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Original article

CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones

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Abstract

A series of new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones were synthesized and evaluated for anticonvulsant, sedative–hypnotic and CNS depression activities. After i.p. injection to mice or rat at doses of 30, 100, and 300 mg/kg body weight 2-styryl quinazolin-4(3*H*)-ones derivatives were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. Rotorod method was employed to determine the neurotoxicity. Out of 18 compounds only **4a**, **4e** and **4p** showed anticonvulsant activity in one or more test models. All except **4l** and **4q** exhibited significant sedative–hypnotic activity via actophotometer screen. Forced swim pool method to determine CNS depressant activity resulted in some potent compounds. It can be concluded that synthesized compounds exhibited better sedative–hypnotic and CNS depressant activities than anticonvulsant activity.

Keywords: Styryl quinazoline-4(3*H*)-ones; 1,3,4-Thiadiazole; MES; Subcutaneous pentylenetetrazole induced seizure; CNS depressants

1. Introduction

The sedative–hypnotic (neurotoxicity) properties of 4(3*H*)-quinazolinone are well documented [1–6]. The prototype sedative–hypnotic in this series is 2-methyl-3-*O*-tolyl 4(3*H*)-quinazolinone **1**, also known as methaqualone. In spite of the fact that literally hundreds of quinazolinone related to **1** have been synthesized and tested for central nervous system (CNS) depression and anticonvulsant activities, none of the anticonvulsant drugs currently contain the 4(3*H*)-quinazolinone ring system. The fact that to date, nearly every derivatives tested a combined neurotoxicity and anticonvulsant screening has exhibited neurotoxicity values (TD_{50}) that are less than, or only slightly higher than, the ED_{50} observed in typical anticonvulsant tests, i.e., protection against maximal electroshock (MES) or subcutaneous metrazol (scMET) induced seizure. Consequently, the protection index (PI) corresponding to the value TD_{50}/ED_{50} is too low to provide sufficient differential between dosages effecting sedation and those leading to protection against seizures. There still existed the possibility that appropriate derivatives of these CNS-active compounds, which obviously cross the blood–brain barrier, might find use as anticonvulsant or CNS depressant if the parent ring system could be appropriately functionalized. Among the few reports in the literature of tentative separation of anticonvulsant and sedative properties of 4(3*H*)-quinazolinone, our attention was drawn to an earlier discovery by Boltze et al. [7] and Wolf et al. [8] that modification of methyl group by some other chemical moieties yielded structural analogs exhibiting protection against MES-induced seizures. 2-(2-Aryl ethenyl) 3-*O*-tolyl 4(3*H*)-quinazolinones **2** and **3** did indeed exhibit protection against MES-induced seizures. Medicinal chemists over the years have substituted different heterocyclic rings at position 3 of 4(3*H*)-quinazolinone to

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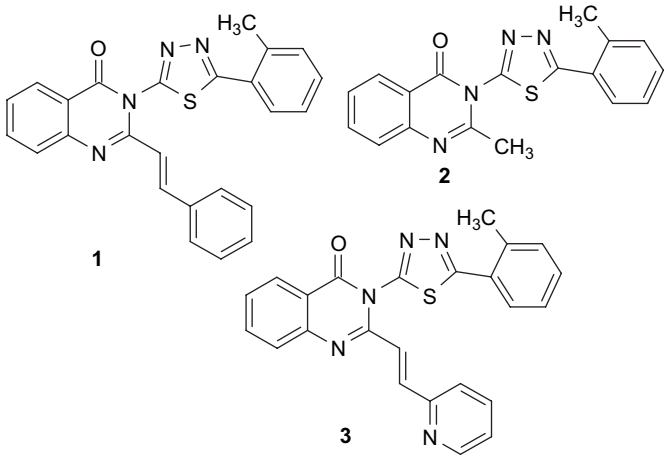
get potent CNS acting drugs. 1,3,4-Thiadiazoles' nucleus itself possesses anticonvulsant, sedative–hypnotic and CNS neurotoxic activities [9,10]. In continuation of our earlier efforts [11–13] to develop CNS acting agents, the present paper reports on the synthesis, anticonvulsant, neurotoxicity, CNS depressant activities and behavioral study of 18 new 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones. Synthesized compounds were expected to show better CNS activity due to the presence of 4(3*H*)-quinazolinone nucleus, substitution of 1,3,4-thiadiazoles' nucleus at third position of 4(3*H*)-quinazolinone and chemical modification of second position of 4(3*H*)-quinazolinone.



2. Chemistry

The synthesis of 3-(1′3′4′-thiadiazolyl)-2-styryl quinazolin-4(3*H*)-one was accomplished as shown in Figs. 1 and 2. 3-(1,3,4-Thiadiazolyl)-2-methyl quinazolinones were obtained by refluxing 2-methylbenzoxazin-4(3*H*)-one **2** [14] with the amine derivative **IV** according to Fig. 1. The amino derivative **IV** [15,16] was obtained by oxidative cyclization of thiosemicarbazone **III** (obtained by condensation of aromatic aldehyde **I** and thiosemicarbazide **II**) in the presence of ferric chloride according to Fig. 2.

3-(1,3,4-Thiadiazolyl)-2-styryl quinazoline was synthesized by a three-step procedure. In this method 3-(1′3′4′-thiadiazolyl)-2-styryl quinazoline **4** was obtained by refluxing equimolar amount of 3-(1′3′4′-thiadiazolyl)-2-methyl quinazoline and aromatic aldehyde in glacial acetic acid. The structures of the new compounds were elucidated by analytical and spectroscopic measurements.

