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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOMETHIAZOLIDINONEDERIVATIVES BEARING PYRIDINE MOIETY: SEARCH FOR ANTIMIROBIAL AGENT

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ABSTRACT:

2-(4-Oxothiazolidin-2-ylidene)acetonitrile and ethyl -2-(4-oxothiazolidin-2-ylidene)acetate (1a,b), were condensed with anthraldehyde (1:1 molar ratio) and gave 4,5-dihydro- 4-oxothiazole derivatives (2a,b). Refluxing of 2-(anthracene-9-yl-methylene) malononitrile in acetic acid with thioglycolic acid gave (3). 4-Thiaz -olidinones containing bis-aryl methylidene moieties (4a-c) and (5a,b) were produced via condensation of either (2a) or (3) with aromatic aldehydes (1:1 molar ratio). Heating of (2a) with α -substituted cinnamionitriles gave the expected substituted thiazolo[3,2-a] pyridines (6a-d), (7) and (9a-c). Thiazolo [3,2-a] pyridine enamino- nitrile (6a) was refluxed with formic acid and phenyl hydrazine to form the corresponding thiazolo [3,2-a] pyridine derivatives (10) and (11) derivatives respectively. The structures of the prepared compounds were confirmed by using spectroscopic techniques; IR, ¹HNMR, ¹³C NMR and Mass spectroscopy. Also, Antibacterial and antifungal activity were evaluated for some of synthesized compounds.

Keywords; 4-Thiazolidinones, thiazolo [3,2-a] pyridines, and anthracene.

1. INTRODUCTION

The increasing cases of microbial resistance pose a major concern to the scientific community and have become a threat for human life worldwide. Moreover, invasive microbial infections caused by multi-drug-resistant Gram-positive bacteria and microbes are difficult to diagnose and treat [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.

To this end, 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 wide spread structural

motif that can be found in many natural products and in several pharmacologically interesting compounds. Therefore the synthesis of pyridine derivatives, aiming to develop new drugs, is an active research area. 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 and screen for their antimicrobial activity. Motivated by these findings and in continuation of our ongoing efforts on the synthesis of heterocycles with potential antimicrobial activities [22-28], we are purposed to synthesize and investigate the antimicrobial activity of a new series from thiazolidinones class having pyridine moiety.

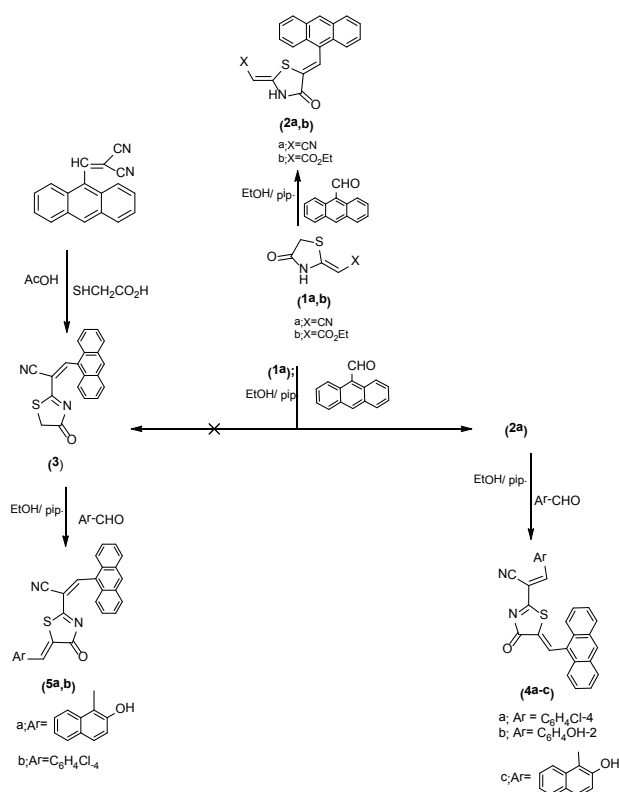
2. RESULTS AND DISCUSSION

The synthesis of the target compounds is depicted in Schemes 1-4. Compound (1) [29] is characterized by the 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 only through another route via the reaction of 2-(anthracen-9-ylmethylene) malononitrile with thioglycolic acid. This, prove that, anthraldehyde condensed first with for 4-thiazolidinone ring (1a) at the most active methylene at position 5 rather than exocyclic methylene at position 3 (Scheme 1). Similarly ethyl 5-(anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene) acetate (2b) was synthesized through condensation of (1b) with anthraldehyde in refluxing ethanol containing few drops of piperidine, (Scheme 1). The structures of the latter products were confirmed by spectroscopic studies and elemental analysis. The IR spectrum of compound (2a), for example, revealed absorption bands at 3183, 2195 and 1707 cm^{-1} corresponding to an NH, cyano and carbonyl characteristics for thiazolidinone. Its $^1\text{H-NMR}$ spectrum revealed signals at δ 5.16 and 11.49 ppm due to methine-H and NH protons. Whereas, $^1\text{H-NMR}$ spectrum of (2b) revealed 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 band at 1653 cm^{-1} assignable to ethylenic carbonyl group. The key starting material (2a) is characterized by the presence of active methylene as well as nitrile 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 (2a) with various aromatic aldehydes (1:1 molar ratio) in ethanol catalytic with piperidine afforded the arylidene derivatives (4a-c). Similarly the arylidene derivatives (5a,b) were obtained through condensation of compound (3) with different aromatic aldehydes (1:1 molar ratio) under reflux conditions. The spectral data of the isolated products were in complete agreement with structures (4) and (5). The IR spectrum for compound (4b) as example revealed absorption bands at 3330, 2204 and 1655 cm^{-1} corresponding to OH, $\text{C}\equiv\text{N}$ and $\text{C}=\text{O}$ function respectively. The $^1\text{H-NMR}$ spectrum of (4a) (DMSO- d_6) 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 $\text{C}_{27}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$.

