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Research Article

A COMPARATIVE STUDY OF SYNTHESIS, CHARATERISATION AND PHARMACOLOGICAL EVALUATION OF FEW QUINOLINE BASED PRECURSORS

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ABSTRACT

Quinoline molecule is synthesized with the substituents at 2nd and 3rd positions, its Schiff bases are derived from 3-formyl-2-mercaptoquinoline and substituted anilines. The prepared Schiff bases have been characterized by elemental analysis, IR, ^{1}H-NMR and mass studies. The compounds have been screened in vitro for antibacterial and antifungal activities by MIC methods. The results have indicated that the biological activity increases and bacterial activity is more as compared to the fungicidal activities. The brine shrimp bioassay was also carried out to study the in vitro cytotoxicity properties of the compounds. One compound has exhibited good activity against H37Rv strain. Only two compounds have exhibited potent cytotoxic activity against *Artemia salina*. Quinoline derivatives at these positions may be promising agents in future pharmacological and medicine applications.

INTRODUCTION

Quinoline a heterocyclic base has proven its potential as anti-inflammatory, analgesics, anti-convulsant, antibacterial, antipyretic, antihypertensive and interferon inducing activity which are reported recently[1]. The synthetic applications of 2-chloro-3-formyl-quinoline have been reported by Meth-cCln *et.al*.[2]. Quinoline derivatives with various substitutions at C-3 position have been synthesized and reported for their analgesic, anti-inflammatory and anti-pyretic activities [3]. Many schiff bases derived from 2-chloro-3-formyl-quinoline have been reported for their antifungal activities [4] and as potential biodynamic agents[5]. The conversion of aryl quinolines into mercaptoquinolines is of vital importance in synthetic chemistry. The ring substituted analogues are important starting materials to construct sulfur containing heterocycles, such as thiophene, thiopyrans, etc., and are fused with a quinoline moiety, with important functional groups, such as –COOR,-COR,-CN and –CONHR, at appropriate positions.[6] These functional groups have been utilized to build various pharmaceutically important heterocycles[7-10].

The Schiff bases derived from 3-formyl-2-mercaptoquinoline have also proven to be important pharmaceutical agents [11-13]. Quinoline derivatives have proven their significance by entering into the field of diagnosis of wide variety of disease like heart disease, brain disorder, cancer, diabetics, tissue hypoxia etc and also to detect the multi-drug resistance. Use of the metal complexes as diagnostic agents is a relatively new area of medicinal research and has flourished rapidly from last 4-5 decades [14-16]. The above facts have promoted us with the present studies on the synthesis, characterization, pharmacology and their comparison studies derived from of quinoline and its schiff bases.

MATERIALS AND METHODS

All chemicals used were of reagent grade and further used without purification. Elemental Analyses (C, H and N) were performed on a Perkin- Elmer 2400 CHN elemental Analyzer Model 1106, Carloerba Strumentazione. The IR spectra of compounds were recorded on a HITACHI-270 IR spectrophotometer in the 4000-250 cm^{-1} region in KBr disks. The proton PMR spectra were recorded in $CDCl_3$ on BRUKER

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300 MHz spectrometer at room temperature using TMS as an internal reference. Mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system using Argon/Xenon (6 KV, 10Am) as the FAB gas. The accelerating voltage was 10 KV and the spectra were recorded at room temperature m-Nitrobenzyl alcohol was used as the matrix.

Synthesis of Quinoline derivatives

General method for the synthesis of compounds

Preparation of 2-chloro-3-formyl-quinoline **(CFQ)** synthesized by the reaction of acetanilide with Vilsmier reaction at 80^0C [19]

Preparation of N-2-chloroquinoline-3-ylmethylene aniline **(SBQ)**

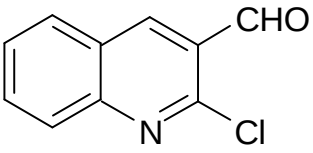
A mixture of 1.064g (0.004 mole), of 2-chloro-3-formyl-quinoline and 0.37ml (0.004 mole) of aniline in ethanol-acetic acid mixture (20ml) (2:1) was stirred at room temperature for 6 hours. After the completion of the reaction (7hours), the solid separated was filtered, washed with excess of cold ethanol, dried and crystallized from ethanol. Slow Evaporation Technique was used to grow the crystals, suitable for diffraction studies in the benzene and ethyl acetate mixture. Yellow colored crystals (benzene+ethyl acetate), yield=92.24%, M.P=162-163^{0}C.

