Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

# Microwave-assisted Synthesis of Few 3-(substituted benzylidine)-amino-2-phenylquinazolin-4(3H)-ones and Evaluation of their Anticonvulsant Activity

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ARTICLE INFO

**Article history:**
Received: 14 July, 2022
Revised: 16 August, 2022
Accepted: 22 August, 2022
Published: 30 September, 2022

**Keywords:**
Anticonvulsant, Microwave, Maximal electroshock seizure, 4-Quinazolinone

**DOI:**
10.25004/IJPSDR.2022.140514

ABSTRACT

Quinazolin-4(3*H*)-one derivatives are recognized as central nervous system (CNS) depressants. Epilepsy, the second most common neurological condition after headache, is characterized by recurrent seizures of cerebral origin. Fifty million people worldwide and an estimated 6 to 10 million people in India suffer from epilepsy. It is of concern that the diagnosis and management of epilepsy is often suboptimal in developing countries. There is a growing need for better, stronger, and safer therapeutic treatments for epilepsy. Quinazoline-4(3*H*)-ones were investigated as a potential next step in creating effective antiepileptic drugs. Herein, we report the synthesis of 3-(substituted benzylidine)-amino-2-phenylquinazolin-4(3H)-ones from 3-amino-2-phenylquinazolin-4(3*H*)-one under microwave irradiation as heating source wherever required. The compounds were evaluated for anticonvulsant potential using maximal electro-shock induced convulsions in mice. The chemical structures of the synthesized compounds were confirmed by fourier transform infra-red (FTIR), proton nuclear magnetic resonance ($^1$H-NMR), and carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) studies. All the compounds were subjected to toxicity studies and then evaluated for their anticonvulsant activity against the maximal electroshock (MES) seizure method. $LD_{50}$ was found to be 1098 mg/kg and the duration of tonic phase was reduced upto 1.1 sec and that of stupor phase was reduced upto 80 seconds. Most of the animals were protected from death after induction of convulsions. The structure-activity relationship of the compounds revealed that the 4(3*H*)-quinazolinone schiff bases; *viz.* 3-(N,N-dimethylamino-benzylidine)-amino-2-phenyl- quinazolin-4(3*H*)-one, 3-(p-chlorobenzylidine)-amino-2-phenyl-quinazolin-4(3*H*)-one and 3-(furan-2-yl methyleneamino)-2-phenylquinazolin-4(3*H*)-one; by significantly shortening the tonic and stupor phases of convulsions compared to controls, these compounds demonstrated strong anticonvulsant potential.

## Introduction

The first quinazoline-4(3H)-one compounds were made from cyanogen and anthranilic acid as early as 1869. These compounds can be divided into three groups based on where the keto or oxo group is located.

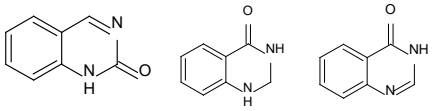

**Fig. 1:** Quinazolin-2(1H)-one 2,3-dihydroquinazolin-4(1H)-one Quinazolin-4(3H)-one

Quinazolinones have demonstrated that these compounds exhibit a broad range of biological actions, including anti-HIV, anti-cancer, anti-fungal, antibacterial, anti-mutagenic, anticonvulsant, anti-inflammatory, central nervous system (CNS) depressant, antimalarial, and antioxidant activity.[1] The therapeutic potential of quinazolinone derivatives in the pharmaceutical and medical industries has received significant attention from chemists in recent decades. According to literature reviews, quinazolinone derivatives are widely known for their anticonvulsant,

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

anti-inflammatory, CNS-depressant, antimicrobial, and anti-cancer properties.[2,3]

