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Synthesis, characterization and pharmacological evaluation of some novel quinoxaline derived chalcones

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ABSTRACT

Quinoxalines derivatives were reported with wide range of biological activities. Hence it was planned to synthesize some novel series of quinoxalines derivatives. Orthopheneylene diamine was reacted with oxalic acid to form quinoxaline 2, 3 Dione. Quinoxaline-2, 3 (1H, 4H)-dione was chlorinated by using Phosphorousoxytrichloride in dimethyl formamide, to form 2, 3- dichloroquinoxaline. This dichloro compound subjected to reaction with 4 amino acetophenone in DMF, refluxed for 5 hours to form 1-(4-(3-chloroquinoxalin-2-ylamino) phenyl) ethanone. Similarly 1-(4-(3-chloroquinoxalin-2-ylamino) phenyl) ethanone then reacted with corresponding aromatic aldehydes to form quinoxaline derived chalcone by claisen Schmidt reaction. All the compounds were characterized by IR, ^{1}H NMR and Mass spectroscopic data and the newly synthesized compounds were screened for anti bacterial, anti oxidant activities.

Key words: Quinoxaline, dimethyl foramide (DMF), disc diffusion method, *p*-NDA, IR, ^{1}H NMR, chalcone, anti oxidant.

INTRODUCTION

In medicinal chemistry there has been lot of interest in quinoxalines as an important class of nitrogen containing heterocyclic. Quinoxaline is also called as benzopyrazine. Diazines are fused to benzene ring to form quinoxaline. Quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinoleutin that are known to inhibit growth of gram positive bacteria. Their derivatives display diverse pharmacological activities like anti-inflammatory [1], anti microbial [2], anti tumor [3], anti herpes activity, anti viral activity [4], 5-HT_3 antagonism [5], anticoagulant[6], antioxidant [7] anticonvulsant action [8] antiplasmodial activity [9] , antimalarial [10] . Considering the significant applications in the field of medicinal chemistry, hence it was intended to develop different derivatives of quinoxalines.

MATERIALS AND METHODS

Orthophenylenediamine,phosphrousoxychloride,oxalicacid,Dimethylsulfoxide(DMSO), Ciprofloxacin, fluconazole, *p*- nitroso dimethyl aniline, ascorbic acid, hydrogen peroxide, ferric Chloride, phosphate. The following experimental methods were used for the characterization of the synthesized compounds. Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectrum was recorded on ELICIO FTIR spectrometer using potassium bromide pellets. ^{1}H-NMR spectra of the compounds in deutiriated

dimethylsulfoxide was recorded on BRUKER Av 400 MHz spectrometer. Mass spectrum was recorded on GCMS QP 5000 shimadzu. Thin layer chromatography was performed using precoated aluminium plates coated with silica gel GF_{254} [E.Merck]. N-hexane: ethyl acetate was used as the eluent. The spots were visualized in the ultraviolet light chamber.

Step-1: Synthesis of 1, 4-Dihydro Quinoxaline-2, 3-Dione:
A solution of oxalic acid dihydrate (0.238mole, 30g) in H_2O (100ml) was heated to 100°C and 4.5 ml conc.HCl was added, followed by O-phenylenediamine (0.204 mole, 22g) with stirring temperature was maintained at 100 °C for 20 min. Completion of the reaction was confirmed by TLC .The mixture was cooled by addition of ice. The precipitate formed was washed with water and recrystalized from ethanol.