In view of the growing biological importance of fused cyanopyridones, particularly thiazolo [1,2-a] pyridines [30-32], it was of interest to synthesize some thiazolo- pyridine derivatives containing anthracenyl moiety on the hope of obtaining more active compounds. Thus, treatment of (2a) with α -cyanocinnamionitriles under reflux conditions in ethanol furnished a single product for which structure (6) was considered (Scheme 2). Both elemental analysis and spectral data of the isolated products were in assignment with the obtained product. The IR spectrum of (6a) as an example showed the presence of absorption bands 3375, 3354, 2200 and 1708 corresponding for NH_2 , $\text{C}\equiv\text{N}$ and $\text{C}=\text{O}$ functions respectively. Its $^1\text{H NMR}$ spectrum exhibited the lack of singlet signal at δ 5.16 specific for the methine proton and the presence a singlet signal at 4.70 due to pyridine- 4H. The mass spectrum showed a molecular ion peak at $m/z = 516$ corre-



Scheme 1

sponding to a molecular formula $C_{30}H_{17}C_1N_4O_S$. Chemically, the structure of (6a) was also confirmed via the reaction of (4a) with one mole of malononitrile under reflux conditions (mp. an mixed mp, and IR spectra). The dihydropyrano [2',3': 4,5] thiazolo[3,2-a] pyridine(7) was achieved as a sole product through one pot reaction of (2a) with p-hydroxybenzaldehyde and malononitrile (1:1:2 molar ratio) (Scheme 2). Actually, the product of this reaction was elucidated on the basis of its spectral data. The IR-spectrum has no absorption band characteristic to a carbonyl group and it revealed the presence of characteristic absorption bands at 3316,3206 and 2201 due to NH_2 and $C\equiv N$, respectively. 1H -NMR spectrum of (7) supported its structure, as it revealed the 4-Hpyrane and 4H-pyridine ring protons as two singlet signals at δ 4.14 and 4.34 ppm respectively beside the other expected signals. Its mass spectrum showed the molecular ion at $m/z = 564$ (41.47) corresponding to a molecular formula $C_{33}H_{20}N_6O_2S$.

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 -ethoxycarbonylcinnamonnitriles in refluxing ethanol containing piperidine gave a product for which (8) and (9) can be formulated. On the basis of ana-

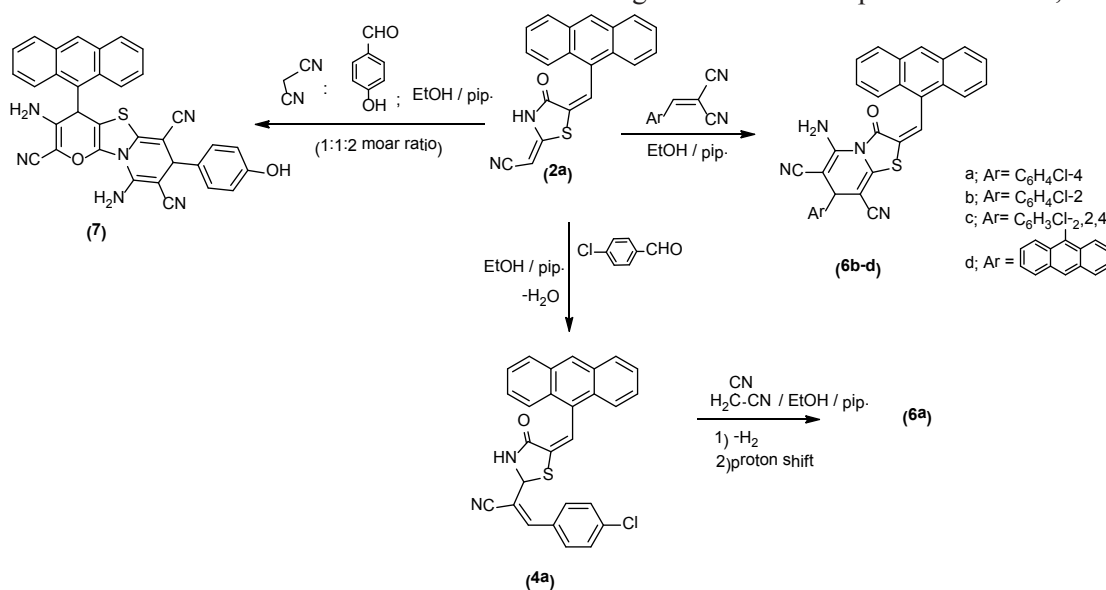
lytical and spectral data structure (8) was readily eliminated. The structure of (9) was confirmed based on the elemental analyses and spectral data. Thus, the IR spectrum of (9a) as example showed the presence bands at 3414, 3289, 2210 and 1714 corresponding for NH_2 , $C\equiv N$ and $C=O$ ester. Its 1H NMR spectrum exhibited triplet signal at 0.83 J=7.5Hz and quartet signal at 3.88 J=7.5 Hz corresponding for the ethoxy ester function beside singlet signal at 5.16 ppm due to pyridine-H. The mechanism of the reaction was proceeds via generation of carbanion of CH_2 which attack β -carbon of cinnamonnitriles followed by proton shift (Scheme3).

