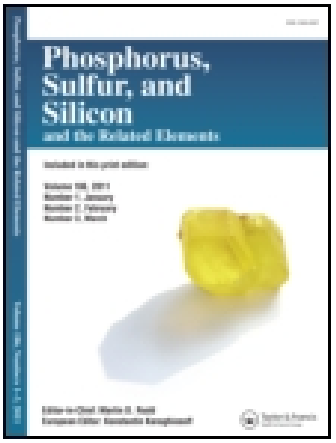


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Three Component Synthesis of New (1,3,4-Thiadiazolamino)Methylphosphonates, Their Glycoside and Oxygenated Alkylthio Analogs

Wael A. El-Sayed [a b] & Omar M. Ali [c d]
[a] Department of Photochemistry , National Research Centre , El-Dokki , Cairo , Egypt
[b] Department of Chemistry, Faculty of Science , NBU University , Arar KSA
[c] Department of Chemistry, Faculty of Science , Menoufia University , Shebin El-Koam , Egypt
[d] Faculty of Medical and Applied Science , Taif University , Taif Saudi Arabia
Accepted author version posted online: 26 Jul 2013.Published online: 03 Dec 2013.

To cite this article: Wael A. El-Sayed & Omar M. Ali (2014) Three Component Synthesis of New (1,3,4-Thiadiazolamino)Methylphosphonates, Their Glycoside and Oxygenated Alkylthio Analogs, Phosphorus, Sulfur, and Silicon and the Related Elements, 189:1, 88-97, DOI: 10.1080/10426507.2013.797417

To link to this article: http://dx.doi.org/10.1080/10426507.2013.797417

Phosphorus, Sulfur, and Silicon, 189:88–97, 2014

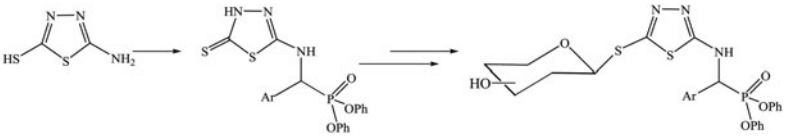
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2013.797417

THREE COMPONENT SYNTHESIS OF NEW (1,3,4-THIADIAZOLAMINO)METHYLPHOSPHONATES, THEIR GLYCOSIDE AND OXYGENATED ALKYLTHIO ANALOGS

Wael A. El-Sayed[1,2] and Omar M. Ali[3,4]

[1]*Department of Photochemistry, National Research Centre, El-Dokki, Cairo, Egypt*
[2]*Department of Chemistry, Faculty of Science, NBU University, Arar KSA*
[3]*Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt*
[4]*Faculty of Medical and Applied Science, Taif University, Taif Saudi Arabia*

GRAPHICAL ABSTRACT



Abstract *A number of (1,3,4-thiadiazol-2-ylamino)methylphosphonate derivatives were synthesized in a three component reaction. The thioglycoside derivatives and oxygenated alkylthio analogs were also prepared by reaction with halo sugars or different acyclic oxygenated alkyl halides.*

Keywords Phosphonates; 1,3,4-thiadiazoles; thioglycosides

INTRODUCTION

1,3,4-Thiadiazoles exhibit a broad spectrum of biological activities, possibly due to the presence of the toxophoric NeCe S moiety.[1] They find applications as antibacterial, antitumor, anti-inflammatory, pesticides, herbicides, dyes, and lubricants agents.[2–6] Organophosphorus compounds play important roles in various areas of functional materials science,[7] biochemistry,[8] and in catalysis chemistry as ligands.[9] Phosphonate containing heterocycles are an important class of active compounds[10] and recent studies have indicated that heterocyclic analogues containing phosphorus showed interesting bioactivities.[11] Various potent antibiotics,[12] enzyme inhibitors,[13] pharmacological agents,[14,15] and herbicides,[16] are 1-aminophosphonic acids, 1-aminoalkyl phosphonates, or their peptide analogs. Their outstanding properties mainly stem from the structural relationship to their carboxylic

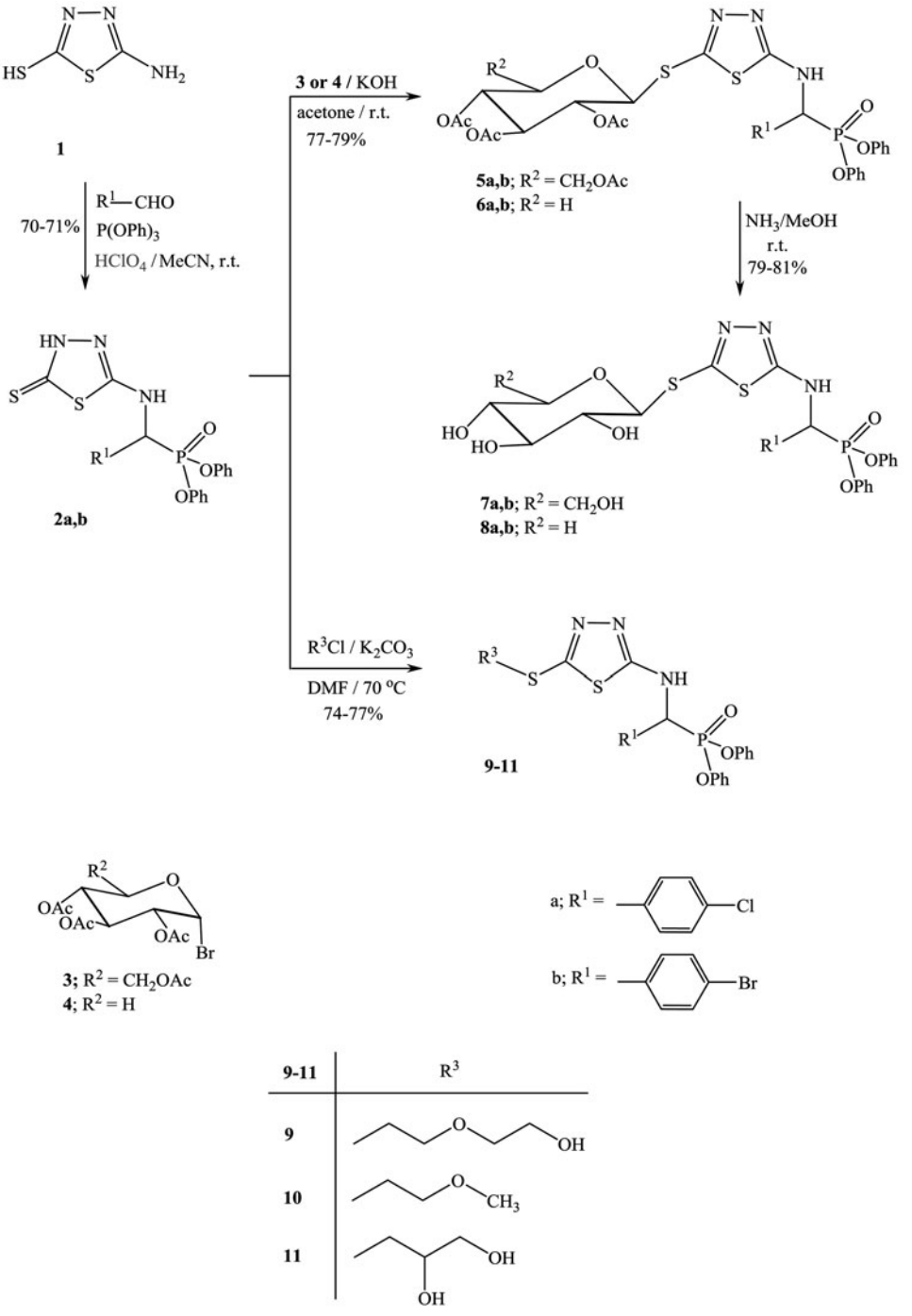
Received 22 January 2013; accepted 16 April 2013.
Address correspondence to Omar M. Ali, Department of Photochemistry, National Research Centre, El-Dokki, Cairo, Egypt; and Department of Chemistry, Faculty of Science, NBU University, KSA. E-mail: omali_66@hotmail.com

