Antimicrobial activity of novel fused nitrogen, sulfur and phosphorus containing-heterocycles and relevant phosphonates with difurylpyridazine species

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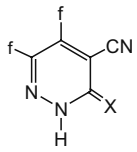
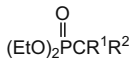
Treatment of 5,6-di(2-furyl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile with phosphonate carboanions stabilised with electron withdrawing group (CO_2R, CN, SR') led, under microwave irradiation and the effect of basic catalysis, to excellent yields of a variety of condensed sulfur, nitrogen and phosphorus-containing heterocycles as major products, along with fused thieno- and thiazole ring systems bearing a phosphonate moiety. On the other hand, fused thiazaphosphinine oxide and thiopyranone phosphonate were obtained in equal yields from the reaction of 5,6-di(2-furyl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile with diethyl vinylphosphonate. Screening results of antimicrobial potency for the products were discussed in terms of structure–activity relationships (SAR), and an attempt was made to define the structural features for lead compounds.

Keywords: phosphacyclenes, thienophosphonates, addition–cyclisation reaction, phosphonate carbanions; α,β-unsaturated carbonitriles

A continuous trend is observed toward the chemistry of phosphorus containing heterocycles,[1,2] largely, because these compounds, especially those that contained more nitrogen and/or sulfur tend to have higher pharmacological and pesticidal activity.[3-6] In connection to our previous work[7-16] on the application of a number of phosphorane and phosphonate carbanions to a variety of nitrogen functions, we studied the antibiotic potency of some fused- and spiro-nitrogen-containing heterophospholes that were isolated from the reactions of Wittig–Horner reagents with α,β-unsaturated nitriles,[17] and diazo–substrates.[18] These results encouraged us to attempt further preparation of a novel series of fused nitrogen- and sulfur-containing heterophosphorus esters and their relevant phosphonates. The antibacterial activity of the products were studied to shed light on the structure-activity relationship (SAR). The methodology used is based on the chemistry of the phosphonate carbanions **3a**–**e** toward 5,6-di(2-furyl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (**1**) (Fig.1). The reactions studied and the products obtained are depicted in Schemes 1, 2, 4, 5, 7 and 8.



1, f = 2-furyl, X = S
2, f = 2-furyl, X = O



3a, $R^1 = H_2$, $R^2 = CO_2Me$
3b, $R^1 = H_2$, $R^2 = CO_2Et$
3c, $R^1 = H_2$, $R^2 = CN$
3d, $R^1 = H_2$, $R^2 = SMe$
3e, $R^1 = H$, $R^2 = (=CH_2)$

Figure 1

Results and discussion

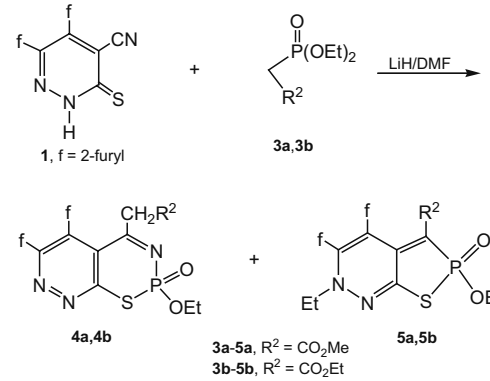
In a parallel work,[17] the required carbonitrile **1** was prepared according to the literature,[19] by ternary condensation of 2-furaldehyde, ethyl cyanoacetate, and hydrazine hydrate in an alcoholic sodium ethoxide solution to give the 3-oxo-4-carbonitrile derivative **2**. Further thiation of **2** with phosphorus pentasulfide in refluxing pyridine gave the thione derivative **1**.

5,6-Di(2-furyl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (**1**) was added to methyl diethoxyphosphonylacetate (**3a**) (or its ethyl derivative **3b**) and lithium hydride (LiH) in dry dimethylformamide (DMF) solution. The reaction mixture was heated under reflux for about 4 days, volatile materials were removed and the residue was subjected to chromatography on silica gel column. Thiazaphosphinines **4a**, **4b** (≈18% yield) and thiaphospholes **5a**, **5b** (≈36% yield) were isolated (Scheme 1). The structures **4** and **5** were assigned on the basis of ^1H, ^{13}C, ^{31}P NMR, IR and MS spectroscopy[20,21] as well as elemental analyses. The IR spectra of **4a** and **4b** showed the characteristic bands at ≈1720, 1260 cm^{-1} due to C(O), ester and P=O groups and the disappearance of the bands at 3160, 2230, 1190 cm^{-1} due to NH, CN and C=S groups of compound **1**.[19] The ^1H NMR spectrum of **4a** (δp = 18.4 ppm[22]) gave two singlets at δ 3.92 and 3.83 ppm due to the methylene and the methyl ester groups. The characteristic signals at δ 1.24 (dt) and 4.17 (dq) ppm were assigned to the phosphorus ester group. The downfield deshielding of the methylene-protons was, however, attributed to the attached hetero-ring. These signals were attested in ^{13}C NMR spectrum of **4a** as follows: δ 39.8 (*C*H_2), 51.3 (*C*H_3O, ester), 16.4 (*C*H_3.C.OP) and 61.3 (*C*H_2OP) ppm.

The formation of **4** is assumed to proceed through structures **6** and **7** to the intermediates of the reaction between nitriles and phosphorus carbanions.[23-27] Subsequent reaction of the phosphonate esters and loss of ethyl alcohol gave rise to the formation of 2-oxo-thiazaphosphinine **4a** and **4b** (Scheme 2).

The latter process was similar to that reported by He *et al.*[28] for the formation of the diazaphospholidinones **8** *via* Mannich-type reaction, involving urea, aldehyde and triphenyl phosphite according to Scheme 3.