Preparation of hydroxy SBQ and its substituent

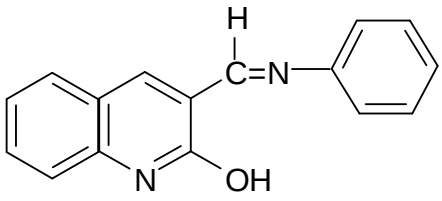
A mixture of above prepared substituted **(SBQ**) (0.01mole) and thiourea (0.01mole) in 20 ml ethanol + ether mixture (2:1) was refluxed on a water bath for 10 hours, the reaction was followed and monitored by TLC (benzene + ethyl acetate) after completion of the reaction (9 hours) the solid separated was filtered, washed with excess of cold water and then dissolved in 15 ml of 5% NaOH solution. Finally the compound formed was isolated by careful addition of HCl. The pale yellow colored compound obtained was filtered, washed with excess of cold water, dried and recrystallised from acetic acid.

Pale yellow crystalline solid (Acetic acid); yield: 78.30%; m.p.291-293; (Fig. 1-3).

Fig. 1

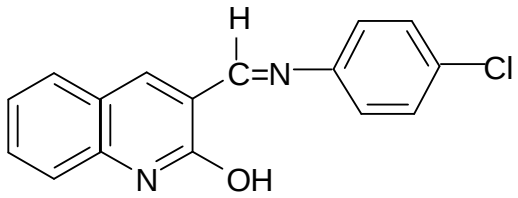


A Structure of CFQ



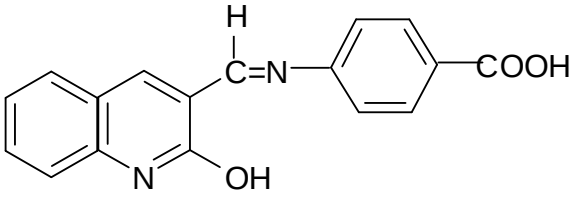
PHQT

B Structure of PQT



CPHQT

C Structure of CPQT



BPHQT

D Structure of BPQT

RESULTS AND DISCUSSION

Chemistry

The synthesized compounds are colored and show solubility in respective solvents.

Table 1 Analytical, magnetic and conductance data of the Quinoline derivatives and transition metal complexes

Formula	Code	C%	H%	N%	S%	Cl%
CFQ	I	62.48 (62.82)	3.03 (3.14)	7.23 (7.32)		18.98 (18.56)
SBQ	II	71.38 (71.80)	4.23 (4.13)	10.32 (10.52)		13.64 (13.32)
PQT	III	72.48 (72.73)	4.43 (4.55)	10.23 (10.61)	11.98 (12.12)	-
CPQT	IV	63.88 (64.12)	3.92 (4.01)	9.11 (9.38)	10.43 (10.72)	11.67 (11.88)
BPQT	V	66.06 (66.23)	3. 56 (3.89)	8.83 (9.09)	10.07 (10.39)	-

They are sparingly soluble in common organic solvents; however, are soluble to a larger extent in DMF and DMSO. The elemental analyses Table.1 are consistent with a stoichiometry of the compounds.

Infrared spectra

The Infrared spectral data of the ligands are listed in Table 2. A high intensity band observed *ca.* 1610 cm^{-1} is attributed to the ν(C=N) vibration. This fact renders the proof for the formation of Schiff base. The low intensity bands arriving in the region of 700-600 cm^{-1} are assignable to the fact of the formation of C-S bonds and further the absorption bands between 2000 and 2500 cm^{-1} indicating the S-H bonding. [22]. Medium intensity bands in the 1600 – 1590 cm^{-1} region are regarded as a combination of C=N and C=C stretching vibrations of aromatic ring. A high intensity band is present in the 1700 – 1730 cm^{-1} region was assigned to $\nu_{C=O}$(lactone

carbonyl) of the COOH group with an additional band around 3100cm^{-1} to the $\nu_{(O-H)}$ vibration of the carboxylic group.

