

Short Note

Naphthalen-2-yl 1-(benzamido(diethoxyphosphoryl)methyl)-1H-1,2,3-triazole-4-carboxylate

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Abstract: We have previously published new biheterocyclic phosphonic α -amino esters of the 1,2,3-triazole-benzimidazole and 1,2,3-triazole-carbazole type. The aim of the present paper was to describe a new phosphonic aminoester bearing a triazole ring substituted in position 5 by an ester group. Thus, according to the same catalytic process used previously, the compound naphthalen-2-yl 1-(benzamido(diethoxyphosphoryl)methyl)-1H-1,2,3-triazole-4-carboxylate was synthesized with an excellent yield and high regioselectivity via the copper (I)-catalyzed alkyne–azide cycloaddition reaction (CuAAC), using diethyl (α -azido(benzamido)methyl)phosphonate (**1**) as a dipole and 2-naphthyl propiolate as a dipolarophile (**2**). The structure of the new compound was fully characterized by 1D (³¹P, ¹H, ¹³C) and 2D (¹H-¹H and ¹H-¹³C) NMR spectroscopy, IR, and HRMS.

Keywords: triazole; α -amino phosphonic ester; 1,3-dipolar cycloaddition; click chemistry; 1D and 2D NMR; HRMS

1. Introduction

Since they were first described in the literature in 1943 by the synthesis of aminomethane phosphonic acid, the study and synthesis of aminophosphonates and their derivatives have continued to proliferate [1]. With these physicochemical properties related to their carboxylic analogs [2], they are known as peptide enzyme inhibitors due to their ability to mimic the transition states of amines and esters in biological processes [3]. The hydrogen acceptor and donor function also make them hold chelating attributes with pharmacological targets [4]. Thus, interesting applications of aminophosphonates have been discovered in several areas of life, ranging from medicine to agrochemistry [5–7]. Their coupling with heterocyclic rings has opened up very interesting avenues in the search for new drugs against cancers [8]. As it happens, phosphonic thieno [2,3-d]pyrimidine derivatives have been recently synthesized and evaluated on human hepatocarcinoma, human gastric carcinoma, and breast cancer cells [9]. It is no longer necessary to discuss their antimicrobial [10], antioxidant [11,12], and antiviral [13] characteristics.

Although they abound in attractive pharmacological properties, methods for their synthesis have not been widely described in scientific journals. According to our research, a few have experimented—the main one being the multicomponent Kabachnik–Fields reaction [14,15] between amines and heterocyclic oxo (aldehyde or ketone) compounds [16]—with trialkyl or dialkyl phosphites. It has been the subject of several publications in

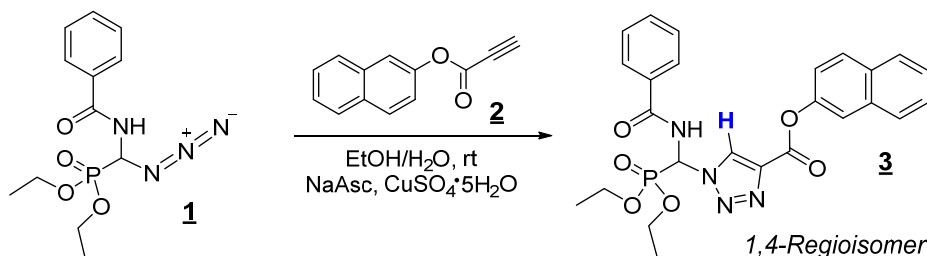
order to improve regioselectivity, reduce reaction times, and use much greener catalysts, which often contain metals [17,18]. Thus remarkable work has been done by previous researchers in our laboratory for the synthesis of triazolic α -amino acid derivatives, using Huisgen's 1,3-dipolar cycloaddition method between an azide and substituted alkyne, giving rise to two regioisomers 1,4 and 1,5 under tedious heating conditions, with rather long reaction times [19–21]. The development of click chemistry, which allows 1,2,3-triazoles to be obtained in a simple and efficient way, has flooded the literature in recent years with their ability to affect the reactivity of biological targets and to influence metabolism and pharmacokinetics [22]. Thus, their hybridization with other pharmacophores such as indole, quinoline, flavone, and other aminoesters have made it possible to evaluate anti-cancer activity [22,23]. For example, Nazariy et al. synthesized a series of triazole molecules, derived from heterocyclic aminoesters [24], showing acceptable efficacy against cancer cells (lung, breast, and prostate cancer). The antiviral activity against the replication of the cantagalo virus was tested on *N*-aminoesters 1,2,3 triazole by Jordão et al. [25]. Recently, the work of Ming-Jie Chu [26] showed an increased efficacy of 1,2,3 triazole derivatives containing the pyrazole ester as inhibitors of topoisomerase II. In addition, some aminophosphonates containing the triazole ring were synthesized [27–29]. They have been the subject of the study of their pharmacological activities such as in the work of Ouahrouch et al. [30] and Makaro et al. [31] on the cytotoxicity of cancer cells.

In the perspective of improving our research work by finding new active formulas, we present in this paper the synthesis of a new triazolic α -aminophosphonate derivative, using the 1,3-dipolar cycloaddition by the “click chemistry” route. In direct connection with the principles of green chemistry and drawing on the reactions found in nature, Sharpless introduced in 2001 the concept of a “chemistry click” [32], which proposes the development and promotion of the use of the most effective and selective reactions possible, in particular those that do not generate by-products. The latter, initiated by Sharpless [33] and his collaborators, has given rise to various applications in the fields of organic synthesis [34–36], functionalization [37] of biomaterials in cell biology [38,39], and the synthesis of biopolymers involved in encapsulation processes [40]. In terms of our study, we prepared diethyl (α -azido(benzamido)methyl)phosphonate (1), which is obtained under dehydrating operating conditions of neutral pH, with an overall yield of 85%, by adopting the strategy of Elachqar et al. [19]. This is composed of six steps, the most strategic of which is the nucleophilic substitution reaction by sodium azide on *N*-benzoylated diethyl α -bromo- α -aminomethylphosphonate. In order to form the triazole cycle, which is in high demand in pharmacology [41], we adopted the catalytic 1,3 dipolar cycloaddition synthesis method between the commercial product, 2-naphthyl propiolate (CAS-91805-17-3), and the phosphonic azide derivative. In very clean and efficient conditions—hence its name of click chemistry [42]—this reaction allowed us to use a less toxic co-solvent, ethanol/water, in equal proportions at room temperature for 12h. We then preferentially used copper(II) sulfate pentahydrate, which is reduced to copper(I) salt by sodium ascorbate, in order to very selectively guide the reaction to the 1,4 regioisomer, namely naphthalene 1-(benzamido(diethoxyphosphoryl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (3) with a 90% yield. In the absence of separation, we were able to purify the cycloadduct by simple recrystallization in anhydrous ethanol. Its molecular structure is confirmed by 1D (^{31}P , ^1H , ^{13}C) and 2D (^1H - ^1H and ^1H - ^{13}C) NMR, infrared, and high-resolution mass spectrometry.

2. Results and Discussion

The key step in our strategy for the synthesis of naphthalene-2-yl 1-(benzamido(diethoxyphosphoryl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (3) was based on the formation of an extremely stable triazole bond between two molecules via a dipolar cycloaddition -1,3 between an azide, diethyl(α -azido(benzamido)methyl)phosphonate (1), and the terminal alkyne, 2-naphthyl propiolate (2) (Scheme1). Thus, we opted for the Huisgen 1,3-dipolar cycloaddition reaction, catalyzed by copper (I) formed in situ by reduction of

the Cu(II) salts ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) by sodium ascorbate. Cu(I) catalysis allowed us to carry out the cycloaddition in a mixture (ethanol/water (1/1)) at room temperature for a reaction time of only 12 h and to selectively obtain 1,4-disubstituted 1,2,3-triazole derivative (**3**), one of the two possible isomers, with an excellent yield of 90% after recrystallization in ethanol.



