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# Novel Quinazolin-3(*H*)-4-one Derivatives by Microwave Synthesis

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The substituted quinazolinones are reported to possesses anticonvulsant activity as they are cyclic amides and exhibit potent AMPAR non-competitive antagonism. The intermediate compound, 2-phenyl-4*H*-3,1-benzoxazin-4-one was synthesized from anthranilic acid and benzoyl chloride and converted to 3-amino-2-phenylquinazolin-4-(3*H*)-one by treating with hydrazine hydrate. The quinazolin-3(*H*)-4-one derivatives were prepared by condensation of amino group with selected aldehydes or ketones. The test compounds were characterized by interpreting UV, IR, Mass and $^1$H NMR spectra.

**Key Words: Microwave synthesis, Quinazolin-4-(3*H*)-one.**

## INTRODUCTION

Quinazolone moiety, the 'lead' compound chosen, exhibited various pharmacological activities like analgesic, antiinflammatory, antibacterial, anticonvulsant[1] *etc*. It is clearly observed that most of the anticonvulsant drugs have a common group *i.e.* a cyclic amide group like azepins, barbiturates, succinimides *etc*. Hence it is proposed to design and synthesize some novel agents, which bearing the cyclic amide with anticonvulsant property. The literature review of quinazolinones reveals that it also possesses anticonvulsant activity as it is a cyclic amide and exhibit potent AMPAR non-competitive antagonism[2]. A three dimensional pharmacophoric group shall include two hydrophobic, one hydrogen bond acceptor and one aromatic feature. In the light of these references we planned to synthesize C-2 and N-3 disubstituted quinazolones with the proposed general structures (Fig. 1).

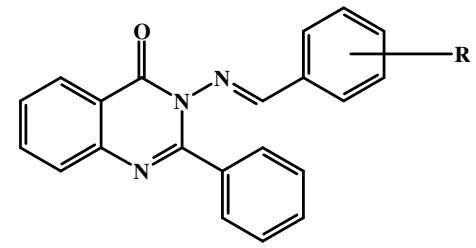


Fig. 1. 2-Phenyl-3-{[(1*E*)-substituted phenylmethylene]amino}quinazolin-4(3*H*)-one

## EXPERIMENTAL

All the chemicals and reagents used were of analytical/synthetic grade. Purity of the compounds was checked by TLC. The melting points were determined by open capillary tube method using thermo electric melting point apparatus (Dalal, Chennai.) and were presented uncorrected. The synthesized compounds were characterized by electronic spectra (UV) in methanol (10-20 µg/mL) in the range 200-400 nm on Jasco V 560 UV/VIS spectrophotometer, IR spectra were recorded using KBr pellets in the range of 4000-500 $cm^{-1}$ on Jasco FTIR model 4100 type A, Proton NMR (300 MHz) spectra were recorded in $CDCl_3$ on Bruker Avance DPX 300. Mass spectra were recorded by FAB+ ionization mode on JEOL JMS600 instrument. Physical data of the newly synthesized compounds were shown in Table-1.

**Synthesis of 2-phenyl-3,1-benzoxazin-4(3*H*)-one (1):** To a stirred solution of anthranilic acid (0.1 mol, 13.7g) in pyridine (60 mL), benzoyl chloride (0.1 mol, 17.57 g) was added drop wise, maintaining the temperature *ca.* 8 ºC for 1 h. Reaction mixture was stirred for another 2 h at room temperature. Whole reaction mixture was neutralized with 5 % $NaHCO_3$ solution[3]. The separated solid was filtered, washed with water and recrystallized from ethanol to get cream coloured crystals [m.w.: 223, Yield (%): 78, m.p.: 120 ºC; $R_f$ (toluene:chloroform(8:2)) 0.7, UV $\lambda_{max}$ (methanol) 313 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$), 3030 (C-H, Ar-H), 1764 (C=O), 1614 (C=N), 1254 (C-O)].

**Synthesis of 3-amino-2-phenylquinazolin-4(3*H*)-one[4,5] (2):** The mixture of the compound **1** (0.05 mol, 11.15 g) and

