Selective amidation of unprotected amino-alcohols using Surfactant-in-Water Technology: A highly desirable alternative to reprotoxic polar aprotic solvents.

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Supporting Information

Contents

1. General Informations

A solution of 2 wt% TPGS-750-M/H_2O was prepared by dissolving TPGS-750-M in deionized water. All commercially available reagents were used without further purification including TPGS-750-M which was purchased from Anthem Biosciences (CAS-No. 1309573-60-1).

^1H and ^{13}C NMR were recorded at 297.8 K on a Bruker® 400 MHz spectrometer. The FID was processesed using MestReNova NMR analysis software. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CDCl_3$ (7.260 ppm) or the central peak of DMSO-d_6 (2.50 ppm). Data are reported as follows: chemical shift, multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *quin* = quintet), and integration. Chemical shifts in ^{13}C chemical spectra are reported in ppm on the δ scale from the central peak of residual $CDCl_3$ (77.16 ppm) or the central peak of DMSO-d_6 (39.51 ppm).

Reaction profile based on analysis of UPLC/MS data using Acquity HSS T3 1.8 µm 2.1 x 50 mm at 60°C with the following eluent system: (A: water + 0.05 % formic acid + 3.75 mM ammonium acetate; B: acetonitrile + 0.04% formic acid); gradient from 5 to 98 % B in 1.4 min; flow 1.0 mL/min.

General procedure A for an amide-bond forming reaction in TPGS-750-M/water

To a mixture of carboxylic acid (2.50 mmol, 1.0 eq), EDC (0.715 g, 3.73 mmol, 1.5eq), HOBt (0.457 g, 3.0 mmol, 1.2 eq), aminoalcohol (3.0 mmol, 1.2 eq) and NMM (0.82 mL, 7.46 mmol, 3.0 eq) was added TPGS-750-M (2 wt% in water, 10 mL). The reaction was allowed to stir for 16-24 hours at 40 °C, until no starting material was detected. The reaction progress was followed by LCMS.

The suspension was cooled to RT, filtered, washed with water (2 x 5.0 mL) and dried at 50 °C under reduced pressure for 12 hours. The resulting product was analyzed by NMR-spectroscopy and HRMS-spectrometry.

General procedure B for an amide-bond forming reaction in acetonitrile or DMF

To a mixture of carboxylic acid (2.50 mmol, 1.0 eq), EDC (0.715 g, 3.73 mmol, 1.5eq), HOBt (0.457 g, 3.0 mmol, 1.2 eq), aminoalcohol (3.0 mmol, 1.2 eq) and NMM (0.82 mL, 7.46 mmol, 3.0 eq) was added acetonitrile or DMF (10 mL). The reaction was allowed to stir for 16-24 hours at room temperature, until no starting material was left. The reaction progress was followed by LCMS.

The solution was diluted with saturated $NaHCO_3$ (10 mL) and EtOAc (20 mL). The phases were allowed to separate and the water phase was extracted with further EtOAc (2 x 10 mL). The combined organic layers were washed with water (25 mL) to remove further HOBt. The water phase was extracted once with EtOAc (25 mL). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The resulting product was analyzed by NMR-spectroscopy and HRMS-spectrometry.

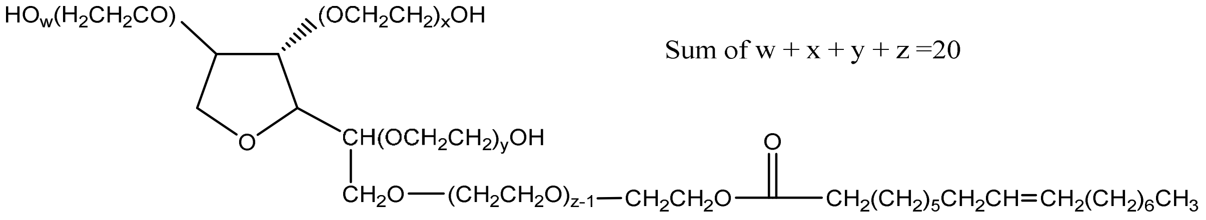
General procedure C for an amide-bond forming reaction in TPGS-750-M/water requiring extractive workup

To a mixture of carboxylic acid (2.50 mmol, 1.0 eq), EDC (0.715 g, 3.73 mmol, 1.5eq), HOBt (0.457 g, 3.0 mmol, 1.2 eq), aminoalcohol (3.0 mmol, 1.2 eq) and NMM (0.82 mL, 7.46 mmol, 3.0 eq) was added TPGS-750-M (2 wt% in water, 10 mL). The reaction was allowed to stir for 16-24 hours at 40 °C, until no starting material was left. The reaction progress was followed by LCMS.

The solution was diluted with saturated $NaHCO_3$ (10 mL) and EtOAc (20 mL). The phases were allowed to separate and the water phase was extracted with further EtOAc (2 x 10 mL). The combined organic layers were washed with water (25 mL) to remove further HOBt. The water phase was extracted once with EtOAc (25 mL). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The resulting product was analyzed by NMR-spectroscopy and HRMS-spectrometry.

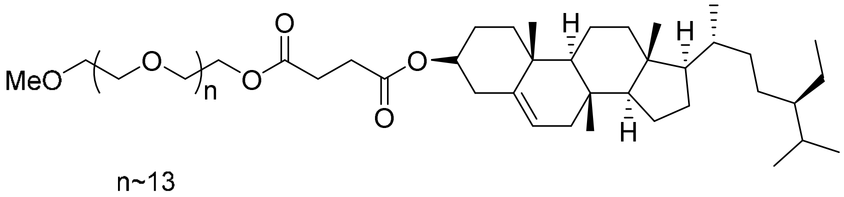
2. Structures of surfactants used in the table 1

TWEEN 80 :

