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To Synthesize and Characterization of Novel Quinoline Derivatives as an Antibacterial and Antifungal Activities

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ABSTRACT

Preparation 7-chloroquinoline was prepared by the 1,2,3 tripropanol to react with sulphuric acid and then add nitrobenzene. Methyl-7-chloroquinoline-3-carboxylate was synthesized by 7-chloro quinoline reacting with pyridine in the presence of acetyl chloride. 7-chloroquinoline-3-carbohydrazide was isolated by the Methyl-7-chloroquinoline-3-carboxylate. These newly synthesized compounds 1-10 have been screened for their antibacterial activity on Escherichia coli, Staphylococcus aureus, and antifungal activity on Candida albicans.

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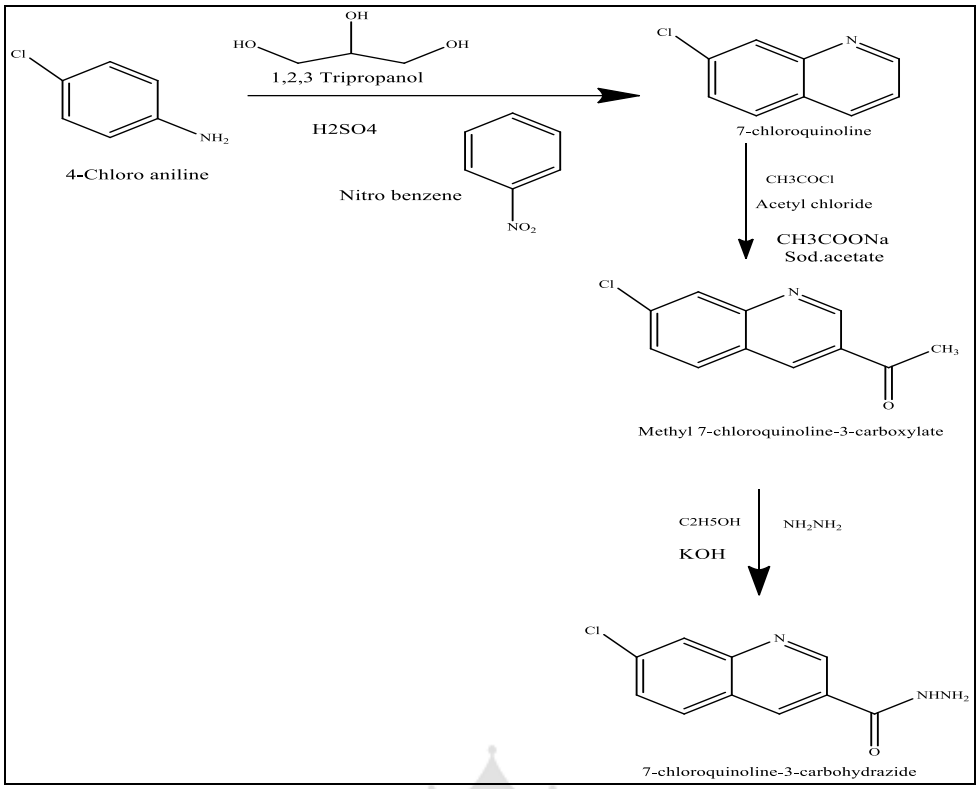
INTRODUCTION:

According to WHO, infectious illnesses account for 22% of all deaths and 27% of disability-adjusted life years (DALYS) globally. Antimicrobial resistance among clinically relevant microorganisms is widely recognized as a serious worldwide public health concern. [2] The majority of today's antimicrobial medications include side effects such as hepatotoxicity and hypersensitivity. [3, 4] The prevalence of infectious diseases, the presence of antimicrobial resistance, and the increased side effects of antimicrobial drugs increase the temptation to design new, more effective, safe, and cost-effective drugs to treat such infectious diseases, making antimicrobial drugs discovery a high priority.

