



SYNTHESIS OF QUINOLONE DERIVATIVES SHOWING ANTIFUNGAL ACTIVITY

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ABSTRACT

We have synthesized a few novel quinoline analogs combining with distinctive substituted fragrant and hetero cyclic aldehydes ring structure to obtain some better antifungal agents. We have successfully synthesized five derivatives from quinoline compound as Qd1, Qd2, Qd3, Qd4, Qd5 and their IUPAC names are.

- a) N-benzylidene-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)benzenesulfonamide.
- b) N-benzylidene-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-N-(4-methoxybenzylidene)benzenesulfonamide.
- c) N-benzylidene-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-N-(3-methoxybenzylidene)benzenesulfonamide.
- d) N-(2-hydroxybenzylidene)-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)benzenesulfonamide.
- e) N-{2-[(1E)-3-oxoprop-1-en-1-yl]benzylidene}-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)benzenesulfonamide.

This work aims to outline the recent advances in quinolone derivatives showing excellent antifungal activity equipped with conventional drugs. This review covers the recent advances in quinolone derivatives as potential antifungal agents.^[1] From the results of the anti-fungal activity it is clearly concluded that the synthesized compounds are promising, great antimicrobial agents.^[2] The substituted quinoline moieties are as of now known for diverse organic exercises. Presence of groups like -methoxy group, -Nitrogen Dioxide, -Bromine, -N-CH₃, at the different positions of phenyl nucleus and heterocyclic system attached to quinoline nucleus showed excellent antifungal activity. As future prospects the Qd3 compound showed significant antifungal activity and may apparently be comparable with the standard drug ketoconazole if it is purified with much better quality and standards.

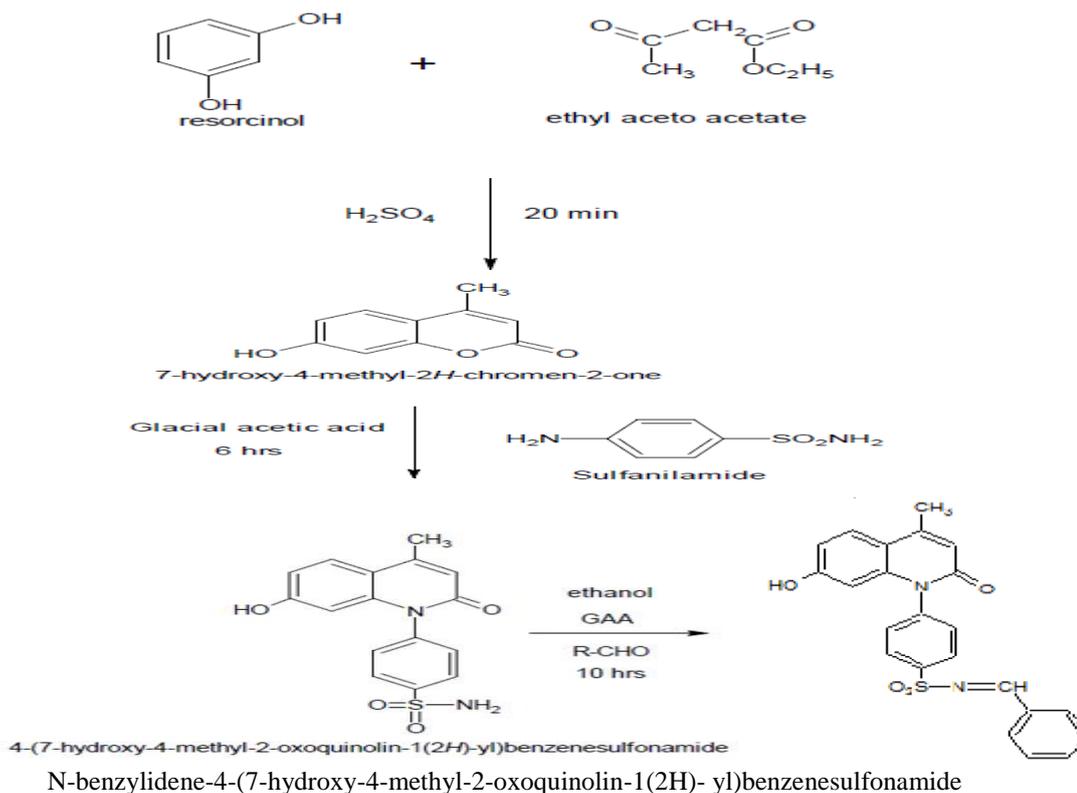
KEYWORDS: Antifungal agents, quinoline, methoxy group.

INTRODUCTION

“Over a few years ago, in the field of medicine antifungal drug discovery was reached by the introduction of a novel class of molecules, known as quinolones.”^[3] Quinolones possess a broad spectrum of chemotherapeutic properties and demonstrate considerable antifungal activities as well. Various quinolone derivatives have been screened for their antifungal activities, and some of them exhibit excellent potency against both drug-susceptible and drug-resistant fungi.^[4] Quinolone is an antibiotic and a member of a large group of broad-spectrum bacteriocidals that share a bicyclic core structure related to the compound 4-quinolone. They are used in human and veterinary medicine to treat bacterial infections, as well as in animal husbandry. Quinolones comprise a relatively large growing and most interesting group of antifungal field of antifungal chemotherapy particularly in the past few years. This is because they potentially offer many of the attributes of an antibiotic. Combining high potency, broad intravenous formulations, high serum levels, and

a large volume of distribution indicating concentration in tissues and a potentially low incidence of side effects.^[5] Quinoline affiliates place as a critical category among the variety of compounds regarded. many heterocyclic compounds, linear anhydrides, cyclic imides, cyclic acetals of dihydroxy alcohols, solvents, dioxanes and tetrahydrofurans, all of which have an open-chain analog chemistry. Heterocyclic intermediates are being utilized increasingly in amalgamation as ensuring bunches, promptly created, and promptly removed.^[6]

SCHEME REACTION FOR Qd1

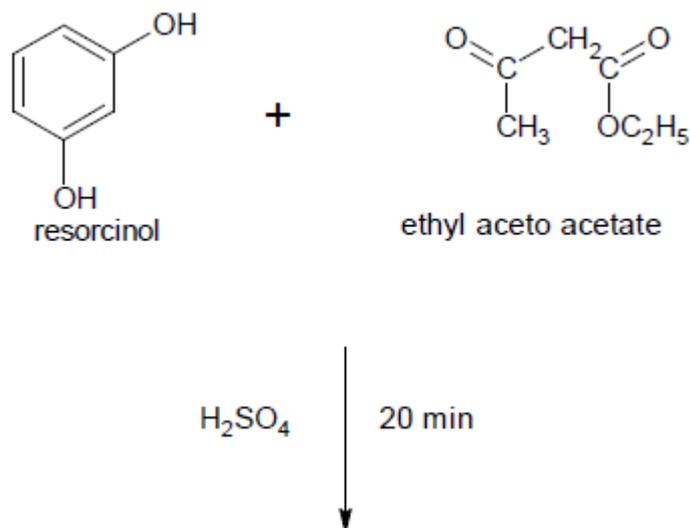


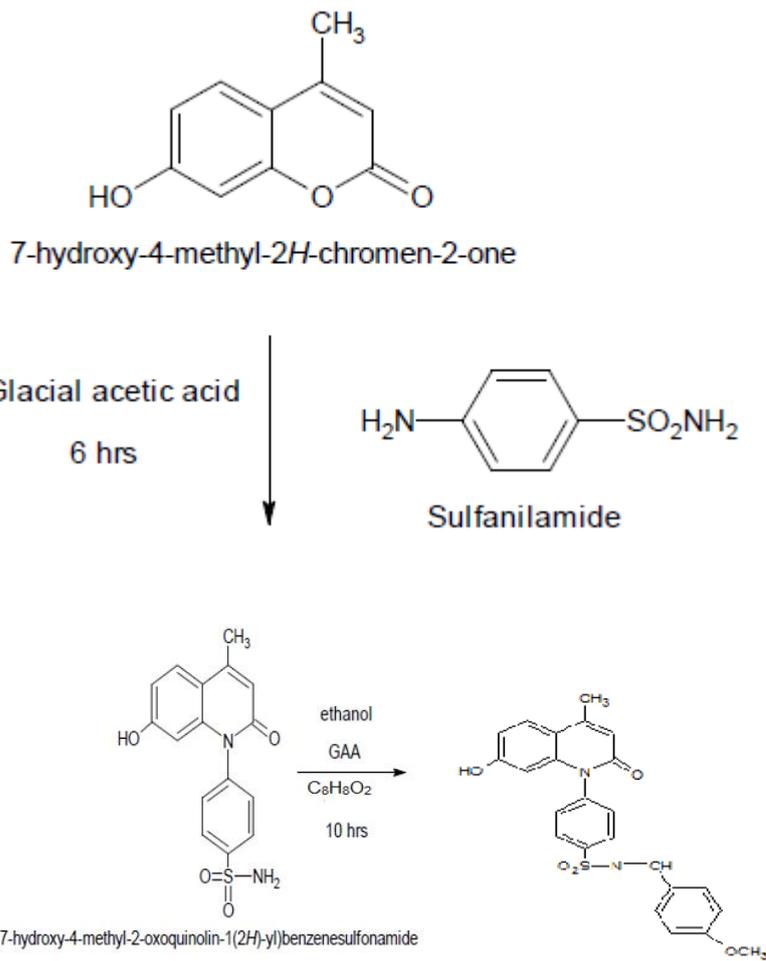
An equimolar arrangement of Resorcinol 3mg is broken up in 4.5ml of ethyl acetoacetate and to this arrangement 5ml of sulphuric acid is included, for 20 mins which gives 7-hydroxy-4-methyl 2H chromen-2-one. Further 7-hydroxy-4-methyl 2H chromen-2-one in the presence of 7ml of glacial acetic acid and 2mg of sulfanilamide is kept beneath reflux for 6hrs which gives 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL)benzenesulfonamide. After cooling to room temperature this arrangement was

included to ice cold water. Then, 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL) benzenesulfonamide in the presence of ethanol GAA and Benzaldehyde is kept under reflux for 10hrs. compound gets isolated as strong, sifted, dried and recrystallized with ethanol which gives Qd1.