counterparts, the α-amino acids. Thus, the phosphonate moiety mimics the tetrahedral intermediate formed during the enzymatic peptide hydrolysis and consequently many reviews have reported their chemistry and biological interest.[17,18] 1-Aminoalkyl phosphonates are also the key substrates in the synthesis of various phosphonopeptides.[19–21] It has been also shown that the presence of a phosphonyl group can influence the biological functions of heterocyclic systems.[22] Owing to such a wide range of applications, the synthesis of phosphonate compounds via C—P bond formation in three component reactions using proper phosphite reagent is enjoying growing interest and is an ever green and widely used method[23,24] in phosphonate synthesis. On the other hand, the glycosylthio heterocycles including modifications of both the glycon and aglycon parts have stimulated extensive research as biological inhibitors.[25–28] Owing to the above facts and our interest in the attachment of sugar moieties to new substituted heterocycles,[29–32] it will be of synthetic and biological interest to synthesize new aminophosphonates linked to glycosylthio derivatives of the 1,3,4-thiadiazole ring system.

RESULTS AND DISCUSSION

Among three-component condensation reactions, the addition of nucleophiles to in situ generated C=N bonds has become an extremely useful process for the synthesis of various nitrogen-containing molecules such as α-amino phosphonates.[33] In this investigation, 5-amino-1,3,4-thiadiazole-2-thiol (**1**)[34] was allowed to react in a three component reaction with *p*-chloro- or *p*-bromobenzaldehyde and triphenyl phosphite in the presence of a catalytic amount of perchloric acid to afford the corresponding aminophosphonate derivatives **2a**,**b**, respectively with 70–71% yields. The ^{1}H NMR spectra of **2a**,**b** showed the C*H*–N signal as singlet at δ 3.91 and 4.01 for **2a** and **2b** respectively, and the NH signals at δ 6.22, 6.05, 11.97, and 12.18.

The key compounds **2a**,**b** were used as starting materials for the synthesis of a number of substituted thiadiazolyl aminophosphonate thioglycosides and acyclic nucleoside analogs. Thus, reaction of **2a**,**b** with 2,3,4,6-tetra-*O*-acetyl-α-D-*gluco*- **3** and 2,3,4-tri-*O*-acetyl-α-D-*xylo*pyranosyl bromide **4** in acetone in the presence of potassium hydroxide afforded the corresponding thioglycoside derivatives **5** and **6**, respectively with 77–79% yields. The IR spectra of the thioglycosides **5a**,**b** and **6a**,**b** showed characteristic absorption bands in the carbonyl frequency region at 1737–1746 cm^{-1} in addition to the NH absorption bands at 3323–3361 cm^{-1}. The ^{1}H NMR spectra showed the signals of the acetyl methyl protons as singlets at δ 1.90–2.15 and the anomeric proton signal as doublet at δ 5.77–5.87 with a coupling constant of 9.8–10.2 Hz indicating the β-orientation of the thioglycosidic bond. The anomeric proton of β-*N*-glucosides having an adjacent C=S was reported[35–38] to appear at higher chemical shift (δ 6.9–7.2) due to the anisotropic deshielding effect of the C=S group.[36,38] The ^{13}C NMR spectra of **5a**,**b** and **6a**,**b** showed a signal at δ 82.11–83.29 corresponding to the anomeric C-1 which also confirmed the β-configuration. The absence of a signal corresponding to a thiocarbonyl carbon atom in the ^{13}C NMR spectra of **5a**,**b** and **6a**,**b** confirmed that the attachment of the sugar moiety has been taken place at the sulfur atom rather than to the nitrogen atom which has also been supported by the chemical shift of the anomeric proton. This attachment also agreed with the mode of their preparation. When the glycosides **5a**,**b** and **6a**,**b** were treated with methanolic ammonia at 0°C, the deacetylated *S*-glucoside derivatives **7a**,**b** and **8a**,**b**, respectively were obtained with 79–81% yields (Scheme 1). Their IR spectra showed absorption bands at 3440–3467 cm^{-1}



Scheme 1 Synthesis of (1,3,4-Thiadiazol-2-yl-amino) methylphosphonates.

and the ^{1}H NMR spectra are in agreement with the assigned structures (see experimental part).

