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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME HITHERTO UNKNOWN 4-OXO-THIAZOLES AND THIAZOLO [3, 2-A] PYRIDINES

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ABSTRACT

*2-(4-Oxothiazolidin-2-ylidene) acetonitrile and ethyl -2-(4-oxothiazolidin-2-ylidene) acetate **(1a, b)**, were condensed with anthralaldehyde (1:1 molar ratio) and gave 4, 5-dihydro-4-oxothiazole derivatives (**2a, b**). Refluxing of 2-(Antharacene-9-yl-methylene) malononitrile in acetic acid with thioglycollic acid gave **(3)**. 4-Thiazolidinones containing bis aryl methylidine moieties (**4a-c**) and (**5a, b**) were produced via condensation of either **(2a)** or **(3)** with different aromatic aldehydes (1:1 molar ratio). Heating of **(2a)** with α-substituted cin- namonitriles gave the expected substituted thiazolo [3, 2-a] pyridines **(6a-d), (8)** and **(10a-c)**. The synthesized compounds have been screened for their antimicrobial activities against some selected species of Gram-positive (G^+). Gram-negative (G^-) bacteria and 3 different types of fungi. They were found to be more active against Gram positive than Gram negative bacteria.*

Keywords: Thiazolidinones; Thizolopyridines ; Antibacterial; Antifungal; Synthesis.

INTRODUCTION

It is well known that, the increasing cases of microbial resistance become a threat for human life worldwide, Moreover, invasive microbial infections caused by multi-drug-resistant *Gram*-positive bacteria and microbes are difficult in diagnosis and treatment [1]. They are the major cause of morbidity and mortality especially in immune suppressed and hospital-acquired patients. To overcome these problems, the development of new and safe antimicrobial agents with better effectiveness is urgently required. As a result of the high antimicrobial activity of heterocyclic compounds, one of the best ways to design new antimicrobial agents is to generate hybrid molecules by combining two bioactive heterocyclic moieties in a single molecular scaffold. Thiazoles are synthetic intermediates and common substructures in numerous biologically active compounds [2-5]. There has been considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities [6-8] and exhibits highly specific activity in vitro against Mycobacterium tuberculosis [9-12]. Furthermore, the pyridine scaffold is a widespread structural motif that can be found in many natural products and in several pharmacologically interesting compounds. Therefore, synthesis of biologically active pyridine derivatives, is the target of different active research areas. Recently, several researchers became interested to cyanopyridine derivatives [13-21]. It is thought of interest to accommodate thiazolidin-4-one and pyridine moiety in a single molecular framework. With this in mind and in continuation of our research on synthesis of biologically active antimicrobial heterocylcles [22-30] we are report here synthesis of some a novel series of thiazolidinones class having pyridine moiety in addition to investigation of their antimicrobial activities.

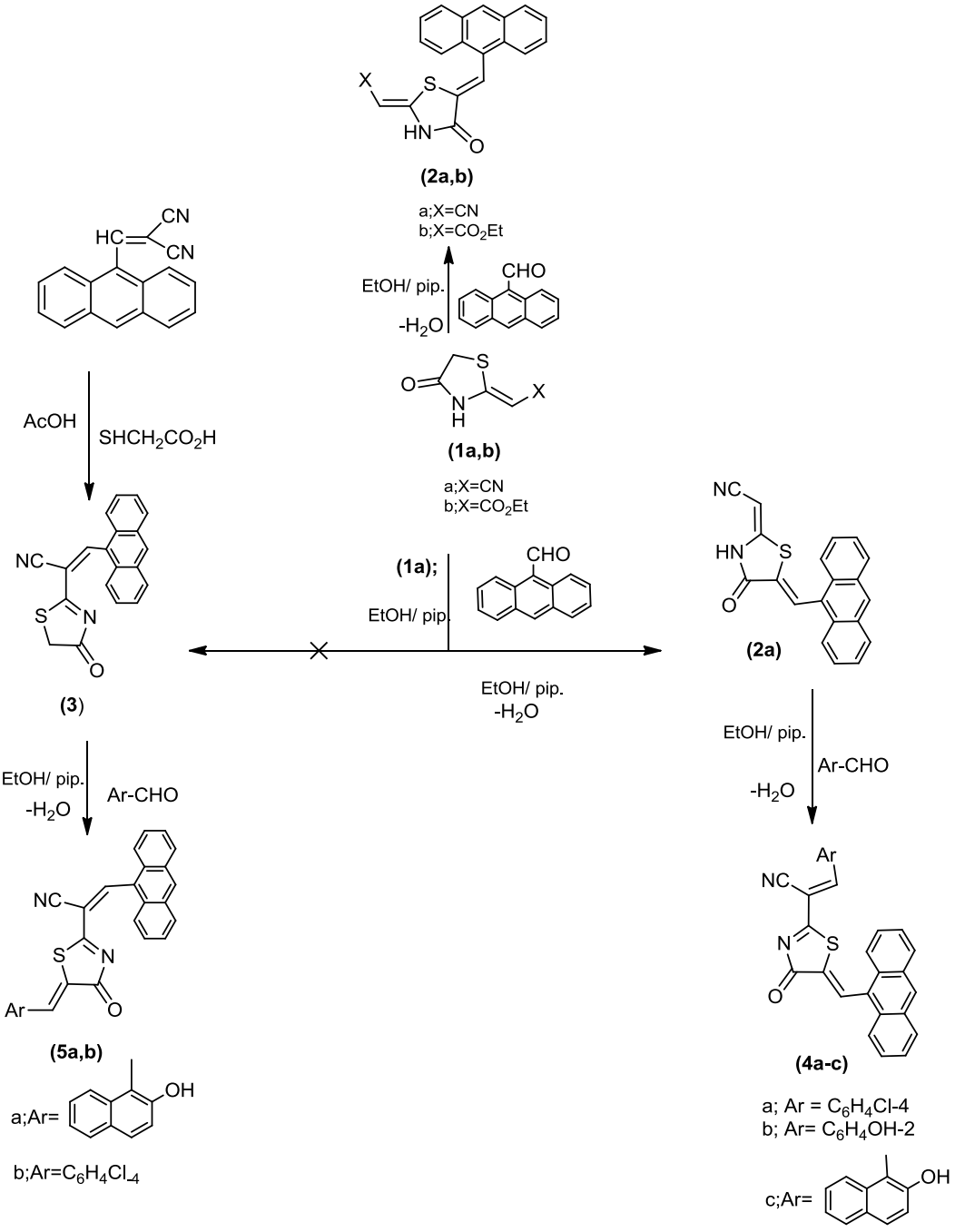
RESULTS AND DISCUSSION

Chemistry

All compounds are stable in air. The theoretical values are in a good agreement with the experimental values. The formulation of these compounds is based on the elemental analysis, IR, Mass spectra, ^{1}H-NMR and ^{13}C-NMR.

