Carboxylic Acid Analogues of Fosmidomycin

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N-Alkylation of *N*-Boc-*O*-benzylhydroxylamine (**1**) with benzyl 4-bromobutyrate (**2**) in DMF gave *N*,*O*-bisprotected benzyl 4-hydroxyamino-butyrate (**3**), which was converted into 4-benzyloxyamino-butyric acid benzyl ester (**4**) with TFA in methylene chloride. Treatment of **4** with formic acid/acetic anhydride or various acid chlorides followed by catalytic hydrogenation led to 4-(*N*-acyl-*N*-hydroxyamino)-butyric acids **6**.

Key words: Non-mevalonate Isoprenoid Biosynthesis, Fosmidomycin, 4-(*N*-Acyl-*N*-hydroxyamino)-butyric Acids

Introduction

Recently we reported on the synthesis of hydroxyurea analogues of Fosmidomycin (**I**) and FR-900098 (**II**) [1]. In continuation of our studies directed to the structural modification of Fosmidomycin we now describe the synthesis of carboxylic acid analogues of **I** and **II**. The bioisosteric replacement of a phosphonic acid function by a carboxylic acid group has been reported by several authors and constitutes an important tool in medicinal and agricultural chemistry [2, 3]. Compounds **I** and **II** are potent inhibitors of the non-mevalonate (DOXP/MEP) pathway of isoprenoid biosynthesis [4, 5]. Both compounds inhibit the 1-desoxy-D-xylulose-5-phosphate (DOXP) reductoisomerase which catalyses the NADPH dependent transformation of 1-desoxy-D-xylulose-5-phosphate into 2-*C*-methyl-D-erythritol-4-phosphate [6]. The DOXP/MEP pathway is for instance present in higher plants, bacteria and the malaria parasite *Plasmodium falciparum*, but not in humans. Therefore, enzymes involved in the DOXP/MEP pathway are promising targets for the development of new herbicidal, antibacterial and antimalaria active compounds (Fig. 1).

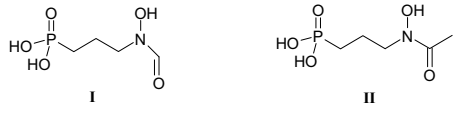

Fig. 1. Fosmidomycin (**I**) and FR 900098 (**II**).

Results and Discussion

The starting materials, *N*-Boc-*O*-benzylhydroxylamine (**1**) and benzyl 4-bromobutyrate (**2**) were prepared according to literature procedures [7, 8]. *N*-Alkylation of **1** with **2** in presence of sodium hydride and catalytic amounts of sodium iodide in dry DMF provided *N*,*O*-bisprotected 4-hydroxyamino-butyrate **3** in 82% yield. Removal of the Boc group with TFA in methylene chloride at room temperature gave **4**, which was isolated after a standard work-up procedure and column chromatography in 61% yield as a pale yellow oil. Formylation of **4** was accomplished with formic acid/acetic anhydride to give **5a**. Treatment of **4** with various acid chlorides afforded O-benzyl protected hydroxamic acids **5b–i**. Catalytic hydrogenation of **5a–i** led to 4-(*N*-acyl-*N*-hydroxyamino)-butyric acids **6a–i** in good to excellent yields (Scheme 1). The structures of all novel compounds **3–6** were confirmed by ^{1}H, ^{13}C NMR spectra, mass spectra and elemental analysis.