On the other hand, the ^{31}P NMR spectrum of the thiaphospholes **5a**, **5b** showed a sharp singlet around δ_p =



Scheme 1

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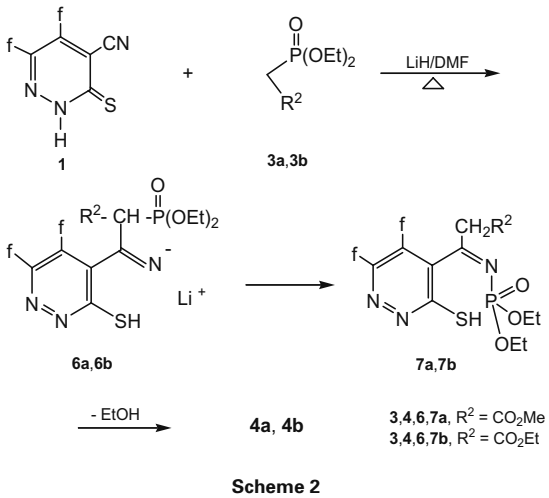
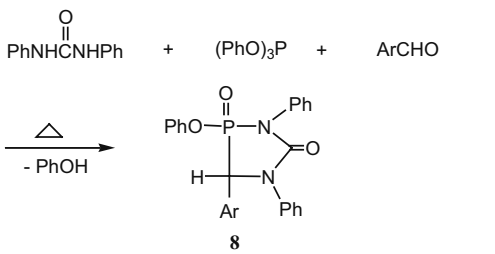
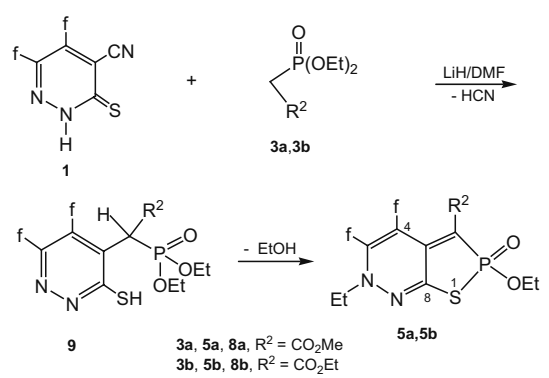


Scheme 2



Scheme 3

17.5 ppm, which is within the range expected for the assigned structure.[29] The distinguishing features of ^{13}C NMR of **5** were the presence of signals around δ ≈128.5 (d, $^{1}J_{p\text{-}c}$ ≈ 74 Hz, *C*-3), ≈147 (d, $^{2}J_{p\text{-}c}$ ≈ 26 Hz, *C*-9), and at ≈153 (d, $^{2}J_{p\text{-}c}$ ≈ 31 Hz, *C*-8). The magnitude of the phosphorus coupling with *C*-3, *C*-8, and *C*-9 are in accord with the suggested structure. A mechanism for the formation of the heterophosphole **5** can be rationalised as occurring through the condensation of **1** with **3a**, **3b** to elaborate the intermediate **9** accompanied with an elimination of an HCN molecule.[30-32] Further intramolecular cyclisation of **9** afforded the phosphole **5** *via* the loss of ethanol molecule (Scheme 4). Regarding the observed N(2) alkylation by the Wittig–Horner (WH) reagent, it is a well established process,[33-37] and similar observation was previously reported in their reactions with pyrimidines,[14-16] pyrroles,[33] and thiazolidinones.[37]



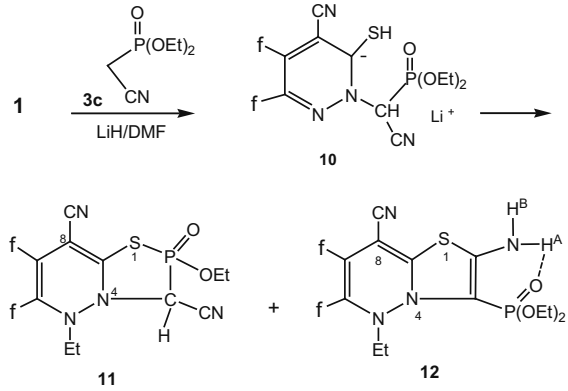
Scheme 4

The use of microwave acceleration in organic synthesis continued to grow.[38-41] Recently, we reported[17] an easy microwave induced one–pot synthesis of phosphorus containing fused heterocycles and/or fused heterocycles bearing a phosphonate ester in excellent yields from the reaction of the parallel oxo-analog of **1**: 5,6-di(2-furyl)-3-oxo-2,3-dihydropyridazin-4-carbonitrile (**2**) with phosphonate carbanions **3a**–**e**. Respectively, when the substrate **1** and the phosphonyl carbanion **3a** (or **3b**) were mixed in DMF solution (3 ml), containing LiH, and irradiated in a microwave oven, the products **4** and **5** were again obtained in higher yield, in ≈20 min.

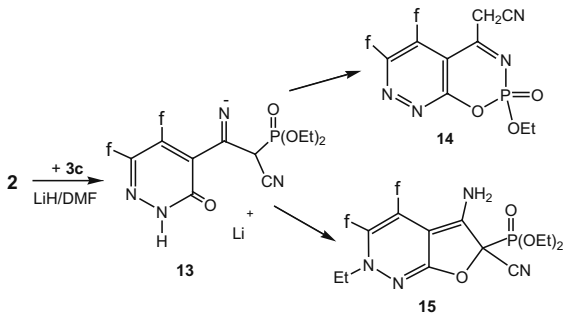
The chemical structures of **11** and **12** were delineated from their spectroscopic properties. Thus, the ^{1}H NMR spectrum of **11** showed a doublet at 5.52 ppm with a coupling constant $^{2}J_{P\text{-}H}$ = 14.8 Hz. The magnitude of $^{2}J_{P\text{-}H}$ (14.8 Hz) relates to the smaller dihedral angle ($\theta_{OP\text{-}H}$),[42] and this suggests that the oxygen (= O) on P-2 and the proton on C-3 are *cis*. In the ^{31}P NMR spectrum are singlet at δ 14.63 ppm indicated only one isomer was formed. The IR spectrum supported the presence of a P=O and two different cyano groups at 1261 and 2339, 2367 cm^{-1}.