The synthesized compounds are depicted in Schemes 1- 4. 4-oxo-thiazole derivative(**1)** [31] is characterized by presence of two active methylene as well as nitrile and carbonyl groups which make it chemically very active so it can be used as a precursor to synthesize many biologically and chemically active ring

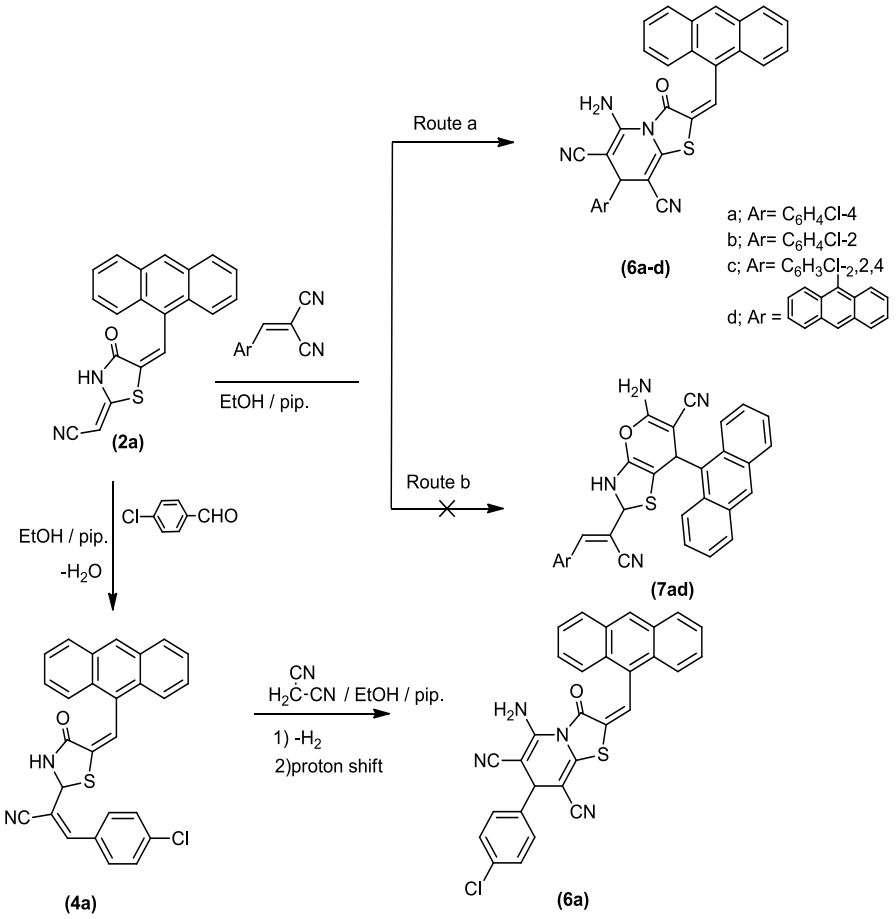
systems. Condensation of acetonitrile **(1a)** with 9-anthranldehyde (1:1 molar ratio) in ethanol containing catalytic amount of piperidine afforded the arylidene derivative as a single product for which (**2a)** or (**3)** seemed possible. Compound (**3)** has been synthesized through another route via the reaction of 2-(anthracen-9-ylmethylene) malononitrile with thioglycolic acid. This, prove that, anthralaldehyde condensed first with 4-thiazolidinone ring **(1a)** at the most active methylene at position number **5** (Scheme 1). Similarly ethyl 5-(anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene) acetate **(2b)** was produced through condensation of **(1b**) with anthraldehyde in refluxing ethanol catalyzed with piperidine. The structures of the latter products were confirmed by spectroscopic studies and elemental analysis. The IR spectrum of compound (**2a)**, for example, revealed



Scheme 1 Synthesis of bis arylmethylidine 4- thiazolidinones.

absorption bands at 3183, 2195 and 1707 cm^{-1} corresponding to an NH, cyano and carbonyl characteristics for thiazolidinone. It's ^1H NMR spectrum revealed signals at δ 5.16 and 11.49 ppm due to methine-H and NH protons. Whereas, ^1H NMR spectrum of (**2b)** showed besides the specific signals for methine and NH at 5.57 and 11.49, there are two signals at 1.08 as triplet and at 3.96 ppm as quartet corresponding for the ester group. IR spectrum of (**3)** assigned stretching absorption frequency at 1653 cm^{-1} assignable to ethyleneic carbonyl group. Condensation of **(2a)** with various aromatic aldehydes (1:1 molar ratio) in ethanolic piperidine solution afforded the bis arylidene derivatives **(4a-c)**. Similarly the other bis arylidene derivatives (**5a, b)** were obtained through condensation of compound **(3)** with different aromatic aldehydes (1:1 molar ratio) with refluxing. The spectral data of the isolated products were in a complete agreement with structure (**4)** and (**5**). The IR spectrum for compound (**4b)** as example revealed absorption bands at 3330, 2204 and 1655 cm^{-1} corresponding to OH, C≡N and C=O functions respectively. The ^1H NMR spectrum of (**4a)** (DMSO–d6) showed multiplet signal at δ 6.58–8.66 region distinctive for aromatic protons beside two singlet signals at 9.01, 9.05 ppm characteristic of two methine protons. The mass spectrum of (**4b)** showed a molecular ion peak at m/z = 432 (0.76%), corresponding to molecular formula $C_{27}H_{16}N_2O_2$.

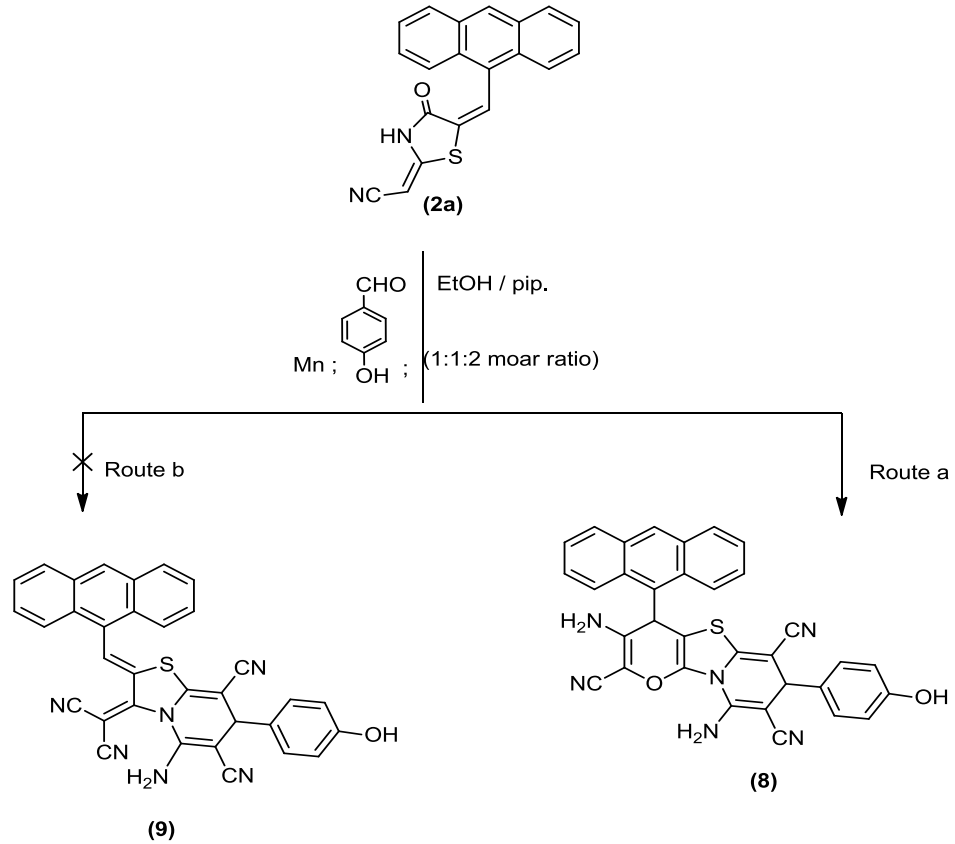
In view of the growing biological importance of fused cyanopyridones, particularly thiazolo [1,2-a] pyridines [32-34] it was of interest to synthesize some thiazolopyridine derivatives containing anthrancenyl moiety on the hope of obtaining more active compounds. Thus, 4-oxo-thiazole derivative **(2a)** was cyclized with α-cyanocinnamonitriles in ethanolic piperidine media to furnish a single product for which structure (**6)** considered (Scheme 2).