In addition, enaminnitrile(6a) was found to react with either formic acid or phenylhydrazine and the corresponding pyrimidine or pyrazole derivatives were obtained (Scheme4). The structures of isolated products (10) and (11) were confirmed by correct elemental and spectral data. IR spectrum of compound(11) appeared lack of stretching absorption band for carbonyl group. Mass spectrum of (11) assigned a molecular ion peak at (604(M^+); 44.36%) corresponding with molecular formula $C_{36}H_{21}C_1N_6S$.

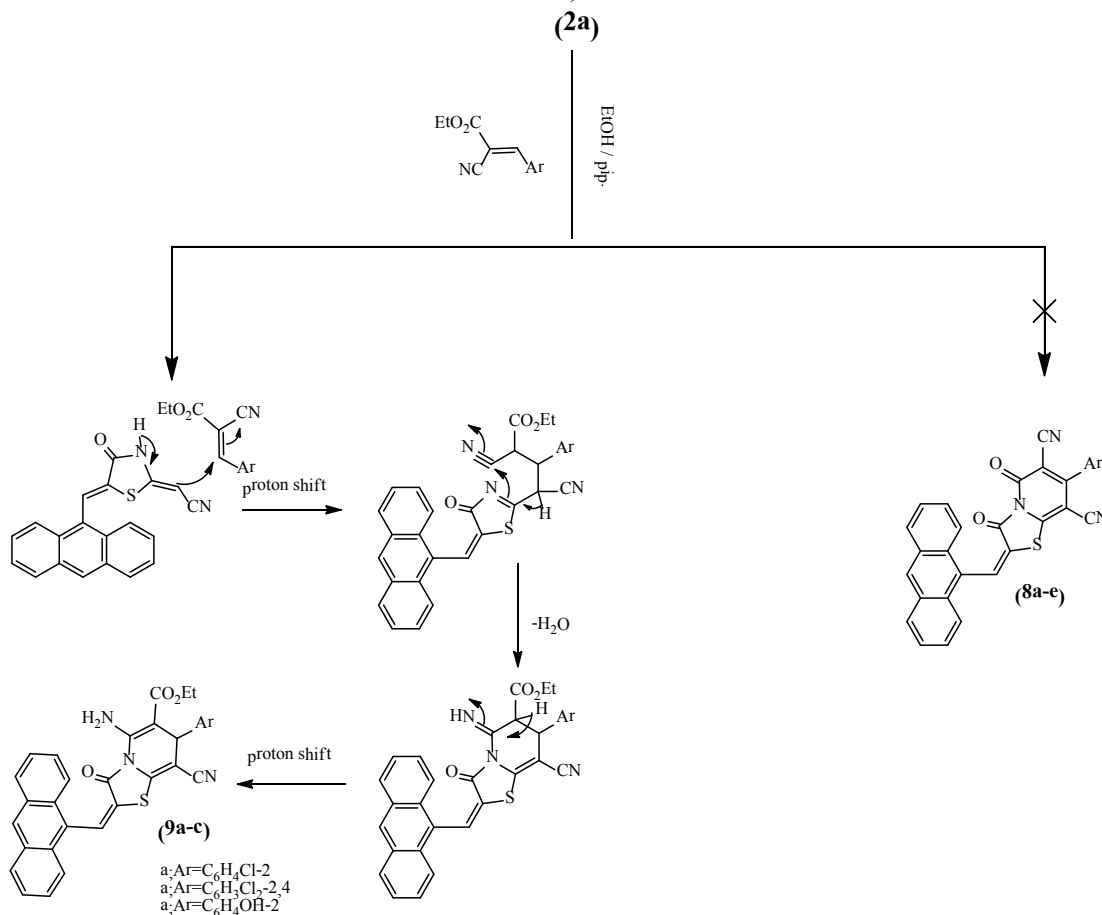
3. ANTIMICROBIAL ACTIVITY

Biological evaluation

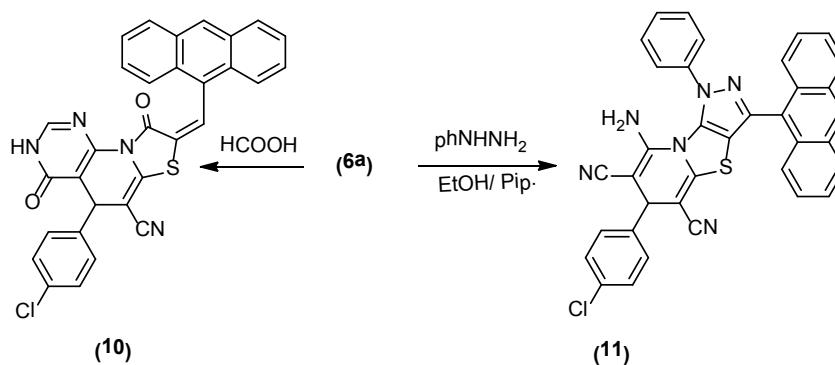
Twelve of the synthesized target compounds were tested for in vitro antibacterial activity against three Gram-positive bacteria, Staphylo-



Scheme2



Scheme3



Scheme4

coccus aureus RCMB 010027, Staphylococcus epidermidis RCMB 010024 and Bacillissubtilis-RCMB 010063; three Gram-negative bacteria, Neisseria gonorrhoeae RCMB 010079, Esh-erichia coli RCMB 010052 and KlebsiellapneumoniaeRCMB 010093. They were also evaluated for their in vitro antifungal potential against the following strains Aspergillus fumigatusRCMB 02564, Aspergillus-clavatusRCMB 02593 and GeotricumCandidumRCMB 05096, and the results were depicted in Table 1, 2. Antimicrobial tests were carried out by the agar well diffusion method using (1 mg/ml) in dimethyl sulfoxide

(DMSO) [33]. The inoculated plates were then incubated for 24 h at 37 °C. Ampicillin, Genta-mycin 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, anti-microbial activity was evaluated by measuring the inhibition zone diameters against the test or-ganisms and compared with standard zone size ranges that determine susceptibility, intermedi-ate susceptibility, or resistance to the screened compounds. Visual bacterial growth is observed only in areas in which the drug concentrations