Table 2 Infrared spectral data of Schiff bases and their metal complexes in cm^{-1}

Sl.No.	Formula	$\nu_{(C-S)}$	$\nu_{(C=N)}$	$\nu_{(C-N-C)}$
1	CFQ	628	1626s	990m
2	SBQ	644	1625s	1001m
3	PQT	643	1623s	1002m
4	CPQT	634	1620s	999m
5	BPQT	678	1622s	1004m

PMR spectra

The Schiff bases exhibit the characteristic resonance at 8.17 ppm due to the azomethine proton. A singlet corresponding to one proton observed at 6.5 ppm is probably due to SH group. Hydrogen bonding leads to deshielding and to an increase in the frequency of the PMR signal of the hydrogen bonded proton. This may explain the observed increase in the chemical shift. The sharp multiplet signals of the phenyl protons are found in the region 6.4-7.6 ppm.

Biology

The antibacterial activity of the compounds were assayed against two bacteria namely, *Escherichia Coli* and *Bacillus Subtilis* by with concentration of 100µg/mL by spread plate method. Similar procedure was followed for the antifungal activity of the above said ligands and metal complexes against two fungi namely, *Candida Albicans* and *Fusarium Solani.* The activity was also assayed for the pure solvent DMF and the standard Norfloxacin for each of antibacterial and Grisiofulvin for antifungal cultures. Further for the active compounds MIC values were determined. Final adjustments were made using optical density measurement for bacteria (absorbance 0.05 at a wavelength of 580nm). For the cytotoxicity study brine shrimp (*A.Salina. L)* eggs were hatched in a shallow rectangular plastic dish (22X32cm), filled with artificial seawater. The antitubercular screening was carried out by Middle brook 7H9 agar medium against H_{37}Rv.

A*ntibacterial and antifungal activities*Antibacterial and antifungal activities of synthesized compounds (**I –V**) were tested against two bacteria such as *S.Aurease* , *Escherichia.Coli* and two fungi *A.Niger*, *C.Albicans*, Norfloxacin for bacteria and Grisiofulvin for fungi were used as standard drugs. The zone of inhibition in mm for compounds are presented in Table III. From the data of it is clear that the cholro exhibit higher antimicrobial activity than that of the non chloro molecules. The compounds were found to be more susceptible towards the bacterial strains as compared to the fungal strains.

Table III Antibacterial and antifungal activity of the compounds (zone of inhibition in mm for 100 µg/mL)

Compound Code	Antibacterial		Antifungal	
	S..Aurease	*E.coli*	*A.niger*	*C. Albicans*
CFQ	19	18	17	15
SBQ	20	21	18	17
PQT	19	20	16	15
CPQT	22	23	16	17
BPQT	19	20	15	14
Norfloxacin	24	24	--	--
Grisiofulvin	--	--	24	24
DMF	04	04	04	04

The compounds SBQ, and CPQT were most active and r compounds **CFQ**, PQT and CPQT were slightly active towards the bacterial strains.

The MICs of the active compounds were carried out as described by Clause [23] with minor modifications. Antifungal activities of the yeast were performed by following the guideleines in NCCLs document M27-A using the microdilution broth method [24]. Solutions of the test compounds and reference drug were dissolved in DMF as a concentration of 12.5 µg ml^{-1}. The twofold dilution of the compounds and reference drug were prepared (6.25, 3.12, 1.56, 0.78,) µg ml^{-1}. The broths were maintained at pH 7.2 with an innoclum of (1-2) X 10^3 cells ml^{-1} by the spectrophotometric method and an aliquot of 100 µl was added to each tube of the serial dilution. The chemical compounds-broth medium serial tuvel dilutions inoculated with each bacterium were incubated on a rotary shaker at 37 ºC for 24 h at 150 rpm. The minimum inhibitory concentrations of the active compounds were recorded as the lowest concentrations of each chemical compounds in the tubes with no growth (i.e. no turbity) of inoculated bacteria and yeast.

