

A convenient route to novel fluorinated 1,2,4,3-triazaphospholo[1,5-*a*]pyridines and pyrido[1,2-*b*][1,2,4,5]triazaphosphinines

Mohammed A. Assiri^{a,b}, Somaia M. Abdel-Kariem^c, Tarik E. Ali^{c*}, and I. S. Yahia^{d,e}

^aAdvanced Materials and Green Chemistry, Chemistry Department, Faculty of Science, King Khalid University, Abha, Saudi Arabia

^bResearch Center for Advanced Materials Science (RCAMS), King Khalid University, Abha, Saudi Arabia.

^cDepartment of Chemistry, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt

^dAdvanced Functional Materials & Optoelectronic Laboratory (AFMOL), Department of Physics, Faculty of Science, King Khalid University, Abha, Saudi Arabia

^eNanoscience Laboratory for Environmental and Bio-medical Applications (NLEBA), Semiconductor Lab., Department of Physics, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt

E-mail: tarik_elsayed1975@yahoo.com; tarekelsaied@edu.asuedu.eg

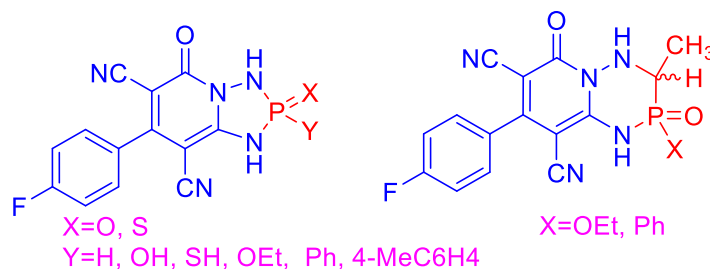
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Abstract

A simple synthetic approach to the construction of novel fluorinated 5-oxo(thioxo)-2-oxido(sulfido)-1,2,4,3-triazaphospholo[1,5-*a*]pyridines **2–14** and pyrido[1,2-*b*][1,2,4,5]triazaphosphinines **16**, **19** and **22**, was achieved. The method depends on the treatment of 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) with some different types of phosphorus reagents such as phosphorus acid, and their esters, phosphorus halides as well as phosphorus sulfides. Structures of all the synthesized products were established by elemental analysis and spectral tools.



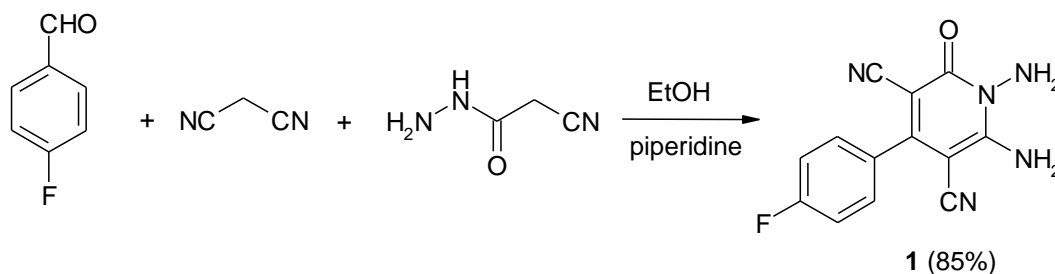
Keywords: 1,6-Diaminopyridine, cyclization, 1,2,4,3-triazaphospholes, 1,2,4,5-triazaphosphinines

Introduction

Phosphorus-nitrogen compounds have gained considerable attention due to their biological and pharmacological effects, such as antimicrobial,¹ insecticidal,² and herbicidal properties.³ Especially, different isomers of triazaphospholes possess multiple biological properties including antibacterial⁴ and antineoplastic activities.⁵ Also, several triazaphosphinine derivatives are present in the pharmaceutical field where they are used as antitumor agents.⁶⁻⁸ On the other hand, the pyridine ring is of considerable interest since it is the key component in a range of bioactive naturally occurring and synthetic compounds.⁹ The pyridine-3,5-dicarbonitrile was chosen as an important structural scaffold for the design of a reaction-based library.¹⁰ A number of the researches reported the biological activities of pyridine dicarbonitrile as being analgesic,¹¹ anti-HIV,¹² anti-Alzheimer,¹³ anticancer,¹⁴ anti-inflammatory and antibacterial agents.¹⁵ Because of the characteristic properties of the fluorine atom, such as its small size, strong electronegativity and the low polarizability of the C–F bond, it has considerable effect on the biological properties of a molecule.¹⁶ The presence of fluorine into a drug causes simultaneous modulation of its electronic, lipophilic, and steric parameters, which lead to a strong influence in the pharmacokinetic and pharmacodynamics properties of drugs.¹⁷ In the light of these facts, and as a continuation of our reported work on construction of bioactive phosphorus heterocycles,¹⁸⁻²⁰ the present work studies the chemical reactivity of 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) towards some different phosphorus reagents, which lead to the formation of novel fluorine compounds containing functionalized 1,2,4,3-triazaphospholo[1,5-a]pyridines and pyrido[1,2-b][1,2,4,5]triazaphosphinines.

Results and Discussion

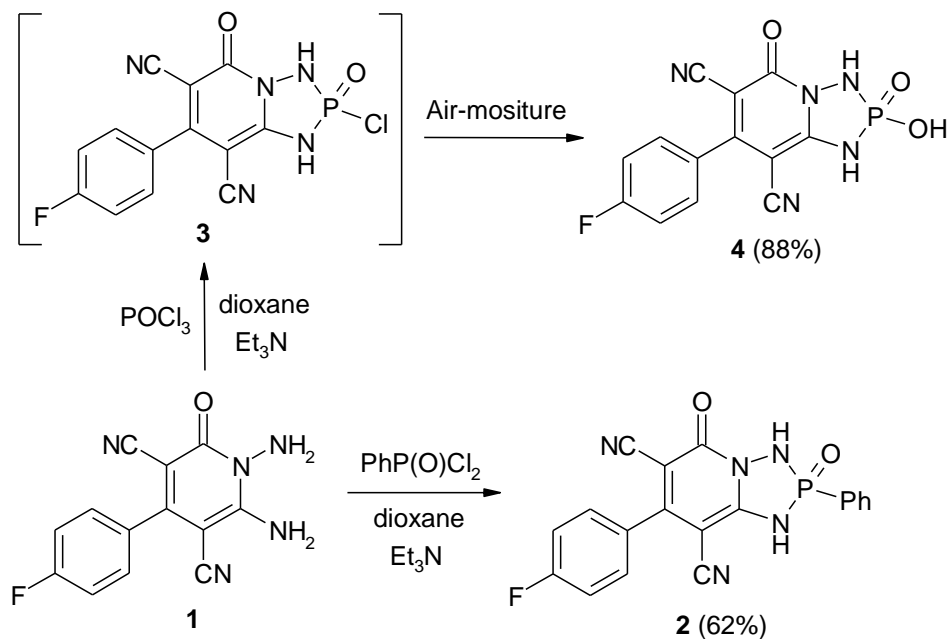
The starting material, 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) was synthesized in one step by the reaction of 4-fluorobenzaldehyde, malononitrile and cyanoacetohydrazide in absolute ethanol containing a few drops of piperidine as a catalyst²¹ (Scheme 1). The chemical structure of compound **1** was in accordance with its spectral data. The IR spectrum exhibited vibrational bands for NH₂, C≡N, and C=O at 3392–3111, 2219 and 1667 cm⁻¹, respectively. The ¹H-NMR spectrum showed signals due to two NH₂ groups at δ 5.68 and 7.97, 8.48 ppm and AB system of phenyl group at δ 7.41 and 7.59 (*J*=9.2 Hz) ppm. Also, the ¹³C-NMR spectrum displayed the aromatic carbon atoms and the nitrile groups at the expected chemical shifts.



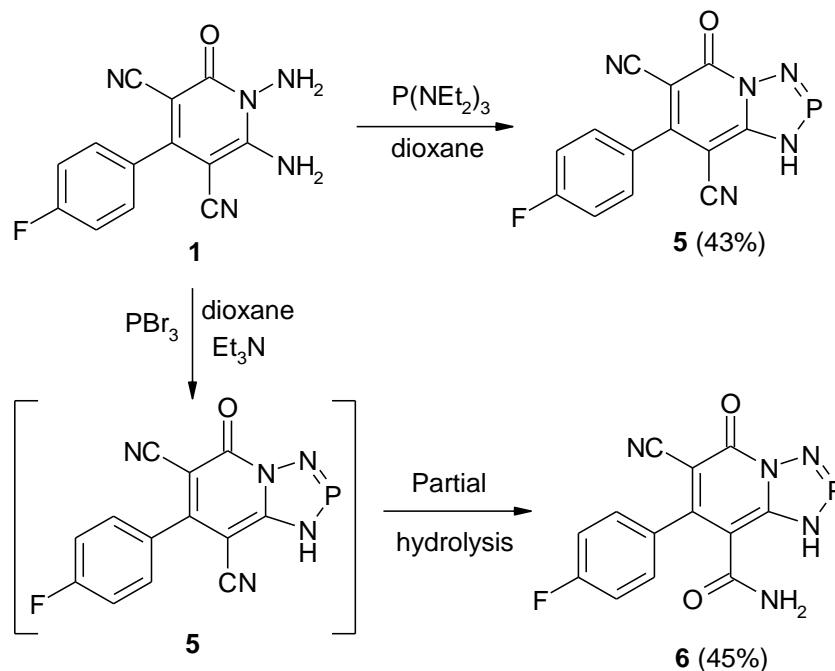
Scheme 1. Synthesis of 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**).

