SUPPORTING INFORMATION

Ammonium Chloride Promoted Ugi-Four Component-Five Center Reaction of α-Substituted α-Isocyano Acetic Acid: A Strong Solvent Effect

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Experimental Section

General information

Melting points were recorded using Reichert melting point apparatus.

Mass spectra were obtained either from an AEI MS-50 instrument using electron impact ionization (EI), from an AEI MS-9 using electron spray (ES), or from a MALDI-TOF type of instrument for the high resolution mass spectra (HRMS).

Proton NMR (^{1}H) spectra were recorded at 300 MHz on a Bruker AC-300 spectrometer. Carbon NMR (^{13}C) spectra were similarly recorded at 75 MHz on a Bruker AC-300 spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence.

Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in deuterochloroform ($CDCl_3$). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, brs: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz).

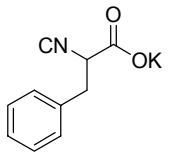
Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer.

Flash chromatography was performed using Kieselgel Si 60, 40-63 μm particle sized silica gel (200-400 mesh). Visualization was achieved under a UVP mineralight UVGL-58

lamp, and by developing the plates with Draggendorf's reagent or potassium permanganate ($KMnO_4$).

All reagents were obtained from commercial suppliers unless otherwise stated. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen. Diethyl ether was dried over sodium wire. Other solvents were dried by distillation from the following: tetrahydrofuran (sodium/benzophenone); dichloromethane (calcium hydride); ethyl acetate (magnesium sulfate). All reactions requiring anhydrous conditions were performed in flame-dried apparatus under a nitrogen atmosphere. Organic extracts were, in general, dried over anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4).

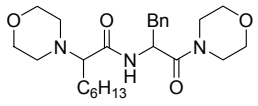
General procedure for the synthesis of 4:



4a

To a solution of the corresponding ester (2.88g, 15.2 mmol) in THF (24.0 mL) and water (6.0 mL) was added potassium hydroxide (853.0 mg, 15.2 mmol) and the resulting mixture was stirred at room temperature for 5 h. The solvent was then removed *in vacuo* and the resulting salt **4a** (3.2 g, 100 %) was used as such without further purification. [1]

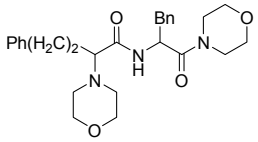
^{1}H NMR (300 MHz, CD_3OD) δ 2.92-3.26 (2H, m, CH_2), 4.28 (1H, m, CH), 7.19-7.28 (5H, m, Ar-H; ^{13}C NMR (75 MHz, CD_3OD) δ 40.2 (t), 64.4 (d), 129.8 (d), 131.2 (d), 132.1 (d), 140.2 (s), 158.1 (s) and 174.4 (s); [Found (ES+): $[M+K]^+$ 251.9838, $C_{10}H_8K_2NO_2$ requires 251.9829].



7a

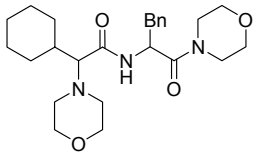
General procedure for the synthesis of 7: Morpholine (106.0 μL, 2.0 eq.) was added to a solution of heptanal (70.0 μL, 1.0 eq.) and ammonium chloride (40.0 mg, 1.5 eq.) in dry toluene (4.0 mL). The mixture was then stirred for 30 min at room temperature. Potassium 2-isocyano-3-phenylpropanoate (107 mg, 1.0 eq.) was added and the reaction was allowed to

