One-pot three-component Kabachnik–Fields reaction: Synthesis of novel α-aminophosphonates containning thiazolylpyrazole moiety

Ashraf A. Sediek,[1,2] Mohamed S. Mudarris[1] and Abeer A. Shaddy[2]

[1]Chemistry Department, Faculty of Sciences and Arts, Al-Kamil Branch, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Chemical Industries Division, National Research Centre, Dokki, Giza, Egypt
asediek@yahoo.com

Abstract: A novel series of thiazolylpyrazole α-aminmethylphosphonate derivatives **4a-l** have been synthesized by Kabachnik–Fields type reaction of equimolar quantities of 5-amino-3-(4-hydroxyphenyl)-1-(4-aryl-thiazol-2-yl)-1*H*-pyrazole-4-carbonitriles, aromatic aldehydes and alkyl phosphites, by using $FeCl_3$ as *Lewis acid catalyst*. The reaction took place *via* imine formation followed by addition of dialkyl phosphite to furnish thiazolylpyrazole α-aminmethylphosphonate derivatives in good yield.

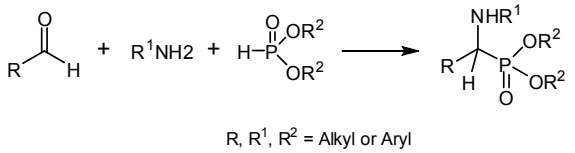
[One-pot three-component Kabachnik–Fields reaction: Synthesis of novel α-aminophosphonates containning thiazolylpyrazole moiety. *Life Sci J* 2014;11(5):9-16]. (ISSN:1097-8135). http://www.lifesciencesite.com. 2

Keywords: α-aminmethylphosphonate; thiazolylpyrazoleo; Kabachnik-Fields reaction

Introduction

α-Aminophosphonates and their derivatives are an important class of bioactive molecules due to their biological importance and wide application in organic chemistry.[1-3] A considerable number of α-aminophosphonate derivatives are known to be antiviral,[4] antifungal, antibacterial[5] and antitumor.[6-12] A large number of studies on their synthesis and biological activities have been reported.[13-18] From this point of view, our attention has been driven to the synthesis of biologically active α-aminophosphonates bearing N-heterocycles moieties.

In the present work we represented the synthesis of different dialkyl [3-(4-hydroxyphenyl)-4-cyano-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5-yl-amino](aryl)methyl-phosphonate **4a-l** derivatives *via* the reaction of 5-amino-3-(4-hydroxyphenyl)-1-(4-arylthiazol-2-yl)-1*H*-pyrazole-4-carbonitriles **1a,b** with a Varity of aromatic aldehydes and dialkyl phosphites (DAPs) **3a,b** (Table-1) through three-component coupling based on Kabachnik-Fields reaction (Scheme A) using 10% mol $FeCl_3$ as catalyst.



Scheme A

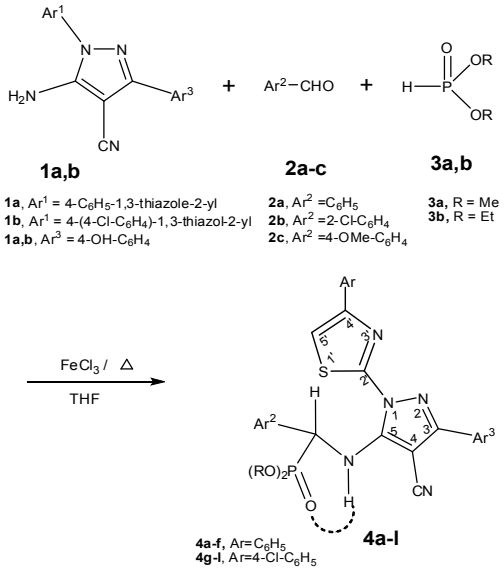
General pathway of the Kabachnik-Fields reaction

In the framework of the scientific research of the project No. 204/856/1433, funded by King Abdulaziz University, the titled compounds and their structure were synthesized and investigated.

Chemistry

α-Aminomethylphosphonates **4a-l** were synthesized by one-pot three component Kabachnik–Fields reaction, by heating a mixture of 5-amino pyrazole derivatives **1a,b** with appropriate aromatic aldehye **2a-c** and dialkyl phosphonates **3a,b** in THF for 5-6 h. They were obtained in good yield (Scheme 1).

The structure of synthesized compounds have been confirmed by mass, infrared spectra (IR) and nuclear magnetic resonance (NMR) spectroscopy which displayed results agreed with the proposed structures **4a-l**.



Scheme 1

The spectroscopic data of compound **4a** gave in IR spectra signals (cm^{-1}) at 3455 (OH-phenyl), 3,355 (NH), 2,198 (CN), 1,235 (P = O) and 1,055 (P–O–C); ^{1}H NMR showed two doublets at δ = 3.64, 3.74 ppm, and J_{H-H} = 6.9, $^3J_{P-H}$ = 11.9 Hz, for 6H of $(CH_3O)_2P$, doublet of doublet at δ = 5.8, 5.9, J_{H-H} = 8.8, $^2J_{P-H}$ = 18.5 Hz, for 1H of HC–P and δ = 8.2 br, for NH; while ^{13}C NMR spectra displayed signals at δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^1J_{P-C}$ = 165.2 Hz, C–P), 155.2, 104.4 (C–4, C–5) of thiazole ring, 123.2 (CN), 53.51 (d, $^2J_{P-C}$ 12.2 Hz, $(CH_3O)_2P$); in ^{31}P NMR, δ (ppm) = 23.4 for phosphonate and in MS spectra showed (m/z %): 541 (M^+, 38).

