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RESEARCH ARTICLE

In Vitro Antibacterial Study of Synthesized 3-Quinolinecarbaldehyde through Vilsmeier Haack Cyclisation of N-Arylacetamide and their Hydrazones

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ABSTRACT

We reported the synthesis and *in vitro* study of 3-Quinolinecarbaldehyde through Vilsmeier Haack cyclisation of N-arylacetamide and their hydrazones. All the intermediates were confirmed by reported physical constants. The synthesized hydrazones were characterized by IR and NMR. They were further tested for their *in vitro* antibacterial activity. Results show that the antibacterial activity of the compound increases logarithmically with an increase in concentration. Although all 3 samples show a similar type of inhibition pattern but QSB3 exhibits more antibacterial activity as compared to other samples.

KEYWORDS

3-Quinolinecarbaldehyde, Hydrazones, N-Arylacetamide, Antibacterial Agents

INTRODUCTION

Chemistry of heterocyclic compounds has evolved with a great place in recent times because of their diverse applications, ease of synthesis and rich distribution in natural sources. Heterocyclic compounds play an important role in Medicinal Chemistry.

Many antibiotics including penicillin and streptomycin also contain heterocyclic ring system. Many pigments such as indigo, hemoglobin and anthocynin are also heterocyclic compounds. Important drugs such as suphathiazol, pyrethrin, rotenine, cocaine, barbiturates also possess heterocyclic system. These compounds are also known to be used as starting material for the synthesis of new drugs.

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Synthetic method for obtaining heterocyclic compound may be divided into ring closure reaction, addition reaction and replacement reaction[1-6].

Quinoline and various analogs of quinoline are well known class of compounds with important biological activities like Antimicrobial[7], anti-inflammatory[8], antileishmanial[9], antituberculosis[10], antimalarial[11], cytotoxicity[12] and HIV-1 Integrase Inhibitors[13]. Naturally occurring quinoline alkaloids and quinoline containing synthetic analogues have played a significant role in medicinal chemistry. Quinoline derivatives have been developed for the treatment of many diseases like malaria[14], HIV[15], tumour[16] and antibacterial infections[17].

Recently, substituted quinolines have also been reported to act as antagonists for endothelin[18], 5HT3[19], NK-3[20] and leukotriene D4 receptor[21]. They also function as inhibitors of gastric

(H+/K+)-ATPase[22], dihydroorotate dehydrogenase[23] and 5-lipoxygenase[24].

Compounds containing azomethine group (-CH=N-) is known as Schiff bases. Schiff bases are very important synthetic conjugates which can be prepared with greater flexibility in reaction conditions as well as pharcamophores of varied nature and activity can be joined together to create newer hybrid compounds with improved activity. Literature survey shows that many Schiff bases exhibit biological activities such as antifungal[25], antibacterial[26], antitumor[27] anti-inflammatory[28].

The main objective of present work is to synthesize 3-quinolinecarbaldhyde by the cyclisation of N-arylacetamide through Vilsmeier Haack reaction for the synthesis of some hydrazones of 3-quinolinecarbaldhyde with different acid hydrazides and *in vitro* evaluation of these synthesized hydrazones for the antibacterial activity.

MATERIALS AND METHOD

Solvents for synthesis were reagent grade and dried by standard procedures. The starting materials such as Aniline, DMF, $POCl_3$, Triflouro acetic acid, acetic anhydride acetone, methanol, ethanol and dichloromethane were obtained from SD-FCL Chemical Limited, Mumbai, India. 4-hydroxy benzoic acid hydrazide, 3-hydroxy naphthoic acid hydrazide and isoniazide were obtained from Sigma-Aldrich chemicals. All compounds were routinely checked by TLC on silica gel G plates using petroleum ether/ethyl acetate (7:3; 6:4; 5:5 etc. by V/V) as solvent system and the developed plates were visualized by UV light and iodine vapours. The detailed synthesis has been shown in Figure 1.

Step-1: Preparation of N-arylacetamide from Aniline

Aniline (10 mmol) was added into the water (50 ml) to produce heterogenous suspension which becomes homogenous after addition of 6N HCl (5 ml) with continuous stirring. The resulting homogenous solution was cooled in an ice bath. In the above solution acetic anhydride (10mmol) was added followed by the addition of solid sodium bicarbonate until there was no effervescence. The precipitated product filtered and dried and finally dried in vacuum desiccators.

