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Synthesis and Antimicrobial Evaluation of Some New Heterocyclic Compounds From Thienopyridines and Thienopyrimidine Derivatives

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***Abstract*:** 4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl pyridine-2-(1*H)*-thiones 1a,b were prepared and reacted with chloroacetonitrile to furnish 3-amino-4-aryl-2-carbamoyl-5-ethoxycarbonyl-6-methyl thieno[2,3-b]pyridine derivative 3a,b. The reaction of 3a with a variety of reagent namely, ethylenediamine, sodium azide, tri ethylorthoformate, 4-chlorobenzaldehyde, carbondisulfide and sodium nitrous acid have been carried out and their products were identified . Most of these products were subjected to further reaction to obtain heterocyclic compounds. The all synthesized derivatives displayed good Antimicrobial activities against some species of bacteria as (*E.colie, P.seudemones and S.aurous*) and some species of fungal as (*Aspergillus, Pencillium and Clado)*

Keywords: Fused heterocyclic system; pyridothienopyrimidine, pyrazolo pyridothienopyrimidine, pyridothienoditriazine and triazolopyridothieno pyrimidine.

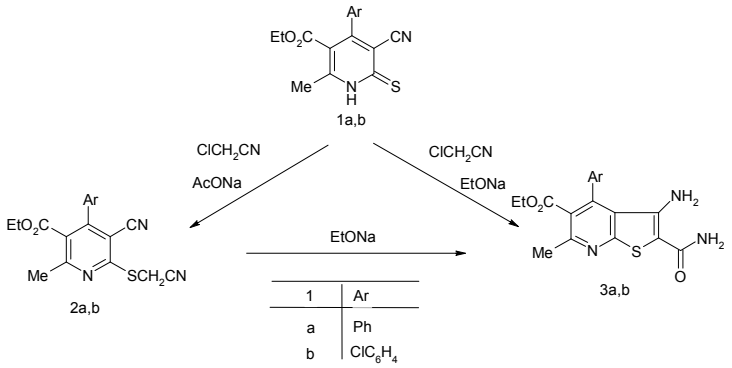
1- Introduction:

Thieno[2,3-b]pyridine ring system has proved to be an interesting class of heterocyclic (1). It has been reported that thienopyridine and pyridothieno pyrimidine derivatives extensively showed variety of activities such as , antibacterial (2-4), antimicrobial (5-6), diabetes mellitus (7-8), analgesic (9-10) and antipyretic (11). Thus, in continuation of our interest in the synthesis of heterocyclic compounds with expected biological activities (12-17), we report herein a convenient routes for the synthesis of novel heterocyclic compounds utilizing thieno pyridine and pyrazolopyridine derivatives.

2- Result and Discussion:-

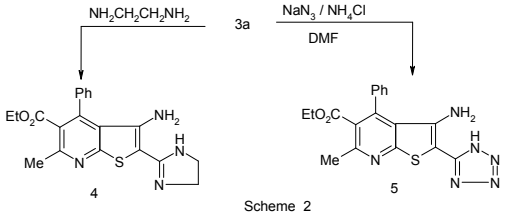
the reaction of 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-(1*H)*-thiones 1a,b with chloroacetonitrile in the presence of sodium acetate gave 2-substituted methylthio-4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl pyridines 2a,b. Upon treatment of these compounds with sodium ethoxide in ethanol, they underwent intermolecular *Thorpe-Ziegler* cyclization to furnish 3-amino-4-aryl-2-carbamoyl-5-ethoxycarbonyl-6-methylthieno

[2,3-b] pyridine 3a,b. The latter thienopyridine derivatives were also prepared *via* direct reaction of compounds 1a,b with chloro acetonitrile in the presence of excess of sodium ethoxide (17), (Scheme 1).



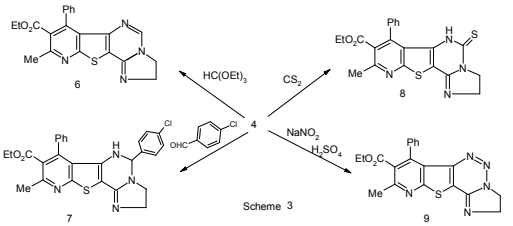
Scheme 1

The reaction of 3a with ethylenediamine gave 3-amino-2-(4,5-dihydroimidazol-2-yl)-5-ethoxycarbonyl-6-methyl-4-phenylthieno[2,3-b]pyridine (4). Treatment of 3a with sodium azide in the presence of ammonium chloride resulted in the formation of the tetrazolyl compound 5. (Scheme 2).



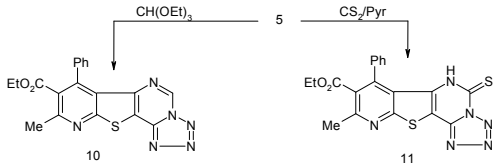
Scheme 2

The reaction of 4 with triethylorthoformate, 4-chlorobenzaldehyde and carbondisulfide gave dihydroimidazolopyridothienopyrimidine derivatives 6, 7 and 8 respectively. On treatment of 4 with sodium nitrate and sulfuric acid the dihydroimidazolopyridothienotriazine derivative 9 was obtained**.** (Scheme 3).



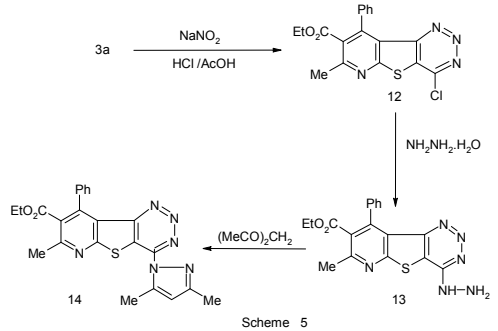
Scheme 3

In the same manner, the compound 5 was reacted with triethylorthoformate under neat conditions and carbondisulfide in pyridine refluxing condition to produce the fused tetra cycliccompounds 10 and 11 respectively. (Scheme 4).