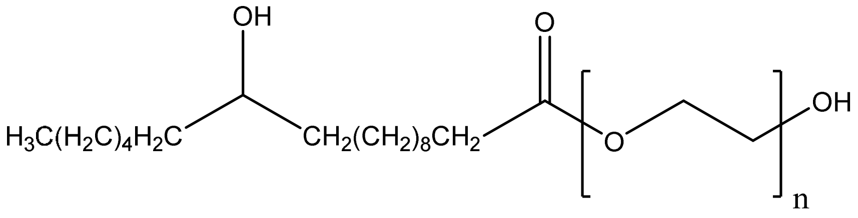


Sum of w + x + y + z =20

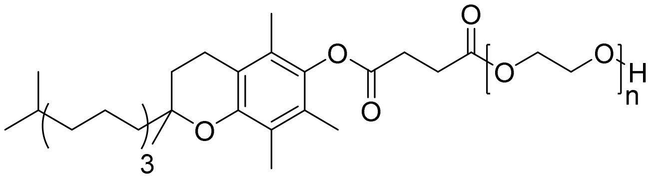
NOK :



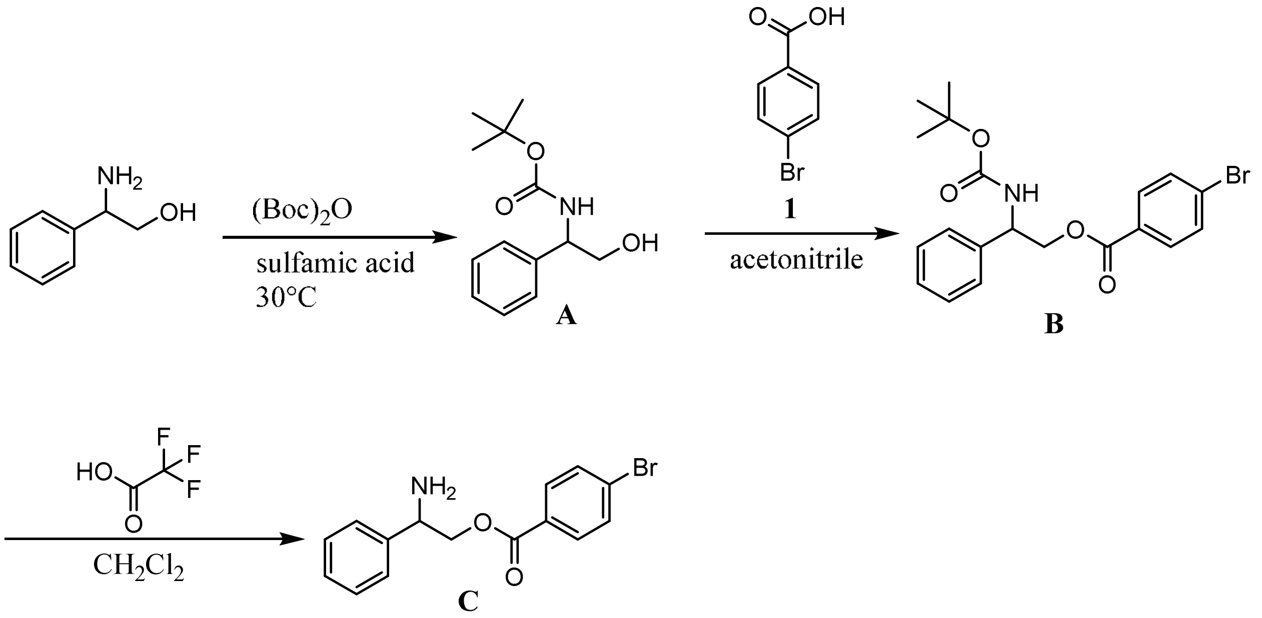
SOLUTOL-HS :



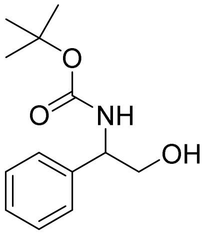
TPGS-1000 :



3. Synthesis of by-products derived from amidation of 4-bromobenzoic acid (1) and 2-amino-2-phenylethan-1-ol (2)



Tert-butyl-(2-hydroxy-1-phenylethyl)carbamate $C_{12}H_{17}NO_3$[1,2] (**A**)



Di-tert-butyl dicarbonate (0.875 g, 4.0 mmol, 1.1eq) and sulfamic acid (0.018 g, 0.182 mmol, 0.05 eq) were stirred together at 30 °C. 2-amino-2-phenylethanol (0.5 g, 3.65 mmol, 1.0 eq) was added to the colourless solution under heavy gas formation. A mixture of acetonitrile : water (1 : 1, 6 mL) was added to the white solid and the suspension was stirred for 30 minutes. The mixture was filtered and the white residue was dried at 50 °C under reduced pressure for 16 hours. Tert-butyl-(2-hydroxy-1-phenylethyl)carbamate was obtained as a white solid in 84% yield.

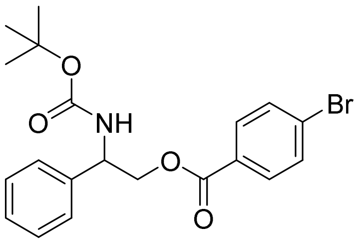
Mp = 137.7 - 138.8 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 7.30 – 7.27 (m, 4H, $H_{arom.}$), 7.23 – 7.17 (m, 2H, $H_{arom.,}$ NH), 4.76 (t, J = 5.8 Hz, 1H, OH), 4.55 – 4.49 (m, 1H, CHNH), 3.48 (t, J = 6.3 Hz, 2H, CH_2), 1.37 (s, 9H, 3 x CH_3) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 155.17 (C=O), 141.8, 128.0, 128.0, 126.8, 126.8, 126.6 (6 x C_{arom}), 77.7 (C), 64.8 (C), 56.8 (C), 28.2 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{12}H_{17}NO_3$, 237.1365 found 237.1438.

