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Synthesis and biological evaluation of novel phosphonyl thiazolo pyrazoles

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A series of novel dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-9-oxo-8-phenyl-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate **11a-g** have been synthesized by the reaction of chalcone derivatives of (*E*)-5-benzylidene-2-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-phenylthiazolidin-4-one **10a-g** with Bestmen Ohira reagent. The chemical structures of newly synthesized compounds have been elucidated by IR, NMR, MS and elemental analysis. The compounds **11a-g** have been evaluated for their nematicidal activity against *Dietylenchus myceliophagus* and *Caenorhabditis elegans*. Compound **11b**, **11c**, **11g** and **11f** show appreciable nematicidal activity.

Keywords: Phosponylpyrazoles, Bestmenohira reagent, click reaction, Knovenagel condensation, cyclisation, nematicidal activity

1,2,3-Triazoles are one of the most important classes of heterocyclic organic compounds, which are reported to present in a plethora of biological activities for diverse therapeutic areas[1]. The 1,2,3-triazole motif is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive and analgesic properties[2]. Polysubstituted five-membered aza heterocyclic's rank the most potent glycosidase inhibitors[3]. Further, this nucleus in combination with or in linking with various other classes of compounds such as amino acids, steroids, aromatic compounds, carbohydrates, *etc*. became prominent in having various pharmacological properties[4]. 1,2,3-Triazole modified carbohydrates have became easily available after the discovery of the Cu(I) catalyzed azide-alkynes 1,3-dipolar cycloaddition reaction[5] and quickly became a prominent class of non-natural sugars. The chemistry and biology of triazole modified sugars is dominated by Triazole glycosides[6]. Therefore, the synthesis and investigation of biological activity of 1,2,3-triazole glycosides is an important objective, which also received the considerable attention by the medicinal chemists.

Thiazoles are familiar group of heterocyclic compounds possessing a wide variety of biological activities and their utility as medicine is very much established[7]. Thiazole nucleus is also an integral part of all the available penicillins which have revolutionized the therapy of bacterial diseases[8]. Chemistry of thiazolidenone ring system is one considerable interest as it core structure in various synthetic pharmaceuticals displaying a broad spectrum biological activities[9]. The thiazolidenone nucleus also appears frequently in the structure of various natural products notably thiamine, compounds possessing cardiac and glycemic benefits such as troglitazone[10] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalyl)–thiazole–4-carboxylicacids[11]. Numerous thiazolidenone derivatives have shown significant bio activities such as antidiarrhoeal[12], anticonvulsant[13], antimicrobial[14], antidiabetic[15], antihistaminic[16], anticancer[17], anti HIV[18], Ca^{+2} channel blocker[19], PAF antagonist[20], cardioprotective[21], antiischemic[22], COX inhibitory[23], antiplatelet activating factor[24], non-peptide thrombin receptor antagonist[25], tumor necrosis factor- α antagonist[26] and nematicidal activities. Organo phosphorus compounds continue to attract much attention because of their various potent biological activities[27] in particular, phosphonates are important synthetic derivatives which can have often act as phosphate and carboxylic acid mimics, and interfere with enzymatic processes. Much of this

activity has been attributed to the relatively inert nature of the C-P bond[27], which is not easily hydrolyzed as compared to the P-O bond found in phosphates. The synthesis and biological activities of important natural and non natural phosphonate derivatives, including Phosponated aza heterocyclics and nucleotides has been reviewed[28]. In view of the importance of heterocyclics bearing a phosphonate group, new synthetic methods that would allow straightforward access to these versatile building blocks are needed[27,29]. Among the various bioactive heterocyclics the pyrazole moiety remains of great interest because of its wide applications in the pharmaceutical and agrochemical industry[30,31]. In addition, pyrazoles also play a central role in coordination chemistry[32].

Nematodes are tiny worms, some of them are plant parasites, and can play an important role in the predisposition of the host plant to the invasion by secondary pathogens[33]. Plants attacked by nematodes show retarded growth and development, as well as loss in the quality and quantity of the harvest. The nematicide use is slated for reduction due to environmental problems, and human and animals health concern. For example, effective nematicides such as dibromochloropropane (DBCD) and ethylene dibromide (EDB) have been withdrawn from the market due to their deleterious effects on human and the environment. Methyl bromide, the most effective and widely used fumigant for soil borne pests including nematodes, has already been banned.

The use of nonfumigant nematicides, based on organophosphates and carbamates, is expected to increase the withdrawal of methyl bromide, which will bring about new environmental concerns. In fact, the highly toxic Aldicarb used to control insects and nematodes has been detected in ground water[34]. Therefore alternative nematode control methods or less toxic nematicides need to be developed[35].One way of searching for such nematicidal compounds is to screen naturally occurring compounds in plants. Several such compounds, *e.g*. alkaloids, phenols, sesquiterpenes, diterpenes, polyacetylenes, and thienyl derivatives have nematicidal activity[36]. For example, α-terthienyl is a highly effective nematicidal compound[37]. Other compounds with nematicidal activity have been isolated from plants, mainly from the family *Asteraceae*[36]. However, compounds of plant origin and their analogs have not been developed into commercial nematicides; hence there is a need to develop commercial synthesis.

Following the successful introduction of nematicidal agents, inspired by the biological profile of triazoles, thiazoles, Phosponylpyrazoles. In continuation of our work on biological active molecules[38-46] it was thought to interest to accomidate all those moieties in single molecular frame work. In this article we wish to report the synthesis of a new class of hybrid heterocyclic's **11a-g** in good yields and their evaluated nematicidal activity.

