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Cyclic *N*-2-Chloroethyl-sulfamide Compounds with a Phosphonate Moiety: Synthesis, Characterization, X-Ray Crystallographic Study and Antimicrobial Evaluation

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Abstract: An efficient access to a novel series of organophosphorus compounds with a cyclosulfamide moiety is described. Starting from α -hydroxyphosphonates, the 2-chloroethyl-(1, 2, 5- thiadiazoline-2-carbonyloxy-1- dioxide) phosphonates compounds were prepared in three steps including an abramov reaction, carbamoylation-sulfamoylation with chlorosulfonyl isocyanate and an intramolecular cyclisation. The spectroscopic methods (¹H NMR, ¹³C NMR, ³¹P NMR, MS and IR) were used to determine the structural characteristics of the synthesized compounds and X-ray crystallographic data were provided for compound 3c. Some selected compounds were screened *in vitro* for their antimicrobial activity against a panel of microorganisms, resulting in a good antibacterial activity compared to standard drugs.

Introduction

Sulfamides compounds bearing a phosphonate moiety have emerged as attractive chemical targets, during the last decades, due to their structural and biological advantages. The sulfamide group has appeared as a good bioisostere of sulfonamide ^[1] or urea ^[2-3] and in drug analogs, it can enhance physico-chemical properties such as water solubility and bioavailability.

Moreover the geometry of both nitrogen atoms as well as the oxygen atoms at the tetrahedral sulfur can be in favor of electrostatic and hydrogen bond interactions to the targeted proteins.⁴ Consequently the biological efficiency of sulfamide compounds as enzyme inhibitors,^[5-6] such as HIV protease,^[7] as well as agonist or antagonist ligands of receptors has led some compounds to the market such as Norprolac (Fig 1, compound 1) used in prolactin-dependent disorder or Famotidine for the treatment of ulcers.^[8]

In the same manner, cyclosulfamide derivatives or (2,5-thiadiazolidine-1,1-dioxide) are considered as sulfonated analogs of cyclic urea compounds,^[9] and have given access to attractive molecules with potential application in medicinal chemistry.^[10]

Indeed, cyclosulfamides offered a wide range of biological activities such as antibacterial ^[11] or protease inhibition of HIV-1^[12] and γ -secretase, ^[13] norovirus inhibitory activity ^[14] (Fig 1, compound 2).

Bifunctional compounds containing both sulfamide and phosphonate moieties have not been so extensively studied compared to their sulfonamido-phosphonate parents.^[15-20] However they have also been characterized as promising anticancer agent such as Fotemustine analog **3** ^[21] or as potent insecticidal ^[22] such as compound **4** (Figure 1).

Because sulfonamide and sulfamide compounds have been widely studied for their antimicrobial activities some sulfonamidocarbonyloxymethylphosphonates were also recently developed in our laboratory, as potential antimicrobial agents against Gram-positive and negative bacteria and have shown significant antibacterial activity ^[23] compared to sulfamethoxazole/trimethoprim as a reference (Figure 1, compound 5).

During the course of our research works, we have also developed several strategies for the synthesis of sulfamidophosphonates compounds. Belhani et al ^[24] reported a simple and new method for the synthesis of a novel α -sulfamidophosphonates (Fig 2, compound 6) via Kabachnik–Fields reaction under ultrasonic (US)

activation and solvent-free conditions with good yields and short reaction times.

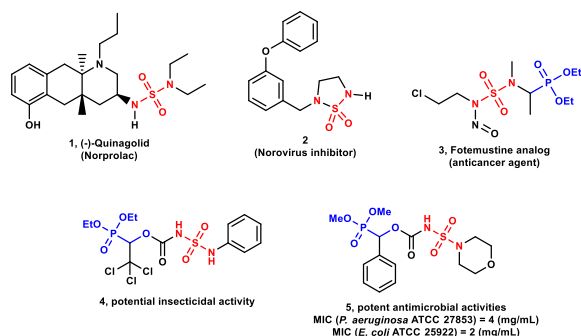


Figure 1. Some examples sulfamide and sulfamidophosphonates compounds with biological interest

In 2017, Bouzina and co-workers^[25] realised the phosphorylation of a series of *N*-acylsulfonamides with trimethylphosphite under US conditions and this process provided in 15 minutes a good yield of product 7 (Fig 2, 88%). If we considered the concomitant role of cyclosulfamide and phosphonate groups in a single molecule, only few syntheses are reported in the literature. Hessania et al^[26] have developed an efficient process for the synthesis of novel phosphonoalkylcyclosulfamide (Fig 2, compound 8), by sulfonylation of diamine with sulfonyl chloride. The synthesis and *in vitro* cytotoxic activities of new sulfamidophosphonates (Fig 2, compound 9) using cyclic-sulfamide, analog of cyclosulfamide, was more recently studied by our group.^[27]

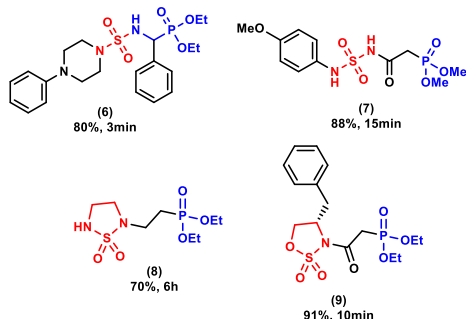
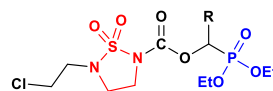


Figure 2. Previous work carried out in our laboratory

In our continuing investigation to the synthesis of new phosphonate derivatives inspired by our previous works,^[28] we report in this paper the synthesis and the antimicrobial evaluation of a new series of 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carbaldehyde-1,1-dioxide tethered to a terminal phosphonate moiety with a substituted carbonyloxymethyl linker (Figure 3).



R: Aryl (H, naphthyl, 4-Cl, 2-F, 4-OMe) or thiophen-2-yl & furan-2-yl

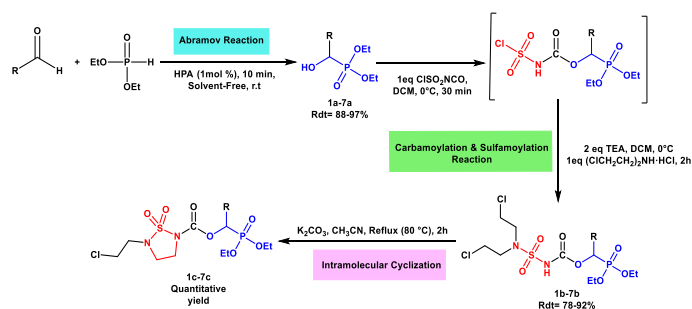
Figure 3. General structure of 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carbaldehyde-1,1-dioxide with phosphonates moiety

Results and Discussion

The synthesis of 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carbaldehyde-1,1-dioxide with phosphonates derivatives **1c-7c** was achieved according to the pathway illustrated in (scheme 1). This strategy was carried out in three steps, starting from commercially available reagents (aldehydes, dialkylphosphite, chlorosulfonyl isocyanate (CSI) and bis (2-chloroethyl) amine hydrochloride).

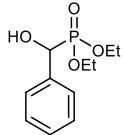
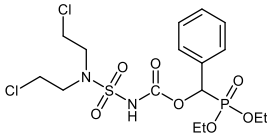
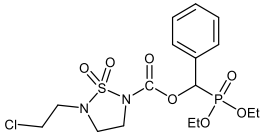
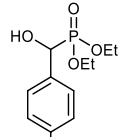
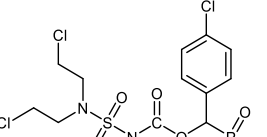
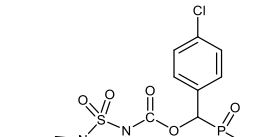
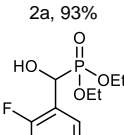
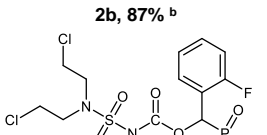
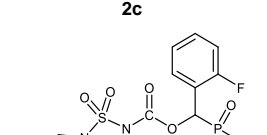
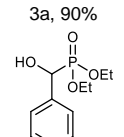
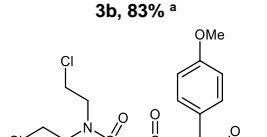
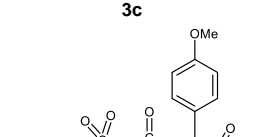
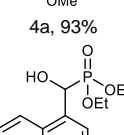
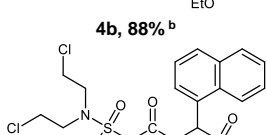
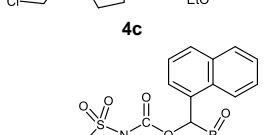
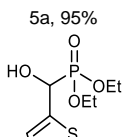
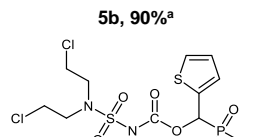
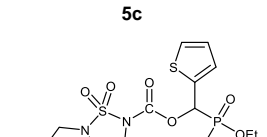
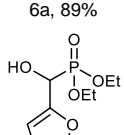
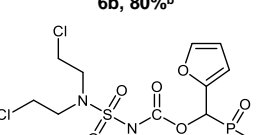
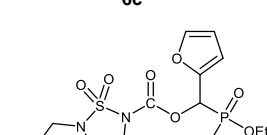
In a first step, the synthesis of the key α -hydroxyphosphonates intermediates was achieved via Abramov reaction,^[29] in solvent free conditions and with a recyclable catalyst, the heteropolyacid HPA following our method recently described.^[30] A series of α -hydroxyphosphonates (**1a-7a**) were prepared involving several aromatic aldehydes (Table 1). The conversions were total within 10 minutes and the phosphonates purified in good to excellent yields. Secondly, carbamoylation of these α -hydroxyphosphonates at 0°C, under anhydrous conditions with commercial chlorosulfonyl isocyanate (CSI), afforded the intermediate compounds (*N*-chlorosulfonyl carbamates) in 30 minutes. The crudes were slowly added to a solution of the hydrochloride form of bis-(2-chloroethyl) amine in the presence of triethylamine at 0°C, to give the sulfamidocarbonyloxymethylphosphonates derivatives **1b-7b** in good yields (78-92%) within 2 hours (Table 1).

