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Synthesis and biological evaluation of some New pyrimidine derivatives

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Abstract

New pyrimidine derivatives comprising azo, schiff's bases, chalcones, and chromene ring moieties were prepared.The newly synthesized compounds have been established on the basis of their m.p., TLC, FT-IR, UV-Vis ,^{1}H-NMR data and element analysis. These compounds were screened for their antimicrobial and *in vitro* antioxidant properties. The results of this investigation revealed that these compounds are potent antimicrobial and antioxidant agent.

Keywords: pyrimidine derivatives; schiff's bases; chalcones; and chromene ring moieties

1.Introduction

Literature revealed that pyrimidine derivatives occupy an important place in medicinal chemistry as they show a variety of microbiological activity [1,2].

Azo dyes, aromatic moieties linked together by azo (-N=N-) chromophores, represent the largest class of dyes used in textile

processing and other industries such as cosmetic, food colorants, printing, and pharmaceutical industries [3,4] .

Schiff-bases are considered as a very important class of organic compounds and have a wide application in many biological aspects[5,6].

Furthermore, chalcone derivatives from nature or synthetic origin exhibit diverse pharmacological activities, such as antimicrobial [7], anticancer [8], antioxidant [9], antitumor [10], anti-inflammatory[11], antitubercular[12] . The main objective of this work is preparing a series of derivatives of pyrimidine. The basic ring was designed to be a pyrimidine with additional derivatives as azo, Schiff bases and chalcones

2. Experimental

2.1 Materials and physical measurements

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected.All reactants and solvents used in this study were reagents grade and they are available from Sigma-Aldrich and Fluka companies. Purity of the compounds was checked on silica coated Merck-TLC plates using water, chloroform benzene and acetone as mobile phase. FTIR measurements were recorded on Shimadzu model FT-IR-8400S. The UV-Visible spectra were measured in ethanol using Shimadzu UV-Vis. 160 a spectrophotometer. ^{1} H -NMR spectra were obtained with a Bruker spectrophotometer model Ultra Shield at 300 MHz in DMSO-*d* solution with the TMS as internal standard. Element analyses were done on EURO EA instrument in Al - Mustansiriya University.

2.1.1 Synthesis of (E)-2-hydroxy-5-(pyrimidin-2-yldiazenyl)benzaldehyde (1):

2-Aminopyrimidine (1.78 mmol) was dissolved by heating and stirring in 16 mL of 85% phosphoric acid. The solution was cooled to 0˚C in an ice bath, and then concentrated nitric acid 8 mL and a

solution of sodium nitrite (0 3.74 mmol) in 4 mL of water was added. The mixture was stirred vigorously and maintained at below 5˚C for 10 minutes. Afterwards salicylaldehyde (0.374 mmol) in 1 mL water was added dropwise with stirring. The dark brown solid was filtered, washed several times with water, then dissolved in 30 mL 10% NaOH, the solution was filtered, the crude product precipitated during neutralization with 10% HCl, then filtered and washed with water several time .Yield: 70 % ; M.p: 245-247 °C ; UV (λmax,nm): 271,373 , ; FTIR (KBr, v, cm^{-1}): 1670 (C=O) ,1545 (N=N),3562-3200(O-H) ; ¹ H -NMR (300 MHz, DMSO-d6, δ, ppm):10.2(s ,1H, aldehyde -H),5.42 (s ,1H, O-H), 8.52-7.21 (m, 6H, Ar).

2.1.2 General procedure for the synthesis of Schiff bases (2-4):

The Schiff base was prepared by reaction of equimole of compound 1 and aromatic amine. Each reactant was dissolved in a minimum amount of ethanol, then mixed together and followed by addition of three drop of glacial acetic acid. The solution was refluxed for 6- 8 h then cools to room temperature and poured in to ice cold water. The solid product was recrystallized from ethanol.

2-((E)-(pyridin-2-ylimino)methyl)-4-((E)-pyrimidin-2-yldiazenyl)phenol (2):

Yield: 77% ; M.p: 166-165 °C ; UV (λmax , nm)212 ,361 ; FTIR (KBr, v, cm^{-1}): 1666 (C=N), 1539 (N=N) . ^{1}H- NMR (300 MHz, DMSO-d6, δ, ppm): 8.92-7.71 (m,11 H, Ar-H,CH=N), 5.52(s, 1H,OH); Anal. % calc./found for $C_{16}H_{12}N_6O$(m.w.304) C,63.15/62.89; H,3.94/3.81;N,27.63/27.48.