The thiadiazolylaminophosphonate derivatives **2a**,**b** have been reacted with different acyclic oxygenated alkyl halides to give a series of oxygenated open chain derivatives of 1,3,4-thiadiazole. Reaction of the **2a**,**b** with 2-(2-chloroethoxy)ethanol, 1-chloro-2-methoxyethane, or 3-chloropropane-1,2-diol in DMF (dimethylformamide) at 70°C afforded the *S*-substituted acyclic analogs **9–11**, respectively with 74–77% yields. The ^{1}H NMR spectra of **10a**,**b** showed signals corresponding to the OCH_3 at δ 3.81 and 3.88 in addition to the CH_2 signals in the range 3.56–4.31. The IR spectra of **11a**,**b** showed the hydroxyl absorption bands at 3482–3485. Their ^{1}H NMR spectra revealed the presence of CH_2 signals at δ 3.66–4.14 in addition to the signals of hydroxyl proton at δ 3.66–5.02.

EXPERIMENTAL

All solvents were dried by standard methods. Melting points were determined with a Kofler block apparatus and are uncorrected. IR spectra (ν/cm^{-1}, KBr pellets) were recorded with a Perkin-Elmer Model 1720 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 with a Bruker AC-300 FT spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C), respectively. The chemical shifts in ppm are expressed on the δ scale using tetramethylsilane as internal standard. Coupling constants J are given in Hz. Mass spectra were measured on a Kratos 50 TC spectrometer. TLC was performed on Merck silica gel 60-F254 pre-coated plastic plates. Microanalyses were performed in the unit of microanalysis at Cairo University, Cairo.

Diphenyl (4-Halophenyl)-(5-mercapto-1,3,4-thiadiazol-2-ylamino)-methyl-phosphonate (2a,b)

General Procedure. $HClO_4$ (0.201 g, 2 mmol) was added to a solution of the aldehyde (2 mmol) and 5-amino-1,3,4-thiadiazole-2-thiol (**1**) (0.266 g, 2 mmol) in dry acetonitrile. The mixture was stirred at reflux for 15 min and then triphenyl phosphite (0.621 g, 2 mmol) was added. After completion of the reaction (6 h), the reaction mixture was quenched with aq. saturated $NaHCO_3$ followed by brine solution and then extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate, 4:1) to afford pure products.

Diphenyl (4-Chlorophenyl)-(5-mercapto-1,3,4-thiadiazol-2-ylamino)-methyl-phosphonate (2a). Yellow powder; Yield: 0.686 g (70%). mp. 243–244°C; IR: 800, 998, 1161, 1253, 1278, 1483, 1618, 2969, 3368 ^{1}H NMR: 3.91 (s, 1H, C*H*N), 6.22 (s, 1H, NH), 7.30–7.42 (m, 3H, Ar-H), 7.47 (d, 2H, J = 8.2, Ar-H), 7.68–7.75 (m, 2H, Ar-H), 7.79 (d, 2H, J = 8.2, Ar-H), 7.84–7.92 (m, 2H, Ar-H), 8.01–8.14 (m, 3H, Ar-H), 12.18 (s, 1H, NH). ^{13}C NMR: 58.7 (*C*HN), 112.1–151.2 (Ar-18C), 160.8 (C=N), 182.1 (C=S). MS (EI): m/z = 490 ([M + H]$^+$). Anal. Calcd. for $C_{21}H_{17}ClN_3O_3PS_2$: C, 51.48; H, 3.50; N, 8.58. Found: C, 51.39; H, 3.42; N, 8.39.

Diphenyl (4-Bromophenyl)-(5-mercapto-1,3,4-thiadiazol-2-ylamino)-methylphosphonate (2b). Yellow powder; Yield: 0.759 g (71%). mp. 231–232°C. IR: 765, 972, 1127, 1245, 1298, 1493, 1620, 2966, 3290. ^{1}H NMR: 4.01 (s, 1H, C*H*N), 6.05 (s, 1H, NH), 7.23–7.35 (m, 3H, Ar-H), 7.39 (d, 2H, J = 8.2, Ar-H), 7.62–7.72 (m, 2H, Ar-H),

7.76 (d, 2H, $J = 8.2$, Ar-H), 7.85–7.92 (m, 2H, Ar-H), 8.12–8.23 (m, 3H, Ar-H), 11.97 (s, 1H, NH). ^{13}C NMR: 58.7 (*C*HN), 114.1–151.6 (Ar-18C), 160.5 (C=N), 181.8 (C=S). MS (EI): m/z = 534 ($[M + H]^+$). Anal. Calcd. for $C_{21}H_{17}BrN_3O_3PS_2$: C, 47.20; H, 3.21; N, 7.86. Found: C, 47.02; H, 3.11; N, 7.69.

Diphenyl (4-Chlorophenyl)-{5-[(O-acetyl-β-D-glycopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonates (5a,b). General procedure: To a solution of **2a,b** (2 mmol) in aqueous KOH (0.112 g, 2 mmol, in 1 mL distilled water) was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-*gluco*- or 2,3,4-tetra-*O*-acetyl-α-D-*xylo*pyranosyl bromide (2.2 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature for 5–7 h. until the reaction was judged complete by TLC ($CHCl_3$/MeOH 99.5:0.5. The solvent was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove the KBr formed. The product was dried, and crystallized from ethanol.