The suggested mechanism for the reaction is depicted in Scheme 2, according to the Kabachnik–Fields reaction,[15,19] the first step of this mechanism assumed to be the formation of Schiff bases **5a-f** by the condensation between heterocyclic amines **1a,b** and aromatic aldehydes **2a,b**, followed by addition of DAPs **3a,b** in the presence of $FeCl_3$ and heating to give dialkyl [3-(4-hydroxyphenyl)-4-cyano-1-(4-arylthiazol-2-yl)-1*H*-pyrazol-5-yl-amino](aryl)methyl-phosphonate **4a-l**.

On the other hand Schiff bases **5a-f** obtained in a good yield by heating amines **1a,b** with aryl aldehydes **2a-c** in ethanol/acetic acid. α-Aminomethylphosphonates **4a-l** can be synthesized in higher yield (~70%) by reacting Schiff bases **5a-f** with DAPs **3a,b** in THF containing 10% mol $FeCl_3$ (**Scheme 3**).

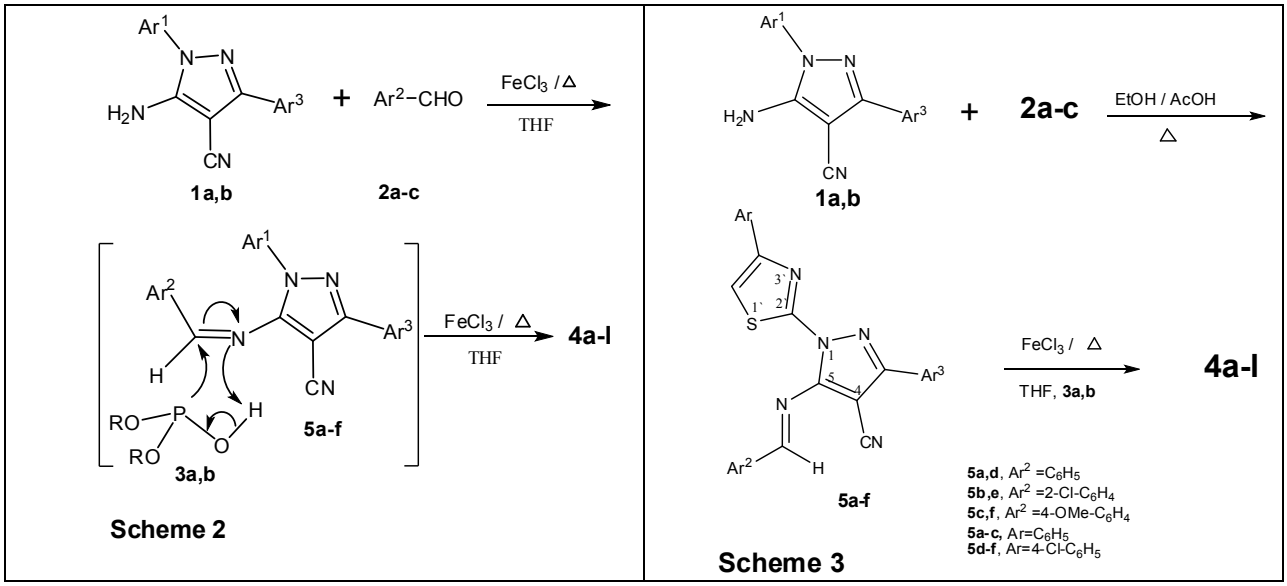
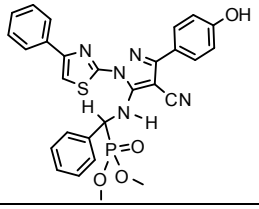
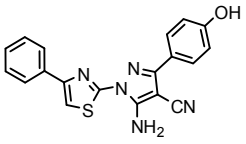
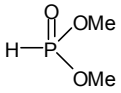
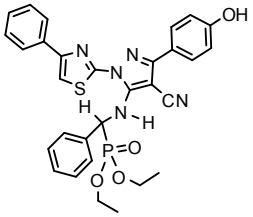
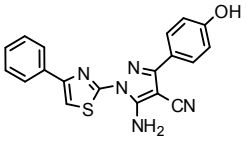
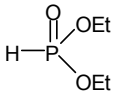
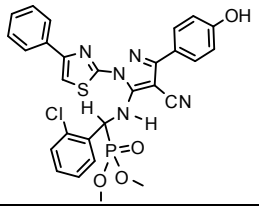
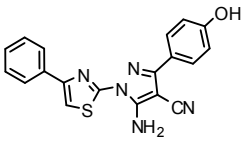
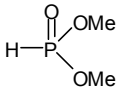
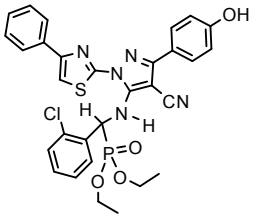
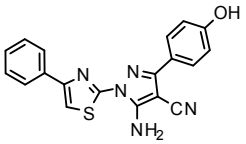
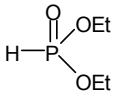
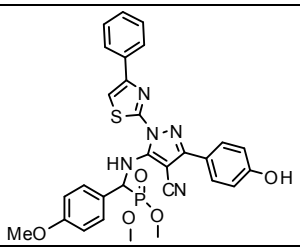
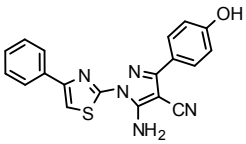
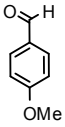
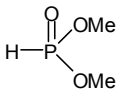
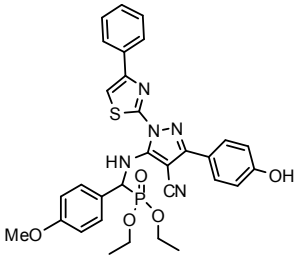
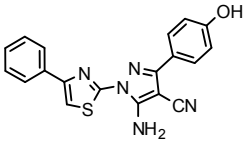
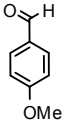
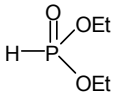
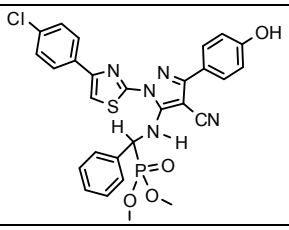
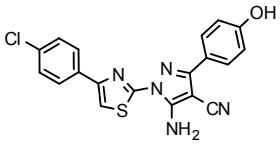
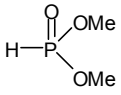
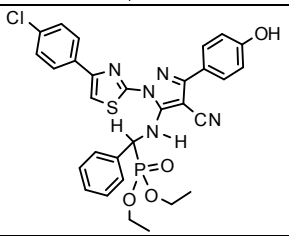
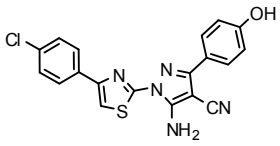
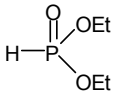
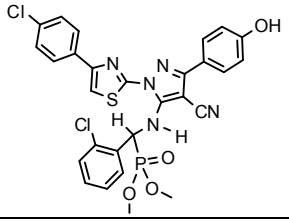
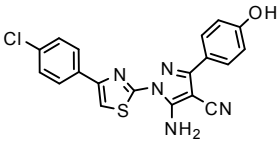
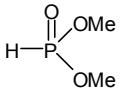
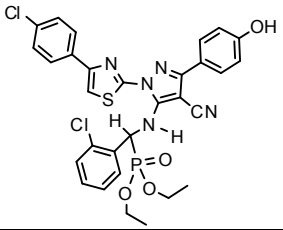
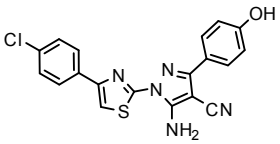
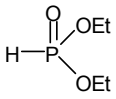
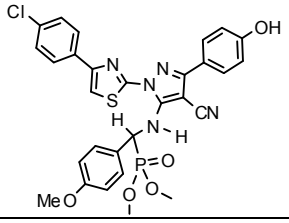
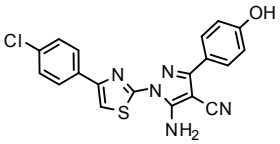
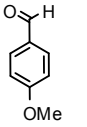
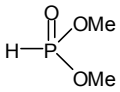
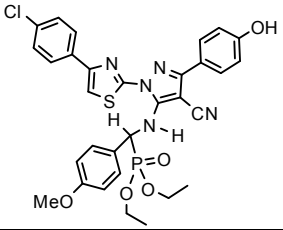
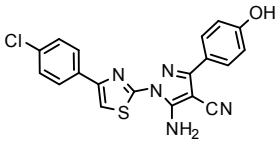
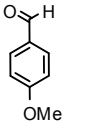
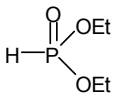