Experimental Section

General Methods: Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400.1 MHz) and ^{13}C NMR (100.62 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6 and $CDCl_3$ as solvents. Mass spectra were recorded on a VG 70–250S (VG An-

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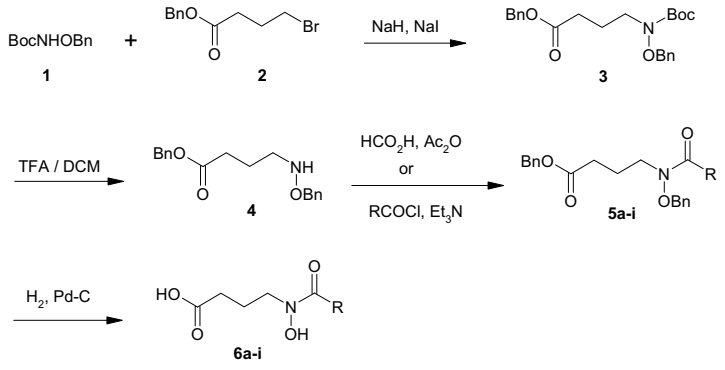

Scheme 1. Synthesis of 4-(*N*-acyl-*N*-hydroxyamino)-butyric acids **6a–i**.

Table 1. 4-(*N*-Acyl-*N*-benzyloxyamino)-butyric acid benzyl esters **5a–i** and 4-(*N*-acyl-*N*-hydroxyamino-butyric acids **6a–i**.

5, 6	**R**	**5** yield [%]	**6** yield [%]
a	H	89	98
b	CH_3	91	83
c	*i*-C_3H_7	99	99
d	*t*-C_4H_9	97	74
e	C_6H_5	98	76
f	2-furyl	88	69
g	4-biphenylyl	48	54
h	4-phenoxy-phenyl	93	86
i	1-naphthyl	96	69

alytical) instrument. Column chromatography was conducted on silica gel (ICN Silica 100–200, active, 60 Å).

4-(N-Benzyloxy-N-tert-butoxycarbonylamino)-butyric acid benzyl ester (**3**)

To a stirred solution of **1** (5 mmol) in dry DMF (20 ml) was added portionwise sodium hydride (5.5 mmol) at 0–5 °C. After stirring for 30 minutes benzyl 4-bromobutyrate (**2**) and catalytic amounts of sodium iodide were added and the reaction mixture was heated at 50 °C for 1.5 h under nitrogen. The mixture was cooled to room temperature, poured into water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The remaining residue was purified by silica gel column chromatography with CH_2Cl_2/hexane (7/3) as an eluent to give **3** as colourless oil (84%). IR (film): ν = 1736, 1701 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.49 (s, 9H, CH_3), 1.89–1.97 (m, 2H, CH_2), 2.39 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.47 (t, ^3J = 6.9 Hz, 2H, CH_2N), 4.81 (s, 2H, $NOCH_2Ph$), 5.10 (s, 2H, OCH_2Ph), 7.30–7.40 (m, 10H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.54 (CH_2), 28.31 (CH_3), 31.45 (CH_2), 48.79 (CH_2N), 66.23 (OCH_2Ph), 76.92 ($NOCH_2Ph$), 81.39 (*C*), 128.19, 128.43, 128.51, 128.55, 129.41, 135.55, 135.99 ($C_{arom.}$), 156.47, 172.83 (*C*=O). $C_{23}H_{29}NO_5$ (399.5): calcd.: C 69.15, H 7.32, N 3.51; found C 68.87, H 7.17, N 3.41.

4-Benzyloxyamino-butyric acid benzyl ester (**4**)

TFA (10 ml) was added to a solution of **3** (10 mmol) in CH_2Cl_2 (10 ml) and the solution was stirred at room temperature for 1 h. After removal of the solvent aqueous K_2CO_3 solution was added to the residue and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and the remaining oil was purified by column chromatography on silica gel with EtOAc/hexane (1/4) as an eluent to give **4** as colourless oil (80%). IR (film): ν = 3412 (NH), 1736, 1701 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.83–1.91 (m, 2H, CH_2), 2.42 (t, ^3J = 7.4 Hz, 2H, CH_2), 2.95 (t, ^3J = 6.9 Hz, 2H, CH_2N), 4.67 (s, 2H, $NOCH_2Ph$), 5.11 (s, 2H, OCH_2Ph), 5.55 (s, 1H, N*H*), 7.25–7.38 (m, 10H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.83 (CH_2), 31.85 (CH_2), 51.15 (CH_2N), 66.18 (OCH_2Ph), 76.29 ($NOCH_2Ph$), 127.80, 128.18, 128.36, 128.41, 128.54, 136.04, 137.93 ($C_{arom.}$), 173.22 (*C*=O). $C_{18}H_{21}NO_3$ (299.4): calcd.: C 72.22, H 7.07, N 4.68; found C 71.88, H 7.28, N 4.72.