The 1,6-diamino groups are ready-made nucleophilic centers for the synthesis of fused phosphorus heterocyclic rings *via* their reaction with phosphorus reagents having labile halogen atoms.²² Thus, treatment

of compound **1** with phenylphosphonic dichloride in dry dioxane containing two equivalent amounts of triethylamine led to the formation of 7-(4-fluorophenyl)-2-oxido-5-oxo-2-phenyl-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (**2**) in moderate yield (Scheme 2). Similarly, compound **1** reacted with phosphorus oxychloride under the same reaction conditions to give the 2-hydroxy-1,2,4,3-triazaphospholo[1,5-*a*]pyridine derivative **4** (Scheme 2). The proposed mechanism for this reaction can be explained by cyclization of 1,6-diaminopyridine **1** with phosphorus oxychloride to give the nonisolable intermediate **3** which underwent hydrolysis by the effect of air-moisture (Scheme 2). In a similar manner, treatment of compound **1** with phosphorus tribromide in dry dioxane containing triethylamine, did not give the expected 7-(4-fluorophenyl)-5-oxo-1,5-dihydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (**5**). This reaction gave the 1,2,4,3-triazaphospholo[1,5-*a*]pyridine-8-carboxamide derivative **6** in moderate yield. However, the product **5** was isolated from the reaction of hexaethylphosphorus triamide with compound **1** in dry dioxane (Scheme 3). We assumed that compound **5** underwent partial hydrolysis *in situ* for one nitrile group because of *by-product* HBr and air-moisture (Scheme 3). The IR spectra of compounds **2**, **4**, **5** and **6** showed absorption bands at regions 3371–3198 (NH₂, NH) and 1229–1227 (P=O) cm⁻¹. Also, the ¹H-NMR spectra of these compounds revealed the NH protons at region δ 8.26–9.15 ppm, while the protons of OH and CONH₂ in compounds **4** and **6** were observed at δ 3.38 and 8.47 ppm, respectively. The ¹³C-NMR spectra of these compounds displayed the expected signals of all carbon atoms. The presence of the carbon atom of CONH₂ in compound **6** at δ 170.6 ppm supported the partial hydrolysis process. Moreover, the molecular ion peaks of these compounds were recorded at *m/z* 391, 331, 297 and 315, respectively, in their mass spectra. The ³¹P-NMR spectrum of compound **2** recorded a singlet at δ 32.1 ppm.

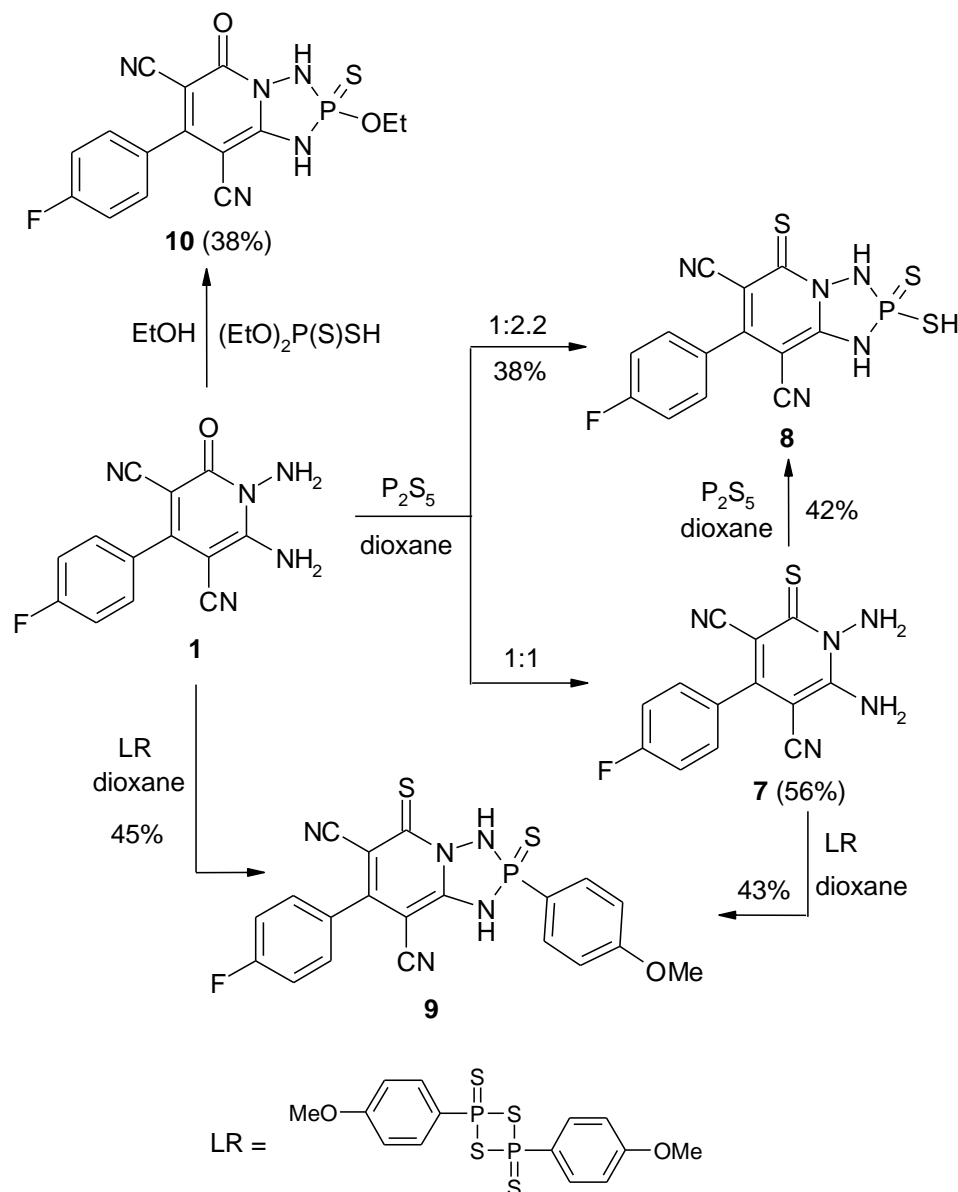


Scheme 2. Reaction of compound **1** with phenylphosphonic dichloride and phosphorus oxychloride.



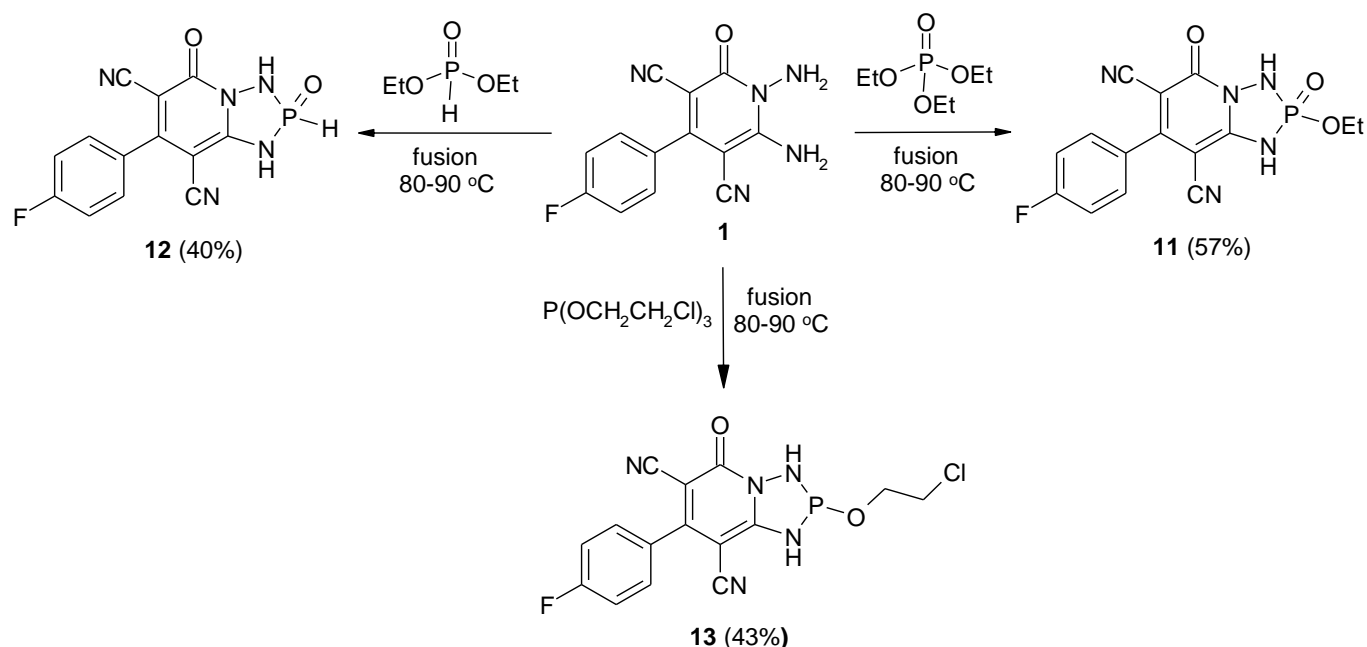
Scheme 3. Reaction of compound **1** with hexaethylphosphorus triamide and phosphorus tribromide.

