A Facile Synthesis of 1,4-benzodiazepine-2,5-diones and Quinazolinones from Amino Acids as Anti-Tubercular Agents

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3. Experimental Section:

3.1. Materials and methods:

All reactions were carried out using round-bottomed flask, unless otherwise stated. All reagents were obtained from commercial suppliers and used without further purification. The starting material, isatoic anhydride procured from Avra chemicals, L-amino acid methyl ester hydrochlorides from Sigma-Aldrich and H$_2$PtCl$_6$ from Rankem. The reactions were monitored by TLC and were visualized under UV lamp (254 nm and 365 nm). Melting points were determined on a Superfit melting point apparatus (India) and were uncorrected. FT-IR was performed using Perkin Elmer Spectrum Two. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on Agilent Technologies (USA) using DMSO or CDCl$_3$ as a solvent and tetramethyl silane as an internal standard. The following abbreviations are used for the multiplicities: s: singlet; d: doublet; t: triplet; m: multiplet, br: broad and coupling constants ($J$) are reported in Hertz (Hz). LC mass spectra were recorded on Waters synapp G-2 using Masslynx 4.1 software with capillary voltage of 2.5-3.5 kV and APCI mode of ionization.

3.2. General Procedure for Synthesis of Intermediates 3a-m:

L-amino acid methyl ester hydrochlorides 2 (0.002 mol, 1.0 equiv.) were dissolved in minimum amount of water (4 mL), to this added Na$_2$CO$_3$ (0.43g, 0.004 mol, 2.0 equiv.). The resulted neutralized solution of amino acid was added drop wise to well-stirred solution of isatoic anhydride 1 (0.45g, 0.0028 mol, 1.4 equiv.) in ACN (8 mL) at room temperature. The resulting mixture was stirred until the completion (2-3 hour) of the reaction (monitored by TLC). The reaction mixture was evaporated under reduced pressure; the remaining residual mass was quenched with saturated K$_2$CO$_3$ solution (20 mL) to remove unreacted isatoic anhydride. The obtained aqueous layer was extracted with EtOAc (2 × 20 mL) and washed with 5% Na$_2$CO$_3$ (2 × 20 mL) and with brine (1 × 20 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to obtain the residual product with almost >95 % purity.

3.3. General Procedure for Synthesis of 1,4-Benzodiazepine-2,5-diones (4a-j):

To a solution of intermediate 3 (0.001 mol, 1.0 equiv.) in THF (3 mL), H$_2$PtCl$_6$ (0.06g, 15 mol %) was added. The resulting mixture was heated to reflux with constant
stirring until the completion (30-40 min) of the reaction (monitored by TLC). The reaction mixture was quenched with saturated Na$_2$CO$_3$ solution (10 mL) and extracted with chloroform (2 × 15 mL). The organic layer was washed with 1N NaOH (1 × 10 mL), 1N HCl (1 × 10 mL), water (1 × 10 mL) and finally with brine (1 × 10 mL). The obtained organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to obtain the crude products. The crude products were purified by either column chromatography (Eluent: EtOAc:Hexane :: 1:2) or recrystallization with MTBE whichever is permissible.

3.4. General Procedure for Synthesis of Quinazolinones (5c & 5e):

To a solution of intermediate 3 (0.001 mol, 1.0 equiv.) in DMF (3 mL), dry/moist H$_2$PtCl$_6$ (0.06g, 15 mol %) was added. The resulting mixture was heated to reflux with constant stirring until the completion (30-40 min) of the reaction (monitored by TLC). The reaction mixture was quenched with saturated Na$_2$CO$_3$ solution (10 mL) and extracted with CHCl$_3$ (2 × 15 mL). The organic layer was washed with 1N HCl (1 × 10 mL), water (1 × 10 mL) and finally with brine (1 × 10 mL). The obtained organic layer was treated with 1N NaOH the product went to aqueous layer, later by acidification, the product was isolated and extracted to organic layer dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure, to obtain the residual products with almost >95 % purity. The obtained product seems astonishing, yielding six membered quinazolinone derivative.
**Characterization Data**