$\text{R}=\text{C}_2\text{H}_5$

SCHEME REACTION FOR Qd2

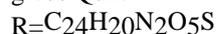




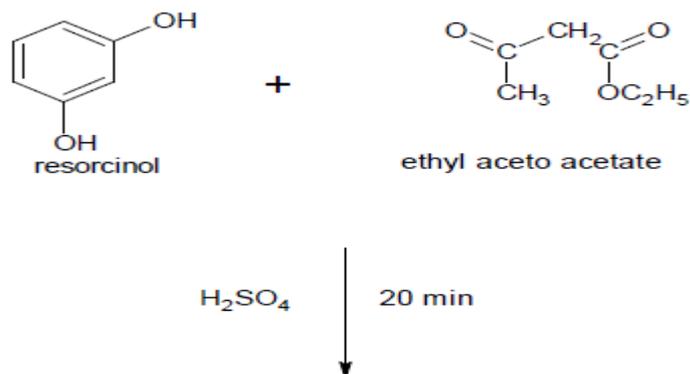
N-benzylidene-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-N-(4-methoxybenzylidene)benzenesulfonamide

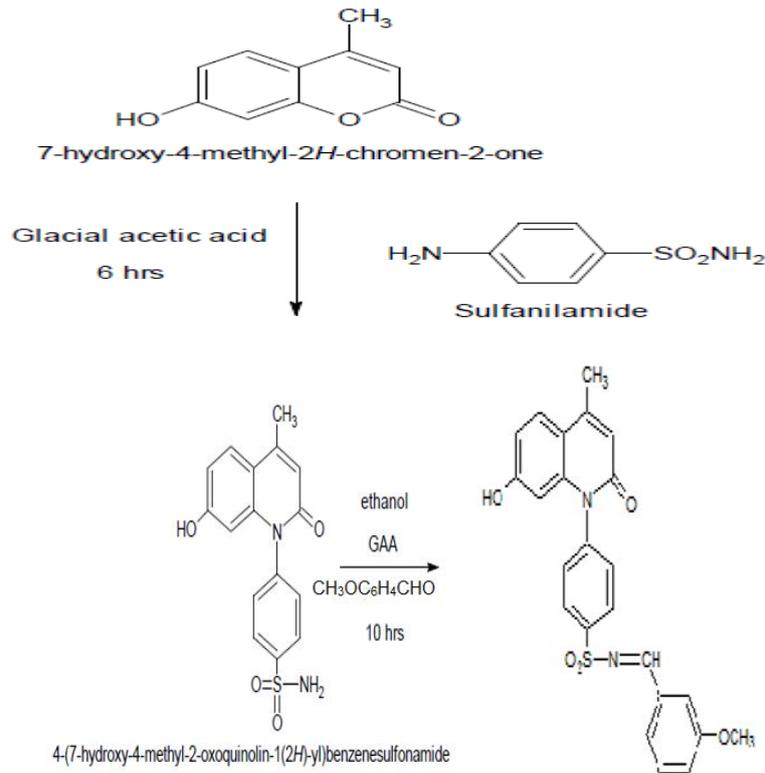
An equimolar arrangement of Resorcinol 3mg is broken up in 4.5ml of ethyl acetoacetate and to this arrangement 5ml of sulphuric acid is included, for 20 mins which gives 7-hydroxy-4-methyl 2H chromen-2-one. Further 7-hydroxy-4-methyl 2H chromen-2-one in the presence of 7ml of glacial acetic acid and 2mg of sulfanilamide is kept beneath reflux for 6hrs which gives 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL)benzenesulfonamide. After cooling to room temperature this arrangement was

included to ice cold water. Then, 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL)benzenesulfonamide in the presence of ethanol GAA and 4-methoxybenzaldehyde is kept under reflux for 10hrs. compound gets isolated as strong, sifted, dried and recrystallized with ethanol which gives Qd2.



SCHEME REACTION FOR Qd3





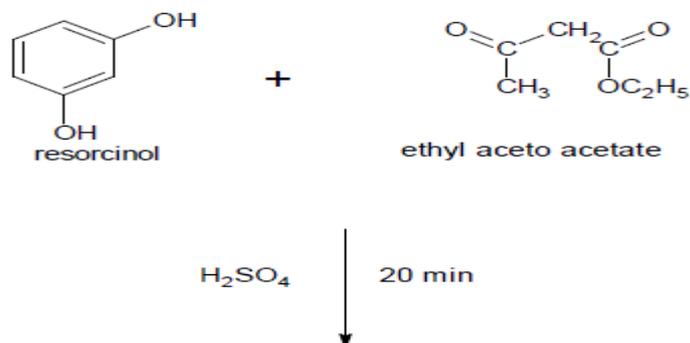
N-benzylidene-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)-N-(3-methoxybenzylidene)benzenesulfonamide

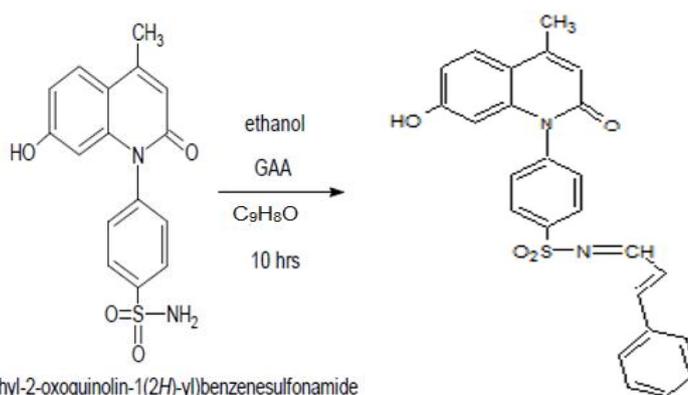
An equimolar arrangement of Resorcinol 3mg is broken up in 4.5ml of ethyl acetoacetate and to this arrangement 5ml of sulphuric acid is included, for 20 mins which gives 7-hydroxy-4-methyl 2H chromen-2-one. Further 7-hydroxy-4-methyl 2H chromen-2-one in the presence of 7ml of glacial acetic acid and 2mg of sulfanilamide is kept beneath reflux for 6hrs which gives 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL)benzenesulfonamide. After cooling to room temperature this arrangement was

included to ice cold water. Then, 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL) benzenesulfonamide in the presence of ethanol GAA and 3-methoxybenzaldehyde is kept under reflux for 10hrs. compound gets isolated as strong, sifted, dried and recrystallized with ethanol which gives Qd3.

R=C₂₄H₂₀N₂O₅S

SCHEME REACTION FOR Qd4





N-{2-[(1E)-3-oxoprop-1-en-1-yl]benzylidene}-4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)benzenesulfonamide

An equimolar arrangement of Resorcinol 3mg is broken up in 4.5ml of ethyl acetoacetate and to this arrangement 5ml of sulphuric acid is included, for 20 mins which gives 7-hydroxy-4-methyl 2H chromen-2-one. Further 7-hydroxy-4-methyl 2H chromen-2-one in the presence of 7ml of glacial acetic acid and 2mg of sulfaniamide is kept beneath reflux for 6hrs which gives 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL)benzenesulfonamide.

After cooling to room temperature this arrangement was

included to ice cold water. Then, 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-YL)benzenesulfonamide in the presence of ethanol GAA and Cinnamaldehyde is kept under reflux for 10hrs. compound gets isolated as strong, sifted, dried and recrystallized with ethanol which gives Qd5.

$R=C_{25}H_{21}N_2O_4S$.

MATERIALS AND METHODOLOGY

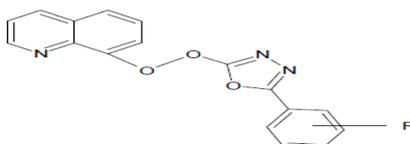
S.NO	Materials used	Make
1.	Weighing machine	Sartorius
2	Volumetric flask	Borosil
3	Pipettes and Burettes	Borosil
4	Beakers	Borosil
5	Digital ultra sonicator	Labman
6	FT-IR	Shimadzu
7	NMR Spectroscopy	Bruker

COMPARATIVE REVIEW LITERATURE

The broad writing study uncovered that compounds containing quinoline moiety have wide assortment of organic exercises.

