Hydroxyurea Analogues of Fosmidomycin

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Benzyloxyureas (**4**) have been prepared by reactions of diethyl 3-benzyloxyamino-propyl-phosphonate (**3**) with isocyanates, potassium cyanate or 1,1'-carbonyldiimidazole / methylamine. Conversion of phosphonic esters **4** into phosphonic acids **6** by means of bromotrimethylsilane and catalytic hydrogenation of **4, 6** afforded the target compounds **5**, **7**.

Key words: Malaria tropica, Fosmidomycin, Hydroxyurea Analogues

Introduction

Replacement of a hydroxamic acid functionality by a hydroxyurea group represents an important tool in medicinal and agricultural chemistry. Both functionalities have attracted considerable interest as pharmacophores in metalloenzyme inhibitors due to their ability to act as chelators for various metal cations [1, 2]. Fosmidomycin (**I**), a phosphono-hydroxamic acid antibiotic, which was described by Fujisawa company in 1980, is assumed to inhibit the bacterial isoprenoid synthesis [3,4]. In 1999 Jomaa [5] identified **I** as potent inhibitor of the 1-desoxy-D-xylulose-5-phosphate (DOXP) reductoisomerase of *Plasmodium falciparum*, the causative agent of *Malaria tropica*. Previously only two hydroxyurea analogues of Fosmidomycin have been described by Fujisawa company [2,6]. This prompted us to synthesize novel hydroxyurea analogues of **I** for structure activity investigations.

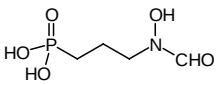


Fig. 1. Fosmidomycin (**I**).

Results and Discussion

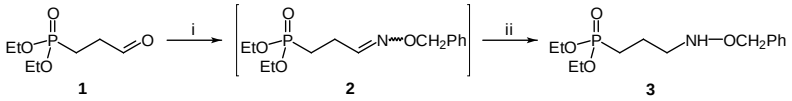
Diethyl 3-benzyloxyamino-propylphosponate (**3**) was prepared from diethyl 3-oxo-propylphosphonate (**1**) [7] and O-benzylhydroxylamine followed by reduction of **2** with sodium cyanoborohydride (Scheme 1).

Treatment of **3** with various isocyanates or potassium cyanate afforded benzyloxyureas **4a,c-f** in excellent yields of 83 – 95% after purification by column chromatography. Benzyloxyurea **4b** was accessible by reacting **3** with 1.05 equivalents of 1,1'-carbonyldiimidazole and subsequent addition of methylamine [8]. The formation of **4a-f** was monitored by running IR spectra from the reaction mixture showing the rapid emergence of a strong (C═O) absorption at 1650 – 1685 cm^{-1}. Dealkylation of phosphonic esters (**4b-e**) by means of bromotrimethylsilane and subsequent aqueous hydrolysis of the trimethylsilyl ester intermediates led to phosphonic acids **6b-e** as crystalline compounds in 83 – 91% yield (Scheme 2).

Catalytic hydrogenation of **4a-f** and **6b,c** provided hydroxyureas **5a-f**, and **7b,c** in good to excellent yields as stable compounds. In contrast to the catalytic hydrogenation of **6b,c** the analogous reaction of **6d,e** only led to crude products. Despite suitable ^{1}H NMR spectra no satisfactory mass spectra or CHN analysis could be obtained. The structures of **4-7** were confirmed by NMR spectra, mass spectra and CHN analyses (Table 1).

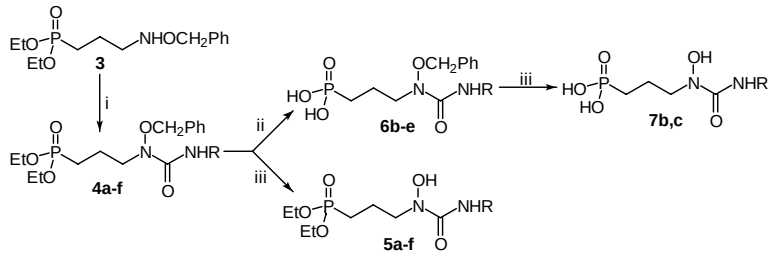
Experimental Section

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 or on a Perkin Elmer Series 1600 FT-IR. ^{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 inter-



Scheme 1.