Scheme 1. Synthetic route for compound (**3**).

It is important to note that, since its discovery independently by the Sharpless [33] and Meldal [43] research teams in 2002, the CuAAC-1,3-dipolar cycloaddition between an alkyne and a copper(I)-catalyzed azide has become one of the major reactions in the chemist's arsenal. The main advantages of this cycloaddition have become clear. This reaction makes it possible to improve the conversion, reduce the reaction time, and carry out the reaction at room temperature. It also tolerates a wide variety of functional groups, is very selective, allows the formation of a rigid and very stable bond between two molecules, and requires little purification because it does not generate any by-products. All these advantages make this reaction very practical to use in all fields of chemical and biological sciences, with many catalytic systems developed and studied.

The structure of the title compound was established on the basis of ^{31}P NMR (Figure 1), ^1H and ^{13}C NMR (Figures 2 and 3), homonuclear (^1H - ^1H) (Figures 4 and 5) and heteronuclear (^1H - ^{13}C) 2D NMR (Figures 6 and 7), infrared spectroscopy (Figure 8), and mass spectrometry (Figure 9). Thus, cycloadduct (**3**) shows in decoupled ^{31}P NMR a single signal at 12.14 ppm (Figure 1A). Meanwhile, in the coupled ^{31}P NMR spectrum (Figure 1B), there is also a single signal centered at 12.15 ppm, but the spread of this signal shows that it is a multiplet due to the coupling of phosphorus with neighboring carbons and hydrogens.

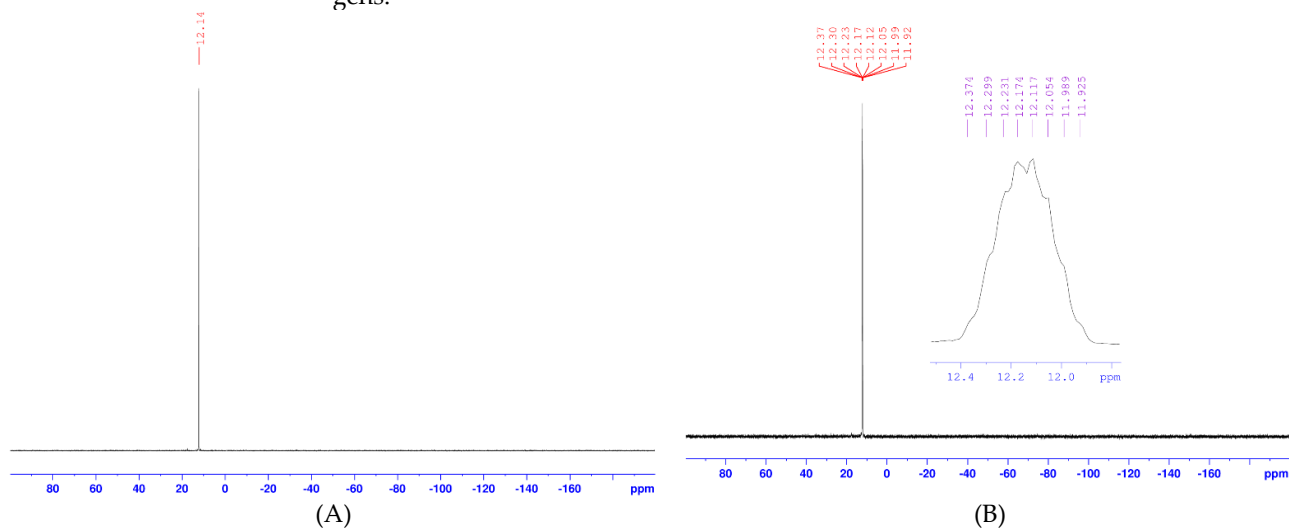


Figure 1. (A). Decoupled ^{31}P NMR spectrum of cycloadduct (**3**). (B) Coupled ^{31}P NMR spectrum of cycloadduct (**3**).

Based on our previous work [34,44], the appearance of a singlet attributable to the triazole proton in position 5, which resonates around 9.04 ppm on the ^1H NMR spectrum (Figure 2) of the cycloadduct (3) compared to that of the azide (1), confirms that the 1,3-dipolar cycloaddition reaction has taken place. Meanwhile, in the ^{13}C J-mod NMR spectrum (Figure 3), a new signal is detected around 158.9 ppm which attests to the presence of the carbonyl carried by the naphthyl.

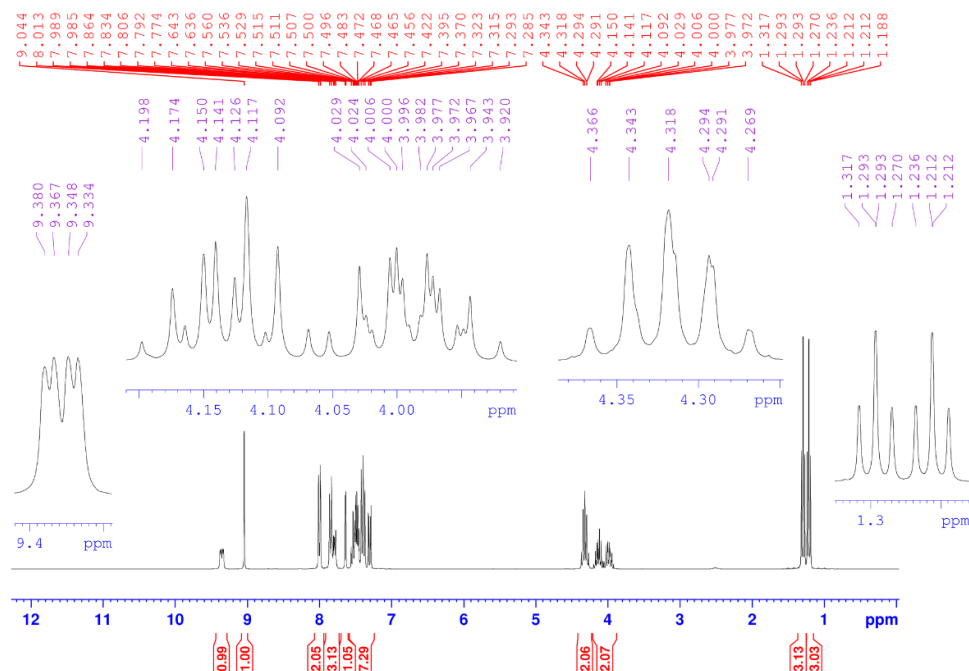


Figure 2. ^1H -NMR spectrum of cycloadduct (3).

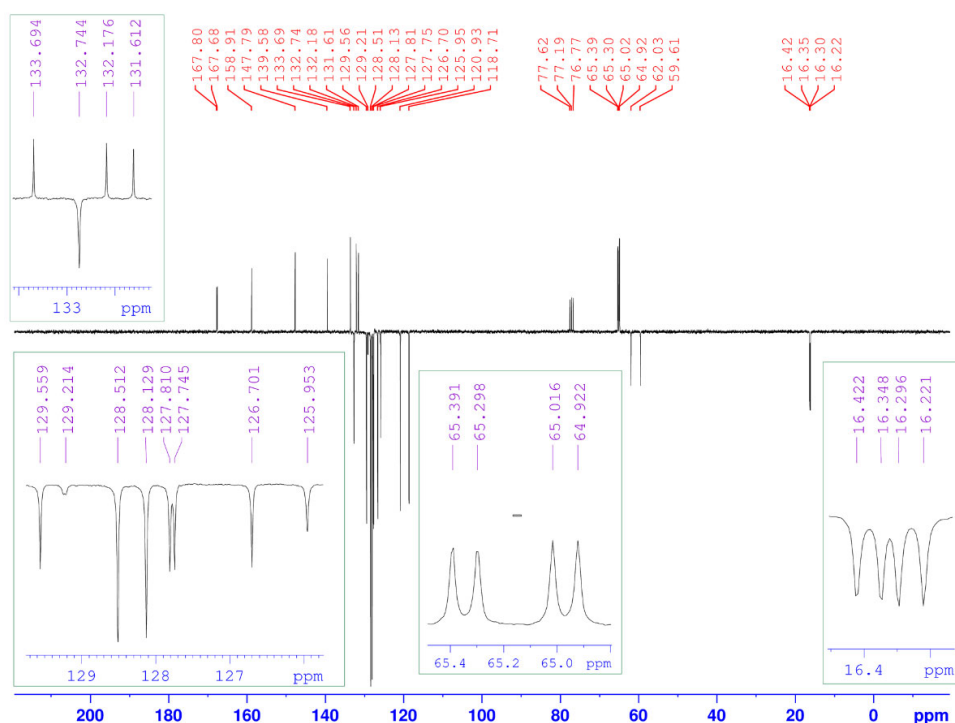


Figure 3. ^{13}C J-mod NMR spectrum of cycloadduct (3).