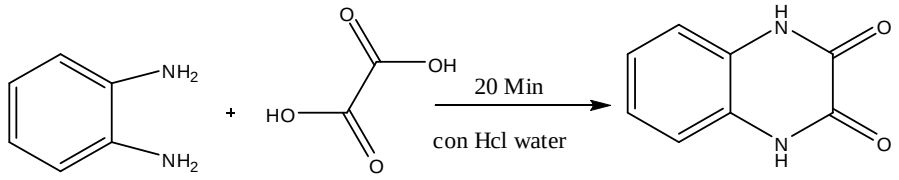
Step-2: Synthesis of 2, 3 dichloro quinoxaline:
A mixture of quinoxaline-2,3-dione (16.2 g, 0.1 mole) freshly distilled phosphorous oxy Trichloride ($POCl_3$, 60ml), and N,N-Dimethylformamide (DMF, 5ml) was refluxed with stirring for 1.5hrs. Completion of the reaction was confirmed by TLC. The cooled reaction mixture was slowly poured into ice-water with stirring and the resulting solid was filtered, washed with water, dried and recrystalized from a mixture of chloroform and n-Hexane.

Step-3: Synthesis of 1-(4-(3-Chloroquinoxalin-2-yl amino) phenyl) ethanone:
4-Aminoacetophenone (8.2 g 0.01 mole) and 2, 3 dichloro quinoxaline were dissolved in N, N- Dimethyl formamide (40 ml). The reaction mixture was refluxed for 5 hours, cooled and poured into crushed ice. Periodically, sodium carbonate solution (0.005, 0.53g in 10 ml water) was added to neutralize HCl evolved during the reaction. The progress of the reaction was monitored on TLC plate. After completion, the solid separated out was filtered, washed with water, dried and recrystalized from alcohol to give 1-(4-(3-Chloroquinoxalin-2-ylamino)phenyl)ethanone.

Step-4: Synthesis of quinoxalines derived chalcones
Equimolar quantities of a 1-(4-(3-Chloroquinoxalin-2-yl amino) phenyl) ethanone with substituted aldehydes was dissolved in alcoholic solution, and then solution of KOH or NaOH (5 ml of 40%) was added to the reaction mixture with constant stirring at room temperature. After 24 h the reaction mixture was neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystalized from ethanol to give quinoxalines derived chalcones.

