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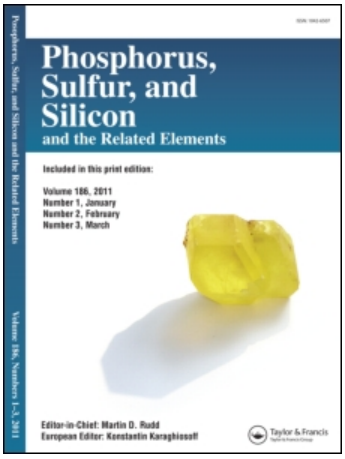

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POLYCYCLIC PYRIDINES: SYNTHESIS OF PYRIDOTHIENOPYRIMIDINES PYRIDOTHIENOTRIAZINES AND PYRIDOTHIENOTRIAZEPINES

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POLYCYCLIC PYRIDINES: SYNTHESIS OF PYRIDOTHIENOPYRIMIDINES PYRIDOTHIENOTRIAZINES AND PYRIDOTHIENOTRIAZEPINES

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Thienopyridines **3a-c** were acetylated with Ac_2O to afford the pyridothienopyrimidines **4a-c**. Also **3a-c** were treated with carbon disulfide in dioxan solution to give **5a-c**. Diazotization of **3a-c** gave the triazine derivatives **6a-c**. Treatment of **3a-c** with triethyl orthoformate in acetic acid gave **7a-c** in good yield. Chlorination of **7a** by $POCl_3$ afforded the chlorine derivatives **8**. Similarly diazotization of the ortho-aminohydrazide **3d** give the corresponding azide **9** which was subjected to Curtius rearrangement in boiling xylene to give the imidazothienopyridine **10**. Compound **12** was obtained by the reaction of **3d** with either formic acid or triethyl orthoformate. Compond **14** was also obtained by the reaction of **3d** with ethyl chloroformate. Refluxing of **3d** with methyl isothiocyanate gave **15**. The interaction of **3d** with acetylacetone furnished the pyrazolyl derivative **16**. The ortho-aminonitrile **3e** reacts with mixture of formic acid and formamide (1:1) to give **7a**, whereas **3e** reacts with formamide alone give **17**. Treatment of **3e** with carbon disulfide in boiling pyridine afforded **18**. Also, acetylation of **3e** with acetic anhydride afforded **4a**.

Finally, treatment of **3e** with triethyl orthoformate in acetic anhydride afford **19**. The reaction of **3e** with phenyl isothiocyanate gave **20**.

Keywords: Pyridothienopyrimidines; pyridothienotriazine; pyrazolothienopyridine and pyridothienotriazepine

INTRODUCTION

Polyfunctionally substituted pyridinethiones are highly reactive compounds that have been extensively utilized in organic heterocyclic synthesis [1,2]. As nucleus for the synthesis of many tri and tetracyclic system,

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they have attracted much attention due to their interesting biological activities [3–7]. The importance of the synthesized compounds as intermediate for the synthesis of the biologically active diaza and folic acid ring systems [8]. Also these compounds have been evaluated pharmacologically and have been found to show activity against diabetes mellitus, as analgesics and antiinflammants[9–11], promptive our interested in the synthesis and chemistry of this class of compounds. In continuation of our research program for the synthesis of tricyclic and tetracyclic pyridine containing ring systems possessing a thienopyridine nucleus, we report here the results of our investigation on the synthesis of tri and tetracyclic pyridines.