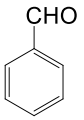
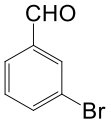
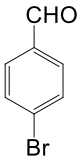
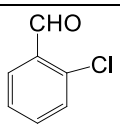
Antimicrobial agents were discovered and developed, resulting in a wide range of chemicals. Quinoline derivatives, for example, are still an important family of therapeutically beneficial antibacterial medicines for infectious disorders like TB. [5–7] Modern chemistry has a huge difficulty in developing a simple process for the manufacture of heterocyclic molecules. Quinoline is a kind of heterocyclic molecule that is present in many natural goods. Many synthetic antimalarial drugs, including chloroquine [8], have been designed using the quinoline structure as a starting point. Blood flukes (Schistosoma mansoni), a common source of sickness in tropical areas, are treated with the tetrahydroquinoline derivative oxamniquine [9]. Quinoline-containing compounds have a wide range of biological actions [10-13], including antifilarial [14], antibacterial [15, 16], and antimalarial [17-22]. DHA topoisomerase II inhibitor [23], lipoxygenase inhibitor [24], and kinase inhibitor [25] are examples of these derivatives that have been widely employed as new inhibitors. Quinoline compounds are widely employed as receptor agonists [26-30], cardio-vascular agents [31], and anticancer drugs [32].

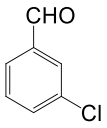
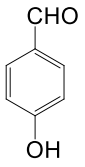
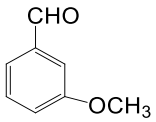
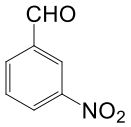
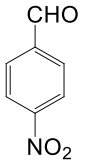
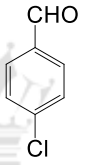
EXPERIMENTAL:



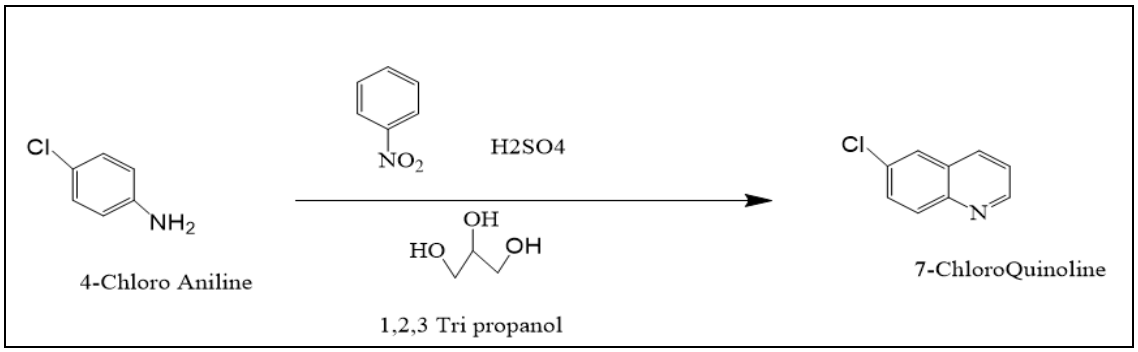
Scheme 1: Synthesis of 7-chloroquinoline-3-carbohydrazide

Table 1:- Lists of Aldehydes

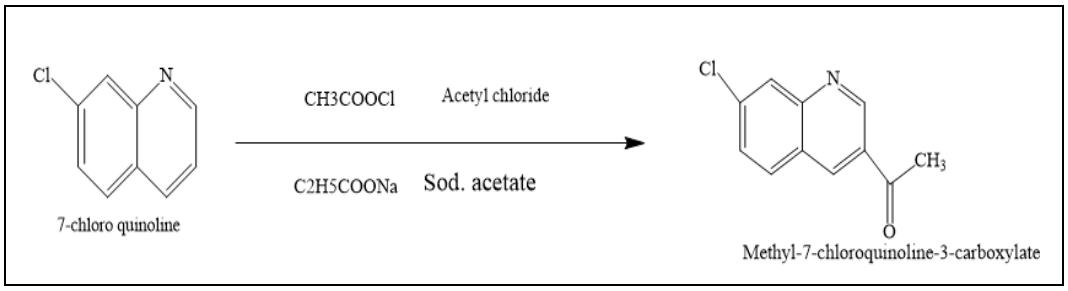
S. No.	R - Aldehyde Name	Structure
Comp -I	Benzaldehyde	
Comp -II	3-Bromo Benzaldehyde	
Comp -III	4-Bromo Benzaldehyde	
Comp -IV	2-Chloro Benzaldehyde	

