Synthesis some of thiazolidinoneand 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 wereprepared by the cyclization of Schiff bases with thioaceticacid to obtain of thiazolidinone compounds (7-12) and with sodium azide to products of tetrazole compounds (13-18). IR, 1H-NMR, and Mass Spectra data have confirmed the structures of synthesized compounds. The synthesized compounds have been screened for their antimicrobial, antifungal, and antioxidant activity.

INTRODUCTION

Acriflavin is an old medicinal drug previously used as an atrypanocidal agent in World War II[1]. ACF has recently been shown to have potential anticancer 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, photophysical, 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]. Acriflavin is a heteroaromatic dye with antibacterial and antiviral effects [7]. More recently, its potential has emerged as an anti-cancer agent if acriflavin has topoisomerase inhibitor activity [8]. Anti-cancer activities in cell lines of pancreatic ductal adenocarcinoma (PDAC)[9] have been shown to be antibacterial drugacriflavin. 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], cardiotonic [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



Keywords: Acriflavine, thiazolidinone, tetrazole, antimicrobial, antifungal, antioxidant. Correspondence: Malath Khalaf Rasheed Department of Chemistry, College of Education, University of Samarra, Samarra, Iraq *Corresponding author: Malath Khalaf Rasheed email-address: dr.malath.rasheed@uosamarra.edu.iq

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 monitory the reaction and to check purity.Microwave irradiations were carried out in modified domestic microwave oven, Universal - 850 Watt, following pictures.



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Synthesis of Schiff bases compounds (1-6). General method:

A mixture of acriflavine (0.004 mol) and deferent aldehydes (0.008 mol) in absolute ethanol (15 ml) and refluxed withcatalytic hydrochloride (2 drops) in a modified domestic microwave oven for 4-10 minutes (200Watt). Progress of the reaction was monitored by TLC (Ethylacetate:Hexane 2:3). After the completion of the reaction, solid product was obtained in reaction mixture, which was filtered, dried, and recrystallized from methanol.

3,6-bis((4-hydroxy-3-methoxybenzylidene)amino)-10methylacridin-10-iumchloride R=2-OCH₃,4-OHC₆H₃.(1) Dark brown solid (yield: 81%; m. p, 75-77°C). IR [KBr] 3356 (O-H); 3086 (C-H aromatic); 1515 (C=C aromatic); 1620 (C=N imine); and 1125 (C-O); ¹H-NMR (DMSO-d6) δ 3.85 [3H, s, CH₃];4.42 [3H, s, CH₃]; 7.17, 7.85 (6H, m, aromatic); 8.86 [1H, s, C-H imine]; and8.86 [1H, s, O-H].C₃₀H₂₆N₃O₄Cl, M/S: 528.01 (M + 1).

10-methyl-3,6-bis(((1E,3E)-4-phenylbut-3-en-1-

ylidene)amino)acridin-10-iumchloride,

R=cinnamaldehyde.(2)

Green solid (yield: 63%; m. p, $132-135^{\circ}$ C). IR [KBr] 3050 (C-H aromatic); 1515 (C=C aromatic); 1644 (C=C alkine); and 1618 (C=N imine);¹H-NMR (DMSO-d6) δ 2.85 [2H, t, CH₂];4.45 [3H, s, CH₃];6.06 [1H, q, C-H];6.44 [1H, d, C-H]; 7.24, 7.75 (8H, m, aromatic); and 8.86 [1H, t, C-H imine].C₃₂H₂₆N₃Cl, M/S: 516.09 (M + 1).

10-methyl-3-(((3S,4R,5R,6R,Z)-3,4,5,6,7-

pentahydroxyheptylidene)amino)-6-(((4R,5R,6R,E)-3,4,5,6,7-pentahydroxyheptylidene)amino)acridin-10-ium chloride

R = Glucose.(3)

Brown solid (yield: 69%; m. p, 90-93°C).IR [KBr]; 3362(O-H); 1515 (C=C aromatic); and 1623 (C=N imine);1115 (C-O); ¹H-NMR (DMSO-d6) δ 2.35 [2H, m, CH₂];4.45 [6H, m, C-Hglucose];4.37 [1H, s, O-H];4.45 [3H, s, CH₃];7.12, 7.45 (7H, m, aromatic); and 8.62 [1H, t, C-H imine].C₂₆H₃₄N₃O₁₀Cl,M/S: 612.07 (M + 1).