Scheme 4

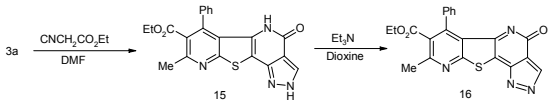
Diazotization of 3a using sodium nitrite in hydrochloric acid and acetic acid mixture gave 4-chloro-8-ethoxycarbonyl-7-methyl-9-phenyl pyrido[3`,2`:4,5]thieno[3,2-e][1,2,3]triazine (12). The reaction of 12 with hydrazine hydrate produced the hydrazinophenylpyrido thienotriazine derivative 13, which was cyclocondensed with acetylacetone to furnish the pyridothienoditriazines 14. (Scheme 5).



Scheme 5

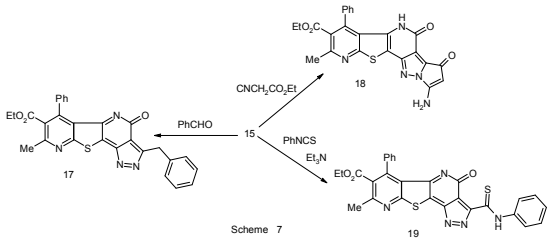
The reaction of 3a with ethylcyanoacetate in the presence of a catalyticamount of dimethyl formamide gave 8-ethoxycarbonyl-9-methyl-5-

oxo-7-phenylpyrazolo[3",4"-c]pyrido [3',2':4,5]thieno[2,3-e]pyridine (15). When the latter compound reacted with 1,4-dioxan containing amounts of triethylamine produced 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenyl pyrazolo[3",4"-c]pyrido[3',2':4,5]thieno[2,3-e] pyridine (16). (Scheme 6).



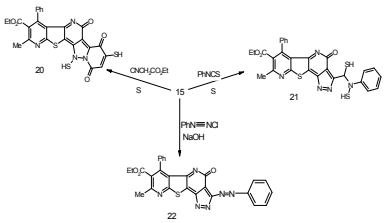
Scheme 6

The reaction of 15 with benzaldehyde produced the fused banzoylmethylpyrazolo pyridothienopyridine derivative 17. Treatment of 15 with active methylene as ethylcyano acetate, in 1,4-dioxan containing catalytic amounts of triethylamine produced amino pyrrolopyrazolopyridothienopyridines 18. Also, the interaction of compound 15 with phenylisothiocyanate in 1,4-dioxane containing catalytic amounts of triethylamine gave 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenyl-3-(phenylthiomethylamide)pyrazolo [3",4"-c]pyrido[3',2':4,5]thieno[2,3-e]pyridine (19). (Scheme 7).



Scheme 7

In the same manner, the reaction of compound 15 with ethyl cyanoacetate or phenylisothiocyanate and elemental sulfur in 1,4-dioxane containing triethylamine produced pyridothienopyridine derivative 20 and pyrazolopyridothienopyridine derivative 21 respectively. Finally, compound 15 was reacted with benzenediazonium chloride to give 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenyl-3-phenylazinopyrazolo[3",4"-c]pyrido [3',2':4,5]thieno[2,3-e]pyridine (22). (Scheme 8).



Scheme 8

3- EXPERIMENTAL

The uncorrected melting points were determined on a thermometer 360 ^{o}C. The IR spectrum were recorded on a VAR AM-2000 FT-IR scimitar series. ^{1}H-NMR spectrum were recorded with operating at 500 and 200 MHz respectively using a JEOL ECP400 NMR meter. ^{13}C-NMR spectrum were determined on DEITA-NMR ECP-400 400MHz spectrometer with tetramethylsilane (TMS). Mass spectrum were taken on Ionization Mode: EI, 70 eV and checking the homogeneity of the compounds were made by TLC (thin layer chromatography).

Synthesis of 4-aryl-3-cyano-2-cyanomethyl sulfanyl-5-ethoxycarbonyl-6-methylpyridine 2a,b.

To a suspended 4-aryl-3-cyano-5-ethoxy carbonyl-6-methylpyridine-2-(1*H)*-thiones 1a,b (20 mmol) and sodium acetate tri hydrate (3 g, 22 mmol) in ethanol (50 ml), chloro acetonitrile (20 mmol) was added. The resulting mixture was heated under reflux for 2 h . The precipitate that formed on cooling was collected and recrystallized from ethanol as pale yellow needles of compounds 2a,b.

3-Cyano-2-cyanomethylsulfanyl-5-ethoxycarbonyl-6-methyl-4-phenylpyridin 2a.

Prepared from 1a. Yield: 80 %; m.p: 120 ^{o}C. Anal. for $C_{18}H_{15}N_3O_2S$ (337.40) Calcd.: C, 64.08; H, 4.48; N,12.45 %. Found: C, 64.12; H, 4.36; N,12.28 %. The IR 9a showed two

absorption bands at 2230, 2220 cm^{-1} for (2 C≡N) and at 1735 cm^{-1} for (C=O of ester). The ^1H NMR (DMSO-d_6) at δ = 7.4 - 7.6 (m, 5H, aromatic protons), 4.0 (q, 2H, OCH_2), 3.8 (s, 2H, SCH_2), 2.6 (s, 3H, CH_3 at C_6) and 0.9 (t, 3H, CH_3 of ester) with disappearance a signal for (NH). ^{13}C NMR (DMSO-d_6) at δ =169 ($C_{amide,}$ C=O), 167($C_{ester,}$ C=O), 148 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 137 ($C_{py,}$ C_6), 128, 129($C_{ph,}$ $C_{2,3,4,5,6}$), 120 ($C_{py,}$ C_5), 118 (CN), 98 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). The mass at m/z = 337 (M^+, 60 %) and 308 (M^+-29, 100 %).