4-(N-Benzyloxy-N-formylamino)-butyric acid benzyl ester (**5a**)

A mixture of formic acid (50 mmol) and acetic anhydride (5 mmol) was stirred for 30 min at room temperature. Afterwards a solution of **4** in formic acid (5 ml) was added at 0–5 °C and the reaction mixture was stirred for 2 h at room temperature. EtOAc (100 ml) was added to the reaction mixture and the solution was washed thrice with cold aque-

ous K_2CO_3 solution, water and 0.5 M HCl. The organic layer was dried over $MgSO_4$, filtrated and the solvent was evaporated to give **5a** as a pale yellow oil (89%). IR (film): ν = 1734, 1676 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.96–1.99 (m, 2H, CH_2), 2.40 (t, ^3J = 6.9 Hz, 2H, CH_2), 3.63–3.65 (m, 2H, CH_2N), 4.80–4.93 (m, 2H, NOCH_2Ph), 5.11 (s, 2H, OCH_2Ph), 7.29–7.37 (m, 10H, $H_{arom.}$), 7.90–8.19 (m, 1H, C*H*O). ^{13}C NMR ($CDCl_3$): δ = 22.21 (*C*H_2), 31.20 (*C*H_2), 43.27 (*C*H_2N), 66.38 (O*C*H_2Ph), 77.70 (NO*C*H_2Ph), 128.27, 128.58, 128.76, 129.15, 129.47, 134.26, 135.85 ($C_{arom.}$), 163.14, 172.51 (*C*=O). $C_{19}H_{21}NO_4$ (327.38): calcd.: C 69.71, H 6.47, N 4.28; found C 69.34, H 6.47, N 4.34. HRMS (FAB): calcd. for $C_{19}H_{21}NO_4$: $[M+H]^+$: 328.1550; found 328.1580.

4-(N-Acyl-N-benzyloxyamino)-butyric acid benzyl esters (**5b–i**)

To a stirred solution of **4** (5 mmol) and triethylamine (5.5 mmol) in dry THF (20 ml) was added the appropriate acid chloride (5.5 mmol) in THF (5 ml) dropwise at 0–5 °C. After stirring at ambient temperature for 2 h the solvent was evaporated and the remaining oil was dissolved in diethyl ether. The solution was subsequently washed with aqueous K_2CO_3 solution, 0.5 M HCl and water. The organic layer was dried over $MgSO_4$, the solvent removed under reduced pressure and the remaining oil purified by column chromatography on silica gel with EtOAc/hexane (3/7) as an eluent to give **5b–h**.

4-(N-Acetyl-N-benzyloxyamino)-butyric acid benzyl ester (**5b**): Pale yellow oil (91%). IR (film): ν = 1732, 1663 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.95–2.02 (m, 2H, CH_2), 2.08 (s, 2H, CH_3), 2.40 (t, ^3J = 7.3 Hz, 2H, CH_2), 3.69 (t, ^3J = 6.3 Hz, 2H, CH_2N), 4.78 (s, 2H, NOCH_2Ph), 5.10 (s, 2H, OCH_2Ph), 7.33–7.37 (m, 10H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 20.46 (*C*H_3), 22.30 (*C*H_2), 31.37 (*C*H_2), 44.45 (*C*H_2N), 66.29 (O*C*H_2Ph), 76.30 (NO*C*H_2Ph), 128.24, 128.55, 128.72, 128.98, 129.22, 134.40, 135.94 ($C_{arom.}$), 172.29, 172.72 (*C*=O). $C_{20}H_{23}NO_4$ (341.4): calcd.: C 70.36, H 6.79, N 4.10; found C 70.00, H 6.64, N 4.46.

