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# UV METHOD DEVELOPMENT FOR THE ESTIMATION OF SACUBITRIL AND VALSARTAN USING HYDROTROPY

**Apoorva Gupta*, Avinash Krishnarao Kondalkar, Narottam Singh, Shankar Singh**

Sun Institute of Pharmaceutical Education and Research (SIPER), Lahar, Bhind, (M.P)

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**ABSTRACT-**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 Schiff's base. The synthesized compounds presented good antioxidant activity and hold the potential to be promising antioxidants. In the present work newer antioxidants based on Quinazoline nucleus were synthesized and evaluated.

The synthesized compounds were characterized for the physicochemical properties such as melting point, color, and solubility. All the compounds were yellowish to brown in colour and were obtained in 57-67% yields using the optimized reaction conditions. The compounds were insoluble in water, slightly soluble in methanol, soluble in chloroform and DMSO.

The confirmation of the structure of the synthesized compounds was done by IR, $^{1}$HNMR and mass spectral studies. All the compounds exhibited the absorption bands of C=O, C=N, C-H, C=C stretching in the IR spectra. 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.

**KEYWORDS**: Quinazoline, isomers, Heterocyclic compounds, Cinnoline,phthalazineAntioxidant Activity

**Corresponding Author: Apoorva Gupta**
**E Mail:** shankarbhaskar77@gmail.com

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**INTRODUCTION: -**

**Quinazoline-** Heterocyclic compounds are a cyclic structure that contains one or more heteroatom (N, O, S) apart from carbon.[1-3] Heterocyclic compounds constitute the largest and most varied family of organic compounds and play a significant role in the pharmaceutical industry and materials science. Heterocyclic ring systems that are derived by fusion with other rings, either carbocyclic or heterocyclic, are essential building blocks and structural units of a variety of bioactive natural products and therapeutic agents. In literature, there are several heterocyclic compounds which contain a different heteroatom. Among them, N-containing heterocyclic compounds have received great attention due to their utility as valuable intermediates for various synthetic transformation and their wide range of application in different areas of science.[4] Aza-fused heterocycles are highly conjugated systems which exhibited interesting pharmacological and photophysical properties. Their DNA intercalating ability makes them suitable candidates as anti-neoplastic and mutagenic agents.[5] Quinazoline is a bicyclic structure containing two fused six-membered rings; one is benzene ring another one is a pyrimidine ring (Figure 1.1). It is a yellowish crystalline compound with molecular formula C8H6N2. Quinazoline is also known by different names like as 5,6-benzo pyrimidine, benzo[a]pyrimidine, 1,3-diazanaphthalene and pheniramine. It is isomeric with the other diazanaphthalene's of the benzothiazine subgroup, cinnoline, quinoxaline and phthalazine (Figure 1.1). Quinazoline scaffold has attracted significant attention due to their existence in several drugs and naturally occurring alkaloids.[6]

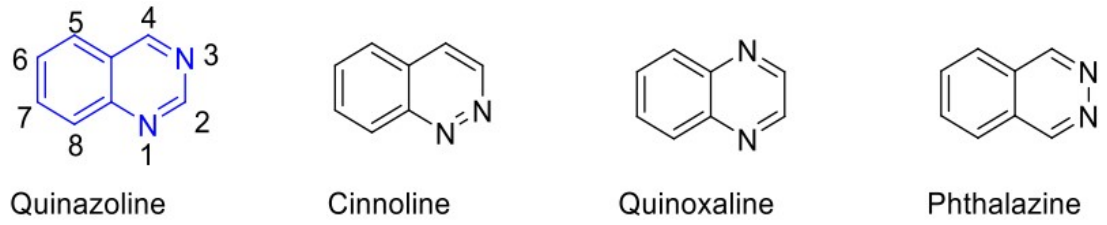



**Figure 1: Quinazoline and its isomers**

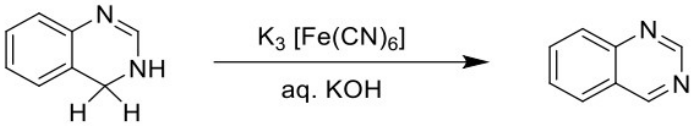
The first reaction for the synthesis of quinazoline was reported in 1895 by August Bachler and Lang through the decarboxylation of the quinazoline-2-carboxylic acid. The discovery of quinazolines commenced with the isolation of quinazoline containing alkaloidswith good antimicrobial activity. The very first time, quinazoline was synthesized by Gabriel in 1903.[8]

Quinazoline and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from several families of the plant kingdom, from microorganisms and animals. Considering the growing number of applications in recent years, there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazoline derivatives.

