Electronic Supplementary Material (ESI) for Chemical Communications.

A mild and selective Pd-mediated methodology for the synthesis of highly fluorescent 2-arylated tryptophans and tryptophan-containing peptides: a catalytic role for Pd^0 nanoparticles?

Thomas J. Williams, Alan J. Reay, Adrian C. Whitwood and Ian J. S. Fairlamb*

Department of Chemistry, University of York, Heslington, York YO10 5DD, United Kingdom

Contents

1 – General Experimental Details

Reagents were purchased from Sigma-Aldrich®, Alfa Aesar® or Fluorochem® and used as received unless otherwise stated. Peptides were purchased from GeneCust Europe (Laboratoire de Biotechnologie du Luxembourg S.A.). Dry methanol was obtained by drying over 3 Å molecular sieves. Dry DMF was obtained from Acros® and degassed by N_2 bubbling with sonication. Petroleum ether refers to the fraction of petroleum that is collected at 40 – 60 °C. Air sensitive procedures were performed using standard Schlenk techniques. Nitrogen gas was oxygen free and dried immediately prior to use by passing through a column of sodium hydroxide pellets and silica. Filtration was performed under gravity through fluted filter paper unless otherwise stated.

TLC analysis was carried out using Merck 5554 aluminium backed silica plates, and visualised using UV light (254 nm) or an iodine tank. All column chromatography was performed using silica gel 60 and a solvent system as stated in the text.

^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectra were recorded on a Jeol ECS/ECX400 (400, 100, 376 and 128 MHz respectively). Alternatively and where specified, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV500 (500 and 126 MHz respectively) spectrometer. ^{1}H Chemical shifts are reported in parts per million and were referenced to residual non-deuterated/partially-deuterated solvent. Coupling constants have been quoted to ±0.2 Hz. ^{1}H NMR chemical shifts are given to two decimal places; ^{13}C NMR chemical shifts are given to 1 decimal place. Spectra were typically recorded at 298 K. ^{13}C, ^{11}B, and ^{19}F spectra were recorded with ^{1}H decoupling. ^{19}F and ^{11}B spectra were externally referenced to $CFCl_3$ and $BF_3.OEt_2$ respectively. Spectra were processed using MestreNova®. Some images were produced as .png, .bmp or jpeg files, or Windows metafiles. Chemical structures were produced in ChemDraw, versions 11 and 12.

IR spectroscopy was performed using a Perkin Elemer Spectrum 2 or a Unicam Research Series FTIR, both using an ATR attachment. Where indicated, reactions were monitored *in situ* using a Mettler Toledo ReactIR™ ic10 with K6 conduit SiComp (silicon) probe and MCT detector. Resolution 4 cm^{-1}, range 4000-650 cm^{-1} and gain adjustment at 1x.

UV-Visible spectroscopy was performed on a Jasco® V-560 spectrometer. A baseline in the appropriate solvent was obtained prior to recording spectra.

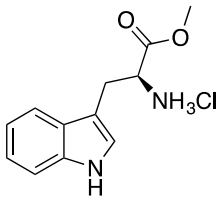
Mass spectrometry was performed using a Bruker Daltronics micrOTOF spectrometer, an Agilent series 1200 LC, or a Thermo LCQ using electrospray ionization (ESI), with less than 5 ppm error for all HRMS. Liquid induction field desorption ionization (LIFDI) mass spectrometry was performed using a Waters GCT Premier mass spectrometer.

Peptide HPLC-MS was performed on a Bruker® HCTultra at the University of Leeds. Chiral stationary phase HPLC was performed with a multiple wavelength, UV-vis diode array detector; integration was performed at 210, 230, and 250 nm. Optical rotations were recorded at 20 °C (using the sodium D line; 259 nm), and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^3 g^{-1}. Melting points were recorded using a Stuart digital SMP3 machine.

Transmission electron microscopy was performed at the University of York, Department of Biology Technology Facility, by Dr. Meg Stark using a Technai 12 BioTWIN microscope, operated at 120 kV. The images were enlarged, and particle sizes measured manually. Statistical analyses were performed and histograms drawn using Microsoft Excel:mac 2010 with AnalystSoft StatPlus:mac LE.2009 (build 5.8.0.0).

2 - Synthesis of Starting Materials

2.1 – Methyl (2S)-2-amino-3-(1H-indol-3-yl)propionate

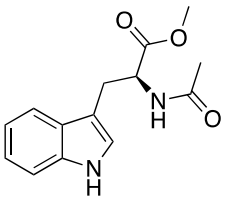


To a Schlenk tube under N_2 was added dry MeOH (50 mL). Thionyl chloride (7.04g, 59 mmol, 4.3 mL, 2.4 eq.) was added dropwise at -15 °C. Tryptophan (5 g, 24.5 mmol, 1 eq.) was then added in three portions, resulting in a white suspension. The reaction mixture was warmed to ambient temperature and stirred for 24 h. During this time, an orange solution was formed. Water (5 mL) was added to the reaction mixture, and the solvent removed under reduced pressure to give product as an off-white solid (2.027 g, 97%).

MP 211 – 213 °C (lit. 214 °C, decomp.)[1]; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.11 (s, 1H), 8.55 (s, 3H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.37 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.24 (d, *J* = 2.5 Hz, 1H), 7.09 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.01 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.28 – 4.17(m, 1H), 3.66 (s, 3H), 3.33 – 3.26 (m, 2H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 170.0, 136.2, 126.9, 125.0, 121.2, 118.6, 118.0, 111.6, 106.5, 52.8, 52.6, 26.3; ESI-MS *m/z* 219 [M+H], 241 [M+K]; ESI-HRMS *m/z* 219.1136 [M+H] (calc. for $C_{12}H_{14}N_2O_2$ 219.1128); IR (solid-state ATR, cm^{-1}) 1747, 1549, 1501, 1437, 1284, 1229, 1210, 1108, 1074, 1007, 730.0.

The racemate was prepared from DL-tryptophan using the method outlined above. The product was obtained as a white solid (5.72 g, 92%).

2.2 - Methyl (2S)-2-acetylamino-3-(1H-indol-3-yl)propioniate, ***1***

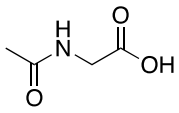


To a three-necked round-bottomed flask fitted with a reflux condenser and purged with N_2, was added methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate (300 mg, 1.38 mmol, 1 eq.). To this was added dry THF (15 mL) and triethylamine (0.2 mL). The mixture was stirred to give a white

suspension. The mixture was cooled to 0 °C, and acetic anhydride (143 µl, 154 mg, 1.51 mmol, 1.1 eq.) added in one portion. The reaction was then stirred for 2 h at 80 °C to give a white suspension. This was added to water (40 mL) and extracted into EtOAc (3 x 50 mL). The organic layers were combined and washed sequentially with 1 M aq. HCl (1 x 40 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (1 x 40 mL). The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give colourless oil. Trituration with Et_2O resulted in product as an off-white solid (327 mg, 91%, *er* 99.9:0.1 by HPLC).

$[\alpha]_D$ = +52.5 (*c* 0.11, $CHCl_3$); MP 156 – 157 °C (lit. 155 – 156 °C)[2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.52 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.19 (ddd, 8.2, 7.0, 1.0 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 5.96 (d, *J* = 8.0 Hz, 1H), 4.95 (dt, *J* = 8.0, 5.2 Hz, 1H), 3.69 (s, 3H), 3.35 (ddd, *J* = 15.0, 5.2 Hz, 0.8, 1H), 3.29 (ddd, *J* = 15.0, 5.2, 0.8 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 169.8, 136.3, 127.8, 122.7, 122.4, 119.7, 118.7, 111.4, 110.2, 53.1, 52.5, 27.7, 23.4; ESI-MS *m/z* 261 [M+H], 283 [M+K]; ESI-HRMS *m/z* 261.1234 [M+H] (calc. for $C_{14}H_{17}N_2O_3$ 261.1234); IR (solid-state ATR, cm^{-1}) 3404, 3317, 1732, 1660, 1521, 1434, 1434, 1221, 848, 747; UV-Vis (DMSO, nm) λ_{max} 282 (ε = 5804 mol dm^{-3} cm^{-1}).
The racemate was prepared from methyl (*2RS*)-2-amino-3-(*1H*-indol-3-yl)propionate using the method outlined above. Product was obtained as a white solid (6.3 g, 83%, *er* 52.1:47.9 by HPLC). $[\alpha]_D$ = +0.353 (*c* 0.11, $CHCl_3$). The remaining data analytical data was identical to that reported above.

2.3 – N-Acetylglycine

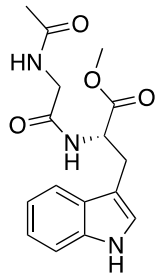


To a round-bottomed flask was added glycine (5 g, 66.6 mmol, 1 eq.) and water (150 mL). To this, acetic anhydride (20.4 g, 200 mmol, 18.9 mL, 3 eq.) was added dropwise and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was then cooled to 4 °C for 16 h, and the resulting precipitate collected by filtration through a sintered funnel to give product as a white solid (4.46 g, 57%).

MP 207 – 208 °C (decomp., lit. 206 – 208 °C)[3]; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.51 (s, 1H), 8.18 (s, 1H), 3.71 (d, *J* = 6.0 Hz, 2H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 171.5, 169.6, 40.6, 22.3; ESI-MS *m/z* 118 [M+H], 140 [M+Na]; ESI-HRMS *m/z* 118.0501 [M+H] (calc. for

$C_4H_8NO_3$ 118.0499); IR (solid-state ATR, cm^{-1}) 3350, 1944, 1897, 1717, 1580, 1547, 1439, 1379, 1351, 1276, 1227, 1137, 993, 902. 682.

2.4 – AcNGlyTrpOMe, ***3***

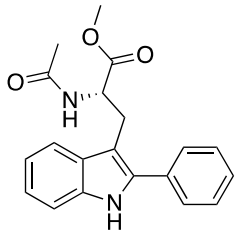


To a Schlenk tube was added methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propionate (190 mg, 0.872 mmol, 1 eq.), *N*-acetylglycine (102 mg, 0.872 mmol, 1 eq.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (167 mg, 0.872 mmol, 1 eq.). The reaction mixture was placed under vacuum and refilled with N_2, and this process repeated twice. Dry CH_2Cl_2 (5 mL) was added, and the mixture stirred for 16 h at ambient temperature. The solvent was removed under reduced pressure. The resulting residue was dissolved in EtOAc (15 mL) and washed with 1 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (1 x 40 mL). The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give product as a white solid (96 mg, 35%).

MP 98 – 102 °C (lit. 178 °C)[4]; ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.31 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.10 – 7.04 (m, 3H), 7.00 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.73 (dd, *J* = 7.0, 5.8 Hz, 1H), 3.83 (d, *J* = 16.6, 1H), 3.78 (d, *J* = 16.6 Hz, 1H), 3.64 (s, 3H), 3.27 (ddd, *J* = 14.6, 7.2, 0.6 Hz, 1H), 3.19 (ddd, *J* = 14.6, 7.2, 0.6 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.9, 173.7, 171.4, 138.0, 128.7, 124.6, 122.5, 119.9, 119.1, 112.3, 110.3, 54.8, 52.7, 49.0, 43.4, 28.4; ESI-MS *m/z* 318 [M+H], 340 [M+Na]; ESI-HRMS *m/z* 318.1433 [M+H] (calc. for $C_{16}H_{20}N_3O_4$ 318.1448); IR (solid-state ATR, cm^{-1}) 3286, 2947, 1737, 1655, 1610, 1508, 1460, 1439, 1372, 1285, 1248, 1215, 1177, 1030.

3 - Experimental Details for C-H Bond Functionalisation

3.1 – Methyl (2S)-2-amino-3-(2-phenyl-1H-indol-3-yl)propanoate, ***2a***

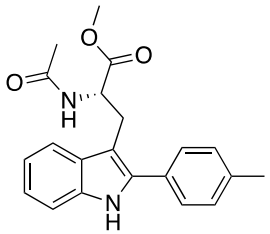


To a microwave tube was added phenylboronic acid (47 mg, 0.384 mmol, 2 eq.), methyl (2*S*)-2-acetylamino-3-(1*H*-indol-3-yl)propioniate (50 mg, 0.192 mmol, 1 eq.), $Cu(OAc)_2$ (3.48 mg, 19.2 μmol, 5 mol%) and $Pd(OAc)_2$ (2 mg, 9.6 μmol, 5 mol%) and acetic acid (5 mL). The reaction mixture was stirred at 40 °C for 16 h. The resulting black reaction mixture was filtered through Celite®, and the solvent removed under reduced pressure to give a brown solid. This was dissolved in EtOAc (10 mL) and washed with sat. aq. $NaHCO_3$. The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a brown solid. This was dry-loaded onto silica gel and purified by flash chromatography eluting with ethyl acetate:petroleum ether (1:1, *v/v*) to give the product as a white solid (60 mg, 93%, *er* 99.9:0.1).

$[\alpha]_D$ = +47.3 (*c* 0.11, $CHCl_3$); MP 83 – 84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.63 – 7.54 (m, 3H), 7.51 – 7.45 (m, 2H), 7.44 – 7.33 (m, 2H), 7.21 (ddd, *J* = 8.0, 7.0, 8.0 Hz, 1H), 7.15 (ddd, J = 8.0, 7.0, 8.0 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.84 (dt, J = 8.0, 5.5 Hz, 1H), 3.56 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.53 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.30 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 170.0 136.4, 136.1, 133.6, 129.9, 129.6, 128.7, 128.6, 123.0, 120.5, 119.4, 111.4, 107.2, 53.2, 52.5 27.0, 23.4.; ESI-MS m/z 337 [M+H], 359 [M+Na], 395 [M+K]; ESI-HRMS m/z 337.1539 [M+H] (calc. for $C_{20}H_{20}N_2O_3$ 337.1547); IR (solid-state ATR, cm^{-1}) 3284, 2961, 1735, 1654, 1525, 1434, 1259, 1094, 1013, 795, 741, 697; UV-Vis (DMSO, nm) λ_{maxima} 308 (ε = 9120 mol dm^{-3} cm^{-1}).

The racemate was obtained according to the method outlined above to give product as a white solid (59 mg, 91%, *er* 50.9:49.1). $[\alpha]_D$ = +0.0353 (*c* 0.11, $CHCl_3$).

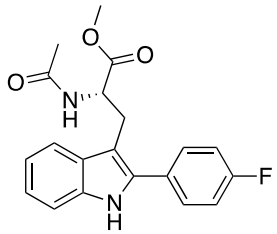
3.2 – Methyl (2S)-2-amino-3-[2-(4-methylphenyl)-1H-indol-3-yl]propanoate, ***2b***



Obtained according to the general method above as a white solid (88% yield).

R_F 0.32 (50% EtOAc/PE); $[\alpha]_D$ = +51.9 (*c* 0.10, $CHCl_3$); MP 97 – 99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.19 (ddd, J= 8.0, 7.0, 1.0 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.82 (dt, *J* = 7.8, 5.4 Hz, 1H), 3.53 (d, *J* = 5.4 Hz, 1H), 3.52 (d, *J* = 5.5Hz, 1H), 3.33 (s, 3H), 2.41 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 169.9, 136.1, 134.4, 134.2, 131.8, 129.9, 129.5, 123.3, 120.5, 119.4, 111.3, 108.2, 52.9, 52.2, 31.8, 29.8, 26.9, 23.0; ESI-HRMS *m/z* 391.0166 [M+H] (calc. for $C_{16}H_{15}F_3I$ 391.1065); IR (solid-state ATR, cm^{-1}) 3331, 2951, 1731, 1657, 1506,1372, 1305, 1215, 1010, 822, 742. UV-Vis (DMSO, nm) λ_{maxima} 310 (ε = 8893 mol dm^{-3} cm^{-1}).

3.3 – Methyl (2S)-2-amino-3-[2-(4-fluorophenyl)-1H-indol-3-yl]propanoate, ***2c***

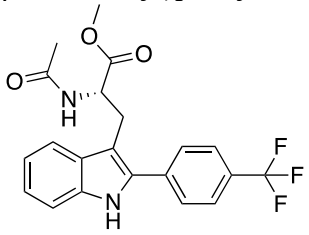


Obtained according to the general method above as a white solid (77% yield).

R_F 0.57 (50% EtOAc/PE); $[\alpha]_D$ = +54.4 (*c* 0.10, $CHCl_3$); MP 213 – 216 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.10 (m, 4H), 5.83 (d, *J* = 8.1 Hz, 1H), 4.82 (dt, *J* = 8.0, 5.4 Hz, 1H), 3.50 (dd, J = 15.0, 5.5 Hz, 1H), 3.46 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.32 (s, 3H), 1.70 (s, 3H); ^{13}C (101 MHz, $CDCl_3$) 172.3, 169.7, 163.6, 160.9, 135.8, 135.1, 130.2 (d, J_{CF} = 8.1), 129.4, 129.3 (d, J_{CF} = 3.5 Hz), 121.6 (d, J_{CF} = 253.0 Hz), 119.5, 116.1, 116.2, 111.1, 106.9, 52.9, 52.2, 26.8, 23.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.83 (m); ESI-MS *m/z* 355 [M+H], 377 [M+Na]; ESI-HRMS *m/z* 355.1443 [M+H] (calc. for

$C_{20}H_{20}FN_2O_3$ 355.1452); IR (solid-state ATR, cm^{-1}) 3332, 2960, 1729, 1659, 1541, 1505, 1444, 1219, 848, 749; UV-Vis λ_{maxima} 306 (ε = 14684 mol dm^{-3} cm^{-1}).

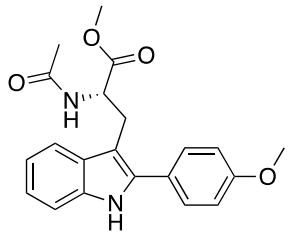
3.4 – Methyl (2S)-2-amino-3-{2-[4-(trifluoromethyl)phenyl]-1H-indol-3-yl}propanoate, ***2d***



Obtained according to the general procedure as a white solid (58% yield).

R_F 0.34 (50% EtOAc/PE); $[\alpha]_D$ = +62.0 (c 0.13, $CHCl_3$); MP 202 – 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.72 – 7.63 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 5.87 (d, *J* = 8.0 Hz, 1H), 4.84 (dt, *J* = 8.0, 5.2 Hz, 1H), 3.59 – 3.48 (m, 2H), 3.29 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 169.9, 136.9, 136.1, 134.3, 129.9 (q, *J* = 31.8 Hz), 129.5, 128.5, 126.1 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 247 Hz), 123.3, 120.4, 119.2, 111.4, 108.2, 53.0, 52.2, 27.0, 23.0; ESI-MS m/z 405 [M+H], 427 [M+Na]; ESI-HRMS m/z 405.1410 [M+H] (calc. for $C_{21}H_{20}F_3N_2O_3$ 405.1421); IR (solid-state ATR, cm^{-1}) 3288, 2925, 2860, 1730, 1651, 1505, 1438, 1285, 1245, 1215, 1027, 835, 743; UV-Vis (DMSO, nm) λ_{max} 318 (ε = 10297 mol dm^{-3} cm^{-1}).