3,6-bis(((E)-4-hydroxybenzylidene)amino)-10-

methylacridin-10-ium chloride

 $R = 4 - OHC_6H_4.(4)$

Dark brown solid (yield: 62%; m. p, 200dec°C). IR [KBr] 3394(O-H); 3042-3096 (C-H aromatic); 1543 (C=C aromatic); 1620-1632 (C=N imine); and);¹H-NMR (DMSO-d6) δ 4.41 [3H, s, CH₃]; 7.04, 7.77 (7H, m, aromatic); and 8.86 [1H, d, C-H imine] 9.78 [1H, s, O-H].C₂₈H₂₂N₃O₂Cl,M/S: 467.95 (M + 1).

3,6-bis(((E)-4-chlorobenzylidene)amino)-10-methylacridin-10-ium chloride

 $R = 4 - ClC_6H_{4.}(5)$

Light brown solid (yield: 84%; m. p, 164-166°C).IR [KBr] 3384 (O-H); 3076 (C-H aromatic); 1515-1589 (C=C aromatic); 1630 (C=N imine); and 713 (C-Cl); 1H-NMR (DMSO-d6) δ 4.39 [3H, s, CH₃]; 7.16, 7.91 (7H, m, aromatic); and 8.78 [1H, d, C-H imine].C₂₈H₂₀N₃Cl₃,M/S: 504.84 504.8 (M + 1).

3,6-bis(((E)-4-bromobenzylidene) amino)-10-methylacridin-10-ium chloride, R=4-BrC₆H₄.(6)

Brown solid (yield: 73%; m.p. 138-140°C). IR [KBr] 3356-3394 (O-H); 3096 (C-H aromatic); 1534 (C=C aromatic); 1627 (C=N imine); and 743 (C-Br); 1H-NMR (DMSO-d6) δ 4.31 [3H, s, CH₃]; 7.17, 7.85 (7H, m, aromatic); and 8.72 [1H, m, C-H imine].C₂₈H₂₀N₃ClBr₂M/S: 593.75 (M + 1).

Synthesis of thiazolidinonecompounds (7-12). General method: Compounds of Schiff bases (1-6), (0.002 mole) were mixed with (0.004mole) of 2-mercptoacetic acid in abs-ethanol (20ml), (0.136 mol) of $ZnCl_2$ 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 TLCeluting with a mixture of *n*-hexane and ethyl acetate (3:2).Cooled, filtered and washed with 5% sodium bicarbonate then with water and crystallized from dioxane.

3,6-bis(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3yl)-10-methylacridin-10-ium chloride,R=2-OCH₃,4-OHC₆H₃.(7) Yellowsolid (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);¹H-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, C-H thiazol ring); and 7.06, 7.96 (7H, m, aromatic); and 10.17 [1H, s, O-H].C₃₄H₃₀N₃O₆S₂Cl,M/S: 676.2 (M + 1).

3,6-bis(2-cinnamyl-4-oxothiazolidin-3-yl)-10-methylacridin-10-ium chloride

R=cinnamaldehyde.(8)

Pale yellowsolid (yield: 54%; m. p, 110-112°C).IR [KBr] 1685 (C=O amide); 1612 (C=C aromatic); 1321 (C-N); 764 and (C-S thio);1H-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-H thiazol ring]; 6.15[1H, q, C-H]; 6.53 [1H, d, C-H]; and 7.06, 7.96 (7H, m, aromatic).C₃₆H₃₀N₃O₂S₂Cl,M/S: 664.28 (M + 1).

10-methyl-3-(4-oxo-2-((2S,3R,4R,5R)-2,3,4,5,6pentahydroxyhexyl)thiazolidin-3-yl)-6-(4-oxo-2-((3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)thiazolidin-3yl)acridin-10-ium chloride,R= Glucose.(9) Yellow solid (yield: 61%; m. p, 169-171°C). $C_{26}H_{34}N_3O_{10}Cl$ (%),IR [KBr] 1685 (C=O amide); 1612 (C=C aromatic); 1321 (C-N); 764 and (C-S thio);¹H-NMR (DMSO-d6) δ 1.97 [2H, t, CH₂]; 3.76 [5H, m, C-Hglucose]; 4.13 (2H, d, CH₂ thiazol ring); 4.39 [1H, s, O-H];4.96 [1H, s, O-H];4.45 [3H, s, CH₃];4.52 [3H, s, CH₃];and 7.10, 7.84 (4H, m, aromatic).C₃₀H₃₈N₃O₁₂S₂Cl,M/S: 760.2 (M + 1).