are below those required for growth inhibition. The experiment was carried out in triplicate and the average zone of inhibition was calculated. In general, most of the tested compounds revealed better activity against the Gram-positive rather than the Gram-negative bacteria. Regarding to the structure activity relationship of the thiazolidinones against Gram-positive bacteria and Gram-negative bacteria, the results revealed that compounds 2b (MIC = 7.81, 3.9, 1.95 $\mu\text{g mL}^{-1}$), 4a (MIC = 15.63, 62.5, 7.81 $\mu\text{g mL}^{-1}$), 4b (MIC = 3.9, 7.81, 15.63, $\mu\text{g mL}^{-1}$), 5 (MIC = 15.63, 7.81, 1.95, 3.9, $\mu\text{g mL}^{-1}$) and 6b (MIC = 1.95, 0.98, 7.81, 1.95, $\mu\text{g mL}^{-1}$) exhibited good spectrum antibacterial profile against the tested organisms. Compounds 2b which contain ester group recorded higher activity than 2a which

contain cyano group. Compounds 4a and 4b which contain 4-chlorophenyl or 2-hydroxyphenyl respectively, showed equal activity against the tests organisms. Also, the equal activity was observed for compounds 4 and 5 which differ in the arylidene positions. Furthermore, meanwhile compound thiazolo[3,2-a]pyridine 6b which contain 2-chlorophenyl revealed the highest activity, compound (6c) which contain dichlorophenyl does not showed any activity towards the tested organisms. On the other hand, compounds 2a, 6c, 9a, 9b, 10 and 11 exhibited weak to moderate growth inhibitory activity against the tested bacteria. Among these compounds 6c, 7 and 9b do not have any activity. The Gram-negative strain *Neisseria gonorrhoeae* RCMB 010079 not affected with any of the tested compounds.