4-(4-Chlolrophenyl)-3-cyano-2-cyanomethyl sulfanyl-5-ethoxycarbonyl-6-methylpyridine 2b.

Prepared from 1b. Yield: 64 %; m.p: 130 °C. Anal. Calcd. for $C_{18}H_{14}ClN_3O_2S$ (371.85): C, 58.14; H, 3.79; N, 11.30 %. Found: C, 58.01; H, 3.58; N, 11.24 %. IR (cm^{-1}) at 2230, 2220 for (2 C≡N) and at 1735 for (C=O of ester). ^1H NMR at δ = 7.3-7.5 (m, 4H, aromatic protons), 4 (q, 2H, OCH_2), 3.8 (s, 2H, SCH_2), 2.6 (s, 3H, CH_3 at C_6) and 0.9 (t, 3H, CH_3 of ester). ^{13}C NMR (DMSO-d_6) at δ = 169 ($C_{amide,}$ C=O), 167 ($C_{ester,}$ C=O), 162 ($C_{py,}$ C_6),152 148 ($C_{py,}$ C_4), 146 ($C_{th,}$ C_2), 138 ($C_{ph,}$ C_1), 134 ($C_{ph,}$ C_4), 128, 129 ($C_{ph,}$ $C_{2,3,5,6}$), 120 ($C_{py,}$ C_5), 118 (CN), 98 ($C_{py,}$ C_3), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). Mass at m/z = 370 (M^+-1, 100 %).

Synthesis of 3-amino-4-aryl-2-carbamoyl-5-ethoxycarbonyl-6-methylthieno[2,3-b] pyridine 3a,b.

Method A

Compounds 2a,b were suspended in sodium ethoxide solution (0.12 g sodium in 30 ml abs. ethanol) and heated under reflux for 5 min. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give canary yellow needles of compounds 415a,b.

3-Amino-2-carbamoyl-5-ethoxycarbonyl-6-methyl-4-phenylthieno[2,3-b]pyridine 3a.

Prepared from 2a. Yield: 81 %; m.p: 300 °C. Anal. Calcd. for $C_{18}H_{17}N_3O_3S$ (355.42): C, 60.83;H, 4.82; N, 11.82 %. Found: C, 60.59; H, 4.68; N, 11.71 %. IR (cm^{-1}) at 3440, 3360 for (NH_2), 1700 for (C=O groups) with disappearance absorption bands for (C≡N). ^1H NMR ($CDCl_3$) at δ = 6.9 - 7.5 (m, 7H, aromatic and amid protons), 4.2 (q, 2H, OCH_2), 3.8 (s, 2H, NH_2), 2.3 (s, 3H, CH_3 at C_6) and 0.9 (t, 3H, CH_3 of ester) with disappearance a signal for (SCH_2).). ^{13}C NMR ($CDCl_3$) at δ = 169 ($C_{amide,}$ C=O), 167 ($C_{ester,}$ C=O), 158 ($C_{py,}$ C_6), 148 ($C_{py,}$ C_4), 146 ($C_{th,}$ C_2), 136 ($C_{ph,}$ C_1),137 ($C_{th,}$ C_3), 134 ($C_{ph,}$ C_4), 128, 129 ($C_{ph,}$ $C_{2,3,5,6}$), 120 ($C_{py,}$ C_5), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). Mass at m/z = 337 (M^+-18, 100 %).

3-Amino-2-carbamoyl-4-(4-chlolrophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-b] pyridine 3b.

Prepared from 2b.Yield: 80 %; m.p: 320 °C. Anal. Calcd. for $C_{18}H_{16}ClN_3O_3S$ (389.64): C, 55.46; H, 4.14; N, 10.78 %.Found: C, 55.32 ; H, 3.99; N, 10.53 %. IR (cm^{-1}) at 3440, 3360 for (NH_2), 1700 for (C=O groups) with disappearance absorption bands for (C≡N). ^1H NMR ($CDCl_3$) at δ = 7.1 - 7.7 (m, 6H, aromatic and amid protons), 3.9 - 4.1 (q&s, 4H, OCH_2 , NH_2), 2.7 (s, 3H, CH_3 at C_6) and 1.0 (t, 3H, CH_3 of ester). Mass at m/z = 371 (M^+, 95 %) and 190 (M^+-181, 100 %).

Method B

To a suspension of compounds 2a,b in sodium ethoxide solution (0.35 g sodium in 40 ml abs. ethanol), chloro acetonitrile (10 mmol) was added. The resulting mixture was refluxed for 20 min. The formed precipitate was collected and recrystallized from ethanol-chloroform mixture to give compounds 3a,b (yield; 57 - 60 %). These products were identical in all aspects to those described in method A.

Synthesis of 3-amino-2-(4,5-dihydro imidazole-2-yl)-5-ethoxycarbonyl-6-methyl-4-phenylthieno[2,3-b]pyridine (4).