Diphenyl (4-Chlorophenyl)-{5-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (5a). Pale yellow solid; Yield: 1.279 g (78%). mp. 146–147°C. IR: 999, 1157, 1223, 1287, 1461, 1618, 1746, 3011, 3323. ^{1}H NMR: 1.95, 2.02, 2.11, 2.13 (4s, 12H, 4 CH_3CO), 4.02 (s, 1H, C*H*N), 4.07−4.11 (m, 1H, H-5), 4.15 (dd, 1H, $J_{6,6'} = 11.4$, $J_{5,6} = 2.8$, H-6), 4.30−4.35 (m, 1H, H-6′), 4.96 (t, 1H, $J_{3,4} = 9.3$, H-4), 5.27 (dd, 1H, $J_{2,3} = 9.6$, $J_{3,4} = 9.3$, H-3), 5.38 (t, 1H, $J_{2,3} = 9.6$, H-2), 5.77 (d, 1H, $J_{1,2} = 10.2$, H-1), 6.15 (s, 1H, NH), 7.29−7.37 (m, 3H, Ar-H), 7.48 (d, 2H, $J = 8.2$, Ar-H), 7.69−7.68 (m, 2H, Ar-H), 7.75 (d, 2H, $J = 8.2$, Ar-H), 7.82−7.91 (m, 2H, Ar-H), 8.10−8.24 (m, 3H, Ar-H) ppm. ^{13}C NMR: 19.3, 19.6, 20.7, 20.8 (4CH_3CO), 62.7 (C-6), 64.2 (C-4), 68.7 (C-3), 69.5 (CHN), 71.3 (C-2), 71.9 (C-5), 82.1 (C-1), 126.1–150.2 (Ar-18C), 156.4, 157.1 (2C=N), 169.7, 170.3, 171.3, 171.5 (4C=O). MS (EI) = 820 ($[M+H]^+$). Anal. Calcd. for $C_{35}H_{35}ClN_3O_{12}PS_2$: C, 51.25; H, 4.30; N, 5.12. Found, C, 51.12; H, 4.22; N, 5.02.

Diphenyl (4-Bromophenyl){5-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (5b). Pale yellow solid; Yield 1.366 g (79%). mp. 140–141°C. IR: 1039, 1124, 1225, 1265, 1459, 1610, 1737, 2985, 3323. ^{1}H NMR: 1.90, 2.04, 2.12, 2.15 (4s, 12H, 4 CH_3CO), 3.96 (s, 1H, C*H*N), 4.07−4.11 (m, 1H, H-5), 4.15 (dd, 1H, $J_{6,6'} = 11.4$, $J_{5,6} = 2.8$, H-6), 4.21−4.26 (m, 1H, H-6′), 4.61 (t, 1H, $J_{3,4} = 9.3$, H-4), 5.40 (dd, 1H, $J_{2,3} = 9.6$, $J_{3,4} = 9.3$ Hz, H-3), 5.66 (t, 1H, $J_{2,3} = 9.6$, H-2), 5.87 (d, 1H, $J_{1,2} = 10.2$, H-1), 6.02 (s, 1H, NH), 6.62−6.76 (m, 3H, Ar-H), 7.28 (d, 2H, $J = 8.2$, Ar-H), 7.70−7.77 (m, 2H, Ar-H), 7.81 (d, 2H, $J = 8.2$, Ar-H), 7.85−7.95 (m, 2H, Ar-H), 8.09–8.24 (m, 3H, Ar-H). ^{13}C NMR: 19.3, 19.7, 20.7, 20.8 (4CH_3CO), 62.6 (C-6), 64.6 (C-4), 68.4 (C-3), 69.6 (CHN), 71.3 (C-2), 71.9 (C-5), 82.1 (C-1), 119.1–150.6 (Ar-18C), 156.2, 157.1 (2C=N), 169.7, 170.4, 171.4, 171.6 (4C=O). MS (EI) = 863 (M^+). Anal. Calcd. for $C_{35}H_{35}BrN_3O_{12}PS_2$: C, 48.62; H, 4.08; N, 4.86. Found: C, 48.49; H, 4.02; N, 4.69.

Diphenyl (4-Chlorophenyl){5-[(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (6a). Pale yellow solid; Yield: 1.220 g (77%). mp. 143–144°C. IR: 708, 1046, 1151, 1228, 1280, 1466, 1616, 1746, 2972, 3324. ^{1}H NMR: 1.95, 2.08, 2.12 (3s, 9H, 3 CH_3CO), 4.02 (s, 1H, C*H*N), 4.15 (dd, 1H, $J_{5,5'} = 11.4$, $J_{4,5} = 2.8$, H-5), 4.30−4.34 (m, 1H, H-5′), 5.21 (t, 1H, $J_{3,4} = 9.3$, H-4), 5.26 (dd, 1H, $J_{2,3} = 9.6$, $J_{3,4} = 9.3$, H-3), 5.33 (t, 1H, $J_{2,3} = 9.6$, H-2), 5.77 (d, 1H, $J_{1,2} = 9.8$, H-1), 6.15 (s, 1H, NH), 7.29−7.39 (m, 3H, Ar-H), 7.44 (d, 2H, $J = 8.2$, Ar-H), 7.70−7.76 (m, 2H, Ar-H), 7.79 (d, 2H, $J = 8.2$, Ar-H), 7.83−7.90 (m, 2H, Ar-H), 8.12−8.26 (m, 3H, Ar-H). ^{13}C NMR: 19.4, 20.7, 20.9 (3CH_3CO), 63.7 (C-5), 64.9 (C-4), 68.8 (C-3), 69.6 (CHN) 71.3 (C-2), 83.2

(C-1), 127.1–150.4 (Ar-18C), 156.4, 157.3 (2C=N), 169.7, 170.4, 171.8 (3C=O). MS (EI) = 748 ([M + H]$^+$). Anal. Calcd. for $C_{32}H_{31}ClN_3O_{10}PS_2$. C, 51.37; H, 4.18; N, 5.62. Found: C, 51.18; H, 4.12; N, 5.71.

Diphenyl (4-Bromophenyl){5-[(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (6b). Pale yellow solid; Yield: 1.236 g (78%). mp. 142–143°C. IR: 701, 1041, 1142, 1231, 1277, 1453, 1614, 1746, 2963, 3361. ^{1}H NMR: 1.97, 2.11, 2.14 (3s, 9H, 3 *CH*$_3$CO), 3.99 (s, 1H, C*H*N), 4.25 (dd, 1H, $J_{5,5'}$ = 11.4, $J_{4,5}$ = 2.8, H-5), 4.27−4.31 (m, 1H, H-5′), 5.28 (t, 1H, $J_{3,4}$ = 9.3, H-4), 5.40 (dd, 1H, $J_{2,3}$ = 9.6, $J_{3,4}$ = 9.3, H-3), 5.45 (t, 1H, $J_{2,3}$ = 9.6, H-2), 5.81 (d, 1H, $J_{1,2}$ = 9.8, H-1), 6.11 (bs, 1H, NH), 7.18−7.24 (m, 3H, Ar-H), 7.28 (d, 2H, J = 8.2, Ar-H), 7.65−7.73 (m, 2H, Ar-H), 7.77 (d, 2H, J = 8.2, Ar-H), 7.82−7.91 (m, 2H, Ar-H), 8.12−8.27 (m, 3H, Ar-H). ^{13}C NMR: 19.4, 20.6, 20.9 (3*CH*$_3$CO), 61.8 (C-5), 67.3 (C-4), 68.8 (C-3), 63.3 (CHN), 70.5 (C-2), 83.3 (C-1), 128.2–150.5 (Ar-18C), 157.4, 160.0 (2C=N), 169.8, 170.7, 171.9 (3C=O). MS (EI) = 791 (M$^+$). Anal. Calcd. for $C_{32}H_{31}BrN_3O_{10}PS_2$: C, 48.49; H, 3.94; N, 5.30. Found: C, 48.31; H, 4.05; N, 5.19.

