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Synthesis, Characterization of heterocyclic compounds and preliminary evaluation of their antibacterial activity and antioxidant agents

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Abstract

Some novel 2-methylquinazolin-4(3H)-ones that carries biphenyl derivatives (A1-A12) were synthesized in better yields and study for their potential antibacterial activities. The structures of the synthesized compounds were proofed on the basis of their spectral data[FTIR, ¹H-NMR] and physical properties. Their antibacterial activities were evaluated by the agar thruogh diffusion method. The results indicated that some of these derivatives have good antimicrobial activities when compared with standard antibiotic.

Keywords: Quinazolinone, Antimicrobial activity, oxazepine ring , cycloaddition reaction ., benzidine

INTRODUCTION

Quinazolinone is aromatic heterocyclic system. Quinazolinone derivatives explain one of the most types of heterocyclic compounds possessing a wide spectrum of biological activity. Medicinally it has been used in various areas as an analgesic and anti-inflammatory[1-3], antioxidant[4,5], Antimicrobial[6-8], antitubercular[9,10], anticonvulsant[11,12], anticancer[13,15]. the quinazolin-4(3H)-one structural motifs containing azomethine (-C=N) functional group has become one of the main areas of interest due to possessing a wide spectrum of biological activities.[16-18].

Oxazepine ring is unsaturated seven-membered hetrocycle. 1,3-Oxazepine ring which contains two hetero atoms are oxygen and nitrogen in positions (1) (3) ,in addition of five carbon atoms [19]. The common methods for preparing oxazepine ring are limited [20]. Recently , cycloaddition reaction, which is a type from a pericyclic reactions is used to synthesis of 1,3-oxazepine ring[21,22]

Literature reviews shows that quinazolinones and oxazepine have antimicrobial activity,, antitumor activity ,anticorrosive activity ,enzymatic activity and anticonvulsant activity.[23-26].

The main objective of this research is synthesis a series of derivatives of quinazolin. The basic ring was designed to be a3-(4'-amino-[1,1'-biphenyl] -4-yl) -2-methylquinazolin-4 (3H) –one (A1) with additional derivatives as Schiff bases and cyclized compounds (Scheme 1).

2- EXPERIMENTAL

Materials and physical measurements

All material chemicals in this study were reagents grade and they are available from Sigma and Aldrich companies. Melting points were determined by Electro thermal capillary apparatus and are uncorrected. Purity of the compounds was checked on silica coated Merck-TLC plates using water,benzene, chloroform and acetone as mobile phase. FTIR measurements were recorded on Shimadzu model FT-IR-8400S. ^{1}HNMR spectra were obtained with a Brukerspectrophotometer model Ultra Shield at 300 MHz in DMSO-*d*6 solution with the TMS as internal standard

Synthesis of 3-(4'-amino-[1,1'-biphenyl] -4-yl) -2-methylquinazolin-4 (3H) –one (A_1):

In a teas tube , (0.001mloe ,0. 161 gm) of 2-methylquinazolin-4(3H)-one compound and (0.001mole ,0.184 gm)of benzidine in oil bath at 180 ^{0}C for 20 min, then cooling and separation molten by ethanol and re-crystallization from methanol

Yield: (88%) : M.P: 194-196 °C , FTIR (ν, cm−1) : 3336 , 3244 (NH_2), 1612 (C=N), (3049,3095)(C-H) Ar., 2945,2865 (C-H) Aliph., 1589–1496 (C=C) Ar.,1672 (C=O), 815,775.696 (CH out of plane) .MS (SCI) (relative intensity %) : m/ z =327 (M+ , 100 %)

SYNTHESIS OF SCHIFF BASES

(0.001mole , 0.327 gm) of compound (A_1) and (0.001mole) of aldehydes (p-hydroxy benzaldehyde. , p-Nitro benzaldehyde. P-N,N-dimethyl benzaldehyde, Pyrrole-2-carbaldehyde, Thiophene-2-carbaldehyde) sequentially and dissolved in 20 ml ethanol absolute with 2-3 drops of glacial acetic acid. . Then reflex (**12-18**) hrs. Then cooling and collect the precipitate and re-crystallization from suitable solvent.