To a suspension of compound 3a (1.6 g, 5 mmol) and ethylenediamine (5 ml) were heated on a water bath for 5 h. and then triturated with ethanol (10 ml). The solid that formed was collected and recrystallized from ethanol-chloroform mixture to give golden yellow crystals. Yield: 80 %; m.p: 170 ^{o}C. Anal. Calcd. for $C_{20}H_{20}N_4O_2S$ (380.46): C, 63.14; H, 5.30; N, 14.73 %. Found: C, 63.25; H, 5.19; N, 14.54 %. IR (cm^{-1}) at 3400, 3320 for (NH_2, NH) and 1720 for (C=O ester). ^{1}H NMR (DMSO-d_6) at δ = 7.2-7.5 (m, 5H, aromatic protons), 4.1(s, 3H, NH and NH_2), 4.0 (q, 2H, OCH_2), 2.7 (t, 2H, CH_2 imidazolo), 2.4 (s, 3H, CH_3 at C_6), 1.4 (t, 2H, CH_2 imidazolo) and 0.9 (t,3H, CH_3 of ester). ^{13}C NMR (DMSO-d_6) at δ = 167 ($C_{ester,}$ C=O), 165 $C_{imid,}$ C_2), 158 ($C_{py,}$ C_6), 155 ($C_{py,}$ C_3), 148 ($C_{py,}$ C_4), 126 ($C_{ph,}$ $C_{2,3,4,5,6}$), 127 ($C_{th,}$ $C_{3,4}$), 126 ($C_{th,}$ $C_{2,5}$), 60 (C, OCH_2), 53 ($C_{imid,}$ C_4), 35 ($C_{imid,}$ C_5), 129, 14 (C, $ArCH_3$) and 13(C, CH_3). Mass at m/z = 380 (M^+, 70 %) and 54 (M^+ -326, 100 %).

Synthesis of 3-amino-5-ethoxycarbonyl-6-methyl-4-phenyl-2-(1H)-tetrazol-2-yl) thieno[2,3-b]pyridine (5).

A mixture of compound 3a (1.4 g, 4 mmol), sodium azide (0.4 g, 6 mmol) and ammonium chloride (0.32 g, 6 mmol) in DMF (15 ml) was heated on a water bath for 2 h. The reaction mixture was cooled, diluted with water and acidified with dilute acetic acid. The solid that formed was collected and recrystallized from ethanol to give golden yellow crystals. Yield: 75 %; m.p: 312 ^{o}C. Anal. Calcd. for $C_{18}H_{16}N_6O_2S$ (380.42): C, 56.83; H, 4.24; N, 22.09 %. Found: C, 56.64; H, 4.06; N, 22.15%. IR (cm^{-1}) at 3430, 3350 for (NH_2, NH) and 1720 cm^{-1} for (C=O ester). ^{1}H NMR ($CDCI_3$) at δ = 8.0 (s, 1H, NH tetrazolo), 7.1 - 7.5 (m, 5H, aromatic protons), 3.9 - 4.1 (s & q, 4H, NH_2 & OCH_2), 2.4 (s, 3H, CH_3 at C_6) and 0.8 (t, 3H, CH_3 of ester). Mass at m/z = 380 (M^+, 45%) and 120 (M^+ -260, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-7-phenyl-2,3-dihydroimidazolo[1″,2″-c]pyrido [3',2':4,5]thieno[2,3-e]pyrimidine (6).

Compound 4 (0.76 g, 2 mmol) in triethylorthoformate (10 ml) was heated under reflux for 4 h. The precipitate that formed while hot was collected and recrystallized from pyridine to give of pale yellow needles. Yield: 80 %; m.p: 285 ^{o}C. Anal. Calcd. for $C_{21}H_{18}N_4O_2S$ (390.45): C, 64.59; H, 4.64; N, 14.34 %. Found: C, 64.47; H, 4.45; N, 14.28 %. IR (cm^{-1}) at 3050 for ($=CH_{aromatic}$), 2950 for ($CH_{aliphatic}$), 1718 for (C=O of ester) and 1620 for ($C=C_{aromatic}$). ^{1}H NMR ($CDCl_3$) at δ = 7.1 - 7.5 (m, 7H, aromatic and CH pyrazolo protons), 4.0 (q, 2H, OCH_2), 2.8 (t, 2H, CH_2 imidazolo), 2.4 (s, 3H, CH_3 at C_9), 1.4 (t, 2H, CH_2 imidazolo) and 1.0 (t, 3H, CH_3 of ester). Mass at m/z = 390 (M^+, 80 %) and 341 (M^+ - 49, 100 %).

Synthesis of 5-(4-chloropyenyl)-8-ethoxy carbonyl-9-methyl-7-phenyl-2,3,5,6-tetra hydroimidazolo[1″,2″-c]pyrido[3',2':4,5] thieno[2,3-e]pyrimidine (7).

A suspension of compound 4 (0.76 g, 2 mmol) and 4-chloro benzaldehyde (0.2 g, 2 mmol) in ethanol (15 ml), few drops of in piperidine was added. The reaction mixture was heated under reflux for 4 h .The solid that formed was on cooling collected and recrystallized from ethanol was collected and recrystallized from dioxane to give yellow crystals. Yield: 81 %; m.p:312 ^{o}C. Anal. Calcd. for $C_{27}H_{23}ClN_4O_2S$ (503.01): C, 64.46; H, 4.60; N, 11.13 %. Found: C, 64.28; H, 3.46; N, 11.00 %. The IR (cm^{-1}) at 3400 - 3350 for NH and 1720 for (C=O of ester). ^{1}H NMR ($CDCl_3$) at δ = 8.0 (s, 1H, NH pyrimidine), 7.1 - 7.6 (m, 11H, aromatic and CH pyrazolo protons), 4.0 (q, 2H, OCH_2), 2.7 (t, 2H, CH_2 imidazolo), 2.4 (s, 3H, CH_3 at C_9), 1.4 (t, 2H, CH_2 imidazolo) and 0.9 (t, 3H, CH_3 of ester). ^{13}C NMR (DMSO-d_6) at δ = 167($C_{ester,}$ C=O), 165 ($C_{py,}$ C_2), 158 ($C_{py,}$ C_6), 148 ($C_{py,}$ C_4), 138 ($C_{ph,}$ C_1), 134 ($C_{ph,}$ C_4), 129 ($C_{ph,}$ $C_{2,3,5,6}$), 126 ($C_{py,}$ $C_{5,6}$), 126 ($C_{th,}$ $C_{2,3}$), 122 ($C_{imid,}$ $C_{4,5}$), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13 (C, CH_3). Mass at m/z = 505 (M^++2, 20 %) and 149 (M^+ -349, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-7-phenyl-5-thioxo-2,3dihydroimidazolo [1″,2″-c]pyrido[3',2':4,5]thieno[2,3-e]pyrimidine (8).