**Compound 4a: 3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione**
Colourless solid; Yield = 62.5% (110 mg); M.P. = 321-324 °C;
IR (thin film): 2820, 1698, 1597 cm\(^{-1}\)
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.32 (s, 1H, -NH), 8.50 (t, 1H, -NH, J = 5.6 Hz), 7.73 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.50-7.46 (m, 1H, Ar-H), 7.19 (t, 1H, Ar-H, J = 6.8 Hz), 7.08 (d, 1H, Ar-H, J = 8 Hz), 3.56 (d, 2H, -CH\(_2\), J = 6 Hz);
\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 171.6, 168.5, 137.6, 132.7, 131.2, 126.0, 124.3, 121.3, 44.9;
LCMS (APCI): m/z calcd. For C\(_9\)H\(_8\)N\(_2\)O\(_2\): 176.0586; found: 176.9819 (M+1)

**Compound 4b: 3-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione**
Light creamy solid; Yield = 63.1% (121 mg); M.P. = 328-330 °C;
IR (thin film): 3015, 1708, 1611 cm\(^{-1}\)
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.32 (s, 1H, -NH), 8.37 (d, 1H, -NH, J = 4.8 Hz), 7.71 (d, 1H, Ar-H, J = 8 Hz), 7.47 (m, 1H, Ar-H), 7.18 (t, 1H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, Ar-H, J = 8 Hz), 3.79-3.76 (m, 1H, -\(\alpha\)CH), 1.20 (d, 3H, -CH\(_3\), J = 6.8 Hz);
\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.6, 168.1, 137.2, 132.7, 131.2, 126.0, 124.3, 121.3, 47.7, 14.2;
LCMS (APCI): m/z calcd. For C\(_{10}\)H\(_{10}\)N\(_2\)O\(_2\): 190.0742; found: 191.0731 (M+1)

**Compound 4c: 3-isopropyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione**
Off-white solid; Yield = 63.6% (144 mg); M.P. = 250-253 °C;
IR (thin film): 2960, 1699, 1563 cm\(^{-1}\)
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.36 (s, 1H, -NH), 8.55 (d, 1H, -NH, J = 6 Hz), 7.73 (dd, 1H, Ar-H, J = 2.2 & 8.8 Hz), 7.50-7.49 (m, 1H, Ar-H), 7.22 (t, 1H, Ar-H, J = 9.6 Hz), 7.09 (d, 1H, Ar-H, J = 10.8 Hz), 3.24-3.19 (m, 1H, -\(\alpha\)CH), 1.9 (br, 1H, -\(\beta\)CH), 0.94-0.87 (m, 6H, -(CH\(_3\))\(_2\));
\(^1^3\)C NMR (100 MHz, DMSO): \(\delta\) 169.8, 166.6, 137.0, 132.0, 130.9, 126.2, 123.9, 120.7, 52.2, 38.7, 35.7;
LCMS (APCI): m/z calcd. For C\(_{12}\)H\(_{14}\)N\(_2\)O\(_2\): 218.1055; found: 219.0239 (M+1)
Compound 4d: 3-isobutyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Off-white solid; Yield = 59% (135 mg); M.P. = 242-243 °C;
IR (thin film): 2907, 1701, 1598, 1320 cm⁻¹
¹H NMR (400 MHz, CDCl₃): δ 10.34 (s, 1H, -NH), 8.41 (d, 1H, -NH, J = 6 Hz), 7.70 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.49-7.45 (m, 1H, Ar-H), 7.18 (t, 1H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, Ar-H, J = 8.4 Hz), 3.58-3.53 (m, 1H, -αCH, J = 6.4 Hz), 1.54-1.50 (m, 2H, -γCH₂), 0.82 (d, 3H, -CH₃, J = 6.4 Hz), 0.74 (d, 3H, -CH₃, J = 6.8 Hz);
¹³C NMR (100 MHz, CDCl₃): δ 171.5, 169.0, 137.0, 132.3, 128.4, 126.9, 124.4, 53.7, 41.3, 24.4, 22.5;
LCMS (APCI): m/z calcd. For C₁₃H₁₆N₂O₂: 232.1212; found: 233.1427 (M+1)⁺