In general IR spectra showed the C=O peak at 1701 cm^{-1}, C=O stretching at 1580 cm^{-1} and C=C stretching (alkene) vibration at 1630 cm^{-1}. The ^{13}C NMR spectrum was at 162.4 for (C-2), 168.3 for (C-4), 112 for (C-11) and 136 for (C-12). Thin layer chromatography (TLC) was run throughout the reaction to optimize the reaction for purity and completion. The physical and chemical data for the newly synthesized compounds are presented in Table 1.

3. Pharmacology

Anticonvulsant evaluation of 3-(1,3,4-thiadiazolyl)-2-styryl quinazolin-4(3*H*)-one was done by the anticonvulsant drug development (ADD) program protocol [17,18]. The profile of anticonvulsant activity was established after i.p. injection by the MES pattern test and the subcutaneous pentylenetetrazole (scPTZ) seizure threshold test. Minimal motor impairment was measured by the rotorod (neurotoxicity, NT) test using doses of 30, 100 and 300 mg/kg at two different time intervals. Same compounds were studied for their CNS behavioral activity in mice using actophotometer and Porsolt's swim pool test in rats.

4. Results and discussion

Initial anticonvulsant activity and neurotoxicity data for the quinazolinone analogs are reported in Table 1, along with the literature data on phenytoin, carbamazepine, sodium valproate, phenobarbital and ethosuximide [19,20]. All the quinazolinone analogs showed potent sedative–hypnotic and CNS depressant activities than anticonvulsant activity. Compounds **4b–4d**, **4f–4o**, **4q** and **4r** did not show any activity in MES as well as scPTZ after 0.5 and 4 h. Compound

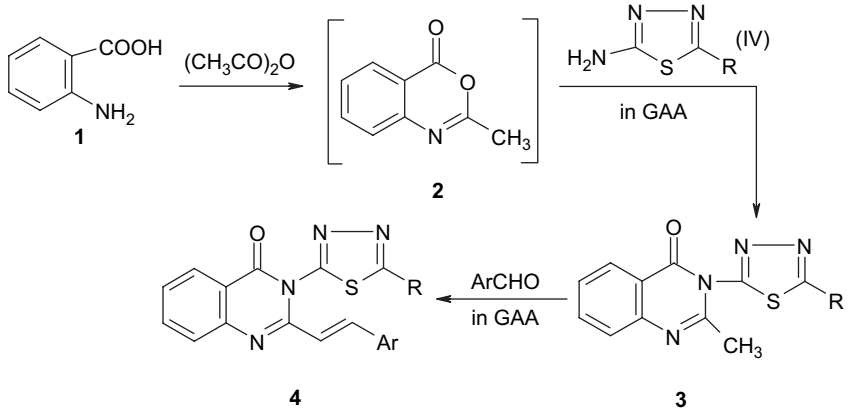


Fig. 1. Scheme for the synthesis of title compounds.

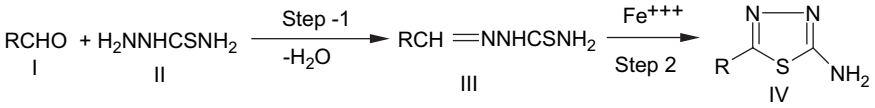


Fig. 2. Scheme for the synthesis of 2-amino-5-aryl 1,3,4-thiadiazoles.

4a showed anticonvulsant activity at 0.5 and 4 h in both test models, whereas **4p** showed anticonvulsant activity at 4 h in MES screen and at 0.5 and 4 h in scPTZ screen. Three compounds namely **4a**, **4e** and **4p** exhibited anticonvulsant activity in scPTZ screen at both 0.5 and 4 h. Compounds **4b**–**4e** and **4g** showed neurotoxicity after 0.5 h at 300 mg/kg body weight. Compounds **4b** and **4q** showed prolonged neurotoxicity level at 300 mg/kg body weight. Compound **4a** displayed activity in the MES screen after 0.5 h (100 mg/kg) and 4 h (300 mg/kg) while it was active at both 0.5 h (300 mg/kg) and 4 h (300 mg/kg) in the scPTZ test. This compound exhibited rapid onset of action and long duration of activity.

Table 1
Anticonvulsant activity and minimal motor impairment of 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones

Code no.	Intraperitoneal injection in mice[a]					
	MES screen		scPTZ screen		Neurotoxicity screen	
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
4a	100	300	300	300[b]	–	–
4b	–	–	–	–	300	300
4c	–	–	–	–	300	–
4d	–	–	–	–	300	–
4e	–	–	300[e]	300	300[c]	–
4f	–	–	–	–	–	–
4g	–	–	–	–	300[d]	–
4h	–	–	–	–	–	–
4i	–	–	–	–	–	–
4j	–	–	–	–	–	–
4k	–	–	–	–	–	–
4l	–	–	–	–	–	–
4m	–	–	–	–	–	–
4n	–	–	–	–	–	–
4o	–	–	–	–	100	–
4p	–	100	300	300	300	–
4q	–	–	–	–	300	300
4r	–	–	–	–	–	–
Phenytoin[f]	30	30	–	–	100	100
Carbamazepine[f]	30	100	100	300	100	300
Sodium valproate[f]	–	–	300	–	–	–
Phenobarbitals[f]	100	30	30	300	100	300
Ethosuximide[f]	–	–	300	–	–	–

[a] Doses of 30, 100 and 300 mg/kg were administered. The values in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 h after the injections were made; the symbol (–) indicates the absence of activity at maximum dose administered (300 mg/kg).
[b] Died during test at 300 mg/kg without seizure.
[c] Neurotoxicity at 100 mg/kg (0.25 h, 1 h).
[d] Loss of righting reflux.
[e] At 100 mg/kg after 0.25 h, 3/5 and after 1 h 4/5 mice were protected.
[f] Data from Refs. [9–11].

