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SYNTHESIS, CHARECTERIZATION AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF 4(3H) QUINAZOLINONE DERIVATIVES

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ABSTRACT

A large number of compounds which contain quinazoline moiety are known in medicinal chemistry as important compounds for their therapeutic value. Recently, there has been an increased interest in the chemistry of 4(3H)-quinazolinone system. Many derivatives of this system showed analgesic, anti-inflammatory, antiulcer, anticonvulsant, antibacterial, antifungal, anticancer and antiproliferative activities. 4(3H)-quinazolinone, a fused nitrogen heterocyclic compound has emerged as a biologically privileged structure, possessing a wide range of biological properties viz. anticancer, antibacterial, antitubercular, antifungal, anti-HIV, anticonvulsant, anti-inflammatory and analgesic activities.The objective of the present research work was to synthesize, characterize and evaluate antimicrobial activity of 4(3H) Quinazolinone derivatives. All the compounds synthesized showed moderate to good activity.

Keywords *– Synthesis, Antimicrobial activity, Quinazolinone.*

1. INTRODUCTION

Emergence of drug resistance has created unmet medical need for the development of new classes of antibiotics. Discovery of new antibacterial agents with new mode of action remains a high priority universally. 4(3H)-quinazolinone, a fused nitrogen heterocyclic compound has emerged as a biologically privileged structure, possessing a wide range of biological properties viz. anticancer, antibacterial, antitubercular, antifungal, anti-HIV, anticonvulsant, anti-inflammatory and analgesic activities. Promising antibacterial properties of quinazolinones have enthused the medicinal chemists to explore and develop this fused heterocyclic system for new antibacterial agents. Utilization of quinazolinone core for the design and synthesis of new antibacterial agents has recently gained momentum [1].

Quinazolinones are very significant heterocyclic compounds because of their potential pharmaceutical and biological activities. Quinazolinone derivatives reveal various medicinal properties such as analgesic, anti-inflammatory and anticancer activities, as well as antimicrobial activity. These heterocycles are valuable intermediates in organic synthesis. Therefore, various procedures have been developed for preparing these important compounds [1-5].

The 4(3H) quinazolinone system possess various activity like anticonvulsant, antimicrobial, antitubercular, anti-inflammatory, antiproliferative and analgesic activity. 4(3H) quinazolinone system possess the various variable sites like position 2 and 3 which can be modified by the introduction of various heterocyclic moietyes to yield the potent antimicrobial agent. The schiff base of

4(3H) quinazolinone with substituted aromatic aldehyde also have the promising antimicrobial activity. The quinazolinone nucleus is found in many bioactive natural products. so because of these reasons much attention is being paid for the synthesis of quinazolinone derivatives.The objective of the present research work was to synthesize, characterize and evaluate antimicrobial activity of novel 4(3H) Quinazolinone derivatives.

2. MATERIALS AND METHODS

Synthesis of 2-Phenyl Benzoxazine 4-One

To a cold solution of 0.1 mol of anthranilic acid in pyridine add 0.2 mol of benzoyl chloride all at once and stir for 30 min. continuously till the odour of pyridine disappears. This mixture was poured in 250ml of ice cold water taken in a beaker. Then add 2-3 drops of hydrochloric acid and stir well. Filter the solid obtained and product was recrystallized from ethanol.

Synthesis of 2-Phenyl 4(3H) Amino Quinazolinone

In the 100ml round bottom flask 0.01 mol of 2-phenyl benzoxazine 4-one and 0.015mol of hydrazine hydrate was refluxed in an oil bath for 6 hrs with occasional shaking, and cooled. The solid formed was recrystallized from toluene.

Synthesis of Ethyl-[(2-Phenyl 3,4- Dihydro 4- Quinazolinone-3-Yl)]Oxy Acetate

Equimolar solution of quinazoline-4-one(0.01mol) and ethyl chloro acetate (0.01mol) in dry acetone (10ml) in the presence of anhydrous potassium carbonate(2.3 g) was stirred over a magnetic stirrer for a period of 24 hrs. The mixture was poured in to 100 ml of ice cold water. The above formed ester was extracted with ether and ester was obtained on removing ether. The product was recrystallized from ethanol.

