Supporting Informations

Proceeding Paper

Synthesis and antimicrobial activity of salicylamide aza-isosteres †

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Materials and Methods

Chemistry

Characterization of investigated compounds

Cbz-Protected Amino Acid Amides

Benzyl (S)-(1-((4-bromophenyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate:

White solid; yield: 76%; m.p. = 143.6–145.6 °C; Rf = 0.62 (EtOAc/n-hexane, 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H, NH), 7.34–7.29 (m, 9H, Ar-H), 5.48 (d, J =8.0 Hz, 1H, NH), 5.11 (dd, J =23.5, 12.4 Hz, 2H, OCH_2), 4.40–4.34 (m, 1H, NHCH), 1.77–1.71 (m, 2H, $CHCH_2$), 1.66–1.59 (m, 1H, CH_2CH), 0.96 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 156.9, 136.8, 135.8, 131.8, 128.6, 128.4, 128.0, 121.3, 116.9, 67.5, 54.3, 40.7, 24.7, 22.9, 21.9. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{20}H_{23}BrN_2O_3Na$: 441.0784; found: 441.0796. Elemental analysis: calcd for $C_{20}H_{23}BrN_2O_3$: C, 57.29; H, 5.53; N, 6.68%; found: C, 57.42 ± 0.18; H, 5.67 ± 0.07; N, 6.48 ± 0.04 %

Benzyl (S)-(1-((4-bromophenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate:

White crystalline solid; yield: 57%; m.p. = 181.5–183.1 °C; Rf = 0.60 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, DMSO-d6): δ 10.23 (br s, 1H, NH), 7.70 (d, J =8.2 Hz, 1H, NH), 7.52 (d, J =8.5 Hz, 2H, Ar-H), 7.44 (d, J =8.6 Hz, 2H, Ar-H), 7.26–7.18 (m, 9H, Ar-H), 7.15–7.07 (m, 1H, Ar-H), 4.89 (s, 2H, OCH_2), 4.36–4.30 (m, 1H, NHCH), 2.97–2.93 (m, 1H, CHH), 2.81–

2.75 (m, 1H, CHH). ^{13}C NMR (125 MHz, DMSO-d6): δ 171.5, 156.7, 138.9, 138.4, 137.6, 132.3, 129.9, 129.0, 128.8, 128.4, 128.2, 127.1, 121.9, 115.6, 66.0, 57.7, 38.0. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{23}H_{21}BrN_2O_3Na$: 475.0628; found: 475.0627. Elemental analysis: calcd for $C_{23}H_{21}BrN_2O_3$: C, 60.94; H, 4.67; N, 6.18%; found: C, 60.17; H, 4.87; N, 6.51 %

Benzyl (S)-(1-((4-bromophenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate:

White crystalline solid; yield: 56%; m.p. = 202.1–203.6 °C; Rf = 0.55 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (br s, 1H, NH), 7.34 (s, 9H, Ar-H), 5.69 (d, *J* =8.4 Hz, 1H, NHCH), 5.14–5.07 (m, 2H, OCH_2), 4.19–4.16 (m, 1H, CH), 1.04–1.01 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 156.9, 138.8, 137.7, 132.2, 129.0, 128.4, 128.4, 121.8, 115.6, 66.1, 61.8, 30.9, 19.8, 19.1. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{19}H_{21}BrN_2O_3Na$: 427.0628; found: 427.0628. Elemental analysis: calcd for $C_{19}H_{21}BrN_2O_3$: C, 56.31; H, 5.22; N, 6.91 %; found: C, 56.16; H, 5.04; N, 6.69 %

Benzyl (S)-(3-methyl-1-oxo-1-((4-(trifluoromethyl)phenyl)amino)butan-2-yl)carbamate:

White crystalline solid; yield: 52%; m.p. = 191.5–193.5 °C; Rf = 0.58 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, DMSO-d6): δ 10.45 (br s, 1H, NH), 7.83 (d, *J* =8.6 Hz, 2H, Ar-H), 7.68 (d, *J* =8.6 Hz, 2H, Ar-H), 7.61–7.59 (m, 1H, NH), 7.37–7.28 (m, 5H, Ar-H), 5.03 (s, 2H, OCH_2), 4.03–3.99 (m, 1H, NHCH), 2.05–1.98 (m, 1H, CH), 0.92–0.90 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d6): δ 171.9, 156.9, 142.9, 137.6, 130.0, 128.5, 128.4, 126.7, 124.2, 123.8, 119.8, 66.1, 61.8, 30.8, 19.8, 19.1. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{20}H_{21}F_3N_2O_3Na$: 417.1397; found: 417.1404. Elemental analysis: calcd for $C_{20}H_{21}F_3N_2O_3$: C, 60.91; H, 5.37; N, 7.10 %; found: C, 61.32; H, 5.45; N, 6.87 %.