Finally, the intramolecular cyclization of these sulfamides (**1b-7b**) was obtained using K_2CO_3 as the base in refluxing acetonitrile for 2 hours. The high acidity of the proton of the *N*-sulfonylcarbamate group is in favor of the expected intramolecular cyclization, and this alkylation step afforded the corresponding cyclic compounds (**1c-7c**) with quantitative yield (Table 1).



Scheme 1. General procedure for the synthesis of 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carbaldehyde-1,1-dioxide with phosphonates derivatives

Table 1. Structures of compounds (1a-7a), (1b-7b) and (1c-7c)

α -Hydroxy phosphonates (1a-7a)	Sulfamidocarbonyloxy methylphosphonates (1b-7b)	5-(2-Chloroethyl)-1, 2, 5- thiadiazoline-2- carboxylate-1, 1-dioxide phosphonates (1c-7c) ^c
		
1a, 97%	1b, 92% ^a	1c
		
2a, 93%	2b, 87% ^b	2c
		
3a, 90%	3b, 83% ^a	3c
		
4a, 93%	4b, 88% ^b	4c
		
5a, 95%	5b, 90% ^a	5c
		
6a, 89%	6b, 80% ^b	6c
		
7a, 88%	7b, 78% ^b	7c

[a] Purification by column chromatography (CH₂Cl₂: MeOH (9.8:0.2)), [b] Recrystallization in diethyl ether/*n*-hexane (1/1), [c] Quantitatively obtained with good purity by simple extraction

The structures of the sulfamidocarbonyloxymethylphosphonates **1b-7b**, as well as their cyclic analogues **1c-7c** were confirmed by usual spectroscopic methods. The infrared spectra of compounds **1b-7b**, exhibited characteristic signals for the NH group (range 3285–3260 cm⁻¹), the phosphonate (P=O, 1255–1234 cm⁻¹), and the carbonyl (C=O, 1750–1730 cm⁻¹) groups, as well as specific bands for symmetric/antisymmetric sulfonyl function SO₂ (1185±10 cm⁻¹/1384±10 cm⁻¹).

The most significant change in the IR spectra data of cyclic compounds **1c-7c** was the disappearance of NH stretching band vibration.

In the ¹H-NMR spectra of the compounds **1b-7b**, the P-CH gave a doublet in a region between 5.89 and 6.33 ppm (with *J*_{H-P} ~ 13.5–16.0 Hz) and the carbamic NH proton appeared as a broad singlet at 9.58–10.62 ppm. The two triplets at 1.03–1.38 ppm attributed to the ethoxy groups of the phosphonate moiety as well as the four multiplets integrating for the twelve methylene protons of the phosphonate and the chloroethyl chains (3.52–4.37 ppm) also confirmed the formation of the targeted compounds. For the cyclic products **1c-7c**, the absence of the carbamic proton signal and the appearance of two triplets attributed to the methylenes of the cyclosulfamide moiety (3.65–3.45 ppm) were in accordance with an intramolecular cyclization.

The ¹³C NMR spectra of compounds **1b-7b** mainly showed the presence of the carbonyl group (150.6 ppm) and in the area

of 64.7-71.7 ppm a doublet with an large coupling constant ($J_{C-P} \sim 174.0-189.0$ Hz) as a characteristic of the trisubstituted carbon in the alpha position of the phosphore. For **1c-7c**, the appearance of four signals between 43 and 45 ppm corresponding to the methylene groups of nitrogen mustard pattern confirmed the formation of the five ring membered *N*-substituted 1,2,5-thiadiazolidine-1,1-dioxide. All these compounds were finally fully characterized with complementary DEPT and HSQC analyses as well as ^{31}P NMR spectra which confirmed the presence of the phosphonate function (13.0-16.0 ppm), and mass spectrometry were also in good accordance with the products formula.

Satisfyingly, we could obtain a single crystal of the fluoro compound **3c** which was submitted to X-ray diffraction analysis. An ORTEP diagram of structure **3c** is shown in figure 4.

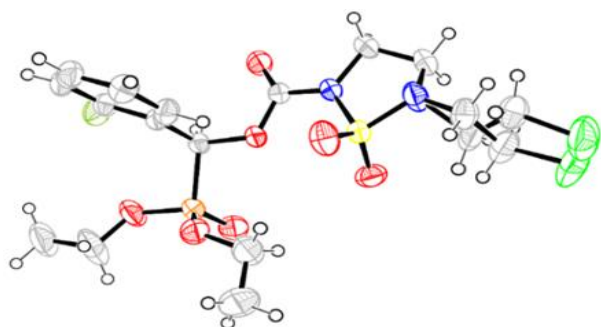


Figure 4. ORTEP diagram of compound **3c** displacement ellipsoids are drawn at the 50% probability level. H atoms are represented as small spheres of arbitrary radius. (With disordered chloroethyl)

Structural resolution revealed that the asymmetric unit consists of one molecule of (IUPAC NAME), which crystallizes in the triclinic crystal system with *p*-1 space group (Table 2).

Table 2. Crystallographic data and refinement parameters for **3c**

Formula	C16 H23 Cl F N2 O7 P S
Formula weight	472.84
Crystal habit, color	Prism, Colorless
Crystal system	Triclinic
Space group	<i>P</i> -1
<i>a</i> (Å)	8.686(2)
<i>b</i> (Å)	9.735(3)
<i>c</i> (Å)	13.705(4)
α (°)	86.165(14)
β (°)	82.181(13)
γ (°)	70.724(13)
Volume (Å ³)	1083.4(5)
<i>Z</i> , <i>Z'</i>	2, 2
Density (calculated, g cm ⁻³)	1.446
Absorption coefficient (mm ⁻¹)	0.394
<i>F</i> (000)	1680
Crystal size (mm)	0.11×0.15×0.18
θ range for data collection (°)	2.217 - 38.538
Reflections collected	11946
Independent reflections	6115
<i>R</i> _{int}	0.0630
Reflections with $I \geq 2\sigma(I)$	6115
Number of parameters	290
Goodness-of-fit on <i>F</i> ²	1.043
Final <i>R</i> indices [$I \geq 2\sigma(I)$]	<i>R</i> ₁ =0.0628, <i>wR</i> ₂ =0.1852
<i>R</i> indices [all data]	<i>R</i> ₁ =0.1155, <i>wR</i> ₂ =0.2128
Largest difference peak and hole (Å ⁻³)	0.583, -0.394
CCDC deposition no.	CCDC 1986194

The structure was refined with disordered chloroethyl with 64:36 ratio. The crystal packing can be described as alternating layers parallel to (*b*, *c*) plane which are connected together with C-H...O and C-H...Cl hydrogen bonds along the *a* and *c* axis (Table 3, Figure 5).

