Al-Azhar Bulletin of Science

Volume 21 | Issue 1 Article 16

6-1-2010
Section: Chemistry

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How to Cite This Article

ELHAGALI, GAMEEL; EL-TAMAMAY, HESSEN; EL-SENUSSI, MA-NSOUR; and ELBASHER, ZAMZAM (2010) "UTILITY OF THIOGLYCOLLIC ACID IN THE SYNTHESIS OF SOME NEWLY THIAZOLIDINONE AND THIAZOLO[3,2-A]PYRIDINE DERIVA-TIVES AS ANTIMICROBIAL AGENTS," *Al-Azhar Bulletin of Science*: Vol. 21: Iss. 1, Article 16.
DOI: https://doi.org/10.21608/absb.2010.7332

UTILITY OF THIOGLYCOLLIC ACID IN THE SYNTHESIS OF SOME NEWLY THIAZOLIDINONE AND THIAZOLO[3,2-A]PYRIDINE DERIVATIVES AS ANTIMICROBIAL AGENTS

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Abstract

A series of thiazolo[3,2-a] pyridine derivatives **3**, **4a-d**, **9a-e**, **11a-e**, and **13** were synthesized through the interaction of 4,5-dihydro-2-ethoxycarbonyl methyllidine-4-thiazolidinone **1** with the corresponding α,β-unsaturated nitrile compounds **2a-e**, **6a-e**, **10a-e**, and **12,** respectively.4-Thiazolidinone derivative **1** was reacted with 2 moles of p-chlorobenzaldehyde to give **14** which was reacted with malononitrile to afford the corresponding thiazolo [3,2-a]pyridine derivative **15**. Acetylation of compound **15** with acetic anhydride furnished N-acetyl amino derivative **16**. The structures of these compounds were elucidated on the basis of their spectral data (IR, ^{1}HNMR and MS).These compounds were also screened for their antimicrobial activity against *pseudomonas aeruginosa, Bacillus subtilis, Penicillium italicum and Syncephalas trumracemosum* by using paper disc diffusion method using *Chloroamphenicol* and *Terbifin* as standard drugs.

***Keywords*:** 4-Thiazolidinone; Thiazolo [3,2-a] pyridines; Antimicrobial activity

Introduction

Diverse biological and medicinal activities as antibacterial, antimicrobial, antifungal, anticonvulsant, anticancer, anti-tuberculosis, antihypertensive, coronary dilator and muscle relaxant activities [1-10] have been found to be associated with 4-thiazolidinone and thiazolopyridine derivatives. Thus, in the courses of our studies devoted to the synthesis of some novel heterocyclic compounds from readily available starting materials [11-19], we report here the synthesis of some novel 4-thiazolidinone **14** and thiazolo [3,2-a] pyridine derivatives **3, 4a-d, 9a-e, 11a-e, 13, 15,** and **16**.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^{1}HNMR spectra were recorded on a Varian Gemini spectrometer (δ; ppm) 200 MHz using TMS as internal standard. Mass spectra were recorded on a Jeol-JMS-600 mass spectrometer. Micro analytical data were obtained from the Micro analytical Center, Faculty of Science, Cairo University. Cairo. Egypt.

Synthesis of 2,3,7-Trihydro-3-oxo-5-amino-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridine (3) and, 2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-ami- no-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridine (4a-d) .

To a solution of **1** (0.01mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml) α-cyanocinnamonitriles **2a-e** (0.01mol) was added. The reaction mixture was heated under reflux. The solid products formed were collected by filtration and recrystallized from ethanol.

Synthesisof2,3,7-Trihydro-2-arylmethylidine-3-oxo-6,8-diethoxycarbonyl-5-am- ino -7-aryl-1,3-thiazolo[3,2-a]pyridine derivatives (9a-e).

Equimolar amount of **1** (0.01mol) and α-ethoxycarbonylcinnamonitriles **6a-e** (0.01mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml) was heated under reflux for 6 h. The solid products formed were collected by filtration and recrystallized from ethanol.

Synthesis of 2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-(amino, or hydroxyl) -6-(formamido, or cyano)-7-aryl-8-ethoxycarbony-l-1,3-thiazolo[3,2-a]pyrid-ines (11a-e).

Equimolar amount of **1** (0.01mol) and α-formamidocinnamonitriles **(10a-e)** (0.01mol) in absolute ethanol (20 ml) having catalytic amount of piperidine (0.5 ml) was heated under reflux for 6 h. The solid products formed were collected by filtration and recrystallized from ethanol.

Synthesis of 2, 3, 7-Trihydro-3-oxo-5-hydroxy--6-cyano-7-aryl-8-ethoxycarb-onyl-1, 3 -thiazolo [3, 2-a] pyridine (13).

To a solution of **1** (0.01mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml) α-formamidocinnamonitile (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h. The solid product formed was collected by filtration and recrystallised from ethanol.

