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RESEARCH ARTICLE

Synthesis, Reactions and Biological Evaluation of Novel 7-Thioxo-pyrido[2,3-*d*][1,2,3]triazine Derivatives Bearing Sulfonamide Moiety

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Abstract

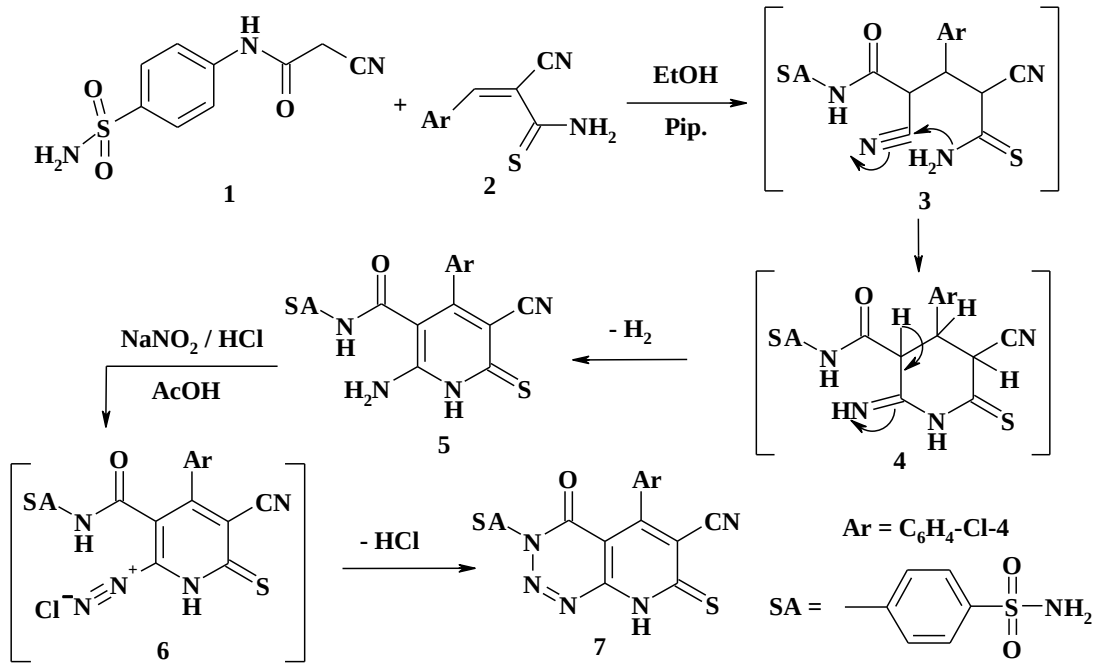
7-Thioxopyrido[2,3-*d*][1,2,3]triazine derivative bearing sulfonamide moiety was synthesized and reacted with different reagents to afford thieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]triazines, oxazinothienopyrido-triazines, pyrimidothienopyridotriazines, pyridazinothienopyridotriazines, pyrazolopyridotriazin-6-amine and pyridazinopyrazolopyridotriazines. The biological evaluation of Sixteen of the newly synthesized compounds was screened as antimicrobial compounds.

Introduction:-

Pyridotriazine derivatives have been found to possess fungicides[1], molluscicidal[2], inhibitors of vascular endothelial growth factor receptor-2[3], anti-inflammatory[4], antimicrobial[5], Phosphodiestarase 10A inhibitors[6] activities. Moreover, Aromatic sulfonamide derivatives exhibit a wide range of bioactivities, including antimicrobial[7], antitumor[8], anti-Alzheimer[9], anticancer[10,11], radiosensitizing[11] Antimalarial[12], anti-hepatitis C virus[13], anti-diabetic[14] activities. All these findings and continuation of our program in the synthesis and biological evaluation of heterocyclic derivatives[15-19], encouraged us to explore the synthesis of new pyridotriazines containing sulfonamides moieties and examine their antimicrobial activities. Incorporation sulfonamide moiety with pyridotriazine moiety may be enhanced the biological activities of the new synthesized compounds.

Results and Discussion:-

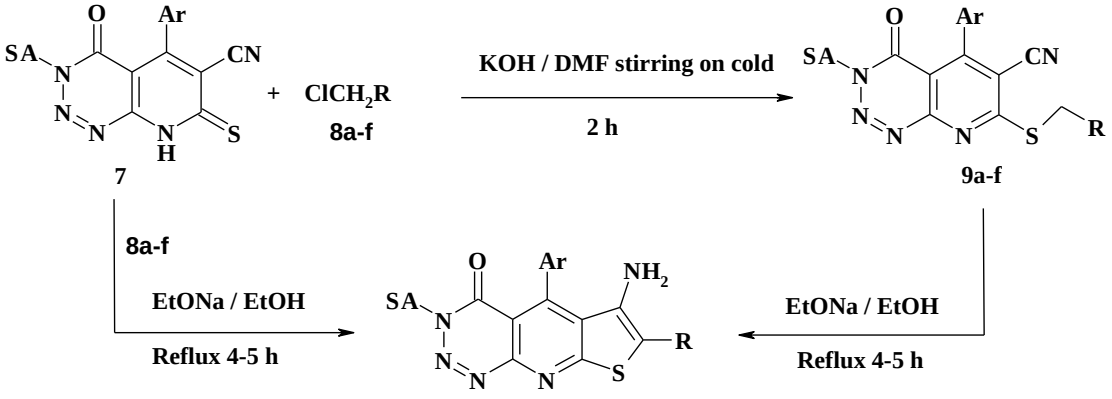
The reaction of 2-cyano-*N*-(4-sulfamoylphenyl)acetamide (**1**)[20] with 3-(4-chlorophenyl)-2-cyanoprop-2-enethioamide (**2**) in ethanol containing few drops of piperedine under reflux afforded the corresponding 2-amino-5-cyano-6-thioxopyridine-3-carboxamide derivative bearing sulfonamide moiety **5**, the structure of **5** was elucidated based on elemental analysis and spectral data. The ^{1}H NMR spectrum of 5 indicated the presence of signals at δ = 7.22, 7.36-7.76, 10.06 and 13.22 ppm due to -SO_2NH_2, NH_2 and two NH protons. (experimental part). Diazotization of **5** using sodium nitrite, hydrochloric acid and acetic acid mixture yielded 6-cyano-7-thioxopyrido[2,3-*d*][1,2,3]triazine-3-ylbenzenesulfonamide derivative **7**, via loss of hydrochloric acid molecule from the nunisolable intermediate diazonium salt **6**, the structure **7** was elucidated based on elemental analysis and spectral data (scheme 1).



Scheme 1: synthesis of 7-thioxopyridotriazine

The ^{1}H NMR spectrum of 7 indicated the absence of the signal due to NH and NH_2 protons in **5** at δ = 10.06 and 7.36-7.76 ppm respectively, and presence of signals at δ = 7.24, 13.22 ppm due to -SO_2NH_2 and NH.

The 7-thioxopyridotriazine derivative **7** was taken as a starting to synthesized new fused biologically active heterocyclic derivatives. Thus, the reaction of 7 with chloroacetonitrile (**8a**) in KOH/DMF solution under stirring at room temperature to give the 7-[(cyanomethyl)thio]- pyrido[2,3-*d*][1,2,3]triazine derivative **9a**. The IR spectrum of **9a** indicated the presence of two cyano function groups at ν = 2220 and 2202 cm^{-1}, and its ^{1}H NMR spectrum revealed the signals of -SCH_2 protons at δ = 4.72 ppm and disappearance of the signal of NH proton of compound 7 (δ = 13.22 ppm) (scheme 2).



