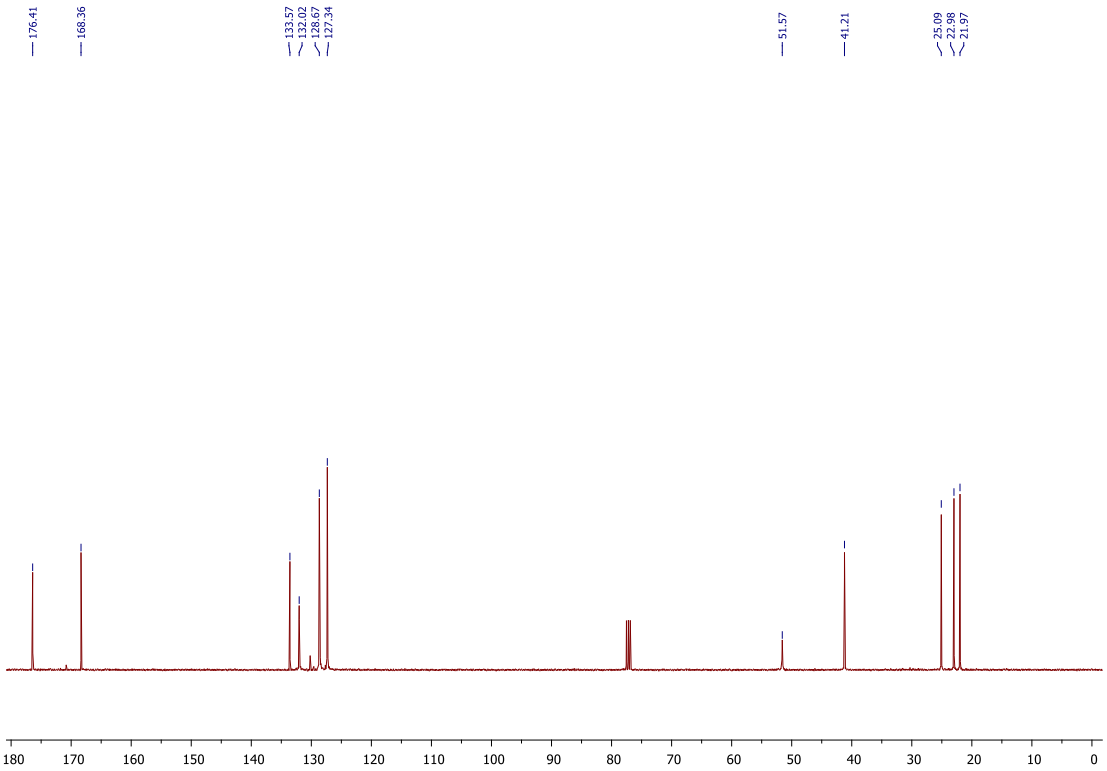

Fig. S40. ^{13}C NMR of *N*-Benzoyl-L-leucine (21).

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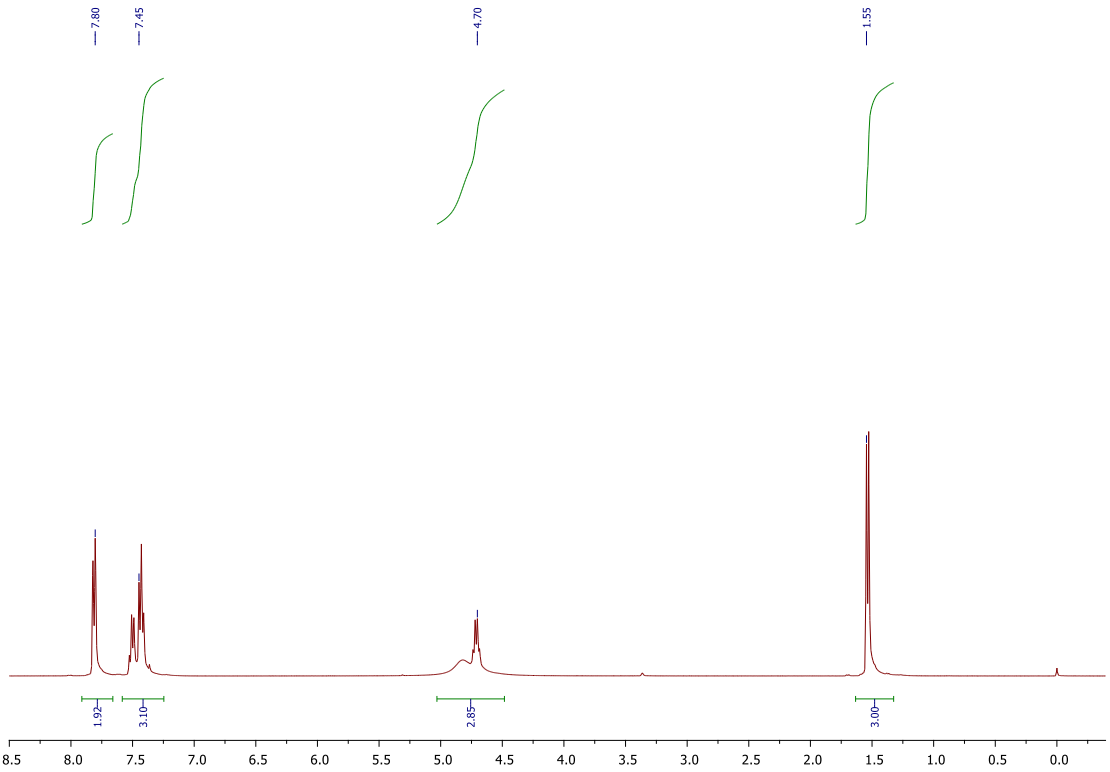