3.5 – Methyl (2S)-2-amino-3-[2-(4-methoxyphenyl)-1H-indol-3-yl]propanoate, ***2e***



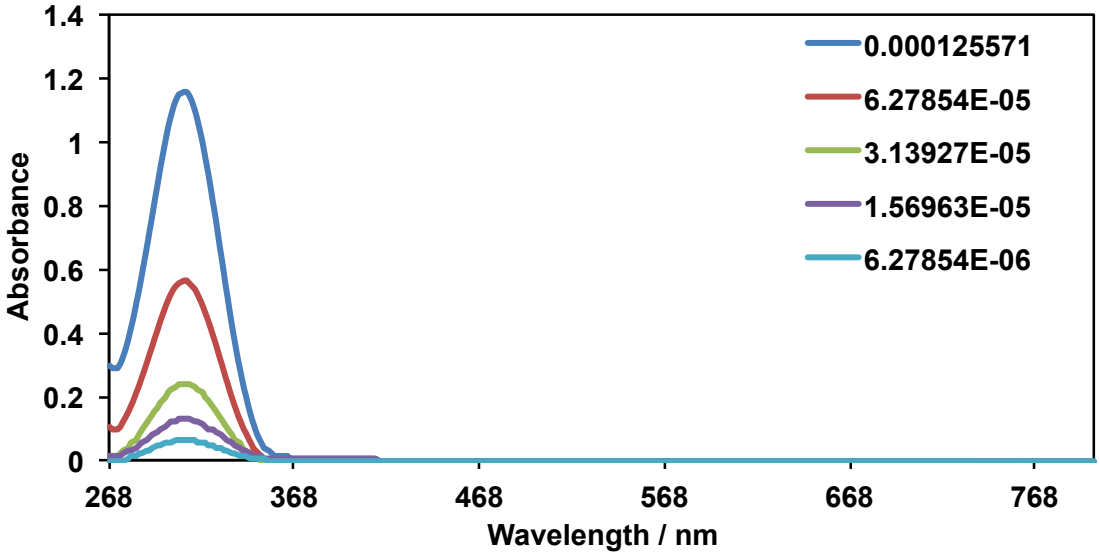
Obtained according to the general procedure as a white solid (28% yield).

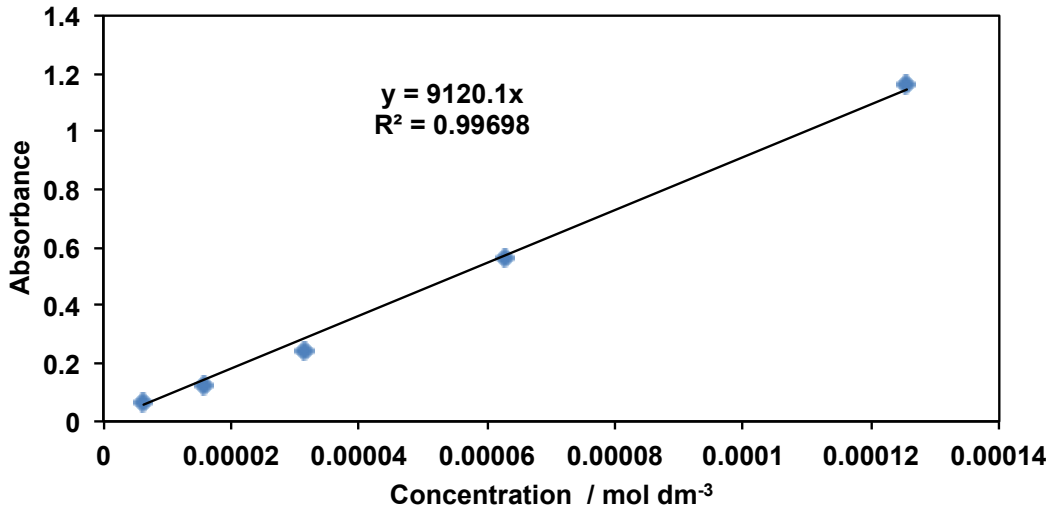
R_F 0.12 (50% EtOAc/PE); $[\alpha]_D$ = +34.9 (c 0.10, $CHCl_3$); MP 202 – 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.78 (d, J = 8.0 Hz, 1H), 4.83 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.87 (s, 3H), 3.48 (m, 2H), 3.35 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.7 159.6, 136.1, 135.6, 129.7, 129.6, 125.6, 122.4, 120.1, 118.8, 114.7, 111.0, 106.3, 55.6, 53.0, 52.2, 26.8, 23.1; ESI-MS *m/z* 367 [M+H], 389 [M+Na]; ESI-

HRMS m/z 367.1644 [M+H] (calc. for $C_{21}H_{23}N_2O_4$ 367.1652); IR (solid-state ATR, cm^{-1}) 3333, 2954, 1728, 1656, 1505, 1458, 1439, 1246, 1216, 1177, 1027, 836, 747; UV-Vis (DMSO, nm) λ_{max} 320 (ε = 11644 mol dm^{-3} cm^{-1}).

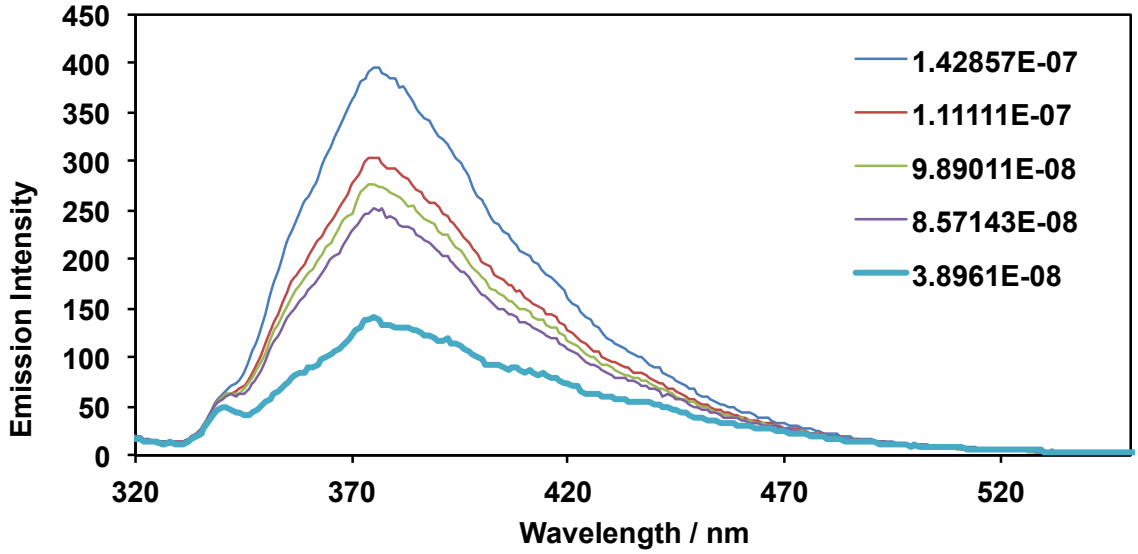
4 – UV-Visible and Fluorescence Data for Analogues

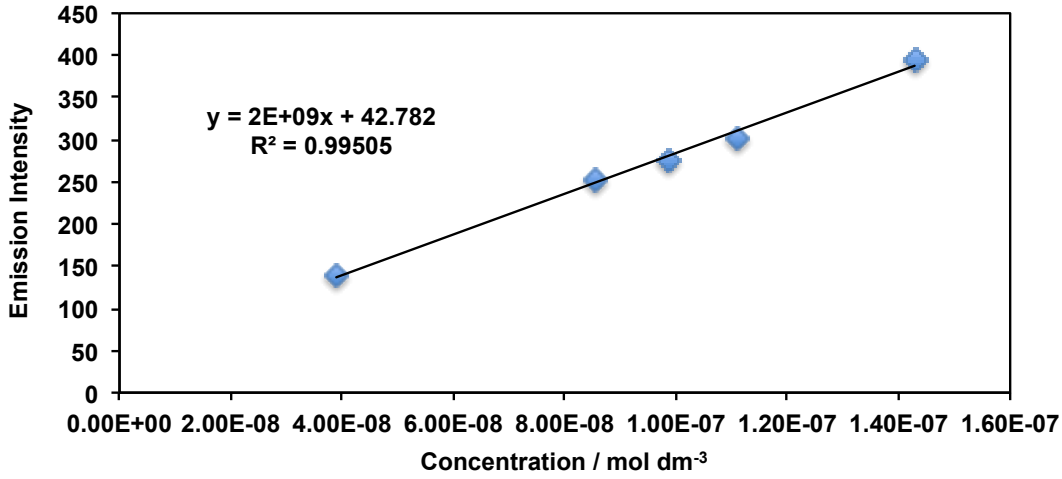
4.1 – UV-Visible spectroscopic analysis of compound **2a** (the concentration range is shown in the figure key, in mol dm^{-3}).



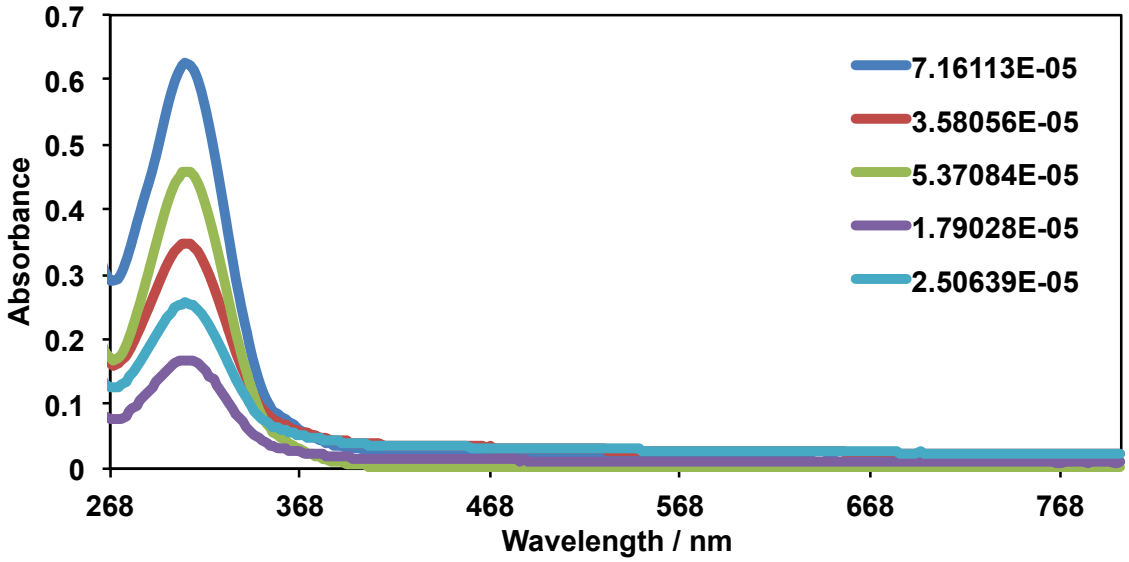


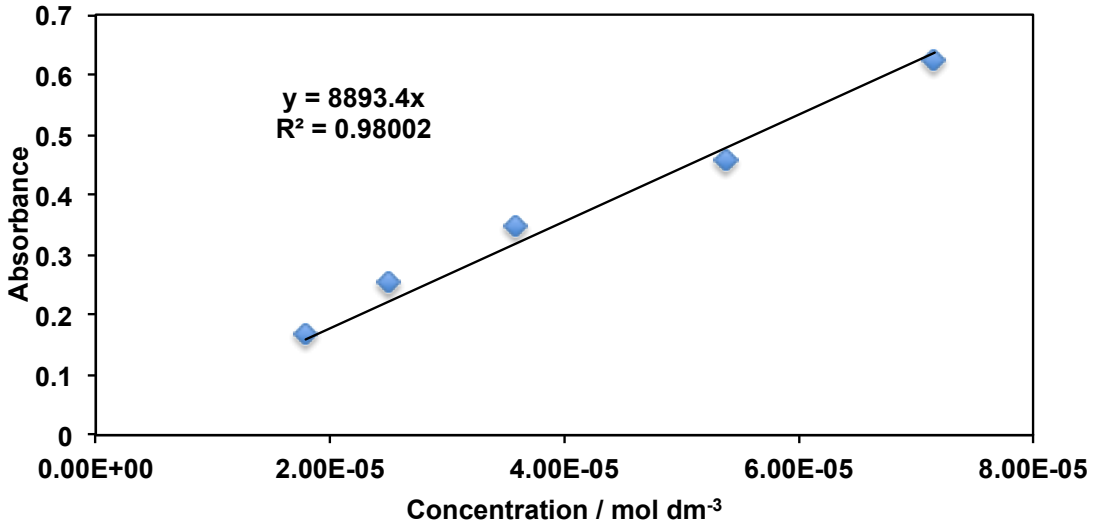
4.2 – Fluorescence spectroscopic analysis of compound **2a** (the concentration range is shown in the figure key, in mol dm^{-3}).



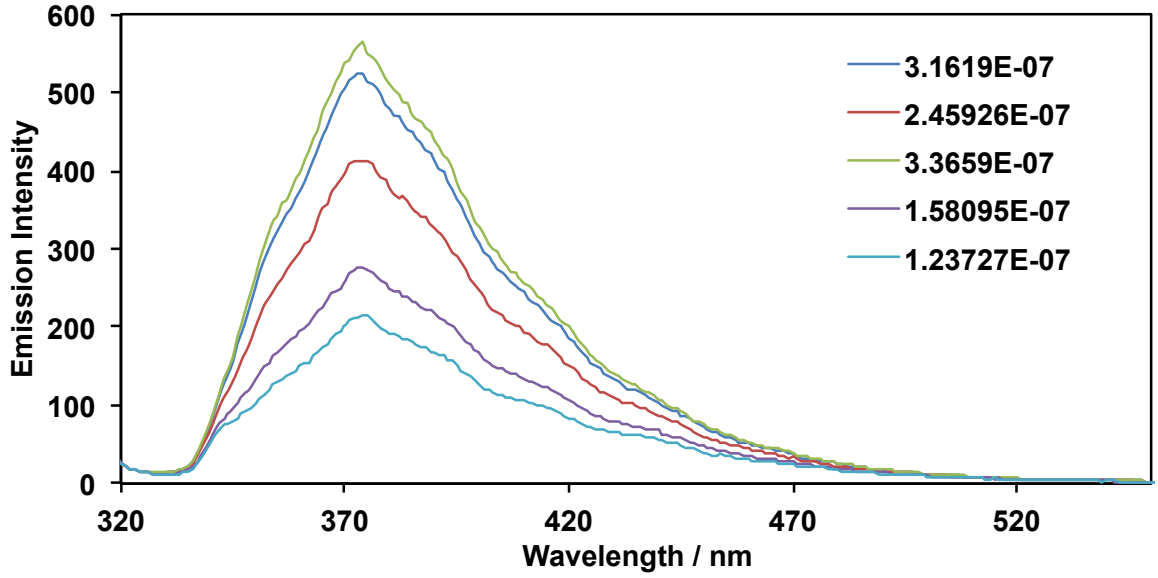


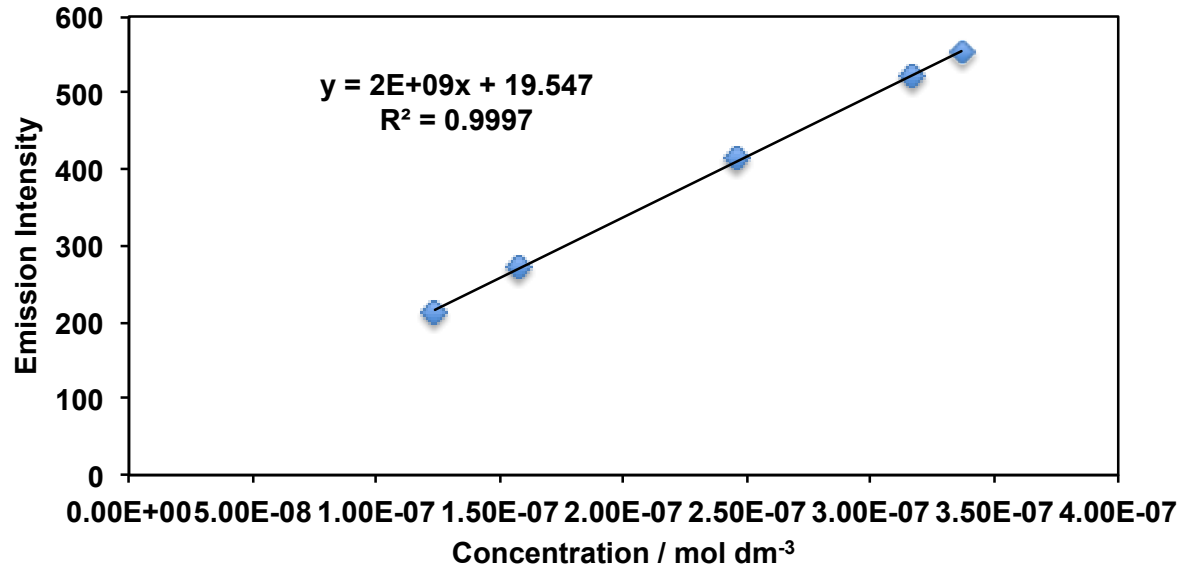
4.3 – UV-Visible spectroscopic analysis of compound **2b** (the concentration range is shown in the figure key, in mol dm^{-3}).



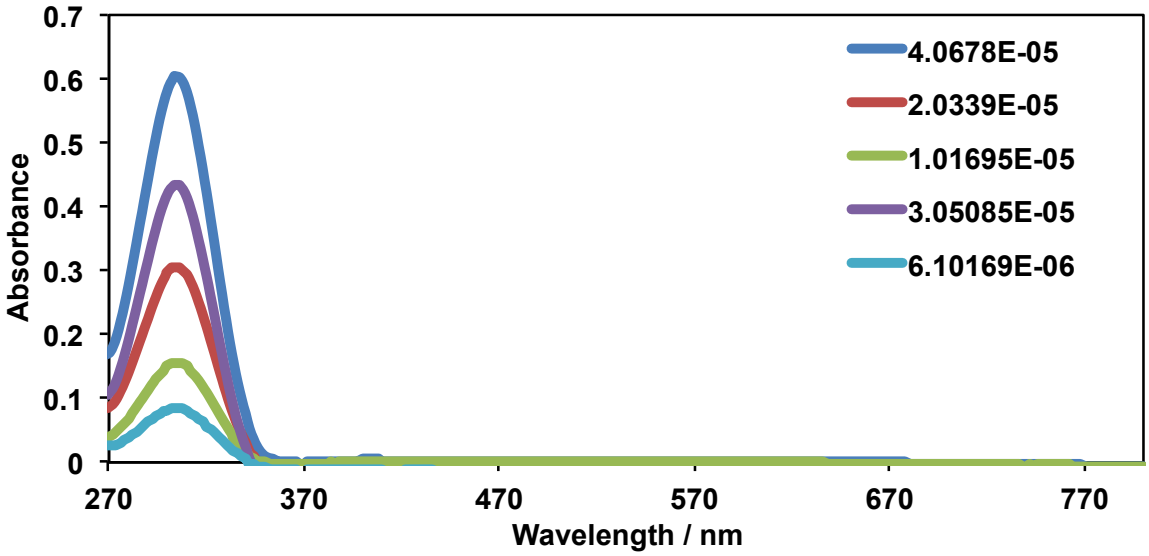


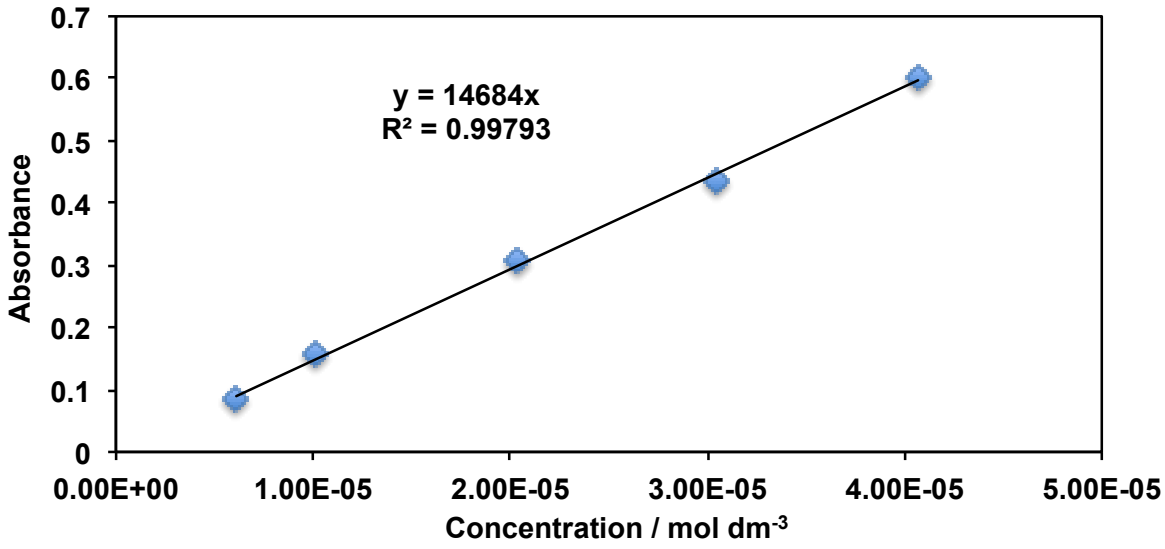
4.4 – Fluorescence spectroscopic analysis of compound **2b** (the concentration range is shown in the figure key, in mol dm^{-3}).