All the compounds were also screened for behavior study and CNS depressant activity. In the behavioral study using actophotometer scoring technique, the entire synthesized compounds showed decrease in locomotor activity where 36% was the lowest and 57% was the maximal decrease in locomotor activity when compared to phenytoin as reported in Table 3. All the compounds except **4m**–**4q** exhibited more than 50% decrease in locomotor activity ($p < 0.05$) after 1 h. Compound **4q** was the least potent compound and **4d** was the most potent compound in the prepared series with 36 and 57% decrease in locomotor activity, respectively. In a similar study with forced swim pool test, the immobility time after administration of the test compounds was compared with carbamazepine (Table 4). Readings of the control groups were taken individually for each compound 24 h prior to compound administration. Experimental results indicate that our compound exhibited better sedative–hypnotic and CNS depressant activities as compared to anticonvulsant activity. Biological activity was also ascertained for PEG because it was used as a vehicle for the synthesized compounds. Except **4c**, **4i** and **4q** other tested compounds were found to exhibit potent CNS depressant activity as indicated by increased immobility time.

Generally compounds possessing higher log *p* value showed higher decrease in locomotor activity. Bulkier compounds are more lipophilic and can cross blood–brain barrier to exert their effect on CNS. Present study explored that substitution of 1,3,4-thiadiazoles at third position and styryl moiety at second position of 4(3*H*)-quinazolinone leads to the development of new chemical entities with potent sedative–hypnotic and CNS depressant activities as compared to anticonvulsant activity.

5. Experimental protocol

5.1. Chemistry

Melting points were determined in one end open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. Infrared (IR) and ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded for the compounds on Perkin Elmer Spectrum RXI Spectrophotometer in KBr pellets and ^{13}C Advance Bruker (300 MHz) instrument, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental analysis (C, N and S) was undertaken with Elemental Vario EL III Carlo Erba 1108 analyzer. The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates and a solvent system of benzene:ethanol (8:2). The spots were developed in iodine chamber and visualized under ultraviolet lamp.

5.1.1. Synthesis of 2-amino-5-aryl 1′3′4′-thiadiazole

The synthesis of 2-amino-5-aryl 1′3′4′-thiadiazole follows the following two steps.

5.1.1.1. Step 1: synthesis of thiosemicarbazones. Aromatic aldehyde **I** (0.2 M) in warm alcohol (300 ml) and thiosemicarbazide **II** (0.2 M) in warm water (300 ml) were mixed slowly with continuous stirring. The product separated immediately on cooling which was filtered with suction, dried and recrystallized from 75% ethanol to yield **III**.

5.1.1.2. Step 2: synthesis of 2-amino-5-aryl 1′3′4′-thiadiazoles. Thiosemicarbazone **III** (0.05 M) was suspended in 300 ml warm water. To this added $FeCl_3$ (0.15 M) in 300 ml water quantitatively, slowly with constant stirring. The contents were heated at 80–90 °C for 45 min. Solution was filtered hot and then citric acid (0.11 M) and sodium citrate (0.05 M) were added. The resulting mixture was divided into four parts and each part is neutralized separately with aq. ammonia (10%). The required amine was separated out, filtered with suction, dried and recrystallized from appropriate solvent.

5.1.2. Synthesis of 2-methyl-3-(1′3′4′-thiadiazole-2′-yl)-4(3H)-quinazolinone

Anthranilic acid **1** (0.01 M) and acetic anhydride were refluxed under anhydrous condition for 4 h. Excess of acetic anhydride was distilled off under reduced pressure. To the mixture obtained, amine **IV** (0.01 M) in glacial acetic acid was added and refluxed for 4 h, and the obtained reaction mixture was poured into crushed ice and kept overnight. The solid which separated out was filtered, thoroughly washed with cold distilled water, dried and recrystallized from hot ethanol.

5.1.3. Synthesis of title compound

The title compound was synthesized following the procedure reported earlier. A solution of **3** (0.01 M) and opportune benzaldehyde (0.01 M) were reacted in glacial acetic acid (10 ml) and refluxed for 12 h. The solid **4** which separated was filtered with suction and recrystallized from dimethylformamide to give pure compound. The physical data of the styryl quinazolinone are given in Table 1. The IR spectra and ^{13}C NMR spectra of the title compounds are as follows.