Diphenyl (4-Halophenyl)-{5-[(β-D-glycopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonates (7 a,b and 8a, b). General Procedure. A solution of **5a,b and 6a,b** (2 mmol) in methanolic ammonia solution (2M in methanol) was stirred at 0°C for 1 h then at room temperature for 8–11 h (TLC). The solvent was evaporated under reduced pressure and the residue was dissolved in absolute ethanol (12 mL) and left over night to slow evaporation of the solvent to initiate the crystallization of the compounds **7a,b** and **8a,b.**

Diphenyl (4-Chlorophenyl)-{5-[(β-D-glucopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (7a). Brownish powder; Yield: 1.056 g (81%). mp. 199–200°C; IR: 804, 1048, 1108, 1205, 1285, 1482, 1618, 3051, 3365, 3467−3440. ^{1}H NMR: 3.41–3.50 (m, 2H, H-6,6′), 3.55–3.59 (m, 1H, H-5), 3.75–3.82 (m, 2H, H-3,4), 3.97 (s, 1H, C*H*N), 4.21 (t, 1H, $J_{2,3}$ = 9.2, H-2), 4.29 (t, 1H, J = 6.4, OH), 4.37–4.41 (m, 1H, OH), 4.92–4.96 (m, 1H, OH), 5.14 (t, 1H, J = 6.2, OH), 5.80 (d, 1H, $J_{1,2}$ = 9.8, H-1), 6.08 (s, 1H, NH), 6.92–7.02 (m, 3H, Ar-H), 7.33–7.40 (d, 2H, J = 8.2, Ar-H), 7.66–7.78 (m, 4H, Ar-H), 7.84–7.92 (m, 2H, Ar-H), 8.02–8.15 (m, 3H, Ar-H). ^{13}C NMR: 63.2 (C-6), 68.3 (C-4), 69.4 (CHN), 72.8 (C-3), 73.5 (C-2), 78.3 (C-5), 91.3 (C-1), 118.2–150.1 (Ar-18C), 157.0, 158.8 (2C=N). MS (EI) = 652 ([M + H]$^+$). Anal. Calcd. For $C_{27}H_{27}ClN_3O_8PS_2$: C, 49.73; H, 4.17; N, 6.44. Found: C, 49.52; H, 4.10; N, 6.25.

Diphenyl (4-Bromophenyl)-{5-[(β-D-glucopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (7b). Brownish powder; Yield: 1.114 g (80%). mp. 203–204°C. IR: 755, 1054, 1122, 1214, 1276, 1482, 1612, 3093, 3348, 3460–3449. ^{1}H NMR: 3.42–3.50 (m, 2H, H-6,6′), 3.56–3.61 (m, 1H, H-5), 3.78–3.88 (m, 2H, H-3,4), 3.91 (s, 1H, C*H*N), 4.20 (t, 1H, $J_{2,3}$ = 9.2, H-2), 4.36 (t, 1H, J = 6.4, OH), 4.46–4.50 (m, 1H, OH), 4.97–5.02 (m, 1H, OH), 5.12 (t, 1H, J = 6.2, OH), 5.79 (d, 1H, $J_{1,2}$ = 9.8, H-1), 6.07 (s, 1H, NH), 6.73–6.87 (m, 3H, Ar-H), 7.44 (d, 2H, J = 8.2, Ar-H), 7.50–7.60 (m, 2H, Ar-H), 7.76–7.92 5 m, 4H, Ar-H), 8.11–8.25 (m, 3H, Ar-H). ^{13}C NMR: 63.7 (C-6), 68.8 (C-4), 69.8 (CHN), 71.1 (C-3), 73.7 (C-2), 78.3 (C-5), 91.3 (C-1), 117.4–150.1 (Ar-18C), 156.8, 158.2 (2C=N). MS (EI) = 696 ([M + H]$^+$). Anal. Cacld. for $C_{27}H_{27}BrN_3O_8PS_2$: C, 46.56; H, 3.91; N, 6.03. Found,%: C, 46.42; H, 3.82; N, 5.95.

Diphenyl (4-Chlorophenyl)-{5-[(β-D-xylopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (8a). Pale yellow solid; Yield: 0.982 g (79%). mp. 198–199°C; IR: 755, 1042, 1123, 1207, 1235, 1472, 1612, 2972, 3357, 3430−3449. ^{1}H NMR: 3.41−3.50 (m, 2H, H-5,5′), 3.80−3.94 (m, 3H, H-3,4 and C*H*N), 4.23 (t, 1H,

$J_{2,3}$ = 9.2, H-2), 4.42 (t, 1H, J = 6.4, OH), 4.50−4.54 (m, 1H, OH), 5.07 (t, 1H, J = 6.2, OH), 5.78 (d, 1H, $J_{1,2}$ = 9.8, H-1), 6.08 (s, 1H, NH), 7.10−7.14 (m, 3H, Ar-H), 7.37 (d, 2H, J = 8.2, Ar-H), 7.61−7.68 (m, 2H, Ar-H), 7.73 (d, 2H, J = 8.2, Ar-H), 7.82−7.91 (m, 2H, Ar-H), 8.08−8.20 (m, 3H, Ar-H). ^{13}C NMR: 63.7 (C-5), 68.7 (C-4), 69.5 (CHN), 71.1 (C-3), 73.5 (C-2), 92.1 (C-1), 122.4–150.2 (Ar-18C), 156.7, 157.4 (2C=N). MS (EI) = 622 ([M + H]$^+$). Anal. Calcd. for $C_{26}H_{25}ClN_3O_7PS_2$: C, 50.20; H, 4.05; N, 6.76. Found: C, 49.97; H, 4.00; N, 6.61.