Step-2: Preparation of 2–Chloro-3-Quinolinecarbaldehyde from N-arylacetamide

Dimethyl formamide (9.13 gm, 0.125m) was cooled to 0˚**C** in a flask equipped with a drying tube and phosphorus oxychloride (53.7 gm, 32.2ml) was added drop wise with stirring to this solution N-aryl acetamides (0.05M) was added and after 5 min the solution was kept under reflux for 16 hrs. The reaction mixture was poured in to ice water (300 ml) and stirred for 30 min at 0-10˚C. When substituted chloro quinolines separated as yellow precipitate, it was filtered, washed with water. It was recrystalized from ethyl acetate into yellow needles M.P. 260˚C, yield 5.5gm.

Step-3: Preparation of 2–Hydroxy-3-Quinolinecarbaldehyde from 2–Chloro-3-Quinolinecarbaldehyde

A mixture of chloroquinolines (0.01 M) and aqueous hydrochloric acid (35 ml; 4 M) was heated under reflux for 4 hrs and then allowed to cool at room temperature. The mixture was poured on to crushed ice. When hydroxy quinolines separated as yellow solid, it was filtered, washed and dried. It was recrystalized from aqueous acetic acid in to yellow sticky needles, M.P. 305˚C yield 1.60 gm.

Step-4: Preparation of 2–Hydroxy-3-Quinolinecarbaldehyde Hydrazones from 2–Hydroxy-3-Quinolinecarbaldehyde

The Schiff's bases were synthesized by condensing 2–Hydroxy-3-Quinolinecarbaldehyde with different acid hydrazides as explained by Anees Pangal et al[29].

The *in vitro* antibacterial activity was performed according to procedure explained by Arpit et al[30]. A standardize inoculums were inoculated with the help of a sterile cotton swab on the surface of the agar plate. Disc of antimicrobial agents were placed on the surface of agar plate.

