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An Aminopyrrolidinyl Phosphonates—A New Class of Antibiotics: Facile Synthesis and Predicted Biological Activity

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Abstract

A novel class of aminopyrrolidinyl phosphonates was synthesized in 74% - 80% isolated yield by the addition of three-fold excess of primary amines to diethyl 4-chloro-1-butynylphosphonates. The reaction was carried out at room temperature and in the absence of solvent or catalyst to give solely compounds which showed predicted biological activity based on PASS program. Some of the synthesized derivatives of antibiotics exhibit properties for the treatment of stroke, the treatment of acute neurological disorders, and can also be acetyl esterase inhibitors.

Keywords

Alkynylphosphonates, Cyclization, Pyrrolidine, β-Aminophosphonates, Amine Addition, Antibiotics

1. Introduction

Natural antibiotics are produced by many microorganisms and are of great interest in medicine and pharmacology [1] [2] [3] [4]. It is well known that some antibiotics, such as K-26, SF-2513, FR-33289, and SF-2312 contain a C-P (carbon-phosphorus) bond that belongs to the category of phosphonates [5] [6] [7] [8]. The targeted synthesis of phosphonates for pharmacological utility is also fairly well described in several reviews [9] [10] [11] [12] [13].

For instance, a pyrrolidinyl phosphonates class (known as antibiotic SF-2312)

is a natural antibiotic which is produced by the actinomycete *Micromonospora* sp. It has not only showed activity as an enolase inhibitor but also found to be one of the most potent natural inhibitors of glycolysis which in turn inhibit cell proliferation [14] [15] [16] [17] [18]. Later, the synthesis of this antibiotic and its analogues has been described by various researchers [19] [20] [21].

In the same context, pharmacologists always agree that the biological activity of both natural and synthetic compounds is related to the chemical structure [22]. Therefore, there are a large number of available computer programs that can evaluate the probability of an organic compound activity to be a drug [23] [24]. For instance, PASS computer program contains a library with information of about 1 million chemical compounds and more than 10,000 biological activities [25]. An algorithm for the practical use of PASS has been described in detail in several publications [26] [27] [28].

Previously, few pyrrolidinylphosphonates and pyrrolidinylphosphonic acids (**1**-**12**, Figure 1) were synthesized for the purpose of testing their biological activity. Generally, they were obtained either from readily available pyrrolidine ring or by multistep cyclization reactions. But there is no one general direct method to produce them and a brief summary for their synthesis is described below:

Initially, the antibiotic SF-2312 (**1**) and its analogue (**3**) were synthesized by a multistep reaction sequence in which ethyl diethoxyphosphorylacetate was converted to N-benzyloxy-2-(diethoxyphosphoryl)-pent-4-enamide followed by oxidative cleavage and hydrolysis [21]. Later, studies showed that their antibiotic activity is due to the inhibition of a glycolytic enzyme called enolase [14] [15] [16]. The reaction of pentanedial with acetamide and acetyl chloride in the presence of phosphorylating agent afforded the pyrrolidinyldiphosphonic acid (**2**) [29]. The combination of the Kabachnik–Fields reaction with a subsequent ring closure of 5-chloro-2-pentanone with ammonia and diethyl phosphonate produced (**4**) [30].

The pyrrolidinylphosphonates (**5**-**6**) were prepared from readily available 2-methylpyrroline and diethyl phosphite [31]. The SF-2312 (**1**) antibiotic analogues (**7**-**10**) were obtained using 1-benzyloxy-3-bromopyrrolidin-2,5-dione through Michaelis-Arbusov reaction with trialkyl phosphites followed by alkylation. However, their biological activity was not determined [19] [20].

Asymmetric synthesis of β-amidophosphonate (**11**) was achieved by Diels–Alder reaction between the vinylphosphonate and chiral aminodiene [32]. Finally, three-component decarboxylative coupling of proline with aldehydes and dialkyl phosphite was used to afford the corresponding pyrrolidinylphosphonates (**12**) [33].

