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# Synthesis and Anticonvulsant activity of New 2-(Substituted aryl/heteryl)-3-(substituted arylidenimino)-6, 8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one Derivatives

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Methyl-3,5-dibromo anthranilate was methylated from 3,5-dibromo anthranilic acid and converted to 3,5-dibromo anthranil hydrazide by reacting with hydrazine hydrate. The hydrazide was condensed with the different *p*- and *m*-substituted aromatic aldehydes in presence of alcohol and concentrated hydrochloric acid to get the 2-(substituted phenyl/heteryl)-3-(substituted arylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one derivatives (**4–14**). The structures of all the synthesized compounds have been confirmed by $^1$H NMR and mass spectral data. All the synthesized compounds were screened for anticonvulsant activity by ICES test method using phenytoin as standard drug. The test compounds **5** and **14** increase seizure threshold current statistically indicating that they are highly significantly ($p < 0.001$) different from control group, whereas all the compounds showed moderate activity in comparison to standard drug.

**Key Words: Synthesis, Quinazolin-4(3H)-one, 1,2,3,4-tetrahydro quinazolin-4(3H)-one, Anticonvulsant.**

## INTRODUCTION

In recent years, large number of pharmacologically important heterocyclic compounds having quinazolinone nucleus have been synthesized in good number. However, there still exists much scope for synthesizing new compounds in this series. A survey of literature shows that quinazolinones possess varied type of biological activities such as analgesic[1], antiinflammatory[2, 3], anticonvulsant[4, 5], antiviral[6], anticancer[7], CNS depressant[8] and antimicrobial[9, 10]. A comparative study of the structure of morphine, pethidine and methadone reveals that the only common feature in all these compounds is the presence of tertiary nitrogen atom and quaternary carbon in β-relationship to it.

Based upon these features and in continuation to our work on 4(3H)-quinazolinones, it was planned to synthesize some new quinazolinone derivatives with tertiary nitrogen atom and quaternary carbon in β-relationship to the tertiary

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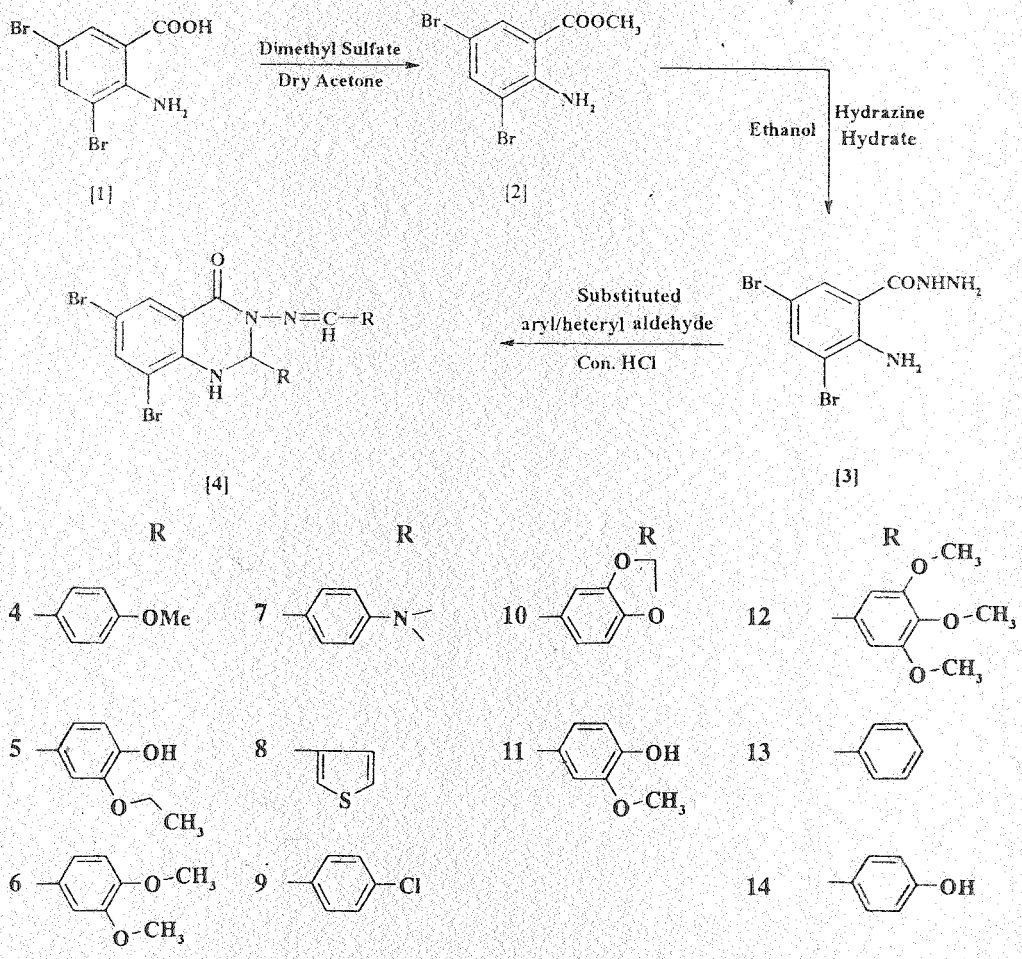
nitrogen atom and electron withdrawing and donating substituted aryl/heteryl moiety at position 2 and 3 of quinazolin-4(3H)-one nucleus. The chemical structures of the synthesized compounds were established on the basis of $^1$H NMR and mass spectral data. The synthesized compounds were tested for their anticonvulsant activity by increasing electroshock seizure (ICES) test method using phenytoin as standard drug.

## EXPERIMENTAL

Melting points of synthesized compounds were recorded in liquid paraffin bath in open capillaries and are uncorrected. All the chemicals were purchased from Merck (India) and SD Fine Chemicals (India). Analytical thin layer chromatographies (TLC) were carried out by precoated silica gel (E. Merck Kieselgel 60 $F_{254}$ layer thickness 0.25 mm) and column chromatographies were performed with silica gel (60–120 mesh). $^1$H NMR spectra were recorded on Bruker 300 MHz spectrophotometer using TMS as internal standard and the mass spectra on Jeol JMS-D 300 double beam spectrophotometer. Microanalyses for C, H, N were performed in Heraeus CHN rapid analyzer and the compounds gave satisfactory chemical analysis (±0.5%).




Scheme-1

**Synthesis of 3,5-dibromo anthranilic acid[11] (1)**

A solution of bromine (0.375 mol ≡ 20 mL) in glacial acetic acid (15 mL) was added in small portions to a hot solution of anthranilic acid (0.124 mol; 17 g) in glacial acetic acid (250 mL) with continuous shaking. The reaction mixture was cooled and the solid mass that separated out was filtered, washed with glacial acetic acid and purified by boiling with water (500 mL) and filtering. This process was repeated five times to remove 5-bromoanthranilic acid and the insoluble mass was crystallized from ethanol to yield 75% (m.p. 228–30°C) of brown coloured crystalline compound (**1**). $^1$H NMR ($CDCl_3$): δ = 7.86 (dd, 1H-Ar), 7.82 (dd, 1H-Ar), 6.3 (s, 2H-$NH_2$). MS m/z: 296 ($M^+$).

**Synthesis of methyl-3,5-dibromo anthranilate (2)**

To a solution of 3,5-dibromo anthranilic acid (0.003 mol; 1 g) and dimethyl sulfate (0.007 mol; 0.924 g ≡ 0.7 mL) in dry acetone (25 mL) was added anhydrous potassium carbonate (3 g) and refluxed for 4 h. After cooling to room temperature the inorganic salt was filtered off and the filtrate was concentrated. The reaction mixture was cooled to room temperature and poured on to crushed ice. The solid mass, which separated out, was filtered, washed with water and crystallized from methanol to yield 66.8% of colourless crystalline compound (**2**), m.p. 78–80°. $^1$H NMR ($CDCl_3$): δ = 3.9 (s, 3H, $CH_3$), 6.3 (s, 2H, $NH_2$), 7.68 (d, 1H, Ar-H), 7.9 (d, 1H, Ar-H). MS m/z: 309 ($M^+$). Anal. Calcd. for $C_8H_7Br_2NO_2$: C, 31.10; H, 2.28; N, 4.53. Found: C, 20.09; H, 2.28; N, 4.51.

**Synthesis of 3,5-dibromo anthranil hydrazide (3)**

To a solution of **2** (0.01 mol, 3 g) in ethanol (20 mL) was added hydrazine hydrate (0.04 mol, 2.3 g ≡ 2.3 mL) and refluxed for 24 h. After cooling to room temperature, the solid mass, which separated, was filtered and crystallized from methanol to yield colourless crystalline compound **3**, m.p. 190–92° (yield 72%). $^1$H NMR ($CDCl_3$): δ = 6.52 (s, 1H, NH), 7.7 (d, 1H, Ar-H), 8.1 (d, 1H, Ar-H), 9.5 (s, 2H, $NH_2$). MS m/z: 309 ($M^+$). Anal.: Calcd. for $C_7H_7Br_2N_3O$: C, 27.21; H, 2.28; N, 13.60; Found: C, 27.10; H 2.2; N, 13.54.

**Synthesis of 2-(substituted aryl/heteryl)-3-(substituted arylidenimino)-6,8-dibromo-1,2,3,4-tetrahydro quinazolin-4(3H)-ones (4–14)**

To a solution of **3** (0.01 mol) in ethanol were added appropriate aldehydes (0.02 mol) and a few drops of concentrated HCl. The reaction mixture was refluxed for 3 h and cooled to room temperature. The solid mass, which separated, was filtered and crystallized to give TCL pure crystals of title compounds **(4–14).**

**2-(4′-Methoxyphenyl)-3-(4″-methoxybenzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (4):** Crystallized from methanol to yield colourless crystalline compound; yield 64%; m.p. 156–158°C; $^1$H NMR ($CDCl_3$) δ = 3.77 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 5.3 (s, 1H, CH), 6.29 (s, 1H, NH), 6.86 (d, 2H, *p*-anisyl), 6.90 (d, 2H, *p*-anisyl), 7.06 and 8.03 (*o*-coupled, d, 2H, dibromo ring), 7.33 (d, 2H, *p*-anisyl), 7.55 (d, 2H, *p*-anisyl) 9.04 (S, 1H, N=CH). MS m/z: 545 ($M^+$). Anal. calcd. for $C_{23}H_{19}Br_2N_3O_3$: C, 50.67; H, 3.51; N, 7.71; Found: C, 50.51; H, 2.49; N, 7.67.

**2-(3′-Ethoxy-4′-hydroxyphenyl)-3-(3″-ethoxy-4″-hydroxybenzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (5):** Crystallized from methanol to give yellow coloured amorphous powder; yield 74%; m.p. 118–120°C; $^1$H NMR ($CDCl_3$) $\delta$ = 1.42 (s, 6H, 2X $OCH_2CH_3$), 4.07 (s, 4H, 2X $OCH_2CH_3$), 5.29 (s, 1H, CH), 6.2 (s, 1H, NH), 6.97 (m, 4H, Ar-H), 7.06 (d, 1H, Ar-H), 7.19 (d, 1H, Ar-H), 7.6 (*m*-coupled, d, 1H, dibromo ring), 8.02 (*m*-coupled, d, 1H, dirbromo ring), 8.9 (s, 1H, N=CH). MS m/z: 605 ($M^+$). Anal. Calcd. for $C_{25}H_{23}Br_2N_3O_5$: C, 49.61; H, 3.83, N, 6.94; Found: C, 49.41; H, 3.83; N, 6.78.

**2-(3′,4′-Dimethoxy phenyl)-3-(3″,4″-dimethoxy benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (6):** Crystallized from ethanol to yield a fluorescent yellowish green coloured crystalline compound; yield 58%; m.p. 176–78°C; $^1$H NMR ($CDCl_3$) $\delta$ = 3.85–3.9 (m, 12H, 4X $OCH_3$), 5.34 (s, 1H, CH), 6.2 (s, 1H, NH), 6.8–7.08 (m, 3H, veteryl ring), 7.42–7.60 (m, 3H, veteryl ring), 7.62 (d, 1H, dibromo ring), 8.02 (d, 1H, dibromo ring), 9.02 (s, 1H, N=CH). MS m/z: 605 ($M^+$). Anal. Calcd. for $C_{25}H_{23}Br_2N_3O_5$: C, 49.61; H, 3.83; N, 6.94; Found: C, 49.73; H, 3.71; N, 6.78.

**2-(4′-Dimethylamino phenyl)-3-(4″-dimethylamino benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (7):** Crystallized from ethanol to yield fluorescent yellowish green coloured crystalline compound; yield 78%; m.p. 244–46°C; $^1$H NMR ($CDCl_3$) $\delta$ = 3.08 (s, 12H, 4X $CH_3$), 5.3 (s, 1H, CH), 6.18 (s, 1H, NH), 6.7 (d, 4H, phenyl), 7.7 (d, 4H, phenyl), 7.8 (d, 1H, dibromo ring), 8.1 (d, 1H, dibromo ring), 9.03 (s, 1H, N=CH). MS m/z: 571 ($M^+$). Anal. Calcd. for $C_{25}H_{25}Br_2N_5O$: C, 52.56; H, 4.41; N, 12.26; Found: C, 52.34; H, 4.39; N, 12.21.

**2-(2′-Thenyl)-3-(2″-thenylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (8):** Crystallized form methanol to yield brown coloured fine crystals; yield 70%; m.p. 180–82°C; $^1$H-NMR ($CDCl_3$) $\delta$ = 5.51 (s, 1H, CH), 6.49 (s, 1H, NH), 6.89–7.08 (m, 3H, thenyl), 7.20–7.42 (m, 3H, thenyl), 7.70 (*m*-coupled d, 1H, dibromo ring), 7.99 (*m*-coupled d, 1H, dibromo ring), 9.67 (s, 1H, N=CH). MS m/z: 497 ($M^+$). Anal. Calcd. for $C_{17}H_{11}Br_2N_3OS_2$: C, 41.07; H, 2.23; N, 8.45; Found: C, 40.90; H, 2.18; N, 8.40.

**2-(4′-Chloro phenyl)-3-(4″-chloro benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (9):** Crystallized from methanol to yield light yellow coloured needle shaped crystals; yield 59.2%; m.p. 178–80°C; $^1$H-NMR ($CDCl_3$) $\delta$ = 5.37 (s, 1H, CH), 6.31 (s, 1H, NH), 7.06 (d, $A_2B_2$ pattern, 1H, dibromo ring), 7.3 (d, $A_2B_2$ pattern, 4H, phenyl), 7.58 (d, 4H, phenyl), 8.01 (d, 1H, dibromo ring), 9.2 (s, 1H, N=CH). MS m/z: 553 ($M^+$). Anal. Calcd. for $C_{21}H_{13}Br_2Cl_2N_3O$: C, 45.52; H, 2.36; N, 7.58; Found: C, 43.33; H, 2.35; N, 7.61.

**2-[(3′,4′-Methylene dioxy)phenyl]-3-[(3″,4″-methylene dioxy)benzylidenimino]-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (10):** Crystallized from ethanol to yield light yellow coloured needle shaped crystals; yield 56%; m.p. 208–10°C; $^1$H NMR ($CDCl_3$) $\delta$ = 5.28 (s, 1H, CH), 6.22 (s, 1H, NH), 5.94 (s, 2H, $CH_2$), 5.99 (s, 2H, $CH_2$), 6.73 (d, 1H, piperonal), 6.78 (d, 1H, piperonal), 6.88 (dd, 1H, piperonal), 7.01 (dd, 1H, piperonal), 7.04 (dd, 1H, piperonal), 7.24 (d, 1H, piperonal), 7.67 (*m*-coupled, d, 1H, dibromo ring), 8.02 (*m*-coupled, d, 1H, dibromo ring), 9.06 (s, 1H, N=CH). MS m/z: 621 ($M^+$). Anal.

Calcd. for $C_{26}H_{27}Br_2N_3O_5$: C, 50.26; H, 4.38; N, 6.76; Found: C, 50.10; H, 4.36; N, 6.78.

**2-(3′-Methoxy-4′-hydroxy phenyl)-3-(3″-methoxy-4″-hydroxy benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (11):** Crystallized from ethanol to yield light yellow coloured crystalline compound; yield 58%; m.p. 216–218°C; $^1$H NMR ($CDCl_3$) $\delta$ = 3.7 (s, 3H, $OCH_3$), 3.8 (s, 3H, $OCH_3$), 6.30 (s, 1H, CH), 6.70 (s, 1H, NH), 6.73 and 6.86 (*o*-coupled, d, 2H, Ar-H), 6.79 and 7.07 (d, 2H, Ar-H), 7.01 and 7.3 (d, 2H, Ar-H) 7.9 (*m*-coupled, d, 1H, dibromo ring), 8.4 (*m*-coupled, d, 1H, dibromo ring), 8.9 (s, 1H, N=CH). MS m/z: 577 ($M^+$). Anal. Calcd. for $C_{23}H_{19}Br_2N_3O_5$: C, 47.86; H, 3.32; N, 7.28; Found: C, 47.66; H, 3.30; N, 7.30.

**2-(3′,4′,5′-Trimethoxy phenyl)-3-(3″,4″,5″-trimethoxy benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (12):** Crystallized from ethanol to yield brownish yellow coloured compound; yield 52%; m.p. 118–120°C; $^1$H NMR ($CDCl_3$) $\delta$ = 3.72 (s, 3H, $OCH_3$), 3.74 (s, 6H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 6.36 (d, 2H, Ar-H), 6.4 (s, 1H, CH), 6.70 (s, 1H, Ar-H), 7.02 (s, 1H, Ar-H), 7.38 (s, 1H, NH), 7.66 (*m*-coupled, d, 1H, dibromo ring), 7.89 (*m*-coupled, d, 1H, dibromo ring), 9.11 (s, 1H, N=CH). MS m/z: 655 ($M^+$). Anal. Calcd. for $C_{27}H_{27}Br_2N_3O_7$: C, 48.74; H, 4.09; N, 6.32; Found: C, 48.54; H, 4.07; N, 6.29.

**2-(Phenyl)-3-(benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (13):** Crystallized from ethanol to yield light yellow coloured needle shaped crystals; yield 76%; m.p. 168–170°C; $^1$H NMR ($CDCl_3$) $\delta$ = 5.41 (s, 1H, NH), 6.36 (s, 1H, CH), 7.36 (*m*-coupled, d, 1H, dibromo ring), 7.35–7.38 (m, 8H, Ar-H), 7.66 (*o*- *m*-coupled, dd, 2H, Ar-H), 8.03 (*m*-coupled, d, 1H, dibromo ring), 9.27 (s, 1H, N=CH). MS m/z: 485 ($M^+$). Anal. Calcd. for $C_{21}H_{15}Br_2N_3O$: C, 51.99; H, 3.12; N, 8.66; Found: C, 51.83; H, 3.11; N, 8.63.

**2-(2′-Hydroxy phenyl)-3-(2″-hydroxy benzylidenimino)-6,8-dibromo-1,2,3,4-tetrahydroquinazolin-4(3H)-one (14):** Crystallized from ethanol to yield yellow coloured crystalline compound; yield 62%; m.p. 228–230°C; $^1$H NMR ($CDCl_3$) $\delta$ = 5.09 (s, 1H, CH), 6.0 (s, 1H, NH), 6.67 (m, 6H, Ar-H), 7.33 (m, 2H, Ar-H), 7.88 (*m*-coupled, d, 1H, dibromo ring), 7.97 (*m*-coupled, d, 1H, dibromo ring), 8.74 (s, 1H, N=CH). MS m/z: 517 ($M^+$). Anal. Calcd. for $C_{21}H_{15}Br_2N_3O_3$: C, 48.77; H, 2.92; N, 8.12; Found: C, 48.52; H, 2.90; N, 8.07.

## Anticonvulsant activity

Albino mice of either sex (weighing 20–25 g) were used for anticonvulsant activity. The animals were housed under standard laboratory conditions with natural light and dark cycle. They were fed on standard pellet diet and water *ad libitum*. Animals were acclimatized to their environment for one week prior to experimentation.

**Method:** Measurement of the seizure threshold for each animal was determined by the increasing current electroshock seizure (ICES) test method[12]. The standard drug phenytoin [25 mg/kg (bw)] and test compounds [100 mg/kg (bw)] as suspension were injected to respective groups and the control group of animals was given equal volume of vehicle (0.5% CMC suspension). After a gap of 30

min of administration of test compounds and standard drug, all the groups of mice were given electroshock *via* ear electrodes (forceps style) using an electro-convulsiometer. The current at which tonic hind limb extension occurred was recorded as the seizure threshold current (STC) for each mouse. If no tonic hind limb extension was observed by a current of 30 mA, electroshock was terminated and this cut-off current was used in the analysis. The statistical significance of differences between control and treatment group was determined and the results are given in Table-1.

### Statistical analysis[13]

The mean values ± SEM were calculated and results were statistically analyzed by one-way analysis of variance (ANOVA) followed by Dunnet's test. "P" values of $p < 0.5$, $< 0.01$ and $< 0.001$ were considered to be significant, highly significant and very highly significant respectively.