3-(4'-((4-hydroxybenzylidene)amino)-[1,1'-biphenyl]-4-yl)-2-methylquinazoline-4-(3H)-one (A_2)

Yield: (76%) : M.P: 290-292 °C , FTIR (ν, cm−1) :1627 (C=N), 3448 (OH) ,(3171, 3051)(C-H) Ar., 2999,2866 (C-H) Aliph., 1585-1491 (C=C) Ar.,1668 (C=O), 837,817,775 (CH out of plane for substituted phenyl ring).). H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.08 (s,3H,CH_3) , (7.4-8.4 m ,16 H, Ar) ,8.9(s ,1H, CH=N), 10.2 (s , 1H, OH)

2-methyl-3-(4-((nitrobenzylidene) amino)-[1,1'-biphenyl] -4-yl)quinazoline-4 (3H)–one (A_3):

Yield: (80%) : M.P: 252-272 °C , FTIR (ν, cm−1) :1627 (C=N), 1515,1340 (NO2) ,(3051,3088)(C-H) Ar., 2945,2843 (C-H) Aliph., 1597-1492 (C=C) Ar.,1666 (C=O), 852,777.686 (CH out of plane for substituted phenyl ring) .H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.21 (s,3H,CH_3) , (6.9- 8.15 m ,16 H, Ar) ,8.57(s ,H, CH=N)

3-{4'-[(4-Dimethylamino-benzylidene)-amino]-biphenyl -4-yl}-2-methyl-3H- quinazolin-4-one(A_4)

Yield: (50 %) : M.P:283-285 °C , FTIR (ν, cm−1): 1628 (C=N), (3078, 3049)(C-H) Ar., 2922,2812 (C-H) Aliph., 1552-1447 (C=C) Ar.,1681 (C=O), 829,813,769 (CH out of plane for substituted phenyl ring).

2-Methyl-3-{4'-[(1H-pyrrol-2-ylmethylene)-amino]-biphenyl -4-yl}-3H- quinazolin-4-one (A_5)

Yield: (52 %) : M.P: 255-257 °C , FTIR (ν, cm−1): 1627 (C=N), 3306,3275 (NH) ,(3192, 3036)(C-H) Ar., 2931,2830 (C-H) Aliph., 1593-1494 (C=C) Ar.,1686 (C=O), 852,817,757 (CH out of plane for substituted phenyl ring). .H-NMR (300 MHz, DMSO-d6, δ, ppm): 1.98 (s,3H,CH_3) , 8.97 (s, H,NH) , (6.2- 8.65) (m ,16 H, Ar , CH=N) .

2-Methyl-3-{4'-[(thiophen-2-ylmethylene)-amino]-biphenyl-4-yl}-3H- quinazolin-4-one(A_6)

Yield: (65 %) : M.P: 140-142°C , FTIR (ν, cm−1) : 1647 (C=N), (3049)(C-H) Ar., 2951,2870 (C-H) Aliph., 1570-1467 (C=C) Ar.,1680 (C=O), 854,815,769 (CH out of plane for substituted phenyl ring). H-NMR1 (300 MHz, 1DMSO-d6, δ, ppm): 1.78 (s,3H,CH_3) , (6.2- 8.65) (m ,16 H, Ar , CH=N) .

SYNTHESIS OF OXAZEPINE DERIVATIVES

A mixture of Schiff bases derivative[(A_2 , A_3] (0.001mole) and anhydrides(naphthalic anhydride, phathalic anhydride, malic anhydride) (0.001mole) was melted in (15mL) solvent (dry benzene). The mixture was stirred and refluxed at 9-10 hours. Excess solvent was distilled; The resulting solid crystals were filtered and recrystallized from solvents

2-(4-hydroxyphenyl)-3-(4'-(2-methyl-4-oxoquinazolin-3(4H)-yl)-[1,1'- biphenyl]-2,3-dihydro-1,3-oxazepine-4,7-dione (A_7):