4-((E)-pyrimidin-2-yldiazenyl)-2-((E)-(pyrimidin-2-ylimino)methyl)phenol (3):

Yield: 50% ; M.p: 260-262 °C ; UV (λmax , nm)257 ,354 ; FTIR (KBr, v, cm^{-1}):3450-3100(OH), 1660 (C=N), 1589 (N=N) . ¹H-

NMR (300 MHz, DMSO-d6, δ, ppm): 8.91-7.51 (m,10 H, Ar-H,CH=N),5.52(s,1H,OH) ; Anal. % calc./found for $C_{15}H_{11}N_7O$(m.w.305) C,59.01/58.80; H,3.60/3.41; N,3.21/3.11.

2-((E)-((4-methylbenzo[d]thiazol-2-yl)imino)methyl)-4-((E)-pyrimidin-2-yldiazenyl)phenol (4):

Yield: 67% ; M.p: 190-188 °C ; UV (λmax , nm)261,433 ; FTIR (KBr, v, cm^{-1}): 1589 (C=N), 1553(N=N) . ^{1}H- NMR (300 MHz, DMSO-d6, δ, ppm): 8.92-7.32 (m, 10H, Ar-H,CH=N), 2.21 (s, 3H,CH_3); Anal. % calc./found for $C_{19}H_{14}N_6OS$ (m.w.374) C, 60.96 / 61.12; H,3.74/3.59 ; N , 22.46 / 22.28; S , 8.55 / 8.32.

21.3 Synthesis of (E)-3-acetyl-6-(pyrimidin-2-yldiazenyl)-2H-chromen-2-one (5):

Compound 1 (0.01mol)in dry chloroform (20mL) were added ethylacetoacetate(0.01mol)and few droup of piperdine.the reaction mixture was heaed nuder reflux for 2 h. and left to cool after distilling off the excess solvent.The solid was filtered ,washed with cold water,dried and recrystallization from toluene. Yield: 70% ; M.p: 123-125 °C ; UV (λmax , nm) : 255 ,332 ; FTIR (KBr, v, cm^{-1}):1737 (C=O of chromen), 1708 (C=O of acetyl),1548(N=N) ; ^{1} H -NMR (300 MHz, DMSO-d6, δ, ppm): 8.89-6.84 (m, 7H, Ar-H), 2.28(s, 3H, acetyl-H) ; Anal. % calc./found for $C_{15}H_{10}N_4O_3$(m.w.294) C,61.22/62.85; H,3.40/3.25; N,19.05/18.86.

2.1.4 Synthesis of Chalcone derivatives (6-9):

An equimolar mixture of compound (C) (0.01 mol) andaromatic aldehydes (0.01mol) was stirred in ethanol(30 ml) and then an aqueous solution of NaOH (40%)was added to it. The reaction mixture was kept overnight at room temperature. The precipitate obtained was filtered ,washed with diethyl ether and recrystallized from ethanol. TLC showed that the reaction was completed by using (benzene ethanol 2:1).

3-((E)-3-(4-chlorophenyl)acryloyl)-6-((E)-pyrimidin-2-yldiazenyl)-2H-chromen-2-one (6):

Yield: 56% ; M.p: 172-174 °C ; UV (λmax , nm)271 ,353; FTIR (KBr, v, cm^{-1}):1670 (C=O), 1635(C=C of chalcon) ,1589 (N=N), . ^{1}H- NMR (300 MHz, DMSO-d6, δ, ppm): 8.83-6.51 (m,11H,Ar-H) 7.32 (d,1H,CH=) ,6.86 (d,1H, O=C-CH) ; Anal. % calc./found for $C_{22}H_{13}N_4O_3Cl$ (m.w.416.5) C,63.38/63.22; H,3.12/3.05; N,13.44/13.38.