Comp –V	3-Chloro Benzaldehyde	
Comp –VI	4-Hydroxy Benzaldehyde	
Comp –VII	3-methoxy Benzaldehyde	
Comp –VIII	3-Nitro Benzaldehyde	
Comp –IX	4-Nitro Benzaldehyde	
Comp -X	4-Chloro Benzaldehyde	

1) Synthesis of 7-chloroquinoline: Taken equimolar (1 mol) quantity of 4-chloro aniline. Then added equimolar (1 mol) solution of 1,2,3 tripropanol by continuous shaking and heating in a conical flask of 500 ml. this reaction is carried out in presence of H2SO4 and added Nitrobenzene in the proper amount. After 30 min of vigorous shaking and gentle warming 7-chloro quinoline is synthesized (33).



2) Synthesis of methyl-7-chloroquinoline-3-carboxylate: The 7-chloro quinoline in equimolar (1 mol) 10 gm quantity is treated with pyridine in a conical flask and continuous shaking. And then added about 10 ml acetyl chloride about 1 ml at a time the reaction is exothermic so it should be cooled and maintain the temp. Below 10oC. After the addition of all the acetyl chloride, the flask is cooled and mixed with 200 ml of ice water. The fine granule of methyl-7-chloroquinoline-3-carboxylate is separated and the crystal is then filtered off on vacuum filter assembly (33).



3) Synthesis of 7-chloroquinoline-3-carbohydrazide: Make the 1 molar solution of Methyl-7-chloroquinoline-3-carboxylate in purified water the this solution is treated with 1 molar solution of hydrazine hydrate in the presence of ethanol and KOH, the equal volume of all solution is taken in 500 ml beaker on a magnetic stirrer and this solution is heated slightly on the water bath for 30 min. then this solution is cooled on an ice bath the fine flakes of 7-chloroquinoline-3-carbohydrazide are precipitated slowly. The compound is filtered on a vacuum pump. Then the compound is washed with cold water to get a pure crystal of 7-chloroquinoline-3-carbohydrazide (33).

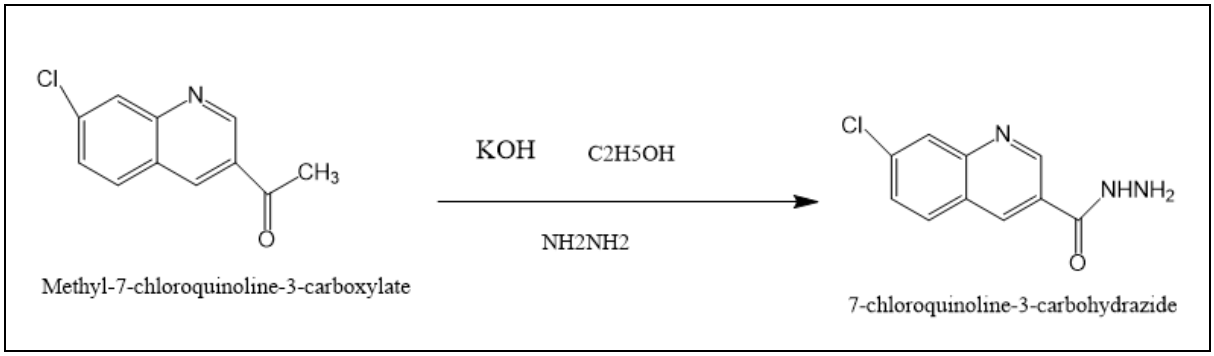


Table 2: Physicochemical parameter of 7-chloroquinoline-3-carbohydrazide

Molecular Formula	$C_{10}H_8ClN_3O$
Molecular Weight	221.64
Melting Point	240-245 ^0C
Percentage Yield	74%

General Procedure for the Preparation of Schiff Bases Compound- (comp 1-10):- An equimolar solution of 7-chloroquinoline-3-carbohydrazide 2.21gm (0.01mol) is dissolved in 10 ml of ethanol and in this solution various substituted aldehydes are added in equimolar qty (0.01mole) and then added 4-6 drops of glacial acetic acid. this reaction mixture is carried out under reflux for 10 h. After cooling to room temperature this solution was added to ice-cold water. The compound gets separated as solid crystalline powdered then the compound is filtered. After filtration, the compounds are dried and recrystallized with ethanol. The melting point is noted in °C, and the yield is mentioned in %. And all the other compounds are prepared by using the same procedure as above (33).