Structure **12**, however, showed in its IR spectrum the characteristic bands due to the amino- (3058, 2853 cm^{-1}) and the cyano groups (2253 cm^{-1}) and the disappearance of the band at 1190 cm^{-1} corresponding to C=S. The ^{1}H NMR spectrum of **12** (δ_P = 28.4 ppm) showed two signals of NH_2 – protons [δ ($_H{}^A$) = 5.78 (br, 1H) and δ ($_H{}^B$) = 9.45 ppm (br, 1H)]. The different chemical shifts of the NH_2 protons are the spectroscopic evidence for the presence of intramolecular hydrogen bond between one of the hydrogens of NH_2 – protons and oxygen atom of the P=O bonding in the phosphonate group. In their ^{13}C NMR, the quaternary -C-3 displayed at δ 121.6 ppm (d, $^{1}J_{P\text{-}C}$ = 136 Hz), while *C*-8 appeared at δ 85.63 (d, $^{4}J_{P\text{-}C}$ = 6.6 Hz) and *C*–9 at δ 144.7 (d, $^{3}J_{P\text{-}C}$ = 9.6 Hz). Note that the findings from the above reaction of the carbonitrile **1** with the phosphonate carbanion **3c** (Scheme 5) vary markedly from the reaction of the oxygen analogue **2** with the same reagent **3c** where oxazaphosphinine **14** and the phosphonate **15** were obtained (Scheme 6).[17]

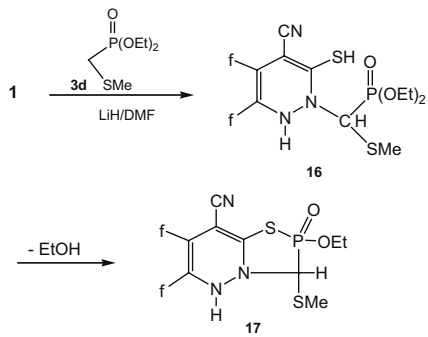
Microwave–assisted reaction of the thione **1** with diethyl α-methylthiomethylphosphonate (**3d**) is a convenient approach to the thiazaphosphole **17**, in 78% yield (Scheme 7). In this case, it is believed that the reaction proceeded again *via* the intermediate **16**, which is parallel to the one depicted in Scheme 5. The ^{1}H NMR spectrum of **17** shows a doublet at 5.16 ppm (J = 18.2 Hz), which as previously discussed[42] indicates that the oxygen (= O) on P-2 and the proton on *C*-3 are *cis*, and that *trans*-configuration can be proposed.



Scheme 5



Scheme 6



Scheme 7

On the other hand, the reaction of **1** with diethyl vinylphosphonate (**3e**), under microwave irradiation condition gave thiopyranone phosphorus esters **22** and 2-oxo-thiazaphosphinine **20** in almost equal yields ≈38% (Scheme 8). The structures **20** and **22** suggested to the products are in good agreement with their analytical and spectral data. The ^{1}H NMR of compound **20** displayed two doublets of doublets at δ 4.61–4.70 ($^2J_{P\text{-}H}$ = 16.9, $J_{H\text{-}H}$ = 6.6 Hz, 3-C*H*) and at 8.02–8.11 ppm ($^3J_{P\text{-}H}$ = 8.5, $J_{H\text{-}H}$ = 6.6 Hz, 4-C*H*) ppm. The phosphorus esters moiety located at 1.24 (dt, $^4J_{P\text{-}H}$ = 4.2, $J_{H\text{-}H}$ = 7.2 Hz, P.O.C.C*H*$_3$) and at δ 4.03 (dq, $^3J_{P\text{-}H}$ = 5.5, $J_{H\text{-}H}$ = 7.2 Hz, POC*H*$_2$). The ^{31}P NMR spectrum showed a sharp singlet at δ_P ($CDCl_3$) = 14.3 ppm, *vs*. H_3PO_4, which is within the range expected for oxothiazaphosphinine.

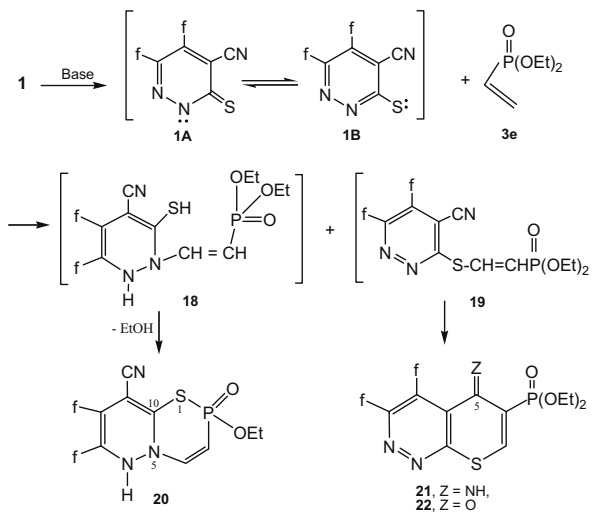
The formation of the products **20** and **22** may be proceeded again *via* the intermediates **18** and **19** depicted in Scheme 8. Partial collapse of the phosphonate moiety of **18**, as previously discussed, would give rise to the formation of compound **20**, accompanied with the extrusion of an ethyl alcohol molecule. On the other hand, hydrolysis of the nitrile group and ring closure would lead to 4-iminothiopyran **21**, which followed by hydrolysis to 4-thiopyranone **22**. A similar transformation of an imino-group to the corresponding carbonyl group, is known for other imino intermediates.[25-27,42-46]

Considering the earlier report,[17] the mechanism of the reaction of **3e** and the vinylphosphonium bromide counterpart (Ph_3P^+–CH=CH_2 Br^-)[47] with **2** have suggested similar initial formation of the nitrogen and the oxygen anions that would attack the vinylphosphorus reagents, however, subsequent transformations were quite different.

Pharmacological evaluation

In a previous investigation,[17] the bioassay indicated the antibacterial and antifungal activities of the synthesised heterophospholes and their relevant phosphonates. Respectively, in a systematic study, the antimicrobial activity of the present products **4a, 4b, 5a, 5b, 11, 12, 17, 20** and **22** was tested at the same concentration, 1 mg/disc.[48,49] The evaluation screened their effect on the organisms: *Bacillus tumefaciens (Bt)*, *Staphylococcus aureus (Sa), Klebsiella pneumoniae (Kp)* (bacteria) and *Aspergillus niger* (*An*), *Aspergillus flavus (Af)*, *Pencillium crysogenous (Pc)* (fungi). Mycostatin (**23)** was used as the reference drug. The results have been recorded in the form of inhibition zone (diameter mm) and activity index in Table 1.