(E)-1-(4-aminophenyl)-3-(2-hydroxy-5-((E)-pyrimidin-2-yldiazenyl) phenyl) prop-2-en-1-one (7):

Yield: 64% ; M.p: 200-201 °C ; UV (λmax , nm)234-314; FTIR (KBr, v, cm^{-1}): 3354 ,3443(NH2), 3225 (OH) ,1651 (C=O), 1633 (C=C chalc.), 1556(N=N), . ^{1}H- NMR (300 MHz, DMSO-d6, δ, ppm): 8.42-6.51 (m,10 H, Ar-H), 7.2 (d,1H,CH=) ,6.8 (d,1H, O=C-CH) ; Anal. % calc./found for $C_{19}H_{15}N_5O_2$(m.w. 345)C,66.08/66.20; H,4.35/4.29; N 20.29/20.10.

(E)-1-(4-nitrophenyl)-3-(2-hydroxy-5-((E)-pyrimidin-2-yldiazenyl) phenyl) prop-2-en-1-one (8):

Yield: 69% ; M.p: 192-194 °C ; UV (λmax , nm)242 ,361 ; FTIR (KBr, v, cm^{-1}): 340-3200 (OH),1667 (C=O chalc.), 1627 (C=C chalc.),1585 (N=N), 1518 ,1342 (NO_2) . ^{1}H- NMR (300 MHz, DMSO-d6, δ, ppm): 8.48-6.95 (m,10 H, Ar-H) 7.22 (d,1H,CH=) , 7.17 (d,1H, O=C-CH) ; Anal. % calc./found for $C_{19}H_{13}N_5O$(m.w.364.5) C,62.55/62.46; H,3.56/3.48; N15.36/15.20.

(E)-1-(4-chlorophenyl)-3-(2-hydroxy-5-((E)-pyrimidin-2-yldiazenyl) phenyl) prop-2-en-1-one (9):

Yield: 78% ; M.p: 186-187 °C ; UV (λmax , nm)221,386 ; FTIR (KBr, v, cm^{-1}):1666 (C=O), 1638 (C=C chalc.),1589 (N=N) ; ^{1}H-NMR (300 MHz, DMSO-d6, δ, ppm): 8.48-6.95 (m,10 H, Ar-H) 7.22 (d,1H,CH=) , 7.17 (d,1H, O=C-CH), 5.34(s, 1H,OH) ; Anal. % calc./found for $C_{19}H_{13}N_4O_2Cl$ (m.w.364.5) C,62.55/63.02; H,3.56/3.38; N,15.36/15.21.

2.2. Biological activities

2.2.1 In vitro antimicrobial activity

The pyrimidine dervatives were screened for their antibacterial activity using two Gram *positive Staphylococcus aureus* and *Streptococcus pyogenes* and gram negative bacteria *Escherichia coli* and *K.pneumonia* using well diffusion method[13].

The antifungal activity was tested against the fungal species *Aspergilus niger* and *Candida albicans* at 10mg/mL concentration using DMSO as solvent. The bacteria and Fungi were sub-cultured in agar and potato dextrose agar medium and were incubated for 24 h for bacteria and 48 h for fungi at 37°C.

2.2.2. Antioxidant activity

The free radical scavenging activity of pyrimidine compound 3-7 towards the radical (DPPH) 1,1-diphenyl-2-picryl hydrazyl was measured as described by reference [16]. The pyrimidine stock solution (1 mg/mL) was diluted to final concentration 20-100 μg/mL. Methanolic DPPH solution (1 mL, 0.3 mmol) was added to sample solution in DMSO (3 mL) at different[14]. concentration. The mixture was shaken vigorously and allowed to stand at room temperature for 30 min.to measured at 517 nm (As) ,using " Shimadzu 175 spectrophotometer ". Methanol was used as the solvent and ascorbic acid as the standard. The methanol solution of DPPH was used as control sample Ac.

