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Synthesis and in vitro antioxidant activity of quinolin-5-ylamine derivatives

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Imines of six new quinolin-5-ylamine derivatives **3(a-c)** and **5(a-c)** were synthesized by the reaction of quinolin-5-ylamine (**1**) with different aldehydes **2(a-c)** and ketones **4(a-c)**. The chemical structures of the compounds were confirmed by UV-visible, FT-IR and ^{1}H NMR spectral study. New compounds were screened for the antioxidant activity by DPPH (2,2-diphenyl-1-picrylhydrazyl) method. Butylated Hydroxytoluene (BHT) was used as standard. All the compounds showed DPPH radical scavenging activity, where compound **3c** was the best radical scavenger.

1. Introduction

Free radical contains an odd number of electrons which makes it unstable, short lived and highly reactive. Therefore, it reacts quickly with other compounds in order to capture the needed electron to gain stability. Generally, free radical attacks the nearest stable molecule, stealing its electron. When the attacked molecule loses its electron, it becomes a free radical itself, beginning a chain reaction cascade resulting in disruption of a living cell[1, 2]. The antioxidants are specifically categorized as natural and synthetic. The natural antioxidants contain a ascorbic acid, phenolic and nitrogen compounds, whereas in synthetic antioxidants it contains phenolic compounds of different alkyl substitution[3, 4]. The primary antioxidants comprise essentially sterically hindered phenols and secondary aromatic amines[5]. These antioxidants act usually both through chain transfer and chain termination. The first step of the reactive radical's termination by this type of antioxidants is hydrogen atom transfer from the antioxidant molecule to the reactive radical intermediate[6]. The water soluble antioxidants react with the cell cytosol in which oxidants are present and the lipid soluble

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antioxidants in the blood plasma protect the cell membranes from lipid peroxidation[7]. The water soluble or lipid soluble compounds are synthesized by the body or obtained through the diet[8]. The amount of protection provided by any antioxidant will depend on its concentration, its reactivity towards the particular reactive oxygen species being considered, and the status of the antioxidants with which it interacts. DPPH is a well-known radical and a scavenger for other radicals.

Schiff bases are used as substrates in the preparation of a number of industrial and biologically active compounds via ring closure, cycloaddition, and replacement reactions[9]. Moreover, Schiff bases are also known to have biological activities such as antimicrobial[10-13], antifungal[14], antitumor[15-17] and herbicides[18]. Quinoline is mainly used as a building block to other specialty chemicals. Its principal use is as a precursor to 8-hydroxyquinoline, which is a versatile chelating agent and precursor to pesticides. The precursors of cyanine dyes are derived from 2- and 4-methyl derivatives by quinoline. Quinoline derivatives are used for functional materials such as fluorescence substances and for medicinal use. It is interesting that above characters change on certain chemical modification. Antioxidant activity of polycyclic pyrimido[4,5-b] quinolines have been reported[19]. Quinolin-5-ylamine is a derivative of quinoline and resembles naphthalene. It consists of one benzene ring and pyridine ring fused together. It consists of one benzene ring and pyridine ring fused together. FT-IR and FT-Raman spectral investigations on 4-aminoquinaldine and 5-aminoquinoline have been reported[20]. Synthesis of some 5-aminoquinoline derivatives has been reported[21-23]. In this respect, the present paper reports the synthesis and antioxidant activity of quinolin-5-ylamine derivatives **3(a-c)** and **5(a-c)**.

2. Experimental

2.1. Materials and Methods

All solvents and reagents were purchased from Sigma-Aldrich, India**.** Melting points were determined by Veego melting point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar. The UV-Visible spectra were recorded on UV-1800 SHIMADZU UV spectrometer with quartz cell of 1.0 cm path length. The FT-IR spectra were recorded using nujol mull on FT-IR Jasco 4100 infrared spectrophotometer and were quoted in cm^{-1}. ^1H NMR spectra was recorded on Bruker DRX -500 spectrometer at 400 MHz using DMSO-d_6 as solvent and TMS as an internal standard. Quinolin-5-ylamine was purchased from Sigma-Aldrich, India.

*2.2. General procedure for the synthesis of Schiff bases of quinolin-5-ylamine with different aldehydes **3(a-c)***

Equimolar concentrations of quinolin-5-ylamine (**1**, 0.003 mol), aryl aldehydes (**2a-c**, 0.003 mol) were dissolved in methanol (20 mL) and 2-3 drops of glacial acetic acid was added to the reaction mixture. It was refluxed for 7-8 h and allowed to stand at room temperature. The progress of the reaction was followed by TLC until the reaction was complete. It was cooled to 0 °C, the precipitate was filtered, washed with diethyl ether and the residue was recrystallized from methanol.