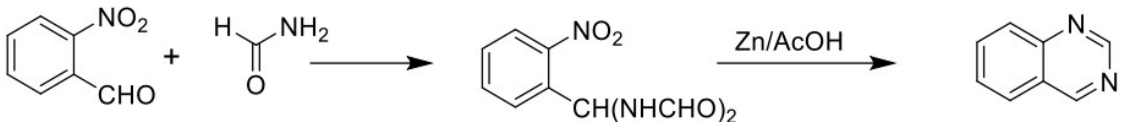
Compounds containing 4(3H)-quinazolinone ring system have showed antitumor, anticonvulsant, antitubercular activities, anti-inflammatory, analgesic, antimicrobial and anticoccidial activities[9-13]. Quinazoline have been frequently used in medicine[14-16], such as quinethazone and metolazone and are 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.[17]

**Synthetic procedures for quinazolines**

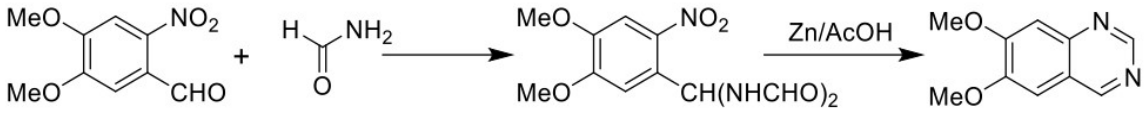
Due to the great importance of quinazoline derivatives across many fields, several synthetic methods have been developed to access quinazoline scaffolds. In 1903, Gabriel described the synthesis of quinazolines by the oxidation of 3,4-dihydroquinazoline.[8]



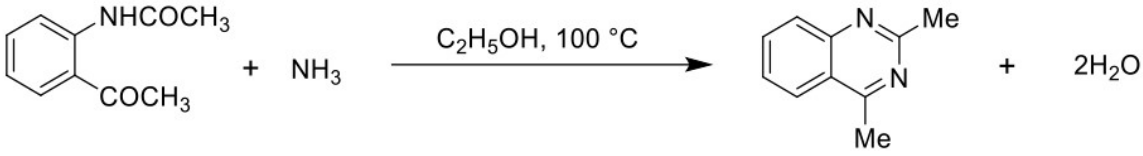
In 1905 Riedel described the synthesis of quinazolines from o-nitro benzaldehyde and amide in the presence of zinc and diluted acetic acid, which leads to corresponding quinazolines with good yields.[18]



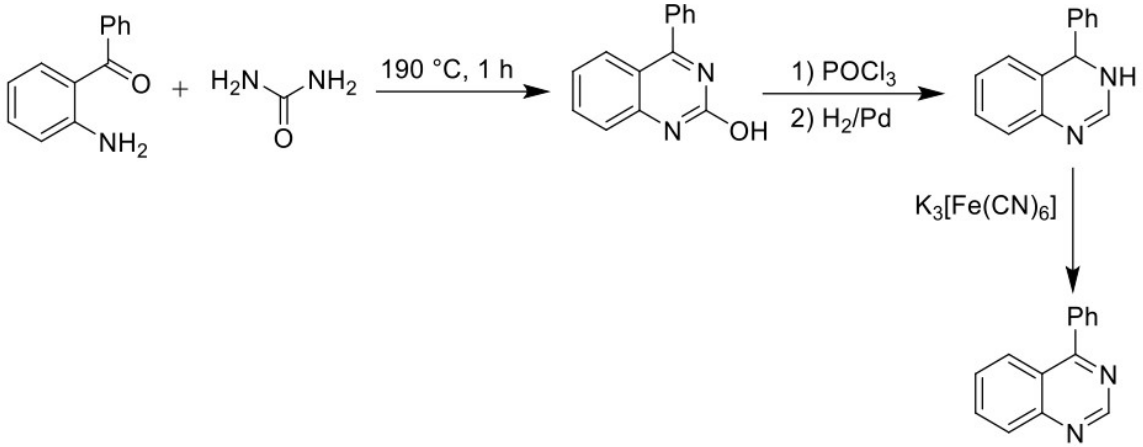

The reaction was modified for the improvement in the reaction yield. This is one of the best methods for quinazolines synthesis which was also applied for the preparation of 6,7-dimethoxyquinazolines by using 6-nitro Vert aldehyde and amide under similar reaction conditions.[19]



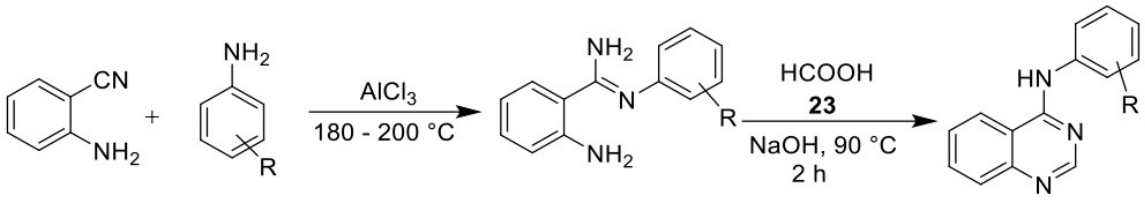

Schofield et al. described the synthesis of 2,4-dimethyl quinazolines from substituted o-amino acetophenone and ammonia in ethanol at 100°C.[20]




Subsequently, the same group synthesized 2-hydroxy-4-phenylquinazolines by the reaction of o-amino benzophenone with urea. The reaction with $POCl_3$ followed by reductive dehalogenation gave dihydroquinoline which on treatment with $K_3[Fe[CN]_6$ gave 4-phenyl quinazoline.