Table 3. Distances (Å) and angles (°) of hydrogen bond for **3c**

D-H...A	<i>d</i> (D-H)	<i>d</i> (H...A)	<i>d</i> (D-A)	D-H-A	Symmetry
Compound 3c					
C3-H3A...O1	0.97	2.54	3.305(2)	136.2	2- <i>x</i> , - <i>y</i> , 1- <i>z</i>
C3-H3B...O5	0.97	2.52	3.320(2)	139.8	<i>x</i> , 1+ <i>y</i> , <i>z</i>
C4-H4B...Cl1A	0.97	2.95	3.915(3)	172.1	- <i>x</i> , <i>y</i> , <i>z</i>
C4-H4B... Cl1B	0.97	2.87	3.827(6)	171.2	- <i>x</i> , <i>y</i> , <i>z</i>
C2A-H2A2...O5	0.97	2.64	3.433(4)	138.9	<i>x</i> , 1+ <i>y</i> , <i>z</i>
C1A-H1A1...O5	0.97	2.37	3.286(4)	157.5	2- <i>x</i> , 1- <i>y</i> , 1- <i>z</i>
C1B-H1B2...O5	0.97	2.62	3.442(7)	143.1	<i>x</i> , 1+ <i>y</i> , <i>z</i>

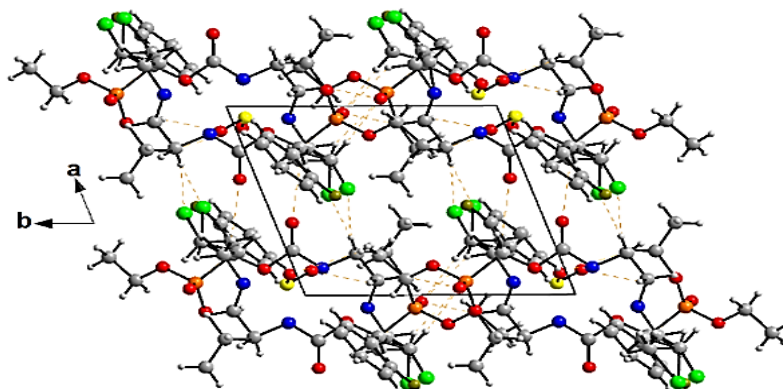


Figure 5. Diagram packing of **3c** viewed along the *c* axis showing layers parallel to (*b*, *c*) and connected with C-H...O and C-H...Cl interactions

In these layers, the arrangement of each molecule induces a strong π - π staking intermolecular interactions. The distance centroid-centroid is 3.7431(12) Å between phenyl rings in the packing crystal, they are oriented face to face with slippage value of 1.730 Å.

Our compounds showed interesting antimicrobial activities on the tested microorganisms. The diameters of inhibition zones range from 10 to 30 mm, compared to an inhibition diameter ranging from 10 to 34 with the standard drugs (gentamycin and amphotericin B). These molecules did not discriminate Gram positive or Gram negative strains, and some also appeared effective on *Candida albicans* (yeasts) showing antifungal activity such as **2b**, **6b** and **5c** (Table 4).

In vitro antibacterial activity being confirmed in the disk diffusion test, the Minimum Inhibition Concentrations (MIC) were then determined. As shown in table 4, all the molecules exhibited good activity between 4 and 0.25 µg/ml for all strains compared to the tested treatment (MIC varied between 8 and 1 µg/ml).

Particularly a MIC of 0.25 µg/ml was observed for compounds **2b**, **4b** on *E. coli* BMR and for compounds **3c** and **5c** on *E. coli* ATCC 25922.

For sulfonamides **2b** to **7b** bearing the *N*-bis chloroethyl terminal moiety, a lipophilic aromatic substituent in the alpha position of the phosphonate function seemed to be preferred on *S. aureus* ATCC 29213. As observed, compound **2b** with a *p*-chlorophenyl substituent was 8 to 16 times more active than the corresponding thiophen analog **6b** or *p*-methoxyphenyl analog **4b**, respectively (Table 5).

It is also to be noted that cyclic compound **5c**, bearing a naphthalene substituent conserved the highest activity on a panel of 5 microorganisms (MIC: 0.25 and 0.5 µg/ml), compared to the cyclic analog **1c** bearing a phenyl substituent (MIC: 1 to 4 µg/ml). Moreover, this thiadiazolidine dioxide derivative **5c** appeared also eight fold more potent than the cyclic morpholino analog **5**, recently published (Fig 1, compound **5**).

Conclusion

In this work, a series of seven *N,N*-bis (2-chloroethyl) sulfamido carbonyloxymethylphosphonate derivatives (**1b-7b**) and their cyclic analogs (**1c-7c**) were synthesized by a carbamoylation-sulfamoylation reaction of seven α -hydroxyphosphonates, followed by intramolecular cyclization. The impact of the aromatic substituent in the alpha position of the phosphonate function for compounds **1b-7b** and **1c-7c** could so be estimated in the biological tests. All the products isolated were fully characterized by spectroscopic methods, supported with RXD analysis of the compound **3c**. *In vitro* antimicrobial activity was studied against eight microbial strains using the disk diffusion and MIC test. The results revealed that these compounds showed a remarkable antimicrobial activities against Gram-positive, Gram-negative bacteria and fungi at low concentrations. Theoretical studies (DFT and docking study) are underway to explore the interactions of these compounds with biological receptors and extended biological studies (anti-diabetics and anti-cancer) could be carried out to identify the pharmacological potential of our products.

Table 4. Antimicrobial activities of the synthetic compounds ^a

Diameter of growth inhibition expressed in mm									
Microorganism	Acetone	2b	4b	6b	7b	1c	3c	5c	Treatment
<i>K. pneumoniae</i> BLSE	11	24	20	19	23	24	23,5	19	29
<i>E. coli</i> BMR	00	22	23,5	22,5	20	25	25	18	29
<i>E. coli</i> ATCC 25922	05	22,5	23	10	00	18,5	21	11	30,5
<i>P. aeruginosa</i>	12	12,5	11,5	18	20	25	21	10	00
<i>P. aeruginosa</i> ATCC27853	00	15	12	19	17	15	11,5	19	10
<i>S. aureus</i>	05	10	10	00	00	00	16	00	34
<i>S. aureus</i> ATCC 29213	00	20	11	21	20	20	22	18	15
<i>C. albicans</i>	10	25	00	30	00	00	00	22	00

[a] All tests were performed in triplicate

Table 5. The minimal inhibitory concentrations (MIC) ^a

Micro organism	Values MIC (µg/ml)							Treatment
	2b	4b	6b	7b	1c	3c	5c	
<i>K. pneumoniae</i> BLSE	2	0.5	4	2	2	2	4	R
<i>E. coli</i> BMR	4	4	4	4	4	4	0.5	1
<i>E. coli</i> ATCC 25922	2	0.5	2	4	2	4	0.5	4
<i>P. aeruginosa</i>	2	2	4	/	4	0.25	0.25	4
<i>P. aeruginosa</i> ATCC27853	0.25	0.25	0.5	1	2	2	0.5	8
<i>S. aureus</i>	0.25	4	2	1	1	1	0.5	8
<i>S. aureus</i> ATCC 29213	4	4	/	/	/	4	/	1
<i>C. albicans</i>	2	/	1	/	/	0.5	/	R

[a] All tests were performed in triplicate and sulfamethoxazole-trimethoprim (SXT) was used as a positive control (MIC = 25 µg/ml)

Experimental Section

The nomenclature of all compounds is performed according to the international denomination of IUPAC; the reagents were obtained from commercial furnisher (Sigma-Aldrich, Alfa Aesar) and used without further purification.

TLC monitored all reactions on silica Merck₆₀ F254 percolated aluminum plates, revealed with UV ($\lambda = 254$ nm) and dipping in Ninhydrine solution followed by heating. Melting points of all compounds were measured in open capillary tubes using StuartTM melting point apparatus SMP3.

IR spectra were recorded on a Perkin-Elmer FT-600 spectrometer. ¹H NMR, ¹³C NMR, ³¹P NMR, DEPT, COSY, and HMQC spectra were recorded at 25 °C with a Bruker spectrometers at 300 or 400, 100, 161.9 MHz, respectively using CDCl₃ as solvent with TMS as an internal standard.

Chemical displacement values (δ) are expressed in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Multiplicity of signals is indicated as following: s (singulet), d (doublet), t (triplet), q (quadruplet), m (multiplet), brs (broad singulet) ...etc.

Low-resolution mass spectra (MS) and High-Resolution Mass Spectrometry (HRMS) were performed in CEISAM laboratory on a Waters Xevo GL-XS Qtof spectrometer coupled with an Acquity H-Class LC apparatus and the ionization sources were performed with electrospray ionization (ESI⁺) method.

The X-ray single-crystal diffraction was performed on a Brüker APEXII diffractometer and the supplemental materials comprises the characterization data of all news products.

2.2. General procedure for the synthesis of α -hydroxyphosphonates derivatives (1a-7a)

According to previous work, [30] we prepared the α -hydroxyphosphonates from diethylphosphite (1 mmol) and several aromatic aldehydes (1 mmol) at room temperature in the presence of H₆P₂W₁₈O₆₂.14H₂O (1 mol %) as catalyst under solvent-free conditions for 10 min. Column chromatography on silica gel eluted with (diethyl acetate: petroleum ether 9.5/0.5) or recrystallization in (diethyl ether/*n*-hexane) gave the pure products in 70-90% yields.