*2.2.1. (6-Bromo-1H-indol-3-ylmethylene)-quinolin-5-yl-amine **(3a)***

The product obtained from quinolin-5-ylamine (**1**) (0.50 g, 0.003 mol) and 6-bromo-1H-indole-3-carbaldehyde (**2a**) (0.50 g, 0.003 mol). FT-IR (KBr, cm^{-1}) *v*: 3450 (N-H), 3080 (Ar C-H), 1610 (C=N), 1500 (C=C). ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.42 (s, 1H, NH), 8.79 (d, 1H, Ar-H), 8.15 (d, 1H, Ar-H), 8.05 (d, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.49 (s, 1H, CH), 7.40 (d, 1H, Ar-H), 7.33 (d, 1H, Ar-H), 7.28 (d, 1H, Ar-H), 7.25 (t, 1H, Ar-H), 7.20 (s, 1H, Pyrrole C-H), 6.95 (t, 1H, Ar-H). Anal. Calcd.: C-61.73; H-3.45; N-12.00; Found: C-61.91; H-3.62; N-12.24 %.

2.2.2. (2-Nitro-benzylidene)-quinolin-5-yl-amine ***(3b)***

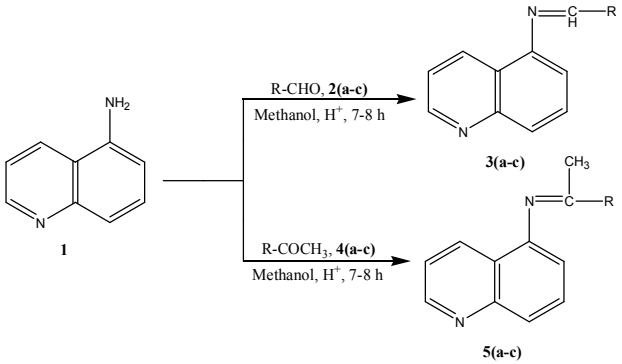
The product obtained from quinolin-5-ylamine (**1**) (0.50 g, 0.003 mol) and 2-nitro-benzaldehyde (**2b**) (0.52 g, 0.003 mol). FT-IR (KBr, cm^{-1}) *v*: 3094 (Ar C-H), 1608 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.80 (d, 1H, Ar-H), 8.60 (t, 1H, Ar-H), 8.35 (s, 1H, CH), 8.20 (d, 1H, Ar-H), 8.15 (d, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 7.85 (d, 1H, Ar-H), 7.65 (t, 1H, Ar-H), 7.50 (t, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.30 (t, 1H, Ar-H). Anal. Calcd.: C-69.31; H-4.00; N-15.15; Found: C-69.24; H-4.32; N-15.34 %.

2.2.3. Quinolin-5-yl-(3,4,5-trimethoxy-benzylidene)-amine ***(3c)***

The product obtained from quinolin-5-ylamine (**1**) (0.50 g, 0.003 mol) and 3,4,5-trimethoxy-benzaldehyde (**2c**) (0.68 g, 0.003 mol). FT-IR (KBr, cm^{-1}) *v*: 3085 (Ar C-H), 1604 (C=N), 1500 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.85 (d, 1H, Ar-H), 8.45 (s, 1H, CH), 8.14 (d, 1H, Ar-H), 8.05 (d, 1H, CH), 7.65 (t, 1H, Ar-H), 7.45 (d, 1H, Ar-H), 7.32 (t, 1H, Ar-H), 6.80 (s, 2H, Ar-H), 3.70 (s, 9H, OCH_3). Anal. Calcd.: C-70.79; H-5.63; N-8.69; Found: C-70.65; H-5.52; N-8.82 %.

2.3. General procedure for the synthesis of Schiff bases of quinolin-5-ylamine with different ketones ***5(a-c)***

Equimolar concentrations of quinolin-5-ylamine (**1**, 0.003 mol), aryl ketones (**4a-c**, 0.003 mol) were dissolved in methanol (20 mL) and 2-3 drops of glacial acetic acid was added to the reaction mixture. It was refluxed for 7-8 h and allowed to stand at room temperature. The progress of the reaction was followed by TLC until the reaction was complete. It was cooled to 0 °C, the precipitate was filtered, washed with diethyl ether and the residue was recrystallized from methanol. New compounds were synthesized by the method summarized in Scheme 1.



