SOME CYCLIZATION REACTIONS WITH 2-(4-OXOTHIAZOLIDIN-2-YLIDENE) ACETONITRILE WITH A-B UNSATURATED NITRILE COMPOUNDS

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Abstract

A novel 2- Cyanomethine- 4,5dihydro-4-oxo-5-(2,4dichlorophenyl) methylidine 1,3 thiazole **(2)** was obtained via the reaction of 4-thiazolidinone **(1)** with 2,4 dichloro-benzaldehyde .Treatment of 4-thiazolodinone derivatives**(2)** with 2,4 dichlorobe-nzaldhyde afforded 2,5-bis arylmethylidine derivatives **(3a-d)**. Cyclization of compound **(2)** with various α-Cyanocinnamonitriles**(4a-c)** afforded the corresponding thiazolopyrid-ine enaminonitrile derivatives **(5a-c).** Reaction of compound **(2)** with α-ethoxycarbonyl cinnamonitriles **(7a-c)** gave the corresponding thiazolo[3,2-a]pyridine enaminoester deri-vatives **(10a-c) .** Also α-formamidocinnamonitriles **(11a-c)** were reacted with compound **(2)** and gave thiazolo [3,2-a] pyridine derivatives **(12a-c).** The reaction of **(5a)** with hydrazine hydrate, carbon disulphide in pyridine and malononitrile afforded the corres-pondding thiazolo pyridine and thiazolonaphthyridine derivatives **(15)**,**(16)** and **(17)**; respectively.

Keywords: 5-Arylmethylidine-4-thiazolinones, thiazolo[3,2-a] pyridines,thiazo-lonaphtjyridine

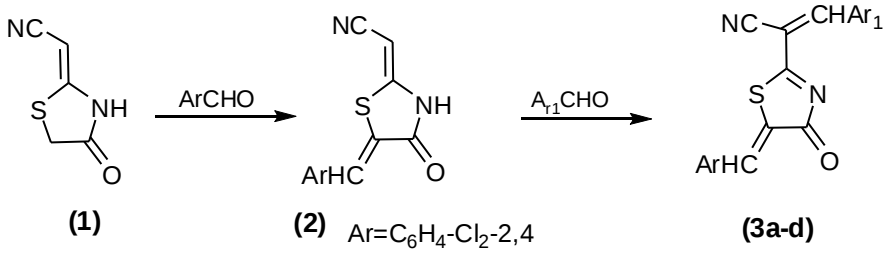
Introduction

In the last decade, much attention have been devoted to construct a new thiazolidinone and thiazolopyridine derivatives and reported their biological activities. A series of novel 4-thiazolidinone and thiazolopyridine derivatives are reported to have diverse biological and medicinal activities as antibacterial[1-4], antimicrobial[5-7], antifungal[8], anticonvulsant[9], anticancer[10], antituberculosis[11], antihypertensive, coronary dilator and muscle relxant[12-14] activities. Thus, we devoted the synthesis of heterocyclic compounds from readily available starting materials[15-21] . The synthesis of some novel thiazolidinones **(3a-d)**, thiazolo[3,2-a]pyridine derivatives (**5a-c), (10a-c)** ,**(12a-c), (15),(16)** and **(17)**from 2-cyano-methylidine-4,5-dihydro-4-thiazolidinone **(1)** as starting material[22]were reported.

Results and discussion

2-Cyanomethylidine-4-oxo-4,5- dihydro-1,3-thiazole **(1)**[22] was condensed with 2,4 dichlorobenzaldehyde in absolute ethanol catalyzed with piperidine to give the corresponding 4-thiazolidinone derivative **(2).** The structure of compound **(2)** was established by correct elemental and spectra data. IR spectrum of thiazolidinone

derivative **(2)** showed absorption bands for (C=O thazolidinone) at 1720 cm^{-1}. ^1H NMR spectrum (DMSO-d6) of compound **(2)** revealed signals at δ 6.20 (s, 1H, methylidene-H), 7.50 – 8.80 (m, 4H, Ar-H +NH). Also, its mass spectrum ($C_{12}H_6N_2Cl_2SO$) displayed a molecular ion peak at m/z (M^+= M-1; 295, 1.08%). Refluxing compound **(2)** with different aromatic aldehydes in ethanol in the presence of piperidine led to the formation of novel thiazolidinone derivatives **(3a-d)**.The structure of compounds (**3a-d)** were confirmed by correct elemental analysis and spectra data. IR spectra of **(3a-d)** showed absorption bands corresponding to (NH, C≡N and C=O thiazolidinone functional groups) .^1H NMR spectrum of **(3b)** recorded on (DMSO-d6) revealed signals at 6.83-7.88 (9H, Ar-H, 2-methine-H), and 10.40 (s,1H, NH). Mass spectrum of **(3b)** displayed a molecular ion peak at m/z (273,1.16%) (M-$C_6H_3Cl_2$); **Scheme(1).**