Result and Discussion

The key intermediate, **8** required for the synthesis of title compound was prepared according to the procedure outlined in the Scheme I. Di acetyl D-Glucal **(2)** prepared from 3,4,6-tri- O-acetyl D-Glucal by treating with triethyl silane and Boron Tri fluoride diethyl etherate, de acylation of **2**, with NaOMe in Methanol at 0°C for 1h gave **3** (77%), which on subsequent treatment with TBDMSCl in Dichloromethane in presence of NEt_3 for 12h afforded TBS ether **4** (80%),on treatment with propargyl bromide in toluene in presence of tetra butyl ammonium hydrogen sulphate produced di ether **5**.After deprotection of TBS ether the propargyl ether converted into Triazole **7** (82%) by using 1,3-Dipolar cycloaddition with *p*-chloro phenyl azide was carried out at ambient temperature in the presence of $CuSO_4$ and sodium ascorbate in a mixture of 1:1 CH_2Cl_2–H_2O. Oxidation of 7 with IBX in acetonitrile afforded compound **8**. Subsequently one pot synthesis of Triazole linked Thiazolidenone glycosides was carried out by the condensation reaction between **8**, primary aromatic amine and a thio glycolic acid in presence of $ZnCl_2$ under microwave irradiation (Scheme I).The reaction is completed in only 5-10 minutes and the compounds, isolated by conventional work-up, **9a-g** are obtained in satisfactory yields, Compound **9a-g** was then reacted with *p*-fluorobenzaldehyde in presence of anhydrous NaOAc in glacial AcOH at reflux temperature gave chalcone derivatives of Triazole linked Thiazolidenone glycosides **10a-g,** on cyclocondensation under conventional and microwave irradiation with Bestmen Ohira reagent in presence of anhydrous KOH gave Compounds **11(a-g)**. The structures of synthesized compounds were confirmed by IR, NMR, MS and elemental analysis. Further the compounds were subject to nematicidal activity testing.

Nematicidal activity

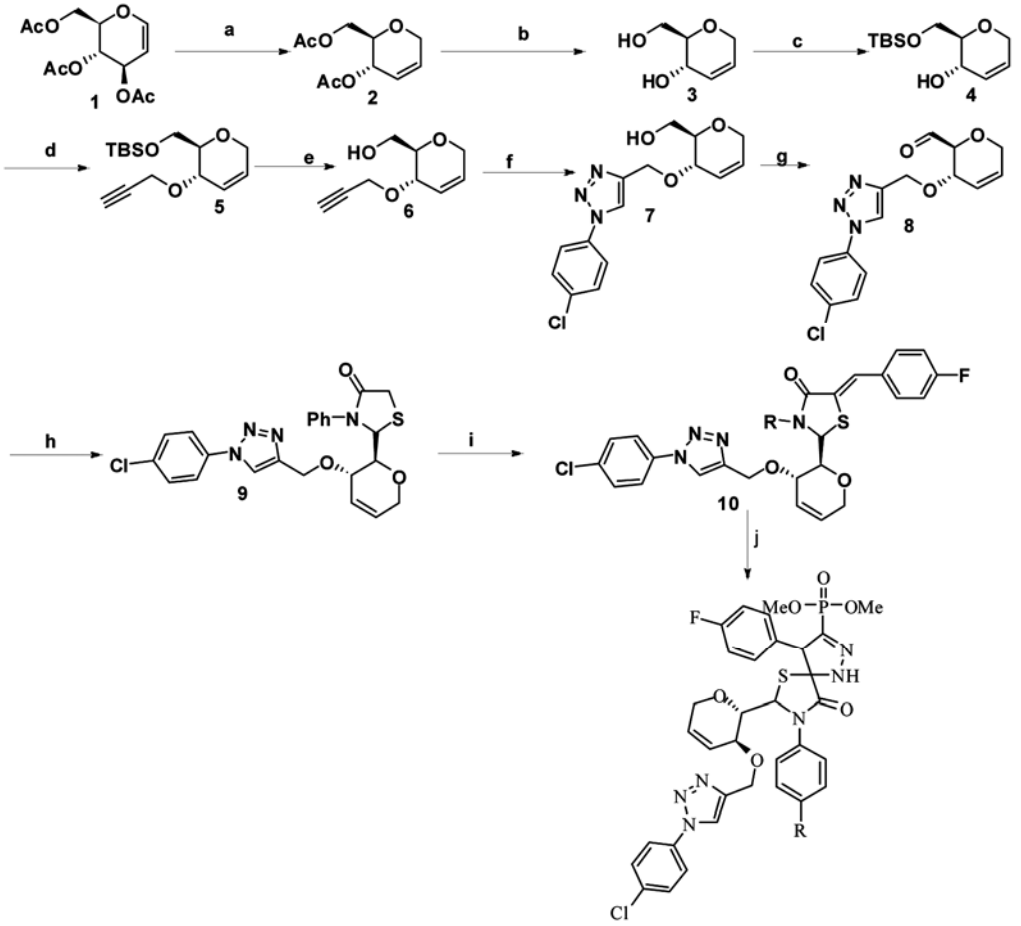
The compounds synthesized 10a-g in this study were also screened for their nematicidal activity against *Dietylenchus myceliophagus* and *Caenorhabditis elegans* by aqueous *in vitro* screening technique[46] at various concentrations. The nematicidal activity of each test compound was compared with the standard drug *Levamisole.* The results have been expressed in terms of LD_{50} *i.e*. median lethal dose at which 50% nematodes became immobile (dead). The screened data reveal that, compounds **11b, 11c, 11f** and **11g** are the most effective against *Dietylenchus myceliophagus* and *Caenorhabditis elegans* the other test compounds showed moderate activity. The LD_{50} values of the test compounds screened are presented in Table I.

Experimental Section

Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Di-methyl 2-oxopropyl phosphonate was purchased from Aldrich for the synthesis of Bestmen Ohira reagent. Reaction progress and homogeneity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck and compounds visualized either by exposure to UV light or dipping in 1% aqueous potassium permanganate solution. Silica gel

Table I — Nematicidal activity of **11a-g**

Compd	LD_{50} Value (ppm)	
	D. myceliophagus	*C. elegans*
11a	740	860
11b	220	280
11c	320	270
11d	501	540
11e	960	900
11f	209	210
11g	310	360
Levamisole	160	180



R: (a) C_6H_5; (b) 4-Cl-C_6H_5; (c) 4-NO_2-C_6H_5; (d) 2-CH_3-C_6H_5; (e) 4-CH_3-C_6H_5;(f) 3-OH-C_6H_5; (g) 2-OH-C_6H_5

Scheme I

chromatographic columns (60–120 mesh) were used for separations. Optical rotations were measured on an Perkin-Elmer 141 polarimeter by using a 2 mL cell with a path length of 1 dm with $CHCl_3$ or $CDCl_3$ as solvent. All melting points are uncorrected and measured using Fisher-Johns apparatus. IR spectra were recorded as KBr disks on a Perkin-Elmer FT-IR spectrometer. Microwave reactions are carried out in mini lab microwave catalytic reactor (ZZKD, WBFY-201). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for^{13}C). Chemical shifts are reported as δ (ppm) against TMS as internal reference and coupling constants *(J)* are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analysis (CHN) determined by a Perkin-Elmer 240 CHN elemental analyzer, were within ± 0.4% of theoretical.

