Design and Synthesis of New Derivatives of 3*H*-Quinazolin-4-One as Potential Anticonvulsant Agents

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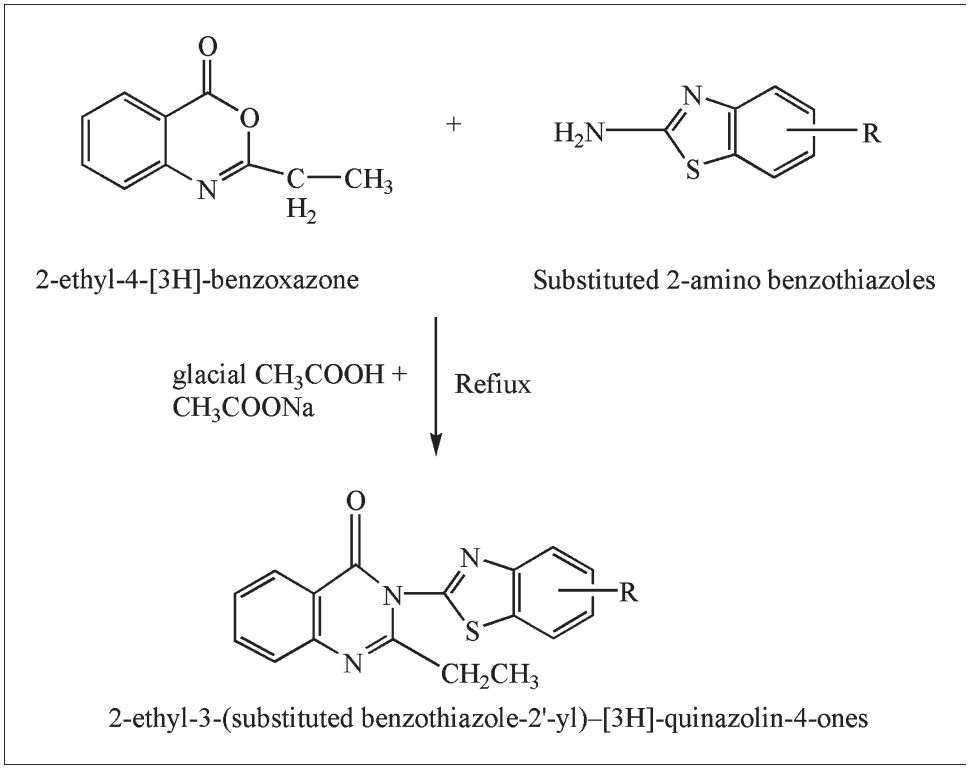

As a part of systematic investigation on synthesis and biological activities, some new derivatives of 2-ethyl-3-(substituted benzothiazole-2′-yl)–[3*H*]-quinazolin-4-ones **3** have been synthesized, and the structures of the compounds were confirmed by elemental analysis and spectral data. The newly synthesized derivatives are then screened for anticonvulsant activity by maximal electroshock method.

