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# A New Route for the Synthesis of Quinazolinones

**A. D. Mishra**
*Prithvi Narayan Campus, Tribhuvan University, Pokhara*
*e-mail: mishraad05@hotmail.com*

## Abstract
Quinazolinone derivatives are highly bioactive heterocyclic compounds with wider range of microbial activities such as anti-malarial, anti-cancer, anti-inflammatory, anti-hypertensive, anti-convulsant, anti-HIV, etc. Solid supported microwave synthesis of some 3-substituted-4-(*2H*)-quinazolinones has been carried out by the reaction of anthranilic acid, formaldehyde and primary aromatic amines. The usage of hazardous reagents and organic solvents has been avoided. The reactions were conducted in presence of acidic alumina where formaldehyde entered into cycloaddition to yield the quinazolinone derivatives. The reactions completed within 2-4 minutes with 82-94% of yields in microwave reactions while it took 5-7 hours for completion affording only 56-68% of the yields in conventional reactions. The synthesized quinazolinone derivatives showed moderate to promising antibacterial and antifungal activities.

**Key words:** *antimicrobial activities, cyclisation, heterocycles, microwave irradiation, quinazolinones, solid support*

## Introduction
Heterocyclic compounds cover a broader area of chemotherapeutic (Wolfe *et al*. 1990). Quinazolinones are important heterocycles with wider range of microbial activities such as anti-malarial, anti-cancer, anti-inflammatory, anti-hypertensive, anti-convulsant, anti-HIV, etc (Tereshina *et al*.1995).These compounds have been synthesized from various precursors by adopting different methods (Zulykama *et al.* 2004, Mishra 2010). Most of the methods are conventional and hazardous from the environmental point of view (Mishra 2009). They take longer time for completion with low yield and involve higher amount of acids, bases and other related chemicals (Mishra 2010, Caddick 1995). The development of some new efficient methodologies for the synthesis of chemotherapeutics is the need of today (Kidwai and Mishra 1999). One of such methods is microwave irradiation technology which is eco-friendly and environment friendly (Metwali and Dosoki 2007). Among the microwave reactions, solution phase and solid phase reactions have drawn the interest of chemists for organic synthesis (Wang *et al*. 2003).

Conventional methods for the synthesis of quinazolinones involves cycloaddition of anthranilic acid derivatives with various reagents including amines, imines, iminohalides, etc. (Gupta and Ajmera 2009, Kidwai and Mishra 2001). Kidwai *et al*. (2001) and Amir *et al.* (2007) synthesized 2-methyl-3-phenyl-4-(*2H*)-quinazolinones by coupling *N* acetylanthranilic acid with the corresponding phosphinoanilines. Quinazolin-4-(*3H*)-one derivatives have been prepared from isatoic anhydride and an orthoester with ammonium acetate or a primary amine, catalyzed by silica-sulphuric acid under solvent free conditions by Salchi *et al.* (2005). Sharma *et al.* (2011) have developed

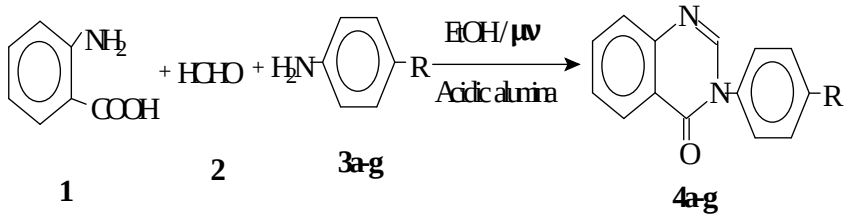
a microwave assisted synthesis of quinazolinones from anthranilic acids, carboxylic acids or acyl chlorides and amines. Hazarkhani *et al.* (2003) described the preparation of various 2-alkyl -4-(*3H*)- quinozolinones using isatoic anhydride, 2-aminobenzimidazole and orthoesters under microwave irradiation. Similarly, Kamal *et al*. (2004) studied the conversion of 2-nitrobenzoic acids to 4-(*3H*)- quinazolinones under microwave irradiations. An efficient synthesis of quinazolinone derivatives has been performed from anthranilic acid, orthoesters and amines in presence of metal catalyst under solvent free conditions by Wang *et al.* (2003). Abdel-Jalil *et al*. (2004) have reported the condensation of anthranilamide with alkyl, aryl or heteroaryl aldehydes in presence of ethanol and cuprous chloride to afford 2-substituted quinazolinones in excellent yield. The one-pot synthesis of quinazolinone derivatives from the reaction of anthranilic acid, trialkyl orthoformate and amines in presence of Lanthanum (III) nitrate hexahydrate or *p*-toluene sulphonic acid, has been reported by Narasimhulu *et al.* (2006).

However, these conventional and microwave methodologies are associated with various drawbacks, like the reaction conditions, availability of reagents and chemical hazards. The synthesis of highly bioactive heterocyclic compounds from simple and easily available reagents under microwave irradiations has been adopted in present synthesis. Some novel 3-substituted-4-(*2H*)-quinazolinones have been synthesized from anthranilic acid, formaldehyde and aromatic amines in solid support under microwave irradiations.

## Methodology

All the chemicals used were purchased from SD Fine Chemicals ltd. Microwave irradiations were carried out in Kenstar Microwave Oven model no. OM9925E at the frequency 2450 MHz and 800 W. IR spectra were recorded on Nicolet 5 PC FT-IR spectrometer in KBr pellets and the frequency was measured in $cm^{-1}$. $^1H$ NMR spectra were recorded on Brucker DRX-300 FT-NMR spectrometer using tetramethyl silane (TMS) as internal reference at 60 MHz with $CDCl_3$ as solvent and chemical shifts δ were measured in ppm. Elemental analysis was performed by means of Heraeus CHN-Rapid analyzer and temperature was measured on AZ Mini Gun Non-contact IR thermometer model no. 8868. All the melting points were determined on a Thomas Hoover Melting Point Apparatus and are uncorrected. The purity of the compounds was checked on silica gel G plates using iodine vapour as visualizing agent. Oxytetracycline and salicylic acid were used as standard drugs for the determination of antibacterial and antifungal activities respectively.

**Scheme 1**




R= a. H b. 4-$CH_3$ c. 4-$CH_2CH_3$ d. 4-$OCH_3$ e. 4-Cl f. 4-Br g. 4-$NO_2$

*General Procedure for the Synthesis of 3-Substituted-4-(2H)-quinazolinones (4a-g)*

## Conventional Method

The equimolar amounts 0.01 moles each of anthranilic acid, formaldehyde and primary aromatic amines **(3a-g)**, were mixed together and dissolved in 25mL of ethanol in round bottomed flask. The resulted mixture was stirred for 10 minutes and refluxed for 5-7 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction the flask content was poured into in 100 mL of cold water to get corresponding 3-substituted-

4-(*2H*)-quinazolinones **(4a-g)**, in solid state. The products were filtered, washed and dried over anhydrous calcium chloride followed by recrystallisation with ethanol. The reaction time and the yields are mentioned in Table 1.Table 2 shows IR and $^1$H NMR spectral characterization data of compounds **(4a-g)**.

**Table 1.** Comparison of reaction time and yield for the synthesis of quinazolinones **4a-g**

| Comp. no. | M.P. ($^0$C) | Reaction Time | | Yield (%) | |
|---|---|---|---|---|---|
| | | Microwave reactions (mins) | Conventional reactions (hrs) | Microwave reactions | Conventional reactions |
| **4a** | 132 | 2.5 | 6.0 | 88 | 62 |
| **4b** | 152 | 3.0 | 6.5 | 85 | 58 |
| **4c** | 158 | 4.0 | 7.0 | 82 | 56 |
| **4d** | 240 | 2.0 | 5.0 | 90 | 62 |
| **4e** | 194 | 2.0 | 5.0 | 93 | 65 |
| **4f** | 200 | 2.5 | 6.0 | 94 | 68 |
| **4g** | 198 | 3.0 | 6.5 | 87 | 60 |

## Microwave Method

Anthranilic acid, formaldehyde and primary aromatic amines **(4a-g)**, in the amount of 0.01 moles each, were mixed together and dissolved in 25 mL of ethanol in a small beaker. The resulted mixture was then adsorbed in 20 g of acidic alumina thoroughly and kept in alumina bath followed by microwave irradiation in the microwave oven for 2-4 minutes with 30 second pulse.

**Table 2.** Spectral characterization data of the compounds **4a-g**

| Comp. no. | IR, υ (Cm$^{-1}$) | $^1$H NMR, δ (ppm) |
|---|---|---|
| **4a** | 3050 (Ar¬H) | 7.4 (m, 9H, Ar¬H) |
| | 1710 (C=O) | 8.1 (S, 1H, Ar¬H) |
| | 1660 (C=N) | |
| | 1570 (C¬N) | |
| **4b** | 3048 (Ar¬H) | 7.3 (m, 8H, Ar¬H) |
| | 1708 (C=O) | 8.0 (S, 1H, Ar¬H) |
| | 1658 (C=N) | 2.2 (S, 3H, ¬$CH_3$) |
| | 1568 (C¬N) | |
| | 2840 (R¬H) | |
| **4c** | 3046 (Ar¬H) | 7.2 (m, 8H, Ar¬H) |
| | 1705 (C=O) | 7.9 (S, 1H, Ar¬H) |
| | 1655 (C=N) | 2.5 (q, 2H, ¬$CH_2$¬) |
| | 1565 (C¬N) | 2.1 (t, 3H, ¬$CH_3$)` |
| | 2838 (R¬H) | |
| **4d** | 3051 (Ar¬H) | 7.3 (m, 8H, Ar¬H) |
| | 1707 (C=O) | 8.2 (S, 1H, Ar¬H) |
| | 1657 (C=N) | 3.8 (S, 3H, ¬$OCH_3$) |
| | 1568 (C¬N) | |
| | 1210 (C¬O) | |
| **4e** | 3056 (Ar¬H) | 7.8 (dd, 2H, Ar¬H) |
| | 1710 (C=O) | 7.5 (dd, 2H, Ar¬H) |
| | 1660 (C=N) | 7.2 (m, 4H, Ar¬H) |
| | 1570 (C¬N) | 8.3 (S, 1H, Ar¬H) |
| | 812 (C¬Cl) | |
| **4f** | 3054 (Ar¬H) | 7.7 (dd, 2H, Ar¬H) |
| | 1708 (C=O) | 7.4 (dd, 2H, Ar¬H) |
| | 1658 (C=N) | 7.1 (m, 4H, Ar¬H) |
| | 1568 (C¬N) | 8.2 (S, 1H, Ar¬H) |
| | 410 (C¬Br) | |
| **4g** | 3060 (Ar¬H) | 7.9 (dd, 2H, Ar¬H) |
| | 1710 (C=O) | 7.6 (dd, 2H, Ar¬H) |
| | 1662 (C=N) | 7.2 (m, 4H, Ar¬H) |
| | 1567 (C¬N) | 8.1 (S, 1H, Ar¬H) |
| | 1420 (N=O) | |

The progress of the reaction was monitored by TLC after each pulse. After the completion of the reaction, the products 3-substituted-4-(*2H*)-quinazolinones **(4a-g)**, were extracted with ethanol (5×10 mL) till the alumina was free of the products in order to make it useful for next reaction. The eluent was recovered by distillation under reduced pressure to get the desired products in solid state. The products **(4a-g)** were obtained in pure state through recrystallisation with ethanol. The reaction time and the yields are mentioned in Table 1.

*Microbiological Evaluation of Quinazolinones (***4a-g***)*

## *In vitro* Antibacterial Activities

The quinazolinone derivatives **4a-g** were evaluated for their *in vitro* antibacterial activities against pathogenic bacteria *Escherichia coli, Rhizobium japonicum, Enterobactor aerogenes, Burkholderia cepacia,* and *Bacillus mojavensis* by the cup-diffusion method (Metwali and Dosoki 2007). The nutrient agar medium (Hi media) was used for microbiological evaluation of the compounds. The suspension of each bacteria was thoroughly spreaded on the surface of the agar medium in Petridishes followed by making several cups (cavities) with the help of presterilized stainless steel cylinder of 8 mm diameter. All the synthesized quinazolinone derivatives **4a-g**, in the concentration of 50 µg/mL were placed in these cavities separately with the help of micropipette and allowed to diffuse for 1 hour. Dimethyl formamide (DMF) was used as the solvent for all the compounds and as a control. These plates were incuvated at 37 $^0$C for 48 hours. The zone of inhibition was measured after incubation and percentage inhibition of the compounds was calculated (Table 3), which gives the biopotentiality of the compounds under evaluation. Oxytetracycline was used as standard drug for study of antibacterial activities.