Synthesis of ethyl-2-(5-(4-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)-3-(4-chlorophenyl) acrylate (14) .

To a solution of **1** (0.01mol) in absolute ethanol (20 mL) containing catalytic amount of piperidine (0.5 mL) p-chlorobenzaldehyde (0.02 mol) was added. The reaction mixture was heated under reflux for 4 h. The solid product formed was collected by filtration and recrystallised from ethanol.

Synthesis of 2,3,7-Trihydro-2-(4-chlorophenylmethylidine)-3-oxo-5-amino--6-cyano-7-(4-chloro)phenyl -8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridine (15)

To a solution of **14** (0.01mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml), malononitrile (0.01mol) was added. The reaction mixture was heated under reflux for 6 h, and then allowed to cool. The solid product formed was collected by filtration and recrystallised from ethanol .

Synthesis of 2,3,7-Trihydro-2-(4-chlorophenylmethylidine)-3-oxo-5-N-acetyl amino-6-cyano-7-(4-chlorophenyl)-8-ethoxycarbonyl-1,3-thiazolo[3,2-a]pyridine (16). A solution of **15** (0.01mol) was boiled in enough quantity of acetic anhydride for 3 h. The solid product formed was collected by filtration.

Table 1. Elemental analysis of the newly synthesized compounds 3-16

.Compd .No	Yield [%]	.Cryst Solvent	M.P [ºC]	Mol. Formula (.M. Wt)	Elemental analysis [%]Calcd./Found		
					C	H	N
3	72	EtOH	36-234	$C_{17}H_{14}ClN_3O_3S$ ((375.5	54.33 54.20	3.72 3.79	11.18 11.30
4a	63	EtOH	240-42	$C_{24}H_{17}F_2N_3O_3S$ 465	61.93 62.01	3.65 3.50	9.03 8.90
4b	63	EtOH	188-90	$C_{28}H_{29}N_5O_3S$.(515)	65.24 65.20	5.63 5.70	13.59 13.40
4c	55	EtOH	270-72	$C_{24}H_{19}N_3O_5S$ (461)	62.47 62.30	4.12 4.10	9.11 9.00
4d	58	EtOH	255-57	$C_{24}H_{19}N_3O_3S$ (429)	67.13 67.09	4.42 4.27	9.79 9.71
9a	71	EtOH	205-07	$C_{26}H_{22}F_2N_2O_5S$ (512)	60.93 60.99	4.29 4.30	5.46 5.52
9b	58	EtOH	196-98	$C_{30}H_{34}N_4O_5S$ (562)	64.05 63.80	6.04 6.00	9.96 10.02
9c	60	EtOH	275-77	$C_{26}H_{24}N_2O_7S$ (508)	61.41 61.49	4.72 4.79	5.51 5.45
9d	74	EtOH	192-94	$C_{26}H_{22}N_4O_9S$ (566)	55.12 55.00	3.88 3.80	9.89 9.90
9e	52	EtOH	239-41	$C_{26}H_{22}Cl_2N_2O_5S$ (545)	57.24 57.10	4.03 3.90	5.13 5.05
11a	70	EtOH	190-92	$C_{24}H_{19}N_3F_2O_4S$ (483)	59.62 59.50	3.93 4.01	8.69 8.50
11b	57	EtOH	240-42	$C_{24}H_{19}Cl_2N_3O_4S$ (516)	55.81 55.90	3.68 3.60	8.13 8.10
11c	74	EtOH	210-12	$C_{28}H_{31}N_5O_4S$ (533)	63.03 62.90	5.81 5.90	13.13 13.00
11d	67	EtOH	240-42	$C_{24}H_{18}N_2O_6S$ (462)	62.33 62.10	3.89 3.70	6.06 5.09
11e	46	EtOH	226-28	$C_{24}H_{18}N_2O_4S$ (430)	66.97 66.90	4.18 4.10	6.51 6.40
13	72	EtOH	240-42	$C_{17}H_{13}N_3O_6S$ (387)	52.71 52.80	3.35 3.30	10.85 10.70
14	69	EtOH	238-40	$C_{21}H_{15}Cl_2NO_3S$ (432)	58.33 58.40	3.47 3.30	3.24 3.10

8 **15**	71	EtOH	258-60	$C_{24}H_{17}Cl_2N_3O_3S$ (498)	57.83 57.70	3.41 3.30	8.43 8.59
16	71	EtOH	188-90	$C_{26}H_{19}Cl_2N_3O_4S$ (540)	57.77 57.60	3.51 3.60	7.77 7.70