DISCUSSION

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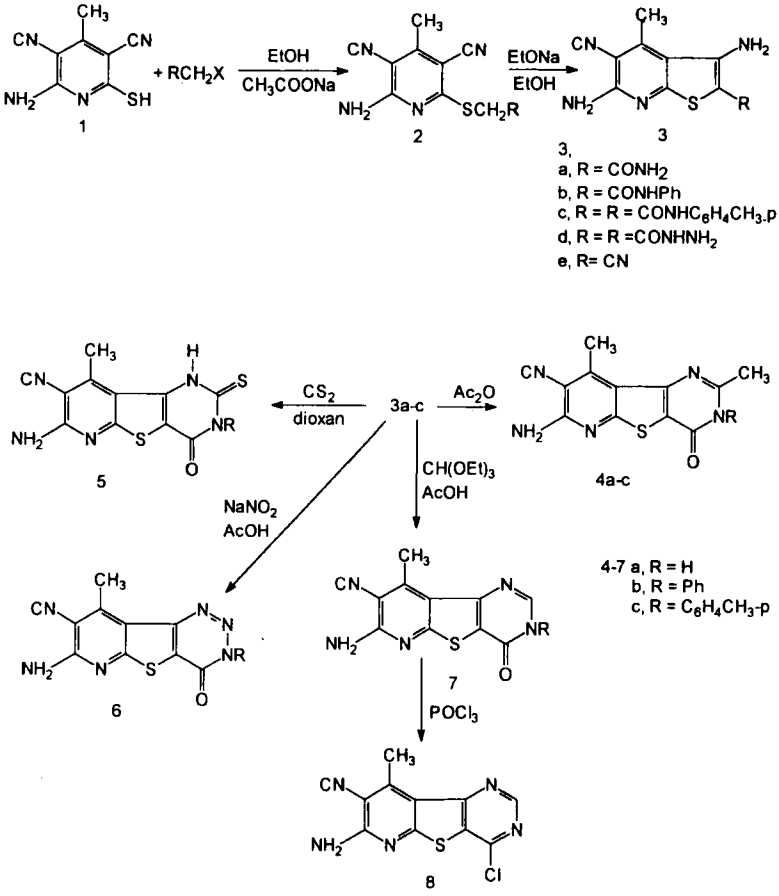
It has been found that compounds **3a-c** which were prepared according the literature [12] were acetylated with acetic anhydride to afford the pyridothienopyrimidine derivatives **4a-c**. The ^{1}H NMR of the products show the presence of two methyl groups at $\delta = 2.1$ and 2.3 ppm corresponding to the methyl group of the pyridine and pyrimidine moieties respectively. The reaction of **3a-c** with carrbon disulfide in dioxan solution afforded **5a-c**. These compounds were confirmed by ^{1}H NMR, mass spectra and elemental analysis. Also, the orthoamides have proved valuable for synthesizing various heterocycles. So, diazotization and self coupling of the amino amide **3a-c** gave the triazine derivatives **6a-c**. Reaction of **3a-c** with triethyl orthoformate in acetic acid gave the pyridothienopyrimidines **7a-c**. Compopund **7a** was chlorinated with $POCl_3$ to give the chloride derivative **8** (Scheme 1).

Similarly, diazotisation of the ortho amino hydrazide **3d** gave the corresponding aminoazide **9** which was subjected to Curtius rearrangement in refluxing xylene to give the imidazothienopyridine **10**. Also the reaction of **3d** with formic acid or triethyl orthoformate in ethanol gave either the N-aminopyrimidine **11** or the triazepine **12**. Structure **11**was ruled out based on ^{1}H NMR which revealed the absence of N-amino at 5.0–6.0 ppm. Moreover ^{1}H NMR data can only be rationalized in term of triazepine structure **12** which revealed a one proton as singlet at $\delta = 7.1$ and 7.5 ppm for two NH groups corresponding to compound **12**. Also, the reaction of **3d** with ethyl chloroformate afforded the N-amino derivative **13** or the triazepine derivative **14**. The structure of compound **14** was based on spectral data (IR, ^{1}H NMR). Similarly, reaction of **3d** with methyl



SCHEME 1

isothiocyanate in anhydrous dioxan gave the triazepine compound **15**. The structure of compound **15** was confirmed by spectral data (IR, ^{1}HNMR and MS). The interaction of **3d** with acetylacetone furnished the pyrazolyl derivative **16**. The ^{1}H NMR of compound **16** showed the presence of three signals at $\delta = 1.9$, 2.3 and 2.8 ppm corresponding to the three methyl groups (Scheme 2).

The ortho aminonitrile **3e** allowed to react with a mixture of formic acid and fomamide to give compound **7a**. The structure of compound **7a** was

