Synthesis some of thiazolidinone and tetrazole compounds derived from acriflavine and evaluation of their antimicrobial, antifungal and antioxidant activity

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ABSTRACT
Some thiazolidinone and tetrazole compounds (7-12), (13-18) were derived from the acriflavine by the synthesis of Schiff bases as intermediate compounds (1-6). Schiff bases compounds were synthesized by reaction the acriflavine with different aldehydes by using microwave method. Thiazolidinone and tetrazole compounds were prepared by the cyclization of Schiff bases with thiourea to obtain thiazolidinone and tetrazole derivatives. The synthesized compounds have been screened for their antimicrobial, antifungal, and antioxidant activity. 

INTRODUCTION
Acriflavine is an old medicinal drug previously used as an atrynpanoidal agent in World War II [1]. ACF has recently been shown to have potential antitumoral activity in mice [2] and has been approved for clinical trials by a FDA. ACF is an antibacterial acridine used in topical antiseptics in addition to anticancer action [3]. ACF inhibits the growth of both chloroquine (CQ) asexual aspects. Sensitive and resistant strains at nanomolar concentration of human malaria parasite, Plasmodium falciparum in vitro [4]. Oligo (acriflavine) was synthesized via chemical oxidative polycondensation by H2O2 (30 %) as the oxidant at an optimum reaction temperature of 110 °C without use of an additional external template. Further characterization was employed using, photophysics, electrophysical, photoelectric, electrochemical, photovoltaic thermogravimetric-differential thermal analysis (TG-DTA), fluorescence (PL), cyclic voltammetry (CV) and differential scanning calorimetry (DSC) measurements [5]. The aim of this study was to encapsulate ACF in reverse micelles and to incorporate this suspension to lipid nanocapsules (LNC) [6]. Acriflavine is a heteroaromatic dye with antibacterial and antiviral effects [7]. More recently, its potential has emerged as an anti-cancer agent if acriflavine has topoisomerase inhibitor activity [8]. Anti-cancer activities in cell lines of pancreatic ductal adenocarcinoma (PDAC) [9] have been shown to be antibacterial drug acriflavine. For the synthesis of biologically active compounds, thiazoles and their analogues serve as precursors [10]. They were reported to have antimicrobial drugs [11], [12], [13]. Analgesic [14], anti-inflammatory [15], anticonvulsant [16], cardiotoxic [17], anticancer [18] antitubercular [19]. and anthelmintic effects [20]. Thiazole and its derivatives are found in various powerful compounds which are naturally and biologically active and can have a broad range of biological activity, so the synthesis of this compound is of important concern [21].

Interest in tetrazole chemistry over the past few years has been increasing rapidly because of its wide range of applications, mainly because of the role played by this heterocyclic functionality in medicinal chemistry as these offer a more favorable pharmacokinetic profile [22]. A wide and increasing number of applications are exhibited tetrazole moiety. They find an essential place in the medical field as it has patented ring systems for the treatment of central nervous system disorders, sexual dysfunction, asthma, obesity, diabetes and various diseases [23]. New tetrazole moiety combinations have been synthesized with various chalcone derivatives. The hydrazine hydrate reaction of these chalcones resulted in the formation of tetrazole-pyrazoline hybrids [24].

MATERIALS AND METHODS
Commercially available compounds were used without further purification unless otherwise noted. On a Shimadzu FT-IR 8400S device, infrared (IR) spectra were recorded and were calibrated using a polystyrene film and m.p's were not corrected. The compounds were identified in disks of potassium bromide (KBr). As a solvent, dimethyl sulfoxide (DMSO-d-6) was used and tetramethylsilane (TMS) was used as an internal standard, on the 400 MHz AV III-HD-800 Bio Spin spectrometer. H-NMR spectra were recorded. In parts per million (ppm) downfield from TMS, chemical shifts were quoted. The mass spectra of some compounds were registered by using the apparatus of kind GC.Mass QP-2013. Thin layer chromatography (TLC) was used to monitor the reaction and to check purity. Microwave irradiations were carried out in modified domestic microwave oven, Universal - 850 Watt, following pictures.
3,6-bis(4-hydroxy-3-methoxybenzylideneamino)-10-methylacridin-10-ium chloride, R=2-OCH₃,4-OHCH₃.(1)

Compounds of Schiff bases (1-6), (0.004 mole) were mixed with (0.004 mole) of 2-mercaptoacetic acid in abs ethanol (20ml), (0.136 mol) of ZnCl₂ anhydrous was then added. The reaction mixture was refluxed for 4-6 minutes (200Watt) by microwave oven. On completion of the reaction as observed by TLC and with a mixture of n-hexane and ethyl acetate (3:2). Cool, filtered and washed with 5% sodium bicarbonate then with water and crystallized from dioxane.