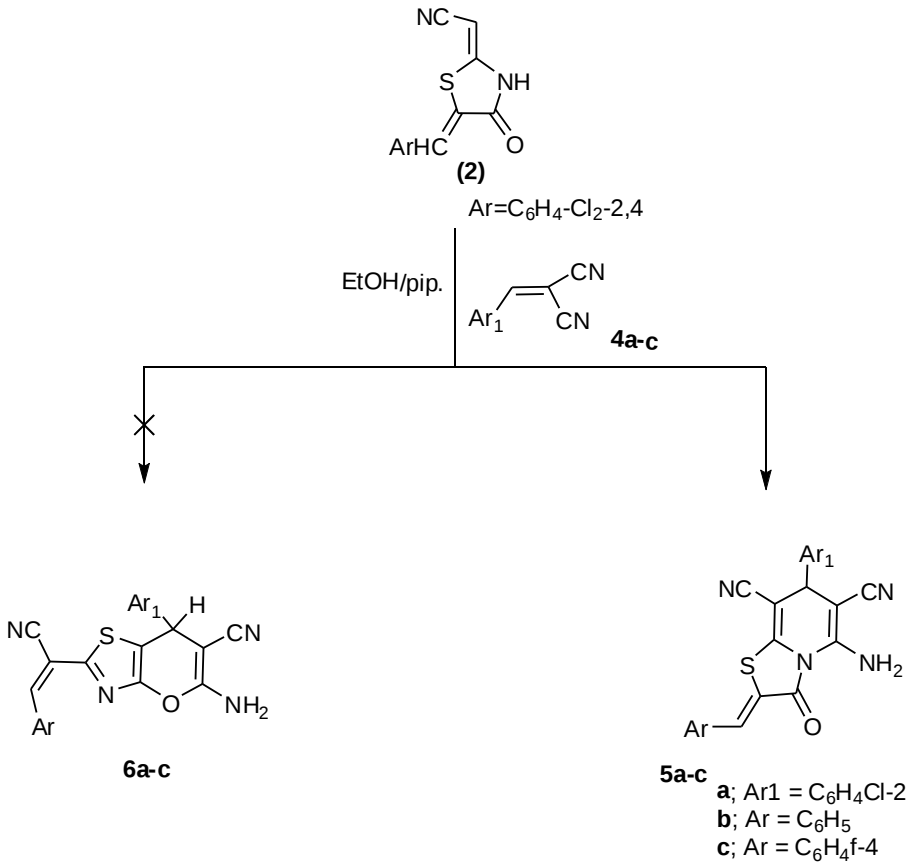
(1) **(2)** Ar=C_6H_4-Cl_2-2,4 **(3a-d)**

a;Ar= Ar1 =$C_6H_3Cl_2$-2,4
b;Ar= $C_6H_3Cl_2$-2,4, Ar1= C_6H_3Cl-2,
c;Ar= $C_6H_3Cl_2$-2,4, Ar1= C_6H_5
d;Ar= $C_6H_3Cl_2$-2,4, Ar1= C_6H_3F-4

Scheme (1)

