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Green Synthesis of Quinazoline derivatives and evaluation of antioxidant potential

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ABSTRACT

In the present work newer antioxidants based on quinalzoline nucleus were synthesized and evaluated. The confirmation of the structure of the synthesized compounds was done by IR, ^{1}HNMR and mass spectral studies. The antioxidant potential of the synthesized compounds was also evaluated and the the data reveals IC_{50} value of 17.4 to 32.6 µg/mL against DPPH radical and 18.3 to 37.4 µg/mL against hydroxy radical. The compounds **4d & 4e** exhibited the best antioxidant activity against DPPH and HRSA assays. The results revealed that higher electron withdrawing potential in the benzene substituent resulted in higher antioxidant capacity. On the other hand compound **4a** with an aliphatic chain exhibited the least antioxidant activity in both the assays.

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Introduction

Heterocyclic compounds are a cyclic structure that contains one or more heteroatom (N, O, S) apart from carbon.[1-3] Quinazoline is a bicyclic structure containing two fused six-membered rings; one is benzene ring another one is a pyrimidine ring. Compounds containing 4(3H)-quinazolinone ring system have showed antitumor, anticonvulsant, antitubercular activities, anti-inflammatory, analgesic, antimicrobial and anticoccidal activities[4-8]. Quinazoline have been frequently used in medicine[9-11], such as quinethazone and metolazone and are used in medicine as diuretics while prazosin is a vasodilator, which is also used as an antihypertensive drug. Quinazolinones are also a class of drugs which function as hypnotic/sedatives that contain a 4-quiazolinone core. Their use has also been proposed in the treatment of cancer.[12]

Microwave assisted synthesis reduces the reaction time and is also known to improve the yield of the product using optimized reaction conditions. The ease of synthesis of the quinazoline molecules has motivated us to design new molecules based on the quinazoline scaffold using microwave irradiation method and evaluate them for their antioxidant action.

Material and Methods

2-aminobenzoic acid, ethanol, hydrazine hydrate, sodium hydroxide, benzoyl chloride, glacial acetic acid and various aromatic aldehyde were procured from Oxford Fine Chemicals LLP, and were used as obtained without any further purification or treatment. All other chemicals used in the study were of laboratory grade. Melting point was determined using electrically heated melting point apparatus, FTIR was determined on Bruker FTIR spectrophotometer, Mass spectra was recorded on API Microsystems LC MS instrument and proton NMR spectra were recorded on Jeol system.

The scheme for the synthesis of the quinazoline derivatives was modified from the previously reported procedures[13,14] (Figure 1).

The entire scheme comprises of 4 steps leading to the formation of the title compounds.

Synthesis of 2-benzamidobenzoic acid

To the 2-aminobenzoic acid (0.002 mol) dissolved in 10% sodium hydroxide (10 mL), benzoyl chloride (0.0022 mol) was added with stirring at room temperature for over 1 h. Upon completion of addition, the reaction mixture was extinguished with cold water to obtain solid residue, which was washed with dilute HCl followed by water and recrystallized from ethanol.

Synthesis of 2-phenyl-4H-benzo[d][1,3] oxazin-4-one

A solution of 2-benzamidobenzoic acid (2 mmol) in acetic anhydride (10 mL) was irradiated with microwave at 350W power for 7 min. The mixture was cooled to room temperature and then poured into crushed ice. The solid residue thus obtained was filtered, dried, and recrystallized with ethanol.

Synthesis of 3-amino-2-phenylquinazolin-4 (3H)-one

A mixture of benzoxazin-4-one (0.002 mmol) and hydrazine hydrate (0.002 mmol) was prepared in in glacial acetic acid (5 mL) and irradiated with microwave at 350W power for 25 min. The completion of reaction was monitored by TLC (n-hexane:ethylacetate, 9:1). On cooling a solid separated that was collected by filtration, washed with water, dried, and recrystallized from ethanol.

General procedure for synthesis of Quinazoline-Schiff bases

0.01 mol of 3-amino-2-phenylquinazolin-4(3H) -one was dissolved in 25 ml of ethanol and to it was added 0.01 mol of the desired aromatic aldehyde. The mixture was irradiated with microwave at 120W power for 1-2 min. The reaction completion was monitored by TLC and was evaporated under reduced pressure. The product obtained was filtered off and recrystallized from ethanol/acetone[15].