The screening results from previous,[17] and present investigations (Table 1) allow the following correlations: (a) data included in Table 1 are in line with those have already been reported[17] that phosphorus containing heterocyclic increases the activity as compared to the relevant heterocycles bearing a phosphonate moiety; (b) phosphorus-containing five membered heterocycles (phospholes, **5a, 5b, 11,** and **17**) have significant activity rather than phosphorus-containing six membered heterocycles (phosphinines, **4a, 4b** and **20**); and (c) compounds **11** and **17** that incorporate [bridged–N–C–P–S] unit are the most active compounds, and that they



Scheme 8

Table 1 Antimicrobial activity of the new compounds **4a**,**b**, **5a**,**b**, **11**, **12**, **17**, **20** and **22**

Micro-organism	Phospholes IZ/AI							Phosphonates IZ/AI		Ref.
	4a	**4b**	**5a**	**5b**	**11**	**17**	**20**	**12**	**22**	**23**
Bt	12.39	12.52	13.0	12.78	13.45	13.98	8.26	8.25	9.01	
	(0.93)	(0.94)	(0.98)	(0.96)	(1.01)	(1.05)	(0.64)	(0.62)	(0.68)	13.32
Sa	12.49	7.89	9.97	8.87	10.08	9.86	7.89	8.43	8.43	
	(1.14)	(0.72)	(0.91)	(0.81)	(0.92)	(0.9)	(0.72)	(0.77)	(0.77)	10.96
Kp	11.55	8.72	11.0	9.26	10.9	12.1	11.88	9.26	8.28	
	(1.06)	(0.8)	(1.01)	(0.85)	(1.0)	(1.11)	(1.09)	(0.85)	(0.76)	10.9
An	8.36	10.34	8.36	11.7	8.15	8.67	8.04	8.26	7.31	
	(0.80)	(0.99)	(0.8)	(1.12)	(0.78)	(0.83)	(0.77)	(0.79)	(0.7)	10.45
Af	9.17	10.4	7.31	10.51	10.4	12.56	11.33	7.1	7.62	
	(0.89)	(1.01)	(0.71)	(1.02)	(1.01)	(1.22)	(1.1)	(0.69)	(0.74)	10.3
*P*c	7.84	9.75	8.41	7.65	9.27	10.13	11.85	6.02	5.54	
	(0.82)	(1.02)	(0.88)	(0.8)	(0.97)	(1.06)	(1.24)	(0.63)	(0.58)	9.56

IZ, Inhibition zone (in mm),
AI, Activity index of tested compounds/inhibition zone of the standard.

represent an optimised pharmacophore hypothesis to explain the complex structure–activity relationship of the active nitrogen containing heterophospholes. The results obtained are encouraging for further optimisation of the antibiotic properties of these compounds. Furthermore, the achieved results led us to conclude that this type of compounds should be studied in detail for their applications in diverse areas; nevertheless, toxicity of these compounds should also be tested, further study is in progress.

Conclusion

In conclusion, the reactions of WH reagents **3a–e** with bifunctional substrates **1** and **2**, on the basis of our present and previous[17] results, proceed smoothly under the effect of basic condition and using microwave irradiation with significante decrease in reaction times and comparably high chemical yields. On the other hand, the results indicated a different behaviour of **3a–e** toward **1** and **2**. This, however, is not surprising as it was reported[50-54] that thiones (C=S) are considered to be "superdipolarophile function". Their permanence was shown by kinetic measurements on their cycloadditions with thiobenzophenone-S-methide and diphenyldiazomethane as 1,3-dipoles. Finally, the results offer a fertile area for future research in which Wittig–Horner reagents may be tailored to produce the desired outcome.

Experimental

Melting points were determined on an Electrothermal melting point apparatus. The IR spectra were recorded on a Perkin Elmer 317 Grating IR spectrophotometer, using KBr. The ^{1}H and ^{13}C NMR spectra were measured using a JEOL, E.C.A-500 MHz spectrometer with $SiMe_4$ as an internal standard. The ^{31}P NMR spectra were recorded with the same instrument, relative to external H_3PO_4 (85%). The mass spectra were performed on a JEOL JMS-A × 500 spectrometer. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. The appropriate precautions in handling moisture-sensitive compounds were observed. Solvents were dried by standard techniques.

Reactions of 5,6-di(2-furyl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile **(1)** *with WH-reagents* **3a, 3b** *under thermal condition: General procedure for preparation of* **4a**, **4b**, **5a** *and* **5b**

To a slurry of 6.4 mmol of lithium hydride dispersion (80% in mineral oil) in 15 ml of anhydrous DMF was added dropwise 672 mg of **3a** (or **3b**) (3.2 mmol) in 5 ml dry DMF at 0 °C. The reaction mixture was further stirred at room temperature for 1 h, and a solution of 0.62 g of the carbonitrile **1**[19] (1.97 mmol) in DMF (10 ml) was introduced all at once, and the mixture was heated under reflux for 4 days (TLC). The reaction mixture was poured into 200 ml of distilled water and HCl (1N) was added at C(5) until the pH became acidic, and extracted with AcOEt (3 × 50 ml). The combined organic phase was dried over anhydrous sodium sulfate, followed by removal of the solvent, under reduced pressure. The resulting residue was chromatographed on silica gel (*n*-hexane/AcOEt) to give the products **4a**, **5a, 4b** and **5b,** respectively. The physical and spectral data of the compounds **4a**, **4b**, **5a** and **5b** are as follows.