A mixture of compound 4 (0.76 g, 2 mmol) and carbon disulphide (1 ml) in pyridine (10 ml) was heated under reflux on a water bath for 8 h. The solid that formed while hot was collected and recrystallized from DMF to give orange crystals. Yield: 65 %; m.p: 240 ^{o}C. Anal. Calcd. for $C_{21}H_{18}N_4O_2S_2$ (422.52): C, 59.69; H, 4.28; N, 13.25 %. Found: C, 59.46; H, 4.19; N, 13.16 %. IR (cm^{-1}) at 3400 - 3350 for NH and 1720 for (C=O of ester). ^{1}H NMR ($CDCl_3$) at δ = 8.0 (s, 1H, NH pyrimidine), 7.1 - 7.9 (m, 7H, aromatic and CH pyrazolo protons), 4.1 (s, 1H, NH), 3.9 (q, 2H, OCH_2), 2.7 (t, 2H, CH_2 imidazolo), 2.5 (s, 3H, CH_3 at C_9), 1.4 (t, 2H, CH_2 imidazolo) and 1.0 (t, 3H, CH_3 of ester). Mass at m/z = 422 (M^+, 95 %) and 341 (M^+ -79, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-7-phenyl-2,3-dihydroimidazolo[1″,2″-c]pyrido [3',2':4,5]thieno[2,3-e][1,2,3]triazine (9).

Sodium nitrite solution 10% (5 ml) was added to a solution of compound 4 (0.76 g, 2 mmol) in concentrated sulphuric acid (5 ml) and glacial acetic acid (5 ml) at 0 °C during 5 min. with stirring. The mixture was allowed to stand at room temperature for 30 min. The solid that precipitated on dilution with water was collected and recrystallized from ethanol as white needles. Yield: 72 %; m.p: 150 ^{o}C. Anal. Calcd. for $C_{20}H_{17}N_5O_2S$ (391.44): C, 61.36; H, 4.37; N, 17.88 %. Found: C, 61.23; H, 4.14; N, 17.57 %. IR (cm^{-1}) at 1720 for (C=O of ester) with the disappearance band of (NH_2). ^{1}H NMR ($CDCl_3$) at δ = 7.1 - 7.5 (m, 7H, aromatic and CH pyrazolo protons), 4.0 (q, 2H, OCH_2), 2.7 (t, 2H, CH_2 imidazolo), 2.5 (s, 3H, CH_3 at C_9), 1.4 (t, 2H, CH_2 imidazolo) and 0.9 (t, 3H, CH_3 of ester). Mass at m/z = 389 (M^+,15 %) and 256 (M^+ -133, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-7-phenyltetrazolo[1″,2″-c]pyrido[3',2':4,5] thieno[2,3-e]pyrimidine (10).

Compound 5 (0.76 g, 2 mmol) in triethylorthoformate (10 ml) was heated under

reflux for 3 h. and then left to cool. The precipitate that formed was collected and recrystallized from dioxane to give of pale yellow needles. Yield: 60%; m.p: 180 °C. Anal. Calcd. for $C_{19}H_{14}N_6O_2S$ (390.42): C, 58.45; H, 3.61; N, 21.53 %. Found: C, 58.38; H, 3.42; N, 21.46 %.

Synthesis of 8-ethoxycarbonyl-6-hydro-9-methyl-7-phenyl-5-thioxotetrazolo[1″,2″-c] pyrido[3',2':4,5]thieno[2,3-e]pyrimidine (11).

A mixture of compound 5 (0.76 g, 2 mmol) and carbon disulphide (1 ml) in pyridine (10 ml) was heated under reflux on a water bath for 12 h. The solid that formed while hot was collected and recrystallized from DMF to give yellow crystals. Yield: 79 %; m.p: 330 °C. Anal. Calcd. for $C_{19}H_{14}N_6O_2S_2$ (422.48): C, 54.01; H, 3.34; N,19.89 %. Found: C, 54.21; H, 3.19; N, 19.69 %. The IR (cm^{-1}) at 1720 for (C=O of ester). ^1H NMR (DMSO-d_6) at δ = 8.0 (s, 1H, CH pyrimidine), 6.7 - 7.5 (m, 5H, aromatic protons), 4.0 (q, 2H, OCH_2) and 2.4 (s, 3H, CH_3 at C_9) and 1.0 (t, 3H, CH_3 of ester). Mass at m/z= 390 (M^+, 60 %) and 97 (M^+ -293, 100 %).

Synthesis of 4-chloro-8-ethoxycarbonyl-7-methyl-9-phenylpyrido[3',2':4,5]thieno[2,3-e][1,2,3]triazine (12).