Synthesis of 2-Phenyl 3,4-Dihydro 4- Quinazolinone 3 Yl Acetyl Hydrazine

A mixture of quinazolinyl ester (0.01mol) and hydrazine hydrate (0.01mol) was refluxed over a water bath for a period of 12-16 hrs. The mixture was poured into beaker containing ice cold water and kept in fridge over night. The product was filtered and washed repeatedly with ice cold water and recrystallized by using absolute alcohol.

2.1 Synthesis of derivatives

DA-1- Synthesis of N-(2-chlorobenzylidene)-2-[(4-oxo-2-phenylquinazolin-4(3*H*)-yl) amino]acetohydrazide- Equimolar quantity of2-(4-Oxoquinazolin-4(3*H*)-ylamino)acetohydrazide and ortho chloro benzaldehyde was refluxed in alcohol for 4 hrs. in the presence of glacial acetic acid, solvent was evaporated and the product was poured into cold water, filtered and dried, the crude solid was recrystallized by using DMF,

Percentage yield-65%, M.P. 219ºC, IR(KBr) 3056.96 cm^{-1} (C-H Ar),3436.91 cm^{-1} (N-H),2921.96 cm^{-1} (C-H,CH_2), 1677.95 cm^{-1} (C=O),1602.74 cm^{-1} (C=C,ring),1550.66 cm^{-1} (C=N,ring),1080.06 cm^{-1} (N-N), 767.62 cm^{-1} (C-Cl)

^{1}HNMR(DMSO)- δ 8.309-8.450 ppm(m,13 H , Ar-H), δ 7.725 ppm(s, 1H,N=CH-Ar), δ 7.594 ppm(s,1H, -NH)

DA-2-- Synthesis of N- (Benzylidene)-2-[(4-oxo-2-phenylquinazolin- 4(3*H*)-yl amino]acetohydrazide- Equimolar quantity of 2-(4-Oxoquinazolin-4(3*H*)- ylamino)acetohydrazide and benzaldehyde was refluxed in alcohol for 4 hrs. in the presence of glacial acetic acid, solvent was evaporated and the product was poured into cold water, filtered and dried, the crude solid was recrystallized by using DMF. Percentage yield-70%, M.P. 215ºC, IR(KBr)- 3056.96 cm^{-1} (C-H aromatic), 3305.76 cm^{-1} (N-H), 2921.96 cm^{-1} (C-H,CH_2), 1679.88 cm^{-1} (C=O), 1560.30 cm^{-1} (C=N,ring), 1091.63 cm^{-1} (N-N)

^{1}HNMR(DMSO)- δ 8.107-8.421 ppm (m,12H,Ar-H), δ 8.613ppm (s, H,NH), δ 2.884-2.957ppm (d,2H,CH_2).

DA-3 Synthesis of N- [1-(2-hydroxy phenyl)ethylidene]2-[(4-oxo-2-phenylquinazolin-4(3*H*)-yl) amino]acetohydrazide.- A mixture of 2-(4-Oxoquinazolin-4(3*H*)-ylamino)acetohydrazide and ortho hydroxy acetophenone in ethanol (20ml) was refluxed for 4 hrs in the presence of few drops of acetic acid. The product formed is filtered, washed with ethanol and recrystallized from aqueous DMF.