2. Results and Discussion

We recently reported the synthesis of N-substituted pyrrolidinyl-methylphosphonate (**14**) by addition of amines to (Z)-diethyl (5-chloropent-1-en-1-yl)phosphonate **13** (Scheme 1) [34].

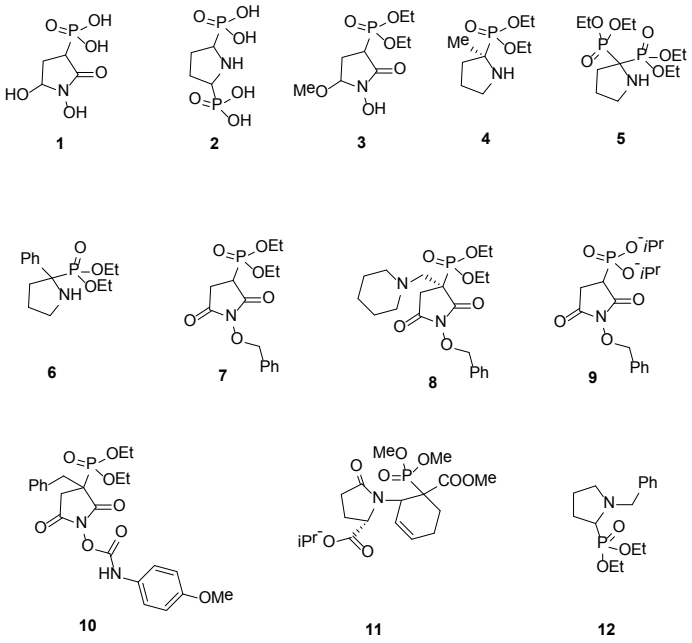
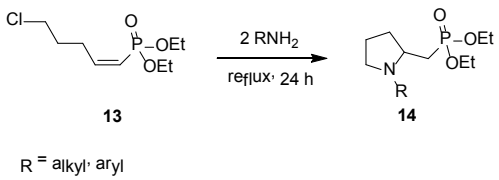


Figure 1. Pyrrolidinyl phosphonates **1-12**.



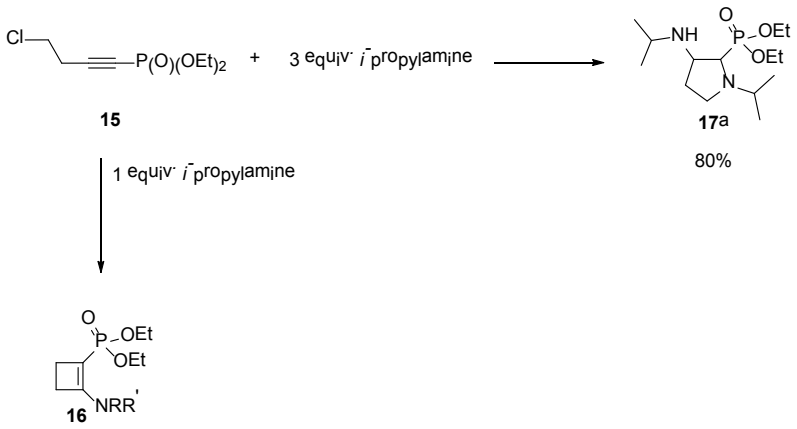
Scheme 1. Formation of pyrrolidines N-substituted pyrrolidinyl-methylphosphonate **14**.

In addition, we investigated the reaction of 4-chloro-1-butentynylphosphonate **15** with an equivalent number of amines which gave 2-amino-cyclobutenylphosphonates [35]. Interestingly, a different novel class of compounds (**17**a-h) was obtained by tuning of the reaction conditions.

Being encouraged by these results, we determined to study amine addition on a shorter chain alkynylphosphonate that has not been explored before. Accordingly, we prepared 4-chloro-1-butentynylphosphonate **15** in our lab by substituting the hydroxy group in but-3-yne-1-ol using thionyl chloride under reflux. After isolation of the product by distillation, it was lithiated using *n*-BuLi, and was reacted with chlorophosphonates.