Reagents: i: NH_2OCH_2Ph, ii: $NaBH_3CN$, HCl



Scheme 2.

Reagents: i: RNCO or KOCN or 1,1'-carbonyldiimidazole (CDI) / methylamine, ii: TMSBr / H_2O, iii: H_2 / Pd-C

Table 1. Benzyloxyureas **4**,**6** and hydroxyureas **5**,**7**.

4-7	**R**	**4** yield [%]	**5** yield [%]	**6** yield [%]	**7** yield [%]
a	H	95	87		
b	CH_3	83	87	92	82
c	C_2H_5	93	89	94	83
d	*i*-C_3H_7	92	99	89	
e	*t*-C_4H_9	83	94	90	
f	Ph	95	90		

nal standard and DMSO-d_6, D_2O and $CDCl_3$ as solvents. Mass spectra were recorded on a VG 70-250S (VG Analytical) instrument. Column chromatography was conducted on silica gel (ICN Silica 100-200, active 60 Å).

*Preparation of diethyl 3-benzyloxyamino-propylphosphonate (***3***)*

To a stirred solution of **1** (5.83 g, 30 mmol) in MeOH (20 ml) was added dropwise a solution of O-benzylhydroxylamine (3.88 g, 31.5 mmol) in MeOH (10 ml). The reaction mixture was refluxed for 1 h, cooled to 20 °C, and MeOH (420 ml) was added. After addition of sodium cyanoborohydride (5.66 g, 90 mmol), conc. HCl (30 ml) was added dropwise over a period of 30 min. After 1 h sodium cyanoborohydride (1.26 g, 20 mmol) was added again and the mixture was stirred for another hour. 200 ml of MeOH were removed under reduced pressure; the remaining residue was treated with 400 ml of ice-water, adjusted to pH 10 with aqueous KOH-solution and extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The remaining oil was purified by silica gel column chromatography with EtOAc as an eluent to give diethyl 3-benzyloxyamino-propylphosphonate (**3**) as a yellow oil (81%). – IR (film): $\nu = 3246$ (NH) cm^{-1}. – ^1H NMR ($CDCl_3$): $\delta = 1.31$ (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.74-1.90 (m, 4H, CH_2), 2.98 (t, J = 6.6 Hz, 2H, NCH_2), 4.02-4.16 (m, 4H, OCH_2CH_3), 4.69 (s, 2H, OCH_2Ph), 5.59 (s, 1H, NH), 7.29-7.35 (m, 5H). – ^{13}C NMR ($CDCl_3$): $\delta = 16.45$ (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 20.62 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 23.26 (d, $^1J_{C,P}$ = 142.4 Hz, PCH_2), 52.2 (d, $^3J_{C,P}$ = 16.8 Hz, NCH_2), 61.5 (d, $^2J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 76.39 (OCH_2Ph), 127.85, 128.40, 128.41, 137.89 ($C_{arom.}$). – $C_{14}H_{24}NO_4P$ (301.3): calcd. C 55.81, H 8.03, N 4.65; found C 55.53, H 7.90, N 4.76.

*General procedures for the preparation of benzyloxyureas (***4***)*

Method A: To a stirred solution of **3** (3.01 g, 10 mmol) in dry CH_2Cl_2 (5 ml) was added the appropriate isocyanate (10.5 mmol) at ambient temperature. After stirring over night the reaction mixture was purified by column chromatography on silica gel with EtOAc as an eluent.

Method B: A solution of KOCN (4.06 g, 50 mmol) in water (15 ml) was added dropwise to a stirred solution of **3** (3.01 g, 10 mmol) in 1 M HCl (50 ml) at 0 °C. After stirring at ambient temperature for 30 min the 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 as an eluent.