stir for 18 h at room temperature. The reaction was then evaporated to dryness. The crude mixture was re-dissolved in ethyl acetate (10.0 mL), washed with water (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Putification by flash column chromatography on silica gel (eluent: ethyl acetate) gave pure *2-Morpholino-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)octanamide* (mixture of stereoisomers) as a white solid (201 mg, 90 %); mp 85-87°C; IR (film): 3367, 2962, 2929, 2861, 1663, 1639, 1499, 1461, 1444, 1268, 1115 and 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 5.1 Hz, CH_3), 1.25 (8H, m, 4 × CH_2), 1.62 (2H, m, CH_2), 2.36-2.51 (4H, m, 2 × CH_2), 2.80 (1H, t, J = 6.5 Hz, CHN), 2.99-3.10 (4H, m, CH_2, CH_2Ph), 3.43-3.70 (10H, m, 5 × CH_2), 5.15 (1H, m, CHNH), 7.19-7.31 (5H, m, Ar-H), 7.53 and 7.59 (1H, 2 × d, J = 8.7 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.5 (t), 28.1 (t), 29.4 (t), 31.6 (t), 39.6 (t), 42.3 (t), 46.1 (t), 48.7 (d), 50.7 (t), 66.2 (t), 66.5 (t), 67.2 (t), 69.4 (d), 127.2 (d), 128.7 (d), 129.4 (d), 136.1 (s), 170.0 (s) and 172.5 (s); *m/z* (ES+) 446 [$(M+H)^+$, 100 %], 468 (94) and 184 (7); [Found (ES+): $[M+Na]^+$ 468.2838, $C_{25}H_{39}N_3O_4Na$ requires 468.2838].



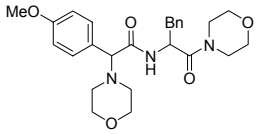
7b

2-Morpholino-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)-4-phenylbutanamide (mixture of stereoisomers) was isolated as a colourless oil (212 mg, 91 %); IR (film) 3368, 2970, 2927, 2862, 1663, 1641, 1496, 1455, 1443, 1268, 1115, 1030 and 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (2H, m, CH_2), 2.46 (4H, m, 2 × CH_2), 2.55-2.76 (2H, m, CH_2), 2.88 (1H, t, J = 6.3 Hz, CHN), 3.00-3.11 (4H, m, 2 × CH_2), 3.38-3.68 (10H, m, 5 × CH_2), 5.17 (1H, q, J = 7.8 Hz, CHNH), 7.14-7.31 (10H, m, Ar-H), 7.61 (1H, d, J = 8.4 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0 (t), 32.8 (t), 39.8 (t), 42.3 (t), 46.1 (t), 48.9 (d), 50.4 (t), 66.2 (t), 66.5 (t), 67.2 (t), 68.2 (d), 126.0 (d), 127.3 (d), 128.4 (d), 128.7 (d), 129.4 (d), 136.0 (s), 141.6 (s), 170.0 (s) and 172.0 (s); *m/z* (ES+) 466 [$(M+H)^+$, 69 %] and 488 (100); [Found (ES+): $[M+H]^+$ 466.2690, $C_{27}H_{36}N_3O_4$ requires 466.2706].



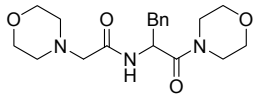
7c

2-Cyclohexyl-2-morpholino-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)acetamide (mixture of stereoisomers) was isolated as a white solid (180 mg, 81 %); mp 157-159°C; IR (film) 3364, 2930, 2858, 1663, 1638, 1500, 1462, 1445, 1268 and 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (1H, m, CH), 0.99-1.25 (4H, m, 2 × CH_2), 1.50-1.74 (6H, m, 3 × CH_2), 2.46-2.55 (5H, m, 2 × CH_2, CHN), 3.02 (4H, m, CH_2, CH_2Ph), 3.43-3.70 (10H, m, 5 × CH_2), 5.19 (1H, m, CHNH), 7.06 (1H, d, J = 7.8 Hz, NH) and 7.14-7.27 (5H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2 (t), 26.5 (t), 26.6 (t), 28.4 (t), 30.5 (t), 36.2 (d), 39.9 (t), 42.3 (t), 46.1 (t), 48.8 (d), 51.1 (t), 66.2 (t), 66.5 (t), 67.2 (t), 75.0 (d), 127.3 (d), 128.7 (d), 129.4 (d), 136.1 (s), 170.1(s) and 170.7 (s)); *m/z* (ES+) 444 [$(M+H)^+$, 52 %] and 466 (100); [Found (ES+): $[M+H]^+$ 444.2888, $C_{25}H_{38}N_3O_4Na$ requires 444.2862].