Diphenyl (4-Bromophenyl)-{5-[(β-D-xylopyranosyl)thio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (8b). Yellow solid; Yield: 1.066 g (80%). mp. 192–193°C. IR: 758, 1040, 1124, 1211, 1239, 1475, 1617, 1617, 3359, 3460−3442. ^{1}H NMR: 3.42−3.51 (m, 2H, H-5,5′), 3.75−3.85 (m, 2H, H-3,4), 3.90 (s, 1H, C*H*N), 4.28 (t, 1H, $J_{2,3}$ = 9.2, H-2), 4.41 (t, 1H, J = 6.4, OH), 4.45–4.49 (m, 1H, OH), 5.18 (t, 1H, J = 6.2, OH), 5.80 (d, 1H, $J_{1,2}$ = 9.8, H-1), 6.02 (s, 1H, NH), 6.95−7.11 (m, 3H, Ar-H), 7.38 (d, 2H, J = 8.2, Ar-H), 7.64−7.71 (m, 2H, Ar-H), 7.74 (d, 2H, J = 8.2, Ar-H), 7.88–7.97 (m, 2H, Ar-H), 8.05−8.18 (m, 3H, Ar-H). ^{13}C NMR: 63.6 (C-5), 68.5 (C-4), 69.7 (CHN), 71.5 (C-3), 73.7 (C-2), 92.4 (C-1), 120.4–151.0 (Ar-18C), 156.9, 157.5 (2C=N). MS (EI) = 666 ([M+H]$^+$). Anal. Calcd. for $C_{26}H_{25}BrN_3O_7PS_2$: C, 46.85; H, 3.78; N 6.30. Found: C, 46.67; H, 3.64; N, 6.50.

General Procedure for the Synthesis of *S*-substituted (1,3,4-Thiadiazol-2-ylamino)methylphosphonate Derivatives 9-11

To a solution of **2a**, **b** (2 mmol) in dry DMF (15 mL) was added K_2CO_3 (0.276 g, 2 mmol) and the mixture was stirred at room temperature for 1 h. 2-(2-Chloroethoxyethanol), 1-chloro-2-methoxyethane or 3-chloropropane-1,2-diol (2 mmol) was added and stirring was continued for 8–10 h (TLC) at 70°C. The solvent was removed under reduced pressure and the residue was triturated with a mixture of diethyl ether:petroleum ether (40−60) [50:50]. The resulting solid was filtered off and recrystallized from ethanol to give the desired products.

Diphenyl (4-Chlorophenyl)-{5-[2-(2-hydroxyethoxy)ethylthio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (9a). Pale yellow solid; Yield: 0.867 g (75%). mp. 148–149°C; IR: 714, 822, 1047, 1122, 1207, 1225, 1468, 1612, 3020, 3314, 3457. ^{1}H NMR: 3.33 (t, 2H, J = 5.2, CH_2), 3.86 (t, 2H, J = 5.6, CH_2), 3.97−4.26 (m, 3H, CH_2 and C*H*N), 4.61 (t, 2H, J = 5.2, CH_2), 4.74−4.78 (m, 1H, OH), 6.24 (bs, 1H, NH), 7.14−7.21 (m, 3H, Ar-H), 7.25 (d, 2H, J = 8.2, Ar-H), 7.68–7.75 (m, 2H, Ar-H), 7.79 (d, 2H, J = 8.2, Ar-H), 7.83−7.91 (m, 2H, Ar-H), 8.10−8.24 (m, 3H, Ar-H). ^{13}C NMR: 47.1, 62.9, 67.5, 70.6 (4CH_2), 73.9 (*C*HN), 111.1−150.2 (Ar-18C), 163.2, 164.4 (2C=N). MS (EI) = 578 ([M + H]$^+$). Anal. Calcd. for $C_{25}H_{25}ClN_3O_5PS_2$: C, 51.95; H, 4.36; N, 7.27. Found: C, 51.32; H, 4.24; N, 7.11.

Diphenyl (4-Bromophenyl)-{5-[2-(2-hydroxyethoxy)ethylthio]-1,3,4-thiadiazol-2-ylamino}methylphosphonate (9b). Pale yellow solid; Yield: 0.959 g (77%). mp. 142–143°C. IR: 820, 1041, 1126, 1212, 1245, 1470, 1615, 2972, 3367, 3479. ^{1}HNMR: 3.42 (t, 2H, J = 5.2, CH_2), 3.92−4.01 (m, 2H, CH_2), 4.15−4.29 (m, 3H, CH_2, and C*H*N), 4.78 (t, 2H, J = 5.2, CH_2), 4.77−4.81 (m, 1H, OH), 6.26 (s, 1H, NH), 7.14−7.23 (m, 3H, Ar-H), 7.28 (d, 2H, J = 8.2, Ar-H), 7.60−7.67 (m, 2H, Ar-H), 7.71 (d, 2H, J = 8.2, Ar-H), 7.85−7.93 (m, 2H, Ar-H), 8.10−8.23 (m, 3H, Ar-H). ^{13}C NMR: 47.5, 62.2, 67.5, 71.1 (4 CH_2), 75.2 (*C*HN), 115.2–150.1 (Ar-18C), 163.9, 164.2 (2C=N). MS

(EI) = 622 ([M + H]$^+$). Anal. Calcd. for $C_{25}H_{25}BrN_3O_5PS_2$: C, 48.24; H, 4.05; N, 6.75. Found: C, 48.36; H, 3.94; N, 6.88.

