An efficient and rapid microwave-assisted synthesis of 1-acetyl-1H-indol-3-YL acetates

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AN EFFICIENT AND RAPID MICROWAVE-ASSISTED SYNTHESIS OF 1-ACETYL-1*H*-INDOL-3-YL ACETATES

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ABSTRACT

*An efficient and rapid synthesis of 1-acetyl-1H-indol-3-yl acetate **1** and its derivatives **7** via the microwave-assisted cyclisation and decarboxylation of 2-[(carboxymethyl)amino]benzoic acids **5** is described. The latter were left to react with acetic anhydride using triethylamine as the base and were subjected to microwave irradiation for 1 minute, at 80 °C with initial power of 300 W. The target 1-acetyl-1H-indol-3-yl acetate **1** and derivatives **7** were isolated in 34-71% yield. In particular, synthesis of 1-acetyl-6-(trifluoromethyl)-1H-indol-3-yl acetate **7f** and 1-acetyl-3-methyl-1H-indol-3-yl acetate **7h** is reported for the first time.*

Keywords: microwave; synthesis; cyclisation; indoxyls; indoles

1. INTRODUCTION

The synthesis of indoles, which are often derived from 1-acetyl-1*H*-indol-3-yl acetates such as **1**, is of considerable synthetic interest, for example due to their antioxidant [1-3], antiobesity [4-5], antimalarial [6-7] and antipyretic [8] properties. Indoles have also found use in microbiology as a result of their antibacterial properties [9] and bacterial detection capabilities [10]. Thus in work conducted by Berlin *et al*. [10], the glycoside 5-bromo-3-indolyl-α-L-arabinofuranoside **2** was used for the detection of α-L-arabinofuranosidase in bacterial colonies, with enzyme catalyzed hydrolysis allowing release of the aglycon 5-bromo-1*H*-indol-3-ol. This unstable moiety is rapidly air oxidized to the insoluble, intensely coloured 5,5'-dibromoindigo **3**, leading to the formation of blue bacterial colonies (Figure **1**). Different coloured indigos are formed when different halogens are present in the benzene ring of indigo; for instance, 6,6'-dichloroindigo leads to a salmon precipitate [11].

Chemical methods for the synthesis of 1-acetyl-1*H*-indol-3-yl acetates such as **1** are available in the literature. For example, 1-acetyl-1*H*-indol-3-yl acetate and its derivatives have been furnished from 2-chlorobenzoic acids [12]. A condensation between the latter and glycine led to the 2-[(carboxymethyl)amino]benzoic acids. A final cyclisation using sodium acetate and acetic anhydride afforded the 1-acetyl-1*H*-indol-3-yl acetates in an overall yield range of 5-68%. Alternatively, Guyen *et al*. [13] reacted 2-amino-5-bromobenzoic acid with chloroacetic acid and 2M Na_2CO_3 to produce 5-bromo-2-[(carboxymethyl)amino]benzoic acid. Ring closure was then achieved using acetic anhydride and sodium acetate, and 1-acetyl-5-bromo-1*H*-indol-3-yl acetate was obtained in an overall yield of 33%. In a further method, Lai *et al*. [14] subjected 2-[(carboxymethyl)amino]benzoic acid to microwave irradiation to afford 2-[acetyl(carboxymethyl)amino]benzoic acid in 92% yield. Further microwave irradiation led to the formation of 1-acetyl-1*H*-indol-3-yl acetate in 86% yield. A further option has been developed by Choi *et al*. [15] who synthesised a range of substituted 2-[(carboxymethyl)amino]benzoic acids in two steps from the respective anthranilic acids. First, the anthranilic acids were reacted with ethyl glyoxylate, sodium cyanoborohydride and 1% acetic acid to produce the 2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid derivatives. The latter ester intermediates were then subjected to base hydrolysis to afford the 2-[(carboxymethyl)amino]benzoic acids in an overall yield range of 77-86%. Reaction of the latter with acetic anhydride and Na_2CO_3 under reflux led to the substituted 1-acetyl-1*H*-indol-3-yl acetates. Whilst each of these strategies has its own advantages and weaknesses, in general the routes are often lengthy, and the

scope of the reactions for accessing a range of indoxyl derivatives has not always been demonstrated. Thus within this paper, an alternative method for the synthesis of 1-acetyl-1*H*-indol-3-yl acetates from 2-[(carboxymethyl)amino]benzoic acids is presented that is rapid, facile and efficient, and allows entry to a range of synthetically useful indoxyls.

2. MATERIALS AND METHODS

All chemicals used in this work were commercially available and were used without further purification. Thin layer chromatography (TLC) was performed on aluminium backed silica gel 60 plates (Merck, Germany) and spots were visualized under UV light (254 nm). Column chromatography was performed manually or by automated column chromatography. When performed manually, sand and silica 60Å (35-70 µm) were used as adsorbents and these were obtained from Fisher Scientific and Fluka, respectively. When automated, a Grace Reveleris system equipped with a C18 Column (120 g) was used and the solvents were acetonitrile (HPLC grade) and 0.1% formic acid. Analysis was monitored at the wavelengths of 210, 254 and 280 nm. Purification in some cases was carried out by preparative high performance liquid chromatography using an Agilent 110 series with PLRP-S 100Å 5 or 8 µM columns, 2 x G1316A preparative pumps, a G2360A preparative autosampler and G1365B MWD detector. The mobile phases used were acetonitrile (HPLC grade) and 0.1% or 1% formic acid. The carrier gas was nitrogen. Analysis was monitored at the wavelengths of 210 and 254 nm. The microwave-assisted reactions were carried out in 10 mL glass vials using a Discover-S CEM (NP-1009) microwave. ^{1}H NMR spectra were recorded at 400 or 500 MHz and ^{13}C NMR spectra were recorded at 100, 125 or 176 MHz, on a Bruker Avance DPX 400, Bruker AV II+ 500 or Bruker AV III 700 spectrometer. Chemical shifts are reported in parts per million (ppm). Coupling constants, *J*, are reported in Hertz (Hz) and peak patterns are represented as follows: s, singlet; b, broad; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet. Infra-red (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR or Perkin Elmer Spectrum RXI Spectrometer and values are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on a Thermo Fisher Scientific LTQ Orbitrap XL mass spectrometer. Melting points were obtained using an Electrothermal digital melting point apparatus.

2.2. Synthetic Strategy

2.2.1. Representative Procedure for Preparation of 2-[(Carboxymethyl)amino]benzoic acid and Derivatives (Scheme 2, Table 1)

The respective 2-aminobenzoic acid (1 equivalent) was dissolved in NaOH (2M). To this was added chloroacetic acid (1.2 equivalents) dissolved in NaOH (2M). The solution was stirred for 3 days at 80°C. The solution was left to cool at room temperature, and addition of HCl (2M) afforded a precipitate. An extraction with diethyl ether was carried out. Further material was retrieved by adjusting the pH of the aqueous solution to 3 via the addition of HCl (2M) and then extracting the aqueous phase with diethyl ether (x2). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The reaction mixture was purified with the appropriate purification method.

2.2.2. Synthesis of 2-[(carboxymethyl)amino]benzoic acid 5a

Synthesised from 2-aminobenzoic acid (**4a**, 3.65 mmol, 1 equiv., 500 mg) and chloroacetic acid (4.38 mmol, 1.2 equiv., 413.7 mg) according to the representative procedure described in 2.2.1. The product was purified by column chromatography on silica gel (using first 9/1= ethyl acetate/methanol and then 9/1/0.1= ethyl acetate/methanol/acetic acid). White/cream solid. Yield: 29%. R_f 0.53 (using 9/1/0.1= ethyl acetate/methanol/acetic acid). ^{1}H NMR (CD_3OD, 400 MHz, ppm): δ 4.01 (2H, s, CH_2), 6.57-6.64 (2H, m, Ar-H), 7.36 (1H, t, J = 8.0 Hz, Ar-H), 7.92 (1H, d, J = 8.0 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm): δ 45.40, 112.13, 112.38, 116.25, 133.26, 135.66, 151.70, 171.77, 174.11. IR (thin film): 3605, 3398, 2871, 1675, 1501, 1458, 741 cm^{-1}. FTMS+ESI calculated for $C_9H_{10}NO_4$ $[M+H]^+$: 196.0610. Found: 196.0604.