Method C: To a suspension of CDI (1.62 g, 10 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise a solution of **3** (3.01 g, 10 mmol) in dry CH_2Cl_2 (10 ml) over a period of 10 min under ice-cooling. After stirring at ambient temperature for 20 min, 5 ml of a 2 M solution of methylamine in THF (10 mmol) was added dropwise. The reaction mixture was stirred for 12 h, washed with 1 M HCl (2×10 ml), and the organic layer was dried over $MgSO_4$. After removal of the solvent the remaining oil was purified by column chromatography on silica gel with EtOAc as an eluent.

*Diethyl 3-(1-benzyloxyureido)propylphosphonate (**4a**):* Method B; yellow oil (95%) – IR (film): ν = 1685 (C═O), 1240 (P═O) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 6H, OCH_2CH_3), 1.71-2.00 (m, 2H, PCH_2CH_2), 3.59 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.02-4.15 (m, 4H, OCH_2CH_3), 4.83 (s, 2H, OCH_2Ph), 5.22 (s, 2H, NH_2), 7.34-7.40 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ = 16.47 (d, $^3J_{C,P}$ = 5.6 Hz, OCH_2CH_3), 20.10 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 23.09 (d, $^1J_{C,P}$ = 142.4 Hz, PCH_2), 48.64 (d, $^3J_{C,P}$ =19.3 Hz, NCH_2), 61.59 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 77.09 (OCH_2Ph), 128.81, 129.0, 129.22, 134.93 ($C_{arom.}$), 160.65 (C—O). – $C_{15}H_{25}N_2O_5P$ (344.4): calcd. C 52.32, H 7.32, N 8.14; found: C 52.21, H 7.52, N 7.81. – HRMS (FAB): calcd. for $C_{15}H_{25}N_2O_5P$: $[M+H]^+$: 345.1580; found 345.1612.

*Diethyl 3-(1-benzyloxy-3-methylureido)propylphosphonate (**4b**:)* Method C; yellow oil (83%). – IR (film): ν = 1674 (C═O), 1240 (P═O), 1055, 1028 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 6H, OCH_2CH_3), 1.71-1.82 (m, 2H, CH_2), 1.87-1.97 (m, 2H, CH_2), 2.74 (d, *J* = 4.8 Hz, 3H, CH_3), 3.56 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.02-4.15 (m, 4H, OCH_2CH_3), 4.79 (s, 2H, OCH_2Ph), 5.65 (m, 1H, NH), 7.34-7.42 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ = 16.47 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 20.04 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 23.16 (d, $^1J_{C,P}$ = 142.4 Hz, PCH_2), 26.72 (CH_3), 49.92 (d, $^3J_{C,P}$ = 19.8 Hz, NCH_2), 61.56 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 77.21 (OCH_2Ph), 128.76, 128.91. 129.13, 135.24 ($C_{aromat.}$), 160.80 (C═O). – $C_{16}H_{27}N_2O_5P$ (358.4): calcd. C 53.62, H 7.59, N 7.82; found C 53.56, H 7.56, N 7.82.

*Diethyl 3-(1-benzyloxy-3-ethylureido)propylphosphonate (**4c**):* Method A; colourless crystals (93%). – M.p. 49 °C (Et_2O / hexane) – IR (KBr): ν = 1655 (C═O), 1240 (P═O), 1037 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.2, 3H, $NHCH_2CH_3$), 1.31 (t, *J* = 7.0 Hz, 6H, OCH_2CH_3), 1.72-1.80 (m, 2H, CH_2), 1.88-1.98 (m, 2H, CH_2), 3.15 (dq *J* = 7.2, *J* = 5.6, 2H, $NHCH_2CH_3$), 3.56 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.02-4.15 (m, 4H, OCH_2CH_3), 4.78 (s, 2H, OCH_2Ph), 5.62 (t, *J* = 5.6 Hz, 1H, NH), 7.34-7.40 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ = 15.15 (CH_3), 16.48 (d, $^3J_{C,P}$ = 5.6 Hz, OCH_2CH_3), 20.03 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 23.19 (d, $^1J_{C,P}$ = 142.4 Hz, PCH_2), 34.85 (NCH_2,), 49.85 (d, $^3J_{C,P}$ = 19.3 Hz, NCH_2), 61.56 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 77.23 (OCH_2Ph), 128.80, 128.94, 129.30, 135.33 ($C_{arom.}$), 160.08 (C═O). – $C_{17}H_{29}N_2O_5P$ (372.4): calcd. C 54.83, H 7.85, N 7.52; found C 54.73, H 7.83, N 7.45.