An estimated 6 to 10 million individuals in India and 50 million people worldwide suffer from epilepsy, which is a heterogeneous mix of illnesses characterized by neuronal hyperexcitability and hypersynchronous neuronal firing. Antiepileptic medications, which are what the anticonvulsant compounds are also commonly referred to as, are now widely available on the market. About 70% of persons with epilepsy successfully manage their seizures using the AEDs that are now available on the market. However, these medications have serious adverse effects such sleepiness, ataxia, digestive issues, hirsutism, and megaloblastic anemia.[4-6] A series of novel 3-{4-[2-amino-4-(substitutedphenyl)-2*H*-[1,3] oxazin/thiazin-6-yl} 2- phenyl-3*H*-quinazolin-4-one derivatives were synthesized and evaluated for their anticonvulsant activity. Compounds; 3-{4-[2-amino-4-(4-nitro-phenyl)-2*H*-[1,3] oxazin-6-yl} 2-phenyl-3H-quinazolin- 4-one have shown significant activity against tonic seizure by the MES model and 3-{4-[2-amino-4-(4-nitro-phenyl)-2*H*-[1,3] thiazin-6-yl} 2-phenyl-3H-quinazolin-4-one against clonic seizure by scPTZ induced seizure model.[7] Quinazolinone and quinazolinedione acetylenic derivatives were synthesized and tested for their anticonvulsant properties. In the seizure threshold test using subcutaneous pentylenetetrazole, only a small number of substances had noticeable action (scMet test). Using the $ED_{50}$ from the MES test as a guide, 1,3-bis-(prop-2-ynyl) -quinazoline-2,4-(1H,3H)-dione was approximately ten times less effective than phenytoin or carbamazepine, but approximately as effective as mesuximide.[8] It was stated that 2-((6,7-dimethoxy-4-oxo-2-phenylquinazolin-3(4H)-yl) amino)-N-(substituted phenyl) acetamides were rationally designed, and *in-vivo* tests were conducted to screen for anticonvulsant properties. Some substances showed excellent anti-seizure activity in mice when used in chemically induced, electroshock, and pharmacoresistant 6-Hz seizure models, with no signs of neurotoxicity or hepatotoxicity.[9]

By combining quinazoline-4(3*H*)-one hydrazide with substituted aromatic aldehydes, a new series of quinazoline-4(3*H*)-one derivatives were created. It was claimed that quinazoline-4(3*H*)-one hydrazide was used to synthesize several schiff bases. Compounds were screened for anticonvulsant activity by isoniazid (INH) and pentylenetetrazole (PTZ) induced convulsions in mice. This demonstrates the anticonvulsant properties of these compounds, which may be brought about by the CNS's ability to potentiate γ-aminobutyric acid (GABA) action. The presence of electron-donating groups like OH, $NH_2$, and $OCH_3$ and electron-withdrawing groups like $CF_3$ at the second and fourth positions of the aromatic ring linked to the hydrazide was the cause of this anticonvulsant effect.[10]

A new "lead" in organic synthesis is the microwave-assisted synthesis. The method makes it easy, effective, clean, affordable, and quick to synthesize a huge number of organic compounds. The substantially accelerated rate of the reaction, the reduction in time, and the improvement in yield and product quality are all significant benefits of this technology.[6] It was shown in 1986 that numerous organic reactions might happen very quickly when exposed to microwave radiation.[11] Because it is more environmental friendly, this technology is seen as a key step towards green chemistry.[12,13]

Despite the wide range of antiepileptic medications available for therapy, about 25% of epileptic patients experience serious side effects, and about 30% of patients have insufficient seizure control. We have reported here the synthesis of a few substituted 3-amino-2-phenylquinazolin-4(3H)-one and 3-(3-aminophenyl)-2-phenyquinazolin-4(3H)-one and their schiff bases under microwave oven that are expected to have anticonvulsant activity because there is a continuing need to develop more antiepileptic drugs that are effective and have improved safety profiles.

## Materials And Methods

All solvents and reagents were purchased from Sigma Aldrich and Merck Ltd. All synthesis were carried out in a scientific microwave oven CATA 2R, 2450 MHz frequency, 800 W melting points were recorded on electrical melting point apparatus in open capillaries and were uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel coated glass plate and products were purified through recrystallization and purity of the compounds was ascertained by single spot-on TLC sheet in solvent system A-chloroform: ethyl acetate (0.2:0.8) or solvent system B-chloroform: ethyl acetate (1:1) and the spots were located by iodine. The FTIR spectra were recorded on FTIR Shimadzu Affinity-1 infrared spectrophotometer. $^1$H-NMR spectra were recorded on Bruker Avance II 400 spectrometer and TMS as an internal standard. The mass spectra of the samples were recorded using the instrument WATERS, Q-TOF MICROMASS (LC-MS) at SAIF, Punjab University, Chandigarh, India.