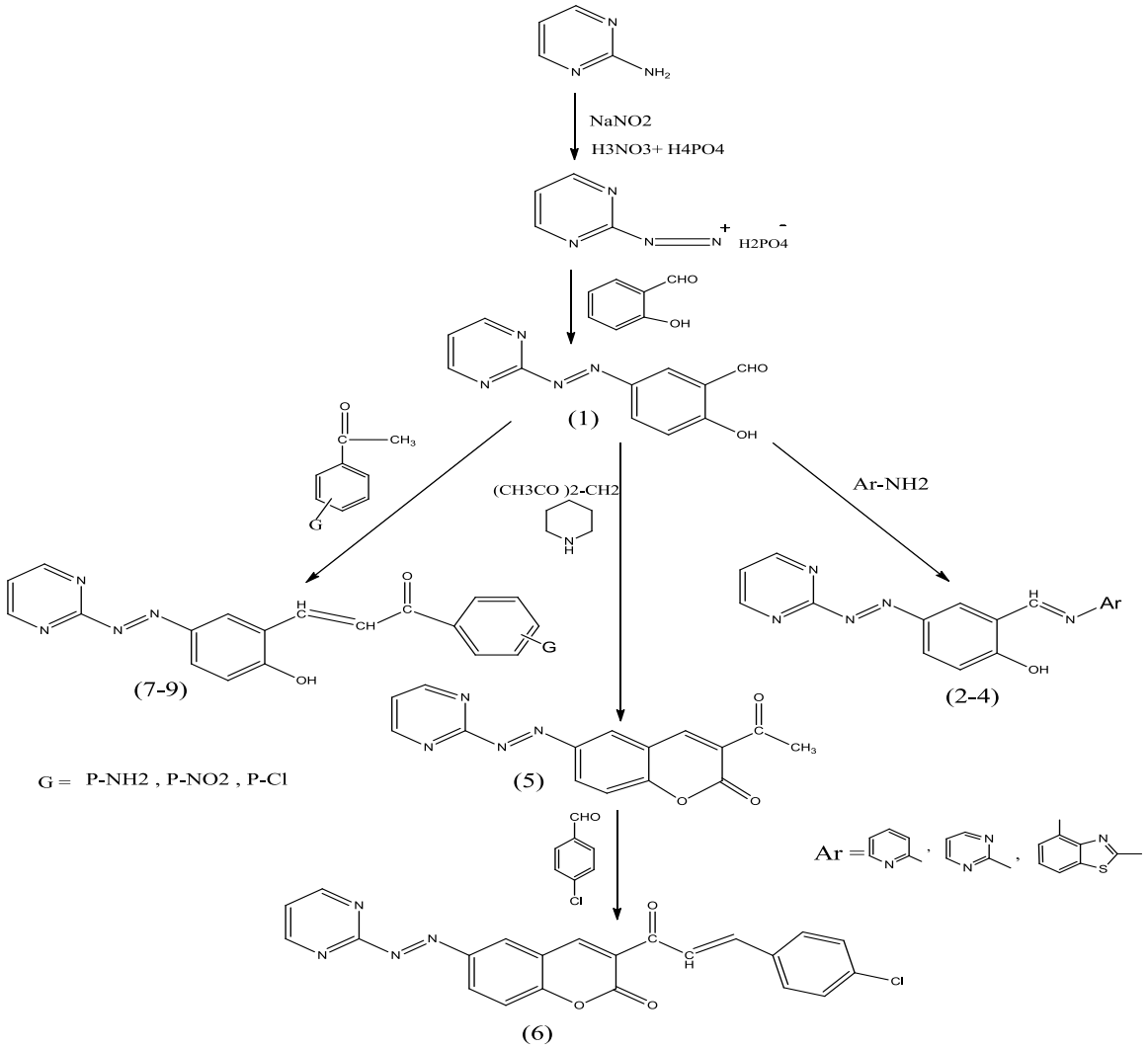
The ability of scavenge calculated using the following formula:

$$\% \text{ Radical scavenging activity} = 100 \times (Ac-As)/Ac \quad (1)$$

3. Results and discussion

3.1. Synthesis

The designated compounds were synthesized according to Schemes 1 . The azo compound 1 was synthesized by diazotiazation of 2-aminopyrimidine and coupling with Salicylaldehyde by following the method reported by Erlenmeyer and Ueberwasser [15].



Scheme 1

The structure of all compounds were proven based on the melting point (m.p), thin layer chromatography (TLC) and spectral data. FTIR absorption bands of azo derivative 1 exhibited the disappearances of two absorption bands due to NH_2 stretching of 2-aminopyrimidine together with the appearance of stretching band at 1545 cm^{-1} due to N=N group,which it also shows stretching abroad band around 3562-3200 cm^{-1} due to the intramolecular hydrogen bonding of O-H group [23].^{1}H-NMR spectrum of azo compound exhibited singlet at 5.42 ppm was attributed to O-H proton, at 8.52-7.21 ppm belong to proton of pyrimidine and salicylaldehyde ring , singlet at 10.2 ppm due to proton of aldehyde group.