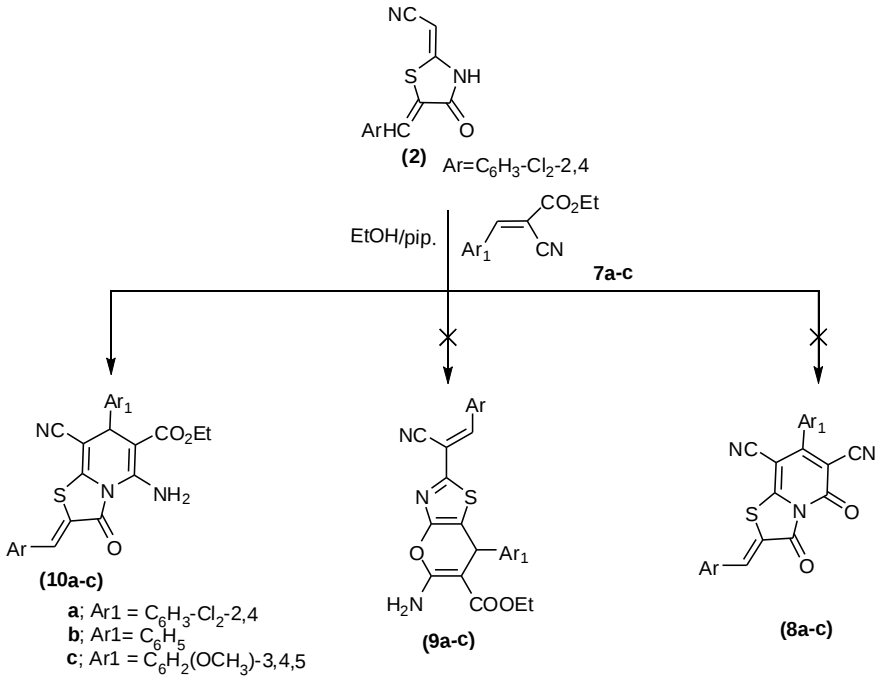
Refluxing of thiazolidinone derivatives **(2)** with α-cyanocinnamonitriles **(4a-c)** in absolute ethanol in presence of catalytic amount of piperidine afforded thiazolo [3,2-a] pyridine enaminonitriles **(5a-c)** , on the basis of elemental and spectral data the reaction proceeds via nucleophile addition of amino group thiazolodinone to β-carbon of arylidine followed by intramolecular cyclization. IR spectra of 1,3-thiazolo-[3,2-a] Pyridine derivatives **(5a-c)** exhibited absorption bands corresponding to NH_2, C≡N and C=O thiazolidinone functional groups.^1H NMR spectrum of thiazolopyridine derivative **(5a)** [DMSO-d6] revealed a signals characteristic for

4.84 (s, 1H, Pyridine- H), 7.30-7.88 (m, 8H, Ar-H , methine-H and NH_2). Also mass spectrum of compound **(5a)** exhibited a molecular ion peak at m/z 484 (0.44%)**; Scheme (2).**



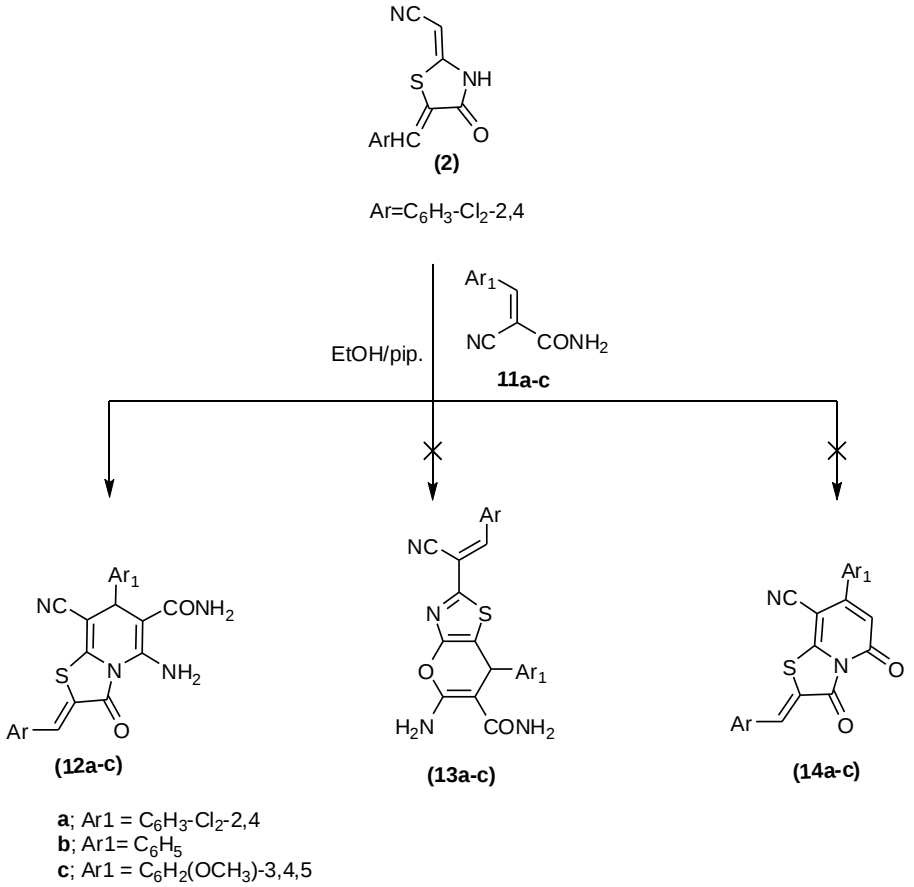
Scheme (2)