*5.1.3.1. Compound **4a**.* IR (cm^{-1}) 1693 (C=O), 1650 (C=C) alkene, 1530 (C=N), 1317 (CN), 688 (CS). ^1H NMR (300 MHz, δ) 5.16 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.6–7.92 (a set of signals, 13H, aromatic protons and olefinic CH). ^{13}C NMR (300 MHz, δ) 168 (C-4), 162.4 (C-2), 112 (C-11), 136 (C-12), 136.5 (C-1″), 135 (C-13), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.0 (C_2″ and C_6″ of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 127.6 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 128.5 (C_4″ of phenyl ring of 1,3,4-thiadiazole ring), 129.4 (C_3″ and C_5″ of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

*5.1.3.2. Compound **4b**.* IR (cm^{-1}) 1700 (C=O), 1611 (C=C) alkene, 1520 (C=N), 1313 (CN), 675 (CS). ^1H NMR (300 MHz, δ) 3.73 (s, 3H, CH_3), 5.74 (d, 1H, olefinic CH, $J = 15.5$ Hz), 6.83–8.00 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (300 MHz, δ) 161 (C-2), 161.5 (C-4), 114.7 (C-11), 136 (C-12), 136.5 (C-1″), 134 (C-13), 55.4 (C_A), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.0 (C_2″ and C_6″ of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 127.6 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 162 (C_4″ of phenyl ring of 1,3,4-thiadiazole ring), 114.6 (C_3″ and C_5″ of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

*5.1.3.3. Compound **4c**.* IR (cm^{-1}) 1691 (C=O), 1640 (C=C) alkene, 1530 (C=N), 1275 (CN), 773 (CS). ^1H NMR (300 MHz, δ) 2.35 (s, 3H, CH_3), 5.84 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.12–7.85 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (300 MHz, δ) 165 (C-2), 168 (C-4), 112 (C-11), 136 (C-12), 133.5 (C-1″), 134.9 (C-13), 21.4 (C_A), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.0 (C_2″ and C_6″ of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 127.6 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 140.3 (C_4″ of phenyl ring of 1,3,4-thiadiazole ring), 128.6 (C_3″ and C_5″ of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

*5.1.3.4. Compound **4d**.* IR (cm^{-1}) 1700 (C=O), 1668 (C=C) alkene, 1591 (C=N), 1326 (CN), 752 (CS). ^1H NMR (300 MHz, δ) 5.52 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.80–7.48 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 165 (C-2), 168 (C-4), 112 (C-11), 136.4 (C-12), 134.6 (C-1″), 135 (C-13), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.0 (C_2″ and C_6″ of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 127.6 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 133.8 (C_4″ of phenyl ring of 1,3,4-thiadiazole ring), 129.4 (C_3″ and C_5″ of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

*5.1.3.5. Compound **4e**.* IR (cm^{-1}) 1700 (C=O), 1614 (C=C) alkene, 1555 (C=N), 1326 (CN), 760 (CS). ^1H NMR (300 MHz, δ) 5.12 (d, 1H, olefinic CH, $J = 15.4$ Hz), 6.41–7.49 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 160.2 (C-2), 168.8 (C-4), 112 (C-11), 136 (C-12), 137.9 (C-1″), 134 (C-13), 112 (C_x of styryl

group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 127.6 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 133.8 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 123.9 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.6. Compound ***4f***. IR (cm^{-1}) 1737 (C=O), 1610 (C=C) alkene, 1532 (C=N), 1269 (CN), 733 (CS). ^{1}H NMR (300 MHz, δ) 5.60 (d, 1H, olefinic CH, $J = 15.6$ Hz), 6.99 (d, 2H, olefinic CH), 6.78–8.01 (a set of signals, 13H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 167 (C-2), 168.9 (C-4), 112 (C-4), 136 (C-12), 134 (C-1″), 134 (C-13), 125 (C_A), 130 (C_B), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 127.6 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 133.8 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 123.9 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.7. Compound ***4g***. IR (cm^{-1}) 1700 (C=O), 1620 (C=C) alkene, 1542 (C=N), 1274 (CN), 740 (CS). ^{1}H NMR (300 MHz, δ) 5.16 (d, 1H, olefinic CH, $J = 15.5$ Hz), 6.6–7.92 (a set of signals, 13H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 158.8 (C-2), 168.6 (C-4), 112 (C-11), 136 (C-12), 136.5 (C-1″), 134.5 (C-13), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 124.3 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 133.8 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 123.9 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 136.3 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 133.7 (C_e of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 128.1 (C_d of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.8. Compound ***4h***. IR (cm^{-1}) 1739 (C=O), 1642 (C=C) alkene, 1542 (C=N), 1334 (CN), 759 (CS). ^{1}H NMR (300 MHz, δ) 3.73 (s, 3H, CH_3), 5.74 (d, 1H, olefinic CH, $J = 15.4$ Hz), 6.83–8.00 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 167 (C-2), 168.6 (C-4), 112 (C-11), 136 (C-12), 128.8 (C-1″), 131.4 (C-13), 55.5 (C_A), 56 (C_B), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 124.3 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 160.9 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 114.6 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 114.6 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 136.3 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 133.7 (C_e of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 128.1 (C_d of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.9. Compound ***4i***. IR (cm^{-1}) 1701 (C=O), 1637 (C=C) alkene, 1530 (C=N), 1267 (CN), 774 (CS). ^{1}H NMR (300 MHz, δ) 2.35 (s, 3H, CH_3), 5.84 (d, 1H, olefinic CH, $J = 15.1$ Hz), 6.12–7.85 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 165 (C-2), 168 (C-4), 112 (C-11), 136 (C-12), 133.5 (C-1″), 131.4 (C-13), 21.4 (C_A), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 124.3 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 140.2 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 129 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 129 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 136.3 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 133.7 (C_e of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 128.1 (C_d of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.10. Compound ***4j***. IR (cm^{-1}) 1734 (C=O), 1634 (C=C) alkene, 1542 (C=N), 1293 (CN), 658 (CS). ^{1}H NMR (300 MHz, δ) 5.52 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.80–7.48 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 167 (C-2), 168.7 (C-4), 112 (C-11), 135.8 (C-12), 134.6 (C-1″), 131.4 (C-13), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 124.3 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 130.2 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 129 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 129 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 136.3 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 133.7 (C_e of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 128.1 (C_d of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.11. Compound ***4k***. IR (cm^{-1}) 1700 (C=O), 1630 (C=C) alkene, 1560 (C=N), 1348 (CN), 591 (CS). ^{1}H NMR (300 MHz, δ) 5.12 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.41–7.49 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 165 (C-2), 168.6 (C-4), 112 (C-11), 136 (C-12), 137.9 (C-1″), 131.6 (C-13), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of

phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 124.3 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 128.9 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 134 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 131.5 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 136.3 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 133.7 (C_e of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 128.1 (C_d of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.12. Compound ***4l***. IR (cm^{-1}) 1708 (C=O), 1608 (C=C) alkene, 1505 (C=N), 1278 (CN), 620 (CS). ^{1}H NMR (300 MHz, δ) 5.60 (d, 1H, olefinic CH, $J = 15.5$ Hz), 6.99 (d, 2H, olefinic CH), 6.78–8.01 (a set of signals, 13H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 167 (C-2), 168 (C-4), 112 (C-11), 136.5 (C-12), 134.9 (C-1″), 131.6 (C-13), 124.2 (C_A), 129.2 (C_B), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 134.9 (C_1'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 126.4 (C_6 of 4(3*H*)-quinazolinone ring), 124.3 (C_b of phenyl at C-2 of 4(3*H*)-quinazolinone ring), 140.2 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 129 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 129 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 136.3 (C_a of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 133.7 (C_e of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 128.1 (C_d of phenyl ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.13. Compound ***4m***. IR (cm^{-1}) 1701 (C=O), 1693 (C=C) alkene, 1562 (C=N), 1274 (CN), 761 (CS). ^{1}H NMR (300 MHz, δ) 5.15 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.5–7.91 (a set of signals, 13H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 164 (C-2), 165 (C-4), 112 (C-11), 136 (C-12), 136.5 (C-1″), 131.9 (C-13).

5.1.3.14. Compound ***4n***. IR (cm^{-1}) 1703 (C=O), 1609 (C=C) alkene, 1559 (C=N), 1251 (CN), 615 (CS). ^{1}H NMR (300 MHz, δ) 3.71 (s, 3H, CH_3), 5.74 (d, 1H, olefinic CH, $J = 15.5$ Hz), 6.82–8.00 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 161.4 (C-2), 168 (C-4), 112 (C-11), 136 (C-12), 128.5 (C-1″), 131.9 (C-13), 55.4 (C_A), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 120.7 (C_b of pyridine at C-2 of 4(3*H*)-quinazolinone ring), 133.8 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 123.9 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 130.2 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 144.3 (C_a of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 158.3 (C_c of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

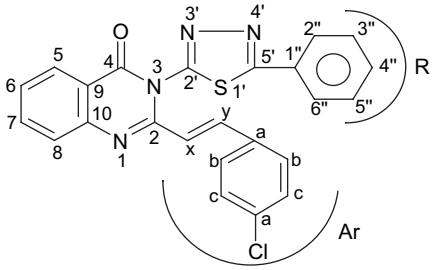
5.1.3.15. Compound ***4o***. IR (cm^{-1}) 1612 (C=O), 1650 (C=C) alkene, 1520 (C=N), 1313 (CN), 615 (CS). ^{1}H NMR (300 MHz, δ) 2.34 (s, 3H, CH_3), 5.83 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.11–7.85 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 165 (C-2), 168 (C-4), 112 (C-11), 136 (C-12), 134.6 (C-1″), 131.4 (C-13), 20.9 (C_A), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 120.7 (C_b of pyridine at C-2 of 4(3*H*)-quinazolinone ring), 161 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 114.7 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 114.7 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 144.3 (C_a of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 158.3 (C_c of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

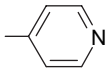
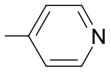
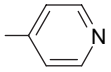
5.1.3.16. Compound ***4p***. IR (cm^{-1}) 1693 (C=O), 1610 (C=C) alkene, 1590 (C=N), 1316 (CN), 667 (CS). ^{1}H NMR (300 MHz, δ) 5.53 (d, 1H, olefinic CH, $J = 15.2$ Hz), 6.81–7.47 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 158.6 (C-2), 168.7 (C-4), 112 (C-11), 136 (C-12), 135.1 (C-1″), 131.6 (C-13), 112 (C_x of styryl group), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 120.7 (C_b of pyridine at C-2 of 4(3*H*)-quinazolinone ring), 137 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 129.8 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 129.8 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 144.3 (C_a of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 158.3 (C_c of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.17. Compound ***4q***. IR (cm^{-1}) 1695 (C=O), 1610 (C=C) alkene, 1530 (C=N), 1322 (CN), 618 (CS). ^{1}H NMR (300 MHz, δ) 5.12 (d, 1H, olefinic CH, $J = 15.4$ Hz), 6.40–7.48 (a set of signals, 12H, aromatic protons and olefinic CH). ^{13}C NMR (δ) 160.1 (C-2), 168.7 (C-4), 112 (C-11), 136 (C-12), 137.9 (C-1″), 131.1 (C-13), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 127.4 (C_2'' of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6'' of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 120.7 (C_b of pyridine at C-2 of 4(3*H*)-quinazolinone ring), 133.8 (C_4'' of phenyl ring of 1,3,4-thiadiazole ring), 129.8 (C_3'' of phenyl ring of 1,3,4-thiadiazole ring), 129.8 (C_5'' of phenyl ring of 1,3,4-thiadiazole ring), 144.3 (C_a of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 158.3 (C_c of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.1.3.18. Compound ***4r***. IR (cm^{-1}) 1708 (C=O), 1600 (C=C) alkene, 1520 (C=N), 1311 (CN), 633 (CS). ^{1}H NMR (300 MHz, δ) 5.61 (d, 1H, olefinic CH, $J = 15.3$ Hz), 6.98 (d, 2H, olefinic CH), 6.77–8.0 (a set of signals, 13H, aromatic