4-(N-Benzyloxy-N-isobutyrylamino)-butyric acid benzyl ester (**5c**): Colourless oil (99%). IR (film): ν = 1734, 1661 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.08 (d, ^3J = 6.9 Hz, 6H, (CH_3), 1.94–2.01 (m, 2H, CH_2), 2.39 (t, ^3J = 7.4 Hz, 2H, CH_2), 2.91 (sept., ^3J = 6.9 Hz, 1H, C*H*), 3.70 (t, ^3J = 6.9 Hz, 2H, CH_2N), 4.79 (s, 2H, NOCH_2Ph), 5.10 (s, 2H, OCH_2Ph), 7.30–7.38 (m, 10H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 19.05 (*C*H_3), 22.33 (*C*H_2), 30.22 (*C*H), 31.29 (*C*H_2), 44.37 (*C*H_2N), 66.28 (O*C*H_2Ph), 76.44 (NO*C*H_2Ph), 128.23, 128.55, 128.71, 128.89, 129.08, 134.52, 135.97 ($C_{arom.}$), 172.79, 178.82 (*C*=O). $C_{22}H_{27}NO_4$ (369.5): calcd.: C 71.52, H 7.37, N 3.97; found C 71.28, H 7.65, N 4.10.

4-(N-Benzyloxy-N-2,2-dimethylpropionylamino)-butyric acid benzyl ester (**5d**): Pale yellow oil (97%). IR (film): ν = 1736, 1647 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.26 (s, 9H, CH_3), 1.95–2.03 (m, 2H, CH_2), 2.41 (t, ^3J = 7.3 Hz, 2H, CH_2), 3.76 (t, ^3J = 7.0 Hz, 2H, CH_2N), 4.83 (s, 2H, NOCH_2Ph), 5.10 (s, 2H, OCH_2Ph), 7.25–7.36 (m, 10H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.03 (*C*H_2), 27.16 (*C*H_3), 31.28 (*C*H_2), 39.52 (*C*$(CH_3)_3$), 44.45 (*C*H_2N), 66.27 (O*C*H_2Ph), 75.05 (NO*C*H_2Ph), 128.21, 128.42, 128.55, 128.57, 128.66, 134.62, 135.96 ($C_{arom.}$), 172.84, 179.45 (*C*=O). $C_{23}H_{29}NO_4$ (383.5): calcd.: C 72.04, H 7.62, N 3.65; found C 71.87, H 7.66, N 3.35.

4-(N-Benzoyl-N-benzyloxyamino)-butyric acid benzyl ester (**5e**): Colourless crystals (98%). M.p. 36 °C (EtOAc/hexane). IR (KBr): ν = 1736, 1647 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.05–2.12 (m, 2H, CH_2), 2.47 (t, ^3J = 7.3 Hz, 2H, CH_2), 3.81 (t, ^3J = 6.8 Hz, 2H, CH_2N), 4.62 (s, 2H, NOCH_2Ph), 5.09 (s, 2H, OCH_2Ph), 7.03–7.05 (m, 2H, $H_{arom.}$), 7.23–7.47 (m, 11H, $H_{arom.}$), 7.62–7.63 (m, 2H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.60 (*C*H_2), 31.31 (*C*H_2), 46.02 (*C*H_2N), 66.34 (O*C*H_2Ph), 76.41 (NO*C*H_2Ph), 128.00, 128.25, 128.27, 128.49, 128.57, 128.83, 129,48, 130.51, 134.06, 134.43, 135.90 ($C_{arom.}$), 170.17, 172.67 (*C*=*O*). $C_{25}H_{25}NO_4$ (403.48): calcd.: C 74.42, H 6.25, N 3.47; found C 74.13, H 6.21, N 3.43. HRMS (FAB): calcd. for $C_{25}H_{25}NO_4$: $[M+H]^+$: 404.1863, found 404.1867.