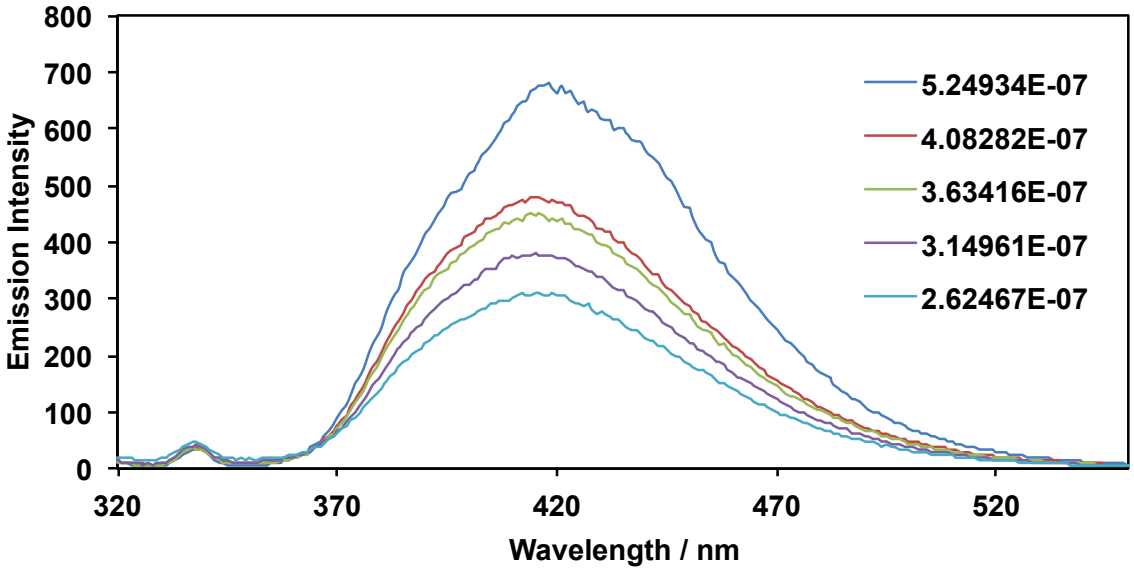


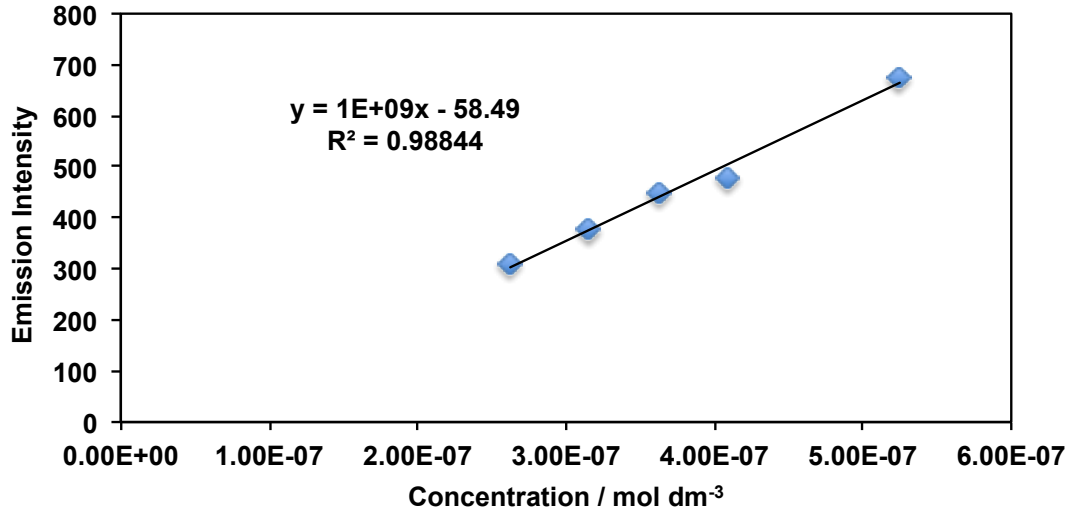
4.5 – UV-Visible spectroscopic analysis of compound **2c** (the concentration range is shown in the figure key, in mol dm^{-3}).



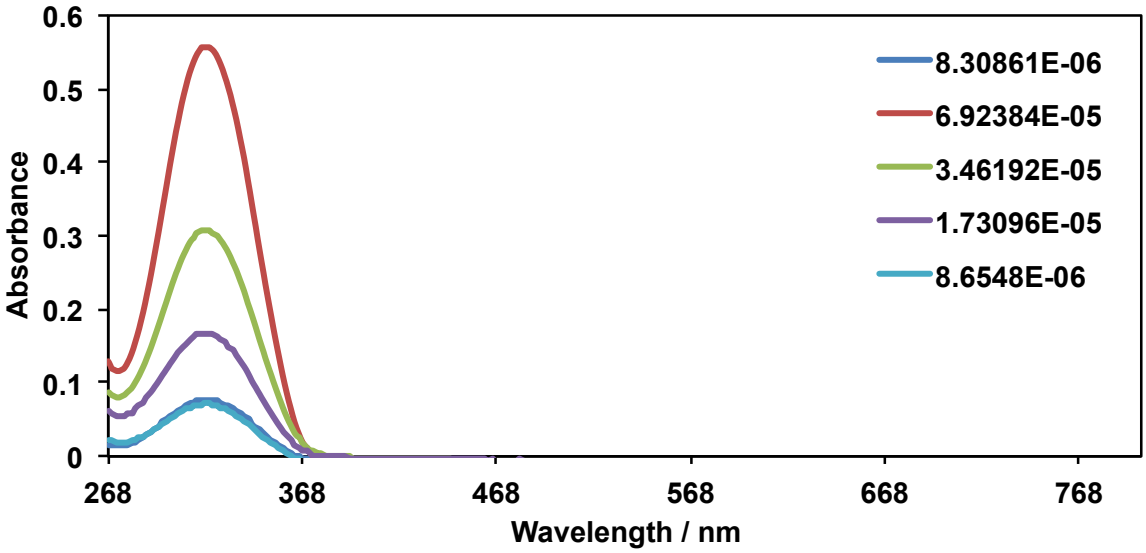


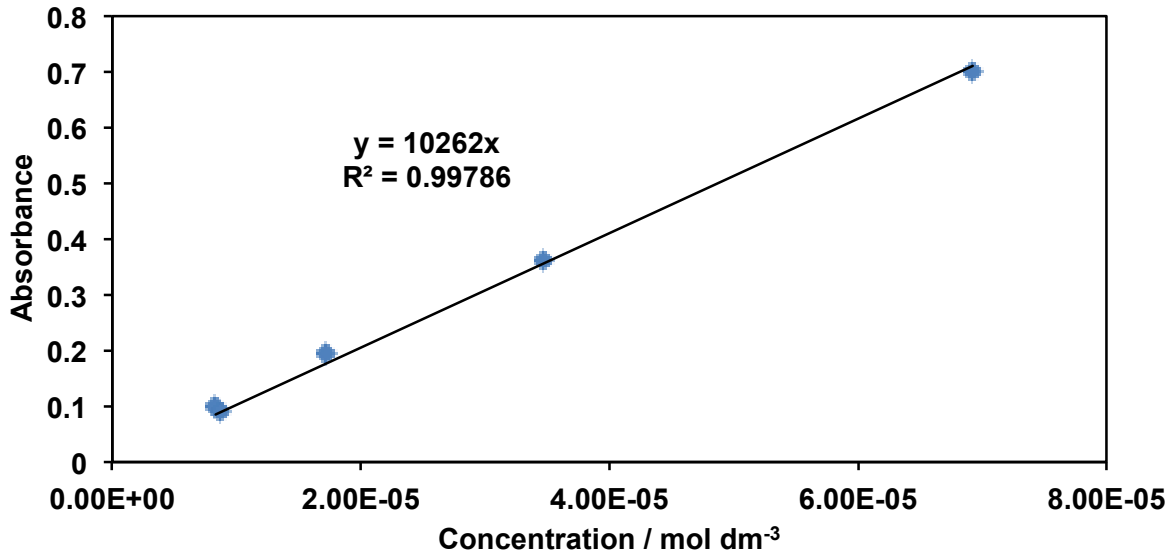
4.6 – Fluorescence spectroscopic analysis of compound **2c** (the concentration range is shown in the figure key, in mol dm^{-3}).



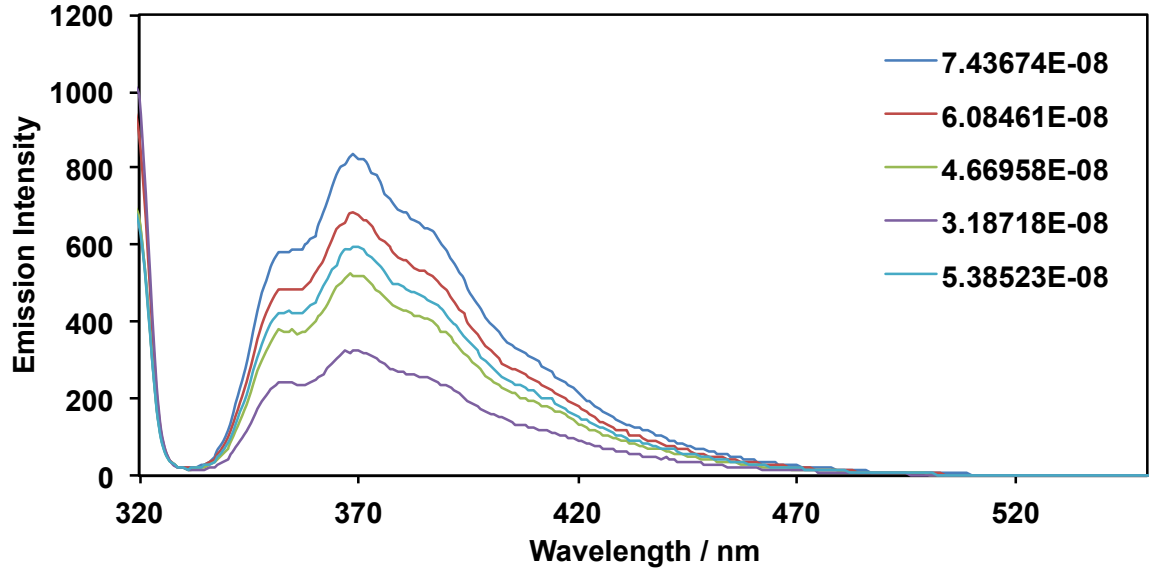


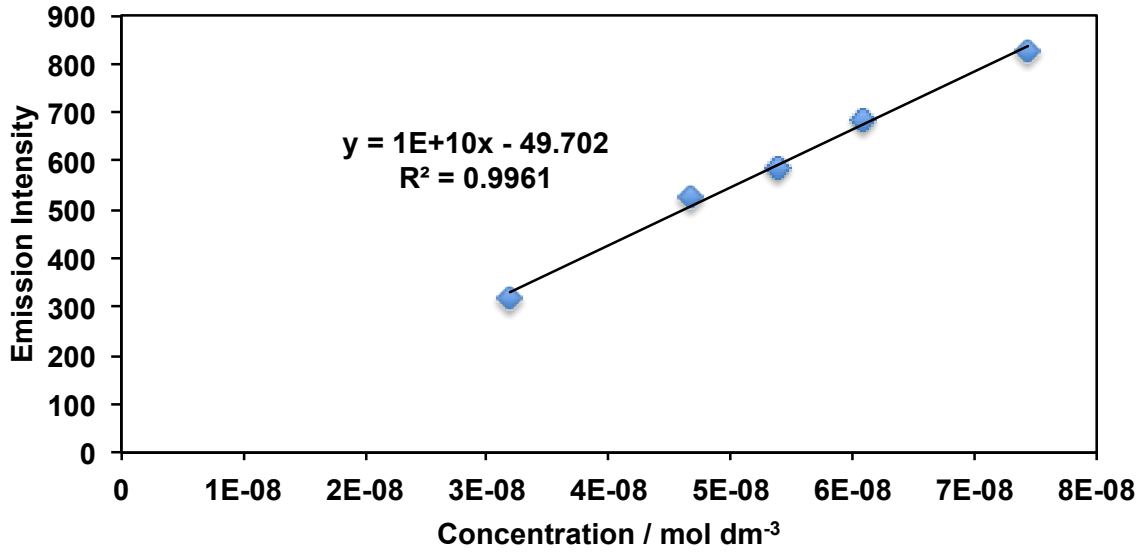
4.7 – UV-Visible spectroscopic analysis of compound **2d** (the concentration range is shown in the figure key, in mol dm^{-3}).



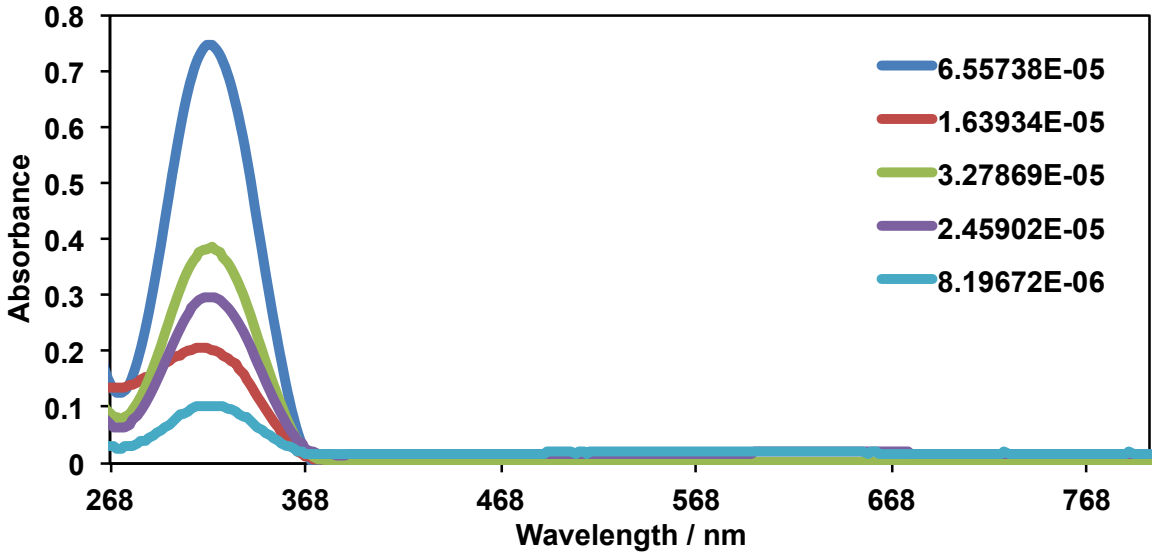


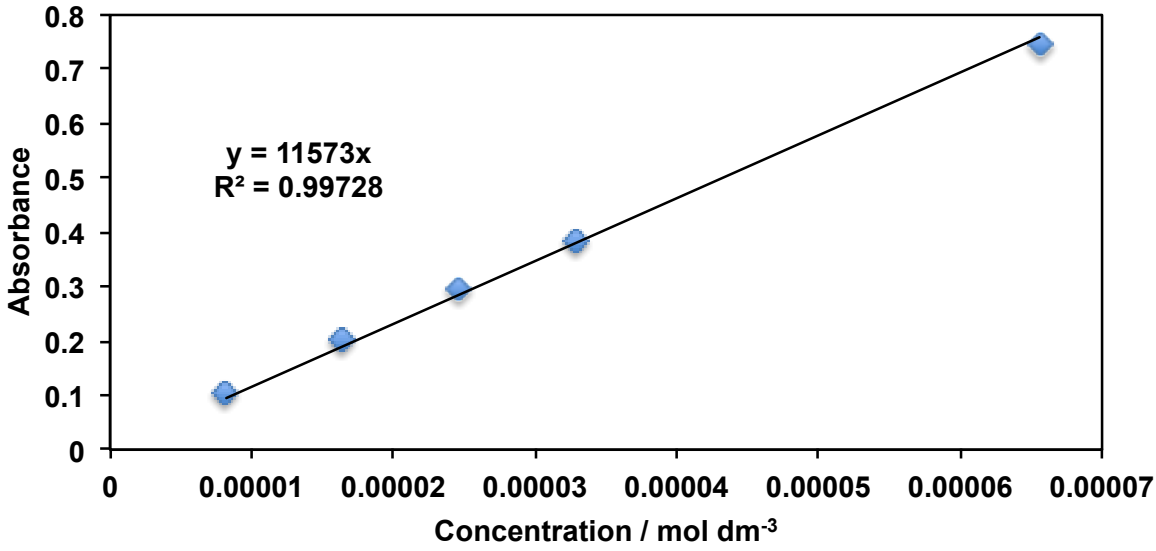
4.8 – Fluorescence spectroscopic analysis of compound **2d** (the concentration range is shown in the figure key, in mol dm^{-3}).