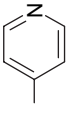
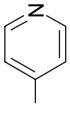
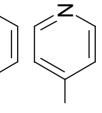
Table 2
Physical data of 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones



Code no.	Ar	R	Yield (%)	M.p. (°C)	Mol. formula[a]	E (C/F)[d]	R_f	log p[b]
4a	*p*-ClC_6H_4	C_6H_5	42	228	$C_{24}H_{15}N_4OS$	N (12.65/12.62), S (7.24/7.22), C (65.08/65.04), H (3.41/3.39)	0.73	4.39
4b	*p*-ClC_6H_4	p-$OCH_3C_6H_4$ C_A	40	240	$C_{25}H_{17}ClN_4OS$	N (11.85/11.83), S (6.78/6.76), C (63.49/63.47), H (3.62/3.60)	0.84	4.44
4c	*p*-ClC_6H_4	p-$CH_3C_6H_4$ C_A	44	232	$C_{25}H_{17}ClN_4OS$	N (12.26/12.24), S (7.02/7.02), C (65.71/65.69), H (3.75/3.73)	0.80	4.89
4d	*p*-ClC_6H_4	*p*-ClC_6H_4	45	250	$C_{24}H_{14}Cl_2N_4OS$	N (11.74/11.73), S (6.72/6.72), C (60.38/60.36), H (2.96/2.94)	0.75	5.10
4e	*p*-ClC_6H_4	*m*-ClC_6H_4	41	250	$C_{24}H_{14}Cl_2N_4OS$	N (11.74/11.74), S (6.72/6.71), C (60.38/60.35), H (2.96/2.94)	0.78	5.10
4f	*p*-ClC_6H_4	-CH=CHC_6H_4 C_A C_B	22	225	$C_{26}H_{17}ClN_4OS$	N (11.95/11.92), S (6.84/6.82), C (66.59/66.58), H (3.65/3.63)	0.74	4.58
4g	*m*-ClC_6H_4	$-C_6H_5$	42	216	$C_{24}H_{15}ClN_4OS$	N (12.65/12.63), S (7.24/7.21), C (65.08/65.06), H (3.41/3.40)	0.63	4.39
4h	*m*-ClC_6H_4	p-$OCH_3C_6H_4$ C_A	35	248	$C_{25}H_{17}ClN_4O_2S$	N (11.85/11.83), S (6.78/6.78), C (63.49/63.46), H (3.62/3.60)	0.52	4.44
4i	*m*-ClC_6H_4	p-$CH_3C_6H_4$ C_A	38	226	$C_{25}H_{17}ClN_4OS$	N (12.26/12.25), S (7.02/7.03), C (65.71/65.69), H (3.75/3.74)	0.68	4.89
4j	*m*-ClC_6H_4	*p*-ClC_6H_4	45	>260[c]	$C_{24}H_{14}Cl_2N_2OS$	N (11.74/11.73), S (6.75/6.74), C (60.38/60.36), H (2.96/2.94)	0.73	5.10
4k	*m*-ClC_6H_4	*m*-ClC_6H_4	45	>260[c]	$C_{24}H_{14}Cl_2N_2OS$	N (11.74/11.72), S (6.72/6.71), C (60.38/60.37), H (2.96/2.94)	0.64	5.10
4l	*m*-ClC_6H_4	-CH=CHC_6H_4 C_A	23	248	$C_{26}H_{17}ClN_4OS$	N (11.95/11.94), S (6.84/6.82), C (66.59/66.58), H (3.65/3.63)	0.58	4.58
4m		$-C_6H_5$	40	210	$C_{23}H_{15}N_5OS$	N (17.10/17.11), S (7.83/7.82), C (67.47/67.46), H (3.69/3.68)	0.62	2.18
4n		p-$OCH_3C_6H_4$ C_A	38	225	$C_{24}H_{17}N_5O_2S$	N (15.93/15.91), S (7.30/7.29), C (65.59/65.57), H (3.90/3.88)	0.68	2.23
4o		p-$CH_3C_6H_4$ C_A	40	216	$C_{24}H_{17}N_5OS$	N (16.54/16.54), S (7.57/7.57), C (68.07/68.04), H (4.05/4.03)	0.52	2.68

(*continued on next page*)

Table 2 (*continued*)

Code no.	Ar	R	Yield (%)	M.p. (°C)	Mol. formula[a]	E (C/F)[d]	R_f	log p[b]
4p		*p*-ClC_6H_4	42	234	$C_{23}H_{14}ClN_5OS$	N (15.78/15.76), S (7.22/7.21), C (62.23/62.21), H (3.18/3.16)	0.64	2.89
4q		*m*-ClC_6H_4	42	230	$C_{23}H_{14}ClN_5OS$	N (15.78/15.77), S (7.22/7.21), C (62.23/62.21), H (3.18/3.16)	0.73	2.89
4r		-CH=CHC_6H_4 (C_A C_B)	30	218	$C_{25}H_{17}N_5OS$	N (16.08/16.07), S (7.36/7.34), C (68.95/68.93), H (3.93/3.91)	0.78	2.37