The analysis of the homonuclear ^1H - ^1H 2D spectrum of compound (3) shows a perfect correlation between neighboring protons (Figures 4 and 5 and Table 1). The two hydrogen atoms of methylene $-\text{CH}_2-$ of the ethoxy group resonate as two split quintuplets because of their different environments [34,35]. This observation was confirmed in both homonuclear and heteronuclear 2D NMR. The definite assignment of the chemical shifts of protons and carbons is shown in Table 1.

Table 1. ^1H (300.13 MHz), ^{13}C (75.47 MHz), and ^{31}P (121.49 MHz) NMR spectral data for the title compound in CDCl_3 , including results obtained by homonuclear 2D shift-correlated COSY and heteronuclear 2D shift-correlated HSQC. Chemical shifts (δ , ppm) and coupling constants (J , Hz, in parenthesis) ^(*).

Position	$\delta(\text{H})$	$\delta(\text{C})$	$\delta(\text{P})$	H-H ^(**)	P-H ^(**)	C-P ^(**)	C-H ^(**)
4	-	139.6	-	-	-	-	-
5	9.04 (1H, s)	129.2	-	H ⁵ -H ⁵	-	-	C ⁵ -H ⁵
6	-	158.9	-	-	-	-	-
7	-	147.8	-	-	-	-	-
8	7.29-7.32 (1H, m)	120.9	-	H ⁸ -H ⁸	-	-	C ⁸ -H ⁸
9	7.77-7.79 (1H, m)	129.6	-	H ⁹ -H ⁹	-	-	C ⁹ -H ⁹
10	-	131.6	-	-	-	-	-
11	7.80-7.86 (1H, m)	127.8	-	H ¹¹ -H ¹¹	-	-	C ¹¹ -H ¹¹
12	7.47-7.51 (1H, m)	126.7	-	H ¹² -H ¹²	-	-	C ¹² -H ¹²
13-14	7.47-7.51 (2H, m)	127.8	-	H ¹³ -H ¹³ H ¹⁴ -H ¹⁴	-	-	C ¹³ -H ¹³ C ¹⁴ -H ¹⁴
15	-	132.2	-	-	-	-	-
16	7.48 (1H, s)	118.7	-	H ¹⁶ -H ¹⁶	-	-	C ¹⁶ -H ¹⁶
17	7.47-7.51 (1H, m)	59.6-65.0 (d, $J_{\text{C-P}} = 182.6$)	-	H ¹⁷ -H ¹⁷ H ¹⁷ -H ²¹	P ¹⁸ -H ¹⁷	C ¹⁷ -P ¹⁸	C ¹⁷ -H ¹⁷
18	-	-	12.14	-	P ¹⁸ -H ¹⁷ P ¹⁸ -H ²¹	P ¹⁸ -C ¹⁷ P ¹⁸ -C ¹⁹ P ¹⁸ -C ^{19'} P ¹⁸ -C ²⁰ P ¹⁸ -C ^{20'} P ¹⁸ -C ²²	-
19	3.92-4.15 (2H, m)	64.9-65.3 (d, $J_{\text{C-P}} = 28.5$)	-	2H ¹⁹ -2H ¹⁹ 2H ¹⁹ -3H ²⁰	-	C ¹⁹ -P ¹⁸	C ¹⁹ -2H ¹⁹
19'	4.29-4.34 (2H, q, $J = 7.2$)	65.0-65.4 (d, $J_{\text{C-P}} = 27.9$)	-	2H ^{19'} -2H ^{19'} 2H ^{19'} -3H ^{20'}	-	C ^{19'} -P ¹⁸	C ^{19'} -2H ^{19'}
20	1.21 (3H, t, $J = 7.2$)	16.2-16.3 (d, $J_{\text{C-P}} = 6.0$)	-	3H ²⁰ -3H ²⁰ 3H ²⁰ -2H ¹⁹	-	C ²⁰ -P ¹⁸	C ²⁰ -3H ²⁰
20'	1.29 (3H, t, $J = 7.2$)	16.3-16.4 (d, $J_{\text{C-P}} = 5.3$)	-	3H ^{20'} -3H ^{20'} 3H ^{20'} -2H ¹⁹	-	C ^{20'} -P ¹⁸	C ^{20'} -3H ^{20'}
21	9.3-9.5 (1H, dd, $J_1 = 4.2$; $J_2 = 9.9$)	-	-	H ²¹ -H ²¹ H ²¹ -H ¹⁷	P ¹⁸ -H ²¹	-	-
22	-	167.6-167.8 (d, $J_{\text{C-P}} = 9.0$)	-	-	-	C ²² -P ¹⁸	-
23	-	133.7	-	-	-	-	-
24; 28	7.98-8.01 (2H, m)	128.5	-	H ²⁴ -H ²⁴ H ²⁸ -H ²⁸	-	-	C ²⁴ -H ²⁴ C ²⁸ -H ²⁸
26	7.51-7.56 (1H, m)	132.7	-	H ²⁶ -H ²⁶	-	-	C ²⁶ -H ²⁶
25; 27	7.47-7.51 (2H, m)	128.1	-	H ²⁵ -H ²⁵ H ²⁷ -H ²⁷	-	-	C ²⁵ -H ²⁵ C ²⁷ -H ²⁷

^(*) Chemical shifts and coupling constants (J) obtained of 1D ^1H and ^{13}C NMR spectra, ^(**) Homonuclear and heteronuclear correlation.