We also studied the reaction of compound **1** with two examples of phosphorus sulfides. Thus, 1,6-diamino-4-(4-fluorophenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**7**) was isolated as a result of sulfuration process when compound **1** reacted with equivalent amount of phosphorus pentasulfide in dry dioxane (Scheme 4). The spectroscopic data of compound **7** confirmed the disappearance of C=O group. In addition, its IR and ^{13}C -NMR spectra revealed new C=S group in them at 1164 cm^{-1} and $\delta\ 179.0\text{ ppm}$, respectively. When this reaction was carried out by using two folds of phosphorus pentasulfide, the 2-sulfanyl-2-sulfido-5-thioxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine **8** was formed (Scheme 4). The product **8** was also isolated *via* treatment of the 1,6-diaminopyridine **7** with phosphorus pentasulfide under the same reaction conditions (Scheme 4). On the other hand, compound **1** was treated with Lawesson's reagent (LR) in dry dioxane to give a moderate yield of 7-(4-fluorophenyl)-2-(4-methoxyphenyl)-2-sulfido-5-thioxo-1,2,3,5-tetrahydro-1,2,4,3-triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (**9**) (Scheme 4). In addition, compound **9** was also obtained from treatment of compound **7** with LR in dry dioxane (Scheme 4). Similarly, treatment of compound **1** with *O,O*-diethyldithiophosphoric acid (formed *in situ*) in absolute ethanol yielded the 2-ethoxy-2-sulfido-1,2,3,5-tetrahydro-1,2,4,3-triazaphospholo[1,5-*a*]pyridine derivative **10** (Scheme 4). In the mass spectra of compounds **8**, **9** and **10**, they revealed their expected molecular ion peaks (M^+). The most characteristic signals in their ^1H -NMR spectra are those of the sulfanyl, methoxy, and ethoxy protons. They appeared at $\delta\ 4.63$ (SH), 3.81 (OCH_3), and 1.08 , 3.46 ($\text{CH}_3\text{CH}_2\text{O}$) ppm. Also, the specific carbon atoms of C=S groups of compounds **8** and **9** were observed at $\delta\ 179.2$ and 178.3 ppm , respectively, in their ^{13}C -NMR spectra. Moreover, the ^{31}P -NMR spectrum of compound **9** displayed a singlet at $\delta\ 54.5\text{ ppm}$ which supported the proposed structure.²³



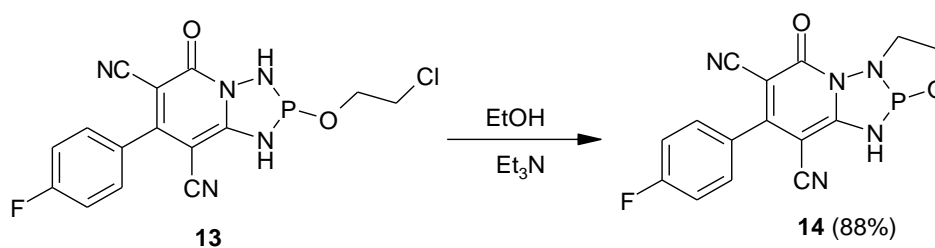
Scheme 4. Reaction of compound **1** with some phosphorus sulfides.

Next, the present study was extended to investigate the interaction of the 1,6-diaminopyridine **1** with three examples of phosphorus esters. Thus, when compound **1** was fused with triethyl phosphate at 80–90 °C, the 2-ethoxy-7-(4-fluorophenyl)-2-oxido-2-oxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (**11**) was isolated (Scheme 5). In the same manner, the 1,2,4,3-triazaphospholo[1,5-*a*]pyridine derivatives **12** and **13** were produced by fusion of compound **1** with diethyl phosphite and tris(2-chloroethyl) phosphite, respectively (Scheme 5). The IR spectra of compounds **11–13** recorded the absorption bands of NH and P=O groups at regions 3295–3429 and 1228–1230 cm^{-1} , respectively. The characteristic protons of these compounds were observed in their $^1\text{H-NMR}$ spectra. For example, the P–H proton was recorded as a doublet at δ 6.47 ($J_{\text{PH}}=711$ Hz) in compound **12**, while the ethoxy protons of compound **11** were resonated as triplet and quartet at δ 1.21 (CH_3) and 3.06 (CH_2) ppm, respectively. Also, the chloroethoxy moiety in compound **13** was displayed as two triplets at δ 3.54 and 3.83 ppm. Furthermore, the carbon atoms of the ethoxy fragments in compounds **11** and **13** were displayed at δ 18.5, 60.0 and 45.0, 62.5 ppm, respectively. Compounds **11–13** recorded the expected molecular ion peaks in their mass spectra.



Scheme 5. Reaction of compound **1** with some phosphorus esters.

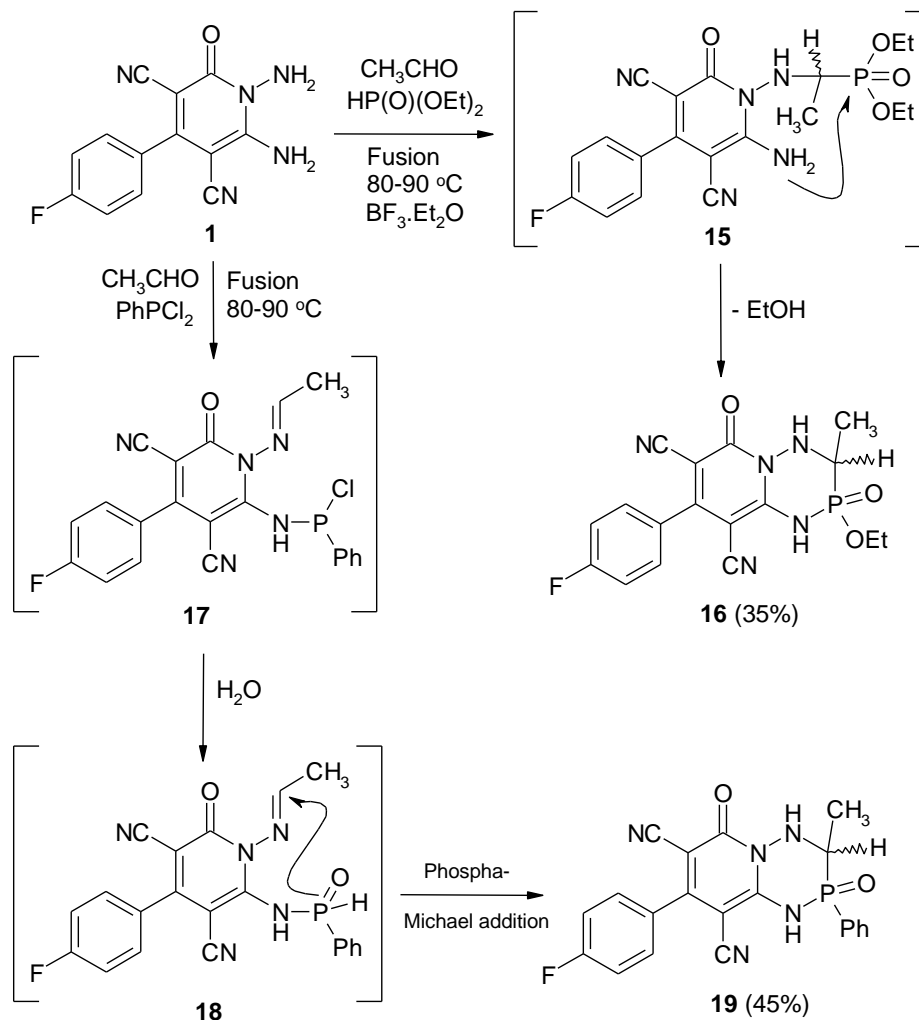
Compound **13** was ready to cyclize into the annulated triheterocyclic system **14** by heating in absolute ethanol containing a few drops of triethylamine (Scheme 6).²⁴ The oxazaphospholotriazaphospholopyridine structure **14** was deduced from analytical and spectroscopic data. In the IR spectrum, the only NH group was observed at 3417 cm^{-1} . In the $^1\text{H-NMR}$ spectrum, the protons of two methylene groups were observed at δ 2.91 and 3.60 ppm, while their resonances in $^{13}\text{C-NMR}$ spectrum were at δ 42.5 and 60.0 ppm. The presence of the molecular ion peak for compound **14** at m/z 341 was the strongest evidence for the cyclization process.