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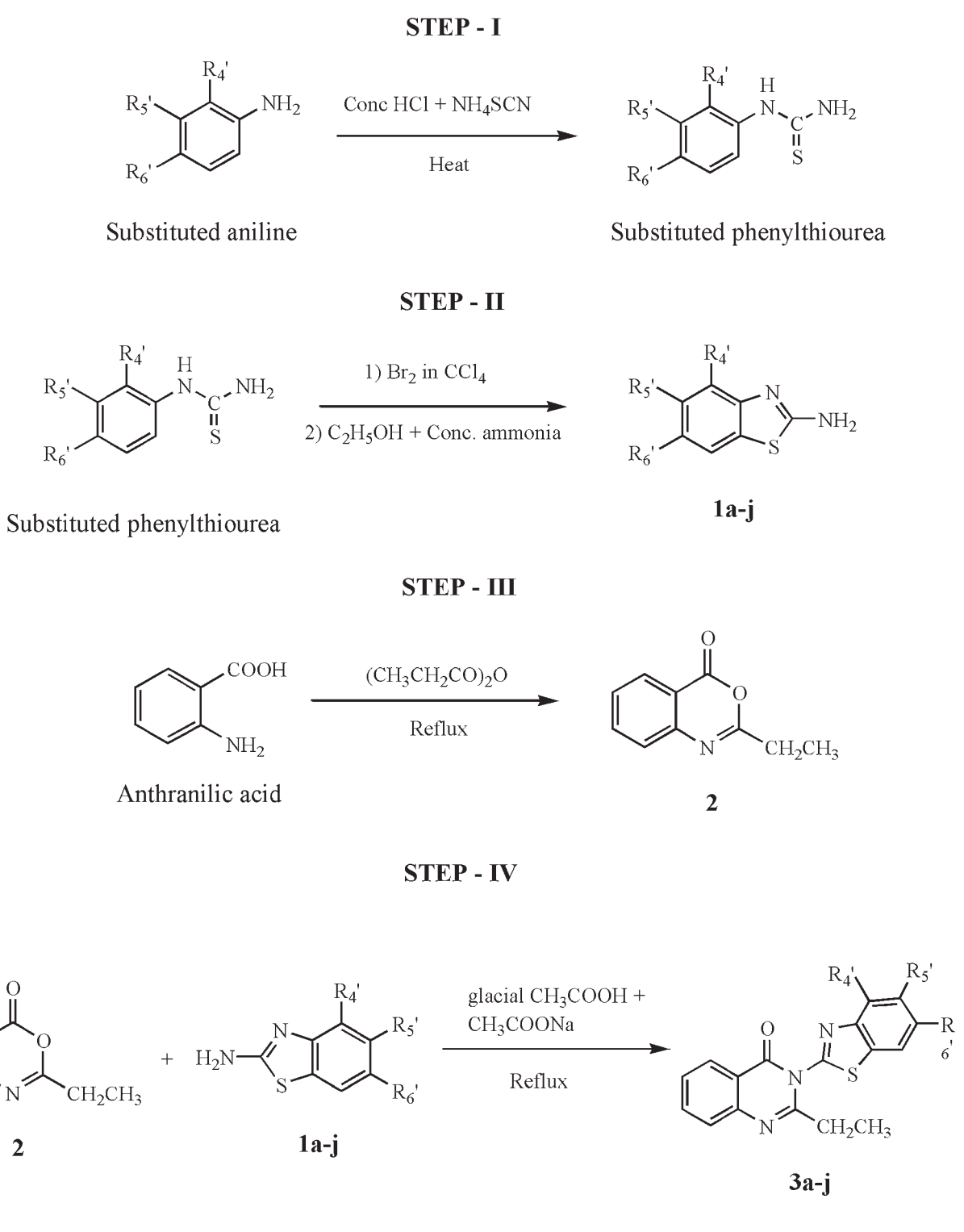
INTRODUCTION

The search for new antiepileptic drugs with reduced toxicity and lower side effects is continuous. 3*H*-quinazolin-4-one represent a very good nucleus for the preparation of new anticonvulsant agents, because such a heterocyclic system possesses the pharmacophoric moiety. From the literature survey, it was found that 3*H*-quinazolin-4-one has been reported to possess different pharmacological effects: anticonvulsant [1], antibacterial [2], bronchodialator [3], antihistaminic [4], antitubercular [5], analgesic [6], antihypertensive [7], and antineoplastic [8]. On the other hand, various therapeutic activities have been reported for benzothiazole moiety: central nervous system (CNS) depressant, muscle relaxant and anticonvulsant [9], local anesthetic [10], antitetanus [11], and anthelmintic [12]. In view of the fact that literally thousands of quinazolinone- and 2-amino benzothiazole-related compounds have been synthesized and tested for CNS depressant and anticonvulsant activity, we have incorporated benzothiazole moiety in quinazoline nucleus to get single molecular framework. As a part of our continued program on the chemistry of 3*H*-quinazolin-4-one ring system, we have recently synthesized a series of 3*H*-quinazolin-4-one derivatives containing benzothiazole ring, with the aim of obtaining

Scheme 1



novel heterocyclic system with potentially enhanced anticonvulsant activity. In this work, 10 new 3*H*-quinazolin-4-one derivatives are synthesized, characterized and evaluated for their anticonvulsant activity.