8-10a, R = CN,
b, R = COOEt
c, R = COOH
d, R = $COCH_3$
e, R = CONH-C_6H_4-SO_2NH_2
f, R = CONH-C_6H_4-SO_2NH-pyrimidin-2-yl

7,9,10, Ar = C_6H_4-Cl-4; SA = C_6H_4-SO_2NH_2-4

Scheme 2: stnthesis of thienopyridotriazines 10a-f

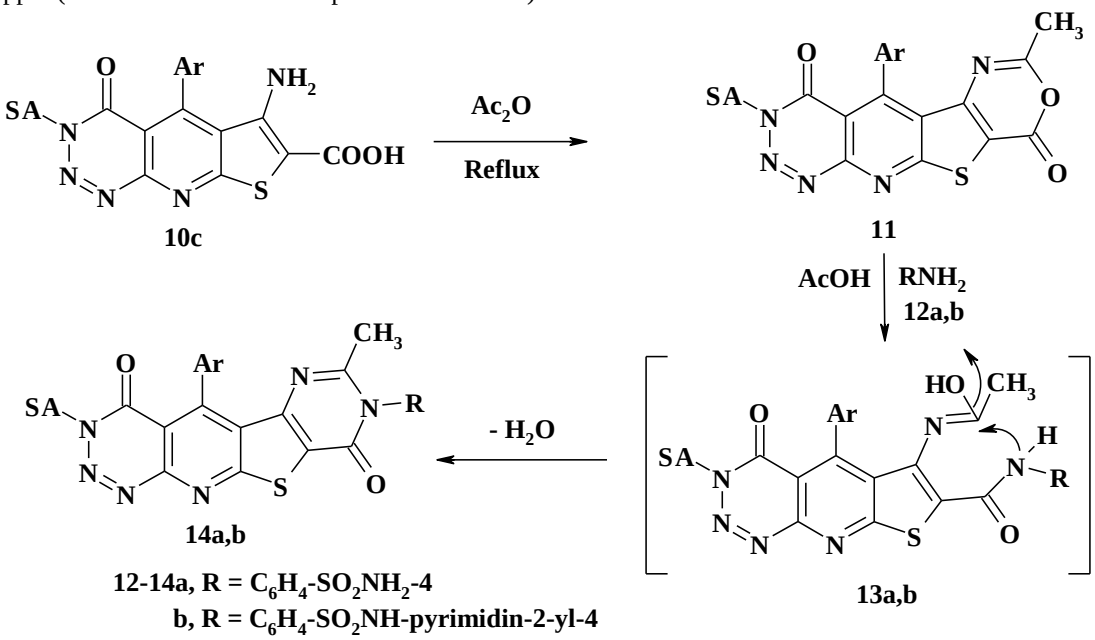
Similarly, compound **7** reacted with the halocompounds 8b-f afforded the corresponding 7-alkylthiopyrido[2,3-*d*][1,2,3]triazine derivative **9b-f** in good yield. The structures of 9b-f were confirmed based on elemental analysis and spectral data (scheme 2 and experimental section).

The structures of **9a–f** were further elucidated via their cyclization into the corresponding 6-aminothieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]triazine
derivatives **10a–f** upon treatment with ethanolic sodium ethoxide under reflux. The structures of **10a–f** were confirmed based on elemental analysis and spectral data. The IR spectra of **10a–f** indicated the absence of CN group instead of the newly born NH_2 group was detected in compounds **10b-f** and presence of only one CN in **10a**, while its ^{1}H NMR spectra revealed the protons of the newly NH_2 and absence of any signals that might be attributed to SCH_2 protons (see Scheme 2 and the Experimental section).

Unequivocal support for the structures of **10a–f** was achieved via its synthesis through an alternate route via the reaction between **7** and **8a-f** in ethanolic sodium ethoxide solution under reflux to give the same reaction products **10a**–**f** as described above (see Scheme 2 and the Experimental section).

Compound **10c** reacted with acetic anhydride under reflux to afford [1,3]oxazino[4″,5″:4′,5′]thieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]benzenesulfonamide derivative **11**. The IR spectrum of the reaction product showed the absorption bands of one NH_2 and two carbonyl groups at ν = 3237, 3103 and 1722 , 1660 cm^{-1} respectively, while its ^{1}H NMR spectrum revealed the disappearance of one NH_2 and OH protons and the signal of the -CH_3 protons were detected at δ = 3032 ppm (see Scheme 3 and the Experimental section).

The reaction of **11** with 4-aminobenzenesulfonamide derivatives **12a,b** in glacial acetic acid under reflux afforded the corresponding pyrimidothienopyridotriazine derivatives **14a,b**. The structures of 14a,b were confirmed based on elemental analysis and spectral data, the ^{1}H NMR spectrum of 14b revealed the signal of NH protons at δ = 11.82 ppm (see Scheme 3 and the Experimental section).