2-((tert-butoxycarbonyl)amino)-2-phenylethyl-4-bromobenzoate $C_{20}H_{22}BrNO_4$[3] (**B**)



tert-butyl (2-hydroxy-1-phenylethyl)carbamate (0.237 g, 1.0 mmol, 0.7 eq), *N1,N1,N2,N2*-tetramethylethane-1,2-diamine (0.23 mL, 1.5 mmol, 1.0 eq) and 1-methyl-1*H*-imidazole (0.12 mL, 1.5 mmol, 1.0 eq) were diluted in acetonitrile (4.0 mL) under inert-gas-atmosphere. The white suspension was cooled to 0 °C and 4-bromobenzoyl chloride (0.329 g, 1.5 mmol, 1.0 eq) was added. The white suspension was allowed to stir 3h at 0°C and further 16 hours at ambient temperature. The mixture was filtered, washed with water and the residue was dried at 50 °C under reduced pressure for 16 hours. (2-((tert-butoxycarbonyl)amino)-2-phenylethyl-4-bromobenzoate was obtained as a white solid in 54% yield.

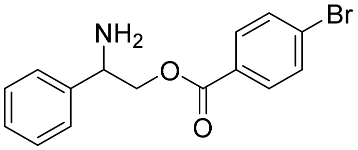
Mp = 99.5 - 101 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 7.87 (d, J = 8.6 Hz, 2H, H_{arom}), 7.75 (d, 2H, J = 8.4 Hz, H_{arom}), 7.71 (d, J = 9.1 Hz, 1H,NH), 7.43 (d, 2H, J = 7.4 Hz, H_{arom}), 7.36 (t, J = 7.4 Hz, 2H, H_{arom}), 7.29 – 7.23 (m, 1H, H_{arom}), 5.03 (m, 1H, CH), 4.40 (dd, 1H, CH_2), 4.33 (dd, 1H, CH_2), 1.36 (s, 9H, CH_3) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 186.3 (COONH), 165.3 (COO), 150.2 (CO(CH$_3$)$_3$), 132.3, 132.3, 131.6, 131.6, 129.2, 128.8, 128.8, 128.0, 127.9, 127.4, 127.4, 110.0 (C_{arom}), 78.6 (COH$_2$), 53.5, (CHN), 28.6 (3x C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{20}H_{22}BrNO_4$, 419.0732 found 419.0805.

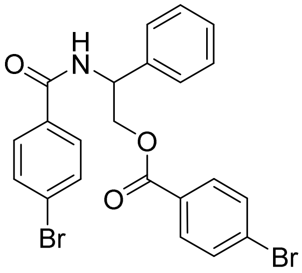
2-amino-2-phenylethyl-4-bromobenzoate[4] (**C**)



2-((tert-butoxycarbonyl)amino)-2-phenylethyl-4-bromobenzoate (0.2 g, 0.476 mmol) was diluted in CH_2Cl_2 (0.7 mL) and Trifluoroacetic acid (0.7 mL) was added. After 2 hours at ambient temperature, the excess of CH_2Cl_2 and Trifluoroacetic acid was removed under reduced pressure. The resulting yellow oil was diluted in $NaHCO_3$ (3.0 mL) and CH_2Cl_2 (5.0 mL). The phases were allowed to separate and the water phase was extracted with further CH_2Cl_2 (2 x 5.0 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. 2-amino-2-phenylethyl 4-bromobenzoate was obtained as a yellow solid in 85% yield.

Mp = 141.5 – 143.5 °C.
^{1}H-NMR (400 MHz, DMSO-d6) δ = 8.77 (s, 2H, N*H*), 8.02 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.79 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.58 (d, *J* = 7.2 Hz, 2H, H_{arom}), 7.50 – 7.44 (m, 3H, H_{arom}), 4.83 (t, *J* = 6 Hz, 1H, CH), 4.58 (d, *J* = 6 Hz, 2H, CH_2) ppm.
^{13}C-NMR (100 MHz, DMSO-d6) δ = 165.1 (*C*=O), 134.9, 132.3, 132.3, 132.1, 129.6, 129.4, 129.4, 128.6, 128.4, 127.9, 127.9 (12x C_{arom}), 70.2 (*C*OH), 65.9 (*C*NH_2) ppm.
HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{15}H_{14}BrNO_2$, 319.0208 found 319.0281.

(*S*)-2-(4-bromobenzamido)-2-phenylethyl-4-bromobenzoate $C_{22}H_{17}Br_2NO_3$[3] **3b**



(*S*)-4-bromo-N-(2-hydroxy-1-phenylethyl)benzamide (0.320 g, 1.0 mmol, 0.7 eq), *N1,N1,N2,N2*-tetramethylethane-1,2-diamine (0.23 mL, 1.5 mmol, 1.0 eq) and 1-methyl-1*H*-imidazole (0.12 mL, 1.5 mmol, 1.0 eq) were diluted in acetonitrile (4.0 mL) under inert-gas-atmosphere. The white suspension was cooled to 0 °C and 4-bromobenzoyl chloride (0.329 g, 1.5 mmol, 1.0 eq) was added. The white suspension was allowed to stir 3 hours at 0°C and further 16 hours at ambient temperature. The mixture was filtered, washed with water and the residue was dried at 50 °C under reduced pressure for 16 hours. (*S*)-2-(4-bromobenzamido)-2-phenylethyl-4-bromobenzoate was obtained as a white solid in 54% yield.

Mp = 198 - 200 °C.

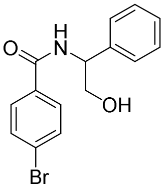
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 9.14 (d, J = 8.3 Hz, 1H, N*H*), 7.82 (d, J = 8.3 Hz, 4H, $H_{arom.}$), 7.73 – 7.68 (m, 4H, $H_{arom.}$), 7.51 (d, J = 7.3 Hz, 2H, $H_{arom.}$), 7.38 (t, J = 7.4 Hz, 2H, $H_{arom.}$), 7.31 – 7.28 (m, 1H, $H_{arom.}$), 5.54 (q, J = 7.2 Hz, 1H, C*H*NH), 4.57 (d, J = 7.0 Hz, 2H, CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 165.4 (C=O), 164.9 (C=O), 139.2, 133.4, 131.9, 131.9, 131.3, 131.3, 131.0, 131.0, 129.5, 129.5, 128.7, 128.5, 128.5, 127.6, 127.0, 127.0, 125.1, 109.5 (18 x C_{arom}), 66.7 (C), 52.1 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{22}H_{17}Br_2NO_3$ 501.9648, found 501.9653.