4-(N-Benzyloxy-N-2-furoylamino)-butyric acid benzyl ester (**5f**): Pale yellow oil (88%). IR (film): ν = 1732, 1643 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.04–2.11 (m, 2H, CH_2), 2.45 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.86 (t, ^3J = 6.9 Hz, 2H, CH_2N), 4.87 (s, 2H, NOCH_2Ph), 5.10 (s, 2H, OCH_2Ph), 6.47 (dd, ^3J= 1.8, 3.6 Hz, 1H, H_{arom}), 7.14 (dd, ^3J = 3.6 Hz, ^4J = 0.8 Hz, 1H, H_{arom}), 7.25–7.40 (m, 10H, $H_{arom.}$), 7.57 (dd, ^3J = 1.8 Hz, ^4J = 0.8 Hz, 1H, OC*H*CH). ^{13}C NMR ($CDCl_3$): δ = 22.37 (*C*H_2), 31.32 (*C*H_2), 45.71 (*C*H_2N), 66.32 (O*C*H_2Ph), 76.70 (NO*C*H_2Ph), 111.57, 117.83, 128.23, 128.56, 128.74, 128.99, 129.23, 134.21, 135.91, 145.24, 145.81 ($C_{arom.}$), 159.32, 172.72 (*C*=O). $C_{23}H_{23}NO_5$ (393.4): calcd.: C 70.22, H 5.89, N 3.56; found

C 69.80, H 5.91, N 3.48. HRMS (FAB): calcd. for $C_{23}H_{23}NO_5$: $[M+H]^+$: 394.1655; found 394.1640.

4-[N-Benzyloxy-N-(4-phenyl-benzoyl)amino]-butyric acid benzyl ester (**5g**): Colourless crystals (48%). M.p. 38 °C (EtOAc/hexane). IR (KBr): ν = 1734, 1639 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.07–2.14 (m, 2H, CH_2), 2.49 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.85 (t, ^3J = 6.7 Hz, 2H, CH_2N), 4.66 (s, 2H, NOCH_2Ph), 5.10 (s, 2H, OCH_2Ph), 7.07–7.73 (m, 19H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.64 (*C*H_2), 31.35 (*C*H_2), 46.05 (*C*H_2N), 66.36 (O*C*H_2Ph), 76.50 (NO*C*H_2Ph), 126.65, 127.20, 128.25, 128.50, 128.57, 128.86, 128.92, 128.97, 129.52, 133.07, 134.05, 135.90, 140.32, 143.38 ($C_{arom.}$), 169.86, 172.70 (*C*=O). $C_{31}H_{29}NO_4$ (479.6): calcd.: C 77.64, H 6.10, N 2.92; found C 77.29, H 6.21, N 3.22.

4-[N-Benzyloxy-N-(4-phenoxy-benzoyl)amino]-butyric acid benzyl ester (**5h**): Colourless oil (93%). IR (film): ν = 1736, 1638 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.05–2.12 (m, 2H, CH_2), 2.47 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.83 (t, ^3J = 6.9 Hz, 2H, CH_2N), 4.64 (s, 2H, NOCH_2Ph), 5.09 (s, 2H, OCH_2Ph), 6.96–7.67 (m, 19H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.60 (*C*H_2), 31.32 (*C*H_2), 45.98 (*C*H_2N), 66.35 (O*C*H_2Ph), 76.35 (NO*C*H_2Ph), 111.57, 119.54, 128.24, 128.52, 128.56, 128.88, 129.49, 129.93, 130.62, 134.06, 135.89, 156.28, 159.53 ($C_{arom.}$), 169.38, 172.69 (*C*=O). $C_{31}H_{29}NO_5$ (495.6): calcd.: C 75.13, H 5.90, N 2.83; found C 74.85, H 6.30, N 3.09. HRMS (FAB): calcd. for $C_{31}H_{29}NO_5$: $[M+H]^+$: 496.2125; found 496.2139.