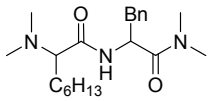
7d

2-(4-Methoxyphenyl)-2-morpholino-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)acetamide (mixture of stereoisomers) was isolated as a white solid (139 mg, 59 %); mp 141-142°C; IR (film): 3371, 2969, 1669, 1637, 1512, 1462, 1442, 1254 and 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18-2.33 (4H, m, 2 × CH_2), 2.98-3.07 (4H, m, 2 × CH_2), 3.21-3.39 (2H, m, CH_2), 3.51-3.72 (8H, m, 4 × CH_2, CHN), 3.78 (3H, 2 × s, OCH_3), 5.06-5.21 (1H, m, CHNH), 6.83 (2H, m, Ar-H), 7.13-7.30 (8H, m, Ar-H), 7.64 and 7.77 (1H, 2 × d, J = 9.0 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1 (t), 42.4 (t), 46.0 (t), 48.6 (d), 52.1 (t), 55.3 (q), 66.2 (t), 66.5 (t), 67.0 (t), 75.5 (d), 114.1 (d), 127.2 (d), 128.7 (d), 129.4 (d), 129.9 (d), 136.1 (s), 159.6 (s), 169.7 (s) and 170.8 (s); *m/z* (ES+) 468 [$(M+H)^+$, 0.5 %], 490 (100), 381 (46), 353 (12) and 266 (6); [Found (ES+): $[M+Na]^+$ 490.2296, $C_{26}H_{33}N_3O_5Na$ requires 490.2318].



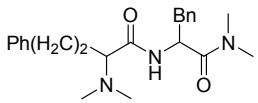
7e

2-Morpholino-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)acetamide was isolated as a coulourless oil (118 mg, 65 %); IR (film): 3366, 2970, 2862, 1666, 1640, 1508, 1445, 1115 and 908 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37-2.51 (4H, m, 2 × CH_2), 2.97-3.10 (6H, m, CH_2N, CH_2Ph, CH_2), 3.36-3.70 (10H, m, 5 × CH_2), 5.16 (1H, m, CHNH), 7.18-7.33 (5H, m, Ar-H), 7.77 (1H, d, J = 8.4 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6 (t), 42.3 (t), 46.1 (t), 48.7 (d), 53.7 (t), 61.9 (t), 66.2 (t), 66.5 (t), 66.9 (t), 127.3 (d), 128.7 (d), 129.5 (d), 136.0 (s), 169.4 (s) and 169.9 (s); *m/z* (ES+) 362 [$(M+H)^+$, 25 %] and 384 (100); [Found (ES+): $[M+Na]^+$ 384.1864, $C_{19}H_{27}N_3O_4Na$ requires 384.1899].



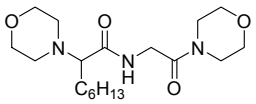
7f

N-[1-(dimethylcarbamoyl)-2-phenylethyl]-2-(dimethylamino)octanamide (mixture of stereoisomers) was isolated as pale yellow solid (172 mg, 95 %); mp 115-116°C; IR (film): 3358, 2930, 1641, 1494, 1455, 1418, and 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.6 Hz, CH_3), 1.26 (8H, m, 4 × CH_2), 1.60 (2H, m, CH_2), 2.22 (6H, s, 2 × CH_3), 2.64 (3H, s, CH_3), 2.73 (1H, dd, J = 6.9 and 5.7 Hz, CHN), 2.85 (3H, s, CH_3), 3.00 (2H, m, CH_2Ph), 5.14 (1H, m, CHNH), 7.19-7.30 (5H, m, Ar-H), 7.51 (1H, d, J = 8.4 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.7 (t), 28.4 (t), 29.5 (t), 31.7 (t), 35.5 (q), 36.9 (q), 39.7 (t), 42.5 (q), 49.6 (d), 69.6 (d), 126.9 (d), 128.4 (d), 129.4 (d), 136.6 (s), 171.3 (s) and 173.0 (s); *m/z* (ES+) 362 [$(M+H)^+$, 100 %], 384 (9) and 142 (33); [Found (ES+): $[M+H]^+$ 362.2816, $C_{21}H_{36}N_3O_2$ requires 362.2808].