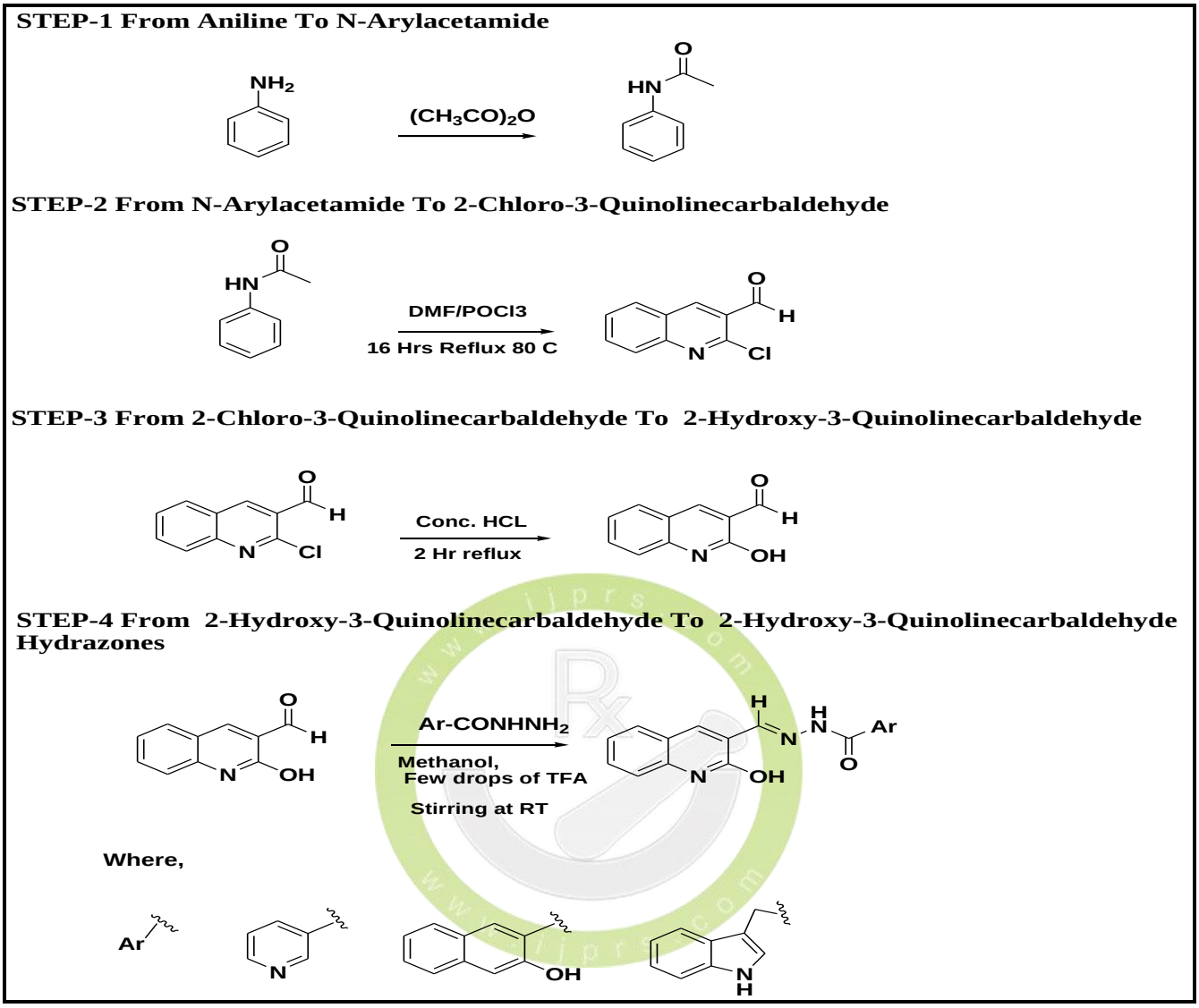


Figure 1: Detailed Scheme for the synthesis of 2–Hydroxy-3-Quinolinecarbaldehyde Hydrazones

The plates were incubated at 37°C for 24 hours and susceptibility is determined on the basis of zone of inhibition. A standard and control strain was also tested for comparison. The diameter of the zone of growth inhibition around each disc were measured and compared with zones of inhibition of standard and control.

RESULTS AND DISCUSSION

Melting points of the synthesized compounds were determined with open capillary tube on a VEEGO melting point apparatus.

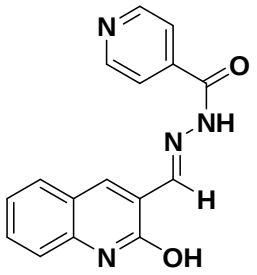
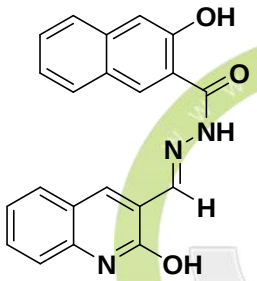
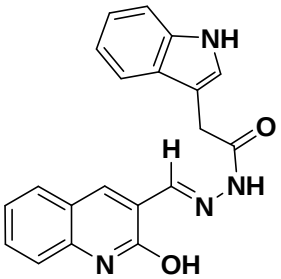
The H^1-NMR was recorded on a 600 MHz at IISc Bangluru.

IR spectra were recorded by "FT- IR Jasco" spectrometer at the centre. The structures of the synthesized compounds have been established on the basis of physical and spectral data. They shows a prominent absorption of -(C=N-) in FTIR. The detailed preliminary analysis of spectral properties is summarized in following Table 1.

Antibacterial Activity

The chemically synthesized compounds were tested for antimicrobial activity. Strains of both Gram positive and Gram negative bacteria were used for experimentation.