Percentage yield-72%, M.P. 229ºC, IR(KBr)- 3033.82 cm-^{1} (C-H aromatic), 3305.76 cm-^{1} (N-H), 2921.96 cm-^{1} (C-H,CH_2), 1662.52 cm-^{1} (C=O), 1508.52 cm-^{1} (C=C,ring)1564.16 cm-^{1} (C=N,ring), 1078.13 cm-^{1} (N-N),3429.2 cm-^{1} (O-H,H-bond)

^{1}HNMR(DMSO)- δ 8.293-8.319 ppm (m, 12H,Ar), δ 2.877-2.949 ppm (d, 2H, CH_2), δ 7.518 ppm (s,1H,-CO-NH-N-), δ 1.25 ppm(s, -CH_3)

DA-4-Synthesis of 2-phenyl-3-{[(5-thioxo-1,3,4-oxadiazolidene-3yl) methyl]amino}quinazolin-4(3*H*)-one- To a solution of 2-(4-Oxoquinazolin-4(3*H*)-ylamino)acetohydrazide (0.001 mol) and potassium hydroxide (0.001 mol) in ethanol,4ml of carbon disulfide was added with stirring , when the addition was complete the reaction mixture was refluxed for 15 hrs, the contents were cooled and solvents were distilled off , the residue was dissolved in ice chilled water, filtered and filtrate was acidified with acetic acid, the solidified product was finally filtered, dried and recrystallized from methanol.

Percentage yield-50%, M.P. 238ºC, IR(KBr)- 3062.76 cm-^{1} (C-H aromatic), 3446.56 cm-^{1} (N-H), 2921.96 cm-^{1} (C-H,CH_2), 1689.52 cm-^{1} (C=O), 1598.88 cm-^{1} (C=C,ring)1566.09 cm-^{1} (C=N,ring), 1035.7 cm-^{1} (N-N),1035.7 cm-^{1} (C-O,oxadiazole ring)

^{1}HNMR(DMSO)- δ 8.121-8.730 ppm(m, 12H, Ar), δ 7.637-7.709 ppm(t, 1H,-NH-CH_2), δ 4.406-40434 ppm(d, 2H, CH_2).

MASS-this compound shows base peak at m/e value 119.06 and parent peak at value 352.369. The fragment peak at m/e value 77.122 is due to loss of phenyl group, the fragment peak at m/e value 208.1 shows the loss of N-NH group from fragment having quinazolinone nucleus.

DA-5- Synthesis of 4-(4-oxo-2-phenyl quinazolin-4(3H)-yl) benzoic acid- To a cold solution of 2-phenyl benzoxazine-one (0.05mol) in anhydrous pyridine (30ml) was added a solution of Para amino benzoic acid(0.1mol) in anhydrous pyridine (30ml) drop wise with constant stirring. When the addition was complete, the reaction mixture was stirred vigorously for 30min at room temperature and subsequently heated under reflux for 6 hr under anhydrous reaction conditions. The reaction mixture was washed repeatedly with cold water and dried, recrystallized from dilute ethanol.

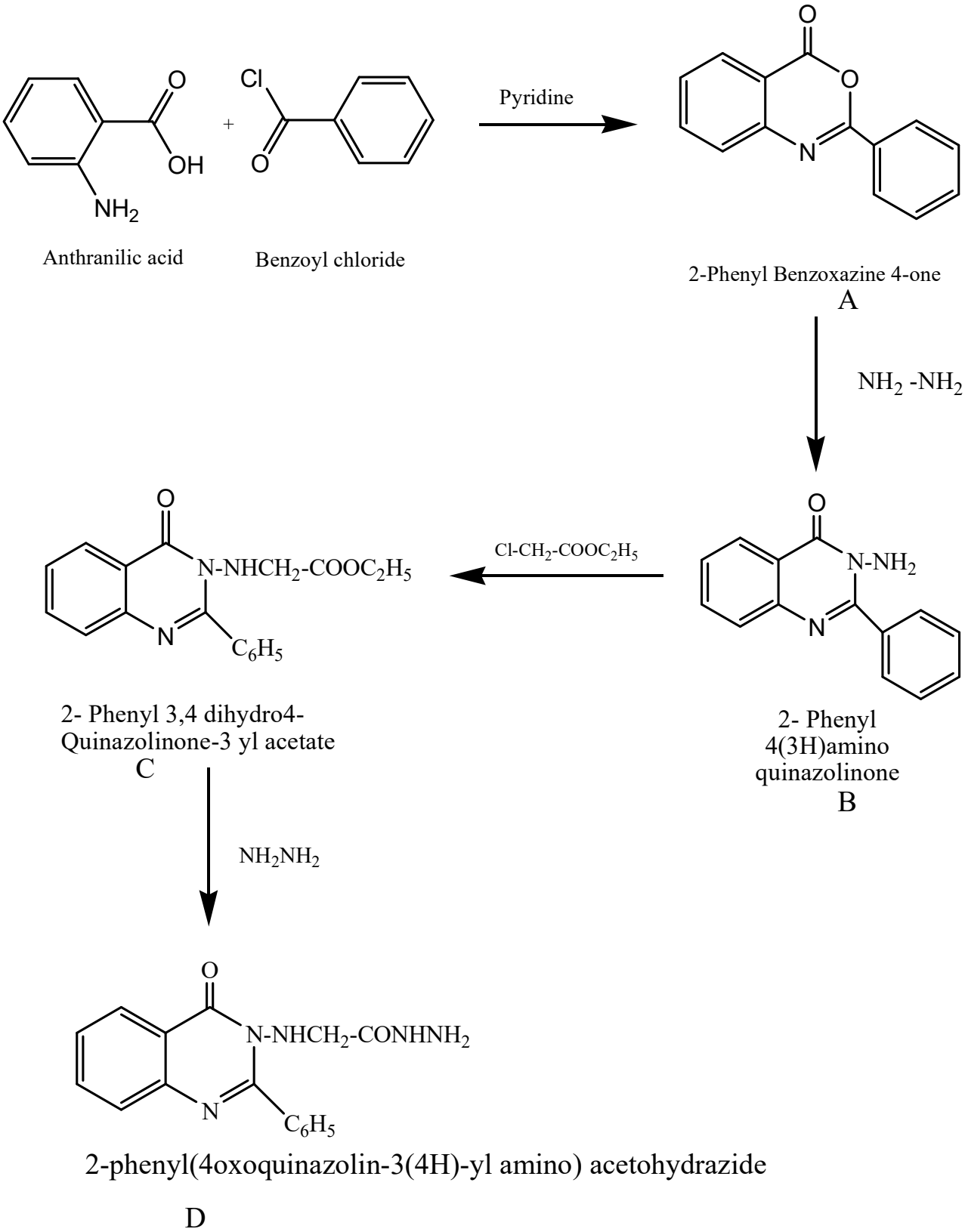
Percentage yield-75%, M.P. 175ºC, IR(KBr)- 3414.35 cm-^{1} (C-O aromatic acid), 1651.73 cm-^{1} (C=O), 1591.95 cm-^{1} (C=C,ring)1524.42 cm-^{1} (C=N,ring).

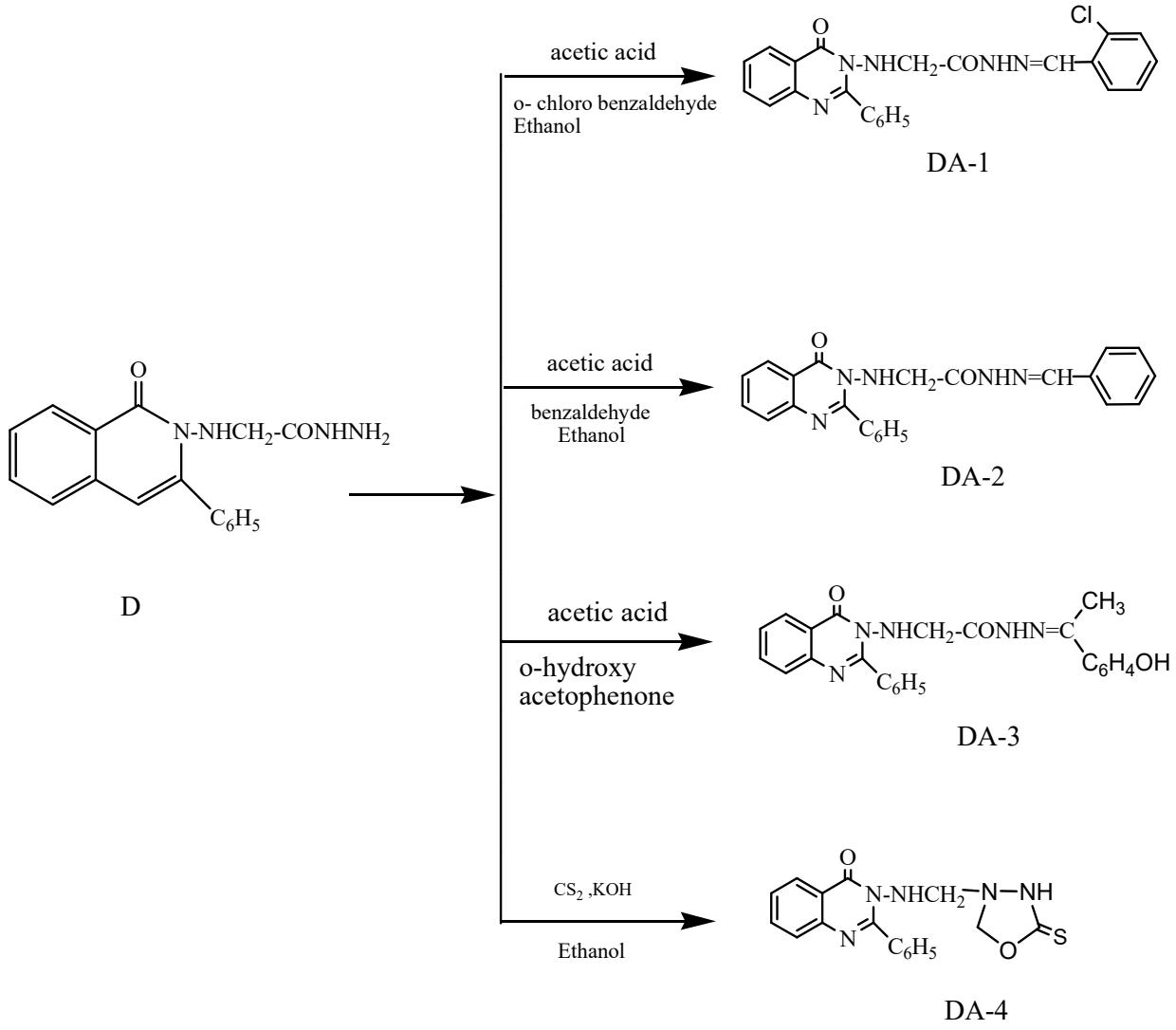
^{1}HNMR (DMSO)- δ 7.631-7.638 ppm(d,Ar-H)

The quinazolinone derivatives were synthesized according to the scheme, the synthetic reaction starts from anthranilic acid and benzoyl chloride to form 2-phenyl benzoxazine 4-one(A), this reaction follows N-acetylation followed by dehydrative cyclization(schtton bauman reaction)[1], the compound A now reacts with hydrazin hydrate over oil bath and forms 2-phenyl 4(3H) amino quinazolinone(B) [6,7] ,the compound B with dry acetone and ethyl chloro acetate in presence of dry potassium carbonate forms 2-phenyl 3,4 dihydro 4-quinazolinone 3-yl acetate(C) [8] , now the compound C reacts with hydrazinre hydrate to form 2-phenyl (4-oxoquinazolinone 4(3H)-yl amino acetohydrazide)(D) [9] .

The compound D used to form various derivatives with aromatic aldehyde and aromatic phenols [10-12].

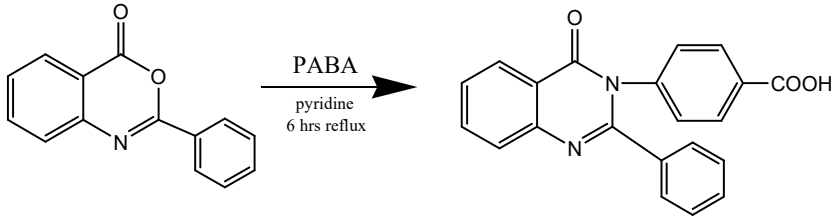
SCHEME


Pyridine
Anthranilic acid
Benzoyl chloride
2-Phenyl Benzoxazine 4-one
A
NH_2 -NH_2
$Cl\text{-}CH_2\text{-}COOC_2H_5$
2- Phenyl
4(3H)amino
quinazolinone
B
2- Phenyl 3,4 dihydro4-
Quinazolinone-3 yl acetate
C
NH_2NH_2
2-phenyl(4oxoquinazolin-3(4H)-yl amino) acetohydrazide
D



3. RESULTS AND DISUSSION

The compound A reacts with PABA to form 4-(2-phenyl 4-oxo quinazoline-4(3H)-yl)benzoic acid.



The structure of the compounds were established by IR,NMR and MASS spectroscopy. The antimicrobial activity of compounds were tested by cup-plate method against gram positive bacteria,gram negative bacteria and fungus. Ofloxacine was taken as standard drug against bacteria in concentration of 10µg/ml and ketoconazole 10µg/ml was taken as standard drug against fungus. *E.coli, klebsiella pneumoniae, B. subtilis, S. aureus bacterial* strains and *A. niger* fungal strain were used for antimicrobial screening. DMF was used as control. The MIC of synthesized compounds was done by broth dilution method.

All the compounds in concentration of 50µg/ml shows the promising antimicrobial activity . the compounds having inductively electron withdrawing but mesomerically electron donating substituent (Cl, OH)shows the better antimicrobial activity(DA-1,DA-3), and the compound DA-4 having 1,3,4 oxadiazole ring shows better antibacterial as well as anti fungal activity.

The zone of inhibition of synthesized compounds against bacterial strains have shown in table 1

S.No.	Compound	Zone of inhibition against			
		Staphylococcus aureus **(+ve)**	***B.subtilis*** **(+ve)**	***Klebsiella*** **(-ve)**	***E. coli*** **(-ve)**
1.	DA_1	7mm	9mm	12 mm	10 mm
2.	DA_2	8mm	8mm	7 mm	6 mm
3.	DA_3	12 mm	8 mm	11 mm	7mm
4.	DA_4	15mm	14mm	15 mm	12mm
5.	DA_5	7 mm	11 mm	9 mm	7 mm
6.	OFLOXACIN (std)	16 mm	16 mm	20 mm	20 mm
7.	DMF (control)	6 mm	6 mm	6 mm	6 mm

The zone of inhibition of synthesized compounds against fungal strain have shown in table 2.

S. No.	**Compound**	**Zone of inhibition (*Aspergillus niger*)**
1	DA-1	11 mm
2	DA-2	8 mm
3	DA-3	9 mm
4	DA-4	10 mm
5	DA-5	9 mm
6	Ketoconazole (standard)	18 mm
7	DMF (control)	6 mm

The MIC of synthesized compounds against bacterial strains have shown in table 3.

Organism	**MIC Value (**μg/ml)				
	DA-1	DA-2	DA-3	DA-4	DA-5
S.aureus	31.25	31.25	31.25	62.5	31.25
B.subtilis	62.5	125	125	125	62.5
E.coli	31.25	31.25	31.25	62.5	62.5
Klebsiella	125	31.25	31.25	31.25	31.25

4. CONCLUSION

In conclusion, the derivative of 4(3H) quinazolinone were synthesized in good yield and the activity of the compounds were tested against bacteria and fungus, all the compounds shows moderate to good activity. The compounds having inductively electron withdrawing but mesomerically electron donating substituent (Cl, OH)shows the better antimicrobial activity(DA-1,DA-3), and the compound DA-4 having 1,3,4 oxadiazole ring shows better antibacterial as well as antifungal activity. The antimicrobial activity seemed to be dependent on the nature of the substituent rather than the basic skeleton of the molecule..

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