Treatment of α-ethoxycarbonyl cinnamonitrile derivatives **(7a-c)** with 4-thiazolidinone **(2)** in refluxing ethanol catalyzed with piperidine gave the novel thiazolo [3,2-a] Pyridine derivatives **(10a-c)** on the basis of elemental and spectral data**; Scheme (3).**



Scheme (3)

Elemental analyses and spectral data were in agreement with thiazolopyridine structure **(10a-c)** and ruled out the other postulated structures **(8a-c)** and **(9a-c)**, respectively. IR spectrum of **(10a)** showed absorption bands at 3494,3386 (NH_2) , 2208 (C≡N) and 1722 (C=O) thiazolodinone .Its ^{1}H NMR spectrum [DMSO-d6] revealed a signals at 0.90 (t, 3H, CH_3), 3.98 (q, 2H, CH_2), 5.13 (s, 1H, Pyridine-H), 7.52 – 7.88 (m, 7H, Ar-H , methine-H) and 8.42 (s, 2H, NH_2). Furthermore my work was extended to synthesize the novel thiazolo[3,2-a] Pyridine derivatives containing amide moiety **(12a-c)**,through interaction of 4-thiazolidinone derivative **(2)** with α-carboxamidocinnamonitriles **(11a-c)** in refluxing ethanol containing minor quantity of piperidine for 6 hours **;Scheme (4).**



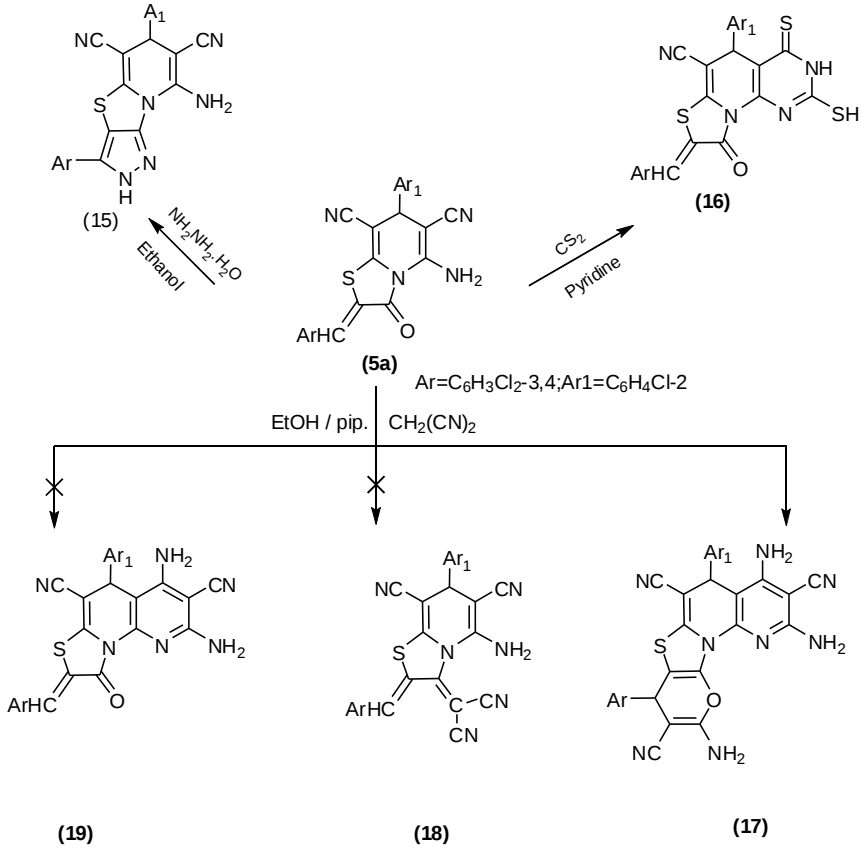
a; Ar1 = C_6H_3-Cl_2-2,4
b; Ar1= C_6H_5
c; Ar1 = $C_6H_2(OCH_3)$-3,4,5