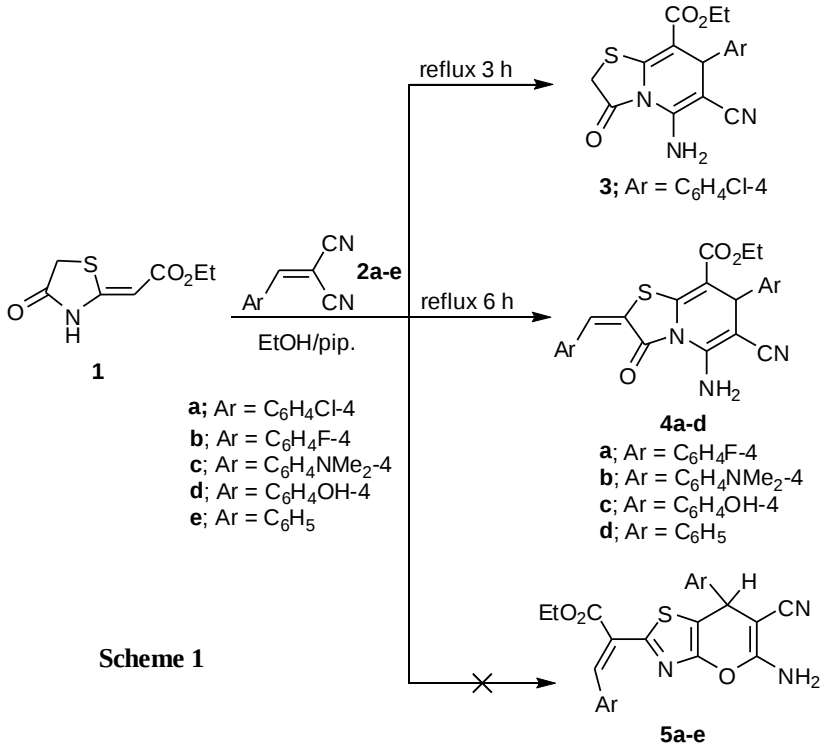
Table 2: Spectral data of the newly synthesized compounds

Comp. .NO	IR(Cm^{-1},ν)	^{1}HNMR(pm); MS: m/z (% abundance)
3	2206 ,(NH_2) 3370 ,3411 (C≡N) and 1714, 1692 (C=O thiazolidinone and ester)	3.79 (s, 2H, CH_2), 4.04 (q, 2H, CH_2, ,(t, 3H, CH_3, J = 7.4 Hz) 1.03 J = 8 Hz) 4.11 (s, 1H, pyridine-H), 7.73-7.68 (d, 4H, Ar-H, J = 7.6 Hz), 8.76 (s, 2H, NH_2)
4a	2180 ,(NH_2) 3370 ,3415 (C≡N) and 1715, 1693 (C=O thiazolidinone and ester)	4.03 (q, 2H, CH_2, J = 8 Hz), 4.51 (s, ,(t, 3H, CH_3, J= 8 Hz) 1.07 1H, pyridine-H), 7.10-7.75 (m, 11H, Ar-H + methine-H+ NH_2) .436 (9.3), 392 (6.7), 370 (100) ,(M^+, 8.5) 465
4b	2187 ,(NH_2) 3320 ,3425 (C≡N) and 1685 (C=O .thiazolidinone and ester)	3.02,3.05 (2s, 12H, 2NMe_2) 4.03 (q, ,(t, 3H, CH_3 , J = 6Hz) 1.07 2H, CH_2, J = 7 Hz), 4.11 (s, 1H, pyridine-H), 7.10-7.75 (m, 11H, Ar-H + methine-H+ NH_2; exchangeable with D_2O)
4c	2180 ,(NH_2) 3333 ,3485 (C≡N) and 1715, 1693 (C=O thiazolidinone and ester)	4.01 (q, 2H, CH_2, J = 6 Hz), 4.41 (s, ,(t, 3H, CH_3, J = 6.8 Hz) 1.04 1H, pyridine-H), 6.62-7.65 (m, 11H, Ar-H + methine-H+ NH_2; exchangeable with D_2O), 9.33, 9.93 (2s, 2H, 2 OH)
4d	2198 ,(NH_2) 3285 ,3378 (C≡N) and 1694 (C=O thiazolidinone and ester)	4.01 (q, 2H, CH_2, J = 6.4 Hz), 4.41 ,(t, 3H, CH_3, J = 6.8 Hz) 1.03 (s, 1H, pyridine-H), 6.62-7.65 (m, 13H, Ar-H + methine-H + NH_2) 352 (100), 324 (3.4), 280 (12.7), 194 ,(M^+, 11) 429 (10.4)
9a	and ,(NH_2) 3277 ,3393 1707, 1692 (C=O thiazolidinone and ester)	3.96, 4.08 (2q, 4H, 2CH_2, J ,(2t, 6H, 2CH_3, J = 7.2 Hz) 1.13 ,1.06 = 6.4 Hz), 4.47 (s, 1H, pyridine-H), 6.96-7.79 (m, 10H, Ar-H + .NH_2), 8.62 (s, 1H, methine-H)
