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RESEARCH ARTICLE
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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL QUINOLINE DERIVATIVES

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Abstract:
In the present study some novel Quinoline derivatives (1 to 11) have been synthesized by the reaction of 7-hydroxy 4-methyl Coumarin and Benzene Sulphonamide derivatives which are formed from starting materials Resorcinol, Ethyl Acetoacetate and Sulphanilamide compounds. The synthesized compounds were evaluated and characterized by TLC, melting point and spectral methods. All synthesized Quinoline derivatives were screened for Anti-bacterial activity and Antifungal activity. Some of the synthesized compounds showed good and moderate Anti-microbial activity.

Keywords: Synthesis, Quinolines, Anti-bacterial and anti-fungal activities.

INTRODUCTION:

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. Many of them are employed in treatment of many infectious diseases due to their specific activity, but their use in treatment is attributed to their inherent toxicity to various pathogens. Among medicinal agents, there is growing interest in the development of newer effective anti-microbial agents. Among the variety of compounds studied, quinoline derivatives forms an important class.
Quinolines are an important class of heterocyclic compound and several derivatives of substituted quinoline which have been found diverse type of biological activity. Quinoline derivatives have been proven to be attractive compounds because of their outstanding different activities like antimicrobial, antibacterial, antimalarial, anticancer, antiviral, anti- inflammatory. Most potent is antimicrobial activity so we thought to synthesize some novel quinoline moiety incorporating with different aromatic and heterocyclic aldehydes moiety.

The conventional methodology was adopted to synthesize the titled compound from starting material resorcinol and ethyl acetoacetate which is heated for 20 min with conc. sulfuric acid to give 7-hydroxy-4-methyl coumarin. The 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H) yl) benzene sulfonamide which is prepared by condensation of 7-hydroxy-4-methyl coumarin and sulfanilamide

with glacial acetic acid for 6 h. and poured in to cold water, precipitate form. 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H) yl) benzene sulfonamide is further reacted with different substituted aromatic and heterocyclic aldehydes in presence of acetic acid as catalyst in ethanol by refluxing for 8 hours to yield the different derivatives of quinoline. The characterization of the various newly synthesized compounds by IR, NMR, Mass spectral data. These compounds were also screened for their anti-microbial activity.

EXPERIMENTAL:

Melting points were determining by using precision melting point apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using n-hexane, ethyl acetate (6:4) and methanol: chloroform (1:9) solvent system and ultraviolet lamp and iodine chambers used as a visualizing agent. IR spectra were recorded using KBr pellets on a SHEMADZU 8000 series spectrophotometer. ^{1}H-NMR spectra on BRUKER- 400-Mhz spectrophotometer using DMSO as solvent and TMS as internal standard (chemical shift values expressed in ppm).

PREPARATION OF 7-HYDROXY-4-METHYL COUMARIN:[1,2]

The main method for the synthesis of coumarins is the Pechmann reaction of substituted phenols with methyl or ethyl acetoacetate in the presence of photonic acid (conc. H_2SO_4), Lewi's acids ($AlCl_3$, $ZnCl_2$/Al_2O_3, etc.), dehydrating agents (P_2O_5) or montmorillonite clay.

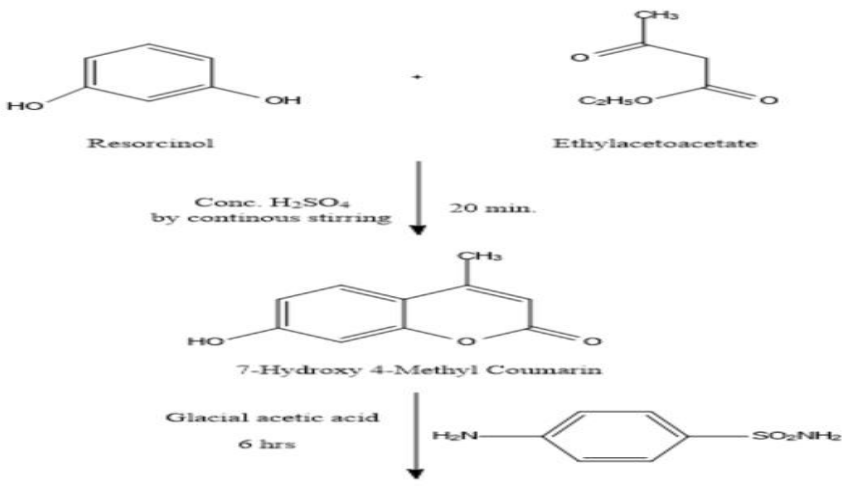
PREPARATION OF4-(7-HYDROXY-4-METHYL-2-OXOQUINOLIN-1(2H)-YL) BENZENE SULFONAMIDE:[3,4]