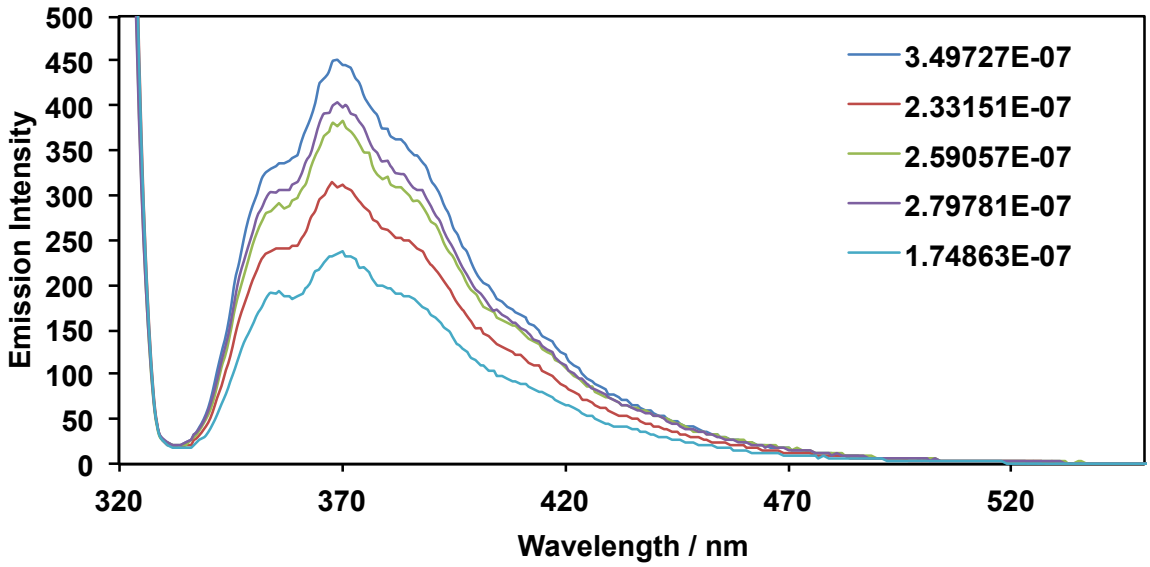


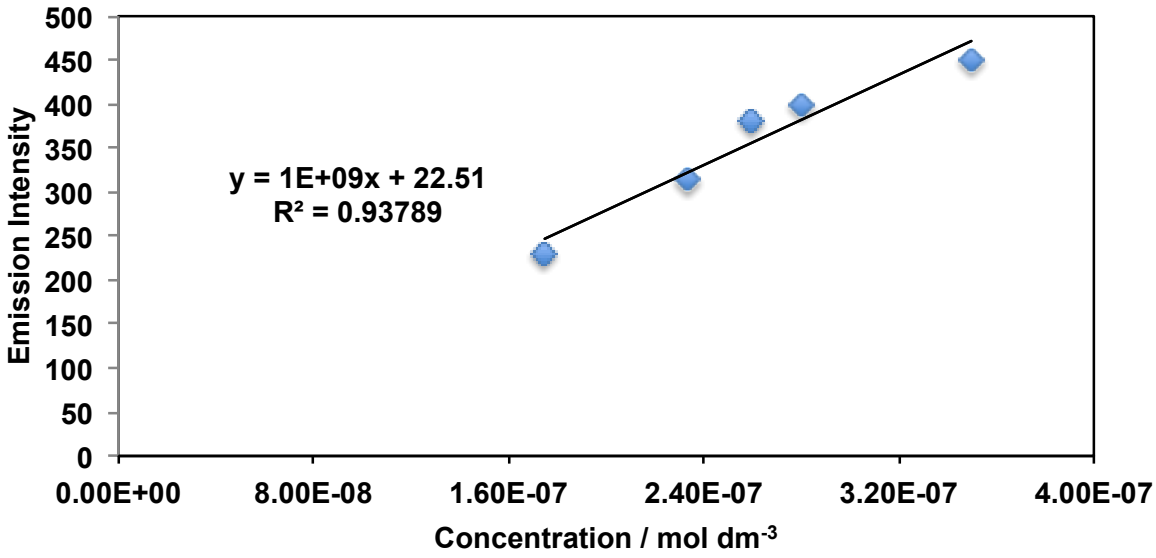
4.9 – UV-Visible spectroscopic analysis of compound **2e** (the concentration range is shown in the figure key, in mol dm^{-3}).





4.10 – Fluorescence spectroscopic analysis of compound **2e** (the concentration range is shown in the figure key, in mol dm^{-3}).





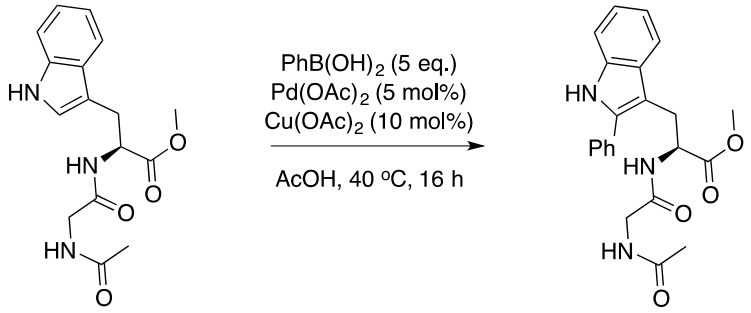
5 – Peptide C-H Bond Functionalisations

5.1 – General Procedure

All peptides were functionalised using a general experimental procedure:

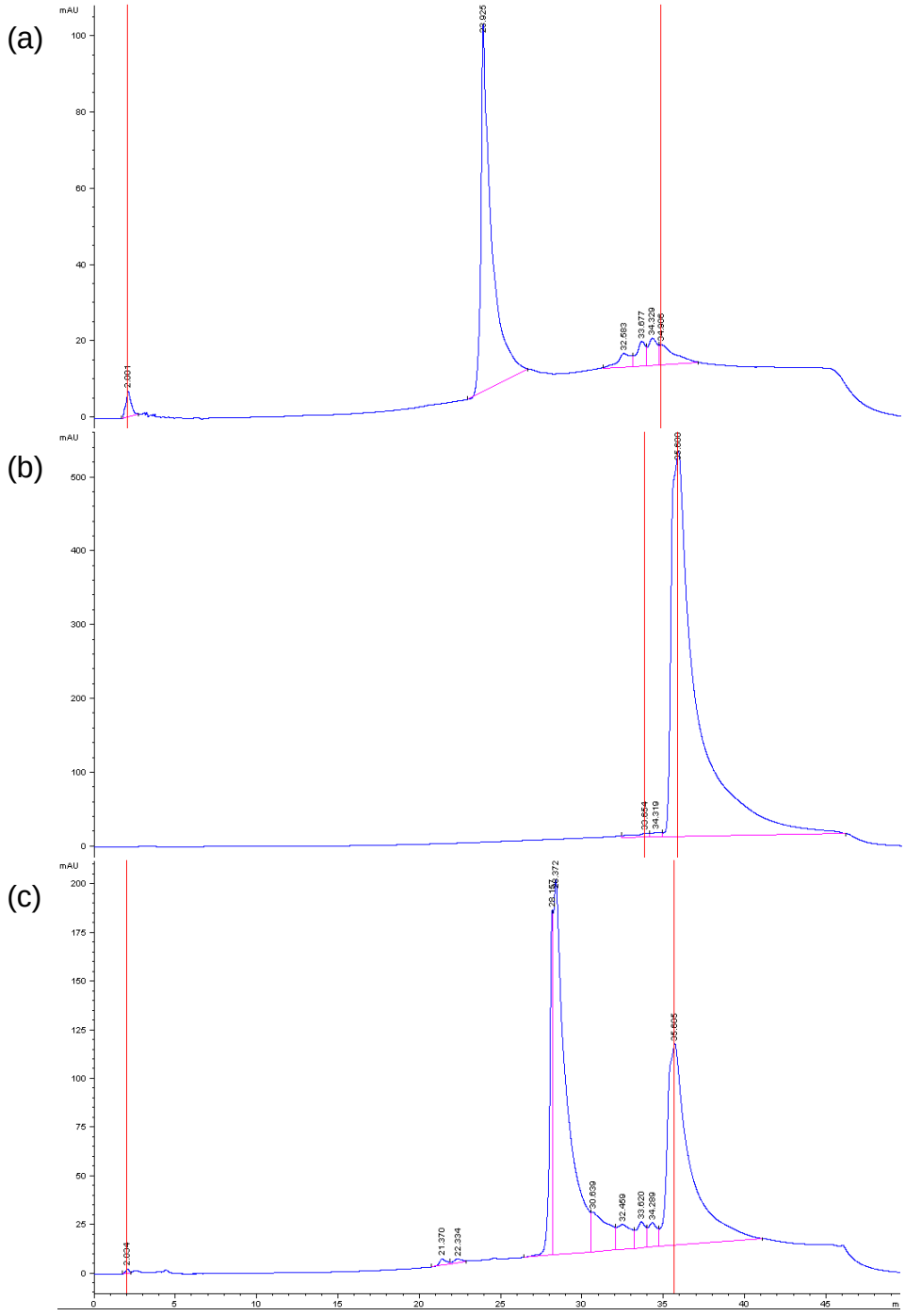
Peptide (10 mg), $PhB(OH)_2$ (5 eq.), $Pd(OAc)_2$ (30 mol%) and $Cu(OAc)_2$ (60 mol%) were dissolved in AcOH (0.5 mL) at 40 °C. The reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure (at a temperature that did not exceed 40 °C) to give a brown residue. This was analysed by HPLC-ESI-MS.

5.2 – Arylated product of NAcGlyTrpOMe, **4**



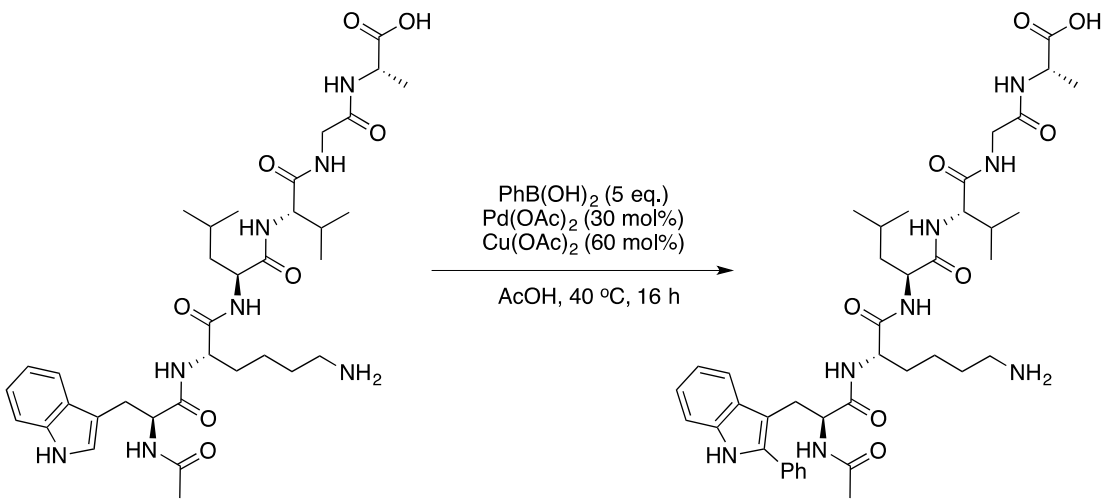
This was dissolved in EtOAc (10 mL) and washed with sat. aq. $NaHCO_3$. The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a brown solid. This was dry-loaded onto silica gel and purified by flash chromatography eluting with ethyl acetate:methanol; (98:1, *v/v*) to give the product as a solid after trituration with Et_2O.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.61 – 7.50 (m, 3H), 7.50 – 7.41 (m, 2H), 7.39 – 7.33 (m, 2H), 7.19 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 7.15 (s, ddd, *J* = 8.2, 7.2, 1.4, 1H), 6.18 (br d, *J* = 7.8 Hz, 1H), 5.95 (br t, *J* = 5.1 Hz, 1H), 4.80 (dt, *J* = 8.0, 5.6 Hz, 1H), 3.66 – 3.38 (m, 4H), 3.34 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.3, 168.3, 136.2, 135.9, 133.2, 129.4, 129.3, 128.4, 128.2, 122.8, 120.2, 118.8, 111.3, 106.5, 77.4, 53.1, 52.3, 42.7, 26.6, 23.0; ESI-MS *m/z* 394 [M+H], 416 [M+Na]; ESI-HRMS *m/z* 394.1763 [M+H] (calc. for $C_{22}H_{24}N_3O_4$ 394.1761).

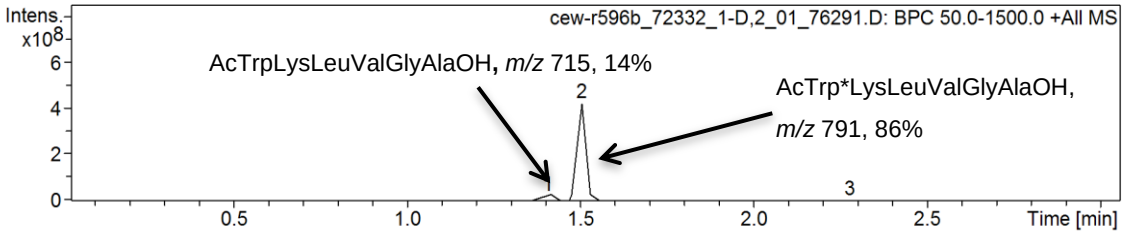


Stacked HPLC chromatographs for the C-H bond functionalisation of dipeptide **3**; (a) dipeptide **3**, (b) biphenyl (Sigma-Aldrich ®), (c) reaction mixture of the C-H bond functionalisation reaction, showing **4** and biphenyl (oxidative coupling side-product).

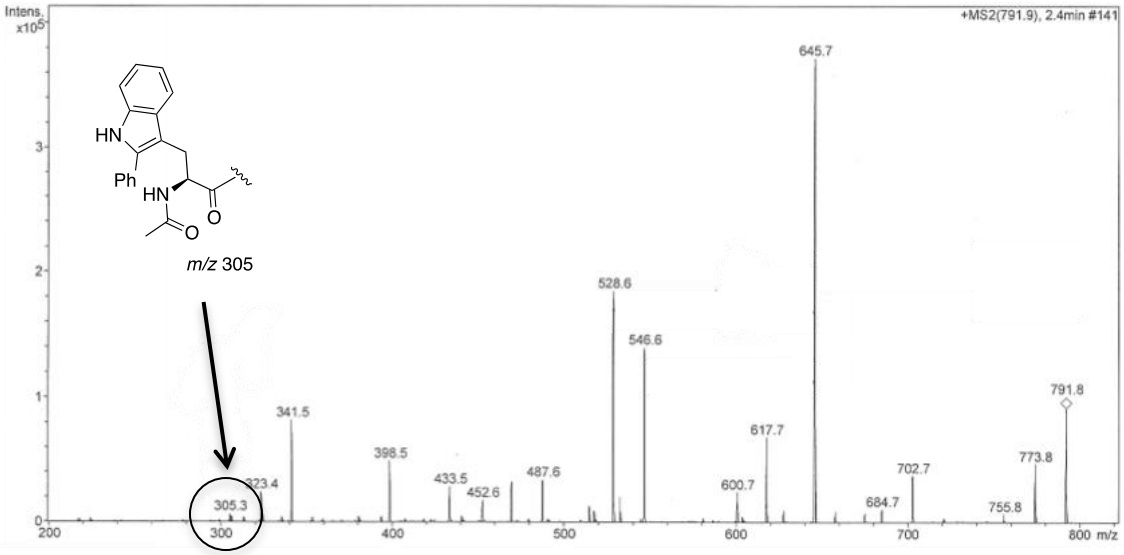
5.3 – Arylated product of AcTrpLysLeuValGlyAlaOH, **6**



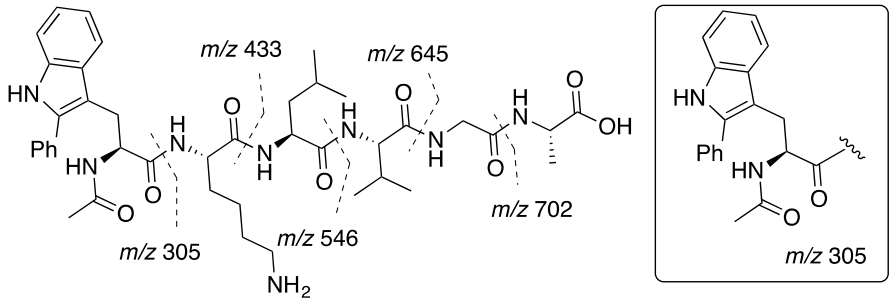
HPLC-MS chromatogram (BPC) of the crude reaction material (arylated tryptophan denoted Trp*).



ESI-MS-MS



Proposed fragmentation pattern by ESI-MS/MS

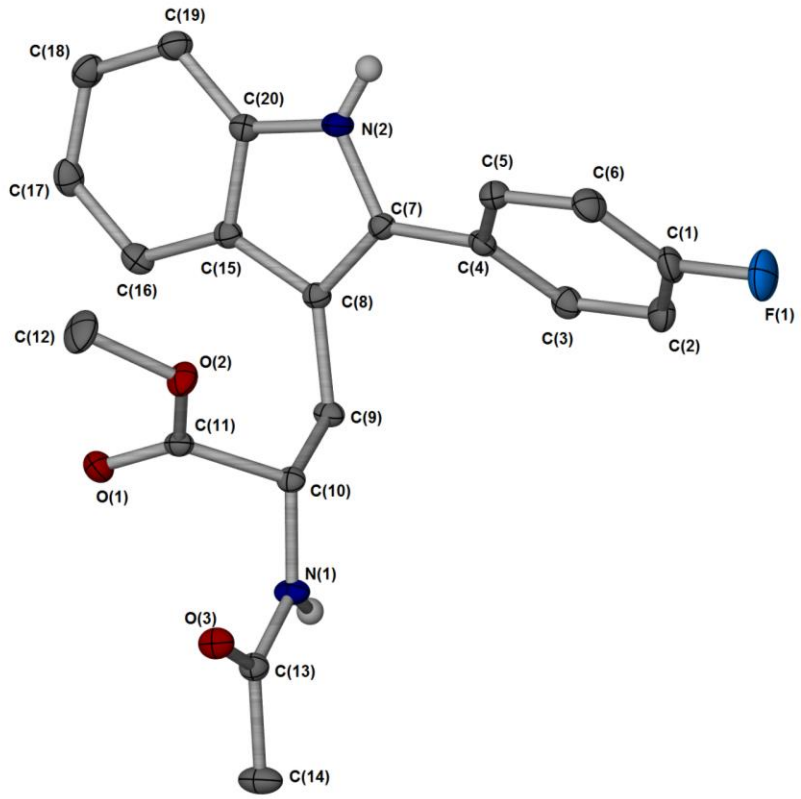


6 – X-Ray Crystallography

Diffraction data were collected at 110 K on an Oxford Diffraction SuperNova diffractometer with Mo-K_α radiation (λ = 0.71073 Å) using a EOS CCD camera. The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement was carried out with "Crysalis".[5] Face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. OLEX2[6] was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithms used for structure solution were direct methods.[7] Refinement by full-matrix least-squares used the SHELXL-97 algorithm within OLEX2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a "riding model" and included in the refinement at calculated positions.

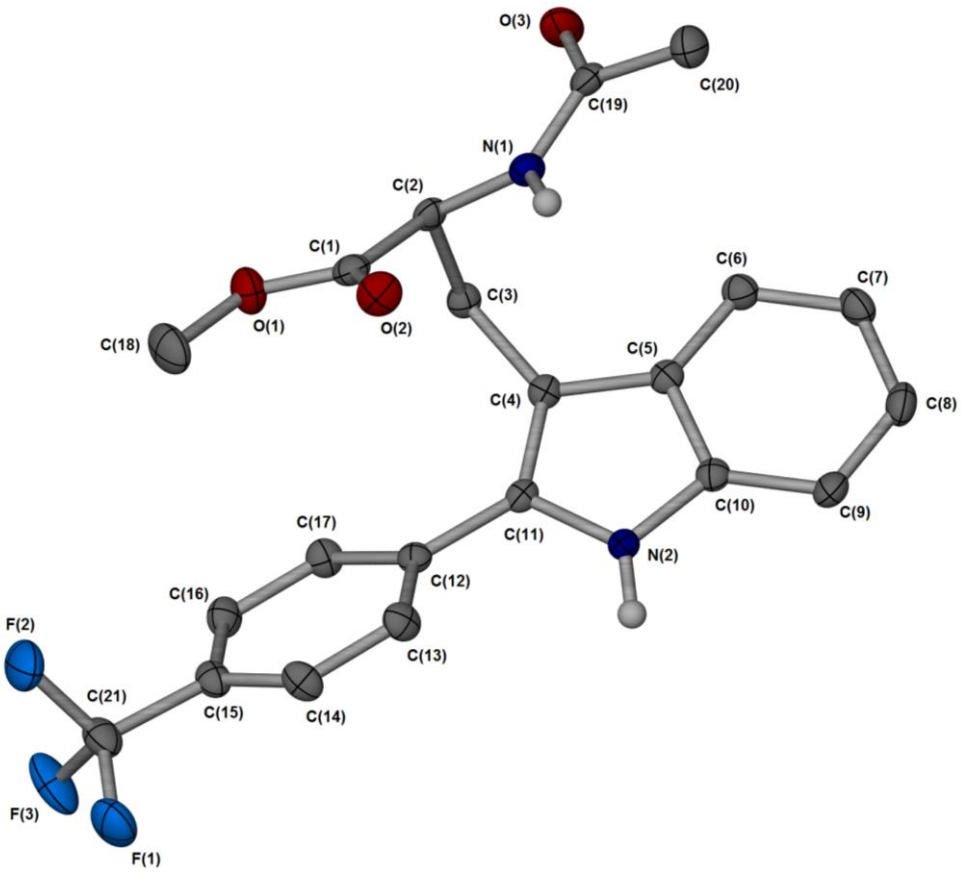
Hydrogen atoms have been omitted for clarity. Crystals were grown by slow evaporation of $CDCl_3$ in a NMR tube.

6.1 – Methyl (2*S*)-2-amino-3-[2-(4-fluorophenyl)-1*H*-indol-3-yl]propanoate **2c**



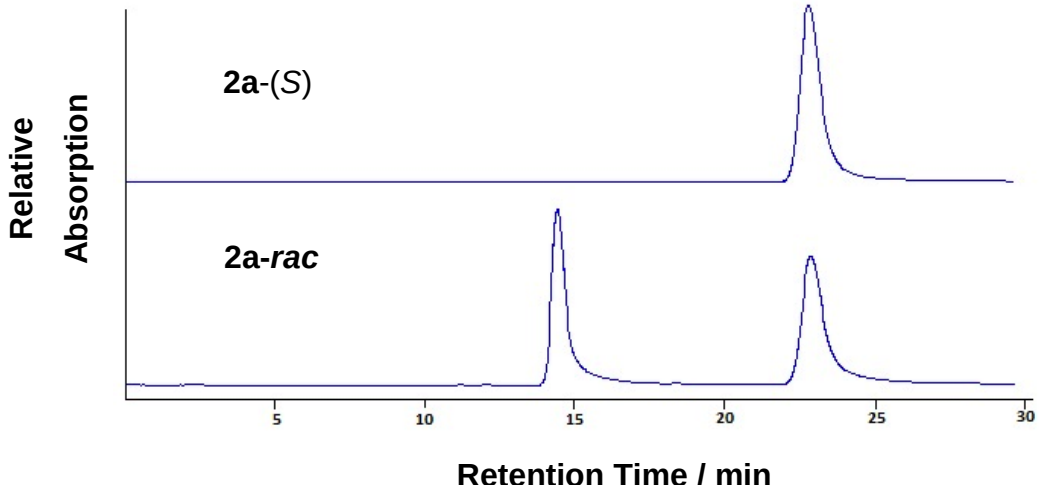
Compound reference	ijsf1202
CCDC reference number	CCDC 968491
Chemical formula	$C_{20}H_{19}F_1N_2O_3$
Formula mass	345.37
Crystal system	Trigonal
a/Å	21.0404(11)
b/Å	21.0404(11)
c/Å	10.4652(7)
α/Å	90.00
β/Å	90.00
γ/Å	120.00
Unit cell volume/Å^3	4012.2(6)
Temperature/K	110.00(10)
Space group	R3
No. of formula units per unit cell, Z	9
No. of reflections measured	9531
No. of independent reflections	5613
R_{int}	0.0271
Final R_1 values (I >2σ(I))	0.0424
Final wR(F^2) values (I >2σ(I))	0.0946
Final R_1 values (all data)	0.0479
Final wR(F^2) values (all data)	0.0995

6.2 – Methyl (2*S*)-2-amino-3-{2-[4-(trifluoromethyl)phenyl]-1*H*-indol-3-yl}propanoate, **2d**



Compound reference	ijsf1201
CCDC reference number	CCDC 968490
Chemical formula	$C_{21}H_{19}F_3N_2O_3$
Formula mass	404.38
Crystal system	Monoclinic
a/Å	8.7492(3)
b/Å	9.0043(3)
c/Å	24.1842(7)
α/Å	90.00
β/Å	98.900(3)
γ/Å	90.00
Unit cell volume/Å^3	1882.30(10)
Temperature/K	110.00(10)
Space group	$P2_1$
No. of formula units per unit cell, Z	4
No. of reflections measured	14377
No. of independent reflections	8188
R_{int}	0.0306
Final R_1 values (I >2σ(I))	0.0480
Final wR(F^2) values (I >2σ(I))	0.1077
Final R_1 values (all data)	0.0572
Final wR(F^2) values (all data)	0.1135

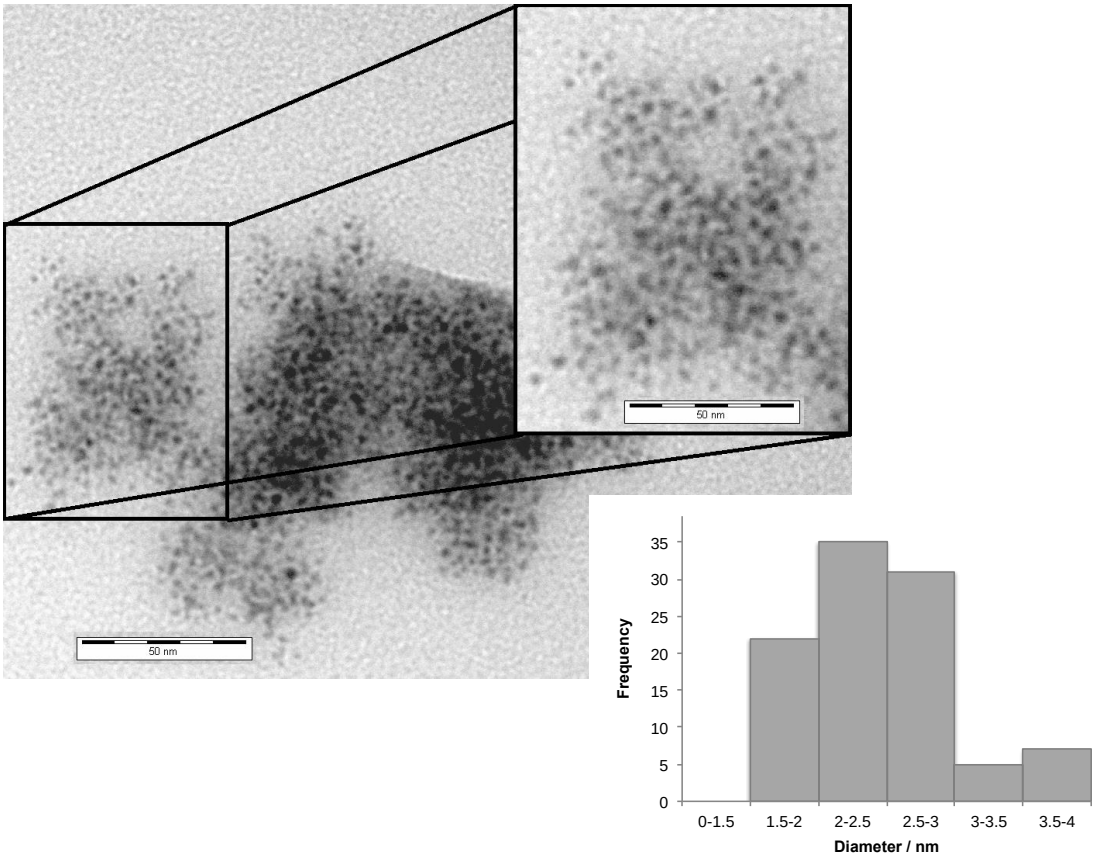
7 – Chiral HPLC trace for compound 2a



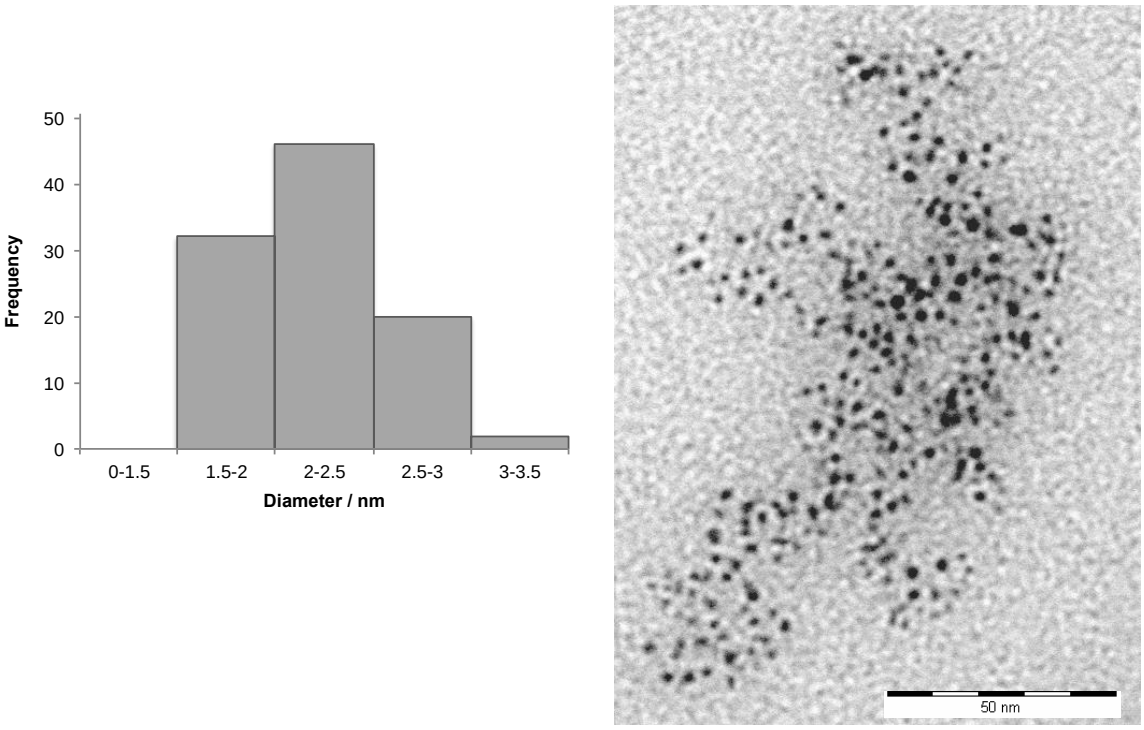
8 – TEM analysis of Pd nanoparticles

To a microwave tube was added phenylboronic acid (47 mg, 0.384 mmol, 2 eq.), methyl (2*S*)-2-acetylamino-3-(1*H*-indol-3-yl)propioniate (50 mg, 0.192 mmol, 1 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 μmol, 5 mol%) and acetic acid (5 mL). The reaction mixture was stirred at 40 °C for 2 h. Two aliquots (1 ml) were removed *via* syringe from the reaction mixture. To one aliquot, PVP (10.6 mg, 10 eq. per theoretical amount of Pd) was added. The solvent of both aliquots was removed under reduced pressure. Each sample was suspended in EtOH, applied to a TEM slide, and the solvent evaporated. They were then analyzed by transmission electron microscopy. Representative images are shown in Figures 5 and 6. The images were enlarged, and particle sizes measured manually. Statistical analyses performed and histograms drawn using Microsoft Excel:mac 2010 with AnalystSoft StatPlus:mac LE.2009 (build 5.8.0.0).

TEM image of Pd^0 nanoparticles isolated from the direct C-H bond functionalisation of tryptophan using $PhI(OAc)_2$/$PhB(OH)_2$, trapped with PVP (inset: histogram showing the distribution of particles by size):



TEM image of Pd^0 nanoparticles isolated from the direct C-H bond functionalisation of tryptophan using $PhI(OAc)_2/PhB(OH)_2$, without PVP (inset: histogram showing the distribution of particles by size).



Simple statistical analyses of the Pd nanoparticles isolated from the direct C-H bond functionalisation of tryptophan using $PhI(OAc)_2/PhB(OH)_2$ (SD = standard deviation, IQR = interquartile range, IQM = interquantile mean).

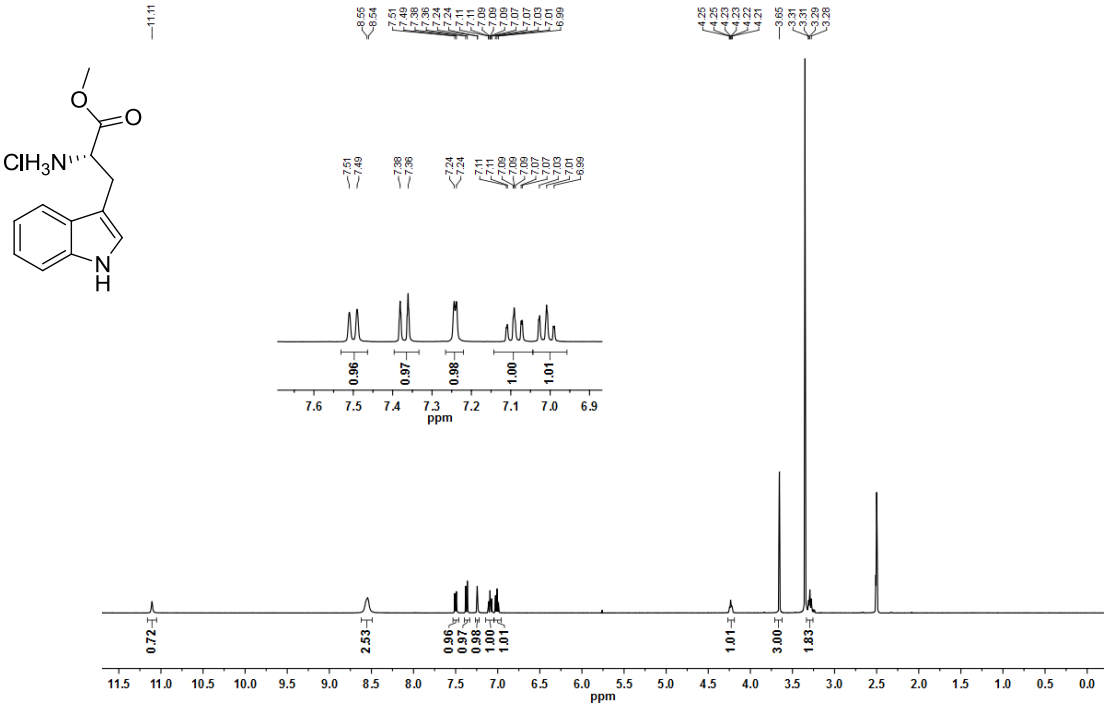
	Mean	**SD**	**Median**	**Mode**	**IQR**	**IQM**
With PVP	2.52	0.52	2.20	2.40	0.680	2.46
Without PVP	2.22	0.32	3.05	2.17	0.435	2.20

9 – ReactIR® - in situ infrared-spectroscopic studies

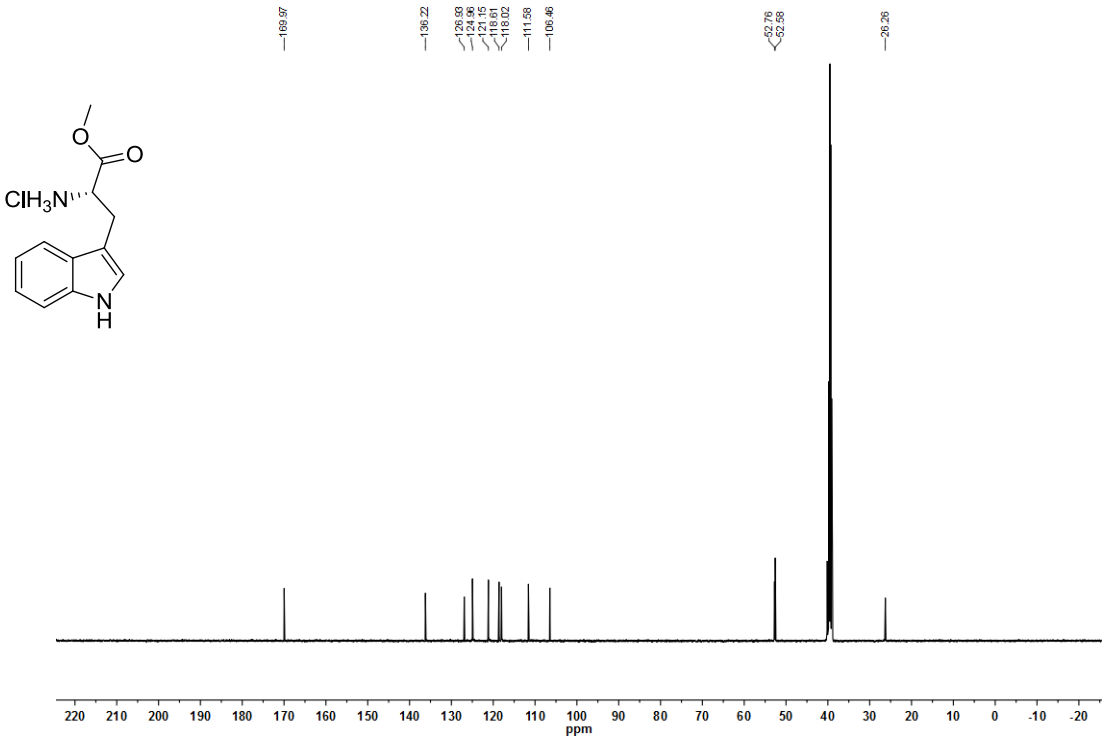
To a three-necked round-bottomed flask with a nitrogen inlet and ReactIR® probe (see general information) was added THF (3 ml). The reaction was monitored by IR at 1616 and 1606 cm^{-1}. This this was added **1** (45 mg, 0.173 mmol, 1 eq.). Once this was fully dissolved, $Pd(OAc)_2$ (39 mg, 0.173 mmol, 1 eq.) was added. The reaction was them monitored for 1.5 h.

10 – NMR Spectra[a]

10.1 – Methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propionate hydrochloride



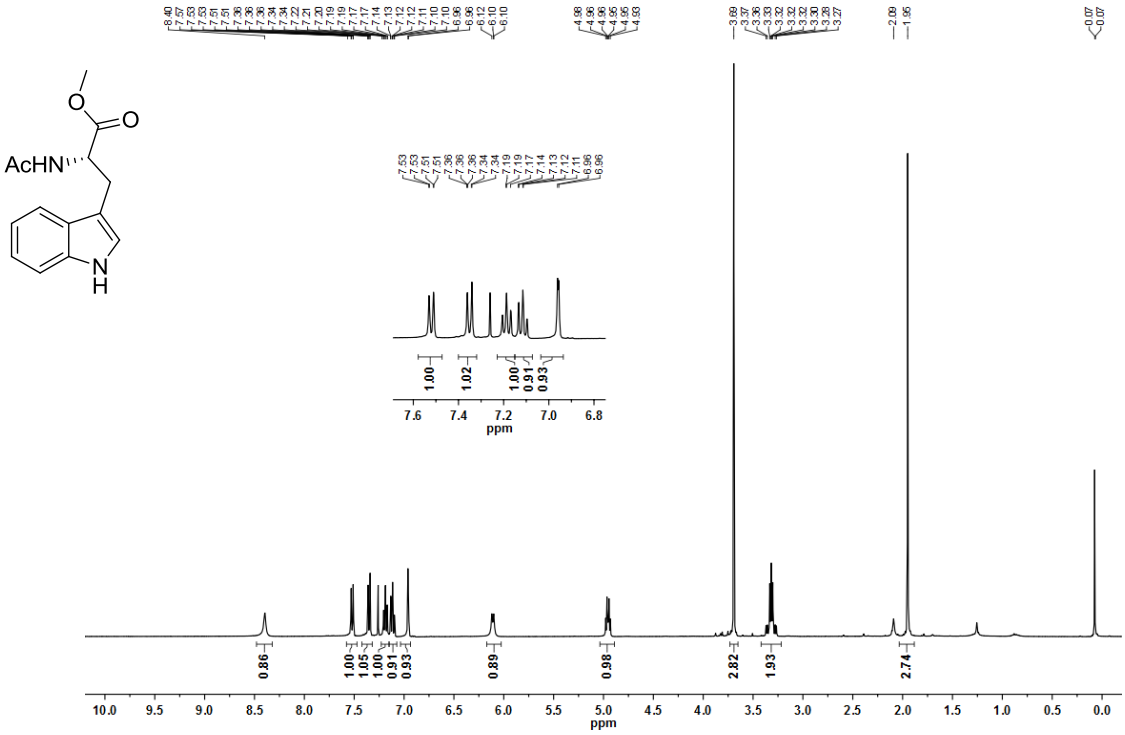
^{1}H NMR spectrum (400 MHz, CD_3OD).