2.2.3. Synthesis of 2-[(carboxymethyl)amino]-5-bromobenzoic acid 5b

Synthesised from 2-amino-5-bromobenzoic acid (**4b**, 2.33 mmol, 1 equiv., 500 mg) and chloroacetic acid (2.79 mmol, 1.2 equiv., 263.8 mg) according to the representative procedure described in 2.2.1. The product was purified by an automated Reveleris flash system equipped with a C18 120 g column, flow of 85 mL/min, solvent system = 3/2 formic acid (0.1%)/acetonitrile, run length of 15 CV and wavelenghts of 210, 254 and 280 nm. White solid. Yield: 8%. R_f 0.59 (using 9/1/0.1=ethyl acetate/methanol/acetic acid). m.p. 223-225°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 4.02 (2H, s, CH_2), 6.57 (1H, d, J = 8.5 Hz, Ar-H), 7.44 (1H, d, J = 9.0 Hz, Ar-H), 7.98 (1H, s, Ar-H). ^{13}C NMR

(CD_3OD, 100 MHz, ppm) δ 45.25, 107.24, 113.67, 114.52, 135.23, 138.02, 150.65, 170.38, 173.60. IR (thin film): 3351, 1736, 1676, 1507, 1572, 1435, 803 cm^{-1}. FTMS+ESI calculated for $C_9H_9{}^{79}BrNO_4$ $[M+H]^+$: 273.9715, and calculated for $C_9H_9{}^{81}BrNO_4$ $[M+H]^+$: 275.9695. Found: 273.9711 and 275.9690, respectively.

2.2.4. Synthesis of 2-[(carboxymethyl)amino]-5-chlorobenzoic acid 5c

Synthesised from 2-amino-5-chlorobenzoic acid (**4c**, 2.92 mmol, 1 equiv., 500 mg) and chloroacetic acid (3.51 mmol, 1.2 equiv., 331.6 mg) according to the representative procedure described in 2.2.1. The product was purified by column chromatography on silica gel (using first 9/1= ethyl acetate/methanol and then 9/1/0.1= ethyl acetate/methanol/acetic acid). Cream coloured solid. Yield: 24%. R_f 0.62 (using 9/1/0.1= ethyl acetate/methanol/acetic acid). m.p. 217-219°C. ^1H NMR (CD_3OD, 400 MHz, ppm) δ 3.98 (2H, s, CH_2), 6.61 (1H, d, J = 9.0 Hz, Ar-H), 7.32 (1H, dd, J = 2.0, 9.0 Hz, Ar-H), 7.84 (1H, d, J = 2.0 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 45.54, 113.28, 114.11, 120.61, 132.23, 135.17, 150.34, 170.58, 173.97. IR (thin film): 3344, 1721, 1678, 1571, 1510, 1435, 808 cm^{-1}. FTMS+ESI calculated for $C_9H_9ClNO_4$ $[M+H]^+$: 230.0220. Found: 230.0215.

2.2.5. Synthesis of 2-[(carboxymethyl)amino]-5-iodobenzoic acid 5d

Synthesised from 2-amino-5-iodobenzoic acid (**4d**, 1.9 mmol, 1 equiv., 500 mg) and chloroacetic acid (2.28 mmol, 1.2 equiv., 215.6 mg) according to the representative procedure described in 2.2.1. The product was purified by column chromatography on silica gel (using first 9/1= ethyl acetate/methanol and then 9/1/0.1= ethyl acetate/methanol/acetic acid). Cream coloured solid. Yield: 9%. R_f 0.58 (using 9/1/0.1= ethyl acetate/methanol/acetic acid). ^1H NMR (CD_3OD, 400 MHz, ppm) δ 3.76 (2H, s, CH_2), 6.41 (1H, d, J = 9.0 Hz, Ar-H), 7.51 (1H, dd, J = 2.0, 9.0 Hz, Ar-H), 8.12 (1H, d, J = 2.0 Hz, Ar-H). ^{13}C NMR (CD_3OD, 176 MHz, ppm) δ 47.32, 74.22, 113.59, 121.65, 139.90, 139.92, 149.05, 174.26, 177.58. IR (thin film): 3358, 1633, 1606, 1560, 1498, 1448, 824 cm^{-1}. FTMS+ESI calculated for $C_9H_9INO_4$ $[M+H]^+$: 321.9576. Found: 321.9572.

2.2.6. Synthesis of 2-[(carboxymethyl)amino]-5-fluorobenzoic acid 5e

Synthesised from 2-amino-5-fluorobenzoic acid (**4e**, 3.23 mmol, 1 equiv., 500 mg) and chloroacetic acid (3.87 mmol, 1.2 equiv., 365.7 mg) according to the representative procedure described in 2.2.1. The product was purified by column chromatography on silica gel (using first 9/1= ethyl acetate/methanol and then 9/1/0.1= ethyl acetate/methanol/acetic acid). Light yellow solid. Yield: 18%. R_f 0.78 (using 9/1/0.1= ethyl acetate/methanol/acetic acid). ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 4.00 (2H, s, CH_2), 6.60 (1H, dd, *J* = 4.5, 9.0 Hz, Ar-H), 7.16 (1H, m, Ar-H), 7.59 (1H, dd, *J* = 3.0, 9.5 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 45.62, 112.30 (d, *J* 6.5 Hz), 113.74 (d, *J* 7.0 Hz), 118.14 (d, *J* 23.0 Hz), 122.82 (d, *J* 23.0 Hz), 148.56, 154.73 (d, *J* 231.5 Hz), 170.62, 173.95. IR (thin film): 3397, 1681, 1569, 1518, 1225, 810 cm^{-1}. FTMS+ESI calculated for $C_9H_9FNO_4$ $[M+H]^+$: 214.0516. Found: 214.0510.

2.2.7. Synthesis of 2-[(carboxymethyl)amino]-4,5-difluorobenzoic acid 5f

Synthesised from 2-amino-4,5-difluorobenzoic acid (**4f**, 2.89 mmol, 1 equiv., 500 mg) and chloroacetic acid (3.47 mmol, 1.2 equiv., 327.7 mg) according to the representative procedure described in 2.2.1. The product was purified by dry loaded column chromatography on silica gel (using first 3/2= diethyl ether/petroleum ether and then 9/1/0.1= ethyl acetate/methanol/acetic acid). Light yellow solid. Yield: 5%. R_f 0.65 (using 9/1/0.1= ethyl acetate/methanol/acetic acid). m.p. 215.5-221°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 3.99 (2H, s, CH_2), 6.49 (1H, dd, *J* = 6.5, 13.5 Hz, Ar-H), 7.75 (1H, dd, *J* = 9.5, 1.5 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 45.54, 100.69 (d, *J* 22.0 Hz), 107.65 (dd, *J* 2.5, 4.5 Hz), 121.0 (dd, *J* 3.0, 19.0 Hz), 142.03 (dd, *J* 13.5, 233.5 Hz), 149.90 (d, *J* 10.0 Hz), 155.95 (dd, *J* 14.0, 250.5 Hz), 170.0, 173.45. IR (thin film): 3390, 1705, 1674, 1594, 1533, 1432, 1256 cm^{-1}. FTMS+ESI calculated for $C_9H_8F_2NO_4$ $[M+H]^+$: 232.0421. Found: 232.0416.

2.2.8. Synthesis of 2-[(carboxymethyl)amino]-4-trifluorobenzoic acid 5g

Synthesised from 2-amino-4-(trifluoromethyl)benzoic acid (**4g**, 2.44 mmol, 1 equiv., 500 mg) and chloroacetic acid (2.93 mmol, 1.2 equiv., 276.5 mg) according to the representative procedure described in 2.2.1. The product was purified by column chromatography on silica gel (using first 7/3= ethyl acetate/petroleum ether and then 9/1/0.02= ethyl acetate/methanol/acetic acid). Cream coloured solid. Yield: 13%. R_f 0.5 (using 9/1/0.1= ethyl acetate/methanol/acetic acid). m.p. 220-224°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 4.07 (1H, s, CH_2), 6.82 (1H, s, Ar-H), 6.86 (1H, d, *J* = 8.5 Hz, Ar-H), 8.07 (1H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ

45.15, 108.86 (d, *J* 4.5 Hz), 111.99 (d, *J* 3.5 Hz), 115.0, 125.33 (d, *J* 271.5 Hz), 134.23, 136.61 (q, *J* 31.5 Hz), 151.55, 170.63, 173.40. IR (thin film): 3351, 2922, 1717, 1674, 1581, 1436, 852 cm^{-1}. FTMS+ESI calculated for $C_{10}H_9F_3NO_4$ $[M+H]^+$: 264.0484. Found: 264.0479.