### General Procedure

#### *Synthesis of 2-phenyl-3,1-benzoxazin-4-one*

2- amino-benzoic acid (Anthranilic acid) was synthesized as per a reported procedure.[14] Benzoyl chloride (0.02 mol) was added to a solution of anthranilic acid (0.01 mol) in pyridine (30 mL), and the mixture was shaken for 5 minutes before being left at room temperature for another 25 min while being shaken occasionally. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 mL), filtered, washed with water, dried and the crude product was recrystallized from absolute ethanol.[15]

**Table 1:** Reaction conditions for 3-(substituted benzylidine)-amino-2-phenylquinazolin-4(3H)-one.

| *Compound code* | *Ar-* | *Microwave power (Watt)* | *Irradiation time (min)* |
|---|---|---|---|
| QA-1 | p-$OCH_3$-$C_6H_5$ | 420 | 15 |
| QB-2 | -$C_6H_5$ | 455 | 17 |
| QC-3 | p-Cl- $C_6H_5$ | 455 | 16 |
| QD-4 | -$C_4H_4O$ | 455 | 20 |
| QE-5 | p-$N(CH_3)_2$ -$C_6H_5$ | 455 | 20 |
| QF-6 | m-$NO_2$- $C_6H_5$ | 455 | 20 |
| QG-7 | p-OH- $C_6H_5$ | 455 | 15 |
| QH-8 | -$C_7H_6N_2$ | 455 | 10 |

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

A mixture of 2-phenyl-3,1-benzoxazin-4-one (0.01 mol), hydrazine hydrate (99%) (0.012 mol) was dissolved in sufficient ethanol and the reaction mixture was irradiated under microwave at power 350 for 8 minutes. Cooled and the product was isolated by filtration and recrystallized from ethanol.[16]

### *Synthesis of 3-(substituted benzylidine)-amino-2-phenylquinazolin-4(3H)-one*

An equimolar mixture of 3-amino-2-phenylquinazolin-4(3*H*)-one and substituted aromatic aldehydes was irradiated under microwave in sufficient ethanol at power and time mentioned in Table 1. The mixture was cooled to room temperature. Solid thus obtained was filtered, air dried and recrystallized (Fig. 1).[17]

All the animal experiments were conducted according to the guidelines of Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environments and Forests, Government of India with their procedures and protocols reviewed and approved by the Institutional Animal Ethical Committee (IAEC), constituted under CPCSEA; (Protocol approval No. MET/IOP/M. PHARM/2013-14/IAEC/2).

### *Acute Toxicity Studies of Synthesized Compounds*

OECD guidelines (no.425) were followed for acute toxicity studies in mice to obtain median lethal dose ($LD_{50}$). Each animal was observed carefully for the signs of toxicity and mortality in the first 30 minutes after dosing and then occasionally for another 4 hours and daily thereafter for a period of 14 days. The number of mice dying during 48 hours period was recorded.

### *Anticonvulsant Activity of Synthesized Compounds*

The anticonvulsant activity of the synthesized compound was determined by evaluation of the ability of the compounds to protect mice against convulsion induced by electroshock models. The maximal electro-shock induced convulsion in animals represents grand mal type of epilepsy. In MES-convulsions electroshock (54 mA and 0.2 s) is applied through the corneal electrodes.

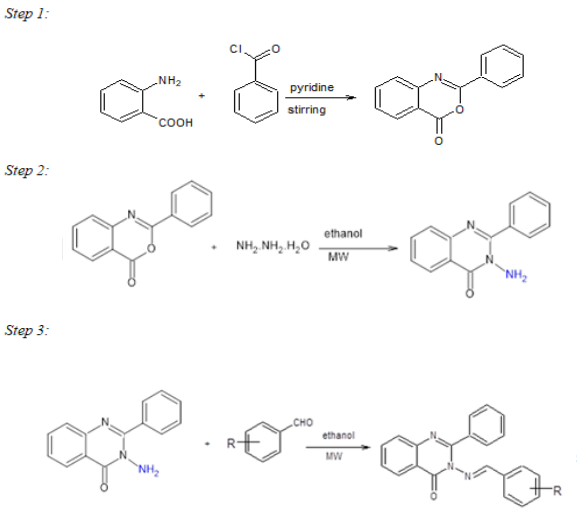


**Figure 1:** Scheme for synthesis of 3-(substituted benzylidine)-amino-2-phenylquinazolin-4(3H)-ones

A substance known to possess anticonvulsant property it reduces or abolishes the extensor phase of MES convulsion. For each compound, a group of 6 male swiss albino mice (22–30 gm) were used. Phenytoin 25 mg/kg was considered as a reference for anticonvulsant effect in all the models. The synthesized compounds, phenytoin were administered 30 minutes before application of electroshock (54 mA and 0.2 s). The hind limb tonic extensions were observed during next 30 minutes.