The yield:(75%); brown, M. p:288-290 °C; FTIR (υ,cm-1) : 3308 (OH) ,3111,3066 υ (CH aromatic), 2997,2858 υ (CH aliphatic), 1593-1471 υ (C=C aromatic), , 1739 υ (C=O lactam), 1712 υ(C=O lactone), 1681 (C=O), 1273 υ(C – N), 817, 775, 692 υ(CH out of plane for substituted phenyl ring). H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.1 (s,3H ,CH3) , 6.9- 8.15(m ,17 H, Ar + CH-N) , 6.7-6.8 (d, 2H ,CH=CH).,9.81(s,1H,OH)

3-(4-hydroxyphenyl)-4-(4'-(2-methyl-4-oxoquinazolin-3(4H)-yl)-[1,1'-biphenyl]-4-yl)-3,4-dihydro dihydrbenzo [2,3-e][1,3]oxazepine-1,5-dione (A_8)

The yield: (70%); off white, M. p:270 - 272 °C; FTIR (υ,cm-1) : 3437 (OH) ,3107,3057 υ (CH aromatic), 2980,2945 υ (CH aliphatic), 1579-1510 υ (C=C aromatic), , 1712 υ (C=O lactam), 1741 υ (C=O lactone), 1658 (C=O), 1300 υ (C – N), 844, 815,775 υ(CH out of plane for substituted phenyl ring). 2.08 (s,3H ,CH_3) , 7.56- 8.55(m ,21 H, Ar + CH-N) ,10.07(s,1H,OH)

3-(4-hydroxyphenyl)-4-(4'-(2-methyl-4-oxoquinazolin-3(4H)-yl)-[1,1'-biphenyl]-4-yl)-3,4-dihydronaphtho[2,3-e][1,3]oxazepine-1,5-dione (A_9)

The yield: 68%; dark green, M. p:143-145 °C; FTIR (υ,cm-1) : 3381 (OH) ,3165,3074 υ (CH aromatic), 2935,2862 υ (CH aliphatic), 1579-1510 υ (C=C aromatic), , 1710 υ (C=O lactam), 1672 υ (C=O lactone), 1654 (C=O), 1220 υ (C – N), 817, 767,700 υ (CH out of plane for substituted phenyl ring). ¹H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.08 (s,3H,CH_3) , 7.23-8.15.(m ,23H, Ar + CH-N) ,9.98(s,1H,OH)

3-(4'-(2-methyl-4-oxoquinazolin-3(4H)-yl)-[1,1'-biphenyl]-4-yl)-2-(4-nitrophenyl)2,3-dihydro-1,3-oxazepine-4,7-dione (A_{10}).

The yield: 66%; yellow, M. p: 220-222°C; FTIR (υ,cm-1) : 3099,3047 υ (CH aromatic), 2931,2887 υ (CH aliphatic), 1595-1467 υ (C=C aromatic), , 1667 υ (C=O lactam), 1712 υ(C=O lactone), 1662 (C=O), 1111 υ(C – N), 828, 773, 690 υ(CH out of plane for substituted phenyl)

H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.08 (s,3H) , (7.2- 8.18 m ,18 H, Ar + CH-N) , 6.6-6.7 (d, 2H ,CH=CH).

(4-(4'-(2-methyl-4-oxoquinazolin-3-(4H)-yl)-[1,1' -biphenyl)-4-yl)-3-(4-nitrophenyl(3,4-dihydrbenzo[e][1,3]oxazepine-1,5-dione (A_{11})

The yield: 71%; yellow, M. p: 297-300°C; FTIR (υ,cm-1) : 3072,3026 υ (CH aromatic), 2937,2891 υ (CH aliphatic), 1595-1467 υ (C=C aromatic), , 1712 υ (C=O lactam), 1737 υ(C=O lactone), 1681 (C=O), 1220 υ (C – N), 818, 711, 694 υ(CH out of plane for substituted phenyl .¹H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.2 (s,3H) , (6.57-8.53.(m ,21H, Ar + CH-N)