7g

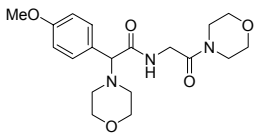
N-(1-(Dimethylcarbamoyl)-2-phenylethyl)-2-(dimethylamino)-4-phenylbutanamide (mixture of stereoisomers) was isolated as a white solid (158 mg, 83 %); mp 107-109°C; IR (film): 3359, 2940, 1641, 1496, 1454, 1418, 1403 and 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (2H, m, CH_2), 2.21 (6H, s, 2 × CH_3), 2.46-2.69 (2H, m, CH_2), 2.73 (3H, s, CH_3), 2.80 (1H, t, J = 6.3 Hz, CHN), 2.88 (3H, s, CH_3), 3.00 (2H, dd, J = 7.6 and 1.8 Hz, CH_2Ph), 5.20 (1H, m, CHNH), 7.14-7.28 (10H, m, Ar-H), 7.59 (1H, d, J = 8.4 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6 (t), 33.0 (t), 35.6 (q), 36.9 (q), 39.7 (t), 42.3 (q), 49.6 (d), 68.7 (d), 125.8 (d), 127.0 (d), 128.3 (d), 128.5 (d), 129.3 (d), 136.5 (s), 142.0 (s), 171.4 (s) and 172.7 (s); *m/z* (ES+) 382 [$(M+H)^+$, 0.6 %], 404 (65) and 162 (100); [Found (ES+): $[M+Na]^+$ 404.2307, $C_{23}H_{31}N_3O_2Na$ requires 404.2314].



7h

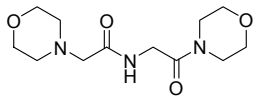
General procedure when potassium isocyanoacetate (4b) is employed: Morpholine (106 µL, 2.0 eq.) was added to a solution of heptanal (70 µL, 1.0 eq.) and ammonium chloride (40 mg, 1.5 eq.) in dry toluene (5 mL). The mixture was then stirred for 30 min at room temperature. Potassium 2-isocyanoacetate (65 mg, 1.0 eq.) was added and the reaction was allowed to stirr for 18 h at 60°C.

The reaction was then evaporated to dryness. The crude obtained was redissolved in ethyl acetate (10 mL), washed with water (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. *2-Morpholino-N-(2-morpholino-2-oxoethyl)octanamide* **7h** was purified by column chromatography on silica gel (100 % ethyl acetate) to give pure title compound as a white solid (152 mg, 85 %); mp 74-75°C; IR (film): 3373, 2961, 2860, 1649, 1507, 1468, 1438 and 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.6 Hz, CH_3), 1.27 (8H, m, 4 × CH_2), 1.68 (2H, m, CH_2), 2.54-2.60 (4H, m, 2 × CH_2), 2.89 (1H, t, J = 6.4 Hz, CHN), 3.43 (2H, m, CH_2), 3.64-3.77 (10H, m, 5 × CH_2), 4.02 (1H, dd, J = 17.4 and 4.2 Hz, CH_2C=O), 4.13 (1H, dd, J = 17.4 and 4.2 Hz, CH_2C=O), 7.76 (1H, t, J = 4.2 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.5 (t), 28.3 (t), 29.5 (t), 31.7 (t), 40.6 (t), 42.3 (t), 44.8 (t), 50.9 (t), 66.4 (t), 66.7 (t), 67.3 (t), 69.6 (d), 166.9 (s) and 173.1 (s); *m/z* (ES+) 356 [$(M+H)^+$, 34 %], 733 (30) and 378 (100); [Found (ES+): $[M+Na]^+$ 378.2362, $C_{18}H_{33}N_3O_4Na$ requires 378.2369].