4. Characterization of amidation products 3 - 26

(*S*) 4-bromo-*N*-(2-hydroxy-1-phenylethyl)benzamide $C_{15}H_{14}BrNO_2$ **3**

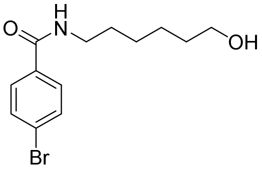


The titled compound was obtained with general procedure A in 95% yield, using general procedure B in 92% yield (acetonitrile) and 99% yield (DMF).

Mp = 178 – 179.5 °C.
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.80 (d, *J* = 8.1 Hz, 1H, N*H*), 7.85 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.69 (d, *J* = 8.6 Hz, 2H, H_{arom}), 7.39 – 7.37 (m, 2H, H_{arom}), 7.33 – 7.29 (m, 2H, H_{arom}), 7.25 – 7.21 (m, 1H, H_{arom}), 5.02 – 5.08 (m, 1H, C*H*NH), 4.95 (t, *J* = 5.9 Hz, 1H, O*H*), 3.73 – 3.60 (m, 2H, CH_2) ppm.
^{13}C-NMR (100 MHz, DMSO-d_6) δ = 165.2 (C=O), 141.2, 133.7, 131.2, 131.2, 129.6, 129.6, 128.1, 128.1, 127.0, 127.0, 126.9, 124.9, (12x C_{arom}), 64.5 (C), 56.1 (C) ppm.
HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{16}H_{14}BrNO_2$ 320.0281, found 320.0284.

Protocole : To a 250 mL reactor was added 4-bromobenzoic acid (10 g, 49.7 mmol, 1eq), TPGS-750-M (100 mL), HOBt (8.07 g, 59.7 mmol, 1.2 eq), EDC (14.31 g, 74.6 mmol, 1.5 eq), (S)-2-amino-2-phenylethanol (8.19 g, 59.7 mmol, 1.2 eq), NMM (16.4 mL, 149.2 mmol, 3 eq) and the remaining TPGS-750-M (50 mL). Then the mixture was heated to 40°C and stirred during 17 hours at 40°C. After, the reaction mixture was cooled to 20 °C and filtered on fritten who the product was washed with water (2 x 75 mL). The powder was dried at 50°C under reduced pressure. (*S*) 4-bromo-*N*-(2-hydroxy-1-phenylethyl)benzamide was obtiened as a white solid in 95% yield.

4-bromo-*N*-(6-hydroxyhexyl)benzamide $C_{13}H_{18}BrNO_2$ **4**



The titled compound was obtained with general procedure A in 93% yield, using general procedure B in 85% yield (acetonitrile) and 88% yield (DMF).

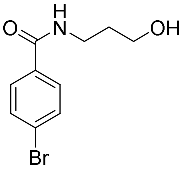
Mp = 117 - 118 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.49 (t, *J* = 5.2 Hz, 1H, N*H*), 7.78 (d, *J* = 8.8 Hz, 2H, H_{arom}), 7.66 (d, *J* = 8.8 Hz, 2H, H_{arom}), 4.31 (t, *J* = 5.2 Hz, 1H, O*H*), 3.37 (q, *J* = 6.5 Hz, 2H, CH_2), 3.23 (q, *J* = 6.5 Hz, 2H, CH_2), 1.53 – 1.28 (m, 8H, 4x CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 165.1 (C=O), 133.8, 131.2, 131.2, 129.2, 129.2, 124.6 (6x C_{arom}), 60.6 (C), 39.2 (C), 32.4 (C), 29.0 (C) 26.4 (C), 25.2 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{13}H_{18}BrNO_2$ 300.0594, found 300.0593.

4-bromo-*N*-(3-hydroxypropyl)benzamide $C_{10}H_{12}BrNO_2$ **5**



The titled compound was obtained with general procedure A in 91% yield, using general procedure B in 75% yield (acetonitrile) and 94% yield (DMF).

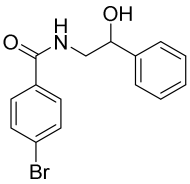
Mp = 71.5 - 73 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.50 (t, *J* = 5.2 Hz, 1H, N*H*), 7.79 – 7.77 (m, 2H, H_{arom}), 7.67 – 7.65 (m, 2H, H_{arom}), 4.45 (t, *J* = 5.2 Hz, 1H, O*H*), 3.46 (q, *J* = 6.2 Hz, 5.2 Hz, 2H, CH_2), 3.28 – 3.33 (m, 2H, CH_2), 1.67 (qi, *J* = 6.5 Hz, 2H, $CH_2CH_2CH_2$) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 165.2 (C=O), 133.7, 131.2, 131.2, 129.2, 129.2, 124.7 (6x C_{arom}), 58.6 (*C*), 36.6 (C), 32.3 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{10}H_{12}BrNO_2$ 258.0124, found 258.0123.

4-bromo-*N*-(2-hydroxy-2-phenylethyl)benzamide $C_{15}H_{14}BrNO_2$ **6**



The titled compound was obtained with general procedure A in 90% yield, using general procedure B in 94% yield (acetonitrile) and 86% yield (DMF).

Mp = 71 - 73 °C.

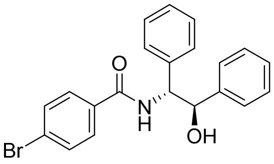
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.62 (t, J = 5.5 Hz, 1H, NH), 7.79 (d, J = 8.6 Hz, 2H, H_{arom}), 7.67 (d, J = 8.5 Hz, 2H, H_{arom}), 7.38 – 7.31 (m, 4H, H_{arom}), 7.27 – 7.21 (m, 1H, H_{arom}), 5.52 (d, J = 4.4 Hz, 1H, OH), 4.80 – 4.76 (m, 1H, CHOH), 3.51 – 3.45 (m, 1H, CH_2), 3.35 – 3.29 (m, 1H, CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 165.4 (C=O), 143.7, 133.7, 131.2, 131.2, 129.4, 129.4, 128.0, 128.0, 127.0, 126.0, 126.0, 124.8, (12x C_{arom}), 71.1 (C), 47.7 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{15}H_{14}BrNO_2$ 320.0281, found 320.0283.