3,6-bis(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-10-methylacridin-10-ium chloride, R=2-OCH₃,4-OHCH₃.(7) Yellow solid (yield: 57%; m.p. 150-152°C). IR [KBr] 3364 (O-H); 1679 (C=O amide); 1554 (C=C aromatic); 1313 (C-N); 815 and (C-S thio); 1-H(NMR (DMSO-d₆) δ 3.77 [3H, s, CH₃]; 4.06.3.95 (2H, d, CH₂); 4.33 [3H, s, CH₃]; 6.44 [1H, s, CH-thiazol ring]; and 7.06, 7.96 (7H, m, aromatic) and 10.17 [1H, s, O-A]. C₆H₅N₂O₂S₃Cl,M/S: 676.2 (M + 1).

10-methyl-3-(4-oxo-2-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylidene)amino)-10-methylacridin-10-ium chloride,

R=2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-10-methylacridin-10-ium chloride, R=2-OCH₃,4-OHCH₃.(8) Pale yellow solid (yield: 54%; m.p. 110-112°C). IR [KBr] 1685 (C=O amide); 1612 (C=O aromatic); 1321 (C-N); 764 and (C-S thio); 1-H(NMR (DMSO-d₆) δ 2.57 [2H, s, CH₂]; 3.95 (2H, d, CH₂ thiazol ring); 4.52 [3H, s, CH₃]; 6.67 [1H, t, C-CH thiazol ring]; 6.15 [1H, q, CH₂]; 6.53 [1H, d, CH]; and 7.06, 7.96 (7H, m, aromatic) C₆H₅N₂O₂S₃Cl,M/S: 664.28 (M + 1).

3,6-bis((E)-4-chlorobenzylidene)amino)-10-methacridin-10-ium chloride, R=...,CH₃CL,R=Cl.(9) 3,6-bis((E)-4-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylidene)amino)-10-methylacridin-10-ium chloride, R=2-OCH₃,4-OHCH₃.(10) Yellow solid (yield: 61%; m.p. 169-171°C). C₆H₅N₂O₂S₃Cl, M/S: 760.2 (M + 1).

3,6-bis(4-chlorobenzylidene)amino)-10-methacridin-10-ium chloride, R=2-ClCH₃,H.(11) Light yellow solid (yield: 71%; m.p. 200-202°C). IR [KBr] 3366(O-H); 3091 (C=O aromatic);1692 (C=O amide); 1558 (C=C aromatic);1329 (C-N); 747 and (C-S thio); 1-H(NMR (DMSO-d₆) δ 4.02 (2H, d, CH₂ thiazol ring); 4.36 [3H, s, CH₃]; 6.54[1H , s, C-CH thiazol ring]; 6.89, 7.87 (7H, m, aromatic) and 10.15 [1H, s, O-H]. C₆H₅N₂O₂S₃Cl,M/S: 616.1 (M + 1).

3,6-bis(4-chlorobenzyldiene)amino)-10-methylacridin-10-ium chloride, R=2-ClCH₃,H.(12) Light yellow solid (yield: 75%; m.p. 300-302°C). IR [KBr] 3356(O-H); 3088 (C=O aromatic);1677 (C=O amide); 1551 (C=C aromatic);1329 (C-N); 747 and (C-S thio);754 (C-Br); 1-H(NMR (DMSO-d₆) δ 3.98 (2H, d, CH₂ thiazol ring); 4.39 [3H, s, CH₃]; 6.66 [1H , s, C-CH thiazol ring]; 7.20, 8.31and (8H, m, aromatic). C₆H₅N₂O₂S₃Cl,M/S: 653.03 (M + 1).
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3.6-bis(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-10-methylacridin-10-ium chloride
R=4-BrC₆H₄(12)
Yellow solid (yield: 63%; m. p. 300dec °C). C₂H₃NBrCl[KBr] 3093 (C-H aromatic), 1668 (C=O amide); 1540 (C=C aromatic); 1350 (C=N); 766 and (C=S thio); 725 (C=Br); 1H-NMR (DMSO-d₆) δ 8.95 (2H, d, C-H thiazol ring); 4.49 (3H, s, CH₃); 6.64 (1H, s, C-H thiazol ring); 7.17, 8.35and (8H, m, aromatic).C₂H₃NBrCl[M/S]: 741.9 (M+1).

Synthesis of tetrazole compounds (13-18).