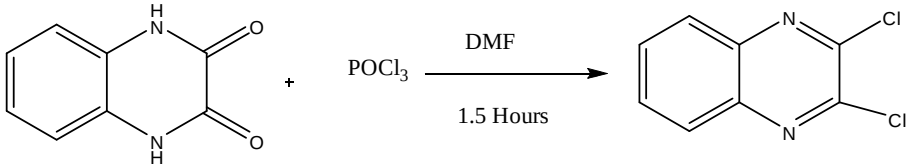
SCHEME: SYNTHESIS OF QUINOXALINE DERIVED CHALCONES

STEP-1



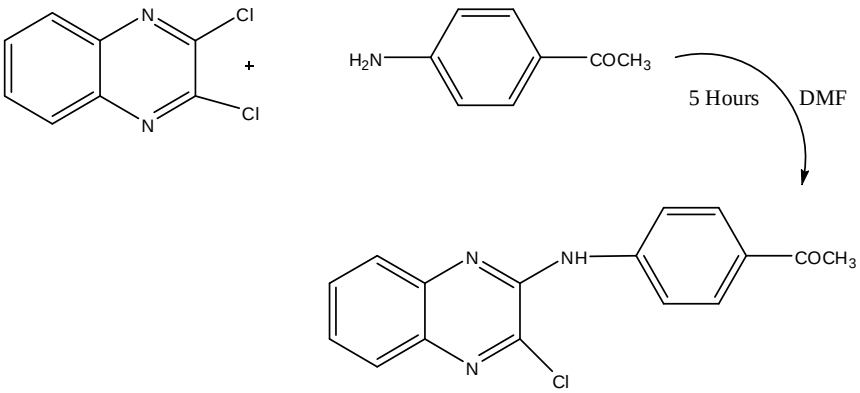
Q

STEP-2



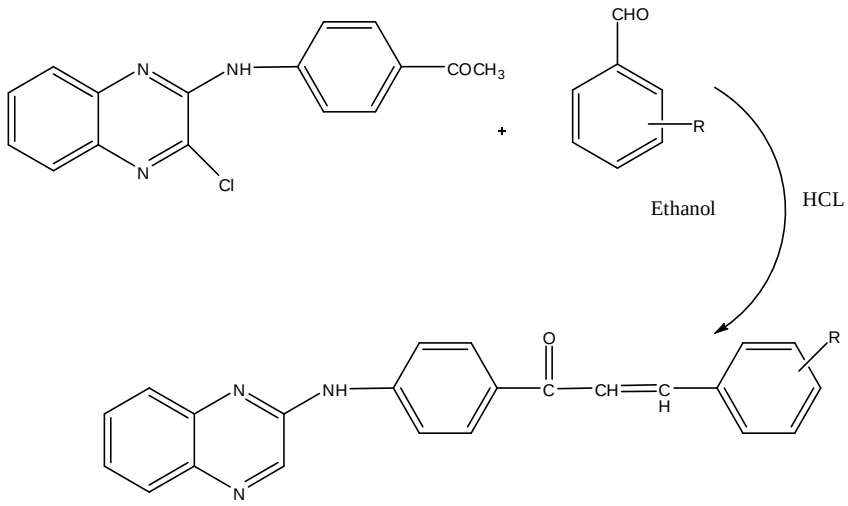
QC

STEP-3



QCAC

STEP-4



QCAC-1

SPECTRAL DATA SYNTHESIZED COMPOUNDS (QCAC 1-12)

Quinoxaline 2,3 (1H,4H) dione (Q) : % yield: 90%; Melting point: 360-362^{o}c R_f=0.76 (n-hexane: ethyl acetate)(7:3); IR KBr cm^{-1}: CH 3042.3001; ^{1}HNMR (400 MHz, DMSO D_6) (δppm): 11.8-12.0(s, 2H, NH), 7.0-7.1(d, 4H, aromatic, j=3.0) mass (*m/z*)=160(100%), 162(M^+).

Dichloro quinoxalines (QC): % yield: 70%; Melting point : 150-152^{o}c R_f=0.34 (n-hexane: ethyl acetate) (7:3); IR KBr cm^{-1}: CH 2938; ^{1}HNMR (400 MHz, DMSO D_6) (δppm): 7.0-7.1(m, 4H, aromatic, j=3.0) mass(*m/z*)= 190(100%), 198(M^+).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)ethanone (QCAC): % yield: 75%; Melting point : 294-296^{o}c R_f=0.34 (n-hexane: ethyl acetate)(7:3); IR KBr cm^{-1}: 1594 (C=C), 1165(C-NH), 1674(CH=CH) ; ^{1}HNMR (400 MHz, DMSO D_6)(δppm): 6.8(d, 2H, CH=CH, j=3.0).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-phenylprop-2-en-1-one(1): % yield: 60%; Melting point: 294-296^{o}c R_f=0.34 (n-hexane: ethyl acetate) (7:3); IR KBr cm^{-1}: 1594 (C=C), 1169(C-NH), 1673(CH=CH); ^{1}HNMR (400 MHz, DMSO D_6) (δppm): 3.8(d, 3H, CH_3, *J*=4.0), 6.8(d, 2H, CH=CH, j=3.0), 7.0-8.4(m, 10H, aromatic), 9.8(s, 1H, NH) mass (*m/z*)=375(100%), 385(M^+).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one(2): % yield: 50%; Melting point: 284-286^{o}c R_f=0.19(n-hexane: ethyl acetate)(8:2); IR KBr cm^{-1}: 1598 (C=C), 1177(C-NH), 1670(CH=CH); ^{1}HNMR (400 MHz, DMSO D_6) (δppm): 3.8(d, 3H, CH_3 *J*=4.0), 6.7(d, 2H, CH=CH, j=3.0), 7.2-8.4(m, 12H, aromatic), 9.8(s, 1H, NH) mass(*m/z*)=175, 254, 415 (100%)(M^+).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(4-hydroxy-3-methoxy phenyl)prop-2-en-1-one(3): % yield: 58%; Reaction time: 18 hours ; Melting point : 274-276^{o}c R_f=0.12 (n-hexane: ethyl acetate)(6:4); IR KBr cm^{-1}: 1603 (C=C) , 1179 (C-NH), 1670(CH=CH), (OCH_3) 2835; ^{1}HNMR (400 MHz ,DMSO D_6)(δppm):3.8(d,3H, CH_3 *J*=4.0), 6.7(d,2H, CH=CH, j=3.0), 7.2-8.4(m,12H,aromatic),9.8(s,1H,NH) mass (*m/z*)=431(100%)(M^+).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(furan-2yl)prop-2-en-1-one(4): % yield: 56.9; melting point (^{0}c): 224-226; R_f Vale : 0.76(n-hexane: ethyl acetate); IR KBr cm^{-1}: 1596.35(C=C), 3339.26(C-NH), 1667.16(CH=CH) ; ^{1}HNMR (400Mz, $DMSOd_6$) (δppm): 3.2-3.3(d, 3H, CH_3) *J=2.4*, 6.7-6.73(d, 2H, CH=CH) *J*= 2.6,7.1-8.3(m, 9H, aromatic), 9.9(s,1H,NH);mass (*m/z*):380(100%),385,386.