*Diethyl 3-(1-benzyloxy-3-isopropylureido)propylphosphonate (**4d**):* Method A; colourless oil (92%). – IR (film): ν = 1666 (C═O), 1240 (P═O), 1056, 1029 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.00 (d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.31 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3), 1.72-1.99 (m, 4H, CH_2), 3.56 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.74-3,85 (m, 1H, $CH(CH_3)_2$), 4.02-4.16 (m, 4H, OCH_2CH_3), 4.76 (s, 2H, OCH_2Ph), 5.44 (d, *J* = 7.6 Hz, 1H, NH), 7.35-7.41 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ = 16.47 (d, $^3J_{C;P}$ = 6.1 Hz, OCH_2CH_3), 20.01 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 22.92 (CH_3), 23.2 (d, $^1J_{C,P}$ = 142.9 Hz, PCH_2), 41.9 (CH), 49.82 (d, $^3J_{C,P}$ =19.3 Hz, NCH_2), 61.56 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 77.24 (OCH_2Ph), 128.84, 128.97, 129.46, 135.41 ($C_{arom.}$), 159.43 (C═O). – HRMS (FAB): calcd. for $C_{18}H_{31}N_2O_5P$: $[M+H]^+$: 387.2050, found: 387.2035; $C_{18}H_{31}N_2O_5P$ (386.4): calcd. C 55.95, H 8.09, N 7.25; found C 56.02, H 7.82, N 7.27.

*Diethyl 3-(1-benzyloxy-3-tert-butylureido)propylphosphonate (**4e**):* Method A; colourless oil (83%). – IR (film): ν = 1682 (C═O), 1244 (P═O), 1056, 1028 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3), 1.73-1.81 (m, 2H, CH_2), 1.86-1.99 (m, 2H, CH_2), 3.54 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.02-4.16 (m, 4H, OCH_2CH_3), 4.75 (s, 2H, OCH_2Ph), 5.57 (s, 1H, NH), 7.36-7.40 (m, 5H). – ^{13}C NMR ($CDCl_3$): δ = 16.47 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.96 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 23.22 (d, $^1J_{C,P}$ = 142.9 Hz, PCH_2), 28.83 $(CH_3)_3$, 49.66 (d, $^3J_{C,P}$ = 19.3 Hz, NCH_2), 61.55 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 77.22 (OCH_2Ph), 128.84, 128.96, 129.61, 135.46 ($C_{arom.}$), 159.24 (C═O). – $C_{19}H_{33}N_2O_5P$ (400.5): calcd. C 56.99, H 8.31, N 7.00; found C 57.04, H 8.49, N 7.10.

*Diethyl 3-(1-benzyloxy-3-phenylureido)propylphosphonate (**4f**):* Method A; yellow oil (95%). – IR (film): ν = 1682 (C═O), 1240 (P═O), 1055, 1028 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 6H, OCH_2CH_3), 1.75-1.83 (m, 2H, CH_2), 1.94-2.05 (m, 2H, CH_2), 3.68 (t, *J* = 7.0 Hz, 2H, NCH_2), 4.02-4.16 (m, 4H, OCH_2CH_3), 4.89 (s, 2H, OCH_2Ph), 7.02-7.06 (m, 1H), 7.24-7.30 (m, 4H), 7.37-7.45 (m, 5H), 7.57 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 16.48 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 20.13 (d, $^2J_{C,P}$ = 4.6 Hz, PCH_2CH_2), 23.16 (d, $^1J_{C,P}$ = 142.9 Hz, PCH_2), 49.22 (d, $^3J_{C,P}$ = 18.8 Hz, NCH_2), 61.62 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 77.71 (OCH_2Ph), 119.21, 123.5, 128.92, 129.01, 129.29, 134.87, 137.84 ($C_{arom.}$), 156.96 (C═O). – $C_{21}H_{29}N_2O_5P$ (420.4): calcd. C 59.99, H 6.95, N 6.66; found C 59.89, H 6.68, N 6.91.