Herein, we report a very facile method for the synthesis of novel aminopyrrolidinyl phosphonates (**17**a-h) and their predicted biological activity using the PASS program.

Thus, when three equivalents of *i*-propylamine were added to (**15**), the pyrrolidine structure diethyl (1-isopropyl-3-(isopropylamino)pyrrolidin-2-yl)phosphonate (**17**a) was gained in 80% yield (Scheme 2). Similarly, products (**17**b-h) were produced in (74% - 79%) isolated yield by treatment of **15** with a different primary amine.



Scheme 2. Formation of pyrrolidinylphosphonate **17**a.

The reaction was carried out at 25˚C for 12 h. and the products **17** were isolated by silica gel column chromatography in good yields (74% - 80%) and were characterized by NMR, GC/MS, and by elemental analysis. The multiplets in the regions ~(1.3 - 2. 0 ppm), ~(2.1 - 3.0 ppm) in the ^{1}H NMR spectrum, precisely the doublet of doublet in the region ~2 ppm that corresponds to the hydrogen on C1 split by phosphorus and the hydrogen on C2 which resonated as a multiplet at ~3 ppm, together with the carbons in the regions ~(30, 32, 45, 55 ppm) in the ^{13}C NMR spectra are indicative of the pyrrolidine ring. Besides, the ^{31}P NMR that resonated chemical shifts at ~31 ppm, the GC/MS and the elemental analysis are all evidence of structure **17**. These results were also supported by 2-D Cosy and ^{1}H-^{13}C HSQCSI NMR of **17**d in which a high correlation was observed.

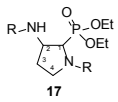
As described above, pyrrolidines **1**-**12** are of predicted biologically active compounds despite the multistep procedures for their preparation.

This process represents a general one-pot method for the synthesis of novel oily amino-pyrrolidinyl phosphonates (**17**a-h) which have not been reported before. In addition, they are thermally and air-stable compounds at room temperature, and are soluble in most organic solvents. Besides, this cyclization reaction is general for both aliphatic and aromatic primary amines as shown in Table 1. In addition, they are of potent biological activity precisely as antibiotics analogous to compounds **1**-**12** as shown in Table 2.

Unlike primary amines, when secondary amines were used, no heterocycles were detected and only 2-amino-cyclobutenylphosphonates **16** were obtained.

A suggested mechanism for this reaction can be attributed to initial addition of the amine on the carbon-carbon double bond to give a zwitterionic intermediate followed by proton transfer. Then, another hydroamination reaction took place on the double bond in the presence of excess amine to give the intermediate (**20**). After, nucleophilic attack of the nitrogen atom on C1 onto the carbon C-Cl by S_N2 fashion, an aminopyrrolidinyl phosphonate (**17**) was produced (Scheme 3) [31] [32] [33] [34].

Table 1. Synthesis of pyrrolidinylphosphonates **17**a-h.



17

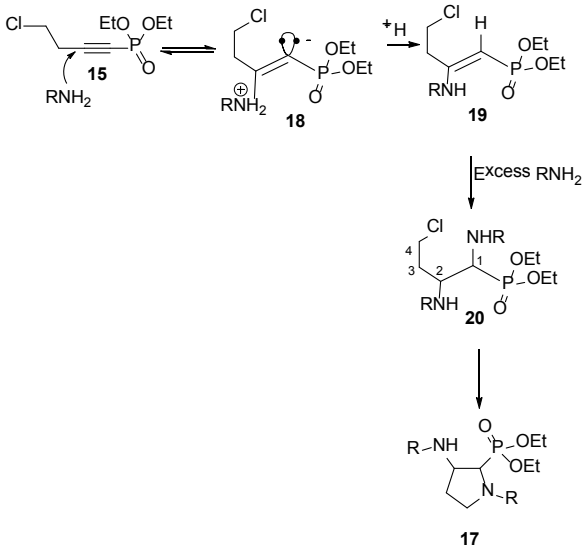
Entry	Products	Amine (3.1 equiv.)	R	Isolated Yield[a], % (reaction conversion)[b]
1	**17a**	*i*-propylamine	*i*-propyl	80 (>98)
2	**17b**	*t*-butylamine	*t*-butyl	74 (>98)
3	**17c**	benzylamine	benzyl	78 (>98)
4	**17d**	amylamine	*n*-pentyl	75 (>98)
5	**17e**	*n*-butylamine	*n*-butyl	77 (>98)
6	**17f**	phenylamine	phenyl	76 (>98)
7	**17g**	*n*-heptylamine	*n*-heptyl	75 (>98)
8	**17h**	2-phenylethylamine	phenylethyl	79 (>98)