The MICs values are shown in Table IV. Only the active compounds **SBQ** and **CPQT,** were evaluated for their minimum inhibitory concentrations. The compounds have shown potent activity towards the bacterial strains as compared to fungal strains. The compounds are more susceptible towards the bacterial strains rather than fungal strains. The halogenated derivatives have shown have activities. Compound **CPQT** was most active exhibiting a MIC value of 0.78 µg / mL active compounds in medium against the bacterial strains. The activities of other compounds are in the range of 3.12-1.56 µg / mL for the bacterial strains.

Table IV MICs* values of the some active compounds.

Compuond Code	Antibacterial		Antifungal	
	S..Aurease	*E.coli*	*A.niger*	*C. Albicans*
CFQ	6.25	6.25	12.5	6.25
SBQ	3.12	1.56	6.25	6.25
PQT	3.12	3.12	6.25	12.5
CPQT	1.56	1.56	12.5	6.25
BPQT	3.12	3.12	6.25	3.12
Grisiofulvin	--	--	1.56	1.56
Norfloxacin	1.56	1.56	--	--

*MICs values were determined as µg / mL active compounds in medium.

Antitubercular assays

The antitubercular screening was carried out by Middle brook 7H9 agar medium against H_{37}Rv Strain [25,26]. Middle brook 7H9 agar medium containing different derivatives **(I-V)**, standard drug as well as control.

Table V Antitubercular Activity*of the compounds. (zone of inhibition in mm)

Code	50 µg/ml	100 µg/ml	150 µg/ml
CFQ	R	R	S
SBQ	R	R	S
PQT	S	S	S
CPQT	R	S	R
BPQT	R	R	S
Standard	S	S	S

*Standard drug: Streptomycin; **R**-Resistance; **S**-Sensitive.

Only compound **PQT** have shown promising activity for this assay. All the other compounds were inactive for this assay (Table V)

Cytotoxicity Bioassay (in vitro studies)

In the present study brine shrimp (*A.Salina. L)* eggs were hatched in a shallow rectangular plastic dish (22X32 cm), filled with artificial seawater, which was prepared [27] with commercial salt mixture and double distilled water. An unequal partition was made in the plastic dish with the help of a perforated device. 50mg of eggs were sprinkled approximately into the large compartment, which was darkened while the matter compartment was opened to ordinary light. After two days, nauplii were collected by a pipette from the lighter side. By dissolving 20mg of each compound in 2ml DMF the samples were prepared. From the stock solutions, 500,50,5µg/mL were transferred to vials (three for each dilution were used for each test sample and LD_{50} is the mean of the three values) one vial was used to as a control with only 2mL DMF and another with the above concentrations of *Bleomycin* as a standard. The solvent was allowed to evaporate overnight. After two days, when shrimp larvae were ready, 1mL of seawater and 10 shrimps were added to each vial (25 shrimps/dilution) and the volume was adjusted with seawater to 5 ml per vial. After 24 h, the numbers of survivors were counted. Data were analyzed by Finney computer program to determine the LD_{50} values [28].

For the active compounds were screened for their cytotoxicity (brine shrimp bioassay) using protocol of Meyer et al. Only four compounds **SBQ**, **PQT** and **CPQT** have exhibited potent cytotoxic activity against *Artemia salina* while all the other compounds were almost inactive for this assay (Table VI).

Table VI Brine shrimp bioassay data of the some active compounds.

Compound Code	LD_{50} (M/ml)
SBQ	5.034×10^{-4}
PQT	6.918×10^{-4}
CPQT	5.187×10^{-4}

CONCLUSIONS

With help of various physico-chemical techniques, geometries of the newly synthesized compounds have been proposed. The compounds **SBQ**, and **CPQT** were found most active and susceptible towards the bacterial strains. The compound **PQT** has shown promising activity against $H_{37}Rv$ Strain for antitubercular assay. The compounds **SBQ**, **PQT** and **CPQT** have exhibited potent cytotoxic activity against Artemia salina with lower LD_{50} values.

Due to insolubility in water and common organic solvents and in fusibility at higher temperatures all the compounds are thought to be polymeric in nature. The tentative structures for the compounds (Fig. 1) were based on elemental analyses, IR, ^1H NMR, and Mass spectral studies.

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