3,6-bis(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-10methylacridin-10-ium chloride $R=4-OHC_{6}H_{4.}(10)$

Off whitesolid (yield: 71%; m. p, 200-202°C). IR [KBr] 3366(O-H); 3091 (C-H aromatic);1692 (C=O amide); 1558 (C=C aromatic);1329 (C-N); 747 and (C-S thio);¹H-NMR (DMSO-d6) δ 4.02 (2H, d, CH₂ thiazol ring); 4.36 [3H, s, CH₃]; 6.54[1H, s, C-H thiazol ring]; 6.89, 7.87 (7H, m, aromatic); and 10.15 [1H, s, O-H].C₃₂H₂₆N₃O₄S₂Cl,M/S: 616.1 (M + 1).

3,6-bis(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-10methylacridin-10-ium chloride

 $R = 4 - ClC_6H_4.(11)$

Light yellow solid (yield: 75%; m. p, 300dec° C).[KBr] 3088 (C-H aromatic);1677 (C=O amide); 1551 (C=C aromatic);1329 (C-N); 747 and (C-S thio);754 (C-Br); ¹H-NMR (DMSO-d6) δ 3.98 (2H, d, CH₂ thiazol ring); 4.39 [3H, s, CH₃]; 6.66[1H, s, C-H thiazol ring]; 7.20, 8.31 and (8H, m, aromatic).C₃₂H₂₄N₃O₂S₂Cl₃,M/S: 653.03 (M + 1).

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3,6-bis(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-10methylacridin-10-ium chloride R= 4-BrC₆H₄.(12)

Yellow solid (yield: 63%; m. p, 300dec °C). $C_{28}H_{20}N_3Br_2Cl,[KBr] 3093$ (C-H aromatic);1668 (C=O amide); 1540 (C=C aromatic);1320 (C-N); 766 and (C-S thio);725 (C-Br); ¹H-NMR (DMSO-d6) $\delta3.95$ (2H, d, CH₂ thiazol ring); 4.49 [3H, s, CH₃]; 6.64[1H, s, C-H thiazol ring];7.17, 8.35and (8H, m, aromatic). $C_{32}H_{24}N_3O_2S_2ClBr_2M/S:741.9$ (M+ 1).

Synthesis of tetrazole compounds (13-18).

General method:

Mixtures 0.01 mole of Schiff basescompounds (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-1yl)-10-methylacridin-10-ium chloride, R=2-OCH₃,4-OHC₆H₃.(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, CH₃]; 4.39 [3H, s, CH₃];8.86 [1H, s, C-H tetrazol ring] 6.85, 8.65 (7H, m, aromatic); and 9.96 [1H, s, N-H tetrazol].C₃₀H₂₈N₉O₄ClM/S: 614.06 (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];2.55 [2H, m, CH₂];3.79 [1H, t, C-H tetrazol ring];4.32 [3H, s, CH₃];6.12 [1H, t, C-H];6.48 [1H, d, C-H]; and 6.57, 7.84 (8H, m, aromatic).C₃₂H₂₈N₉Cl,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-((3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)-4,5-dihydro-1Htetrazol-1-yl)acridin-10-ium chloride, R= Glucose.(15) Yellow solid (yield: 61%; m. p, 220-222°C). IR [KBr];

3402(O-H); 1579 (C=C aromatic); 1449 (N=N azo); 1258 (C-N); 1129 (C-O); and 1086 (N-N). ¹H-NMR (DMSO-d6)

 $\delta1.76$ [1H, s, N-H tetrazol];2.35 [2H, m, CH₂];4.57 [5H, m, C-Hglucose]; 5.13[1H, s, C-H tetrazol ring]4.39 [1H, s, O-H];4.96 [1H, s, O-H];4.45 [3H, s, CH₃];7.12, 8.45 (4H, m, aromatic).C₂₆H₃₆N₉O₁₀ClM/S: 698.1 (M + 1).

3,6-bis(5-(4-hydroxyphenyl)-4,5-dihydro-1H-tetrazol-1-yl)-10-methylacridin-10-ium chloride, $R=4-OHC_6H_4$. (16) Yellow solid (yield: 71%; m. p, 181-183°C). IR [KBr] 3389(O-H); 3042-3096 (C-H aromatic); 1543 (C=C aromatic);1459 (N=N azo); 1263 (C-N); 1132 (C-O); and 1053 (N-N).¹H-NMR (DMSO-d6) δ 2.33 [1H, s, N-H tetrazol];4.40 [3H, s, CH₃]; 8.86 [1H, d, C-H tetrazol ring] 6.69, 7.86 (7H, m, aromatic); and 10.23 [1H, s, O-H].C₂₈H₂₄N₉O₂Cl,M/S: 554.01 (M + 1).

