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Paper

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Synthesis and biological screening of diethyl [*N*-(thiazol-2-yl)carbamoyl]methylphosphonates

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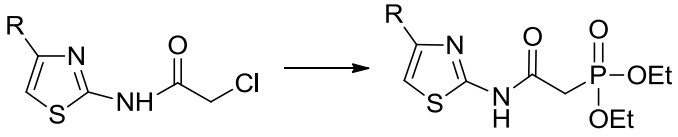
Abstract

A three-step synthesis, involving condensation of bromomethyl aryl ketones with urea to afford 2-aminothiazoles, their chloroacetylation and subsequent solvent-free Arbuzov phosphonation has afforded a series of novel diethyl [*N*-(thiazol-2-yl)carbamoyl]methylphosphonates **3a**-**3f** in good overall yields; the 4-carboxythiazole analogue **3g** was obtained by selective hydrolysis of the corresponding ethyl ester **3f**. The phosphonate esters exhibited significant anti-cancer activity (nM - low µM IC_{50} values) against SH-SY5Y cells and, in one case, 7.6 µM MIC90 anti-TB activity against the virulent *M. tuberculosis* H_{37}Rv strain; the chloroacetamido precursors all exhibited some antimalarial (*Pf*LDH) activity, three with IC_{50} values in the range 1.0 - 8.9 µM.



Keywords: 2-(2-Chloroacetamido)thiazoles , *N*-(thiazol-2-yl)carbamoyl]methylphosphonates, synthesis, biological activities

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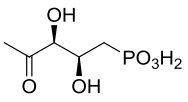
Introduction

The enzyme,1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) regulates a non-mevalonate pathway in the biosynthesis of isoprenoid-derived compounds in *Plasmodium falciparum* (*Pf*), but is not found in humans[1,2]. This enzyme has been validated as a target for the development of antimalarial drugs capable of selectively inhibiting reduction of 1-deoxy-D-xylulose-5-phosphate **1** in resistant *P. falciparum* strains[3-5]. The naturally occurring antibiotic, fosmidomycin [3-(*N*-formyl-*N*-hydroxyamino)propylphosphonic acid[4,5] and its *N*-acetyl derivative, FR900098 **2**[6,7], are known to inhibit *Pf*DXR, and various analogues of these compounds have been prepared. In our own group, research has focussed on the synthesis and antimalarial activity of phosphonated *N*-aryl- and *N*-heteroaryl-carboxamides, such as compound **3**[8,9] and, more recently, phosphoramidate analogues[6] of fosmidomycin.



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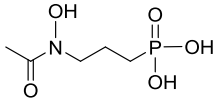

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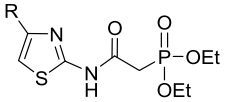