Diphenyl (4-Chlorophenyl)-[5-(2-methoxyethylthio)-1,3,4-thiadiazol-2-ylamino]methylphosphonate (10a). Yellow solid; Yield: 0.833 g (76%). mp. 134–135°C. IR: 712, 833, 1029, 1186, 1245, 1289, 1488, 1610, 3056, 3352. ^{1}H NMR: 3.56 (t, 2H, J = 5.4, CH_2), 3.81 (s, 3H, OCH_3), 3.98−4.18 (m, 3H, CH_2, and C*H*N), 6.05 (s, 1H, NH), 7.24−7.31 (m, 3H, Ar-H), 7.35 (d, 2H, J = 8.2, Ar-H), 7.65−7.71 (m, 2H, Ar-H), 7.75 (d, 2H, J = 8.2, Ar-H), 7.87−7.96 (m, 2H, Ar-H), 8.08−8.21 (m, 3H, Ar-H). ^{13}C NMR: 55.7 (OCH_3), 61.0, 62.6 (2 CH_2), 72.9 (*C*HN), 118.1−150.2 (Ar-18C), 162.9, 163.7 (2C=N). MS (EI) = 548 ([M + H]$^+$). Anal. Calcd. for $C_{24}H_{23}ClN_3O_4PS_2$: C, 52.60; H, 4.23; N, 7.67. Found,%: C, 52.48; H, 4.19; N, 7.50.

Diphenyl (4-Bromophenyl)-[5-(2-methoxyethylthio)-1,3,4-thiadiazol-2-ylamino]methylphosphonate (10b). Yellow solid; Yield: 0.912 g (77%). mp. 137–138°C. IR: 830, 1031, 1180, 1242, 1285, 1477, 1615, 3077, 3371. ^{1}H NMR: 3.57 (t, 2H, J = 5.4, CH_2), 3.88 (s, 3H, OCH_3), 4.12–4.31 (m, 3H, CH_2, and C*H*N), 6.21 (s, 1H, NH), 7.03–7.16 (m, 3H, Ar-H), 7.36 (d, 2H, J = 8.2, Ar-H), 7.65–7.73 (m, 2H, Ar-H), 7.77 (d, 2H, J = 8.2, Ar-H), 7.90–7.98 (m, 2H, Ar-H), 8.14–8.25 (m, 3H, Ar-H). ^{13}C NMR: 58.2 (OCH_3), 62.9, 67.5 (2 CH_2), 73.9 (*C*HN), 111.1–149.2 (Ar-18C), 160.5, 161.3 (2C=N). MS (EI) = 591 (M^+). Anal. Cacld. for $C_{24}H_{23}BrN_3O_4PS_2$: C, 48.65; H, 3.91; N, 7.09. Found,%: C, 48.51; H, 3.74; N, 7.20.

Diphenyl (4-Chlorophenyl)-[5-(2,3-dihydroxypropylthio)-1,3,4-thiadiazol-2-ylamino]methylphosphonate (11a). Pale yellow solid; Yield: 0.835 g (74%). mp. 182–183°C. IR: 755, 840, 1042, 1120, 1214, 1261, 1458, 1612, 2966, 3482. ^{1}H NMR: 3.66−3.72 (m, 3H, CH_2, and OH), 3.91−4.01 (m, 2H, CH_2), 4.22−4.31 (m, 2H, C*H*N, and C*H*OH), 4.58−4.62 (m, 1H, OH), 6.14 (bs, 1H, NH), 7.22−7.31 (m, 3H, Ar-H), 7.36 (d, 2H, J = 8.2, Ar-H), 7.61−7.69 (m, 2H, Ar-H), 7.73 (d, 2H, J = 8.2, Ar-H), 7.88−7.96 (m, 2H, Ar-H), 8.10−8.22 (m, 3H, Ar-H). ^{13}C NMR: 43.2, 66.2 (2 CH_2), 72.1 (*C*HN), 73.1 (C*H*OH), 119.1−150.9 (Ar-18C), 161.1, 163.2 (2C=N). MS (EI) = 564 ([M + H]$^+$). Anal. Cacld. for $C_{24}H_{23}ClN_3O_5PS_2$: C, 51.11; H, 4.11; N, 7.45. Found: C, 50.95; H, 4.02; N, 7.36.

Diphenyl (4-Bromophenyl)-[5-(2,3-dihydroxypropylthio)-1,3,4-thiadiazol-2-ylamino]methylphosphonate (11b). Pale yellow solid; Yield: 0.913 g (75%). mp. 179–180°C. IR: 827, 1040, 1118, 1211, 1258, 1468, 1615, 2972, 3485. ^{1}H NMR: 3.79−3.85 (m, 3H, CH_2, and OH), 4.05−4.14 (m, 2H, CH_2), 4.28−4.38 (m, 2H, C*H*N, and C*H*OH), 4.98−5.02 (m, 1H, OH), 6.15−6.19 (bs, 1H, NH), 7.25−7.37 (m, 3H, Ar-H), 7.41 (d, 2H, J = 8.2, Ar-H), 7.59−7.67 (m, 2H, Ar-H), 7.72 (d, 2H, J = 8.2, Ar-H), 7.88−7.98 (m, 2H, Ar-H), 8.12−8.24 (m, 3H, Ar-H). ^{13}C NMR: 44.2, 66.6 (2 CH_2), 72.8 (*C*HN), 73.2 (C*H*OH), 118.3−151.3 (Ar-18C), 161.5, 163.4 (2C=N). MS (EI) = 607 (M^+). Anal. Cacld. for $C_{24}H_{23}BrN_3O_5PS_2$: C, 47.37; H, 3.81; N, 6.91. Found: C, 47.14; H, 3.68; N, 7.11.

CONCLUSION

New (1,3,4-thiadiazol-2-ylamino) methylphosphonate derivatives were synthesized by a three component reaction of aromatic aldehyde, thiadiazolylamine, and triphenyl phosphite. Glycosylation and alkylation, of the phosphonates linked to thiadiazole thioles, with acyclic oxygenated halides lead to the formation of the *S*-substituted derivatives.