9b	and ,(NH_2) 3246 ,3354 1704, 1683 (C=O thiazolidinone and ester)	3.01 (s, 6H, NMe_2), 3.73 (s, ,(2t, 6H, 2CH_3, J = 7 Hz) 1.22 ,1.07 6H, NMe_2), 3.75, 3.85 (2q, 4H, 2CH_2, J = 6.4 Hz), 4.40 (s, 1H, pyridine-H), 6.83-7.48 (m, 11H, Ar-H + methine-H + NH_2) .490 (31.6), 442 (100), 177(37.3) ,(M^+, 24.3) 562
9c	and ,(NH_2) 3429 ,3468 1692 (C=O thiazolidinone and ester)	4.00, 4.03 (2q, 4H, 2CH_2, J ,(2t, 6H, 2CH_3, J = 5.6 Hz) 1.18 ,1.07 = 6.8 Hz), 4.40 (s, 1H, pyridine-H), 6.83-7.48 (m, 11H, Ar-H + methine-H + NH_2)
9e	and (NH_2) 3267 ,3388 1715, 1693 (C=O thiazolidinone and ester)	3.99, 4.09 (2q, 4H, 2CH_2, J ,(2t, 6H, 2CH_3, J = 5.2 Hz) 1.18 ,1.08 = 7.4 Hz), 4.78 (s, 1H, pyridine-H), 7.76-8.66 (m, 11H, Ar-H + methine-H + NH_2)
11a	and ,(NH_2) 3370 ,3415 1695, 1660 (C=O thiazolidinone, ester and amide)	4.03 (q, 2H, CH_2, J = 8 Hz), 4.53 (s, ,(t, 3H, CH_3, J = 6.8 Hz) 1.05 1H, pyridine-H), 6.37-8.61 (m ,11H, Ar-H + methine-H+ NH_2), 8.85 (s, 2H, $CONH_2$) 436 (9.3), 392 (6.7), 370 (100) ,(M^+, 8.5) 495
11c	and (NH_2) 3377 ,3488 1686, 1664 (C=O thiazolidinone, ester and .amide)	2.88, 3.02 (2s, 12H, 2 NMe_2), 4.15 ,(t, 3H, CH_3, J = 6.8 Hz) 1.22 (q, 2H, CH_2, J = 8 Hz), 4.69 (s, 1H, pyridine-H), 6.51-7.79 (m, 11H, Ar-H + methine-H+ NH_2), 8.82 (s, 2H, $CONH_2$)
11d	2180 (C≡N) ,(OH) 3370 and 1693, 1664 (C=O .thiazolidinone and ester)	4.12 (q, 2H, CH_2, J = 7.8 Hz), 4.79 ,(t, 3H, CH_3, J = 6.8 Hz) 1.16 (s, 1H, pyridine-H), 7.10-7.75 (m, 9H, Ar-H + methine-H), 8.90 (s, 1H, OH), 9.23 (s, 1H, OH), 9.88 (s,1H,OH)