1. Irfan Mohammed et al. synthesized Novel 5-aryl(8-quinolineoxymethyl)-1,3,4-oxadiazol subsidiaries. In show consider we created a productive strategy for

planning 1, 3, 4-oxadiazoles, commencing from hydrazides and substituted aldehydes. The response of hydrazides with substituted aldehydes within the nearness of ethanol to abdicate schiff's bases and advance treating with Chloramine-T to create 5-aryl (8-quinolineoxymethyl)-1, 3, 4-oxadiazoles. The compounds hence gotten were recognized by ghostly information and screened for their antimicrobial action.^[7]

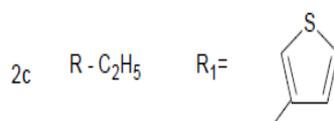
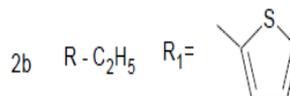
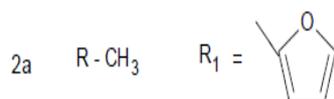
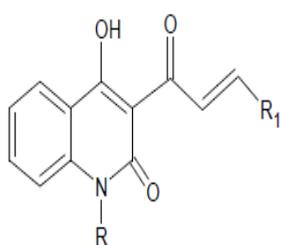
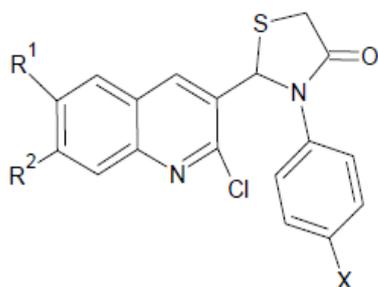


No.	R	No	R
4a	H	4e	4-OH
4b	4-Cl	4f	4-Me
4c	4-Br	4g	4-OMe
4d	4-NO ₂	4h	4-N(CH ₃) ₂

2. Vartale S.P. et. al., were synthesized 6/7-Substituted Quinolines-4-thiazolidinones. A arrangement of add up

to fifteen novel Quinoline Schiff bases [4a-e,5a-e,6a-e] were arranged from 6/7 substituted quinoline

carbaldehyde. All quinoline schiff bases were refluxed with thioacetic corrosive in nearness of anhydrous zinc chloride and dissolvable N,N-dimethyl formamide to managed novel arrangement of 4- thiazolidinone (7a-e,8a-e,9a-e). All synthesized 4-thiazolidinone were screened for their antimicrobial action.^[8]



ACTIVITY

Benzene sulphonamide is a Schiff base from which quinolones derivatives are prepared. It is a compound from which potent antifungal derivatives are extracted. By changing hydroxyl and ethyl group on quinolone nucleus activity is identified.

Broth dilution method is used for screening Antifungal activity as described.

Broth double dilution method

The broth double weakening approach was used to evaluate the minimum inhibitory concentration (MIC) of the sample compounds that perhaps the classical approach produces accurate, and precise results for the quantity of antimicrobial expert needed to suppress microorganism growth. Minimum inhibitory concentration (MIC) determination by the double weakening technique of the broth.^[10]

- MIC of the entire test (synthesized compounds) was determined using the above method.
- Following controls were also incorporated :-

3. Muhammad A. et.al., synthesized a quinoline based chalcones. An arrangement quinoline-based chalcones have been arranged by the condensation of quinoline-3-carbaldehyde with acetophenone and N- substituted-3-acetyl-4-hydroxy-2-quinolines with heterocyclic carbaldehydes. The arranged chalcones have been screened for antimicrobial action. The arranged chalcones have appeared noteworthy antimicrobial exercises.^[9]

- Drug control- Ketoconazole as reference standard was used.
- Solvent control DMF and DMSO were used as solvent controls.
- C. Sabourauds Dextrose Broth (SDB) and Malt Extract Glucose Yeast Extract Peptone Broth (MGYP) have been used as a nutrient medium for micro-organism development and *C.albicans* MIC determination.
- D. All compounds dissolved in DMF and dissolved in DMSO as a standard.
- E. All compounds have been diluted in series.
- F. Sabourauds Dextrose Broth (SDB) and Malt Extract Glucose Yeast Extra Peptone Broth (MGYP) have been used to dilute the sample compounds and conventional drug solution to obtain the necessary concentration.
- G. Test organisms have been introduced using saline solutions or broth to serially diluted solution.
- H. Then the plates were incubated at 37°C for 48 hrs.
- I. The growth of micro organism in the test compound solutions and control drug was seen after incubation

Dilution method

The sterilized media was cooled to 45⁰C with delicate shaking to bring around uniform cooling and after that vaccinated with 18-24 hrs ancient culture beneath aseptic conditions, blended well by tender shaking. This was poured in (properly marked) sterile Petri dish and allowed the medium to be set. After hardening the Petri dish were exchanged to laminar stream unit.^[10] At that point the circle which were already arranged were carefully kept on the cemented media by utilizing sterilized forceps. Petri dish was kept because it is for one-hour dissemination at room temperature and after that for hatching at 37⁰C for 24 hours in a hatchery.

The magnitude of inhibition diameter was evaluated in millimeters after 24 hours.

Antifungal activity

Method used for screening:- The sample compounds were mixed in DMF to provide 8000µg / ml, which was then diluted serially to obtain 250-500µg / ml serial dilutions.

As a standard, ketoconazole was dissolved in sterile DMSO. Also testing for sterile DMF, DMSO.

IMPACT

From the information of the anti-fungal action it is clearly concluded that the synthesized compounds are

promisingly critical, great antimicrobial agents. The substituted quinoline moieties are as of now known for diverse organic exercises. Here we have synthesized a few novel quinoline analogs combining with distinctive substituted fragrant and hetero cyclic aldehydes ring framework to urge some better antifungal agent.

Based on the screening outcomes, it is obviously shown that the scheme's compounds showed excellent antifungal activity equipped with conventional drugs. This is because of the presence of groups like **-methoxy group**, **-Nitrogen Dioxide**, **-Bromine**, **-N-CH₃**, at the different positions of phenyl nucleus and heterocyclic system attached to quinoline nucleus.

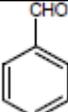
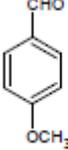
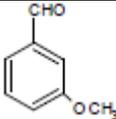
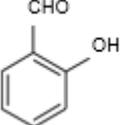
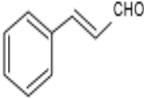
SIGNIFICANCE

The prepared compounds are having potent antifungal activity. Which is comparable with the marketed product. So, the prepared derivatives can be used as a topical drug dosage form to prevent and treat fungal infections.

In the scheme reaction of compound quinoline derivative "R" position changes to aldehyde. As the position changes the activity decrease.

So, in the last step while reflux we are adding aldehyde to form new quinolone derivative.

Table no. 1: List of aldehydes.

COMP NO.	ALDEHYDE NAME	STRUCTURE
Qd-1	Benzaldehyde	
Qd-2	4-methoxybenzaldehyde	
Qd-3	3-methoxybenzaldehyde	
Qd-4	Salisialdehyde	
Qd-5	Cinnamaldehyde	

RESULTS GENERAL PROCEDURE FOR THE PREPARATION OF NOVEL QUINOLINE DERIVATIVES WITH SCHIFF BASES COMPOUND

An equimolar arrangement of benzenesulfonamide 2.86gm (0.01mol) is broken up in 10 ml of ethanol and to this arrangement substituted aldehydes in equimolar qty (0.01mole) is included with 4-6 drops of cold acidic

corrosive was included, this response blend is kept beneath reflux for 10 h. After cooling to room temperature this arrangement was included to ice cold water. Compound gets isolated as strong, sifted, dried and recrystallized with ethanol. Dissolving point is famous in 0C, the abdicate is specified in %. And all the other compounds are arranged by utilizing the same strategy as over.

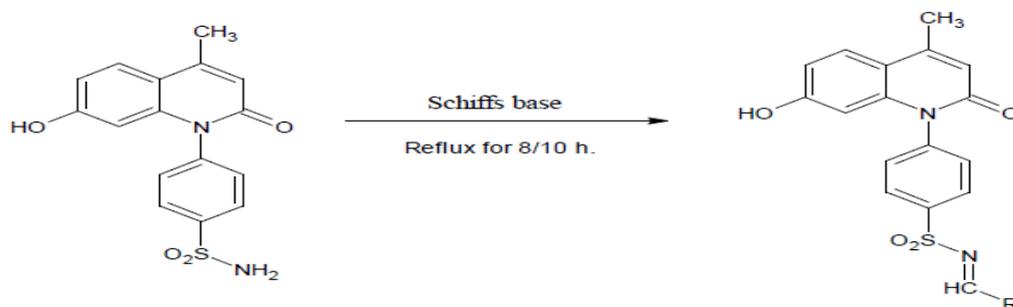


Table no. 2: Physicochemical parameters of quinoline derivatives.

S.NO	Compound code	R	Molecular Formula	Molecular Weight	Melting point (°C)
1	Qd-1		C ₂₃ H ₁₈ N ₂ O ₄ S	418.12	258-260 ⁰ C
2	Qd-2		C ₂₄ H ₂₀ N ₂ O ₅ S	448.27	130-132 ⁰ C
3	Qd-3		C ₂₄ H ₂₀ N ₂ O ₅ S	448.25	191-193 ⁰ C
4	Qd-4		C ₂₃ H ₁₈ N ₂ O ₅ S	434.24	270-272 ⁰ C
5	Qd-5		C ₂₅ H ₂₁ N ₂ O ₄ S	445.12	272-274 ⁰ C

SPECTRAL DATA

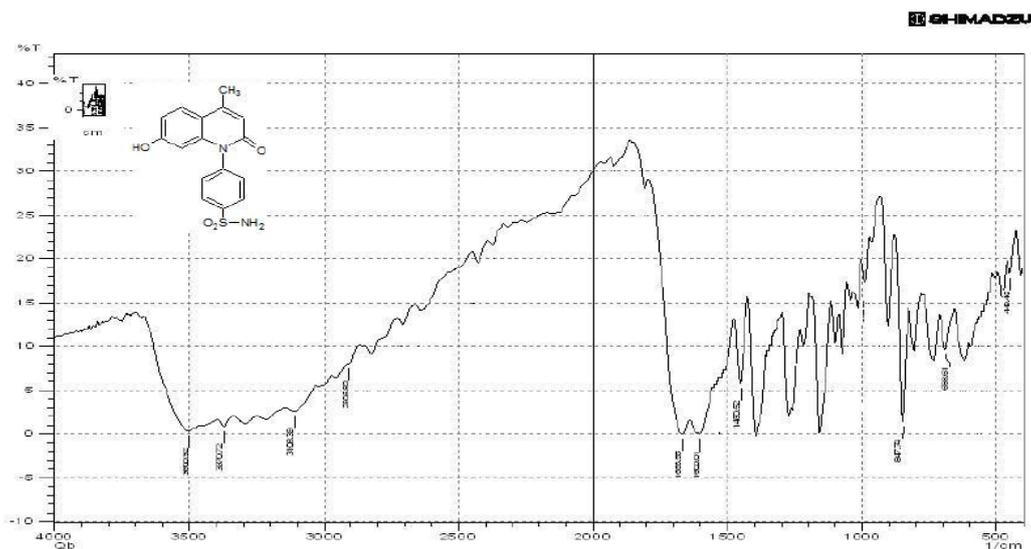


Figure no. 1: ir spectra of 4-(7-hydroxy-4-methyl-2-oxoquinolin-1(2h)- yl)benzenesulfonamide.