Table - 1

No.	Product Structure	Amine	Aldehyde	Phosphie
4a				
4b				

4c				
4d				
4e				
4f				
4g				
4h				
4i				

4j				
4k				
4l				

Experimental

All chemicals used were purchased from Aldrich. Solvents were distilled and dried by standard techniques. The reactions were monitored by thin layer chromatography (TLC) on Merck precoated silica GF254 aluminum plates. Melting points were measured on Stuart scientific melting point apparatus SMP30 and are uncorrected. ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectra were recorded on Bruker spectrometer 400 MHz. ^{1}H and ^{13}C NMR spectra were measured using TMS as the internal standard, whereas ^{31}P NMR spectra were recorded relative to external H_3PO_4 (85%). Mass spectrometry was performed on a Konik MS Q12 spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet IS 10 spectrophotometer using KBr pellets. 5-amino-3-(4-hydroxyphenyl)-1-(4-arylthiazol-2-yl)-1*H*-pyrazole-4-carbonitriles **1a,b** prepared as reported in literature.[20]

General procedure for the one-pot preparation of 4a–l

A mixture of 5-Amino-3-(4-hydroxyphenyl)-1-(4-arylthiazol-2-yl)-1*H*-pyrazole-4-carbonitriles **1a** (1.717 g, 0.005 mol) or **1b** (1.889 g, 0.005 mol), aldehyde **2a-c** (0.005 mol) and trimethyl **3a** or triethyl phosphite **3b** (0.008 mol in tetrahydrofuran (10 ml) and $FeCl_3$ (10 mol %) was heated at 70 ^{o}C for appropriate reaction time, After completion of the reaction (TLC), EtOAc (10 mL) was added to the mixture. The mixture was washed with H_2O (10 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the resulting α-aminophosphonates were collected and crystallized from the proper solvent.

dimethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino](phenyl)methylphosphonate ***4a***

Pale-yellow crystals; yield = 61%; m.p. = 218-219 ^{o}C (AcOEt); IR (KBr): ν = 3455 (OH), 3,355 (NH), 2,198 (CN), 1,235 (P = O), 1,055 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.64, 3.74 (2d, J_{H-H} = 6.9, $^{3}J_{P-H}$ = 11.9 Hz, 6H, $(CH_3O)_2P$), 5.8, 5.9 (dd, J_{H-H} = 8.8, $^{2}J_{P-H}$ = 18.5 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.07–8.26 (m, 15H, Ar–H, thiazole-H), 9.55 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^{1}J_{P-C}$ = 165.2 Hz, C–P), 152.8, 141.3, 139.2, 132.2, 129.4, 128.5, 127.5, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4`, C–5`–thiazole), 123.2 (CN), 16.6 (d, $^{3}J_{P-C}$ 7.2 Hz, $(CH_3CO)_2P$), ^{31}P NMR ($CDCl_3$): δ (ppm) = 23.4; MS (m/z %): 557 (M^{+}, 38), 448 (100).

diethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino](phenyl)methylphosphonate ***4b***

Pale-yellow crystals; yield = 60%; m.p. = 229-230 ^{o}C (AcOEt); IR (KBr): ν = 3450 (OH), 3,350 (NH), 2,200 (CN), 1,233 (P = O), 1,050 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.15, 1.17 (2d, J_{H-H} = 5.9, $^{4}J_{P-H}$ = 3.9 Hz, 6H, $(CH_3CO)_2P$), 3.9, 4.1 (2dq, $^{3}J_{P-H}$ = 9.8 Hz, 4H $(CH_2O)_2P$), 5.8, 5.9 (dd, J_{H-H} = 8.8, $^{2}J_{P-H}$ = 18.5 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.07–8.26 (m, 15H, Ar–H, thiazole-H), 9.56 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–

4), 159.3 (d, C–5), 51.6, 54.8 (d, $^{1}J_{P–C}$ = 165.2 Hz, C–P), 152.8, 141.3, 139.2, 132.2, 129.4, 128.5, 127.5, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4`, C–5`–thiazole), 123.2 (CN), 53.51 (d, $^{2}J_{P–C}$ 12.2 Hz, $(CH_3O)_2P$), 55.6 (d, $^{2}J_{P–C}$ = 8.4 Hz, $(CH_2O)_2P$); MS (m/z %): 585 (M^+, 35), 448 (100).

dimethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino](2-chlorophenyl)methyl-phosphonate ***4c***
Pale-yellow crystals; yield = 57%; m.p. = 207-208 °C (AcOEt); IR (KBr): *ν* = 3460 (OH), 3,360 (NH), 2,210 (CN), 1,230 (P = O), 1,050 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.6, 3.7 (2d, $J_{H–H}$ = 6.9, $^{3}J_{P–H}$ = 11.7 Hz, 6H, $(CH_3O)_2P$), 5.7, 5.8 (dd, $J_{H–H}$ = 8.6, $^{2}J_{P–H}$ = 18.3 Hz, 1H, HC–P), 8.1 (br, 1H, NH), 7.17–8.2 (m, 14H, Ar–H, thiazole-H), 9.6 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.1 (d, C–3), 78.4 (d, C–4), 159.1 (d, C–5), 51.4, 54.6 (d, $^{1}J_{P–C}$ = 164.2 Hz, C–P), 152.6, 141.1, 139.1, 132.3, 129.2, 128.3, 127.2, 130.2, 128.2 (C–Ar) 155.3, 104.2 (C–4`, C–5`–thiazole), 122.8 (CN), 53.4 (d, $^{2}J_{P–C}$ 11.8 Hz, $(CH_3O)_2P$); MS (m/z %): 592 (M^+, 35), 482 (100).

diethyl [3-(4-hydroxyphenyl)-4-cyano-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-yl-amino](2-chloro-phenyl)methylphosphonate ***4d***
Pale-yellow crystals; yield = 56%; m.p. = 218-219 °C (AcOEt); IR (KBr): *ν* = 3455 (OH), 3,355 (NH), 2,195 (CN), 1,235 (P = O), 1,055 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.15, 1.17 (2d, $J_{H–H}$ = 5.9, $^{4}J_{P–H}$ = 3.9 Hz, 6H, $(CH_3CO)_2P$), 3.9, 4.1 (2dq, $^{3}J_{P–H}$ = 9.8 Hz, 4H $(CH_2O)_2P$), 5.8, 5.9 (dd, $J_{H–H}$ = 8.8, $^{2}J_{P–H}$ = 18.5 Hz, 1H, HC–P), 8.3 (br, 1H, NH), 7.07–8.26 (m, 14H, Ar–H, thiazole-H), 9.62 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^{1}J_{P–C}$ = 165.2 Hz, C–P), 152.8, 141.3, 139.2, 132.2, 129.4, 128.5, 127.5, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4`, C–5`–thiazole), 123.2 (CN), 16.7 (d, $^{3}J_{P–C}$ 7.1 Hz, $(CH_3CO)_2P$), 55.5 (d, $^{2}J_{P–C}$ = 8.2 Hz, $(CH_2O)_2P$); MS (m/z %): 620 (M^+, 35), 482 (100).

dimethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino](4-methoxyphenyl)methyl-phosphonate ***4e***
Pale-yellow crystals; yield = 58%; m.p. = 226-227 °C (AcOEt); IR (KBr): *ν* = 3460 (OH), 3,358 (NH), 2,198 (CN), 1,235 (P = O), 1,055 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.64, 3.74 (2d, $J_{H–H}$ = 6.9, $^{3}J_{P–H}$ = 11.9 Hz, 6H, $(CH_3O)_2P$), 3.86 (s, 3H, Phenyl-OCH_3), 5.8, 5.9 (dd, $J_{H–H}$ = 8.8, $^{2}J_{P–H}$ = 18.5 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.07–8.26 (m, 14H, Ar–H, thiazole-H), 9.64 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^{1}J_{P–C}$ = 165.2 Hz, C–P), 152.8, 141.3, 139.2, 132.2, 129.4, 128.5, 127.5, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4`, C–5`–thiazole), 128.6 (CN), 56.4 (Phenyl-OCH_3), 53.54 (d, $^{2}J_{P–C}$ 12.2 Hz, $(CH_3O)_2P$); MS (m/z %): 587 (M^+, 28), 478 (100).