((2R,3S)-3-Acetoxy-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate, 2

Tri-*O*-acetyl-D-glucal (**1**) (3.0 g, 11. 02 mmol) was dissolved in anhydrous dichloromethane(5 mL).The solution was cooled to 0°C, tri ethyl silane (1.53 g,13.22 mmol) was added and the mixture was stirred for 5 min. Thereafter, boron trifluoride diethyl etherate (690 μL of a40 w% solution in diethyl ether, 11.02 mmol) was added drop-wise and the reaction mixture was stirred for 90 min. The mixture was poured into a saturated solution of $NaHCO_3$. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel (PE/EtOAc, 3:1) yielded the title compound (2.24 g, 10.42 mmol, 95%) as a colourless syrup. $[\alpha]^D_{20}$: +115.5° (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87-5.84 (m, 2H, =CH), 4.95 (t, 1H, OCH), 4.03-3.99 (m, 1H, CH), 4.12- 4.09 (m, 4H, OCH_2), 2.20 (s, 6H, CO C H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 127.2, 125.8, 73.6, 65.1, 64.0, 62.5, 21.1; MS: *m/z* (M^++H) 215. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.82; H, 6.35%.

(2R,3S)-2-((tert-Butyldimethylsilyloxy)methyl)-3,6-dihydro-2*H*-pyran-3-ol, 4

Diacetate **2** (17.22 mmol) was treated by a catalytic amount of sodium methoxide in methanol (100 mL) at RT. After evaporation of the solvent,the free hydroxyl unsaturated glycoside was obtained in quantitative yield and used without further purification. This diol was treated with 2.50 equiv of TBD MSCl (3.14 g, 21.14 mmol), 2.6 equiv of NEt_3 (3.2 mL,22.4 mmol), and 0.05 equiv of imidazole (30 mg, 0.43 mmol) in CH_2Cl_2 (30 mL) at RT for *ca*. 24 h (until TLC analysis showed no more starting material). After addition of 25 mL of water and extraction with 3×30 mL of CH_2Cl_2, the organic layer was dried. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography using petroleum ether/ethyl acetate as the eluent yielded the title compound (1.94 g, 10.42 mmol, 85%) as a colourless syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.0-5.82 (m, 2H, =CH), 5.42 (d, *J*=6.5Hz, 1H, CH), 4.50 (brs, 1H, OH), 4.20-4.12 (m, 1H, CH), 3.91-3.80 (m, 4H, CH_2), 0.98 (s, 9H, t-Bu), 0.24 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.5, 125.6, 84.6, 81.5, 73.6, 62.7, 25.6, 18.1; MS: *m/z* (M^++Na) 267. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.62; H, 9.75%.

tert-Butyldimethyl(((2R,3S)-3-(prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)silane, 5

To a solution of alcohol **4** (400 mg, 1.63 mmol, 1.0 equiv) in toluene (1.6 mL) was added a 35% aqueous solution of NaOH (1.6 mL), propargyl bromide (80% solution in toluene, 363 μL, 2.4 mmol, 1.5equiv), and n-Bu_4NHSO_4 (280 mg, 0.82 mmol, 0.5 equiv). After 6 h of vigorous stirring at RT, Et_2NH (1.6 mL) was added. The reaction mixture was stirred for 1 h, poured into ice water, cautiously neutralized by addition of a 3M solution of hydrochloric acid, and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexane/EtOAc 85:15) to afford propargyl ether as colorless oil (0.345g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03-5.80 (m, 2H, =CH), 4.69 (t, *J*= 3.9Hz 1H, CH), 3.68 (dd, *J*= 8.9Hz, 4.1Hz, 1H, OCH), 3.99-3.89 (m, 6H, CH_2), 3.20 (s, 1H, CH), 0.96 (s, 9H, t-Bu), 0.23 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.2, 124.9, 78.0, 76.2, 74.2, 64.2, 63.2, 58.5, 25.3, 18.5; MS: *m/z* (M^++H) 283. Anal. Calcd for $C_{15}H_{26}O_3Si$: C, 63.78; H, 9.28. Found: C, 63.62; H, 8.95%.

((2R,3S)-3-(Prop-2-ynyloxy)-3,6-dihydro-2*H*-pyran-2-yl)methanol, 6

To a stirred solution of **5** (0.325g) in tetrahydro-furan catalytic amount of TBAF was added and stirred the reaction mixture at RT for 15 min, extracted the product with ethyl acetate (20 mL). The

combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (60-120 mesh, hexane/EtOAc 70:30) to afford alcohol as yellow oil (0.285 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95-5.75 (m, 2H, =CH), 4.65 (d, *J*=3.9Hz, 1H,CH), 4.52 (brs, 1H, OH), 4.09-4.11 (m, 4H, OCH_2), 3.64 (dd, *J*= 4.1Hz, 8.9Hz, 1H, OCH), 3.76 (d, *J*=6.8Hz, 2H, OCH_2), 3.28 (s, 1H, CH): ^{13}C NMR (75 MHz, $CDCl_3$): δ 127.2, 125.6, 78.3, 76.1, 74.1, 64.2, 61.4, 58.0; MS: *m/z* (M^++H) 169. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.10. Found: C, 64.02; H, 6.95%.