3,6-bis(5-(4-chlorophenyl)-4,5-dihydro-1H-tetrazol-1-yl)-10methylacridin-10-ium chloride, R=4-ClC₆H₄.(17) Brown solid (yield: 66%; m. p, 170-172°C).IR [KBr] 3087 (C-

Biowii solid (yield: 00 %, iii. p, 1/0-1/2-C).ik [KBi] 5087 (C-H aromatic);1589 (C=C aromatic); 1419 (N=N azo); 1223 (C-N); 1114 (C-O); and 1034 (N-N). and 721 (C-Cl); ¹H-NMR (DMSO-d6) δ 2.33 [1H, s, N-H tetrazol];4.39 [3H, s, CH₃]; 5.21 [1H, s, C-H tetrazol ring]; 7.05, 7.92 (7H, m, aromatic).C₂₈H₂₂N₉Cl₃,M/S: 590.9 (M + 1).

3,6-bis(5-(4-bromophenyl)-4,5-dihydro-1H-tetrazol-1-yl)-10methylacridin-10-ium chloride, R= 4-BrC₆H₄.(18) Pale yellow solid (yield: 65%; m. p, 189-191°C). IR [KBr] 3079(C-H aromatic);1577 (C=C aromatic); 1422 (N=N azo); 1226 (C-N); and 1038 (N-N).and 771 (C-Br); ¹H-NMR (DMSO-d6) δ 2.53 [1H, s, N-H tetrazol];4.44 [3H, s, CH₃]; 5.51 [1H, s, C-H tetrazol ring]; 7.11, 8.17 (7H, m, aromatic).C₂₈H₂₂N₉ClBr₂,M/S: 234.1 (M + 1). M/S: 679.8 (M + 1).

RESULTS AND DISCUSSION

The reaction of acriflavine with deferent aldehydes to products of Schiff bases afforded the intermediate compounds (1-6). As expected, the conversion of the Schiff bases into the thiazolidinonederivatives (7-12) by it's the reaction with 2- mercptoacetic acid, alsoconversion of 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 the all structures (1-18) was based on their IR, ¹H-NMR, and the Mass spectradata. The results were matching for existing in the literature [25,26,27].



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Biological activity

The biological activities of some the synthesize Schiff bases, thiozolidinone and tetrazole weretested against one type of bacterial including Gramnegative, *E. Coli*, and one type of fungiincluding *Candida albicans* by disc and well diffusion method [28,29]. In addition to antioxidant activity [30]as shown in Tables1, 2which 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*yeastwhen compared with standard drug (Nystatin).

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

Table1: inhiption activity data of some prepared compounds against Escherichia coli and Candida albicans

Zone of inhibition (mm)											
Escherichia coli					Candida albicans						
Comp. No.	St ₁ . 10 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml	St ₂ . 10 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml			
1	8	7.5	8	8.4	20.8	15.2	16.5	18.1			
2	10	7.6	9	10.2	20.6	12.5	15.1	17.7			
3	8.4	9	9.2	9.8	20	12.7	15.2	16.8			
4	9.2	10	10.2	10.4	20.5	13.9	15.5	15.1			
5	8	9.8	10	10.2	20.8	13.3	16.1	19.5			
6	10	8	8.2	8	20.7	13.6	16.8	17.4			
8	8.2	8	9.1	9.5	20.8	15.6	15.9	17.9			
9	10	10.2	10.5	10.8	20.5	13.6	16.4	17.3			
12	8.8	9.3	9.6	10	20.7	15.7	16.6	18.3			
14	8	7.6	8.9	10.5	20	16.1	16.5	17.6			
16	8.5	8	9.4	10	20.8	15.1	15.3	16.7			
18	9	10	10.3	10.5	20.8	15.5	16.1	18.1			

Standard (St₁.) = Neomycin sulfate

Standard (St₂.) =Nystatin

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Figure1: inhiption activity data of some prepared compounds against Escherichia coli.