## Results And Discussion

### Chemistry

A synthesis of few substituted 3-amino-2-phenylquinazolin-4(3*H*)-one and their schiff bases under microwave oven which are expected to have anticonvulsant activity. The synthesis of novel compound comprised of four steps; firstly, the anthranilic acid was prepared, then from anthranilic acid benzoxazinone were prepared and then by using hydrazine hydrate and aniline derivatives quinazolinones were prepared from which the final compound as their schiff bases were synthesized. The substituted quinazolinones, derivatives were prepared by microwave technique at power 420 or 455 W. (60–65% of total capacity of the oven) The microwave technique is rapid and efficient resulting in reduced reaction times; up to 10–20 minutes The compounds were obtained in moderate to good yields ranging from 64–82%. The synthesized compounds were confirmed based on IR, wherein the characteristic peak for C=N (Imine) was observed within 1600–1693 $cm^{-1}$, $^1$H-NMR wherein the characteristic δ-valve for C-H benzylidene proton was observed within 8.13–8.70 ppm and $^{13}$C- NMR studies.

**Table 2:** Anticonvulsant effect of few 3-(substituted benzylidine)- amino-2-phenylquinazolin-4(3H)-ones in mice using MES method.

| *S. no.* | *Compound code* | *Dose (mg/kg)* | *Duration in seconds (Mean ± SEM)* | | | *Recovery/Death* |
|---|---|---|---|---|---|---|
| | | | *Tonic* | *Straub tail* | *Stupor* | |
| 1 | Electroshock (control) | 54 mA for 0.2 sec | 5 ± 0.000 | Present | 184 ± 0.8367 | Recovery |
| 2 | Phenytoin | 25 | 2.6 ± 0.5477 | Absent | 42 ± 2.074 | Recovery |
| 3 | QA-1 | 110 | 1.8 ± 0.7456 | Absent | 113 ± 1.643 | Recovery |
| | | 150 | 1.4 ± 0.2388** | Absent | 81.2 ± 1.304** | Recovery |
| 4 | QB-2 | 110 | 2.1 ± 0.5482 | Absent | 133 ± 2.074 | Recovery |
| | | 150 | 2.0 ± 0.4472 | Absent | 124 ± 1.384 | Death |
| 5 | QC-3 | 110 | 1.4 ± 0.2388** | Absent | 115 ± 1.2345* | Recovery |
| | | 150 | 1.2 ± 0.4140** | Absent | 80 ± 0.5624** | Recovery |
| 6 | QD-4 | 110 | 1.6 ± 0.1267* | Absent | 84 ± 2.550** | Recovery |
| | | 150 | 1.2 ± 0.2344** | Absent | 51.2 ± 0.8367 | Recovery |
| 7 | QE-4 | 110 | 1.3 ± 0.1145* | Absent | 135 ± 0.2356* | Recovery |
| | | 150 | 1.1 ± 0.1325** | Absent | 100 ± 0.1456* | Recovery |
| 8 | QF-6 | 110 | 1.6 ± 0.2477* | Absent | 183 ± 1.000NS | Recovery |
| | | 150 | 1.4 ± 0.2302* | Absent | 147 ± 3.000* | Recovery |
| 9 | QG-7 | 110 | 1.9 ± 0.2617* | Absent | 104 ± 1.155* | Recovery |
| | | 150 | 1.7 ± 0.2491* | Absent | 91.2 ± 0.716* | Recovery |
| 10 | QH-8 | 110 | 1.8 ± 0.1627* | Absent | 110 ± 0.248* | Recovery |
| | | 150 | 1.6 ± 0.3790* | Absent | 99.5 ± 0.506* | Recovery |

N=6, in each group; *$p$ <0.05; **: $p$ <0.01; NS: Non significant; one-way ANOVA followed by Dunnett's test. Value expressed as Mean ± SEM.

### *2-phenyl-3,1-benzoxazin-4-one*

Grayish solid in 86% 3.78 g, mp: 180–184°C, $R_f$ value: 0.8 (solvent system A), IR $V_{max}$ (KBr $cm^{-1}$): 1157(C-O), 1645(C=N), 1670(C=C), 1747(C=O).

### *3-amino-2-phenylquinazolin-4(3H)-one*

Yellowing white solid in 72% 3.8g, mp: 290°C dec., $R_f$: 0.7 (solvent system A), IR $V_{max}$ (KBr $cm^{-1}$): 1213(C-N), 1541 (C=N), 1595(C=C), 1701(C=O), 3481($NH_2$).

