ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 8, pp. 1455–1461. © Pleiades Publishing, Ltd., 2020.

# Synthesis, Characterization, and Biological Evaluation of 2-(*p*-Nitrophenyl)quinazolin-4(3*H*)-one Derivatives

**V. N. Giradkar[a], U. D. Kabra[a,b], R. S. Diwakar[a], R. T. Lohiya[a,*], and M. J. Umekar[c]**

[a] *Department of Pharmaceutical Chemistry, Smt. Kishoritai Bhoyar College of Pharmacy, Nagpur, 441002 India*
[b] *Department of Pharmaceutical Chemistry, Parul Institute of Pharmacy, Parul University, Vadodara, 391760 India*
[c] *Principal of Smt. Kishoritai Bhoyar College of Pharmacy, Nagpur, 441002 India*
**e-mail: rtlohiya@gmail.com*

Received February 24, 2020; revised February 29, 2020; accepted March 02, 2020

**Abstract**—A series of novel 2-(4-nitrophenyl)-3-(R-benzothiazol-2-yl)quinazolin-4(3*H*)-ones **4a–4g** (R = Alk, AlkO, Hal, $NO_2$) were synthesized from the corresponding substituted 2-aminobenzothiazoles and 2-(4-nitrophenyl)-4*H*-3,1-benzoxazin-4-one via a nucleophilic addition reaction. The structures of the novel compounds were assigned on the basis of the elemental analyses and FTIR, $^1$H NMR, and mass spectra. The synthesized compounds were tested for anticonvulsant, antimicrobial, and antioxidant activities. All the compounds increased the seizure latency compared to control. Compound **4b** (R = 6-$NO_2$) exhibited significant anticonvulsant activity, comparable to that of the standard drug Phenytoin. Antimicrobial activity testing revealed moderate to good activity in all the test compounds, and **4a** (R = H) and **4b** compared in activity with the standard drug Chloramphenicol. The antioxidant activity of compounds **4a**, **4d** (R = 5-Br), and **4f** (R = 4,6-$Me_2$) ($IC_{50}$ 39.30, 15.55, and 42.95 μg/mL, respectively) was found to be higher compared to the standard drug ascorbic acid ($IC_{50}$ 48.30 μg/mL).

**Keywords:** quinazolinone, benzothiazole, anticonvulsant, antimicrobial, antioxidant

**DOI:** 10.1134/S1070428020080175

## INTRODUCTION

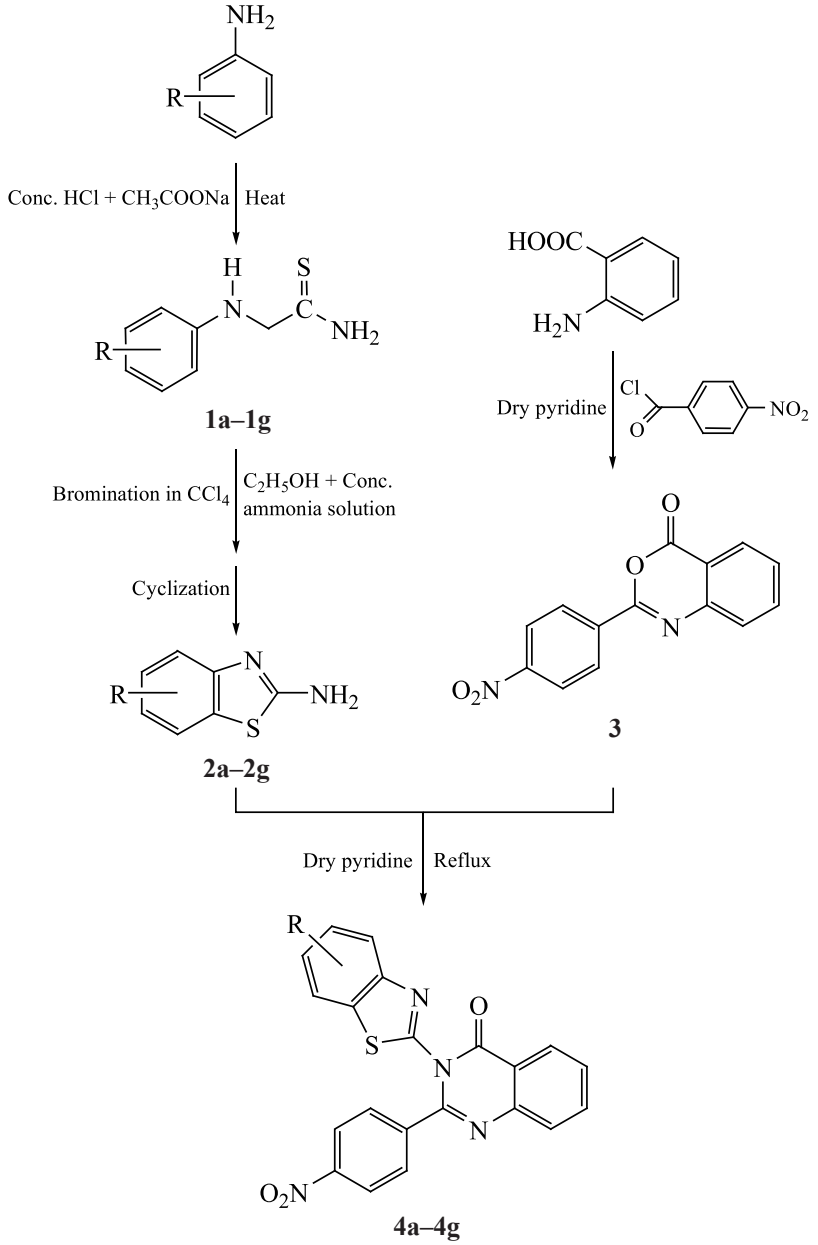
Quinazolinone belongs to the class of fused heterocycles, which have diverse biological activities, including antibacterial, antioxidant, antifungal, anticonvulsant, anticancer, antidiabetic, and anti-inflammatory [1–6]. Therefore, the quinazolinone scaffold has been incorporated into variety of drugs: Diproqualone (analgesic), Gefitinib (anticancer), and Piriqualone (anticonvulsant) [7]. Inspection of the literature showed that different substituents at the $N^2$ or $N^3$ position of the quinazolinone nucleus modulate the biological activity [8]. Para substitution in the 2-phenyl group of quinazolinone was found to induce a higher biological activity than *meta*- or *ortho*-substitution; furthermore, electron-acceptors substituents, like $NO_2$, F, or Cl, yielded more potent biologically active compounds [9–11]. One of the most useful moieties, which can be introduced in the $N^3$ position of the quinazolinone ring to enhance the biological activity, is benzothiazole [12]. Alkyl, alkoxy, or halogen substituents at different positions of the benzothiazole nucleus improved the activity and potency of the starting compounds. Benzothiazole and its derivatives showed such interesting biological activities, including anticonvulsant, antibacterial, anti-inflammatory, antifungal, antioxidant, and anticancer [13–19]. In view of the significant biological potential of both quinazolinone and benzothiazole, we set ourselves the goal to synthesize, characterize, and assess the biological activity of a series of compounds comprising both the quinazolinone and benzothiazole rings.

## RESULTS AND DISCUSSION

2-(4-Nitrophenyl)-3-(R-benzothiazol-2-yl)quinazolin-4(3*H*)-ones **4a–4g** were synthesized by the reaction sequence shown in the scheme. The structures of the intermediate and final products were confirmed by their $^1$H NMR, IR, and mass spectra and elemental analyses (Scheme 1).

Compounds **4a–4g** were screened for anticonvulsant, antibacterial, and antioxidant activity. Among all the synthesized compounds, compound

**Scheme 1.**




**1**, **2**, **4**, R = H (**a**), 6-$NO_2$ (**b**), 4-EtO (**c**), 5-Br (**d**), 4-Cl (**e**), 6-MeO (**f**), 4,6-$Me_2$ (**g**).

**4b** showed significant anticonvulsant activity in the pentylenetetrazole (PTZ)-induced seizure assay in mice, comparable with the activity of the standard drug Phenytoin. Compounds **4a**, **4d**, and **4e** showed medium activity, and compound **4c** was the least active (Table 1). Using the cup-plate assay, the synthesized compounds were tested for antibacterial activity against Gram-positive (*S. aureus* and *B. subtilis*) and Gram-negative bacteria (*E. coli* and *P. aeruginosa*). Two of the synthesized compounds, specifically, **4a** and **4b**, were found to be potent antibacterial agents comparing in activity with the standard drug Ciprofloxacin (Table 2). The in vitro antioxidant activity of the synthesized compounds was evaluated by the DPHH assay. Compounds **4a**, **4d**, and **4f** displayed antioxidant activity better than the standard drug ascorbic acid (Table 3).

## EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich and used without further purification. The melting points were determined in open capillary tubes using

**Table 1.** Anticonvulsant activity of compounds **4a–4g** by the PTZ-induced seizure assay in mice[a]

| Entry no. | Compound no. | Seizure score | Latency time, s |
|---|---|---|---|
| 1 | **4a** | 2.2 | 96.6 |
| 2 | **4b** | 0 | – |
| 3 | **4c** | 4.8 | 100.4 |
| 4 | **4d** | 1.8 | 211.6 |
| 5 | **4e** | 1 | 284.8 |
| 6 | **4f** | 2.8 | 112.4 |
| 7 | **4g** | 4.8 | 33 |
| 8 | Saline (control) | 6 | 31.8 |
| 9 | Phenytoin (standard) | 0 | – |

[a] Values are expressed as mean ($n$ = 5).

a Thermoink precision melting point apparatus and are uncorrected. The purity and homogeneity of compounds was controlled by TLC on silica gel G plates in chloroform–toluene (3 : 1); compounds were applied as methanol solutions with capillary tubes; spots were visualized by exposure to iodine vapor or UV light. The elemental analyses were obtained on a Heraus Carlo Erba 1108 CHN analyzer. The IR spectra were recorded for KBr pellets on a Shimadzu 8400s FTIR spectrophotometer. The $^1$H NMR spectra were recorded for DMSO-$d_6$ on a Bruker Advance III 400 MHz spectrometer, internal standard TMS. The mass spectra were obtained on a Shimadzu LC-MS 8040 instrument.

**Synthesis of substituted phenylthiourea 1a–1g** [20]. A solution of ammonium thiocyanate (20 g in 30 mL of water) was slowly added to a warm mixture of substituted aniline (0.2 mol) and conc. HCl (20–25 mL). The resulting mixture was refluxed until turbidity appeared and then poured into cold water. The precipitate of substituted phenylthiourea that formed was filtered off, washed with water, dried, and recrystallized from dilute ethanol (70 vol %).

**Synthesis of substituted 2-aminobenzothiazoles 2a–2g** [21]. In a beaker, the synthesized substituted phenylthiourea **1a–1g** (0.1 mol) in $CCl_4$ (150 mL) was taken. The solution was brominated using a solution of bromine (5 vol % in $CCl_4$) until the orange-yellow color persists. The slurry was kept overnight; the dibromide precipitate that formed was filtered off and washed with $CCl_4$ until the yellow color disappeared. The

**Table 2.** Antibacterial activity of compounds **4a–4g** by the cup-plate assay[a]

| Entry no. | Compound no. | Zone of inhibition, mm | | | |
|---|---|---|---|---|---|
| | | *B. subtilis* | *S. aureus* | *E. coli* | *P. aeruginosa* |
| 1 | **4a** | 19 | 14 | 13 | 16 |
| 2 | **4b** | 18 | 14 | 15 | 15 |
| 3 | **4c** | – | – | – | – |
| 4 | **4d** | 14 | 11 | 10 | 11 |
| 5 | **4e** | 14 | 10 | – | – |
| 6 | **4f** | 13 | 10 | 12 | 13 |
| 7 | **4g** | – | – | – | – |
| 8 | DMSO (control) | – | – | – | – |
| 9 | Ciprofloxacin (standard) | 20 | 16 | 16 | 18 |

[a] (–) No inhibition.

**Table 3.** In vitro antioxidant activity of compounds **4a–4g** by the DPPH assay

| Entry no. | Compound no. | Inhibition, % | | | | | $IC_{50}$, μg/mL |
|---|---|---|---|---|---|---|---|
| | | 20 μg/mL | 40 μg/mL | 60 μg/mL | 80 μg/mL | 100 μg/mL | |
| 1 | **4a** | 52.87 | 51.51 | 39.39 | 54.54 | 42.42 | 39.30 |
| 2 | **4b** | 21.21 | 27.27 | 30.30 | 39.39 | 43.93 | 121.08 |
| 3 | **4c** | 30.30 | 36.36 | 50 | 43.93 | 59.09 | 78.60 |
| 4 | **4d** | 50 | 59.09 | 60.60 | 68.18 | 72.72 | 15.55 |
| 5 | **4e** | 13.63 | 31.81 | 43.93 | 45.45 | 66.66 | 76.21 |
| 6 | **4f** | 34.84 | 51.51 | 62.12 | 68.18 | 72.72 | 42.95 |
| 7 | **4g** | 10 | 13.93 | 38.33 | 50.30 | 55.90 | 85.34 |
| 8 | Ascorbic acid (standard) | 42.42 | 45.45 | 54.54 | 59.09 | 66.66 | 48.50 |

precipitate was dissolved in a rectified spirit (200 mL), and the solution was made basic with a concentrated ammonia solution to precipitate the target substituted 2-aminobenzothiazole. The precipitate was filtered off, washed with water, dried, and recrystallized from dilute ethanol (70 vol %).

**Synthesis of 2-(4-nitrophenyl)-4*H*-3,1-benzoxazin-4-one (3)** [22]. *p*-Nitrobenzoyl chloride (0.01 mol) was added to a stirred solution of anthranilic acid (0.01 mol) in dry pyridine (15 mL). The reaction mixture was further stirred. Small samples of the reaction mixture were taken periodically to check benzoxazin formation: anthranilic acid, *p*-nitrobenzoyl chloride, and pyridine are water-soluble, while benzoxazin not, and it precipitates. Once benzoxazin had formed, the entire reaction mixture was poured into 250 mL of water containing 10% sodium bicarbonate. The product was filtered off, dried, and recrystallized from ethanol (70 vol %).

**Synthesis of 2-(4-nitrophenyl)-3-(substituted benzothiazol-2-yl)quinazolin-4(3*H*)-ones 4a–4g** [23]. 2-Aminobenzothiazole **2a–2g** (0.005 mol) was added in portions to a stirred solution of benzoxazinone **3** (0.005 mol) in dry pyridine (15 mL). The reaction mixture was refluxed for about 9–12 h, and the hot solution was poured into a beaker containing 100 g of crushed ice and 5 mL of conc. HCl. The solid that separated was filtered off, dried, and recrystallized from glacial acetic acid.

**3-(Benzothiazol-2-yl)-2-(4-nitrophenyl)quinazolin-4(3*H*)-one (4a).** Yield 2.76 g (86%), brown crystals, mp 128–132°C, $R_f$ 0.48. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 205, 256.4, 292.4. IR spectrum, ν, $cm^{-1}$: 3080 (C–H), 1697 (C=O), 1690 (C=N), 1456 (C=C), 1540 (N=O), 680 (C–S). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 8.75–7.69 m ($12H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 403.95 (1.5) $[M]^+$, 400.1 (100.0), 401.1 (25.2), 402.1 (8.2). Found, %: C 63.97; H 3.06; N 13.96. $C_{21}H_{12}N_4O_3S$. Calculated, %: C 63.99; H 3.02; N 13.99.

**3-(6-Nitrobenzothiazol-2-yl)-2-(4-nitrophenyl)-quinazolin-4(3*H*)-one (4b).** Yield 2.61 g (95%), yellow crystals, mp 152–154°C, $R_f$ 0.47. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 256.4, 370. IR spectrum, ν, $cm^{-1}$: 3050 (C–H), 1717 (C=O), 1636 (C=N), 1456 (C=C), 1506 (N=O), 680 (C–S). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 8.66–7.52 m ($11H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 446.1 (23.0) $[M]^+$, 445.0 (100.0), 447.0 (5.0), 447.1 (3.7), 446.0 (2.6), 448.0 (1.1). Found, %: C 56.68; H 2.43; N 15.77. $C_{21}H_{11}N_5O_5S$. Calculated, %: C 56.63; H 2.49; N 15.72.

**3-(4-Ethoxybenzothiazol-2-yl)-2-(4-nitrophenyl)-quinazolin-4(3*H*)-one (4c).** Yield 2.97 g (86%), white crystals, mp 124–126°C, $R_f$ 0.30. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 206.2, 256.4, 296. IR spectrum, ν, $cm^{-1}$: 3070 (C–H), 1684 (C=O), 1636 (C=N), 1456 (C=C), 1541 (N=O), 602 (C–S). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.19 t (3H, $OCH_2CH_3$, $J$ 2.3 Hz), 4.25 q (2H, $OCH_2CH_3$, $J$ 2.0 Hz), 8.13– 6.39 m ($11H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 445.10 (27.3) $[M]^+$, 444.09 (100.0), 446.09 (5.9), 446.10 (3.0), 447.09 (1.2). Found, %: C 62.19; H 3.68; N 12.64. $C_{23}H_{16}N_4O_4S$. Calculated, %: C 62.15; H 3.63; N 12.61.

**3-(5-Bromobenzothiazol-2-yl)-2-(4-nitrophenyl)-quinazolin-4(3*H*)-one (4d).** Yield 1.21 g (48%), brown

crystals, mp 120–122°C, $R_f$ 0.47. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 208.4, 250, 304. IR spectrum, ν, $cm^{-1}$: 3080 (C–H), 1717 (C=O), 1670 (C=N), 1456 (C=C), 1541 (N=O), 600 (C–S), 520 (C–Br). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 8.64–7.26 m ($11H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 478.98 (22.5) $[M]^+$, 479.97 (100.0), 477.97 (97.9), 480.97 (24.9), 481.97 (4.9), 479.98 (3.2), 481.98 (3.1), 478.97 (2.2), 482.97 (1.0). Found, %: C 52.66; H 2.35; N 11.62. $C_{21}H_{11}BrN_4O_3S$. Calculated, %: C 52.62; H 2.31; N 11.69.

**3-(4-Chlorobenzothiazol-2-yl)-2-(4-nitrophenyl)-quinazolin-4(3*H*)-one (4e).** Yield 1.31 g (70%), brown crystals, mp 142–144°C, $R_f$ 0.21. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 208.8, 256.2, 294. IR spectrum, ν, $cm^{-1}$: 3060 (C–H), 1680 (C=O), 1640 (C=N), 1456 (C=C), 1540 (N=O), 680 (C–S), 760 (C–Cl). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 8.66–7.27 m ($11H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 435.03 (23.0) $[M]^+$, 434.02 (100.0), 436.02 (36.8), 437.02 (9.1), 436.03 (3.3), 435.02 (2.3), 438.02 (1.7), 438.03 (1.1). Found, %: C 58.10; H 2.60; N 12.92. $C_{21}H_{11}ClN_4O_3S$. Calculated, %: C 58.00; H 2.55; N 12.88.

**3-(6-Methoxybenzothiazol-2-yl)-2-(4-nitrophenyl)quinazolin-4(3*H*)-one (4f).** Yield 2.36 g (66%), gray crystals, mp 130–134°C, $R_f$ 0.58. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 205.2, 256.2, 293.4. IR spectrum, ν, $cm^{-1}$: 3070 (C–H), 2840 ($OCH_3$), 1680 (C=O), 1660 (C=N), 1456 (C=C), 1520 (N=O), 710 (C–S). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 3.74 s (3H, $OCH_3$, *J* 3.2 Hz), 7.95–7.01 m ($11H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 431.08 (24.1) $[M]^+$, 430.07 (100.0), 432.07 (4.9), 432.08 (3.8), 431.07 (2.3), 433.07 (1.2). Found, %: C 61.42; H 3.33; N 13.09. $C_{22}H_{14}N_4O_4S$. Calculated, %: C 61.39; H 3.28; N 13.02.

**3-(4,6-Dimethylbenzothiazol-2-yl)-2-(4-nitrophenyl)quinazolin-4(3*H*)-one (4g).** Yield 0.55 g (19%), black crystals, mp 124–126°C, $R_f$ 0.30. UV spectrum ($CH_3OH$), $\lambda_{max}$, nm: 210, 273.2, 331.2. IR spectrum, ν, $cm^{-1}$: 2960 (C–H), 1716.65 (C=O), 1635.64 (C=N), 1456.26 (C=C), 1541.12 (N=O), 669.30 (C–S). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 2.35 s (3H, 6-$CH_3$, *J* 3.0 Hz), 2.51 s (3H, 4-$CH_3$, *J* 3.0 Hz), 8.19–7.52 m ($10H_{arom}$). Mass spectrum, *m/z* ($I_{rel}$, %): 431.70 (1.2) $[M]^+$, 428.09 (100.0), 429.10 (25.2), 430.09 (4.9), 430.10 (3.9), 429.09 (2.3). Found, %: C 64.51; H 3.80; N 13.13. $C_{23}H_{16}N_4O_3S$. Calculated, %: C 64.47; H 3.76; N 13.08.

**Animals.** Swiss albino mice of either sex, 8–10 weeks old and weighing between 25–30 g were used. Animals were housed in perspex cages under standard conditions of temperature (26 ± 2°C) and 12 : 12 h light : dark cycles. Animals were allowed to acclimatize to laboratory conditions with free access to food and water for a period of 1 week before testing. All the experimental protocols were approved by the Institutional Animal Ethical Committee (IAEC) and experiments were conducted in accordance with the guidelines provided by the Committee for the Purpose of Control Supervision of Experimental Animals (CPCSEA).

**Biological screening. Anticonvulsant activity.** The anticonvulsant activity of compounds **4a–4g** was determined by the pentylenetetrazole (Metrazol or PTZ)-induced seizure assay [24]. Mice were divided randomly into different groups (control, standard, and test) consisting of five animals each. The compounds were administered intraperitoneally, 30 min prior to subcutaneous injection of PTZ (60 mg/kg). Doses of the test compounds were equimolar to the intraperitoneal dose 30 mg/kg of the standard drug Phenytoin. The animals were observed for 30 min after the PTZ injection. The latency to the onset of first generalized tonic-clonic seizures and behavioral changes were monitored. The seizure scores were assigned as follows. An animal in a group was assigned score 0, 1, 3, or 6 if it showed (a) no behavioral signs, (*b*) any myoclonic jerks, (*c*) Straub tail reaction (score 1 for jerk + score 2 for Straub tail), or (*d*) clonus (score 1 for jerk + score 2 for Straub tail + score 3 for clonus). The seizure scores were calculated for each individual animal in a particular group after the PTZ injection. Furthermore, a cumulative kindling score was calculated by adding the score of all the animals in a group divided by the total number of animals in this group. The maximum score an animal could get after PTZ injection was 6. The data were analyzed by One Way ANOVA followed by Dunnett's test using Graph Pad Prism software. A value of $P < 0.05$ was considered as statıstically significant. The results are listed in Table 1.

**Antibacterial activity.** The antibacterial activity of compounds **4a–4g** was determined using the cup-plate assay by measuring the zone of inhibition [25]. The test organisms were Gram-positive (*S. aureus* and *B. subtilis*) and Gram-negative bacteria (*P. aeruginosa* and *E. coli*) at a concentration of 100 μg/mL, and Ciprofloxacin (100 μg/mL) and DMSO were used as the standard

drug and negative control, respectively. Nutrient agar was used as a culture medium. The agar was poured into a sterile Petri dish and inoculated with the test microorganism with a glass spreader. After drying, cups 6 mm in diameter were punched in the agar plates with a sterile cork borer. The cups were then impregnated with the standard drug and test compounds. The plates were then incubated at 37°C for 24 h, after which the zones of inhibition were measured and recorded. Control was also maintained employing 0.1 mL of DMSO. The results are presented in Table 2.

**Antioxidant activity.** The free radical scavenging activity of compounds **4a–4g** was determined using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay [26]. A stock solution of DPPH (100 μg/mL) in methanol was prepared. Methanol solutions of the test compounds of different concentrations (20–100 μg/mL) were prepared, and 1.0 mL of each was diluted with 3.0 mL of methanol. To these solutions, 0.1 mL of the stock solution of DPPH was added, and the resulting solutions were incubated at room temperature for 30 min to complete reaction, after which absorbance was recorded at 516 nm on a UV–VIS spectrophotometer against methanol as a blank. Ascorbic acid was used as control. The DPPH free radical scavenging activity was calculated using the following formula:

$$\% \text{ Scavenging} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100\%,$$

where, $A_{\text{control}}$ and $A_{\text{sample}}$ are the absorbances of the control and test compounds, respectively.

To assess the antioxidant activity, $IC_{50}$ values (the effective concentration, at which 50% of the radicals are scavenged), were also calculated. The results are listed in Table 3.

## CONCLUSIONS

In the present study we synthesized a series of novel 2-(4-nitrophenyl)-4(3*H*)-quinazolin-4(3*H*)-one derivatives, which showed profound anticonvulsant, antioxidant, and antibacterial activities. These results allow the synthesized quinazolinone derivatives to be considered as useful templates for further development of more potent agents.

## ACKNOWLEDGEMENT

The authors wish to express their deep gratitude to Dr. Milind J. Umekar, Principle of Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur for motivating and providing the necessary facility to carry out the research work. The author is also grateful to the Perfomics Analytical Labs LLP, Hyderabad, Sophisticated Analytical Instruments Facility STIC, Kochi and UDPS, Nagpur, for providing spectral data.

## CONFLICT OF INTEREST

The authors is no conflict of interest.

## REFERENCES

1. Kusuma, P.K. and Vedula, G., *Biosci. Biotech. Res. Asia*, 2016, vol. 13, p. 1121. https://doi.org/10.13005/bbra/2141
2. Mishra, A.D., *Nepal J. Sci. Technol*., 2011, vol. 12, p. 133. https://doi.org/10.3126/njst.v12i0.6491
3. Abuelizz, H.A., El Dib, R., Marzouk, M., Anouar, El-H., Maklad, Y.A., Attia, H.N., and Al-Salahi, R., *Molecules*, 2017, vol. 22, p. 1. https://doi.org/10.3390/molecules22071094
4. Hosseinzadeh, L., Aliabadi, A., Rahnama, M., Sadeghi, H.M.M., and Khajouei, M.R., *Res. Pharm. Sci*., 2017, vol. 12, p. 290. https://doi.org/10.4103/1735-5362.212046
5. Saeedi, M., Mohammadi-Khanaposhtani, M., Pourrabia, P., Razzaghi, N., Ghadimi, R., Imanparast, S., Faramarzi, M.A., Bandarian, F., Esfahani, E.N., Safavi, M., Rastegar, H., Larijani, B., Mahdavi, M., and Akbarzadeh, T., *Bioorg. Chem*., 2019, vol. 83, p. 161. https://doi.org/10.1016/j.bioorg.2018.10.023
6. Osarumwense, P.O., Edema, M.O., and Usifoh, O., *IOSR-JAC*, 2018, vol. 11, p. 12. https://doi.org/10.9790/5736-1104011215
7. Hosseinzadeh, L., Aliabadi, A., Kalantari, M., Mostafavi, A., and Khajouei, M.R., *Res. Pharm. Sci*., 2016, vol. 11, p. 210.
8. Karumanchi, A.D., Sarangapani, M., and Sriram, *Int. J. Drug Dev. Res*., 2014, vol. 6, p. 259.
9. Ibrahim, M.K., El-Adl, K., and Al-Karmalawy, A.A., *Bull. Fac. Pharm. Cairo Univ*., 2015, vol. 53, p. 101–116. https://doi.org/10.1016/j.bfopcu.2015.05.001
10. Paneersalvam, P., Raj, T., Ishar, M.P.S., Singh, B., Sharma, V., and Rather, B.A., *Indian. J. Pharm. Sci*., 2010, vol. 72, p. 375. https://doi.org/10.4103/0250-474X.70488
11. Zayed, M.F. and Hassan, M.H., *Saudi Pharm. J*., 2014, vol. 22, p. 157. https://doi.org/10.1016/j.jsps.2013.03.004
12. Pawar, S., Pisal, P., Deodhar, M., Kale, A., and Nigade, G., *Int. J. Pharm. Pharm. Sci*., 2018, vol. 10, p. 57. https://doi.org/10.22159/ijpps.2018v10i10.28480

13. Prabhu, P.P., Panneerselvam, T., Shastry, C.S., Sivakumar, A., and Pande, S.S., *J. Saudi Chem. Soc*., 2015, vol. 19, p. 181. https://doi.org/10.1016/j.jscs.2012.02.001
14. Ajeet and Kumar, A., *Am. J. Pharm. Sci*., 2013, vol. 1, p. 116. https://doi.org/10.12691/ajps-1-6-2
15. Gupta, A., *Asian. J. Pharm. Clin. Res*., 2018, vol. 11, p. 416. https://doi.org/10.22159/ajpcr.2018.v11i9.28095
16. Shakya, A.K., Kumar, A., and Siddiqui, H.H., *Indian J. Heterocycl. Chem*., 2016, vol. 25, p. 243.
17. Dhamak, K.B., Gaware, V.M., and Somwanshi, S.B., *Int. J. Pharm. Pharm. Res*., 2015, vol. 3, p. 112.
18. Gollapalli, N., Karumudi, B.S., Kota, C., Gudipati, M., Suresh, P.V., and Ramarao, N., *Indo Am. J. Pharm. Res*., 2015, vol. 5, p. 1288.
19. Devmurari, V.P., Pandey, S., Goyani, M.B., Nandanwar, R.R., Jivani, N.P., and Perumal, P., *Int. J. ChemTech. Res*., 2010, vol. 2, p. 681.
20. Kabra, U., Chopde, C., and Wadodkar, S., *J. Heterocycl. Chem*., 2011, vol. 48, p. 1351. https://doi.org/10.1002/jhet.754
21. Ugale, V.G., Wadodkar, S.G., and Chopde, C.T., *Asian J. Res. Chem*., 2011, vol. 4, p. 1717.
22. Ganguli, S., Panigrahi, M.K., Singh, P., and Shukla, P.K., *Int. J. Pharm. Pharm. Sci*., 2012, vol. 4, p. 434.
23. Laddha, S.S., Wadodkar, S.G., and Meghal, S.K., *Arkivoc*, 2006, vol. 11, p. 1. https://doi.org/10.3998/ark.5550190.0007.b01
24. Vogel, H.G., *Drug Discovery and Evaluation Pharmacological Assays*, New York: Springer, 2002.
25. Upadhaye, G.J. and Asnani, A.J., *IJPSR*, 2017, vol. 8, p. 1214. https://doi.org/10.13040/IJPSR.0975-8232.8 (3).1314-18
26. Kumar, C.T.K., Keshavayya, J., Ravi, B.N., and Patil, S.R., *Int. J. Innov. Res. Dev*., 2016, vol. 5, p. 13.