All the synthesized compounds were characterized for melting point, solubility, yield and elucidation of the structure. The structure elucidation was performed by spectroscopic analysis (NMR, Mass and IR). The melting points were determined by open capillary method and are uncorrected using a electrically heated melting point determination apparatus. The purity and homogeneity of the compounds was determined by thin layer chromatography, using silica gel G as the stationary phase on glass plates. Iodine vapors were used for development of the chromatogram. The solvent system used for running the compounds was n-hexane:ethylacetate

(9:1).The solubility of all the synthesized compounds was qualitatively determined in different solvents. A small amount of the sample was shaken in 1 mL of solvent in a test tube and was visually inspected for the absence of the solid particles in the test tube.

Evaluation of antioxidant action[16]

In-vitro antioxidant activity

The *in vitro* antioxidant activity of the synthesized compounds **4a-e** was determined by two different methods using ascorbic acid as the standard.

DPPH Method

The free radical scavenging activity of the synthesized molecules was measured in terms of hydrogen donating or radical scavenging ability using the stable radical DPPH. The test samples (10–100 □L) were prepared in DMSO and were mixed with 1.0 mL of DPPH solution and filled up with methanol to a final volume of 4 mL. Absorbance of the resulting solution was measured at 517 nm in a visible spectrophotometer. Ascorbic acid was used as the reference compound. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. Radical scavenging activity was expressed as the inhibition percentage of free radical by the sample and was calculated using the following formula:

$$\%\ inhibition = \frac{(Ao - At)}{Ao}\ X\ 100$$

where □o is the absorbance of the control (blank, without sample) and □□ is the absorbance in the presence of the test samples. All tests were performed in triplicate and the results were expressed as mean values ± standard deviations.

Hydroxyl radical scavenging method

The test samples (10–100 □L) were prepared in DMSO and 1 mL of iron EDTA solution, 0.5mL of EDTA solution, 1 mL of DMSO and 0.5mL of ascorbic acid were added to it. The mixture was incubated in a boiling water bath at 80 to 90°C for 15 min. After incubation, 1 mL of ice cold TCA and 3mL of Nash reagent were added and the reaction mixture was incubated at room temperature for 15 min. The absorbance was read at 412 nm. The % hydroxyl radical scavenging activity is calculated by the following formula

$$\%\ HRSA = \frac{Abs\ control - Abs\ sample}{Abs\ control} \times 100$$

Where, HRSA is the Hydroxyl Radical Scavenging Activity, Abs control is the absorbance of control and Abs sample is the absorbance of the test solution.

Results and Discussion

The structure elucidation of the synthesized compounds was confirmed by interpretation of the IR, ^{1}HNMR and Mass spectra of the compounds. The IR spectra were observed for the characteristic peaks obtained due to the presence of the functional groups. All the compounds exhibited the peaks of aromatic C=C stretching, C-H stretching, C-N and C=N stretching and C=O stretching. The occurrence of absorption bands for C=O and C=N may occur at the same frequency and Fermi resonance peaks were the diagnostics of a carbonyl group in the compounds. The ^{1}HNMR spectra of all the compounds exhibited chemical shifts of aromatic hydrogen and imine hydrogen. They also exhibited any peak that may arise due to certain functional groups like –OH. The mass spectra of the compounds were examined for the presence of molecular ion peak or the isotopic peaks to confirm the formation of the compounds. Table 1 presents the structures and spectral data of compounda 4a-e.

The synthesized compounds were subjected to determination of yield, melting point and R_f value (Table 2).

Antioxidant Activity

The antioxidant activity displayed by the synthesized compounds against DPPH and hydroxyl radicals is presented in table 3.

The compounds **4d & 4e** exhibited the best antioxidant activity against DPPH and HRSA assays. The results revealed that higher electron withdrawing potential in the benzene substituent resulted in higher antioxidant capacity. On the other hand compound **4a** with an aliphatic chain exhibited the least antioxidant activity in both the assays.

