Synthesis and Insecticidal Evaluation of some newly Designed pyridine-2(1H)-thion derivatives and their thienopyrimidine Analogue

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Abstract: Given the importance of pesticide in the field of pest control, specially cotton leaf worm *spodopttera littoralis*, we have studied the reaction of 4,6-disubstituted phenyl-3-cyanopyridien-2(1*H*)thiones **5a-d** with dialkyl chloro-phosphate. The formed s-(3-cyano(4,6-(4-substituted phenyl)pyridine-2yl)-*O,O*-dialkyl phosphor-thioate **7a-h** were separated and identified. Also, the reactions of enaminonitriles **8a-d** with formic acid, formamide, carbon disulfide and trichloro acetonitrile were studied to obtain (9.10.11 and 12) a-d. The insecticidal activity of some synthesized organophosphorous compounds as well as some thieno[3,2-*d*]pyrimidin derivatives was evaluated and tabulated.

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1. Introduction:

3-Cyano-2(*1H*)-pyridinethiones [1,2] and their related compounds were found to be very reactive substances for the synthesis of many different heterocyclic systems which exhibited biological activities such as antibacterial, pesticidal, antifungal, acaricidal and neurotropic activities [3-10]. Also, 3-Cyano-pyridine-2(*1H*)-thion compounds have gained considerable interest due to their importance as intermediates for the synthesis of the biologically active deazafolic acid and deaza amino protein ring system [11,12].

Several thieno[2,3‑*b*]pyridine derivatives are known to possess antibacterial [13], antihypertensive [14] and gonadotropinreleasing hormone antagonizing activity[15,16], antitumor and antiangiogenesis or dual activity, essentially by acting as inhibitors of tyrosine kinase receptors I [17], II [18] III [19], or nonreceptors (IV) [20] which have been implicated in the growth and progression of various human cancers, therefore, have been crucial in the development of anticancer therapies.

Pyridothienopyrimidine derivatives have found applications as analgesics, antipyretics [21] and anti‑inflammatories [22].

Moreover, thienopyrimidine derivatives as annulated five-membered heteroaromatic ring systems are structurally analogues of biogenic purines with a very wide spectrum of biological activities. Pyrimidine and thienopyrimidine are reported to possess significant analgesic [23,24], fungicidal [25], antiviral [26] and anti-inflammatory [27–30] activities. Also, some thieno[2,3-*d*]pyrimidines show CNS depressing activity [28] and are useful as muscle relaxants, sedatives [30], diuretics [31], pesticides and herbicides [32]. Numerousthieno [2,3-*d*]pyrimidines have been proved to use in case of cerebral ischemia, malaria, tuberculosis, Alzheimer's and Parkinson's diseases.[33]

Motivated by the aforementioned biological and pharmacological importance and as a part of our program directed towards developing new approaches to a variety of heterocycles, we report here on the synthesis and insecticidal potency of some new organophosphorous derivatives of 3-cyanopyridine-2(*1H*)-thione and on the synthesis of some new thienopyrimidine derivatives.

2. Materials and Methods

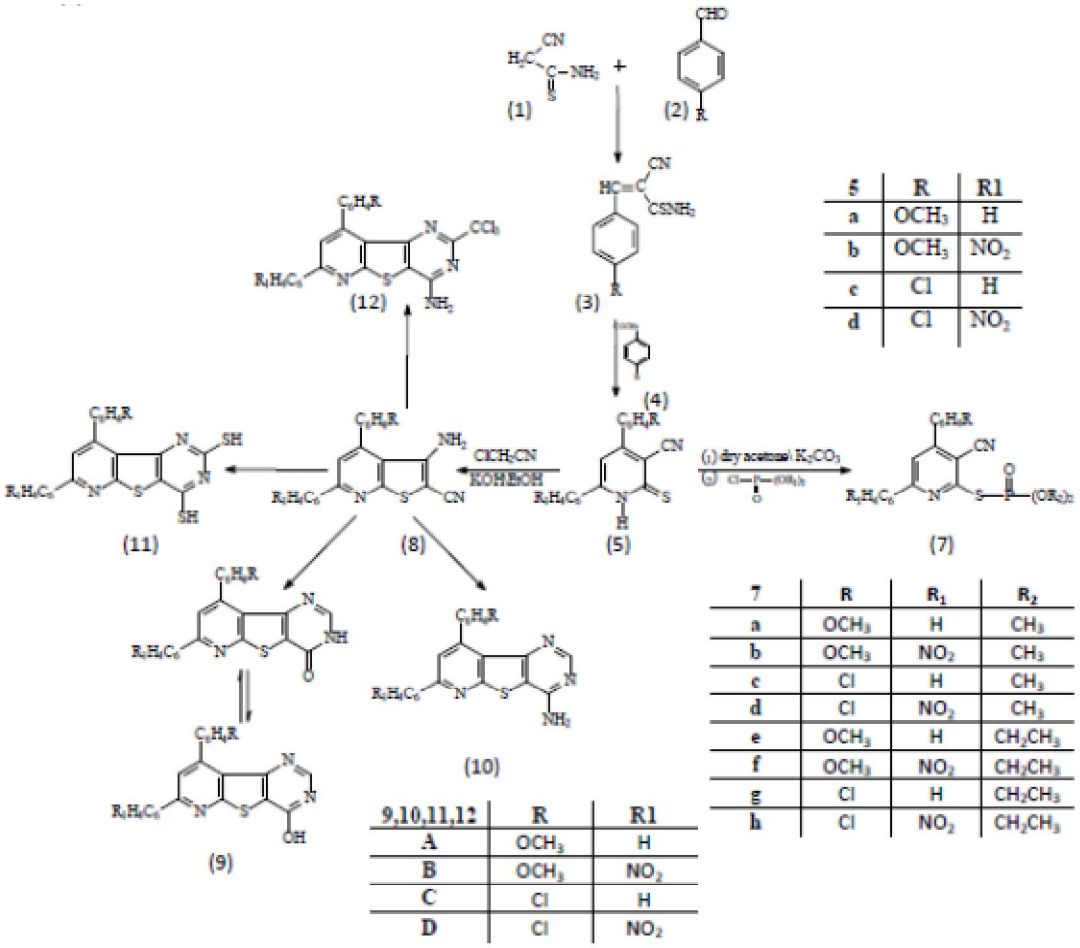
A. Chemistry:

Cyanothioacetamide **(1)** allowed to condense with aromatic aldehyde **(2)** in boiling ethanol in the presence of few drops peperidine as a basic catalyst to afford the corresponding colored arylidene cyanothioaceatmide derivatives **(3a,b)**.

The reaction of benzylidene derivatives **(3a,b)** with acetophenone and p-nitroacetophenone as an active hydrogen bearing reagent was studied for the first time. Thus, when arylidene **(3a,b)** allowed to react with acetophenone and\or p-nitroacetophenone **(4)** under reflux in boiling ethanol containing a catalytic amount of piperedine as basic medium, 3-cyanopyridine-2(*1H*)-thione **(5a-d)**were obtained in good yield.

3-cyanopyridine-2(*1H*)-thione and their derivatives constitute an important class of heterocyclic compounds of considerable interest due to the diversity of chemical conversion and possibilities of practical applications too.

The reaction of 3-cyanopyridine-2(*1H*)-thione **(5a,b)** with dialkyl chlorophosphate **(6a,b)** was also conducted for the first time in heterocyclic organic synthesis. Therefore, compound **(5 a,b)** was reacted with dialkyl chlorophosphate **(6a,b)** in dry acetone in the presence anhydrous dry potassium carbonate (K_2CO_3) as a basic medium to neutralize the eliminated hydrochloric acid to furnish in each case one single product S-3-cyano-4,6-di(4-substituted phenyl)pyridin-2-yl-*O,O*-dialkylphosphorothioate (**7a-h) (**TLC control).



5	R	R1
a	OCH_3	H
b	OCH_3	NO_2
c	Cl	H
d	Cl	NO_2

7	R	R_1	R_2
a	OCH_3	H	CH_3
b	OCH_3	NO_2	CH_3
c	Cl	H	CH_3
d	Cl	NO_2	CH_3
e	OCH_3	H	CH_2CH_3
f	OCH_3	NO_2	CH_2CH_3
g	Cl	H	CH_2CH_3
h	Cl	NO_2	CH_2CH_3

9,10,11,12	R	R1
A	OCH_3	H
B	OCH_3	NO_2
C	Cl	H
D	Cl	NO_2

Synthesis of s-(3-cyano-4-(4-substituted phenyl)-6(-4-substituted pheny)pyridinyl-2-yl)O,O-dialkyl phosphorothioate 7a-h.

Pyridine thiones **5a-d** (10 mmol) was stirred with 5 gm of k_2CO_3 in 40 ml dry acetone for 1 hr. (15 mmol) of dialkyl chlorophosphate was added drop wisely with continuous stirring for another 2 hrs. The reaction mixture was then refluxed for 4 hrs (TLC control). The reaction was then filtered off to get rid of K_2CO_3, evaporated under reduced pressure using rotatory evaporator. The residual resins was dissolved in ethanol and precipitated on crushed ice to obtain an organophosphorous derivatives **7a-h**.

Synthesis of 9-(4-substituted phenyl)-7-(4-substituted phenyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine 9a-d.

Enaminonitrile **8a-d** (10 mmol) was refluxed in an excess amount of formic acid for 10 hrs (TLC control). The reaction mixture was then poured onto ice/cold water mixture with continuous stirring. The formed precipitate was filtered off, washed with cold water and recrystalized from aproper solvent to give **9a-d**.