To a chilled solution of compound 3a (0.76 g, 2 mmol) in a mixture of acetic acid (10 ml) and concentrated hydrochloric acid (7 ml), a sodium nitrite solution 10% (4 ml) was added with stirring at 0 °c during 5 min. The stirring was continuing for 3 h. The formed precipitated was collected and recrystallized from ethanol-chloroform mixture to give white plated. Yield: 72 %; m.p: 200 °C. Anal. Calcd. for $C_{18}H_{13}ClN_4O_2S$ (384.84): C, 56.18; H, 3.40 ; N,14.56 %. Found: C, 55.88; H, 3.26; N,14.33 %. IR (cm^{-1}) at 3420 - 3330 for (NH) and 1712 for (C=O of ester). ^1H NMR ($CDCI_3$) at δ = 6.8 - 7.8 (5H, aromatic protons), 4.1 - 4.0 (s & q, 3H, NH, OCH_2), δ 2.3 (s, 3H, CH_3 at C_9) and 1.0 (t, 3H, CH_3 of ester). The mass at m/z = 421 (M^+-1, 60 %) and 80 (M^+ -342, 100 %).

Synthesis of 8-ethoxycarbonyl-4-hydrazino -7-methyl-9-phenylpyrido[3',2':4,5]thieno [2,3-e][1,2,3]triazine (13).

A mixture of compound 12 (0.76 g, 2 mmol) and hydrazine hydrate 99% (4 ml) in ethanol (30 ml) was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from dioxane to give yellow crystals. Yield: 70 %; m.p: 240 °C. Anal. Calcd. for $C_{18}H_{16}N_6O_2S$ (380.42): C, 56.83; H, 4.24; N, 22.09 %. Found: C, 56.62; H, 4.09; N, 22.21 %. IR (cm^{-1}) at 3450, 3400 for (NH-NH_2) and 1724 (C=O of ester). ^1H NMR $CDCI_3$ at δ = 7.1 -7.6 (m, 5H, aromatic protons), 4.2 - 4.0 (s & q, 3H, OCH_2 , NH), 2.6 (s, 3H, CH_3 at C7), 2.0 (s, 2H, NH_2) and 0.9 (t, 3H, CH_3 of ester). Mass at m/z = 380 (M+, 60 %) and 366 (M^+ -14, 100 %).

Synthesis of 4-(3,5-dimethylpyrazolo-1-yl)-8-ethoxycarbonyl-7-methyl-9-phenylpyrido [3',2':4,5]thieno[2,3-e][1,2,3]triazine (14).

A compound 13 (0.76 g, 2 mmol) and acetylacetone (2 ml, 20mmol) in ethanol (15 ml) was heated under reflux for 5 h. The precipitate that formed while hot was collected and recrystallized from ethanol-chloroform mixture as greenish crystals of 14. Yield: 30 %; m.p: 320 °C. Anal. Calcd. for $C_{23}H_{20}N_6O_2S$ (444.52): C, 62.14; H, 4.53; N,18.79 %. Found: C, 62.36; H, 4.77; N, 18.46

%. IR (cm^{-1}) at 1725 for (C=O of ester) with disappearance absorption bands of (NH_2). ^1H NMR $CDCI_3$ at δ = 7.2 -7.6 (m, 5H, aromatic protons), 4.1 (q, 2H, OCH_2), 2.7 (s, 6H, $2CH_3$ pyrazolo), 2.5 (s, 3H, CH_3 at C_7) and 0.8 (t, 3H, CH_3 of ester). Mass at m/z = 444 (M^+, 15 %) and 312 (M^+ -123, 100 %).

Synthesis of 1,6-dihydro-8-ethoxycarbonyl-9-methyl-5-oxo-7-phenylpyrazolo[3",4"-c] pyrido[3',2':4,5]thieno[2,3-e] pyridine (15).

A mixture of 3a (3.7 g,10mmol) in dimethylformamide (30ml), ethyl cyanoacetate (1.1 ml, 10 mmol) was added. The reaction mixture was heated under reflux for 5 h. The solid that formed while hot was collected and recrystallized from dioxane to give pale yellow crystals. Yield: 82 %; m.p: 330 °C. Anal. for $C_{21}H_{16}N_4O_3S$ (404.44) Calcd.: C, 62.36; H, 3.99; N, 13.85 %. Found: C, 62.11; H, 3.82; N, 13.67 %. IR (cm^{-1}) at 3420, 3320 for (2 NH), at 1716 for (C=O groups). ^1H NMR $CDCI_3$ at δ = 8.0 - 8.1 (s, 2H, NH pyrazolo and NH pyridine), 7.2 -7.6 (m, 6H, aromatic and CH pyrazolo protons), 4.0 (q, 2H, OCH_2), 2.4 (t, 3H, CH_3 at C_9) and δ 0.8 (t, 3H, CH_3 at ester). ^{13}C NMR ($CDCI_3$) at δ = 167(Cester, C=O), 165 (Cpy, C=O), 158 (Cpy, C6), 148 (Cpy, C4), 138 (Cph, C1), 133(Cpyr, $C_{3,5}$), 129 (C_{ph}, $C_{2,3,4,5,6}$), 125 (Cth, $C_{2,5}$), 122 (Cpy, $C_{3,5}$), 120 (C_{py}, C_3), 105 (C_{pyr}, C_4), 60 (OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). Mass at m/z = 404 (M^+, 90 %) and 57 (M^+ -347, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenylpyrazolo[3",4"-c]pyrido [3',2':4,5]thieno[2,3-e]pyridine (16).

A mixture of compound 15 (2 g, 5 mmol) in 1,4-dioxane (20 ml), triethylamine (1 ml) was added. The reaction mixture was heated under reflux for 5 h. and then left to cool. The precipitate that formed was collected and recrystallized from dioxane to give brown crystals of compound 16. Yield: 65 %; m.p: 322 °C. Anal. for $C_{21}H_{14}N_4O_3S$ (402.43) Calcd.: C, 62.68; H, 3.51; N, 13.92 %.Found: C, 62.55; H, 3.42; N, 13.80 %. IR (cm^{-1}) at 1716 for (C=O groups) with the disappearance absorption bands of (NH). Mass at m/z = 402 (M^+, 20 %) and 363 (M^+ -39, 100 %).