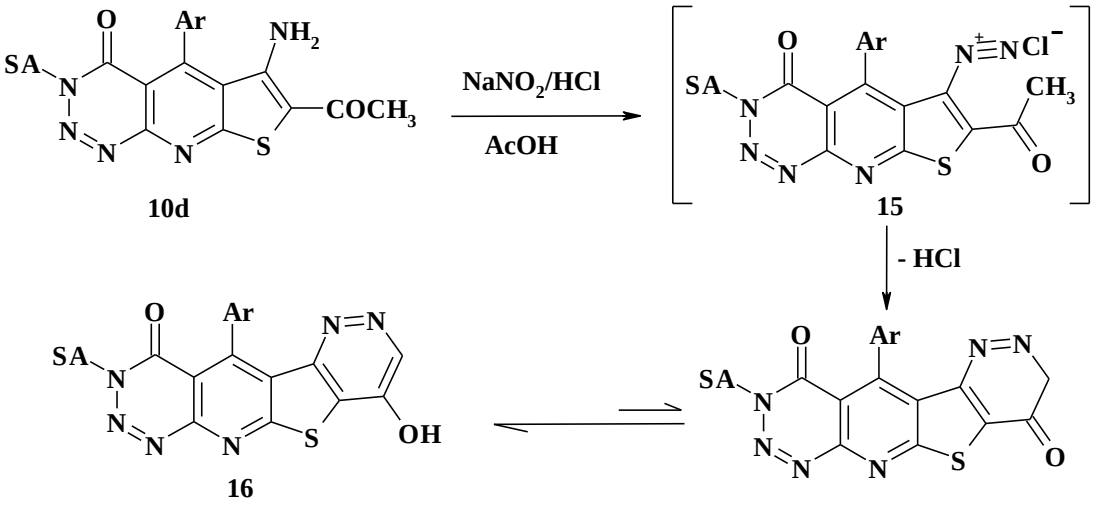


12-14a, R = C_6H_4-SO_2NH_2-4
b, R = C_6H_4-SO_2NH-pyrimidin-2-yl-4

10c, 11, 13a,b, 14,b; Ar = C_6H_4-Cl-4; SA = C_6H_4-SO_2NH_2-4

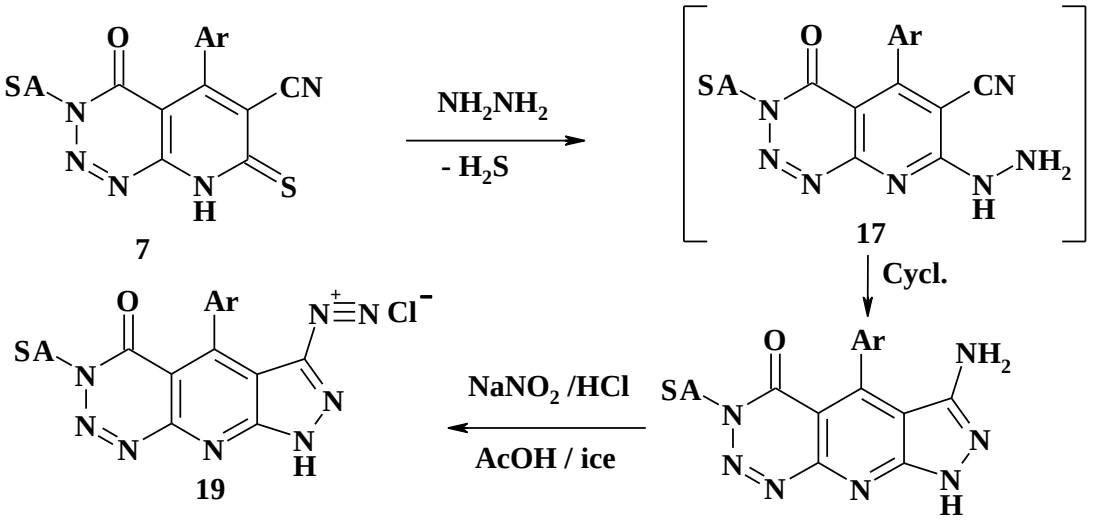
Scheme 3: synthesis of pyrimidothienopyridotriazines 14a-b

Diazotization and self coupling of **10d** afforded the 9-hydroxy-pyridazinothienopyridotriazine derivative **16**. The ^{1}H NMR spectrum of **16** revealed a broad signal at δ = 12.4 ppm which may be attributed to OH proton and absence of any signals may be attributed to CH_2 protons, the above data enhance the enol form of compound **16** rather than the keto form (see Scheme 4 and the Experimental section).



Scheme 4: synthesis of pyridazinothienopyridotriazine 16

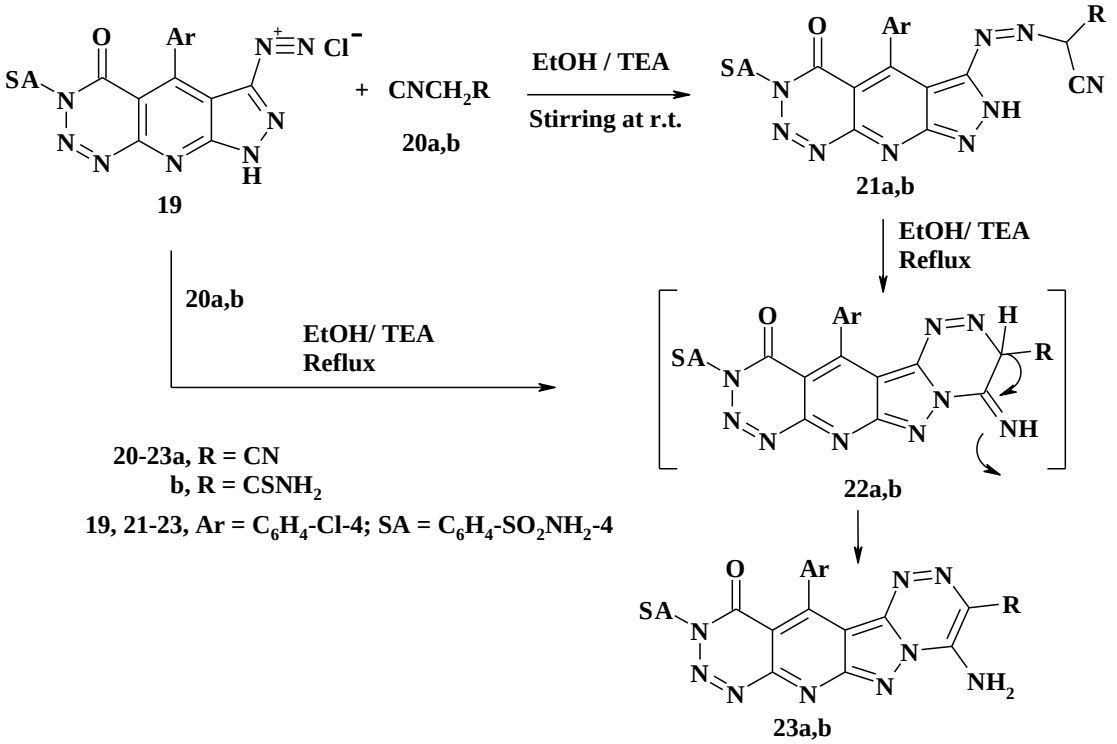
Treatment of **7** with hydrazine hydrate under reflux afforded the corresponding 4-[6-amino-5-(4-chlorophenyl)-4-oxo-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-3-yl]benzenesulfonamide (**18**), the structure of **18** was elucidated based on elemental analysis and spectral data. Thus its IR spectrum revealed the absorption bands due to two NH_2 and NH, and absence of any absorption bands may be attributed to CN function group, while its 1H NMR revealed the signal of the newly born NH_2 at δ = 4.90 ppm (see Scheme 4 and the Experimental section).
Compound **18** upon diazotization afforded the stable isolated[17] 5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-4,8-dihydro-3*H*-pyrazolo-[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazine-6-diazonium chloride (**19**) (see Scheme 5 and the Experimental section).



Scheme 5: synthesis of pyrazolopyridotriazine derivatives 18 and 19

The diazonium salt **19** reacted with malononitrile (**20a**) in ethanol triethylamine (TEA) solution under stirring at room temperature yielded 4-{5-(4-chlorophenyl)-6-[(dicyanomethyl)diazenyl]-4-oxo-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-3-l}benzenesulfonamide (**21a**), which its IR spectrum indicated the presence of the absorption band at ν = 2209 cm^{-1} due to CN function group, while its ^{1}H NMR spectrum indicated

the signal of only one NH at δ = 13.12 ppm. These data enhance the azo form of compound **21a** rather than the hydrazo form (see Scheme 6 and the Experimental section).
Similarly, **19** reacted with 2-cyanoethanethioamide (**20b**) to give pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-6-ylethanthioamide derivative **21b** (see Scheme 6 and the Experimental section).
Compounds **21a,b** underwent cyclization into the corresponding [1,2,4]triazinopyrazolopyrido[1,2,3]triazine derivatives **23a,b** via reflux their solutions in ethanol/TEA. Compounds **23a,b** were formed via nucleophilic addition of the nitrogen into the carbon of the cycno group in **21a,b** to give the nunisolable intermediate **22a,b** which aromatized forming the final products **23a,b** (see Scheme 6 and the Experimental section).