Synthesis of 9-(4-substituted phenyl)-7-(4-substituted phenyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-amin 10a-d:

Enaminonitrile **8a-d** (10 mmol) was refluxed for 10 hrs (TLC control) with formamide in the presence of formic acid and dimethyl formamide all as ternary mixture. The reaction mixture was then poured on ice/cold water mixture. The formed solid product was filtered off, washed several times with cold water,

dried and recrystalized from suitable solvent to yield **10a-d.**

Synthesis of 9-(4-substituted phenyl)-7-(4-substituted phenyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-2,4-dithiol 11a-d.

Solution of enaminonitrile **8a-d** (10 mmol) in pyridin was refluxed with carbon disulphide (10 mmol) for 3hrs (TLC control). After complete the reaction the mixture was left to cool then the excess pyridine was evaporated under reduced pressure using rotatory evaporator. The residual resine dissolved in least volume of ethanol and poured on ice/cold water mixture. The solution was acidified with few drops of diluted HCl. The precipitated solid was filtered off, washed with cold water, dried and recrystalized from suitable solvent to obtain **11a-d.**

Synthesis of 9-(4-substituted phenyl)-7-(4-substituted phenyl)-2-trichloromethyl pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-2,4-dithiol 12a-d.

Solution of (10 mmol) enaminonirle 8a-d in benzene containing few drops of triethyl amine as a basic medium, was refluxed with (10 mmol) trichloroacetonutrile for 2 hrs (TLC control). After the reaction completed, the reaction mixture was evaporated under reduced pressure using rotatory evaporator to get rid off benzene. The residual resin was dissolved in least amount of ethanol. The ethanolic solution was poured drop wisely onto ice/cold water mixture containing few drops of diluted HCl. The solid product was filtered off, washed with cold water, dried and recrystalized from proper solvent to get **12 a-d**.

All melting points are uncorrected and were determined on an electric melting point (electrothermal 9200A) apparatus. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 1H-Gemini 300 MHz and /or Jeol JNM-EX using TMS as internal reference. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer operating at 70 ev. Microanalytical data were obtained from the Microanalytical Data Center at Cairo University.

B.Bioassay

The cotton leaf worm strain in the present study was taken from field colony and reared in central agricultural pesticide laboratory. This strain was obtained from Sharkia governorate. The strain was kept under laboratory conditions at 25 ± 2 °C and 65 ± 5 % relative humidity away from any chemical pressure.

1. Chemical used.

The newly synthesized heterocyclic compounds.

2. Method of bioassay technique.

The leaf dipping technique was adopted on the 4th instar larvae to simulate the actual treatments under field conditions [34]. A stock solution of each chemical was freshly prepared. Subsequent water dilutions were made. Discs of 5 cm diameter were made from cotton leaves collected from unsprayed fields. The leaves were washed, dried, immersed in a test solution for 10 sec and allowed to dry on corrugated kitchen foil at ambient temperature for 1-1.5 hr. Leaf discs immersed in distilled water as control treatment. On drying, the leaf discs were placed in individual Petri dishes (9 cm diameter). Each treatment (concentration) was replicated 5 times, including water solvent control. 10 of 4th instar larvae were placed on each leaf disc (replication) and thus the total number of tested larvae per concentration was 50. The bioassay was kept at temperature 25±2 °C and 65±5 % relative humidity to determine the different biological criteria. Mortality was assessed after 72 hrs exposure to tested compounds.

3. Result and Discussion:

A. Illucidation of chemical compounds

As a part of our program directed for the development of a new simple and efficient procedure for the synthesis of biologically active heterocyclic nitrogenous compounds utilizing readily available intermediates [35], we have investigated the reaction of 3-cyanopyridine-2(*1H*)thione (**5a-d)** derivatives with some electrophilic reagent. The investigation has resulted in the development of novel procedure for the synthesis of 3-cyanopyridine-2(*1H*)thione and their fused heterocyclic derivatives. These compounds seem to promising for further chemical transformation and biological evaluation studies. Therefore, the reaction of compound (**5a-d)** with chloroacetonitrile in alcoholic potassium hydroxide proceeded via thrope-ziegler cycloaddition reaction [36,37] with the formation of thieno[2,3-*b*]pyridine derivatives **(8a-d)**. Compond (**8)** is a typical enaminonitrile which can undergo many cycloaddition reaction to afford different heterocyclic compounds.

The IR spectrum of compound **(7a)** showed new absorption bands at 1050 cm^{-1} corresponding to (OCH_3) of phosphate ester linkage, also, absorption at 1250 cm^{-1} of (P=O) group. More evidence for the formation of our target compound came from the mass spectrum of compound **(7a)** which revealed the presence of molecular ion peak at m /e = 426 corresponding to molecular formula $C_{21}H_{19}N_2O_4PS$ with 3.56% as relative a abundance. Another evidence for the formation of the designed skeleton obtained from the ^{1}H NMR spectrum of compound **(7a)** which illustrated new signals at δ (ppm) 3.8(2s, 6H) corresponding to two methoxy of phosphate ester group. Another evidence for the formation of the

suggested skeleton was the data of compound **(7h)** as another example of this structure category. The IR spectrum of this compound showed the presence of two absorption bands at 1030 cm^{-1} and 980 $cm^{-1}$of phosphate ester groups, also the absorption band at 1300 cm^{-1} of the (P=O) group. Also, 1H-NMR spectrum of compound **(7h)** revealed the strong evidence for the formed structural skeleton, where it revealed two new signals at δ (ppm) 4.5 (q, 4H, 2 CH_2 group) and 1.3 (t, 6H, $2CH_3$ group).