[a]After silica gel chromatography; [b]>98% as determined by GC/MS and ^{31}P NMR.

Table 2. Predicted biological activity of compounds **1**-**17**.

No.	Experimental reported Activity, (Pa)*	Predicted theoretical biological activity, (Pa)*	Related reference
1	Inhibitor of the glycolytic enzyme enolase 2	Stroke treatment (0.761); Neuroprotector (0.744); Acute neurologic disorders treatment (0.663); Antineoplastic (sarcoma) (0.646); Antinephrotoxic (0.587); Antiseborrheic (0.578)	(15, 16, 21)
2	Not reported	Stroke treatment (0.979); Antiviral (0.897); Antiviral (HIV) (0.887) Antinephrotoxic (0.701); Bone formation stimulant (0.653)	(29, 31)
3	Not reported	Antibiotic Glycopeptide-like (0.984); Stroke treatment (0.538) Antischistosomal (0.510)	(21)
4	Not reported	Antiarthritic (0.963); Anti-inflammatory (0.942); Acute neurologic disorders treatment (0.765); Bone formation stimulant (0.615) Antinephrotoxic (0.608); Stroke treatment (0.567) Leukopoiesis stimulant (0.542); Bone diseases treatment (0.539)	(30)
5	Not reported	Bone formation stimulant (0.813); Bone diseases treatment (0.803) Acute neurologic disorders treatment (0.650); Antinephrotoxic (0.604) Antiosteoporotic (0.560); Leukopoiesis stimulant (0.526)	(31)
6	Not reported	Acute neurologic disorders treatment (0.834); Stroke treatment (0.583) Bone formation stimulant (0.574); Bone diseases treatment (0.536) Anesthetic general (0.517); Leukopoiesis stimulant (0.506)	(31)
7	Not reported	Acetylesterase inhibitor (0.618); Anticonvulsant (0.533)	(19, 20)
8	Not reported	Anticonvulsant (0.664); Acetylesterase inhibitor (0.637); Acute neurologic disorders treatment (0.513)	(19, 20)
9	Not reported	Acetylesterase inhibitor (0.687); Myasthenia Gravis treatment (0.562)	(19, 20)
10	Not reported	Cognition disorders treatment (0.765)	(19, 20)
11	Not reported	Calcium regulator (0.548); Antihypertensive (0.503)	(32)
12	Not reported	Acute neurologic disorders treatment (0.852); Stroke treatment (0.582) Bone diseases treatment (0.580); Bone formation stimulant (0.531)	(33)
17a	Not reported	Acetylesterase inhibitor (0.611); Insulinotropin antagonist (0.568)	Present study
17b	Not reported	Spasmolytic, urinary (0.954)	Present study
17c	Not reported	Acetylesterase inhibitor (0.572); Immunostimulant (0.522)	Present study
17d	Not reported	Acetylesterase inhibitor (0.618); Immunostimulant (0.544)	Present study
17e	Not reported	Acetylesterase inhibitor (0.618); Immunostimulant (0.544)	Present study
17f	Not reported	Purinergic P2Y2 antagonist (0.512)	Present study
17g	Not reported	No activities with Pa > 0.5	Present study
17h	Not reported	General pump inhibitor (0.600)	Present study

*Only activities with Pa > 0.5 are shown.