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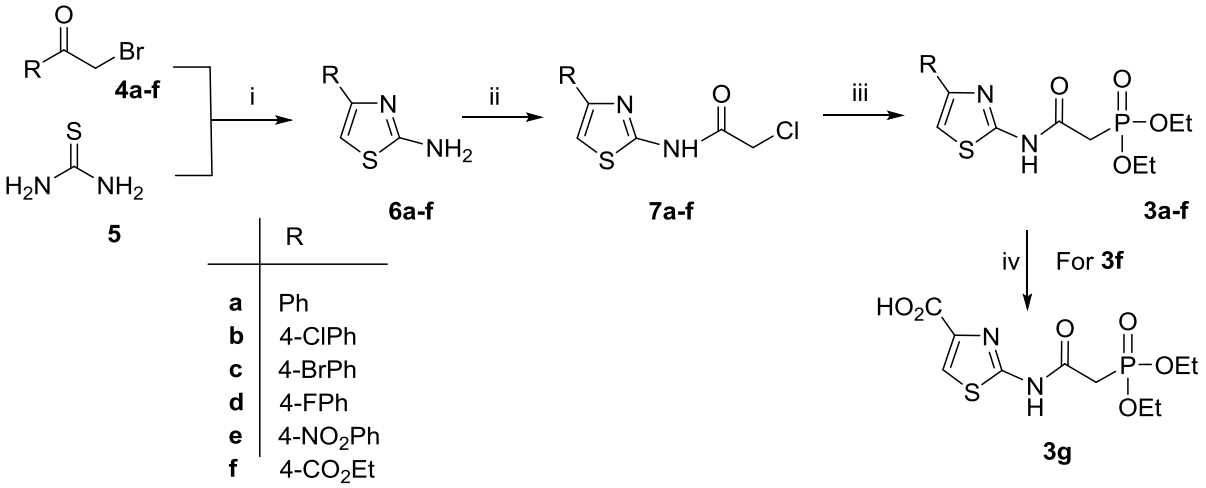
The thiazole scaffold is well represented in medicinal systems. Mjambili *et al*. have prepared a library of *N*-aryl substituted 2-(pyridin-2-yl)thiazol-4-amines and explored their anti-TB and antimalarial activity, and compounds containing electronegative *para* substituents were shown to inhibit *P. falciparum* with sub-micromolar IC_{50} values[11]. The anti-cancer potential of certain thiazole-based compounds has been investigated, the most active of which, ethyl 2-[3-(diethylamino)propanamido]thiazole-4-carboxylate, exhibited a GI_{50} value of 0.08 μM against the RPMI-8226 leukemia cell line and broad-spectrum activity against 60 tumour cell lines with a GI_{50} value of 38.3 μM[12,13]. Jaishree *et al*. showed that 2-methyl-4-trifluoromethylthiazole-5-carboxamides exhibited promising anti-parasitic and insecticidal properties, but without herbicidal effect.[14]

In this communication, we discuss: (i) the synthesis of a series of [*N*-(thiazol-2-yl)carbamoylmethylphosphonate esters **3** as fosmidomycin analogues which satisfy the Lipinski "Rule of Five"; and (ii) screening of these compounds and their synthetic precursors for antimalarial, anti-cancer and anti-tuberculosis activity.

Result and Discussion

The aminothiazole scaffolds **6a-e** were obtained using conventional Hantzsch condensation of the α-bromo ketones **4a-f** with thiourea (Scheme 1). On completion of each of the reactions, the desired product was precipitated out by pouring the reaction mixture into ice-cold water. The known thiazole derivatives **3a-f**[15-17] were thus isolated in excellent yields (93–100%; Table 1) and subsequently treated with chloroacetyl chloride in the presence of triethylamine in dichloromethane, using a modification of the method reported by Xu *et al*.[18] to afford the 2-(2-chloroacetamido)thiazole analogues **7a**-f in yields ranging from 54 to 100%. Solvent-free Arbuzov phosphonation of the 2-(2-chloroacetamido)thiazoles **7a-f** was effected by boiling with triethyl phosphite at 110 ^{0}C for 9 h. Excess triethyl phosphite was removed by stirring the crude products with hexane. Column chromatography afforded the desired phophonate esters **3a-e** in 68-98% yield, while treatment of the carbethoxy analogue **3f** with methanolic potassium hydroxide, followed by acidification, permitted selective

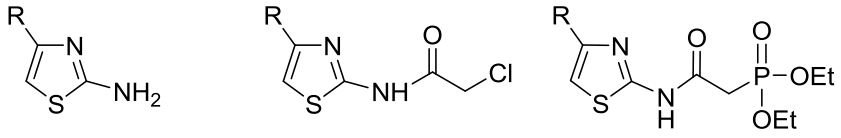
hydrolysis of the carboxlic ester moiety to give diethyl [(4-carboxythiazol-2-yl)carbamoyl]methylphosphonate **3g** in 59% yield. The phosphonate esters **3a-g** are all new and were fully characterised using 1- and 2-D NMR, IR and HRMS methods.



Reagents and conditions: i) EtOH, 70 °C, 1 h; ii) Chloroacetyl chloride, 0 °C - rt, 2 h; iii) $(EtO)_3P$, 110 °C, 9h; and iv) KOH, MeOH, rt, 2h, then 20% HCl.

Scheme 1

Table 1. Yields (%) of the intermediates **6a-f** and **7a-f** and the diethyl [*N*-(thiazol-2-yl)carbamoyl]-methylphosphonates **3a-g**.