Scheme 6: synthesis of triazinopyrazolopyridotriazines 23a,b

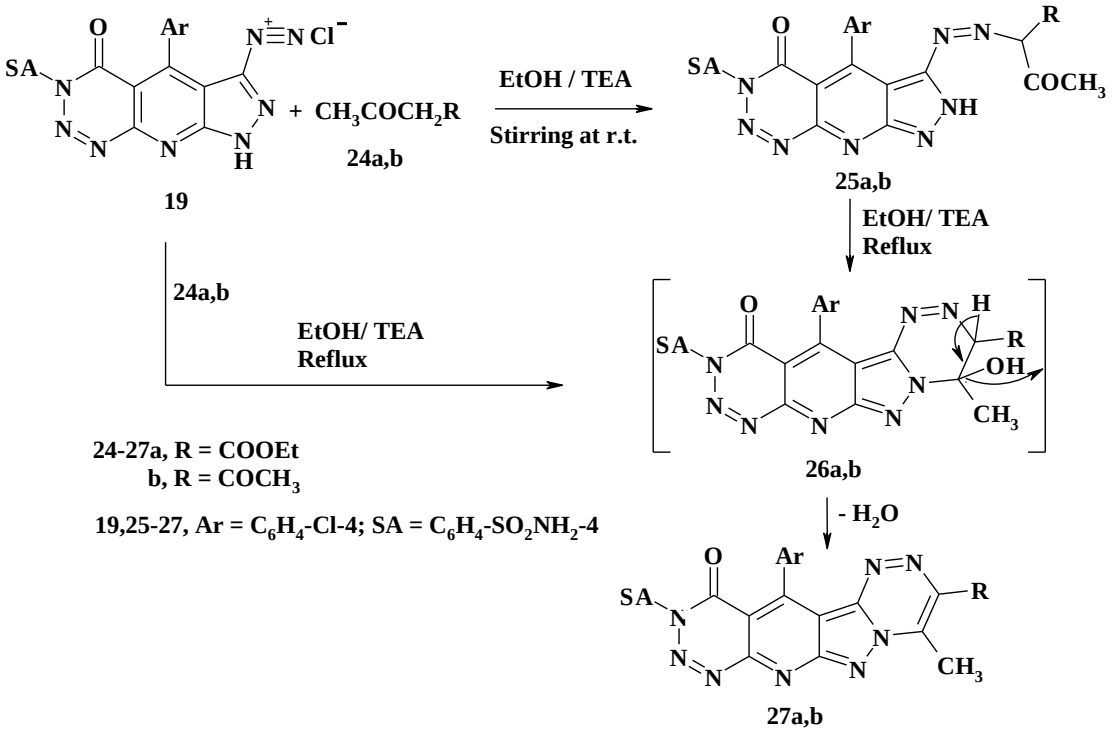
The elemental and spectral analyses were found in good agreement with the assigned structures **23a,b**. The IR spectrum of **23b** revealed the absence of any absorption bands may be attributed to the cyano function group, while its ^{1}H NMR revealed the presence of three signals at δ = 3.63, 6.59 and 7.32 ppm may be attributed to 3NH_2 protons.

Compounds **23a,b** can also be prepared by conducting the reaction directly between **19** and **20a,b** under reflux in ethanol triethylamine (TEA) solution. Compounds **23a,b** prepared via this way were found identical in all aspects with the **23a,b** prepared previously.

Coupling of the diazonium salt **19** with ethyl 3-oxobutanoate (**24a**) and pentane-2,4-dione (**24b**) with stirring at room temperature in ethanol triethylamine (TEA) solution yielded the hydrazo form **25a,b**. The IR spectrum of **25a** indicated the presence of three absorption bands at ν = 1734, 1713 and 1663 cm^{-1} for three C=O function group, while its ^{1}H NMR spectrum indicated the presence of only one signal may be attributed to NH proton at δ = 12.66 ppm. Also the IR and 1H NMR spectrum of **25b** were found in good agreement with the assigned structures (see Scheme 7 and the Experimental section).

In the same manner, cyclization of **25a,b** into the corresponding [1,2,4]triazinopyrazolo-pyrido[1,2,3]triazine derivatives **27a,b** was achieved via reflux their solutions in ethanol/TEA. The ^{1}H NMR spectrum of 27a indicated the presence of the signals of -OCH_2CH_3 at δ = 1.21-1.28 ppm as triplet (J = 7.2 Hz) and 4.16-4.26 ppm as quartet (J

= 7.2 Hz), this indicated that cycliztion of **25a** into **27a** proceeded through loss of one molecule of water (see Scheme 7 and the Experimental section).



Scheme 7: synthesis of triazinopyrazolopyridotriazines 27a,b

Compounds **27a,b** can also be prepared by conducting the reaction directly between **19** and **24a,b** under reflux in ethanol triethylamine (TEA) solution. Compounds **27a,b** prepared via this way were found identical in all aspects with the **27a,b** prepared previously (see Scheme 7 and the Experimental section).

Biological Activity:-

Sixteen of the newly synthesized compounds were screened for their in vitro antibacterial activities against Gram positive bacteria; Staphylococcus aureus (G +ve), Gram negative bacteria; Pseudomonas aeruginosa (G -ve) and for their Antifungal activities against Aspergillus

Niger and Fusarium Oxysporum by the agar diffusion technique[21]. 1 mg/ml solution in dimethylformamide (DMF) was used. The bacteria are maintained on nutrient agar. DMF showed no inhibition zones. The agar media were inoculated with different microorganism's culture tested after 24 hours of inoculation at 37 °C for bacteria and for antifungal tested after 72 hours of inoculation at 28 °C. The diameter of inhibition zone (cm) was measured. The data obtained is summarized in table (1).

The results indicated that most of the tested compounds exhibit slightly, moderately to highly active against bacteria but are slightly to moderately active against fungi. Compound **10a**, was found to be highly active against Staphylococcus aureus (G +ve) and moderately active against Pseudomonas aeruginosa (G -ve) bacteria, while compound **14a** to be highly active against Pseudomonas aeruginosa (G -ve) bacteria.

Experimental:-

Melting points were measured with a Gallenkamp apparatus and are uncorrected.. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm-1). The ^{1}H NMR spectra were recorded in DMSO-d6 at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Elemental analysis were carried out by the Micro analytical Research Center, Faculty of Science, Cairo University. Compound **1** was prepared according literature procedure[20].

Synthesis of 2-Amino-4-(4-chlorophenyl)-5-cyano-*N*-(4-sulfamoyl-phenyl)-6-thioxo-1,6-dihydropyridine-3-carboxamide (5):-

A mixture of **1** (10 mmol) and **2** (10 mmol) in ethanol (30 ml) containing a catalytic amount of piperidine (0.5 ml) was heated under reflux for 6 h, then cooled. The solid product that formed was collected by filtration, dried and crystallized from ethanol to give **5** as yellow crystals, (87%), m.p. 252 ◦C, IR υ (cm^{-1}): 3436, 3186 ($2NH_2$ and 2NH), 2202 (CN), 1645 (CO). ^{1}H NMR (DMSO-*d*6): δ 7.22 (s, 2H, NH_2), 7.36 (s, 2H, NH_2), 7.46–7.78 (m, 8H, Ar–H), 10.06 (s, 1H, NH) and 13.24 (s, 1H, NH). Anal. for $C_{19}H_{14}ClN_5O_3S_2$ (459.92): Calcd.: C, 49.62; H, 3.07; Cl, 7.71; N, 15.23; S, 13.94 %. Found: C, 49.85; H, 3.27; Cl, 7.50; N, 15.46; S, 13.70 %.