Methyl (2-ethoxy-5,6-di(2-furyl)-2H-pyridazino[4,3-e][1,3,2]-2-oxothiazaphosphinin-4-yl)acetate **(4a)**: Yield, 19%. M.p. 182–184 °C (from $CHCl_3$). IR (cm^{-1}): ν = 1722 (C=O, ester), 1610 (furans), 1258 (P=O), 1120 (P–O–C). ^{1}H NMR δ: 1.24 (dt, $J_{H\text{-}H}$ = 6.5, $^4J_{P\text{-}H}$ = 3.8 Hz, 3H, H_3CC.OP), 3.83 (s, 3H, H_3CO, ester), 3.92 (s, 2H, H_2C.C(4)), 4.17 (dq, $J_{H\text{-}H}$ = 6.5, $^3J_{P\text{-}H}$ = 5.5 Hz, 2H, H_2COP), 6.71, 7.27 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ & $H^{4'}$, furyls), 7.63, 7.88 (2d, J_{HH} = 4, 2H, 2 × $H^{5'}$-furyls) ppm. ^{13}C NMR δ: 16.4 (*C*H$_3$C.O), 39.8 (d, $^3J_{P\text{-}C}$ = 14 Hz, *C*H$_2$.C(4)), 51.3 (*C*H$_3$O, ester), 61.3 (*C*H$_2$O), 102.8 (d, $^4J_{PC}$ = 5.3 Hz, 5-*C*), 106.2, 106.7, 110.2, 110.6 (2 × (3'*C* and 4'*C*), furyls), 119.8 (d, $^3J_{PC}$ = 7.3 Hz, 10-*C*), 134.4 (d, $^2J_{P\text{-}C}$ = 32 Hz, 4-*C*), 142.4, 142.7, 146.3, 148.1 (2', 5'-*C*, furyls), 148.8 (d, $^2J_{PC}$ = 23 Hz, 9-*C*), 152.2 (6-*C*), 164.2 (*C*=*O*, ester) ppm. ^{31}P NMR δ = 18.4 ppm. MS: *m/z* (EI) (%): 432 (14) [M$^+$–1], 418 (9), 402 (23), 374 (18), 359 (26), 309 (78) [M$^+$–92, SP(O)(OEt)], 235 (100) [359-124, SP(O)(OEt)], 235 (30), 169 (38), 67 (46). Anal. Calcd for $C_{18}H_{16}N_3O_6PS$ (433.4): C, 49.88; H, 3.72; N, 9.70; P, 7.14; S, 7.40. Found: C, 49.92; H, 3.67; N, 9.74; P, 7.21; S, 7.35%.

Ethyl 2-ethoxy-5,6-di(2-furyl)-2H-pyridazino[4,3-e][1,3,2]-2-oxo-thiazaphosphinin-4-yl)acetate (**4b**): Yield, 17%. M.p. 173–175 °C (from C_2H_5OH). IR (cm^{-1}): ν 1720 (C=O, ester), 1608 (furans), 1268 (P=O), 1049 (P–O–C). ^{1}H NMR δ: 0.97 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, H_3C.CO, ester), 1.17 (dt, $J_{H\text{-}H}$ = 6.6, $^4J_{P\text{-}H}$ = 3.5 Hz, 3H, H_3CC.OP), 3.56 (q, $J_{H\text{-}H}$ = 7.2 Hz, 2H, H_2CO, ester), 3.88 (d, 2H, d, $^4J_{P\text{-}H}$ = 4.3 Hz, 2H, H_2C.C(4)), 4.01(dq, $J_{H\text{-}H}$ = 6.6, $^3J_{P\text{-}H}$ = 5.8 Hz, 2H, H_2COP), 6.71, 7.27 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ & $H^{4'}$, furyls), 7.63, 7.88 (2d, J_{HH} = 4, 2H, 2 × $H^{5'}$-furyl rings) ppm. ^{13}C NMR δ: 14.1, 16.4 (*C*H$_3$C.O, *C*H$_3$C.OP), 40.2 (d, $^3J_{P\text{-}C}$ = 16.4 Hz, *C*H$_2$C(4)), 55.2 (*C*H$_2$O, ester), 61.7 (*C*H$_2$OP), 103.6 (5-*C*), 98.6, 106.7, 110.2, 110.6 (2 × (3'*C* and 4'*C*), furyls), 119.2 (d, $^3J_{PC}$ = 7.3 Hz, 10-*C*), 134.5 (d, $^2J_{P\text{-}C}$ = 33.7 Hz, 4-*C*), 142.6, 142.9, 147.1, 148.1 (2', 5'-*C*, furyls), 150.7 (6-*C*), 151.8 (d, $^2J_{P\text{-}C}$ = 27.7 Hz, 9-*C*), 169.42 (*C*=*O*, ester) ppm. ^{31}P NMR δ_P = 16.4 ppm. MS: *m/z* (EI) (%): 446 (12) [M$^+$–1], 417 (13), 401 (18), 373 (28), 359 (36), 323 (75) [M$^+$–124, SP(O)(OEt)], 235 (100) [359-124, SP(O)(OEt)], 169 (47), 67 (47). Anal. Calcd for $C_{19}H_{18}N_3O_6PS$ (447.4): C, 51.00; H, 4.05; N, 9.39; P, 6.92; S, 7.16. Found: C, 50.88; H, 3.98; N, 9.79; P, 7.27; S, 7.07%.

Methyl 2-ethoxy-6-ethyl-4,5-di(2-furyl)-2,6-dihydro-2-oxo-[1,2]thiaphospholo[5,4-c]-pyridazine-3-carboxylate (**5a**): Yield, 38%. M.p. 138–141 °C (from cyclohexane). IR (cm^{-1}): ν 1702 (C=O, ester), 1610 (furyls), 1262 (P=O), 1072 (P–O–C). ^{1}H NMR δ: 0.87 (t, $J_{H\text{-}H}$ = 6.6 Hz, 3H, H_3CC.N), 1.15 (dt, $J_{H\text{-}H}$ = 6.8, $^4J_{P\text{-}H}$ = 3.8 Hz, 3H, H_3CC.OP), 3.64 (q, $J_{H\text{-}H}$ = 6.8 Hz, 2H, H_2CN), 3.84 (s, 3H, H_3CO, ester), 4.04 (dq, $J_{H\text{-}H}$ = 6.8, $^3J_{P\text{-}H}$ = 5.6 Hz, 2H, H_2COP), 6.68, 7.22 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ and $H^{4'}$, furyls), 7.66, 7.97 (2d, $J_{H\text{-}H}$ = 4, 2H, 2 × $H^{5'}$-furyl rings) ppm. ^{13}C NMR δ: 12.2, 16.3 (*C*H$_3$C.N, *C*H$_3$C.OP), 42.7 (*C*H$_2$–N), 54.3 (*C*H$_3$O, ester), 61.9 (*C*H$_2$OP), 96.7 (d, $^3J_{P\text{-}C}$ = 28.7 Hz, 4-*C*), 99.6, 106.7, 110.2, 110.6 (3'*C* and 4'*C*, furyls), 120.1 (d, $^4J_{P\text{-}C}$ = 6.4 Hz, 5-*C*), 128.3 (d, $^1J_{P\text{-}C}$ = 74.8 Hz, 3-*C*–P), 147.2 (d, $^2J_{P\text{-}C}$ = 26.8 Hz, 9-*C*), 145.3, 146.4, 147.6, 148.5 (2', 5'-*C*, furyls), 153.8 (d, $^2J_{P\text{-}C}$ = 31.7 Hz, 8-*C*), 157.2 (*C*=*O*, ester) ppm. ^{31}P NMR δ_P = 17.2 ppm. MS: *m/z* (EI) (%): 433 (22) [M$^+$–1], 418 (13), 402 (23), 374 (38), 345 (40), 221 (100) [345-124, SP(O)(OEt)], 154 (18),