Figure2: inhiption activity data of some prepared compounds against*Candida albicans*. Table 2: antioxidantdata of some synthesized compounds and thestandard (St.)Gallic acid

Comp.No.	25µg/cm ³	50µg/cm ³	100µg/cm ³	150µg/cm ³	200µg/cm ³
St. Gallic acid	0.192	0.203	0.34	0.495	0.689
1	0.293	0.308	0.333	0.355	0.471
3	0.226	0.311	0.359	0.320	0.332
6	0.273	0.329	0.458	0.580	0.605
8	0.227	0.365	0.416	0.436	0.521
9	0.322	0.355	0.298	0.358	0.475
11	0.283	0.308	0.333	0.355	0.378
12	0.326	0.322	0.359	0.333	0.365
18	0.225	0.329	0.458	0.58	0.705



Figure 3: Total antioxidantdata of synthesized compoundscompared with Gallic acid

REFERENCES

- Wainwright, M. (2001) AcridineA neglected antibacterialchromophore. J. Antimicrob. Chemother. 47, 1–13.
- Lee, K., Zhang, H., Qian, D. Z., Rey, S., Liu, J. O., and Semenza, G. L. (2009) Acriflavine inhibits HIF-1 dimerization, tumor growth, and vascularization. Proc. Natl. Acad. Sci. U.S.A. 106, 17910–17915.
- 3. Browning, C. H. (1943) Aminoacridine compounds as surface antiseptics. Br. Med. J. 1, 341–343.
- 4. Srikanta Dana, Dhaneswar Prusty, Devender Dhayal, Mohit Kumar Gupta, Ashraf Dar,
- 5. Sobhan Sen,Pritam Mukhopadhyay, Tridibesh Adak, and Suman Kumar Dhar.Potent
- Antimalarial Activity of Acriflavine in Vitro and In Vivo. Chem. Biol. 2014, 9, 2366–2373.
- Feyza Kolcu and İsmet Kaya. Synthesis, characterization and photovoltaic studies of oligo (acriflavine) *via* chemical oxidative polymerization.<u>RSC</u> <u>Adv.</u>, 2017, 7, 8973-8984.
- 8. Yoann Montigaud, Bernard Ucakar, Balaji Krishnamachary, Zaver M.Bhujwalla, Olivier Feron, Véronique Préat, Fabienne Danhier, Bernard acriflavine-loaded Gallez[,]Pierre Danhier.Optimized lipid nanocapsules as a safe and effective delivery system to treat breast cancer. International Journal of PharmaceuticsVolume 551, Issues 1-2, 15 November 2018, Pages 322-328.

- Wainwright M. Acridine a neglected antibacterial chromophore.J Antimicrob Chemother. 2001; 47:1–13. doi:10.1093/jac/47.1.1
- Hassan S, Laryea D, Mahteme H, et al. Novel activity of acriflavineagainst colorectal cancer tumor cells. Cancer Sci.2011; 102:2206–2213. doi:10.1111/j.1349-7006.2011.02097.
- Ashenafi Bulle, Jeroen Dekervel, Lise Deschuttere, David Nittner, Eric Van Cutsem, Chris Verslype, Jos van Pelt.Anti-Cancer Activity of Acriflavine as Metabolic Inhibitor of OXPHOS in Pancreas Cancer Xenografts.OncoTargets and Therapy 2020:13 6907– 6916.
- Ali I., Lone M.N., Al-Othman Z.A., Al-Warthan A., Sanagi M.M. Heterocyclic scaffolds: centrality in anticancer drug developmentCurr. Drug Target, 16 (2015), pp. 711-734.
- Pawar C.D, Sarkate A.P, Karnik K.S ,Bahekar S.S, Pansare D.N, Shelke R.N, Jawale C.S Shinde, D.B. Synthesis and antimicrobial evaluation of novel ethyl 2-(2-(4-substituted)acetamido)-4-subtituted-thiazole-5carboxylate derivativesBioorg. Med. Chem. Lett., 26 (2016), pp. 3525-3528.
- Mohammad H, Reddy P.V.N, Monteleone D, Mayhoub A.S, Cushman M, Seleem M.N. Synthesis and antibacterial evaluation of a novel series of synthetic phenylthiazole compounds against methicillin-resistant *Staphylococcus aureus* (MRSA)Eur. J. Med. Chem., 94 (2015), pp. 306-316.