2.3. General procedure for the synthesis of *N,N*-Bis (2-chloroethyl) sulfamidocarbonyloxymethylphosphonates derivatives (1b-7b)

N,N-bis (2-chloroethyl) sulfamidocarbonyloxymethylphosphonates derivatives were obtained in 2 steps: firstly, a solution of α -hydroxyphosphonates (1.1 eq) in anhydrous DCM (5 mL) was slowly added dropwise to a stirred solution of chlorosulfonyl isocyanate (CSI) (1 eq, 500.00 mg, 3.53 mmol) dissolved in DCM at 0 °C for 30 min. In a second step, the resulting solution were slowly added to a solution of bis (2-chloroethyl) amine hydrochloride (1 eq, 630.56 mg, 3.53 mmol) in anhydrous DCM (10 mL) at 0 °C in the presence of triethylamine (2 eq, 715.02 mg, 7.07 mmol), the resulting reaction solution was then stirred at room temperature for 2h. Finally, the reaction mixture was diluted with dichloromethane (100 mL), washed with HCl (0.1N) until acidic pH then extracted with water up to neutral pH. The organic layer was dried over anhydrous sodium sulfate (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was crystallized in a mixture of diethyl ether/*n*-hexane (1:1) or purified by column chromatography on silica gel (eluent: CH₂Cl₂: MeOH (9.8:0.2) to afford the desired *N,N*-bis (2-chloroethyl) sulfamidocarbonyloxymethylphosphonates derivatives (1b-7b) in excellent yields.

(Diethoxyphosphoryl) (phenyl) methyl (N,N-bis(2-chloroethyl) sulfamoyl) carbamate: the product (1b, C₁₆H₂₅Cl₂N₂O₇PS) was obtained as a colorless oil (160 mg, 92% yield); R_f 0.48 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3267 (NH), 1741 (CO), 1366 and 1155 (SO₂), 1232 and 1042 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 16.43 ppm; ¹H NMR (300 MHz, CDCl₃) δ 1.03 (t, *J*_{HH} 7.2 Hz, 3H, CH₃-CH₂), 1.32 (t, *J*_{HH} 7.2 Hz, 3H, CH₃-CH₂), 3.51-3.75 (m, 8H, 4CH₂), 3.83-3.97 (m, 1H, CH₂-CH₃), 4.13-4.24 (m, 2H, CH₂-CH₃), 4.29-4.35 (m, 1H, CH₂-CH₃), 5.89 (d, *J*_{HP} 13.8 Hz, 1H, *CH),

7.32-7.34 (m, 3H, H-Ar), 7.47-7.49 (m, 2H, H-Ar), 10.62 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (d, ³*J*_{CP} 5.0 Hz, CH₃), 16.4 (d, ³*J*_{CP} 6.0 Hz, CH₃), 41.5 (2CH₂-Cl), 52.2 (2CH₂-N), 63.7 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 64.1 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 71.7 (d, ¹*J*_{CP} 174.0 Hz, *CH), 128.2 (d, *J*_{CP} 6.0 Hz, CH-Ar), 128.6 (CH-Ar), 129.3 (CH-Ar), 129.4 (CH-Ar), 132.4 (C-Ar), 150.6 (d, *J*_{CP} 12.0 Hz, CO) ppm; MS (ESI⁺) *m/z* = 491.1 [M+H]⁺; HRMS (ESI⁺): *m/z* [M+H]⁺ calcd for C₁₆H₂₅N₂O₇PSCl: 491.0569; found: 491.0575

(4-Chlorophenyl) (diethoxyphosphoryl) methyl (N,N-bis(2-chloroethyl) sulfamoyl) carbamate: the product (2b, C₁₆H₂₄Cl₃N₂O₇PS) was obtained as a white powder (162 mg, 87% yield); m.p. 138-140 °C; R_f 0.5 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3268 (NH), 1741 (CO), 1343 and 1165 (SO₂), 1260 and 1024 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 15.95 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.13 (t, *J*_{HH} 6.8 Hz, 3H, CH₃-CH₂), 1.36 (t, *J*_{HH} 6.8 Hz, 3H, CH₃-CH₂), 3.59-3.73 (m, 8H, 4CH₂), 3.82-3.86 (m, 1H, CH₂-CH₃), 3.96-4.04 (m, 1H, CH₂-CH₃), 4.18-4.23 (m, 2H, CH₂-CH₃), 5.90 (d, *J*_{HH} 14.0 Hz, 1H, *CH), 7.35 (d, *J*_{HH} 8.4 Hz, 2H, H-Ar), 7.44 (d, *J*_{HH} 2.0 Hz, 1H, H-Ar), 7.46 (d, *J*_{HH} 2.0 Hz, 1H, H-Ar), 10.22 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (d, ³*J*_{CP} 5.0 Hz, CH₃), 16.4 (d, ³*J*_{CP} 6.0 Hz, CH₃), 41.5 (2CH₂-Cl), 52.2 (2CH₂-N), 63.9 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 64.1 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 70.7 (d, ¹*J*_{CP} 174.0 Hz, *CH), 128.9 (CH-Ar), 129.5 (d, *J*_{CP} 7.0 Hz, CH-Ar), 131.0 (CH-Ar), 135.5 (C-Ar), 150.4 (d, *J*_{CP} 13.0 Hz, CO) ppm; MS (ESI⁺) *m/z* = 549.0 [M+Na]⁺; HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₆H₂₄N₂O₇NaPSCl₃: 547.0004; found: 547.0005

Diethoxyphosphoryl) (2-fluorophenyl) methyl (N,N-bis (2-chloroethyl) sulfamoyl) carbamate: the product (3b, C₁₆H₂₄Cl₂FN₂O₇PS) was obtained as a colourless oil (149 mg, 83% yield); R_f 0.52 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3277 (NH), 1754 (CO), 1369 and 1157 (SO₂), 1231 and 1025 (PO) cm⁻¹; ³¹P NMR (121.5 MHz, CDCl₃) δ 15.77 (d, *J*_{FP} 5.7 Hz) ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.12 (t, *J*_{HH} 7.2 Hz, 3H, CH₃-CH₂), 1.38 (t, *J*_{HH} 7.2 Hz, 3H, CH₃-CH₂), 3.61-3.73 (m, 8H, 4CH₂), 3.86-3.90 (m, 1H, CH₂-CH₃), 3.97-4.03 (m, 1H, CH₂-CH₃), 4.23-4.27 (m, 2H, CH₂-CH₃), 6.33 (d, *J*_{HH} 14.0 Hz, 1H, *CH), 7.10 (t, *J*_{HH} 8.4 Hz, 1H, H-Ar), 7.19 (t, *J*_{HH} 7.6 Hz, 1H, H-Ar), 7.34-7.41 (m, 1H, H-Ar), 7.67 (t, *J*_{HH} 8.2 Hz, 1H, H-Ar), 10.11 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 16.2 (d, ³*J*_{CP} 6.0 Hz, CH₃), 16.6 (d, ³*J*_{CP} 6.0 Hz, CH₃), 41.8 (2CH₂-Cl), 52.5 (2CH₂-N), 64.1 (d, ²*J*_{CP} 5.0 Hz, CH₂-CH₃), 64.4 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 64.7 (d, ¹*J*_{CP} 177.0 Hz, *CH), 115.7 (d, *J*_{CP} 2.0 Hz, CH-Ar), 124.7 (C-Ar), 129.6 (C-Ar), 131.3 (C-Ar), 150.6 (CO) ppm; MS (ESI⁺) *m/z* = 531.0 [M+Na]⁺; HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₆H₂₄N₂O₇FNAPSCl₂: 531.0303; found: 531.0301

(Diethoxyphosphoryl) (4-methoxyphenyl) methyl (N,N-bis(2 chloroethyl) sulfamoyl) carbamate: the product (4b, C₁₇H₂₇Cl₂N₂O₈PS) was obtained as a white powder (163 mg, 88% yield); m.p. 116-118 °C; R_f 0.40 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3260 (NH), 1739 (CO), 1338 and 1158 (SO₂), 1253 and 1026 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 16.67 ppm; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, *J*_{HH} 7.2 Hz, 3H, CH₃-CH₂), 1.36 (t, *J*_{HH} 7.2 Hz, 3H, CH₃-CH₂), 3.58-3.66 (m, 8H, 4CH₂), 3.86-3.78 (m, 1H, CH₂-CH₃), 3.81 (s, 3H, OCH₃), 3.81-4.00 (m, 1H, CH₂-CH₃), 4.19-4.24 (m, 2H, CH₂-CH₃), 5.88 (d, *J*_{HH} 13.5 Hz, 1H, *CH), 6.87 (d, *J*_{HH} 8.4 Hz, 2H, H-Ar), 7.45 (d, *J*_{HH} 1.8 Hz, 1H, H-Ar), 7.48 (d, *J*_{HH} 1.8 Hz, 1H, H-Ar), 10.18 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (d, ³*J*_{CP} 6.0 Hz, CH₃), 16.5 (d, ³*J*_{CP} 5.0 Hz, CH₃), 41.5 (2CH₂-Cl), 52.2 (2CH₂-N), 55.3 (OCH₃), 63.6 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 64.1 (d, ²*J*_{CP} 7.0 Hz, CH₂-CH₃), 71.0 (d, ¹*J*_{CP} 177.0 Hz, *CH), 114.1 (CH-Ar), 124.3 (CH-Ar), 130.0 (d, *J*_{CP} 6.0 Hz, C-Ar), 130.0 (d, *J*_{CP} 6.0 Hz, C-Ar), 150.9 (d, *J*_{CP} 13.0 Hz, CO), 160.4 (C-Ar) ppm; MS (ESI⁺) *m/z* = 543.1 [M+Na]⁺; HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₇H₂₇N₂O₈NaSCl₂P: 543.0508; found: 543.0500