((2R,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)methanol, 7

To a solution containing alkyne **6** (0.250 g, 0.778 mmol), *p*-chlorophenyl azide (0.130 g, 0.849 mmol) in dichloromethane (10 mL) and water (10 mL) were added $CuSO_4.5H_2O$ (0.110 g) and sodium ascorbate (0.114 g). The resulting suspension was stirred at RT for 6h. After this time, the mixture was diluted with 5 mL dichloromethane and 5 mL water. The organic phase was separated, dried with sodium sulphate and concentrated at reduced pressure the crude product was purified by column chromatography on silica gel (60-120 mesh, hexane/EtOAc 65:35) to afford **7** (0.290 g, 75%) as a white powder. m.p.149-151°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, Ar-H), 7.56 (d, *J*=9.2Hz, 2H, Ar-H), 7.45 (d, *J*=8.9Hz, 2H, Ar-H), 5.85-5.79 (m, 2H, =CH), 4.59 (s, 2H, OCH_2), 4.50 (brs, 1H, OH), 3.88-3.99 (m, 4H, OCH_2), 3.8-3.75 (m, 2H, OCH); ^{13}C NMR (75MHz, $CDCl_3$): δ 140.9, 134.5, 134.1, 128.4, 127.5, 125.4, 122.1, 11.5, 78.6, 68.5, 65.7, 64.2, 62.4; MS: *m/z* (M^++H) 322. Anal. Calcd for $C_{15}H_{16}ClN_3O_3$: C, 55.90; H, 5.01, N, 13.06. Found: C, 55.65, H, 4.95. N, 12.86%.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-phenylthiazolidin-4-one, 9a-g

To a solution of alcohol **7** (0.120 g, 0.465 mmol) in CH_2Cl_2 (5 mL), catalytic amount of IBX was added at 0°C and stirred at RT for 30 min. The reaction mixture was filtered and washed with CH_2Cl_2 (2×10 mL). It was dried (Na_2SO_4) and evaporated to give aldehyde 7 (0.110 g) in quantitative yield as a yellow liquid, which was used as such for the next reaction.

To a stirred mixture of **8** (0.110g, 0.373 mmol), aromatic amine (0.373 mmol) and anhydrous thioglycolic acid (0.140 g, 0.211 mmol) in dry toluene (5 mL), $ZnCl_2$ (0.100 g, 0.751 mmol) was added after 2 min and irradiated in microwave bath reactor at 280 W for 4-7 min at 110°C. After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The ethyl acetate layer was washed with 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel (60- 120 mesh) with hexane - ethyl acetate as eluent.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-phenylthiazolidin-4-one, 9a: m.p. 157-159°C. Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04(s, 1H, Ar-H), 7.50 (d, *J*=9.2H_Z, 2H, Ar-H), 7.40(d, *J*=8.9 H_Z, 2H, Ar-H), 7.10-6.20 (m, 5H, Ar-H), 5.80-5.71 (m, 2H, =CH), 4.90 (d, *J*=5.2 Hz, 1H, CH-S), 4.52 (s, 2H, OCH_2), 4.09-3.94 (m, 2×CH), 3.79 (d, *J*=6.6 Hz, 2H, OCH_2), 3.72 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 144.1, 141.8, 134.1, 128.2, 125.6, 122.4, 119.4, 85.6, 72.6, 66.4, 64.0, 51.4, 33.9; MS: *m/z* (M^++H) 469. Anal. Calcd for $C_{23}H_{21}ClN_4O_3S$: C, 58.91; H, 4.51; N, 11.95. Found: C, 58. 68; H, 4.35; N, 11.66%.

(R)-3-(4-Chlorophenyl)-2-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)thiazolidin-4-one, 9b: m.p. 226-228°C. Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, Ar-H), 7.54 (d, *J*=9.4H_Z, 4H, Ar-H), 7.42(d, *J*=8.6H_Z, 4H, Ar-H), 5.84-5.75 (m, 2H, =CH), 4.94 (d, *J*=5.2 Hz, CH-S), 4.50 (s, 2H, OCH_2), 4.06-3.96 (m, 2H, 2×CH), 3.80 (t, 2H, OCH_2), 3.72 (s, 2H, CH_2): δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 144.2, 139.2, 134.2, 129.2, 125.5, 122.2, 119.4, 85.4, 72.8, 65.4, 63.4, 51.2, 34.1; MS: *m/z* (M^++Na) 525. Anal. Calcd for $C_{23}H_{20}Cl_2N_4O_3S$: C, 54.88; H, 4.00, N, 11.13. Found: C, 54.58, H, 3.75. N, 10.86%.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-(4-nitrophenyl)thiazolidin-4-one, 9c: m.p.211-213°C. Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J*=8.7Hz, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 7.61 (d, *J*=9.4H_Z, 2H, Ar-H), 7.46 (d, *J*=8.5H_Z, 2H, Ar-H), 6.84 (d, *J*=9.8Hz, 2H, Ar-H), 5.86-5.79 (m, 2H, =CH), 4.96 (d, *J*=5.2Hz, CH-S), 4.55 (s, 2H, OCH_2),

4.05-3.95 (m, 2H, 2×CH), 3.85 (d, *J*=6.9Hz, 2H, OCH_2), 3.82 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 144.0, 141.8, 134.2, 128.5, 125.4, 119.5, 85.4, 72.4, 65.9, 63.6, 51.5, 34.6; MS: *m/z* (M^++H) 514. Anal. Calcd for $C_{23}H_{20}ClN_5O_5S$: C, 53.75; H, 3.92, N, 13.63. Found: C, 53.58, H, 3.75. N, 13.39%.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-*o*-tolylthiazolidin-4-one, 9d: m.p.191-193°C. Yield 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H, Ar-H), 7.56 (d, *J*=9.2 Hz, 2H, Ar-H), 7.49 (d, *J*=8.7 Hz, 2H, Ar-H), 7.45-7.39 (m, 4H, Ar-H), 5.76 (m, 2H, =CH), 4.93 (d, *J*=5.2 Hz, 1H, CHS), 4.60 (s, 2H, OCH_2), 4.05-3.96 (m, 2H, CH), 3.90 (t, 2H, OCH_2), 3.81 (s, 2H, CH_2), 2.1 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 144.2, 138.2, 134.2, 130.7, 128.6, 125.6, 122.0, 119.5, 116.5, 85.4, 72.6, 65.8, 63.4, 52.0, 32.3, 17.5; MS: *m/z* (M^++H) 483. Anal. Calcd for $C_{24}H_{23}ClN_4O_3S$: C, 59.68; H, 4.80, N, 11.60. Found: C, 59.48; H, 4.55; N, 11.49%.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-*p*-tolylthiazolidin-4-one, 9e: m.p.195-198°C. Yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, Ar-H), 7.51 (d, *J*= 9.2 Hz, 2H, Ar-H), 7.45 (d, *J*=8.7Hz, 2H, Ar-H), 7.25 (d, *J*=8.2Hz, 2H, Ar-H), 6.84 (d, *J*= 9.4 Hz, 2H, Ar-H), 5.72-5.68 (m, 2H, =CH), 4.95 (s, 1H, CHS), 4.59 (s, 2H, OCH_2), 4.04-3.99 (m, 2H, CH), 3.98 (t, 2H, OCH_2), 3.90 (s, 2H, CH_2), 2.32 (s, 3H, CH_3): ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 144.2, 138.6, 136.2, 14.1, 133.2, 129.4, 127.5, 122.5, 119.5, 85.4, 72.0, 66.4, 63.5, 51.5, 34.0, 21.4; MS: *m/z* (M^++H) 483. Anal. Calcd for $C_{24}H_{23}ClN_4O_3S$: C, 59.68; H, 4.80, N, 11.60. Found: C, 59.58, H, 4.65. N, 11.43%.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-(3-hydroxyphenyl)thiazolidin-4-one, 9f: m.p. 218-219°C. Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.40 (brs, 1H, Ph-OH), 8.08 (s, 1H, Ar-H), 7.58 (d, *J*=9.3 Hz, 2H, Ar-H), 7.49 (d, *J*=8.6 Hz, 2H, Ar-H), 6.83-6.76 (m, 4H, Ar-H), 5.72-5.68 (m, 2H,= CH), 4.94 (d, *J*=5.2Hz, 1H, CHS), 4.64 (s, 2H, OCH_2), 4.12 (t, 2H, OCH_2), 4.01-3.94 (m, 2H, CH), 3.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 158.2, 143.8, 134.5, 130.4, 128.6, 125.6, 122.4, 119.5, 114.8, 106.5, 85.4, 72.5, 66.4, 63.4, 51.5, 34.1; MS: *m/z* (M^++Na) 507. Anal. Calcd for $C_{23}H_{21}ClN_4O_4S$: C, 59.96; H, 4.36; N, 11.55. Found: C, 59.28; H, 4.65; N, 11.43%.