Scheme 6. Cyclization of compound **13** into **14**.

The 1,6-diamino groups as active nucleophilic centers can be used to react with aldehyde and dialkyl phosphite under the *Kabachnik-Fields* reaction condition to form new 1,2,4,5-triazaphosphinine (cyclic α -aminophosphonate).^{25,26} Thus, compound **1** condensed with acetaldehyde in the presence of diethyl phosphite or phenyl dichlorophosphine at room temperature, followed by heating under reflux to yield two isomeric forms of pyrido[1,2-*b*][1,2,4,5]triazaphosphinines **16** and **19**, respectively (Scheme 7). The formation of product **16** took place easily *via* condensation of the more chemically active N-amino group with acetaldehyde, followed by phospho-*Michael* addition of phosphorus atom to form the nonisolable α -aminophosphonate **15**. The latter intermediate underwent cyclization by removal of ethanol molecule (Scheme 7).²⁷ Also, the formation of compound **19** occurred easily *via* condensation of the two amino groups with acetaldehyde and phenyl dichlorophosphine affording the nonisolable intermediate **17** which underwent

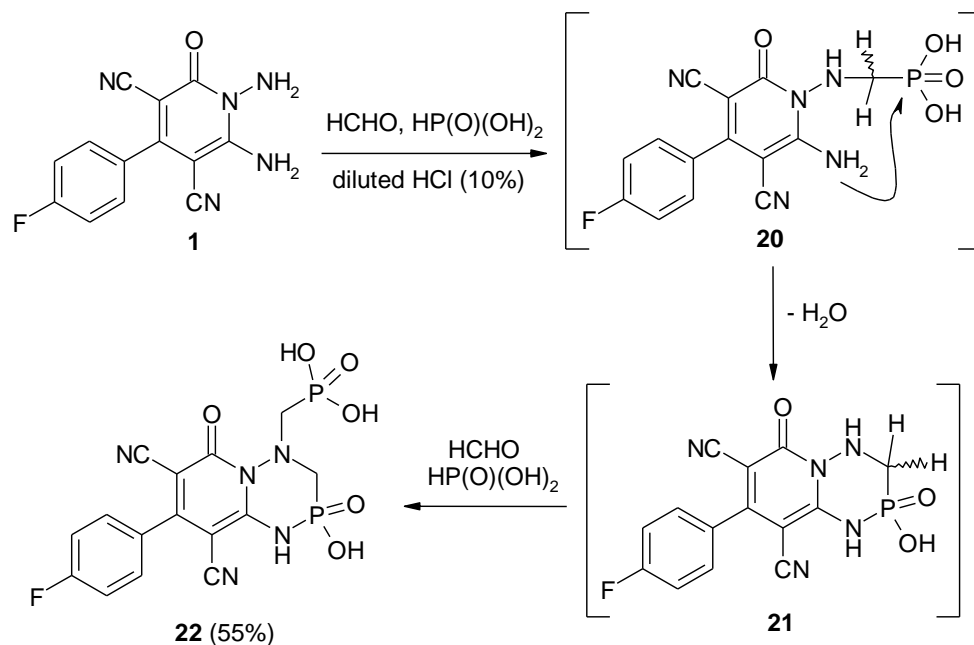
hydrolysis of labile chlorine atom by the eliminated water to form the intermediate **18**. This intermediate could easily transform into the isolated product **19** *via* phospho-*Michael* addition reaction (Scheme 7).²⁸ The IR spectra of compounds **16** and **19** recorded the absorption bands of P=O groups at 1236 and 1237 cm⁻¹, respectively. In their ¹H-NMR spectra, the P-CH protons appeared at δ 4.50 (q, $J_{\text{PCH}}=18.6$ Hz) and 4.14–4.20 (m) ppm, respectively, while the carbon atoms of the P-CH moieties in their ¹³C-NMR spectra, were resonated at δ 53.5 (d, $J_{\text{PC}}=150$ Hz) and 45.5 (d, $J_{\text{PC}}=138$ Hz) ppm for **16** and **19**, respectively. The phosphorus chemical shift of compound **16** showed a singlet at δ 22.2 ppm in its ³¹P-NMR spectrum which confirmed the proposed structure. The mass spectra of **16** and **19** recorded the expected molecular ion peaks at m/z 387 and 419, respectively.



Scheme 7. Reaction of compound **1** with acetaldehyde in the presence of diethylphosphite and phenyl dichlorophosphine.

An addition of phosphorous acid to an acidic solution of compound **1** in the presence of formaldehyde led to the formation of the interesting novel pyrido[1,2-*b*][1,2,4,5]triazaphosphinyl methyl phosphonic acid **22** (Scheme 8). The reaction took place smoothly *via* condensation of N-amino group with formaldehyde, followed by phospho-*Michael* addition of phosphorous acid to form the nonisolable aminophosphonic acid **20**. The latter acid underwent cyclization by removal of water molecule to give the nonisolable pyrido[1,2-*a*][1,2,4,5] triazaphosphinine **21**, that underwent additional methylphosphorylation process at N-1 to isolate the

novel pyrido[1,2-*a*][1,2,4,5]triazaphosphinylmethyl phosphonic acid **22** (Scheme 8).²⁹ The IR spectrum of compound **22** showed absorption bands at 3418 (br, OH, NH), 2964 (CH_{aliphatic}) and 1230 (P=O) cm⁻¹. In its ¹H-NMR spectrum, the protons of P-CH₂ fragments were displayed as a multiplet at δ 4.54–5.15 ppm, while the carbon atoms of these fragments were recorded as two doublets at δ 45.0 and 50.5 ppm in the ¹³C-NMR spectrum. The ³¹P-NMR spectrum of compound **22** was the strongest evidence for the proposed structure, due to the presence of two signals at δ 11.7 and 19.2 ppm.³⁰ Finally, its molecular ion peak (M⁺) was observed at *m/z* 408, in the mass spectrum.



Scheme 8. Reaction of compound **1** with formaldehyde in the presence of phosphorous acid.

Conclusions

We suggested a simple method for the synthesis of some novel functionalized 1,2,4,3-triazaphospholo[1,5-*a*]pyridines **2–14** and pyrido[1,2-*b*][1,2,4,5]triazaphosphinine **16, 19** and **22** by the reaction of 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) with some different phosphorus reagents under mild reaction conditions.

Experimental Section

General. The melting points were determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectra were measured on a Perkin-Elmer 293 spectrophotometer using KBr disks. ¹H-NMR spectra were recorded on a Bruker 400 and 600 MHz spectrometer. ¹³C- and ³¹P-NMR spectra were recorded on a Bruker 600 MHz spectrometer operating at 150 and 242 MHz, respectively. Chemical shifts are reported in ppm with respect to the references and are stated relative to tetramethylsilane (TMS) for ¹H- and ¹³C-NMR and to 85% phosphoric acid for the ³¹P-NMR. Mass spectra were recorded on a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 eV. Elemental microanalysis was performed Perkin-Elmer 2400II at the

Chemical War department, Ministry of Defense. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) and elemental microanalysis.