Benzyl (S)-(4-methyl-1-oxo-1-((4-(trifluoromethyl)phenyl)amino)pentan-2-yl)carbamate:

White crystalline solid; yield: 44%; m.p. = 143.7–145.7 °C; Rf = 0.65 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 10.43 (br s, 1H, NH), 7.84 (d, *J* =8.5 Hz, 2H, Ar-H), 7.68 (d, *J* =8.7 Hz, 3H, Ar-H), 7.36–7.35 (m, 4H, Ar-H), 5.03 (s, 2H, OCH_2), 4.25–4.19 (m, 1H, NHCH), 1.69–1.64 (m, 1H, CH), 1.61–1.54 (m, 1H, CHH), 1.49–1.42 (m, 1H, CHH), 0.90–0.88 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d6): δ 172.9, 156.8, 143.2, 137.6, 129.0, 128.5, 128.4, 126.7, 126.4, 124.1, 123.8, 119.8, 66.1, 54.6, 24.9, 23.6, 22.1. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{21}H_{23}F_3N_2O_3Na$: 431.1553; found: 431.1562. Elemental analysis: calcd for $C_{21}H_{23}F_3N_2O_3$: C, 61.76; H, 5.68; N, 6.86 %; found: C, 62.16; H, 5.68; N, 7.13 %.

Benzyl (S)-(1-oxo-3-phenyl-1-((4-(trifluoromethyl)phenyl)amino)propan-2-yl)carbamate:

White crystalline solid; yield: 31%; m.p. = 190.3–191.5 °C; Rf = 0.60 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, DMSO-d6): δ 10.56 (br s, 1H, NH), 7.87–7.84 (m, 3H, Ar-H), 7.75–7.73 (m, 2H, Ar-H), 7.40–7.31 (m, 9H, Ar-H), 7.27–7.18 (m, 2H, Ar-H), 5.02 (s, 2H, OCH_2), 4.52–4.46 (m, 1H, NHCH), 3.12–3.07 (m, 1H, CHH), 2.94–2.88 (m, 1H, CHH). ^{13}C NMR (125 MHz, DMSO-d6): δ 171.9, 156.7, 143.1, 138.3, 137.6, 129.9, 128.9, 128.8,

128.4, 128.2, 127.1, 126.7, 124.2, 123.9, 119.9, 66.1, 57.8, 37.9. HRMS (MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{24}H_{21}F_3N_2O_3Na$: 465.1397; found: 465.1404. Elemental analysis: calcd for $C_{24}H_{21}F_3N_2O_3$: C, 65.15; H, 4.75; N, 6.33 %; found: C, 65.27; H, 5.07; N, 6.67 %.

Deprotected amine intermediates

(S)-2-Amino-3-methyl-N-phenylbutanamide:
Yellow crystalline solid; yield: 97%; m.p. = 119.2–122.0 °C; Rf = 0 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, CD3OD): *δ* 7.69–7.67 (m, 2H, Ar-H), 7.42–7.38 (m, 2H, Ar-H), 7.22–7.19 (m, 1H, Ar-H), 3.94 (d, *J* =6.1 Hz, 1H, NHCH), 3.38–3.36 (m, 1H, NH), 2.43–2.31 (m, 1H, CH), 1.21 (dd, *J* =10.7, 7.0 Hz, 6H, 2 × CH_3). (Signals of the NH_2 protons were not observed in the spectrum.) ^{13}C NMR (125 MHz, CD_3OD): *δ* 166.7, 137.9, 129.0, 124.8, 120.3, 59.2, 30.6, 17.7, 16.8. HRMS (MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{11}H_{16}N_2ONa$: 215.1155; found: 215.1103