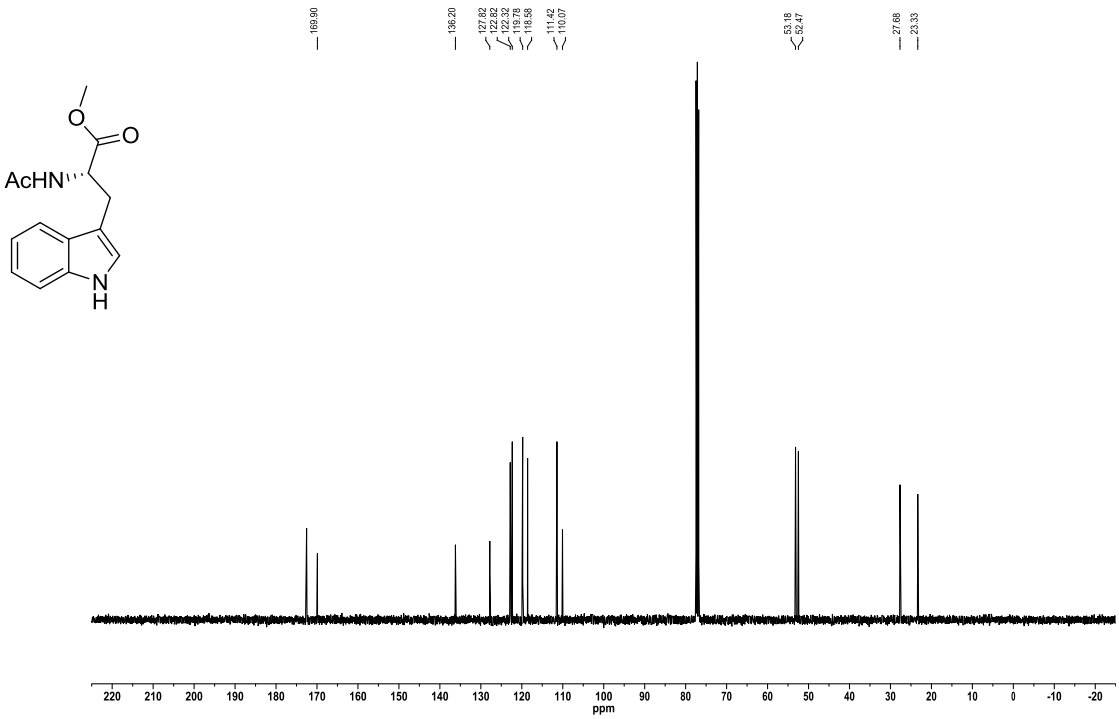
^{13}C NMR spectrum (101 MHz, CD_3OD).

[a] Note: traces of ethyl acetate and grease are visible in some NMR spectra.

10.2 – Methyl (2*S*)-2-acetylamino-3-(1*H*-indol-3-yl)propionate, **1**

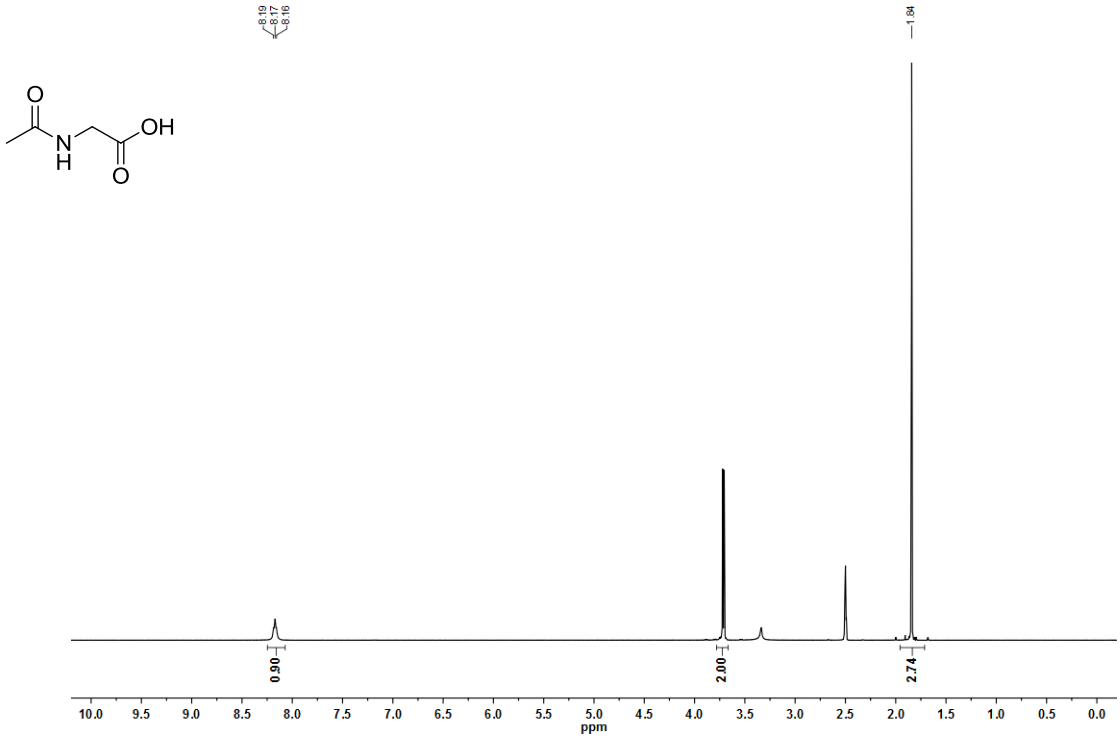


^{1}H NMR spectrum (400 MHz, $CDCl_3$).

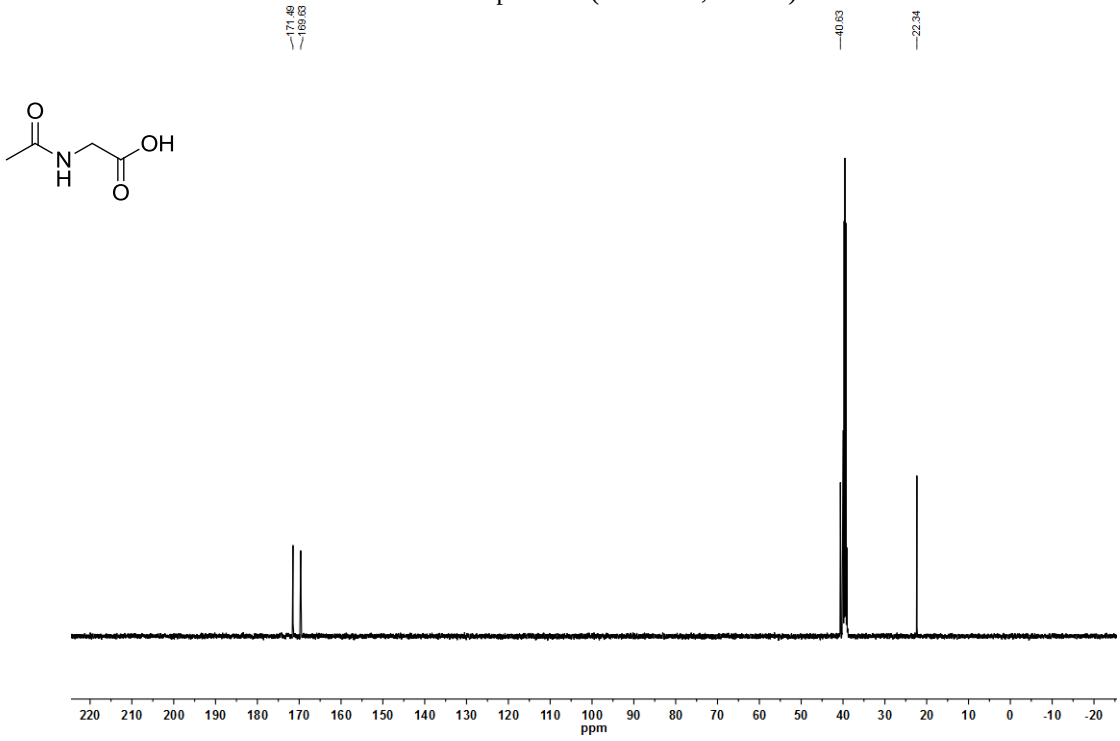


^{13}C NMR spectrum (101 MHz, $CDCl_3$)

10.3 – *N*-Acetylglycine

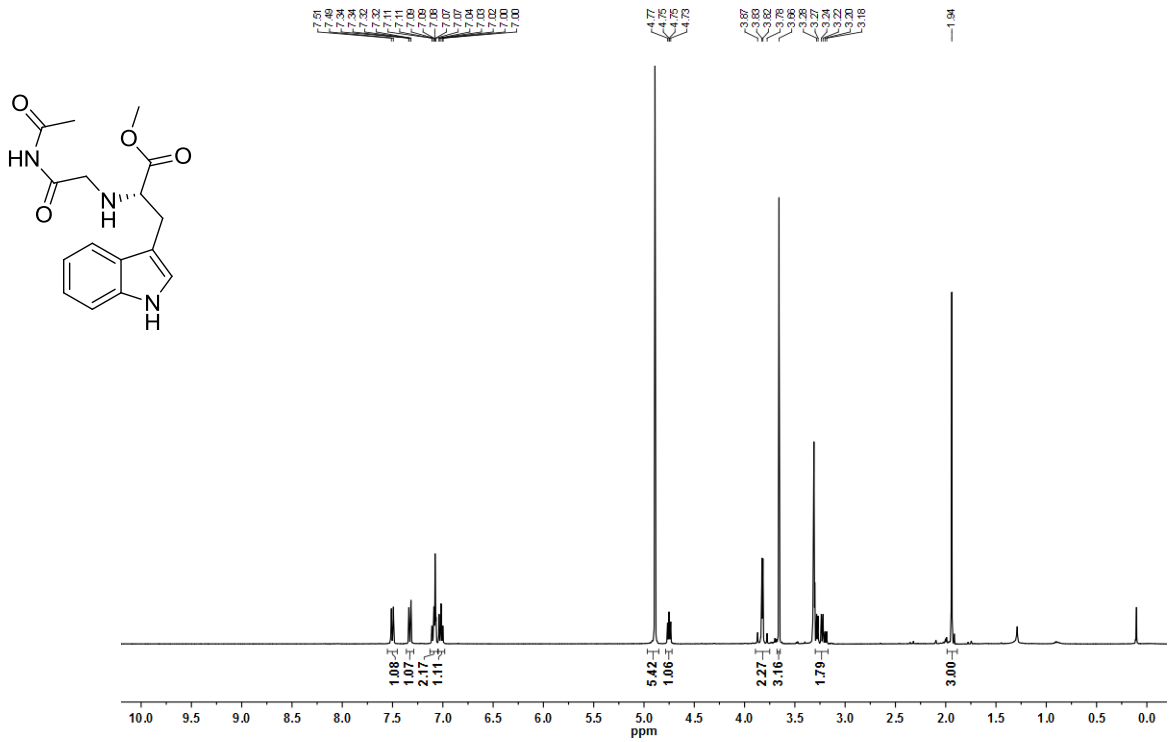


^{1}H NMR spectrum (400 MHz, MeOD).

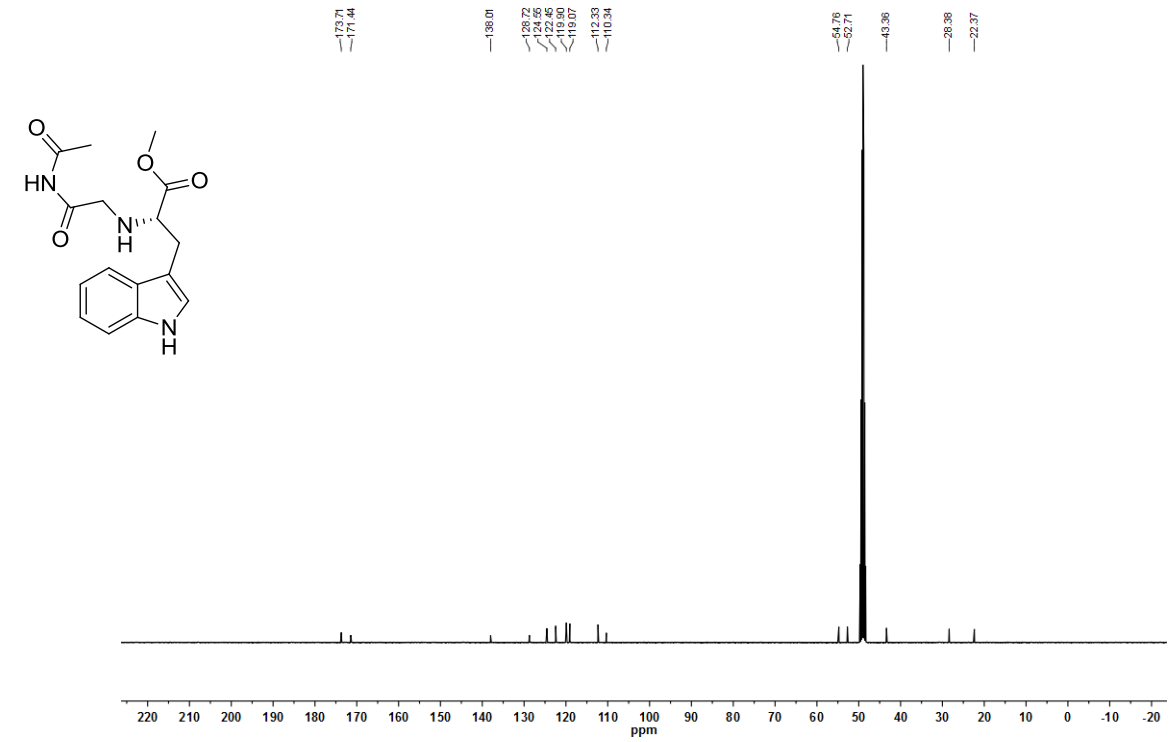


^{13}C NMR spectrum (101 MHz, MeOD).

10.4 – AcNGlyTrpOMe, **3**

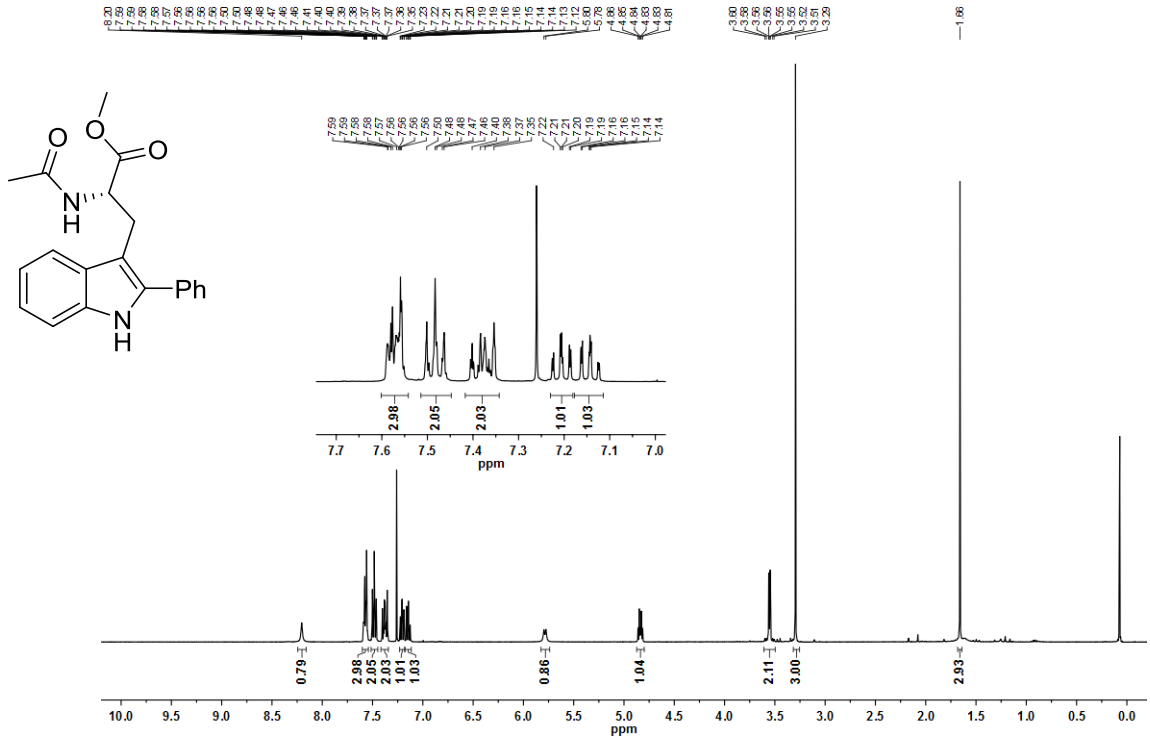


^{1}H NMR spectrum (400 MHz, CD_3OD).

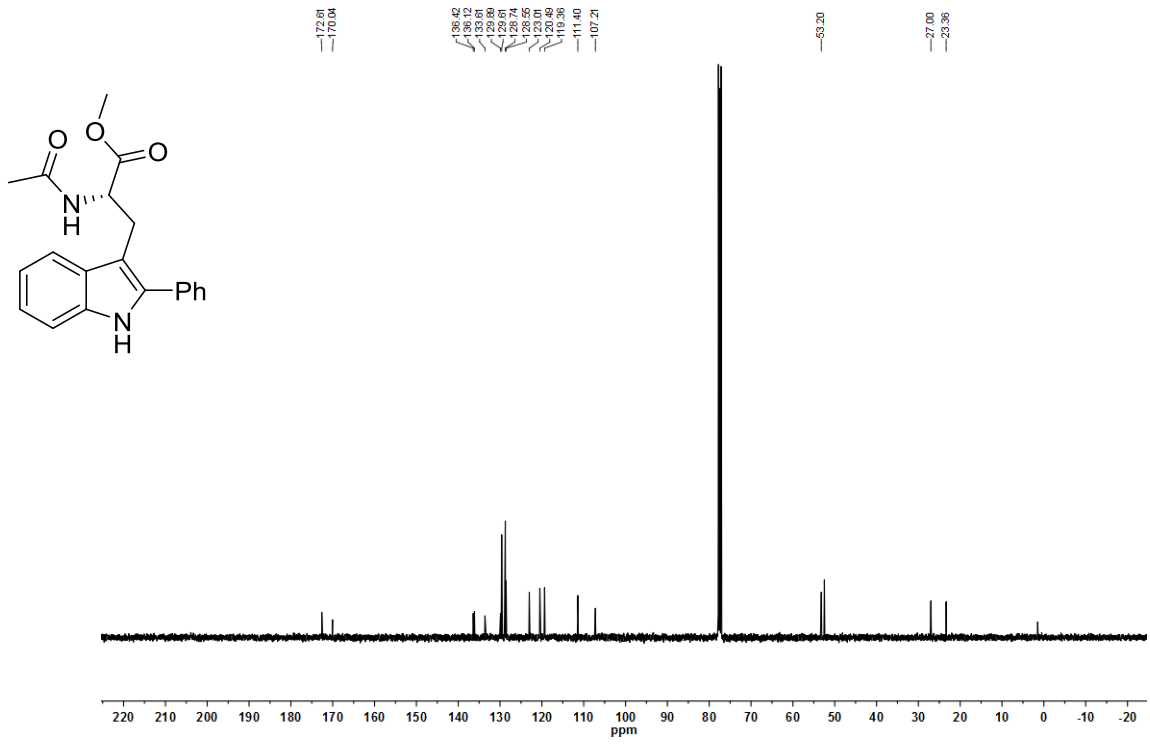


^{13}C NMR spectrum (101 MHz, CD_3OD).