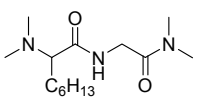
7i

2-(4-Methoxyphenyl)-2-morpholino-N-(2-morpholino-2-oxoethyl)acetamide was isolated as a white solid (29 mg, 15 %); mp 156-157°C; IR (film): 3374, 2970, 1651, 1510, 1465, 1438 and 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (4H, m, 2 × CH_2), 3.40 (2H, m, CH_2), 3.65-3.80 (14H, m, CH, OCH_3, 5 × CH_2), 4.02 (1H, dd, J = 17.3 and 4.5 Hz, CH_2C=O), 4.15 (1H, dd, J = 17.3 and 4.5 Hz, CH_2C=O), 6.85 (2H, d, J = 8.7 Hz, 2 × ArCH), 7.27 (2H, d, J = 8.7 Hz, 2 × ArCH), 7.97 (1H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.8 (t), 42.3 (t), 44.8 (t), 52.2 (t), 55.3 (q), 66.3 (t), 66.7 (t), 67.1 (t), 75.6 (d), 114.1 (d), 127.6 (s), 130.0 (d), 159.6 (s), 166.8 (s) and 171.7 (s); *m/z* (ES+) 378 [$(M+H)^+$, 14 %], 400 (100) and 291 (43); [Found (ES+): $[M+Na]^+$ 400.1811, $C_{19}H_{27}N_3O_5Na$ requires 400.1848].



7j

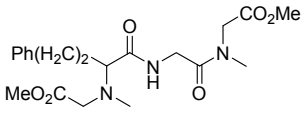
2-morpholino-N-(2-morpholino-2-oxoethyl)acetamide was isolated as a white solid (46 mg, 34 %); mp 148-149°C; Anal. calcd. for $C_{12}H_{21}N_3O_4$ (271.15): C 53.12, H 7.80, O 23.59; found C 52.65, H 7.61, O 23.52; IR (film): 3370, 2972, 1651, 1516, 1438, 1418 and 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (4H, m, 2 × CH_2), 3.07 (2H, s, CH_2N), 3.44 (2H, m, CH_2), 3.66-3.78 (10H, m, 5 × CH_2), 4.10 (2H, d, J = 4.8 Hz, CH_2NH), 8.01 (1H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.6 (t), 42.3 (t), 44.9 (t), 53.9 (t) 61.8 (t), 66.4 (t), 66.7 (t), 67.1 (t), 166.8 (s) and 170.2 (s); *m/z* (ES+) 272 [$(M+H)^+$, 8 %] and 294 (100).



7k

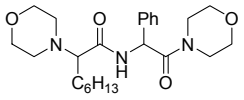
General procedure when the hydrochloric salt of the amine is employed: dimethylamine hydrochloride (122 mg, 3.0 eq.) was added to a solution of heptanal (70 μL, 1.0 eq.) and triethylamine (210 μL, 3.0 eq.) in dry toluene (5 mL). The mixture was then stirred for 30 min at room temperature. Potassium 2-isocyanoacetate (65 mg, 1.0 eq.) was added and the reaction was allowed to stir for 18 h at 60°C.

The reaction was then evaporated to dryness. The crude obtained was redissolved in ethyl acetate (10 mL), washed with water (2 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. *N-[(Dimethylcarbamoyl)methyl]-2-(dimethylamino)octanamide* was purified by column chromatography on silica gel (5 % methanol in dichloromethane) to give pure title compound as a colourless oil (105 mg, 77 %); IR (film): 3366, 2930, 1647, 1506, 1417, and 1406 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.8 Hz, CH_3), 1.27 (8H, m, 4 × CH_2), 1.66 (2H, m, CH_2), 2.30 (6H, s, 2 × CH_3), 2.79 (1H, t, J = 6.3 Hz, CH), 3.00 (6H, s, 2 × CH_3NC=O), 4.03 (1H, dd, J = 17.4 and 4.5 Hz, CH_2C=O), 4.12 (1H, dd, J = 17.4, 4.5 Hz, CH_2C=O), 7.62 (1H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 26.6 (t), 29.0 (t), 29.5 (t), 31.7 (t), 35.5 (q), 36.0 (q), 40.8 (t), 42.7 (q), 69.9 (d), 168.2 (s) and 173.7 (s); *m/z* (ES+) 272 [$(M+H)^+$, 100 %], 294 (52) and 142 (32); [Found (ES+): $[M+Na]^+$ 294.2145, $C_{14}H_{29}N_3O_2Na$ requires 294.2157].