Scheme 3. Suggested mechanism for the synthesis of the compounds **17**.

This suggested mechanism is also supported by the fact that when secondary amines were used, no hetero cycles were detected and only 2-amino-cyclobutenylphosphonates **16** were obtained. In addition, this reaction was restricted to 4-chloro-1-butynylphosphonate **15**. When longer chloro alkynylphosphonates chains were used no heterocyclic structure was observed apparently due to the proximity of the chloro substituted carbon to the conjugated system of the triple bond and the phosphonate group. After the synthesis of compounds (**17**a-h), their biological activity was screened utilizing the PASS program and were found to be of predicted pharmacological usefulness as listed in Table 2.

3. Conclusion

In conclusion, a novel aminopyrrolidinyl phosphonate class of compounds (**17**a-h) was smoothly obtained by addition of primary amines to 4-chloro-1-butynylphosphonate in the absence of solvent or catalyst and relatively in a satisfactory isolated yield. In addition, manifestations of biological activities of the above compounds were observed using PASS program. This reaction can be of interest for the related chemist's community to apply this reaction to other functional groups instead of phosphonates and for the biologists to test their predicted biological activity.

4. Experimental

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded from solutions in $CDCl_3$ on a Varian Mercury 300 spectrometer at 300, 75.5, and 121.4 MHz, respectively; the chemical shifts were measured relative to TMS (^{1}H, ^{13}C) and H_3PO_4. The mass spectra (EI) were recorded on an HP G1800A GCD GC/MS instrument using a 30-m methyl silicone column.

Synthesis of Diethyl (4-chlorobut-1-yn-1-yl)phosphonate (15)

Since the starting material 4-chlorobut-1-yne was not commercially available as usual, it was prepared in our lab [35].

Synthesis of aminopyrrolidinyl phosphonates (17a-h)

Typical procedure for the synthesis of diethyl (1-isopropyl-3-(isopropylamino)pyrrolidin-2-yl)phosphonate 17a.

To diethyl (4-chlorobut-1-yn-1-yl)phosphonate (0.22 g, 1 mmol) was added (0.23 g, 3.5 mmol) of isopropylamine in a 10 mL round bottom flask. After stirring at 25˚C for 12 h. the reaction mixture was washed with 0.1 N NaOH solution and the product was extracted with (2 × 20 mL CH_2Cl_2), dried over $MgSO_4$, concentrated using a rotary evaporator and the oily product was separated on a silica gel column and was obtained in 80% isolated yield (10% methanol:90% dichloromethane), which was then analyzed by GC/MS, elemental analysis, and NMR spectroscopy.

^{1}H NMR (300 MHz, Chloroform d): δ 1.01 (d, 6H, J_{HH} = 6.3 Hz), 1.11 (d, 6H, J_{HH} = 6.3 Hz), 1.30 (t, 6H, J_{HH} = 6.9 Hz), 1.65 - 2.30 (overlap, 3H), 2.65 - 70 (m, 1H), 2.78 - 2.88 (overlap, 2H), 3.02 - 3.15 (m, 1H), 3.42 - 3.48 (m, 1H), 4.03 - 4.12 (m, 4H); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 31.38; ^{13}C NMR (75.5 MHz, Chloroform d): 15.8 (d, $^3J_{PC}$ = 6.8), 15.8, 15.9, 32.0 (d, $^1J_{PC}$ = 126.7 Hz), 44.4, 50.8 (d, $^2J_{PC}$ = 3.2 Hz), 53.1, 60.4 (d, $^2J_{PC}$ = 8.6 Hz), 62.1, 63.2; MS(EI):*m/z* (%) 306 (10.5), 305 (15.1), 287 (20.0), 235 (22.3), 168 (35.0), 152 (18.8), 123 (30.0), 110 (41.3), 84 (100), 70 (56.7), 42 (19.9); Anal. Calcd. for $C_{14}H_{31}N_2O_3P$: C, 54.88; H, 10.20; N, 9.14; P, 10.11. Found: C, 55.09; H, 10.37; N, 8.95; P, 9.97.