TABLE-1
PHYSICAL DATA OF THE NEWLY SYNTHESIZED COMPOUNDS

| Compound | Substituent (R) | m.f. | m.w. | m.p. (ºC)* | $R_f$ @ | Microwave method** | | Conventional method | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Time (min) | Yield (%) | Time (min) | Yield (%) |
| **3a** | Ph | $C_{21}H_{15}N_3O$ | 325.3 | 196 | 0.53 | 1.5 | 95 | 120 | 75 |
| **3b** | -*p*-Cl | $C_{21}H_{14}N_3OCl$ | 359.8 | 215 | 0.45 | 2.0 | 95 | 180 | 75 |
| **3c** | 2,3(Cl)$_2$ | $C_{21}H_{13}N_3OCl_2$ | 394.3 | 220 | 0.4 | 2.0 | 94 | 180 | 76 |
| **3d** | *p*-F | $C_{21}H_{14}N_3OF$ | 343.4 | 185 | 0.48 | 2.0 | 93 | 180 | 78 |
| **3e** | *o*-OH | $C_{21}H_{15}N_3O_2$ | 341.4 | 185 | 0.51 | 1.5 | 94 | 150 | 80 |
| **3f** | *m*-$NO_2$ | $C_{21}H_{14}N_4O_3$ | 370.4 | 130 | 0.43 | 1.0 | 95 | 120 | 80 |
| **3g** | *p*-$OCH_3$ | $C_{22}H_{17}N_3O_2$ | 355.4 | 195 | 0.51 | 1.0 | 94 | 120 | 80 |
| **3h** | *o*-$OCH_3$ | $C_{23}H_{17}N_3O_2$ | 355.4 | 205 | 0.49 | 0.5 | 95 | 120 | 76 |
| **3i** | 3,4($OCH_3$) | $C_{23}H_{19}N_3O_3$ | 385.4 | 195 | 0.52 | 1.0 | 96 | 150 | 78 |
| **3j** | 3-$OCH_3$ 4-OH | $C_{22}H_{17}N_3O_3$ | 371.4 | 230 | 0.6 | 1.0 | 95 | 180 | 76 |
| **3k** | 3,5($OCH_3$)$_2$-4(OH) | $C_{23}H_{19}N_3O_4$ | 401.4 | 215 | 0.53 | 1.0 | 94 | 150 | 78 |
| **3l** | *p*-N,N($CH_3$)$_2$ | $C_{23}H_{20}N_4O$ | 368.4 | 235 | 0.45 | 1.5 | 94 | 180 | 75 |
| **3m** | Indole-3-carboxaldehyde | $C_{23}H_{18}N_4O$ | 366.4 | 230 | 0.51 | 2.0 | 94 | 180 | 78 |
| **4** | Isatin | $C_{22}H_{14}N_4O_2$ | 366.3 | 245 | 0.68 | 2.0 | 95 | 180 | 79 |

*Melting point determined in open en capillary tube; @ $R_f$ (Toluene: Chloroform: Methanol) 8:1:1; **microwave irradiation at 400 watts

hydrazine hydrate 99 % (0.1 mol, 4.94 g) in ethanol (50 mL) was refluxed for 3 h and cooled. The separated solid was recrystallized from ethanol [m.w.: 237.25, Yield (%): 83, m.p.: 172 ºC, $R_f$ (toluene:chloroform (8:2) 0.62, UV $\lambda_{max}$ (methanol) 270 nm, IR spectrum (KBr, $\nu_{max}$, $cm^{-1}$) 3316 ($NH_2$), 1659 (C=O), 1602 (C=N)].

**Synthesis of 2-phenyl-3-{[(1*E*)-substituted phenyl methylene]amino}quinazolin-4-(3*H*)-one (3)**

**Conventional method:** A mixture of the compound **2** (0.002 mol, 0.47 g), substituted arylaldehydes/ketone (isatin) (0.002 mol) and 2-3 drops of glacial acetic acid in ethanol (50 mL) were placed in a round bottom flask and refluxed for 3-4 h. After completion of the reaction (monitored by TLC), the solvent was removed by distillation and the product recrystallized from ethanol[6,7].

**Microwave assisted synthesis[8]:** A mixture of the compound **2** (0.002 mol, 0.47 g), different aldehydes/ketone (0.002 mol) and 2-3 drops of glacial acetic acid in ethanol (5 mL) were placed in a beaker and irradiated (400 W) in an unmodified domestic microwave oven for 1-2 min[9,10]. After completion of the reaction (monitored by TLC), the solvent was removed and the residue recrystallized from ethanol.

**2-Phenyl-3-{[(1*E*)-phenylmethylene]amino}quinazolin-4-(3*H*)-one (3a):** General procedure was adopted using benzaldehyde (0.104 g) and irradiated for 1.5 min. UV ($\lambda_{max}$) 304 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3061 (Ar-H) 1648 (C=O), 1601 (C=N), 1519(C-N).

**3-{[(1*E*)-(4-Chlorophenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3b):** General procedure is adopted using *p*-chloro benzaldehyde (0.25 g) and irradiated for 2 min UV ($\lambda_{max}$) 308 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 1654 (C=O), 1604 (C=N), 697 (C-Cl) $^1$H NMR ($CDCl_3$) δ ppm. 6.8-8.4 (Ar-H,15H) MS: m/z, 359 [$M^+$].