Synthesis of 1,6-diamino-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (1). A mixture of 4-fluorobenzaldehyde (0.27 ml, 2.5 mmol), malononitrile (0.165 g, 2.5 mmol) and cyanoacetohydrazide (0.25 g, 2.5 mmol) in absolute ethanol (30 ml) containing a few drops of piperidine, was heated under reflux for 5 h. After cooling, the formed solid was filtered and recrystallized from DMF to afford beige crystals in 85% yield (0.57 g); mp 315–317 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3392, 3292 (NH₂), 3187, 3111 (NH₂), 2219 (2 C≡N), 1667 (C=O), 1613 (C=C). ¹H-NMR (400 MHz, DMSO-*d*₆): 5.68 (s, 2H, NH₂), 7.41 (td, 2H, *J* 9.2 and 2.8 Hz, Ar-H), 7.59 (td, 2H, *J* 9.2 and 2.0 Hz, Ar-H), 7.97 (s, 1H, NH), 8.48 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 74.5 (C-5), 86.6 (C-3), 115.5 (C≡N), 116.0 (C≡N), 130.6 (C-4), 130.9 (C-2',6'), 156.6 (C-3',5'), 158.6 (C-1'), 159.1 (C-6), 161.8 (C-4'), 164.3 (C=O). MS (EI, *m/z*): 269 (M⁺, 100%). Anal. calcd. for C₁₃H₈FN₅O (269.23): C, 57.99; H, 2.99; N, 26.01%. Found: C, 57.63; H, 2.61; N, 25.62%.

Synthesis of 7-(4-fluorophenyl)-2-oxido-5-oxo-2-phenyl-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (2). A solution of phenylphosphonic dichloride (0.35 ml, 2.5 mmol) in dry dioxane (5 ml), was added dropwise to a solution of compound **1** (0.675 g, 2.5 mmol) in dry dioxane (30 ml) in presence of a catalytic amount of triethylamine (0.35 ml, 5 mmol) at 5–10 °C for 30 minutes. The mixture was heated under reflux for 4 hours then filtered off to remove triethyl ammonium chloride. The filtrate was concentrated into its third volume and left to cool. The formed solid was filtered off and crystallized from EtOH to give pale yellow solid in 62% yield (0.61 g); mp 287–289 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3294, 3198 (2 NH), 2218 (2 C≡N), 1671 (C=O), 1629 (C=C), 1229 (P=O). ¹H-NMR (400 MHz, DMSO-*d*₆): 6.92 (dd, 1H, *J* 8.4 and 4.2 Hz, Ph-H), 7.18–7.26 (m, 4H, Ph-H and Ar-H), 7.40–7.41 (m, 3H, Ph-H and Ar-H), 7.50 (dd, 1H, *J* 7.8 and 2.4 Hz, Ar-H), 8.79 (s, 1H, NH), 9.15 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 75.0 (C-5), 87.1 (C-3), 116.2 (C≡N), 116.4 (C≡N), 120.2 (C-3'',5''), 127.6 (C-2'',6''), 130.3 (C-4), 132.1 (C-2',6'), 135.4 (C-4''), 137.4 (C-1''), 156.2 (C-3',5'), 157.8 (C-1'), 158.5 (C-6), 161.5 (C-4'), 165.0 (C=O). ³¹P-NMR (242 MHz, DMSO-*d*₆): 32.1 ppm. MS (EI, *m/z*): 393 (M+2, 20%). Anal. calcd. for C₁₉H₁₁FN₅O₂P (391.30): C, 58.32; H, 2.83; N, 17.89%. Found: C, 58.03; H, 2.55; N, 17.57%.

Synthesis of 7-(4-fluorophenyl)-2-hydroxy-2-oxido-5-oxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (4). A solution of phosphorus oxychloride (0.25 ml, 2.5 mmol) in dry dioxane (5 ml), was added dropwise to a solution of compound **1** (0.675 g, 2.5 mmol) in dry dioxane (30 ml) in presence of a catalytic amount of triethylamine (0.35 ml, 5 mmol) at 5–10 °C for 30 minutes. The mixture was heated under reflux for 10 hours then filtered off to remove triethyl ammonium chloride. The filtrate mixture was concentrated into its third volume and left to cool. The formed solid was filtered off and crystallized from diluted ethanol to give white solid in 88% yield (0.73 g); mp 303–306 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3390 (br, OH), 3294, 3198 (2 NH), 2218 (2 C≡N), 1671 (C=O), 1629 (C=C), 1229 (P=O). ¹H-NMR (400 MHz, DMSO-*d*₆): 3.38 (br, 1H, OH), 7.38–7.43 (m, 2H, Ar-H), 7.50 (d, 1H, *J* 8.4 Hz, Ar-H), 7.58–7.62 (m, 1H, Ar-H), 8.26 (s, 1H, NH), 8.82 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 75.4 (C-5), 86.1 (C-3), 115.5 (C≡N), 115.8 (C≡N), 130.6 (C-4), 133.3 (C-2',6'), 155.4 (C-3',5'), 157.0 (C-1'), 159.8 (C-6), 160.8 (C-4'), 164.8 (C=O). MS (EI, *m/z*): 333 (M+2, 8%), 332 (M+1, 9%), 331 (M⁺, 13%). Anal. calcd. for C₁₃H₇FN₅O₃P (331.20): C, 47.14; H, 2.13; N, 21.14%. Found: C, 46.83; H, 1.85; N, 20.79%.

Synthesis of 7-(4-fluorophenyl)-5-oxo-1,5-dihydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (5). Hexaethylphosphorus triamide (0.68 ml, 2.5 mmol) was added to a solution of compound **1** (0.675 g, 2.5 mmol) in dry dioxane (30 ml). The mixture was heated under reflux for 10 hours. The solution was concentrated to its half volume and left to cool. The oily product was treated with ethyl acetate to give solid which was filtered off and crystallized from diluted ethanol to give pale yellow solid in yield 43% (0.32 g); mp

200–201 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3297 (NH), 3050 (C–H_{arom}), 2214 (2 C≡N), 1665 (C=O). ¹H-NMR (400 MHz, DMSO-*d*₆): 7.28 (d, 2H, *J* 9.0 Hz, Ar–H), 7.65 (d, 2H, *J* 7.2 Hz, Ar–H), 8.71 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 75.5 (C–5), 82.9 (C–3), 110.7 (C≡N), 112.6 (C≡N), 133.7 (C–4), 133.9 (C–2',6'), 156.0 (C–3',5'), 158.0 (C–1'), 160.1 (C–6), 161.8 (C–4'), 164.9 (C=O). MS (EI, *m/z*): 297 (M⁺, 18%). Anal. calcd. for C₁₃H₁₅FN₅OP (297.18): C, 52.54; H, 1.70; N, 23.57. Found: C, 52.19; H, 1.53; N, 23.22%.

Synthesis of 6-cyano-7-(4-fluorophenyl)-5-oxo-1,5-dihydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-8-carboxamide (6). A solution of phosphorus tribromide (0.25 ml, 2.5 mmol) in dry dioxane (5 ml), was added dropwise to a solution of compound **1** (0.67 g, 5 mmol) in dry dioxane (60 ml) in presence of a catalytic amount of triethylamine (0.7 ml, 10 mmol) at 5–10 °C for 30 minutes. The mixture was heated under reflux for 10 hours. The reaction mixture was concentrated into its third volume and left to cool. The obtained oily product was dissolved in distilled water (15 ml). The formed solid was filtered off and crystallized from diluted ethanol to give yellow solid in 45% yield (0.35 g); mp 294–297 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3371, 3283 (NH₂), 3200 (NH), 2215 (C≡N), 1682 (C=O), 1666 (C=O), 1607 (C=C). ¹H-NMR (400 MHz, DMSO-*d*₆): 7.41 (td, 2H, *J* 8.8 and 3.0 Hz, Ar–H), 7.58 (td, 2H, *J* 8.8 and 3.2 Hz, Ar–H), 8.47 (br, 2H, NH₂), 8.79 (br, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 78.5 (C–5), 86.6 (C–3), 116.2 (C≡N), 130.6 (C–4), 130.9 (C–2',6'), 156.6 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 161.8 (C–4'), 164.2 (C=O), 170.6 (C=O). MS (EI, *m/z*): 315 (M⁺, 55%). Anal. calcd. for C₁₃H₇FN₅O₂P (315.20): C, 49.53; H, 2.23; N, 22.21%. Found: C, 49.10; H, 1.94; N, 21.89%.

Synthesis of 1,6-diamino-4-(4-fluorophenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (7). A mixture of phosphorus pentasulfide (0.55 g, 2.5 mmol) and compound **1** (0.675 g, 2.5 mmol) in dry dioxane (40 ml), was heated under reflux for 5 hours. The reaction mixture was concentrated into its half volume and left to cool. The formed solid was filtered off and crystallized from ethanol to give orange crystalline solid in 56% yield (0.40 g); mp 285–286 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3374, 3283, 3204 (2 NH₂), 2216 (2 C≡N), 1604 (C=C), 1164 (C=S). ¹H-NMR (400 MHz, DMSO-*d*₆): 5.68 (s, 2H, NH₂), 7.41 (td, 2H, *J* 8.8 and 2.4 Hz, Ar–H), 7.59 (td, 2H, *J*=8.0 and 2.8 Hz, Ar–H), 8.47 (s, 2H, NH₂). ¹³C-NMR (100 MHz, DMSO-*d*₆): 74.4 (C–5), 86.6 (C–3), 115.6 (C≡N), 116.2 (C≡N), 130.6 (C–4), 131.0 (C–2',6'), 156.6 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 161.8 (C–4'), 179.0 (C=S). MS (EI, *m/z*): 285 (M⁺, 100%). Anal. calcd. for C₁₃H₈FN₅S (285.30): C, 54.72; H, 2.82; N, 24.54; S, 11.23%. Found: C, 54.33; H, 2.54; N, 24.11; S, 10.85%.

