3-Quinonlinecarbaldehyde thiosemicarbazones: Synthesis from N-arylacetamide, Characterization, Antibacterial and Antioxidant activities

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Abstract— **Four different Schiff bases of 3-quinolinecarbaldehydes are synthesized from differently substituted thiosemicarbazides. The structures of compounds are established using modern analytical technique FT-IR, 1H-NMR and mass spectral data. Antimicrobial screening results are also presented against clinical isolates of pathogenic strains of Staphylococcus aureus, and E. coli. Simultaneously, antioxidant activities also have been carried out using DPPH radical scavenging properties to understand other functional applications of compounds. Depending on the structures of four synthesized compound, the compound d showed higher free radical neutralizing abilities as well as antimicrobial activities that may be due to the presence of 6-flouro group of the quinoline which might be facilitating the flow of electrons through polarization of electron density of the quinoline ring.**

Index Terms—**3-quinilinecarbaldehyde, Thiosemicarbazide, Schiff's bases, antimicrobial, DPPH scavenging.**

I. INTRODUCTION

In recent years nitrogen containing heterocyclic compounds like quinoline has received considerable attention due to their biological and pharmaceutical activities. Quinoline, also known as benzpyridine is a heterocyclic aromatic organic compound which has few anti-microbial properties but its derivatives are known to possess a considerable amount of effect on microbial strains[1-3].

Quinoline and its derivatives have always attracted the interests of both synthetic and biological chemists alike because of its diverse chemical and pharmacological properties. It is found in several natural compounds and pharmacologically active substances displaying a broad range of biological activities[3-5].

Literature survey had revealed that the chemistry of hydrazine derivatives such as thiosemicarbazide and its hydrazones is of immense interest owing to their wide synthetic and analytical applications and biological activities[6]. Thiosemicarbazides and their condensation products with different aldehydes display interesting biological activities and have therefore attracted considerable pharmaceutical interest. They have been evaluated for last 50 years as anticancer[7], antiHIV[8], antibacterial[9], antiviral[10] and antifungal due to their ability to diffuse through the semipermeable membrane of cell lines[11-14]. They also play an important role in the regulation of plant growth[15]. Due to their abundance in plants and ease of synthesis, this class of compounds has generated great interest for possible therapeutic uses.

The important role displayed by quinoline and its derivatives for various therapeutic and biological activities prompted us to synthesize a new range of thiosemicarbazones. These are important synthetic conjugates that can be prepared with greater flexibility in reaction conditions as well as pharcamophores of varied nature. Such strategies can be used to create newer hybrid compounds with improved activity[16-17].

In the present report, following four poly substituted quinolinecarbaldehyde such as 2-hydroxy quinolinecarbaldehyde(**1**), 2-chloroquinolinecarbaldehyde **(2)**, 6-flouro-2-hydroxy-quinolinecarbaldehyde **(3)** and 6-flouro-2-chloro-quinolinecarbaldehyde**(4)** are used with thiosemicarbazide for the syntheses of four (**a**, **b**, **c** and **d**) thiosemicarbazone.

II. EXPERIMENTAL

Solvents used for syntheses (acetone, methanol, ethanol and dichloromethane) were of AR grade and further dried before their use by standard procedures. The starting materials such as aniline, DMF, POCl3, triflouro acetic acid, acetic anhydride were obtained from SD-FCL Chemical Limited, Mumbai, India. N-aryl-acetamide, phosphoryl chloride and thiosemicarbazide were purchased from Sigma-Aldrich. All compounds were routinely checked by TLC on silica gel plates using petroleum ether/ethyl acetate as solvent system and the developed plates were visualized by UV light and iodine vapours. The detailed synthesis has been shown in Scheme-1.

Four different 3-quinoline carbaldehyde thiosemicarb-zones **a, b, c** and **d** were synthesized through multistep reactions. Starting from cyclization of N-arylacetamide in the presence of Vilsemier- Haack (DMF/$POCl_3$) reagent gives rise to 2-chlro-3-quinolinecarbaldehyde. Subsequent treatment by conc*entrated* acid and preceded condensation with various acid hydrazides produce proposed hydrazones as reported by Sreenivasulu Enamula et al[18] **(Scheme – I)**. Further structural characterization antimicrobial and antioxidant activities were reported in this work.