*General procedure for the preparation of phosphonic acids (**6b-e**)*

To a stirred solution of **4b-f** (2 mmol) in dry CH_2Cl_2 (5 ml) bromotrimethylsilane (6 mmol) was added at room temperature. After 24 h the solvent was removed under reduced pressure, the remaining residue was dissolved in THF (3 ml) and treated with water (0.1 ml). After stirring for 10 minutes EtOAc was added and a white precipitate was formed. Finally **6b-f** were isolated by filtration.

*3-(1-Benzyloxy-3-methylureido)propyphosphonic acid (**6b**):* Colourless crystals (92%). – M.p. 102 °C

(EtOAc/MeOH). – IR (KBr): ν = 3361 (NH), 2813, 2196 (POH), 1625 (C═O), 1267, 1231 (P═O) cm^{-1}. – ^{1}H NMR (DMSO-d_6, D_2O): δ = 1.44-1.58 (m, 2H, CH_2) 1.62-1.77 (m, 2H, CH_2), 2.62 (s, 3H, NCH_3), 3.38 (t, J = 7.12 Hz, 2H, NCH_2), 4.77 (s, 2H, OCH_2Ph), 7.35-7.49 (m, 5H). – ^{13}C NMR (DMSO-d_6, D_2O): δ = 20.62 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 25.42 (d, $^1J_{C,P}$ = 136.8 Hz, PCH_2), 27.22 (NCH_3), 49.94 (d, $^3J_{C,P}$ = 19.3 Hz, NCH_2), 76.68 (OCH_2), 129.13, 129.30, 130.1, 136.41 ($C_{arom.}$), 161.26 (C═O). – $C_{12}H_{19}N_2O_5P$ (302.3): calcd. C 47.68, H 6.34, N 9.27; found C 47.52, H 6.41, N 9.19.

3-(1-Benzyloxy-3-ethylureido)propylphosphonic acid (**6c**)*:* Colourless crystals (94%). – M.p. 87 °C (EtOAc/MeOH). – IR (KBr): ν = 3350 (NH), 2870, 2364 (POH), 1605 (C═O), 1236 (P═O) cm^{-1}. – ^{1}H NMR (DMSO-d_6, D_2O): δ = 0.95 (t, J = 7.12 Hz, 3H, CH_3), 1.44-1.59 (m, 2H, CH_2), 1.62-1.79 (m, 2H, CH_2), 3.05 (q, J = 7.12 Hz, 2H, NCH_2), 3.39 (t, J = 7.12 Hz, 2H, NCH_2), 4.77 (s, 2H, OCH_2Ph), 7.35-7.49 (m, 5H aromat. H). – ^{13}C NMR (DMSO-d_6, D_2O): δ = 15.96 (CH_3), 20.62 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 25.45 (d, $^3J_{C,P}$ = 136.8 Hz, PCH_2), 34.99 (NCH_2), 49.79 (d, $^1J_{C,P}$ = 19.3 Hz, NCH_2), 76.61 (OCH_2), 129.18, 129.30, 130.25, 136.47 (aromat. C), 160.58 (C=O). – $C_{13}H_{21}N_2O_5P$ (316.3): calcd. C 49.37, H 6.69, N 8.86; found C 49.19, H 6.97, N 8.50.