2.2.9. Representative Procedure for Preparation of 2-[(2-Ethoxy-2-oxoethyl)amino]benzoic acid and Derivatives (Scheme 3, Table 2)

The respective 2-aminobenzoic acid (1 equivalent) was left to stir in methanol, acetic acid (0.74 equivalents) and ethyl glyoxylate (1.5 equivalents, 50% in toluene) for 2.25 hours at room temperature. Then $NaBH_3(CN)$ (1.5 equivalents) was added and the reaction was left to stir for an additional 1.75 hours at room temperature. The solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate. This was then washed twice with saturated NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The reaction mixture was purified with the appropriate purification method.

2.2.10. Synthesis of 2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6a

Synthesised from 2-aminobenzoic acid (**4a,** 7.3 mmol, 1 equiv., 1 g), acetic acid (5.4 mmol, 0.74 equiv., 308.8 µL), ethyl glyoxylate (10.95 mmol, 1.5 equiv., 2.17 mL) and $NaBH_3(CN)$ (10.95 mmol, 1.5 equiv., 687.8 mg) according to the representative procedure described in 2.2.9. Product **6a** was used for the next step without purification.

2.2.11. Synthesis of 5-bromo-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6b

Synthesised from 2-amino-5-bromobenzoic acid (**4b**, 4.65 mmol, 1 equiv., 1 g), acetic acid (3.44 mmol, 0.74 equiv., 196.9 µL), ethyl glyoxylate (6.98 mmol, 1.5 equiv., 1.383 mL) and $NaBH_3(CN)$ (6.98 mmol, 1.5 equiv., 438.5 mg) according to the representative procedure described in 2.2.9. The product was purified by column chromatography (using 7/3=ethyl acetate/petroleum ether). White solid. Yield: 89%. R_f 0.63 (using 7/3=ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 1.31 (3H, t, *J* = 7.0 Hz, CH_3), 3.99 (2H, s, CH_2), 4.27 (2H, q, *J* = 7.0 Hz, CH_2), 6.44 (1H, d, *J* = 9.0 Hz, Ar-H), 7.46 (1H, d, *J* = 8.0 Hz, Ar-H), 8.10 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 14.19, 44.98, 61.66, 107.13, 111.22, 113.19, 134.89, 138.18, 149.39, 169.93, 172.34. IR (thin film): 3336, 1734, 1671, 1566, 1508, 1454, 804, 679 cm^{-1}. FTMS+ESI calculated for $C_{11}H_{13}{}^{79}BrNO_4$ $[M+H]^+$: 302.0022, and calculated for $C_{11}H_{13}{}^{81}BrNO_4$ $[M+H]^+$: 304.0002. Found: 302.0026 and 304.0003, respectively.

2.2.12. Synthesis of 5-chloro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6c

Synthesised from 2-amino-5-chlorobenzoic acid (**4c**, 5.85 mmol, 1 equiv., 1 g), acetic acid (4.33 mmol, 0.74 equiv., 247.5 µL), ethyl glyoxylate (8.77 mmol, 1.5 equiv., 1.739 mL) and $NaBH_3(CN)$ (8.77 mmol, 1.5 equiv., 551.2 mg) according to the representative procedure described in 2.2.9. The product was purified by column chromatography (using 7/3=ethyl acetate/petroleum ether). Cream coloured solid. Yield: 80%. R_f 0.32 (using 7/3=ethyl acetate/petroleum ether). m.p. 145-147°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 1.31 (3H, t, *J* = 7.0 Hz, CH_3), 4.00 (2H, s, CH_2), 4.27 (2H, q, *J* = 7.0 Hz, CH_2), 6.49 (1H, d, *J* = 9.0 Hz, Ar-H), 7.34 (1H, dd, *J* = 2.5, 9.0 Hz, Ar-H), 7.96 (1H, d, *J* = 2.5 Hz Ar-H), 8.07 (1H, b, -NH-). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 14.18, 45.03, 61.65, 110.63, 112.81, 120.44, 131.93, 135.50, 149.06, 169.99, 172.59. IR (thin film): 3352, 1739, 1673, 1567, 1511, 1452, 809 cm^{-1}. FTMS+ESI calculated for $C_{11}H_{13}{}^{35}ClNO_4$ $[M+H]^+$: 258.0528, and calculated for $C_{11}H_{13}{}^{37}ClNO_4$ $[M+H]^+$: 260.0498. Found: 258.0528 and 258.0497, respectively.

2.2.13. Synthesis of 5-iodo-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6d

Synthesised from 2-amino-5-iodobenzoic acid (**4d**, 3.8 mmol, 1 equiv., 1 g), acetic acid (2.81 mmol, 0.74 equiv., 161 µL), ethyl glyoxylate (5.7 mmol, 1.5 equiv., 1.131 mL) and $NaBH_3(CN)$ (5.7 mmol, 1.5 equiv., 358.5 mg) according to the representative procedure described in 2.2.9. The product was purified by column chromatography (using 1/1=ethyl acetate/petroleum ether). Cream coloured solid. Yield: 90%. R_f 0.31 (using 1/1=ethyl acetate/petroleum ether). m.p. 169-173.5°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 1.28 (3H, t, *J* = 7.0 Hz, CH_3), 4.04 (2H, s, CH_2), 4.23 (2H, q, *J* = 7.0 Hz, CH_2), 6.44 (1H, d, *J* = 9.0 Hz, Ar-H), 7.58 (1H, dd, *J* = 2.0, 9.0 Hz, Ar-H), 8.15 (1H, d, *J* = 2.0 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 14.50, 45.43, 62.39, 75.54, 114.58, 114.95, 141.37, 143.68, 151.09, 170.30, 172.08. IR (thin film): 3326, 2957, 2922, 2851, 1731, 1670, 1606, 1563, 1503, 805 cm^{-1}. FTMS+ESI calculated for $C_{11}H_{13}INO_4$ $[M+H]^+$: 349.9889. Found: 349.9884.

2.2.14. Synthesis of 5-fluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6e

Synthesised from 2-amino-5-fluorobenzoic acid (**4e**, 6.45 mmol, 1 equiv., 1 g), acetic acid (4.77 mmol, 0.74 equiv., 273 µL), ethyl glyoxylate (9.68 mmol, 1.5 equiv., 1.918 mL) and $NaBH_3(CN)$ (9.68 mmol, 1.5 equiv., 608 mg) according to the representative procedure described in 2.2.9. The product was purified by column chromatography

(using 7/3=ethyl acetate/petroleum ether). Cream coloured solid. Yield: 83%. R_f 0.69 (using 7/3=ethyl acetate/petroleum ether). m.p. 166-168°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 1.30 (3H, t, *J* = 7.0 Hz, CH_3), 4.07 (2H, s, CH_2), 4.24 (2H, q, *J* = 7.0 Hz, CH_2), 6.62 (1H, dd, *J* = 4.5, 9.0 Hz, Ar-H), 7.17 (1H, ddd, *J* = 3.0, 8.0, 11.0 Hz, Ar-H), 7.61 (1H, dd, *J* = 3.0, 9.5 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 14.49, 45.91, 62.30, 112.52, 113.75 (d, *J* 7.0 Hz), 118.16 (d, *J* 23.0 Hz), 122.77 (d, *J* 23.0 Hz), 148.56, 154.81 (d, *J* 231.5 Hz), 170.62, 172.42. IR (thin film): 1734, 1670, 1558, 1429, 805 cm^{-1}. FTMS+ESI calculated for $C_{11}H_{13}FNO_4$ $[M+H]^+$: 242.0829. Found: 242.0822.