4-(4'-(2-methyl-4-oxoquinazolin-3-(4H)-yl)-[1,1'-biphenyl)-4-yl)-3-(4-nitrophenyl(3,4-dihydronaphtho[2,3-e][1,3]oxazepine-1,5-dion (A_{12})

The yield: 76%; yellow, M. p: 188-190 °C; FTIR (υ,cm-1) : 3072,3026 υ (CH aromatic), 2933,2837 υ (CH aliphatic), 1591-1496 υ (C=C aromatic), , 1739 υ (C=O lactam), 1770 υ(C=O lactone), 1693 (C=O), 1232 υ(C – N), 842, 817, 773 υ(CH out of plane for substituted phenyl

¹H-NMR (300 MHz, DMSO-d6, δ, ppm): 2.23 (s,3H) , 6.63-8.2.(m ,23H, Ar + CH-N)

BIOLOGICAL ACTIVITY

The antimicrobial activities of all the newly synthesized derivatives were tested by the agar disc-diffusion method on five micro-organism . Both gram positive , gram negative bacteria and fungal were used. Gram positive bacteria include *Staphylococcus aureus and Streptococcus eipidermidis* and two gram negative bacteria *E.Coli* ,*Klebsielllasp microorganisms* . Fungal strains namely *Candida albicans*. The test was performed at 100mg/mL concentration. The bacteria and fungi were carried out in agar and potato dextrose agar medium and these plates were incubated for 24 h for bacteria and 48h for fungi at 37 °C.[27]

ANTIOXIDANT ACTIVITY

The free radical scavenging activity of compounds(A_2,A_3,A_7,A_9,**)** towards the radical (DPPH) 1,1-diphenyl-2-picryl hydrazyl was measured as described by reference [28]. Briefly**,**the sample solution (1 mg/mL) was diluted to final concentration of 20-100 µg/mL. To this (1 mL, 0.3 mmol) of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) solution in methanol was added to sample solution in DMSO (3 mL) at different concentration. The mixture solution was incubated and allowed to stand at room temperature for 30 min. the absorbance was then measured at 517 nm (As), using “Shimadzu175 spectrophotometer”.

The methanol solution of DPPH was used as control sample Ac. The free radical scavenging activity was expressed as follows:

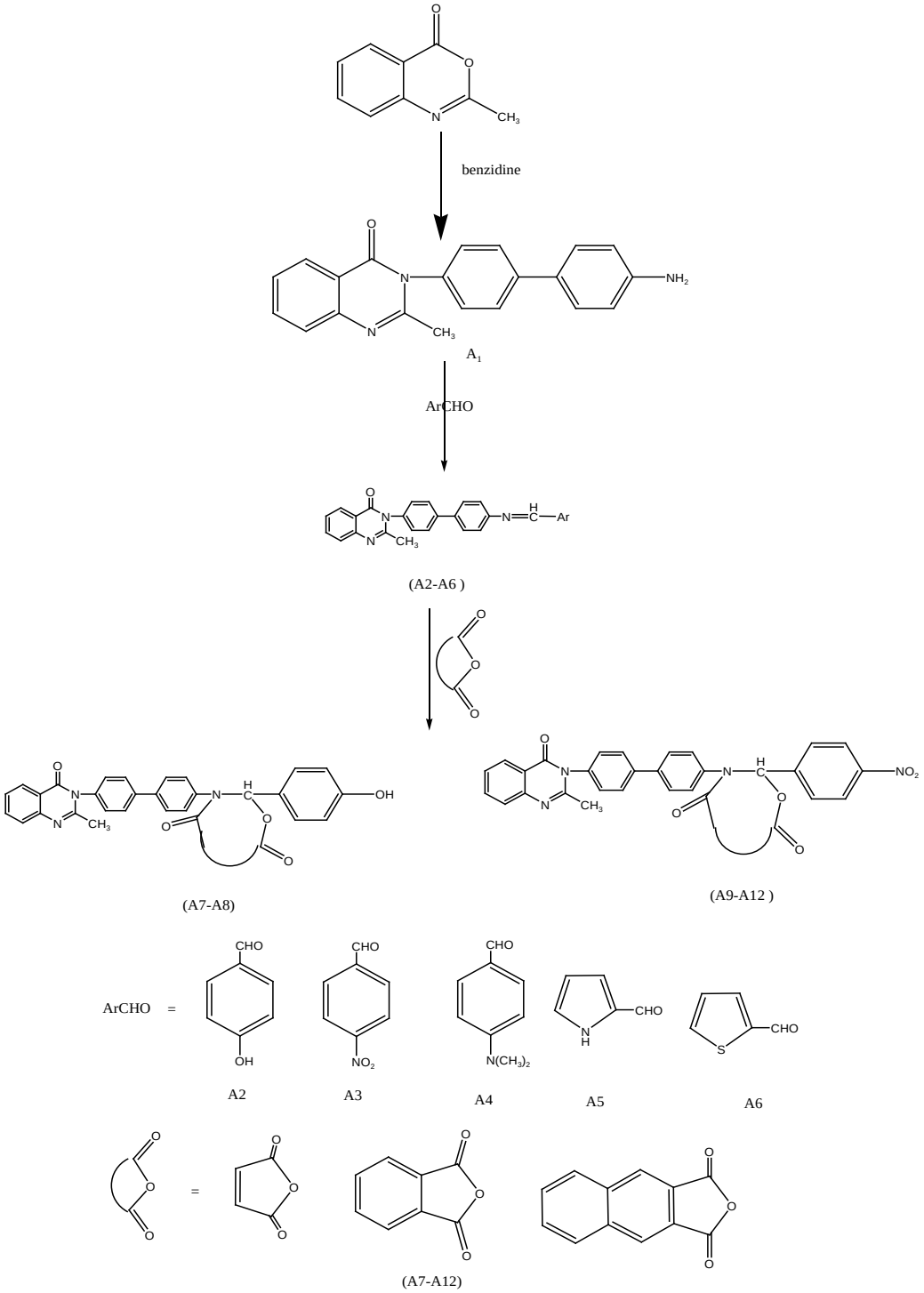
% Radical scavenging activity = 100 × (Ac-As)/(Ac-Ab)

Where *Ac* was the absorbance of the control, *As* for the sample and *Ab* for the blank (MeOH+DMSO) Methanol was used as the solvent and ascorbic acid as the standard.

3. Results And Discussion

Compounds (A1–A12) were synthesized according to the steps illustrated in Scheme 1

3-(4'-amino-[1,1'-biphenyl] -4-yl) -2- methylquinazolin-4 (3H) –one (A_1) was synthesized by heating 2-methylquinazolin-4(3H)-one and benzidine in oil bath , producing (A_1) in 88% yield. The FT-IR spectrum showed stretching bands at 3336 , 3244 cm^{-1} for (NH_2) group, 1672 cm^{-1} for (C=O),and 1612 cm^{-1} for (C=N). The ^1H NMR spectrum the appearance of a singlet signal at 9.34 ppm for NH group and multi signals at 6.52- 7.96 ppm for hydrogen aromatic, singlet signal at 1.96 corresponding to (CH_3)..MS (SCI) (relative intensity %) : m/ z =327 (M+ , 100 %) .



Scheme (1)

Table 1. Antimicrobial screening of compounds (A1-A3 , A7-A12)

Compounds	inhibition zone (mm) at 100 mg/mL				
	Gram positive		Gram negative		Fungi
	S. aureus	*S.epidermidis*	*E.coli*	*Klebsiellas pp*	*Candida albican*
A1	12	11	7	9	9
A2	12	13	11	8	10
A3	13	10	12	10	10
A7	15	8	10	12	11
A8	11	15	13	8	11
A9	13	11	10	12	15
A10	11	10	13	8	14
A11	7	13	12	8	13
A12	12	13	9	12	11
Amoxicillin	20	21	12	18	-
Fluconazole	-	-	-	-	22