Synthesis of 3-banzoyl-8-ethoxycarbonyl-9-methyl-5-oxo-7-phenylpyrazolo[3",4"-c] pyrido[3',2':4,5]thieno[2,3-e]pyridine (17).

To a suspension of compound 15 (2 g, 5 mmol) in 1,4-dioxane (25 ml), piperidine (1 ml) and benzaldehyde (0.2 ml, 2 mmol) was heated under reflux for 5 h. The solid that formed on cooling was collected and recrystallized from dioxane to give pale yellow crystals of compound 17. Yield: 76 %; m.p: 318 °C. Anal. Calcd. for $C_{28}H_{20}N_4O_3S$ (492.55): C, 68.28; H, 4.09; N, 11.37 %. Found: C, 68.10; H, 3.87; N, 11.21 %. IR (cm^{-1}) at 1710 for (C=O groups). Mass at m/z = 493 (M^+,70 %) and 467 (M^+ -25, 100 %).

Synthesis of 3-amino-11-ethoxycarbonyl-12-methyl-5,8,-dioxo-10-phenylpyrralo [1''',2'''-b]pyrazolo[3",4"-c]pyrido[3',2':4,5] thieno[2,3-e]pyridine (18).

To a mixture 338 (2 g, 5 mmol), ethyl cyanoacetate (1 ml, 10 mmol) in 1,4-dioxane (20 ml) and triethylamine (1 ml) was added. The reaction mixture was heated under reflux for 5 h. and then left to cool. The solid that formed was collected and recrystallized from ethanol-dimethylformamide (1 : 1) mixture to give pale yellow crystals of compound 18. Yield: 85 %; m.p: 338 °C. Anal. Calcd. for

$C_{24}H_{17}N_5O_4S$ (471.49): C, 61.14; H, 3.63; N, 14.85 %. Found: C, 60.89; H, 3.49; N, 14.64 %. IR (cm^{-1}) at 3420,3350 for (NH_2), at 1720 for (C=O groups). ^1H NMR $CDCI_3$ at δ = 7.9 (s, H, NH pyridine), 7.1-7.7 (m, 7H, aromatic and NH2 protons), 5.1 (s, H, CH pyrralo), 4.0 (q, 2H, OCH_2), 2.8 (s, 3H, CH_3 at C10) and 1.3 (t, 3H, CH_3 ester). 13C NMR $CDCI_3$ at δ = 187 (C_{pyrr}, C=O),165 (C_{py}, C_3), 167(C_{ester}, C=O), 162 (C_{py}, C_6), 157 (C_{pyrr}, C_3), 158 (C_{pyr}, C_6), 138 (C_{ph}, C1), 129 (C_{ph}, $C_{2,3,4,5,6}$), 126 (C_{py}, $C_{5,6}$), 125 (C_{th}, C_3), 122 (C_{py}, $C_{2,3}$),105(C_{pyr}, C_4), 84 (C_{pyrr}, C_4), 60 (C, OCH_2), 14 (C, $ArCH_3$) and 13(C, CH_3). Mass at m/z =472 (M^++1, 60 %) and 296 (M^+ -175, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenyl-3-N-(phenylthiomethylamido) pyrazolo[3",4"-c]pyrido[3',2':4,5]thieno [2,3-e]pyridine (19).

A mixture of compound 15 (2 g, 5 mmol), phenylisothiocyanate (0.67 ml, 5 mmol) in 1,4-dioxane (20 ml) and triethylamine (1 ml) was heated under reflux for 5 h, and then left to cool. The precipitate that formed was collected and recrystallized from dimethylformamide to give pale yellow crystals. Yield: 60 %; m.p: 130 °C. Anal. for $C_{28}H_{19}N_5O_3S_2$ (537.61) Calcd.: C, 62.55; H, 3.56 ; N, 13.02 %. Found: C, 62.21; H, 3.38 ; N, 13.09 %. IR (cm^{-1}) at 3280 for (NH), at 1720 for (C=O groups). Mass at m/z = 462 (M^+ -75, 80 %) and 438 (M^+ -99, 100 %).

Synthesis of 9-ethoxycarbonyl-4-hydrothio -10-methyl-2,5,6-trioxo-8-phenylindolazino [3",4"-c]pyrido[3',2':4,5]thieno[2,3-e] pyridine (20).

A mixture of compound 15 (2 g, 5 mmol), ethyl cyanoacetate (1.1 ml, 10 mmol) in 1,4-dioxane (20 ml) with elemental sulfur (3.2 g, 10 mmol) and triethylamine (1 ml) was added. The reaction mixture was heated under reflux for 5 h. and then left to cool. The precipitate that formed was collected and recrystallized from dioxane to give brown crystals. Yield: 60 % ; m.p: 300 °C. Anal. Calcd. for $C_{25}H_{16}N_4O_5S_3$ (548.61): C, 54.73; H, 2.94; N, 10.21%. Found: C, 54.65; H, 2.64; N, 10.05 %. IR (cm^{-1}) at 1710 for (C=O groups). ^1H NMR ($CDCI_3$) at δ = 7.2 -7.4 (m, 6H, aromatic and CH at C_4 protons), 4.0 (q, 2H, OCH_2), 2.5 (s, 3H, CH_3 at C_{13}), 1.5 (s, 2H, 2SH) and 1.0 (t, 3H, CH_3 of ester). Mass at m/z = 550 (M^++2, 90 %) and 485 (M^+ -63, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenyl-3-(N-thiophenylthioamide) pyrazolo[3",4"-c]pyrido[3',2':4,5]thieno [2,3-e]pyridine (21).