7a)- Yield 72 % (ethanol) mp = 173-176 ºC. IR spetrum ν (cm^{-1}); 3100 (CH-aromatic), 2950 (CH-aliphatic), 2230 (C≡N), 1250 (P=O) and 1050 (P-O-CH_3). ^{1}H NMR spectrum ($CDCl_3$) δ (ppm) 8.3 -7.0 (m, 9H, aromatic proton), 7.7 (s, 1H, pyridine proton), 3.9 (s, 3H, OCH_3) and 3.7, 3.6 (2s, 6H, 2 OCH_3 of phosphorous group). Found C 59.43, H 4.32, N 6.32, S 7.65 and P 7.30. calculated for $C_{21}H_{19}N_2O_4PS$ (426.36), C 59.15, H4.49,N 6.57, P 7.26 and S 7.52. Ms: m/z = 426.0; 3.56%.

7b)- Yield 69 % (ethanol), mp = 191-193 ºC. IR spectrum ν (cm^{-1}); 3120 (CH-aromatic), 2965 (CH-aliphatic), 2220 (C≡N), 1635 (C=N), 1520, 1515 (NO_2), 1275 (P=O) and 1080 (P-O-CH_3).

Found C52.98, H 3.92, N 8.73, P 6.82 and S 6.59. calculated for $C_{21}H_{18}N_3O_6PS$ (471.42), C53.50, H 3.85, N 8.91, P 6.57 and S 6.80. Ms: m/z = 471; 4.51%.

7c)- Yield 61% (ethylacetate) mp = 160-162 ºC. IR spectrum ν (cm^{-1}); 3078 (CH-aromatic), 2950 (CH-aliphatic), 2235(C≡N), 1620 (C=N), 1260 (P=O) and 1070 (P-O-CH_3).

Found C 54.61, H 4.01,Cl 7.51, N 6.21, P 6.44 and S 6.83.calculated for $C_{21}H_{15}ClN_2O_4PS$ (460.87),C 54.77, H 4.20, N 7.28, P 6.32 and S 6.91. Ms: m/z = 460; 2.45 %.

7d)- Yield 75% (acetic acid), mp+198-200) ºC. IR spectrum ν (cm^{-1}); 3120 (CH-aromatic), 2980 (CH-aliphtic), 2225 (C≡N), 1630 (C=N), 1520,1517 (NO_2), 1235 (P=O) and 1090 (P-O-CH_3). ^{1}H NMR spectrum (DMSO-d6) δ (ppm) = 8.7-7.6 (m, 8H, aromatic protons), 7.8 (s, 1H, pyridine ring proton) and 3.8, 3.7 (2s, 6H, 2- OCH_3 of phosphorous group).

Found C 51.01, H 3.42, Cl 7.21, N 8.84, P 6.32 andS 6.53. calculated for $C_{20}H_{15}ClN_3O_5PS$ (475.84), C 50.48, H 3.18, Cl 7.45, N 8.83, P 6.51 and S 6.72. Ms: m/z = 474.0; 2.15 %.

7e)- Yield 60 % (ethanol) mp = 149-151 ºC IR spectrum ν (cm^{-1}); 3110 (CH-aromatic), 2985 (CH-aliphatic), 2217 (C≡N), 1640 (C=N), 1220 (P=O) and 1030, 950 (P-O-CH_2CH_3).

Found C 60.95, H 4.95, N 6.33, P 6.59 and S 7.25. calculated for $C_{23}H_{23}N_2O_4PS$ (454.48), C60.78, H 5.10, N 6.16, P 6.82 and S 7.06. Ms: m/z = 454.0; 4.61%.

7f)- Yield 64 % (methanol) mp = 163-166 ºC IR spectrum ν (cm^{-1}) 3150 (CH-aromatic), 2960 (CH-aliphatic), 2229 (C≡N), 1650 (C=N), 1518, 1514 (NO_2), 1250 (P=O) and 1040, 980 (P-O-CH_2CH_3). ^{1}H NMR spectrum (DMSO-d6) δ (ppm) = 8.6-7.0 (m, 8H, aromatic proton), 7.9 (s, 1H, pyridine ring proton), 4.5 (q, 4H, $2CH_2$), 3.8 (s, 3H, OCH_3) and 1.3 (t, 6H, $2CH_3$). Found C55.51, H 4.25, N 8.69, P 6.35 and S 6.18. calculated for $C_{23}H_{22}N_3O_6PS$ (499.48), C55.31, H 4.44, N 8.41, P 6.20 and S 6.42. ms: m/z = 500.0; 5.61 %.