(R)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-3-(4-hydroxyphenyl)thiazolidin-4-one, 9g: m.p.273-275°C, Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.42 (brs, 1H, Ph-OH), 8.05 (s, 1H, Ar-H), 7.56 (d, *J*=9.2 Hz, 2H, Ar-H), 7.46 (d, *J*=8.4 Hz, 2H, Ar-H), 7.32 (d, *J*=8.6 Hz, 2H, Ar-H), 7.02 (d, *J*=8.8Hz, 2H, Ar-H), 5.89-5.80 (m, 2H,=CH), 4.96 (d, *J*=5.4 Hz, 1H, CHS), 4.66 (s, 2H, OCH_2), 4.09 (d, *J*=2H, OCH_2), 4.04-3.98 (m, 2H, CH), 3.94 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 154.1, 144.4, 134.9, 134.8, 128.8, 127.2, 125.6, 123.2, 119.4, 116.4, 85.4, 72.6, 66.5, 64.0, 51.6, 34.5; MS: *m/z* (M^++H) 485. Anal. Calcd for $C_{23}H_{21}ClN_4O_4S$: C, 59.96; H, 4.36, N, 11.55. Found: C, 59.38, H, 4.75. N, 11.33%.

General procedure for the synthesis of 10a-g

A mixture of compound **9a** (0.01 mol), *p*-fluorobenzaldehyde (0.02 mol) and sodium acetate (0.01 mol) in anhydrous glacial acetic acid (20 mL), was refluxed for 3 h. The reaction mixture was concentrated and then poured into ice cold water, the solid thus separated, was filtered, washed with water and crystallized from glacial acetic acid. To afford pure **10a** as yellow solid.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-5-(4-fluorobenzylidene)-3-phenylthiazolidin-4-one, 10a: m.p. 235-237°C. Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H, Ar-H), 7.80 (s, 1H, CH =C), 7.72 (d, *J*=9.6Hz, 2H, Ar-H), 7.40 (d, *J*=9.2H_Z, 2H, Ar-H), 7.45 (d, *J*=8.9H_Z, 2H, Ar-H), 7.19 (d, *J*= 8.2 Hz, 2H, Ar-H), 7.02-6.80 (m, 5H, Ar-H), 5.80-5.74 (m, 2H, =CH), 4.90 (d, *J*=5.2 Hz, 1H, CH-S), 4.52 (s, 2H, OCH_2), 4.09-3.94 (m, 2H, 2×CH), 3.79 (d, *J*=6.6 Hz, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 162.1, 144.1, 141.8, 139.8, 134.1, 130.4, 128.2, 125.6, 124.6, 122.4, 119.4, 115.5, 85.6, 72.6, 66.4, 64.0, 51; MS: *m/z* (M^++H) 575. Anal. Calcd for $C_{30}H_{24}ClFN_4O_3S$: C, 62.66; H, 4.21, N, 9.74. Found: C, 62. 48; H, 4.15; N, 9.56%.