3-(1-Benzyloxy-3-isopropylureido)propylphosphonic acid (**6d**)*:* Colourless crystals (89%). – M.p. 88 °C (EtOAc/MeOH). – IR (KBr): ν = 3406 (NH), 2813, 2343 (POH), 1601 (C═O), 1207 (P═O) cm^{-1}. – ^{1}H NMR (DMSO-d_6, D_2O): δ = 0.93 (d, J = 6.62 Hz, 6H, CH_3), 1.43-1.58 (m, 2H, CH_2), 1.61-1.76 (m, 2H, CH_2), 3.37 (t, J = 6.87 Hz, 2H, NCH_2), 3.53-3.56 (m, 1H, CH), 4.73 (s, 2H, OCH_2Ph), 7.30-7.45 (m, 5H). – ^{13}C NMR (DMSO-d_6, D_2O): δ = 20.75 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 23.25 (CH_3), 25.48 (d, $^1J_{C,P}$ = 136.8 Hz, PCH_2), 42.31 (CH), 49.75 (d, $^3J_{C,P}$ = 19.3 Hz, NCH_2), 76.70 (OCH_2), 129.46, 129.60, 130.58, 136.62 ($C_{arom.}$), 160.10 (C═O). – $C_{14}H_{23}N_2O_5P$ (330.3): calcd. C 50.91, H 7.02, N 8.48; found C 51.05, H 6.80, N 8.58.

3-(1-Benzyloxy-3-tert-butylureido)propylphosphonic acid (**6e**)*:* Colourless crystals (90%). – M.p. 101 °C (EtOAc/MeOH). – IR (KBr): ν = 3409 (NH), 2740, 2340 (POH), 1595 (C═O), 1215 (P═O) cm^{-1}. – ^{1}H NMR (DMSO-d_6, D_2O): δ = 1.01 (s, 9H, CH_3), 1.47-1.62 (m, 2H, CH_2), 1.66-1.81 (m, 2H, CH_2), 3.43 (t, J = 6.87 Hz, 2H, NCH_2), 4.76 (s, 2H, OCH_2Ph), 7.43 (s, 5H). – ^{13}C NMR (DMSO-d_6, D_2O): δ = 20.61 (d, $^2J_{C,P}$ = 4.1 Hz, PCH_2CH_2), 25.42 (d, $^1J_{C,P}$ = 136.8 Hz, PCH_2), 29.08 (CH_3), 49.41 (d, $^3J_{C,P}$ = 19.8 Hz, NCH_2), 50.2 (C-quart), 76.56 (OCH_2), 129.28, 129.4, 130.52, 136.32 ($C_{arom.}$), 159.29 (C═O). – $C_{15}H_{25}N_2O_5P$ (344.3): calcd. C 52.32, H 7.32, N 8.14; found C 52.35, H 7.12, N 8.25.

*General procedure for the preparation of hydroxyureas (***5**, **7***)*

4a-f and **6b,c** were hydrogenated in MeOH using catalytic amounts of 10% Pd/C for 3 h. The suspension was filtrated and the solvent was evaporated.

*Diethyl 3-(1-hydroxyureido)-propylphosphonate (***5a***):* Yellow oil (87%). – IR (film): ν = 1659 (C═O), 1236, 1213 (P═O), 1053, 1026 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.33 (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.81-2.01 (m, 4H, CH_2), 3.61 (t, J = 5.9 Hz, 2H, NCH_2), 4.01-4.15 (m, 4H, OCH_2CH_3), 5.32 (s, 2H, NH_2), 9.58 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$): δ = 16.36 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.60 (d, $^2J_{C,P}$ = 5.6 Hz, PCH_2CH_2), 22.33 (d, $^1J_{C,P}$ = 140.9 Hz, PCH_2), 49.38 (d, $^3J_{C,P}$ = 7.1 Hz, NCH_2), 62.15 (d, $^2J_{C,P}$ = 7.1 Hz, OCH_2CH_3), 161.60 (C═O). – $C_8H_{19}N_2O_5P$: HRMS (FAB): calcd. for $C_8H_{19}N_2O_5P$: $[M+H]^+$: 255.1111; found 255.1152.