4-(N-Benzyloxy-N-1-naphthoylamino)-butyric acid benzyl ester (**(5i**): Colourless oil (96%). IR (film): ν = 1732, 1651 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.93–2.25 (m, 2H, CH_2), 2.32–2.69 (m, 2H, CH_2), 3.47–4.17 (m, 2H, CH_2N), 4.35–4.86 (m, 2H, NOCH_2Ph), 5.07 (s, 2H, OCH_2Ph), 6.50–6.94 (m, 1H, $H_{arom.}$), 7.05–7.36 (m, 1H, $H_{arom.}$), 7.44–7.51 (m, 1H, $H_{arom.}$), 7.85–7.94 (m, 1H, $H_{arom.}$). ^{13}C NMR ($CDCl_3$): δ = 22.75 (*C*H_2), 31.37 (*C*H_2), 45.72 (*C*H_2N), 66.35 (O*C*H_2Ph), 76.72 (NO*C*H_2Ph), 124.73, 124.83, 125.01, 126.30, 127.00, 128.25, 128.32, 128.36, 128.56, 128.70, 129.70, 129.96, 133.05, 133.42, 135.26 ($C_{arom.}$), 164.26, 172.54 (*C*=O). $C_{29}H_{27}NO_4$(453.5): calcd.: C 76.80, H 6.00, N 3.09; found C 75.83, H 5.87, N 3.08. HRMS (FAB): calcd. for $C_{29}H_{27}NO_4$: $[M+H]^+$: 454.2019, found 454.2040.

4-(N-Acyl-N-hydroxyamino)-butyric acids (**6a–i**)

Benzyl esters **5a–h** (2 mmol) were hydrogenated in MeOH using catalytic amounts of 10% Pd-C for 1 h. The suspension was filtrated and the solvent was evaporated to give **6a–i**.

4-(N-Formyl-N-hydroxyamino)-butyric acid (**6a**): Yellow oil (98%). IR (KBr): ν = 3142, 2941 (OH), 1707, 1653 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.71–1.80 (m, 2H, CH_2), 2.22 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.40–3.48 (m, 2H, CH_2N), 7.88 (s, 0.5H, C*H*O), 8.25 (s, 0.5H, C*H*O), 10.90 (s, 2H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 21.48, 22.31 (*C*H_2), 30.19, 30.53 (*C*H_2), 45.06, 48.30 (*C*H_2N), 157.06, 161.75, 173.85 (*C*=O). $C_5H_9NO_4$ (147.1): calcd.: C 40.82, H 6.17, N 9.52; found C 40.87, H 6.31, N 9.31.

4-(N-Acetyl-N-hydroxyamino)-butyric acid (**6b**): Colourless crystals (83%). M.p. 70 °C (EtOAc/hexane). IR (KBr): ν = 3138, 2829 (OH), 1711, 1670, 1616, 1589 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.70–1.77 (m, 2H, CH_2), 1.97 (s, 2H, CH_3), 2.21 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.69 (t, ^3J = 6.9 Hz, 2H, CH_2N), 9.71 (s, 1H, O*H*), 12.01 (s, 1H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 20.66 (*C*H_3), 22.26 (*C*H_2), 31.12 (*C*H_2), 44.70 (*C*H_2N), 170.75, 174.41 (*C*=O). $C_6H_{11}NO_4$ (161.2): calcd.: C 44.72, H 6.88, N 8.69; found C 44.89, H 6.81, N 8.52.