16	2193 ,(NH_2) 3370 ,3415 (C≡N) and 1725, 1693 (C=O .thiazolidinone and ester)	1.93 (s, 3H, $COCH_3$), 3.99 (q, 2H, ,(t, 3H, CH_3, J = 7.2 Hz) 1.03 CH_2, J = 6 Hz) ,4.47(s,1H, pyridine-H) 7.09-7.76 (m, 9H, Ar-H + methine-H), 12.00 (s, 1H NH)

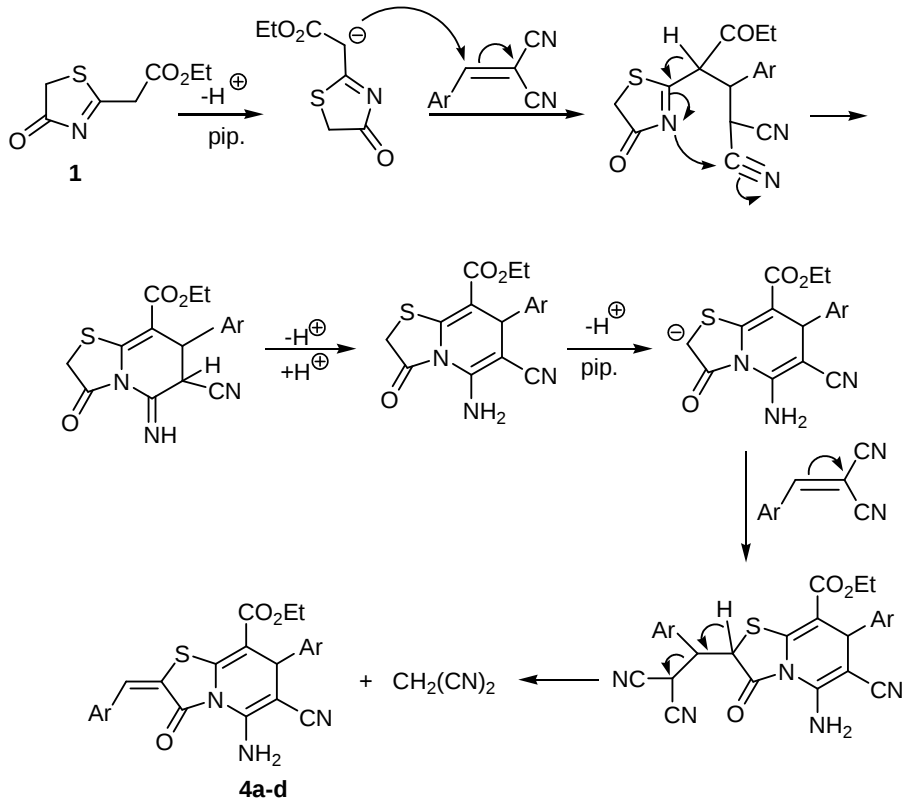
Results and Discussion

The reactivity of 4,5-dihydro-2-ethoxycarbonylmethylidine-4-oxo-1,3-thiazole **(1)** which was produced from the reaction of the ethylcyanoacetate and thioglycollic acid [20] towards some different α,β-unsaturated nitrile compounds was investigated. Thus, compounds **3** and **4a-d** were produced via refluxing of compound **1** with either α-cyanocinnamonitriles **2a** or **2b-e** in absolute ethanol catalyzed with piperidine for 3h and 6h, respectively. On the basis of elemental and spectral data these products were assigned to *2,3,7*-Trihydro-3-oxo-5-amino-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a] pyridine **(3**) and, 2,3,7-Trihydro-2-arylmethylid-ine-3-oxo-5-amino-6-cyano-7-aryl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a] pyridine **(4a -d)** and the structure of **(5a-d**) was ruled out ; Scheme 1.



Scheme 1

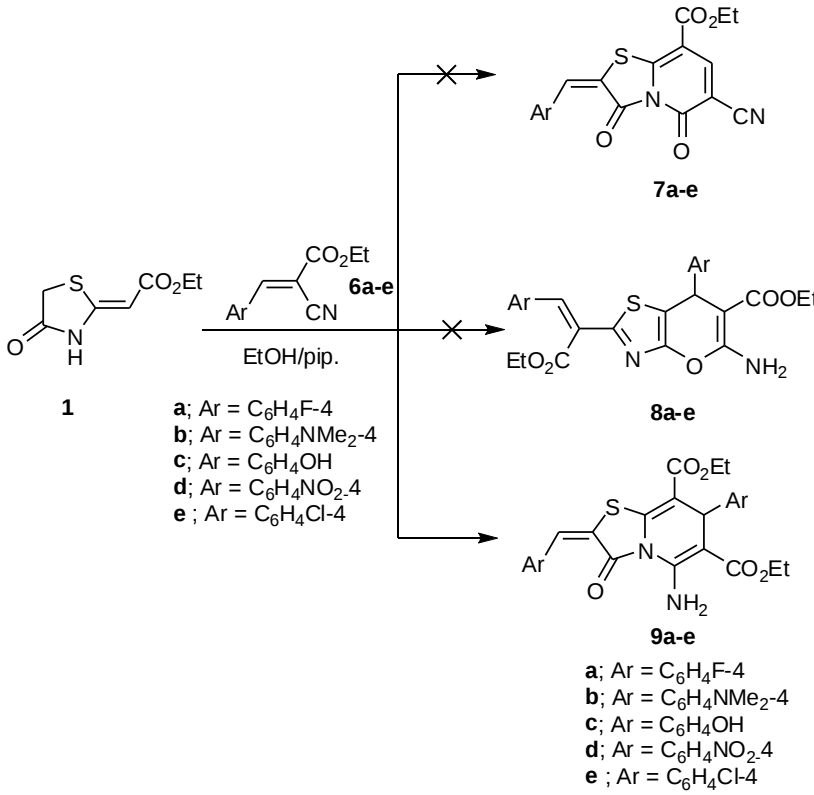
The mechanistic equations for thiazolopyridines **4a-d** formation can be illustrated as follows; Scheme 2.



Scheme 2

The elemental and spectral data were in agreement with thiazolo[3,2-a]pyridine structure **3**, and **4a-d**, the IR spectrum of thiazolopyridine derivative **3** exhibited intensive absorption bands for (NH_2, C≡N, C=O thiazolidinone and ester functional groups) at 3411, 3370, 2206, 1714, and 1692 cm^{-1}, respectively. Moreover, its ^{1}HNMR spectrum revealed in addition to a characteristic signal corresponding to pyridine-H at δ 4.11 ppm, other significant signal was observed at δ 3.79 ppm (s, 2H, CH_2-aliphatic). Also; IR spectra of compounds **4a-d** revealed intensive absorption bands for (NH_2, C≡N, C=O thiazolidinone and ester functional groups).