Scheme 2 Synthesis of thiazolo [3, 2-a] pyridine enamininitriles

Both elemental analysis and spectral data of the isolated products were in accord with the proposed structure **(6a-d)**. The IR spectrum of (**6b)** as an example showed the appearance of absorption frequencies at 3388, 3266, 2197 and 1715 for NH_2, C≡N and C=O functions respectively; Fig. 1. Also, the ^1H NMR spectrum of (**6a)** exhibited the lack of singlet signal at δ 5.16 specific for the methine proton and occurred a singlet signal at 4.70 due to pyridine-H. Its mass spectrum showed a molecular ion peak at m/z = 516 alike to a molecular formula $C_{30}H_{17}ClN_4OS$. Chemically, thiazolo [3,2-a] pyridine derivative of structure (**6a)** was also proved via refluxing of (**4a)** with one mole of malononitrile (m. p. and mixed m.p., and IR spectrum). The dihydropyrano [2',3': 4,5] thiazolo [3,2-a] pyridine **(8)**.was achieved as a sole product through one pot reaction of (**2a)** with p-hydroxy benzaldehyde and malononitrile (1:1:2 molar ratio) (Scheme 3). Actually, the product of this reaction was elucidated on the basis of its spectral data. The IR spectrum showed absence of absorption band characteristic to a carbonyl group and exhibited characteristic absorption bands at 3316, 3206 and 2201 due to NH_2 and C≡N, respectively. Also, ^1H NMR spectrum supported structure **(8)** and rejected **(9)** structure, that's because occurrence of the 4H-pyridine and 4H- pyran ring protons as two singlet signals at δ 4.14 and 4.34 ppm respectively beside the other expected signals. Its mass spectrum showed a molecular ion at m/z = (564; 41.47%) corresponding to a molecular formula $C_{33}H_{20}N_6O_2S$; Fig. 2**.**

The foregoing results prompted us to investigate the applicability and synthetic potency of (**2)** to develop a facile and convenient route to thiazolopyridines of an expected pharmaceutical interest. Thus, reaction of **(2a)** with α–ethoxy carbonyl cinnamonnitriles in refluxing ethanolic piperidine gave a product for which (**10)** and **(11)** can be formulated. On the basis of analytical and spectral data structure **(11)** was readily eliminated and (**10)** structure was acceptable. Thus, the IR spectrum of **(10a)** showed the presence frequencies. NH_2, C≡N and C=O ester, thiazolidinone at 3414, 3289,

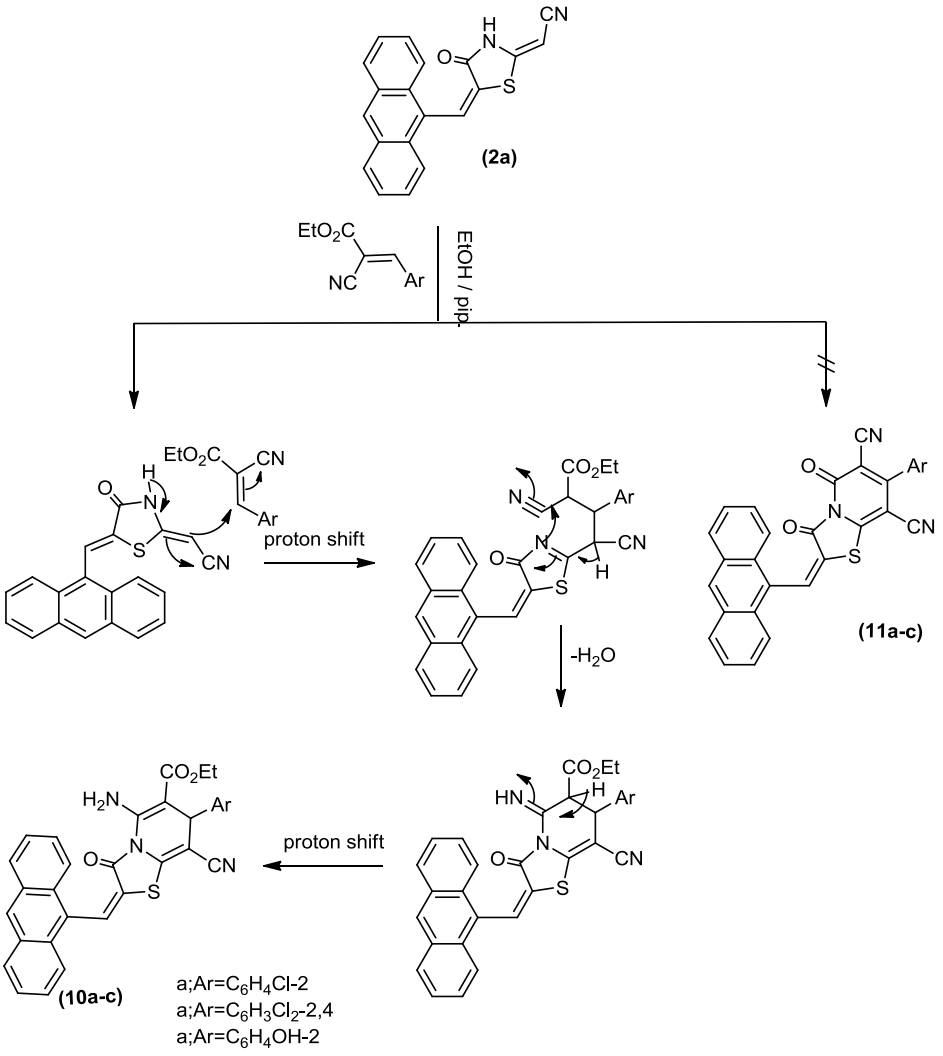


Scheme 3 Synthesis of pyrano [2, 3-4,5]thiazolo[3,2-a]pyridine.