4-(N-Hydroxy-N-isobutyrylamino)-butyric acid (**6c**): Colourless crystals (99%). M.p. 69 °C (EtOAc/hexane). IR (KBr): ν = 3161, 2935, 2515 (OH), 1709, 1585 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 0.99 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.70–1.77 (m, 2H, CH_2), 2.19 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.02 (sept., ^3J = 6.9 Hz, 1H, C*H*), 3.50 (t, ^3J = 6.9 Hz, 2H, CH_2N), 10.80 (s, 2H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 18.75 (*C*H_3), 21.79 (*C*H_2), 28.90 (*C*H), 30.66 (*C*H_2), 46.55 (*C*H_2N), 174.02, 176.37 (*C*=O). $C_8H_{15}NO_4$ (189.2): calcd.: C 50.78, H 7.99, N 7.40; found C 50.67, H 8.04, N 7.08. HRMS (FAB): calcd. for $C_8H_{15}NO_4$: $[M+H]^+$: 190.1080; found 190.1090.

4-(N-2,2-Dimethylpropionyl-N-hydropxyamino)-butyric acid (**6d**): Colourless crystals (74%). M.p. 95 °C (EtOAc/hexane). IR (KBr): ν = 3111, 2955 (OH), 1707, 1593, 1572 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.18 (s, 9H, CH_3), 1.71–1.78 (m, 2H, CH_2), 2.19 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.50 (t, ^3J = 6.9 Hz, 2H, CH_2N), 9.42 (s, 1H, O*H*), 11.99 (s, 1H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 22.03 (*C*H_2), 27.38 (*C*H_3), 31.11 (*C*H_2), 38.70 (*C*$(CH_3)_3$), 48.64 (*C*H_2N), 174.46, 176.78 (*C*=O). $C_9H_{17}NO_4$ (203.2): calcd.: C 53.19, H 8.43, N 6.89; found C 53.10, H 8.30, N 6.99.

4-(N-Benzoyl-N-hydroxyamino)-butyric acid (**6e**): Colourless crystals (76%). M.p. 89 °C (EtOAc/hexane) IR (KBr): ν = 3140, 3055, 2914 (OH),

1709, 1595 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.81–1.89 (m, 2H, CH_2), 2.29 (t, ^3J = 7.3 Hz, 2H, CH_2), 3.65 (t, ^3J = 6.7 Hz, 2H, CH_2N), 7.38–7.47 (m, 3H, $H_{arom.}$), 7.58–7.60 (m, 2H, $H_{arom.}$), 9.84 (s, 1H, O*H*), 12.03 (s, 1H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 21.76 (*C*H_2), 30.65 (*C*H_2), 47.96 (*C*H_2N), 127.63, 128.03, 129.80, 135.01 ($C_{arom.}$), 168.54, 173.93 (*C*=O). $C_{11}H_{13}NO_4$ (223.2): calcd.: C 59.19, H 5.87, N 6.27; found C 59.03, H 5.86, N 6.21. HRMS (FAB): calcd. for $C_{11}H_{13}NO_4$: $[M+H]^+$: 224.0924; found 224.0920.

4-(N-2-Furoyl-N-hydroxyamino)-butyric acid (**6f**): Colourless crystals (69%). M.p. 113 °C (EtOAc/hexane). IR (KBr): ν = 3134, 2887 (OH), 1715, 1597 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.79–1.78 (m, 2H, CH_2), 2.26 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.66 (t, ^3J = 6.9 Hz, 2H, CH_2N), 6.62 (dd, ^3J= 1.8, 3.6, 1H, H_{arom}), 7.18 (dd, ^3J = 3.6 Hz, ^4J = 0.8 Hz, 1H, H_{arom}), 7.86 (dd, ^3J = 1.8 Hz, ^4J = 0.8 Hz, 1H, H_{arom}), 10.21 (s, 1H, O*H*), 11.93 (s, 1H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 22.14 (*C*H_2), 31.10 (*C*H_2), 47.99 (*C*H_2N), 111.86, 117.56, 145.65, 146.00 ($C_{arom.}$), 158.53, 174.36 (*C*=O). $C_9H_{11}NO_5$ (213.2): calcd.: C 50.71, H 5.20, N 6.57; found C 50.60, H 5.25, N 6.21.