Table 1: Summarized Results of Spectral Analysis

Sr. No.	Name	Structure of Hydrazones	Yield (%)	M. P. (˚c)	Spectral Properties
1	QSB1	 (E)-N'-((2-hydroxyquinolin-3-yl)methylene)isonicotinohydrazide	78%	202˚C	**FTIR (cm^{-1}):**1095(C-O), 1647.56 (-C=N), 3195.86 (-NH), 3051.27 (-OH), 2958.27 (-CH), 1660.41 (-C=O), 1057.03 (-N-N), 1500 to 1600 (Aromatic region). **H^1-NMR** (*dmso)* (δ, ppm,): 12.1 (s, 1H, -OH), 12.05 (s, 1H, NH), 9.05 (s, 1H, -CH=N), 8.95 (s, 1H), 8.40 (d, 2H), 8.30 (m, 3H), 8.0 (d, 1H), 7.90 (t, 1H), 7.70 (t, 1H)
2	QSB2	 (E)-3-hydroxy-N'-((2-hydroxyquinolin-3-yl)methylene)naphthalene-2-carbohydrazide	80%	196˚C	**FTIR (cm^{-1}):**1095(C-O), 1647.56 (-C=N), 3265.86 (-NH), 2958.27 (-CH), 1660.41 (-C=O), 1057.03 (-N-N), 3051.27 (-OH), 1500 to 1600 (Aromatic region), 2958.27 (-CH). **H^1-NMR** (*dmso*) (δ, ppm,): 7.25 (s, 1H), 7.35(dd, 2H), 7.65(q, 2H), 7.8(dd, 2H), 7.1(t, 2H), 8.45(d, 2H), 8.7(s, 1H), 11.4(s, 1H, -OH), 12.1(s, 1H, -OH), 12.3(s, 1H, -NH)
3	QSB3	 (E)-N'-((2-hydroxyquinolin-3-yl)methylene)-1H-indole-3-carbohydrazide	70%	320˚C	**FTIR (cm^{-1}):**1095(C-O), 1647.56 (-C=N), 3265.86 (-NH), 2958.27 (-CH), 1660.41 (-C=O), 1057.03 (-N-N), 1500 to 1600 (Aromatic region). 3051.27 (-OH) **H^1-NMR** (*$CDCl_3$*) (δ, ppm): 7.25 (m, 4H), 7.35(dd, 1H), 7.65(dd, 1H), 7.8(dd, 1H), 7.1(t, 1H), 8.7(s, 1H), 7.25 (s, 1H, olefinic), 6.9 (s, 1H), 11.4 (s, 1H, indolic -NH), 3.5 (s, 2H), 12.3(s, 1H, -NH), 11.4(s, 1H, -OH)

Amoxicillin (25 μg/mL^{-1}) was used as standard which shows a zone of inhibition of 8mm. The compounds were serially diluted and different dilutions were tested against *Staphylococcus aureus* and *E. coli*.

Comparison of all three samples at a concentration 50, 100, 150 and 200 μgs/ml respectively for their zone of inhibition in mms is done. All three compounds lack Antibacterial activity against Gram positive bacteria *Staphylococcus aureus*. Results show that the antibacterial activity of the compound increases logarithmically with an increase in concentration. Although all 3 samples show a similar type of inhibition pattern but QSB3 exhibits more antibacterial activity as compared to other samples (Table 2).

Table 2: Results of Anti-bacterial Activity (Zone of Inhibition in mm)

No.	Conc. (μg/ml)	QSB1	QSB2	QSB3
1	50	8	8	8
2	100	10	9	10
3	150	12	9	12
4	200	13	12	14

Since the compounds show activity against *E. coli* as a representative organism from the Gram negative *Enterobacteriaceae* family. All three samples can be screened for other enteric organisms which are known pathogens like *Salmonell*, *Pseudomonas*, *Vibrio* etc. Also Antifungal, Antiviral, Cytotoxic and anti-inflammatory activities can also be carried out.

CONCLUSION

We reported the synthesis and *in vitro* study of 3-Quinolinecarbaldehyde through Vilsmeier Haack Cyclisation of N-Arylacetamide and their Hydrazones. All the intermediates were confirmed by reported physical constants. The synthesized hydrazones are characterized by IR and NMR. They are further tested for their *in vitro* antibacterial activity. All the synthesized compounds are moderately active when compared with standard Amoxicillin. Since the compounds show activity against *E coli* as a representative organism from the Gram negative *Enterobacteriaceae* family. All samples can be screened for other enteric organisms which are known pathogens like *Salmonella*, *Pseudomonas*, *Vibrio* etc. Also Antifungal, Antiviral, Cytotoxic and anti-inflammatory activities can also be carried out.

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