(S)-4-Methyl-1-oxo-1-(phenylamino)pentan-2-aminium bromide:
Yellow crystals; yield: 95%; m.p. = 106.2–110.1 °C. ^{1}H NMR (400 MHz, CD_3OD): *δ* 7.68–7.66 (m, 2H, Ar-H), 7.42–7.38 (m, 2H, Ar-H), 7.23–7.19 (m, 1H, Ar-H), 4.13–4.09 (m, 1H, CH), 3.38–3.36 (m, 3H, NH_3+), 1.90–1.81 (m, 3H, CH_2CH), 1.12–1.10 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, CD_3OD): *δ* 167.7, 137.8, 128.8, 124.7, 120.1, 52.5, 40.5, 24.3, 22.0, 20.9. HRMS (MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{12}H_{18}N_2ONa$ [M(free base) + Na]$^+$: 229.1311; found: 229.1314. Elemental analysis: calcd for $C_{12}H_{19}BrN_2O$: C, 50.19; H, 6.67; N, 9.75%; found: C, 49.88 ± 0.07; H, 6.83 ± 0.03; N, 9.61 ± 0.01 %

(S)-2-Amino-N,3-diphenylpropanamide:
Yellow crystalline solid; yield: 92%; Rf = 0 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, CD_3OD): *δ* 7.58–7.56 (m, 2H, Ar-H), 7.42–7.35 (m, 7H, Ar-H), 7.21–7.17 (m, 1H, Ar-H), 4.33–4.30 (m, 1H, NHCH), 3.78–3.56 (m, 2H, CH_2), 3.26–3.21 (m, 1H, NH). (Signals of the NH_2 protons were not observed in the spectrum.) ^{13}C NMR (125 MHz, CD_3OD): *δ* 137.6, 134.3, 129.4, 128.9, 128.7, 127.7, 124.7, 120.1, 55.2, 37.6. HRMS (MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{15}H_{16}N_2ONa$: 263.1155; found: 263.1099.

(S)-2-Amino-3-methyl-N-(4-(trifluoromethyl)phenyl)butanamide:
Greenish-gray waxy solid; yield: 67%; Rf = 0 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, CD_3OD): *δ* 7.88 (d, *J* =8.4 Hz, 2H, Ar-H), 7.68 (d, *J* =8.6 Hz, 2H, Ar-H), 3.38–3.36 (m, 1H, NHCH), 3.34 (d, *J* =5.6 Hz, 1H, NH), 2.15–2.04 (m, 1H, CH), 1.10 (d, *J* =6.9 Hz, 3H, CH_3), 1.04 (d, *J* =7.0 Hz, 3H, CH_3). (Signals of the NH_2 protons were not observed in the spectrum.) ^{13}C NMR (125 MHz, CD_3OD): *δ* 174.6, 141.9, 125.9, 125.8, 119.6, 119.6, 61.0, 32.5, 18.6, 16.5. HRMS (MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{12}H_{15}F_3N_2ONa$: 283.1034; found: 283.1031.

(S)-2-Amino-4-methyl-N-(4-(trifluoromethyl)phenyl)pentanamide:
Gray waxy solid; yield: 91%; Rf = 0 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, CD_3OD): *δ* 8.64 (d, *J* =8.5 Hz, 2H, Ar-H), 8.44 (d, *J* =8.8 Hz, 2H, Ar-H), 4.14–4.12 (m, 2H, CH_2), 2.64–2.53 (m, 1H, NH), 2.48–2.41 (m, 1H, NHCH), 2.34–2.27 (m, 1H, CH), 1.82–1.78 (m, 6H, 2 × CH_3). (Signals of the NH_2 protons were not observed in the spectrum.) ^{13}C NMR (125 MHz, CD_3OD): *δ* 175.7, 141.9, 125.9, 125.8, 119.6, 54.1, 44.2, 24.7, 22.3, 21.2. HRMS

(MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{13}H_{17}F_3N_2ONa$: 297.1185; found: 297.1185.

(S)-2-Amino-3-phenyl-N-(4-(trifluoromethyl)phenyl)propanamide:
Gray waxy solid; yield: 79%; m.p. = 94.0–95.4 °C; Rf = 0 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 7.84–7.82 (m, 2H, Ar-H), 7.68–7.66 (m, 2H, Ar-H), 7.32–7.24 (m, 5H, Ar-H), 3.03–2.99 (m, 1H, NH), 2.77–2.73 (m, 1H, NHCH), 2.52–2.50 (m, 2H, CH_2). (Signals of the NH_2 protons were not observed in the spectrum.) ^{13}C NMR (125 MHz, DMSO-d6): δ 175.5, 143.6, 139.7, 130.5, 129.3, 127.4, 126.6, 124.5, 120.4, 58.6, 42.1, 37.6.