Table no. 3: ir-spectral data of 4-(7- hydroxy -4- methyl -2- oxoquinolin -1 (2h) -yl) benzenesulfonamide.

S.No.	Wave number (cm ⁻¹)	Functional group assigned
1	3500	O-H Str.
2	3370	N-H Str.
3	3108	C-H str.
4	1666	C=O str.
5	1180	C-N str.
6	666	C-S str.

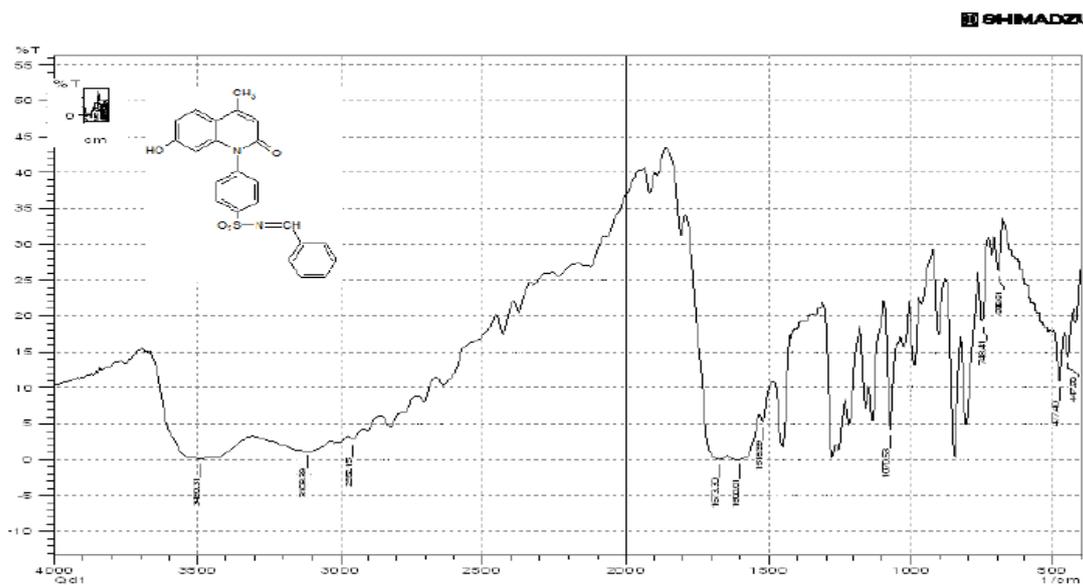


Figure no. 2: IR Spectra of Qd-1.

Table no 4: IR spectral data of Qd-1.

S.No.	Wave number (cm ⁻¹)	Functional group assigned
1	3500	O-H Str.
2	3108	C-H Str.
3	1673	C=O str.
4	1518	C=N str.
5	1070	C-N str.
6	666	C-S str.

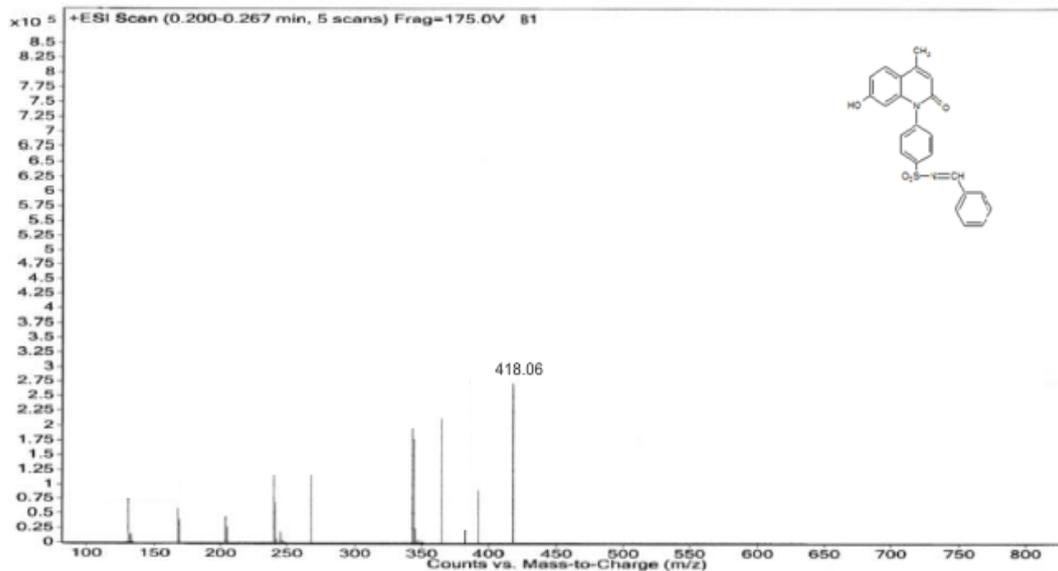


Figure no 3: MASS Spectra of Qd-1.

MASS spectral data of compound Qd-1

The molecular weight of the compound is 418.12 and the mass spectral data matching the same as 418 m/e it shows that the M^+ peak.

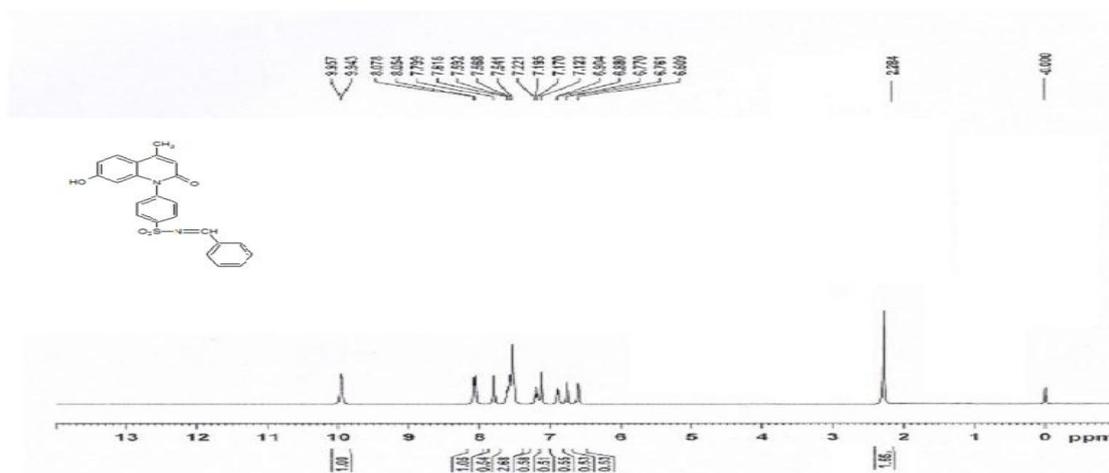


Figure no 4: ^1H NMR Spectra of Qd-1.

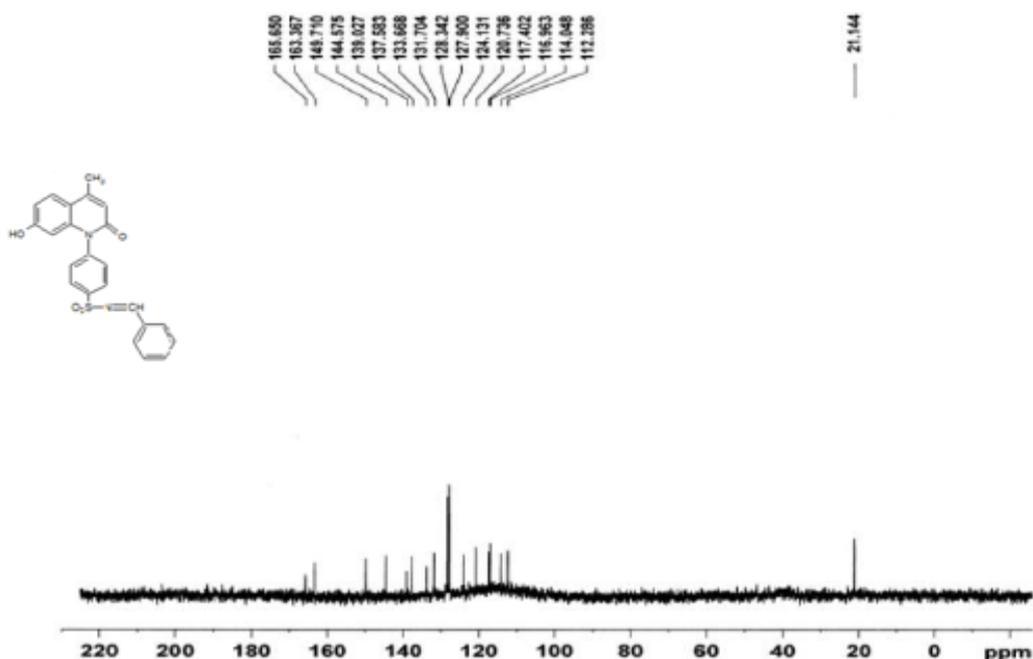


Figure no: ¹³C NMR Spectra of Qd-1.

Spectral data of compound Qd-1

Table no 5: Spectral data of compound Qd-1.