2210 and 1714 Its ^{1}H NMR spectrum exhibited triplet signal at 0.83 J=7.5Hz and quartet signal at 3.87 J = 7.5 Hz corresponding for the ethoxy ester function beside singlet signal at 5.16 ppm due to pyridine-H.; Fig. 3. The mechanism of the reaction was proceeds via generation of carbanion of CH_2 which attack β-carbon of cinnamonitriles followed by proton shift (Scheme 4).

Biological evaluation

In general, most of the tested compounds revealed better activity against the Gram-positive rather than the Gram-negative bacteria, it may be concluded that the antimicrobial activity of the compounds is related to cell wall structure of the bacteria. It is possible because the cell wall is essential to the survival of bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan. *Gram*-positive bacteria possess a thick cell wall containing many layers of peptidoglycan and teichoic acids, but in contrast, *Gram*-negative bacteria have a relatively thin cell wall consisting of a few layers of peptidoglycan surrounded by a second lipid membrane containing lipopolysaccharides and lipoproteins. These differences in cell wall structure can produce differences in antibacterial susceptibility and some antibiotics can kill only *Gram*-positive bacteria and is infective against Gram-negative pathogens (Koch, A.L., 2003, El-Sherif, A.A., 2015). The results of the antibacterial activity and activity inxed percent of the synthesized compounds are recorded in Tables 1 and 2. The results revealed that:



Scheme 4. Synthesis of thiazolo [3, 2-a] pyridine enaminoester derivatives.

1- The activity of the compounds against E. coli is better than against Klebsiella pneumoniae.

2- Activity of these compounds against E. coli decreased in the order *Gentamycin* > 2b > 4a ≈ 5 > 6c > 10a ≈ 4b > 2a and against *Klebsiella pneumoniae* decreased in the order Gentamycin > 6b > 4b ≈ 2b > 5 > 4a > 10a > 2a under experimental conditions.

3- Antibacterial activity of these compounds versus gram positive bacteria indicates that, these compounds have better activity versus *Staphylococcus epidermidis* than *Staphylococcus aureus*. Activity of these compounds *against Staphylococcus epidermidis* decreased in the order Ampicillin > 6b > 2b > 4b > 4a > 2a > 5 > 10a and against *Klebsiella pneumoniae* decreased in the order Ampicillin > 6b > 4b > 2b ≈ 5 > 10a > 4a > 2a.

4- The synthesized compounds have no antibacterial activity versus *Neisseria gonorrhoeae*.

5- Compound 2b which contain ester group has a higher activity than 2a which contain cyano group.

6- Compounds 4a and 4b which contain 4-chlorophenyl or 2-hydroxyphenyl respectively have approximately equipotent activities against the tested organisms.

7- Compound 10b has no biological activity versus the investigated five types of gram positive and gram negative bacteria.

8- Compounds 2a, 6c, 10a, and 9b exhibited weak to moderate growth inhibitory activity versus the tested bacteria.

9- Equal potencies was observed for compounds 4 and 5 which differ in the arylidene positions.

10- The fungal strain *Aspergillus-clavatus* (RCMB 02593) is not affected with any of the tested compounds (Table 3).

11- Compounds 7, 10c and 10b have no antifungal activity versus the selected types of fungal species (Table 4).

12- Compounds 2b and 6b have a good and higher activity against *Aspergillus fumigates*, and *Geotricum Candidum fungal species.*

13- Regarding the minimum inhibitory concentration of the tested compounds against the antifungal strains, the results revealed that compounds 2b (MIC = 3.9, 1.95 µg ml^{-1}), 4b (MIC = 3.9, 1.95, µg ml^{-1}) and 6b (MIC = 3.9, 1.95, µg ml^{-1}) proved to be equipotent to with respect to *Aspergillus fumigates* (RCMB 02564), and *Geotricum Candidum* (RCMB 05096) (Table 5).

14-The antibacterial and antifungal activities were given in Figs 1 and 2respectively.

Table 1. Antibacterial activity of the synthesized compounds

	Inhibition zone diameter in mm					
	Gram Positive Bacteria			**Gram Negative Bacteria**		
	Staphylococcus aureus	*Staphylococcus epidermidis*	*Bacillus subtillis*	*Neisseria gonorrhoeae*	*Esherichia coli*	*Klebsiella pneumoniae*
2a	15.2 ± 0.58	17.2 ± 0.63	19.2 ± 0.42	NA[a]	15.6 ± 0.72	16.2 ± 0.63
2b	18.2 ± 0.25	19.6 ± 0.58	22.4 ± 0.63	NA	19.2 ± 0.72	20.6 ± 0.63
4a	16.7 ± 0.72	18.2 ± 1.2	20.3 ± 0.43	NA	18.9 ± 1.2	20.1 ± 0.81
4b	19.4 ± 0.58	18.3 ± 0.63	20.3 ± 0.63	NA	17.3 ± 1.2	20.6 ± 2.1
5	18.2 ± 0.72	13.3 ± 0.44	19.2 ± 0.63	NA	18.9 ± 0.72	20.3 ± 1.2
6b	21.1 ± 0.63	21.9 ± 0.72	22.3 ± 0.53	NA	18.3 ± 0.72	22.4 ± 0.25
6c	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA
9a	17.2 ± 0.72	12.4 ± 0.72	17.3 ± 0.67	NA	17.2 ± 0.72	17.9 ± 0.58
9b	NA	NA	NA	NA	NA	NA
St.	28.9 ± 0.14	25.4 ± 0.18	34.6 ± 0.35	22.3 ± 0.58	23.4 ± 0.3	26.3 ± 0.15

[a]NA: not detected

Table 2. Activity index for the antibacterial activity of the synthesized compounds

	Activity index %					
	Staphylococcus aureus	***Staphylococcus epidermidis***	***Bacillus subtillis***	***Neisseria gonorrhoeae***	***Esherichia coli***	***Klebsiella pneumoniae***
2a	52.60	67.72	55.49	-	66.67	61.60
2b	62.98	77.17	64.74	-	82.05	78.33
4a	57.79	71.65	58.67	-	80.77	76.43
4b	67.13	72.05	58.67	-	73.93	78.33
5	62.98	52.36	55.49	-	80.77	77.19
6b	73.01	86.22	64.45	-	78.21	85.17
6c	-	-	-	-	-	-
7	-	-	-	-	-	-
9a	59.52	48.82	50.00	-	73.50	68.06
9b	-	-	-	-	-	-
Standard[a]	100	100	100	100	100	100

[a]Gentamycin is used as standard for gram negative bacteria and Ampicillin is used as standard for gram positive bacteria

Table 3. Antifungal activity of the synthesized compounds.