Comparison : A. S. Aboraia, S. W. Yee, M. S. Gomaa, N. Shah, A. C. Robotham, B. Makowski, D. Prosser, A. Brancale, G. Jones, C. Simons, *Bioorg. Med. Chem.* **2010**, *18*, 4939–4946.

4-bromo-*N*-((1*R*, 2*R*) 2-hydroxy-1,2-diphenylethyl)benzamide $C_{21}H_{18}BrNO_2$ **7**



The titled compound was obtained with general procedure A in 82% yield, using general procedure B in 88% yield (acetonitrile) and 87% yield (DMF).

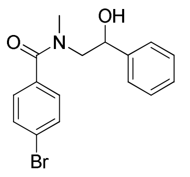
Mp = 235 - 237 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ = 8.71 (d, J = 9.2 Hz, 1H, NH), 7.63 – 7.58 (m, 4H, H_{arom}), 7.45 – 7.40 (m, 4H, H_{arom}), 7.31 – 7.18 (m, 6H, H_{arom}), 5.46 (d, J = 5.3 Hz, 1H, OH), 5.12 (t, J = 8.9 Hz, 1H, CHNH), 4.93 – 4.89 (m, 1H, CHOH) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 164.2 (C=O), 143.5, 141.1, 133.6, 131.1, 131.1, 129.3, 129.3, 128.3, 128.3, 127.6, 127.6, 127.5, 127.5, 127.0, 126.8, 126.8, 126.7, 124.7 (18x C_{arom}), 74.5 (C), 59.0 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{21}H_{18}BrNO_2$, 396.0594 found 396.0600.

4-bromo-*N*-(2-hydroxy-2-phenylethyl)-N-methylbenzamide $C_{16}H_{16}BrNO_2$ **8**



The titled compound was obtained with general procedure A in 80% yield, using general procedure B in 90% yield (acetonitrile) and 86% yield (DMF).

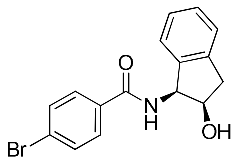
Mp = 133 - 135 °C.

^{1}H-NMR (500 MHz, DMSO-d_6) δ = 7.58 (d, J = 8.4 Hz, 2H, H_{arom}), 7.31 (d, J = 6.7 Hz, 4H, H_{arom}), 7.27 – 7.22 (m, 3H, H_{arom}), 5.22 (d, J = 4.6 Hz, 1H, O*H*), 4.86 (s, 1H, C*H*OH), 3.52 (d, J = 7.5 Hz, 2H, CH_2), 2.96 (s, 3H, CH_3) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 170.0, 169.2, 143.5, 143.0, 131.2, 131.0, 129.2, 128.9, 128.1, 127.2, 126.0, 125.8, 122.5, 122.1, 70.42, 69.7, 58.0, 55.12, 33.18 ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{16}H_{16}BrNO_2$ 334.0437, found 334.0441.

4-bromo-*N*-((2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-benzamide $C_{16}H_{14}BrNO_2$ **9**



The titled compound was obtained with general procedure A in 96% yield, using general procedure B in 90% yield (acetonitrile) and 96% yield (DMF).

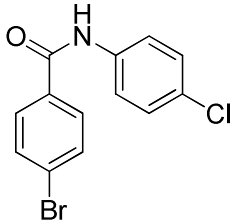
Mp = 186.5 – 187.5 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.41 (d, *J* = 8.5 Hz, 1H, N*H*), 7.92 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.67 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.17 – 7.27 (m, 4H, H_{arom}), 5.42 – 5.46 (m, 1H, C*H*NH), 5.10 (d, *J* = 4.5 Hz, 1H, O*H*), 4.50 – 4.54 (m, 1H, C*H*OH), 3.08 – 3.13 (m, 1H, CH_2), 2.91 – 2.86 (m, 1H, CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 165.8 (C=O), 141.6, 141.0, 133.6, 131.1, 131.1, 129.8, 129.8, 127.4, 126.3, 124.9, 124.8, 124.4 (12 x C_{arom}), 72.1 (C), 57.6 (C), 39.7 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{16}H_{14}BrNO_2$ 332.0281, found 332.0282.

4-bromo-*N*-(4-chlorophenyl)benzamide $C_{13}H_9BrClNO_2$ **10**



The titled compound was obtained with general procedure A in 95% yield.

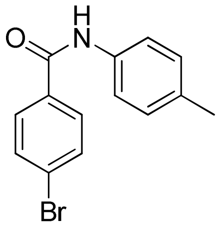
Mp = 219 – 220.5 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.42 (s, 1H, N*H*), 7.90 (d, *J* = 8.6 Hz, 2H, $H_{arom.}$), 7.81 (d, *J* = 8.9 Hz, 2H, $H_{arom.}$), 7.75 (d, *J* = 8.6 Hz, 2H, $H_{arom.}$), 7.41 (d, *J* = 8.9 Hz, 2H, $H_{arom.}$) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 164.6 (C=O), 137.9, 133.7, 131.4, 131.4, 129.8, 129.8, 128.5, 128.5, 127.4, 125.5, 121.9 121.9 (12 x C_{arom}) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{13}H_9BrClNO_2$ 309.9629, found 309.9626.

4-bromo-*N*-(*p*-tolyl)benzamide $C_{14}H_{12}BrNO$ **11**



The titled compound was obtained with general procedure A in 94% yield.