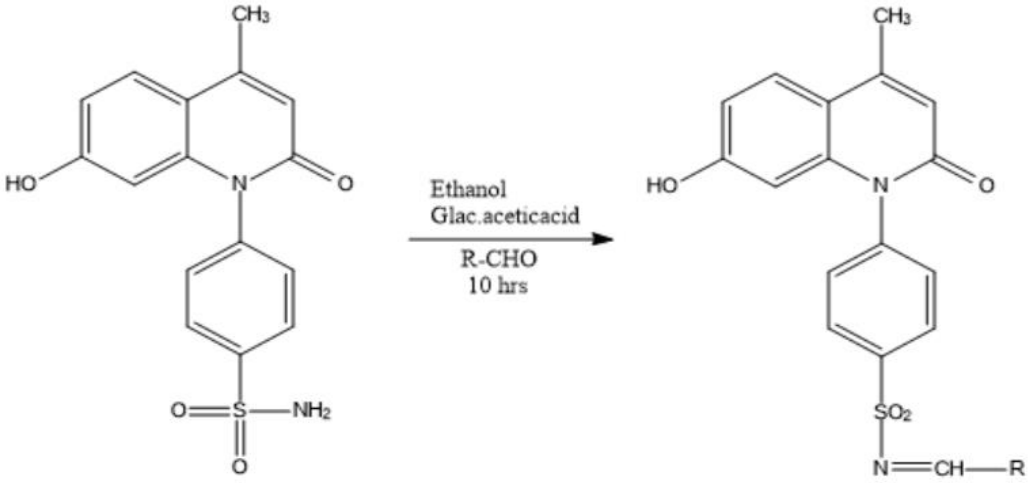
An equimolar (0.06) mix. of first step (7-hydroxy-4-methyl coumarin) and sulfanilamide was refluxed for 6 h. with glacial acetic acid and the progress of reaction was maintained by TLC. After completion of reaction contents were poured in to crushed ice to form solid mass which was collected and recrystallized from ethanol or chloroform.

GENERAL PROCEDURE FOR THE PREPRATION OF SCHIFF BASES COMPOUND-(Qd-1-11):[5,6]

An equimolar solution of 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H) yl) benzene sulfonamide 3.27gm (0.01mol) is dissolved in 10 ml of ethanol and to this solution substituted aldehydes in equimolar qty (0.01mole) is added with 4-6 drops of glacial acetic acid was added, this reaction mixture is kept under reflux for 10 h. After cooling to room temperature this solution was added to ice cold water. Compoundgets separated as solid, filtered, dried and re-crystallized with ethanol.

SCHEME:

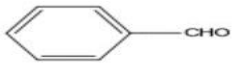




4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl) benzene sulphonamide

Quinoline derivatives

Where **R=**

(1) 

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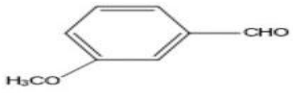
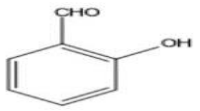
(3) 

(4) 

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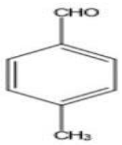
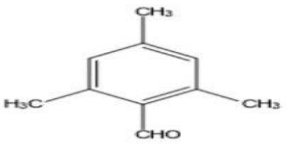
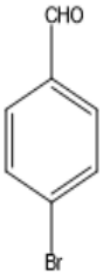
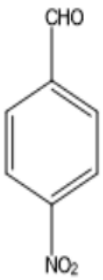
(6) 

(7) 

(8) 

(9) 

(10) 

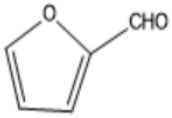
(11) 

Table 1: PHYSICAL DATA OF QUINOLINE DERIVATIVES (1-11):