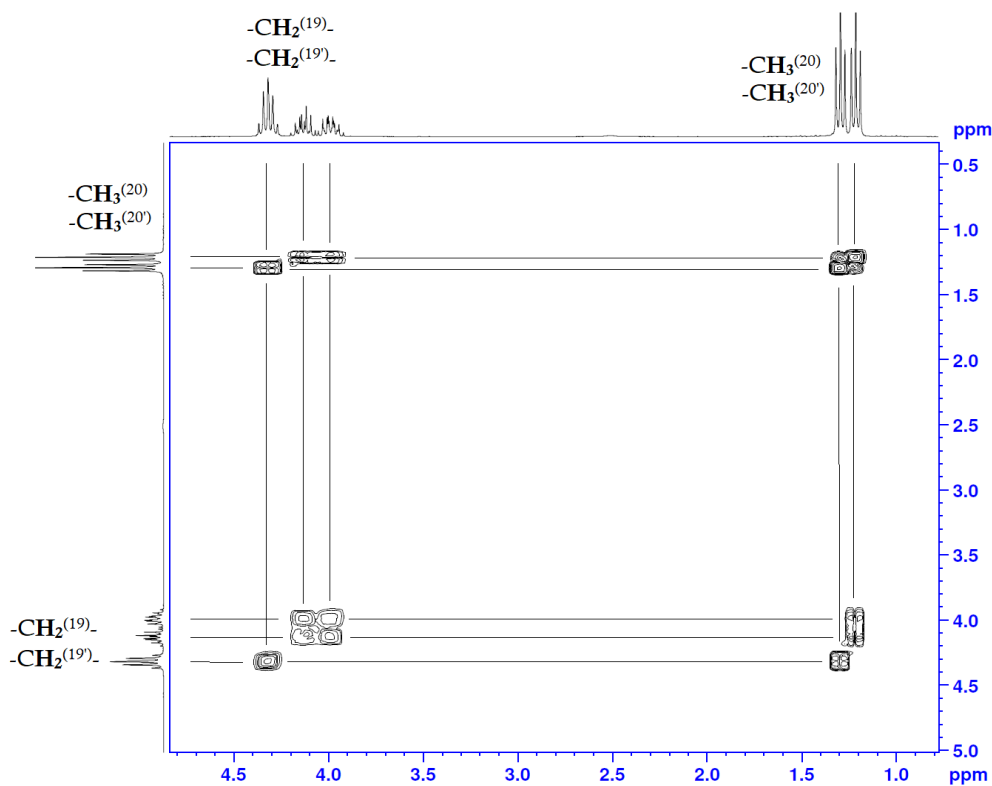


Figure 4. Two-dimensional COSY spectrum of the cycloadduct (3) (Aliphatic part).

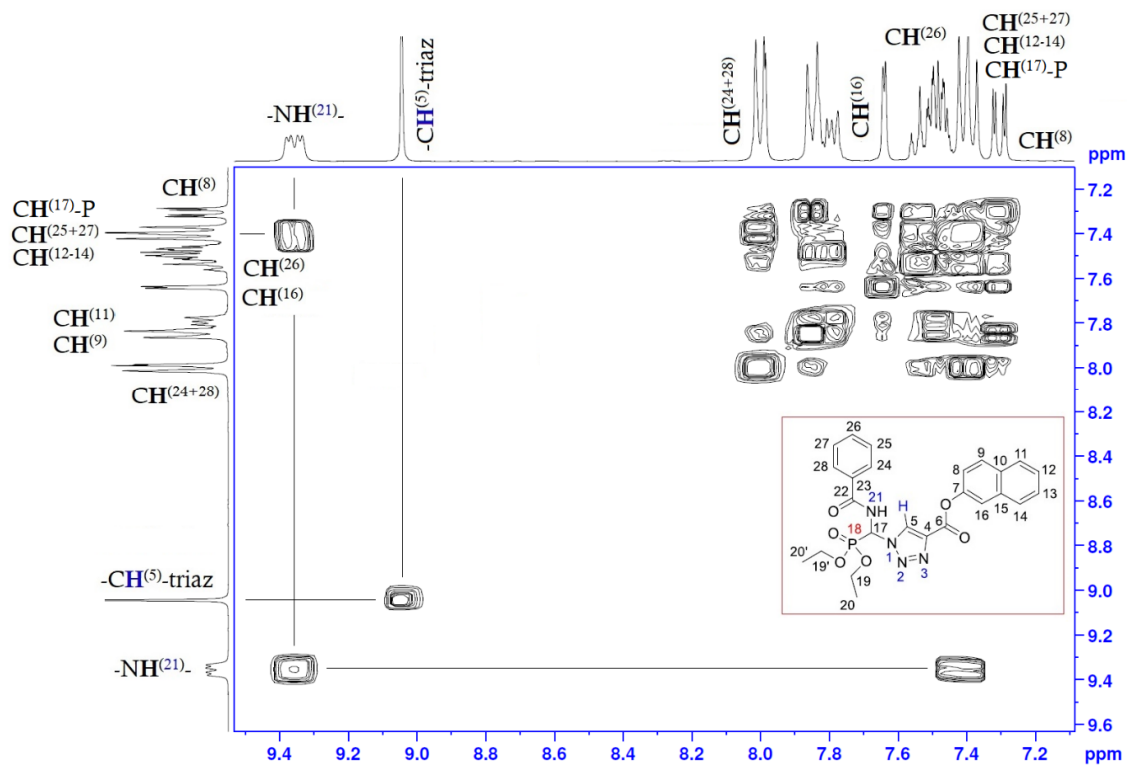


Figure 5. Two-dimensional COSY spectrum of the cycloadduct (3) (Aromatic part).

The interpretation of the heteronuclear 2D-NMR spectrum of the cycloadduct shows a perfect correlation between protons and adjacent carbons, on the one hand, and between protons and neighboring carbons and between phosphorus and neighboring carbons and hydrogens, on the other hand (Figures 6 and 7 and Table 1).

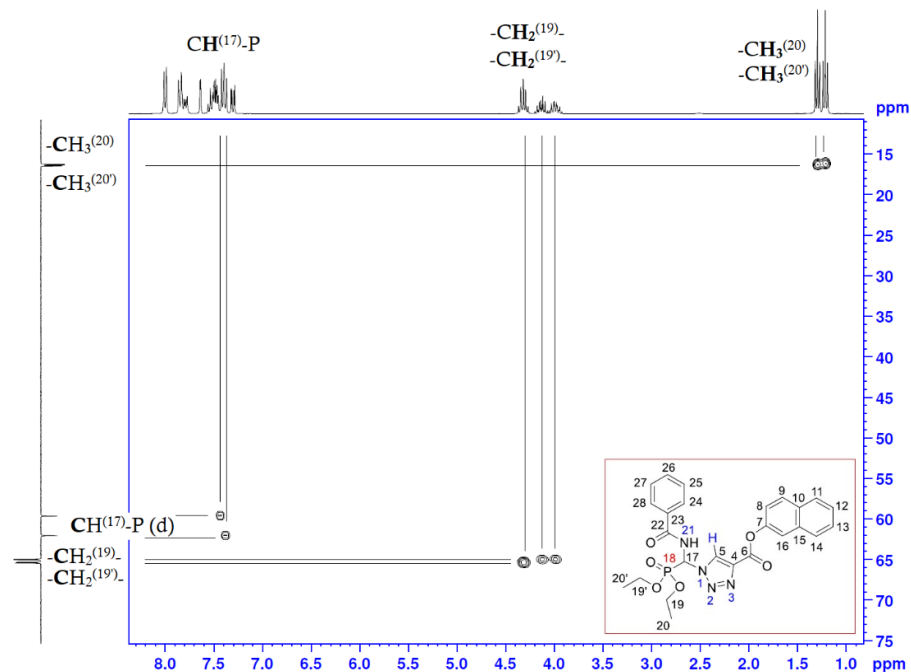


Figure 6. Two-dimensional HSQC spectrum of the cycloadduct (3) (Aliphatic part).

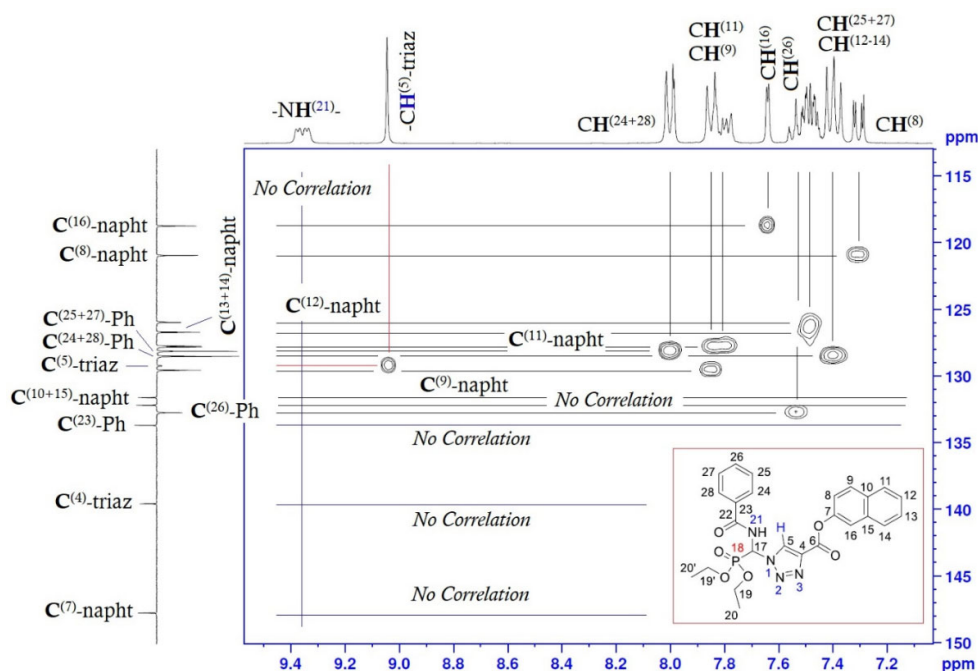


Figure 7. Two-dimensional HSQC spectrum of the cycloadduct (3) (Aromatic part).