7g)- Yield 61 % (benzene) mp =139-141 ºC IR spectrum ν (cm^{-1}) 3090 (CH-aromatic), 2940 (CH-aliphatic), 2222 (C≡N), 1640 (C=N), 1290 (P=O) and 1090, 970 (P-O-CH_2CH_3)

Found C 57.72, H4.21, Cl 7.34, N6.29, P 6.41 and S 6.82. Calculated for $C_{22}H_{20}ClN_2O_3PS$ (458.90), C57.58, H4.39, Cl 7.73, N 6.10, P 6.75 and S 6.97. Ms: m/z = 458.0; 2.55 %.

7h)- Yield 72 % (ethanol + benzene) mp = 152-156 ºC IR spectrum ν (cm^{-1}) 3140 (CH-aromatic) 2930 (CH-aliphatic), 2232 (C≡N), 1650 (C=N), 1522,1518 (NO_2), 1300 (P=O) and 1030, 980 (P-O-CH_2CH_3).^{1}H NMR spectrum (DMSO-d6) δ (ppm) = 8.6-7.5 (m, 8H, aromatic proton), 7.9 (s, 1H, pyridine ring proton), 4.2 (q,4H, $2CH_2$), and 1.2 (t, 6H, $2CH_3$).

Found C 52.31, H3.99, Cl 7.21, N 8.51, P 6.04 and S 6.21. Calculated for $C_{21}H_{19}CLN_3O_5PS$ (503.96), C52.44,H 3.88, Cl 7.04, N 8.34, P 6.15 and S 6.35. Ms: m/z = 504; 3.45 %.

The compound (**8**) was reacted with formic acid to give the corresponding thieno[3,2-*d*]pyrimidine derivatives **(9a-d)**. The evidence for the formed skeletone are the compatible spectroscopic findings as well as the correct elemental analysis of the synthesized compounds. It is evident from IR and ^{1}H NMR spectrum of compound **9d**, as an example, that it could be present in the lactam – lactim dynamic equilibrium where as the lactam or oxo form is thermodynamically more stable due to the fact that oxo form is more stabilized by 54.4 $kj.mol^{-1}$ than the enol form [38, 39].

9a)- Yield 83 % (ethyl acetate) mp = 250-253 ºC IR spectrum ν (cm^{-1}) 3390 (OH), 3130 (CH-aromatic), 2930 (CH-aliphatic) and 1645 (C=N). Found C68.25, H 4.08, N 11.10 and S 8.12. Calculated for $C_{22}H_{15}N_3O_2S$ (385.44), C68.55, H 3.92, N 10.90 and S 8.32.Ms: m/z = 385.0; 3.15 %.

9b)- Yield 79 % (ethanole) mp = 261-263 ºC IR spectrum ν (cm^{-1}) 3280 (OH), 3090 (CH-aromatic), 2870 (CH-aliphatic) 1649 (C=N) and 1520, 1515 (NO_2). Found C61.15,H 3.45, N 12.88 and S 7.66. Calculated for $C_{22}H_{14}N_4O_4S$ (430.44), C61.39, H 3.28, N 13.02 and S 7.45. Ms: m/z =430.0, 6.14 %.

9c)- Yield 71 % (benzen) mp = 240-242 ºC IR spectrum ν (cm^{-1}) 3320 (OH), 3150 (CH-aromatic),

2980 (CH- aliphatic), and 1640 (C=N). found C64,38, H 2.99, Cl 9.21, N 10.98 and S 8.38. Calculated for $C_{22}H_{12}ClN_3OS$ (389.86), C64.70, H 3.10, Cl 9.09, N 10.78 and S 8.22. Ms: m/z = 390.0; 5.13 %.

9d)- Yield 70 % (ethanol) mp = 235-238 ºC IR spectrum ν (cm^{-1}) 3250 (OH), 3120 (CH-aromatic), 2920 (CH-aliphatic), 1638 (C=N) and 1522, 1517 (NO_2). ^{1}H NMR spectrum (DMSO-d6) δ (ppm) = 11.5 (s,1H, OH), 8.4-7.6 (m,8H, aromatic protons), 7.9 (s, 1H, pyrimidine ring proton) and 7.8 (s, 1H, pyridine ring proton). Found C57.73, H 2.78, Cl 7.95, N 12.58 and S 7.51. Calculated for $C_{21}H_{11}ClN_4O_3S$ (434.86), C58.0, H 2.55, Cl 8.15, N 12.88 and S 7.37. Ms: m/z = 435.0; 4.66 %.

Also, compound **(8a-d)** allowed to react with formamide in the presence of formic acid and dimethylformamide (DMF) as ternary mixture to obtain thieno[2,3-*b*]pyrimidine deivatives **(10a-d)**.