¹ H NMR (δ ppm)	2.28 (3H, s, -CH ₃), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 9.94, 9.95 (2H, s, s, amide NH).
¹³ C NMR (δ ppm)	165.65, 163.36, 149.71, 144.57, 116.96, 114.04, 112.28
MS Qbd1	345, 418(M+1), 243, 132

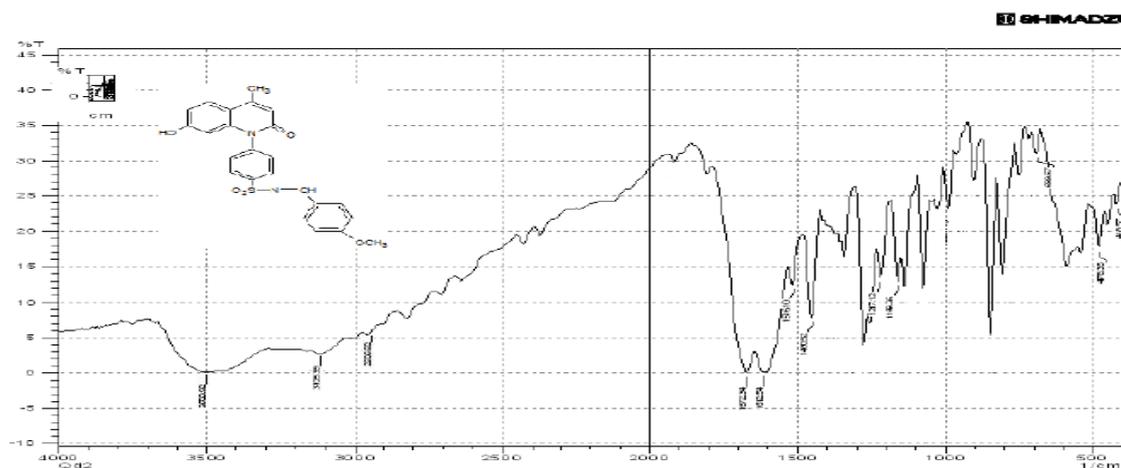


Figure no. 6: IR Spectra of compound Qd-2.

Table no 6: IR spectral data of compound Qd-2.

Sr.No.	Wave number (cm ⁻¹)	Functional group assigned
1	3500	O-H Str.
2	3108	C-H Str.
3	1672	C=O str.
4	1516	C=N str.
5	1180	C-N str.
6	680	C-S str.

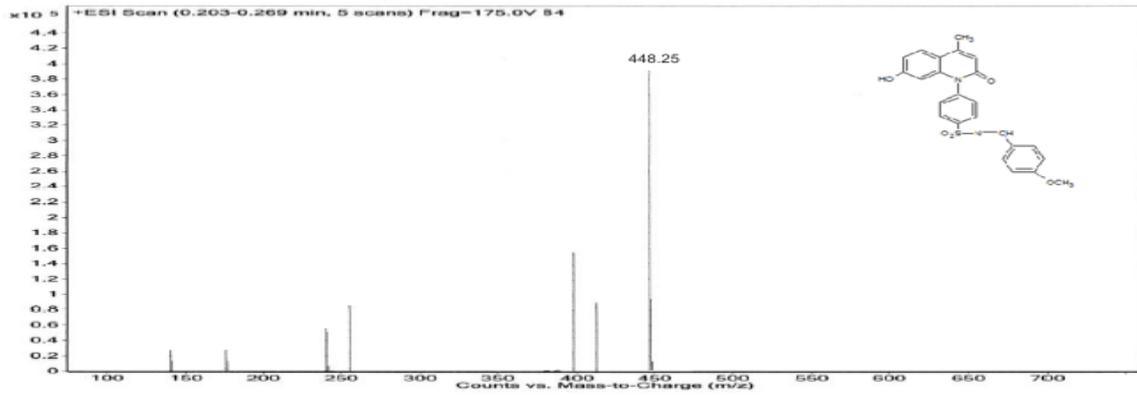


Figure no 7: MASS Spectra of Qd-2.

MASS spectral data of compound Qd-2

The molecular weight of the compound is 448.27 and the mass spectral data matching the same as 448 m/e it shows that the M⁺ peak.

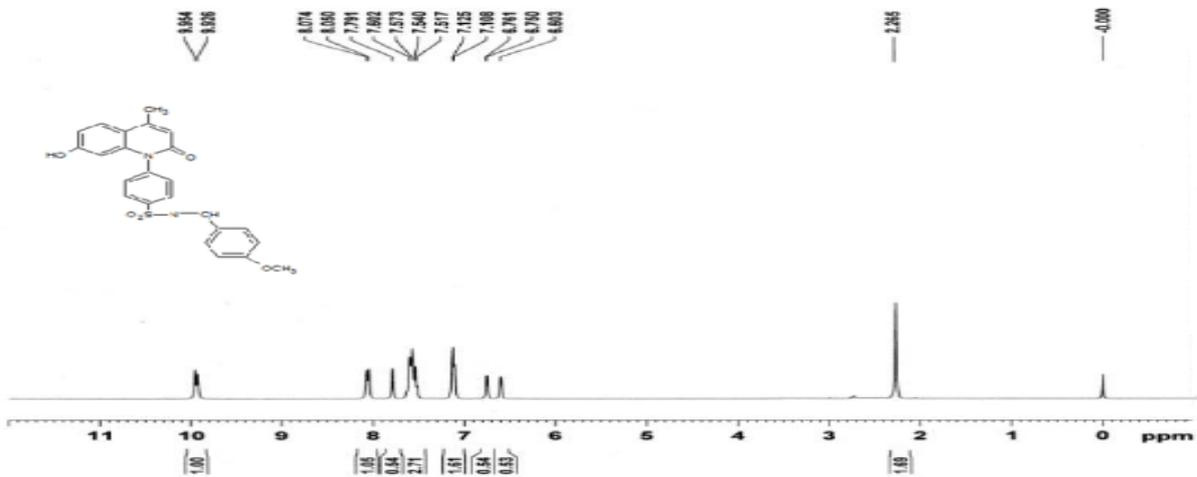


Figure no 8: ¹H NMR Spectra of Qd-2.

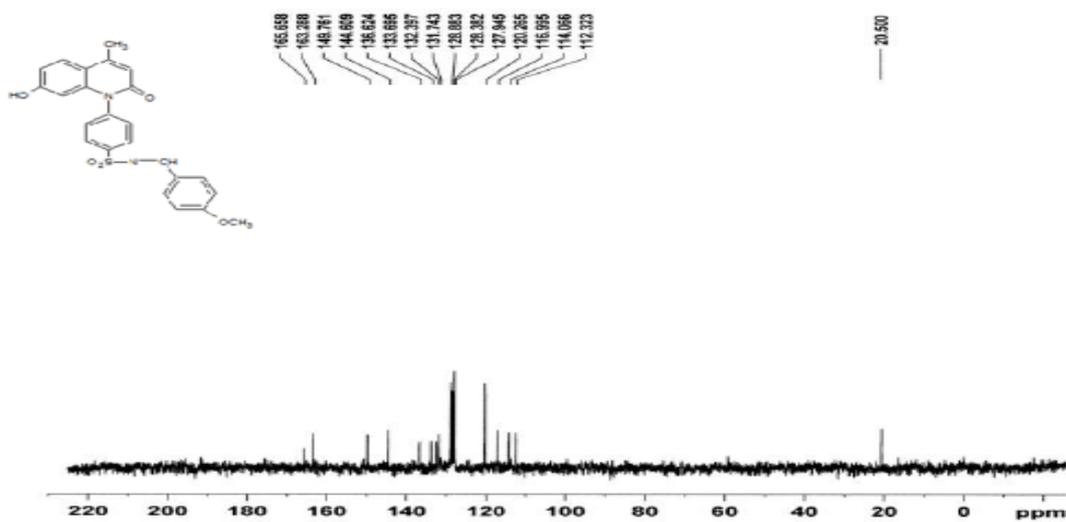


Figure no. 9: ¹³C NMR Spectra of Qd-2.

Spectral data of compound Qd-2

Table no. 7: Spectral data of compound Qd-2.

¹ HNMR (δ ppm)	2.28 (3H, s, -CH ₃), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 9.94, 9.95 (2H, s, s, amide NH).
¹³ CNMR (δ ppm)	165.65, 163.36, 149.71, 144.57, 116.96, 114.04, 112.28
MS Qd2	448(M+1), 261,134,135.

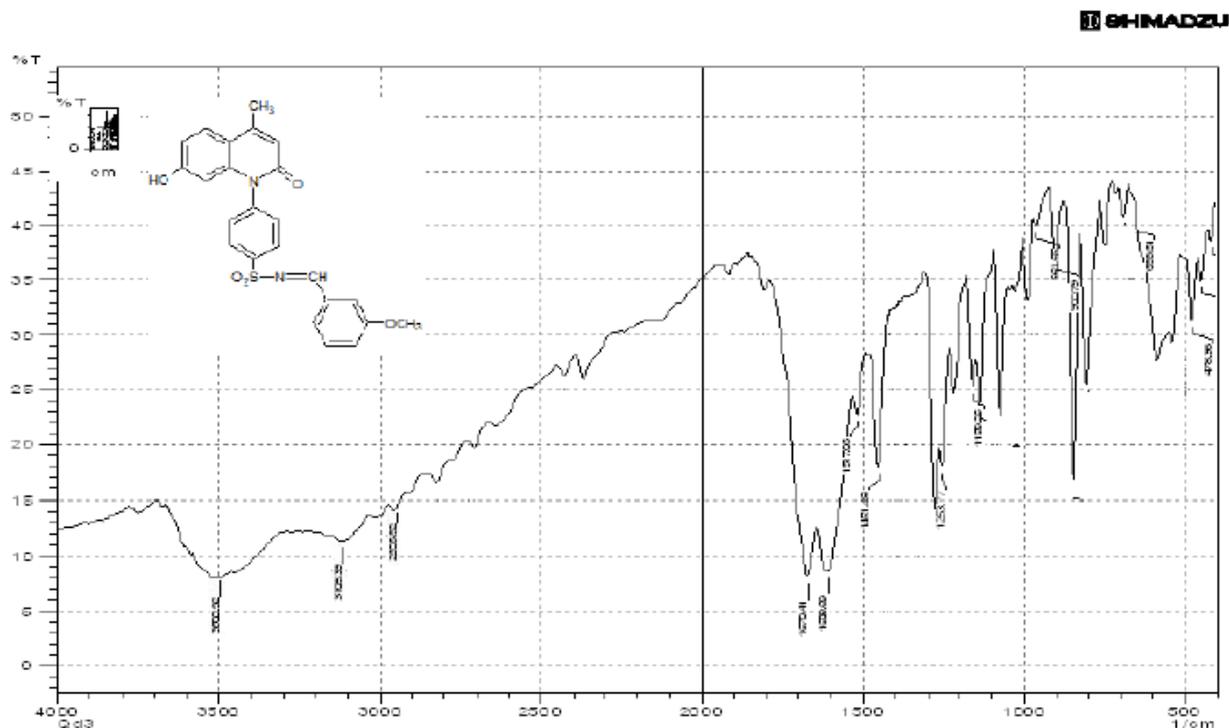


Figure no 10: IR Spectra of Qd-3.