87 (67), 67 (53). Anal. Calcd for $C_{19}H_{19}N_2O_6PS$ (434.4): C, 52.53; H, 4.41; N, 6.45; P, 7.13; S, 7.38. Found: C, 52.57; H, 4.47; N, 6.51; P, 7.24; S, 7.46%.

Ethyl 2-ethoxy-6-ethyl-4,5-di(2-furyl)-2,6-dihydro-2-oxo[1,2]thiaphospholo[5,4-c]-pyridazine-3-carboxylate (**5b**): Yield, 35%. M.p. 127–129 °C (from pentane). IR (cm^{-1}): ν 1710 (C=O, ester), 1612 (furyls), 1258 (P=O), 1096 (P–O–C). ^1H NMR δ: 0.86, 0.89 (2t, $J_{H\text{-}H}$ = ~ 6.6 Hz, 2 × 3H, H_3CC.N, H_3CC.O, ester), 1.22 (dt, $J_{H\text{-}H}$ = 6.8, $^4J_{P\text{-}H}$ = 4.1 Hz, 3H, H_3CC.OP), 3.66 (q, $J_{H\text{-}H}$ = 6.6 Hz, 2H, H_2CN), 3.84 (q, $J_{H\text{-}H}$ = 6.6 Hz, 2H, H_2CO, ester), 4.21 (dq, $J_{H\text{-}H}$ = 6.6, $^3J_{P\text{-}H}$ = 5.6 Hz, 2H, H_2COP), 6.72, 7.24 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ and $H^{4'}$, furyls), 7.64, 7.86 (2d, J_{HH} = 4, 2H, 2 × $H^{5'}$-furyl rings) ppm. ^{13}C NMR δ: 12.2, 14.4, 16.3 (CH_3C.N, CH_3C.O, CH_3C.OP), 44.1 (CH_2N), 58.3 (CH_2O, ester), 61.9 (CH_2OP), 97.6 (d, $^3J_{P\text{-}C}$ = 28.7 Hz, 4-*C*), 98.8, 106.7, 110.2, 110.6 (2 × (3'*C* and 4'*C*), furyls), 119.2 (d, $^4J_{P\text{-}C}$ = 6.8 Hz, 5-*C*), 129.3 (d, $^1J_{P\text{-}C}$ = 77.8 Hz, 3-*C*-P), 147.2 (d, $^2J_{P\text{-}C}$ = 27.6 Hz, 9-*C*), 144.6, 148.2, 148.5 (2', 5'-C, furyls), 154.3 (d, $^2J_{P\text{-}C}$ = 32.3 Hz, 8-*C*), 154.7 (*C*=O, ester) ppm. ^{31}P NMR δ_P = 17.8 ppm. MS: *m/z* (EI) (%): 447 (26) [M^+-1], 418 (19), 402 (12), 374 (32), 345 (49), 221 (100) [345-124, SP(O)(OEt)], 154 (21), 88 (67), 67 (55). Anal. Calcd for $C_{20}H_{21}N_2O_6PS$ (448.4): C, 53.56; H, 4.72; N, 6.25; P, 6.91; S, 7.15. Found: C, 53.63; H, 4.80; N, 6.32; P, 6.84; S, 7.12%.

Reactions of carbonitrile **(1)** *with WH reagents* ***3a,3b*** *under microwave-irradiation: genera1 procedure for preparation of* **4a, 4b, 5a,** *and* **5b**

1.2 mmol of **1** was added to a mixture of 3 mmol of LiH in 8 ml dry DMF and 1.5 mmol Wittig–Horner reagent **3a, 3b** in a Pyrex glass beaker. Microwave irradiation was applied for ≈ 20 min. After the completion of the reaction (TLC analysis), the mixture was poured onto ice-cold water, acidified (HCl, 1N), extracted (AcOEt), dried, and evaporated till dryness. The resulting residue was chromatographed on silica gel (*n*-hexane/AcOEt) to give pure samples of **4a** (28%) and **5a** (45%) or **4b** (27%) and **5b** (48%).

Reactions of carbonitrile **1** *with WH-reagents* **3c, 3d, 3e** *under microwave-irradiation: preparation of* **11, 12, 17, 20, 22**

As described in the general procedure, a mixture of 1.2 mmol of **1,** 3 mmol of LiH in 8 ml dry DMF and 1.5 mmol of WH-reagent **3c–e** in a Pyrex glass beaker was subjected to microwave irradiation for ≈ 20–35 min. After the completion of the reaction (TLC analysis), acidification, and the usual work up the pure samples of **11** and **12** (from **1** + **3c**)**; 17** (from **1** + **3d**)**;** or **20** and **22** (from **1** + **3e**), respectively. The physical and spectral data of these products are as follows:

2-Ethoxy-5-ethyl-6,7-di(2-furyl)-2,3-dihydro-2-oxo-5H-[1,4,2]thiazaphospholo[4,5-b]-pyridazine-3,8-dicarbonitrile (**11**): Yield, 51%. M.p. 156–158 °C (from CH_2Cl_2). IR (cm^{-1}): ν 2367, 2339 (2CN), 1610 (C=C, furyl), 1261 (P=O), 1117 (P–O–C). ^1H NMR δ: 0.86 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H, H_3CC.N), 1.25 (dt, $J_{H\text{-}H}$ = 7.2, $^4J_{P\text{-}H}$ = 4.6 Hz, 3H, H_3CC.OP), 3.54 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H, H_2CN), 4.15 (dq, $J_{H\text{-}H}$ = 7.2, $^3J_{P\text{-}H}$ = 5.4 Hz, 2H, H_2COP), 5.52 (d, $^2J_{P\text{-}H}$ = 14.8 Hz, 1H, *H*COP), 6.74, 7.34 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ and $H^{4'}$, furyls), 7.76, 7.89 (2d, $J_{H\text{-}H}$ = 4, 2H, 2 × $H^{5'}$-furyl rings) ppm. ^{13}C NMR δ: 12.6, 16.8 (CH_3C.N, CH_3C.OP), 44.7 (CH_2–N), 48.8 (d, $^1J_{P\text{-}C}$ = 211 Hz, 3-*C*), 61.9 (CH_2OP), 78.3 (d, $^3J_{P\text{-}C}$ = 21.7 Hz, 8-*C*), 104.7 (7-*C*), 98.6, 106.7, 110.2, 110.6 (2 × (3'*C* and 4'*C*), furyls), 114.2 (d, $^2J_{P\text{-}C}$ = 22.6 Hz, *C*N-C(3)), 124.3 (d, $^4J_{P\text{-}C}$ = 7.4 Hz, *C*N-C(8)), 135.4. (6-*C*), 142.5, 143.2, 147.6, 148.5 (2', 5'-*C*, furyls), 161.3 (d, $^2J_{P\text{-}C}$ = 35.6 Hz, 9-*C*), ppm. ^{31}P NMR δ_P = 14.6 ppm. MS: *m/z* (EI) (%): 427 (18) [M^+-1], 401 (16), 398 (26), 375 (36), 356 (66), 232 (100) [356-124, SP(O)(OEt)], 154 (16), 87 (51), 67 (43). Anal. Calcd for $C_{19}H_{17}N_4O_4PS$ (428.4): C, 53.27; H, 4.00; N, 13.08; P, 7.23; S, 7.48. Found: C, 53.33; H, 4.11; N, 13.14; P, 7.27; S, 7.54%.

Diethyl (2-amino-8-cyano-5-ethyl-6,7-di(2-furyl)-5H-[1,3]thiazolo-[3,2-b]pyridazin-3-yl)phosphonate (**12**): Yield, 33%; M.p. 190–192 °C (from $CHCl_3$). IR (cm^{-1}): ν 3058, 2853 (NH_2), 2253 (CN), 1610 (furans), 1232 (P=O, bonded), 1073 (P–O–C). ^1H NMR δ: 0.89 (t, $J_{H\text{-}H}$ = 7.5 Hz, 3H, H_3CC.N), 1.14 (dt, J_{HH} = 6.5, $^4J_{PH}$ = 3.8 Hz, 6H, H_3CC.OP), 3.54 (q, $J_{H\text{-}H}$ = 7.3 Hz, 2H, H_2CN), 3.98 (dq, J_{HH} = 6.5, $^3J_{P\text{-}H}$ = 5.5 Hz, 4H, H_2COP), 5.78 (br, 1H, N*H*^{A}), 6.67, 7.43 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ and $H^{4'}$, furyls), 7.69, 7.84 (2d, $J_{H\text{-}H}$ = 4, 2H, 2 × $H^{5'}$-furyl rings), 9.45 (br, 1H, N*H*^{B}) ppm. ^{13}C NMR δ: 12.35, 16.4 (CH_3C.N, CH_3C.OP), 45.4 (CH_2N), 64.2 (CH_2OP), 85.63 (d, $^4J_{P\text{-}C}$ = 6.6 Hz, 8-*C*), 100.1 (7-*C*), 98.6, 106.7, 110.2, 110.6 (2 × (3'*C* and 4'*C*), furyls), 114.3 (*C*N.C(8)), 121.6 (d, $^1J_{P\text{-}C}$ = 136 Hz, 3-*C*-P), 130.8 (d, $^2J_{P\text{-}C}$ = 32.6 Hz, 2-*C*-NH_2), 141.6 (6-*C*), 139.4, 142.5, 144.8, 146.3 (2', 5'-*C*, furyls), 144.7 (d, $^3J_{P\text{-}C}$ = 9.6 Hz, 9-*C*) ppm. ^{31}P NMR δ_P = 28.4 ppm. MS: *m/z* (EI) (%): 473 (18) [M^+–1], 448 (20), 443 (11), 422 (31), 419 (13), 393 (26), 257 (100) [393-136, P(O)(OEt)$_2$], 249 (28), 217 (44), 163 (38), 67 (40). Anal. Calcd for $C_{21}H_{23}N_4O_5PS$ (474.5): C, 53.16; H, 4.89; N, 11.81; P, 6.53; S, 6.75. Found: C, 53.23; H, 4.83; N, 11.74; P, 6.61; S, 6.81%.

2-Ethoxy-6,7-di(2-furyl)-3-methylthio-2,3-dihydro-2-oxo-5H-[1,4,2]-thiazaphospholo[4,5-b]pyridazine-8-carbonitrile (**17**): Yield, 78%. M.p. 146–148 °C (from cyclohexane). IR (cm^{-1}): ν 3425 (NH), 2310 (CN), 1610 (C=C, furyl), 1261 (P=O), 1054 (P–O–C). ^1H NMR δ: 1.34 (dt, $J_{H\text{-}H}$ = 6.5, $^4J_{P\text{-}H}$ = 4.8 Hz, 3H, H_3CC.OP), 2.86 (dd, $J_{H\text{-}H}$ = 6.3 Hz, $^4J_{P\text{-}H}$ = 6.3 Hz, 3H, H_3CS), 4.21 (dq, $J_{H\text{-}H}$ = 7.0, $^3J_{P\text{-}H}$ = 5.4 Hz, 2H, H_2COP), 5.16 (d, $^2J_{P\text{-}H}$ = 18.2 Hz, 1H, HCP), 6.74, 7.34 (2d, J_{HH} = 4.7, 4H, 2 × $H^{3'}$ and $H^{4'}$, furyls), 7.76, 7.85 (2d, J_{HH} = 4.4, 2H, 2 × $H^{5'}$-furyl rings), 9.84 (s (br), 1H, *H*N) ppm. ^{13}C NMR δ: 15.8 (CH_3C.O), 16.3 (d, $^3J_{P\text{-}C}$ = 8.8 Hz, CH_3S), 54.3 (d, $^1J_{P\text{-}C}$ = 186.4 Hz, 3-*C*H), 62.2 (CH_2O), 78.4 (d, $^3J_{P\text{-}C}$ = 11.6 Hz, 8-C), 110.4 (8-*C*CN), 106.9 (7-*C*), 98.6, 109.7, 110.2, 111.6 (2 × (3'*C* and 4'*C*), furyls), 136.4 (6-*C*), 143.3, 143.8, 147.6, 148.5 (2', 5'-C, furyls), 166.3 (d, $^2J_{P\text{-}C}$ = 36.3 Hz, 9-*C*) ppm. ^{31}P NMR δ_P = 14.63 ppm. MS: *m/z* (EI) (%): 419 (11) [M^+-2], 393 (19), 372 (56), 346 (60), 222 (100) [346-124, SP(O)(OEt)], 144 (26), 87 (35), 67 (61). Anal. Calcd for $C_{17}H_{16}N_3O_4PS_2$ (421.43): C, 48.45; H, 3.83; N, 9.97; P, 7.35; S, 15.22. Found: C, 48.55; H, 3.88, N, 9.86; P, 7.43; S, 15.31%.