General method:
Mixtures 0.01 mole of Schiff bases compounds (1-6) and sodium azide dissolved in 20 ml of tetrahydrofuran(THF) and 2 ml of distilled water and refluxed the mixture by microwave oven for 6 minutes 200Watt. On completion of the reaction as observed by TLC eluting with a mixture of n-hexane and ethyl acetate (3:2), and left to stand for 24 hr. The solid product was precipitated, filtered off and recrystallized from absolute ethanol.

3.6-bis(5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-tetrazol-1-yl)-10-methylacridin-10-ium chloride, R=2-OCH₃,4-OHCH₂(13)
Silver solid (yield: 57%; m. p. 113-116 °C). IR [KBr] 3400 (O-H); 3248 (N-H tetrazole ring); 1572 (C=C aromatic); 1473 (N=N azo); 1224 (C=N); 1125 (C-O) and 1015(N-N). 1H-NMR (DMSO-d₆) δ 3.77 [3H, s, CH₂]; 4.39 [3H, s, CH₃]; 5.86 [1H, s, C-H tetrazol ring] 6.85, 8.65 (7H, m, aromatic); and 9.96 [1H, s, N-H tetrazol].C₂H₃N₂OCl[M/S]: 614.0 (M+1).

3.6-bis(5-cinnamyl-4,5-dihydro-1H-tetrazol-1-yl)-10-methylacridin-10-ium chloride
R=cinnamaldehyde,(14)
Off whitesolid (yield: 54%; m. p. 200dec °C). IR [KBr] 3254 (N-H tetrazole ring); 1572 (C=C aromatic); 1461 (N=N azo); 1282 (C-N); and 1119 (N-N). 1H-NMR (DMSO-d₆) δ 1.76 [1H, s, N-H tetrazol]; 2.32 [3H, s, CH₂]; 6.12 [1H, t, C-H]; 6.48 [1H, d, C-H]; and 6.57, 7.84 (8H, m, aromatic).C₂H₃N₂OCl[M/S]: 573.5 (M+1).

10-methyl-3-(5-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)-4,5-dihydro-1H-tetrazol-1-yl)-6-(5-(3H, s, CH₃); 3.97 [1H, t, C-H tetrazol ring]; 4.32 [3H, s, CH₂]; 6.12 [1H, t, C-H]; 6.48 [1H, d, C-H]; and 6.57, 7.84 (8H, m, aromatic).C₂H₃N₂OCl[M/S]: 573.5 (M+1).

RESULTS AND DISCUSSION

The reaction of acriflavine with different aldehydes to products of Schiff bases afforded the intermediate compounds (1-6). As expected, the conversion of the Schiff bases into the thiazolidonederivatives (7-12) by it’s the reaction with 2-mercaptoacetic acid, alsoconversionof the Schiff bases into the tetrazole derivatives (13-18) by it’s the reaction with sodium azide. Modified domestic microwave oven was used in methods; this modified has been made by us. The prepared compounds illustrated in scheme (1). The conversion could be monitored by TLC analysis of the reaction mixture. The assignment of all structures (1-18) was based on their IR, 1H-NMR, and the Mass spectra data. The results were matching for existing in the literature [25,26,27].

![Scheme 1: Synthesis of the thiazolidine and tetrazole derivatives](image-url)
Biological activity

The biological activities of some of the synthesized Schiff bases, thiazolidinone and tetrazole were tested against one type of bacterial including Gram-negative, *E. Coli*, and one type of fungi including *Candida albicans* by disc and well diffusion method [28,29]. In addition to antioxidant activity [30] as shown in Tables 1, 2, which the zone of inhibition was measured in mm. Figures 1, 2, 3.

The results revealed that compounds showed high activity against *E. Coli* bacteria when compared with standard drug (Neomycin sulfate) and showed good activity against *Candida albicans* yeast when compared with standard drug (Nystatin).

The antioxidant data of some synthesized compounds were revealed good results compared to standard (St.) Gallic acid. Table 2, Figure 3.

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<th>Comp. No.</th>
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<th>Candida albicans</th>
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<td>Zone of inhibition (mm)</td>
<td>Zone of inhibition (mm)</td>
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<td></td>
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<td>5 mg/ml</td>
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Standard (St1) = Neomycin sulfate  
Standard (St2) = Nystatin
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Figure 1: inhibition activity data of some prepared compounds against *Escherichia coli*.

Figure 2: inhibition activity data of some prepared compounds against *Candida albicans*.

Table 2: antioxidant data of some synthesized compounds and the standard (St.) Gallic acid

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<th>Comp.No.</th>
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<th>100µg/cm³</th>
<th>150µg/cm³</th>
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REFERENCES
Synthesis of some thiazolidinone and tetrazole compounds derived from acriflavine and evaluation of their antimicrobial, antifungal and antioxidant activity