Table (1): Antimicrobial activity of some newly synthesized compounds

Compound no.	Staphylococcus aureus (G +ve)	Pseudomonas aeruginosa (G -ve)	Aspergillus niger (fungi)	Fusarium Oxysporum (fungi)
5	++	++	-	+
7	+	+	-	-
9a	++	+	+	+
9d	-	++	-	+
9e	-	+	+	-
10a	+++	++	-	+
10d	-	-	+	+
10e	+	+	+	-
11	+	+	+	++
14a	-	+++	+	-
16	+	-	++	-
18	+	-	+	-
21a	++	+	-	+
23a	++	-	-	-
25a	-	++	+	-
27a	++	-	++	-
DMF	-	-	-	-
Chloramp-henicol	+++	+++	-	-
Clotrima-zole	-	-	+++	+++

Inhibition Zone = 0.1 - 0.5 cm beyond control = + (slightly active); Inhibition Zone = 0.6 - 1.0 cm beyond control = + + (moderately active); Inhibition Zone = 1.1 - 1.5 cm beyond control = + + + (highly active); Inhibition Zone = 0.0 cm beyond control = − (inactive).

Synthesis of compounds 7, 16 and 19

General procedure:-

A solution of each of compounds **5, 10d and 18** (10 mmol) in acetic acid (20 ml) containing 2mL of concentrated HCl was stirred in an ice bath and then a cold saturated solution of 15 mmol of sodium nitrite in water was added. The reaction mixture was stirred for 1 h and the solid product thus formed was filtered off, washed with water and crystallized from the proper solvent to give compounds 7, 16 and 19 respectively.

4-[5-(4-Chlorophenyl)-6-cyano-4-oxo-7-thioxo-7,8-dihydropyrido-[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]benzenesulfonamide (7):

It obtaine from dioxane as brown crystals (74%), m.p.283°C, IR υ (cm^{-1}): 3403, 3349 3364 (NH_2 and NH), 2222 (CN) and 11686 (CO). ^{1}H NMR (DMSO-*d*6): δ 7.24 (s, 2H, NH_2), 7.34-7.65 (m, 8H, Ar-H) and 13.22 (s, 1H, NH). Anal. for $C_{19}H_{11}ClN_6O_3S_2$ (470.91): Calcd.: C, 48.46; H, 2.35; Cl, 7.53; N, 17.85; S, 13.62 %. Found: C, 48.75; H, 2.60; Cl, 7.20; N, 17.66; S, 13.95 %.

Synthesis of 9a-f:- General procedure:-

A mixture of compound **7** (10 mmol) and each of the compounds **8a**–**f** (10 mmol) in DMF (50 ml) containing KOH (12 mmol) were stirred at room temperature for 2 h, then poured onto ice-cold water and acidified with dil. HCl. The solid products were filtered off, washed with water and crystallized from ethanol to give compounds **9a**–**f**, respectively.

4-[5-(4-chlorophenyl)-6-cyano-7-[(cyanomethyl)thio]-4-oxopyrido-[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]benzenesulfonamide (9a):

Yellow crystals (72%), m.p.215ºC, IR υ (cm^{-1}): 3384, 3264 (NH_2), 2220, 2202 (2CN) and 1664 (CO). ^{1}H NMR (DMSO-*d*6): δ 4.72 (s, 2H, CH_2), 6.75 (s, 2H, NH_2) and 7.48-7.02 (m, 8H, Ar-H). Anal. for $C_{21}H_{12}ClN_7O_3S_2$ (509.94): Calcd.: C, 49.46; H, 2.37; Cl, 6.95; N, 17.85; S, 12.58 %. Found: C, 49.85; H, 2.65; Cl, 7.20; N, 17.56; S, 12.85 %.

Ethyl {[5-(4-chlorophenyl)-6-cyano -4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydropyrido[2,3-*d*][1,2,3]triazin-7-yl]thio}acetate (9b):

Yellow crystals (80%), m.p.207ºC, IR υ (cm^{-1}):3245, 3067 (NH_2), 2222 (CN), 1725 (CO-ester) and 1675 (ring-CO). ^{1}H NMR (DMSO-*d*6): δ 1.04-1.09 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 4.18-4.31(q, 2H, $O\underline{CH_2}CH_3$, J = 7.2 Hz), 5.65 (s, 2H, SCH_2CO) and 7.58-7.73 (m, 10H, Ar-H and NH_2). Anal. for $C_{23}H_{17}ClN_6O_5S_2$ (557): Calcd.: C, 49.60; H, 3.08; Cl, 6.36; N, 15.09; S, 11.51 %. Found: C, 49.89; H, 2.79; Cl, 6.10; N, 15.36; S, 11.75 %.

{[5-(4-Chlorophenyl)-6-cyano-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydropyrido[2,3-*d*][1,2,3]-triazin-7-yl]thio}acetic acid (9c)

Yellow crystals (71%), m.p.220ºC, IR υ (cm^{-1}): 3500-2500 (br. OH), 3359, 3256 (NH_2), 2212 (CN), 1724 (CO-acid) and 1666 (ring-CO). ^{1}H NMR (DMSO-*d*6): δ 5.45 (s, 2H SCH_2CO), 7.31-7.56 (m, 10H, Ar-H and NH_2) and 13.54 (s, 1H, COOH). Anal. for $C_{21}H_{13}ClN_6O_5S_2$ (528.94): Calcd.: C, 47.68; H, 2.48; Cl, 6.70; N, 15.89; S, 12.12 %. Found: C, 47.79; H, 2.73; Cl, 6.96; N, 15.56; S, 12.55 %.

4-[5-(4-Chlorophenyl)-6-cyano-4-oxo-7-[(2-oxopropyl)thio]pyrido-[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]benzenesulfonamide (9d):

Yellow crystals (75%), m.p.230ºC, IR υ (cm^{-1}): 3283, 3104 (NH_2), 2216 (CN), 1715 ($COCH_3$) and 1677 (ring-CO). ^{1}H NMR (DMSO-*d*6): δ 2.87 (s, 3H, CH_3), 4.32 (s, 2H, SCH_2CO), 7.38 (s, 2H, NH_2) and 7.46-7.79 (m, 8H, Ar-H). Anal. for $C_{22}H_{15}ClN_6O_4S_2$ (526.97): Calcd.: C, 50.14; H, 2.87; Cl, 6.73; N, 15.95; S, 12.17%. Found: C, 50.39; H, 2.53; Cl, 6.96; N, 15.58; S, 12.43 %.

2-{[5-(4-Chlorophenyl)-6-cyano-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydropyrido[2,3-*d*][1,2,3]-triazin-7-yl]thio}-*N*-(4-sulfamoylphenyl)-acetamide (9e):

Yellow crystals (77%), m.p.224ºC, IR υ (cm^{-1}): 3367, 3350, 3283, 3245 ($2NH_2$ and NH), 2223 (CN), 1695, 1665 (2CO). ^{1}H NMR (DMSO-*d*6): δ 4.15 (SCH_2CO), 6.95, (s, 2H, NH_2), 7.07 (s, 2H, NH_2), 7.52- 8.07 (m, 12H, Ar-H) and 11.74 (s, 1H, NH). Anal. for $C_{27}H_{19}ClN_8O_6S_3$ (683.13): Calcd.: C, 47.47; H, 2.80; Cl, 5.19; N, 16.40; S, 14.08%. Found: C, 47.19; H, 2.56; Cl, 5.46; N, 16.68; S, 14.39 %.