2-Ethoxy-7,8-di(2-furyl) 2-oxo-2H,6H-pyridazino[1,6-e][1,5,2]-thiazaphosphinine-9-carbonitrile (**20**): Yield, 38%. M.p. 176–178 °C (from MeCN). IR (cm^{-1}): ν 3433 (NH), 2328 (CN), 1610 (furyls), 1262 (P=O), 1162 (P–O–C). ^1H NMR δ: 1.24 (dt, $J_{H\text{-}H}$ = 7.2, $^4J_{P\text{-}H}$ = 4.2 Hz, 3H, H_3CC.OP), 4.03 (dq, $J_{H\text{-}H}$ = 7.2, $^3J_{P\text{-}H}$ = 5.5 Hz, 2H, H_2COP), 4.61–4.7 (dd, $J_{H\text{-}H}$ = 6.6, $^2J_{P\text{-}H}$ = 16.9 Hz, 1H, 3-C*H*), 6.76, 7.24 (2d, J_{HH} = 4.7, 4H, $H^{3'}$ and $H^{4'}$, furyls), 7.76, 7.85 (2d, J_{HH} = 4.4, 2H, 2 × $H^{5'}$-furyl rings), 8.02–8.11 (dd, $J_{H\text{-}H}$ = 6.6 Hz, $^3J_{P\text{-}H}$ = 8.5 Hz, 1H, 4-C*H*), 8.94 (s (br), 1H, *H*N) ppm. ^{13}C NMR δ: 16.8 (CH_3C.OP), 62.2 (CH_2OP), 78.5 (d, $^3J_{P\text{-}C}$ = 14.6 Hz, 9-*C*-CN), 98.6 (d, $^1J_{P\text{-}C}$ = 102 Hz, 3-*C*), 132.6 (8-*C*), 98.6, 106.7, 110.2, 110.6 (3'*C* and 4'*C*, furyls), 121.7 (*C*N), 129.3 (d, $^2J_{P\text{-}C}$ = 18.6 Hz, 4-*C*), 140.4 (7-*C*), 142.6, 144.5, 145.4, 147.3 (2', 5'-*C*, furyls), 168.3 (d, $^2J_{P\text{-}C}$ = 33.8 Hz, 10-*C*), ppm. ^{31}P NMR δ_P = 14.3 ppm. MS: *m/z* (EI) (%): 386 (16) [M^+–1], 361(37), 237 (100) [361-124, SP(O)(OEt)], 154 (21), 87 (51), 67 (43). Anal. Calcd for $C_{17}H_{14}N_3O_4PS$ (387.35): C, 52.71; H, 3.64; N, 10.85; P, 7.99; S, 8.28. Found: C, 52.79; H, 3.68; N, 10.78; P, 7.92; S, 8.34%.

Diethyl [3,4-di(2-furyl)-5-oxo-5H-thiopyrano[2,3-c]pyridazin-6-yl] phosphonate (**22**): Yield, 40%. M.p. 217–220 °C (from CH_3OH). IR (cm^{-1}): ν 1688 (C=O), 1610 (furyls), 1258 (P=O), 1080 (P–O–C). ^1H NMR δ: 1.23 (dt, J_{HH} = 6.8, $^4J_{P\text{-}H}$ = 3.8 Hz, 6H, H_3CC.OP), 3.98 (dq, $J_{H\text{-}H}$ = 6.5, $^3J_{P\text{-}H}$ = 5.5 Hz, 4H, H_2COP), 6.47, 7.02 (2d, $J_{H\text{-}H}$ = 4.7, 4H, $H^{3'}$ and $H^{4'}$, furyls), 7.24 (d, $^3J_{P\text{-}H}$ = 9.5 Hz, 1H, *H*C(7)), 7.78, 7.84 (2d, J_{HH} = 4.4, 2H, 2 × $H^{5'}$-furyl rings); ^{13}C NMR δ: 14.6 (CH_3C.OP), 61.7 (CH_2OP), 91.6, 104.7, 110.2, 110.8 (3'*C* and 4'*C*, furyls), 126.2, (d, $^1J_{P\text{-}C}$ = 112 Hz, 6-*C*-P), 129.7 (d, $^3J_{P\text{-}C}$ = 16.6 Hz, 10-*C*), 132.5 (d, $^4J_{P\text{-}C}$ = 8.6 Hz, 4-*C*), 141.6 (3-*C*), 144.8, 146.4, 148.7 (2', 5'-*C*, furyls), 151.8 (d, $^2J_{P\text{-}C}$ = 36.7 Hz, 7-*C*), 161.4 (9-*C*), 163.8 (5-*C*=*O*) ppm. ^{31}P NMR δ_P = 28.4 ppm. MS: *m/z* (EI) (%): 431(55) [M^+–1], 296 (100) [M^+–136, P(O)(OEt)$_2$], 268 (33), 267 (37), 252 (25), 229 (48), 163 (17), 67 (47). Anal. Calcd for $C_{19}H_{17}N_2O_6PS$ (432.4): C, 52.77; H, 3.96; N, 6.48; P, 7.16; S, 7.42. Found: C, 52.88; H, 3.91; N, 6.55; P, 7.27; S, 7.51%.

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