10a)- Yield 81 % (1,4-dioxane) mp > 300 ºC. IR spectrum ν (cm^{-1}) 3320,3310 (NH_2), 3120 (CH-aromatic), 2950 (CH- aliphatic) and 1645 (C=N). ^{1}H NMR spectrum (DMSO-d6) δ (ppm) = 8.4 (s, 1H, pyrimidine proton), 8.3-7.0 (m, 8H, aromatic protons), 7.8(s, 1H, pyridine proton), 7.7 (s, 2H, NH_2) and 3.8 (s, 3H, OCH_3). Found C68.58, H 4.42, N 14.81and S 8.12. Calculated for $C_{22}H_{16}N_4OS$ (384.45), C69.73, H4.19, N 14.57 and S 8.34. Ms: m/z = 384.0; 3.11 %.

10b)- Yield 78 % (1,4-dioxane) mp > 300 ºC. IR spectrum ν (cm^{-1}) 3290,3280 (NH2), 3110 (CH-aromatic), 2910 (CH- aliphatic), 1643 (C=N) and 1520, 1516 (NO_2). Found C61.40, H 3.62, N 16.45 and S 7.32. Calculated for $C_{22}H_{15}N_5O_3S$ (429.45), C 61.53, H 3.52, N 16.31 and S 7.47. Ms: m/z = 430.0; 2.15 %.

10c)- Yield 72 % (acetic acid) mp > 300 ºC IR spectrum ν (cm^{-1}) 3310, 3290 (NH_2), 3110 (CH-aromatic), 2950 (CH- aliphatic) and 1635 (C=N). Found C 64.71, H 3.21, Cl 9.30, N 14.29 and S 8.41. Calculated for $C_21H_{13}ClN_4S$ (388.87), C64.86, H 3.37, Cl 9.12, N 14.41 and S 8.25. Ms: m/z = 389.0; 8.14 %.

10d)- Yield 75 % (acetic acid) mp > 300 ºC IR spectrum ν (cm^{-1}) 3320, 3305 (NH2), 3110 (CH-aromatic), 2920 (CH- aliphatic), 1643 (C=N) and 1523, 1520 (NO_2). Found C58.02, H 2.85, Cl 8.29, N 16.01 and S 7.51. Calculated for $C_{21}H_{12}ClN_5O_2S$ (433.87), C 58.17, H 2.79, Cl 8.17, N 16.14 and S 7.39. Ms: m/z =434.0; 10.15 %.

On the other hand the reaction of thienopyridine **(8a-d)** with carbondisulphide in pyridine proceed with addition, followed by thiazine – pyrimidine ring transformation via Dimorth rearrangement [40-43] to afford **(11a-d).** While the reaction with trichloroacetonitrile in benzene in the presence of few drops of triethylamine as a basic medium varnish thieno[2,3-b]pyrimidine derivatives **(12a-d)**.

11a)- Yield 80 % % (1,4-dioxane) mp = 298-300 ºC. IR spectrum ν (cm^{-1}) 3090 (CH-aromatic), 2930 (CH-aliphatic), 2570 (SH) and 1642 (C=N). Found C60.85, H 3.62, N 9.51 and S 22,06. Calculated for $C_{22}H_{15}N_3OS_3$ (433.57), C 60.94, H 3.49, N 9.69 and S 22.19. Ms: m/z = 433.0; 7.41 %.

11b)- Yield 77% (acetic acid) mp > 300 ºC. IR spectrum ν (cm^{-1}) 3080 (CH-aromatic), 2930 (CH-aliphatic), 2590 (SH) and 1640 (C=N).^{1}H NMR spectrum ($CDCl_3$) δ (ppm) = 13.9 (s, 2H, SH), 8.4 – 7.0 (m, 8H, aromatic protons), 7.7 (s, 1H, pyridine ring proton} and 3.8 (s, 3H, OCH_3). Found C56.08, H 2.86, N 11.54 and S 20.28. Calculated for $C_{22}H_{14}N_4O_3S_3$ (478.57), C55.21, H 2.95, N 11.71 and S 20.11. Ms: m/z = 478.0; 5.14%.

11c)- Yield 69 % (acetic acid) mp = 285-289 ºC. IR spectrum ν (cm^{-1}) 3095 (CH- aromatic), 2980 (CH-aliphatic), 2580 (SH) and 1630 (C=N). Found C 57.75, H 2.59, Cl 8.25 N 9.7 and S 22.15. Calculated for $C_{21}H_{12}ClN_3S_3$ (437.99), C 57.59, H 2.76, Cl 8.09, N 9.95 and S 21.96. Ms: m/z = 438; 3.10 %.

11d)- Yield 68 % (acetic acid) mp > 300 ºC. IR spectrum ν (cm^{-1}) 3090 (CH- aromatic), 2910(CH-aliphatic), 2555 (SH) and 1635 (C=N). Found C52.11, H 2.50, Cl 7.22, N 11.45 and S 19.71. Calculated for $C_{21}H_{11}ClN_4O_2S_2$ (482.79), C52.22, H 2.3, Cl 7.34, N 11.60 and S 19.92. Ms: m/z = 438.0; 6.21 %.