To mixture of compound 15 (2 g, 5 mmol), phenylisothiocyanate (0.67 ml, 5 mmol) in 1,4-dioxane (20 ml) with elemental sulfur (3.2 gm., 10 mmol) and triethylamine (1 ml) was added. The reaction mixture was heated under reflux for 5 h. and then left to cool. The precipitate that formed was collected and recrystallized from dioxane to give dark brown crystals of compound 21. Yield: 60 %; m.p: 120 °C. Anal. Calcd. for $C_{28}H_{21}N_5O_3S_3$ (571.69): C, 58.83; H, 3.70; N, 12.25 %.Found: C, 58.58; H, 3.57; N, 12.01 %. IR (cm^{-1}) at 1710 for (C=O groups). ^1H NMR ($CDCI_3$) showed at δ = 7.2-7.4 (m, 10H, aromatic protons), 4.3 (t, H, CHS), 4.1 (q, 2H, OCH_2), 2.4 (s, 3H, CH_3 at C_9) and 1.5 (s, 2H, 2SH) and 0.9 (t, 3H, CH_3 of ester). Mass at m/z = 571 (M+, 10 %) and 256 (M^+ -315, 100 %).

Synthesis of 8-ethoxycarbonyl-9-methyl-5-oxo-7-phenyl-3-phenyldiazinopyrazolo [3",4"-c]pyrido[3',2':4,5]thieno[2,3-e] pyridine (22).

To a cold solution (0 - 5°c) of compound 15 (2 g, 5 mmol) in ethanol (20 ml) containing sodium hydroxide (1 g) and diazotized aniline was gradually added while stirring during 5 min. The formed upon cooling in ice-bath was collected and recrystallized from 1,4-dioxane to give reddish brown crystals of compound 22. Yield: 76 %; m.p: 140 °C. Anal. for $C_{27}H_{18}N_6O_3S$ (506.54) Calcd: C, 64.02; H, 3.58; N, 16.59 %.Found: C, 64.15; H, 3.36; N, 16.31 %. IR (cm^{-1}) at 1710 for (C=O groups). ^1H NMR ($CDCI_3$) at δ = 6.8 - 8.0 (m, 10H, aromatic protons), 4.0 (q, 2H, OCH_2), 2.6 (s, 3H, CH_3 at C_8) and 1.0 (t, 3H, CH_3 of ester). Mass at m/z = 507 (M^++1, 20 %) and 77 (M^+ - 429, 100 %).

3- Results

Biological activities:

Study all new compound derivative were screened in vitro for antimicrobial activity against three species of bacteria (*E.colie, P.seudemones and S.aurous*) and three fungal species of (*Aspergillus, Pencillium and Clado*) using wells method. (Table 1).

Table 1: Antibacterial and antifungals activities of some new synthesized compounds.

Com.No.	Aspergillus	Pencillium	Clado	E.colie	Pseudemones	S.aurous
1a	-	-	++	+	++	+++
1b	-	-	-	++	+++	-
2a	++	+	+	++	+	+
2b	-	++	++	-	-	+
3a	++	+	+	++	+	+
3b	++	++	++	-	-	+
4	-	++	-	+++	++	++
5	-	++	++	+++	++	++
6	++	++	++	++	++	++
7	++	-	-	++	++	++
8	++	-	-	+++	-	++
9	++	++	++	++	++	+++
10	-	+++	++	++	+++	+++
11	++	++	-	+	++	+++
12	+	++	++	++	++	++
13	-	-	++	++	++	++
14	++	-	+	+	++	+++
15	++	-	+	+	-	+++
16	++	-	+	+++	++	++
17	+	-	+	++	-	-
18	++	-	-	++	+++	+
19	++	++	+	++	+++	++
20	+++	++	+++	++	-	-
21	++	+++	+++	++	+++	-
22	++	++	+++	+	++	-

-: No activity; +: moderate activity (inhibition zone 5-10 mm); ++: strong activity (inhibition zone 11-15 mm); +++: very strong activity (inhibition zone 16-20 mm).

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تخليق وتقدير الفعالية البيولوجية لبعض المركبات الجديدة غير متجانسة الحلقة المتعلقة بمشتقات الثينوبيريدين و الثينوبيرميدين.

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المستخلص .صمم هذا البحث لتحضير بعض مشتقات ٤- اريل-٣-سينو-٥-ايثوكسي كربونيل-٢-ميثيل ثيون من تفاعله كلورو استونيتريل و نتج مشتقات ٣- امينو-٤-اريل -٢-كربواميل -٥-ايثوكسي كربونيل - ٦- ميثيل ثينو(٣,٢-ب) بيريدين ٣-ا،ب . وتفاعل ٣-ا،ب مع عديد من الكواشف مثل ايثلين امين، صوديوم ازيد ، تراي ايثيل اورثوفورمات ،٤- كلوروبنزالدهيد، كربون داي كبريد ، صوديوم نيتريل .
معظم هده النواتج مركبات غير متجانسة الحلقة. تم استنتاج بنية المركبات المحضرة حديثا من تحليل العنصر وكذلك البيانات الطيفية من (IR، H^1 NMR، C^{13} NMR والكتله الذرية). أيضا، تم اختبار دراسة الأنشطة البيولوجية لجميع المركبات التي تم توليفها في المختبر لأنشطة مضادة للميكروبات مثل بعض انواع البكتيريا و الفطريات حيث كان لها تاثيرات مختلفة .