The treatment of compound **1** with α-ethoxycarbonylcinnamonitriles **6a-e** in boiling ethanol containing a little quantity of piperidine for 4 h resulted in the formation of thiazolopyridines **9a-e ;** Scheme 3.



Scheme 3

On the basis of elemental analysis and spectral data, the other possible structures **7a-e** and **8a-e** were ruled out. IR spectra of compounds **9a-e** displayed presence of absorption bands for amino groups at 3393, 3277, 3254, 3246, 3468, 3429, 3396, 3270, 3393, 3254, 3335 and 3265 cm^{-1}, respectively and absence of sensitive absorption bands for (C≡N groups). Their ^{1}HNMR data showed the presence of characteristic signals for pyridine-H. Mass spectrum of **(9b**; $C_{30}H_{34}N_4O_5S$) showed a molecular ion peak at m/z (562; 24.3%) and a base peak was found in the spectrum at m/z (442). Also, the fragmentation pattern of compound (**9d;** $C_{26}H_{22}N_4O_9S$**)** exhibited a molecular ion peak at m/z (566; 63%) and a base peak at m/z 549. The fragmentation pattern of thiazolopyridine **9b** can be illustrated in Chart **I** .

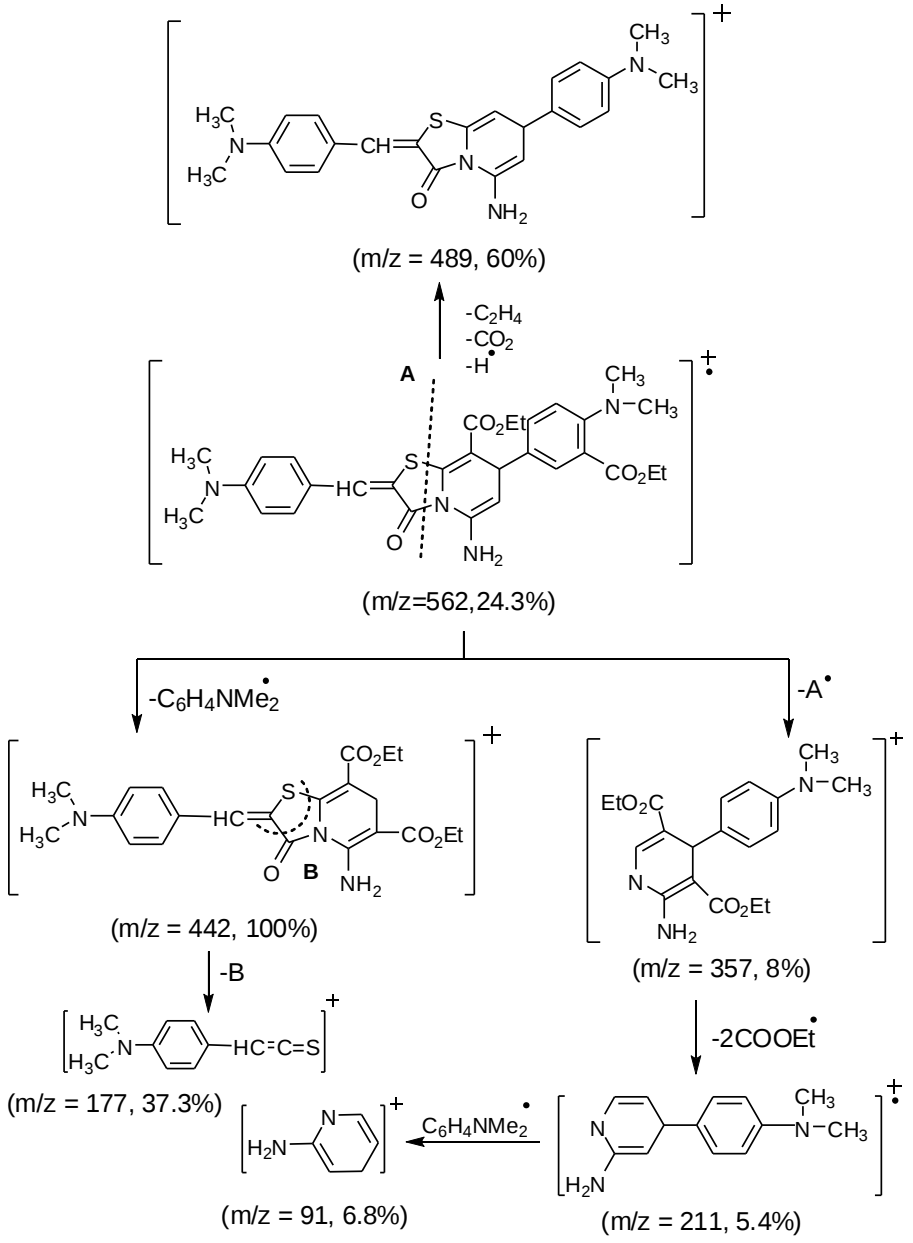
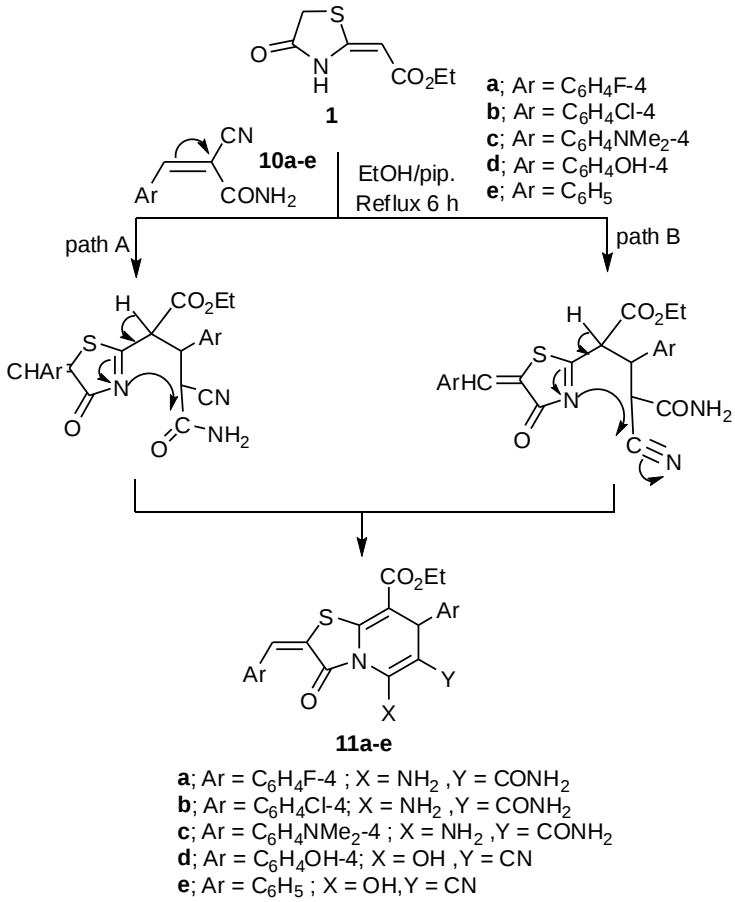