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(2-nitrophenyl)prop-2-en-1-one(5): % yield: 52. Melting point (^{0}c): 208-210 ^{O}C; R_f Value : 0.97(n-hexane: ethyl acetate); IR(KBrcm^{-1}): 1466.85(C=C), 1177.54(C-NH), 1618.59(CH=CH); ^{1}HNMR(400Mz, $DMSOd_6$) (δppm): 3.43.43(s, 3H, CH_3), 4.4-4.5(s, 1H, NO_2) 7.28.4(m, 11H, aromatic). 9.8(s, 1H, NH), 4-12.5(s, 1H, CH_2).13.7(s, 1H, CH_2); mass (*m/z*): 174.190, 194(100%), 430(M^{+1}).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one(6): % yield: 52.7; melting point (^{0}c): 208-210 ^{O}C ; R_f Value: 0.97(n-hexane: ethyl acetate); IR(KBrcm^{-1}): 1466.85(C=C), 1177.54(C-NH), 1618.59(CH=CH); ^{1}HNMR(400Mz, $DMSOd_6$)(δppm): 3.4-3.43(s, 3H, CH_3), 4.4-4.5(s, 1H, NO_2) 7.28.4(m, 11H, aromatic). 9.8(s, 1H, NH), 4-12.5(s, 1H, CH_2).13.7(s, 1H, CH_2); mass (*m/z)* : 174.190, 194(100%), 430(M^{+1}).

3-(2-chlorophenyl)-1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)prop-2-en-1-one(7): % yield: 53.7; melting point (^{0}c): 274-276; R_f Value: 0.114(n-hexane: ethyl acetate); IR (KBr cm^{-1}): 1482.08(C=C), 1131.13(C-NH), 1621.19(CH=CH); ^{1}HNMR (400MHz DMSO d_6) (ð ppm): 3.8(singlet, 3H, CH_3), 5.1(d, 2H, CH=CH) *J*=3.6 7.21 8.3(m, 10H, aromatic), 9.7(s, 1H,C-NH), 10.3-10.4(t, 1H, CH_2); mass(*m/z*):135, 190, 247, 421(M^{+1}).