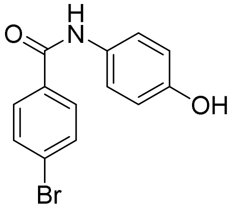
Mp = 235.5 – 236.5 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ = 10.22 (s, 1H, N*H*), 7.90 (d, *J* = 8.5 Hz, 2H, *H*$_{arom\cdot}$), 7.73 (d, *J* = 8.5 Hz, 2H. *H*$_{arom\cdot}$), 7.64 (d, *J* = 8.5 Hz, 2H, *H*$_{arom\cdot}$), 7.15 (d, *J* = 8.5 Hz, 2H, *H*$_{arom\cdot}$), 2.28 (s, 3H, C*H*$_3$) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 164.3 (C=O), 136.4, 134.1, 132.8, 131.3, 131.3, 129.7, 129.7, 129.0, 129.0, 125.2, 120.4, 120.4 (12 x C$_{arom}$), 20.5 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{14}H_{12}BrNO$ 290.0175, found 290.0176.

4-bromo-*N*-(4-hydroxyphenyl)benzamide $C_{13}H_{10}BrNO_2$ **12**



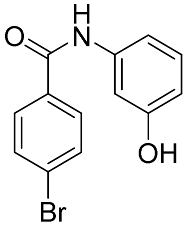
The titled compound was obtained with general procedure A in 50% yield.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ = 10.09 (s, 1H, RCON*H*), 9.28 (s, 1H, CO*H*), 7.89 (d, *J* = 7.8 Hz, 2H, *H*$_{arom}$), 7.72 (d, *J* = 7.8 Hz, 2H, *H*$_{arom}$), 7.52 (d, *J* = 8.3 Hz, 2H, *H*$_{arom}$), 6.74 (d, 2H, *J* = 8.3 Hz, *H*$_{arom}$) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 163.9 (O*C*N), 153.8, 134.20, 131.3, 131.3, 130.5, 129.7, 129.7, 125.01, 122.3, 122.3, 115.0, 115.0 (12x *C*$_{arom}$) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{13}H_{10}BrNO_2$, 290.9895 found 290.9968.

4-bromo-N-(3-hydroxyphenyl)benzamide $C_{13}H_{10}BrNO_2$ **13**



The titled compound was obtained with general procedure A in 40% yield.

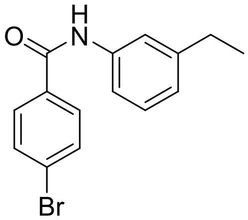
Mp = 213 – 215 °C

^{1}**H-NMR** (400 MHz, DMSO-d$_6$) δ = 10.18 (s, 1H, RCON*H*), 9.43 (s, 1H, O*H*), 7.89 (d, *J* = 7.9 Hz, 2H, *H*$_{\text{arom}}$), 7.72 (d, *J* = 7.9 Hz, 2H, *H*$_{\text{arom}}$), 7.34 (s, 1H, Harom), 7.13 (m, 2H, *H*$_{\text{arom}}$), 6.52 (d, *J* = 6.9 Hz, 1H, *H*$_{\text{arom}}$) ppm.

^{13}**C-NMR** (100 MHz, DMSO-*d*$_6$) δ = 177.2 (O*C*N), 164.9, 158.0, 140.4, 131.8, 131.8, 130.3, 130.3, 129.7, 129.7, 125.7, 111.6, 100.0, 107.9 (12x *C*arom) ppm.

HRMS (ESI) *m/z*: (M + H)$^+$ calc. for $C_{13}H_{10}BrNO_2$, 290.9895 found 290.9968.

4-bromo-N-(3-ethylphenyl)benzamide $C_{15}H_{14}BrNO$ **16**



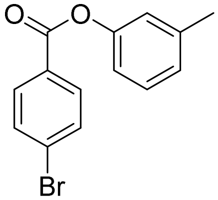
The titled compound was obtained with general procedure A.

^{1}**H-NMR** (400 MHz, DMSO-d$_6$) δ = 10.25 (s, 1H, N*H*), 7.93 (d, *J* = 8.5 Hz, 2H, *H*$_{\text{arom}}$), 7.76 (d, *J* = 8.5 Hz, 2H, *H*$_{arom}$), 7.60 (m, 2H, *H*$_{\text{arom}}$), 7.26 (t, *J* = 7.8 Hz, 1H, *H*$_{\text{arom}}$), 6,97 (d, *J* = 7.8 Hz, 1H, H$_{\text{arom}}$), 2.61 (q, *J* = 8 Hz, 3H, C*H*$_2$), 1.20 (t, *J* = 8 Hz, 2H, C*H*$_3$) ppm.

^{13}**C-NMR** (100 MHz, DMSO-*d*$_6$) δ = 164.9 (N*C*O) 144.6, 139.4, 134.5, 131.8, 131.8, 130.23, 130.23, 129,0, 125.7, 123.8, 120.2, 118.3 (12x *C*$_{\text{arom}}$), 28.8 (*C*), 16.01 (*C*) ppm.

HRMS (ESI) *m/z*: (M + H)$^+$ calc. for $C_{15}H_{14}BrNO$, 303.0259 found 303.0336.

m-tolyl 4-bromobenzoate $C_{15}H_{11}BrO_2$ **17**



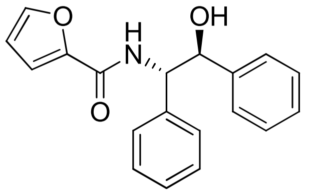
The titled compound was obtained with general procedure A.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.06 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.86 (d, *J* = 8.7 Hz, 2H, H_{arom}), 7.36 (t, *J* = 7.7 Hz, 1H, H_{arom}), 7.15 – 7.04 (m, 3H, H_{arom}), 2.35 (s, 3H, CH_3) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 164.4 (O*C*O) 150.9, 139.8, 132.6 ,132.6, 132.15, 132.15, 131.74, 129.8, 128.7, 127.2, 122.7, 119.3 (12x C_{arom}), 21,27 (*C*) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{15}H_{11}BrO_2$, 289.9942 found 290.0015.

N-((1*S*, 2*S*)-2-hydroxy-1,2-diphenylethyl)furan-2-carboxamide $C_{19}H_{17}NO_3$ **18**



The titled compound was obtained with general procedure A in 92% yield.