2-Oxo-1,2-dihydropyridine-3-carbonyl chloride:

Yellowish crystals; yield: 87%; m.p. = 234–236 °C. Elemental analysis: calcd for $C_6H_4ClNO_2$: C, 45.74; H, 2.56; N, 8.89%; found: C, 45.87 ± 0.05; H, 2.56 ± 0.01; N, 8.81 ± 0.01%

Final Coupling with Acyl Chlorides (2-Hydroxynicotinic Acid Series)

2-Hydroxy-N-((S)-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)nicotinamide:
White crystals; yield: 81%; m.p. = 282.4–284.9 °C; Rf = 0.46 (DCM/MeOH, 10:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.54 (br s, 1H, OH), 10.23 (s, 1H, NH), 10.15 (d, *J* =7.95 Hz, 1H, CHNH), 8.35–8.33 (m, 1H, Ar-H), 7.74–7.73 (m, 1H, Ar-H), 7.63–7.62 (m, 2H, Ar-H), 7.33–7.29 (m, 2H, Ar-H), 7.07–7.04 (m, 1H, Ar-H), 6.50–6.47 (m, 1H, Ar-H), 4.75–4.71 (m, 1H, CH_2CH), 1.68–1.61 (m, 3H, $CHCH_2$), 0.96–0.93 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d6): δ 171.9, 164.1, 163.4, 145.3, 140.8, 140.1, 129.9, 124.6, 121.2, 120.5, 107.4, 53.2, 43.0, 25.8, 24.1, 23.1. HRMS (MALDI-TOF): m/z [M + Na]$^+$ calcd for $C_{18}H_{21}N_3O_3Na$: 350.1475; found: 350.1391. Elemental analysis: calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84 %; found: C, 66.28 ± 0.28; H, 6.47 ± 0.08; N, 12.41 ± 0.05 %.

2-Hydroxy-N-((S)-1-oxo-3-phenyl-1-(phenylamino)propan-2-yl)nicotinamide:
White crystals; yield: 87%; m.p. = 277.6–279.5 °C; Rf = 0.46 (DCM/MeOH, 10:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.52 (br s, 1H, OH), 10.23 (d, *J* =7.8 Hz, 1H, CHNH), 10.22 (s, 1H, NH), 8.29–8.27 (m, 1H, Ar-H), 7.72–7.71 (m, 1H, Ar-H), 7.58–7.57 (m, 2H, Ar-H), 7.33–7.29 (m, 2H, Ar-H), 7.27–7.26 (m, 4H, Ar-H), 7.21–7.18 (m, 1H, Ar-H), 7.07–7.05 (m, 1H, Ar-H), 6.47–6.44 (m, 1H, Ar-H), 4.91 (q, *J* =7.7 Hz, 1H, $CHCH_2$), 3.15 (dd, *J* =13.9, 5.5 Hz, 1H, CHCHH), 3.00 (dd, *J* =13.5, 8.4 Hz, 1H, CHCHH). ^{13}C NMR (125 MHz, DMSO-d6): δ 170.8, 164.2, 163.3, 145.2, 140.9, 139.9, 138.2, 130.4, 129.9, 129.4, 127.7, 124.6, 121.1, 120.5, 107.4, 56.1, 39.7. Elemental analysis: calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63 %; found: C, 69.67 ± 0.03; H, 5.34 ± 0.02; N, 11.24 ± 0.02 %.

2-Hydroxy-N-((S)-3-methyl-1-oxo-1-(phenylamino)butan-2-yl)nicotinamide:
White crystals; yield: 70%; m.p. = 282.4–284.6 °C; Rf = 0.50 (DCM/MeOH, 10:1, v/v). ^{1}H NMR (400 MHz, DMSO-d6): δ 12.56 (br s, 1H, OH), 10.29 (d, *J* =8.1 Hz, 1H, CHNH), 10.24 (s, 1H, NH), 8.40–8.37 (m, 1H, Ar-H), 7.80–7.76 (m, 1H, Ar-H), 7.70–7.65 (m, 2H, Ar-H), 7.37–7.33 (m, 2H, Ar-H), 7.12–7.07 (m, 1H, Ar-H), 6.54–6.51 (m, 1H, Ar-H), 4.63 (dd, *J* =8.1, 6.0 Hz, 1H, NHCH), 2.18–2.13 (m, 1H, CH), 1.01–0.98 (m, 6H, 2 × CH_3). ^{13}C NMR (125

MHz, DMSO-d6): δ 170.5, 163.9, 163.0, 144.8, 140.2, 139.4, 129.4, 124.0, 120.8, 120.0, 106.9, 59.0, 46.3, 31.9, 20.0, 18.6. Elemental analysis: calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41 %; found: C, 65.63 ± 0.07; H, 6.33 ± 0.08; N, 13.42 ± 0.01 %.