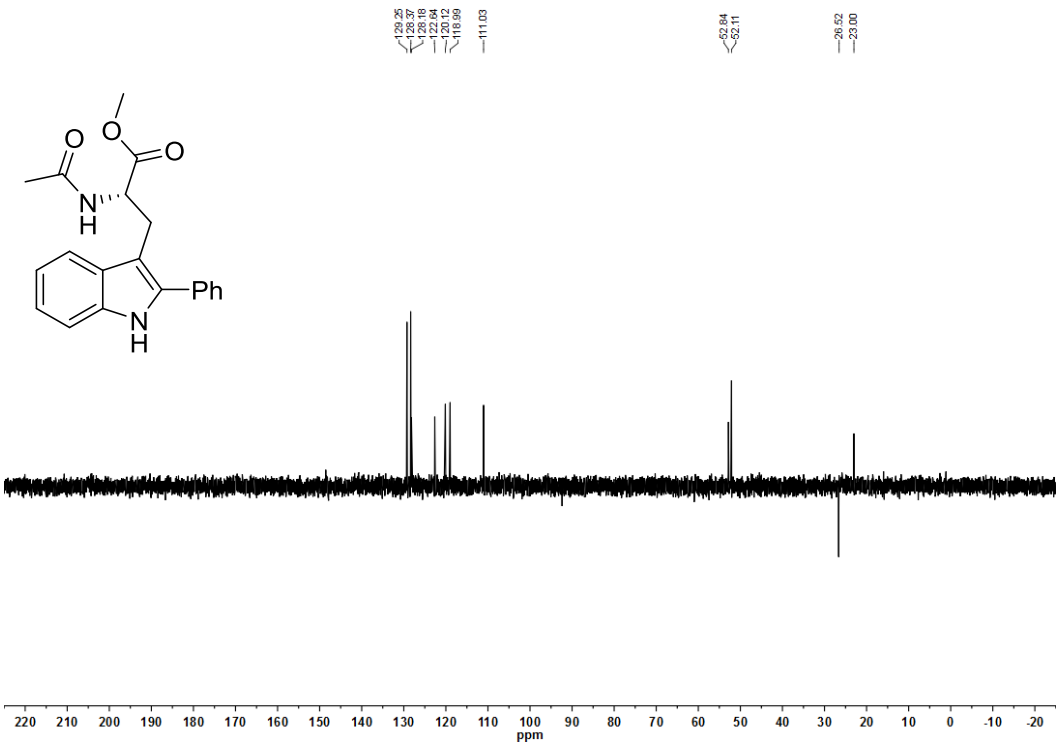
10.5 – Methyl (2*S*)-2-acetyl-3-[2-phenyl-1*H*-indol-3-yl]propanoate, **2a**



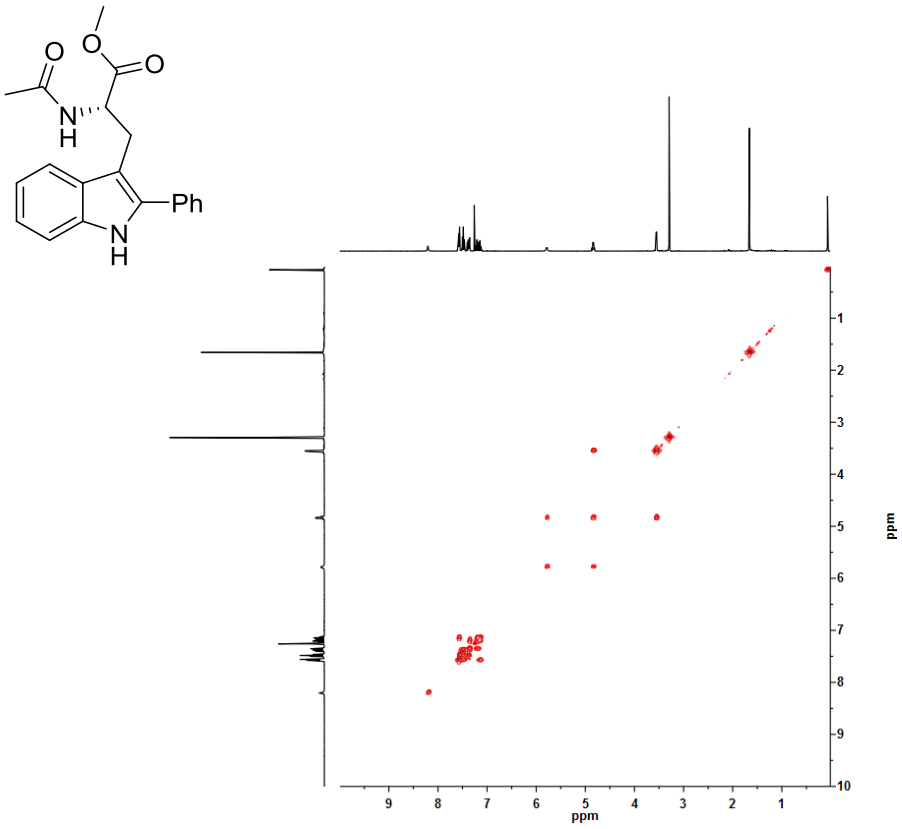
^{1}H NMR spectrum (400 MHz, $CDCl_3$).



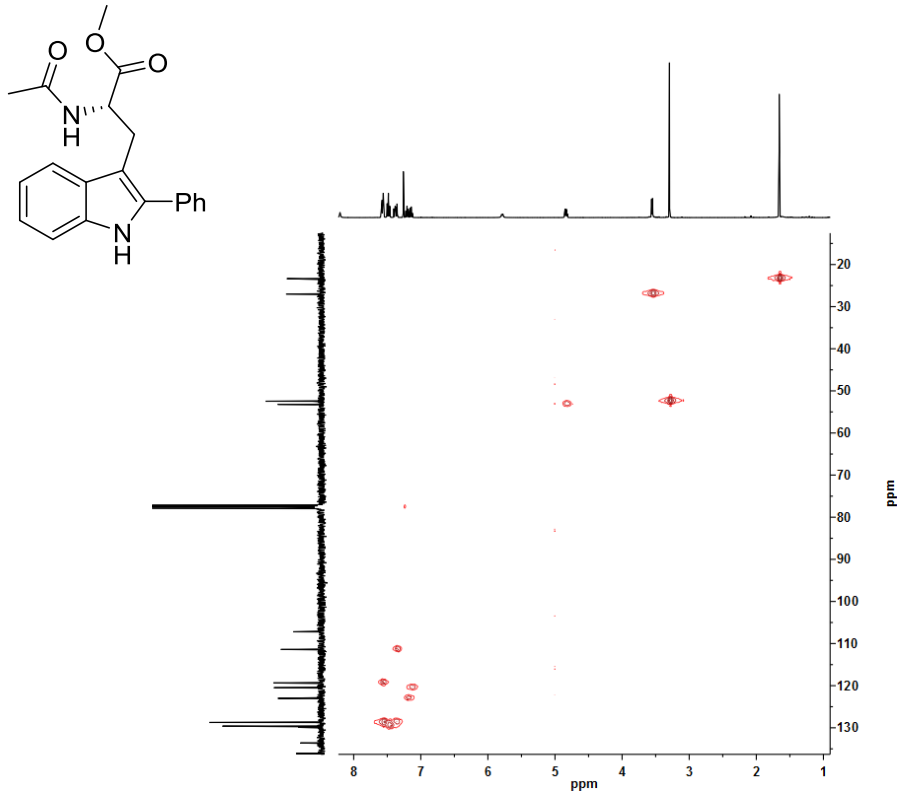
^{13}C NMR spectrum (101 MHz, $CDCl_3$).



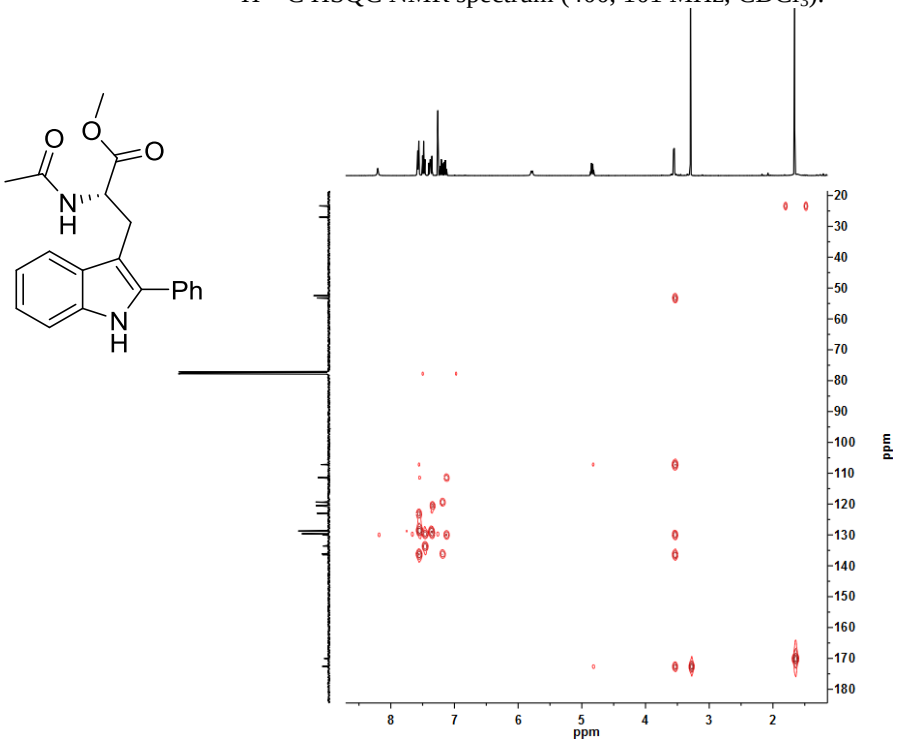
^{13}C NMR DEPT 135 spectrum (101 MHz, $CDCl_3$).



^{1}H-^{1}H COSY NMR spectrum (400 MHz, $CDCl_3$).

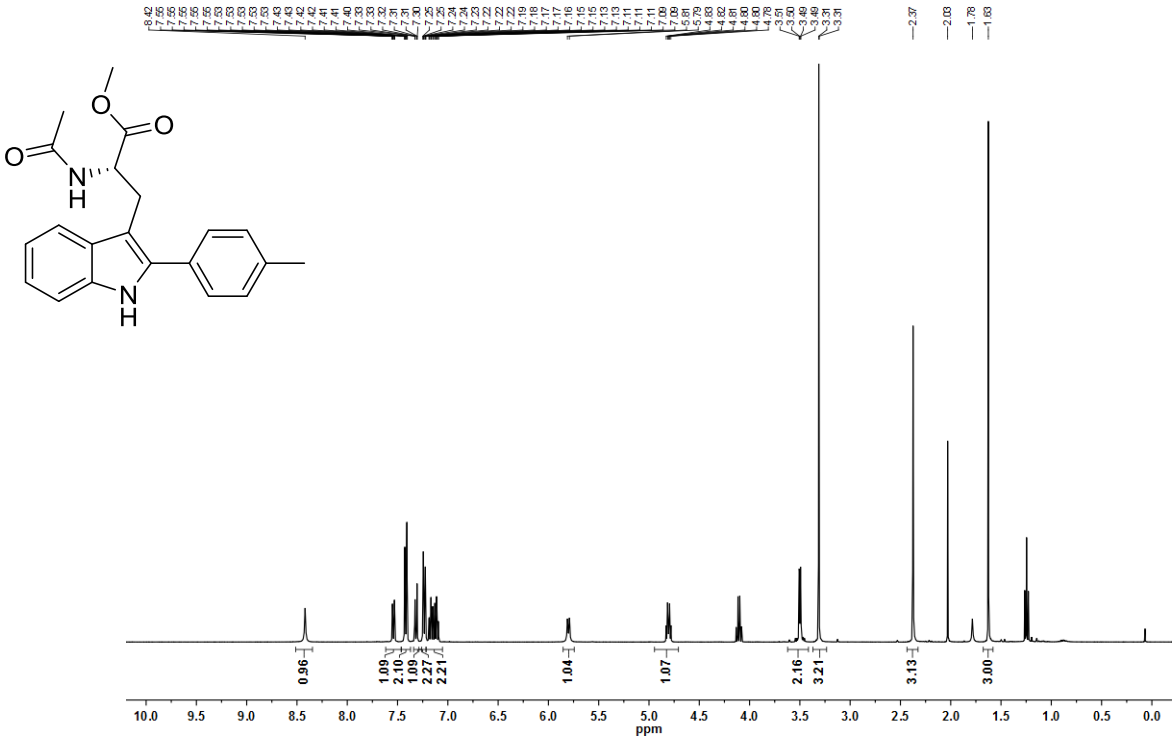


^{1}H-^{13}C HSQC NMR spectrum (400, 101 MHz, $CDCl_3$).

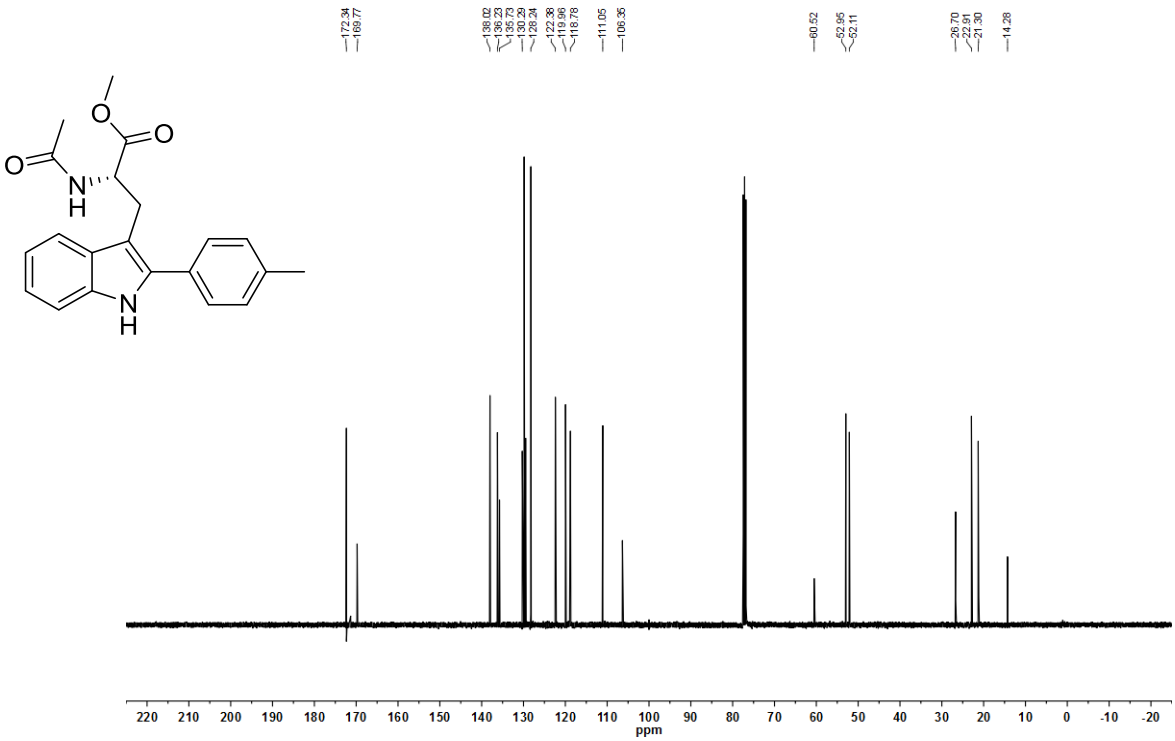


^{1}H-^{13}C HMBC NMR spectrum (400, 101 MHz, $CDCl_3$).

10.6 – Methyl (2*S*)-2-acetyl-3-[2-(4-methylphenyl)-1*H*-indol-3-yl]propanoate, **2b**

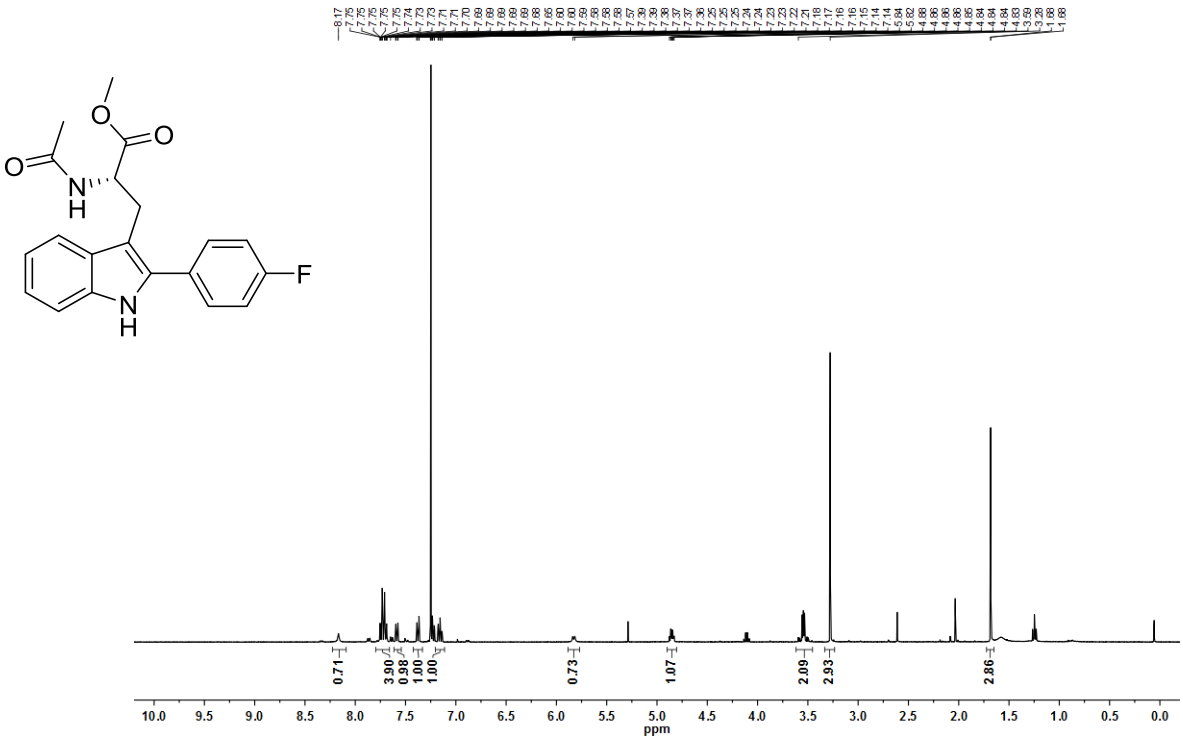


^{1}H NMR spectrum (400 MHz, $CDCl_3$).