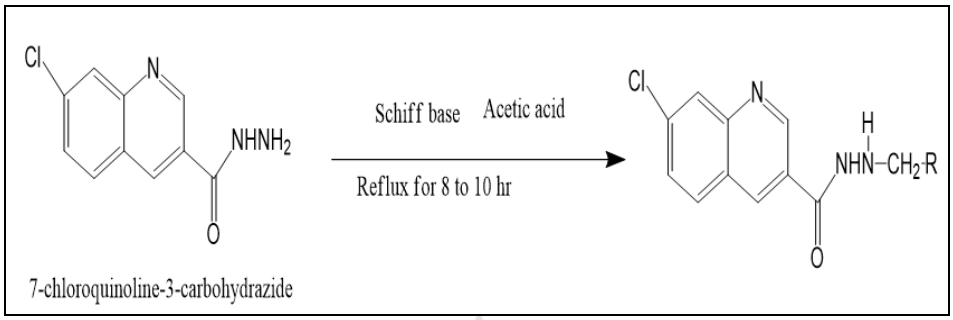
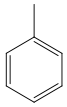
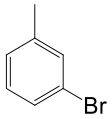
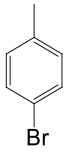
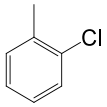
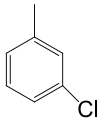
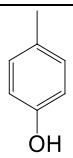
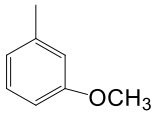
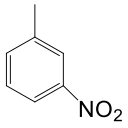
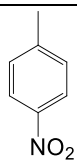
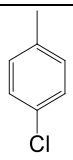


Table 3: Physico-Chemical Parameter Of Quinoline Derivatives

S. No.	Compound Code	R	Molecular Formula	Molecular Weight	Melting Point (^{O}C)
1	Comp –I		$C_{17}H_{14}ClN_3O$	311.77	224.6
2	Comp –II		$C_{17}H_{13}BrClN_3O$	390.66	214.76
3	Comp –III		$C_{17}H_{13}BrClN_3O$	390.66	243.65
4	Comp –IV		$C_{17}H_{13}Cl_2N_3O$	346.21	225.7
5	Comp –V		$C_{17}H_{13}Cl_2N_3O$	346.21	223.6

6	Comp –VI		$C_{17}H_{14}ClN_3O_2$	327.76	235.6
7	Comp –VII		$C_{18}H_{16}ClN_3O_2$	341.79	216.7
8	Comp –VIII		$C_{17}H_{13}ClN_4O_3$	356.76	225.8
9	Comp –IX		$C_{17}H_{13}ClN_4O_3$	356.76	228.5
10	Comp -X		$C_{17}H_{13}Cl_2N_3O$	346.21	238.9