Table no 8: IR spectral data of compound Qd-3.

Sr.No.	Wave number (cm ⁻¹)	Functional group assigned
1	3500	O-H Str.
2	3100	C-H Str.
3	1670	C=O str.
4	1517	C=N str.
5	1160	C-N str.
6	680	C-S str.

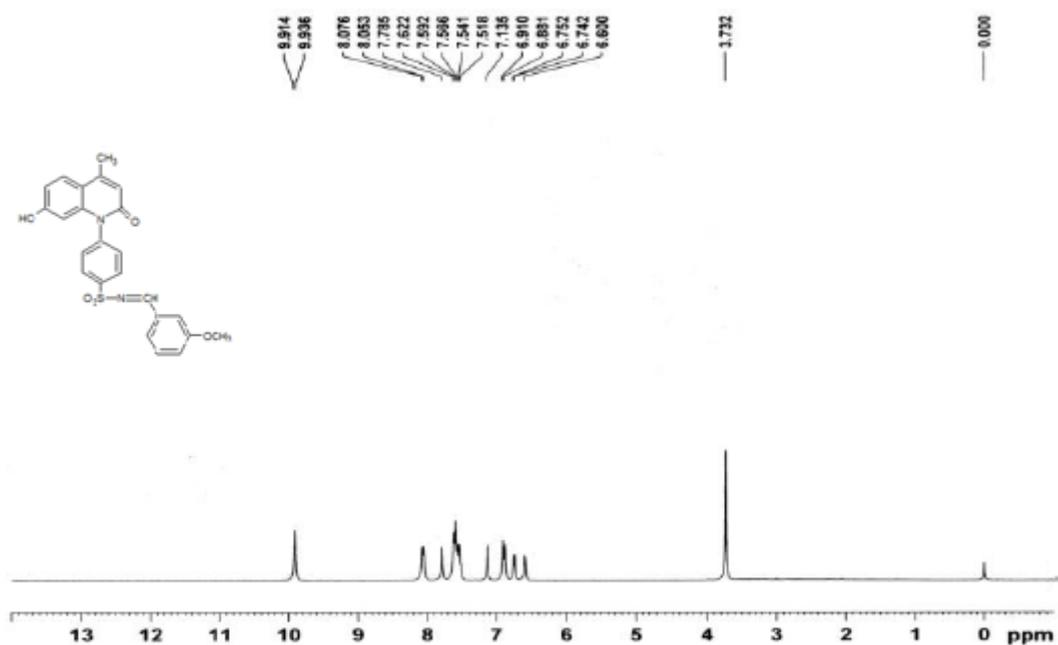


Figure no 11: ¹H NMR Spectra of Qd-3.

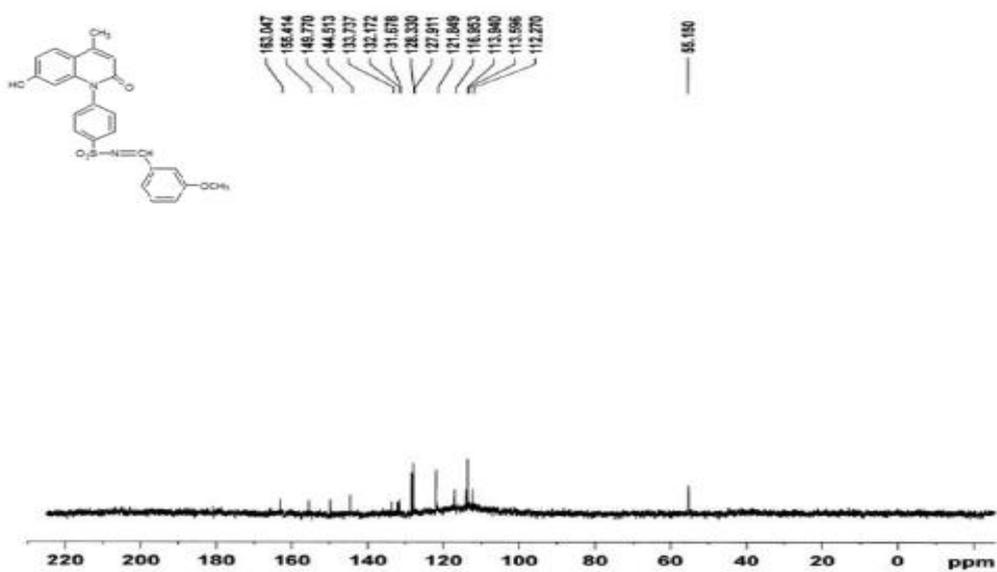


Figure no. 12: ¹³C NMR Spectra of Qd-3.

MASS Spectra of Qd-3

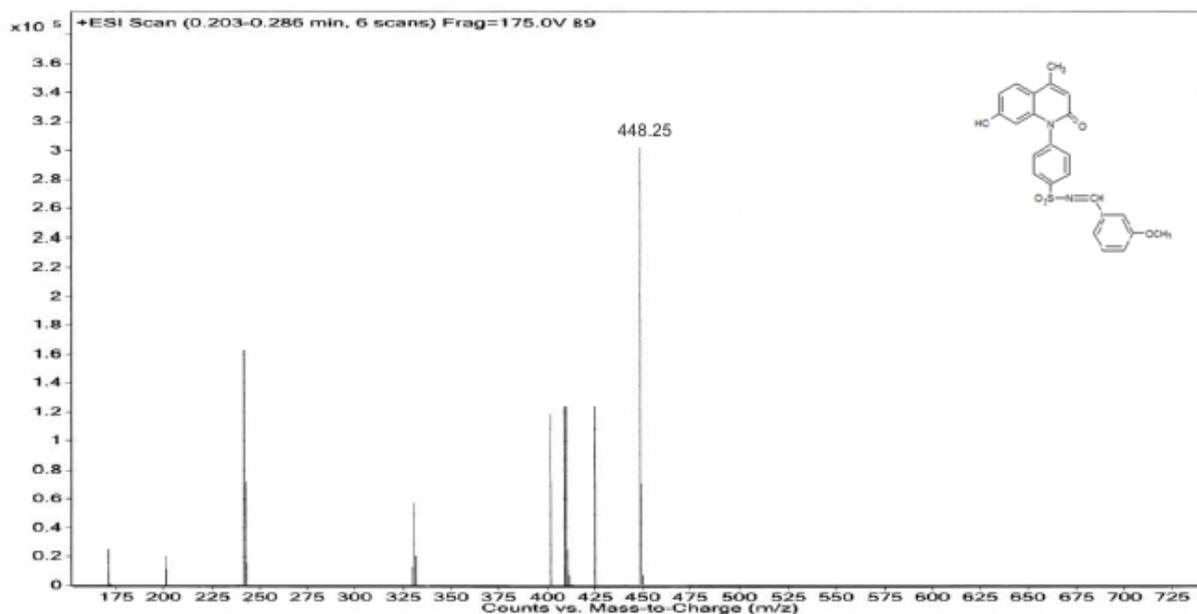


Figure no 13: MASS spectral data of compound Qd-3.

The molecular weight of the compound is 448.25 and the mass spectral data matching the same as 448m/e it shows that the M^+ peak.

Table no. 9: Spectral data of compound Qd-3.

¹ HNMR (δ ppm)	2.28 (3H, s, -CH ₃), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 9.94, 9.95 (2H, s, s, amide NH).
¹³ CNMR (δ ppm)	165.65, 163.36, 149.71, 144.57, 116.96, 114.04, 112.28
MS Qd3	400, 410, 448(M+1), 243, 139,174.