Compound 4e: 3-(sec-butyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 59.9% (139 mg); M.P. = 245-248 °C;
IR (thin film): 3211, 1711, 1552, 1525 cm⁻¹
¹H NMR (400 MHz, CDCl₃): δ 10.34 (s, 1H, -NH), 8.41 (d, 1H, -NH, J = 6 Hz), 7.70 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.49-7.45 (m, 1H, Ar-H), 7.18 (t, 1H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, Ar-H, J = 8.4 Hz), 3.58-3.53 (m, 1H, -αCH, J = 6.4 Hz), 1.54-1.50 (m, 2H, -γCH₂), 0.82 (d, 3H, -CH₃, J = 6.4 Hz), 0.74 (d, 3H, -CH₃, J = 6.8 Hz);
¹³C NMR (100 MHz, CDCl₃): δ 171.1, 169.0, 137.0, 132.3, 128.4, 126.9, 124.4, 120.8, 39.3, 27.1, 16.4, 10.9;
LCMS (APCI): m/z calcd. For C₁₃H₁₆N₂O₂: 232.1212; found: 233.0291 (M+1)⁺

Compound 4f: 1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione
creamy solid; Yield = 70.3% (152 mg); M.P. = 321-324 °C;
IR (thin film): 2914, 1713, 1622, 1369 cm⁻¹
¹H NMR (400 MHz, DMSO): δ 10.45 (s, 1H, -NH), 7.76 (dd, 1H, Ar-H, J = 1.6 & 6 Hz), 7.50-7.46 (m, 1H, Ar-H), 7.21-7.18 (m, 1H, Ar-H), 7.11 (d, 1H, Ar-H, J = 7.6 Hz), 4.08 (t, 1H, -αCH), 3.59-3.54 (m, 1H, -δCH₂), 3.46-3.40 (m, 1H, -δCH₂), 1.96-1.77 (m, 4H, -β&γCH₂);
\( ^{13} \text{C NMR} \) (100 MHz, DMSO): \( \delta \) 171.2, 165.0, 136.8, 132.5, 130.7, 127.0, 124.2, 121.7, 56.6, 47.3, 26.2, 23.5;

\( \text{LCMS (APCI):} \) m/z calcd. For C\(_{12}\)H\(_{12}\)N\(_2\)O\(_2\): 216.0899, found: 217.0070 (M+1)^+

**Compound 4g: 3-benzyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione**

Off-white solid; Yield = 63.5\% (169 mg); M.P. = 280-281 °C;

\( \text{IR (thin film):} \) 3340, 1695, 1596, 1050 cm\(^{-1}\)

\( ^{1} \text{H NMR} \) (400 MHz, DMSO): \( \delta \) 10.40 (s, 1H, -NH), 8.50 (d, 1H, -NH, J = 6.4 Hz), 7.48 (t, 1H, Ar-H, J = 7.2 Hz), 7.30-7.07 (m, 8H, Ar-H), 3.90-3.85 (m, 1H, -\( \alpha \)CH), 3.14-3.09 (m, 1H, -CH\(_2\)), 2.87-2.81 (m, 1H, -CH\(_2\));

\( ^{13} \text{C NMR} \) (100 MHz, DMSO): \( \delta \) 171.7, 168.1, 138.4, 137.2, 132.7, 130.8, 129.8, 128.6, 126.8, 124.4, 121.4, 54.3, 33.7

\( \text{LCMS (APCI):} \) m/z calcd. For C\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\): 266.1055, found: 267.0137 (M+1)^+

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**Compound 4h: 3-((1H-indol-3-yl)methyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione**

Light brownish solid; Yield = 77.8\% (239 mg); M.P. = 251-253 °C;

\( \text{IR (thin film):} \) 3105, 1756, 1699, 1640, 1365 cm\(^{-1}\)

\( ^{1} \text{H NMR} \) (400 MHz, DMSO): \( \delta \) 10.85 (s, 1H, indole-NH), 10.42 (s, 1H, -NH), 8.45 (d, 1H, -NH, J = 4.4 Hz), 7.63 (d, 1H, Ar-H, J = 6.8 Hz), 7.47-7.46 (m, 2H, Ar-H), 7.30 (d, 1H, indole-Ar-H, J = 7.6 Hz), 7.22 (s, 1H, indole-Ar-H), 7.15 (t, 1H, Ar-H, J = 6.8, 7.2 Hz), 7.09 (d, 1H, indole-Ar-H, J = 7.6 Hz), 7.01 (t, 1H, indole-Ar-H, J = 6.4 Hz), 6.88 (t, 1H, indole-Ar-H, J = 6.8 Hz), 3.87 (m, 1H, -CH\(_2\)), 3.23-3.20 (m, 1H, -\( \beta \)CH\(_2\)), 3.01-3.95 (m, 1H, -\( \beta \)CH\(_2\));

\( ^{13} \text{C NMR} \) (100 MHz, DMSO): \( \delta \) 171.9, 168.0, 137.2, 136.5, 132.7, 130.8, 127.4, 124.7, 124.3, 121.4, 118.8, 118.6, 111.8, 110.1, 53.3, 24.0;

\( \text{LCMS (APCI):} \) m/z calcd. For C\(_{18}\)H\(_{15}\)N\(_3\)O\(_2\): 305.1164, found: 306.0160 (M^+1)
Compound 4i: 4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 66.8% (127mg); M.P. = 188-192 °C;
IR (thin film): 2842, 1685, 1596, 1050 cm⁻¹
¹H NMR (400 MHz, CDCl₃): δ 10.50 (s, 1H, -NH), 7.72 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.49-7.45 (m, 1H, Ar-H), 7.19 (t, 1H, Ar-H, J = 7.6 Hz), 7.09 (d, 1H, Ar-H, J = 8 Hz), 3.81 (s, 2H, -CH₂), 3.09 (s, 3H, N-CH₃);
¹³C NMR (100 MHz, CDCl₃): δ 170.2, 167.0, 137.4, 132.4, 131.3, 126.6, 124.3, 121.2, 52.6, 36.3;
LCMS (APCI): m/z calcd. For C₁₀H₁₀N₂O₂: 190.0742; found: 190.9944 (M⁺+1)

Compound 4j: 3-phenyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 63.5% (160 mg); M.P. = 289-291 °C;
IR (thin film): 3076, 1693, 1595, 1505, 1298 cm⁻¹
¹H NMR (400 MHz, CDCl₃): δ 8.65 (s, 1H, -NH), 7.96 (d, 1H, -NH, J = 7.6 Hz), 7.47 (t, 1H, Ar-H, J = 7.6 Hz), 7.34 (broad, 5H, Ar-H), 7.25 (t, 1H, Ar-H, J = 7.2 Hz), 7.06 (d, 1H, Ar-H, J = 3.6 Hz), 6.99 (d, 1H, Ar-H, J = 8 Hz), 4.99 (d, 1H, N-CH, J = 3.2 Hz);
¹³C NMR (100 MHz, CDCl₃): δ 171.0, 168.6, 135.5, 133.2, 131.4, 128.9, 128.8, 127.7, 125.3, 120.7, 58.0, 29.6;
LCMS (APCI): m/z calcd. for C₁₅H₁₂N₂O₂: 252.0899; found: 253.0992 (M⁺+1)