Final Coupling via Carbodiimide Activation (Pyrazine-2-carboxylic Acid Series)

S)-N-(3-Methyl-1-oxo-1-(phenylamino)butan-2-yl)pyrazine-2-carboxamide:

White crystalline solid; yield: 27%; m.p. = 202.1–203.6 °C; Rf = 0.25 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.44 (br s, 1H, NH), 8.81 (br s, 1H, NH), 8.64–8.62 (m, 2H, Ar-H), 8.54–8.53 (m, 1H, Ar-H), 7.57 (d, *J* =8.0 Hz, 2H, Ar-H), 7.31–7.28 (m, 2H, Ar-H), 7.12–7.09 (m, 1H, Ar-H), 4.74–4.71 (m, 1H, NHCH), 2.49–2.39 (m, 1H, CH), 1.16–1.12 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 164.1, 147.6, 145.1, 144.5, 143.9, 138.2, 129.7, 125.4, 120.8, 60.6, 31.9, 20.3, 19.2. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{16}H_{18}N_4O_2Na$: 321.1322; found: 321.1328. Elemental analysis: calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78 %; found: C, 64.38; H, 6.20; N, 18.34 %.

(S)-N-(3-Methyl-1-oxo-1-((4-(trifluoromethyl)phenyl)amino)butan-2-yl)pyrazine-2-carboxamide:

White crystalline solid; yield: 31 %; m.p. = 142.9–144.8 °C; Rf = 0.22 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 10.67 (br s, 1H, NH), 9.22 (d, *J* =1.4 Hz, 1H, Ar-H), 8.92 (d, *J* =2.5 Hz, 1H, Ar-H), 8.80–8.79 (m, 1H, Ar-H), 8.66 (d, *J* =9.1 Hz, 1H, NH), 7.83 (d, *J* =8.6 Hz, 2H, Ar-H), 7.70 (d, *J* =8.7 Hz, 2H, Ar-H), 4.63–4.60 (m, 1H, NHCH), 2.30–2.20 (m, 1H, CH), 0.99–0.94 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d6): δ 171.3, 163.8, 149.1, 145.1, 144.7, 143.2, 128.8, 127.3, 126.5, 124.9, 120.5, 59.9, 32.4, 20.8, 19.3. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{17}H_{17}F_3N_4O_2Na$: 367.1376; found: 367.1385. Elemental analysis: calcd for $C_{17}H_{17}F_3N_4O_2$: C, 55.74; H, 4.68; N, 15.29 %; found: C, 56.05; H, 4.79; N, 15.27 %.

(S)-N-(4-Methyl-1-oxo-1-(phenylamino)pentan-2-yl)pyrazine-2-carboxamide:

White crystalline solid; yield: 44%; m.p. = 139.0–140.5 °C; Rf = 0.33 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, CD_3OD): δ 9.29–9.28 (m, 1H, Ar-H), 8.86 (d, *J* =2.4 Hz, 1H, Ar-H), 8.77–8.76 (m, 1H, Ar-H), 7.63 (d, *J* =8.0 Hz, 2H, Ar-H), 7.38–7.34 (m, 2H, Ar-H), 7.18–7.14 (m, 1H, Ar-H), 3.38–3.36 (m, 1H, NHCH), 1.98–1.90 (m, 1H, NH), 1.87–1.75 (m, 2H, CH_2), 1.72–1.54 (m, 1H, CH), 1.08 (d, *J* =5.9 Hz, 6H, 2 × CH_3). (An additional NH proton signal was not observed in the spectrum.) ^{13}C NMR (125 MHz, CD_3OD): δ 171.6, 163.8, 147.5, 144.6, 143.7, 143.5, 138.2, 128.7, 124.5, 120.4, 52.8, 41.4, 25.0, 22.3, 21.0. HRMS (MALDI-TOF): m/z $[M + Na]^+$ calcd for $C_{17}H_{20}N_4O_2Na$: 335.1479; found: 335.1482. Elemental analysis: calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94 %; found: C, 67.37; H, 7.45; N, 15.80 %.