Synthesis of 7-(4-fluorophenyl)-2-sulfanyl-2-sulfido-5-thioxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (8). **Method A.** A mixture of phosphorus pentasulfide (0.55 g, 2.5 mmol) and compound **7** (0.285 g, 1 mmol) in dry dioxane (20 ml), was heated under reflux for 8 hours. The reaction mixture was concentrated into its half volume and left to cool. The formed solid was filtered off and crystallized from ethanol to give orange solid in 42% yield (0.16 g); mp 240–242 °C. **Method B.** A mixture of phosphorus pentasulfide (1.22 g, 5.5 mmol) and compound **1** (0.675 g, 2.5 mmol) in dry dioxane (40 ml), was heated under reflux for 8 hours. The reaction mixture was concentrated into its half volume and left to cool. The formed solid was filtered off and crystallized from ethanol to give orange crystalline solid in yield 38% (0.36 g); mp 242–243 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3303, 3199 (2 NH), 2700 (br, SH), 2216 (2 C≡N), 1608 (C=C), 1163 (C=S), 764 (P=S). ¹H-NMR (400 MHz, DMSO-*d*₆): 4.63 (brs, 1H, SH), 7.12 (t, 2H, *J* 7.2 Hz, Ar–H), 7.48 (t, 2H, *J* 8.0 Hz, Ar–H), 8.99 (s, 1H, NH), 9.55 (brs, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 75.7 (C–5), 85.8 (C–3), 111.2 (C≡N), 112.4 (C≡N), 131.9 (C–4), 132.9 (C–2',6'), 156.0 (C–3',5'), 158.3 (C–1'), 159.6 (C–6), 161.2 (C–4'), 179.2 (C=S). MS (EI, *m/z*): 381 (M+2, 2%), 380 (M+1, 7%), 379 (M⁺, 35%). Anal. calcd. for C₁₃H₇FN₅PS₃ (379.39): C, 41.15; H, 1.86; N, 18.46; S, 25.35%. Found: C, 40.79; H, 1.59; N, 18.08; S, 25.02%.

Synthesis of 7-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-oxo-2-sulfido-5-thioxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (9). Lawesson's reagent (0.5 g, 1.25 mmol) was added to a solution of compound **1** (0.330 g, 1.25 mmol) or compound **7** (0.356, 1.25 mmol) in dry dioxane (30 ml). The mixtures were heated under reflux for 8 hours. The solutions were concentrated to their half volumes and left

to cool. The oily products were treated with diethyl ether to give solids which were filtered off and crystallized from diluted ethanol to give orange solids in 45% yield (0.25 g) and 43% (0.24 g), respectively; mp 278–280 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3310, 3199 (2 NH), 3073 (C–H_{arom}), 2965 (C–H_{aliph}), 2217 (2 C≡N), 1637, 1617 (C=C), 1079 (O–C), 844 (P=S). ¹H-NMR (400 MHz, DMSO-*d*₆): 3.81 (s, 3H, OCH₃), 6.53 (s, 1H, NH), 7.39–7.45 (m, 4H, Ar–H), 7.57–7.63 (m, 4H, Ar–H), 8.76 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 55.0 (OCH₃), 74.5 (C–5), 86.6 (C–3), 115.8 (C≡N), 116.2 (C≡N), 121.5 (C–3'',5''), 130.5 (C–2'',6''), 130.7 (C–4), 130.8 (C–2',6'), 132.0 (C–1''), 153.6 (C–4''), 156.6 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 161.9 (C–4'), 178.3 (C=S). ³¹P-NMR (242 MHz, DMSO-*d*₆): 54.5 ppm. MS (EI, *m/z*): 453 (M⁺, 20%). Anal. calcd. for C₂₀H₁₃FN₅OPS (453.46): C, 52.97; H, 2.89; N, 15.44; S, 14.14%. Found: C, 52.59; H, 2.61; N, 15.09; S, 13.79%.

Synthesis of 2-ethoxy-7-(4-fluorophenyl)-5-oxo-2-sulfido-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (10). A solution of phosphorus pentasulfide (1.11 g, 5 mmol) in absolute ethanol (30 ml) was heated under reflux for 1 hour to give *O,O*-diethyldithiophosphoric acid (formed *in situ*). Compound **1** (0.675 g, 5 mmol) was added to the previous ethanolic solution. The mixture was heated under reflux for 8 hours. The reaction mixture was concentrated into its half volume and left to cool. After adding some water, the formed solid was filtered off and crystallized from diluted ethanol to give yellow crystals in 38% yield (0.35 g); mp 298–300 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3392, 3291 (2 NH), 2214 (2 C≡N), 1667 (C=O), 1630 (C=C), 1111 (P–O–C), 704 (P=S). ¹H-NMR (400 MHz, DMSO-*d*₆): 1.08 (t, 3H, *J* 7.2 Hz, CH₃), 3.46 (q, 2H, *J* 7.2 Hz, CH₂), 7.41 (td, 2H, *J* 8.8 and 2.0 Hz, Ar–H), 7.59 (td, 2H, *J* 6.4 and 2.4 Hz, Ar–H), 8.47 (s, 1H, NH), 9.26 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 18.5 (CH₃), 56.0 (CH₂), 74.5 (C–5), 86.6 (C–3), 115.5 (C≡N), 116.2 (C≡N), 130.6 (C–4), 130.9 (C–2',6'), 156.6 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 161.8 (C–4'), 164.2 (C=O). MS (EI, *m/z*): 375 (M⁺, 35%). Anal. calcd. for C₁₅H₁₁FN₅O₂PS (375.32): C, 48.00; H, 2.95; N, 18.65; S, 8.52%. Found: C, 47.63; H, 2.61; N, 18.28; S, 8.09%.

Synthesis of 2-ethoxy-7-(4-fluorophenyl)-2-oxido-5-oxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (11). A mixture of triethyl phosphate (0.85 ml, 5 mmol) and compound **1** (0.67 g, 2.5 mmol) was fused on water bath for 10 hours. The oily product was dissolved in hot diluted ethanol and left to cool. The formed solid was filtered off and dried to give red solid in 57% yield (0.52 g); mp 262–265 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3429 (br, 2 NH), 2976, 2935 (C–H_{aliph}), 2213 (2 C≡N), 1660 (C=O), 1600 (C=C), 1228 (P=O), 1093 (P–O–C). ¹H-NMR (400 MHz, DMSO-*d*₆): 1.21 (t, 3H, *J* 7.2 Hz, CH₃), 3.06 (q, 2H, *J* 7.2 Hz, CH₂), 5.69 (brs, 1H, NH), 7.41 (td, 2H, *J* 9.2 and 2.4 Hz, Ar–H), 7.58 (td, 2H, *J* 8.4 and 2.8 Hz, Ar–H), 8.49 (brs, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 18.5 (CH₃), 60.0 (CH₂), 74.5 (C–5), 86.6 (C–3), 115.6 (C≡N), 116.2 (C≡N), 130.6 (C–4), 131.0 (C–2',6'), 156.5 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 161.8 (C–4'), 164.2 (C=O). MS (EI, *m/z*): 361 (M+2, 5%), 360 (M+1, 18%). Anal. calcd. for C₁₅H₁₁FN₅O₃P (359.25): C, 50.15; H, 3.08; N, 19.49. Found: C, 49.78; H, 2.81; N, 19.12%.