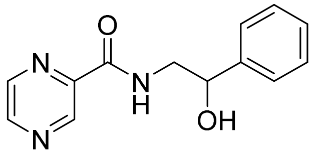
Mp = 214.5 - 216 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.45 (d, *J* = 9.1 Hz, 1H, N*H*), 7.78 (s, 1H, $H_{arom.}$), 7.38 – 7.35 (m, 4H, $H_{arom.}$), 7.28 – 7.18 (m, 6H, $H_{arom.}$), 7.00 (d, 1H, *J* = 3.9 Hz, $H_{arom.}$), 6.57 – 6.56 (m, 1H, $H_{arom.}$), 5.49 (d, *J* = 5.1 Hz, 1H, O*H*), 5.09 (t, *J* = 8.5 Hz, 1H, C*H*NH), 4.97 – 4.94 (m, 1H, C*H*OH) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 156.5 (C=O), 147.6, 144.9, 143.2, 140.8, 128.3, 128.3, 127.6, 127.6, 127.5, 127.5, 127.0, 126.8, 126.8, 126.7, 113.5, 111.8, (16 x $C_{\text{arom.}}$) 74.2 (C), 58.3 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{19}H_{17}NO_3$ 308.1281, found 308.1282.

N-(2-hydroxy-2-phenylethyl)pyrazine-2-carboxamide $C_{13}H_{13}N_3O_2$ **19**



The titled compound was obtained with general procedure C in 95% yield.

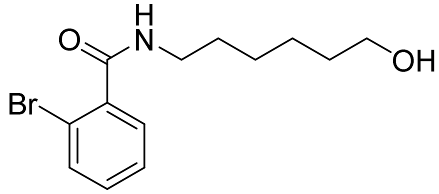
Mp = 121.5 - 123 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ = 9.18 (d, *J* = 1.3 Hz, 1H, N*H*), 8.87 (d, *J* = 2.4 Hz, 1H, *H*$_{\text{arom}}$), 8.74 – 8.68 (m, 2H, *H*$_{\text{arom}}$), 7.40 – 7.31 (m, 4H, *H*$_{\text{arom}}$), 7.27 – 7.23 (m, 1H, *H*$_{\text{arom}}$), 5.61 (d, *J* = 4.5 Hz, 1H, O*H*), 4.84 – 4.80 (m, 1H, C*H*), 3.63 – 3.57 (m, 1H, C*H*$_2$), 3.46 – 3.39 (m, 1H, C*H*$_2$) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 162.6 (C=O), 147.6, 144.5, 143.4, 143.3, 143.3, 128.1, 128.1, 128.1, 127.1, 125.9, 125.9, 70.9 (C), 46.8 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{13}H_{13}N_3O_2$ 244.1081, found 244.1082.

2-bromo-*N*-(6-hydroxyhexyl)benzamide $C_{13}H_{18}BrNO_2$ **20**



The titled compound was obtained with general procedure C in TPGS-750-M in 77% yield.

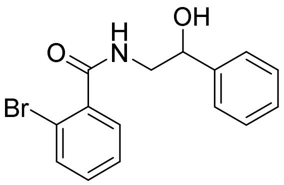
Mp = 63 - 65 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ = 8.36 (t, *J* = 5.2 Hz, 1H, N*H*), 7.63 (d, *J* = 8.0 Hz, 1H, *H*$_{\text{arom}}$) 7.44 – 7.40 (m, 1H, *H*$_{\text{arom}}$), 7.36 – 7.32 (m, 2H, *H*$_{\text{arom}}$), 4.33 (t, *J* = 5.2 Hz, 1H, O*H*), 3.39 (q, *J* = 6.5 Hz, 2H, C*H*$_2$), 3.20 (q, *J* = 6.5 Hz, 2H, C*H*$_2$), 1.52 – 1.32 (m, 8H, 4 x C*H*$_2$) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 167.0 (C=O), 139.5, 132.6, 130.6, 128.7, 127.5, 118.9 (6x C$_{\text{arom}}$), 60.7 (C), 38.9 (C), 32.5 (C), 28.9 (C), 26.3 (C), 25.2 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{13}H_{18}BrNO_2$ 300.0594, found 300.0595.

2-bromo-*N*-(2-hydroxy-2-phenylethyl)benzamide $C_{15}H_{14}BrNO_2$ **21**



The titled compound was obtained with general procedure A in 63% yield.

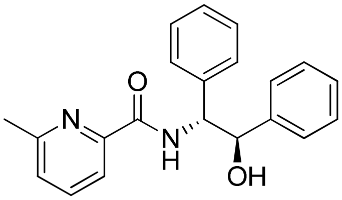
Mp = 116 - 117 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.42 (t, J = 5.6 Hz, 1H, NH), 7.62 (dd, J = 7.9, 1.1 Hz, 1H, H_{arom}), 7.42 – 7.24 (m, 8H, H_{arom}), 5.47 (d, J = 4.5 Hz, 1H, OH), 4.77 – 4.73 (m, 1H, CHNH), 3.47 – 3.34 (m, 2H, CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 167.2 (C=O), 143.6, 139.0, 132.6, 130.7, 128.8, 128.0, 128.0, 127.4, 127.1, 126.2, 126.2, 118.9, (12x C_{arom}), 71.1 (C), 47.1 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{15}H_{14}BrNO_2$ 320.0281, found 320.0281.

N-((1*R*, 2*R*)-2-hydroxy-1,2-diphenylethyl)-6-methylpicolinamide $C_{21}H_{20}N_2O_2$ **22**



The titled compound was obtained with general procedure A in 93% yield.

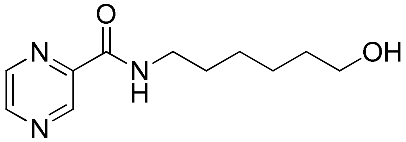
Mp = 126 - 128 °C.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.98 (d, J = 8.9 Hz, 1H, NH), 7.85 (t, J = 7.7 Hz, 1H, H_{arom}.), 7.76 (d, J = 7.5 Hz, 1H, H_{arom}.), 7.47 (d, J = 7.5 Hz, 1H, H_{arom}.), 7.14 – 7.25 (m, 10H, H_{arom}.), 5.84 (d, J = 4.3 Hz, 1H, OH), 5.18 – 5.22 (m, 1H, CHNH), 5.11 – 5.13 (m, 1H, CHOH), 2.58 (s, 3H, CH_3) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6) δ = 162.7 (C=O), 157.1, 148.9, 141.8, 139.4, 138.0, 127.9, 127.9, 127.9, 127.5, 127.5, 127.5, 127.5, 127.1, 126.8, 126.6, 126.6, 126.2, 118.8 (17 x C_{arom}), 74.5 (C), 58.4 (C), 24.0 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{21}H_{20}N_2O_2$ 333.1598, found 333.1602.