(R,Z)-3-(4-Chlorophenyl)-2-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-5-(4-fluorobenzyli dene) thiazolidin-4-one, 10b: m.p. 216-218°C. Yield 72%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H, Ar-H), 7.75 (s, 1H, CH=C), 7.62 (d, *J*=9.5 Hz, 2H, Ar-H), 7.52 (d, *J*=9.4 H_Z, 4H, Ar-H), 7.40 (d, *J*=8.6 H_Z, 4H, Ar-H), 7.19 (d, *J*=8.1Hz, 2H, Ar-H), 5.84-5.75 (m, 2H ,=CH), 4.94 (d, *J*=5.2Hz, 1H, CH-S), 4.52 (s, 2H, OCH_2), 4.06-3.94 (m, 2H, 2×CH), 3.80 (t, 2H, OCH_2): δ ^{13}C NMR (75 MHz,$CDCl_3$): δ 170.5, 162.1, 144.2, 139.2, 134.2, 130.4,129.2, 125.5, 124.1, 122.2, 119.4, 85.4, 72.8, 65.4, 63.4, 51.2; MS: *m/z* (M^++Na) 632. Anal. Calcd for $C_{30}H_{23}Cl_2FN_4O_3S$: C, 59.12; H, 3.80, N, 9.19. Found: C, 59.01; H, 3.45; N, 8.96%.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2, 3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-5-(4-fluorobenzylidene)-3-(4-nitrophenyl) thiazolidin-4-one, 10c: m.p.221-223°C. Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, *J*=8.7Hz, 2H, Ar-H), 8.09 (s, 1H, Ar-H), 7.69 (d, *J*=9.1Hz, 2H,Ar-H), 7.65 (s, 1H, CH =C), 7.61 (d, *J*=9.4H_Z, 2H, Ar-H), 7.46 (d, *J*=8.5H_Z, 2H, Ar-H), 7.18 (d, *J*=8.3Hz, 2H, Ar-H), 6.84 (d, *J*=9.8Hz, 2H, Ar-H), 5.86-5.79 (m, 2H, =CH), 4.96 (d, *J*=5.2Hz, CH-S), 4.55 (s, 2H, OCH_2), 4.05-3.95 (m, 2H, 2×CH), 3.85 (d, *J*=6.9 Hz, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 162.1, 144.0, 141.8, 134.2, 130.4, 128.5, 125.4, 119.5, 115.4, 85.4, 72.4, 65.9, 63.6, 51.5; MS: *m/z* (M^++H) 620. Calcd for $C_{30}H_{23}ClFN_5O_5S$: C, 58.11; H, 3.74, N, 11.29. Found: C, 57.98; H, 3.55; N, 11.09%.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-5-(4-fluorobenzylidene)-3-*o*-tolylthiazolidin-4-one, 10d: m.p. 201-203°C. Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H, Ar-H), 7.69 (d, *J*=8.5Hz, 2H, Ar-H), 7.62 (s, 1H, CH =C), 7.56 (d, *J*=9.2 Hz, 2H, Ar-H), 7.49 (d, *J*=8.7 Hz, 2H, Ar-H), 7.45-7.39 (m, 4H, Ar-H), 7.10 (d, *J*=9.1 Hz, 2H, Ar-H), 5.76 (m, 2H, =CH), 4.93 (d, *J*=5.2 Hz, 1H, CHS), 4.60 (s, 2H, OCH_2), 4.05-3.96 (m, 2H, CH), 3.90 (t, 2H, OCH_2), 2.1 (s, 3H, CH_3): δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 162.9, 144.6, 137.2, 133.2, 130.6, 130.4, 128.2, 125.9, 122.7, 119.2, 116.2, 115.4, 84.4, 72.1, 65.3, 63.1, 52.5, 32.0, 17.5; MS: *m/z* (M^++H) 589. Anal. Calcd for $C_{31}H_{26}ClFN_4O_3S$: C, 63.21; H, 4.45; N, 9.51. Found: C, 62.75; H, 4.25; N, 9.29%.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2 ,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl) -5-(4-fluorobenzylidene)-3-*p*-tolylthiazolidin-4-one, 10e: m.p. 205-215°C, Yield 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H, Ar-H), 7.69 (s, 1H, CH =C), 7.65 (d, *J*=9.1Hz, 2H, Ar-H), 7.54 (d, *J*=9.2Hz, 2H, Ar-H), 7.42 (d, *J*=8.7Hz, 2H, Ar-H), 7.35 (d, *J*=8.2 Hz, 2H, Ar-H), 7.18 (d, *J*=8.8 Hz, 2H, Ar-H), 6.80 (d, *J*=9.4Hz, 2H, Ar-H), 5.70-5.69 (m, 2H, =CH), 4.94 (s, 1H, CHS), 4.55 (s, 2H, OCH_2), 4.04-3.98 (m, 2H, CH), 3.96 (t, 2H, OCH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 162.5, 144.1, 139.5, 137.6, 135.2, 133.2, 130.4, 129.1, 127.5, 124.1, 122.5, 119.5, 115.3, 85.1, 72.5, 66.1, 63.2, 51.2, 21.6; MS: *m/z* (M^++H) 589. Anal. Calcd for $C_{31}H_{26}ClFN_4O_3S$: C, 63.21; H, 4.45; N, 9.51. Found: C, 62.98; H, 4.25; N, 9.33%.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-5-(4-fluorobenzylidene)-3-(3-hydroxyphenyl) thiazoli din-4-one, 10f: m.p. 218-219°C. Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.42 (brs, 1H, Ph-OH), 8.08 (s, 1H, Ar-H), 7.71 (d, *J*=9.7Hz, H, Ar-H), 7.65 (s, 1H, CH=C), 7.59 (d, *J*=9.3Hz, 2H, Ar-H), 7.44 (d, *J*=8.6Hz, 2H, Ar-H), 7.15 (d, *J*=8.4 Hz, 2H, Ar-H), 6.80-6.78 (m, 4H, Ar-H), 5.70-5.68 (m, 2H, =CH), 4.92 (d, *J*=5.2Hz, 1H, CHS), 4.64 (s, 2H, OCH_2), 4.10 (t, 2H, OCH_2), 4.01-3.98 (m, 2H, CH); ^{13}C NMR (75 MHz,$CDCl_3$): δ 170.5, 162.1, 158.2, 143.8, 139.8, 134.5, 130.8, 128.6, 125.6, 124.1, 122.4, 119.5, 115.7, 114.8, 106.5, 85.4, 72.5, 66.4, 63.4, 51.5; MS: *m/z* (M^++H) 591. Anal. Calcd for $C_{30}H_{24}ClFN_4O_4S$: C, 60.96; H, 4.09; N, 9.48. Found: C, 60.58; H, 3.85; N, 9.13%.

(R,Z)-2-((2S,3S)-3-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-5-(4-fluorobenzylidene)-3-(4-hydroxyphenyl) thiazo lidin-4-one, 10g: m.p.283-285°C. Yield 62%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.42 (brs, 1H, Ph-OH), 8.05 (s, 1H, Ar-H), 7.85 (d, *J*=9.3Hz, 2H, Ar-H), 7.65 (s, 1H, CH=C), 7.56 (d, *J*=9.2Hz, 2H, Ar-H), 7.46 (d, *J*=8.4 Hz, 2H, Ar-H), 7.32 (d, *J*=8.6Hz, 2H, Ar-H), 7.19 (d, *J*=8.3 Hz, 2H, ArH), 7.02 (d, *J*=8.8Hz, 2H, Ar-H), 5.89-5.80 (m, 2H, =CH), 4.96 (d, *J*=5.4 Hz, 1H, CHS), 4.66 (s, 2H, OCH_2), 4.09 (d, *J*=2H, OCH_2), 4.04-3.98 (m, 2H, CH), ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 162.5, 154.1, 144.4, 139.8, 134.9, 134.8, 130.4, 128.8, 127.2, 125.6, 123.2, 119.4, 116.4, 115.9, 85.4, 72.6, 66.5, 64.0, 51.6; MS: *m/z* (M^++H) 591. Anal. Calcd for $C_{30}H_{24}ClFN_4O_4S$: C, 60.96; H, 4.09; N, 9.48. Found: C, 60.58; H, 3.95; N, 9.23%.