Chart (I): Fragmentation pattern of compound **(9b).**

4-Thiazolidinone **1** , on refluxing with α-formamidocinnamonitriles **10a-e** for 6 h, the reaction consumed 2 moles of α-formamidocinnamonitriles and give products which were formulated as thiazolopyridine derivatives **11a-e** on the basis of the correct elemental and spectral data; Scheme 4.

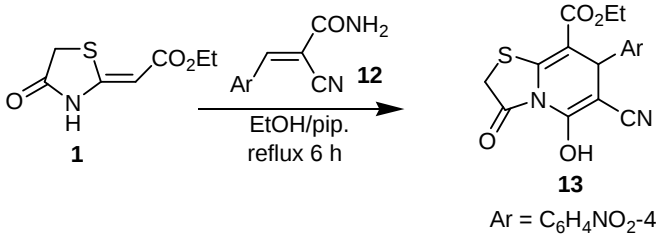


Scheme 4

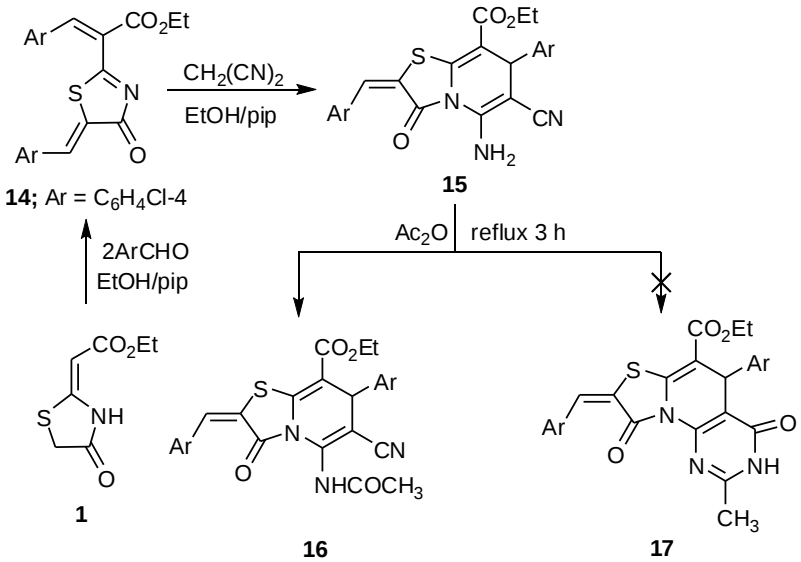
IR spectra of compounds **11a-c** showed the presence of absorption bands corresponding to (NH_2, C=O amide, ester, and thiazolidinone) .Whereas for compounds **11d,e** revealed absorption bands corresponding to hydroxyl and cyano functional groups at 3370, 2180 , and 3393, 2193cm^{-1}, respectively. Moreover; their ^{1}HNMR data displayed significant absorption signals corresponding to pyridine-H.