### *3-(4-methoxybenzylideneamino)-2-phenylquinazolin-4(3H)-one(QA-1)*

White crystalline solid in 66% 1.17 g, mp: 120–124°C, $R_f$: 0.68 (solvent system B), IR $V_{max}$ (KBr $cm^{-1}$): 1151 (C-N), 1180(C-O), 1357($CH_3$), 1500(C=C),1600(N=C-H), 1670(C=N), 1701(C=O); $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-$d_6$): $\delta$ 3.79 (s, 3H, $CH_3$), 7.30 (ddd, 2H, aromatic), 7.40–7.73 (m, 10H, aromatic), 8.17 (ddd, 1H, aromatic), 8.53 (s, 1H, imine C-H). $^{13}$C-NMR ($\delta$c ppm, DMSO-$d_6$): 56.0, 114, 119, 126, 127, 128, 130, 134, 147, 151, 160, 165.

### *3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one (QB-2)*

White crystalline solid in 64% 1.04 g, mp: 76–80°C, $R_f$: 0.8 (solvent system B), IR $V_{max}$ (KBr $cm^{-1}$): 1128 (C-N), 1519(C=C), 1622(N=C-H), 1674(C=N), 1712(C=O), $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-d6): 7.37-7.73 (m, 11H, aromatic), 8.10–8.24 (ddd, 3H, aromatic), 8.64 (s, 1H, imine C-H); $^{13}$C-NMR ($\delta$c ppm, DMSO-$d_6$): 119, 126, 127, 128, 129, 134, 147, 151, 165.

### *3-(4-chlorobenzylideneamino)-2-phenylquinqzolin-4(3H)-one (QC-3)*

Off White solid in 79% 1.41 g, mp:140–144°C, $R_f$: 0.6 (solvent system B), IR $V_{max}$ (KBr $cm^{-1}$): 755(C-Cl), 1138(C-N), 1676(C=N), 1625(N=C-H), 1703(C=O), 1595(C=C), $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-$d_6$): 7.36 (2H, ddd, aromatic), 7.42–7.74 (m, 10H, aromatic), 8.15 (ddd, 1H, aromatic), 8.61 (s, 1H, imine C-H); $^{13}$C-NMR ($\delta$c ppm, DMSO-$d_6$): 119, 126, 127, 128, 129, 134, 147, 152, 164.

### *3-(furan-2-ylmethyleneamino)-2-phenylquinazolin-4(3**H**)-one(QD-4)*

White solid in 70% 1.10 g, mp: 80–84°C, $R_f$: 0.75, (solvent system B), IR $V_{max}$ (KBr $cm^{-1}$): 3062 (furan C-H), 1107 (C-N), 1693(C=N), 1643(N=C-H), 1714(C=O), 1593(C=C); $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-$d_6$): 6.37 (dd, 1H, aromatic), 6.93 (dd, 1H, aromatic), 7.39-7.72 (m, 9H, aromatic), 8.19 (ddd, 1H, aromatic), 8.36 (s, 1H, imine C-H); $^{13}$C-NMR ($\delta$c ppm, DMSO-$d_6$): 112, 114, 119, 126, 127, 128, 133, 144, 146, 149, 152, 166.

### *3-((4-N,N-dimethylamino)benzylideneamino)-2-phenylquinazolin-4(3H)-one(QE-5)*

Yellowish solid in 82% 1.50 g, mp:60–64°C, $R_f$: 0.6 (solvent system B); IR $V_{max}$ (KBr $cm^{-1}$): 1124(C-N),1670(C=N), 1649(N=C-H), 1751(C=O), 1589(C=C); 2906(C-H); $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-$d_6$): 2.77 (s, 6H, -$CH_3$), 6.73 (dd, 2H, aromatic), 7.33-7.63 (m, 10H, aromatic), 8.17 (dd, 1H, aromatic ), 8.56 (s, 1H, imine C-H); $^{13}$C NMR ($\delta$c ppm,

DMSO-$d_6$):40.3 , 112.0 , 119, 126, 127, 128, 129, 134, 147, 151, 152, 165.

### *3-(3-nitrobenzylideneamino)-2-phenylquinazolin-4(3H)-one (QF-5)*

Yellowish solid in 80% 1.48 g, mp:130–134°C, $R_f$: 0.76 (solvent system B), IR $V_{max}$ (KBr $cm^{-1}$): 1344(NO2 grp), 1091(C-N), 1687(C=N), 1645(N=C-H), 1714(C=O), 1595(C=C); $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-$d_6$): 7.36–7.68 (m, 9H, aromatic), 8.10–8.36 (ddd, 2H, aromatic ), 8.63–8.77 (dd, 2H, aromatic 8.70 (s, 1H, imine C-H); $^{13}$C-NMR ($\delta$c ppm, DMSO-$d_6$): 118, 123, 124, 126, 127, 128, 129, 136, 145, 146, 147, 150, 164.