2.2.15. Synthesis of 4,5-fluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6f

Synthesised from 2-amino-4,5-difluorobenzoic acid (**4f**, 5.78 mmol, 1 equiv., 1 g), acetic acid (4.28 mmol, 0.74 equiv., 244.6 µL), ethyl glyoxylate (8.67 mmol, 1.5 equiv., 1.718 mL) and $NaBH_3(CN)$ (8.7 mmol, 1.5 equiv., 544.8 mg) according to the representative procedure described in 2.2.9. The product was purified by column chromatography (using 7/3=ethyl acetate/petroleum ether). White solid. Yield: 82%. R_f 0.46 (using 7/3=ethyl acetate/petroleum ether). m.p. 175-178°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 1.29 (3H, t, *J* = 7.0 Hz, CH_3), 4.03 (2H, s, CH_2), 4.23 (2H, q, *J* = 7.0 Hz, CH_2), 6.49 (1H, dd, *J* = 6.5, 13.5 Hz, Ar-H), 7.75 (1H, dd, *J* = 9.5, 11.5 Hz, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 14.48, 45.79, 62.42, 100.76 (d, *J* 21.0 Hz), 107.84, 121.03 (d, *J* 19.0 Hz), 142.10 (dd, *J* 14.0, 234.0 Hz), 149.91 (d, *J* 11.0 Hz), 155.92 (dd, *J* 14.0, 249.0 Hz), 170.02, 171.93. IR (thin film): 1734, 1681, 1585, 1535, 1429 cm^{-1}. FTMS+ESI calculated for $C_{11}H_{12}F_2NO_4$ $[M+H]^+$: 260.0734. Found: 260.0729.

2.2.16. Synthesis of 4-trifluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6g

Synthesised from 2-amino-4-(trifluoromethyl)benzoic acid (**4g**, 4.88 mmol, 1 equiv., 1 g), acetic acid (3.61 mmol, 0.74 equiv., 206.4 µL), ethyl glyoxylate (7.32 mmol, 1.5 equiv., 1.45 mL) and $NaBH_3(CN)$ (7.32 mmol, 1.5 equiv., 459.7 mg) according to the representative procedure described in 2.2.9. Product **6g** was used for the next step without purification.

2.2.17. Synthesis of 5-methyl-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6h

Synthesised from 2-amino-5-methylbenzoic acid (**4h**, 6.62 mmol, 1 equiv., 1 g), acetic acid (4.9 mmol, 0.74 equiv., 280.2 µL), ethyl glyoxylate (9.93 mmol, 1.5 equiv., 1.968 mL) and $NaBH_3(CN)$ (9.93 mmol, 1.5 equiv., 624 mg) according to the representative procedure described in 2.2.9. The product was purified by dry loaded column chromatography (using 3/2=ethyl acetate/petroleum ether). White solid. Yield: 83%. R_f 0.74 (using 3/2=ethyl acetate/petroleum ether). m.p. 151.1-152.2°C. ^{1}H NMR ($CDCl_3$, 400 MHz. ppm) δ 1.31 (3H, t, *J* = 7.0 Hz, CH_3), 2.25 (3H, s, CH_3), 4.01 (2H, s, CH_2), 4.26 (2H, q, *J* = 7.0 Hz, CH_2), 6.47 (1H, d, *J* = 8.5 Hz, Ar-H), 7.23 (1H, dd, *J* = 2.0, 8.5 Hz, Ar-H), 7.82 (1H, d, *J* = 1.5 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 14.20, 20.14, 45.24, 61.39, 109.66, 111.43, 124.83, 132.57, 136.69, 148.62, 170.51, 173.72. IR (thin film): 3348, 1735, 1670, 1571, 1524, 802 cm^{-1}. FTMS+ESI calculated for $C_{12}H_{16}NO_4$ $[M+H]^+$: 238.1079. Found: 238.1075.

2.2.18. Synthesis of 3-methyl-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid 6i

Synthesised from 2-amino-3-methylbenzoic acid (**4i**, 6.62 mmol, 1 equiv., 1 g), acetic acid (4.9 mmol, 0.74 equiv., 280.2 µL), ethyl glyoxylate (9.93 mmol, 1.5 equiv., 1.968 mL) and $NaBH_3(CN)$ (9.93 mmol, 1.5 equiv., 624 mg) according to the representative procedure described in 2.2.9. Product **6i** was used for the next step without purification.

2.2.19. Representative Procedure for Preparation of 2-[(Carboxymethyl)amino]benzoic acid and Derivatives (Scheme 3, Table 2)

The respective 2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid was left to react in methanol and NaOH (1M) for 3 hours. Precipitation with HCl (1M) afforded the final desired product with characterization data as provided before.

2.2.20. Synthesis of 2-[(carboxymethyl)amino]benzoic acid 5a

Synthesised from impure 2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6a**) according to the representative procedure described in 2.2.19. Overall yield: 96%. Data was as presented previously in 2.2.2

2.2.21. Synthesis of 2-[(carboxymethyl)amino]-5-bromobenzoic acid 5b

Synthesised from 5-bromo-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6b**, 1.66 mmoles, 500 mg) according to the representative procedure described in 2.2.19. Yield: 90%. Data was as presented previously in 2.2.3

2.2.22. Synthesis of 2-[(carboxymethyl)amino]-5-chlorobenzoic acid 5c

Synthesised from 5-chloro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6c**, 1.95 mmoles, 500 mg) according to the representative procedure described in 2.2.19. Yield: 91%. Data was as presented previously in 2.2.4

2.2.23. Synthesis of 2-[(carboxymethyl)amino]-5-iodobenzoic acid 5d

Synthesised from 5-iodo-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6d**, 1.43 mmoles, 500 mg) according to the representative procedure described in 2.2.19. Yield: 67%. Data was as presented previously in 2.2.5

2.2.24. Synthesis of 2-[(carboxymethyl)amino]-5-fluorobenzoic acid 5e

Synthesised from 5-fluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6e**, 2.07 mmoles, 500 mg) according to the representative procedure described in 2.2.19. Yield: 89%. Data was as presented previously in 2.2.6

2.2.25. Synthesis of 2-[(carboxymethyl)amino]-4,5-difluorobenzoic acid 5f

Synthesised from 4,5-difluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6f**, 1.93 mmoles, 500 mg) according to the representative procedure described in 2.2.19. Yield: 76%. Data was as presented previously in 2.2.7

2.2.26. Synthesis of 2-[(carboxymethyl)amino]-4-trifluorobenzoic acid 5g

Synthesised from impure 4-trifluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6g**) according to the representative procedure described in 2.2.19. Overall yield: 52%. Data was as presented previously in 2.2.8

2.2.27. Synthesis of 2-[(carboxymethyl)amino]-5-methylbenzoic acid 5h

Synthesised from 5-methyl-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6h**, 2.1 mmoles, 0.5 g) according to the representative procedure described in 2.2.19. White solid. Yield: 100%. R_f 0.64 (using 9/1/0.1=ethyl acetate/methanol/acetic acid). m.p. 210-212°C. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 2.22 (3H, s, CH_3), 3.99 (2H, s, CH_2), 6.53 (1H, d, *J* = 8.5 Hz, Ar-H), 7.20 (1H, d, *J* = 8.5 Hz, Ar-H), 7.73 (1H, s, Ar-H). ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 20.25, 45.55, 112.05, 112.56, 125.40, 133.08, 136.52, 149.79, 171.83, 174.20. IR (thin film): 3373, 1713, 1633, 1599, 1571, 1435, 1397 cm^{-1}. FTMS+ESI calculated for $C_{10}H_{12}NO_4$ $[M+H]^+$: 210.0766. Found: 210.0759.

2.2.28. Synthesis of 2-[(carboxymethyl)amino]-3-methylbenzoic acid 5i

Synthesised from 3-methyl-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6i**) according to the representative procedure described in 2.2.19. The product was purified by preparative HPLC using a PLRP-S 100Å 8 µm column, flow of 72 mL/min, solvent system 9/1 formic acid (1%)/acetonitrile and wavelength of 210 nm. Golden rod crystalline solid. Overall yield: 6%. m.p. 168-172°C. ^{1}H NMR (D_2O, 400 MHz, ppm) δ 2.29 (3H, s, CH_3), 3.67 (2H, s, CH_2), 7.20 (1H, t, *J* = 7.5 Hz, Ar-H), 7.34 (1H, d, *J* = 7.5 Hz, Ar-H), 7.69 (1H, d, *J* = 7.5 Hz, Ar-H). ^{13}C NMR (D_2O, 100 MHz, ppm) δ 16.64, 51.50, 126.81, 127.25, 128.89, 131.70, 134.86, 137.72, 173.41, 173.49. FTMS+ESI calculated for $C_{10}H_{12}NO_4$ $[M+H]^+$: 210.0766. Found: 210.0760.