TABLE-1
ANTICONVULSANT ACTIVITY OF 2-(SUBSTITUTED ARYL/ HETERYL)-3-(SUBSTITUTED ARYLIDENIMINO)-6, 8-DIBROMO-1,2,3,4-TETRAHYDROQUINAZOLIN-4-ONE DERIVATIVES (ICES METHOD)

| Compounds | Seizure threshold current (mA) | Compounds | Seizure threshold current (mA) |
|---|---|---|---|
| | Mean ± S.D | | Mean ± S.D |
| 4 | 15.00 ± 1.10† | 11 | 15.00 ± 1.10† |
| 5 | 18.67 ± 12.07‡ | 12 | 14.00 ± 0.00 |
| 6 | 15.33 ± 2.07† | 13 | 15.00 ± 1.10† |
| 7 | 13.33 ± 1.03 | 14 | 16.00 ± 1.79‡ |
| 8 | 15.33 ± 1.03† | Control | 13.00 ± 1.10 |
| 9 | 15.33 ± 1.03† | Phenytoin | 27.00 ± 1.10 |
| 10 | 14.67 ± 1.03* | | |

*$p < 0.5$, †$p < 0.01$, ‡$p < 0.001$, when compared with control (n = 6).

## RESULTS AND DISCUSSION

The increasing current electroshock seizure test is used for assessment of anticonvulsant and pro-convulsant activity in a small number of animals. Moreover, this test was used to evaluate the weak anticonvulsant effect. Increasing current electroshock produced serial symptoms as follows: (1) vocalization and struggling (2) generalized clonic seizure with loss of righting reflux (3) tonic flexion (4) tonic extension (5) death. Tonic extension of the hind limb was selected as the end point.

Among the 2-(substituted aryl/heteryl)-3-(substituted arylidenimino)-6,8-dibromo-1,2,3,4-tetrahydro quinazolin-4(3H)-one derivatives, at a dose of 100 mg/kg (bw), compounds **5** and **14** increased seizure threshold current (STC) statistically indicating them to be highly significant ($p < 0.001$) from control group

and compounds **4, 6, 8, 9, 11** and **13** were sligiitly statistically significant ($p < 0.01$). Compound **10** showed statistically significant ($p < 0.05$) increase in STC. All compounds were highly statistically significantly ($p < 0.001$) different in comparison to standard drug phenytoin. From the study, it was concluded that quinazolinone nucleus possesses a weak anticonvulsant property.

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## REFERENCES

1. L. Fisnerova, J. Grimova, Z. Roubal, Matwova Eva and Brunova, *Cesk. Farm.*, **35**, 447 (1986); *Chem. Abstr.*, **106**, 131555q (1987).
2. M.A. Kahil, R. Soliman, A.M. Fraghaly and A.A. Bekhit, *Arch. Pharm. (Weinheim)*, **327**, 27 (1994); *Chem. Abstr.*, **121**, 9311b (1194).
3. N.A. Santagati, E. Bousquet, A. Spadaro and G. Resonsisvalle, *IL Farmaco*, **54**, 780 (1999).
4. R.R. El-Naser Ossman and S. El-Sayed Barakat, *Arzneimittelforschung*, **44**, 915 (1994); *Chem. Abstr.*, **122**, 160590h (1995).
5. S.H. El-Flksy, *Pharmazie*, **48**, 894 (1993).
6. S.S. Carroll, J.S.M. Geib and D.B. Olsen, *J. Biol. Chem.*, **269**, 32351 (1994).
7. D.J. Bark, Y.K. Park, H.I. Heo, M. Lee, Z. Yang and M. Choi., *Biorg. Med. Chem. Lett.*, **8**, 3287 (1998).
8. S.R. Nautiyal, R.A. Vee and D.D. Mukerji, *Indian J. Pharm. Sci.*, **50**, 26 (1988).
9. A.D. Farghaly and A.M. Moharra, *Bull. Chim. Farm.*, **138**, 280 (1999).
10. D. Raffa, G. Daidone, D. Schillaci, B. Maggio and F. Plewscia, *Pharmazie*, **54**, 251 (1999); *Chem. Abstr.*, **131**, 295254h (1999).
11. A.S. Wheeler and W.M. Oats, *J. Am. Chem. Soc.*, **32**, 770 (1910).
12. Y. Kitano, C. Usui, K. Takamuna, M. Hirohashi and M. Nomura, *J. Pharmacol. Toxicol. Methods*, **35**, 25 (1996).
13. G.N. Snedocor and E.G. Corchran, Statistical Methods, Oxford & IBH Publishing Co., New Delhi, p. 33 (1967).

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