Mass spectrum of compound **11b** displayed a molecular ion peak at m/z 471 (M^+ = M-OEt, 2.4%) and a base peak at m/z 404.

In case of α-formamidocinnamonitriles **12** (Ar = $C_6H_4NO_2$-4), the reaction consumed one mole and a product was formulated as thiazolopyridine **13** on the basis of the analytical and spectral data.



IR spectrum of compound **13** showed the presence of absorption bands corresponding to (C≡N) at 2220 cm^{-1}. Mass spectrum for thiazolopyridine (**13**; $C_{17}H_{13}N_3O_6S$) showed a molecular ion peak at m/z [(M^+ = M-OEt); (342; 24.4%)], and a base beak at m /z 84. Thiazolo[3,2-a] pyridine **15** have the same aryl group (p-chlorophenyl) at 2 and 7 positions produced by the reaction of malononitrile with compound **14**. The structure of compound **15** was confirmed by its acetylation with acetic anhydride for 3h and gave 5-*N*-acetylamino derivative **16 ;** Scheme 5.



Scheme 5

The structures of compounds **14-16** were deduced from their spectral and analytical data. Mass spectrum of compound (**14**; $C_{21}H_{15}Cl_2NO_3S$) showed a molecular ion peak at m/z (M+1; 433 ,6.7%) and a base peak was found in the spectrum at m/z (168). IR spectrum of compound **15** showed the presence of absorption bands corresponding to (NH_2), (C≡N) and (C=O Thiazolidinone and ester), at 3329, 3214, 2220,1715,and 1680 cm^{-1}, respectively.^{1}HNMR spectrum of the 5-*N*-acetyl amino derivative **16** exhibited two characteristic signals at δ 1.93 ppm and 4.47 ppm arising from (s, 3H, $COCH_3$) and (s, 1H, pyridine-H), respectively.

Antimicrobial activity

Most of the newly synthesized compounds (**3, 4a, 4c, 9d, 9e, 15,** and **16**) were evaluated invitro for their antibacterial activity against two strains of bacteria *pseudomonas aeruginosa*, *and bacillus subtilis*. Also, the antifungal activity against *penicillum italicum*, and syncephalas *trumracemosum* using paper disc diffusion m-ethod [21] 1mg ml^{-1} solution in dimethylformamide DMF was used. The bacteria and fungi were grown on nutrient agar and Czap-ek's –Dox agar media, respectively. DMF as a negative control zones. The agar media were incubated with different microorganism cultures tested. After 25 h of incubation at 30˚C for bacteria and 48 h for fungi, the diameter of Inhibition Zone (mm) was measured. *Chloroamphenicol* and *Terbifin* 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 3. Antimicrobial activity of some newly synthesized compounds.

Compd. No.	Bacteria		Fungi	
	Bacillus Subtilis	Pseudomonas Aeruginosa	Syncephalas Trumracemosum	Penicillum talicum
3	(-)	(-)	(+)	(-)
4a	(-)	(+)	(+)	(++)
4c	(+)	(-)	(-)	(-)
9d	(-)	(-)	(+)	(+)
9e	(+)	(++)	(+)	(+)
15	(++)	(+)	(+)	(+)
16	(+)	(-)	(-)	(-)
Chloroamp-henicol	(++)			
Terbifin			(++)	

Symbols: High activity; (0.6-1.0 mm) (++). Low activity ; (0.1-0.5 mm) (+).
No activity; (-).

Conclusion

Among the series of newly synthesized 2,3,7-trihydro-2-(p-florophe-nylm-ethylidine)-3-oxo-5-amino-6-cyano-7-p-florophenyl-8-ethoxycarbonyl-1,3-thiazolo [3,2-a]pyridine **4a**, 2,3,7-trihydro-2(p-chlorophenylmethylidine)-3-oxo -5-amino-6-cyano-7-p-clorophenyl-8-ethoxycarbonyl-1,3-thiazolo [3,2-a] pyridi-ne **9e**, and 2, 3, 7-trihydro-2-(p-chlorophenylmethylidine)-3-oxo-5-amino -6-cy-ano-7-(p-chloro-phe-nyl-8-ethoxycarbonyl-1,3-thiazolo[3,2-a] pyridine **15** showed the highest activity against *Penicillum italicum*, *Pesudomonas aeruginosa* and *Bacillus Subtilis* , respe-ctively. The highest activity may be due to the presence of p-flourophenyl and p-chlorophenyl moieties in their structures.

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