2.2.29. Representative Procedure for Preparation of 1-Acetyl-1H-indol-3-yl acetate and Derivatives (Scheme 4, Table 3)

In a microwave tube, the reaction mixture containing the respective 2-[(carboxymethyl)amino]benzoic acid (1 equivalent), acetic anhydride (59 equivalents) and triethylamine (3 equivalents), was subjected to sonication for 0.25 minutes for uniform mixing and was then irradiated by microwave at an initial power of 300W for 1 minute

at 80°C. The respective organic solvent was added to the mixture and this was washed twice with saturated $NaHCO_3$. The organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification using the appropriate purification technique furnished the desired 1-acetyl-1*H*-indol-3-yl acetate.

2.2.30. Synthesis of 1-acetyl-1H-indol-3-yl acetate 1

Synthesised from 2-[(carboxymethyl)amino]benzoic acid (**5a**, 0.51 mmoles, 100 mg), acetic anhydride (30.25 mmoles, 2.854 mL) and triethylamine (1.54 mmoles, 214.5 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with ethyl acetate. The product was purified by column chromatography (using 3/2=ethyl acetate/petroleum ether). Orange solid. Yield: 40%. R_f 0.83 (using 3/2 ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.39 (3H, s, CH_3COO), 2.62 (3H, s, CH_3CON), 7.31 (1H, t, *J* = 8.0 Hz, Ar-H), 7.40 (1H, t, *J* = 8.0 Hz, Ar-H), 7.55 (1H, d, *J* = 8.0 Hz, Ar-H), 7.72 (1H, s, Ar-H), 8.47 (1H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.06, 23.94, 113.31, 116.70, 117.47, 123.59, 123.76, 126.22, 132.88, 134.64, 167.88, 168.74. IR (thin film): 1739, 1693, 1602, 1440, 1381, 733 cm^{-1}. FTMS+ESI calculated for $C_{12}H_{11}NO_3$ $[M+H]^+$: 218.0817. Found: 218.0812.

2.2.31. Synthesis of 1-acetyl-5-bromo-1H-indol-3-yl acetate 7a

Synthesised from 2-[(carboxymethyl)amino]-5-bromobenzoic acid (**5b**, 0.92 mmoles, 250 mg), acetic anhydride (54 mmoles, 5.099 mL) and triethylamine (2.75 mmoles, 383.2 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with ethyl acetate. The product was purified by column chromatography (using 3/2= petroleum ether/ethyl acetate). Light yellow solid. Yield: 59%. R_f 0.73 (using 3/2 petroleum ether/ethyl acetate). m.p. 121-124°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.39 (3H, s, CH_3COO), 2.61 (3H, s, CH_3CON), 7.48 (1H, dd, *J* = 9.0, 1.5 Hz, Ar-H), 7.69 (1H, d, *J* = 1.5 Hz, Ar-H), 7.73 (1H, s, Ar-H), 8.35 (1H, d, *J* = 9.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.01, 23.79, 114.34, 117.10, 118.19, 120.31, 125.20, 129.08, 131.46, 133.54, 167.68, 168.60. IR (thin film): 1757, 1707, 1592, 1568, 1445 cm^{-1}. FTMS+ESI calculated for $C_{12}H_{11}{}^{79}BrNO_3$ $[M+H]^+$: 295.9923, and calculated for $C_{12}H_{11}{}^{81}BrNO_3$ $[M+H]^+$: 297.9902. Found: 295.9919 and 297.9897, respectively.

2.2.32. Synthesis of 1-acetyl-5-chloro-1H-indol-3-yl acetate 7b

Synthesised from 2-[(carboxymethyl)amino]-5-chlorobenzoic acid (**5c**, 0.79 mmoles, 180 mg), acetic anhydride (46.37 mmoles, 4.375 mL) and triethylamine (2.36 mmoles, 328.9 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with dichloromethane. The product was purified by column chromatography (using 3/2= petroleum ether/ethyl acetate). Light green solid. Yield: 61%. R_f 0.56 (using 3/2 petroleum ether/ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.38 (3H, s, CH_3COO), 2.60 (3H, s, CH_3CON), 7.33 (1H, dd, *J* = 2.0, 9.0 Hz, Ar-H), 7.50 (1H, d, *J* = 2.0 Hz, Ar-H), 7.73 (1H, s, Ar-H), 8.38 (1H, d, *J* = 9.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.0, 23.74, 114.49, 117.26, 117.85, 124.75, 126.39, 129.49, 131.13, 133.70, 167.68, 168.56. FTMS+ESI calculated for $C_{12}H_{11}ClNO_3$ $[M+H]^+$: 252.0427. Found: 252.0423.

2.2.33. Synthesis of 1-acetyl-5-iodo-1H-indol-3-yl acetate 7c

Synthesised from 2-[(carboxymethyl)amino]-5-iodobenzoic acid (**5d**, 0.47 mmoles, 150 mg), acetic anhydride (27.57 mmoles, 2.602 mL) and triethylamine (1.4 mmoles, 195.6 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with ethyl acetate. The product was purified by column chromatography (using 4/1= petroleum ether/ethyl acetate). Yellow solid. Yield: 53%. R_f 0.41 (using 4/1 petroleum ether/ethyl acetate). m.p. 125-131°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.38 (3H, s, CH_3COO), 2.59 (3H, s, CH_3CON), 7.65 (1H, dd, *J* = 1.5, 9.0 Hz, Ar-H), 7.68 (1H, s, Ar-H), 7.88 (1H, d, *J* = 1.5 Hz, Ar-H), 8.22 (1H, d, *J* = 9.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.02, 23.85, 87.74, 113.99, 118.52, 125.69, 126.45, 132.03, 133.27, 134.73, 167.68, 168.64. IR (thin film): 1751, 1701, 1592, 1563, 1444 cm^{-1}. FTMS+ESI calculated for $C_{12}H_{11}INO_3$ $[M+H]^+$: 343.9784. Found: 343.9778.

2.2.34. Synthesis of 1-acetyl-5-fluoro-1H-indol-3-yl acetate 7d

Synthesised from 2-[(carboxymethyl)amino]-5-fluorobenzoic acid (**5e**, 0.58 mmoles, 123 mg), acetic anhydride (34.06 mmoles, 3.214 mL) and triethylamine (1.73 mmoles, 241.6 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with dichloromethane. The product was purified by column chromatography (using 3/2= petroleum ether/ethyl acetate). Light green solid. Yield: 49%. R_f 0.58 (using 3/2 petroleum ether/ethyl acetate). m.p. 142-143°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.38 (3H, s, CH_3COO), 2.60 (3H, s, CH_3CON), 7.11 (1H, t, *J* = 9.0 Hz, Ar-H), 7.19 (1H, d, *J* = 8.0 Hz, Ar-H), 7.75 (1H, s, Ar-H), 8.43 (1H, d, *J* =

4.5 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.02, 23.67, 103.37 (d, *J* 25.0 Hz), 114.06 (d, *J* 24.5 Hz), 114.80, 118.09 (d, *J* 9.0 Hz), 124.56 (d, *J* 10.0 Hz), 129.23, 134.21 (d, *J* 4.0 Hz), 159.6 (d, *J* 240.5 Hz), 167.73, 168.50. IR (thin film): 1753, 1694, 1449 cm^{-1}. FTMS+ESI calculated for $C_{12}H_{11}FNO_3$ $[M+H]^+$: 236.0723. Found: 236.0718.