(Diethoxyphosphoryl) (naphthalen-1-yl) methyl (N,N-bis(2-chloroethyl) sulfamoyl) carbamate: the product (5b, C₂₀H₂₇Cl₂N₂O₇PS) was obtained as a yellow oil (173 mg, 90% yield); R_f 0.45 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3262 (NH), 1746 (CO), 1367 and 1157 (SO₂), 1230 and 1042 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 16.39 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.06 (t, *J*_{HH} 6.8 Hz, 3H, CH₃), 1.38 (t, *J*_{HH} 7.2 Hz, 3H, CH₃), 3.52-

3.74 (m, 8H, 4(CH₂)), 3.90-4.09 (m, 1H, CH₂-CH₃), 4.24-4.27 (m, 2H, CH₂-CH₃), 4.33-4.37 (m, 1H, CH₂-CH₃), 6.13 (d, ¹J_{H-P} 14.0 Hz, 1H, CH*), 7.48-7.54 (m, 2H, H-Ar), 7.68-7.70 (m, 1H, H-Ar), 7.78-7.85 (m, 3H, H-Ar), 8.01 (brs, 1H, H-Ar), 10.41 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (d, ³J_{C-P} 5.0 Hz, CH₃), 16.5 (d, ³J_{C-P} 6.0 Hz, CH₃), 41.5 (s, 2(CH₂-Cl)), 52.2 (s, 2(CH₂-N)), 63.8 (d, ²J_{C-P} 5.0 Hz, CH₂), 64.1 (d, ²J_{C-P} 7.0 Hz, CH₂), 71.7 (d, ¹J_{C-P} 174.0 Hz, C*), 125.2 (d, ¹J_{C-P} 4.0 Hz, CH-Ar), 126.6 (CH-Ar), 126.9 (CH-Ar), 127.8 (CH-Ar), 128.0 (d, ¹J_{C-P} 8.0 Hz, CH-Ar), 128.1 (CH-Ar), 128.6 (CH-Ar), 129.8 (C-Ar), 132.9 (C-Ar), 133.6 (C-Ar), 150.6 (d, ¹J_{C-P} 12.0 Hz, CO) ppm; MS (ESI⁺) m/z = 563.1 [M+Na]⁺; HRMS (ESI⁺): m/z [M+Na]⁺ calcd for C₂₀H₂₇N₂O₇NaSCl₂P: 563.0551; found: 563.0551

(Diethoxyphosphoryl) (thiophen-2-yl) methyl (N,N-bis(2-chloroethyl)sulfamoyl) carbamate: the product (6b, C₁₄H₂₃Cl₂N₂O₇PS₂) was obtained as a white powder (141 mg, 80% yield); m.p. 130-132 °C; R_f 0.42 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3280 (NH), 1745 (CO), 1340 and 1150 (SO₂), 1251 and 1045 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 15.10 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, J_{H-H} 7.2 Hz, 3H, CH₃), 1.35 (t, J_{H-H} 7.2 Hz, 3H, CH₃), 3.64-3.74 (m, 8H, CH₂), 3.91-3.96 (m, 1H, CH₂-CH₃), 4.05-4.11 (m, 1H, CH₂-CH₃), 4.21-4.25 (m, 2H, CH₂-CH₃), 6.23 (d, ¹J_{H-P} 14.8 Hz, 1H, CH*), 7.01-7.03 (m, 1H, H-vinyl), 7.32 (brs, 1H, H-vinyl), 7.38 (d, J_{H-H} 4.8 Hz, 1H, H-vinyl), 9.58 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (CH₃), 16.4 (CH₃), 41.5 (2CH₂-Cl), 52.2 (2CH₂-N), 64.1 (t, ²J_{C-P} 6.0 Hz, CH₂), 66.2 (d, ¹J_{C-P} 181.0 Hz, C*), 127.0 (CH-vinyl), 128.3 (CH-vinyl), 129.9 (CH-vinyl), 133.4 (C-vinyl), 150.1 (d, ¹J_{C-P} 9.0 Hz, CO) ppm; MS (ESI⁺) m/z = 519.0 [M+Na]⁺; HRMS (ESI⁺): m/z [M+Na]⁺ calcd for C₁₄H₂₃N₂O₇NaPS₂Cl₂: 518.9972; found: 518.9959

(Diethoxyphosphoryl) (furan-2-yl) methyl (N,N-bis(2-chloroethyl)sulfamoyl) carbamate: the product (7b, C₁₄H₂₃Cl₂N₂O₈PS) was obtained as a brown powder (133 mg, 78% yield); m.p. 124-126 °C; R_f 0.40 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 3285 (NH), 1732 (CO), 1349 and 1144 (SO₂), 1230 and 1030 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 14.12 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.17 (t, J_{H-H} 7.2 Hz, 3H, CH₃), 1.31 (t, J_{H-H} 7.2 Hz, 3H, CH₃), 3.64-3.73 (m, 8H, CH₂), 3.96-4.06 (m, 1H, CH₂-CH₃), 4.08-4.18 (m, 1H, CH₂-CH₃), 4.20-4.24 (m, 2H, CH₂-CH₃), 6.06 (d, ¹J_{H-P} 16.0 Hz, 1H, CH*), 6.36-6.37 (m, 1H, H-vinyl), 6.62 (t, J_{H-H} 2.4 Hz, 1H, H-vinyl), 7.42-7.43 (m, 1H, H-vinyl), 10.23 (s, 1H, NH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.1 (d, ³J_{C-P} 6.0 Hz, CH₃), 16.4 (d, ³J_{C-P} 6.0 Hz, CH₃), 41.6 (s, 2CH₂-Cl), 52.3 (s, 2CH₂-N), 64.1 (t, ²J_{C-P} 8.0 Hz, CH₂), 66.3 (d, ¹J_{C-P} 189.0 Hz, C*), 111.0 (CH-vinyl), 112.7 (d, ¹J_{C-P} 5.0 Hz, CH-vinyl), 144.1 (CH-vinyl), 145.6 (C-vinyl), 150.5 (d, ¹J_{C-P} 11.0 Hz, CO) ppm; MS (ESI⁺) m/z = 503.0 [M+Na]⁺; HRMS (ESI⁺): m/z [M+Na]⁺ calcd for C₁₄H₂₃N₂O₈NaPSCl₂: 503.0190; found: 503.0187

2.4. General procedure for the synthesis of cyclic compounds (1c-7c)

N, N-bis(2-chloroethyl) sulfamidocarbonyloxyphosphonates 1b (100.00 mg, 203.53 μmol) was dissolved in dry acetonitrile (20 mL) at room temperature then we added K₂CO₃ (23.13 mg, 203.53 μmol). The mixture was heated to reflux under stirring for 2 h. The reaction mixture was evaporated, diluted with ethyl acetate (30 mL) and then extracted with water. The organic layer was combined and dried over anhydrous sodium sulfate (Na₂SO₄), filtered and concentrated *in vacuo*. All products (1c-7c) were obtained pure without further treatment with a total transformation of the starting material.