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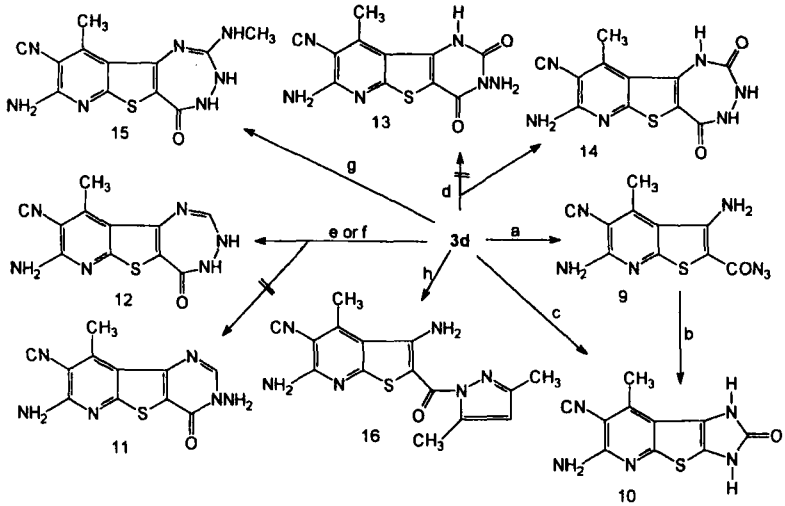

SCHEME 2

confirmed by mp and mixed mp. Also, **3e** reacts with formamide to give the amino pyrimidine derivative **17**. The tetracyclic ring **18** was prepared by reaction of **3b** with carbon disulfide in boiling pyridine. The compound **18** was confirmed by spectral data. The IR spectrum of **18** revealed the absence of CN peak, ^{1}H NMR revealed the presence of dueterable signal for four protons corresponding to **4** NH group. Treatment of compound **3e** with triethyl orthoformate in acetic anhydride afforded the ethoxymethyleneamino derivative **19**. Acetylation of **3e** with acetic anhydride in boiling pyridine give the pyridothienopyrimidine **4a**. The compound **4a** was confirmed by mp. and mixed mp. The reaction of **3e** with phenylisothiocyanate afforded the tetracyclic ring **20** (Scheme 3).

BIOLOGICAL ACTIVITIES

Most of the synthesized compounds have been tested against four different bacteria. The result of the antimicrobial studies presented in Table (I)

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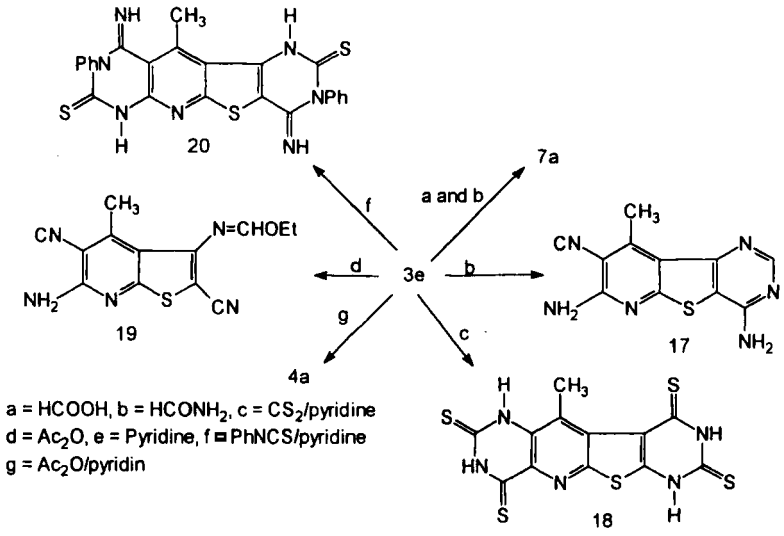

SCHEME 3

revealed the prepared compounds show antimicrobial activity against Staphyllococcus aurous, Streptococcus mitor, Fsherichia coli and Nisscria sica.

TABLE I

No of Compounds	*staphyllococcus aurous*	*streptococcus mitor*	*Esherichia coli*	*Nisseria sica*
4a	+	++	+	++
5a	++	++	+	++++
6a	+	++	+	+++
7a	+	++	+	++
8	++	+++	+	++++
12	+	+	+	++++
15	++	+++	+	+++
17	++	+++	+	++++
18	+	++	+	+
19	+	+++	++	+++
20	+++	++	+	++++

++++ = very severe effect +++ = severe effect ++ = moderate effect, + = slight effect
--=Negative

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EXPERIMENTAL

All melting points are uncorrected and were determined on a Gellankamp apparatus, IR spectra were recorded on Schimadzu 470 spectrophotometer in potassium bromide discs; ^{1}H NMR spectra were recorded on a Varian EM-390 (90 Mhz) spectrophotometer using TMS as an internal standard, Mass spectrometer MS 30 (AEL) at 70ev. Analytical data were obtained from the microanalytical data center at Cairo University

Preparation of compounds 4a-c. General procedure

Compound **3a-c** (2g) were dissolved in acetic anhydride (20 ml) and refluxed for 3h. The reaction mixture was poured onto ice water and left to stand for 12h. The solid product was formed filtered off and recrystllized from the proper solvent.