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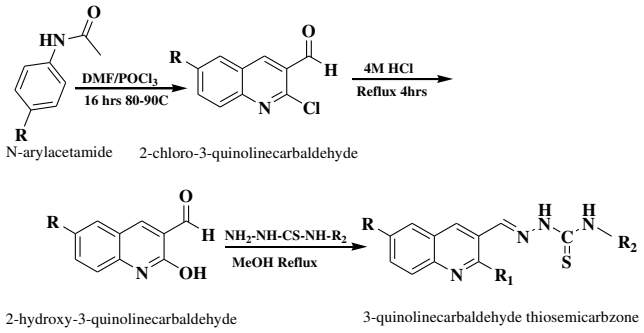

Where (a) R = H, R_1 = Cl, $R_2 = C_2H_5$ (c) R = H, R_1 = OH, $R_2 = CH_3$
(b) R = H, R_1 = Cl, $R_2 = CH_3$ (d) R = F, R_1 = OH, $R_2 = CH_3$

Figure 1: Stepwise synthesis of thiosemicarbazones

The final products were purified on a silica gel chromatographic column using petroleum ether/ethyl acetate in proportion of 7:3 by V/V as solvent system.The purity of compounds wasroutinely checked by TLC on silica gel plates visualizing under UV light and iodine vapours. 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 SHIMADZU 600 MHz at Savitribai Phule Pune University, Pune while IR spectra were recorded on JASCO FT- IR-4100 spectrometer.

The chemically synthesized four compounds (**a**, **b**, **c** and **d**) were tested for antimicrobial activity. Strains of both Gram positive and Gram negative bacteria were used for experimentation. Amoxicillin (25 $\mu g/mL^{-1}$) 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*.

The earlier studies attracted us to check antioxidant activities of these thiosemicarbazones. In the present work, we have used DPPH radical scavenging activities as per the procedure reported[19]. 2, 2-Diphenyl-l, 2 - picrylhydrazil (DPPH) is a stable free radical which has an unpaired valence electron at one atom of nitrogen bridge and scavenging of (DPPH) radical is the basis of popular DPPH antioxidant assay[20]. The IC_{50} values for even the standard antioxidants like ascorbic acid and butyrate hideoxytoulene (BHT) were also considered for the limiting concentrations. Aliquots of eight sample concentrations (1, 5, 10, 20, 25, 50, 100, 150 ml) prepared in methanol were taken in eight different test tubes. Samples were accurately dissolved in methanol to make the required concentration by dilution techniques. DPPH was weighed & dissolved to make 0.004% of DPPH solution. To dissolve homogenously magnetic stirrer was used. After making the desired sample concentrations, 5ml of 0.004 % DPPH solution was applied on each test tube by micropipette to make a total volume of 10 ml. The room temperature was recorded & solutions were kept for 30 min to complete the reaction. DPPH was applied into blank test tube at the same time where methanol was taken as blank. After 30 minutes the absorbance of each test tube were taken by single beam spectrophotometer. IC_{50} were measured from the plot of % inhibition verses concentration.

III. Results and Discussion

All the intermediates were confirmed by reported physical constants. The structures of the synthesized compounds (**a**, **b**, **c** and **d**) were established on the basis of physical and spectral data. The proposed structures are shown in the following **Table 1.**

Antimicrobial Studies:

The chemically synthesized four compounds (**a**, **b**, **c** and **d**) were tested for antimicrobial activities. Strains of both Gram positive and Gram negative bacteria were used for experimentation. Amoxicillin (25 $\mu g/mL^{-1}$) 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 inhibition zone diameter in mm for fourcompounds at a concentration 50, 100, 150 and 200 µg/ml respectively against Gram negative bacteria *E. Coli* is shown in **Table 2**. All four compounds lack antibacterial activity against Gram positive bacteria *S. aureus*. The values indicate that the antibacterial activity of the compounds increases logarithmically with an increase in concentration. Although all four the compounds show a similar type of inhibition pattern, the compound **d**exhibits more antibacterial activity as compared to others. Since the compounds show activity against *E coli* as a representative organism from the Gram negative *Enterobacteriaceae* family. All four compounds can be screened for other enteric organisms who are known pathogens like *Salmonell, Pseudomonas , Vibrio* etc.

Table 2: Comparison of antimicrobial activities

No	Conc. (µg/ml)	a	b	c	d
1	50	8	8	8	10
2	100	10	9	10	11
3	150	12	9	12	13
4	200	13	12	14	15

Antioxidant activities:

The use of 2, 2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) assay provides an easy and rapid way to evaluate antioxidants by spectrophotometry[20]. DPPH free radical method is an antioxidant assay based on electron-transfer process that produces a violet solution in ethanol. This free radical, stable at room temperature, is reduced in the presence of an antioxidant molecule (probably the synthesized conjugates) giving rise to colourless ethanol solution. From the values given in the following **Table 3**, it is seen that **c** and **d** have lowest IC_{50} values compared to **a** and **b.** Based on such observations we can conclude that **c** and **d** are more potent antioxidant compounds than **a** and **b**.