According to the 2D COSY spectrum (Figure 4), the amidic proton shows a good homonuclear correlation with the -CH-P proton. Meanwhile, the 2D HSQC spectrum (Figure 6) shows that this last carbon is in the form of a doublet with $J_{C-P} = 182.6$ Hz thanks to its coupling with the phosphorus atom.

The 2D HSQC spectrum (Figure 7) exhibits that each carbon is correlated with its neighboring hydrogen atom and that the amidic proton is uncorrelated. The same spectrum also shows that the quaternary carbons, namely C4, C7, C10, and C15, in addition to C23, do not show any correlation.

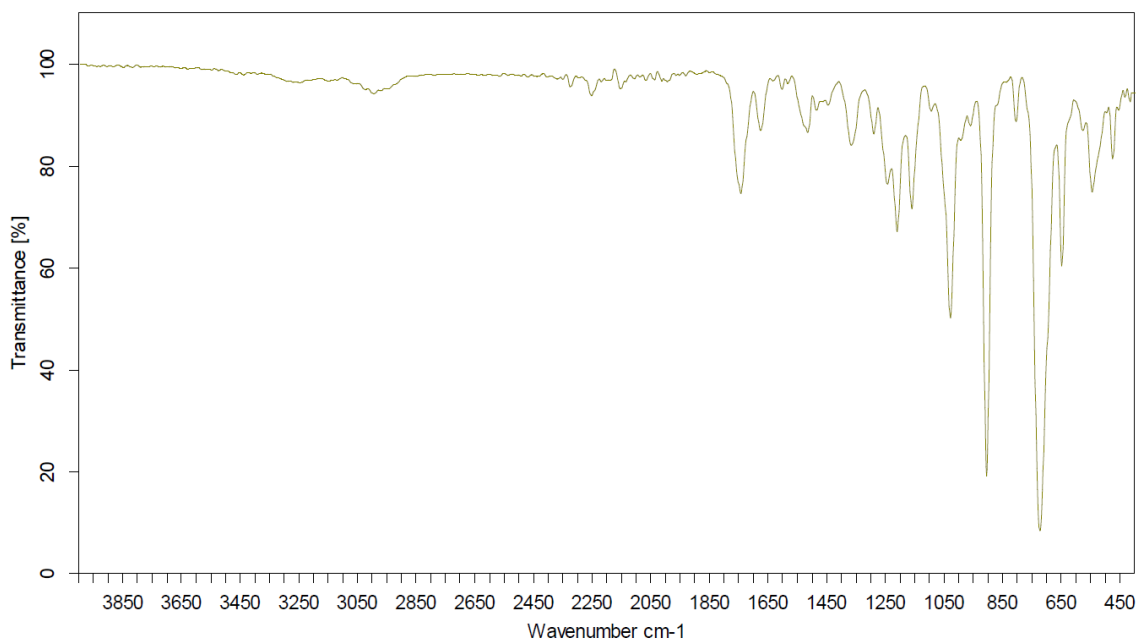


Figure 8. IR spectrum of the cycloadduct (3).

In the IR spectrum (Figure 8), the absorption bands between 1650 and 1750 cm^{-1} were assigned to two C=O stretching vibrations. This spectrum also exhibits a strong band at 1250 cm^{-1} , corresponding to the valence vibrations of the $\nu(\text{P}=\text{O})$ function, and a medium band at 1050 cm^{-1} , associated with the valence vibrations of the $\nu(\text{P}-\text{O}-\text{C})$ link. In addition, the C-N stretching vibrations were observed at 1245 and 1290 cm^{-1} .

The exact mass of $[\text{M} + \text{Na}]^+$ ion, determined by ESI-HRMS (Figure 9), was found to be $531,14039$ ($531,14039$ as calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_4\text{O}_6\text{PNa}^+$).

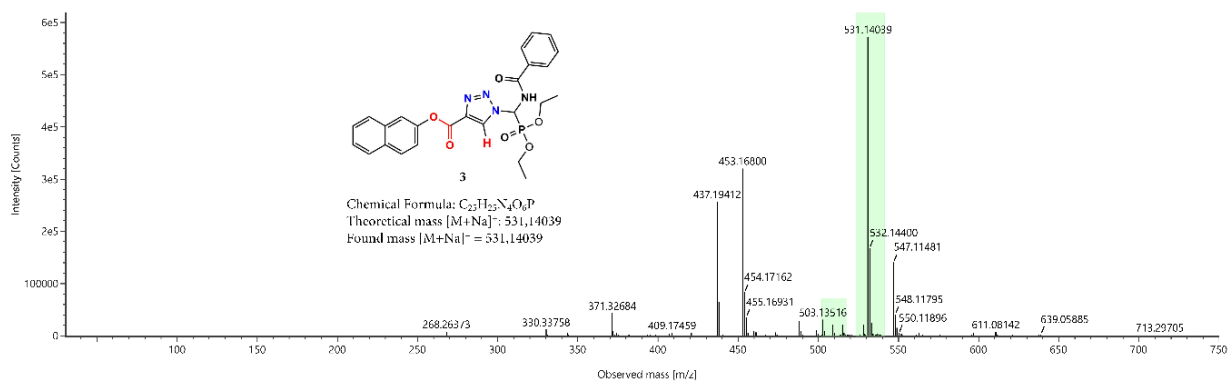


Figure 9. HRMS spectrum of the cycloadduct (3).

All these interpretations allowed us to propose for the cycloadduct (3) the nomenclature of the 1,4-regioisomer, which is naphthalen-2-yl 1-(benzamido(diethoxyphosphoryl)methyl)-1*H*-1,2,3-triazole-4-carboxylate.

3. Materials and Methods

All the reagents and solvents were commercial products, originating from Sigma-Aldrich. They were used without any prior purification. The melting point was measured using an electrothermal melting point instrument without correction. NMR analyses were performed on a Bruker AM 300 spectrometer (^1H operating at 300.13 MHz, ^{13}C operating at 75.47 MHz). The solvent used is specified for each compound, and the chemical shifts (δ) are expressed relative to the tetramethylsilane (TMS), using as internal reference the residual signals of the deuterated solvents. The coupling constants (J) are expressed in hertz (Hz), and the abbreviations used to define the different types of resonances are: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, and dd = split doublet. Thin-layer chromatography was carried out on a Merck 60F₂₅₄ silica plate. The spots were revealed in UV at 254 nm and 365 nm, or with a p-anisaldehyde or iodine solution. Column chromatography was carried out on silica gel (silica Fluka gel, particle size of 40 to 63 μm , 230-400 mesh). Product to be purified was adsorbed on silica (solid deposit) or dissolved in the eluent (liquid deposit) and then deposited on silica. The IR spectrum was produced in a KBr pellet, at room temperature, using an FTIR Bruker Vertex 70 spectrometer (Cit  de l'Innovation, USMBA, Fez, Morocco). High-resolution mass spectrum was recorded with Vion IMS QToF Ion Mobility Quadrupole Time-of-flight Mass Spectrometry (Waters) with electrospray ionization ESI eighter in positive mode. The compound was initially dissolved in CDCl_3 and further diluted 1:100 with acetonitrile. MS spectra processing and isotope model simulations were performed with the UNIFI workstation.