Conclusion

The objective of the present investigation was to develop newer molecules based on quinazoline nucleus with antioxidant action. The objective was achieved by modifying the quinazoline nucleus as Schiffs base. The synthesized compounds presented good antioxidant activity and hold the potential to be promising antioxidants.

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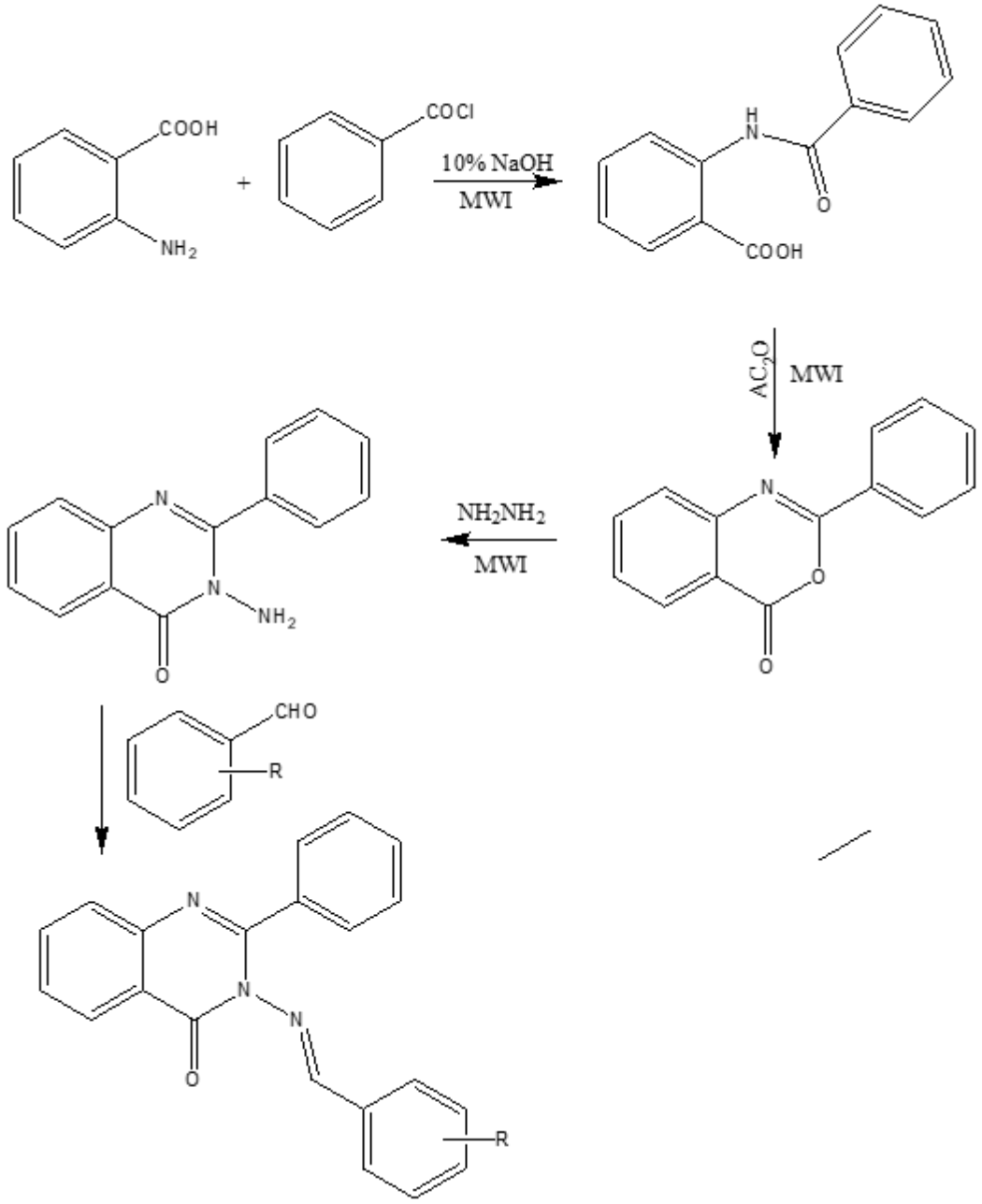