One-electron oxidation of the compound **d** in 200 ug/ml solution may produce a phenoxyl radical at 2-hydroxy position of quinoline ring, indicating that the phenolic moiety of compound participates in free radical scavenging reactions. Depending on the structure, the compound **d** possesses higher free radical neutralizing abilities as well as antimicrobial activities that may be due to the presence of 6-flouro group of the quinoline. This might facilitate the polarization of electron density of the molecule.

Table 3: DPPH radical scavenging activities in terms of IC_{50} values of compounds

Compounds	IC_{50}
a	2.4
b	4.0
c	5.6
d	6.4

Table 1: Spectral Characterization of synthesized compounds

SR. No.	Name Code	YIELD (%)	M. P. (°C)	Spectral Assignments
1	a	78%	202	**FTIR (cm^{-1}):**710-770(C-Cl), 1647.56 (-C=N), 3195.86 (-NH), 2958.27 (-CH), 1660.41 (-C=S), 1057.03 (-N-N), 1500 to 1600 (Aromatic region). **^{1}H-NMR** (*dmso)* (δ, ppm,): 9.77 ppm, 6.29 mm(s,1H ,HC=N), 8.67 ppm, 6.72 mm (s, 1H, NH), 8.34 ppm, 6.64 mm (s, 1H, NH), 8.45ppm, 5.81 mm (d, 1h), 7.94-7.50, 6.12 + 6.33 + 6.32 + 6.31 mm (m, 4H), 3.84ppm, 13.00 mm (q, 2H), 1.38 ppm, 20.42 mm (t, 3H)
2	b	80%	196	**FTIR (cm^{-1}):**1095(C-O), 1647.56 (-C=N), 3265.86 (-NH), 2958.27 (-CH), 1660.41 (-C=S), 1057.03 (-N-N), 3051.27 (-OH), 1500 to 1600 (Aromatic region), 2958.27 (-CH). **^{1}H-NMR** (*dmso*) (δ, ppm,): 11.87 ppm, 2.03 mm (s, 1H, HC=N), 9.22 ppm, 2.07 mm (s, 1H-NH), 8.45ppm,2.12 mm (d, 1H), 8.52 ppm, 2.07 mm (s, 1H, -NH), 8.1-7.6 ppm, (4.17+2.17+2.32) mm (m, 4H),3.15 ppm, 6.79 mm (s, 3H)
3	c	70%	320	**FTIR (cm^{-1}):**710-770 (C-Cl), 1647.56 (-C=N), 3265.86 (-NH), 2958.27 (-CH), 1660.41 (-C=S), 1057.03 (-N-N), 1500 to 1600 (Aromatic region). **^{1}H-NMR** (*CDCl3*) (δ, ppm): 12.02 ppm, 1.91 mm (s , 1HH, -OH), 11.70 ppm, 1.98 mm (s, 1H, HC=N), 8.68 ppm, 4.58 mm (s, 1H, -NH), 8.60 ppm, 4.58 mm (d, 1H), 8.28 pmm, 2.00 mm (s,1H, -NH), 7.6-7..2 ppm, (2.32+2.09+4.41) mm (m, 4H),3.05 ppm, 7.50 mm (s, 3H)
4	d	70%	202	**FTIR (cm^{-1}):**710-770(C-Cl), 1647.56 (-C=N), 3195.86 (-NH), 2958.27 (-CH), 1660.41 (-C=S), 1057.03 (-N-N), 1500 to 1600 (Aromatic region). **^{1}H-NMR** (*dmso)* (δ, ppm,): 11.91 ppm, 1.48 mm (s, 1H, HC=N), 9.17 pmm, 1.51 mm (s, 1H, -NH), 8.73 ppm, 1.65 mm (d, 1H), 8.50 ppm, 1.56 mm (s, 1H, -NH), 8.0-7.3 ppm, (1.64+3.67+0.75) mm (m, 4H), 3.15ppm, 5.36mm (s, 3H)

IV. Conclusion

In the present study, we have made an attempt to elaborate 3-Quinolinecarbaldehyde thiosemicarbazides as main pharmacophore. All the intermediates were confirmed by reported physical constants. The synthesized thiosemicarbazides are characterized by IR and H1-NMR. They are further tested for their in vitro antibacterial and antioxidant activities. 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. The results of antioxidant activities in terms of DPPH radical scavenging properties indicate the probable application of these compounds as antioncogenic agents in future research. The contest of development of new molecules has become more interesting and challenging with the advent in the field of drug design and discovery due to various multi resistant strains of pathogenic micro-organism. It has been observed that in this competition, pathogens have the upper hand since they can more easily evolve and develop a mechanism to fight the drug action. So, it is necessary to develop drugs which can easily act against the resistant strains.

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