In total, 2.2 mmol of diethyl (α -azido(benzamido)methyl)phosphonate (1) and 2.2 mmol of 2-naphthyl propiolate (2) were stirred in 10 mL of an ethanol–water mixture (1:1), and 0.05 equivalents of copper sulfate pentahydrate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) and 0.1 equivalent of sodium ascorbate (Na-Asc) were added. TLC analysis indicated complete consumption of the reagents after 12 h of stirring at room temperature. After filtration of the formed precipitate, the solvent was evaporated under reduced pressure and the reaction crude was washed with water and extracted with methylene chloride. The organic phase was then dried with sodium sulfate, and the solvent was removed under reduced pressure. The resulting yellowish-white powder was recrystallized in anhydrous ethanol to obtain a pure white powder product.

*Naphthalen-2-yl 1-(benzamido(diethoxyphosphoryl)methyl)-1*H*-1,2,3-triazole-4-carboxylate* (3). Yield = 92% (white solid); R_f = 0.41 (ethyl acetate/hexane 3/2); m.p. = 169–170 $^\circ\text{C}$; ^1H -NMR (300.13 MHz, CDCl_3) δ_{H} , ppm: 1.21 (t, 3H, $-\text{CH}_2-\text{CH}_3$, $^3J = 7.2$ Hz), 1.29 (t, 3H, $-\text{CH}_2-\text{CH}_3$, $^3J = 7.2$ Hz), 3.92–4.15 (m, 2H, $-\text{O}-\text{CH}_2-\text{CH}_3$), 4.29–4.34 (q, 2H, $-\text{O}-\text{CH}_2-\text{CH}_3$, $^3J = 7.2$ Hz), 7.29–7.32 (m, 1H, $1\text{H}_{\text{naph}(8)}$), 7.47–7.51 (m, 5H_{arom} ($3\text{H}_{\text{naph}(12-14)} + 2\text{H}_{\text{benz}(25+27)}$) + 1H, $-\text{CH}-\text{P}$), 7.48 (s, 1H, $1\text{H}_{\text{naph}(16)}$), 7.51–7.56 (m, 1H, $1\text{H}_{\text{benz}(26)}$), 7.77–7.86 (m, 2H, $2\text{H}_{\text{naph}(9+11)}$), 7.98–8.01 (m, 2H, $2\text{H}_{\text{benz}(24+28)}$), 9.04 (s, 1H, $-\text{CH}_{\text{triaz}(5)}$), 9.3–9.5 (dd, 1H, $-\text{NH}-$, $J_1 = 4.2$ Hz, $J_2 = 9.9$ Hz). ^{13}C -NMR (75.47 MHz, CDCl_3) δ_{C} , ppm: 16.2–16.3 (d, 1C, $-\text{CH}_3$, $J_{\text{C-P}} = 6.0$ Hz), 16.3–16.4 (d, 1C, $-\text{CH}_3$, $J_{\text{C-P}} = 6.0$ Hz), 59.6–65.0 (d, 1C, $-\text{CH}-\text{P}$, $J_{\text{C-P}} = 182.6$ Hz), 64.9–65.3 (d, 1C, $-\text{CH}_2-$, $J_{\text{C-P}} = 28.5$ Hz), 65.0–65.4 (d, 1C, $-\text{CH}_2-$, $J_{\text{C-P}} = 27.9$ Hz), 118.7 (1C, $1\text{C}_{\text{naph}(16)}$), 120.9 (1C, $1\text{C}_{\text{naph}(8)}$), 126.7 (1C, $1\text{C}_{\text{naph}(12)}$), 127.8 (3C, $3\text{C}_{\text{naph}(11+12+14)}$), 128.5 (2C, $2\text{C}_{\text{benz}(24+28)}$), 129.2 (1C, $1\text{C}_{\text{triaz}(5)}$), 129.6 (1C, $1\text{C}_{\text{naph}(9)}$), 131.6 (1C, $1\text{C}_{\text{naph}(10)}$), 132.2 (1C, $1\text{C}_{\text{naph}(15)}$), 132.7 (1C, $1\text{C}_{\text{benz}(26)}$), 133.7 (1C, $1\text{C}_{\text{benz}(23)}$), 139.6 (1C, $1\text{C}_{\text{triaz}(4)}$), 147.8 (1C, $1\text{C}_{\text{naph}(7)}$), 158.9 (1C, $1\text{CO}_{(6)}$), 167.6–167.8 (d, 1C, $1\text{CO}_{(22)}$, $J_{\text{C-P}} = 9.0$ Hz). IR ($\nu(\text{cm}^{-1})$): 3050 (N-H), 1750 (C=O), 1650 (C=O), 1250 (P=O), 1245-1290 (C-N), 1050 (P-O). HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_4\text{O}_6\text{PNa}^+$ 531,14039, found 531,14039.

4. Conclusions

In summary, the 1,3-dipolar cycloaddition reaction between the azide (**1**) and the terminal heterocyclic alkyne (**2**) provides regioselective access to the 1,4-isomer with an excellent yield. The identification and structure determination of the obtained product was carried out by different spectroscopic methods also based on literature data. The evaluation of the anticorrosion and biological activities of the synthesized product is the subject of ongoing work.

Supplementary Materials: The following materials are available online, Figure S1: Decoupled ^{31}P NMR spectrum of cycloadduct (**3**). Figure S2: Coupled ^{31}P NMR spectrum of cycloadduct (**3**). Figure S3: ^1H -NMR spectrum of cycloadduct (**3**). Figure S4: ^{13}C J-mod NMR spectrum of cycloadduct (**3**). Figure S5: ^1H - ^1H COSY NMR spectrum of compound (**3**). Figure S6: Expanded region of ^1H - ^1H COSY NMR spectrum (0.5–5.0 ppm and 0.5–5.0 ppm) of cycloadduct (**3**). Figure S7: Expanded region of ^1H - ^1H COSY NMR spectrum (7.2–9.5 ppm and 7.2–9.5 ppm) of cycloadduct (**3**). Figure S8: Expanded region of ^1H - ^1H COSY NMR spectrum (7.25–8.1 ppm and 7.25–8.1 ppm) of cycloadduct (**3**). Figure S9: ^1H - ^{13}C HSQC NMR spectrum of cycloadduct (**3**). Figure S10: Expanded region of ^1H - ^{13}C HSQC NMR spectrum (1.0–8.0 ppm and 15–75 ppm) of cycloadduct (**3**). Figure S11: Expanded region of ^1H - ^{13}C HSQC NMR spectrum (7.1–9.5 ppm and 113–150 ppm) of cycloadduct (**3**). Figure S12: IR spectrum of cycloadduct (**3**). Figure S13: LC-HRMS Chromatogram of cycloadduct (**3**). Figure S14: HRMS spectrum of cycloadduct (**3**) showing a $[\text{M} + \text{H}]^+$ ion at m/z 508,15953. Figure S15: HRMS spectrum of cycloadduct (**3**) showing a $[\text{M} + \text{Na}]^+$ ion at m/z 531,14039.