Scheme 4

IR spectra of thiazolo [3,2a] Pyridine derivatives **(12a-c)** exhibited absorption bands corresponding to NH_2, C≡N and C=O (thiazolodinone).^{1}H NMR spectrum of **(12a)** in (DMSO-d6) revealed characteristic signals at 4.85 (s, 1H. Pyridine-H), 8.24(s,2H,NH_2),7.30-7.80 (m,7H,Ar-H+methine-H). Also mass spectrum of compound **(12a)** showed molecular ion peak at m/z (M^+; M +1; 537, 0.5.56 %). The elemental and spectral data of **(12c)**, were in a complete accordance with the assigned a structure. Mass spectrum of **(12c)** showed a molecular ion peak at m/z (556, 0.28%). Also,^{1}H NMR spectrum of compound **(12c)** exhibited characteristic signals for 3OCH_3 at 3.76, 3.78 and 3.82, respectively.

The reactivity of thiazolo [3,2-a] pyridine **(5a)** towards hydrazine hydrate in refluxing ethanol was also investigated. A single product as examined by TLC was produced. The structure of the obtained product was assigned as 3,10-(diaryl)-8-amino-9,11-dicyano- pyrazolo[3,4-4',5'] thiazolo [3, 2-a] pyridine **(15**) based on its

elemental analysis and spectral data. IR spectrum of (**15)** was free of C=O thiazolidinone absorption bands in the region 1690-1712cm^{-1} and presence of absorption band at 2206 for cyano group . In conjunction with the interest in the chemistry and biological activity of polycondensed thiazolo[3,2-a]pyridine derivative **(5a)** was reacted with carbon disulphide and malononitrile to give the corresponding polycondensed thiazolo [3,2-a]-1,8- naphthyridine derivatives **(16 , 17**), respectively. The structure of the latter products was deduced from their elemental analyses and spectral data. IR spectra of thiazolo[3,2-a] -1,8-naphthyridines **(16**) showed absorption bands for thiazolidinone group in the regions 1690-1720.^{1}H NMR spectrum of compound **(16)** showed significant signals for SH and pyridine-H moieties Mass spectrum of compound **17** ($C_{25}H_{13}Cl_3N_6OS$; 616) showed a molecular ion peak at m/z 574 (M-NH_2CN;0.03%)(Scheme 5)



Scheme 5

Table I: Physical data of the synthesized compounds:

Copd. No.	Yield %	Crystal Solvent	M.P [°C]	Molecular Formula	Elemental Analysis Caled/Found[%] C	H	N
2	60	EtOH	210-212	$C_{12}H_6N_2Cl_2SO$ (296)	48.64 48.42	2.03 2.00	9.45 9.33
3a	55	EtOH	205-207	$C_{19}H_8N_2Cl_4SO$ (452)	50.25 50.23	1.78 1.82	6.17 6.32
3b	50	EtOH	190-192	$C_{19}H_9N_2Cl_3SO$ (418)	54.37 54.22	2.16 2.32	6.67 6.55
3c	57	EtOH	198-200	$C_{19}H_{10}N_2Cl_2SO$ (384)	59.32 59.52	2.60 2.44	7.29 7.12
3d	67	EtOH	200-202	$C_{19}H_9N_2Cl_2FSO$ (402)	56.59 56.70	2.25 2.35	6.95 6.75
5a	66	CH_3OH	195-197	$C_{22}H_{11}N_4Cl_3SO$ (484)	54.39 54.24	2.28 2.19	11.53 11.70
5b	60	CH_3OH	208-210	$C_{22}H_{12}N_4Cl_2SO$ (450)	58.55 58.62	2.68 2.59	12.41 12.42
5c	54	EtOH	163-165	$C_{22}H_{11}N_4Cl_2FSO$ (468)	56.30 56.50	2.36 2.20	11.94 12.00
10a	63	EtOH	185-187	$C_{24}H_{15}N_3Cl_4SO_3$ (565)	50.81 51.02	2.67 2.42	7.41 7.51
10b	65	EtOH	225-227	$C_{24}H_{17}N_3Cl_2SO_3$ (497)	57.84 58.00	3.44 3.29	8.43 8.42
10c	61	EtOH	175-177	$C_{27}H_{23}N_3Cl_2SO_6$ (587)	55.11 55.31	3.94 3.77	7.14 7.19
12a	66	EtOH	215-217	$C_{22}H_{12}N_4Cl_4SO_2$ (536)	49.09 49.22	2.25 2.02	10.41 10.45
12b	60	EtOH	220-222	$C_{22}H_{14}N_4Cl_2SO_2$ (468)	56.30 56.51	3.01 2.80	11.94 11.95
12c	57	EtOH	210-212	$C_{25}H_{20}N_4Cl_2SO_5$ (558)	53.76 53.79	3.88 3.45	10.03 10.10
15	51	EtOH/ Benzene	230-32	$C_{22}H_{11}N_6Cl_3S$ 496	53.22 53.94	2.21 2.02	16.93 16.45
16	62	EtOH/ Benzene	251-53	$C_{23}H_{11}N_4Cl_3OS$ 560	49.28 49.22	1.96 2.02	10.00 10.45
17	79	EtOH/ Benzene	310-311	$C_{28}H_{15}N_8Cl_3OS$ 616	54.54 54.75	2.36 2.02	15.27 14.45