Condensation compound 1 with aromatic amine in absolute ethanol gave Schiff bases (2-4). The formation of these Schiff bases was indicated by the presence in their FT IR spectra of the azomethine CH=N stretching at 1589-1666 cm^{-1} While ^{1}H-NMR spectrum of compound 4 exhibited singlet signal at 2.21 ppm was assigned to proton of methyl group and a multiplet signals at 8.92-7.32 ppm due to aromatic proton and proton of CH=N group.

The Knoevenagel condensation can be successfully applied to the cyclization of azo compound 1 with ethylacetoacetate in the presence of piperidine leads to coumarin dervative 5 [16].

The structure of compound 5 was confirmed by their FTIR spectra through disappearance of the O-H stretching frequency and C=O of aldehyde together with the appearance of bands at 1737 cm^{-1} assignable to C=O of chromen ring and C=O of acetyl group at 1708 cm^{-1}, are good evidence for the structure given to this compound. ^{1}H-NMR spectrum of compound 5 exhibited singlet signals 2.28 ppm was assigned to proton of acetyl group pm was assigned to three protons of p-substituted methoxy group, doublet of doublet signals and a multiplet signals at 8.89-6.84 ppm due to 7H aromatic proton.

On the other hand, the reaction of compound 5 with p-chlorobenzaldehyde afforded chalcones deravtive 6 . FTIR spectrum of 6 showed a bands at 1670 , 1635 cm^{-1} due to(C=C and C=O) of α, β –unsaturated compound respectively. ^{1}H-NMR spectrum of chalcone compound 6 exhibited two dublet signal at 7.32ppm ,6.83ppm for one proton CH= and O=C-CH , while a multiplet signals at 8.83-6.51 ppm due to 11 H aromatic protons.

Moreover, condensation of compound 1 with substituted acetophenone afforded chalcones 7-9 . FTIR spectra of chalcones showed a bands at 1638-1627 cm^{-1} and 1667-1651 cm^{-1} due to (C=C and C=O) of α, β- unsaturated respectively

The ^{1} H-NMR of chalcon 8 showed singlet signal 5.32 ppm assigned to OH proton of hydroxyl group and two dublet signals at 7.22 (d,1H,CH=) ,7.17 (d,1H, O=C-CH) , which is interference with a multiplet signals at 8.48-6.95 ppm due to 10 H aromatic protons.