Compound 5c: 3-methyl-2-(4-oxoquinazolin-3(4H)-yl)butanoic acid
Colourless solid; Yield = 72% (178 mg); M.P. = 218-220 °C;
IR (thin film): 3075, 1682, 1596, 1506, 1263 cm⁻¹
¹H NMR (400 MHz, DMSO): δ 13.1 (br, 1H, -COOH), 8.39 (s, 1H, =CH), 8.13 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.86-7.82 (m, 1H, Ar-H), 7.68 (d, 1H, Ar-H, J = 8 Hz), 7.55 (t, 1H, Ar-H, J = 8 Hz), 4.94 (d, 1H, N-CH, J = 9.6 Hz), 2.64-2.58 (m, 1H, CH), 1.11 (d, 3H, -CH₃, J = 6.4 Hz), 0.74 (d, 3H, -CH₃, J = 6.4 Hz);
¹³C NMR (100 MHz, DMSO): δ 171.0, 160.5, 147.8, 147.4, 135.2, 127.8, 126.8, 121.5, 63.1, 28.8, 20.8, 19.5;
LCMS (API): m/z calcd. For C₁₂H₁₂N₂O₂: 246.1004, found: 247.0138 (M⁺+1)
Compound 5e: 3-methyl-2-(4-oxoquinazolin-3(4H)-yl)pentanoic acid
Off-white solid; Yield = 78% (203 mg); M.P. = 203-205 °C;
IR (thin film): 3297, 1706, 1686, 1615, 1552 cm⁻¹
¹H NMR (400 MHz, DMSO): δ 13.1 (br, 1H, -COOH), 8.47 (s, 1H, =CH), 8.14 (d, 1H, Ar-H, J = 7.6 Hz), 7.84 (t, 1H, Ar-H J = 7.6 Hz), 7.69 (d, 1H, Ar-H, J = 8.4 Hz), 7.55 (t, 1H, Ar-H, J = 7.6 Hz), 5.05 (d, 1H, -αCH, J = 9.6 Hz), 1.21 (m, 1H, -βCH), 1.07 (d, 3H, -CH₃, J = 6.4 Hz), 1.10-0.94 (m, 2H, -CH₂), 0.76 (t, 3H, -CH₃, J = 7.2 Hz);
¹³C NMR (100 MHz, DMSO): δ 171.2, 160.5, 147.7, 147.2, 135.2, 127.8, 127.7, 126.8, 121.4, 61.4, 34.8, 25.3, 16.7, 10.7;
LCMS (API): m/z calcd. For C₁₄H₁₆N₂O₃: 260.1161, found: 261.0240 (M+1)⁺

Compound 3a: methyl (2-aminobenzoyl)glycinate
Creamy solid; Yield = 58.8% (241 mg); M.P. = 114-116 °C;
IR (thin film): 2943, 1697, 1647, 1543 cm⁻¹
¹H NMR (400 MHz, CDCl₃): δ 7.39 (d, 1H, Ar-H, J = 7.6 Hz), 7.20 (t, 1H, Ar-H, J = 7.6 Hz), 6.67-6.63 (m, 2H, Ar-H), 6.67-6.63 (m, 1H, -NH), 5.50 (broad, 2H, -NH₂); 4.18 (d, 2H, -CH₂, J = 5.2 Hz), 3.78 (s, 3H, -OCH₃);
³C NMR (100 MHz, CDCl₃): δ 170.1, 167.8, 142.2, 133.9, 126.3, 118.6, 117.8, 116.1, 50.8, 42.1;
LCMS (APCI): m/z calcd. for C₁₀H₁₂N₂O₃: 208.0848; found: 209.0011 (M+1)⁺

Compound 3b: methyl (2-aminobenzoyl)alaninate
Light yellowish solid; Yield = 58.4% (257 mg); M.P. = 101-104 °C;
IR (thin film): 3076, 1693, 1595, 1505 cm⁻¹
¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, 1H, Ar-H, J = 7.2 Hz), 7.24 (t, 1H, Ar-H, J = 7.8 Hz), 6.66-6.57 (m, 2H, Ar-H), 6.66-6.57 (m, 1H, -NH), 5.53 (broad, 2H, -NH₂); 4.26 (m, 1H, -αCH), 3.76 (s, 3H, -OCH₃), 1.01 (d, 3H, -CH₃, J = 6.2 Hz);
³C NMR (100 MHz, CDCl₃): δ 171.5, 168.9, 141.5, 133.4, 129.2, 121.1, 118.1, 117.9, 52.7, 50.2, 18.9;
LCMS (APCI): m/z calcd. for C₁₁H₁₄N₂O₃: 222.1004; found: 222.9917 (M⁺+1)
**Compound 3c: methyl (2-aminobenzoyl)valinate**

Off-white solid; Yield = 56.1% (230mg); M.P. = 96-98 °C;