Table II: Spectral data of some synthesized compounds:

Compd. No.	IR (KBr . Cm^{-1})	^1H NMR [DMSO-d6] (δ . PPM), and or MS. m/z (%)
2	3250 (NH) 3074 (CH-arom), 2202 (C≡N)), 1720 (C=O) thiazolidinone	6.20 (s, 1H, methylidene-H), 7.50– 8. 80 (m, 5H, Ar-H + NH+methylidine-H) 295 [(M -1); 1.08] ,78(57.17),46(100),
3a	3370 (NH), 2204 (C≡N) ,1720 (C=O) thiazolidinone	452 (M^+, 3.02) ,46(100),64(62.73), 78(48.60)
3b	3211 (NH), 2926 (CH-aliph.), 2202 (C≡N), 1718 (C=O) thiazolidinone	6.83–7.88 (9H, Ar-H + 2-methine-H), 10.40 (s, 1H, NH).
3c	3280 (NH), 2922 (CH-aliph), 2270 (C≡N), 1714 (C=O) thiazolidinone	7.36-7.89(m,10H,Ar-H+2-methine-H),10.02(s,1H,NH) 384 (M^+ ; 0.99) ,77(22),43(100),
3d	3270 (NH), 2928 (CH-aliph), 2202(C≡N) , 1720 (C=O) thiazolidinone	7.31-7.79(m,9H,Ar-H+2-methine-H) , 3.02(s,1H,NH) 401 (M-1 ; 0.78) ,140(7.11),43(100) , 75(10.36)
5a	3366, 3300 (NH_2), 2942 (CH-aliph.), 2200 (C≡N), 1718 (C=O) thiazolidinone	4.84 (s, 1H, Pyridine-H), 7.30–7.88 (m,10H, Ar-H + methine-H+NH_2) 484 (M^+ ·0.44) ,78(59.38),45(100) ,
5b	3456, 3358 (NH_2), 2930(CH-aliph), 2200 (C≡N), 1718 (C=O) thiazolidinone.	7.31-7.83(8H,Ar-H+methine-H),8.13 (s,2H,NH_2)
5c	3630, 3550 (NH_2), 2930 (CH-aliph), 2206(C≡N), 1750 (C=O) thiazolidinone	466(M-2; 6.98), 91(10.91),61(93.5),
10a	3494,3386 (NH_2), 2968 (CH-aliph.), 2208 (C≡N), 1722 (C=O) thiazolidinone	0.90 (t, 3H, CH_3), 3.98 (q, 2H, CH_2), 5.13 (s, 1H, Pyridine-H), 7.52 – 7.88 (m, 7H, Ar-H + methine-H), 8.42 (s, 2H, NH_2) 565 (M^+ ·0.07) , 86(68.65),83(100) ,
10b	3546,3494 (NH_2), 2926(CH-aliph), 2220 (C≡N), 1750 (C=O) thiazolidinone	498 (M+1 ·7.72) ,52(100) ,63(40.22) , 147(19.72)
10c	3504 , 3396 (NH_2), 3090 (CH-Ar.), 2936 (CH-aliph.), 2206 (C≡N), 1722 (C=O) thiazolidinone	1.19 (t, 3H, CH_3), 4.14 (q, 2H, CH_2),5.10(s,1H,pyridine-H), 7.50 – 7.71 (m, 6H, Ar-H + methine-H), 8.33 (s, 2H, NH_2) 587 (M^+ ; 12.7) , 292(33.10),44(100) ,
12a	3426, 3368 (NH_2), 2926 (CH-Aliph.), 2204 (C≡N), 1718 (C=O) thiazolidinone	4.85 (s, H, Pyridine-H), 7.30 – 7.80 (m, 7H, Ar-H + methine-H), 8.24 (s, 2H, NH_2)537 (M+1 ; 5.56) ,44(100) , 204(64.90)
12 b	3540,3450(NH_2), 2952(CH-aliph), 2204(C≡N) , 1750(C=O)thiazolidinone,1658 (C=O) amide	468(M^+;20.21) 77(60,23),171(65,57)
12c	3460, 3406 (NH_2), 3002 (CH-Ar.), 2934 (CH-Aliph.), 2218 (C≡N), 1698,1586 (C=O thiazolidinone) and amide	3.76,3.78,3.82 (s, 9H,3OCH_3), 4.81 (s, 1H, pyridine-H), 7.22 – 7.96 (m, 5H, Ar-H), 8.14 (s, 2H, NH_2) 558 (M^+ ; 0.28) ,263(100) , 188(21.68) 162(28.91)
15	3460, 3334 (NH_2),3211(NH) 3002 (CH-Ar.), 2206 (C≡N),	4.04 (s, 1H, pyridine-H), 7.22 – 7.39 (m, 9H, Ar-Hand NH_2, NH)
16	3415(SH), 3211(NH) 3002 (CH-Ar.), 1696(C=O thiazolidinone) .	4.30 (s, 1H, pyridine-H), 7.22 – 7.39 (m, 8H, Ar-H, methine-H),8.74 (s, 1H ,NH),10.52(s,1H,SH)
17	3412,3330(NH_2), 2940 (CH-aliph), 2214(C≡N)	574 (M^+;(M-2NH_2;0.03) 397(0.03) , 198(24.08),65(100)