(Diethoxyphosphoryl) (phenyl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (1c, C₁₆H₂₄ClN₂O₇PS) was obtained as a white powder (92.58 mg, 100% yield); m.p. 110-112 °C; R_f 0.60 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1735 (CO), 1357 and 1152 (SO₂), 1260 and 1021 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 15.05 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.22-1.29 (m, 6H, 2CH₃), 3.46-3.49 (m, 2H, (CH₂)_{cyc}-NCH₂), 3.56 (t, J_{H-H} = 6.8 Hz, 2H, CH₂-CH₂-Cl), 3.73 (t, J_{H-H} = 6.8 Hz, (CH₂)_{cyc}-NCO), 3.92 (t, J_{H-H} = 6.8 Hz, 2H, CH₂-Cl), 4.03-4.17 (m, 4H, 2CH₂-CH₃), 6.13 (d, J_{H-P} = 13.6 Hz, 1H, *CH), 7.32-7.39 (m, 3H, H-Ar), 7.50-7.53 (m, 2H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³J_{C-P} = 2.0 Hz, CH₃), 16.4 (d, ³J_{C-P} = 3.0 Hz, CH₃), 41.6

(CH₂)_{cyc}-NCO), 43.4 (CH₂-Cl), 45.2 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂), 63.8 (d, ²J_{C-P} = 6.0 Hz, 2CH₂-CH₃), 73.0 (d, ¹J_{C-P} = 168.0 Hz, *CH), 127.5 (d, ¹J_{C-P} = 5.0 Hz, CH-Ar), 128.5 (d, ¹J_{C-P} = 2.0 Hz, CH-Ar), 128.8 (d, ¹J_{C-P} = 2.0 Hz, CH-Ar), 132.6 (C-Ar), 149.2 (d, ¹J_{C-P} = 10.0 Hz, CO) ppm; MS (ESI⁺) m/z = 455.1 [M+H]⁺; HRMS (ESI⁺): m/z [M+H]⁺ calcd for C₁₆H₂₅N₂O₇PSCl: 455.0808; found: 455.0809

(4-chlorophenyl)(diethoxyphosphoryl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (2c, C₁₆H₂₃Cl₂N₂O₇PS) was obtained as an colorless oil (93.07 mg, 100% yield); R_f 0.68 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1749 (CO), 1361 and 1156 (SO₂), 1229 and 1018 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 14.51 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.25-1.29 (m, 6H, 2CH₃), 3.45-3.48 (td, J₁ = 4.0 Hz, J₂ = 6.8 Hz, 2H, (CH₂)_{cyc}-NCH₂), 3.56 (t, J_{H-H} = 6.4 Hz, 2H, CH₂-CH₂-Cl), 3.71 (t, J_{H-H} = 6.4 Hz, (CH₂)_{cyc}-NCO), 3.90 (t, J_{H-H} = 6.8 Hz, 2H, CH₂-Cl), 4.04-4.19 (m, 4H, 2CH₂-CH₃), 6.07 (d, J_{H-P} = 13.6 Hz, 1H, *CH), 7.32 (d, J_{H-H} = 8.4 Hz, 2H, H-Ar), 7.43 (d, J_{H-H} = 2.0 Hz, 1H, H-Ar), 7.46 (d, J_{H-H} = 2.0 Hz, 1H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³J_{C-P} = 2.0 Hz, CH₃), 16.4 (d, ³J_{C-P} = 3.0 Hz, CH₃), 41.5 (CH₂)_{cyc}-NCO), 43.5 (CH₂-Cl), 45.1 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂), 63.9 (d, ²J_{C-P} = 6.0 Hz, 2CH₂-CH₃), 72.3 (d, ¹J_{C-P} = 168.0 Hz, *CH), 128.5 (d, ¹J_{C-P} = 2.0 Hz, CH-Ar), 128.9 (d, ¹J_{C-P} = 5.0 Hz, CH-Ar), 131.3 (d, ¹J_{C-P} = 2.0 Hz, C-Ar), 134.9 (d, ¹J_{C-P} = 3.0 Hz, C-Ar), 149.1 (d, ¹J_{C-P} = 11.0 Hz, CO) ppm; MS (ESI⁺) m/z = 511.0 [M+Na]⁺; HRMS (ESI⁺): m/z [M+Na]⁺ calcd for C₁₆H₂₃N₂O₇NaPSCl₂: 511.0238; found: 511.0238

(Diethoxyphosphoryl)(2-fluorophenyl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (3c, C₁₆H₂₃ClFN₂O₇PS) was obtained as a white crystal (92.84 mg, 100% yield); m.p. 106-108 °C; R_f 0.70 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1740 (CO), 1323 and 1157 (SO₂), 1258 and 1025 (PO) cm⁻¹; ³¹P NMR (121.48 MHz, CDCl₃) δ 14.43 (d, J_{F-P} = 4.6 Hz) ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (t, J_{H-H} = 7.2 Hz, 6H, 2CH₃), 3.45-3.49 (td, J₁ = 3.6 Hz, J₂ = 6.4 Hz, 2H, (CH₂)_{cyc}-NCH₂), 3.56 (t, J_{H-H} = 6.4 Hz, 2H, CH₂-CH₂-Cl), 3.72 (t, J_{H-H} = 6.4 Hz, (CH₂)_{cyc}-NCO), 3.91 (t, J_{H-H} = 6.4 Hz, 2H, CH₂-Cl), 4.10-4.21 (m, 4H, 2CH₂-CH₃), 6.46 (d, J_{H-P} = 13.2 Hz, 1H, *CH), 7.05 (t, J_{H-H} = 9.6 Hz, 2H, H-Ar), 7.18 (t, J_{H-H} = 7.6 Hz, 2H, H-Ar), 7.29-7.33 (m, 1H, H-Ar), 7.63 (br t, J_{H-H} = 7.6 Hz, 1H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³J_{C-P} = 5.0 Hz, 2CH₃), 41.6 (CH₂)_{cyc}-NCO), 43.4 (CH₂-Cl), 45.2 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂), 63.8 (d, ²J_{C-P} = 7.0 Hz, CH₂-CH₃), 63.9 (d, ²J_{C-P} = 7.0 Hz, CH₂-CH₃), 66.3 (d, ¹J_{C-P} = 172.0 Hz, *CH), 115.2 (CH-Ar), 115.5 (CH-Ar), 124.5 (C-Ar), 124.5 (CH-Ar), 129.3 (CH-Ar), 130.6 (C-Ar), 130.7 (C-Ar), 149.0 (CO) ppm; MS (ESI⁺) m/z = 495.1 [M+Na]⁺; HRMS (ESI⁺): m/z [M+Na]⁺ calcd for C₁₆H₂₃N₂O₇NaPSCl: 495.0533; found: 495.0534

(Diethoxyphosphoryl)(4-methoxyphenyl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (4c, C₁₇H₂₆ClN₂O₈PS) was obtained as an colorless oil (93.01 mg, 100% yield); R_f 0.65 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1740 (CO), 1323 and 1157 (SO₂), 1258 and 1025 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 15.44 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.25-1.30 (td, J₁ = 2.4 Hz, J₂ = 6.8 Hz, 6H, 2CH₃), 3.46-3.50 (td, J₁ = 1.6 Hz, J₂ = 6.4 Hz, (CH₂)_{cyc}-NCH₂), 3.56 (t, J_{H-H} = 6.8 Hz, 2H, CH₂-CH₂-Cl), 3.73 (t, J_{H-H} = 6.4 Hz, (CH₂)_{cyc}-NCO), 3.81 (s, 3H, OCH₃), 3.92 (t, J_{H-H} = 6.4 Hz, 2H, CH₂-Cl), 4.07-4.17 (m, 4H, 2CH₂-CH₃), 6.07 (d, J_{H-P} = 12.8 Hz, 1H, *CH), 6.89 (d, J_{H-H} = 8.8 Hz, 2H, H-Ar), 7.44 (d, J_{H-H} = 2.0 Hz, 1H, H-Ar), 7.47 (d, J_{H-H} = 1.6 Hz, 1H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³J_{C-P} = 5.0 Hz, 2CH₃), 41.6 (CH₂)_{cyc}-NCO), 43.4 (CH₂-Cl), 45.2 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂), 55.3 (OCH₃), 63.7 (d, ²J_{C-P} = 7.0 Hz, 2CH₂-CH₃), 72.7 (d, ¹J_{C-P} = 170.0 Hz, *CH), 114.1 (CH-Ar), 124.6 (CH-Ar), 129.3 (d, ¹J_{C-P} = 5.0 Hz, C-Ar), 149.2 (d, ¹J_{C-P} = 11.0 Hz, CO), 160.1 (C-Ar) ppm; MS (ESI⁺) m/z = 507.1 [M+Na]⁺; HRMS (ESI⁺): m/z [M+Na]⁺ calcd for C₁₇H₂₆N₂O₈NaSClP: 507.0734; found: 507.0734

(Diethoxyphosphoryl) (naphthalen-1-yl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (5c, C₂₀H₂₆ClN₂O₇PS) was obtained as a white powder (93.27 mg, 100% yield); m.p. 150-152 °C; R_f 0.63 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1734 (CO),