(S)-N-(4-Methyl-1-oxo-1-((4-(trifluoromethyl)phenyl)amino)pentan-2-yl)pyrazine-2-carboxamide:

White crystalline solid; yield: 25 %; m.p. = 82.8–85.7 °C; Rf = 0.29 (n-

hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 10.55 (br s, 1H, NH), 9.21 (d, *J* =1.5 Hz, 1H, Ar-H), 8.92 (d, *J* =2.5 Hz, 1H, Ar-H), 8.88 (d, *J* =8.4 Hz, 1H, NH), 8.79–8.78 (m, 1H, Ar-H), 7.84 (d, *J* =8.8 Hz, 2H, Ar-H), 7.70 (d, *J* =8.7 Hz, 2H, Ar-H), 4.80–4.75 (m, 1H, NHCH), 1.90–1.82 (m, 1H, CH), 1.72–1.62 (m, 2H, CH_2), 0.95–0.93 (m, 6H, 2 × CH_3). ^{13}C NMR (125 MHz, DMSO-d6): δ 172.4, 164.2, 149.0, 145.4, 144.8, 144.7, 143.5, 127.3, 126.6, 124.8, 124.6, 120.5, 53.6, 25.9, 24.6, 22.8. HRMS (MALDI-TOF): m/z [M + Na]$^{+}$ calcd for $C_{18}H_{19}F_3N_4O_2Na$: 381.1533; found: 381.1541. Elemental analysis: calcd for $C_{18}H_{19}F_3N_4O_2$: C, 56.84; H, 5.04; N, 14.73 %; found: C, 57.88; H, 5.43; N, 13.70 %.

(S)-N-(1-Oxo-3-phenyl-1-(phenylamino)propan-2-yl)pyrazine-2-carboxamide:

White crystalline solid; yield: 44 %; m.p. = 162.8–164.8 °C; Rf = 0.23 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94–8.91 (br s, 1H, NH), 8.39–8.36 (br s, 1H, NH), 8.25–8.16 (m, 2H, Ar-H), 7.91–7.89 (m, 1H, Ar-H), 7.01–6.82 (m, 9H, Ar-H), 6.72–6.66 (m, 1H, Ar-H), 4.74–4.71 (m, 1H, NHCH), 2.96–2.91 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 163.5, 147.7, 144.1, 143.9, 143.0, 137.3, 136.5, 129.4, 129.0, 128.9, 127.2, 124.7, 120.1, 55.8, 38.6. HRMS (MALDI-TOF): m/z [M + Na]$^{+}$ calcd for $C_{20}H_{18}N_4O_2Na$: 369.1322; found: 369.1328. Elemental analysis: calcd for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17 %; found: C, 69.55; H, 5.11; N, 15.96 %

(S)-N-(1-Oxo-3-phenyl-1-((4-(trifluoromethyl)phenyl)amino)propan-2-yl)pyrazine-2-carboxamide:

White crystalline solid; yield: 46 %; m.p. = 217–219 °C; Rf = 0.22 (n-hexane/EtOAc, 1:1, v/v). ^{1}H NMR (500 MHz, DMSO-d6): δ 10.64 (br s, 1H, NH), 9.14 (d, *J* =1.4 Hz, 1H, Ar-H), 8.94 (d, *J* =8.1 Hz, 1H, NH), 8.90 (d, *J* =2.5 Hz, 1H, Ar-H), 8.78–8.77 (m, 1H, Ar-H), 7.82 (d, *J* =8.5 Hz, 2H, Ar-H), 7.71 (d, *J* =8.7 Hz, 2H, Ar-H), 7.31 (d, *J* =7.3 Hz, 2H, Ar-H), 7.27–7.24 (m, 2H, Ar-H), 7.20–7.17 (m, 1H, Ar-H), 5.01–4.97 (m, 1H, NHCH), 3.24 (d, *J* =7.1 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d6): δ 171.2, 163.9, 149.1, 145.2, 144.7, 143.4, 138.2, 130.4, 129.4, 127.7, 127.3, 126.6, 124.6, 120.5, 56.2, 38.5. HRMS (MALDI-TOF): m/z [M + Na]$^{+}$ calcd for $C_{21}H_{17}F_3N_4O_2Na$: 415.1376; found: 415,13812. Elemental analysis: calcd for $C_{21}H_{17}F_3N_4O_2$: C, 60.87; H, 4.14; N, 13.52 %; found: C, 61.45; H, 4.13; N, 13.62 %