Experimental:

Meting points are recorded on a (sturartscientific.co.uk) melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrometer using KBr pellets. ^{1}H NMR spectrum were recorded on a Varian Gemini spectrometer 300 (300 MHz) using tetramethylsilane (TMS) as internal standard and mass spectra on a ShimadzuGC-MS-QP-100 (Japan) mass spectrometer. Elemental Analysis was performed on a Perkin-Elmer 240 C micro-analyzer. The physical and spectral data are collected in tables I and II respectively. Elemental Analysis was carried out at Micro-analytical Center of Cairo University and National Research Center

5-(2,4-dichlorobenzylidene)-4-oxothiazolidin-2-ylidene) acetonitrile(2)

To a solution of 4-thiazolidinone (1) (0.01 mol), the aromatic aldehydes (0.01mol) in presence of absolute ethanol (20 ml) having a few drops of piperidine(0.05ml) were added.The reaction mixture was refluxed for 4 hours, then allowed to cool. The solid product formed was collected and recrystallized from ethanol to give (2).

2,5-Diarylmethylidine-4-oxo-4,5-dihydrothiazol-2-yl)-3-aryl-acrylonitrile (3a-e)

To a solution of **(2)** (0.01 mol), the aromatic aldehydes (0.01 mol) in presence of absolute ethanol (20 ml) having a few drops of piperidine (0.05ml) were added. The reaction mixture was refluxed for 4 hours, then allowed to cool. The solid products formed were collected and recrystallized from ethanol to give **(3a-e)**.

5-amino-7-aryl-2-(arylmethylene)-3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]pyridine- 6,8-dicarbonitrile (5a-c)

To a solution of **(2)** (0.01 mol) malononitrile (0.01 mol) in presence of absolute ethanol (20 ml) having a few drops of piperidine (0.05ml) was added.The reaction mixture was refluxed for 4 hours, then allowed to cool. The solid products formed were collected and recrystallized from ethanol to give **(5a-c)**.

Ethyl5-amino-7-aryl-8-cyano-2-(arylmethylene)-3-oxo-3,7-dihydro-2H-thiaz-olo [3,2-a]pyridine-6-carboxylate(10a-c)

To a solution of **(2)** (0.01 mol) ethylcyanoacetate (0.01 mol) in presence of absolute ethanol (20 ml) having a few drops of piperidine (0.05ml) was added. The reaction mixture was refluxed for 4 hours , then allowed to cool. The solid products

formed were collected and recrystallized from ethanol to give **(10a-c).**

5-amino-7-aryl-2-(arylmethylene)-6-carbamoyl-8-cyano3-oxo-3,7-dihydro-2H-thiazolo[3,2-a]pyridine(12a-c).