IR (thin film): 2896, 1688, 1605, 1514, 1227 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 (d, 1H, Ar-H, J = 7.2 Hz), 7.22-6.81 (m, 3H, Ar-H), 7.22-6.81 (m, 1H, -NH), 5.48 (broad, 2H, -NH$_2$); 4.57-4.49 (m, 1H, -$^\alpha$CH), 3.76 (s, 3H, -OCH$_3$); 1.69-1.63 (m, 1H, -$^\beta$CH), 0.98-0.87 (m, 6H, -(CH$_3$)$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.6, 168.4, 148.9, 133.7, 126.4, 121.2, 120.1, 119.0, 54.3, 50.4, 36.7, 16.5, 16.4;

LCMS (APCI): m/z calcd. for C$_{13}$H$_{18}$N$_2$O$_3$: 250.1317; found: 251.0417 (M+1)$^+$

**Compound 3d: methyl (2-aminobenzoyl)leucinate**

Light creamy solid; Yield = 63.2 % (335mg); M.P. = 98-101 °C;

IR (thin film): 2974, 1679, 1595, 1543, 1359 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 (d, 1H, Ar-H, J = 7.6 Hz), 7.24 (t, 1H, Ar-H, J = 7.6 Hz), 6.76-6.68 (m, 2H, Ar-H), 6.76-6.68 (m, 1H, -NH), 5.57 (broad, 2H, -NH$_2$); 4.29-4.26 (m, 1H, -$^\alpha$CH), 3.78 (s, 3H, -OCH$_3$), 1.70-1.68 (m, 2H, -$^\beta$CH), 1.51-1.49 (m, 1H, -$^\gamma$CH), 0.93 (d, 3H, -CH$_3$, J = 6.8 Hz), 0.82 (d, 3H, -CH$_3$, J = 6.8 Hz);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.9, 168.4, 148.9, 133.7, 126.4, 121.2, 120.5, 119.4, 53.7, 50.4, 41.0, 26.5, 19.9, 19.8;

LCMS (APCI): m/z calcd. for C$_{14}$H$_{20}$N$_2$O$_3$: 264.1474; found: 265.1349 (M+1)$^+$

**Compound 3e: methyl 2-(2-aminobenzamido)-3-methylpentanoate**

Light rosy solid; Yield = 64.5% (342 mg); M.P. = 91-92 °C;

IR (thin film): 2974, 1697, 1505, 1543, 1359 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 (d, 1H, Ar-H, J = 7.6 Hz), 7.25 (t, 1H, Ar-H, J = 7.6 Hz), 6.81-6.66 (m, 2H, Ar-H), 6.81-6.66 (m, 1H, -NH), 5.44 (broad, 2H, -NH$_2$); 4.36-4.31 (m, 1H, -$^\alpha$CH), 3.80 (s, 3H, -OCH$_3$); 1.57-1.54 (m, 1H, -$^\beta$CH), 1.52-1.48 (m, 2H, -$^\gamma$CH), 0.92 (d, 3H, -CH$_3$, J = 6.8Hz), 0.84 (d, 3H, -CH$_3$, J = 6.8 Hz);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.1, 168.7, 140.0, 133.2, 128.4, 121.2, 120.4, 120.1, 119.0, 54.7, 43.4, 38.4, 33.4, 26.1, 19.7;

LCMS (APCI): m/z calcd. for C$_{14}$H$_{20}$N$_2$O$_3$: 264.1474; found: 265.1295(M+1)$^+$
**Compound 3f: methyl (2-aminobenzoyl)prolinate**

Colourless floppy solid; Yield = 66% (330 mg); M.P. = 116-118 °C;
IR (thin film): 3075, 2832, 1761, 1694, 1593, 1507, 1228 cm⁻¹

**¹H NMR** (400 MHz, CDCl₃): δ 7.29 (d, 1H, Ar-H, J = 6.8 Hz), 7.17 (t, 1H, Ar-H, J = 6.8 Hz), 6.81-6.76 (m, 2H, Ar-H), 6.81-6.76 (m, 1H, -NH), 5.47 (broad, 2H, -NH₂); 4.50-4.46 (m, 1H, -α CH), 3.69 (s, 3H, -OCH₃), 3.47-3.43 (m, 1H, -δ CH₂), 2.01-1.81 (m, 4H, -β&γ CH₂);