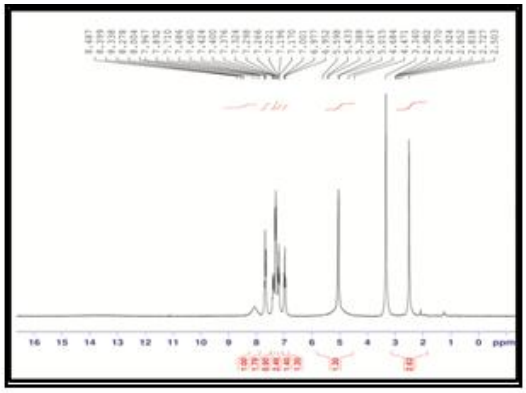


Figure 1: ^{1}H-NMR spectrum of compound 8

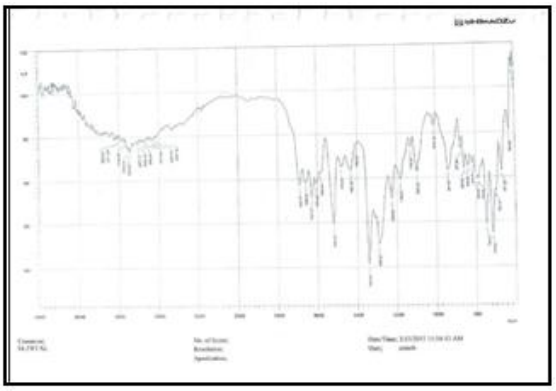


Figure 2: FTIR spectrum of compound 8

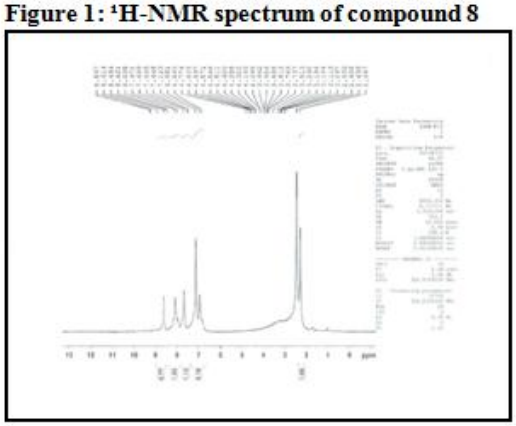


Figure3: ^{1}H-NMR spectrum of compound 5

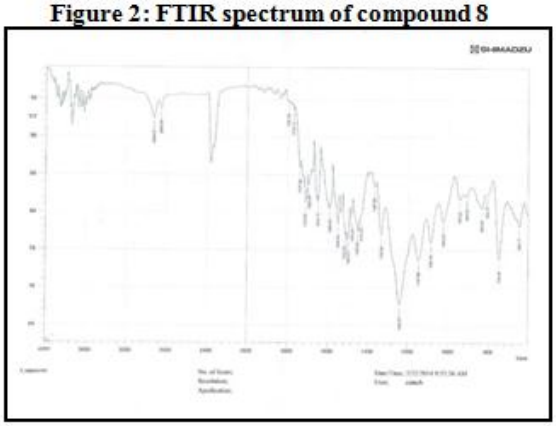


Figure 4: FTIR spectrum of compound 5

3.2.1. Antimicrobial activity

The experiments were performed in triplicate inorder to minimize errors. Pyrimidine carrying azo , , Schiff base , coumarin, chalcone moieties , which is responsible for antimicrobial activity. These compounds showed moderate to considerable of antibacterial and antifungal activity compared to the standard drugs chloramphenicol and fluconazole as positive control at dose of 10mg/mL . It seems that the compound 7 is very significant for activity against both bacterial and fungal species due to the presence of phenyloxy moiety in chalcone and NH2 as electron releasing group . The results of antimicrobial studies are given in Table 1 and Figure 2.

3.2.2. *In vitro* Antioxidant activity

The reducing abilities of the pyrimidine compounds 3- 7 were determined by their interaction with the free stable radical 1,- 1-diphenyl-2-picryl-hydrazine (DPPH) at five different concentration for 30 min. The highest scavenger activity observed in chalcon 7 is probably due to the presence of phenolic moiety. The results of antioxidant screening were depicted in Table 2 and Figure 2 .

Table 1. Antimicrobial evaluation compound 3-7.

	Antibacterial Activity				Antifungal	
	Zone of inhibition (mm)					
	Gram negative		Gram positive		Fungi	
Compound	E.coli	K.pneumonia	S.aureus	S.pyogenes	A.niger	C.albicans
3	7	8	6	8	9	8
4	13	14	7	9	10	12
5	14	12	14	16	12	12
6	18	17	12	18	14	16
7	18	19	15	20	15	17
Chloramphenicol	24	26	23	25	-	-
Fluconazole	-	-	-	-	26	25