12a)- Yield 82 % (benzene) mp = 272-275 ºC. IR spectrum ν (cm^{-1}) 3390,3310 (NH2), 3110 (CH-aromatic), 2900 (CH- aliphatic) and 1640 (C=N). ^{1}H NMR spectrum (DMSO-d6) δ (ppm) = 8.4 (s, 1H, pyrimidine ring proton), 8.3-7.0 (m, 8H, aromatic protons), 7.8 (s, 1H, pyridine ring proton), 7.7 (s, 2H, NH_2) and 3.8 (s, 3H, OCH_3). Found C54.97, H 2.86, Cl 20.99, N 11.31 and S 6.52. Calculated for $C_{23}H_{15}Cl_3N_4OS$ (501.82), C 55.05, H 3.01, Cl 21.19, N 11.16 and S 6.39.Ms: m/z = 502.0; 9.14 %.

12b)- Yield 86 % (ethanol) mp > 300 ºC. IR spectrum ν (cm^{-1}) 337050, 3310 (NH2), 3090 (CH- aromatic), 2890 (CH- aliphatic), 1630 (C=N) and 1520, 1518 (NO2). Found C 50.41, H 2.71, Cl 19.29, N 12.69 and S 6.01. Calculated for $C_{23}H_{14}Cl_3N_5O_3S$ (546.81), C 50.52, H 2.58, Cl 19.43, N 12.81 and S 5.86. Ms: m/z = 546.0; 8.23 %.

12c)- Yield 79 % (benzene) mp =250-253 ºC. IR spectrum ν (cm^{-1}) 3400, 3320 (NH2), 3120 (CH-aromatic), 2980 (CH- aliphatic) and 1635 (C=N). Found C51.98, H 2.51, Cl 27.83, N 11.21 and S 6.21. Calculated for $C_{22}H_{13}Cl_4N_4S$ (506.23), C52.20, H 2.39, Cl 28.01, N 11.07 and S 6.33.Ms: m/z = 506.0; 6.35 %.

12d)- Yield 72 % (ethanol) mp = 292-295 ºC. IR spectrum ν (cm^{-1}) 3410, 3340 (NH2), 3080 (CH-aromatic), 2940 (CH-aliphatic), 1650 (C=N) and 1518, 1515 (NO2). Found C47.81, H 2.16, Cl 25.85, N 12.56 and S 5.71. Calculated for $C_{22}H_{11}Cl_4N_5O_2S$

(548.23), C 47.94, H 2.01, Cl 25.73, N 12.70 and S 5.82. Ms: m/z = 548.0; 2.23 %.

B. The insecticidal activity of some synthesized compounds.

The cotton leaf worm *Spodoptera lettoralis* (Boisd) is a serious pest causing enormous losses to many economically important cultivated crops such as cotton, soybean, groundnut, tobacco and vegetables [44], it has been found to cause 26-100% yield loss in the field [45]. The present study aimed to evaluate the newly synthesized organophosphorous derivatives and some other thienopyrimidine derivatives against cotton leaf worm.

Table 1: The insecticidal activity of some synthesized organophosphorous derivatives of pyridinethione

		Concentration ppm				LC_{50}	slope	Toxicity Index
		250	500	750	1000			
% of Mortality	7a	16.95	63.15	86.25	94.82	429.73	3.603	57.13
	7d	40.11	75.98	85.72	95.17	301.70	0.320	81.73
	7f	17.57	80.73	96.26	99.62	361.06	0.461	67.99
	7h	50.97	87.12	96.25	98.47	245.49	3.630	100

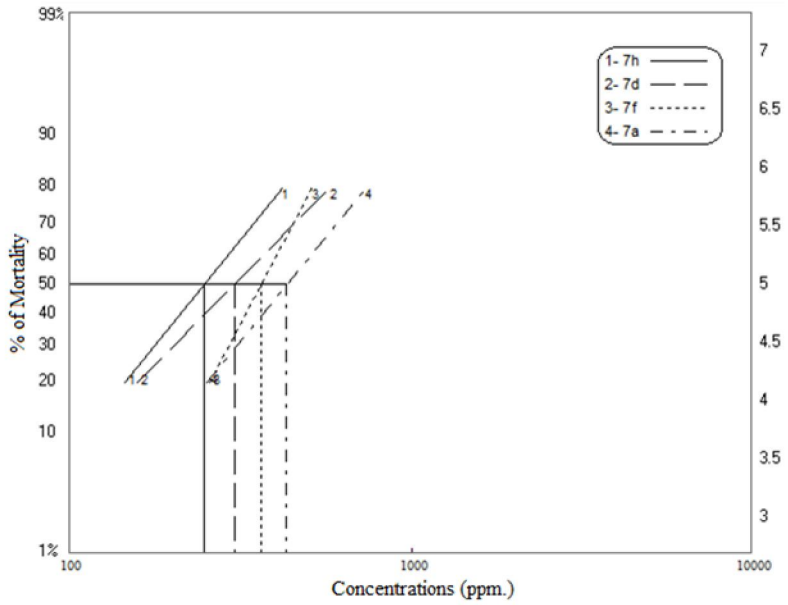


Fig.(1): Ldp lines of some synthesized organophosphorous 7a, 7d, 7f and 7h against *spodoptera lettoralis*