**¹³C NMR** (100 MHz, CDCl₃): δ 171.6, 167.4, 140.1, 136.4, 130.5, 124.5, 118.6, 118.1, 55.1, 49.2, 36.4, 24.8, 20.7;

**LCMS (APCI):** m/z calcd. for C₁₃H₁₆N₂O₃: 248.1161; found: 249.1007 (M+1)⁺

**Compound 3g: methyl (2-aminobenzoyl)phenylalaninate**

Light sandy brown solid; Yield = 68.1% (409 mg); M.P. = 120-121 °C;
IR (thin film): 3348, 2847, 1541, 1264 cm⁻¹

**¹H NMR** (400 MHz, CDCl₃): δ 7.39 (d, 1H, Ar-H, J = 7.6 Hz), 7.24 (t, 1H, Ar-H, J = 7.6 Hz), 6.80-6.63 (m, 7H, Ar-H), 6.70-6.63 (m, 1H, -NH), 5.50 (broad, 2H, -NH₂); 4.81-4.78 (m, 1H, -α CH), 3.81 (s, 3H, -CH₃), 2.88-2.74 (m, 2H, -CH₂);

**¹³C NMR** (100 MHz, CDCl₃): δ 171.5, 169.4, 141.7, 137.5, 133.6, 126.9, 126.4, 124.1, 123.9, 122.2, 122.0, 58.1, 53.4, 34.8;

**LCMS (APCI):** m/z calcd. for C₁₇H₁₈N₂O₃: 298.1317; found: 299.0332 (M+1)⁺

**Compound 3h: methyl (2-aminobenzoyl)tryptophanate**

Light brownish solid; Yield = 66.5% (446 mg); M.P. = 118-119 °C;
IR (thin film): 3456, 2949, 1532, 1057 cm⁻¹

**¹H NMR** (400 MHz, CDCl₃): δ 10.69 (s, 1H, indole-NH), 7.66 (d, 1H, Ar-H, J = 7.0 Hz), 7.57-7.53 (m, 2H, Ar-H), 7.46-6.89 (m, 6H, Ar-H), 7.46-6.89 (m, 1H, -NH), 5.61 (broad, 2H, -NH₂), 4.62 (m, 1H, -α CH), 3.58 (s, 3H, -OCH₃), 3.09-2.97 (m, 2H, -β CH₂);
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.2, 168.7, 142.6, 136.7, 133.4, 132.9, 131.7, 129.8, 124.7, 122.8, 121.1, 119.1, 112.1, 110.6, 60.2, 51.0, 23.7;  
**LCMS (APCI):** m/z calcd. for C$_{19}$H$_{19}$N$_3$O$_3$: 337.1426; found: 338.0373 (M+1)$^+$

![Compound 3j: methyl (S)-2-(2-aminobenzamido)-2-phenylacetate](image)

**Compound 3j: methyl (S)-2-(2-aminobenzamido)-2-phenylacetate**  
Colourless solid; Yield = 56.5% (327 mg); M.P. = 116-118 °C;  
**IR (thin film):** 3447, 2973, 1572, 1066 cm$^{-1}$  
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61 (t, 1H, Ar-H, J = 6.8 Hz), 7.24-6.82 (m, 8H, Ar-H), 5.68 (broad, 2H, -NH$_2$), 5.01 (d, 1H, $^\alpha$CH, J = 4.1 Hz), 3.77 (s, 3H, -OCH$_3$);  
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.1, 167.9, 141.7, 134.5, 132.7, 129.4, 128.9, 128.8, 126.11, 118.8, 118.2, 117.6, 116.4, 61.2, 51.9;  
**LCMS (APCI):** m/z calcd. for C$_{16}$H$_{16}$N$_2$O$_3$: 284.1161; found: 285.0210 (M+1)$^+$

![Compound 3k: methyl (2-aminobenzoyl)serinate](image)