Synthesis of diethyl (1-(tert-butyl)-3-(tert-butylamino)pyrrolidin-2-yl)phosphonate 17b.

Identical to procedure **17**a except adding t-butylamine and was obtained in 74% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): δ 1.09 (s, 9H), 1.11 (s, 9H), 1.31 (dt, 6H, J_{HH} = 7.2 Hz, $^3J_{HP}$ = 2.1 Hz), 1.63 - 2.22 (overlap, 3H), 2.61 - 2.67 (overlap m, 2H), 3.21 - 3.45 (m, 1H), 4.06 - 4.13 (m, 4H); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 30.38; ^{13}C NMR (75.5 MHz, Chloroform d): 16.4 (d, $^3J_{PC}$ = 6.3), 28.8, 30.0, 34.5 (d, $^1J_{PC}$ = 132.4 Hz), 39.7, 47.0, 50.6, 50.8 (d, $^2J_{PC}$ = 3.0 Hz), 60.4 (d, $^2J_{PC}$ = 8.6 Hz); MS(EI): *m/z* (%) 334 (0.70), 319 (2.5), 289 (7.8), 277 (17.8), 244 (27.8), 220 (70.5), 186 (51.1), 136 (100), 89 (55.1), 57 (67.8); Anal. Calcd. for $C_{16}H_{35}N_2O_3P$: C, 57.46; H, 10.55; N, 8.38; P, 9.26. Found: C, 58.18; H, 10.73; N, 8.21; P, 9.12.

Synthesis of diethyl(1-benzyl-3-(benzylamino)pyrrolidin-2-yl)phosphonate 17c.

Identical to procedure **17**a except adding benzylamine and was obtained in 78% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): ^{1}H NMR (300 MHz, Chloroform d): δ 1.26 (dt, 6H, J_{HH} = 6.9 Hz, $^3J_{HP}$ = 1.51 Hz), 1.69 - 2.18 (overlap, 3H), 2.64 - 283 (m, 2H), 3.05 - 3.14 (m, 1H), 3.76 (s, 2H), 3.77 (s, 2H), 4.00 - 4.11 (m, 4H), 7.21 - 7.33 (overlap, 10); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 30.98; ^{13}C NMR (75.5

MHz, Chloroform d): 16.1 (d, $^{3}J_{PC}$ = 7.4), 30.5, 40.8, 47.5 (d, $^{1}J_{PC}$ = 126.7 Hz), 45.5, 55.0, 60.2 (d, $^{2}J_{PC}$ = 4.0 Hz), 60.9 (d, $^{2}J_{PC}$ = 5.7 Hz), 127.7, 127.0, 128.2, 141.5; MS(EI): *m/z* (%) 402 (3.1), 401 (4.7), 325 (15.4), 311(17.7), 295 (17.9), 266 (30.4), 218 (44.9), 186 (22.3), 136 (60.1), 104 (33.6), 91 (100), 77 (55.8), 65 (18.8), 54 (26.8); Anal. Calcd. for $C_{22}H_{31}N_2O_3P$: C, 65.65; H, 7.76; N, 6.96; P, 7.70. Found: C, 65.47; H, 7.64; N, 7.10; P, 7.81.

Synthesis of diethyl (1-pentyl-3-(pentylamino)pyrrolidin-2-yl)phosphonate17d.