Synthesis of 7-(4-fluorophenyl)-2-oxido-5-oxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (12). A mixture of diethyl phosphite (0.7 ml, 5 mmol) and compound **1** (0.67 g, 2.5 mmol) was fused on water bath for 6 hours. The oily product was dissolved in hot diluted ethanol and left to cool. The formed solid was filtered off and dried to give orange solid in 40% yield (0.31 g); mp 204–206 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3430, 3300 (br, 2 NH), 2216 (2 C≡N), 1667 (C=O), 1604 (C=C), 1230 (P=O). ¹H-NMR (400 MHz, DMSO-*d*₆): 6.47 (1H, d, *J* 711 Hz, P–H), 6.22 (t, 1H, *J* 6 Hz, NH), 7.39 (dd, 2H, *J* 9.2 and 1.2 Hz, Ar–H), 7.53–7.57 (m, 2H, Ar–H), 8.38 (brs, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 76.0 (C–5), 82.0 (C–3), 115.6 (C≡N), 115.9 (C≡N), 130.4 (C–4), 130.6 (C–2',6'), 156.0 (C–3',5'), 158.0 (C–1'), 159.0 (C–6), 161.0 (C–4'), 164.0 (C=O). MS (EI, *m/z*): 315 (M⁺, 18%). Anal. calcd. for C₁₃H₇FN₅O₂P (315.20): C, 49.53; H, 2.23; N, 22.21%. Found: C, 49.16; H, 1.90; N, 21.86%.

Synthesis of 2-(2-chloroethoxy)-7-(4-fluorophenyl)-5-oxo-1,2,3,5-tetrahydro[1,2,4,3]triazaphospholo[1,5-*a*]pyridine-6,8-dicarbonitrile (13). A mixture of tris(2-chloroethyl)phosphite (0.9 ml, 5 mmol) and compound **1**

(0.67 g, 2.5 mmol) was fused on water bath for 8 hours. The oily product was dissolved in hot diluted ethanol and left to cool. The formed solid was filtered off and dried to give red solid in 43% yield (0.41 g); mp 205–208 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3295, 3396 (2 NH), 2904 (C–H_{aliph}), 2217 (2 C≡N), 1666 (C=O), 1631 (C=C), 1050 (P–O–C). ¹H-NMR (400 MHz, DMSO-*d*₆): 3.54 (t, 2H, *J* 5.6 Hz, CH₂Cl), 3.83 (t, 2H, *J* 4.8 Hz, CH₂O), 5.67 (brs, 1H, NH), 7.41 (t, 2H, *J*=8.8 Hz, Ar–H), 7.58 (t, 2H, *J*=8.4 Hz, Ar–H), 8.47 (br, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 45.0 (CH₂Cl), 62.5 (CH₂O), 74.5 (C–5), 86.6 (C–3), 115.6 (C≡N), 116.2 (C≡N), 130.6 (C–4), 130.9 (C–2',6'), 156.6 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 161.0 (C–4'), 164.0 (C=O). MS (EI, *m/z*): 379 (M+2, 5%), 377 (M⁺, 12%). Anal. calcd. for C₁₅H₁₀ClFN₅O₂P (377.7): C, 47.70; H, 2.66; N, 18.54%. Found: C, 47.35; H, 2.29; N, 18.19%.

Synthesis of 8-(4-fluorophenyl)-6-oxo-2,3,6,10-tetrahydro[1,3,2]oxazaphospholo[3',2':2,3][1,2,4,3]triazaphospholo[1,5-*a*]pyridine-7,9-dicarbonitrile (14). A solution of compound **13** (0.38 g, 1 mmol) was heated in absolute ethanol containing a few drops of triethylamine for 12 hours. After cooling, the solution was poured into ice. The formed solid was filtered off and crystallized from diluted ethanol to give brick red solid in 88% yield (0.3 g); mp 123–125 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3417 (br, NH), 2964 (C–H_{aliph}), 2219 (2 C≡N), 1660 (C=O), 1603 (C=C), 1039 (P–O–C). ¹H-NMR (400 MHz, DMSO-*d*₆): 2.91 (s, 2H, CH₂N), 3.60 (brs, 2H, CH₂O), 7.41 (td, 2H, *J* 8.8 and 2.0 Hz, Ar–H), 7.59 (td, 2H, *J* 8.0 and 2.4 Hz, Ar–H), 7.97 (s, 1H, NH). ¹³C-NMR (150 MHz, DMSO-*d*₆): 42.5 (CH₂N), 60.0 (CH₂O), 74.5 (C–5), 86.6 (C–3), 115.4 (C≡N), 116.2 (C≡N), 130.6 (C–4), 130.9 (C–2',6'), 156.6 (C–3',5'), 158.6 (C–1'), 159.1 (C–6), 162.0 (C–4'), 164.3 (C=O). MS (EI, *m/z*): 343 (M+2, 1%), 342 (M+1, 6%), 341 (M⁺, 35%). Anal. calcd. for C₁₅H₉FN₅O₂P (341.24): C, 52.79; H, 2.65; N, 20.52%. Found: C, 52.43; H, 2.36; N, 20.19%.

Synthesis of 2-ethoxy-8-(4-fluorophenyl)-3-methyl-2-oxido-6-oxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-*b*][1,2,4,5]triazaphosphinine-7,9-dicarbonitrile (16). A mixture of compound **1** (0.675 g, 2.5 mmol) and acetaldehyde (0.132 g, 3 mmol) was warmed for 2 hour at 35–40 °C, then added diethyl phosphite (0.4 ml, 2.85 mmol) and two drops of trifluoroboron etherate. The reaction mixture was heated under reflux on water bath for 10 hours. The reaction mixture was treated with ethyl acetate, giving crude solid which was crystallized from diluted ethanol to give pale yellow solid in 35% yield (0.34 g); mp 252–254 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3299, 3200 (2 NH), 3050 (C–H_{arom}), 2925, 2858 (C–H_{aliph}), 2216 (2 C≡N), 1667 (C=O), 1236 (P=O), 1000 (P–O–C). ¹H-NMR (400 MHz, DMSO-*d*₆): 1.24 (t, 3H, *J* 7.2 Hz, CH₃), 1.85 (d, 3H, *J* 2.5 Hz, CH₃), 3.97 (q, 2H, *J* 7.2 Hz, CH₂), 4.50 (q, 1H, *J* 18.6 Hz, P–CH), 7.45 (d, 2H, *J* 9.8 Hz, Ar–H), 7.70 (d, 2H, *J* 11.2 Hz, Ar–H), 7.80 (s, 1H, NH), 10.06 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 15.9 (CH₃), 35.0 (CH₃), 53.5 (d, *J*=150 Hz, P–CH), 63.0 (CH₂), 75.8 (C–5), 85.1 (C–3), 110.9 (C≡N), 112.0 (C≡N), 133.5 (C–4), 134.0, 134.7 (C–2',6'), 155.6 (C–3',5'), 158.1 (C–1'), 159.3 (C–6), 162.2 (C–4'), 167.3 (C=O). ³¹P-NMR (242 MHz, DMSO-*d*₆): 22.2 ppm. MS (EI, *m/z*): 387 (M⁺, 8%). Anal. calcd. for C₁₇H₁₅FN₅O₃P (387.30): C, 52.72; H, 3.90; N, 18.08. Found: C, 52.39; H, 3.63; N, 17.84%.

Synthesis of 8-(4-fluorophenyl)-3-methyl-2-oxido-6-oxo-2-phenyl-1,3,4,6-tetrahydro-2H-pyrido[1,2-*b*][1,2,4,5]triazaphosphinine-7,9-dicarbonitrile (19). A mixture of compound **1** (0.675 g, 2.5 mmol) and acetaldehyde (0.132 g, 3 mmol) was warmed for 2 hour at 35–40 °C, then added *P,P*-dichlorophenylphosphine (0.34 ml, 2.5 mmol) and heated under reflux on water bath for 10 hours. The reaction mixture was treated with cold water, giving crude solid which was crystallized from diluted ethanol to give pale yellow solid in 45% yield (0.47 g); mp 232–234 °C. IR (KBr), (ν_{\max} , cm^{-1}): 3370, 3304 (2 NH), 2217 (2 C≡N), 1666 (C=O), 1611 (C=C), 1237 (P=O). ¹H-NMR (400 MHz, DMSO-*d*₆): 2.08 (d, 3H, *J* 2.4 Hz, CH₃), 4.14–4.20 (m, 1H, P–CH), 6.92 (dd, 1H, *J* 8.4 and 4.2 Hz, Ph–H), 7.18–7.26 (m, 4H, Ar–H and Ph–H), 7.40–7.41 (m, 3H, Ar–H and Ph–H), 7.50 (dd, 1H, *J* 7.8 and 2.4 Hz, Ph–H), 8.79 (s, 1H, NH), 9.15 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆): 34.4 (CH₃), 45.5 (d, *J* 138 Hz, P–CH), 75.0 (C–5), 82.0 (C–3), 116.2 (C≡N), 116.4 (C≡N), 120.3 (C–3'',5''), 127.6, 127.8 (C–2'',6''), 130.2 (C–4), 132.0 (C–2',6'), 135.4 (C–4''), 137.4 (C–1''), 156.2 (C–3',5'), 157.8 (C–1'), 159.1 (C–6), 161.6

(C-4'), 167.5 (C=O). MS (EI, m/z): 419 (M^+ , 8%). Anal. calcd. for $C_{21}H_{15}FN_5O_2P$ (419.34): C, 60.15; H, 3.61; N, 16.70%. Found: C, 59.82; H, 3.29; N, 16.34%.