**Compound 3k: methyl (2-aminobenzoyl)serinate**  
Creamy solid; Yield = 61.3% (292mg); M.P. = 133-134 °C;  
**IR (thin film):** 3447, 2973, 1572, 1066 cm$^{-1}$  
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36 (d, 1H, Ar-H, J = 7.2 Hz), 7.23 (t, 1H, Ar-H, J = 7.0 Hz), 6.71-6.59 (m, 2H, Ar-H), 6.71-6.63 (m, 1H, -NH), 5.47 (broad, 2H, -NH$_2$); 4.63-4.59 (m, 1H, $^\alpha$CH), 3.80 (s, 3H, -OCH$_3$), 2.01 (d, 2H, $^\beta$CH$_2$, J = 6.8 Hz);  
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.8, 168.3, 148.7, 133.7, 130.1, 128.3, 118.7, 116.8, 60.4, 56.7, 50.1;  
**LCMS (APCI):** m/z calcd. for: C$_{11}$H$_{14}$N$_2$O$_4$: 238.0954; found: 238.9813 (M+1)$^+$
**Compound 3l: methyl 2-(2-aminobenzamido)-3-hydroxybutanoate**

Creamy solid; Yield = 59.7% (301 mg); M.P. = 127-128 °C;

IR (thin film): 3447, 2973, 1572, 1066 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.39 (d, 1H, Ar-H, J = 7.0 Hz), 7.21 (t, 1H, Ar-H, J = 7.0 Hz), 6.81-6.56 (m, 2H, Ar-H), 6.81-6.67 (m, 1H, -NH), 5.51 (broad, 2H, -NH\(_2\)); 4.63-4.59 (m, 1H, -\(\alpha\)CH), 3.76 (s, 3H, -OCH\(_3\)), 2.32 (m, 1H, -\(\beta\)CH), 1.21 (d, 3H, -CH\(_3\), J = 6.2 Hz);

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 169.9, 168.4, 140.1, 133.7, 126.1, 121.5, 118.3, 118.0, 57.4, 51.3, 44.3, 20.8;

LCMS (APCI): m/z calcd. for C\(_{12}\)H\(_{16}\)N\(_2\)O\(_4\): 252.1110; found: 253.0058 (M+1)^+  

**Compound 3m: methyl (2-aminobenzoyl)tyrosinate**

Light buff solid; Yield = 59% (371 mg); M.P. = 132-134 °C;

IR (thin film): 3447, 2973, 1572, 1066 cm\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.46 (d, 1H, Ar-H, J = 6.2 Hz), 7.30 (t, 1H, Ar-H, J = 6.2 Hz), 7.23 (dd, 2H, Ar-H, J = 1.6 & 6.0 Hz), 7.01-6.76 (m, 4H, Ar-H), 7.01-6.76 (m, 1H, -NH), 5.66 (broad, 2H, -NH\(_2\)); 4.52-4.49 (m, 1H, -\(\alpha\)CH), 3.77 (s, 3H, -OCH\(_3\)), 2.69-2.53 (m, 2H, -CH\(_2\));

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.2, 168.4, 151.1, 148.6, 131.2, 131.0, 130.2, 130.0, 128.4, 118.8, 118.4, 116.8, 115.6, 115.1, 56.4, 51.4, 28.4;

LCMS (APCI): m/z calcd. for C\(_{17}\)H\(_{18}\)N\(_2\)O\(_4\): 314.1267; found: 315.0268 (M+1)^+
Spectra for Compounds

$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4a
Mass: 176.0586
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4b
Mass: 190.0742
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4c
$^1$H NMR and Mass Spectra for Compound 4d
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4f
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4g
Mass: 266.1055
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4h
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound $4i$
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 4j
Mass: 252.0899
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 5c
Mass: 246.1004
$^1$H NMR, $^{13}$C NMR and Mass Spectra for Compound 5e
Mass: 260.1161
$^1$H NMR and Mass Spectra for Compound 3a

Mass: 208.0848
Mass Spectrum for Compound 3c

Mass Spectrum for Compound 3g
Mass Spectrum for Compound 3k

Mass: 238.0954

Mass Spectrum for Compound 3m

Mass: 314.1267