Table 1; Antibacterial activity of the synthesized compounds

	Gram Positive Bacteria			Gram Negative Bacteria		
	<i>S.aureus</i>	<i>S.epidermidis</i>	<i>B.subtilis</i>	<i>N.gonorrhoeae</i>	<i>E.coli</i>	<i>K.pneumoniae</i>
2a	0.58 ± 15.2	0.63 ± 17.2	0.42 ± 19.2	NA	0.72 ± 15.6	0.63 ± 16.2
2b	0.25 ± 18.2	0.58 ± 19.6	0.63 ± 22.4	NA	0.72 ± 19.2	0.63 ± 20.6
4a	0.72 ± 16.7	1.2 ± 18.2	0.43 ± 20.3	NA	1.2 ± 18.9	0.81 ± 20.1
4b	0.58 ± 19.4	0.63 ± 18.3	0.63 ± 20.3	NA	1.2 ± 17.3	2.1 ± 20.6
5	0.72 ± 18.2	0.44 ± 13.3	0.63 ± 19.2	NA	0.72 ± 18.9	1.2 ± 20.3
6b	0.63 ± 21.1	0.72 ± 21.9	0.53 ± 22.3	NA	0.72 ± 18.3	0.25 ± 22.4
6c	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA
9a	0.72 ± 17.2	0.72 ± 12.4	0.67 ± 17.3	NA	0.72 ± 17.2	0.58 ± 17.9
9b	NA	NA	NA	NA	NA	NA
10	0.63 ± 11.6	0.72 ± 13.2	0.42 ± 14.6	NA	0.58 ± 13.1	1.2 ± 16.2
11	0.43 ± 11.9	0.43 ± 11.2	0.63 ± 13.2	NA	0.73 ± 11.4	1.2 ± 13.3
.St	0.14 ± 28.9	0.18 ± 25.4	0.35 ± 34.6	0.58 ± 22.3	0.3 ± 23.4	0.15 ± 26.3

Table 2; Antifungal activity of the synthesized compounds

	Fungi		
	<i>A.fumigatus</i>	<i>A.clavatus</i>	<i>G.candidum</i>
2a	0.72 ± 16.3	NA	0.63 ± 18.2
2b	0.63 ± 19.4	NA	0.63 ± 21.3
4a	0.58 ± 17.2	NA	0.63 ± 19.2
4b	0.63 ± 19.1	NA	0.58 ± 21.2
5	0.72 ± 17.6	NA	0.63 ± 18.4
6b	0.63 ± 19.3	NA	0.38 ± 21.3
6c	NA	NA	NA
7	NA	NA	NA
9a	0.63 ± 14.1	NA	0.58 ± 15.2
9b	NA	NA	NA
10	0.63 ± 11.2	NA	0.72 ± 14.2
11	0.58 ± 12.6	NA	0.72 ± 14.3
.St	0.14 ± 28.9	NA	0.35 ± 34.6

Regarding the activity of the tested compounds against the antifungal strains, the results revealed that compounds 2b (MIC = 3.9, 1.95 $\mu\text{g mL}^{-1}$), 4b (MIC = 3.9, 1.95, $\mu\text{g mL}^{-1}$) and 6b (MIC = 3.9, 1.95, $\mu\text{g mL}^{-1}$) proved to be equipotent to Amphotericin against *Aspergillus fumigatus* (RCMB 02564), and *GeotricumCandidum* (RCMB 05096). On the other hand, none of the tested compounds showed any activity towards the strain *Aspergillusclavatus* (RCMB 02593). While, compounds 2a, 6c, 9a, 9b, 10 and 11 exhibited weak to moderate growth inhibitory activity against the tested strains.

Conclusions

We have described herein an efficient and convenient synthesis of some thiazolidinone and thiazolopyridine derivatives. Twelve of the prepared compounds evaluated for their in vitro antibacterial and antifungal activities. The best antimicrobial activity was observed for 5-Amino-2-(anthracen-9-ylmethylene)-7-(2-chlorophenyl)-3-oxo-3,7-dihydro-2H-thiazolo [3,2-a] pyridine-6,8-dicarbonitrile (6b) followed by 2-[5-(anthracen-9-yl-methylene)-4-oxothiazolidin-2-yl]-3-(2-hydroxyphenyl)acrylonitrile (4b).

Antimicrobial Activity as MICS ($\mu\text{g} / \text{ml}$) of tested samples against tested microorganisms:

4. EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (ν ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^1H 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. Micro analytical data were obtained from the Micro analytical Research Centre, Faculty of Science, Cairo University.

2-[5-(Anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene]acetonitrile (2a) and ethyl 2-[5-(anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene]acetate (2b)

General procedure

A mixture of anthraaldehyde (0.01mol) was heated under reflux for 2h with either 1a or 1b (0.01mol) in absolute ethanol (20 mL) catalyzed with piperidine. The solid product formed was collected by filtration and recrystallized from ethanol.

2-[5-(Anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene]acetonitrile(2a).

Browns crystals; Mp 125-27 $^{\circ}\text{C}$ (72 % yield).