	Inhibition zone diameter in mm		
	Fungi		
	*Aspergillus fumigates (*RCMB 02564)	*Aspergillus-clavatus* (RCMB 02593)	*Geotricum Candidum (*RCMB 05096)
2a	16.3 ± 0.72	NA	18.2 ± .063
2b	19.4 ± 0.63	NA	21.3 ± 0.63
4a	17.2 ± 0.58	NA	19.2 ± 0.63
4b	19.1 ± 0.63	NA	21.2 ± 0.58
5	17.6 ± 0.72	NA	18.4 ± 0.63
6b	19.3 ± 0.63	NA	21.3 ± 0.38
6c	NA	NA	NA
7	NA	NA	NA
9a	14.1 ± 0.63	NA	15.2 ± 0.58
9b	NA	NA	NA
St.	28.9 ± 0.14	NA	34.6 ± 0.35

[a]NA: not detected

Table 4. Activity index percent for the antibacterial activity of the synthesized compounds

	Activity index		
	Aspergillus fumigates	***Aspergillus clavatus***	***Geotricum Candidum***
2a	56.40	-	52.60
2b	67.13	-	61.56
4a	59.52	-	55.49
4b	66.09	-	61.27
5	60.90	-	53.18
6b	66.78	-	61.56
6c	-	-	-
7	-	-	-
9a	48.79	-	43.93
9b	-	-	-
Standard	100.00	-	100.00

Table 5. Minimum inhibitory concentration MIC (µg/ml) of the synthesized compounds against the tested microorganisms.

	Minimum inhibitory concentration (µg/ml)					
	2b	4a	4b	5	6b	Standard
FUNGI *Aspergillus fumigatus (RCMB 02564)*	3.9	15.63	3.9	7.81	3.9	Amphotericin B 0.98
Aspergillus clavatus (RCMB 02593)	NA[a]	NA	NA	NA	NA	1.95
Geotricum candidum (RCMB 05096)	1.95	3.9	1.95	7.81	1.95	0.49
Gram Positive Bacteria: *Staphylococcus aureus (RCMB 010027)*	7.81	15.63	3.9	15.63	1.95	*Ampicillin* 0.49
Staphylococcus epidermidis (RCMB 010024)	3.9	62.5	7.81	7.81	0.98	0.49
Bacillis subtilis (RCMB 010063)	1.95	15.63	3.9	1.95	0.98	0.24
Gram negativeBacteria: *Neisseria gonorrhoeae (RCMB 010079)*	NA	NA	NA	NA	NA	*Gentamycin* 0.98
Escherichia coli (RCMB 010052)	3.9	15.63	7.81	3.9	7.81	1.95
Klebsiella pneumoniae (RCMB 0010093)	3.9	7.81	1.95	3.9	1.95	0.49

[a]NA: not detected

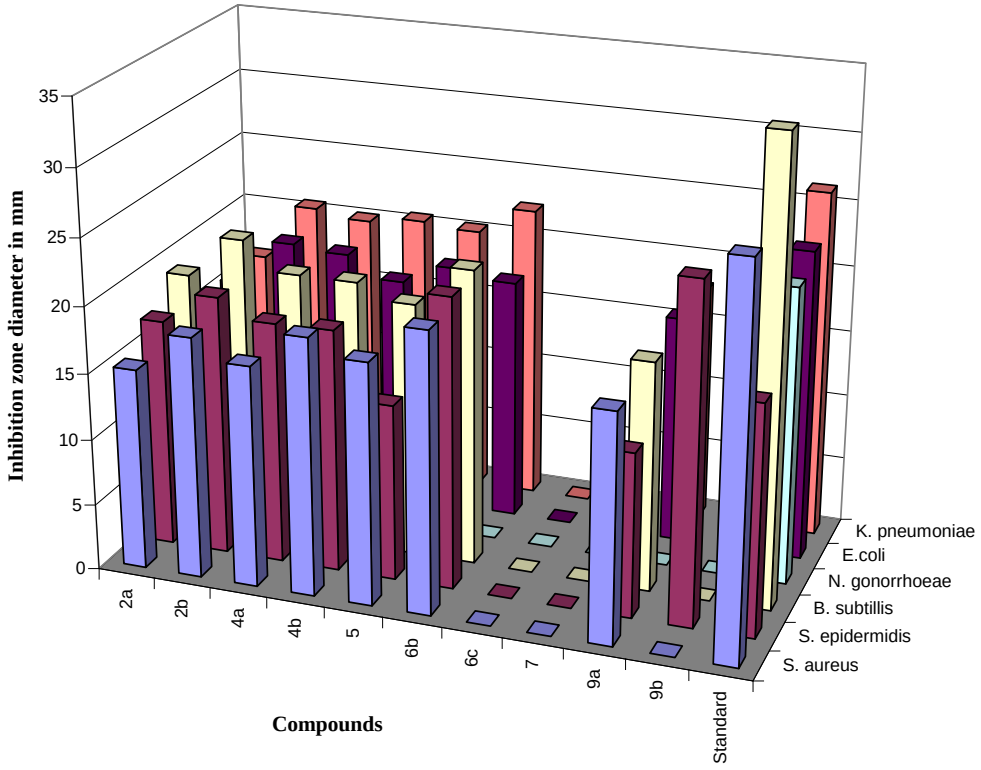


Fig. 1. Antibacterial activity of the synthesized compounds

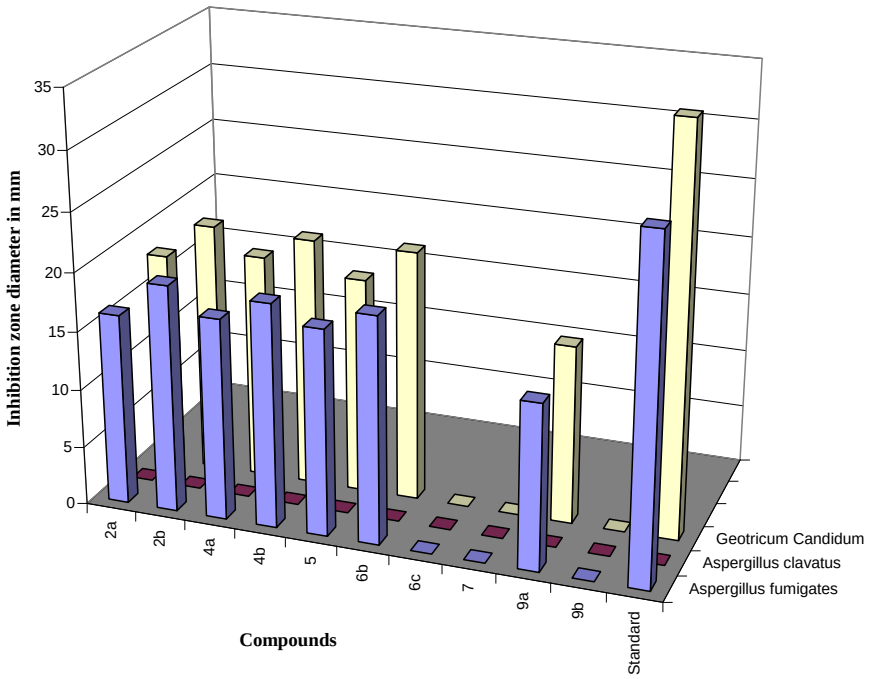


Fig.2. Antifungal activity of the synthesized compounds

CONCLUSIONS

We have described herein an efficient and convenient method for synthesis of some thiazolidinoe and thiazolopyridine derivatives. The antibacterial and antifungal activities were investigated for ten of the prepared compounds. The best antimicrobial activity was observed for compound **2b** versus E. coli, **6b** versus *Klebsiella pneumoniae*. Also, compound **6b** was active versus both investigated types of gram positive bacteria (*Staphylococcus epidermidis* and *Klebsiella pneumoniae).* Compounds **2b** and **6b** have a good and higher activity against *Aspergillus fumigates*, and *Geotricum Candidum fungal species.*