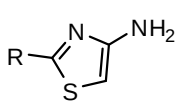
R		Yield (%)				
Ph	**6a**	99	**7a**	54	**3a**	98
p-ClPh	**6b**	100	**7b**	100	**3b**	89
p-BrPh	**6c**	93	**7c**	64	**3c**	68
p-FPh	**6d**	94	**7d**	64	**3d**	70
p-NO_2Ph	**6e**	94	**7e**	88	**3e**	70
COOEt	**6f**	100	**7f**	70	**3f**	87
COOH	-	-	-	-	**3g**	59[a]

[a]**3g** obtained from hydrolysis of the carbethoxy precursor **3f.**

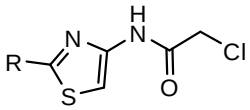
It is apparent from the data summarised in Table 2 that, at low concentrations, the phosphonate esters **3a-c,e,g** exhibit encouragingly effective inhibition of the SH-SY5Y cell line with IC_{50} values in the nanomolar to very low micromolar range but little, if any, activity against the HeLa cell line[19,20] ($\geq$ 95% viability at 20 μ M),

thus reflecting clear selectivity against the former cell line. Compounds **7a-f**, however, exhibit 15-40% inhibition of the HeLa cells at 20 μ M.

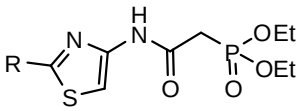
Table 2. Bioassay results for compounds **6a-f**, **7a-f** and **3a-g**



6a-f



7a-f



3a-g

		Anti-cancer		***Antimalarial***		***Anti-TB***	
	R	SH-SY5Y IC_{50} (µM)	HeLa cells % Viability[a]	*Pf*LDH % Viability	IC_{50}(µM)	MIC90 (µM)	MIC99 (µM)
6a	Ph	-	90	85	-	-	-
6b	*p*-ClPh	-	98	81	-	-	-
6c	*p*-BrPh	-	≤100	88	-	-	-
6d	*p*-FPh	-	≤100	83	-	-	-
6e	*p*-NO_2Ph	-	95	84	-	-	-
6f	COOEt	-	75	68	-	-	-
7a	Ph	-	80	18	1.86	-	-
7b	*p*-ClPh	-	85	40	-	-	-
7c	*p*-BrPh	-	80	32	-	-	-
7d	*p*-FPh	-	60	16	8.87	-	-
7e	*p*-NO_2Ph	-	55	14	1.04	-	-
7f	COOEt	-	65	68	-	-	-
3a	Ph	0.87	100	115	-	> 20.0	> 20.0
3b	*p*-ClPh	0.0018	100	115	-	> 20.0	> 20.0
3c	*p*-BrPh	2.1	100	102	-	7.62	> 20.0
3d	*p*-FPh	> 1 mM	95	102	-	> 20.0	> 20.0
3e	*p*-NO_2Ph	590	100	105	-	> 20.0	> 20.0
3f	COOEt	> 1 mM	≤100	99	-	> 20.0	> 20.0
3g	COOH	4.6	≤100	102	-	> 20.0	> 20.0
Controls			100				
Chloroquine			-	-	0.0143	-	-
Rifampicin			-	-	-	0.0015	0.0016

[a] At 20 μ M.

The resazurin-based whole-cell *Pf*LDH bioassay was conducted to explore the antimalarial activities of the crucial intermediates and final compounds using 20 µM as the cut-off concentration before determining IC_{50} values for compounds with significant levels of inhibition. The results (Table 1) show that the unsubstituted aminothiazole intermediates **6a-f** exhibit low levels of inhibition (66-88% *Pf*LDH viability), whereas the 2-(2-chloroacetamido)thiazole intermediates **7a-e** exhibit significant activity at 20 µM, with IC_{50} values of 8.87, 1.86 and 1.04 µM for compounds **7d, 7a** and **7e** , respectively.The phosphonate esters **3a-g**, which were designed

primarily as potential inhibitors of *P. falciparum* 1-deoxy-1-D-xylulose-5-phosphate reductoisomerase (*Pf*DXR), unfortunately showed no discernible *Pf*LDH inhibition.