The data presented in table (2) and illustrated in fig.(2) revealed the insecticidal efficiency of some synthesized thieno[2,3-*b*]pyrimidine derivatives against cotton leaf worm *spodoptera lettoralis*. From these data we conclude that the pyrimidine derivative **12d** with LC_{50} 370.91 ppm was the more potent compound, while derivative **9a** with LC_{50} 1458.50 ppm was the least effective one. On contrast both of compound **10b** and **11c** showed moderate effect where they recorded LC_{50} values at 645.39 and 524.73 ppm respectively.

Table 2: The insecticidal activity of some synthesized thieno[2,3-b]pyrimidine derivatives

		Concentration ppm					LC_{50}	slope	Toxicity Index
		250	500	1000	1500	2000			
% of Mortality	9a	29.95	37.48	45.52	50.33	53.75	1458.50	0.686	25.43
	10b	34.16	45.63	57.47	64.17	68.68	645.39	0.9904	57.47
	11c	30.73	43.07	56.13	63.56	68.55	524.73	0.871	70.69
	12d	36.95	63.90	70.15	78.26	83.14	370.91	1.333	100

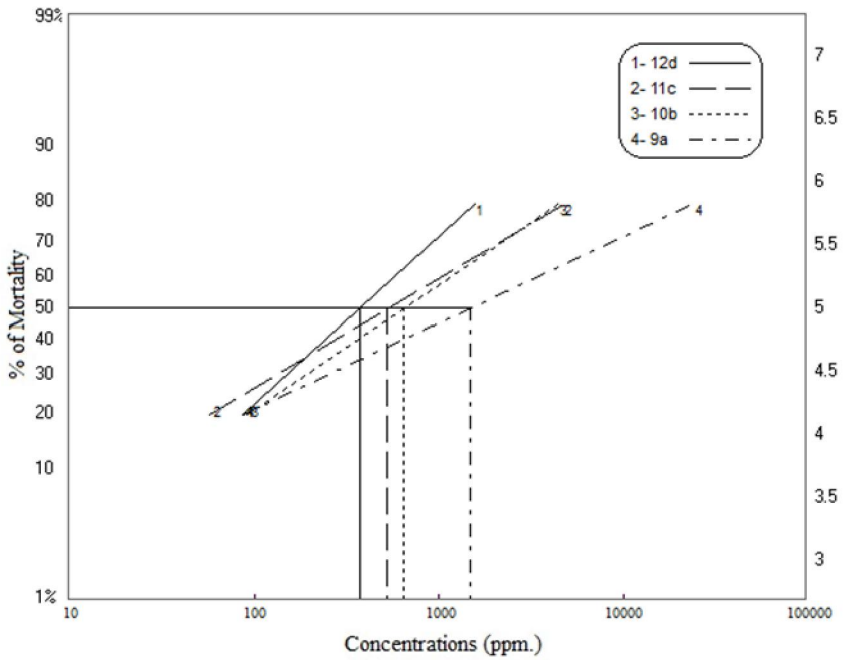


Fig.(2): Ldp lines of some synthesized thieno[2,3-*b*]pyrimidine 9a, 10b, 11c and 12d against *spodoptera lettoralis*

Tables (1and 2) and figures (1and 2) represented the insecticidal activity data of some synthesized phosphothioate derivatives of pyridine thione. From these data we detected that the phosphothioate derivative **(7h)** was the more effective compound where it recorded LC_{50} at 245.49 ppm followed by compound **(7d)** and **(7f)** with LC_{50} 301.70 and 361.06 respectively. On the other hand compound **(7a)** was the least efficient compound among the other tested organophosphorous derivatives against cotton leaf worm *spodoptera lettoralis* insect where its LC_{50} 429.73 ppm.

This order may attributed to the presence of electron withdrawing derivatives as NO_2 group and Cl attached to benzene ring at *p*-position which led decreasing electron density around the molecule thus facilitate the absorption of compound through the cells and increasing the leaving tendency of phosphoester group. The rate of acetylcholinesterase inhibition depends on the leaving group where higher tendency of leaving group results in higher affinity of the inhibitor to the enzyme [46,47].

The overall assay decided that phosphothioate derivatives are more efficient against *spodoptera lettoralis* than the other tested thieno [2,3-*b*] pyrimidine. Compound **7h** was the most potent one among all of the tested compounds, while pyrimidine derivative **9a** was the less effective one against the tested *spodoptera lettoralis.*

The tested organophosphorous derivatives might be used in a proper formulation form to control cotton leaf worm *spodoptera lettoralis.*

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