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7-Amino-2,9-dimethyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d] pyrimidine-8-carbonitile 4a

Compound **4a** was obtained as yellow crystals from DMF/Ethanol; yield 40%; mp 355°C; IR ν cm^{-1} 3390–3225 (NH_2); 3225–3100 (NH); 2200 (CN); 1651 (CO); ^{1}H NMR (DMSO-d_6) δ = 2.1 (s, 3H, CH_3); 2.3 (s, 3H, CH_3); 6.4(5, 2H, NH_2); 12.2 (s, 1H, NH); Ms: m/z = 271; Found: C, 53.3; H, 3.0; N, 25.9; S, 12.0; calcd for $C_{12}H_9N_5OS$: C, 53.13; H, 3.34; N, 25.81; S, 11.82%.

7-Amino-2,9-dimethyl-4-oxo-3,4-dihydro-3-phenylpyrido[3′,2′:4,5] thieno[3,2-d] pyrimidine-8-carbonitrile. 4b

Compound **4b** was crystallized from DMF/EtOH as yellow crystals; yield 45%; mp >360°C; IR ν cm^{-1} 3355–3220 (NH_2); 3220–3150 (NH); 2200 (CN); 1655 (CO); ^{1}H NMR (DMSO-d6) δ = sample is insoluble; Found: C, 62.5; H, 3.9: N, 20.3; calcd or $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16%

7-Amino-2,9-dimethyl-4oxo-3,4-dihydro-3-p-tolylpyrido[3′,2′:4,5] thieno[3,2-d] pyrimidine-8-carbonitrile (4c)

Compound **4c** was obtained as yellow crystals from DMF/EtOH; yield 60%; mp 350°C; IRν cm^{-1} 3390–3210 (NH_2); 2200 (CN); 1673 (CO); ^{1}H

NMR (DMSO-d_6) δ = 2.2 (s, 3H, CH_3) 2.4 (s, 3H, CH_3); 3.1 (s, 3H, CH_3); 5.5 (s, 2H, NH_2); 7.2–7.6 (m, 4H, Ar-H); MS: m/z = 347; Found: C, 62.5; H, 3.8; N, 20.3; S, 9.4; calcd for $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16; S, 9.23%.

Preparation of compound 5a-c. General procedure

A suspension of compounds **3a-c** (0.01mol) and carbon disulfide (2ml) in dioxan (20 ml) was refluxed for 8h. The reaction mixture was poured onto ice/water and neutralized with dilute HCl. The solid product formed was collected by filtration and recrystallized from the proper solvent.

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7-Amino-9-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2′,3′:4,5] thieno [3,2-d]pyrimidine-8-carbonitrile 5a

Compound **5a** was obtained as orange crystals from dioxan, yield 40%; mp. 306 °C; IR νcm^{-1} 3445–3300 (NH_2); 3300–3100 (NH); ^1H NMR (DMSO-d_6) δ = 4.0.3 (s, 3H, CH_3); 6.4 (s, 2H, NH_2); 7.8 (s 2H, 2NH); MS: m/z = 289; Found: C, 45.8; H, 2.5; N, 24.3; S, 22.3; calcd for $C_{11}H_7N_5OS_2$: C, 45.66; H, 2.44; N, 24.21; S, 22.16%

7-Amino-9-methyl-3-phenyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido [2′,3′:4,5] thieno[3,2-d]pyrimidine-8-carbonitrile 5b

Compound **5b** was obtained as yellow crystals from DMF/EtOH; mp. 318–320°C; yield 60 %; IRν cm^{-1} 3400–3300 (NH_2); 2200 (CN); 1650 (CO); ^1H NMR (DMSO-d_6) δ = 3.1 (s, 3H, CH_3); 6.9–7.5 (m, 7H, Ar-H and NH_2); MS: m/z = 365; Found: 56.0; H, 3.2; N, 19.2; S, 17.7; calcd for $C_{17}H_{11}N_5OS_2$: C, 55.88; H, 3.03; N, 19.16; S, 17.55%.