2-{[5-(4-Chlorophenyl)-6-cyano-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydropyrido[2,3-*d*][1,2,3]-triazin-7-yl]thio}-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]acetamide (9f):

Yellow crystals (76%), m.p.233ºC, IR υ (cm^{-1}): 3420, 3338, 3225 (NH_2 and 2NH), 2203 (CN) and 1654, 1629 (2CO). ^{1}H NMR (DMSO-*d*6): δ 4.31 (SCH_2CO), 7.34, (s, 2H, NH_2), 7.53- 8.10 (m, 15H, Ar-H), 11.71(s, 1H, NH) and 13.15 (s, 1H, NH). Anal. for $C_{31}H_{21}ClN_{10}O_6S_3$ (761.20): Calcd.: C, 48.91; H, 2.78; Cl, 4.66; N, 18.40; S, 12.64%. Found: C, 48.69; H, 2.46; Cl, 4.42; N, 18.69; S, 12.37 %.

Synthesis of 10a-f: general procedure:

Method A: A solution of each of the compounds **9a**–**f** (10 mmole) in ethanolic sodium ethoxide (10 m mole of Na in 50 mL ethanol), was heated under reflux for 4-5 hours, then cooled and poured onto ice-cold water and acidified with dil. HCl. The solid products were filtered off, washed with water and crystallized from the proper solvent to give compounds **10a**–**d**, respectively.

Method B: A solution of each of the compounds **7** (10 mmole) in ethanolic sodium ethoxide (10 m mole of Na in 50 mL ethanol), and each of the compounds **8a-f** (10 mmole) was heated under reflux for 4-5 hours, then cooled and poured onto ice-cold water and acidified with dil. HCl. The solid products were filtered off, washed with water and crystallized from the proper solvent to give compounds **10a**–**d**, respectively.

4-[6-Amino-5-(4-chlorophenyl)-7-cyano-4-oxo-3,4-dihydrothieno-[3',2':5,6]pyrido[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]benzenesulfonamide (10a):

Yellow crystals from ethanol/dioxane mixture (63%), m.p. 290ºC, IR υ (cm^{-1}): 3432, 3196 (2 NH_2), 2207 (CN), and (CO). ^{1}H NMR (DMSO-*d*6): δ 5.58 (s, 2H, NH_2) and 7.05-7.49 (m, 10H, Ar-H and NH_2). Anal. for $C_{21}H_{12}ClN_7O_3S_2$ (509.94): Calcd.: C, 49.46; H, 2.37; Cl, 6.95; N, 17.85; S, 12.58 %. Found: C, 49.22; H, 2.18; Cl, 6.70; N, 17.58; S, 12.35 %.

Ethyl 6-amino-5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydrothieno[3',2':5,6]-pyrido[2,3-*d*][1,2,3]triazine-7-carboxylate (10b):

Brown crystals from dioxane (60%), m.p. 248ºC IR υ (cm^{-1}): 3370, 3252 ($2NH_2$), 1675 (CO-ester) and 1635 (ring-CO). ^{1}H NMR (DMSO-*d*6): δ 1.22-1.26 (t, 3H, $OCH_2\underline{CH_3}$, J = 7.2 Hz), 4.15-4.42(q, 2H, $O\underline{CH_2}CH_3$, J = 7.2 Hz), 7.30(s, 2H, NH_2) and 7.38-7.8.01 (m, 10H, Ar-H and NH_2). Anal. for $C_{23}H_{17}ClN_6O_5S_2$ (557): Calcd.: C, 49.60; H, 3.08; Cl, 6.36; N, 15.09; S, 11.51 %. Found: C, 49.87; H, 3.35; Cl, 6.62; N, 15.40; S, 11.25 %.

6-Amino-5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydrothieno[3',2':5,6]-pyrido[2,3-*d*][1,2,3]triazine-7-carboxylic acid (10c):

It was obtained as brown crystals from ethanol /Dioxane, yield 66%; mp 282◦C, IR υ (cm^{-1}): 3450-2500 (br. OH), 3463, 3216,3193 ($2NH_2$), 1735 (CO-acid) and 1671 (ring-CO). ^{1}H NMR (DMSO-*d*6): δ 6.24 (s, 2H NH_2), 7.01 (s, 2H NH_2), 7.18-7.80 (m, 8H, Ar-H) and 8.56 (s, 1H, OH). Anal. for $C_{21}H_{13}ClN_6O_5S_2$ (528.94): Calcd.: C, 47.68; H, 2.48; Cl, 6.70; N, 15.89; S, 12.12 %. Found: C, 47.40; H, 2.21; Cl, 6.30; N, 15.60; S, 12.40 %.

4-[7-Acetyl-6-amino-5-(4-chlorophenyl)-4-oxo3,4-dihydrothieno-[3',2':5,6]pyrido-[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]benzenesulfonamide (10d):

It was obtained as brown crystals from DMF/ethanol, yield 64%; mp 285°C, , IR υ (cm^{-1}): 3436, 3218, 3198 $2(NH_2)$ and 1727, 1677 (2CO). ^{1}H NMR (DMSO-*d*6): δ 2.25 (s, 3H, CH_3), 7.37 (s, 2H, NH_2) and 7.49 -7.79 (m, 10H, Ar-H and NH_2). Anal. for $C_{22}H_{15}ClN_6O_4S_2$ (526.97): Calcd.: C, 50.14; H, 2.87; Cl, 6.73; N, 15.95; S, 12.17%. Found: C, 50.42; H, 2.49; Cl, 6.48; N, 15.65; S, 12.33 %.

6-amino-5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-*N*-(4-sulfamoylphenyl]-3,4-dihydrothieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]-triazine-7-carboxamide (10e):

It was obtained as brown crystals from EtOH/ dioxane, yield 69%; mp 268◦C, IR υ (cm^{-1}): 3327, 3253, 3177, 3107 ($3NH_2$ and NH) and 1699, 1667 (2CO). ^{1}H NMR (DMSO-*d*6): δ 5.88, (s, 2H, NH_2), 7.22 (s, 2H, NH_2), 7.31- 7.87 (m, 14H, Ar-H and NH_2) and 9.59 (s, 1H, NH). Anal. for $C_{27}H_{19}ClN_8O_6S_3$ (683.13): Calcd.: C, 47.47; H, 2.80; Cl, 5.19; N, 16.40; S, 14.08%. Found: C, 47.76; H, 2.50; Cl, 5.50; N, 16.63; S, 14.36 %.

6-amino-5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-*N*-[4-(pyrimidin-2-ylsulfamoyl)-phenyl]-3,4-dihydrothieno[3',2':5,6]-pyrido[2,3-*d*][1,2,3]triazine-7-carboxamide (10f):

It was obtained as brown crystals from DMF/ethanol, yield 62%; mp 294°C, IR υ (cm^{-1}): 3422, 3254, 3212, 3155 ($2NH_2$ and 2NH), and 1667, 1627 (2CO). ^{1}H NMR (DMSO-*d*6): δ 6.20 (s, 2H, NH_2), 7.30 (s, 2H, NH_2), 7.35- 8.03 (m, 15H, Ar-H), 8.39 (s, 1H, NH) and 10.37 (s, 1H, NH). Anal. for $C_{31}H_{21}ClN_{10}O_6S_3$ (761.20): Calcd.: C, 48.91; H, 2.78; Cl, 4.66; N, 18.40; S, 12.64%. Found: C, 48.65; H, 2.50; Cl, 4.95; N, 18.12; S, 12.25 %.