*Diethyl 3-(1-hydroxy-3-methylureido)propylphosphonate (***5b***):* Yellow oil (87%). – IR (film): ν = 1651 (C═O), 1230 (P═O), 1055, 1026 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.82-1.99 (m, 4H, PCH_2CH_2), 2.81 (d, J = 4.8 Hz, 3H, CH_3), 3.56 (t, J = 5.98 Hz, 2H, NCH_2), 4.00-4.13 (m, 4H, OCH_2CH_3), 6.01 (m, 1H, NH), 9.33 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$): δ = 16.33 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.69 (d, $^2J_{C,P}$ = 5.6 Hz, PCH_2CH_2), 22.34 (d, $^1J_{C,P}$ = 140.9 Hz, PCH_2), 26.64 (CH_3), 50.38 (d, $^3J_{C,P}$ = 8.7 Hz, NCH_2), 62.04 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 161.98 (C═O). – $C_9H_{21}N_2O_5P$ (268.3): calcd. C 40.30, H 7.89, N 10.44; found C 40.52, H 7.67, N 10.34.

*Diethyl 3-(1-hydroxy-3-ethylureido)propylphosphonate (***5c***):* Yellow oil (89%). – IR (film): ν = 1645 (C═O), 1230, 1210 (P═O), 1055, 1026 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.14 (t, J = 7.3 Hz, 3H, CH_3) 1.32 (t, J = 7.0 Hz, 6H, OCH_2CH_3), 1.83-2.00 (m, 4H, CH_2), 3.26 (dq J = 7.3, J = 5.8, 2H, $NHCH_2CH_3$), 3.56 (t, J = 7.1 Hz, 2H, NCH_2), 4.00-4.13 (m, 4H, OCH_2CH_3), 6.03 (t, J = 5.8 Hz, 1H, NH), 9.29 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$): δ = 15.43 (CH_3), 16.37 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.68 (d, $^2J_{C,P}$ = 5.6 Hz, PCH_2CH_2), 22.37 (d, $^1J_{C,P}$ = 140.9 Hz, PCH_2), 34.83 ($NHCH_2CH_3$,), 50.29 (d, $^3J_{C,P}$ = 7.6 Hz, NCH_2), 62.06 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 161.23 (C═O). – $C_{10}H_{23}N_2O_5P$ (282.3): calcd. C 42.55, H 8.21, N 9.92; found C 42.85, H 8.34, N 9.81.

*Diethyl 3-(1-hydroxy-3-isopropylureido)propylphosphonate (***5d***):* Yellow oil (99%). – IR (film): ν = 1651 (C═O), 1231, 1211 (P═O), 1055, 1028 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.16 (d, J = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.32 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 1.84-2.00 (m, 4H, CH_2), 3.55 (t, J = 6.0 Hz, 2H, NCH_2), 3.87-3.96 (m, 1H, $NHCH(CH_3)_2$), 4.00-4.13 (m, 4H, OCH_2CH_3), 5.90 (d, J = 7.9 Hz, 1H, NH), 9,27 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$): δ = 16.38 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.78 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2),

22.48 (d, $^1J_{C,P}$ = 141.4 Hz, PCH_2), 23.27 (CH_3), 41.87 (CH), 50.36 (d, $^3J_{C,P}$ = 9.2 Hz, NCH_2), 62.02 (d, $^2J_{C,P}$ = 6.6 Hz, OCH_2CH_3), 160.64 (C═O). – HRMS (FAB): calcd. for: $[M+H]^+$: 297.1580; found 297.1582. – $C_{11}H_{25}N_2O_5P$ (296.3): calcd. C 44.59, H 8.50, N 9.45; found C 44.78, H 8.50, N 8.89.

*Diethyl 3-(1-hydroxy-3-tert-butylureido)propylphosphonate (***5e***):* Red oil (94%). – IR (film): ν = 1661 (C═O), 1236, 1213 (P═O), 1055, 1026 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.32 (m, 15 H, OCH_2CH_3, CH_3), 1.84-1.99 (m, 4H, CH_2), 3.52 (t, J = 5.95 Hz, 2H, NCH_2), 4.00-4.14 (m, 4H, OCH_2CH_3), 6.06 (s, 1H, NH), 9.26 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$): δ = 16.40 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.91 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 22.62 (d, $^1J_{C,P}$ = 141,4 Hz, PCH_2), 29.25 (CH_3), 50,16 ($C(CH_3)_3$) 50.32 (d, $^3J_{C,P}$ = 9,7 Hz, NCH_2), 61,98 (d, $^2J_{C,P}$ =6.6 Hz, OCH_2CH_3), 160.57 (C═O). – $C_{12}H_{27}N_2O_5P$ (310.3): calcd. C 46.44, H 8.77, N 9.03; found C 46.29, H 8.88, N 8.84.