EXPERIMENTAL

Material and methods

All melting pints (m.p.) are uncorrected, IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^{1}H NMR 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. ^{13}C NMR spectra were run out at 75 MHz. Micro analytical data were obtained from the Micro analytical Research Centre, faculty of science, Cairo University. The reactions were monitored by thin layer chromatography (TLC) using TLC sheets with UV fluorescent silica gel Merck 60f 254 plates using UV lamp and different solvents as mobile phases.

Chemistry

General procedure for synthesis 2-[5-(Anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene) acetonitrile (2a) and ethyl 2-[5-(anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene) acetate (2b)

A mixture of anthraldehyde (0.01 mol) was heated for 2 h with either **(1a)** or **(1b)** (0.01 mol) in absolute ethanol (20 mL) and piperidine (0.05 mL). The solid product was precipitated out of heating then collected and recrystallized from suitable solvent.

2-[5-(Anthracen-9-ylmethylene)-4-oxothiazolidine-2-ylidene) acetonitrile (2a)

Browns crystals (EtOH); Yield 72 %; m. p :125-127 ºC; IR (KBr, ύ, cm^{-1}): 3183 (NH), 3055 (CH- arom.), 2923 (CH- aliph.), 2195 (C≡N) and 1707 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6): δ/ppm 5.16 (s, 1H, methine-

H), 7.51-8.75 (m, 10H, Ar-H+methine-H), and 11.49 (s, 1H, NH; cancelled with D_2O); Anal. Calcd for $C_{20}H_{12}N_2OS$ (328): C, 73.15; H, 3.68; N, 8.53; Found: C, 73.42; H, 3.81, N, 8.85.

Ethyl 2-[5-(anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene) acetate (2b)

Yellows crystals (EtOH); Yield 77 %; m. p: 245-247 ºC ; IR (KBr, ύ, cm^{-1}): 3246 (NH), 3008 (CH-arom.), 2892 (CH-aliph.) and 1689 (2 C=O thiazolidinone and ester); ^1H NMR (DMSO-d_6): δ/ppm 1.08 (t, 3H, CH_3), 3.96 (q, 2H, CH_2), 5.57 (s,1H, methine-H), 7.49-8.74(m, 9H, Ar-H), 9.01 (s,1H, methine-H) and 11.49 (s, 1H, NH; exchangeable with D_2O); Anal. Calcd for $C_{22}H_{17}NO_3S$ (375): C, 70.38; H, 4.56; N, 3.73. Found: C, 70.52; H, 4.81; N, 3.52.

Synthesis 2-(Anthracen-9-yl)-2-(4-oxothiazolidin-2-ylidene) acetonitrile (3)

To a solution of 2-**(**anthracene-9-yl-methylene) malononitrile (0.01 mol) in acetic acid (20 mL), thioglycollic acid (0.01 mol) was added. The solution was refluxed for 2 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Yellow powder (EtOH); Yield 54 %; m. p: 160-162 ºC; IR (KBr, ύ, cm^{-1}):3323 (NH), 3049 (CH-arom.), 2929 (CH-aliph.), 2193((C≡N) and 1653 (C=O thiazolidinone); Anal. Calcd for $C_{20}H_{12}N_2OS$ (328): C, 73.15; H, 3.68; N, 8.53. Found: C, 73.61; H, 3.25; N, 8.31.

General procedure for synthesis 2-[5-(Anthracen-9-yl-methylene)-4-oxo-4, 5-dihydroth- iazolidin-2-yl)]-3-aryl-acrylonitrile (4a-c)

A mixture of 4-thiazolidinone derivative (**2a**) (0.01 mol) and aromatic aldehydes (0.01 mol), in absolute ethanol (20 mL) and piperidine (0.05 mL) was refluxed for 3 h. The solid product formed was collected by filtration and recrystallized from suitable solvent.

2-[5-(Anthracen-9-yl-methylene)-4-oxo-4, 5-dihydrothiazolidin-2-yl)]-3-(4-chloro-phenyl) -acrylonitrile (4a)

Reddish brown crystals (ETOH); Yield 67; %m. p: 150-152 ºC; IR (KBr, ύ, cm^{-1}): 3056 (CH-arom.), 2978 (CH-aliph.), 2195 (C≡N) and 1709 (C=O thiazolidinone); ^1H NMR (DMSO-d_6): δ/ppm 6.58-8.66 (m, 13H, Ar-H), 9.01, 9.05 (2s, 2H, methine-H); Anal. Calcd for $C_{27}H_{15}ClN_2OS$ (450): C, 71.91; H, 3.35; N, 6.21 Found: C, 72.71; H, 3.79, N, 6.09.

2-[5-(anthracen-9-yl-methylene)-4, 5 dihydro-4oxo-thiazolidin-2-yl)]-3-(2-hydroxyphenyl)-acrylonitrile (4b).

Brown crystals (EtOH); Yield 78 %. m. p: 130-132 ºC; IR (KBr, ύ, cm^{-1}): 3330 (br, OH), 3055 (CH-arom.), 2204 (C≡N) and 1655 (C=O thiazolidinone); MS m/z (%):432 (M^+, 0.76); Anal. Calcd for $C_{27}H_{16}N_2O_2S$ (432.49) C; 74.98; H, 3.73; N, 6.48 Found: C; 74.62; H, 3.98; N, 6.19.

2-[5-(Anthracen-9-yl-methylene)-4-oxo-4, 5-dihydrothiazolidin-2-yl)]-3-(2-hydroxy-naphthalen-1-yl) acrylonitrile (4c)

Brown crystals (EtOH); Yield 67; m. p. 160-162 ºC; IR (KBr, ύ, cm^{-1}): 3221 (br-OH), 2205(C≡N) and 1651 (C=O thiazolidinone); ^1H. NMR (DMSO-d_6): δ/ppm 6.98-8.21 (m, 15H, Ar-H), 9.01, 9.04 (2s, 2H, methine-H), 11.01(s, 1H, OH); Anal. Calcd for $C_{31}H_{18}N_2O_2S$ (482.55): C, 77.16; H, 3.76; N, 5.81 Found: C, 77.32; H, 3.52, N; 5.41.