Apart from the *para*-bromophenyl product **3c**, which exhibited an MIC90 value of 7.62 µM, all other compounds in this series (**3**) showed little if any inhibitory effect (MIC90 and MIC99 values $\geq$ 20 µM) on the growth of *M. tuberculosis* $H_{37}Rv$[19]. The relatively high predicted Log P value of 3.87 for compound **3c** may contribute to its absorption across the lipophilic membrane of *M. tuberculosis* $H_{37}Rv$, whereas the Log P values for the other compounds **3a, 3b, 3d, 3e, 3f** and **3g** (2.98, 3.62, 3.18, 1.54 and 1.10, respectively) are all lower.

Conclusions

The novel diethyl [*N*-(thiazol-2-yl)carbamoyl]methylphosphonates (**3**) were successfully obtained in good overall yields. Although designed as potential antimalarial agents, these compounds failed to exhibit any activity against *Pf*LDH, whereas their chloroacetamido precursors (**7**) all exhibited antimalarial (*Pf*LDH) activity, three with IC_{50} values in the range 1.0 - 8.9 µM. The title compounds did, however, exhibit significant and selective anti-cancer activity (nM - low µM IC_{50} values) against SH-SY5Y cells and, in one case, 7.6 µM MIC90 anti-TB activity against the virulent *M. tuberculosis* $H_{37}Rv$ strain.

Experimental Section

General. Reagents were supplied by Sigma-Aldrich and used without further purification. Tetrahydrofuran (THF) and methylene chloride were stored over 4 Å molecular sieves. The reaction progress and purity of the compounds were checked by thin layer chromatography (TLC) on pre-coated Merck® silica gel G60 F_{254} plates, and viewed under UV light at 254 and 365 nm. Melting points were recorded, uncorrected, using a Reichert hot-plate microscope. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance II 600 MHz, Bruker Avance III HD 400 MHz and Bruker Fourier 300 MHz spectrometers. The NMR chemical shifts are reported in ppm downfield from tetramethylsilane (TMS), and the coupling constants are given in Hertz (Hz). NMR analyses were carried out in deuterated solvents, such as DMSO-d_6, $CDCl_3$, acetone-d_6 and methanol-d_4 for standard NMR experiments, and the spectra were calibrated using solvent signals [δ_H: 7.26 ppm for residual $CHCl_3$, 2.50 ppm for residual DMSO, 2.05 ppm for residual acetone and 3.31 for residual MeOH; δ_C: 77.2 ppm ($CDCl_3$), 39.5 ppm (DMSO-d_6), 29.8 ppm (acetone-d_6) and 49.0 ppm (MeOH-d_4)]. Infrared (IR) spectra were obtained using a Perkin Elmer (R) Spectrum 400 Frontier / FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Waters API Q-TOF Ultima spectrometer (University of Stellenbosch, Stellenbosch, South Africa). NMR spectra for all compounds and the bioassay procedures are provided in the Supporting Information.

The known 2-aminothiazoles (6) were obtained following reported methods.[16-18] A mixture of thiourea (1.2 mmol) and 2-bromoacetophenone (1 mmol) in EtOH (2 mL) was stirred at 70 °C for 1h. The reaction mixture was cooled to room temperature, poured into ice-cold water, and the resulting precipitate was filtered and dried to give the desired compounds: [**6a** (99%) as a white solid, mp 150-152 °C (Lit.[26] 149-150 °C) ; **6b** (100%) as a white solid, mp 162-165 °C (Lit.[26] 163-164 °C); **6c** (0.236 g, 93%) as a white solid, mp 179-181 °C (Lit.[26] 180-181 °C); **6d** (98%) as a white solid, mp 203.6-204.2 °C (Lit.[28/22] 204.0-204.5 °C); **6e** (94%) as a bright yellow solid, mp 287-288 °C (Lit.[26,27] 285-286 °C); **6f** (100%) as a white solid, mp 172-174 °C (Lit.[29-31] 172 °C).