To a solution of **(2)** (0.01 mol) and cyanoacetamide (0.01 mol) in presence of absolute ethanol (20 ml) having a few drops of piperidine (0.05ml).The reaction mixture was refluxed for 4 hours, then allowed to cool. The solid products formed were collected and recrystallized from ethanol to give (12a-c).

3,10-diaryl-8-amino-9,11-dicyano-pyrazolo[3,4-4',5']thiazolo[3,2-a]pyridine (15)

To a solution of **(5a)** (0.01 mol) hydrazine hydrate (0.01 mol) in presence of absolute ethanol (20 ml) was added.The reaction mixture was refluxed for 3 hours, then allowed to cool. The solid products formed were collected and recrystallized from ethanol/ benzene mixture to give (15)

2-arylmethylidine-2,3,10-trihydro-8-imino-3-oxo-9-thioxo-10-aryl-11-cyano-thiazolo[3,2-a]pyridine(16)

To a solution of **(5a)** (0.01 mol) carbon disulphide (0.01 mol) in presence of pyridine(20 ml) was added .The reaction mixture was refluxed for 6 hours, then allowed to cool. The solid products formed were collected and recrystallized from ethanol/ benzene mixture to give (16)

3,12-dihydro-4,11,14-tricyano-6,10-diamino-3,12-diaryl-pyrano[2,3-4',5']-thiazolo-[3,2-a]1,8-naphthyridine(17)

To a solution of **(5a)** (0.01 mol), carbon disulphide (0.01 mol) in presence of pyridine(20 ml) was added .The reaction mixture was refluxed for 6 hours, then allowed to cool. The solid products formed were collected and recrystallized from ethanol/ benzene mixture to give (17)

Antimicrobial Activity:

The most of the synthesized compounds were screened in vitro for their antimicrobial activity. The diameter of inhibition zone was measured as an indicator for the activity of the compounds; Ampillicin is used as reference drug.

The results for antibacterial activities depicted in table 3 revealed that compounds **2** and **3b** exhibited good activities against the reference drug, while

other compounds **3d**, **5a**,**5c,10c** and **12a** showed moderate activity against the reference chemotherapeutic, on the other hand most of the prepared compounds **2a** and **10c** exhibited high antifungal activities against the reference drugs.

Invitro antimicrobial activity

Most of the newly synthesized compounds **(2,3b,3d,5a,5c,10c and 12a)** were evaluated in vitro for their antibacterial activity against four strains of bact-eria *bacillus subtillus , Staphelococcus aureus, E.coli and pseudomonas aeruginosa* . Also, the antifungal activity against *Candida albicans* and, *Aspergillus nigar* using paper disc diffusion method[23]. 1mg mL^{-1} solution in dimethylformamide DMF was used. The bacteria and fungi were grown on nutrient agar and Czapek's –Dox agar media, respectively. DMF as a negative control zones. The agar media were incubated with different microorganism cultures tested. After 24 h of incubation at 30 ˚C for bacteria and 48 h for fungi, the diameter of Inhibition Zone (mm) was measured. *Amikacin* used as reference drugs for antibacterial and antifungal activities, respectively.

Most of the synthesized compounds were found to possess various antimicrobial activities towards all the microorganisms used (Table III)

Table III. Antimicrobial activity of some newly synthesized compounds

Test Organism / Sample	Bacillus subtillus	Staphylococcus Aureus	E.coli	Pseudomonas aeruginosa	Candida albicans	Aspergillus nigar
2	21	22.5	20.5	23	22	19
3b	21	18.5	20	19	20	_
3d	18.5	19	17.5	18.5	16.5	-
5a	17	16	18.5	17	17	_
5c	17.8	15	16	20	17	_
10c	16.5	17	19	21	17.5	15
12a	18	17.5	18.5	21	19.5	-
ST	**29**	**31**	**34**	**32**	**25**	**_**

-Inhibation zone (m.m)
Symbols: High activity; (20-30 mm) (+++).
Moderate activity: (10-19) (++)
Low activity ; (1 - 9 mm) (+).
No activity; (-).
St = standard which is Amikacin

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