7-Amino-9-methyl-3-p-tolyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido [2′,3′:4,5] thieno[3,2-d]pyrimidine-8-carbonitrile 5c

Compound **5c** was obtained as orange crystals from; mp. 330°C; yield 70%; IRν cm^{-1} 3390–3310 (NH_2); 2210 (CN); 1650 (CO); ^1H NMR (DMSO-d_6) δ = 2.9 (s, 3H, CH_3); 3.5 (s, 3H, CH_3); 7.2–7.7 (m, 6H, Ar-H and NH_2); 8;9 (s, 1H, NH); MS: m/z = 379; Found: C, 57.1; H, 3.6; N,

18.6; S, 17.0: calcd for $C_{18}H_{13}N_5OS_2$: C, 56.98; H, 3.45; N, 18.46; S, 16.90%.

Preparation of compounds 6a- c. General procedure

To a cold solution of compounds **3a-c** (0.01 mol) in acetic acid (30 ml) a cold solution of sodium nitrite (1g in 2 ml H_2O) was added drop wise with stirring. The stirring was continued for 1 hour and left to stand at room temperature for 1 hour. The solid precipitate formed was collected by filtration and recrystallized from the appropriate solvent.

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7-Amino-9-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d] triazine-8-carbonitrile 6a

Compound **6a** was obtained as red crystals from dioxan; yield 60%; mp 260 °C; IR ν cm^{-1} 3395–3250 (NH_2), 3250–3170 (NH); 2200 (CN); 1656 (CO); ^1H NMR (DMSO-d_6) δ = 2.8 (s, 3H, CH_3); 7.1 (s, 2H, NH_2); 8.5 (s, 1H, NH); MS: m/z = 258; Found: C, 46.7; H, 2.4; N, 32.7; S, 12.5; calcd for $C_{10}H_6N_6OS$: C, 46.51; H, 2.34; N, 32.54; S, 12.41%.

7-Amino-9-methyl-4-oxo-3,4-dihydro-3-phenylpyrido[3′,2′:4,5]thieno [3,2-d] triazine-8-carbonitrile 6b

Compound **6b** was obtained as gray crystals from dioxan; yield 54%; mp 350 C; IR ν cm^{-1} 3356–3175 (NH_2), 2200 (CN); 1667 (CO); Ms: m/z = 334; ^1H NMR (DMSO-d_6) δ = 3.0 (s, 3H, CH_3), 7.1–7.7 (m, 6H, Ar-H and NH_2); 9.0 (s, 1H, NH); Found: C, 57.6; H, 3.3; N, 25.4; S, 9.7; calcd for $C_{16}H_{10}N_6OS$: C, 57.48; H, 3.01; N, 25.14; S, 9.59%.

7-Amino-9-methyl-4-oxo-3,4-dihydro-3-p-tolylpyrido[3′,2′:4,5]thieno [3,2-d]triazine-8-carbonitrile 6c

Compound **6c** was obtained as colourless crystals from dioxan; yield 66%; mp 350°C; IRν cm^{-1} 3475–3190 (NH_2), 2220 (CN); 1660 (CO); Ms: m/z = 348; ^1H NMR (DMSO-d_6) δ = 2.9 (s, 3H, CH_3); 3.5 (s, 3H, CH_3); 7.0–7.6 (m, 5H, Ar-H and NH_2); 8.8 (s, 1H, NH); Found: C, 58.8; H, 3.5;

N, 24.5; S, 9.4; calcd for $C_{17}H_{12}N_6OS$: C, 58.61; H, 3.47; N, 24.12; S, 9.20%.

Preparation of compounds 7a-c. General procedure

To a solution of compound **3a-c** (0.01 mol) in acetic acid (30 ml), triethyl orthoformate (3 ml) was added. The reaction mixture was refluxed for 3h. then poured on water and left to stand for 5h. The solid product formed was filtered off and recrystallized from the appropriate solvent.

7-Amino-9-methyl-4-oxo-3,4-dihydropyrido[3′,2′:4,5]thieno[3,2-d] pyrimidine-8-carbonitrile7a

Compound **7a** was obtained as red crystals from ethanol; yield 37%; mp 230°C; IR ν cm^{-1} 3370–3220 (NH_2); 3220–3165 (NH); 2190 (CN); 1663 (CO) MS: m/z = 257; Found: C, 51.5; H, 2.8; N, 27.6; S, 12.7; calcd for $C_{11}H_7N_5OS$: C, 51.36; H, 2.74; N, 27.22; S, 12.46%.