General procedure for the synthesis of Pyrazole phosphonates, 11a-g

To a stirred mixture of **10a** (1 mmol), and Bestmen Ohira Reagent (2.5mmol) in dry EtOH (10 mL) was

added KOH (2.5mmol) at RT, after 2 min and irradiated in microwave bath reactor at 500 W for 4-7 min at 50°C.The crude product thus obtained was purified by column chromatography on silica gel (60-120 mesh) with hexane-ethyl acetate as eluent. Under conventional method the reaction mixture in EtOH (10 mL) was stirred at RT for the appropriate time (Table II).

Dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-9-oxo-8-phenyl-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate, 11a: m.p.245-247°C. Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.06 (brs, 1H, -NH), 8.03 (s, 1H, Ar-H), 7.70 (d, *J*=9.6Hz, 2H, Ar-H), 7.30 (d, *J*=9.2H_Z, 2H, Ar-H), 7.45 (d, *J*=8.9H_Z, 2H, Ar-H), 7.19 (d, *J*=8.2Hz, 2H, Ar-H), 6.95-6.70 (m, 5H, Ar-H), 5.80-5.74 (m, 2H, =CH), 4.80 (d, *J*=5.2Hz, 1H, CH-S), 4.42 (s, 2H, OCH_2), 4.09-3.94 (m, 2H, 2×CH), 3.78 (s, 6H, OCH_3), 3.69 (d, *J*=6.6Hz, 2H, OCH_2), 3.52 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 160.1, 155.2, 144.1, 141.6, 136.2, 134.1, 129.2, 127.5, 125.6, 122.1, 119.1, 115.8, 86.6, 72.9, 63.8, 53.8, 44.5, 34.9; MS: *m/z* (M^++H) 725. Anal. Calcd for $C_{33}H_{31}ClFN_6O_6PS$: C, 54.66; H, 4.31, N, 11.59. Found: C, 54.48, H, 4.05. N, 11.36%.

Dimethyl8-(4-chlorophenyl)-7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-9-oxo-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate, 11b: m.p.206-208°C. Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.11 (brs,1H,-NH), 8.19 (s, 1H, Ar-H), 7.60 (d, *J*=9.5Hz, 2H, Ar-H), 7.54 (d, *J*=9.4H_Z, 4H, Ar-H), 7.30 (d, *J*=8.6H_Z, 4H, Ar-H), 7.22 (d, *J*=8.1Hz, 2H, Ar-H), 5.80-5.78 (m, 2H, = CH), 4.92 (d, *J*=5.2Hz, 1H, CH-S), 4.52 (s, 2H, OCH_2), 4.06-3.94 (m, 2H, 2×CH), 3.80 (t, 2H, OCH_2), 3.68 (s, 6H, OCH_3), 3.54 (s, 1H, CH); ^{13}C NMR (75 MHz,$CDCl_3$): δ 170.9, 162.1, 155.4, 144.2, 139.8, 134.6, 129.5, 125.8, 124.1, 122.0, 119.2, 115.4, 86.1, 72.5, 64.4, 53.5, 44.8, 34.9; MS: *m/z* (M^++Na) 781. Anal. Calcd for $C_{33}H_{30}Cl_2FN_6O_6PS$: C, 52.18; H, 3.98; N, 11.06. Found: C, 51.91; H, 3.65; N, 10.86%.

Dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-8-(4-nitrophenyl)-9-oxo-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate, 11c: m.p.231-233°C. Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.06 (brs, 1H, -NH), 8.23 (d, *J*=8.7Hz, 2H, Ar-H), 8.06 (s, 1H, Ar-H), 7.65 (d, *J*=9.1Hz, 2H, Ar-H), 7.51 (d, *J*=9.4H_Z, 2H, Ar-H), 7.41 (d, *J*=8.5H_Z, 2H, Ar-H), 7.10 (d, *J*=8.3Hz, 2H, Ar-H), 6.64 (d, *J*=9.8Hz, 2H, Ar-H), 5.76-5.59 (m, 2H, =CH), 4.86 (d, *J*=5.2Hz, 1H, CH-S), 4.35 (s, 2H, OCH_2), 4.01-3.93 (m, 2H, 2×CH), 3.72 (s, 6H, OCH_3), 3.65 (d, *J*=6.9 Hz, 2H, OCH_2), 3.45 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 162.1, 150.0, 147.8, 144.0, 136.8, 131.4, 128.8, 127.2, 122.0, 119.5, 115.4, 86.4, 72.4, 65.9, 63.9, 53.5, 44.5, 34.8; MS: *m/z* (M^++H) 780. Calcd for $C_{33}H_{30}ClFN_7O_8PS$: C, 51.47; H, 3.93; N, 12.73. Found: C, 51.18; H, 3.55; N, 12.49%.

Dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-9-oxo-8-o-tolyl-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate, 11d: m.p.221-223°C. Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.10 (brs, 1H, -NH), 8.02 (s, 1H, Ar-H), 7.59 (d, *J*=8.5Hz, 2H, Ar-H), 7.59 (d, *J*=9.2 Hz, 2H, Ar-H), 7.44 (d, *J*=8.7 Hz, 2H, Ar-H), 7.42-7.40 (m, 4H, Ar-H), 7.12 (d, *J*=9.1Hz, 2H, Ar-H), 5.76 (m, 2H, =CH), 4.92 (d, *J*=5.2Hz, 1H, CHS), 4.62 (s, 2H, OCH_2), 4.09-3.99 (m, 2H, CH), 3.74 (s, 6H, OCH_3), 3.62 (s, 1H, CH), 3.80 (t, 2H, OCH_2), 2.12 (s, 3H, CH_3): ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 160.1, 155.1, 144.4, 138.6, 136.2, 134.3, 130.7, 128.6, 127.2, 122.0, 119.2, 116.9, 115.4, 86.1, 72.8, 63.8, 53.5,