RESULTS AND DISCUSSION

Synthesis of the titled compounds **3a–j** has been carried out as being depicted in Scheme 1. The starting

substituted 2-amino benzothiazole **1a–j** and 2-ethyl-4[3*H*]-benzoxazone **2** were prepared according to the known procedures from commercially available aniline, substituted anilines, and anthranilic acid. Finally, the mixture of substituted 2-amino benzothiazole **1a–j** and 2-ethyl-4-[3*H*]-benzoxazone **2** were refluxed in the presence of glacial acetic acid and sodium acetate to afford corresponding 2-ethyl-3-(substituted benzothiazole-2′)–[3*H*]-quinazolin-4-ones **3a–j**. All the synthesized compounds were characterized by their physical, analytical, and spectral data. The infrared (IR), mass spectra (MS) and ^{1}H NMR data of all the synthesized compounds were in conformity with the structure assigned, and detail spectra are given in the Experimental section.

The titled compounds were assessed for their anticonvulsant activity by subjecting the animals to maximal electroshock (MES) test. The reduction in time or abolition of tonic extensor phase of MES convulsion was considered as anticonvulsant activity of the drug. All the synthesized compounds have shown profound anticonvulsant activity as evident from marked reduction in duration of hind limb extension as compared to control. Furthermore, we calculated the % potency of the synthesized compounds with respect to standard drug, phenytoin (considering as 100%). The order of potency was found to be, **3b** > **3c** > **3j** > **3d** > **3f** > **3e**> **3a** > **3g** > **3h** > **3i**. The difference in the potencies of these compounds might be due to the different substituents on the aromatic ring, which influences the biological activity by altering the lipophilicity and thereby facilitating penetration across the blood brain barrier.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries using a Thermoink precision melting point cum boiling point apparatus and are uncorrected. The purity and homogeneity of the compounds was checked by thin layer chromatography (TLC). All the analytical samples were prepared in methanol (compound:-methanol, 1:2) and the solvent system used as mobile phase was chloroform:toluene (3:1). The solutions of the compounds were spotted on glass plate coated with silica gel G using glass capillaries and the spots were exposed to iodine vapors. Elemental analysis for C, H, and N was determined using Heraus Carlo Erba 1108 CHN analyzer. IR spectra were recorded using KBr pellets on Shimadzu Fourier Transform Infrared Spectrophotometer (FTIR-8400s). ^{1}H NMR spectra were recorded on Bruker W.M. 400 spectrometer (Bruker AG, Fallanden, Switzerland) at 300 MHz in $CDCl_3$ using tetramethylsilane (TMS) as internal standard (chemical shift in δ ppm). Coupling constants (*J*) were reported in Hz. Mass spectra were obtained on matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)-TOF.

General method for preparation of substituted phenylthiourea [13]. In round bottom flask, aniline (18.6 mL, 0.2 mol) and concentrated hydrochloric acid (20–25 mL) were taken and warmed. Saturated solution of ammonium thiocynate (20 g) was added slowly to the above solution and boiled until turbidity appeared. The turbid solution was then poured in cold water, which gave precipitate of phenylthiourea. The substituted phenylthioureas were prepared by using required quantity of substituted anilines.

General method for preparation of substituted 2-amino benzothiazole 1a–j [14]. In a conical flask, phenylthiourea (15.2 g, 0.1 mol) was taken. To it carbon tetrachloride (150 mL) was added, and then it was brominated by using bromine solution (5%, v/v) in carbon tetrachloride till orange-yellow color persists. The slurry was kept overnight. The precipitated dibromide obtained was filtered, washed with carbon tetrachloride until the yellow color disappeared. The precipitate of dibromide was dissolved in rectified spirit (200 mL) and basified with concentrated ammonia solution, which gave precipitate of 2-amino benzothiazole. It was then filtered, washed with water, dried and recrystallized from dilute alcohol (70%, v/v). The substituted 2-amino benzothiazole were prepared by using required quantity of substituted phenylthioureas.