Synthesis of 4-[5-(4-Chlorophenyl)-7-methyl-4,9-dioxo-3,4-dihydro- 9*H*-[1,3]oxazino[4″,5″:4′,5′]thieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]-triazin-3(4*H*)-yl]benzenesulfonamide (11):

A solution of **10c** (10 mmole) in 30 mL acetic anhydride was heated under reflux for 4 hours, then cooled. The solid formed was collected by filtration and crystallized from ethanol to give **11** as green crystals (64% yield), m.p. = 244 ^{0}C, IR υ (cm^{-1}): 3237,3103 (NH_2) and 1722, 1660 (2CO). ^{1}H NMR (DMSO-*d*6): δ 3.32 (s, 3H, CH_3), 7.24 (s, 2H, NH_2) and 7.38-7.96 (m, 8H, Ar-H). Anal. for $C_{23}H_{13}ClN_6O_5S_2$ (552.96): Calcd.: C, 49.96; H, 2.37; Cl, 6.41; N, 15.20; S, 11.60%. Found: C, 49.75; H, 2.60; Cl, 6.70; N, 15.56; S, 11.35 %.

Synthesis of 14a,b:

A solution of 11 (10 mmole) and each of 12a,b (10 mmole) in 50 mL glacial acetic acid was heated under reflux for 5 hours, then cooled. The solid products formed were collected by filtration and crystallized from ethanol dioxane mixture to give **14a,b** respectively.

4-[5-(4-Chlorophenyl)-7-methyl-4,9-dioxo-8-(4-sulfamoylphenyl)- 3,4-dihydro-9*H*-pyrimido[4″,5″:4′,5′]thieno[3',2':5,6]pyrido[2,3-*d*]-[1,2,3]triazin-3(4*H*)-yl]-benzenesulfonamide (14a):

Brown crystals (60% yield), m.p. = 297°C, IR υ (cm^{-1}): 3327, 3252, 3191, 3103 ($2NH_2$) and 1691, 1667 (2CO). ^{1}H NMR (DMSO-*d*6): δ 3.32 (s, 3H, CH_3), 7.31 (s, 2H, NH_2) and 7.51-7.74 (m, 12H, Ar-H and NH_2). Anal. for $C_{29}H_{19}ClN_8O_6S_3$ (707.15): Calcd.: C, 49.25; H, 2.71; Cl, 5.01; N, 15.85; S, 13.60%. Found: C, 49.55; H, 2.33; Cl, 5.31; N, 15.58; S, 13.35 %.

4-[5-(4-Chlorophenyl)-7-methyl-4,9-dioxo-8-(4-sulfamoylphenyl)- *N*-[4-(pyrimidin-2-ylsulfamoyl)-phenyl]-3,4-dihydro-9*H*-pyrimido-[4″,5″:4′,5′]thieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]-benzenesulfonamide (14b):

Pale brown crystals (54% yield), m.p. = 290ºC, IR υ (cm^{-1}): 3367, 3241 (NH_2 and NH) and 1698, 1669 (2CO). ^{1}H NMR (DMSO-*d*6): δ 3.09 (s, 3H, CH_3), 7.28 (s, 2H, NH_2), 7.37-7.85 (m, 15H, Ar-H) and 11.82 (s, 1H, NH). Anal. for $C_{29}H_{19}ClN_8O_6S_3$ (707.15): Calcd.: C, 49.25; H, 2.71; Cl, 5.01; N, 15.85; S, 13.60%. Found: C, 49.55; H, 2.33; Cl, 5.31; N, 15.58; S, 13.35 %.

4-[5-(4-Chlorophenyl)-9-hydroxy-4,-oxo-3,4-dihydropyridazino-[3″,4″:4′,5′]thieno[3',2':5,6]pyrido[2,3-*d*][1,2,3]triazin-3(4*H*)-yl]-benzenesulfonamide (16):

It was obtained as brown crystals from Dioxane (52% yield), m.p. = 247ºC, IR υ (cm^{-1}): 3420 (br, OH), 3367, 3245 (NH_2) and 1668 (2CO). ^{1}H NMR (DMSO-*d*6): δ 3.31 (br., 1H, OH), 7.34 (s, 2H, NH_2) and 7.53-7.69 (m, 9H, Ar-H). Anal. for $C_{22}H_{12}ClN_7O_4S_2$ (537.95): Calcd.: C, 49.12; H, 2.25; Cl, 6.59; N, 18.23; S, 11.92%. Found: C, 49.35; H, 2.54; Cl, 6.90; N, 18.47; S, 11.70 %.

Synthesis of 4-[6-amino-5-(4-chlorophenyl)-4-oxo-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-3-yl]benzene-sulfonamide (18):

A solution of **7** (10 mmole) in 30 mL hydrazine hydrate was heated under reflux for 5 hours, then cooled. The solid formed was collected by filtration and crystallize from DMF/ ethanol to give compound **18** as yellow crystals (75% yield), m.p. = 322-324ºC, IR υ (cm^{-1}): 3339, 3255, 3191, 3107 ($2NH_2$ and NH) and 1686 (CO). ^{1}H NMR (DMSO-*d*6): δ 4.90 (s, 2H, NH_2), 7.22 (s, 2H, NH_2), 7.33-7.58 (m, 8H, Ar-H) and 12.68 (s, 1H, NH). Anal. for $C_{19}H_{13}ClN_8O_3S$ (468.87): Calcd.: C, 48.67; H, 2.79; Cl, 7.56; N, 23.90; S, 6.84%. Found: C, 48.36; H, 2.55; Cl, 7.80; N, 23.66; S, 6.57 %.

5-(4-Chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazine-6-diazonium chloride (19):

It was obtained as yellow crystals from Dioxane (72% yield), m.p. = 285ºC decompose, IR υ (cm^{-1}): 3334, 3262, 3107 (NH_2 and NH) and 1663 (CO).

Synthesis of compounds 21a,d and 25a,b:

General procedure:

A solution of **19** (10 mmole) in ethanol (30 mL) containing triethyl amine (TEA) (0.5 mL) was treated with each of **20a,b** and **24a,b** (10 mmole) and stirred at room temperature for 2 hours. The formed solid products were collected with filtration and crystallized from the proper solvent to give **21a,b** and **25a,b** respectively.

4-{5-(4-Chlorophenyl)-6-[(dicyanomethyl)diazenyl]-4-oxo-4,8-di-hydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-3-yl}-benzenesulfonamide (21a):

It obtained as green crystals from ethanol (68% yield), m.p. = 228ºC, IR υ (cm^{-1}): 3434, 3354, 3127 (NH_2 and NH), 2209 (CN) and 1666 (CO). ^{1}H NMR (DMSO-*d*6): δ 3.30 (s, 1H, CH), 7.30 (s, 2H, NH_2), 7.34-7.59 (m, 8H, Ar-H) and 13.12 (s, 1H, NH). Anal. for $C_{22}H_{12}ClN_{11}O_3S$ (545.92): Calcd.: C, 48.40; H, 2.22; Cl, 6.49; N, 28.22; S, 5.87%. Found: C, 48.66; H, 2.59; Cl, 6.70; N, 28.49; S, 5.58 %.

2-Cyano-2-{[5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-6-yl]-diazenyl}ethanethioamide (21b):

It was obtained as Pale green crystals (65% yield), m.p. = 237º C, , IR υ (cm^{-1}): 3442, 3298, 3150 ($2NH_2$ and NH), 2201 (CN) and 1698 (CO). ^{1}H NMR (DMSO-*d*6): δ 3.78 (s, 1H, CH), 6.46 (s, 2H, NH_2), 7.33 (s, 2H, NH_2), 7.48-7.78 (m, 8H, Ar-H) and 12.10 (s, 1H, NH). Anal. for $C_{22}H_{14}ClN_{11}O_3S_2$ (580.0): Calcd.: C, 45.56; H, 2.43; Cl, 6.11; N, 26.56; S, 11.06%. Found: C, 45.86; H, 2.69; Cl, 6.41; N, 26.27; S, 11.29 %.