3-(4-chlorophenyl)-1-(4-(3-chloroquinoxalin-2ylamino)phenyl)prop-2-en-1-one(8): % yield: 53.7; melting point(^{0}c): 274-276; R_f Value: 0.114(n-hexane: ethyl acetate); IR (KBr cm$^{-1)}$: 1482.08(C=C), 1131.13(C-NH), 1621.19(CH=CH); ^{1}HNMR (400MHz DMSO d_6) (ð ppm): 3.8(singlet, 3H, CH_3), 5.1(d, 2H, CH=CH) *J*=3.6, 7.21-8.3(m, 10H, aromatic), 9.7(s, 1H, C-NH), 10.3-10.4(t, 1H, CH_2); mass(*m/z*):135, 190, 247, 421(M^{+1}).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one(9): % yield: 58.7; brown crystals; melting point(^{0}c): 198-200; R_f Value: 0.27(n-hexane: ethyl acetate); IR (KBr cm^{-1}): 1457.85(C=C), 1177.56 (C-NH), 1680.91(CH=CH); ^{1}HNMR (400Mz DMSO d_6) (δppm): 2.9(s, 2H, CH_2), 3.6(S, 3H, CH_3), 6.8-6.9(d. 2H, CH=CH) *J*=0.35, 7.21-8.3(m, 6H, aromatic), 9.8(s, 1H, NH), 10.3-10.4(s, 1H, OH); Mass (*m/z*): 280, 376, 384(100%), 400(M^+).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one(10): % yield: 57.7; melting point (^{0}c): 198-200^{O}C; R_f Value: 0.27, (n-hexane: ethyl acetate); IR KBr cm^{-1}: 1457.85(C=C), 1177.56 (C-NH), 1680.91(CH=CH); ^{1}HNMR(400MHz DMSO d_6 (δppm)= 2.9(S, 2H, CH_2), 3.6(S, 3H, CH_3), 6.8-6.9(d. 2H, CH=CH) *J*=0.35, 7.21-8.3(m, 6H aromatic), 9.8(s, 1H, NH), 10.3-10.4(s, 1H, OH)); mass (*m/z)*280, 376, 384(100%), 400(M^+).

1-(4)-1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)-5-phenylpenta-2,4-dien-1-one(11): % yield: 53.7: melting point (^{0}c): 298-300; R_f Value: 0.75, (n-hexane: ethyl acetate); IR (KBr cm^{-1}): 1616.17(C=N), 1180.57(C-NH), 1616.17(CH=CH); ^{1}HNMR(400MHz DMSO d_6) (δppm)=3.4(S, 3H, CH_3), 5.6(dd, 4H, CH=CH), *J*=4.07.1-8.4(m, a10H, aromatic), 9.3(s, 1H, NH) MS (m/z):190, 222, 411(100%)(M^+).

1-(4-(3-chloroquinoxalin-2-ylamino)phenyl)(4(dimethylamino)phenyl) prop-2-en-1-one(12): % yield: 45.4; melting point(^{0}c): 300-302; R_f Value: 0.54; IR KBr cm^{-1}: 1595.45(C=C), 1174.74(C-NH), 1658.09(CH=CH); ^{1}HNMR(400MHz, DMSO, d_6) (δppm): 3.51-3.8(doublet, 6H, CH_3) *J*=3.4, 6.(d, 2H, CH=CH) *J= 2.4*, 7.2-8.7(m, 12H, aromatic), 9.2(s, 1H, NH); MS (*m/z*): 428(100%) (M^+).

Antibacterial activity microbial strains

All the compounds were tested for their antibacterial activity against *Bacillus subtilis(BS)* (ATCC 6633), *Staphylococcus aureus(SA)* (ATCC 25923), *Klebsiella pneumonia(KP)* (ATCC 13883), *Escheria coli* (ATCC 25922) using disc diffusion method . DMSO was run as a control and test was performed at different concentrations (, 50,100 and 150 µg/ ml) using a solvent DMSO. Ciprofloxacin was used as a standard drug.