The general procedure for the preparation of the known 2-(2-chloroacetamido)thiazoles (7) involved a modification of the procedure reported by Xu and collegues[18]. A solution of 2-amino-4-phenylthiazole **6a** (0.530 g, 3 mmol) and Et_3N (560 µL, 4 mmol) in dichloromethane (15 mL) was cooled to 0-5 °C in an ice-bath and stirred for 30 min. 2-Chloroacetyl chloride (578 µL, 6.6 mmol) in dry dichloromethane (1.5 mL) was then added slowly, and the reaction mixture was allowed to warm to room temperature and stirred until the amine was completely consumed (*ca*. 1 h, as monitored by TLC). The reaction mixture was diluted with dichloromethane and washed successively with water and saturated brine. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the residue was recrystallised from ethanol to give compound **7a** (0.413 g, 54%) as light-grey crystals, mp 170-171 °C (Lit.[18,20,26] 171-173 °C). The remaining analogues were obtained similarly [**7b** (100%) as a brown solid, mp 194-195 °C (Lit.[27] mp not cited); **7c** (64%) as a brown solid, mp 241-243 °C (Lit.[27] mp not cited); **7d** (64%) as a brown solid, mp 135-137 °C (Lit.[28] 135 °C); **7e** (0.262 g, 88%) as a yellow solid, mp 174-176 °C (Lit.[29] 175 °C); **7f** (70%) as a light-brown solid, mp 213-216 °C (Lit.[30] 216 °C).

General procedure for the preparation of the diethyl [*N*-(thiazol-2-yl)carbamoyl]methylphosphonates (3). A mixture of 2-(2-chloroacetamido)-4-phenylthiazole **7a** (0.063 g, 0.25 mmol) and triethyl phosphite (22 µL, 0.13 mmol) in an oven-dried round-bottomed flask was refluxed (*ca*. 110 °C) for 9 h under nitrogen[1,2]. The reaction mixture was cooled to room temperature and then stirred 3 times with hexane (3 x 700 µL for 20 min each, followed each time by decantation of the hexane layer to remove excess triethyl phosphite). The residual solvent was evaporated under reduced pressure, and the crude product was chromatographed [using silica gel; eluting with hexane/EtOAc (4:1)] to yield the diethyl [4-phenylthiazol-2-yl)carbamoyl]methylphosphonate.

Diethyl [4-phenylthiazol-2-yl)carbamoyl]methylphosphonate (3a). Brown solid (0.087 g, 98%), mp 78-80 °C; [HRMS: *m/z* calculated for $C_{15}H_{20}N_2O_4PS$ (MH^+) 355.0881. Found 355.0876]; ν_{max} / cm^{-1} 1679 (C=O) and 3168 (NH); δ_H (400 MHz; $CDCl_3$) 10.96 (1H, br s, NH), 7.80 (2H, d, ^3J 8 Hz, ArH), 7.36-7.29 (2H, m, ^3J 7.1-7.4 Hz, ArH), 7.01 (1H, s, thiazolyl-H), 4.28-4.21 (4H, m, 2 x OCH_2), 3.17 (2H, d, $^2J_{P,H}$ 24 Hz, PCH_2) and 1.39 (6H, t, $^3J_{H,H}$ 8.0 Hz, 2 x CH_3); δ_C (100 MHz; $CDCl_3$) 162.4 (C=O, $^2J_{C,P}$ 5 Hz), 157.3, 150.2, 134.7, 128.7, 128.0, 126.3, 107.8 (ArC and thiazolyl-C), 63.5 (OCH_2, $^2J_{C,P}$ 6.4 Hz), 35.9 (PCH_2, $^1J_{C,P}$ 131 Hz) and 16.5 (CH_3, $^3J_{C,P}$ 5.9 Hz).