Ethyl 3-oxo-2-{[5-(4-chlorophenyl)-4-oxo-3-(4-sulfamoylphenyl)-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-6-yl]-diazenyl}butanoate (25a):

It was obtained as Reddish brown crystals from ethanol (69% yield), m.p. = 217ºC, , IR υ (cm^{-1}): 3399, 3216 (NH_2 and NH), and 1734, 1713, 1663 (3CO). ^{1}H NMR (DMSO-*d*6): δ 1.23-1.30 (t, 3H, $OCH_2\underline{CH_3}$, J= 7.2 Hz), 3.08 (s, 3H, $COCH_3$), 3.13 (s, 1H, CH), 4.14-4.25 (q, 2H, $O\underline{CH_2}CH_3$, J= 7.2 Hz), 6.72 (s, 2H, NH_2), 7.28-7.59 (m, 8H, Ar-H) and 12.66 (s, 1H, NH). Anal. for $C_{25}H_{20}ClN_9O_6S$ (610.0): Calcd.: C, 49.22; H, 3.30; Cl, 5.81; N, 20.67; S, 5.26%. Found: C, 49.51; H, 3.58; Cl, 5.59; N, 20.39; S, 5.55 %.

4-{6-[(1-Acetyl-2-oxopropyl)diazenyl]-5- (4-chlorophenyl)-4-oxo-4,8-dihydro-3*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-3-yl}-benzenesulfonamide (25b):

It obtained as brown crystals from ethanol (69% yield), m.p. = 223ºC, IR υ (cm^{-1}): 3392, 3266 (NH_2 and NH), and 1728, 1668 (3CO). ^{1}H NMR (DMSO-*d*6): δ 2.87 (s, 6H, $2COCH_3$), 4.32 (s, 1H, CH), 5.13 (s, 1H, NH) and 7.38-7.73 (m, 10H, Ar-H and NH_2). Anal. for $C_{24}H_{18}ClN_9O_5S$ (579.97): Calcd.: C, 49.70; H, 3.13; Cl, 6.11; N, 21.74; S, 5.53%. Found: C, 49.41; H, 3.42; Cl, 6.41; N, 21.50; S, 5.80 %.

Synthesis of 23a,b and 27a,b:

General procedure:-

Method A:- cyclization of 21a,b and 23a,b: a solution of each of **21a,b** and **23a,b** (10 mmole) in ethanol (30 mL) containing TEA (0.5 mL) was heated under reflux for 4 hours, then cooled. The solid products formed were collected by filtration and crystallized from the proper solvent to give **23a,b** and **27a,b** respectively.

Method B:- reaction of 19 with the halo-compounds 20a,b and 24a,b:

A solution of **19** (10 mmole) in ethanol (30 mL) containing triethyl amine (TEA) (0.5 mL) was treated with each of **20a,b** and **24a,b** (10 mmole) and heated under reflux for 4 hours. The solid products formed after cooling were collected by filtration and crystallized from the proper solvent to give **23a,b** and **27a,b** respectively.

4-[9-Amino-5-(4-chlorophenyl)-8-cyano-4-oxo-3,4-dihydro[1,2,4]-triazino[4″,3″:1′,5′]pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin-3-yl]benzenesulfonamide (23a):

It was obtained as brown crystals from ethanol / Doixane mixture (62% yield), m.p. > 300ºC, IR υ (cm^{-1}): 3412, 3316, 3266, 3201 ($2NH_2$), 2214 (CN) and 1676 (CO). ^{1}H NMR (DMSO-*d*6): δ 3.10 (s, 2H, NH_2), 7.28 (s, 2H, NH_2) and 7.36-7.68 (m, 8H, Ar-H). Anal. for $C_{22}H_{12}ClN_{11}O_3S$ (545.92): Calcd.: C, 48.40; H, 2.22; Cl, 6.49; N, 28.22; S, 5.87%. Found: C, 48.18; H, 2.01; Cl, 6.75; N, 28.52; S, 5.60 %.

5-(4-Chlorophenyl)-8-cyano-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydro[1,2,4]triazino[4″,3″:1′,5′]pyrazolo[4',3':5,6]pyrido[2,3-*d*]-[1,2,3]triazine-8-carbothioamide (23b):

It was obtained as brown crystals from ethanol / Doixane (59% yield), m.p. = 298ºC, IR υ (cm^{-1}): 3407, 3198, 3150 ($3NH_2$) and 1660 (CO). ^{1}H NMR (DMSO-*d*6): δ 3.36 (s, 2H, NH_2), 6.59 (s, 2H, NH_2), 7.32 (s, 2H, NH_2) and 7.38-7.67 (m, 8H, Ar-H). Anal. for $C_{22}H_{14}ClN_{11}O_3S_2$ (580.0): Calcd.: C, 45.56; H, 2.43; Cl, 6.11; N, 26.56; S, 11.06%. Found: C, 45.26; H, 2.14; Cl, 6.38; N, 26.85; S, 11.34 %.

Ethyl 5-(4-chlorophenyl)- 9-methyl-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydro[1,2,4]triazino[4″,3″:1′,5′]pyrazolo[4',3':5,6]pyrido[2,3-*d*]-[1,2,3]triazine-8-carboxylate (27a):

It was obtained as Dark brown crystals from ethanol / Dioxane (55% yield), m.p. = 288ºC, , IR υ (cm^{-1}): 3301, 3104 (NH_2), and 1726, 1671 (2CO). ^{1}H NMR (DMSO-*d*6): δ 1.21-1.28 (t, 3H, $OCH_2\underline{CH_3}$, J= 7.2 Hz), 2.48 (s, 3H, $COCH_3$), 4.16-4.26 (q, 2H, $O\underline{CH_2}CH_3$, J= 7.2 Hz), 6.67 (s, 2H, NH_2) and 7.33-7.54 (m, 8H, Ar-H). Anal. for $C_{25}H_{18}ClN_9O_5S$ (591.98): Calcd.: C, 50.72; H, 3.06; Cl(5.99; N, 21.29; S, 5.42%. Found: C, 50.42; H, 3.36; Cl, 5.71; N, 21.02; S, 5.72 %.

4-{8-Acetyl-5-(4-Chlorophenyl)-9-methyl-4-oxo-3,4-dihydro[1,2,4]-triazino[4″,3″:1′,5′]pyrazolo[4',3':5,6]pyrido[2,3-*d*][1,2,3]triazin -3-yl}-benzenesulfonamide (27b):

It was obtained as dark brown crystals from ethanol / Dioxane (59% yield), m.p. > 300ºC, IR υ (cm^{-1}): 3478, 3212 (NH_2), and 1697, 1669 (2CO). ^{1}H NMR (DMSO-*d*6): δ 2.14 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.18 (s, 2H, NH_2) and 7.38-7.80 (m, 8H, Ar-H). Anal. for $C_{24}H_{16}ClN_9O_4S$ (561.95): Calcd.: C, 51.29; H, 2.87; Cl, 6.31; N, 22.43; S, 5.71%. Found: C, 51.01; H, 2.60; Cl, 6.65; N, 22.70; S, 5.49 %.

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