[a] Elemental analyses for C, H, N and S were within ±0.4% of the theoretical value.
[b] log p was generated using Hyperchem software.
[c] Melting point of the compound at their decomposition.
[d] Element (Calculated %/Found %).

protons and olefinic CH). ^{13}C NMR (δ) 161.6 (C-2), 168.6 (C-4), 112 (C-11), 136.4 (C-12), 135.4 (C-1″), 131.9 (C-13), 124.8 (C_A), 130.8 (C_B), 122.1 (C_8 of 4(3*H*)-quinazolinone ring), 126.9 (C_{10} of 4(3*H*)-quinazolinone ring), 126.2 (C_2″ of phenyl ring of 1,3,4-thiadiazole ring), 125.7 (C_6″ of phenyl ring of 1,3,4-thiadiazole ring), 127.1 (C_6 of 4(3*H*)-quinazolinone ring), 120.7 (C_b of pyridine at C-2 of 4(3*H*)-quinazolinone ring), 127.2 (C_4″ of phenyl ring of 1,3,4-thiadiazole ring), 128.4 (C_3″ of phenyl ring of 1,3,4-thiadiazole ring), 128.4 (C_5″ of phenyl ring of 1,3,4-thiadiazole ring), 144.3 (C_a of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 158.3 (C_c of pyridine ring at C-2 of 4(3*H*)-quinazolinone ring), 136 (C_y of styryl group), 147.8 (C_9 of 4(3*H*)-quinazolinone ring).

5.2. Pharmacology

The anticonvulsant evaluation was undertaken by the National Institute of Neurological Disorders and Strokes, NIH (USA) using their reported procedure. Male albino mice (CF-1 strain or Swiss, 18–25 g) and rats (Sprague–Dawley or Wistar, 100–150 g) were used as experimental animals. The tested compounds were suspended in polyethylene glycol 400.

5.2.1. Anticonvulsant screening

Initially all the compounds were administered i.p. in a volume of 0.01 ml/g body weight for mice and 0.004 ml/g body weight for rats at doses of 30, 100, 300 mg/kg to one to four animals. Activity was established using the MES and scPTZ tests and these data are presented in Table 2.

5.2.2. Neurotoxicity screening

Minimal motor impairment was measured in mice by the rotorod test. The mice were trained to stay on an accelerating rotorod that rotates at six revolutions per minute. The rod diameter was 3.2 cm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials.

5.2.3. Behavioral testing

The title compounds (100 mg/kg) were screened for their behavioral effect using actophotometer [21] at 30 min and 1 h after drug administration. The behavior of animals inside the photocell was recorded as a digital score. Increased scores suggest good behavioral activity. Percentage decrease in locomotor activity is calculated with the help of activity score of control (24 h prior) and score after 1 h of drug treatment. Mean values were taken for the calculations. The control group animal was administered with PEG 400. The observations are tabulated in Table 3.

5.2.4. CNS depressant activity

The forced swim pool method described earlier was followed [22]; Wistar rats were placed in a chamber (diameter 45 cm, height 20 cm) containing water up to a height of 15 cm at 25 ± 2 °C. Two swim sessions were conducted: an initial 15 min pretest followed by a 5 min test session 24 h

Table 3
Behavioral study of 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones

Code no.[a]	Activity score[b]			% Inhibition
	Control (24 h prior)	Post-treatment		
		After 0.5 h	After 1 h	
4a	405.55 ± 21.32	300.91 ± 26.52	137.16 ± 10.26	53
4b	316.62 ± 10.36	281.39 ± 9.69	103.78 ± 4.89	51
4c	420.71 ± 9.48	372.44 ± 22.17	149.41 ± 15.24	52
4d	238.80 ± 12.21	180.52 ± 15.26	45.54 ± 10.19	57
4e	460.91 ± 11.14	359.81 ± 9.18	140.18 ± 17.64	56
4f	384.82 ± 7.26	241.91 ± 7.24	137.45 ± 13.28	51
4g	450.24 ± 14.74	465.82 ± 14.19NS	343.36 ± 7.28	48
4h	239.40 ± 15.76	187.62 ± 15.20	72.62 ± 6.19	49
4i	445.67 ± 10.70	297.41 ± 19.84	172.50 ± 4.52	50
4j	358.32 ± 26.84	245.32 ± 20.20	110.12 ± 14.92	54
4k	400.42 ± 16.20	287.24 ± 6.19	125.08 ± 19.86	55
4l	362.31 ± 6.42	389.19 ± 10.24NS	400.20 ± 14.29NS	–
4m	395.56 ± 8.93	304.08 ± 10.24	172.36 ± 3.28	45
4n	382.67 ± 9.32	310.22 ± 16.79	177.42 ± 21.91	42
4o	416.50 ± 13.41	430.20 ± 21.20NS	362.48 ± 13.36NS	40
4p	350.12 ± 15.72	292.36 ± 4.65	165.52 ± 10.15NS	41
4q	362.02 ± 24.91	286.48 ± 26.27	181.73 ± 22.34NS	36
4r	417.10 ± 15.82	315.32 ± 8.36	198.91 ± 15.68	42
Phenytoin[c]	456.40 ± 31.12	161.02 ± 12.32	107.42 ± 30.11	64

[a] The compounds were tested at a dose of 100 mg/kg i.p.
[b] Each score represents the means ± SEM of six mice significantly different from the control score at $p < 0.05$ and NS at $p > 0.05$ denotes not significant (Student's *t*-test).
[c] Tested at 30 mg/kg p.o.