S.NO	Compound code	Molecular Formula	Molecular Weight	Melting Point (^{0}C)
1	Qd-1	$C_{23}H_{18}N_2O_4S$	418.12	258-260^{0}C
2	Qd-2	$C_{24}H_{20}N_2O_5S$	448.27	130-132^{0}C
3	Qd-3	$C_{24}H_{20}N_2O_5S$	448.25	191-193^{0}C
4	Qd-4	$C_{23}H_{18}N_2O_5S$	434.24	270-272^{0}C
5	Qd-5	$C_{25}H_{21}N_2O_4S$	445.12	272-274^{0}C
6	Qd-6	$C_{24}H_{20}N_2O_4S$	432.27	256-258^{0}C
7	Qd-7	$C_{24}H_{20}N_2O_4S$	432.27	208-210^{0}C
8	Qd-8	$C_{26}H_{24}N_2O_4S$	460.32	274-276^{0}C
9	Qd-9	$C_{23}H_{17}N_2O_4Br$ S	497.14	268-270^{0}C
10	Qd-10	$C_{23}H_{17}N_3O_6S$	463.24	245-247^{0}C
11	Qd-11	$C_{21}H_{16}N_2O_5S$	408.20	260-262^{0}C

SPECTRAL DATA OF THE QUINOLINE DERIVATIVES:

Qd-1: IR: 3500(0-H), 3108(C-H), 1673(C=O), 1518(C=N), 1070(C-H), 666(C-S).
HNMR: 2.32[s, 1H(CH_3)], 5.99[s, 1H(OH)], 6.32[s, 1H, (N=CH)],
6.63-8.08[m, 12H(Ar-H)], 9.95[s, 1H(CH)].
Mass: 418 m/e (M^+ peak).

Qd-2: IR: 3500(O-H), 3108(C-H), 1672(C=O), 1516(C=N), 1180(C-N), 680(C-S).
HNMR: 2.31[s, 3H(CH_3)], 2.48[s, 3H(OCH_3)], 5.97[s, 1H, (OH)], 6.62[s, 1H(N=CH)],
6.73-8.03[m, 11H(Ar-H)], 9.79[s, 1H(CH)].
Mass: 448 m/e (M^+ peak).

Qd-3: IR: 3500(0-H), 3100(C-H), 1670(C=O), 1517(C=N), 1160(C-N), 680(C-S)
Qd-4: IR: 3500(0-H), 3100(C-H), 1672(C=O), 1517(C=N), 1160(C-N), 680(C-S)
Qd-5: IR: 3500(0-H), 3100(C-H), 1672(C=O), 1516(C=N), 1158(C-N), 686(C-S)
Qd-6: IR: 3500(0-H), 3100(C-H), 1672(C=O), 1517(C=N), 1159(C-N), 690(C-S)
Qd-7: IR: 3500(0-H), 3100(C-H), 1673(C=O), 1517(C=N), 1136(C-N), 686(C-S)
HNMR: 2.30[s, 3H(CH_3)], 2.49[s, 3H(OCH_3)], 5.95[s, 1H, (OH)], 6.62[s, 1H(N=CH)],
6.63-7.41[m, 11H(Ar-H)], 9.88[s, 1H(CH)].
Mass: 432 m/e (M^+ peak).

Qd-8: IR: 3500(0-H), 3100(C-H), 1672(C=O), 1519(C=N), 1180(C-N), 682(C-S)
Qd-9: IR: 3500(0-H), 3100(C-H), 1686(C=O), 1518(C=N), 586(C-Br), 1158(C-N), 686(C-S)
Qd-10: IR: 3500(0-H), 3100(C-H), 1672(C=O), 1557(C=N), 1380(-NO2), 1159(C-N), 690(C-S)
Qd-11: IR: 3500(0-H), 3100(C-H), 1672(C=O), 1517(C=N), 1274(C-O),1160(C-N), 680(C-S)

ANTI-BACTERIAL ACTIVITY:

In screening, the test compounds were first dissolved in sterile Dimethyl formamide (DMF) which has shown the inhibition of E. coli, so later sterile 1,4– Dioxane was used to dissolve the test compounds which was filter sterilized by using membrane filter of 0.2u, as its boiling point is below 121^{o}C and thermo-instable. Compounds were tested for its antibacterial activity at 50-100 ug/ml concentration. Ciprofloxacin was used as standard which was dissolved in sterile water.1, 4-Dioxane, water also tested as control.