2.2.35. Synthesis of 1-acetyl-5,6-difluoro-1H-indol-3-yl acetate 7e

Synthesised from 2-[(carboxymethyl)amino]-4,5-difluorobenzoic acid (**5f**, 0.65 mmoles, 150 mg), acetic anhydride (38.31 mmoles, 3.614 mL) and triethylamine (1.95 mmoles, 271.7 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with dichloromethane. The product was purified by column chromatography (using 3/2=petroleum ether/ethyl acetate). Cream coloured solid. Yield: 71%. R_f 0.63 (using 3/2 petroleum ether/ethyl acetate). m.p. 122-125°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.38 (3H, s, CH_3COO), 2.60 (3H, s, CH_3CON), 7.28 (1H, dd, *J* = 8.0, 9.5 Hz, Ar-H), 7.74 (1H, s, Ar-H), 8.35 (1H, dd, *J* = 7.0, 11.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.00, 23.56, 104.90 (d, *J* 21.0 Hz), 106.07 (d, *J* 24.5 Hz), 114.24 (d, *J* 4.0 Hz), 119.25 (d, *J* 7.5 Hz), 127.87 (d, *J* 9.5 Hz), 133.94, 148.33 (dd, *J* 15.0, 243.5 Hz), 149.80 (dd, *J* 15.5, 245.5 Hz), 167.61, 168.54. IR (thin film): 1754, 1706, 1609, 1468 cm^{-1}. FTMS+ESI calculated for $C_{12}H_{10}F_2NO_3$ $[M+H]^+$: 254.0629. Found: 254.0622.

2.2.36. Synthesis of 1-acetyl-6-(trifluoromethyl)-1H-indol-3-yl acetate 7f

Synthesised from 2-[(carboxymethyl)amino]-4-trifluorobenzoic acid (**5g**, 0.76 mmoles, 200 mg), acetic anhydride (44.86 mmoles, 4.233 mL) and triethylamine (2.28 mmoles, 318.1 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with ethyl acetate. The product was purified by preparative HPLC equipped with a PLRP-S 100Å 8µm column, flow of 50 mL/min, solvent system 3/2 acetonitrile/formic acid (0.1%) and wavelength of 210 nm. White solid. Yield: 68%. R_f 0.63 (using 3/2 petroleum ether/ethyl acetate). m.p. 115-121°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.40 (3H, s, CH_3COO), 2.64 (3H, s, CH_3CON), 7.55 (1H, d, *J* = 8.5 Hz, Ar-H), 7.64 (1H, d, *J* = 8.5 Hz, Ar-H), 7.86 (1H, s, Ar-H), 8.80 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.03, 23.83, 114.36 (dd, *J* 3.5, 8.0 Hz), 115.66,

118.01, 120.54 (dd, *J* 3.5, 7.0 Hz), 123.14, 125.86 (d, *J* 2.0 Hz), 128.25 (q, *J* 32.0 Hz), 131.89, 134.03, 167.71, 168.67. IR (thin film): 1766, 1715, 1571, 1437, 824 cm^{-1}. FTMS+ESI calculated for $C_{13}H_{11}F_3NO_3$ $[M+H]^+$: 286.0691. Found: 286.0686.

2.2.37. Synthesis of 1-acetyl-5-methyl-1H-indol-3-yl acetate 7g

Synthesised from 2-[(carboxymethyl)amino]-5-methylbenzoic acid (**5h**, 0.72 mmoles, 150 mg), acetic anhydride (42.33 mmoles, 3.994 mL) and triethylamine (2.15 mmoles, 300.2 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with dichloromethane. The product was purified by column chromatography (using 4/1 dichloromethane/hexane). Pale yellow solid. Yield: 67%. R_f 0.68 (using 4/1=dichloromethane/hexane). m.p. 113-115°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.37 (3H, s, CH_3COO), 2.45 (3H, s, CH_3Ar), 2.58 (3H, s, CH_3CON), 7.20 (1H, d, *J* = 8.5 Hz, Ar-H), 7.31 (1H, s, Ar-H), 7.65 (1H, s, Ar-H), 8.31 (1H, d, *J* = 6.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.05, 21.39, 23.82, 113.38, 116.37, 117.28, 123.79, 127.55, 131.19, 133.47, 134.48, 167.92, 168.57. IR (thin film): 1760, 1695, 1452, 1376, 820 cm^{-1}. FTMS+ESI calculated for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974. Found: 232.0968.

2.2.38. Synthesis of 1-acetyl-7-methyl-1H-indol-3-yl acetate 7h

Synthesised from 2-[(carboxymethyl)amino]-3-methylbenzoic acid (**5i**, 0.54 mmoles, 112 mg), acetic anhydride (31.61 mmoles, 2.982 mL) and triethylamine (1.61 mmoles, 224.2 µL) according to the representative procedure described in 2.2.29. Extractions were carried out with dichloromethane. The product was purified by preparative HPLC equipped with a PLRP-S 100Å 8µm column, flow of 30 mL/min, solvent system 3/2 acetonitrile/formic acid (0.1%) and wavelength of 210 and 254 nm. Light pink solid. Yield: 34%. R_f 0.32 (using 4/1 dichloromethane/petroleum ether). m.p. 72-74°C. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 2.37 (3H, s, CH_3COO), 2.57 (3H, s, CH_3Ar), 2.62 (3H, s, CH_3CON), 7.18-7.25 (2H, m, Ar-H), 7.37 (1H, d, *J* = 7.5 Hz, Ar-H), 7.69 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 21.08, 22.74, 24.42, 114.52, 114.96, 124.15, 125.33, 127.07, 129.31, 132.60, 134.32, 167.77, 167.94. IR (thin film): 1766, 1720, 1369, 776 cm^{-1}. FTMS+ESI calculated for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974. Found: 232.0967.

3. RESULTS AND DISCUSSION

At the outset of the programme the optimisation of two different synthetic methods for the synthesis of 2-[(carboxymethyl)amino]benzoic acids, that are key intermediates en-route to the final indoxyl targets, was undertaken, and the general approach is illustrated in Scheme 1. Initially, the method reported by Guyen *et al*. [13] was used, with modifications, for the synthesis of 2-[(carboxymethyl)amino]benzoic acid and a range of further functionalised derivatives (Scheme 2, Table 1). Thus reaction of the 2-aminobenzoic acids **4a**-**4g** with chloroacetic acid in sodium hydroxide (2M) at 80°C for 3 days, led to isolation of the 2-[(carboxymethyl)amino]benzoic acids **5a**-**5g** in 5-29% yield after purification by chromatography. Attempts to purify **5h** with both column chromatography and a Reveleris flash system equipped with a C18 reverse phase column were unsuccessful.

Given the low yields afforded during this first step in the synthesis of the indoxyl targets, an alternative route to the 2-[(carboxymethyl)amino]benzoic acids **5** was sought, and the method reported by Choi *et al*. [15] was utilised with small modifications. Thus 2-aminobenzoic acids **4** were subjected to a reductive alkylation using ethyl glyoxylate, acetic acid and sodium cyanoborohydride, to afford the ester intermediates **6b**-**6f** and **6h** in 80-90% yield (Scheme 3, Table 2, step 1). After a base hydrolysis with sodium hydroxide (1M) and precipitation with hydrochloric acid (1M), the 2-[(carboxymethyl)amino]benzoic acids **5b**-**5f** and **5h** were furnished in 67-100% yield (Scheme 3, Table 2, step 2). The syntheses of 5-iodo-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6d**), 4,5-difluoro-2-[(2-ethoxy-2-oxoethyl)amino]benzoic acid (**6f**), 2-[(carboxymethyl)amino]-4-trifluorobenzoic acid (**5g**) and 2-[(carboxymethyl)amino]-3-methylbenzoic acid (**5i**) are reported for the first time.

With the key 2-[(carboxymethyl)amino]benzoic acid intermediates **5** in hand, the next and final step for entry to the diacetylindoxyl targets **1** and **7** involved cyclisation and decarboxylation of the 2-[(carboxymethyl)amino]benzoic acids. As a starting point, the method used by Rodríguez-Domínguez *et al*. [12] with modifications, was employed. Thus, compound **5a** was heated at reflux for 5 hours with acetic anhydride and anhydrous sodium acetate (Scheme 4). After purification via column chromatography, 1-acetyl-1*H*-indol-3-yl acetate (**1**) was isolated in 26% yield. With the aim of improving the yield and encouraged by the work by Lai *et al*. [14] where 1-acetyl-1*H*-indol-3-yl acetate was furnished through microwave activation in two steps from 2-[(carboxymethyl)amino]benzoic acid, it was also decided to attempt to synthesise **1** from **5a**, using microwave irradiation. Thus compound **5a** was subjected to microwave irradiation for four minutes at 80°C and initial power of 300W in the presence of sodium carbonate,

H_2O and acetic anhydride. 1-Acetyl-1*H*-indol-3-yl acetate was furnished directly from **5a**, in 35% yield, after purification via column chromatography. Different conditions (Scheme 4, Table 3) were employed for the microwave activation of **5a** to investigate whether this would lead to an increase in reaction yield. An increase in microwave reaction time reduced the reaction yield (entry 2, Table 3), however when the reaction time was reduced, a small increase in yield was noticed (entry 3, Table 3). Changing the base to triethylamine in the absence of H_2O led to isolation of 1-acetyl-1*H*-indol-3-yl acetate in 40% yield (entry 4, Table 3). The synthesis of derivatives of **1** was pursued using these optimised conditions as illustrated in Scheme 5, Table 4. All derivatives were afforded in good to very good yields and all 1-acetyl-1*H*-indol-3-yl acetates except for **7h**, were obtained in higher yields compared to **1**. The lower yield obtained for formation of **1** correlates with the formation of a number of by-products as evidenced by thin layer chromatographic analysis of its reaction mixture. Also, the low solubilities of the starting materials **5a** and **5i** in acetic anhydride and triethylamine are likely to have contributed to the lower yields obtained for 1-acetyl-1*H*-indol-3-yl acetates **1** and **7h**, compared to **7a**-**7g**. All of the 1-acetyl-1*H*-indol-3-yl acetates were purified via column chromatography, with the novel **7f** and **7h** derivatives being purified via preparative HPLC.