Determination of the *in vitro* antimicrobial activity by the disc-diffusion method

The antimicrobial activity of the compounds was determined by means of the disc-diffusion method. Cultures of each bacteria were inoculated to nutrient agar broth and incubated at 37 ^{0}C for 16 h, then adjusted to OD625 ¼ 0.08–0.1 (approximately 1 x 10^7 –1x 10^8CFU/ml). The bacterial suspensions (100 ml) was placed on to agar in a 60-mm Petri dish and spread homogeneously with a Drigalski tip. Discs (6.0-mm diameter) were impregnated with 50, 100 and 150 µg/ ml concentrations in DMSO solution of the compounds (QCAC 1-12) and placed on the surface of the agar containing each bacterium, which was incubated at 37 ^{0}C for 24 h. The inhibition zones were measured with a caliper considering the total diameters. Similarly, each plate carried a blank disc containing 50, 100 and 150 µg/ ml concentrations in DMSO and an anti-biotic disc (100 µg/ml for ciprofloxacin.

Anti fungal activity Microbial Strains

All the compounds were tested for their antifungal activity against *Aspergillus flavus* and *Aspergillus niger* (NCCS 1196) by disc diffusion method DMSO was run as a control and test was performed at different concentrations (100 and 150 µg/ml) using a solvent DMSO. Fluconazole was used as a standard drug.

Determination of the in vitro antifungal activity by the disc-diffusion method

The fungal activity of the compounds was determined by means of the disc-diffusion method. Cultures of each bacteria were inoculated to potato dextrose broth and incubated at 37 ^{0}C for 16 h, then adjusted to BOD625 ¼ 0.08–0.1 (approximately 1 x 10^7 –1x 10^8CFU/ml). The Fungal suspensions was placed on to dextrose in a 60-mm Petri dish and spread homogeneously with a Drigalski tip. Discs (6.0-mm diameter) were impregnated with 100 and 150 µg/ ml concentrations in DMSO solution of the compounds (QCAC 1-12) and placed on the surface of the dextrose broth containing each fungal strain, which was incubated at 37 ^{0}C for 24 h. The inhibition zones were measured with a caliper considering the total diameters. Similarly, each plate carried a blank disc containing 100 and 150 µg/ ml concentrations in DMSO and an anti-biotic disc (100µg/ml for Fluconazole).

Antioxidant Activity by P-NDA (P-Nitroso Dimethyl Aniline) Radical Scavenging Method[11]

To a solution containing ferric chloride (0.1mM, 0.5ml), EDTA(0.1mM, 0.5ml), ascorbic acid (0.1mM, 0.5ml), hydrogen peroxide (2mm, 0.5ml) and p-nitroso dimethyl aniline (0.01mM, 0.5ml) in phosphate buffer (p^H 7.4, 20mm) were added various concentrations of the test compounds in distilled DMSO or dissolving solvent or alcohol to produce final volume of 3ml. Absorbance was measured at 440nm.

$$\textbf{1.}\quad p\text{-NDA radical Scavenging activity(\%)} = \frac{[\text{Abs (sample)-Abs (standard)}]}{[\text{Abs (sample)}]} \times 100$$

Where, Abs- Absorbance,

RESULTS AND DISCUSSION

Anti bacterial activity:

The results presented in the below table-1 suggested that compounds **QCAC-1,5,6,8** were highly active against gram positive bacteria and compounds **QCAC-1.5,6,4** and **7** show better activity against gram positive bacteria. Rest of the compounds was less potent when compared to the above mentioned compounds. The anti bacterial activity of these compounds may due to permeability of the microbial cell.

Antifungal Activity

The antifungal activity was tested against strain such as *A.niger* and *A.flavus*, using fluconazole as standard antifungal. **Compounds QCAC 5,6,7,8,9,10** were found to be more potent than standard. Rest of the compounds showed moderate activity against *A. niger* and *A.flavus*. The results were tabulated in the table-2.