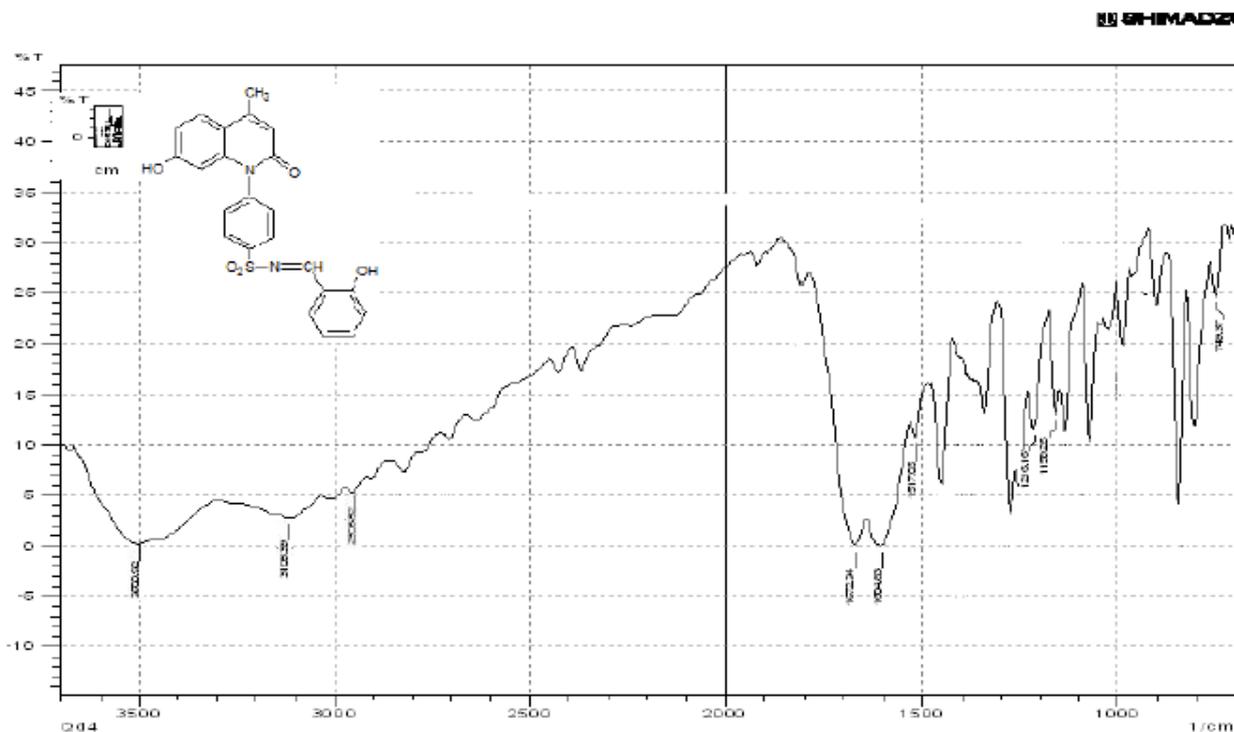
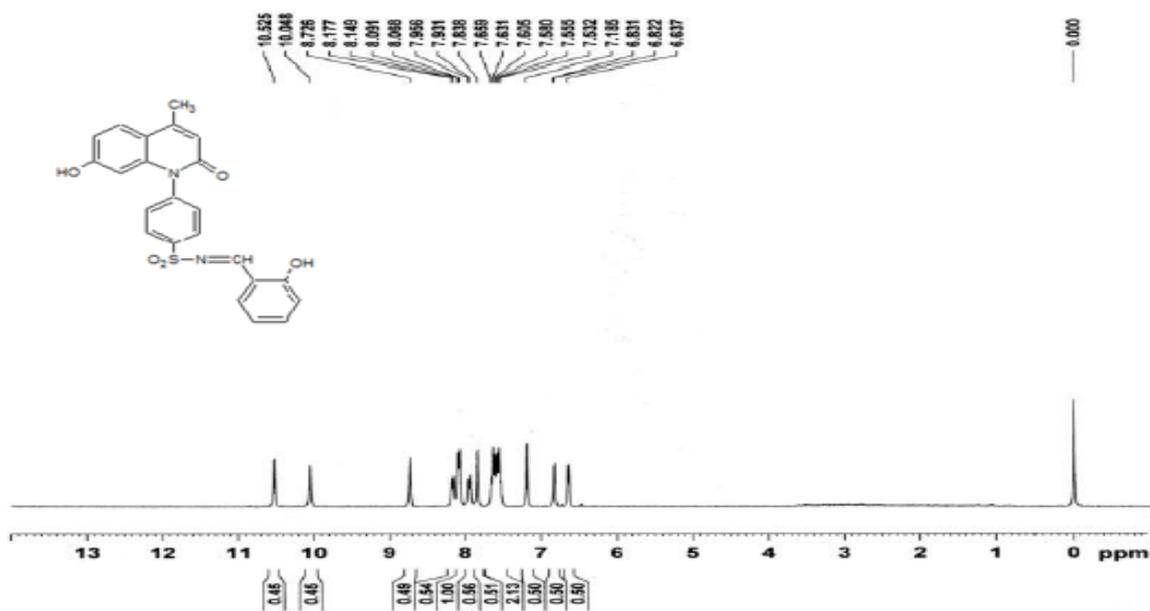
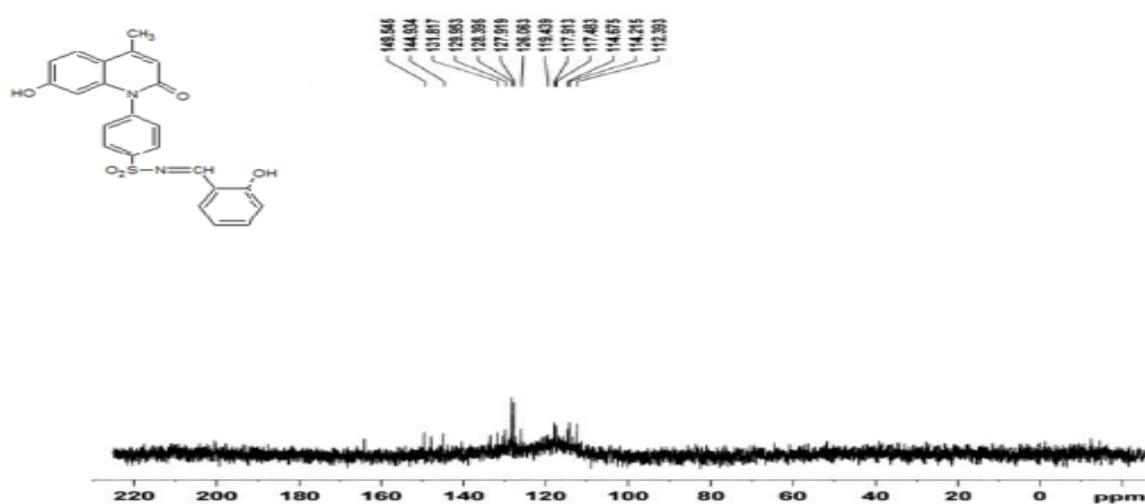


Figure no 14: IR Spectra of Qd-4.

Table no 10: IR spectral data of compound Qd-4.

Sr.No.	Wave number (cm ⁻¹)	Functional group assigned
1	3500	O-H Str.
2	3100	C-H Str.
3	1672	C=O str.
4	1517	C=N str.
5	1160	C-N str.
6	680	C-S str.

Figure no 15: ¹H NMR Spectra of Qd-4.Figure no. 16: ¹³C NMR Spectra of Qd-4.

MASS Spectra of Qd-4

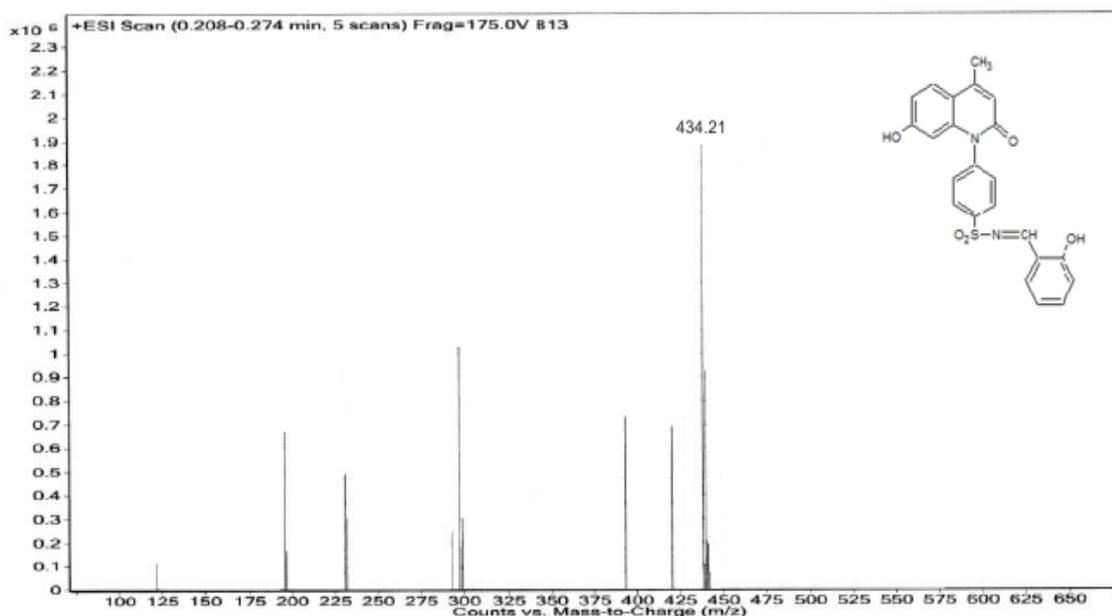


Figure no. 17: MASS Spectra.

MASS spectral data of compound Qd-4

The molecular weight of the compound is 434.24 and the mass spectral data matching the same as 434m/e it shows that the M^+ peak.

Table no. 11: Spectral data of compound Qd-4.

$^1\text{H NMR}$ (δ ppm)	2.28 (3H, s, -CH ₃), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 9.94, 9.95 (2H, s, s, amide NH).
$^{13}\text{C NMR}$ (δ ppm)	165.65, 163.36, 149.71, 144.57, 116.96, 114.04, 112.28
MS Qd4	415, 434(M+1), 384, 296, 190, 122.