Sample Tested microorganisms	2b	4a	4b	5	6b	
	(Minimum inhibitory concentration ($\mu\text{g}/\text{ml}$))					
FUNGI						
<i>Aspergillusfumigatus</i> (RCMB 02564)	3.9	15.63	3.9	7.81	3.9	Amphotericin B 0.98
<i>Aspergillusclavatus</i> (RCMB 02593)	NA	NA	NA	NA	NA	1.95
<i>Geotricumcandidum</i> (RCMB 05096)	1.95	3.9	1.95	7.81	1.95	0.49
Gram Positive Bacteria:						
<i>Staphylococcus aureus</i> (RCMB 010027)	7.81	15.63	3.9	15.63	1.95	Ampicillin 0.49
<i>Staphylococcusepidermidis</i> (RCMB 010024)	3.9	62.5	7.81	7.81	0.98	0.49
<i>Bacillissubtilis</i> (RCMB 010063)	1.95	15.63	3.9	1.95	0.98	0.24
Gram negativeBacteria:						
<i>Neisseria gonorrhoeae</i> (RCMB 010079)	NA	NA	NA	NA	NA	Gentamycin 0.98
<i>Escherichia coli</i> (RCMB 010052)	3.9	15.63	7.81	3.9	7.81	1.95
<i>Klebsiellapneumoniae</i> (RCMB 0010093)	3.9	7.81	1.95	3.9	1.95	0.49

^1H 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); IR (KBr) cm^{-1} : = 3183 (NH), 3055 (CH-arom.), 2923 (CH-aliph.), 2195 ($\text{C}\equiv\text{N}$) and 1707 (C=O thiazolidinone); Anal. Calcd. for $\text{C}_{20}\text{H}_{12}\text{N}_2\text{O}_5$ (328.07): C; 73.15, H; 3.68; N; 8.53 Found: C; 73.52 H; 3.81, N; 8.85.

Ethyl 2-[5-(anthracen-9-ylmethylene)-4-oxothiazolidin-2-ylidene] acetate (2b). Yellow crystals; Mp 245-47°C (77 % yield). ^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); IR (KBr) cm^{-1} = 3246 (NH), 3008 (CH-arom.), 2892 (CH-aliph.) and 1689 (C=O thiazolidinone and ester); Anal. Calcd. for $\text{C}_{22}\text{H}_{17}\text{NO}_3\text{S}$ (375.09): C; 70.38, H; 4.56; N; 3.73. Found: C; 70.52 H; 4.81, N; 3.52.

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), thioglycolic acid (0.01 mol) was added. The solution was heated under reflux for 2h. The solid product formed was collected by filtration and recrystallized from ethanol.

Yellow powder; Mp 160-62 °C (54 % yield). IR (KBr): cm^{-1} = 3323 (NH), 3049 (CH-arom.), 2929 (CH-aliph.), 2193 ($\text{C}\equiv\text{N}$) and 1653 (C=O thiazolidinone); Anal. Calcd. for $\text{C}_{20}\text{H}_{12}\text{N}_2\text{OS}$ (328.07): C; 73.15, H; 3.68; N; 8.53 Found C; 73.61 H; 3.25, N; 8.31.

2-[5-(Anthracen-9-yl-methylene)-4-oxo-4,5-dihydrothiazolidin-2-yl]-3-aryl-acrylonitrile (4a-c).

General procedure

A mixture of 4-thiazolidinone derivative 2a (0.01 mol) and aromatic aldehydes (0.01 mol), in absolute ethanol (20 mL) catalyzed with piperidine was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from ethanol.

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

Reddish brown crystals; Mp 150-52 °C (67 % yield). ^1H NMR (DMSO- d_6) δ /ppm 6.58-8.66 (m, 13H, Ar-H), 9.01, 9.05 (2s, 2H, methine-H); IR (KBr) cm^{-1} = 3056 (CH-arom.), 2978 (CH-aliph.), 2195 ($\text{C}\equiv\text{N}$) and 1709 (C=O thiazolidinone); Anal. Calcd. for $\text{C}_{27}\text{H}_{15}\text{ClN}_2\text{OS}$ (450.94) C; 71.91, H; 3.35; N; 6.21 Found: C; 72.01 H; 3.89, N; 6.19.

2-[5-(anthracen-9-yl-methylene)-4-oxothiazolidin-2-yl]-3-(2-hydroxyphenyl) acrylonitrile (4b).

Brown crystals; Mp 130-32 °C (78 % yield). IR (KBr) cm^{-1} = 3330 (br, OH), 3055 (CH-arom.), 2204 ($\text{C}\equiv\text{N}$) and 1655 (C=O thiazolidinone); MS m/z (%): 432 (M^+ , 0.76); Anal. Calcd. for $\text{C}_{27}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ (432.09) 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; Mp 160-62 °C (67% yield). ^1H NMR (DMSO- d_6) δ /ppm 6.98-8.21 (m, 15H, Ar-H), 9.01, 9.04 (2s, 2H, methine-H), (s, 1H, OH); IR (KBr) : cm^{-1} = 3221 (br. OH), 2205 ($\text{C}\equiv\text{N}$) and 1651 (C=O thiazolidinone); Anal. Calcd. for $\text{C}_{31}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (482.11) C; 77.16, H; 3.76; N; 5.81 Found: C; 77.32; H; 3.52, N; 5.41.

3-(Anthracen-9-yl)-2-(5-(arylmethylidene)-4-oxo-4,5-dihydrothiazol-2-yl) acrylonitriles (5a, b)

To a solution of 4-thiazolidinone derivative 3 (0.01 mol) in absolute ethanol (20 mL) catalyzed with piperidine either α -hydroxynaphthaldehyde or p-chlorobenzaldehyde (0.01 mol) was added. The solution was heated under reflux for 3h. The solid product formed was collected by filtration and recrystallized from ethanol.

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

Brown crystals, Mp 160-62 °C (67 % yield). IR (KBr) : cm^{-1} = 3375 (br. OH), 3052 (CH-arom.), 2927 (CH-aliph), 2206 ($\text{C}\equiv\text{N}$) and 1662 (C=O); MS m/z (%): 481 ($\text{M}-1$), (56.70); Anal.

Calcd. for C₃₁H₁₈N₂O₂S (482.11): C; 77.16, H; 3.76; N; 5.81 Found: C; 77.65; 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; Mp 100-02°C (75 % yield). ¹H NMR (DMSO-d₆) δ/ppm 6.59-8.10 (m, 13H, Ar-H), 8.20, 8.99 (2s, 2H, methine-H); IR (KBr)cm⁻¹: = 3056 (CH-arom.), 2927 (CH-aliph), 2198(C≡N) and 1658 (C=O thiazolidinone); Anal. Calcd for C₂₇H₁₅N₂ClOS (450.94) 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]pyridine-6,8-dicarbonitriles (6a-d)

A mixture of 4-thiazolidinone derivative 2a(0.01mol) and α-cyanocinnamionitrile (0.01mol), in absolute ethanol (20 mL) catalyzed with piperidine was heated under reflux for 6h. The solid product formed was collected by filtration and recrystallized from ethanol.

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, Mp 160-62°C (73%yield). ¹H NMR (DMSO-d₆) δ/ppm 4.70 (s, 1H, pyridine-H), 6.37-8.80 (m, 16H, Ar-H + methine-H + NH₂; exchangeable with D₂O); IR (KBr) cm⁻¹: = 3331, 3354 (NH₂), 3051 (CH-arom.), 2200 (C≡N) and 1708 (C=O thiazolidinone); MS m/z (%): 516, (M+, 6.89); Anal. Calcd. for C₃₀H₁₇ClN₄OS (517.00) 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[3,2-a]pyridine-6,8-dicarbonitrile (6b)

Yellow powder; M.p 295-97°C (67 %yield); ¹H NMR (DMSO-d₆)δ/ppm 5.09 (s, 1H, pyridine-H), 7.35-7.98 (m, 16H, Ar-H + methine-H + NH₂; exchangeable with D₂O); IR (KBr): cm⁻¹: = 3388, 3286 (NH₂), 3050 (CH-arom.) 2197 (C≡N) and 1715 (C=O thiazolidinone); Anal. Calcd. for C₃₀H₁₇ClN₄OS (517.00) 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-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6c)

Yellow powder; Mp 290-92°C (61%yield). ¹H NMR (DMSO-d₆) δ/ppm 5.10 (s, 1H, pyridine-H), 7.55-7.91 (m, 15H, Ar-H + methine-H + NH₂; exchangeable with D₂O); IR (KBr, cm-1): = 3384, 3289 (NH₂), 3055 (CH-arom.) 2198 (C≡N) and 1721 (C=O thiazolidinone); Anal. Calcd. for C₃₀H₁₆Cl₂N₄OS (551.45) C; 65.34, H; 2.92; N; 10.16 Found: C; 65.72, H; 3.23, N; 10.42.

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; Mp 170-72°C (61%yield). ¹H NMR (DMSO-d₆) δ/ppm 5.10 (s, 1H, pyridine-H), 7.55-7.91 (m, 21H, Ar-H + methine-H + NH₂; exchangeable with D₂O); IR (KBr): cm⁻¹ = 3332, 3207 (NH₂), 3051 (CH-arom.), 2006 (C≡N) and 1707 (C=O thiazolidinone); Anal. Calcd for C₃₈H₂₂N₄OS (582.15) 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 (7)

To a solution of 4-thiazolidinone derivative 2a (0.01mol) in absolute ethanol (20 mL) catalyzed with piperidine, p-hydroxybenzaldehyde (0.01mol) and malononitrile (0.02mol) (1:1:2 molar ratio) were added. The reaction mixture was heated under reflux for 6h. The solid product formed was collected by filtration and recrystallized from ethanol.

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 (7)

Yellow powder; Mp 140-42°C (58%yield); ¹H NMR (DMSO-d₆) δ/ppm 4.14 (s, 1H, pyran-H), 4.34 (s, 1H, pyridine-H), 6.36-8.20 (m, 17H, Ar-H + 2NH₂; exchangeable with D₂O) and 10.34 (br, 1H, OH; exchangeable with D₂O); IR (KBr): cm⁻¹ = 3316, 3206 (broad NH₂), and 2201 (C≡N); MS m/z (%): 564 (M+, 41.47); Anal. Calcd. for C₃₃H₂₀N₆O₂S (564.14) 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)-

7-aryl-8-cyano-3-oxo-3,7-dihydro-2H - t hiazolo [3,2-a] pyridine-6-carboxylate (9a-c)

A mixture of 4-thiazolidinone derivative 2a(0.01mol), and α -cyanocinnamionitriles (0.01mol), in absolute ethanol (20 mL) catalyzed with piperidine was heated under reflux for 6h. The solid product formed was collected by filtration and recrystallized from ethanol.