Synthesis of {[7,9-dicyano-8-(4-fluorophenyl)-2-hydroxy-2-oxido-6-oxo-1,2,3,6-tetrahydro-4H-pyrido[1,2-b][1,2,4,5]triazaphosphinine-4-yl]methyl}phosphonic acid (22). A solution of phosphorous acid (0.41 g, 5 mmol) in distilled water (5 ml) was added dropwise to an acidic solution of compound **1** (0.67 g, 5 mmol) in diluted hydrochloric acid (30 ml, 5%) in presence of formaldehyde (1 ml). The mixture was heated under reflux for 10 hours. The solvent was evaporated. After adding some cold water, the formed solid was filtered off and crystallized from diluted DMF to give yellow solid in 55% yield (0.56 g); mp 259–260 °C. IR (KBr), (ν_{max} , cm^{-1}): 3418 (br OH and NH), 3077 (C-H_{arom}), 2964, 2898 (C-H_{aliph}), 2218 (2 C≡N), 1667 (C=O), 1603 (C=C), 1230 (P=O). ¹H-NMR (400 MHz, DMSO- d_6): 4.54–5.15 (m, 4H, 2 P-CH₂), 3.68 (br, 3H, P-OH), 7.43 (td, 2H, J 8.8 and 2.4 Hz, Ar-H), 7.58 (td, 2H, J 9.2 and 4.0 Hz, Ar-H), 10.34 (s, 1H, NH). ¹³C-NMR (100 MHz, DMSO- d_6): 45.0 (P-CH₂), 50.5 (P-CH₂), 76.3 (C-5), 90.4 (C-3), 114.8 (C≡N), 115.8 (C≡N), 130.5 (C-4), 130.6 (C-2',6'), 154.4 (C-3',5'), 154.8 (C-1'), 159.7 (C-6), 161.9 (C-4'), 164.4 (C=O). ³¹P-NMR (242 MHz, DMSO- d_6): 11.7 and 19.2 ppm. MS (EI, m/z): 409 ($M+1$, 6%), 408 (M^+ , 32%). Anal. calcd. for $C_{15}H_{12}FN_5O_6P$ (408.26): C, 44.13; H, 2.96; N, 17.15%. Found: C, 43.61; H, 2.61; N, 16.83%.

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References

- Holla, B. S.; Ashok, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 981.
<https://doi.org/10.1080/10426500601088853>
- Eugenia, F. C.; Laichici, M.; Gheorghe, F. C.; Vlascici, D. *J. Serb. Chem. Soc.* **2006**, *71*, 1031.
<https://doi.org/10.2298/JSC0610031F>
- He, L. N.; Zhuo, R. X.; Chen, R.Y.; Li, K.; Zhang, Y. J. *Heteroat. Chem.* **1999**, *10*, 105.
[https://doi.org/10.1002/\(SICI\)1098-1071\(1999\)10:2<105::AID-HC3>3.0.CO;2-V](https://doi.org/10.1002/(SICI)1098-1071(1999)10:2<105::AID-HC3>3.0.CO;2-V)
- Ali, T. E. *Eur. J. Med. Chem.* **2009**, *44*, 4539.
<https://doi.org/10.1016/j.ejmech.2009.06.022>
- Abdou, W. M.; Ganoub, N. A.; Sabry, E. *Monatsh Chem.* **2016**, *147*, 619.
<https://doi.org/10.1007/s00706-015-1542-4>
- Chen, R. Y.; Mao, L. J.; Chen, X. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *165*, 91.
<https://doi.org/10.1080/10426500008076328>
- Chen, R. Y.; Mao, L. J. *Heteroat. Chem.* **1994**, *5*, 125.
<https://doi.org/10.1002/hc.520050208>
- Chen, R. Y.; Mao, L. J.; Chen, X. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *89*, 83.
<https://doi.org/10.1080/10426509408020436>
- Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880.
<https://doi.org/10.1021/jo00002a077>
- Reddy, T. R. K.; Mutter, R.; Heal, W.; Guo, K.; Gillet, V. J.; Pratt, S.; Chen, B. *J. Med. Chem.* **2006**, *49*, 607.

<https://doi.org/10.1021/jm050610f>

11. Manna, F.; Chimenti, F.; Bolasco, A.; Filippelli, A.; Palla, A.; Filippelli, W.; Lampa, E.; Mercantini, R. *Eur. J. Med. Chem.* **1992**, *27*, 627.
[https://doi.org/10.1016/0223-5234\(92\)90141-M](https://doi.org/10.1016/0223-5234(92)90141-M)
12. El-Hawash, S. M.; Abdel Wahab, A. E.; El-Demellawy, M. A. *Arch. Pharm.* **2006**, *339*, 14.
<https://doi.org/10.1002/ardp.200500161>
13. Samadi, A.; Marco-Contelles, J.; Soriano, E.; Alvarez-Perez, M.; Chioua, M.; Romero, A.; Gonzalez-Lafuente, L.; Gandia, L.; Roda, J. M.; Lopez, M. G.; Villarroya, M.; Garcia, A.G.; Rios, C. D. L. *Bioorg. Med. Chem.* **2010**, *18*, 5861.
<https://doi.org/10.1016/j.bmc.2010.06.095>
14. Cocco, M. T.; Congiu, C.; Lilliu, V.; Onnis, V. *Bioorg. Med. Chem.* **2007**, *15*, 1859.
<https://doi.org/10.1016/j.bmc.2006.11.031>
15. Behbehani, H.; Ibrahim, H. M.; Makhseed, S.; Elnagdi, M. H.; Mahmoud, H. *Eur. J. Med. Chem.* **2012**, *52*, 51.
<https://doi.org/10.1016/j.ejmech.2012.03.004>
16. Begue, J. P.; Delpon, D. B. *J. Fluorine Chem.* **2006**, *127*, 992.
<https://doi.org/10.1016/j.jfluchem.2006.05.006>
17. Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27.
[https://doi.org/10.1016/S0022-1139\(02\)00201-4](https://doi.org/10.1016/S0022-1139(02)00201-4)
18. Ali, T. E.; El-Edfawy, S. M. *Res. Chem. Intermed.* **2016**, *42*, 1329.
<https://doi.org/10.1007/s11164-015-2088-0>
19. Ali, T. E.; Ibrahim, M. A.; El-Edfawy, S. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 819.
<https://doi.org/10.1080/10426507.2017.1287183>
20. Abdel-kariem, S. M.; Ali, T. E. *J. Heterocycl. Chem.* **2017**, *54*, 2916.
<https://doi.org/10.1002/jhet.2902>
21. Al-Najjar, A. A.; Amer, S. A.; Raid, M.; Elghamry, I.; Elnagdi, M. H. *J. Chem. Res.* **1996**, 296.
22. Yang H.; and Lu, R. *Synth. Commun.* **1994**, *24*, 59.
<https://doi.org/10.1080/00397919408012626>
23. Prasad, G. S.; Babu, B. H.; Reddy, C. D.; Raju, C. N.; Reddy C. S. *Synthet. Commun.* **2008**, *38*, 85.
<https://doi.org/10.1080/00397910701649148>
24. Ali, T. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 88.
<https://doi.org/10.1080/10426500802713309>
25. Ali, T. E. *Arkivoc* **2014**, 21.
26. Beck, J.; Gharbi, S.; Herteg-Fernea, A.; Vercheval, L.; Bebrone, C.; Lassaux, P.; Zervosen, A.; Marchand-Brynaert, J. *Eur. J. Org. Chem.* **2009**, 85.
27. Octaviano, J. Z.; Martinez, A. H.; Guevara, A. O.; Elizalde, I. L.; Hopfl, H. *Heteroat. Chem.* **2006**, *17*, 75.
<https://doi.org/10.1002/hc.20178>
28. Wang, B.; Miao, Z. W.; Haung, Y.; Chen, R. Y. *Heterocycles* **2006**, *68*, 2123.
<https://doi.org/10.3987/COM-06-10838>
29. Aime, S.; Cavallotti, C.; Gianolio, E.; Giovenzana, G. B.; Palmisano, G.; Sisti, M. *Tetrahedron* **2002**, *43*, 8387.
[https://doi.org/10.1016/S0040-4039\(02\)01950-0](https://doi.org/10.1016/S0040-4039(02)01950-0)
30. Vuano, B. M.; Acebal, S. G.; Sala, O.; Brioux, O.; Pieroni, O. I. *J. Mol. Struct.* **2004**, *690*, 77.