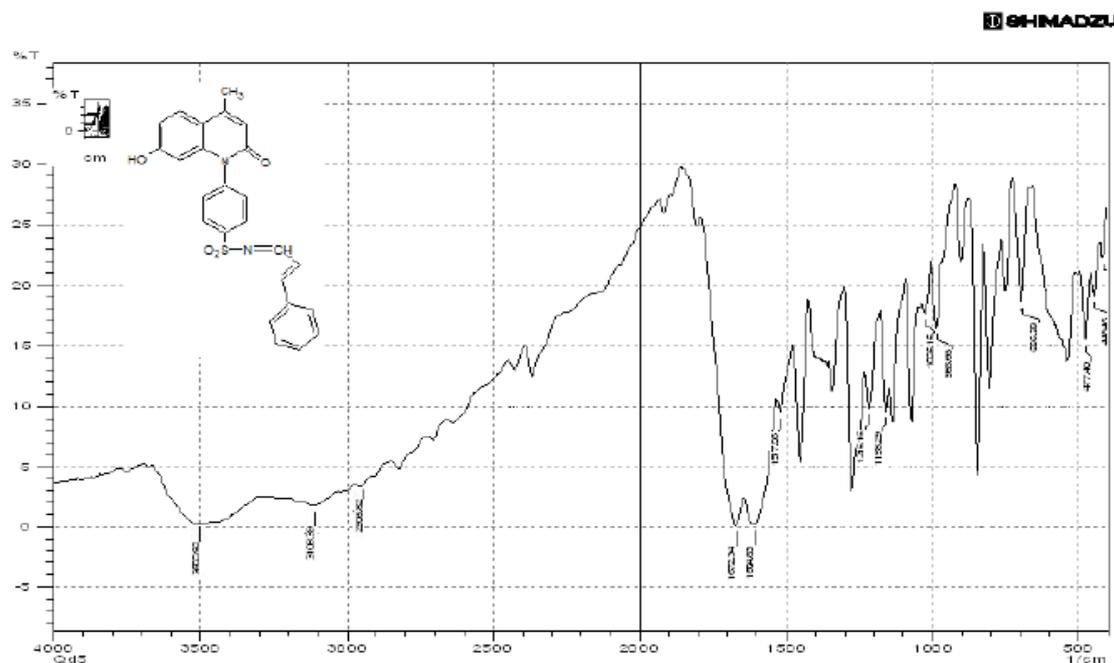
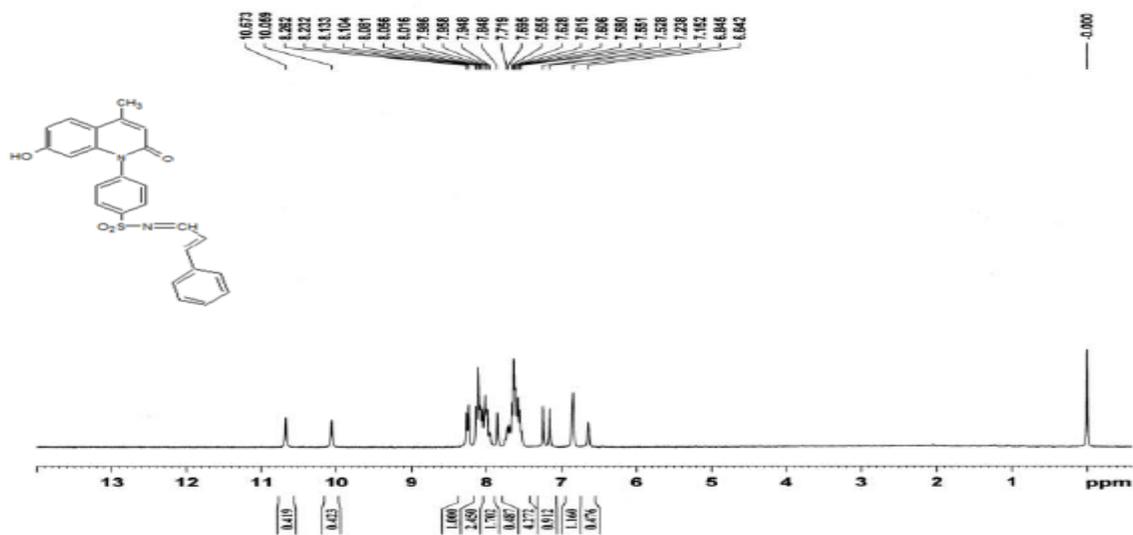
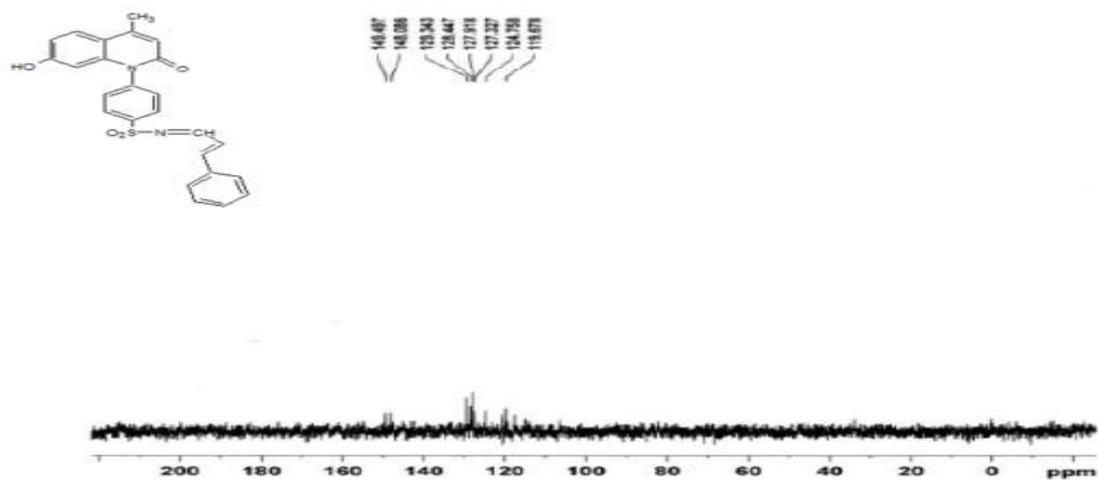


Figure no 18: IR Spectra of Qd-5.

Table no 12: IR spectral data of compound Qd-5.

Sr.No.	Wave number (cm ⁻¹)	Functional group assigned
1	3500	O-H Str.
2	3100	C-H Str.
3	1672	C=O str.
4	1516	C=N str.
5	1158	C-N str.
6	686	C-S str.

Figure no. 19: ¹H NMR Spectra of Qd-5.Fig. 20: ¹³C NMR Spectra of Qd-5.

MASS Spectra of Qd-5

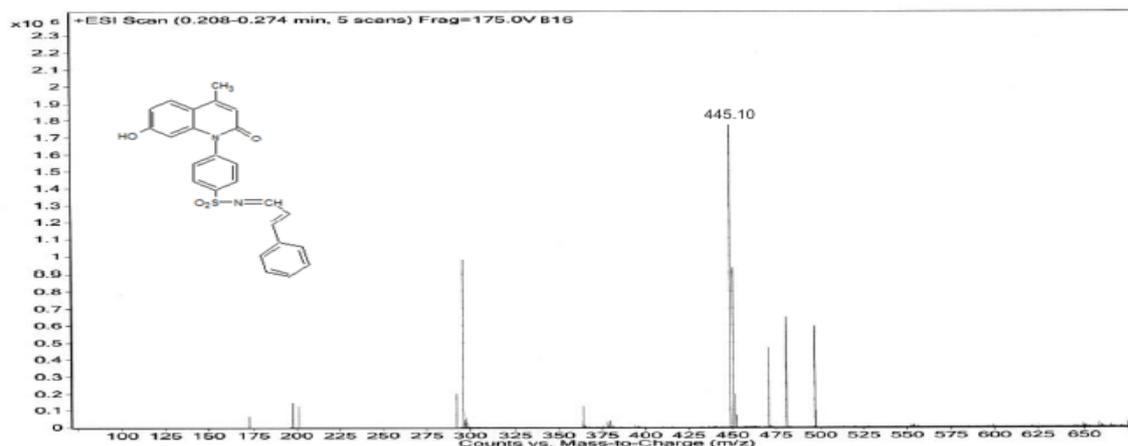


Fig. 21: MASS Spectra of Qd-5.

MASS spectral data of compound Qd-5

The molecular weight of the compound is 445.12 and the mass spectral data matching the same as 445m/e it shows that the M^+ peak.

Table no. 13: Spectral data of compound Qd-5.

^1H NMR (δ ppm)	2.28 (3H, s, -CH ₃), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 9.94, 9.95 (2H, s, s, amide NH).
^{13}C NMR (δ ppm)	165.65, 163.36, 149.71, 144.57, 116.96, 114.04, 112.28
MS Qd 5	445(M+1), 467, 480, 492, 296,192,172.

Table 14: Anti-fungal activity result of synthesized quinoline derivatives.

Sr. No.	compound	Zone of inhibition in diameter (mm)	
		<i>C.albicans</i>	<i>A.niger</i>
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	S	35	33

Zone of inhibition of synthesized compounds [Qd1-Qd5]

(Against Fungi) Note: - 0-15 mm poor activity, 15-25 mm moderate activity, 25above good. Standard(S) = Ketoconazole



Figure no 22: Anti Fungal Activity.

CONCLUSION

From the information of the anti-fungal action it is clearly concluded that the synthesized compounds are promisingly critical, great antimicrobial agents. The substituted quinoline moieties are as of now known for diverse organic exercises. Here we have synthesized a few novel quinoline analogs combining with distinctive substituted fragrant and hetero cyclic aldehydes ring framework with see to urge some better antifungal agent.

Based on the screening outcomes, it is obviously shown that the scheme's compounds showed excellent antifungal activity equipped with conventional drugs. This is because of the presence of groups like **-methoxy group**, **-Nitrogen Dioxide**, **-Bromine**, **-N-CH₃**, at the different positions of phenyl nucleus and heterocyclic system attached to quinoline nucleus.

From the over comes about one can set up that the synthesized substituted quinoline can be wealthy source for the investigation. Subsequently in look of modern era of the dynamic compounds, it may be worth whereas to investigate the plausibility in this zone or by making or presenting diverse useful bunches to auxiliary amines or by cyclization as substitutions, which may comes about into superior pharmacological agents.

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