*Diethyl 3-(1-hydroxy-3-phenylureido)propylphosphonate (***5f***):* Yellow oil (91%). – IR (film): ν = 1682 (C═O), 1215 (P═O), 1053, 1028 (POC) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 1.88-2.07 (m, 4H, CH_2), 3.69 (t, J = 6.0 Hz, 2H, NCH_2), 4.00-4.14 (m, 4H, OCH_2CH_3), 6,96-7.04 (m, 1H), 7.23-7.30 (m, 2H), 7.36-7.47 (m, 2H), 8.03 (s, 1H, NH), 9.81 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$): δ = 16.33 (d, $^3J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 19.70 (d, $^2J_{C,P}$ = 5.1 Hz, PCH_2CH_2), 22.36 (d, $^1J_{C,P}$ = 140.9 Hz, PCH_2), 49.66 (d, $^3J_{C,P}$ = 6.1 Hz, NCH_2), 62.24 (d, $^2J_{C,P}$, J = 7.1 Hz, OCH_2CH_3), 119.05, 123.00, 128.90, 138.50 ($C_{arom.}$), 157.90 (C═O). – HRMS (FAB): calcd. for $C_{14}H_{23}N_2O_5P$: $[M+H]^+$: 331.1424, found 331.1447. – $C_{14}H_{23}N_2O_5P$ (330.3): calcd. C 50.91, H 7.02, N 8.48; found C 50.81, H 7.31, N 8.15.

*3-(1-Hydroxy-3-methylureido)propylphosphonic acid (***7b***):* Colourless crystals (82%). – M.p. 131 °C (EtOAc/MeOH). – IR (KBr): ν = 3402 (NH), 2870, 2312 (POH), 1618 (C═O), 1240 (P═O) cm^{-1}. – ^{1}H NMR (DMSO-d_6, D_2O): δ = 1.46-1.62 (m, 2H, CH_2) 1.64-1.80 (m, 2H, CH_2), 3.39 (s, 3H, NCH_3), 3.38 (t, J = 7.12 Hz, 2H, NCH_2). – ^{13}C NMR (DMSO-d_6, D_2O): *delta* = 20.9, 25.35 (d, $^1J_{C,P}$ = 136.8 Hz, PCH_2), 27.01 (NCH_3), 51.55 (d, $^3J_{C,P}$ = 18.3 Hz, NCH_2), 162.35 (C═O). – $C_5H_{13}N_2O_5P$ (212.1): calcd. C 28.31, H 6.18, N 13.20; found C 28.65, H 6.19, N 12.81.

*3-(1-Hydroxy-3-ethylureido)propyphosphonic acid (***7c***):* Colourless crystals (83%). – M.p. 104 °C (EtOAc/MeOH). – IR (KBr): ν = 3408 (NH), 2870, 2364 (POH), 1604 (C═O), 1226 (P═O) cm^{-1}. – ^{1}H NMR (DMSO-d_6, D_2O): δ = 1.04 (t, J = 7.12 Hz, 3H, CH_3), 1.49-1.84 (m, 4H, CH_2), 3.09 (q, J = 7.12 Hz, 2H, NCH_2), 3.39 (t, J = 7.12 Hz, 2H, NCH_2). – ^{13}C NMR (DMSO-d_6, D_2O): δ = 16.31 (CH_3), 21.07 (d, $^2J_{C,P}$ = 3.6, Hz, PCH_2CH_2), 25.33 (d, $^1J_{C,P}$ = 136.8 Hz, PCH_2), 35.15 (NCH_2), 51.60 (d, $^3J_{C,P}$ = 19.3 Hz, NCH_2), 162.08 (C═O). – $C_6H_{15}N_2O_5P$ (226.2): calcd. C 31.86, H 6.69, N 12.39; found C 31.88, H 6.66, N 12.29.

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