4-[N-Hydroxy-N-(4-phenyl-benzoyl)amino]-butyric acid (**6g**): Pale pink crystals (54%). M.p. 158 °C (EtOAc/hexane). IR (KBr): ν = 3188 (OH), 1699, 1601 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.58–1.92 (m, 2H, CH_2), 2.32 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.69 (t, ^3J = 6.9 Hz, 2H, CH_2N), 7.38–7.42 (m, 1H, $H_{arom.}$), 7.47–7.51 (m, 2H, $H_{arom.}$), 7.66–7.75 (m, 6H, $H_{arom.}$), 10.36 (s, 1H, O*H*), 11.51 (s, 1H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 22.25 (*C*H_2), 31.17 (*C*H_2), 48.46 (*C*H_2N), 126.34, 126.81, 127.16, 128.20, 128.26, 129.32, 129.37, 134.29, 139.75, 141.98 ($C_{arom.}$), 168.71, 174.43 (*C*=O). $C_{17}H_{17}NO_4$ (299.3): calcd.: C 68.22, H 5.72, N 4.68; found C 68.13, H 5.77, N 4.38.

4-[N-Hydroxy-N-(4-phenoxy-benzoyl)amino]-butyric acid (**6h**): Colourless crystals (86%). M.p. 125 °C (EtOAc/hexane). IR (KBr): ν = 3240, 3170, 2939 (OH), 1701, 1603 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.82–1.89 (m, 2H, CH_2), 2.29 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.66 (t, ^3J = 6.9 Hz, 2H, CH_2N), 6.96–7.01 (m, 2H, $H_{arom.}$), 7.06–7.09 (m, 2H, $H_{arom.}$), 7.18–7.22 (m, 1H, $H_{arom.}$), 7.41–7.46 (m, 2H, $H_{arom.}$), 7.66–7.70 (m, 2H, $H_{arom.}$), 10.07 (s, 1H, O*H*), 11.85 (s, 1H, O*H*). ^{13}C NMR (DMSO-d_6): δ = 22.22 (*C*H_2), 31.16 (*C*H_2), 48.51 (*C*H_2N), 117.38, 119.71, 124.49, 129.91, 130.56, 131.01, 156.14, 158.71 ($C_{arom.}$), 168.26, 174.42 (*C*=O). $C_{17}H_{17}NO_5$ (315.3): calcd.: C 64.75, H 5.43, N 4.44; found C 64.60, H 5.58, N 4.71.

4-(N-Hydroxy-N-1-naphthoylamino)-butyric acid (**6i**): Pale yellow crystals (69%) M.p. 122 °C (EtOAc/hexane). IR (film): ν = 3111, 3060, 2871 (OH), 1711, 1618 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 1.68–2.01 (m, 2H, CH_2), 2.08–2.45 (m, 2H, CH_2), 6.60–3.92 (m, 2H, CH_2N), 7.45–7.47 (m, 1H, $H_{arom.}$), 7.51–7.56 (m, 3H, $H_{arom.}$), 7.80–7.82 (m, 1H, $H_{arom.}$), 7.95–7.96 (m, 2H, $H_{arom.}$), 10.76 (s, 2H, OH). ^{13}C NMR (DMSO-d_6): δ = 22.32 (*C*H_2), 31.22 (*C*H_2), 47.40 (*C*H_2N), 124.69, 125.35, 126.47, 126.87, 128.54, 128.96, 129.66, 133.24, 134.72 ($C_{arom.}$), 169.26, 174.42 (*C*=O). $C_{15}H_{15}NO_4$ (273.3): calcd.: C 65.93, H 5.53, N 5.13; found C 65.74, H 5.73, N 5.24. HRMS (FAB): calcd. for $C_{15}H_{15}NO_4$: $[M+H]^+$: 274.1080; found 274.1081.

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