1330 and 1165 (SO₂), 1264 and 1017 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 15.01 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (t, *J*_{HH} = 7.2 Hz, 3H, CH₃), 1.28 (t, *J*_{HH} = 7.2 Hz, 3H, CH₃), 3.49 (t, *J*_{HH} = 6.4 Hz, 2H, (CH₂)_{cyc}-NCH₂), 3.56 (t, *J*_{HH} = 6.4 Hz, 2H, CH₂-CH₂-Cl), 3.73 (t, *J*_{HH} = 6.4 Hz, (CH₂)_{cyc}-NCO), 3.91-3.94 (td, *J*₁ = 1.6 Hz, *J*₂ = 6.4 Hz, 2H, CH₂-Cl), 4.05-4.20 (m, 4H, 2CH₂-CH₃), 6.30 (d, *J*_{HP} = 13.6 Hz, 1H, *CH), 7.47-7.50 (m, 2H, H-Ar), 7.63 (brd, *J*_{HH} = 8.4 Hz, 1H, H-Ar), 7.81-7.86 (m, 3H, H-Ar), 8.01 (brs, 1H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³*J*_{C-P} = 2.0 Hz, CH₃), 16.4 (d, ³*J*_{C-P} = 3.0 Hz, CH₃), 41.6 (CH₂)_{cyc}-NCO, 43.3 (CH₂-Cl), 45.2 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂, 63.8 (d, ²*J*_{C-P} = 6.0 Hz, 2CH₂-CH₃), 73.2 (d, ¹*J*_{C-P} = 168.0 Hz, *CH), 124.8 (d, *J*_{C-P} = 4.0 Hz, CH-Ar), 126.3 (CH-Ar), 126.6 (CH-Ar), 127.2 (CH-Ar), 126.7 (CH-Ar), 128.3 (CH-Ar), 130.1 (C-Ar), 133.0 (C-Ar), 133.4 (C-Ar), 149.2 (d, *J*_{C-P} = 10.0 Hz, CO) ppm; MS (ESI⁺) *m/z* = 527.1 [M+Na]⁺; HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₂₀H₂₆N₂O₇NaSClP: 527.0788; found: 527.0785

(Diethoxyphosphoryl) (thiophen-2-yl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (6c, C₁₄H₂₂ClN₂O₇PS₂) was obtained as an colorless oil (92,67 mg, 100% yield); R_f 0.50 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1744 (CO), 1366 and 1155 (SO₂), 1224 and 1018 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 13.89 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (m, 6H, 2CH₃), 3.46 (t, *J*_{HH} = 6.4 Hz, 2H, (CH₂)_{cyc}-NCH₂), 3.55 (t, *J*_{HH} = 6.4 Hz, 2H, CH₂-CH₂-Cl), 3.70 (t, *J*_{HH} = 6.4 Hz, (CH₂)_{cyc}-NCO), 3.91 (t, *J*_{HH} = 6.8 Hz, 2H, CH₂-Cl), 4.14-4.20 (m, 4H, 2CH₂-CH₃), 6.36 (d, *J*_{HP} = 13.6 Hz, 1H, *CH), 6.99-7.01 (dd, *J*₁ = 3.6 Hz, *J*₂ = 5.2 Hz, 1H, H-Ar), 7.29-7.30 (m, 1H, H-Ar), 7.34-7.36 (2t, *J*₁ = 1.2 Hz, *J*₂ = 5.2 Hz, 1H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³*J*_{C-P} = 2.0 Hz, CH₃), 16.4 (d, ³*J*_{C-P} = 3.0 Hz, CH₃), 41.6 (CH₂)_{cyc}-NCO, 43.4 (CH₂-Cl), 45.1 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂, 64.0 (d, ²*J*_{C-P} = 7.0 Hz, CH₂), 64.1 (d, ²*J*_{C-P} = 6.0 Hz, CH₂), 68.5 (d, ¹*J*_{C-P} = 176.0 Hz, *CH), 126.9 (CH-Ar), 127.6 (CH-Ar), 129.1 (CH-Ar), 133.9 (C-Ar), 149.2 (CO) ppm; MS (ESI⁺) *m/z* = 483.0 [M+Na]⁺; HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₄H₂₂N₂O₇NaPS₂Cl: 483.0197; found: 483.0192

(Diethoxyphosphoryl)(furan-2-yl) methyl 5-(2-chloroethyl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide: the product (7c, C₁₄H₂₂ClN₂O₈PS) was obtained as an colorless oil (92,42 mg, 100% yield); R_f 0.52 (DCM/MeOH) (9.8 :0.2); FTIR (KBr): 1719 (CO), 1305 and 1162 (SO₂), 1228 and 1025 (PO) cm⁻¹; ³¹P NMR (161.9 MHz, CDCl₃) δ 13.05 ppm; ¹H NMR (400 MHz, CDCl₃) δ 1.29 (q, *J*_{HH} = 7.2 Hz, 6H, 2CH₃), 3.46 (t, *J*_{HH} = 6.8 Hz, 2H, (CH₂)_{cyc}-NCH₂), 3.56 (t, *J*_{HH} = 6.4 Hz, 2H, CH₂-CH₂-Cl), 3.71 (t, *J*_{HH} = 6.4 Hz, (CH₂)_{cyc}-NCO), 3.92 (t, *J*_{HH} = 6.4 Hz, 2H, CH₂-Cl), 4.18-4.25 (m, 4H, 2CH₂-CH₃), 6.21 (d, *J*_{HP} = 15.2 Hz, 1H, *CH), 6.39 (t, *J*_{HH} = 1.6 Hz, 1H, H-Ar), 6.67 (t, *J*_{HH} = 2.8 Hz, 1H, H-Ar), 7.46 (t, *J*_{HH} = 1.2 Hz, 1H, H-Ar) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 16.3 (d, ³*J*_{C-P} = 4.0 Hz, CH₃), 16.4 (d, ³*J*_{C-P} = 4.0 Hz, CH₃), 41.6 (CH₂)_{cyc}-NCO, 43.5 (CH₂-Cl), 45.1 (CH₂-CH₂-Cl), 48.8 (CH₂)_{cyc}-NCH₂, 63.9 (t, ²*J*_{C-P} = 7.0 Hz, 2CH₂), 65.9 (d, ¹*J*_{C-P} = 175.0 Hz, *CH), 110.9 (CH-Ar), 112.5 (d, *J*_{C-P} = 5.0 Hz, CH-Ar), 143.9 (CH-Ar), 145.8 (C-Ar), 149.2 (d, *J*_{C-P} = 9.0 Hz, CO) ppm; MS (ESI⁺) *m/z* = 467.0 [M+Na]⁺; HRMS (ESI⁺): *m/z* [M+Na]⁺ calcd for C₁₄H₂₂N₂O₈NaPSCl: 467.0419; found: 467.0421

2.5. Crystallographic data

Data collection was performed, at 295(2) K, on a Bruker APEXII diffractometer, CCD area detector equipped with a graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). The crystallographic data and experimental details for structural analysis are summarized in (Table S1, SI). The reported structures were solved by direct methods with SIR2002 [31] to locate all the non-H atoms which were refined anisotropically with SHELXL97 [32] using full matrix least squares on F² procedure from within the WinGX [33] suite of software used to prepare material for publication. All the H atoms were located in difference Fourier maps and were placed in the calculated positions and constrained to ride on their parent atoms.

2.6. Antimicrobial activity

Antimicrobial activity of the selected synthetic compounds (**2b**, **4b**, **6b**, **7b**, **1c**, **3c** and **5c**) were determined using the clinical and reference microorganisms by mean of an agar diffuse on method described by Toty et al [34] and Demoulin et al [35] with some modifications. Briefly, the microbial cell suspensions were prepared and adjusted to an OD of 0.08 to 0.1 read at 625nm, referring to 10⁸. UFC / ml (CLSI, 2007). Each cell suspension was spread uniformly on the Mueller Hinton (MH) agar medium and incubated 20 min at 37 °C allowing the formation of a homogeneous microbial mat. Following this incubation, three paper discs (Whatman No. 3) of 6 mm in diameter were impregnated with either 10μl of synthetic compounds (**2b**, **4b**, **6b**, **7b**, **1c**, **3c** and **5c**), (test disc) and put in contact with the MH agar medium being previously populated with one species or another of the microorganisms. Experimental controls include acetone or antibiotic (gentamycin)/anti-fungus (amphotericin-B) impregnated discs.

The preparations were then incubated overnight at 37 °C and each test was performed in triplicate. The absence of microbial growth results in a clear halo around the disc and the diameter of the zone of inhibition (DZI) were measured.

The solid dilution technique is used and recommended by the institute of clinical and laboratory standards (CLSI, 2007) to assess the sensitivity of micro-aerophilic bacteria to antibacterial agents. The MIC determination tests are carried out according to the standard dilution method, respectively, on semi-solid bikes of the Mueller Hinton (MHA) type for bacteria; and Saboureaud agar recommended for yeasts.

A base 2 dilution range is made, in acetone, from 50 μl of our compounds to test. The range of concentrations thus published is between 1 and 0.03 mg.mL⁻¹. The contents of each tube are immediately returned to a sterile Petri dish after stirring for 15 seconds. 2 μL spots of an inoculum standardized to 10⁸ UFC.mL⁻¹ (i.e. 2.10⁵UFC per spot) are deposited on the agar plates. Gentamycin / amphotericin B is used as a positive control, acetone is used as a negative control. The dishes are incubated for 24 h at 37 °C. The MIC of the synthetic molecules is defined from the first dish in the range devoid of bacterial growth. The test is carried out in three successive technical repetitions.