General procedure for synthesis 3-(Anthracen-9-yl)-2-(5-(arylmethylidine)-4-oxo-4, 5-dihydrothiazol-2-yl) acrylonitrile (5a, b)

To a solution of 4-thiazolidinone derivative (**3**) (0.01 mol) in absolute ethanol (20 mL) and piperidine (0.5 mL) either α-hdroxy naphthaldeehyde or p-chloro benzaldehyde (0.01 mol) was added. The solution was heated for 3 h. The solid product formed was collected by filtration and recrystallized from suitable solvent.

3-(Anthracen-9-yl)-2-(5-(2-hydroxynaphthylidine)-4-oxo-4, 5-dihydrothiazol-2-yl) acrylonitrile (5a)

Brown crystals (EtOH); Yield 65 %. m. p.: 160-162 ºC; IR (KBr, ύ, cm^{-1}): 3375 (br. OH), 3052 (CH- arom.), 2927 (CH- aliph.), 2206(C≡N) and 1662 (C=O); MS m/z (%):481 (M^+-1, 56.70); Anal. Calcd for $C_{31}H_{18}N_2O_2S$

(482.55): C, 77.16; H, 3.76; N, 5.81 Found: C, 77.45; H, 3.92; N; 5.98.

3-(Anthracen-9-yl)-2-(5-(4-chlorobenzylidene)-4-oxo-4, 5-dihydrothiazol-2-yl) acrylonitrile (5b)

Brown crystals (EtOH); Yield. 75 %; m. p.: 100-102. ºC; IR (KBr, ύ, cm^{-1}): 3056 (CH-arom.), 2927 (CH- aliph.), 2198 (C≡N) and 1658 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6): δ/ppm 6.59-8.10 (m, 13H, Ar-H), 8.20, 8.99 (2s, 2H, methine-H); Anal. Calcd for $C_{27}H_{15}N_2ClOS$ (450): C, 71.91; H, 3.35; N, 6.21 Found: C, 72.01; H, 3.79; N; 6.10.

5-Amino-2-(anthracen-9-ylmethylene)-7-aryl-3-oxo-3, 7-dihydro-2H-thiazolo [3, 2-a]pyridi -ne-6, 8-dicarbonitriles (6a-d)

A mixture of 4-thiazolidinone derivative (**2a**) (0.01 mol) and α-cyanocinnamonitrile (0.01 mol), in absolute ethanolic (20 mL) and piperidine (0.5 mL) was refluxed for 6 h. The solid products formed were collected by filtration and recrystallized from suitable solvent.

***5-Amino-2-(anthracen-9-ylmethylene)-7-(4-chlorophenyl)-3-oxo-3, 7-dihydro-2H-thiazolo [3, 2-a] pyridine-6, 8-dicarbonitrile* (6a).**

Brown powder (EtOH); Yield. 75 %; m. p.: 160-162ºC; IR (KBr, ύ, cm^{-1}): 3331, 3354 (NH_2), 3051 (CH. arom.) , 2200 (C≡N) and 1708 (C=O thiazolidinone) ^{1}H NMR (DMSO-d_6):δ/ppm 4.70 (s, 1H, pyridine-H), 6.37-8.80 (m, 16H, Ar-H + methine-H + NH_2 ,exchangeable with D_2O); MS m/z (%): 516, (M^+, 6.89); Anal. Calcd for $C_{30}H_{17}ClN_4OS$ (516): C, 69.69; H, 3.31; N, 10.84 Found: C, 70.12; H, 3.64; N, 10.37.

5-Amino-2-(anthracen-9-ylmethylene)-7-(2-chlorophenyl)-3-oxo-3,7-dihydro-2H-thiazolo

Yellow powder (EtOH); m. p: 295-297; Yield. 71 %; IR (KBr, ύ, cm^{-1}): 3388, 3266 (NH_2), 3050 (CH- arom.) 2197 (C≡N) and 1715 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6): δ/ppm 5.09 (s, 1H, pyridine-H), 7.35-7.98 (m, 16H, Ar-H + methine-H+ NH_2, exchangeable with D_2O); Anal. Calcd for $C_{30}H_{17}Cl\ N_4OS$ (516): C, 69.69; H, 3.31; N, 10.84 Found: C, 69.87; H, 3.04; N, 10.63.

***5-Amino-2-(anthracen-9-ylmethylene)-7-(2,4-dichlorophenyl)-3-oxo-3,7-dihydro-2H-thiaz -olo [3, 2-a]pyridine-6, 8-dicarbonitrile* (6c).**

Yellow. Powder; Yield. 61%; m. p.: 290-292ºC; IR (KBr, ύ, cm^{-1}):: 3384, 3289(NH_2), 3055 (CH- arom.), 2198 (C≡N) and 1721 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6): δ/ppm 5.10 (s, 1H, pyridine-H),7.55-7.91 (m, 15H, Ar-H + methine-H+ NH_2 ,exchangeable with D_2O); Anal. Calcd for $C_{30}H_{16}\ Cl_2\ N_4OS$ (551): C, 65.34; H, 2.92; N, 10.16 Found: C, 65.72; H, 3.13; N, 10.32.

***5-Amino-2-(anthracen-9-ylmethylene)-7-(2, 4-anthracen-9-yl)-3-oxo-3, 7-dihydro-2H-thiazolo [3, 2-a] pyridine-6, 8-dicarbonitrile* (6d).**

Brown powder (EtOH); Yield. 61%; m. p.: 170-172.ºC ; IR (KBr, ύ, cm^{-1}):; 3332, 3207 (NH_2), 3051 (CH.-arom.), 2006 (C≡N) and 1707 (C=O thiazolidinone); ^{1}H NMR (DMSO-d_6):δ/ppm 5.10 (s, 1H, pyridine-H), 7.55-7.91 (m, 21H, Ar-H + methine-H+; NH_2, exchangeable with D_2O); Anal. Calcd for $C_{38}\ H_{22}\ N_4OS$: (582) C, 78.33; H, 3.81; N, 9.62 Found: C, 78.73, H, 3.21;N; 9.13.

3,9-Diamino-4-(anthracen-9-yl)-7-(4-hydroxyphenyl)-4,7-dihydropyrano[2',3':4,5]thiazolo [3, 2-a]pyridine-2, 6, 8-tricarbonitrile (8)

To a solution of 4-thiazolidinone derivative (**2a**) (0.01 mol) in absolute ethanol (20 mL) and piperidine (0.05 mL), p-hydroxy benzaldehyde (0.01 mol) and malononitrile (0.02 mol) (1:1:2 moalr ratio) were added. The reaction mixture was refluxed for 6 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Yellow powder; Yield 58%; m. p.: 140-142 ºC; IR (KBr, ύ, cm^{-1}): 3316, 3206 (broad NH_2), and 2201(C≡N); ^{1}H NMR (DMSO-d_6): δ/ppm 4.14 (s, 1H, pyridine-H), 4.34 (s, 1H, pyran-H), 6.36-8.20 (m, 17H, Ar-H + $2NH_2$, exchangeable with D_2O) and 10.34 (br, 1H, OH, exchangeable with D_2O); MS m/z (%): 564 (M^+, 41.47); Anal. Calcd for $C_{33}H_{20}\ N_6O_2S$

(564.62) C, 70.20; H, 3.57; N, 14.88 Found: C, 69.83; H, 3.33, N, 14.25.