Author Contributions: S.A.K.F. performed the experiments; H.F., B.L, and A.A. conceived and designed the experiments; M.A. realized and collected NMR and HRMS spectra; O.K., S.H., S.B., Y.A., and A.A. analyzed the data; Y.A. and A.A. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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References

1. Kafarski, P.; Lejczak, B. BIOLOGICAL ACTIVITY OF AMINOPHOSPHONIC ACIDS. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215. <https://doi.org/10.1080/10426509108029443>.
2. Macchiarulo, A.; Pellicciari, R. Exploring the Other Side of Biologically Relevant Chemical Space: Insights into Carboxylic, Sulfonic and Phosphonic Acid Bioisosteric Relationships. *J. Mol. Graph. Model.* **2007**, *26*, 728–739. <https://doi.org/10.1016/j.jmgm.2007.04.010>.
3. Turhanen, P.A.; Demadis, K.D.; Kafarski, P. Editorial: Phosphonate Chemistry in Drug Design and Development. *Front. Chem.* **2021**, *9*, 755–758. <https://doi.org/10.3389/fchem.2021.695128>.
4. Olszewski, T.K. Synthesis of heterocyclic substituted phosphonates, phosphonic and phosphinic acids. *Targets Heterocycl. Syst.* **2020**, *24*, 84. <https://doi.org/10.17374/targets.2021.24.84>.
5. Awad, M.K.; Abdel-Aal, M.F.; Atlam, F.M.; Hekal, H.A. Molecular Docking, Molecular Modeling, Vibrational and Biological Studies of Some New Heterocyclic α -Aminophosphonates. *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.* **2019**, *206*, 78–88. <https://doi.org/10.1016/j.saa.2018.07.083>.
6. López-Francés, A.; Del Corte, X.; Martínez De Marigorta, E.; Palacios, F.; Vicario, J. Ugi Reaction on α -Phosphorated Ketimines for the Synthesis of Tetrasubstituted α -Aminophosphonates and Their Applications as Antiproliferative Agents. *Molecules* **2021**, *26*, 1654. <https://doi.org/10.3390/molecules26061654>.

7. Zhou, X.; Ye, Y.; Liu, S.; Shao, W.; Liu, L.; Yang, S.; Wu, Z. Design, Synthesis and Anti-TMV Activity of Novel α -Aminophosphonate Derivatives Containing a Chalcone Moiety That Induce Resistance against Plant Disease and Target the TMV Coat Protein. *Pestic. Biochem. Physiol.* **2021**, *172*, 104749. <https://doi.org/10.1016/j.pestbp.2020.104749>.
8. Balam, S.K.; Soora Harinath, J.; Krishnammagari, S.K.; Gajjala, R.R.; Polireddy, K.; Baki, V.B.; Gu, W.; Valasani, K.R.; Avula, V.K.R.; Vallela, S.; et al. Synthesis and Anti-Pancreatic Cancer Activity Studies of Novel 3-Amino-2-Hydroxybenzofused 2-Phospha- γ -Lactones. *ACS Omega* **2021**, *6*, 11375–11388. <https://doi.org/10.1021/acsomega.1c00360>.
9. Guo, Y.-C.; Li, J.; Ma, J.-L.; Yu, Z.-R.; Wang, H.-W.; Zhu, W.-J.; Liao, X.-C.; Zhao, Y.-F. Synthesis and Antitumor Activity of α -Aminophosphonate Derivatives Containing Thieno[2,3-d]Pyrimidines. *Chin. Chem. Lett.* **2015**, *26*, 755–758. <https://doi.org/10.1016/j.ccllet.2015.03.026>.
10. Abdel-Megeed, M.F.; Badr, B.E.; Azaam, M.M.; El-Hiti, G.A. Synthesis and Antimicrobial Activities of a Novel Series of Heterocyclic α -Aminophosphonates. *Arch. Pharm.* **2012**, *345*, 784–789. <https://doi.org/10.1002/ardp.201200109>.
11. Tellamekala, S.; Gundluru, M.; Sarva, S.; Nadiveedhi, M.R.; Sudileti, M.; Allagadda, R.; Chippada, A.R.; Cirandur, S.R. Meglumine Sulfate-Catalyzed One-Pot Green Synthesis and Antioxidant Activity of α -Aminophosphonates. *Synth. Commun.* **2019**, *49*, 563–575. <https://doi.org/10.1080/00397911.2018.1563795>.
12. Thaslim Basha, S.; Sudhamani, H.; Rasheed, S.; Venkateswarlu, N.; Vijaya, T.; Naga Raju, C. Microwave-Assisted Neat Synthesis of α -Aminophosphonate/Phosphinate Derivatives of 2-(2-Aminophenyl)Benzothiazole as Potent Antimicrobial and Antioxidant Agents. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, *191*, 1339–1343. <https://doi.org/10.1080/10426507.2016.1192629>.
13. Zhang, P.; Tang, C.; Chen, Z.; Wang, B.; Wang, X.; Jin, L.; Yang, S.; Hu, D. Design, Synthesis, and Antiviral Activity of α -Aminophosphonates Bearing a Benzothioephene Moiety. *Phosphorus Sulfur Silicon Relat. Elem.* **2014**, *189*, 530–540. <https://doi.org/10.1080/10426507.2013.829837>.
14. Bazine, I.; Cheraiet, Z.; Bensegueni, R.; Bensouici, C.; Boukhari, A. Synthesis, Antioxidant and Anticholinesterase Activities of Novel Quinoline—Aminophosphonate Derivatives. *J. Heterocycl. Chem.* **2020**, *57*, 2139–2149. <https://doi.org/10.1002/jhet.3933>.
15. Varga, P.R.; Keglevich, G. Synthesis of α -Aminophosphonates and Related Derivatives; The Last Decade of the Kabachnik–Fields Reaction. *Molecules* **2021**, *26*, 2511. <https://doi.org/10.3390/molecules26092511>.
16. Hamed, M.A.; Shaban, E.; Kafafy, H.; El Gokha, A.A.A.; El Sayed, I. Synthesis and Characterization of Novel Azo Disperse Dyes Containing α -Amino Phosphonate and Their Dyeing Performance on Polyester Fabric. *Egypt. J. Chem.* **2017**, *60*, 4–8. <https://doi.org/10.21608/ejchem.2017.1562.1122>.
17. Kaur, G.; Shamim, M.; Bhardwaj, V.; Gupta, V.K.; Banerjee, B. Mandelic Acid Catalyzed One-Pot Three-Component Synthesis of α -Aminonitriles and α -Aminophosphonates under Solvent-Free Conditions at Room Temperature. *Synth. Commun.* **2020**, *50*, 1545–1560. <https://doi.org/10.1080/00397911.2020.1745844>.
18. Guezane-Lakoud, S.; Toffano, M.; Aribi-Zouiouche, L. Promiscuous lipase catalyzed a new P-C bond formation: Green and efficient protocol for one-pot synthesis of α -aminophosphonates. *Heteroat. Chem.* **2017**, *28*, e21408. doi:10.1002/hc.21408.
19. Elachqar, A.; El Hallaoui, A.; Roumestant, M.L.; Viallefont, P. Synthesis of Heterocyclic α -Aminophosphonic Acids. *Synth. Commun.* **1994**, *24*, 1279–1286. doi:10.1080/00397919408011729.
20. Achamlale, S.; Mabrouk, H.; Elachqar, A.; El Hallaoui, A.; El Hajji, S.; Alami, A.; Bellan, J.; Mazières, M.R.; Wolf, J.G.; Pierrot, M. Synthesis and Thermal Isomerization of Carboxylic and Phosphonic α -Aminoesters Substituted With a Triazole Ring. *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 357–367. <https://doi.org/10.1080/10426500600919959>.
21. Boukallaba, K.; Elachqar, A.; El Hallaoui, A.; Alami, A.; El Hajji, S.; Labriti, B.; Martinez, J.; Rolland, V. Synthesis of New α -Heterocyclic α -Aminophosphonates. *Phosphorus Sulfur Silicon Relat. Elem.* **2006**, *181*, 819–823. <https://doi.org/10.1080/10426500500272046>.
22. Xu, Z.; Zhao, S.-J.; Liu, Y. 1,2,3-Triazole-Containing Hybrids as Potential Anticancer Agents: Current Developments, Action Mechanisms and Structure-Activity Relationships. *Eur. J. Med. Chem.* **2019**, *183*, 111700. <https://doi.org/10.1016/j.ejmech.2019.111700>.
23. Taha, M.A.M.; El-Badry, S.M. Antimicrobial Assessment of Some Heterocyclic Compounds Utilizing Ethyl 1-Aminotetrazole-5-Carboxylate. *J. Korean Chem. Soc.* **2010**, *54*, 414–418. <https://doi.org/10.5012/jkcs.2010.54.4.414>.
24. Pokhodylo, N. Synthesis of 1,2,3-Triazole Derivatives and Evaluation of Their Anticancer Activity. *Sci. Pharm.* **2013**, *81*, 663–676. <https://doi.org/10.3797/scipharm.1302-04>.
25. Jordão, A.K.; Afonso, P.P.; Ferreira, V.F.; de Souza, M.C.B.V.; Almeida, M.C.B.; Beltrame, C.O.; Paiva, D.P.; Wardell, S.M.S.V.; Wardell, J.L.; Tiekink, E.R.T.; et al. Antiviral Evaluation of N-Amino-1,2,3-Triazoles against Cantagalo Virus Replication in Cell Culture. *Eur. J. Med. Chem.* **2009**, *44*, 3777–3783. <https://doi.org/10.1016/j.ejmech.2009.04.046>.
26. Chu, M.-J.; Wang, W.; Ren, Z.-L.; Liu, H.; Cheng, X.; Mo, K.; Wang, L.; Tang, F.; Lv, X.-H. Discovery of Novel Triazole-Containing Pyrazole Ester Derivatives as Potential Antibacterial Agents. *Molecules* **2019**, *24*, 1311. <https://doi.org/10.3390/molecules24071311>.
27. Danne, A.B.; Akolkar, S.V.; Deshmukh, T.R.; Siddiqui, M.M.; Shingate, B.B.A.J. *Iran. Chem. Soc.* **2019**, *16*, 953–961. <https://doi.org/shaik>.
28. Vorobyeva, D.V.; Karimova, N.M.; Vasilyeva, T.P.; Osipov, S.N.; Shchetnikov, G.T.; Odinets, I.L.; Rösenthaller, G.-V. Synthesis of Functionalized α -CF₃- α -Aminophosphonates via Cu (I)-Catalyzed 1, 3-Dipolar Cycloaddition. *J. Fluor. Chem.* **2010**, *131*, 378–383.
29. Tripolszky, A.; Tóth, E.; Szabó, P.T.; Hackler, L.; Kari, B.; Puskás, L.G.; Bálint, E. Synthesis and In Vitro Cytotoxicity and Antibacterial Activity of Novel 1,2,3-Triazol-5-Yl-Phosphonates. *Molecules* **2020**, *25*, 2643. <https://doi.org/10.3390/molecules25112643>.