Preparation of 2-ethyl-4-[3*H*]-benzoxazone 2 [15]. In round bottom flask, anthranilic acid (13.7 g, 0.1 mol) and propionic anhydride (13.0 mL, 0.1 mol) were taken and refluxed on heating for 30 min. Then excess of propionic anhydride was removed under vacuum. The separated solid was again refluxed with acetic anhydride (10.2 mL, 0.1 mol) for 30 min. Then excess of acetic anhydride was removed under vacuum. The separated white amorphous solid was washed several times with petroleum ether (60:80), dried and recrystallized using dilute ethanol. The yield of the product was 13.9 g (79.42%) and m.p. 84–86°C.

General procedure for preparation of titled compounds 3a–j. In round bottom flask, 2-amino benzothiazole **1a** (1.5 g, 0.01 mol) and 2-ethyl-4-[3*H*]-benzoxazone **2** (1.75 g, 0.01 mol) were taken. To this mixture, glacial acetic acid (20 mL) and anhydrous sodium acetate (1.5g) were added. The mixture was refluxed for 25 h on oil bath at about 115–120°C. Then the mixture was cooled and poured on 100–150 g crushed ice. The precipitate was filtered, washed with cold water, dried and recrystallized with glacial acetic acid. After recrystallization, the product was washed with benzene and then several times with water and dried. The remaining 2-ethyl-3-(substituted benzothiazole-2′-yl)–3*H*-quinazolin-4-ones were prepared by using 0.025 mol of each of substituted 2-amino benzothiazole and 2-ethyl-4-[3*H*]-benzoxazone using the above described procedure. The physical constants are recorded in Table 1.

2-Ethyl-3-(benzothiazole-2′-yl)-3H-quinazolin-4-one (3a). R_f: 0.46 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1620 (C═N), 1720 (C═O), 3065 (C─H), 2850 (CH_2, CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.4–8.23 (m, 8H, Ar─H), 0.9 (t, J = 4.5 Hz, 3H, CH_2CH_3), 1.4 (q, 2H, J = 2.5, 6.8 Hz, CH_2CH_3); MS *m*/*z*: 307 (M^+).

2-Ethyl-3-(4′-methyl benzothiazole-2′-yl)-3H-quinazolin-4-one (3b). R_f: 0.58 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1622 (C═N), 1718 (C═O), 3025 (C─H), 2850 (CH_2, CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.35–7.93 (m, 7H, Ar─H), 2.35 (s, 3H, CH_3), 0.7 (t, 3H, J = 5.0 Hz, CH_2CH_3), 1.1 (q, J = 2.5, 6.8 Hz, 2H, CH_2CH_3); MS *m*/*z*: 321.36 (M^+).

2-Ethyl-3-(5′-methyl benzothiazole-2′-yl)-3H-quinazolin-4-one (3c). R_f: 0.54 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1622 (C═N), 1720 (C═O), 3025 (C─H), 2800 (CH_2, CH_3)

Table 1

Characterization data of compounds **3a–j**.