Diethyl {*N*-[4-(4-chlorophenyl)thiazol-2-yl]carbamoyl}methylphosphonate (3b). Brown solid (0.087 g, 89%), mp 86-89 °C; [HRMS: *m/z* calculated for $C_{15}H_{19}ClN_2O_4PS^{35}$ (MH^+) 389.0492. Found 389.0488]; ν_{max} / cm^{-1} 1680 (C=O) and 3169 (NH); δ_H (400 MHz; $CDCl_3$) 10.99 (1H, br s, NH), 7.72 (2H, d, $^3J_{H,H}$ 7.8 Hz, ArH), 7.36 (2H, d, $^3J_{H,H}$ 7.8 Hz, ArH), 6.99 (1H, s, thiazolyl-H), 4.27 (4H, m, 2 x OCH_2), 3.23 (2H, d, $^2J_{P,H}$ 21 Hz, PCH_2) and 1.40 (6H, t, $^3J_{H,H}$ 6.8 Hz, 2 x CH_3); δ_C (100 MHz; $CDCl_3$) 162.5 (C=O, $^2J_{C,P}$ 4.7 Hz), 157.5, 149.1, 133.9, 133.2, 129.0, 127.7, 108.1 (ArC and thiazolyl-C), 63.7 (OCH_2, $^2J_{C,P}$ 6.5 Hz), 35.7 (PCH_2, $^1J_{C,P}$ 131 Hz) and 16.6 (CH_3, $^3J_{C,P}$ 5.8 Hz).

Diethyl {*N*-[4-(4-bromophenyl)thiazol-2-yl]carbamoyl}methylphosphonate (3c). Brown solid (0.074 g, 68%), mp 96-98 °C; [HRMS: *m/z* calculated for $C_{15}H_{19}BrN_2O_4PS^{79}$ (MH^+) 432.9987. Found 432.9979]; ν_{max} / cm^{-1} 1680 (C=O) and 3160 (NH); δ_H (400 MHz; $CDCl_3$) 11.02 (1H, br s, NH), 7.65 (2H, d, $^3J_{H,H}$ 8.3 Hz, ArH), 7.51 (2H, d, $^3J_{H,H}$ 8.3 Hz, ArH), 6.98 (1H, s, thiazolyl-H), 4.25 (4H, m, 2 x OCH_2), 3.22 (2H, d, $^2J_{P,H}$ 22 Hz, PCH_2) and 1.38 (6H, t, $^3J_{H,H}$ 7.0 Hz, 2 x CH_3); δ_C (100 MHz; $CDCl_3$) 162.4 (C=O, $^2J_{C,P}$ 4.5 Hz), 157.5, 149.0, 133.6, 131.8, 127.9, 121.9, 108.1 (ArC and thiazolyl-C), 63.6 (OCH_2, $^2J_{C,P}$ 6.5 Hz), 35.6 (PCH_2, $^1J_{C,P}$ 130.6 Hz) and 16.5 (CH_3, $^3J_{C,P}$ 6.0 Hz).

Diethyl {*N*-[4-(4-fluorophenyl)thiazol-2-yl]carbamoyl}methylphosphonate (3d) Brown solid (0.0651 g, 70%), mp 72-74 °C; [HRMS: *m/z* calculated for $C_{15}H_{19}FN_2O_4PS$ (MH^+) 373.0787. Found 373.0786]; ν_{max} / cm^{-1} 1680 (C=O) and 3159 (NH); δ_H (400 MHz; $CDCl_3$) 10.89 (1H, br s, NH), 7.74 (2H, dd, $^3J_{H,H}$ =8.3 Hz, $^4J_{F,H}$ 5.6, ArH), 7.06 (2H, t, $^3J_{F,H}$ $^3J_{H,H}$ 8.4 Hz, ArH), 6.92 (1H, s, thiazolyl-H), 4.20 (4H, m, 2 x OCH_2), 3.18 (2H, d, $^2J_{P,H}$ 21 Hz, PCH_2) and 1.38 (6H, t, $^3J_{H,H}$ 7.0 Hz, 2 x CH_3); δ_C (100 MHz; $CDCl_3$) 162.8 ($^1J_{F,C}$ 247 Hz, ArC), 162.3 (C=O, $^2J_{C,P}$ 4.6 Hz), 157.3,

149.3, 130.9 ($^4J_{F,C}$ 2.7 Hz, ArC), 128.0 ($^3J_{F,C}$ 8.1 Hz, ArC), 115.6 ($^2J_{F,C}$ 22 Hz, ArC), 107.3, 63.5 ($^2J_{C,P}$ 6.5 Hz, OCH_2), 35.6 ($^1J_{C,P}$ 131 Hz, PCH_2), 16.5 ($^3J_{C,P}$ 6.0 Hz, CH_3).