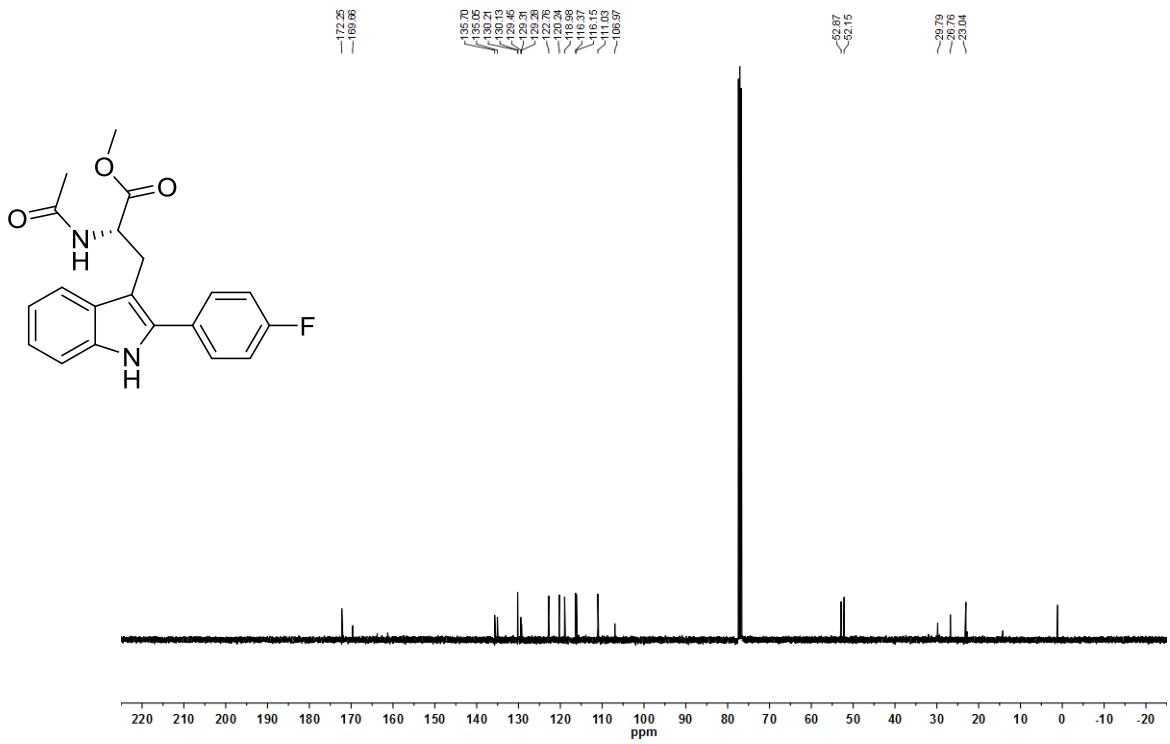


^{13}C NMR spectrum (101 MHz, $CDCl_3$).

10.7 – Methyl (2*S*)-2-amino-3-[2-(4-fluorophenyl)-1*H*-indol-3-yl]propanoate, **2c**

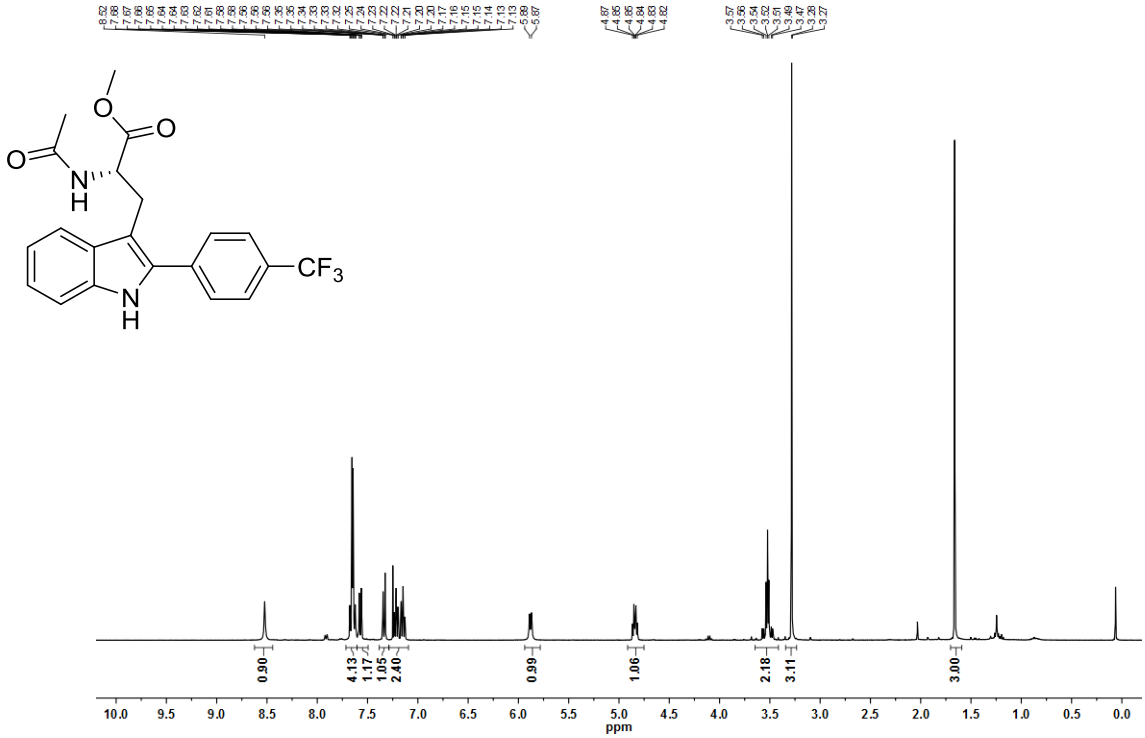


^{1}H NMR spectrum (400 MHz, $CDCl_3$).

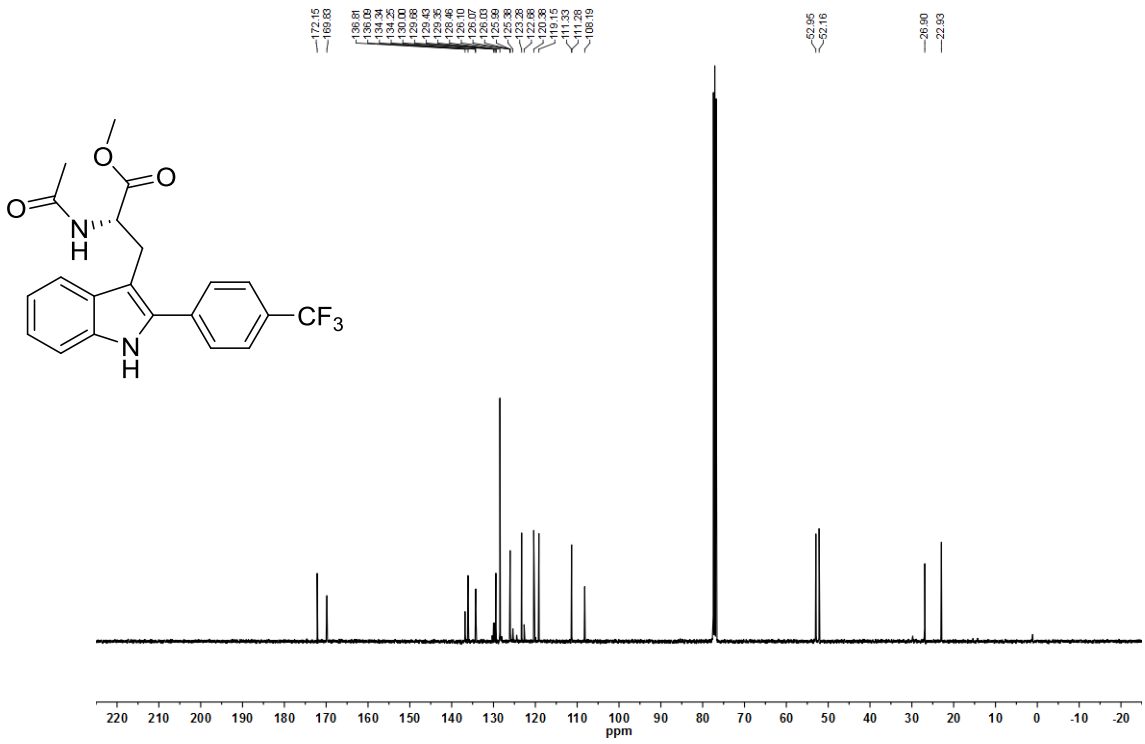


^{13}C NMR spectrum (101 MHz, $CDCl_3$).

10.8 – Methyl (2*S*)-2-acetyl-3-{2-[4-(trifluoromethyl)phenyl]-1*H*-indol-3-yl}propanoate, **2d**

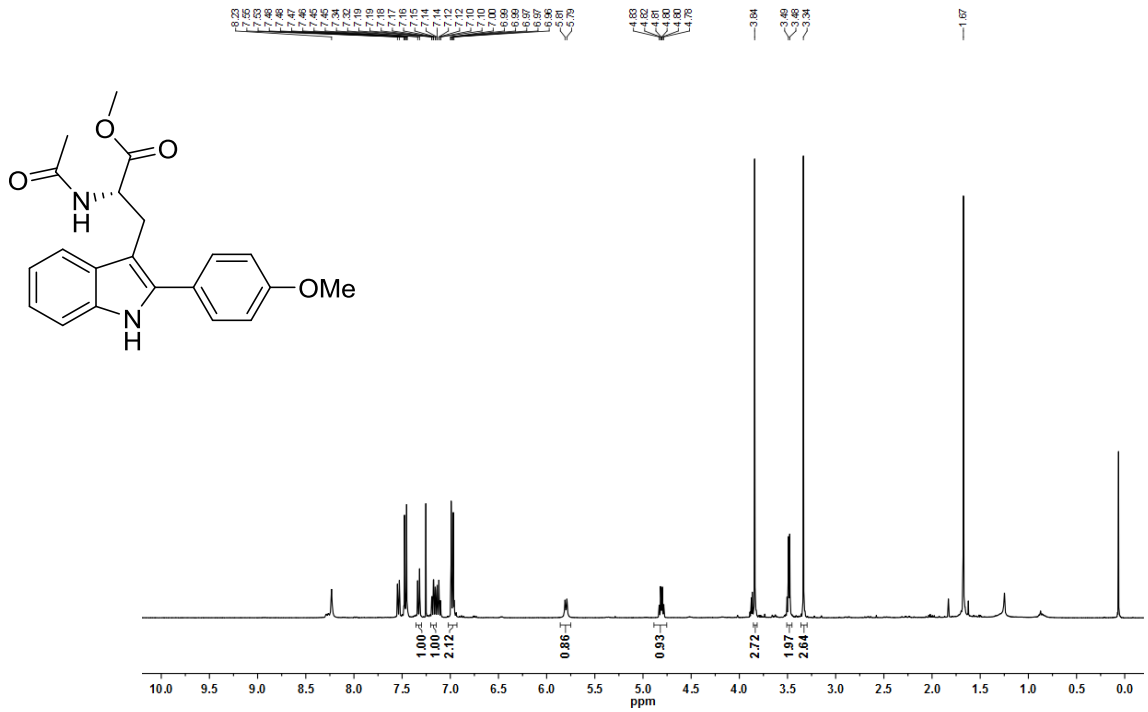


^{1}H NMR spectrum (400 MHz, $CDCl_3$).

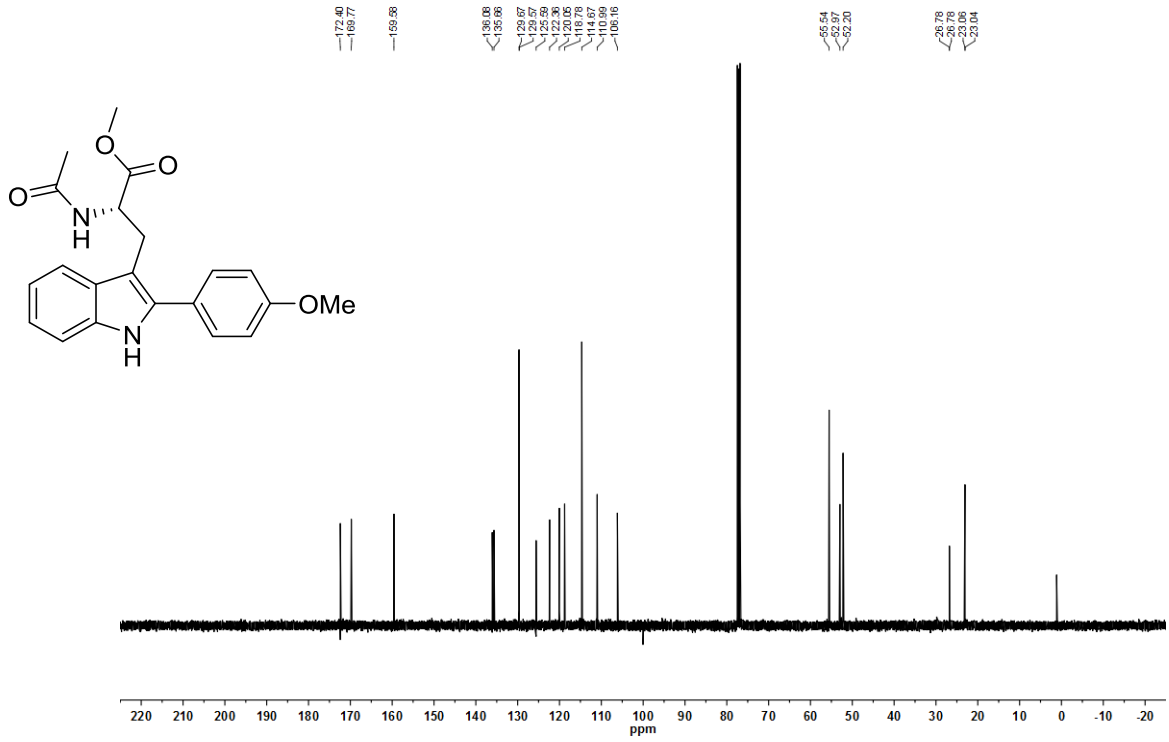


^{13}C NMR spectrum (101 MHz, $CDCl_3$).

10.9 – Methyl (2*S*)-2-amino-3-[2-(4-methoxyphenyl)-1*H*-indol-3-yl]propanoate, **2e**

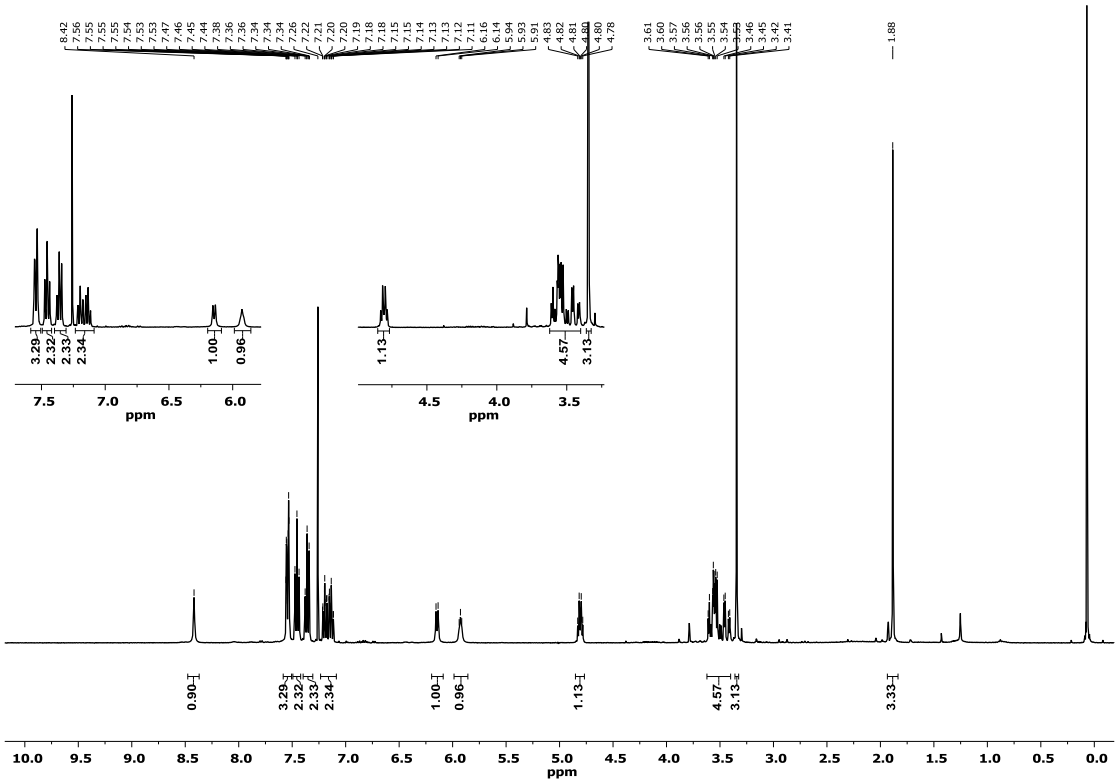


^{1}H NMR spectrum (400 MHz, $CDCl_3$).

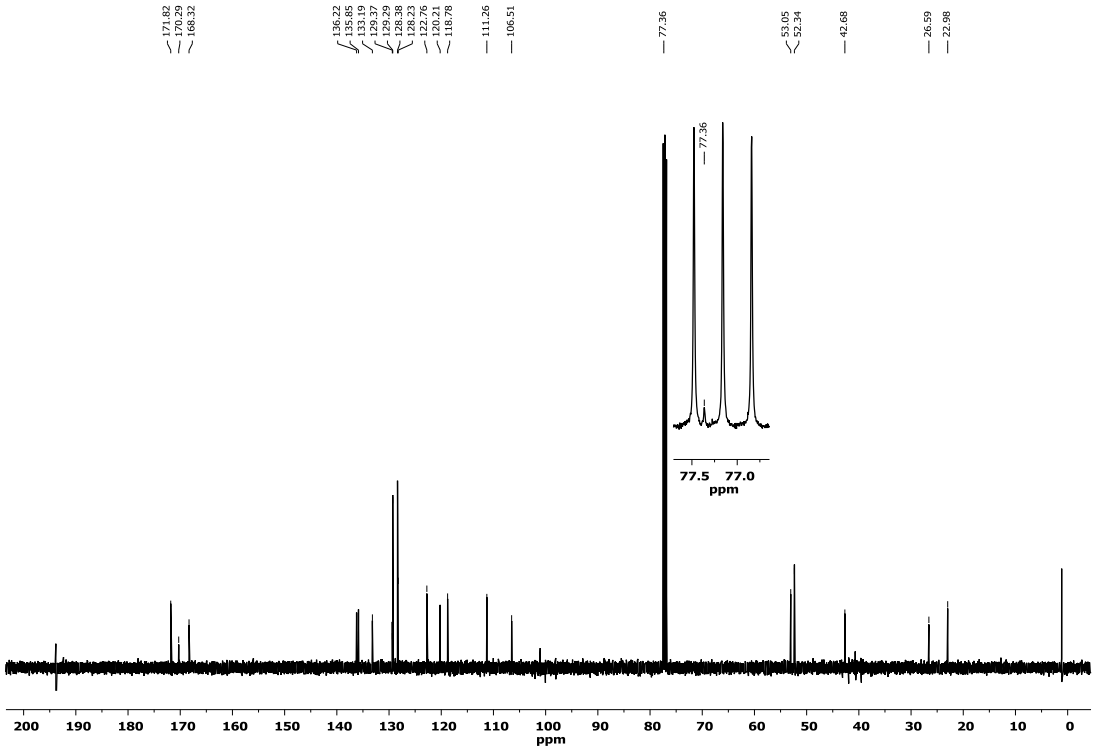


^{13}C NMR spectrum (101 MHz, $CDCl_3$).

10.10 – AcNGlyTrpOMe, **4**



^{1}H NMR spectrum (400 MHz, $CDCl_3$).



^{13}C NMR spectrum (101 MHz, $CDCl_3$) (an artifact and grease impurity is observed at δ 193.84 and δ 1.15).

11 – References

1. D. R. Appleton, R. C. Babcock, B. R. Copp *Tetrahedron* 2001, **57**, 10181-10190
2. E. F. Evans, N. J. Lewis, I. Kapfer, G. Macdonald, Taylor, R. J. K. *Synth. Comm*., 1997, **27**, 1819-1825
3. B. S. Holla, K.V. Malini, B. K. Sarojini, B. Poojary *Synth. Comm.* 2005**, 35**, 333-340
4. K. Hasizume, Y. Shimonishi, *Bull. Chem. Soc. Jpn.* 1981, *54*, 3806-3810
5. CrysAlisPro (X-ray diffraction software).
6. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339-341.
7. G. M. Sheldrick, SHELXS-97, 1997