Figure 1 Scheme for synthesis of quinazolines

Table 1 Spectral data and structure of 4a-e

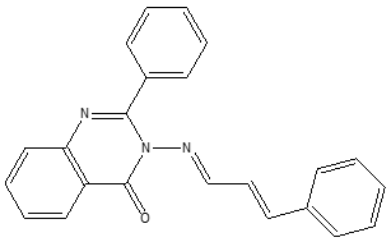
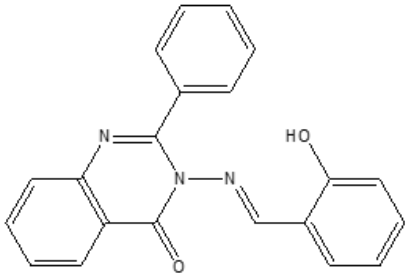
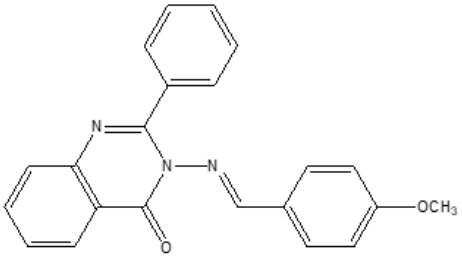
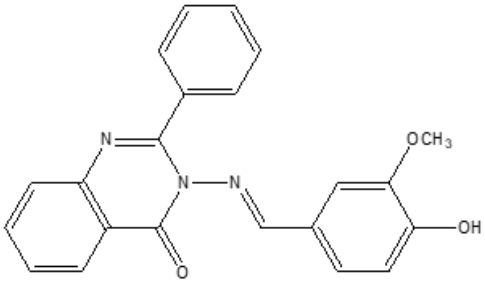
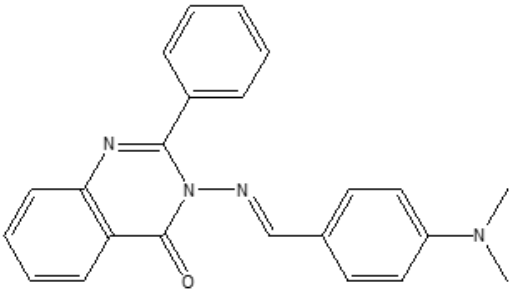
S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Structure
4a	7.2-7.9 Ar H, 8.1 imine H, 5.3-6.5 H of C=C	3202.53, 3042.73, 1678.80, 1510.55, 1428.04	
4b	7.2-7.9 Ar H, 8.1 imine H, 6.8 H adj to OH, 5.0 OH	3705.25, 3104.67, 2970.38, 1639.00, 1456.90, 1289.63, 1082.70	
4c	7.2-7.9 Ar H, 8.1 imine H, 8.2 H adj to OCH_3	3100.40, 2970.97, 1639.54, 1456.90, 1289.17	
4d	7.2-7.9 Ar H, 8.1 imine H, 6.8 H adj to OH, 5.0 OH	3733.07, 3107.54, 2967.05, 1653.56, 1477.79, 1289.54, 1082.15	
4e	7.2-7.69 Ar H, 8.1 imine H	3112.47, 2933.32, 1651.13, 1477.24, 1284.08	

Table 2 Physicochemical properties of 4a-e

Compound code	Yield (%)	Color	R_f Value	Melting point (°
4a	57	Yellow	0.63	280-282
4b	63	Brownish Yel-	0.72	226-228
4c	67	Yellow	0.61	249-251
4d	62	Yellow	0.62	273-275
4e	59	Brown	0.61	268-271

Table 3 IC_{50} values of 4a-e

Compound	IC_{50} (µg/mL)	
	DPPH	HRSA
4a	32.6 ± 0.53	37.4 ± 0.05
4b	24.1 ± 0.47	23.7 ± 0.25
4c	22.7 ± 0.29	21.8 ± 0.14
4d	19.5 ± 0.03	19.9 ± 0.17
4e	17.4 ± 0.07	18.3 ± 0.73
Ascorbic Acid	12.2 ± 0.11	13.6 ± 0.65