Identical to procedure **17**a except adding amylamine and was obtained in 75% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): δ 0.89 (t, 3H, J_{HH} = 5.7 Hz), 0.92 (t, 3H, J_{HH} = 5.7 Hz), 1.31 (dt, 6H, J_{HH} = 7.2 Hz, $^{3}J_{HP}$ = 2.1 Hz), 1.21 - 1.34 (overlap, 8H), 1.40 - 1.51 (m, 2H), 1.53 - 1.70 (m, 2H), 1.80 - 2.21 (overlap, 3H), 2.55 - 2.80 (overlap, 4H), 2.81 - 2.90 ((m, 1H), 3.00 - 3.05 (m, 1H), 3.06 - 3.15 (m, 1H), 4.06 - 4.15 (m, 4H); ^{31}P NMR (121.4 MHZ, Chloroform d): δ31.47; ^{13}C NMR (75.5 MHz, Chloroform d): 13.9, 14.1, 16.4 (d, $^{3}J_{PC}$ = 6.3), 22.4, 22.6, 26.4, 27.9, 29.2, 29.5, 29.8, 30.1 (d, $^{1}J_{PC}$ = 137.4 Hz), 32.3, 46.5, 47.1, 48.9 (d, $^{2}J_{PC}$ = 3.0 Hz), 55.4, 61.4 (d, $^{2}J_{PC}$ = 8.6 Hz); MS(EI): *m/z* (%) 362 (0.8), 319 (0.9), 279 (1.1), 264 (8.4), 256 (2.0), 222 (15.0), 194 (42.9), 142 (28.1), 128 (100), 98 (28.8), 82 (14.3), 56 (34.4), 43 (49.8), 29 (64.2); Anal. Calcd. for $C_{18}H_{39}N_2O_3P$: C, 59.64; H, 10.84; N, 7.73; P, 8.54. Found: C, 59.77; H, 10.97; N, 7.60; P, 8.41.

Synthesis of diethyl (1-butyl-3-(butylamino)pyrrolidin-2-yl)phosphonate 17e.

Identical to procedure **17**a except adding butylamine and was obtained in 77% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): δ 0.88 (t, 3H, J_{HH} = 5.7 Hz), 0.96 (t, 3H, J_{HH} = 5.7 Hz), 1.31 (dt, 6H, J_{HH} = 7.2 Hz, $^{3}J_{HP}$ = 2.1 Hz), 1.35 - 1.48 (overlap, 10H), 1.60 - 2.17 (overlap, 7H), 2.90 - 3.10 (m, 1H), 4.03 - 4.15 (m, 4H); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 31.85; ^{13}C NMR (75.5 MHz, Chloroform d): 13.6, 14.0, 16.2 (d, $^{3}J_{PC}$ = 6.5), 23.0, 23.8, 28.3, 29.8, 30.3, 31.5 (d, $^{1}J_{PC}$ = 140.2 Hz), 33.5, 48.1, 49.3 (d, $^{2}J_{PC}$ = 3.2 Hz), 50.0, 53.1, 62.0 (d, $^{2}J_{PC}$ = 8.4 Hz); MS(EI):*m/z* (%) 334 (0.9), 333 (1.0), 319 (16.8), 304 (40.2), 289 (17.6), 276 (66.1), 219 (32.2), 189 (100), 135 (47.8), 89 (41.0), 57 (44.1); Anal. Calcd. for $C_{16}H_{35}N_2O_3P$: C, 57.46; H, 10.55; N, 8.38; P, 9.26. Found: C, 57.63; H, 10.70; N, 8.19; P, 9.09.

Synthesis of diethyl (1-phenyl-3-(phenylamino)pyrrolidin-2-yl)phosphonate 17f.

Identical to procedure **17**a except adding phenylamine and was obtained in 76% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): ^{1}H NMR (300 MHz, Chloroform d): δ 1.22 (dt, 6H, J_{HH} = 6.9 Hz, $^{3}J_{HP}$ = 2.1 Hz), 1.73 - 2.20 (overlap, 3H), 2.58 - 2.80 (m, 2H), 3.00 - 3.10 (m, 1H), 4.08 - 4.13 (m, 4H), 7.21 - 7.35 (overlap, 10); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 30.98; ^{13}C NMR (75.5 MHz, Chloroform d): 16.2 (d, $^{3}J_{PC}$ = 6.8), 29.8, 39.9, 48.8 (d, $^{1}J_{PC}$ = 132.1 Hz), 47.0, 61.0 (d, $^{2}J_{PC}$ = 2.8

Hz), 62.5 (d, $^{2}J_{PC}$ = 5.7 Hz), 127.9, 128.8, 129.2, 141.0; MS(EI): *m/z* (%) 374 (0.7), 373 (1.2), 297 (30.0), 255 (20.1), 220 (100), 189 (35.9), 137 (28.7), 89 (18.7), 77 (67.9), 65 (30.0); Anal. Calcd. for $C_{20}H_{27}N_2O_3P$: C, 64.16; H, 7.27; N, 7.48; P, 8.27. Found: C, 63.98; H, 7.13; N, 7.60; P, 8.41.