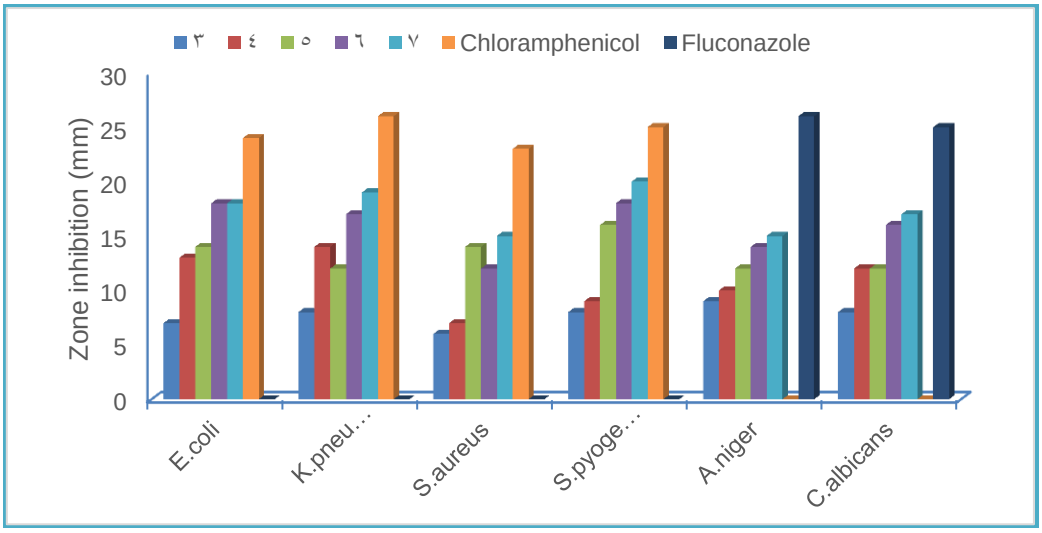


Figure 1. Antimicrobial evaluation of compounds 3-7 .

Table 2: Antiradical activity of compounds 3-7 (expressed as % inhibition)

	10	20	30	40	50	60	70	80	90
3	11	23	30	40	51	61	72	81	90
4	14	25	33	42	54	64	74	82	91
5	13	25	35	44	55	65	75	84	92
6	13	28	38	45	56	66	78	86	93
7	14	29	39	47	57	67	79	88	94
Ascorbic acid	9	16	28	34	44	56	65	76	85

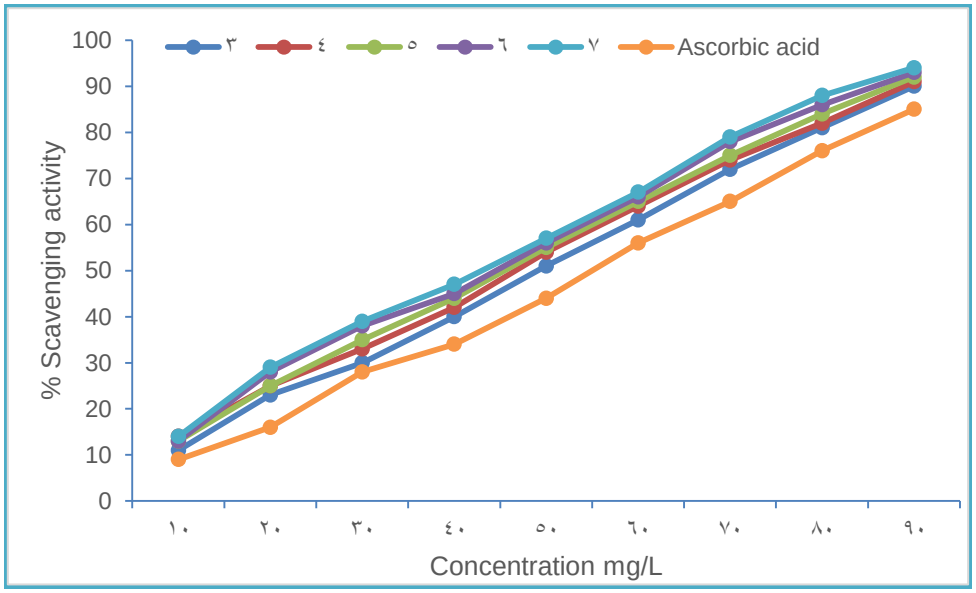


Figure 2. % Scavenging activity of the compounds 3-7 using DPPH

التخليق والتقييم الحيوي لبعض مشتقات البيريميدين الجديدة

فريال ولي عسكر

الجامعة المستنصرية/كلية العلوم/قسم الكيمياء

الخلاصة

مشتقات البريميدين الجديدة التي تضم الآزو ،قواعد شيف الجالكونات ،حلقة الكرومين. المركبات المحضرة الجديدة انشئت على اساس درجات انصهارها ،كروموتوغرافيا الطبقة الرقيقة،الاشعة فوق البنفسجية والمرئية ،الرنيين النووي المغناطيسي للبروتون والتحليل الدقيق للعناصر. تم فحص الفعالية البايولوجية ومضادات الاكسدة للمركبات المحضرة خارج الجسم. نتائج الفحص وجدت ان المركبات المحضرة لها فعالية بايولوجية قوية وتعتبرمضادات اكسدة قوية.

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