**3-{[(1*E*)-(2,4-Dichlorophenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3c):** General procedure was adopted using 2,4 dichloro benzaldehyde (0.35 g) and irradiated for 2 min. UV ($\lambda_{max}$) 317 nm, IR (KBr $\nu_{max}$, $cm^{-1}$) 1649 (C=O), 1584 (C=N), 1521 (C-N), 700 (C-Cl).

**3-{[(1*E*)-(4-Fluorophenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3d):** General procedure was adopted using *p*-fluorobenzaldehyde (0.24 g) and irradiated for 2 min. UV (λmax) 305 nm. IR (KBr, $\nu_{max}$, $cm^{-1}$) 1672 (C=O), 1509 (C-N), 1368 (C-F).

**3-{[(1*E*)-(2-Hydroxyphenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3e):** General procedure was adopted using salicylaldehyde (0.23 g) and irradiated for 1.5 min. UV ($\lambda_{max}$) 332 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3200 (Ar-OH) 3051 (Ar-H Str) 1649 (C=O) $^1$H NMR, ($CDCl_3$) δ ppm 8.6 (s,Ar-OH), MS, m/z, 341 [$M^+$].

**3-{[(1*E*)-(3-Nitrophenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)- one (3f):** General procedure was adopted using 3-nitrobenzaldehyde (0.32 g) and irradiated for 1 min. UV ($\lambda_{max}$) 272 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3059 (Ar-H) 1686 (C=O), 1530 ($NO_2$).

**3-{[(1*E*)-(4-Methoxyphenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3g):** General procedure was adopted using *p*-anisaldehyde (0.27 g) and irradiated for 1 min. UV ($\lambda_{max}$) 320 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 1651 (C=O), 1512 (C-N), 1279 (C-O-C), $^1$H NMR ($CDCl_3$) δ ppm: 3.8, (s, 3H, $OCH_3$), 8.4-6.7(Ar-H, 15H); MS, m/z: 355 [$M^+$].

**3-{[(1*E*)-(2-Methoxyphenyl)methylene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3h):** General procedure was adopted using *o*-methoxybenzaldehyde (0.27 g) and irradiated for 0.5 min. UV ($\lambda_{max}$) 331 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 1686 (C=O), 1652 (C=O) 1603 (C=N), 1524 (C-N).

**3-{[(1*E*)-(3, 4-Dimethoxyphenyl)methyl-ene]amino}-2-phenyl quinazolin-4-(3*H*)-one (3i):** General procedure was adopted using 3,4-dimethoxy benzaldehyde (0.33 g) and irradiated for 1 min. UV ($\lambda_{max}$) 331 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 1673 (C=O) 1599 (C=N) 1510 (C-N str) 1267 (C-O-C).

**3-{[(1*E*)-(4-Hydroxy-3-methoxyphenyl)methylene]-amino}-2-phenyl quinazolin-4-(3*H*)-one (3j):** General procedure was adopted using 4-hydroxy-3-methoxy benzaldehyde (0.30 g) and irradiated for 1 min. UV ($\lambda_{max}$) 332 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3053 (Ar-H) 1650 (C=O), 1599 (C=N), 1512 (C-N).

**3-{[(1*E*)-(4-Hydroxy-3,5-dimethoxyphenyl)methylene]-amino}-2-phenyl quinazolin-4-(3*H*)-one (3k):** General procedure was adopted using 4-hydroxy-3,5-dimethoxy benzaldehyde( 0.36 g) and irradiated for 1 min UV ($\lambda_{max}$) 336

nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3217 (Ar-OH), 1649 (C=O) 1514 (C-N) 1324 (C-O-C).

**3-({(1*E*)-[4-(Dimethylamino)phenyl]methylene}-amino)-2-phenyl quinazolin-4(3*H*)-one (3l):** General procedure was adopted using 4-dimethylamino benzaldehyde (0.29 g) and irradiated for 1.5 min. UV ($\lambda_{max}$) 364 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 1645 (C=O), 1600(C-N), 1359 ($N(CH_3)_2$.

**3-{[(1*E*)-2,3-Dihydro-1*H*-indol-3-ylmethylene]amino}-2-phenyl quinazolin-4(3*H*)-one (3m):** General procedure was adopted using indole 3-carboxaldehyde (0.29 g) and irradiated for 2 min. UV ($\lambda_{max}$) 340 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3215 (N-H), 3053 (Ar-H), 1650 (C=O), 1600 (C=N) 1509 (C-N).

**3-{[(3*E*)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]amino}-2-phenyl quinazolin-4(3*H*)-one (4):** General procedure was adopted using isatin (0.29 g) and irradiated for 2 min. UV ($\lambda_{max}$) 346 nm, IR (KBr, $\nu_{max}$, $cm^{-1}$) 3242 (NH-) 1725 (C=O, isatin), 1650 (C=O), 1604 (C=N), 1530 (C-N).

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