Synthesis of diethyl (1-heptyl-3-(heptylamino)pyrrolidin-2-yl)phosphonate 17g.

Identical to procedure **17**a except adding heptylamine and was obtained in 75% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): δ 0.88 (t, 3H, J_{HH} = 5.7 Hz), 0.96 (t, 3H, J_{HH} = 5.7 Hz), 1.28 (dt, 6H, J_{HH} = 7.2 Hz, $^{3}J_{HP}$ = 2.1 Hz), 1.30 - 1.60 (overlap, 16H), 1.74 - 2.18 (overlap, 13H), 2.93 - 3.20 (m, 1H), 4.04 - 4.10 (m, 4H); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 32.25; ^{13}C NMR (75.5 MHz, Chloroform d): 13.6, 14.0, 16.0 (d, $^{3}J_{PC}$ = 6.1), 22.2, 22.7, 26.9, 27.0, 27.9, 28.2, 28.8, 29.0, 29.4, 29.8, 31.0 (d, $^{1}J_{PC}$ = 135.8 Hz), 33.3, 45.2, 46.9 (d, $^{2}J_{PC}$ = 3.2 Hz), 49.0, 53.0, 60.8 (d, $^{2}J_{PC}$ = 8.6 Hz); MS(EI): *m/z* (%) 418 (0.7), 417 (0.9), 412 (11.2), 396 (14.8), 345 (20.7), 289 (49.6), 235 (33.8), 189 (100), 135 (60.3), 87 (57.7), 43 (45.8); Anal. Calcd. for $C_{22}H_{47}N_2O_3P$: C, 63.12; H, 11.32; N, 6.69; P, 7.40. Found: C, 62.91; H, 11.17; N, 6.81; P, 7.56.

Synthesis of diethyl (1-phenethyl-3-(phenethylamino)pyrrolidin-2-yl)phosphonate17h.

Identical to procedure **17**a except adding phenylethylamine and was obtained in 79% isolated yield.

^{1}H NMR (300 MHz, Chloroform d): ^{1}H NMR (300 MHz, Chloroform d): δ 1.24 (dt, 6H, J_{HH} = 6.9 Hz, $^{3}J_{HP}$ = 1.67 Hz), 1.58 - 2.18 (overlap, 3H), 2.14 - 2.85 (overlap, 7H), 4.04 - 4.15 (m, 4H), 7.17 - 7.31 (overlap, 10); ^{31}P NMR (121.4 MHZ, Chloroform d): δ 31.78; ^{13}C NMR (75.5 MHz, Chloroform d): 16.2 (d, $^{3}J_{PC}$ = 7.2), 31.3, 32.8, 41.5, 49.5 (d, $^{1}J_{PC}$ = 132.9 Hz), 48.2, 55.6, 57.9, 61.0 (d, $^{2}J_{PC}$ = 4.2 Hz), 60.9 (d, $^{2}J_{PC}$ = 5.7 Hz), 127.7, 127.0, 128.2, 141.5; MS(EI): *m/z* (%) 430 (0.7), 429 (0.8), 353 (18.9), 325 (32.1), 276 (100), 234 (22.8), 188 (45.9), 135 (57.7), 105 (77.8), 77 (46.8), 69 (66.7); Anal. Calcd. for $C_{24}H_{35}N_2O_3P$: C, 66.96; H, 8.19; N, 6.51; P, 7.19. Found: C, 67.08; H, 8.31; N, 6.37; P, 7.06.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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