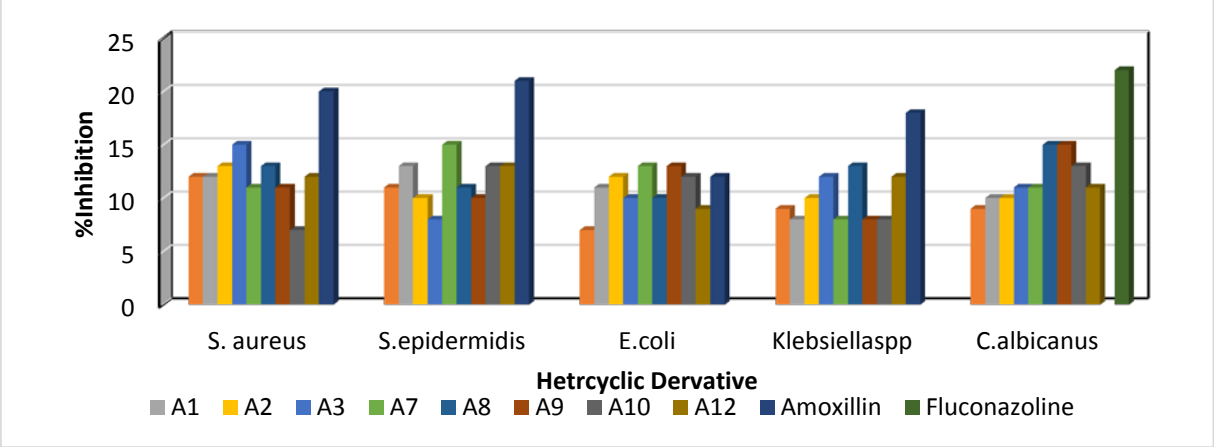


Figure (1):- Antimicrobial evaluation of compounds(A1-A3 , A7-A12)

The Schiff's bases (A_2-A_6) were obtained by reacting 3-(4'-amino-[1,1'-biphenyl] -4-yl) -2-methylquinazolin-4 (3H) –one (A_1)) with substituted aromatic aldehyde in presence of ethanol with few drops of glacial acetic acid. the Schiff's bases derivatives were obtained in good yield. The structures of all the newly synthesized compounds were confirmed by FT-IR and 1H NMR

The FT-IR spectra showed disappearance stretching bands of (NH_2), and appearance stretching bands at 1627–1647 cm^{-1} for imines , 1686-1666 cm^{-1} for The ^1H NMR spectra of compounds showed singlet and multi signals at 8.9-8.57 and 6.9- 8.15 ppm for CH=N and aromatic hydrogen's respectively.

To synthesis oxazepine derivatives (A_7-A_{11}) , the Schiff bases (A_2,A_3) were reacted with aromatic anhydrides in presence of sodium carbonate as catalysis and dioxane as solvent. , The structures of all the newly synthesized compounds were confirmed by FT-IR and 1H NMR.

The FT-IR spectral showed disappearance of bands of N=CH group at (1627–1647) cm-1 for the schiff bases , conversely observed new two bands at (1710, 1742) cm-1 which due to lactam and lactone carbonyl groups of oxazepine ring The 1H-NMR spectra of compounds(A_7-A_{12}) showed multi signals at 7.56- 8.55 ppm for CH-N and aromatic hydrogen's respectively.

Biological activity1.3

The synthesized 2-methylquinazolin-4(3H)-ones derivatives carrying schiff base and 1, 3-oxazepan moieties, which are accountable for antimicrobial activity.The amoxicilline and Fluconazole were used as standard for comparison of antibacterial and antifungal activities respectively. Its appear that the compounds (A1-A3 , A7-A12) possess significant antibacterial and moderate antifungal activities.. Table (1) and Figure (1)

3.2: Antioxidant activity Study:

Antioxidant screening (DPPH radical scavenging activity)

The scavenging activity results of some of synthetic compounds showed in table (2):

From the results in table (2) and figure (2), the conc. (100) µg/ml is the most scavenging activity compared with other concentrations of compounds (A3-4c),

The DPPH is used in the laboratory and is widely used to evaluate the effectiveness of antioxidants. DPPH has absorption at 515 nm and disappears when DPPH is reduced to an antioxidant or becomes radical .The diamagnetic molecule is stable. As a result, the color changes from purple to yellow. This change in color is taken as an indicator of the ability of hydrogen to donate to tested compounds.