7-Amino-9-methyl-4-oxo-3,4-dihydro-3-phenylpyrido[3′,2′:4,5]thieno [3,2-d] pyrimidine-8-carbonitrile 7b

Compound **7b** was obtained as gray crystals from dioxan; yield 65%; mp 320°C; IR ν cm^{-1} 3375–3195 (NH_2), 2220 (CN); 1674 (CO); ^1H NMR (DMSO-d_6) δ = 2.7 (s, 3H, CH_3); 7.0–7.7 (m, 8H, Ar-H and NH_2); Found: C, 62.4; H, 3.4; N, 21.2; S, 9.8: calcd for $C_{17}H_{11}N_5OS$: C, 61.26; H, 3.30; N, 21.02; S, 9.62%.

7-Amino-9-methyl-4-oxo-3,4-dihydro-3-p-tolylpyrido[3′,2′:4,5]thieno [3,2-d] pyrimidine-8-carbonitrile 7c

Compound **7c** was obtained as yellow crystals from dioxan; yield 60%; mp 358°C; IR ν cm^{-1} 3330–3200 (NH_2), 2195 (CN); 1640 (CO); ^1H NMR (DMSO-d_6) δ = 2.8 (s, 3H, CH_3); 3.3 (s, 3H, CH_3); 7.0–7.6 (m, 7H, Ar-H and NH_2); Found: C, 62.4; H, 3.8; H, 20.4; S, 9.4; calcd for $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16; S, 9.23%.

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7-Amino-4-chloro-9-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile 8

A suspension of compound **7a** (0.01 mol) in $POCl_3$ (10 ml) was refluxed for 2 h. then left to stand. The reaction mixture was poured onto ice/water and the solid product formed was filtered off, washed with water several times, dried and recrystallized from ethanol as yellow crystals, yield 74%; mp 266°C; IR ν cm^{-1} 3330–3200 (NH_2) 2200 (CN); ^1H NMR (DMSO-d_6) δ = 2.9 (s, 3H, CH_3); 7.0 (br, 3H, Ar-H and NH_2); Found: C, 48.3; H, 2.0; N, 25.6; S, 11.8; calcd for $C_{11}H_5N_5SCl$: C, 48.10; H, 1.83; N, 25.49; S, 11.67%.

3,6-Diamino-5-cyano-4-methylthieno[2,3-b]pyridine-2-carboazide 9

To a cold solution of **8** (0.05 mol) in acetic acid (20ml), a cold solution of sodium nitrite (0.5g in H_2O) was added drop wise with stirring. The stirring was continued for ½ hour and let to stand at room temperature for 1 hour. The precipitate was collected and recrystallized from ethanol as colourless crystals; mp 323°C; yield 40%; IR *ν* cm^{-1} 3455–3145 (NH_2), 2205 (CN), 1659 (CO); ^1H NMR (DMSO-d_6) δ = 2.8 (s, 3H, CH_3); 6.1 (s, 2H, NH_2); 6.9 (s, 2H, NH_2); Ms: m/z = 273; Found: C, 44.2; H, 2.8; N, 36.0; S, 11.9; calcd for $C_{10}H_7N_7OS$: C, 43.95; H, 2.56; N, 35.88; S, 11.73%

6-amino-8-methyl-2-oxo-1,2,3-trihydroimidazo[4′,5′:2,3]thieno[2,3-b]pyridine-7-carbonitrile 10

The carboxyazide **9** (0.01 mol.) was refluxed in xylene (20 ml) for 30 minutes and then allowed to cool. The solid product formed was filtered off, washed with petrolium ether, dried and recrystallized from dioxan as yellow crystals; mp 333 °C; yield 55%; IR *ν* cm^{-1}3375–3160 (NH_2, NH); 2190 (CN); 1666 (CO); ^1H NMR (DMSO-d_6) δ = 2.7 (s, 3H, CH_3); 6.2 (s, 2H, NH_2); 8.5 (s, 1H, NH); 8.7 (s, 1H, NH); Found: C, 49.1; H, 3.0; N, 28.7; S, 13.2; calcd for $C_{10}H_7N_5OS$: C, 48.97; H, 2.88; N, 28.55; S, 13.07%.