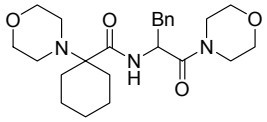
7l

Methyl 2-(N-(1-((N-methoxycarbonylmethyl-N-methylcarbamoyl)methylcarbamoyl)-3-phenyl propyl)-N-methylamino)acetate was isolated as a colourless oil (135 mg, 66 %); IR (film): 3361, 2955, 1749, 1656, 1495, 1454, 1262, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87-1.95 and 2.08-2.17 (2H, 2 × m, CH_2), 2.41 (3H, s, CH_3N), 2.61-2.84 (2H, m, CH_2Ph), 3.07 (3H, s, CH_3NC=O), 3.26 (1H, m, CH), 3.35 (1H, d, J = 17.1 Hz, CH_2N), 3.44 (1H, d, J = 17.1 Hz, CH_2N) (3.70 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.03-4.17 (4H, m, CH_2NH, CH_2NC=O), 7.20-7.27 (5H, m, Ar-H), 7.83 (1H, brs, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.6 (t), 33.2 (t), 35.3 (q), 39.4 (q), 41.0 (t), 49.4 (t), 51.8 (q), 52.3 (q), 55.5 (t), 66.2 (d), 126.0 (d), 128.4 (d), 128.5 (d), 141.6 (s), 169.0 (s), 169.4 (s), 171.8 (s) and 173.1 (s); *m/z* (ES+) 408 [$(M+H)^+$, 32 %], 430 (100) and 220 (13).



7m

2-Morpholino-N-(2-morpholino-2-oxo-1-phenylethyl)octanamide (mixture of stereoisomers) was isolated as a white solid (201 mg, 90 %); mp 82-84°C; IR (film): 3369, 2961, 2929, 2861, 1645, 1496, 1462, 1441, 1271, 1115 and 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, m, CH_3), 1.12-1.26 (8H, m, 4 × CH_2), 1.53-1.68 (2H, m, CH_2), 2.33-2.61 (4H, m, 2 × CH_2), 2.81 (1H, m, CHN), 2.99-3.28 (2H, m, CH_2), 3.39-3.78 (10H, m, 5 × CH_2), 5.82 and 5.84 (1H, 2 × d, J = 7.9 Hz, CHNH), 7.27-7.37 (5H, m, Ar-H), 8.18 and 8.22 (1H, 2 × d, J = 7.9 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (q), 22.5 (t), 25.7 (t), 28.4 (t), 29.3 (t), 31.6 (t), 42.6 (t), 45.9 (t), 50.9 (t), 53.6 (d), 66.0 (t), 66.6 (t), 67.2 (t), 69.5 (d), 127.6 (d), 128.4 (d), 129.1 (d), 137.6 (s), 168.3 (s) and 172.0 (s); *m/z* (ES+) 432 [$(M+H)^+$, 84 %] and 454 (100).



7n

1-Morpholino-N-(1-morpholino-1-oxo-3-phenylpropan-2-yl)cyclohexanecarboxamide was isolated as a white solid (117 mg, 54 %); mp 122-124°C; IR (film): 3366, 2937, 2861, 1636, 1495, 1456, 1444, 1215 and 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (2H, m, 2 × CH), 1.51-1.57 (6H, m, 3 × CH_2), 1.60-1.76 (2H, m, 2 × CH), 2.49 (4H, m, 2 × CH_2), 2.96-3.09 (4H, m, CH_2Ph, CH_2), 3.33-3.65 (10H, m, 5 × CH_2), 5.12 (1H, q, J = 8.4 Hz, CHNH), 7.19-7.30 (5H, m, Ar-H), 7.40 (1H, d, J = 8.4 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (t), 25.8 (t), 29.5 (t), 30.5 (t), 39.7 (t), 42.3 (t), 46.0 (t), 46.7 (t), 48.9 (d), 65.2 (s), 66.2 (t), 66.5 (t), 67.8 (t), 127.1 (d), 128.6 (d), 129.4 (d), 136.2 (s), 170.2 (s) and 174.7 (s); *m/z* (ES+) 430 [$(M+H)^+$, 18 %], 452 (100) and 365 (51) ; [Found (ES+): $[M+Na]^+$ 452.2496, $C_{24}H_{35}N_3O_4Na$ requires 452.2525].

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[1] Takiguchi, K.; Yamada, K.; Mamoru, S.; Nanami, K.; Kimiaki, H.; Kazuo, M. *Agric. Biol. Chem.* **1989**, *53*, 77-82.