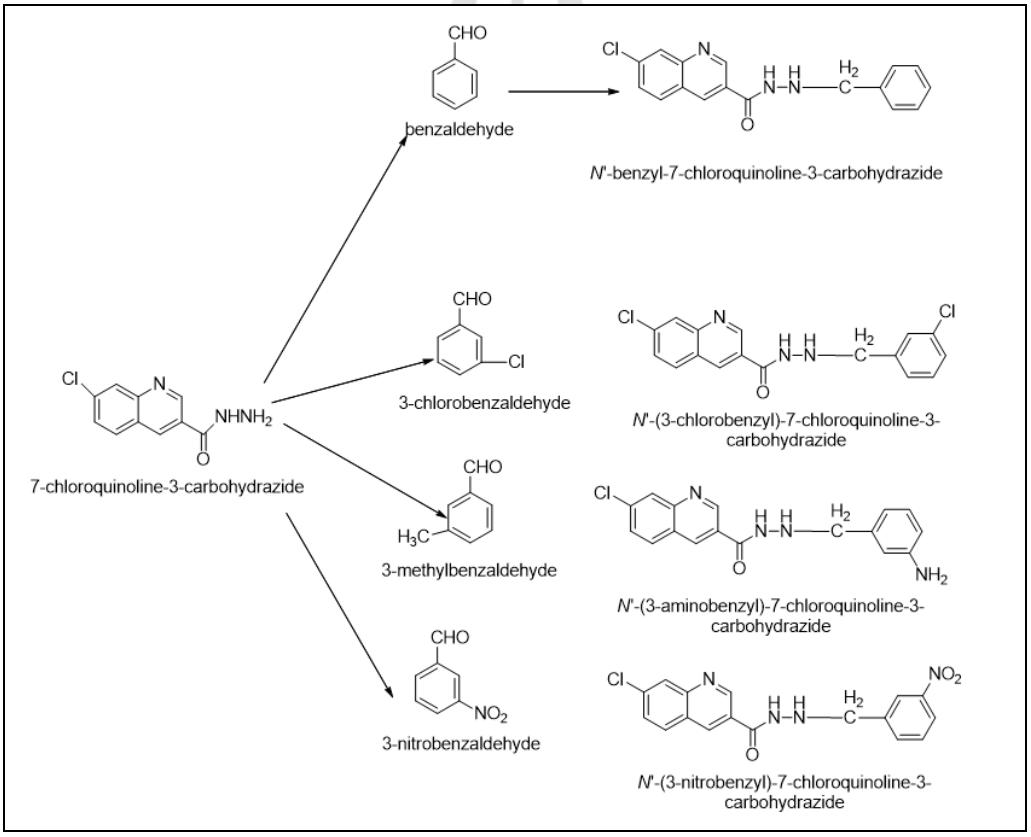
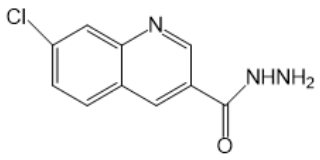


Figure 1: 7-chloroquinoline-3-carbohydrazide derivatives



7-chloroquinoline-3-carbohydrazide

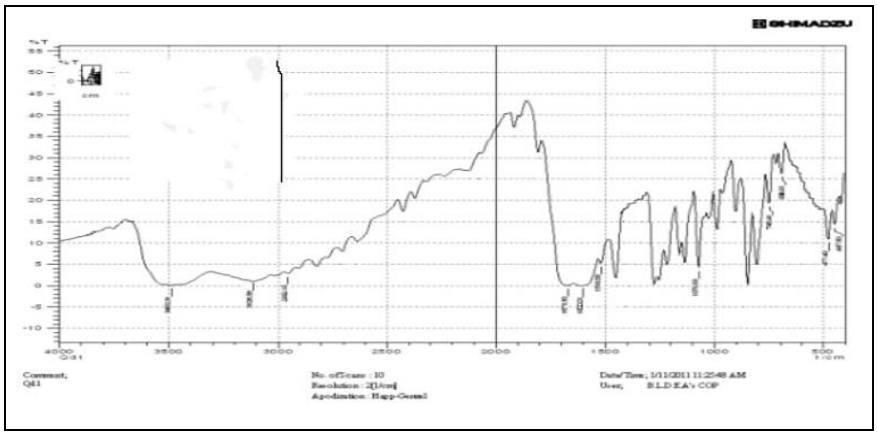


Figure 2: IR Spectra of 7-chloroquinoline-3-carbohydrazide

PHARMACOLOGICAL EVALUATION OF VARIOUS QUINOLINE DERIVATIVES:

Anti-Bacterial Activity: All the compounds synthesized in the present investigation were screened for their antibacterial activity by Cup plate Method. Antibacterial activities were tested on nutrient medium against, Staphylococcus aureus, and Escherichia coli which are representative types of Gram-positive and Gram-negative organisms respectively. The antibacterial activity of the compounds was assessed by the disc-diffusion bmethod.

Preparation Of Discs: Discs of 6-7 mm in diameter were punched from No: 1 Whattmann filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at 140 °C for 60 minutes. Then standard and test solutions were added to each disc and discs were air-dried.