REFERENCES

1. Omar, A. M. E.; Aboul Wafa, O. M. *J. Heterocycl. Chem.* **1986,** 23, 1339-1341.
2. Kurtzer, F. In: A. R. Katritzky, and A. J. Boulton (Eds.), *Advances in Heterocyclic Chemistry*, Vol. 5, 1,2,4-Thiadiazoles; Academic Press: New York, 1965, p. 165.
3. Foroumadi, A.; Mirzaei M.; Shafiee, A. *Farmaco* **2001,** 56, 621-623.
4. Awad, L. F.; El Ashry, E. S. H. *Carbohydr. Res.* **1998,** 312, 9-22.
5. Varvarasou, A.; Sistra-Papastaikoud, T.; Tsantili-Kakoulidou, A.; Vamvakides, A. *Farmaco* **1998,** 53, 320-326.
6. Holla, B. S.; Poorjary, K. N.; Rao B. S.; Shivananda, M. K. *Eur. J. Med. Chem.* **2002,** 37, 511-517.
7. (a) Bock, T.; Möhwald, H.; Mülhaupt, R. *Macromol. Chem. Phys.* **2007,** 208, 1324-1340. (b) Evans, O. R.; Manke, D. R.; Lin, W. *Chem. Mater.* **2002,** 14, 3866-3874.
8. Dang, Q.; Liu, Y.; Cashion, D. K.; Kasibhatla, S. R.; Jiang, T.; Taplin, F.; Jacintho, J. D.; Li, H.; Sun, Z.; Fan, Y.; DaRe, J.; Tian, F.; Li, W.; Gibson, T.; Lemus, R.; Van Poelje, P. D.; Potter, S. C.; Erion, M. D. *J. Med. Chem.* **2011,** 54, 153-165.
9. Birkholz, M. N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009,** 38, 1099-1018.
10. Engel, R.; Cohen, J. I. *Synthesis of Carbon–Phosphorus Bonds, 2nd ed.*; CRC Press: Boca Raton, FL, 2003.
11. Li, X. S.; Zhang, D. W.; Pang, H.; Shen, F.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Org. Lett.* **2005,** 7, 4919-4922.
12. Atherton, F. R.; Hassal, C. H.; Lambert, R. W. *J. Med. Chem.* **1987,** 30, 1603-1607.
13. Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade R.; Wood, J. M. *J. Med. Chem.* **1989,** 32, 1652-1661.
14. Hassal, C. H. in Hahn, F. E. Ed., *Antibiotics*; Springer: Berlin, **1983**; Vol. VI, Alafosfalin (Ro 03-7008, Alaphosphin), pp. 1-11.
15. Atherton, F. R.; Hall, M. J.; Hassal, C. H.; Lambert R. W.; Lloyd, W. J.; Ringrose, P. S. *Antimicrom. Agents Chemother.* **1979,** 15, 696-705.
16. Barder, A. *Aldrichim. Acta* 1988**,** 21, 15.
17. Gulyukina, N. S.; Makukhin, N. N.; Beletskaya, I. P. Russ. *J. Org. Chem.* **2011,** 47, 633-649.
18. Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010,** 17, 264-289.
19. Maier L.; Spoerri, H. *Phosphorus Sulfur Silicon Relat. Elem.* **1991,** 61, 69-75.
20. Giannousi P. P.; Bartlett, P. A. *J. Med. Chem.* **1987,** 30, 1603-1609.
21. Kafarski P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991,** 63, 193-115.
22. (a) Dang, Q.; Brown, B. S.; Liu, Y.; Rydzewski, R. M.; Robinson, E. D.; van Poelje, P. D.; Reddy, M. R.; Erion, M. D. *J. Med. Chem.* **2009,** 52, 2880-2898. (b) Moonen, K.; Laureyn, I.; Stevens, Ch. *Chem. Rev.* **2004,** 109, 6177-6115. (c) Koparir, P.; Karaarslan, M.; Orek, C.; Koparir, M. *Phosphorus Sulfur Silicon Relat. Elem.* **2011,** 86, 2368-2376.
23. Keglevich, G.; Sipos, M.; Takacs, D.; Ludanyi, K. *Heteroatom Chem.* **2008,** 19, 288-292.
24. Enders, D. Saint-Dizier, A. Lannou, M. I. Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29-49.
25. Khalifa, N. M.; Ramla, M. M.; Amr, A. E. E.; Abdulla, M. M. *Phosphorus Sulfur Silicon Relat. Elem.* **2008,** 183, 3046-3062.
26. Blanc-Muesser, M.; Vigne, L.; Driguez, H.; Lehmann, J.; Steck, J.; Urbahns, K. *Carbohydr. Res.* **1992,** 224, 59-71.
27. Mereyala, H. B.; Gurijala, V. R. *Carbohydr. Res.* **1993,** 242, 277-280.
28. El Ashry, E. S. H.; Rashed, N.; Awad, L. F.; Ramadan, E.; Abdel-Mageed, S. M.; Rezki, N. *Nucleosides Nucleotides Nucleic Acids* **2007,** 26, 423-435.
29. El-Sayed, W. A.; Rashad, A. E.; Awad, S. M.; Ali, M. M. *Nucleosides, Nucleotides Nucleic Acids* **2009,** 28, 261-274.
30. El-Sayed, W. A.; Fathi, N. M.; Gad W. A.; El-Ashry, E. S. H. *J. Carbohydr. Chem.* **2008,** 27, 357-372.
31. El-Sayed, W. A.; Ali, O. M.; Hathoot M. M.; Abdel-Rahman, A. A.-H. *Z. Naturforsch.* **2010,** 65C, 22-29.

32. Abbas, H. S.; El Sayed W. A.; Fathy, N. M. *Eur. J. Med.Chem.* **2010,** 45, 973-982.
33. Xianli Gao, W.; Bing Wang, W. M.; Chao Cao, Z. H.; Xincheng, S. L. *Chin. J. Org. Chem.* **2009,** 29, 1429-1433.
34. Talath, S.; Gadad, A. K. *Eur. J. Med. Chem.* **2006,** 41, 918-924.
35. Ibrahim, Y. A.; Abbas A. A.; Elwahy, A. H. M. *Carbohydr. Lett.* **1999,** 3, 331-338.
36. Mansour, A. K.; Ibrahim, Y. A.; Eid M. M.; Abdel-Hady, S. A. L. *J. Carbohydr. Nucleosides Nucleotides* **1981,** 8, 81-99.
37. Ibrahim, Y. A. *Carbohydr. Lett.* **1996,** 1, 425-432.
38. Mansour, A. K.; Ibrahim Y. A.; Khalil, N. S. A. M. *Nucleosides Nucleotides Nucleic Acids* **1999,** 18, 2256-2283.