Bujok and his colleagues synthesized quinazolines from 2-aminobenzonitrile and anilines in the presence of anhydrous aluminium-chloride.[21] In the first step, amidines were formed which on treatment with formic acid and sodium hydroxide furnished 4-arylamino quinazolines with good to excellent yields (70-92%). Quinazolines were not observed with 3,4-dichloroaniline or nitro anilines under this reaction condition; this may be due to reduced nucleophilicity of the amino group.




## EXPERIMENTAL AND RESULTS

### *Chemical Characterization*

The synthesized compounds were subjected to determination of yield, melting point, solubility, and structure elucidation. The physicochemical properties are shown in Table 1

**Table 1: Yield and color of synthesized compounds**

| Compound code | Aldehyde Used | Yield (%) | Color |
|---|---|---|---|
| 4a | Cinnamaldehyde | 57 | Yellow |
| 4b | Salicylaldehyde | 63 | Brownish Yellow |
| 4c | Anisaldehyde | 67 | Yellow |
| 4d | Vanillin | 62 | Yellow |
| 4e | 4-dimethylamino benzaldehye | 59 | Brown |

### *Structure Elucidation*

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.

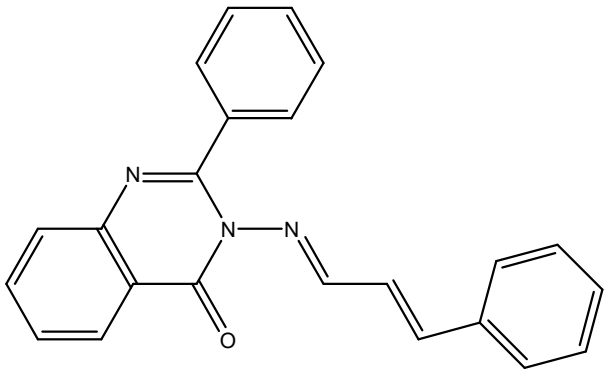



**Fig2: 4a; IUPAC Name** - 2-phenyl-3-((E)-((E)-3-phenylallylidene)amino)quinazolin-4(3H)-one

**Table 2: IR and 1H NMR data of 4a**

| S. No. | NMR signals (ppm relative to TMS) | Wave number ($cm^{-1}$) | Due to… |
|---|---|---|---|
| 1 | 7.2-7.9 Ar H, 8.1 imine H, 5.3-6.5 H of C=C | 3202.53 | Ar/Het C-H Str |
| 2 | | 3042.73 | Ar C-C Str |
| 3 | | 1678.80 | C=N Str |
| 4 | | 1510.55 | N=N Str |
| 5 | | 1428.04 | C-N Str |

MS – 351.4 ($M^+$)

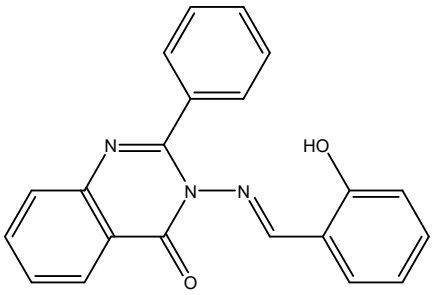



**Fig 3: 4b; IUPAC Name** - (E)-3-(2-hydroxybenzylideneamino)-2-phenylquinazolin-4(3H)-one

**Table 3: IR and 1H NMR data of 4b**

| S. No. | NMR signals (ppm relative to TMS) | Wave number ($cm^{-1}$) | Due to… |
|---|---|---|---|
| 1 | 7.2-7.9 Ar H, 8.1 imine H, 6.8 H adj to OH, 5.0 OH | 3705.25 | O-H str |
| 2 | | 3104.67 | Ar/Het C-H Str |
| 3 | | 2970.38 | Ar C-C Str |
| 4 | | 1639.00 | C=N Str |
| 5 | | 1456.90 | N=N Str |
| 6 | | 1289.63 | C-N Str |
| 7 | | 1082.70 | C-O Str |

MS – 342.2 ($M^+$+1)

**ANTIOXIDANT ACTIVITY**

The antioxidant activity displayed by the synthesized compounds against DPPH and hydroxyl radicals is presented in table 4.

**Table 4: $IC_{50}$ 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 |

The compounds 4d & 4eexhibited 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.

## SUMMARY

In the present work newer antioxidants based on quinazoline nucleus were synthesized and evaluated.The synthesized compounds were characterized for the physicochemical properties such as melting point, color, and solubility. All the compounds were yellowish to brown in colour and were obtained in 57-67% yields using the optimized reaction conditions. The compounds were insoluble in water, slightly soluble in methanol, soluble in chloroform and DMSO.

The confirmation of the structure of the synthesized compounds was done by IR, $^1$HNMR and mass spectral studies. All the compounds exhibited the absorption bands of C=O, C=N, C-H, C=C stretching in the IR spectra. 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.The antioxidant potential of the synthesized compounds was also evaluated and 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.

## 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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CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED