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## Synthesis and evaluation of some novel 3-[5-phenyl-1,3,4-oxadiazole- 2-yl]-2-(substituted styryl)-quinazoline-4(3H)-ones for antibacterial activity

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**ABSTRACT**

*A series of 3-(5-phenyl-1,3,4-oxadiazole-2-yl)-2-(substituted styryl)-quinazoline-4(3H)-ones **3(a-h)** were synthesized by reacting 2-methyl-3-(5-phenyl-1,3,4-oxadiazole-2-yl)-quinazoline-4(3H)-one **2** and substituted benzaldehydes in glacial acetic acid. 2-methyl-3-(5-phenyl-1,3,4-oxadiazole-2-yl)-quinazoline-4(3H)one **2** was obtained by refluxing 2-methylbenzoxazin-4(3H)-one with the 2-amino-5-phenyl-1,3,4-oxadiazole **1**. 2-Amino-5-phenyl-1,3,4-oxadiazole **1** was prepared by oxidative cyclization of benzaldehyde semicarbazone and bromine in the presence of glacial acetic acid. All the compounds were screened for antibacterial activity by using cup plate method. Out of these compounds unsubstituted styryl compounds showed significant activity.*

**Key words**: 4(3H)-quinazolinones, 1,3,4-oxadiazoles, antibacterial activity.

## INTRODUCTION

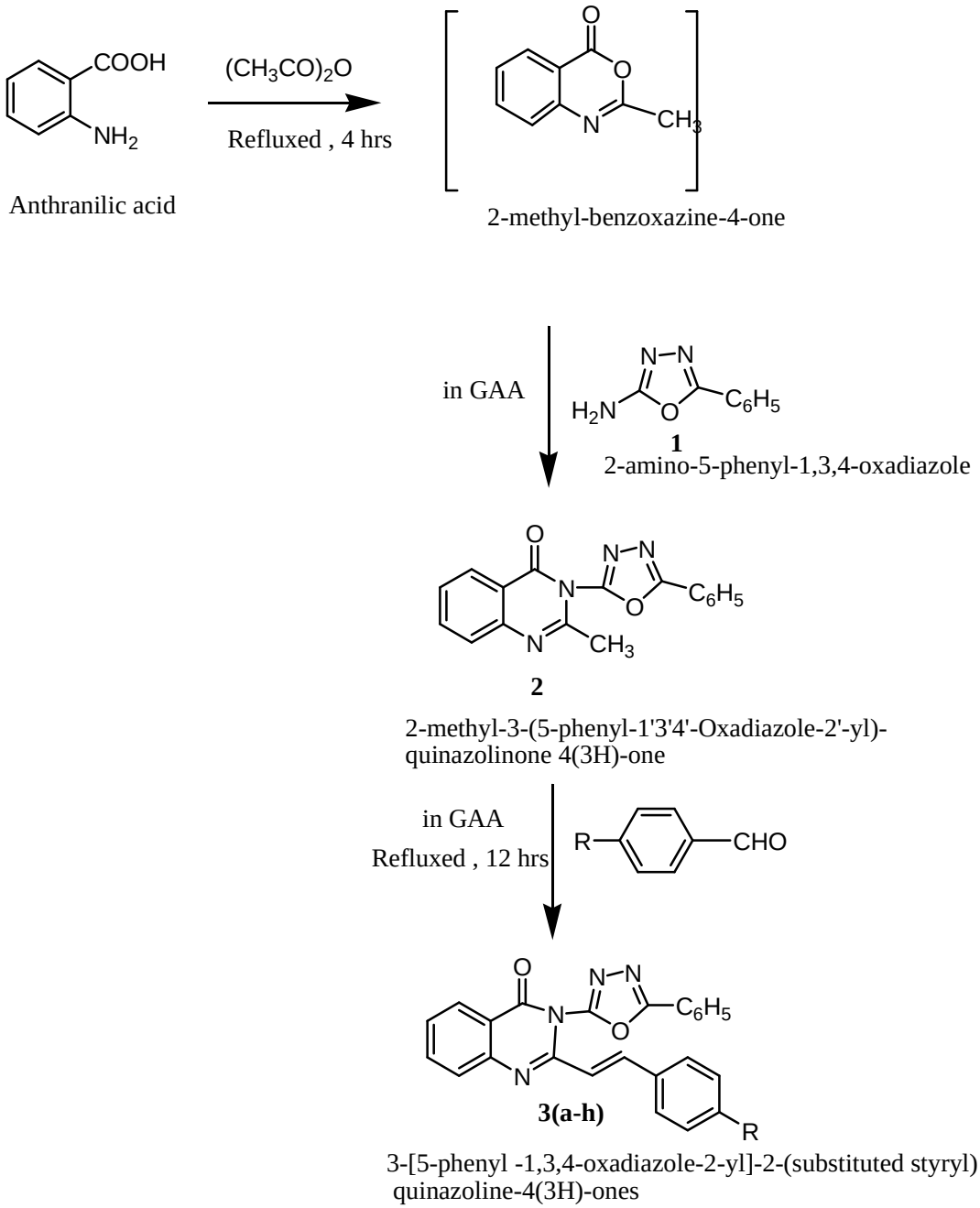
Quinazolinone derivatives are found to show CNS depressant[1], anticancer[2], antibacterial[3], antiinflammatory[4-5] antifungal[6] properties, etc. 1,3,4-oxadiazoles itself possesses antiinflammatory[7], insecticidal[8], antibacterial[9], antimicrobial[10-11] and anticonvulsant[12] activities. In hope of getting synergistic response due to the presence of both quinazolinone and 1,3,4-oxadiazole moieties the present work is aimed to synthesize title compounds and evaluated for their antibacterial activity using cup plate method method.

## EXPERIMENTAL SECTION

All the melting points reported in this series were determined in one end open capillaries using Thermonik Precision Melting Point cum Boiling Point Apparatus Model C-PMB-2, and are uncorrected. Purity of the compounds was confirmed by Thin layer chromatography using silica

gel glass plates and a solvent system. The IR spectra were recorded using KBr Pellets on a Perkin-Elmer 1760 spectrophotometer ($cm^{-1}$). $^1H$ NMR spectra were recorded on GE Omega 400 MHz spectrometer or Bruker Avance (300 MHz) spectrometer, using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a JEOL-JMS-D-300 spectrometer. All solvents are procured from Aldrich and Sigma and are used without further purification.

**Scheme**




**Synthesis of 2-amino-5-phenyl-1,3,4-oxadiazole 1**

Benzaldehyde semicarbazone (0.79gm), sodium acetate (1.5gm) dissolved in glacial acetic acid with continuous stirring. Bromine in acetic acid was added carefully with stirring till a light yellow compound was obtained. The reaction mixture was poured into crushed ice. The resulting solid was filtered, washed with cold water, dried and recrystallized from hot ethanol (95%).

**Synthesis of 2-methyl-3-[5-phenyl-1,3,4-oxadiazole-2-yl]-quinazoline-4(3H)-one 2**

Anthranilic acid (0.01 M) and acetic anhydride were refluxed under anhydrous condition for 4 h. Excess of acetic anhydride was distilled off under reduced pressure. To the mixture obtained, 2-amino-5-phenyl-1,3,4-oxadiazole **1** (0.01 M) in glacial acetic acid was added and refluxed for 4 h and the obtained reaction mixture was poured into crushed ice and kept overnight. The solid which separated out was filtered, thoroughly washed with cold distilled water, dried and recrystallized from hot ethanol (95%).

**Synthesis of 3-[5-phenyl-1,3,4-oxadiazole-2-yl]-2-(substituted styryl)-quinazoline-4(3H)-ones 3(a-h)**

The title compound was synthesized following the procedure reported earlier[13]. A solution of **2** (0.01 M) and substituted benzaldehydes (0.01 M) were reacted in glacial acetic acid (10ml) and refluxed for 12h. The solid **3(a-h)** which separated was filtered with suction and recrystallized from hot ethanol (95%).

**Table 1 – Physicochemical data of the compounds 3a-h**

| Compound | R | Yield (%) | m.p.˚C |
|---|---|---|---|
| **3a** | H | 78 | 198 |
| **3b** | 4-$OCH_3$ | 62 | 208 |
| **3c** | 4-$CH(CH_3)_2$ | 70 | 218 |
| **3d** | 4-Cl | 62 | 232 |
| **3e** | 4-N $(CH_3)_2$ | 68 | 219 |
| **3f** | 4-$NO_2$ | 72 | 232 |
| **3g** | 4-$CH_3$ | 74 | 208 |
| **3h** | 4-OH | 58 | 225 |

**Antibacterial activity**

The new derivatives obtained from the reaction sequence were screened by four test organisms such as *Bacillus subtilis, Escherichia coli, Staphylococcus aureus* (gram-positive) and *Proteus vulgaris* (gram-negative) by using Streptomycin and penicillin as standard drug.

**Cup Plate Method:**

Antibacterial activity was performed by cup plate method by measuring zone of inhibition. All the test compounds were screened for antibacterial activity against bacterial strains *Bacillus subtilis, Staphylococcus aureus* (gram-positive), *Escherichia coli* and *Proteus vulgaris* (gram-negative) at a concentration of 100 µg/ml. Streptomycin and penicillin were used as standard drugs at a concentration of 100 µg/ml. Nutrient agar was used as culture medium & dimethylsulfoxide (DMSO) was used as solvent control. Laminar airflow bench was swapped with 70 % alcohol and UV lamp was switched on. After 30 min, the UV lamp was switched off. All the reagents, media, inoculums and glassware were placed in laminar airflow bench observing all aseptic conditions. The plates were inoculated within minutes of the preparation of suspension, so that the density does not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculums had dried, cups of diameter 6mm were made in the agar plate with a sterile cork borer. The drugs solutions were added to these cups with a micropipette and the plates were then incubated at 37 $^0$C for 24 hours. The zone of inhibition was measured using mm scale. Table 2

**Table 2 - Antibacterial activity of the compounds 3a-3h**

| Compound | R | *B. subtilis* (mm) | *E. coli* (mm) | *S. aureus* (mm) | *P. vulgaris* (mm) |
|---|---|---|---|---|---|
| **3a** | H | 15 | 14 | 15 | 14 |
| **3b** | 4-$OCH_3$ | 8 | 7 | 8 | 10 |
| **3c** | 4-$CH(CH_3)_2$ | 8 | 8 | 10 | 9 |
| **3d** | 4-Cl | 10 | 8 | 10 | 10 |
| **3e** | 4-N $(CH_3)_2$ | 7 | 5 | 6 | 6 |
| **3f** | 4-$NO_2$ | NA | NA | 7 | 6 |
| **3g** | 4-$CH_3$ | 6 | 5 | 6 | 6 |
| **3h** | 4-OH | NA | 6 | 6 | 5 |
| | Penicillin | 16 | 17 | NA | NA |
| | Streptomycin | NA | NA | 15 | 16 |

*NA: No activity.*

Controls were maintained employing 0.1ml of dimethylsulfoxide (DMSO). A blank test was done to check the antimicrobial activity of DMSO.

## RESULTS AND DISCUSSION

Synthesis of title compounds by the earlier described method resulted in products with good yield.

The final products were purified by the recrystallization techniques with methanol. The newly synthesized compounds **3(a-h)**were established on the basis of IR and $^1$H NMR spectroscopy method.

**3-(5-Phenyl-1,3,4-oxadiazole-2-yl)-2-styrylquinazoline-4(3H)-one (3a):**
3179(ArC-H), 1699 (C=O), 1598(C=N), 1210(C-N), 1088cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole). $^1$HNMR (400 MHz, δ), 5.18 (d,1H, olefinic CH), 6.6-7.98(a set of signals, 14H, aromatic protons and olefinic CH).

**2-(4-Methoxystyryl)-3-(5-phenyl-1,3,4-oxadiazole-2-yl)quinazoline-4(3H)-one (3b):**
3186(ArC-H), 1676(C=O), 1583(C=N), 1300(C-N), 1088cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole). $^1$HNMR (300 MHz, δ) 3.9(s, 3H, $OCH_3$), 5.76(d, 1H, olefinic CH), 6.86-8.05 ( a set of signals, 13H, aromatic protons and olefinic CH).

**2-(4-Isopropylstyryl)-3-(5-phenyl-1,3,4-oxadiazole-2-yl)quinazoline-4(3H)-one (3c):**
3186(ArC-H), 1691(C=O), 1553(C=N), 1300(C-N), 1001cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole).

**2-(4-Chlorostyryl)-3-(5-phenyl-1,3,4-oxadiazole-2-yl)quinazoline-4(3H)-one (3d):**
3125(ArC-H), 1683(C=O), 1501(C=N), 1121(C-N), 1075cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole). $^1$HNMR (300 MHz,δ) 5.52 (d, 1H, olefinic CH), 6.82-7.49 ( a set of signals, 13H, aromatic protons and olefinic CH).

**2-(4-Dimethylaminostyryl)-3-(5-phenyl-1,3,4-oxadiazole-2-yl)quinazoline-4(3H)-one (3e):**
3143(ArC-H), 1811(C=O), 1556(C=N), 1275 (C-N), 1066cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole). $^1$HNMR (300 MHz,δ) 3.00(d, 6H, $N(CH_3)_2$) 5.71(d, 1H, olefinic CH ), 6.83-8.14( a set of signals, 13H, aromatic protons and olefinic CH).

**2-(4-Methylstyryl)-3-(5-phenyl-1,3,4-oxadiazole-2-yl)quinazoline-4(3H)-one (3g):**
3179(ArC-H), 1735(C=O), 1457(C=N), 1207(C-N), 1023cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole).

**2-(4-Hydroxystyryl)-3-(5-phenyl-1,3,4-oxadiazole-2-yl)quinazoline-4(3H)-one (3h):**
3122(ArC-H), 1800(C=O), 1497(C=N), 1297(C-N), 1079cm$^{-1}$ (C-O-C of 1,3,4-oxadiazole).

Among the series of the compounds unsubstituted styryl compounds showed significant activity. Substitution either by electron-releasing or electron-attracting moieties at the styryl group resulted in decreased activity. (Table 2)

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