diethyl [4-cyano-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5-ylamino](4-methoxyphenyl)methyl-phosphonate ***4f***
Pale-yellow crystals; yield = 57%; m.p. = 241-242 °C (AcOEt); IR (KBr): *ν* = 3455 (OH), 3,345 (NH), 2,205 (CN), 1,230 (P = O), 1,045 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.15, 1.17 (2d, $J_{H–H}$ = 5.9, $^{4}J_{P–H}$ = 3.9 Hz, 6H, $(CH_3CO)_2P$), 3.9, 4.1 (2dq, $^{3}J_{P–H}$ = 9.8 Hz, 4H $(CH_2O)_2P$), 3.87 (s, 3H, Phenyl-OCH_3), 5.8, 5.9 (dd, $J_{H–H}$ = 8.8, $^{2}J_{P–H}$ = 18.5 Hz, 1H, HC–P), 8.1 (br, 1H, NH), 7.1–8.25 (m, 14H, Ar–H, thiazole-H), 9.64 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.5 (d, C–3), 78.4 (d, C–4), 159.1 (d, C–5), 51.4, 54.6 (d, $^{1}J_{P–C}$ = 165.2 Hz, C–P), 152.6, 141.2, 139.1, 132.1, 129.3, 128.4, 127.4, 130.2, 128.2 (C–Ar) 155.1, 104.3 (C–4`, C–5`–thiazole), 123.2 (CN), 56.5 (Phenyl-OCH_3), 16.6 (d, $^{3}J_{P–C}$ 7.2 Hz, $(CH_3CO)_2P$), 55.6 (d, $^{2}J_{P–C}$ = 8.4 Hz, $(CH_2O)_2P$); ^{31}P NMR ($CDCl_3$): δ (ppm) = 23.2; MS (m/z %): 615 (M^+, 38), 478 (100).

dimethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylamino](phenyl)methyl-phosphonate ***4g***
Pale-yellow crystals; yield = 61%; m.p. = 214-215 °C (AcOEt); IR (KBr): *ν* = 3450 (OH), 3,348 (NH), 2,202 (CN), 1,230 (P = O), 1,040 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.6, 3.7 (2d, $J_{H–H}$ = 6.9, $^{3}J_{P–H}$ = 11.5 Hz, 6H, $(CH_3O)_2P$), 5.6, 5.7 (dd, $J_{H–H}$ = 8.6, $^{2}J_{P–H}$ = 18.4 Hz, 1H, HC–P), 8.1 (br, 1H, NH), 7.2–8.26 (m, 14H, Ar–H, thiazole-H), 9.65 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.5 (d, C–3), 78.2 (d, C–4), 159.2 (d, C–5), 51.3, 54.5 (d, $^{1}J_{P–C}$ = 165.1 Hz, C–P), 152.7, 141.2, 139.1, 132.1, 129.2, 128.3, 127.4, 130.2, 128.2 (C–Ar) 155.3, 104.2 (C–4`, C–5`–thiazole), 123.3 (CN), 53.53 (d, $^{2}J_{P–C}$ 11.7 Hz, $(CH_3O)_2P$); ^{31}P NMR ($CDCl_3$): δ (ppm) = 22.6; MS (m/z %): 592 (M^+, 24), 483 (100).

diethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylamino](phenyl)methylphosphonate ***4h***
Pale-yellow crystals; yield = 60%; m.p. = 216-217 °C (AcOEt); IR (KBr): *ν* = 3455 (OH), 3,355 (NH), 2,200 (CN), 1,235 (P = O), 1,050 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.15, 1.17 (2d, $J_{H–H}$ = 5.9, $^{4}J_{P–H}$ = 3.9 Hz, 6H, $(CH_3CO)_2P$), 3.9, 4.1 (2dq, $^{3}J_{P–H}$ = 9.8 Hz, 4H $(CH_2O)_2P$), 5.8, 5.9 (dd, $J_{H–H}$ = 8.8, $^{2}J_{P–H}$ = 18.5 Hz, 1H, HC–P), 8.4 (br, 1H, NH), 7.07–8.26 (m, 14H, Ar–H, thiazole-H), 9.64 (s, 1H, OH); ^{13}C

NMR ($CDCl_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^1J_{P–C}$ = 165.2 Hz, C–P), 152.8, 141.3, 139.2, 132.2, 129.4, 128.5, 127.5, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4`, C–5`–thiazole), 123.2 (CN), 16.6 (d, $^3J_{P–C}$ 7.2 Hz, $(CH_3CO)_2P$), 55.6 (d, $^2J_{P–C}$ = 8.4 Hz, $(CH_2O)_2P$); MS (m/z %): 620 (M^+, 35), 483 (100).

dimethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylamino](2-chlorophenyl)methyl-phosphonate ***4i***

Pale-yellow crystals; yield = 57%; m.p. = 203-204 °C (AcOEt); IR (KBr): *ν* = 3450 (OH), 3,360 (NH), 2,196 (CN), 1,235 (P = O), 1,045 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 3.68, 3.76 (2d, $J_{H–H}$ = 6.5, $^3J_{P–H}$ = 11.3 Hz, 6H, $(CH_3O)_2P$), 5.2, 5.7 (dd, $J_{H–H}$ = 8.7, $^2J_{P–H}$ = 18.2 Hz, 1H, HC–P), 8.1 (br, 1H, NH), 7.2–8.26 (m, 13H, Ar–H, thiazole-H), 9.7 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.5 (d, C–3), 78.1 (d, C–4), 159.1 (d, C–5), 51.5, 54.1 (d, $^1J_{P–C}$ = 164.1 Hz, C–P), 152.7, 141.1, 139.1, 132.3, 129.5, 128.6, 127.4, 130.2, 128.2 (C–Ar) 155.3, 104.5 (C–4`, C–5`–thiazole), 122.8 (CN), 53.52 (d, $^2J_{P–C}$ 11.7 Hz, $(CH_3O)_2P$); MS (m/z %): 626 (M^+, 28), 518 (100).

diethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylamino](2-chlorophenyl)methyl-phosphonate ***4j***

Pale-yellow crystals; yield = 59%; m.p. = 212-213 °C (AcOEt); IR (KBr): *ν* = 3455 (OH), 3,340 (NH), 2,190 (CN), 1,230 (P = O), 1,045 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.16, 1.17 (2d, $J_{H–H}$ = 5.9, $^4J_{P–H}$ = 3.8 Hz, 6H, $(CH_3CO)_2P$), 3.8, 4.1 (2dq, $^3J_{P–H}$ = 9.6 Hz, 4H $(CH_2O)_2P$), 5.6, 5.8 (dd, $J_{H–H}$ = 8.8, $^2J_{P–H}$ = 18.3 Hz, 1H, HC–P), 8.2 (br, 1H, NH), 7.1–8.26 (m, 13H, Ar–H, thiazole-H), 9.72 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.4 (d, C–3), 78.2 (d, C–4), 159.4 (d, C–5), 51.4, 54.5 (d, $^1J_{P–C}$ = 165.1 Hz, C–P), 152.6, 141.4, 139.2, 132.2, 129.2, 128.5, 127.3, 130.1, 128.1 (C–Ar) 155.2, 104.4 (C–4`, C–5`–thiazole), 123.2 (CN), 16.4 (d, $^3J_{P–C}$ 7.1 Hz, $(CH_3CO)_2P$), 55.4 (d, $^2J_{P–C}$ = 8.4 Hz, $(CH_2O)_2P$); MS (m/z %): 654 (M^+, 30), 518 (100).

dimethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylamino](4-methoxyphenyl)-methylphosphonate ***4k***

Pale-yellow crystals; yield = 56%; m.p. = 224-225 °C (AcOEt); IR (KBr): *ν* = 3460 (OH), 3,355 (NH), 2,200 (CN), 1,245 (P = O), 1,050 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 3.62, 3.72 (2d, $J_{H–H}$ = 6.7, $^3J_{P–H}$ = 11.8 Hz, 6H, $(CH_3O)_2P$), 3.88 (s, 3H, Phenyl-OCH_3), 5.7, 5.8 (dd, $J_{H–H}$ = 8.6, $^2J_{P–H}$ = 18.1 Hz, 1H, HC–P), 8.1 (br, 1H, NH), 7.1–8.26 (m, 13H, Ar–H, thiazole-H), 9.7 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.5 (d, C–3), 78.2 (d, C–4), 159.4 (d, C–5), 51.4, 54.4 (d, $^1J_{P–C}$ = 165.1 Hz, C–P), 152.4, 141.1, 139.2, 132.2, 129.2, 128.3, 127.2, 130.1, 128.1 (C–Ar) 155.2, 104.2 (C–4`, C–5`–thiazole), 123.2 (CN), 56.2 (Phenyl-OCH_3), 53.49 (d, $^2J_{P–C}$ 11.8 Hz, $(CH_3O)_2P$); MS (m/z %): 622 (M^+, 35), 513 (100).

diethyl [1-(4-(4-chlorophenyl)thiazol-2-yl)-4-cyano-3-(4-hydroxyphenyl)-1H-pyrazol-5-ylamino](4-methoxyphenyl)methyl-phosphonate ***4l***

Pale-yellow crystals; yield = 61%; m.p. = 238-239 °C (AcOEt); IR (KBr): *ν* = 3455 (OH), 3,350 (NH), 2,200 (CN), 1,240 (P = O), 1,055 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.15, 1.17 (2d, $J_{H–H}$ = 5.9, $^4J_{P–H}$ = 3.9 Hz, 6H, $(CH_3CO)_2P$), 3.8, 4.1 (2dq, $^3J_{P–H}$ = 9.7 Hz, 4H $(CH_2O)_2P$), 3.87 (s, 3H, Phenyl-OCH_3), 5.6, 5.7 (dd, $J_{H–H}$ = 8.8, $^2J_{P–H}$ = 18.3 Hz, 1H, HC–P), 8.1 (br, 1H, NH), 7.1–8.26 (m, 13H, Ar–H, thiazole-H), 9.72 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ (ppm) = 152.6 (d, C–3), 78.3 (d, C–4), 159.3 (d, C–5), 51.6, 54.8 (d, $^1J_{P–C}$ = 165.1 Hz, C–P), 152.6, 141.3, 139.1, 132.2, 129.4, 128.5, 127.4, 130.1, 128.1 (C–Ar) 155.2, 104.5 (C–4`, C–5`–thiazole), 123.1 (CN), 56.3 (Phenyl-OCH_3), 16.4 (d, $^3J_{P–C}$ 7.2 Hz, $(CH_3CO)_2P$), 55.4 (d, $^2J_{P–C}$ = 8.2 Hz, $(CH_2O)_2P$); MS (m/z %): 649 (M^+, 35), 513 (100).

General procedure for the preparation of Schiff bases 5a-f

To a mixture of 5-amino-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitrile **1a** or **1b** (20 mmol) and aryl aldehydes **2a-c** (20 mmol) in 100 ml ethanol/acetic acid (9:1 v/v). The reaction mixture was refluxed for 4 h. The solid thus precipitated was collected and washed several times with ethanol and recrystallized from ethanol to give the Schiff bases **5a-f** as yellow crystals, Yield (~85%).

(E)-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-5-(phenyl-methyleneamino)-1H-pyrazole-4-carbonitrile ***5a***

m.p. = 188–189 °C); IR (KBr): *ν* = 3450 (OH), 2,200 (CN), 1,610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 9.4 (s, 1H, OH), 8.32 (s, 1H, HC=N, exocyclic), 7.17–8.1 (m, 15H, Ar–H, thiazole-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 164.4 (HC=N, exocyclic), 146.2.2.7 (C–3), 167.3 (C–5), 82.3 (C–4), 143.3, 138.2, 132.2, 129.4, 128.5, 127.5, 128.1, 126.1, 120.2 (C–Ar) 156.2, 104.8 (C–4`, C–5`–thiazole), 123.4 (CN); MS (m/z %): 447 (M^+, 38), 357 (21), 77 (100).

(E)-5-(2-chlorophenyl-methyleneamino)-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitrile ***5b***

m.p. = 184–185 °C); IR (KBr): ν = 3450 (OH), 2,200 (CN), 1,620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 9.2 (s, 1H, OH), 8.42 (s, 1H, HC=N, exocyclic), 7.17–8.1 (m, 14H, Ar–H, thiazole-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 161.2 (HC=N, exocyclic), 146.3 (C–3), 167.1 (C–5), 82.1 (C–4), 143.3, 138.2, 132.2, 129.4, 128.5, 127.5, 128.1, 126.1, 120.2 (C–Ar) 153.2, 107.8 (C–4`, C–5`–thiazole), 121.6 (CN); MS (m/z %): 482 (M^+, 38), 357 (25), 77 (100).

(E)-3-(4-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-5-(4-methoxyphenyl-methyleneamino)-1H-pyrazole-4-carbonitrile ***5c***

m.p. = 196–197 °C); IR (KBr): ν = 3450 (OH), 2,198 (CN), 1,620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 9.4 (s, 1H, OH), 8.48 (s, 1H, HC=N, exocyclic), 3.82 (s, 3H, Phenyl-OCH_3) 7.17–8.1 (m, 14H, Ar–H, thiazole-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 163.2 (HC=N, exocyclic), 55.8 (Phenyl-OCH_3), 148.4 (C–3), 167.1 (C–5), 81.6 (C–4), 143.3, 138.4, 132.6, 129.4, 128.5, 127.5, 128.1, 126.1, 121.2 (C–Ar) 154.2, 106.4 (C–4`, C–5`–thiazole), 121.4 (CN); MS (m/z %): 477 (M^+, 38), 357 (18), 77 (100).

(E)-[1-(4-(4-chlorophenyl)-thiazol-2-yl)]-3-(4-hydroxyphenyl)-5-(2-chlorophenyl-methyleneamino)-1H-pyrazole-4-carbonitrile ***5d***

m.p. = 182–183 °C); IR (KBr): ν = 3460 (OH), 2,195 (CN), 1,615 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 9.3 (s, 1H, OH), 8.42 (s, 1H, HC=N, exocyclic), 7.3–8.4 (m, 14H, Ar–H, thiazole-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 162.2 (HC=N, exocyclic), 143.2, 137.6, 133.2, 129.4, 128.4, 127.5, 128.1, 126.1, 120.8 (C–Ar) 154.2, 106.4 (C–4`, C–5`–thiazole), 121.4 (CN); MS (m/z %): 482 (M^+, 38), 392 (22), 77 (100).

(E)-[1-(4-(4-chlorophenyl)-thiazol-2-yl)]-3-(4-hydroxyphenyl)-5-(2-chlorophenyl-methyleneamino)-1H-pyrazole-4-carbonitrile ***5e***

m.p. = 179–180 °C); IR (KBr): ν = 3450 (OH), 2,195 (CN), 1,620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 9.4 (s, 1H, OH), 8.45 (s, 1H, HC=N, exocyclic), 7.2–8.3 (m, 13H, Ar–H, thiazole-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 162.2 (HC=N, exocyclic), 143.2, 137.6, 133.2, 129.4, 128.4, 127.5, 128.1, 126.1, 122.2 (C–Ar) 154.2, 106.4 (C–4`, C–5`–thiazole), 121.4 (CN); MS (m/z %): 515 (M^+, 38), 392 (22), 77 (100).

(E)- [1-(4-(4-chlorophenyl)-thiazol-2-yl)]-3-(4-hydroxyphenyl)-5-(4-methoxyphenyl-methyleneamino)-1H-pyrazole-4-carbonitrile ***5f***

p. = 190–191 °C); IR (KBr): ν = 3455 (OH), 2,195 (CN), 1,610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 9.5 (s, 1H, OH), 8.45 (s, 1H, HC=N, exocyclic), 3.86 (s, 3H, Phenyl-OCH_3) 7.22–8.2 (m, 13H, Ar–H, thiazole-H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 163.2 (HC=N, exocyclic), 55.6 (Phenyl-OCH_3), 148.6 (C–3), 167.2 (C–5), 81.4 (C–4), 143.2, 137.4, 133.2, 129.4, 128.4, 127.5, 128.1, 126.1, 121.2 (C–Ar) 154.2, 106.4 (C–4`, C–5`–thiazole), 121.4 (CN); MS (m/z %): 512 (M^+, 38), 392 (16), 77 (100).

Acknowledgement

This Project was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant no. (204/856/1433). The authors, therefore, acknowledge with thanks DSR technical and financial support.

References

1. Kafaraki P., Lejczak B., Biological Activity of Aminophosphonic Acid *Phosphorus Sulfur Silicon Relat Elem*, 63, 191, **1991**.
2. Panl A. B., Willam, B. K., Phosphinic acid dipeptide analogs: potent, slow-binding inhibitors of aspartic peptidases *J Am Chem Soc,* 106, 4282, **1984**.
3. Vo-Quang Y., Gravey A. M., Stmonneau, R., Towards new inhibitors of D-alanine:D-alanine ligase: The synthesis of 3-amino butenylphosphonic and aminophosphonamidic acids *Tetrahedron Lett,* 28, 6167, **1987**.
4. Baylis E. K., Campbell, C. D., Dingwall J. G., 1-Aminoalkylphosphonous acids. Part 1. Isosteres of the protein amino acids *J Chem Soc Perkin Trans 1*, 2845, **1984**.
5. Prasad G. S., Krishna J. R., Manjunath M., Reddy O. V. S., Krishnaiah M., Reddy C. S., Puranikd V. G., Synthesis, NMR, X-ray crystallography and bioactivity of some α-aminophosphonates *ARKIVOC,* 13, 133, **2007**.
6. Jing-Zi L., Bao-An S., Hui-Tao F., Bhadury P. S., Wan W.-T., Yang S., Xu W., Wu J., Jin L.-H., Wei X., Hu D.-Y., Zeng S., Synthesis and in vitro study of pseudo-peptide thioureas containing α-aminophosphonate moiety as potential antitumor agents *Eur. J. Med. Chem*., 45, 5108, **2010**.
7. Naydenova E. D., Todorov P. T., Mateeva P. I., Zamfirova R. N., Synthesis and biological activity of novel small peptides with aminophosphonates moiety as NOP receptor ligands *Amino Acids*, 39, 1537, **2010**.
8. Naydenova E. D., Todorov P. T., Topashka-Ancheva M. N., Momekov G. Ts., Yordanova T. Z., Konstantinov S. M.; Troev K. D., Novel N-(phosphonomethyl) glycine derivatives: Design, characterization and biological activity *Eur. J. Med. Chem*., 43, 1199, **2008**.
9. Bloemink MJ, Diederen JJH, Dorenbos JP, Heetebrij RJ, Keppler BK, Reedijik J., Calcium

Ions Do Accelerate the DNA Binding of New Antitumor-Active Platinum Aminophosphonate Complexes *Eur J Inorg Chem*, 10, 1655, **1999**.
10. Tusek-Bozic L., Juribasic M., Traldi P., Scarcia V., Furlani A., Synthesis, characterization and antitumor activity of palladium(II) complexes of monoethyl 8-quinolylmethylphosphonate *Polyhedron*, 27, 1317, **2008**.
11. Wang B., Miao Z. W., Wang, J., Chen R. Y., Zhang X. D., Synthesis and biological evaluation of novel naphthoquinone fused cyclic aminoalkylphosphonates and aminoalkylphosphonic monoester *Amino Acids*, 35, 463, **2008**.
12. Rao X, Song Z, He L., Synthesis and antitumor activity of novel α-aminophosphonates from diterpenic dehydroabietylamine *Heteroatom Chem*, 19, 512, **2008**.
13. Mohamed F. Abdel-Megeed, Badr E. Badr, Mohamed M. Azaam and Gamal A. El-Hiti, Synthesis, antimicrobial and anticancer activities of a novel series of diphenyl 1-(pyridin-3-yl)ethylphosphonates *Bioorganic & Medicinal Chemistry*, 20, 2252, **2012**.
14. C. Bhupendra Reddy, K. Suresh Kumar, M. Anil Kumar, M. Veera Narayana Reddy, B. Satheesh Krishna, M. Naveen, M.K. Arunasree, C. Suresh Reddy, C. Devendranath Reddy and C. Naga Raju, PEG-SO3H catalyzed synthesis and cytotoxicity of α-aminophosphonates *European Journal of Medicinal Chemistry*, 47 553, **2012**.
15. B. Kaboudin, Novel Methods for the Synthesis of Phosphonate Esters on the Solid Surface *Phosphorus Sulfur Silicon Relat Elem*, 177, 1749–1751, **2002**.
16. Mona H. N. Arsanious, Yevette A. Issac, and Leila S. Boulos, Reactions of phosphite esters and trisdialkylaminophosphines with 5-substituted 1,3,4-thiadiazol derivatives *Heteroatom Chemistry*, 12:7, 594, **2001**.
17. De-Qing Shi, Yan-Ming Wang and Ru-Yu Chen, Synthesis and stereoselectivity of a new type of unsaturated phosphonates *Heteroatom Chemistry*, 11:5, 261, **2000**.
18. Wafaa, M. Abdou; Reham, F. Barghash; Mohamed, S. Bekheit, Multicomponent reactions in a one-pot synthesis of α-aminophosphonates and α –aminophosphonic diamides with anti-inflammatory properties *Monatsh Chem*, 142, 649, **2011**.
19. Matveeva, E. D; Zefirov, N. S., On the mechanism of the Kabachnik-Fields reaction: Does a mechanism of nucleophilic amination of α-hydroxyphosphonates exist? *Dokl Chem*, 420, 137, **2008**.
20. a) Amer Anwar Amer, Synthesis and Reactions of Some New Thiazolylpyrazole Derivatives and Related Compounds *Phosphorus Sulfur Silicon Relat Elem*, 183:9, 2330, **2008**.
b) A. P. Novikova, N. M. Perova, L. Egorova, and E. I. Bragina, Synthesis and properties of 1,3,4-thiiadiazine derivatives. 1-Investigation of the condensation of substituted phenacyl bromides and bromoacetylpyridines with thiosemecarbazide *Chemistry of Heterocyclic Compounds,* 27:6, 666, **1991**.

3/5/2014