30. Ouahrouch, A.; Taourirte, M.; Schols, D.; Snoeck, R.; Andrei, G.; Engels, J.W.; Lazrek, H.B. Design, Synthesis, and Antiviral Activity of Novel Ribonucleosides of 1,2,3-Triazolylbenzyl-aminophosphonates. *Arch. Pharm.* **2016**, *349*, 30–41. <https://doi.org/10.1002/ardp.201500292>.
31. Makarov, M.V.; Rybalkina, E.Y.; Khrustalev, V.; Roeschenthaler, G.V. Modification of 3,5-Bis(Arylidene)-4-Piperidone Pharmacophore by Phosphonate Group Using 1,2,3-Triazole Cycle as a Linker for the Synthesis of New Cytostatics. *Med. Chem. Res.* **2015**, *24*, 1753–1762. <https://doi.org/10.1007/s00044-014-1262-z>.
32. Kolb, H.C.; Finn, M.G.; Sharpless, K.B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
33. Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, K.B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes. *Angew. Chemie. Int. Ed.* **2002**, *41*, 2596–2599. [https://doi.org/10.1002/1521-3773\(20020715\)41:14<2596::AID-ANIE2596>3.0.CO;2-4](https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4).
34. Khadir Fall, S.A.; Achamlale, S.; Aouine, Y.; Nakkabi, A.; Faraj, H.; Alami, A. Diethyl [(4-((9H-Carbazol-9-Yl)Methyl)-1H-1,2,3-Triazol-1-Yl)(Benzamido)Methyl]Phosphonate. *Molbank* **2020**, 2020, M1167. <https://doi.org/10.3390/M1167>.
35. Khadir, F.S.A.; Boukhssas, S.; Achamlale, S.; Aouine, Y.; Nakkabi, A.; Faraj, H.; Alami, A. Synthesis and Characterization of the Structure of Diethyl [(4-((1H-Benzo[d]Imidazol-1-Yl)Methyl)-1H-1,2,3-Triazol-1-Yl)(Benzamido)Methyl]Phosphonate Using 1D and 2D NMR Experiments. *Eur. J. Adv. Chem. Res.* **2021**, *2*, 1–7. <https://doi.org/10.24018/ejchem.2021.2.1.42>.
36. Dioukhane, K.; Aouine, Y.; Boukhssas, S.; Nakkabi, A.; Faraj, H.; Alami, A. Synthesis and Characterization of a Novel Biheterocyclic α -Amino Acid Precursor of the Triazole-Tetrazole Type, via the Copper (I) Catalyzed Alkyne-Azide Cycloaddition Reaction (CuAAC). *Eur. J. Adv. Chem. Res.* **2021**, *2*, 7–15. <https://doi.org/10.24018/ejchem.2021.2.2.53>.
37. Xi, W.; Scott, T.F.; Kloxin, C.J.; Bowman, C.N. Click Chemistry in Materials Science. *Adv. Funct. Mater.* **2014**, *24*, 2572–2590. <https://doi.org/10.1002/adfm.201302847>.
38. Kim, E.; Koo, H. Biomedical Applications of Copper-Free Click Chemistry: In Vitro, in Vivo, and Ex Vivo. *Chem. Sci.* **2019**, *10*, 7835–7851. <https://doi.org/10.1039/C9SC03368H>.
39. Habnoui, S.E.; Darcos, V.; Garric, X.; Lavigne, J.-P.; Nottelet, B.; Coudane, J. Mild Methodology for the Versatile Chemical Modification of Polylactide Surfaces: Original Combination of Anionic and Click Chemistry for Biomedical Applications. *Adv. Funct. Mater.* **2011**, *21*, 3321–3330. <https://doi.org/10.1002/adfm.201100412>.
40. Yvorra, T.; Steinmetz, A.; Retailleau, P.; Lantz, O.; Schmidt, F. Synthesis, Biological Evaluation and Molecular Modelling of New Potent Clickable Analogues of 5-OP-RU for Their Use as Chemical Probes for the Study of MAIT Cell Biology. *Eur. J. Med. Chem.* **2021**, *211*, 113066. <https://doi.org/10.1016/j.ejmech.2020.113066>.
41. Kharb, R.; Sharma, P.C.; Yar, M.S. Pharmacological Significance of Triazole Scaffold. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1–21. <https://doi.org/10.3109/14756360903524304>.
42. N’Guyen, T.T.T.; Oussadi, K.; Montembault, V.; Fontaine, L. Synthesis of ω -Phosphonated Poly(Ethylene Oxide)s through the Combination of Kabachnik-Fields Reaction and “Click” Chemistry. *J. Polym. Sci. Part Polym. Chem.* **2013**, *51*, 415–423. <https://doi.org/10.1002/pola.26399>.
43. Tornøe, C.W.; Christensen, C.; Meldal, M. Peptidotriazoles on solid phase: [1,2,3]-Triazoles by regioselective copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem.* **2002**, *67*, 3057–3064. <https://doi.org/10.1021/jo011148j>.
44. Achamlale, S.; Alami, A.; Aouine, Y. STRUCTURE ASSIGNMENT OF N-PROTECTED 2-(1H-1,2,3- TRIAZOL-1-YL)-GLYCINE DERIVATIVES BY CHEMICAL AND SPECTROSCOPIC METHODS. *Moroc. J. Heterocycl. Chem.* **2019**, *18*, 61–69. <https://doi.org/10.48369/IMIST.PRSM/jmch-v18i3.18502>.