Diethyl {*N*-[4-(4-nitrophenyl)thiazol-2-yl]carbamoyl}methylphosphonate (3e). Brown solid (0.070 g, 70%), mp 88-90 ^oC; [HRMS: *m/z* calculated for $C_{15}H_{19}N_3O_6SP$ (MH^+) 400.0732. Found 400.0717]; ν_{max} / cm^{-1} 1683 (C=O) and 3165 (NH); δ_H (400 MHz; acetone-d_6) 10.84 (1H, br s, NH), 8.25 (2H, d, $^3J_{H,H}$ 8.8 Hz ArH), 8.10 (2H, d, $^3J_{H,H}$ 8.8 Hz, ArH), 7.66 (1H, s, thiazolyl-H), 4.24 (4H, m, 2 x OCH_2), 3.38 (2H, d, $^2J_{P,H}$ 22 Hz, PCH_2) and 1.83 (6H, t, $^3J_{H,H}$ 7.1 Hz, 2 x CH_3); δ_C (100 MHz; acetone-d_6) 164.2 (C=O, $^2J_{C,P}$ 5.7 Hz), 159.0, 148.2, 147.8, 141.4, 127.5, 124.7, 112.6 (ArC and thiazolyl-C), 63.5 (OCH_2, $^2J_{C,P}$ 6.2 Hz), 35.9 (PCH_2, $^1J_{C,P}$ 130.1 Hz) and 16.7 (CH_3, $^3J_{C,P}$ 6.0 Hz).

Diethyl *[N*-(4-carbethoxythiazol-2-yl)carbamoyl]methylphosphonate (3f). Brown solid (0.154 g, 87%), mp 74-75 ^oC; [HRMS: *m/z* calculated for $C_{12}H_{20}N_2O_6PS$ (MH^+) 351.0780. Found 351.0773]; ν_{max} / cm^{-1} 1683 (NC=O), 1721 (OC=O) and 3165 (NH); δ_H (400 MHz; $CDCl_3$) 11.08 (1H, br s, NH), 7.78 (1H, s, thiazolyl-H), 4.36 (2H, q, $^3J_{H,H}$ 7.0 Hz, OCH_2), 4.32-4.15 (4H, m, 2 x OCH_2), 3.25 (2H, d, $^2J_{P,H}$ 22 Hz, PCH_2) and 1.45-1.33 (9H, overlapping m, CH_3); δ_C (100 MHz; $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (NC=O, d, $^2J_{C,P}$ 5.2 Hz), 161.7 (OC=O), 158.0, 142.0, 122.3 (ArC and thiazolyl-C), 63.4 (OCH_2, d, $^2J_{C,P}$ 6.4 Hz), 61.5 (OCH_2), 35.7 (PCH2, d, $^1J_{C,P}$ 132 Hz), 16.5 (CH_3, $^3J_{C,P}$ 5.9 Hz) and 14.4 (CH_3).

Diethyl [*N*-(4-carboxythiazol-2-yl)carbamoyl]methylphosphonate (3g). A solution of diethyl [(4-carbethoxythiazol-2-yl)carbamoyl]methylphosphonate **3f** (0.088 g, 0.25 mm) and KOH (0.093 g, 0.5 mmol) in MeOH (2 mL) was stirred at room temperature for 2 h.[31] Addition of 20% HCl (2 mL) gave the desired product **3g** as a brown viscous oil (0.0478 g, 59%); [HRMS: *m/z* calculated for $C_{10}H_{16}N_2O_6PS$ (MH^+) 323.0467. Found 323.0456]; ν_{max} / cm^{-1} 1697 (C=O), 2508-3586 (br, COOH) and 3183 (NH); δ_H (400 MHz; $CDCl_3$) 11.26 (br s, COOH), 11.02 (1H, br s, NH), 7.97 (1H, s, thiazolyl-H), 4.38 (4H, m, 2 x OCH_2), 3.43 (2H, d, $^2J_{P,H}$ 21 Hz, PCH_2) and 1.56-1.49 (6H, m, CH_3); δ_C (100 MHz; $CDCl_3$) 168.2 (COOH), 163.5 (C=O), 158.1, 142.1, 122.4 (thiazolyl-C), 63.5 (OCH_2), 35.8 (CH_2) and 16.5 (CH_3).

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