N-(6-hydroxyhexyl)pyrazine-2-carboxamide $C_{11}H_{17}N_3O_2$ **23**



The titled compound was obtained with general procedure C in 85% yield.

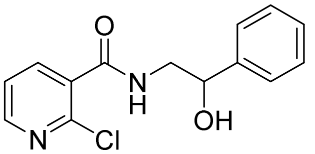
Mp = 89 – 90.5 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ = 9.17 (d, *J* = 1.5 Hz, 1H, N*H*), 8.93 (t, *J* = 6.1 Hz, 1H, H_{arom}), 8.87 (d, *J* = 2.5 Hz, 1H, H_{arom}), 8.73 (m, 1H, H_{arom}), 4.26 (bs, 1H, O*H*), 3.36 (t, *J* = 6.2 Hz, 2H, CH_2), 3.29 (q, *J* = 6.9 Hz, 2H, CH_2), 1.53 (qi, *J* = 6.7 Hz, 2H, CH_2), 1.43 – 1.36 (m, 2H, CH_2), 1.278 – 1.27 (m, 4H, 2 x CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 162.7 (C=O), 147.3, 145.0, 143.5, 143.2 (4 x $C_{\text{arom.}}$), 60.7 (C), 38.8 (C), 32.5 (C), 29.1 (C), 26.4 (C), 25.3 ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{11}H_{17}N_3O_2$ 224.1394, found 224.1397.

2-chloro-*N*-(2-hydroxy-2-phenylethyl)nicotinamide $C_{14}H_{13}ClN_2O_2$ **24**



The titled compound was obtained with general procedure C in 85% yield.

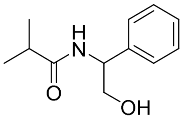
Mp = 120 - 122 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ = 8.68 (t, *J* = 5.9 Hz, 1H, RCON*H*), 8.45 (dd, *J* = 7.8 Hz, 2.0 Hz, 1H, H_{arom}), 7.80 (dd, *J* = 7.5 Hz, 2.2 Hz, 1H, H_{arom}), 7.48 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H, H_{arom}), 7.42 – 7.34 (m, 4H, H_{arom}), 7.27 (m, 1H, H_{arom}), 5.55 (d, *J* = 4.6 Hz, 1H, C*H*), 3.51- 3.45 (m, 1H, CH_2), 3.40 – 3.33 (m, 1H, CH_2) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 165.6 (O*C*N), 150.5, 147.0, 144.0, 138.5, 133.6, 128.5, 128.5, 127.6, 126.7, 126.7, 123.4 (11x C_{arom}), 71.6 (*C*OH), 47.6 (*C*NH$_2$) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{14}H_{13}ClN_2O_2$, 276.0666 found 276.0738.

(*R*)-*N*-(2-hydroxy-1-phenylethyl)isobutyramide $C_{12}H_{17}NO_2$ **25**



The titled compound was obtained with general procedure C in 81% yield.

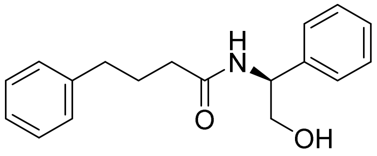
Mp = 185.5 – 120.5 °C.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ = 8.09 (d, *J* = 8.6 Hz, 1H, N*H*), 7.36 – 7.20 (m, 5H, *H*$_{arom\cdot}$), 7.22 (m, 1H, *H*$_{arom}$), 4.84 – 4.79 (m, 2H, O*H*, CH$_3$C*H*), 3.54 (d, *J* = 5.2 Hz, 2H, C*H$_2$*), 2.49 (m, 1H, C*H*NH), 1.11 (d, *J* = 7.0 Hz, 3H, C*H$_3$*), 0.98 (d, *J* = 7.0 Hz, 3H, C*H$_3$*) ppm.

^{13}C-NMR (100 MHz, DMSO-d$_6$) δ = 175.7 (C), 141.6, 128.0, 128.0, 126.8, 126.6, 126.7 (6 x C$_{arom}$), 64.7 (C), 54.7 (C), 33.9 (C), 19.7 (C), 19.6 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{12}H_{17}NO_2$, 207.1259 found 208.1332.

(*S*)-*N*-(2-hydroxy-1-phenylethyl)-4-phenylbutanamide $C_{18}H_{21}NO_2$ **26**



The titled compound was obtained with general procedure A in 98% yield.

Mp = 92.5 - 94 °C.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ = 8.18 (d, *J* = 8.2 Hz, 1H, N*H*), 7.31 – 7.15 (m, 10H, *H*$_{arom\cdot}$), 4.89 – 4.81 (m, 2H, C*H*NH, O*H*), 3.56 – 3.52 (m, 2H, C*H$_2$*), 2.55 (t, *J* = 7.6 Hz, 2H, C*H$_2$*), 2.17 (t, *J* = 7.6 Hz, 2H, C*H$_2$*), 1.80 (qi, *J* = 7.6 Hz, 2H, C*H$_2$*) ppm.

^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ = 171.5 (C=O), 141.8, 141.5, 128.3, 128.3, 128.3, 128.3, 128.0, 128.0, 126.9, 126.9, 126.7 ,125.7 (12 x C$_{arom}$), 64.7 (C), 54.9 (C), 34.9 (C), 34.7 (C), 27.2 (C) ppm.

HRMS (ESI) *m/z*: $(M + H)^+$ calc. for $C_{18}H_{21}NO_2$ 284.1645, found 284.1650.

5. References

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