Table-1: Anti-Microbial Activity of synthesized Compounds (QCAC 1-12) against Bacterial strain

Compounds	Mean Zone of inhibition											
	BS			*SA*			*K.p*			*E.Coli*		
	50	100	150	50	100	150	50	100	150	50	100	150
	µg/disc			µg/disc			µg/disc			µg/disc		
Control	-			-			-			-		
QCAC-1	R	06	16	R	09	16	R	11	15	R	13	18
QCAC-2	R	08	11	R	11	11	R	08	12	R	09	12
QCAC-3	R	07	09	R	07	11	R	R	10	R	10	09
QCAC-4	R	06	11	R	08	11	R	06	14	R	07	16
QCAC-5	R	09	18	R	10	18	R	08	15	R	R	17
QCAC-6	R	08	19	R	06	19	R	10	15	R	R	16
QCAC-7	R	10	15	R	08	15	R	10	16	R	07	15
QCAC-8	R	07	17	R	09	15	R	R	13	R	06	18
QCAC-9	R	09	11	R	07	11	R	09	12	R	06	07
QCAC-10	R	09	11	R	07	11	R	09	12	R	06	07
QCAC-11	R	-	08	R	11	09	R	11	09	R	-	07
QCAC-12	R	06	07	R	R	12	R	06	12	R	11	11
standard	10	12	15	10	13	15	10	14	17	10	13	15

Table-2: Anti-Fungal Activity of synthesized Compounds (4a-l) against Fungal Strains

compounds	Mean Zone of inhibition			
	Aspergillus flavus		*Aspergillus niger*	
	150	200	150	200
	µg/disc		µg/disc	
Control	-	-	-	-
QCAC-1	07	14	08	11
QCAC-2	07	08	09	13
QCAC-3	06	09	07	11
QCAC-4	08	13	10	11
QCAC-5	09	18	11	16
QCAC-6	R	18	R	17
QCAC-7	08	17	R	18
QCAC-8	09	17	08	17
QCAC-9	R	16	06	18
QCAC-10	R	17	06	17
QCAC-11	07	15	08	11
QCAC-12	R	09	08	13
standard	16	17	15	17

Table-3: Anti-oxidant Activity of synthesized Compounds (4a-l)against Free Radicals

Compounds	% Radical scavenging method Concentrations (mg/ml)					
	5(mg/ml)	10(mg/ml)	25(mg/ml)	50(mg/ml)	100(mg/ml)	IC_{50}
Control	-	-	-	-	-	-
QCAC-1	10.9	20.86	40.21	58.53	64.75	1.95
QCAC-2	42.69	46.39	51.49	58.67	65.35	1.25
QCAC-3	35.2	42.98	4.58	57.6	64.16	1.9
QCAC-4	15.56	29.46	44.74	49.25	58.80	1.8
QCAC-5	30.8	35.19	39.6	46.2	36.7	4.19
QCAC-6	5.5	1.68	47.23	52.9	58.9	2.3
QCAC-7	20.74	5.5	20.37	15.70	58.70	2.9
QCAC-8	54.05	24.3	45.13	59.23	62.63	1.5
QCAC-9	43.45	48.53	58.5	64.22	65.67	0.99
QCAC-10	43.45	48.53	58.5	64.22	65.67	0.99
QCAC-11	42.69	46.39	51.49	58.67	65.35	1.25
QCAC-12	48.38	49.3	59.9	62.8	64.71	0.73
standard	23.3	66.78	80.45	82.45	85.46	0.64

Anti oxidant activity

All the synthesized compounds (QCAC 1-12) were evaluated for *in vitro* antioxidant activity by radical scavenging method and compared with that of the standard ascorbic acid at 440nm. The percentages of inhibition of various concentrations of the synthesized compounds along with the standard were measured and were tabulated in table-3.

The anti oxidant activity of the compounds **QCAC- 2,8,9,10,11** and **12** shown moderate activity when compared with standard ascorbic acid. Rest of the compounds shown poor activity.

CONCULSION

The compounds bearing nitro, chloro and methoxy groups have shown prominent activity when compared to compounds without these groups. It was also confirmed that the groups in para position showed better activity when compared to the groups in ortho position. Further investigation in this area may help to bring more potent drugs for the treatment of bacterial and fungal infections.

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