Fig. S41. ^{1}H NMR of *N*-Benzoyl-L-alanine (22).

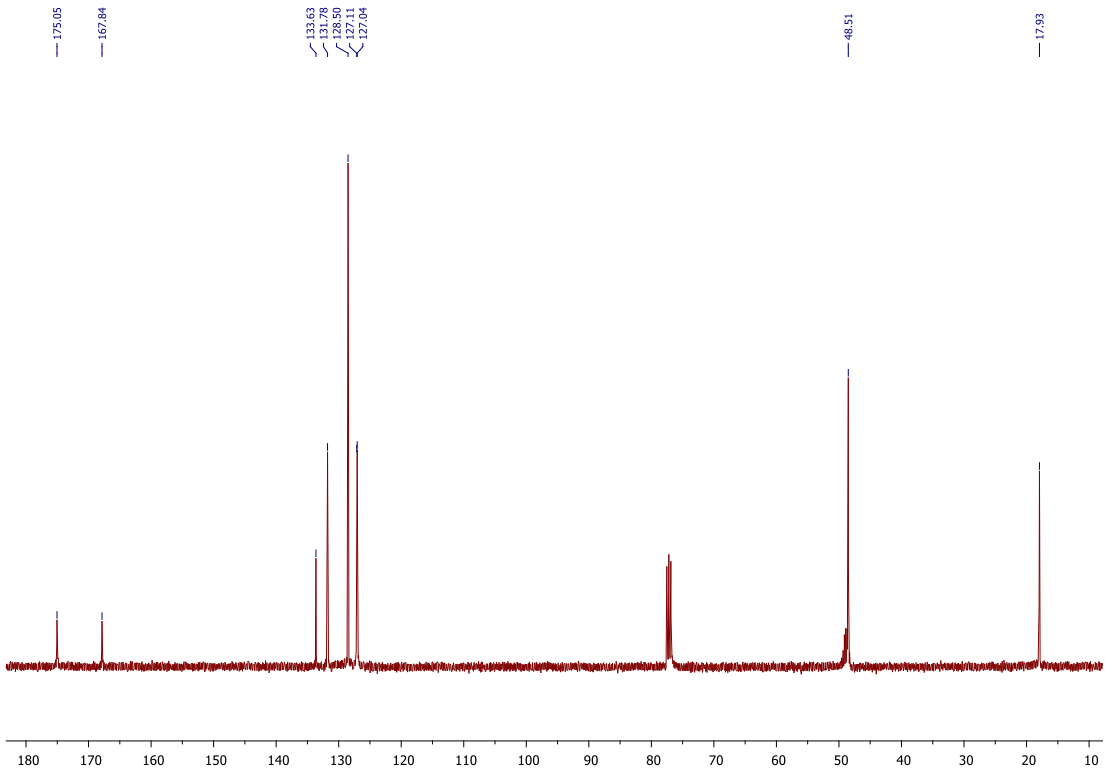

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Fig. S42. ^{13}C NMR of *N*-Benzoyl- L-alanine (22).

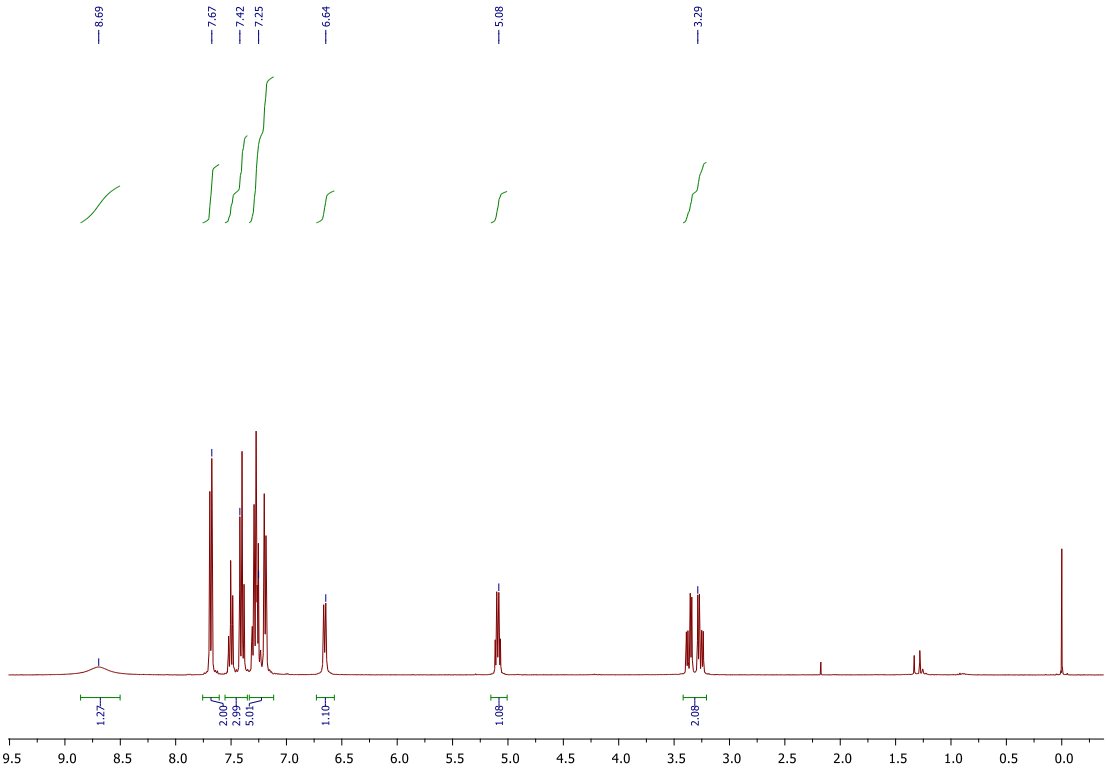

Fig. S43. ^{1}H NMR of *N*-Benzoyl-L-phenylalanine (23).

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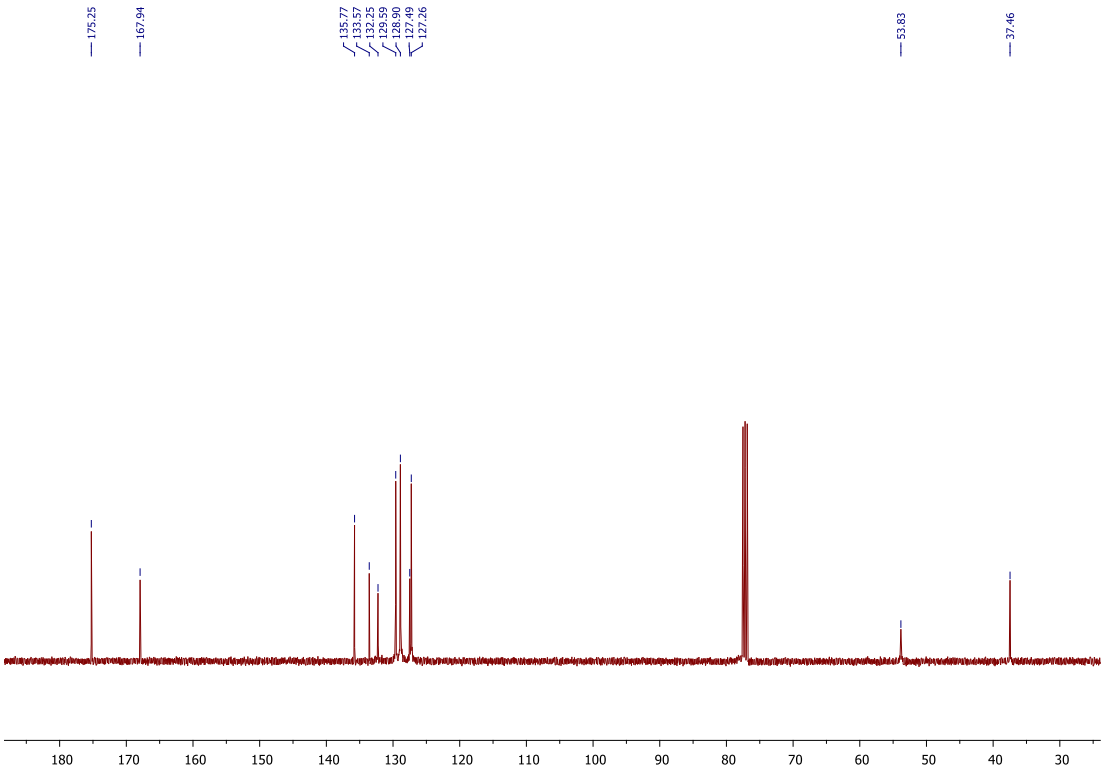

Fig. S44. ^{13}C NMR of *N*-Benzoyl-L-phenylalanine (23).