Method Of Testing: The sterilized media was cooled to 45 °C with gentle shaking to bring about uniform cooling and then inoculated with 18-24 hrs old culture under aseptic conditions, mixed well by gentle shaking. This was poured into sterile Petri dishes (properly labeled) and allowed the medium to set. After solidification, all the Petri dishes were transferred to a laminar flow unit. Then the discs which were previously prepared were carefully kept on solidified media by using sterilized forceps. These Petri dishes were kept as

it is for one-hour diffusion at room temperature and then for incubation at 370C for 24 hours in an incubator. The extent diameter of inhibition after 24 hours was measured as the zone of inhibition in millimeters and the results. [34]

Methods used for screening: In screening, the test compounds were first dissolved in sterile Dimethylformamide (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 a membrane filter of 0.2u, as its boiling point is below 121oC 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 was also tested as a control.

Anti-Fungal Activity: The broth double dilution method was used to evaluate the minimal inhibitory concentration (MIC) of the test compounds the classical method yields accurate, precise and quantitative results for the amount of antimicrobial agent that is needed to inhibit growth of microorganisms. Determination of minimum inhibitory concentration (MIC) by broth double dilution method.

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

✓ Drug control- Ketoconazole as reference standard was used.

✓ Solvent control DMF and DMSO were used as solvent controls.

- Sabourauds Dextrose Broth (SDB) and Malt extract Glucose Yeast extract peptone broth (MGYP) were used as nutrient medium for growth of the micro organism and MIC determination for C. albicans.
- All the compounds were dissolved in DMF and standard dissolved in DMSO.
- All the compounds were serially diluted.
- Test compounds were dissolved in sterile DMF and Ketoconazole was dissolved in the sterile DMSO.
- The test compounds and standard drug solution were diluted using Sabourauds Dextrose Broth (SDB) and Malt extract Glucose Yeast extract peptone broth (MGYP) so as to get the required concentration.

- To serially diluted the solution, test organisms were added using saline solutions or broth.
- Then the plates were incubated at 37 °C for 48 hrs.
- The growth of microorganisms in the test compound solutions and control drug was seen after incubation. [35]

RESULTS AND DISCUSSION:

- All the reactions were monitored by TLC, structure, and purity of the anticipated compounds were characterized by physical constant and FTIR spectral studies initially followed by NMR and Mass spectroscopy.
- From the TLC we ensured to declare the completion of reaction. The TLC plates were visualized either by iodine vapors or by viewing in a UV chamber. The reaction products of all the reactions were purified by different workup processes to remove unreacted starting material if any and recrystallization using suitable solvents.
- From the literature survey it reveals that quinoline have been reported for number of pharmacological activities and some molecules have shown significant activities and some compounds shows moderate and good activities.
- The synthesized all quinoline derivatives were screened for anti bacterial activity using DMF as a solvent against the organisms, S. aureus and E. coli. And antifungal activity using Candida albicans. By disc diffusion method on nutrient agar media. The standard drug used was ciprofloxacin for antibacterial and Ketoconazole as standard for antifungal activity.
- The antimicrobial screening results presented on above table reveals that compounds Comp-1, a Comp-2, Comp-3 and Comp-4 exhibited poor activity at 50µg/ml, but at 100µg/ml they have shown medium activity against S. aureus, and medium activity against E. coli. And Comp-5, Comp-6, Comp-7, Comp-8, Comp-9 and Comp-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 Comp-2, Comp-3 Comp-6, Comp-9, and Comp-10 compounds Showed the 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. The Discussion part mainly deals with the synthesized compounds against the antibacterial and antifungal activity.

- The Comp-5, Comp-6, Comp-7, Comp-8, Comp-9, and Comp-10 have shown good antibacterial activity due to the presence of electron-donating group OCH_3, OH, Cl group which is attached to the phenyl ring.

- The anti-fungal activity shows that Comp-2, Comp-3 Comp-6, Comp-9, and Comp-10 have shown good antifungal activity it also may be due to the presence of electron-donating group OCH_3, OH, CH_3 and Cl group which is attached to the phenyl ring system.

CONCLUSION:

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

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