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8-Amino-10-methyl-5-oxo-1,2,3,4,5-pentahydropyrido[3′,2′;4,5] thieno[2,3-e]triazepine-9-carbonitrile 12

Method A

A solution of compound **8** (0.01mol) in formic acid (30 ml), was refluxed for 3h. The solid product formed was collected by filtration and recrystallized from dioxan as colourless crystals m.p 250°C; yield 35%; IR ν cm^{-1} 3350–3170 (NH_2, NH); 2220 (CN); 1655 (CO). ^1H NMR (DMSO-d_6) δ = 2.7 (s, 3H, CH_3); 4.0 (s, 1H, CH); 4.4 (s, 2H, NH_2); 7.1 (s, 1H, NH); 7.5 (s, 1H, NH); Found: C, 48.7; H, 3.1: N, 31.0; S, 12.0; calcd for $C_{11}H_7N_6OS$: C, 48.70; H, 2.60; N, 30.98; S, 11.82%.

Method B for preparation of 12 and 19. General procedure

A suspension of **3d** or **3e** (0.01 mol) and triethyl orthoformate (3 mol) in acetic anhydride (30 ml) was refluxed for 3h. The reaction mixture was poured onto water and left to stand overnight. The solid precipitate formed was filtered off and recrystallized from ethanol as red crystals; yield 45%; mp and mixed m.p as **12**.

8-Amino-10-methyl-2,5-dioxo-1,2,3,4,5-pentahydropyrido[3′,2′;4,5] thieno[2,3-e]triazepine-9-carbonitrile 14

A suspension of **3d** (0.01 mol) and ethyl chloroformate (0.01 mol) in benzene (30 ml) was treated with little amount of triethylamine and refluxed for 3h. The solvent was evaporated under vacuo. The solid precipitate formed was triturated with petroleum ether, filtered off and recrystallized from ethanol as yellow crystals; yield 44%; mp 230°C; IR ν cm^{-1} 3380–3190 (NH_2, NH); 2220 (CN); 1655 (CO). ^1H NMR (DMSO-d_6) δ = 2.9 (s, 3H, CH_3); 4.4 (s, 2H, NH_2); 7.4 (s, 2H, 2NH); 7.9 (s, 1H, NH); MS: m/z = 288; Found: C, 46.0; H, 3.1; N, 29.3; S, 11.3: calcd for $C_{11}H_8N_6O_2S$: C, 45.83; H, 2.80; N, 29.15; S, 11.12:

8-Amino-10-methyl-2-methylamino-3,4,5-trihydropyrido[2,3:4,5] thieno[3,2-e]triazepine-9-carbonitrile 15

To a solution of compound **8** (0.01 mol) in anhydrous dioxan (30 ml), methyl isothiocynate (0.01 mol) was added. The reaction mixture was

refluxed for 4 hours. The solid product formed after cooling was collected by filtration and recrystallized from dioxan as yellow crystals; mp 250°C; yield 40%; IR cm^{-1} 3335–3165 (NH_2-NH); 2220 (CN); 1641 (CO); ^1H. NMR (DMSO-d_6) δ = 2.3 (s, 3H, CH_3); 7.0 (s, 1H. NH); 7.2 (s, 1H, NH); 7.5 (s, 1H, NH); 8.0 (br, 2H, 2NH); Found: C, 47.9; H, 3.7; N, 33.7; S, 10.8; calcd for $C_{12}H_{10}N_7OS$: C, 47.99; H, 3.36; N, 32.65; S, 10.68%.

2-[3,5-Dimethylpyrazolyl-1-yl]-3,6-diamino-4-methylthieno[2,3-b]-pyridine-5-carbonitrile 16

A mixture of compound **8** (0.01 mol) and acetyl acetone (0.02 mol) in ethanol (30 ml) was treated with a few drops of piperidine. The reaction mixture was refluxed for 3 hours. The solid product formed after cooling was collected by filtration and recrystallized from DMF/dioxan as orange crystal; yield 35%; mp.>350°C; IR ν cm^{-1} 3390–3095 (NH_2), 2205 (CN), 1657 (CO); ^1H. NMR (DMSO-d_6) δ = 1.9 (s, 3H, CH_3); 2.3 (s, 3H, CH_3); 2.8 (s, 3H, CH_3); 6.1 (s, 1H, CH); 6.8–7.1 (br, 4H, $2NH_2$); Ms: m/z = 326; Found: C, 55.1; H, 4.7; N, 25.8; S, 10.0; calcd for for $C_{15}H_{14}N_6OS$: C, 55.20; H, 4.32; N, 25.75; S, 9.82%.