Table 4
CNS study on 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones by forced swim pool test

Code no.[a]	Immobility time[b] (s)	
	Control (24 h prior)	Post-treatment (after 1 h)
PEG	110.32 ± 8.26	127.51 ± 2.48NS
4a	56.18 ± 17.14	103.26 ± 11.26
4b	125.92 ± 13.28	177.08 ± 17.18
4c	154.36 ± 15.93	150.10 ± 21.93NS
4d	75.41 ± 7.74	117.93 ± 14.21
4e	80.50 ± 9.20	127.48 ± 13.62
4f	62.32 ± 18.42	73.83 ± 4.91NS
4g	117.01 ± 20.37	132.69 ± 7.24
4h	134.31 ± 18.72	163.21 ± 11.64
4i	92.20 ± 15.80	100.76 ± 13.29NS
4j	113.18 ± 7.62	163.75 ± 20.18
4k	121.73 ± 5.91	175.83 ± 18.93
4l	134.94 ± 3.28	187.91 ± 9.41
4m	48.12 ± 16.98	83.23 ± 3.27
4n	132.23 ± 21.22	168.42 ± 8.17
4o	108.41 ± 11.82	131.51 ± 13.16
4p	57.56 ± 13.21	99.82 ± 12.20
4q	137.32 ± 12.48	142.36 ± 23.16NS
4r	76.91 ± 19.98	114.42 ± 26.83
Carbamazepine[c]	138.82 ± 15.09	240.30 ± 14.10

[a] The compounds were tested at a dose of 100 mg/kg (oral).
[b] Each value represents the means ± SEM of six rats significantly different from the control at $p < 0.05$ and NS denotes not significant at $p < 0.05$ (Student's *t*-test).
[c] Tested at 30 mg/kg (i.p.).

later. The animals were oral drug administrated (100 mg/kg) with the test compound 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period was measured. The results are presented in Table 4.

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References

[1] W.L.F. Armarego, Adv. Heterocycl. Chem. 24 (1979) 1–62.
[2] L. Fisnerova, B. Brunova, Z. Kocfeldova, J. Tikalova, E. Maturova, J. Grimova, Collect. Czech. Chem. Commun. 56 (1991) 2373–2381.
[3] S. Saxena, M. Verma, A.K. Saxena, K. Shanker, Indian J. Pharm. Sci. 53 (1991) 48–52.
[4] D. Gravier, J.P. Dupin, F. Casadebaig, G. Hou, M. Boisseau, H. Bernard, Pharmazie 47 (1992) 91–94.
[5] M.J. Yu, J.R. McCowan, N.R. Mason, J.B. Deeter, L.G. Mendelsohn, J. Med. Chem. 35 (1992) 2534–2542.
[6] Y. Kurogi, Y. Inoue, K. Tsutsumi, S. Nakamura, K. Nagao, H. Yohsitsugu, Y. Tsuda, J. Med. Chem. 39 (1996) 1433–1437.
[7] K.H. Boltze, H.D. Dell, H. Lehwald, D. Loranz, M. Ruberg-Schweer, Arzneim-Forsch./Drug Res. 13 (1963) 688–692.
[8] J.F. Wolfe, T.L. Rathman, M.C. Sleevi, J.A. Campbell, T.D. Greenwood, J. Med. Chem. 33 (1990) 161–166.
[9] S.K. Jain, P. Mishra, Asian J. Chem. 12 (2000) 1341–1343.

[10] V. Jatav, S.K. Kashaw, P. Mishra, J. Indian Chem. Soc. 83 (2006) 1165–1170.
[11] N. Aggarwal, P. Mishra, J. Pharm. Pharm. Sci. 7 (2004) 260–264.
[12] N. Aggarwal, P. Mishra, J. Zhejiang Univ. 6B (2005) 617–621.
[13] V. Jatav, P. Mishra, S. Kashaw, J.P. Stables, Eur. J. Med. Chem., in press, doi:10.1016/j.ejmech.2007.02.004.
[14] M.J. Kornet, T. Varia, W. Beaven, J. Heterocycl. Chem. 20 (1983) 1553–1558.
[15] N. Deshpande, Y.V. Rao, R.P. Kandlikar, A.D. Rao, V.M. Reddy, Indian J. Pharmacol. 18 (1986) 127–131.
[16] R.K. Saksena, R. Yasmeen, Indian J. Chem., Sect. B 25 (1986) 438–442.
[17] R.I. Krall, J.K. Penry, B.G. White, H.J. Kupferberg, E.A. Swinyard, Epilepsia 19 (1978) 409–428.
[18] R.J. Pester, J.J. Cereghino, G.D. Gladding, B.J. Hessie, H.J. Kupferberg, B. Seoville, B. White, Cleve. Clin. Q. 51 (1984) 293–305.
[19] J.R. Dimmock, R.N. Puthucode, J.M. Smith, M. Hetherington, J.W. Quail, U. Pugazhenthi, T. Lechler, J.P. Stables, J. Med. Chem. 39 (1996) 3984–3997.
[20] P.T. Flaherty, T.D. Greenwood, A.L. Manheim, J.F. Wolfe, J. Med. Chem. 39 (1996) 1509–1513.
[21] J.R. Boisser, P. Simon, Arch. Int. Pharmacodyn. Ther. 158 (1965) 212–220.
[22] R.D. Porsolt, G. Anton, N. Blanet, M. Jalfre, Eur. J. Pharmacol. 47 (1978) 379–391.