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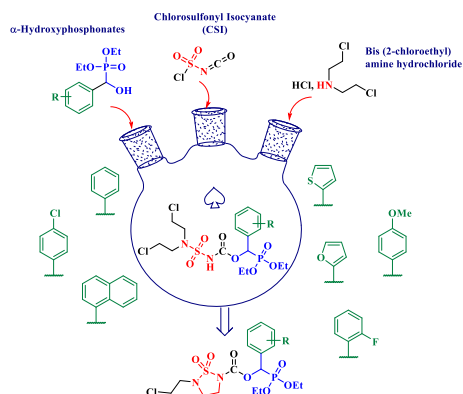
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- [1] A. J. Zych, S. Q. Lam, D. M. Jenkins, R. J. Herr, P. C. Ting, J. F. Lee, R. Kuang, H. Wu, D. W. Kim, R. G. Aslanian, S. Wainhaus, T. A. Black, A. Cacciapuoti, P. M. McNicholas, Y. Xu, S. S. Walker, *Bioorg. Med. Chem. Lett.* **2012**, 22, 4896-4899.
- [2] B. Özgeriş, S. Göksu, L. P. Köse, İ. Gülçin, R. E. Salmas, S. Durdagi, F. Tümer, C. T. Supuran, *Bioorg. Med. Chem.* **2016**, 24, 2318-2329.
- [3] B. Ozgeris, Y. Akbaba, O. Ozdemir, H. Türkez, S. Göksu, *Arch. Med. Res.* **2017**, 48, 513-519.
- [4] J. D. Park, D. H. Kim, S. J. Kim, J. R. Woo, S. E. Ryu, *J. Med. Chem.* **2002**, 45, 5295-5302.
- [5] J. Y. Winum, A. Scozzafava, J. L. Montero, C.T. Supuran, *Med. Res. Rev.* **2006**, 26, 767-792.
- [6] J. Y. Winum, A. Scozzafava, J. L. Montero, C.T. Supuran, *Expert Opin. Ther. Pat.* **2006**, 16, 27-47.

- [7] A. Ax, W. Schaal, L. Vrang, B. Samuelsson, A. Hallberg, A. Karlen, *Bioorg. Med. Chem.* **2005**, *13*, 755-764.
- [8] J. J. Jun, X. Q. Xie, *ChemistrySelect*. **2021**, *6*, 430-469.
- [9] G. Ahlsén, J. Hultén, C. F. Shuman, A. Poliakov, M. T. Lindgren, M. Alterman, B. Samuelsson, A. Hallberg, U. H. Danielson, *Antivir. Chem. Chemother.* **2002**, *13*, 27-37.
- [10] J. J. Jun, D. Duscharla, R. Ummanni, P. R. Hanson, S. V. Malhotra, *ACS. Med. Chem. Lett.* **2021**, *12*, 202-210.
- [11] S. J. Kim, M-H. Jung, K. H. Yoo, J-H. Cho, C-H. Oh, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5815-5818.
- [12] A. Spaltenstein, M. R. Almond, W. J. Bock, D. G. Cleary, E. S. Furfine, R. J. Hazen, W. M. Kazmierski, F. G. Salituro, R. D. Tung, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159-1162.
- [13] T. Sparey, D. Beher, J. Best, M. Biba, J. L. Castro, E. Clarke, J. Hannam, T. Harrison, H. Lewis, A. Madin, M. Shearman, B. Sohal, N. Tsou, C. Welch, J. Wrigley, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4212-4216.
- [14] D. Dou, S. R. Mandadapu, K. R. Alliston, Y. Kim, K-O. Chang, W. C. Groutas, *Eur. J. Med. Chem.* **2012**, *47*, 59-64.
- [15] J. Joossens, O. Mouhamed-Ali, I. El-Sayed, G. Surpateanu, P. Van der Veken, A.-M. Lambeir, B. Setyono-Han, J. A. Foekens, A. Schneider, W. Schmalix, A. Haemers, K. Augustyns, *J. Med. Chem.* **2007**, *50*, 6638-6646.
- [16] Z. Chen, W. Xu, K. Liu, S. Yang, H. Fan, P. S. Bhadury, D-Y. Huang, Y. Zhang, *Molecules*. **2010**, *15*, 9046-9056.
- [17] N. Alimoradi, M. R. Ashrafi-Kooshk, M. Shahlaei, S. Maghsoudi, H. Adibi, R. P. McGeary, R. Khodarahmi, *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 20-28.
- [18] R. Karpowicz, J. Lewkowski, M. Stasiak, A. Czopor, P. Tokarz, A. Król, D. Rogacz, P. Rychter, *Phosphorus, Sulfur Relat. Elem.* **2018**, *193*, 423-436.
- [19] S. Bhagat, M. Supriya, S. Pathak, D. Sriram, A. K. Chakraborti, *Bioorg. Chem.* **2019**, *82*, 246-252.
- [20] K. Bechlem, M. Aissaoui, B. Belhani, K. Otmane Rachedia, S. Bouacida, R. Bahadi, S-E., Djouad, R. Ben Mansour, M. Bouaziz, F. Almalki, T. Ben Hadda, M. Berredjem, *J. Mol. Struct.* **2020**, *1210*, 127990-128016.
- [21] J. Y. Winum, J. L. Bouissière, I. Passagne, A. Evrard, V. Montero, P. Cuq, J. L. Montero, *Eur. J. Med. Chem.* **2003**, *38*, 319-324.
- [22] H. Timmler, R. Wegler, G. Unterstenhafer, Procédé de Fabrication de Dérivés Phosphorylés de Sulfonyle Urethanes, FR1, 403, 523A, 18 June 1965.
- [23] A. Bouzina, K. Bechlem, H. Berredjem, B. Belhani, I. Bechecker, J. Lebreton, M. Le Borgne, Z. Bouaziz, C. Marminon, M. Berredjem, *Molecules*. **2018**, *23*, 1682-169.
- [24] B. Belhani, M. Berredjem, M. Le Borgne, Z. Bouaziz, J. Lebreton, N. E. Aouf, *RSC. Adv.* **2015**, *5*, 39324-39329.
- [25] A. Bouzina, B. Belhani, N-E. Aouf, M. Berredjem, *RSC. Adv.* **2015**, *5*, 46272-46275.
- [26] S. Hessainia, M. Berredjem, S. Ouarna, Z. Cheraiet, N-E. Aouf, *Phosphorus, Sulfur Silicon Relat. Elem.* **2013**, *188*, 719-725.
- [27] H. K'tir, Z. Aouf, T. O. Souk, R. Zerrouki, M. Berredjem, N-E. Aouf, *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 555-559.
- [28] a) S. Boughaba, Z. Aouf, O. Bechiri, M. Mathe-Allainmat, J. Lebreton, N-E. Aouf, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2021**, *196*, 28-35. b) S. Boughaba, S. Bouacida, Z. Aouf, O. Bechiri, N-E. Aouf, *Curr. Org. Chem.* **2018**, *22*, 1335-1341. c) A. Amira, Z. Aouf, H. K'tir, Y. Chemam, R. Ghodbane, R. Zerrouki, N - E. Aouf, *ChemistrySelect*. **2021**, *6*, 6137-6149.
- [29] V. Abramov, *Dokl. Akad. Nauk SSSR*. **1950**, *73*, 487-489.
- [30] Z. Aouf, S. Boughaba, S. Lakrou, O. Bechiri, N-E. Aouf, *Chem. Chem. Technol.* **2020**, *14*, 154-160.
- [31] M.C. Burla, R. Caliendo, M. Camalli, B. Carrozzini, G.L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **2005**, *38*, 381-388.
- [32] G. M. Sheldrick, *J. Acta Cryst.* **2008**, *64*, 112-122.
- [33] L. J. Farrugia, *J. Appl. Cryst.* **2012**, *45*, 849-854.
- [34] A. A. Toty, N. Guessennnd, C. Bahi, A. M. Kra, D. A. Otokore, M. Dosso, *Bull. Soc. r. sci. Liège*. **2013**, *82*, 12-21.
- [35] L. Demoulin, M. Medard, J. Kellens, *J. Kellens, Pathol. Biol.* **1982**, *30*, 201-205.

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Seven *N,N*-bis(2-chloroethyl) sulfamidocarbonyloxymethylphosphonate derivatives and their cyclic compounds were synthesized in three steps (Abramov reaction, carbamoylation-sulfamoylation with CSI reagent and intramolecular cyclisation). A single crystal of compound 3c was designated for single crystal X-ray diffraction analysis. Some compounds were selected to examine the antimicrobial activity against clinical and reference microorganisms.