Antioxidants can interact with DPPH and produce 1.1 - diphenyl - 2 - picryl - hydrazine. The limiting capabilities of the compounds examined were determined by their interaction with stable free-standing 1.1-di- vinyl-2-picryl-hydrazine (DPPH) in five different concentrations for 30 minutes 1.1 - - Diphenyl-2-picryl-hydrazine. The limiting

capabilities of the compounds examined were determined by their interaction with stable free-standing 1.1-di- phyl-2-picryl-hydrazine (DPPH) in five special concentrations for 30 minutes

The highest scavenger activity observed in compound (A3,A4), this is probably due to the presence of hydroxyl and nitro group . Mostly electron withdrawing substituent's deactivate aromatic ring and have no capability to bind the free radicals.

CONCLUSION

In the present work**,** all the quinazolinone derivatives were synthesized and characterized FTIR 1HNMR ,.Some of the synthesized derivatives was screened for the microbial activity. Results showed that synthesized quinazolinone derivatives have good to moderate anti-bacterial and anti-fungal activities

Table (2): scavenging activity of some of synthetic compounds

Comp. No.	scavenging activity % µg/ml				
	12.5	**25**	**50**	**75**	**100**
A2	43.3	50.6	56.4	64.5	69.36
A3	32.53	37.5	43.3	46.5	54.9
A9	24.7	30.4	35.1	41.8	50.3
A10	29.8	35.2	41.4	43.5	52.3
standard	61.4	71.79	80.22	89.3	94.3

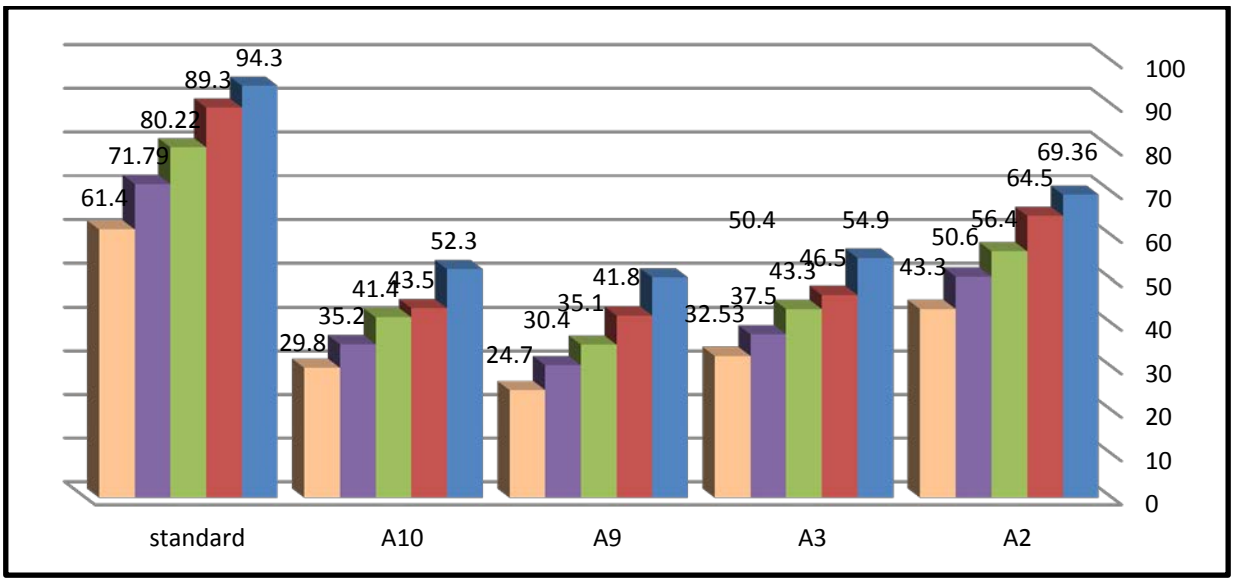


Figure 2. % Scavenging activity of the compounds using DPPH.

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