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 (9a).

Yellow powder; Mp 255-57 °C (67%yield). ¹H NMR (DMSO-d₆) δ /ppm 0.83 (t, J=7.5Hz, 3H, CH₃), 3.88(q, J=7.5 Hz, 2H, CH₂), 5.16(s,1H, pyridine-H), 7.25-7.96 (m,16H,Ar-H + methine-H+ NH₂ exchangeable with D₂O); IR (KBr) :cm⁻¹ = 3414,3289(NH₂), 2210 (C \equiv N) and 1714 ,1660(C=O ester and thiazolidinone); Anal. Calcd for C₃₂H₂₂C₁N₃O₃S (563.50): 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-dihydro-2H -thiazolo[3,2-a]pyridine-6-carboxylate (9b)

Yellow powder; Mp 220-22°C (68%yield). ¹H NMR (DMSO-d₆) 0.92(t, J=7.5Hz, 3H, CH₃), 3.89(q, J=7.5Hz, 2H, CH₂), 5.10 (s,1H, pyridine-H), 7.38-9.05 (m, 15H,Ar-H + methine-H ; NH₂; exchangeable with D₂O); IR (KBr): cm⁻¹= 3392,3276 (NH₂), 2206 (C \equiv N) and 1713,1665 (C=O ester and thiazolidinone) ; Anal. Calcd for C₃₂H₂₁C₁₂N₃OS (598.00) C; 64.22, H; 3.54; N; 7.02 Found: C; 64.52, H; 3.23, N; 7.42.

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 (9c)

Yellow powder; Mp225-27°C (61%yield). ¹H NMR (DMSO-d₆) 1.09 (t, J=7.5Hz, 3H, CH₃), 3.96 (q, J=7.5Hz, 2H, CH₂), 5.56 (s,1H, pyridine-H), 7.56-8.27 (m, 17H, Ar-H + methine-H+NH₂; exchangeable with D₂O), 12.20 (br, 1H, OH; exchangeable with D₂O); IR (KBr): cm-1= 3429,3289 (NH₂), 2198(C \equiv N) and 1721 (C=Oester and thiazolidinone); Anal. Calcd.for

C₃₂H₂₃N₃O₄S (545.14): C; 70.44, H; 4.25; N; 7.70; Found: C; 70.11, H; 4.66, N; 7.12.

8-(anthracen-9-ylmethylene)-5-(4-chlorophenyl)-4,9-dioxo-4,5,8,9-tetrahydro-3H -thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carbonitrile (10)

A mixture of 2a(0.01mol) and formic acid (0.01mol) was heated under reflux for 6h.The solid product formed was collected by filtration and recrystallized from ethanol.

8-(anthracen-9-ylmethylene)-5-(4-chlorophenyl)-4,9-dioxo-4,5,8,9-tetrahydro-3H -thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carbonitrile (10)

Brown powder; Mp 225-27°C (59%yield. ¹H NMR (DMSO-d₆), 4.97 (s,1H,pyridine-H), 5.20 (s,1H, pyrimidine-H),7.20-8.22 (m, 13H,Ar-H), 8.88 (s,1H,methine-H), 9.64 (s,1H,NH; exchangeable with D₂O); IR (KBr) : cm⁻¹ =3181(NH), 2227 (C \equiv N) and 1712 (C=O); Anal. Calcd. for C₃₁H₁₇C₁N₄O₂S (545.50) C; 68.32, H; 3.14; N; 10.28 Found: C; 68.21, H; 2.98, N; 10.52.

8-amino-3-(anthracen-9-yl)-6-(4-chlorophenyl)-1-phenyl-1,6-dihydropyrazolo-[3',4': 4,5] thiazolo[3,2a]pyridine-5,7-dicarbonitrile (11)

To a solution of 2a (0.01mol)in absolute ethanol (20 mL), phenylhydrazine (0.01mol) was added. The reaction mixture was heated under reflux for 6h.The solid product formed was collected by filtration and recrystallized from ethanol.

8-amino-3-(anthracen-9-yl)-6-(4-chlorophenyl)-1-phenyl-1,6-dihydropyrazolo-[3',4': 4,5] thiazolo[3,2a]pyridine-5,7-dicarbonitrile (11)

Brown powder, (56%yield), Mp.190-92°C. IR (KBr): cm⁻¹= 3432, 3216 (NH₂) and 2211(C \equiv N); MS m/z (%):604(M+), 44.36); Anal.Calcd.for C₃₆H₂₃C₁N₆S (604.50) C; 71.40, H; 3.50; N; 13.89, Found: C; 71.03, H; 3.71, N; 14.12.

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