Scheme 1

2.3.1. (1-Phenyl-ethylidene)-quinolin-5-yl-amine ***(5a)***

The product obtained from quinolin-5-ylamine (**1**) (0.50 g, 0.003 mol) and acetophenone (**4a**) (0.41 g, 0.003 mol). FT-IR (KBr, cm^{-1}) *v*: 3080 (Ar C-H), 1605 (C=N), 1510 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.80 (d, 1H, Ar-H), 8.14 (d, 1H, Ar-H), 8.00 (d, 1H, Ar-H), 7.65 (m, 2H, Ar-H), 7.60 (t, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 7.35 (m, 3H, Ar-H), 7.30 (t, 1H, Ar-H), 0.98 (s, 3H, CH_3). Anal. Calcd.: C-82.90; H-5.73; N-11.37; Found: C-82.98; H-5.56; N-11.51 %.

2.3.2. 3-[1-(Quinolin-5-ylimino)-ethyl]-benzonitrile ***(5b)***

The product obtained from quinolin-5-ylamine (**1**) (0.50 g, 0.003 mol) and 3-acetylbenzonitrile (**4b**) (0.50 g, 0.003 mol). FT-IR (KBr, cm^{-1}) *v*: 3094 (Ar C-H), 1608 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.82 (d, 1H, Ar-H), 8.20 (d, 1H, Ar-H), 8.15 (d, 1H, Ar-H), 7.95 (d, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.47 (t, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.32 (t, 1H, Ar-H), 0.95 (s, 3H, CH_3). Anal. Calcd.: C-79.68; H-4.83; N-15.49; Found: C-79.49; H-4.64; N-15.56 %.

2.3.3. (1-Naphthalen-2-yl-ethylidene)-quinolin-5-yl-amine ***(5c)***

The product obtained from quinolin-5-ylamine (**1**) (0.50 g, 0.003 mol) and 1-(naphthalen-2-yl)ethanone (**4c**) (0.59 g, 0.003 mol). FT-IR (KBr, cm^{-1}) *v*: 3080 (Ar C-H), 1610 (C=N), 1505 (C=C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.80 (d, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.10 (d, 1H, Ar-H), 8.05 (d, 1H, CH), 7.95 (d, 1H, Ar-H), 7.90 (d, 1H, Ar-H), 7.62 (t, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 7.45 (d, 1H, Ar-H), 7.32 (m, 2H, Ar-H), 7.25 (t, 1H, Ar-H), 0.98 (s, 3H, CH_3). Anal. Calcd.: C-85.11; H-5.44; N-9.45; Found: C-85.32; H-5.24; N-9.50 %.

2.4. Antioxidant activity

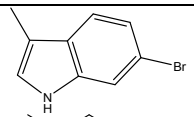
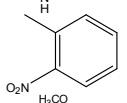
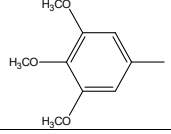
The free radical scavenging activity of the synthesized compounds was studied *in vitro* by 1, 1-diphenyl-2-picrylhydrazyl (DPPH) assay method[24]. Stock solution of the drug was diluted to different concentrations (100 and 200 μg/mL) in methanol. Methanolic solution of the synthesized compounds (2 mL) was added to 0.003 % (w/v) methanol solution of DPPH (1 mL). The mixture was shaken vigorously and allowed to stand for 30 min. Absorbance at 517 nm was determined and the percentage of scavenging activity was calculated. Ascorbic acid was used as the standard drug. The inhibition ratio (I %) of the tested compounds was calculated according to the following equation: $I\ \% = (Ac\text{-}As) / Ac \times 100$, where *Ac* is the absorbance of the control and *As* is the absorbance of the sample. The concentration of compounds providing 50 % scavenging of $DPPH^{\cdot}$ (IC_{50}) was calculated from the plot of percentage inhibition against concentration (μg/mL)[25, 26].

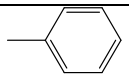
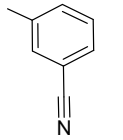
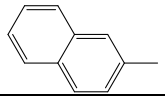
3. Results and discussion

The synthetic route of the compounds is outlined in Scheme 1. The reactions of quinolin-5-ylamine with different aldehydes and ketones were carried out in the presence of methanol. The synthesized compounds were characterized by UV-visible, FT-IR and ^{1}H NMR spectral studies. The elemental analyses data showed good agreement between the experimentally determined values and the theoretically calculated values within ± 0.4 %. The chemical structures and physical data of all the synthesized compounds are given in Table 1. The electronic absorption spectra of the synthesized compounds showed new bands, and the appearance of longer wavelength absorption band in the UV region confirms the formation of compounds.