**Table 3.** *In vitro* antibacterial and antifungal activities of the compounds **4a-g**

| Comp. no. | Antibacterial | | | | Antifungal Activities | |
|---|---|---|---|---|---|---|
| | *E.coli* | *Rhizobium Japonicum* | *Enterobactor aerogenes* | *Bacillus mojavensis* | *Asperigllus niger* | *Aspergillus flavus* |
| **4a** | +++ | ++ | ++ | +++ | +++ | +++ |
| **4b** | + | ++ | - | ++ | + | + |
| **4c** | - | ++ | - | - | ++ | - |
| **4d** | ++ | ++ | +++ | ++ | +++ | ++ |
| **4e** | ++ | ++++ | +++ | ++++ | ++++ | +++ |
| **4f** | ++ | +++ | +++ | +++ | ++++ | +++ |
| **4g** | - | ++ | - | ++ | ++ | + |
| ot* & sa** | ++++ | ++++ | +++++ | ++++ | +++++ | ++++ |

*Oxytetracycline - Reference drug for antibacterial activities:
-: No measurable activity; +:2-4 mm; ++:5-8 mm; +++:9-14 mm; ++++:15-18 mm; +++++:19-22 mm.
** Salicylic acid - Reference drug for antifungal activity:
-: No measurable activity; +:3-7 mm; ++:8-12 mm; +++:13-18 mm; ++++:19-21 mm; +++++:23-28 mm.

### In vitro Antifungal Activities

All the synthesized quinazolinone derivatives **(4a-g)** were evaluated for their antifungal activities against *Aspergillus niger* and *Aspergillus flavu*s by paper-disc diffusion method (Metwali and Dosoki 2007). Saburoud's dextrose agar (Hi-media) was used as culture medium in sterilized petridishes. The suspensions of these fungi are spreaded on the surface of the culture medium with the help of sterilized triangular loop. Then the quinazolinone derivatives were dissolved in DMF with concentration of 50 µg/mL and applied to different paper-discs which were placed on the solid surface of the agar medium. The petridishes were then incuvated for 72 hours at 28 $^0$C. The zones of inhibition around the discs were measured and percentage inhibition of the compounds under experiment were calculated (Table 3) which shows the biopotentiality of the compounds 4a-g against the tested fungal strains. Salicylic acid was used as standard drug for study of antifungal activities.

## Results and Discussion

The synthesis of various 3-substituted-4-(*2H*)-quinazolinones **(4a-g)** was carried out by the reaction of anthranilic acid and substituted primary aromatic amines **(3a-g)** with formaldehyde under conventional and microwave irradiation methods. Formaldehyde links anthranilic acid and aniline molecules to furnish 3-aryl substituted-4-(*2H*)-quinazolinones **(4a-g)** in excellent yield. Microwave reactions were completed within 2-4 minutes affording 82-94% of the products, whereas the conventional reactions took 5-7 hours for the completion yielding 56-68% of the products. Microwave reactions have been proved efficient in terms of reaction time, degree of purity, easy work-up and the usage of non-toxic solvents in limited amount. On the top of this inorganic solid supports can be reused without causing any chemical hazards in the environment.

Formation of the products **(4a-g)** is confirmed by different physical characterization and spectral analysis. The IR absorption of cyclic keto group appears at 1705-1710 $cm^{-1}$ . The appearance of IR bands at 1655-1662 and at 1565-1570 $cm^{-1}$ has confirmed the C=N and C¬N bonds in the products. The aromatic protons have shown the absorption at 3046-3060 $cm^{-1}$ with the variation of substitutions. The other substitutions and the functional groups have shown their characteristic absorptions in IR spectra (Table 2). All the aromatic protons have shown δ value at 7.1-7.8 ppm according to the variations of substituents in the aromatic rings. One of the protons in the diazo-ring has shown $^1$H NMR signal at 7.9-8.3 ppm which is much down field in comparison to other aromatic protons and is justified as the proton is present on the carbon atom in between two nitrogen atoms in the heterocyclic ring of the products **(4a-g)**. The aliphatic protons on substituent groups have shown their characteristic signals in $^1$H NMR spectra (Table 2).

All the quinazolinone derivatives **(4a-g)** were evaluated for their antifungal and antibacterial activities and have shown moderate to excellent antifungal and antibacterial activities (Table 3). The compounds **4a**, **4d**, **4e** and **4f** have shown excellent antibacterial and antifungal activities and **4c** and **4g** are proved to be poor antimicrobial therapeutics. The compound **4b** showed moderate biopotentiality.

Microwave assisted synthesis of various 3-substituted-4-(2H)-quinazolinones **(4a-g)**, by the reaction of anthranilic acid, substituted primary aromatic amines **(3a-g)** and formaldehyde under inorganic solid support yielded up to 94 % of the products within 2-4 minutes of reaction time. This synthetic method has proved as rapid, excellent and environment friendly tool in the synthetic chemistry. The usage of harmful reagents and solvents has been eliminated which makes this method one step more economic for the synthesis of biologically active compounds comparing the conventional methods. The synthesized quinazolinone derivatives have shown moderate to excellent antibacterial and antifungal activities against the tested microbial strains.

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