Table 2: Anti-Bacterial data of synthesized quinoline derivatives:

S. No.	Compound	Zone of inhibition diameter (mm)	
		E. coli	***S. Aureus***
1	Qd-1	10	07
2	Qd-2	24	22
3	Qd-3	22	23
4	Qd-4	19	18
5	Qd-5	14	15
6	Qd-6	20	21
7	Qd-7	1	19
8	Qd-8	22	23
9	Qd-9	24	23
10	Qd-10	24	22
11	Qd-11	12	10
12	S	34	31
13	C	-	-

Zone of inhibition of synthesized compounds [Qd1-Qd11] against bacteria.
Note: 0-15 mm poor activity, 15-25 mm moderate activity, 25 above good.
Standard(S)= Ciprofloxacin **Control**(C)= DMF

ANTI-FUNGAL ACTIVITY:

In screening the test compounds were dissolved in DMF, so as togive 8000 µg/ml which was then serially diluted so as to get serial dilutions of 250-500 µg/ml.

Ketoconazole used as standard, was dissolved in sterile DMSO. Sterile DMF, DMSO werealso tested as control.

Table 3: Anti-Fungal data of synthesized quinoline derivatives:

S. No.	Compound	Zone of inhibition in diameter (mm)	
		C. albicans	***A. niger***
1	Qd-1	12	10
2	Qd-2	24	23
3	Qd-3	27	24
4	Qd-4	16	17
5	Qd-5	10	12
6	Qd-6	15	16
7	Qd-7	12	14
8	Qd-8	18	19
9	Qd-9	21	19
10	Qd-10	20	21
11	Qd-11	05	07
12	S	35	33
13	C	-	-

Zone of inhibition of synthesized compounds [Qd1-Qd11] against fungi.
Note: 0-15 mm poor activity, 15-25 mm moderate activity, 25above good.
Standard(S)= Ketoconazole **Control**(C)= DMF

RESULTS:

The antimicrobial screening results presented on above table reveals that compounds **Qd-2, Qd-3, Qd-8, Qd-9, and Qd-10** exhibited poor activity at 50µg/ml, but at 100µg/ml they have shown moderate activity against S. aureus, and moderate activity against E. coli.

And **Qd-2, Qd-3, Qd-8, Qd-9, Qd-10** have shown the very good activity against S. aureus at 100µg/ml when compared with the standard drug Ciprofloxacin.

The same compounds also screened for the anti-fungal activity against Candida albicans the compounds **Qd-2, Qd-3, Qd-8, Qd-9, Qd-10** showed highest degree of inhibition at 250µg/ml and 500µg/ml against C. albicans when compared with the standard drug Ketoconazole.However, the activities shown by all the compounds tested were less than that of the standard.

DISCUSSION:

The discussion part mainly deals with the about the synthesized compounds against the antibacterial and antifungal activity. The compounds **Qd-2, Qd-3, Qd-8, Qd-9, Qd-10** have shown good anti-bacterial activity due to the presence of electron donating group **-OCH_3, -$N(CH_3)_2$, CH_3** group which is attached at 4 fourth position of the phenyl ring system and the compounds **Qd-9** and **Qd-10** may be due to the presence of electron withdrawing group like **NO_2, Br** are attached at the second and fourth position of the phenyl ring system.

The anti-fungal activity shown that **Qd-2, Qd-3, Qd-8, Qd-9, Qd-10** have shown good antifungal activity it also may be due to the presence of electron donating group **-OCH_3, -$N(CH_3)_2$, -CH_3** group which is attached at 4 fourth position of the phenyl ring system and electron withdrawing group like **-NO_2, Br** are attached at the second and fourth position of the phenyl ring system. However, the activities shown by all the compounds tested were less than that of the standard.

CONCLUSION:

From the data of the Table no.2 & 3 of antibacterial and anti-fungal activity it is clearly concluded that the synthesized compounds are promisingly significant, good antimicrobial agents.

The substituted quinoline moieties are already known for different biological activities. Here we have synthesized some novel quinoline analogues combining with different substituted aromatic and hetero cyclic aldehydes ring system with view to get a good antibacterial and antifungal agent.

As per the results of screening it is clearly indicated that the compounds of the schemehave shown good antibacterial and antifungal activity equipotent with the standard drugs. This is because of the presence of groups like **-OCH_3, -NO_2, -Br, -N-CH_3**, at the different positions of phenyl nucleus and heterocyclic system attached to quinoline nucleus.

From the above results one can establish that the synthesized substituted quinoline canbe rich source for the exploration. Therefore, in search of new generation of the active compounds, it may be worth, while to explore the possibility in this area or by making or introducing different functional groups to secondary amines or by cyclization as substitutions,which may result into better pharmacological agents.

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