The absence of NH_2 and C=O absorption bands in the IR spectra confirmed that the compounds were synthesized. The appearance of a medium to strong absorption band at around 1600 cm^{-1} is due to the stretching vibration of C=N bond formation in the synthesized compounds. The proton spectral data agree with respect to the number of protons and their chemical shifts with the proposed structures. The proton spectral data of the intermediate, quinolin-5-ylamine (**1**) shows resonance at δ 5.50 ppm (s, 2H, NH_2). In all the synthesized compounds, the above resonance disappeared.

Table 1. Chemical structures and physical data of the synthesized compounds (**3a-c**) and **5(a-c)**

Compound	R	Molecular Formula	Mol. Wt.	Yield (%)	M.R. (°C)	UV-visible (nm)
3a		$C_{18}H_{12}BrN_3$	349.02	65.4	82-84	380
3b		$C_{16}H_{11}N_3O_2$	277.3	62.0	118-122	285
3c		$C_{19}H_{18}N_2O_3$	278.3	68.4	88-90	252

5a		$C_{17}H_{14}N_2$	246.3	63.2	110-112	407
5b		$C_{18}H_{13}N_3$	271.3	63.8	123-125	349
5c		$C_{21}H_{16}N_2$	296.3	61.3	102-104	364

DPPH is a well-known radical and a scavenger for other radicals. DPPH has two major applications in laboratory research: (a) to monitor the chemical reactions involving radicals. (b) The number of initial radicals can be counted from the change in the optical absorption at 520 nm or in the electron paramagnetic resonance signal of the DPPH. The *in vitro* scavenging assay of DPPH radicals was performed spectrophotometrically with BHT as positive control. Percentages of DPPH radical scavenging activity were tabulated in Table 2. All the compounds showed antioxidant activity (Fig. 1). The percentage scavenging effect of the compound **3c** at 200 µg/mL is 58.0 %. Compounds **3a**, **3b**, **5a**, **5b** and **5c** showed weak activity. The compound **3c** showed higher radical inhibition activity due to the presence of methoxy group (electron donating group) in the aromatic ring.

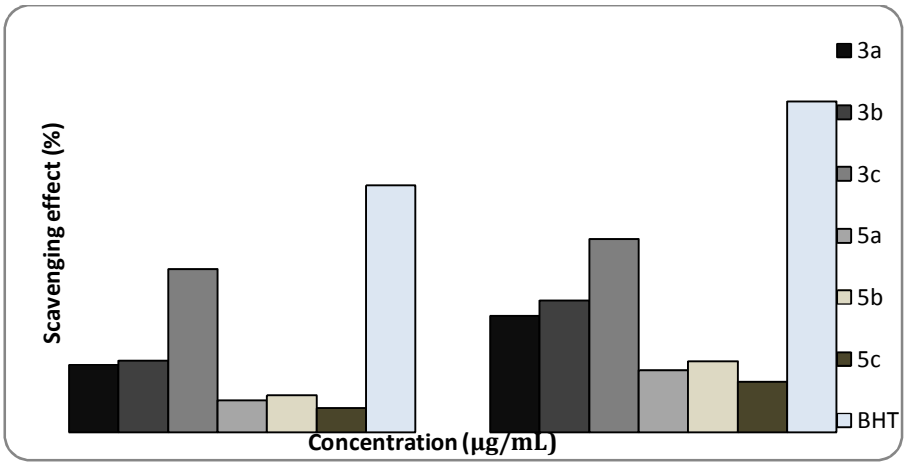


Fig. 1.

Table 2 DPPH radical scavenging activity of the tested compounds

Compound	Scavenging effect (%)	
	Concentration of the tested compounds (µg/mL)	
	100	200
3a	20.2	34.9
3b	21.4	39.5
3c	49.0	58.0
5a	09.6	18.5
5b	11.0	21.3
5c	07.2	15.2
BHT	74.1	99.3

4. Conclusion

In conclusion, a series of new quinolin-5-ylamine derivatives **3(a-c)** and **5(a-c)** were synthesized in good yield, characterized by different spectral studies and their antioxidant activity have been evaluated. All the compounds showed DPPH radical scavenging activity, where compound **3c** was the best radical scavenger.

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