4. CONCLUSION

A range of 2-[(carboxymethyl)amino]benzoic acids **5,** that are key intermediates for the synthesis of the indoxyl targets **1** and **7**, were synthesised using two different methods. The synthetic method to the benzoic acids **5** via intermediates **6,** was found to be superior to the direct entry method from 2-aminobenzoic acids **4** (summarised in Scheme 6) both in terms of yield and purification. Optimisation of the final step, by using microwave irradiation, and altering the base, solvent and reaction time, allowed rapid entry to a range of indoxyl derivatives **1** and **7** in good yield. Thus, an efficient method for the synthesis of 1-acetyl-1*H*-indol-3-yl acetates, including novel derivatives, from 2-[(carboxymethyl)amino]benzoic acids has been developed.

LIST OF ABBREVIATIONS

Ar = Aromatic

^{13}C NMR = Carbon Nuclear Magnetic Resonance

^{1}H NMR = Proton Nuclear Magnetic Resonance

CV = Column Volume

Equiv. = Equivalent

ESI = Electron Spray Ionisation

FTMS = Fourier Transform Mass Spectrometry

HPLC = High Performance Liquid Chromatography

MHz = Megahertz

m.p. = Melting Point

µL = Microlitre

µM = Micrometer

mL = Millilitre

mmoles = Millimoles

M = Molar

MW = Microwave

nM = Nanometer

R_f = Retention factor

rt = room temperature

UV = Ultraviolet

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPORTING INFORMATION

Supplementary data including spectroscopic data for this article can be accessed by contacting the corresponding author.

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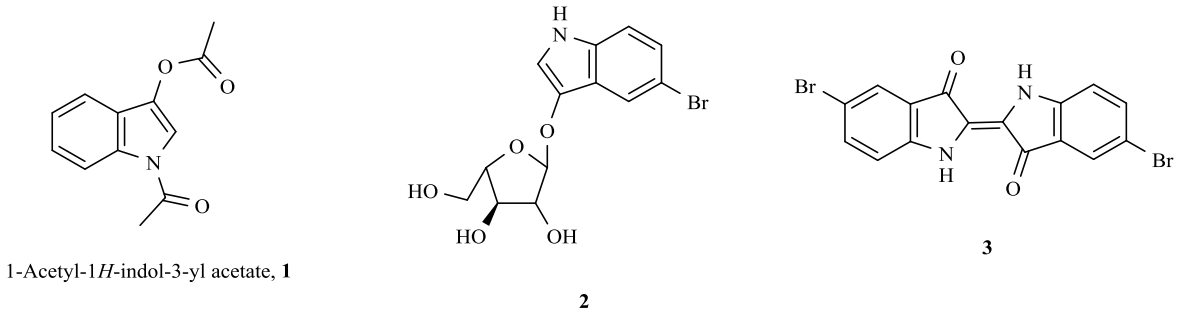
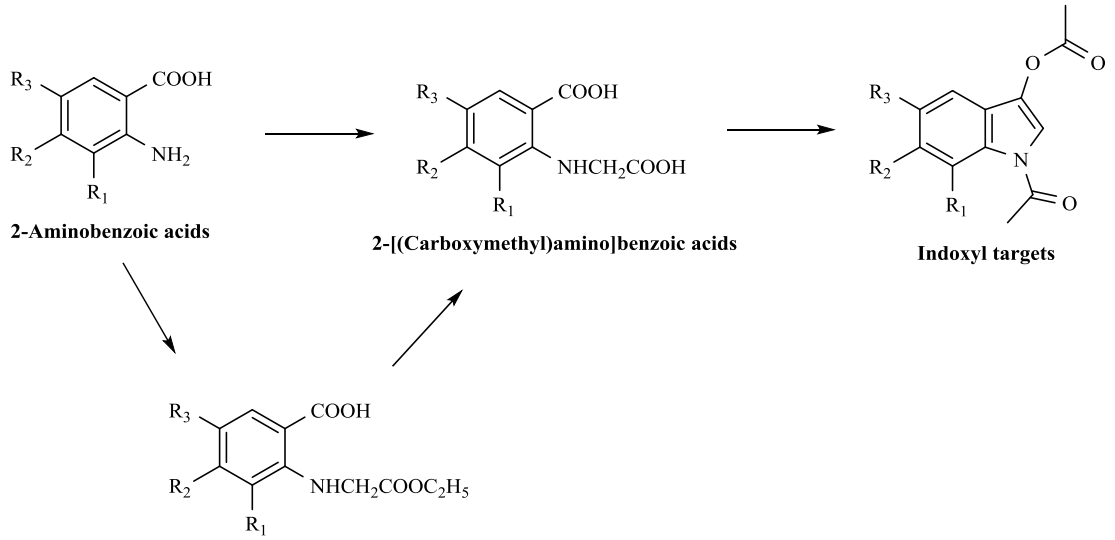
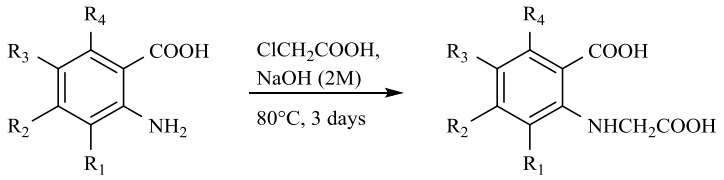


Figure 1. Structures of 1-acetyl-1*H*-indol-3-yl acetate and indoles of microbiological importance.



Scheme 1. Summary of the approaches investigated herein for the synthesis of the indoxyl targets.

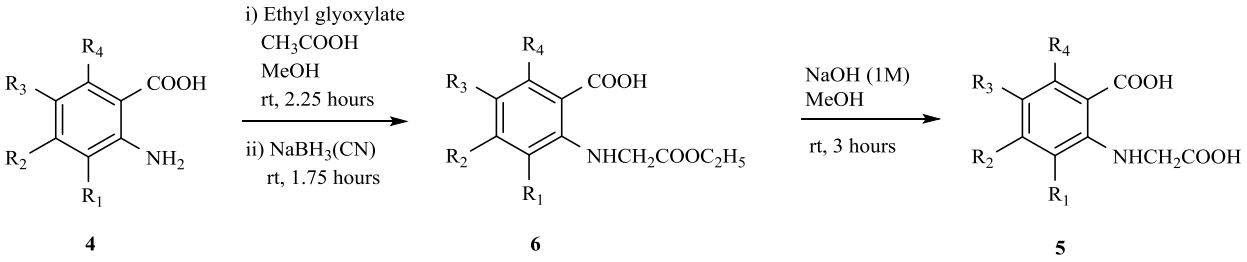


4 **5**

Starting material	Product	Yield (%)
4a, $R_{1,2,3,4}$ = H	**5a**, $R_{1,2,3,4}$ = H	29

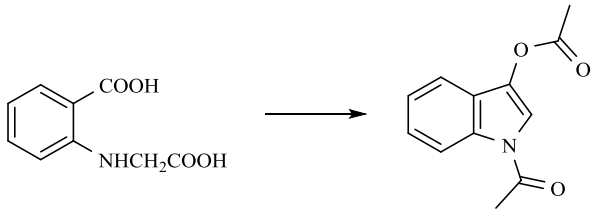
4b, $R_{1,2,4}$ = H, R_3 = Br	**5b**, $R_{1,2,4}$ = H, R_3 = Br	8
4c, $R_{1,2,4}$ = H, R_3 = Cl	**5c**, $R_{1,2,4}$ = H, R_3 = Cl	24
4d, $R_{1,2,4}$ = H, R_3 = I	**5d**, $R_{1,2,4}$ = H, R_3 = I	9
4e, $R_{1,2,4}$ = H, R_3 = F	**5e**, $R_{1,2,4}$ = H, R_3 = F	18
4f, $R_{1,4}$ = H, $R_{2,3}$ = F	**5f**, $R_{1,4}$ = H, $R_{2,3}$ = F	5
4g, $R_{1,3,4}$ = H, R_2 = CF_3	**5g**, $R_{1,3,4}$ = H, R_2 = CF_3	13
4h, $R_{1,2,4}$ = H, R_3 = CH_3	**5h**, $R_{1,2,4}$ = H, R_3 = CH_3	Not obtained pure

Scheme 2, Table 1. Synthesis of 2-[(carboxymethyl)amino]benzoic acids.