### *3-(4-hydroxybenzylideneamino)-2-phenylquinazolin-4(3H)-one (QG-7)*

White crystalline solid in 71% 1.21 g, mp:110–114°C, $R_f$: 0.73 (solvent system B), IR $V_{max}$ (KBr $cm^{-1}$): 3350(OH), 1178(C-N), 1600(C=N), 1620(N=C-H), 1714(C=O), 1487(C=C); $^1$H-NMR (400 MHz, $\delta$ ppm, DMSO-$d_6$): 7.22(ddd, 2H, aromatic), 7.38-7.71 (m, 11H, aromatic), 8.22 (s, 1H, imine C-H). 8.53 (s, 1H, OH); $^{13}$C-NMR ($\delta$c ppm, DMSO-d6): 116, 119, 125, 126, 127, 128, 130, 134, 146, 147, 150, 157, 164.

### *3-(benzimidazol-2-ylmethylene) amino-2-phenylquinazolin-4(3H)-one(QH-7)*

Brown solid in 72% 1.31 g, mp:182–186°C, $R_f$: 0.68 (solvent system B); $^1$H-NMR (400 MHz, δ ppm, DMSO-$d_6$): 7.10 (ddd, 1H, aromatic), 7.35-7.73 (m, 10H, aromatic) 7.99 (ddd, 1H, aromatic), 8.13 (s, 1H, imine C-H,), 8.55 (s, 1H, N-H); $^{13}$C-NMR (δc ppm, DMSO-$d_6$): 114, 118, 119, 126, 127, 128, 138, 143, 146, 150, 151, 164.

## Pharmacological Evaluation

### *Determination of $LD_{50}$ (Acute Toxicity Study)*

$LD_{50}$ was calculated by using the software AOT425StatPgm. $LD_{50}$ was calculated as 1098 mg/kg. The actual doses taken for evaluation of activity of the synthesized compounds were dose I: 110 mg/kg (approx. 1/10$^{th}$ that of $LD_{50}$) and dose II: 160 mg/kg (approx.1.5 times of dose I).

### *Anticonvulsant Activity Study*

The maximal electroshock induced seizures is feasible animal model to evaluate the compound for potential as anticonvulsant activity. A 54 mA current applied to the ear pinna electrodes for 0.2 seconds was enough to cause the classic tonic-clonic convulsions with the recognizable stupor phase and straub tail phases. Here, the absence of straub tail stages, the shortening of the duration of these distinct phases, and the recovery of the animals were noticed and compared to the control. Observations were recorded in Table 2. The duration of severe tonic phase was reduced up to 1.1 to 2.1 seconds, and that of stupor phase was reduced up to 51.2 to 183 seconds compared to control.

In the present investigation, quinazolinone derivatives were synthesized to achieve enhanced anticonvulsant effect. Reaction times were significantly shortened by the use of microwave technology in synthesis, reaching only a few minutes. With good yield, a number of quinazolinone derivatives were created, their anticonvulsant properties were assessed, and spectral data were used to describe them. The quinazolin-4(3*H*)-one schiff bases; 3-(N,N-dimethylaminobenzylidine)-amino-2-phenylquinazolin-4(3*H*)-one, 3-(p-chlorobenzylidine)-amino-2-phenylquinazolin-4(3*H*)-one, 3-(furan-2-ylmethyleneamino)-2-phenylquinazolin-4(3*H*)-one showed substantial anticonvulsant potential by shortening the tonic and stupor phases of convulsions compared to control.

## Acknowledgment

Authors are thankful to Principal, Management of Mumbai Education Trust's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik, India for providing the necessary facility to undertake this research and Director, SAIF, Punjab University for providing the necessary instrumental faculty for structural analysis of compounds.

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HOW TO CITE THIS ARTICLE: Rishipathak DD, Karanjikar CV, Udavant PB. Microwave-assisted Synthesis of Few 3-(substituted benzylidine)-amino-2-phenylquinazolin-4(3H)-ones and Evaluation of their Anticonvulsant Activity. Int. J. Pharm. Sci. Drug Res. 2022;14(5):602-607. **DOI:** 10.25004/IJPSDR.2022.140514