Ethyl-5-amino-2-(anthracen-9-ylmethylene)-7aryl-8-cyano-3-oxo-3, 7-dihydro-2H-thiazolo [3, 2-a]pyridine-6-carboxylate (10a-c)

A mixture of 4-thiazolidinone derivative (**2a**) (0.01 mol), and α-cyanocinnamonitriles (0.01mol), in absolute ethanol (20 mL) and piperidine (0.5 ml) was refluxed for 6 h. The solid products formed were collected by filtration and recrystallized from suitable solvent.

***Ethyl-5-amino-2-(anthracen-9-ylmethylene)-7-(2-chlorophenyl)-8-cyano-3-oxo-3, 7-dihydro-2H -thiazolo[3,2-a]pyridine-6-carboxylate* (*10a*)**

Yellow powder; Yield 67%; m. p.: 255-257 ºC; IR (KBr, ύ, cm^{-1}): 3414, 3289 (NH_2), 2210 (C≡N) and 1714, 1660 (C=O ester and thiazolidinone); ^{1}H NMR (DMSO-d_6): δ/ppm 0.89 (t, J=7.5Hz, 3H, CH_3), 3. 87 (q, J=7.5 Hz, 2H, CH_2), 5.16 (s, 1H, pyridine-H), 7.25-7.96 (m, 16H, Ar-H + methine-H+ NH_2, exchangeable with D_2O); Anal. Calcd for $C_{32}H_{22}ClN_3O_3S$ (564.05): C, 68.14; H, 3.93; N, 7.45. Found: C, 68.55, H, 3.65; N, 7.13.

***Ethyl-5-amino-2-(anthracen-9-ylmethylene)-8-cyano-7-(2, 4-dichlorophenyl)-3-oxo-3, 7-dih- ydro-2H -thiazolo[3,2-a]pyridine-6-carboxylate* (*10b*)**

Yellow powder (EtOH); Yield 68%; m. p.: 220-222ºC; IR (KBr, ύ, cm^{-1}): 3392, 3276 (NH_2), 2206 (C≡N) and 1713,1665 (C=O ester and thiazolidinone; ^{1}H NMR (DMSO-d_6) :δ/ppm 0.92 (t, J=7.5Hz, 3H, CH_3), 3.89 (q, J=7.5Hz, 2H, CH_2), 5.10 (s, 1H, pyridine-H), 7.38-9.05 (m, 15H, Ar-H + methine-H, NH_2, exchangeable with D_2O); Anal. Calcd for $C_{32}H_{21}Cl_2N_3OS$: (598 .50): C, 64.22; H, 3.54; N, 7.02 Found: C, 64.52; H, 3.23; N, 7.32.

***Ethyl-5-amino-2-(anthracen-9-ylmethylene)-8-cyano-7-(2-hydroxyphenyl)-3-oxo-3,7-dihydro -2H-thiazolo[3,2-a]pyridine-6-carboxylate* (*10c*)**

Yellow powder (EtOH); Yield. 61%; m. p.: 225-227ºC; IR (KBr, ύ, cm^{-1}): 3429, 3289 (NH_2), 2198 (C≡N) and 1721 (C=O ester and thiazolidinone); ^{1}H NMR (DMSO-d_6) δ/ppm 1.09 (t, J=7.5Hz, 3H, CH_3), 3.96 (q, J=7.5Hz, 2H, CH_2), 5.56 (s, 1H, pyridine-H), 7.56-8.27 (m, 16H, Ar-H + methine-H+NH_2, exchangeable with D_2O), 12.20 (br, 1H, OH, exchangeable with D_2O); Anal. Calcd for $C_{32}H_{23}N_3O_4S$ (545.61): C, 70.44; H, 4.25, N, 7.70; Found: C, 70.11; H, 4.66; N; 7.12.

Biological evaluation

The synthesized target compounds were tested *in vitro* antibacterial activity against three Gram-positive bacteria, *Staphylococcus aureus* (RCMB 010027), *Staphylococcus epidermidis* (RCMB 010024) and *Bacillis subtillis* (RCMB 010063); three Gram-negative bacteria, *Neisseria gonorrhoeae* (RCMB 010079), *Escherichia coli* (RCMB 010052) and *Klebsiella pneumoniae* (RCMB 010093). They were also evaluated for their in vitro antifungal potential against the following strains*: Aspergillus fumigatus* (RCMB 02564), *Aspergillus-clavatus* (RCMB 02593) and *Geotricum Candidum* (RCMB 05096). The results of the antimicrobial activities were depicted in Tables 1 and 2. Antimicrobial tests were carried out by the agar well diffusion method using (1 mg/ml) in dimethyl sulfoxide (DMSO) [35]. The inoculated plates were then incubated for 24 h at 37 C. Ampicillin, Gentamycin and Amphotericin B (1 mg/mL) were used as standard references for Gram positive bacteria, Gram negative bacteria and antifungal activity, respectively. After incubation time, antimicrobial activity was evaluated by measuring the inhibition zone diameters against the test organisms and compared with standard zone size ranges that determine susceptibility, intermediate susceptibility, or resistance to the screened compounds. Visual bacterial growth is observed only in the areas in which the drug concentrations is below those required for growth inhibition. The experiment was carried out in triplicate and the average zone of inhibition was calculated.

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الملخص العربي

مشتقات ٢(٤-أوكزوثيازولدينون-٢-يلدين) أسيتونيتريل و إيثيل (٤-أوكزوثيازولدينون-٢-يلدين) أسيتات (1a,b) تكاثفت مع الأنثراليديهيد (نسب جزيئية1:1) أعطت مشتقات 4,5 ثنائى هيدرو -4 أوكزو ثيازول (2a,b) . بتسخين 2 (أنثرالديهيد -9 –يل-ميثلين)مالونونيتريل فى حمض الخليك مع حمض ثيوجليكوليك امكن الحصول على (3) . تكاثف (2a) أو(3) مع الالد يهيدات الأروماتية المختلفة (نسب جزيئية1:1) أعطت ثنائى اريل ميثيليدين -4 ثيازوليدينون (4a-c) و(5a,b) وكذلك (2a)تفاعل مع مشتقات α سيانو سينامونيتريل واعطى مشتقات الثيازولو [3, 2-a] بريدين .(10a-c),(8), (6a-d) وكذلك تم إختبار نشاطية هذة المركبات تجاه النشاط البيولوحى وقد أعطت نتائج مرضية .