4,7-Diamino-9-methylpyrido[2′,3′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile 17

A mixture of **3b** (0.01 mol) and formamide (20 ml) was refluxed for 1h. After cooling the precipitated was filtered off and wash several times it is obtained as red crystals from ethanol, yield 45%; mp. 330°C; IR ν cm^{-1}3366–3145 (NH_2), 2195 (CN); ^1H. NMR (DMSO-d_6) δ = 2.9 (s, 3H, CH_3); 7.0 (s, 1H, CH); 7.5 (br, 4H, $2NH_2$); Ms: m/z = 256; Found: C, 51.5; H, 2.8; N, 32.9; S, 12.7: calcd for $C_{11}H_8N_6S$: C, 51.55; H, 3.15; N, 32.79; S, 12.51%.

11-Methyl-1,2,3,4,7,8,9,10-octahydropyrimidine[5,4-b]thieno[3′,2′:2,3]pyrido[2,3-d]pyrimidine-1,3,7,9-tetrathione 18

A suspension of compounds **3b** (0.01mol) and carbon disulphide (2ml) in pyridine (20) was refluxed for 8h. The reaction mixture was poured onto ice/water and neutralized with dilute HCl. The solid product formed was-

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collected by filration and recrstallized from dioxan as orange crystals, yield 40%; mp. 300°C; IR ν cm^{-1} 3445–3115 (NH);); ^1H NMR (DMSO-d_6) $\delta = 3.0$ (s, 3H, CH_3): 7.8 (s, 4H, 4 NH); Ms: m/z = 381; Found: C, 37.9; H, 2.0; N, 18.5; S, 24.4; calcd for $C_{12}H_7N_5S_5$: C, 37.79; H, 1.85; N, 18.36; S, 24.02%.

2-Acetylamino-5-ethoxymethyleneamino-4-methylthieno[2,3-b]-pyridine-3,6-dicarbonitrite 19

It is recrystalized from ethanol as brown crystals yield 75%; mp. 352°C; IR ν cm^{-1} 3575–3205 (NH_2); 3205–3100 (NH); 2190 (CN); 1700(CO); ^1H NMR (DMSO- d_6) $\delta = 1.6$ (s, 3H, CH_3); 2.1(s, H, CH_3); 3.8 (s, 3H, CH_3); 4.4 (q, 2H, CH_2); 8.1 (s, 1H, CH); 8.3 (s, 1H, NH); Found: C, 55.3; H, 4.3; N, 21.5; S, 9.9; calcd for $C_{15}H_{13}N_5O_2S$: C, 55.04; H, 4.00; N, 21.39; S, 9.79%.

11-Methyl-3,9-diphenyl-4,10-diimino-1,2,7,8-tetrahydropyrimido [5,4-b]thieno[3′,2′:2,3]pyrido[2,3-d]pyrimidine-2,8-dithione 20

A mixture of compound **3b** (0.01mol) and phenyl isothiocyanate (0.01mol) in pyridine (20ml) was refluxed for 8h. The reaction mixture was poured onto ice/ water. The solid product formed was collected by filtration and recrystalized from DMF/dioxan (1/3) as yellow crystals yield 40%; mp>350°C; IR ν cm^{-1} 3145 (NH); ^1H. NMR (DMSO-d_6) $\delta = 3.0$ (s, 3H, CH_3); 7.0–7.8 (m, 10H, Ar-H); 8.2 (s, 1H, 2NH); 8.7 (s, 2H, 2NH); Found: C, 57.9; H, 3.6; N, 19.7; S, 19.4; calcd for $C_{24}H_{17}N_7S_3$: C, 57.70; H, 3.43; N, 19.62; S, 19.25%.

BIOLOGICAL TESTING

The newly synthesized compounds were dissolved in propylene glycol (10 mg/20 ml) and transferred to a filter paper disc (10 mm) diffusion plate method [13]. The bacterial suspension was prepared by adding 20 ml of distilled water to 10-d-old cultures of the test bacteria grown on a nutrient agar of NA. The spore suspension was prepared by adding 20 ml of distilled water to 10-d-od cultures of the test bacteria.

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