Synthesis some of thiazolidinoneand tetrazole compounds derived from acriflavine and

evaluation of their antimicrobial, antifungal and antioxidant activity

- 15. Thore S.N, Gupta S.V, Baheti K.G. Synthesis and pharmacological evaluation of 5-methyl-2phenylthiazole-4-substituted heteroazoles as a potential anti-inflammatory and analgesic agentsJ. Saudi Chem. Soc., 20 (2016), pp. S46-S52.
- Nastasă C, Tiperciuc B, Pârvu A, Duma M, Ionuț I, Oniga O. Synthesis of new *N*-substituted 5-arylidene-2,4-thiazolidinediones as anti-inflammatory and antimicrobial agents Arch. Pharm. Chem. Life Sci., 346 (2013), pp. 481-490.
- Das D, Sikdar P, Bairagi M. Recent developments of 2aminothiazoles in medicinal chemistryEur. J. Med. Chem., 109 (2016), pp. 89-98.
- Duan L.M, Yu H.Y, Jia C.J, LiY.L. Design and discovery of 2-(4-(1H-tetrazol-5-yl)-1H-pyrazol-1-yl)-4-(4-phenyl)thiazole derivatives as cardiotonic agents via inhibition of PDE3Bioorg. Med. Chem., 23 (2015), pp. 6111-6117.
- Turan-Zitouni G, Altintop M.D, Ozdemir A, KaplancıklZ.A, Çiftçi G.A, Temel H.E. Synthesis and evaluation of bis-thiazole derivatives as new anticancer agentsEur. J. Med. Chem., 107 (2016), pp. 288-294
- Parekh N.M, Mistry B.M, Pandurangan M, Shinde S.K, PatelInR.V. vestigation of anticancer potencies of newly generated Schiff base imidazolylphenylheterocyclic-2ylmethylenethiazole-2-aminesChin. Chem. Lett., 28 (2017), pp. 602-606.
- Dhumal S.T, Deshmukh A.R, Bhosle M.R, Khedkar V.M, Nawale L.U, Sarkar D, Mane R.A. Synthesis and antitubercular activity of new 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffoldsBioorg. Med. Chem. Lett., 26 (2016), pp. 3646-3651.
- 22. Amnerkar N.D, Bhongade B.A, Bhusari K.P, Synthesis and biological evaluation of some-(6-substituted-1,3benzothiazol-2-yl)amino-1,3-thiazole-2-amines and their Schiff bases, Arab. J. Chem. 8 (2015) 545–552.
- Weiam Hussein, Gülhan Turan-Zitouni.Synthesis of new thiazole and thiazolyl derivatives of medicinal significant-a short review.*MOJ Biorg Org Chem.* 2018;2(2):52–55.
- 24. Yashika Bhalla, Erra Puri, Prakriti Monga, Sameer Sapra, Medicinal and chemical aspects of Tetrazoles: an overview, *Innovations in Pharmacy Planet*, 1(1), 2013, 20-30.
- 25. Arulmozhi R, Abirami N, Helen Kavitha P.A Pharmacological Expedition of Tetrazole Compounds Towards Medical Field - An Overview. Int. J. Pharm. Sci. Rev. Res., 46(1), September - October 2017; Article No. 21, Pages: 110-114.
- 26. Heidi S. Abd ElMonaem1, Naglaa I. Abdel-Aziz, Mohammad A. Morsy, Farid A. Badria, Fardous ElSenduny, Mahmoud B. El-Ashmawy1, Mohamed A. Moustafa.Synthesis, *In Vitro* ntiproliferative Evaluation and Molecular Docking of New tetrazole-chalcone and tetrazole-pyrazoline Hybrids.Journal of Applied Pharmaceutical Science 8 (05); 2018: 075-087.
- 27. Donald L,Pavia. Introduction to Spectroscopy. 5th Ed.Paperback 2015; Pp 784.
- Silverstein RM, Webster FX, Kiemle D, Bryce DL. Spectrometric identification of organic compounds. 7th d., John Wiley & Sons. *New York*, US. 2005; Pp 142, 154.
- 29. Iqbal C.M. and Atta-ur-Rahman "Applications of NMR Spectroscopy", (2015),167-169.
- Yarbrough ML, Lainhart W, Burnham CA (2018) Epidemiology, clinical characteristics, and antimicrobial susceptibility profiles of human clinical isolates of Staphylococcus intermedius group. J Clin Microbiol 56(3): e01788-17.

- Peng Z, Jin D, Kim HB, Stratton CW, Wu B, Tang YW, Sun X (2017) Update on antimicrobial resistance in Clostridium difficile: resistance mechanisms and antimicrobial susceptibility testing. J Clin Microbiol 55(7):1998–2008.
- 32. Hatem Karim Mohammed, D. (2020) MSc dissertation, University of Samarra, Samarra, Iraq.