Table II — Synthesis of phosphonyl pyrazoles **11a-g**

Compd	R	Mol. Formula	Reaction time		Yield (%)	
			A (h)	B (min)	A	B
11a	C_6H_5	$C_{33}H_{31}ClFN_6O_6PS$	3.5	6	62	89
11b	4-Cl-C_6H_4	$C_{33}H_{30}Cl_2FN_6O_6PS$	2.5	4	60	85
11c	4-NO_2-C_6H_4	$C_{33}H_{30}ClFN_7O_8PS$	2.0	5	61	84
11d	2-CH_3-C_6H_4	$C_{34}H_{33}ClFN_6O_6PS$	3.0	6	65	86
11e	4-CH_3-C_6H_4	$C_{34}H_{33}ClFN_6O_6PS$	3.2	4	69	85
11f	3-OH-C_6H_4	$C_{35}H_{31}ClFN_6O_7PS$	2.0	5	72	89
11g	4-OH-C_6H_4	$C_{35}H_{35}ClFN_6O_7PS$	3.0	4	71	82

A: Conventional method; **B**: Microwave Irradiation method

44.9, 34.8, 17.9; MS: *m/z* (M^++H) 739. Anal. Calcd for $C_{34}H_{33}ClFN_6O_6S$: C, 55.25; H, 4.50; N, 11.37. Found: C, 55.01; H, 4.25; N, 11.09%.

Dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-9-oxo-8-*p*-tolyl-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate, 11e: m.p.209-211°C. Yield 76%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.01 (brs, 1H, -NH), 8.07 (s, 1H, Ar-H), 7.62 (d, *J*=9.1 Hz, 2H, Ar-H), 7.50 (d, *J*=9.2 Hz, 2H, Ar-H), 7.40 (d, *J*=8.7Hz, 2H, Ar-H), 7.32 (d, *J*=8.2Hz, 2H, Ar-H), 7.18 (d, *J*=8.8Hz, 2H, Ar-H), 6.70 (d, *J*=9.4Hz, 2H, Ar-H), 5.60-5.59 (m, 2H, =CH), 4.90 (s, 1H, CHS), 4.45 (s, 2H, OCH_2), 4.01-3.99 (m, 2H, CH), 3.94 (t, 2H, OCH_2), 3.75 (s, 6H, OCH_3), 3.62 (s, 1H, CH), 2.30 (s, 3H, CH_3); ^{13}C NMR (75MHz, $CDCl_3$): δ 170.9, 160.1, 155.0, 144.1, 138.7, 136.8, 133.4, 130.4, 129.1, 127.2, 122.0, 119.1, 115.3, 86.1, 72.9, 68.1, 63.9, 53.5, 44.5, 34.8, 21.6; MS: *m/z* (M^++H) 739. Anal. Calcd for $C_{31}H_{26}ClFN_4O_3S$: C, 55.25; H, 4.50; N, 11.37. Found: C, 54.98; H, 4.25; N, 11.03%.

Dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-8-(3-hydroxyphenyl)-9-oxo-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylpho sphonate, 11f: m.p.228-229°C. Yield 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.09 (brs, 1H, -NH), 9.40 (brs, 1H, Ph-OH), 8.04 (s, 1H, Ar-H), 7.61 (d, *J*=9.7Hz, 2H, Ar-H), 7.52 (d, *J*=9.3Hz, 2H, Ar-H), 7.42 (d, *J*=8.6Hz, 2H, Ar-H), 7.13 (d, *J*=8.4Hz, 2H, Ar-H), 6.70-6.68 (m, 4H, Ar-H), 5.73-5.70(m, 2H, =CH), 4.82 (d, *J*=5.2Hz, 1H, CHS), 4.54(s, 2H, OCH_2), 4.14 (t, 2H, OCH_2), 4.0-3.97 (m, 2H, CH), 3.70 (s, 6H, OCH_3), 3.57 (s, 1H, CH); ^{13}C NMR(75MHz,$CDCl_3$): δ 170.2, 156.1, 155.2, 144.8, 136.8, 129.6, 128.2, 127.5, 122.4, 119.4, 115.4, 106.5, 86.4, 72.5, 66.4, 63.4, 53.5, 44.9, 34.3; MS: *m/z* (M^++H) 741. Anal. Calcd for $C_{33}H_{31}$ $ClFN_6O_7PS$: C, 53.48; H, 4.22; N, 11.34. Found: C, 53.18; H, 4.01; N, 11.13%.

Dimethyl 7-((2S,3S)-3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)-4-(4-fluorophenyl)-8-(4-hydroxyphenyl)-9-oxo-6-thia-1,2,8-triazaspiro[4.4]non-2-en-3-ylphosphonate, 11g: m.p.293-295°C. Yield 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.85 (brs, 1H, -NH), 9.32 (brs, 1H, Ph-OH), 8.02 (s, 1H, Ar-H), 7.65 (d, *J*=9.3Hz, 2H, Ar-H), 7.59 (d, *J*=9.2Hz, 2H, Ar-H), 7.49 (d, *J*=8.4Hz, 2H, Ar-H), 7.30 (d, *J*=8.6Hz, 2H, Ar-H), 7.16 (d, *J*=8.3Hz, 2H, ArH), 7.0 (d, *J*= 8.8Hz, 2H, Ar-H), 5.89-5.82 (m, 2H, =CH), 4.96 (d, *J*=5.4 Hz, 1H, CHS), 4.56 (s, 2H, OCH_2), 4.07 (d, *J*=2H, OCH_2), 4.02-3.99 (m, 2H, CH), 3.82 (s, 6H, OCH_3), 3.62 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 160.5, 154.3, 144.6, 136.2, 134.9, 134.3, 130.4, 129.8, 127.2, 125.6, 123.2, 119.8, 116.1, 86.4, 73.6, 66.5, 64.0, 53.6, 44.8, 34.9; MS: *m/z* (M^++Na) 763. Anal. Calcd for $C_{33}H_{31}ClFN_6O_7PS$: C, 53.48; H, 4.22; N, 11.34. Found: C, 53.18; H, 3.99; N, 11.13%.

Conclusion

In conclusion, a series of a new class of hybrid heterocyclics **11 a-g** has been synthesized. The nematicidal activity of these compounds was evaluated against *Dietylenchus myceliophagus* and *Caenorhabditis elegans*. Among synthesized compounds **11b, 11c, 11f** and **11g** are the most effective against *Dietylenchus myceliophagus* and *Caenorhabditis elegans* the other test compounds showed moderate activity.

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