Compound	$R^{4'}$	$R^{5'}$	$R^{6'}$	Molecular formula	Molecular weight	Reflux time (h)	m.p.	Yield (%)	Elemental analysis calculated (found) C	H	N
3a	H	H	H	$C_{17}H_{13}N_3OS$	307.08	25	158	77	67.01 (67.13	4.52 4.36	13.59 13.56)
3b	CH_3	H	H	$C_{18}H_{15}N_3OS$	321.40	25	180	72	67.27 (67.02	4.70 4.62	13.07 13.26)
3c	H	CH_3	H	$C_{18}H_{15}N_3OS$	321.40	28	182	75	67.27 (67.38	4.70 4.65	13.07 13.25)
3d	OCH_3	H	H	$C_{18}H_{15}N_3O_2S$	337.40	25	266	69	64.08 (64.15	4.48 4.50	12.45 12.42)
3e	H	H	OCH_3	$C_{18}H_{15}N_3O_2S$	337.40	25	312	67	64.08 (64.12	4.48 4.43	12.45 12.48)
3f	OC_2H_5	H	H	$C_{19}H_{17}N_3O_2S$	351.42	25	174	64	64.94 (64.89	4.88 4.90	11.96 11.95)
3g	H	Cl	H	$C_{17}H_{12}N_3OSCl$	341.82	30	178	74	59.73 (59.65	3.52 3.47	12.29 12.32)
3h	H	H	Br	$C_{17}H_{12}N_3OSBr$	386.27	30	136	61	52.86 (52.90	3.13 3.15	10.88 10.82)
3i	H	H	NO_2	$C_{17}H_{12}N_4O_3S$	352.37	30	126	58	57.95 (57.80	3.43 3.48	15.90 15.79)
3j	CH_3	H	CH_3	$C_{19}H_{17}N_3OS$	335.42	27	222	65	68.03 (67.94	5.11 5.09	12.53 12.50)

cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.35–8.03 (m, 7H, Ar—H), 2.35 (s, 3H, CH_3), 0.8 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.3 (q, J = 2.5, 8.9 Hz, 2H, CH_2CH_3); MS m/z: 321.45 (M^+).

2-Ethyl-3-(4′-methoxy benzothiazole-2′-yl)-3H-quinazolin-4-one (3d). R_f: 0.40 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1618 (C=N), 1720 (C=O), 2810 (O—CH_3), 3025 (C—H), 2865 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.06–7.9 (m, 7H, Ar—H), 3.73 (s, 3H, OCH_3), 1.1 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.6 (q, J = 2.5, 9.0 Hz, 2H, CH_2CH_3); MS m/z: 337.63 (M^+).

2-Ethyl-3-(6′-methoxy benzothiazole-2′-yl)-3H-quinazolin-4-one (3e). R_f: 0.25 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1624 (C=N), 1720 (C=O), 2814 (O—CH_3), 3025 (C—H), 2850 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.06–8.12 (m, 7H, Ar—H), 3.73 (s, 3H, OCH_3), 1.2 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.6 (q, J = 2.5, 9.0 Hz, 2H, CH_2CH_3); MS m/z: 337.85 (M^+).

2-Ethyl-3-(4′-ethoxy benzothiazole-2′-yl)-3H-quinazolin-4-one (3f). R_f: 0.36 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1382 (C—H in CH_3), 1635 (C=N), 1720 (C=O), 3075 (C—H), 2890 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.10–7.84 (m, 7H, Ar—H), 0.9 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.4 (q, 2H, J = 2.4, 9.0 Hz, CH_2CH_3), 1.2–1.6 (q, J = 4.0, 10.5 Hz, 2H, CH_2—CH_3), 3.5–4.2 (t, J = 6.5 Hz, 3H, CH_2—CH_3); MS m/z: 351.80 (M^+).

2-Ethyl-3-(5′-chloro benzothiazole-2′-yl)-3H-quinazolin-4-one (3g). R_f: 0.35 (chloroform:toluene 3:1), IR (KBr) υ_{max} 712 (Ar—Cl), 1624 (C=N), 1724 (C=O), 3050 (C—H), 2850 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.4–8.17 (m, 7H, Ar—H), 0.8 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.3 (q, J = 2.4, 9.0 Hz, 2H, CH_2CH_3); MS m/z: 342.03 (M^+).

2-Ethyl-3-(6′-bromo benzothiazole-2′-yl)-3H-quinazolin-4-one (3h). R_f: 0.33 (chloroform:toluene 3:1), IR (KBr) υ_{max} 612 (C—Br), 1622 (C=N), 1722 (C=O), 3065 (C—H), 2850 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.4–8.29 (m, 7H, Ar—H), 1.0 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.5 (q, J = 2.4, 9.0 Hz, 2H, CH_2CH_3); MS m/z: 386.65 (M^+).