Starting material	Product	Yield (%)	Product	Yield (%)
4a, $R_{1,2,3,4}$ = H	**6a**, $R_{1,2,3,4}$ = H	See experimental	**5a**, $R_{1,2,3,4}$ = H	96 (overall yield)
4b, $R_{1,2,4}$ = H, R_3 = Br	**6b**, $R_{1,2,4}$ = H, R_3 = Br	89	**5b**, $R_{1,2,4}$ = H, R_3 = Br	90
4c, $R_{1,2,4}$ = H, R_3 = Cl	**6c**, $R_{1,2,4}$ = H, R_3 = Cl	80	**5c**, $R_{1,2,4}$ = H, R_3 = Cl	91
4d, $R_{1,2,4}$ = H, R_3 = I	**6d**, , $R_{1,2,4}$ = H, R_3 = I	90	**5d**, $R_{1,2,4}$ = H, R_3 = I	67
4e, $R_{1,2,4}$ = H, R_3 = F	**6e**, $R_{1,2,4}$ = H, R_3 = F	83	**5e**, $R_{1,2,4}$ = H, R_3 = F	89
4f, $R_{1,4}$ = H, $R_{2,3}$ = F	**6f**, $R_{1,4}$ = H, $R_{2,3}$ = F	82	**5f**, $R_{1,4}$ = H, $R_{2,3}$ = F	76
4g, $R_{1,3,4}$ = H, R_2 = CF_3	**6g**, $R_{1,3,4}$ = H, R_2 = CF_3	See experimental	**5g**, $R_{1,3,4}$ = H, R_2 = CF_3	52 (overall yield)
4h, $R_{1,2,4}$ = H, R_3 = CH_3	**6h**, $R_{1,2,4}$ = H, R_3 = CH_3	83	**5h**, $R_{1,2,4}$ = H, R_3 = CH_3	100
4i, R_1 = CH_3, $R_{2,3,4}$ = H	**6i**, R_1=CH_3, $R_{2,3,4}$= H	See experimental	**5i**, R_1 = CH_3, $R_{2,3,4}$ = H	6 (overall yield)

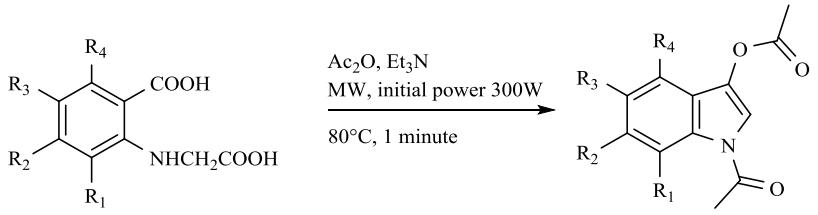
Scheme 3, Table 2. Synthesis of 2-[(carboxymethyl)amino]benzoic acids.



5a **1**

Compound **5a** (1 Molar equiv.)						
Entry	Na_2CO_3 (Molar equiv.)	Et_3N (Molar equiv.)	H_2O (Molar equiv.)	Ac_2O (Molar equiv.)	Reaction time (min)	Yield **1** (%)
1	1.6	-	10.7	73.1	4	35
2	1.6	-	10.7	73.1	10	20
3	1.6	-	10.7	73.1	1	37
4	-	3	-	59	1	40

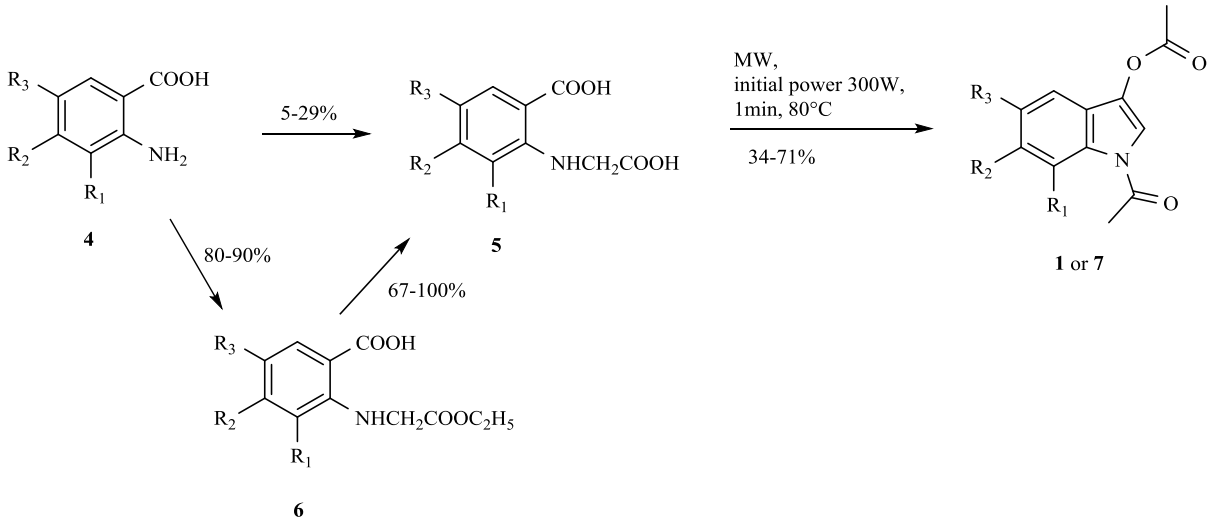
Scheme 4, Table 3. Summary of yields (%) obtained during optimisation process. All reactions were carried out under microwave irradiation at 80 ˚C and initial power of 300 W with stirring.



5 **1** or **7**

Starting material	Product	Yield (%)
5a, $R_{1,2,3,4}$ = H	**1**, $R_{1,2,3,4}$ = H	40
5b, $R_{1,2,4}$ = H, R_3 = Br	**7a**, $R_{1,2,4}$ = H, R_3 = Br	59
5c, $R_{1,2,4}$ = H, R_3 = Cl	**7b**, $R_{1,2,4}$ = H, R_3 = Cl	61
5d, $R_{1,2,4}$ = H, R_3 = I	**7c**, $R_{1,2,4}$ = H, R_3 = I	53
5e, $R_{1,2,4}$ = H, R_3 = F	**7d**, $R_{1,2,4}$ = H, R_3 = F	49
5f, $R_{1,4}$ = H, $R_{2,3}$ = F	**7e**, $R_{1,4}$ = H, $R_{2,3}$ = F	71
5g, $R_{1,3,4}$ = H, R_2 = CF_3	**7f**, $R_{1,3,4}$ = H, R_2 = CF_3	68
5h, $R_{1,2,4}$ = H, R_3 = CH_3	**7g**, $R_{1,2,4}$ = H, R_3 = CH_3	67
5i, R_1 = CH_3, $R_{2,3,4}$ = H	**7h**, R_1 = CH_3, $R_{2,3,4}$ = H	34

Scheme 5, Table 4. Synthesis of 1-acetyl-1*H*-indol-3-yl acetates. Reagents and conditions: Acetic anhydride, triethylamine, microwave, initial power 300 W, 80 °C, 1 min.



Scheme 6. Summary of the approaches investigated in this programme.