2-Ethyl-3-(6′-nitro benzothiazole-2′-yl)-3H-quinazolin-4-one (3i). R_f: 0.41 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1494 (C— NO_2), 1620 (C=N), 1720 (C=O), 3025 (C—H), 2850 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ in ppm) 7.4–9.05 (m, 7H, Ar—H), 0.9 (t, J = 5.0 Hz, 3H, CH_2CH_3), 1.3 (q, J = 2.1, 8.5 Hz, 2H, CH_2CH_3); MS m/z: 352.72 (M^+).

2-Ethyl-3-(4′,6′-dimethyl benzothiazole-2′-yl)-3H-quinazolin-4-one (3j). R_f: 0.37 (chloroform:toluene 3:1), IR (KBr) υ_{max} 1382 (C—H in CH_3), 1624 (C=N), 1720 (C=O), 3025 (C—H), 2850 (CH_2, CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ

Table 2

Anticonvulsant activity.

Treatment groups	Mean duration of hind limb extension, mean (± SEM)	% potency of anticonvulsant drugs
Control	28.80 (± 2.79)	–
Standard	7.40** (± 0.67)	100.0
3a	9.40** (± 0.71)	73.90
3b	8.00** (± 1.17)	91.89
3c	8.20** (± 0.87)	89.18
3d	8.80** (± 1.34)	81.08
3e	9.20** (± 1.15)	75.68
3f	9.00** (± 0.89)	78.38
3g	9.40**(± 0.46)	72.97
3h	9.60** (± 0.73)	70.27
3i	9.80** (± 1.00)	67.57
3j	8.40** (± 0.67)	86.49

**$P < 0.01$.

in ppm) 7.15–7.9 (m, 6H, Ar—H), 2.35 (s, 3H, CH_3, in sixth position of benzothiazole), 2.37 (s, 3H, CH_3, in fourth position of benzothiazole) 0.7 (t, $J = 5.0$ Hz, 3H, CH_2CH_3), 1.1 (q, $J = 2.1$, 8.5 Hz, 2H, CH_2CH_3); MS *m/z*: 335.76 (M^+).

Anticonvulsant activity. The title compounds were tested for anticonvulsant activity against maximal electroshock-induced convulsion in mice according to the method reported by Turner [16] . Male Swiss Albino mice weighing between 20 and 25 g, obtained from National Center for Laboratory Animal Sciences, Hyderabad, India, were used in this study. Animals were housed in wire-mesh cages under the laboratory conditions (26 ± 2°C), 12–12 h light/dark. Animals were allowed to acclimatize with free access to food and water for a 24-h period before testing. During the course of experiment, the general behavior of animal was normal. All the experimental protocols were approved by the institutional animal ethical committee, and experiments were conducted in accordance with the standard guidelines. The animals were divided into three groups (control, standard, and test) and each group consisted of five animals. The homogenous suspension of the test compounds **3a–j** and standard drug phenytoin were prepared in 10% (w/v) polyethylene glycol in saline. All the test compounds were administered intraperitoneally (ip) at an equimolar dose with respect to standard drug phenytoin, 30 min prior to the start of the experiments. The maximal electroshock seizures (MES) was induced by electroconvulsometer (Techno Instruments, India). The animals were subjected to electroshock (45 mA/0.2 s) *via* the corneal electrodes. The anticonvulsant effect was assessed by recording the tonic hind limb extension. Absence of seizure component like hind limb tonic extension with drug treatment was considered to be evidence of protection. The data were analyzed by one-way ANOVA followed by Dennett's test using Sigma Stat software. A value of $P < 0.05$ was considered as statistical significance. All the values were expressed as mean ± SEM (Table 2). The % potency of anticonvulsant drugs is calculated by the formula given below:

$$\%\text{potency} = 100 \times \left[1 - \left(\frac{\text{mean value of compound} - \text{mean value of standard}}{\text{mean value of standard}}\right)\right]$$

CONCLUSION

The newly synthesized 3*H*-quinazolin-4-one derivatives showed potential anticonvulsant activity against maximal electroshock-induced convulsion in mice, with variable potency.

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