SYNTHESIS AND ANTICONVULSANT ACTIVITY (CHEMO SHOCK) OF N-1(SUBSTITUTED-4)[(4-OXO-3-PHENYL-3, 4-DIHYDRO-QUINAZOLINE-2-YLMETHYL) SEMICARBAZONES

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INTRODUCTION

Epilepsy is regarded as a multifactor and symptomatically highly diversified neurological disorder result from long-lasting plastic changes in the brain affecting neurotransmitter release, the properties of receptors and channels, synaptic reorganization and astrocyte activity. It afflicts more than 60 million people worldwide according to epidemiological studies [1.2]. Different chemical classes such as hydantoin, barbiturates, benzodiazepines, gamma-aminobutyric acid (GABA) analogs, dibenzazepines, and carbamates are known to be part of anti-epileptic scaffolds [3-8]. Several of these drugs are known to act through modulating the GABAergic and glutamate/aspartate systems. Glutamate, the major fast excitatory neurotransmitter in the brain, play a significant role in brain development, affecting neuronal migration, neuronal differentiation, axonogenesis, and neuronal survival [9,10]. Glutamate activates a number of pharmacologically distinct subtypes [11,12] and plays an essential role in long-term potentiation [13] brought on the identification that most excitatory neurotransmission in the central nervous system (CNS) is mediated by glutamate receptors. They are important mediators of a wide range of neuronal functions from primary sensory perception to cognition [14-17]. Glutamate receptors also play a role in a number of neurodegenerative diseases and epilepsy [18]. L-glutamate can be synthesized in nerve terminals from α-ketoglutarate (formed from gluconeogenesis and the tricarboxylic acid cycle) by the enzyme glutamate dehydrogenase, and from glutamine by the glutaminase enzyme [19,20]. The release of glutamate gets elevated in epilepsy. The majority of antiepileptic drugs reduce the release of excitatory glutamate by blocking sodium or calcium channels, activation of GABA, inhibition of glutamate receptor, and activation of peroxisome proliferator-activated receptor alpha. Epileptic seizures occur when the excitability in certain brain circuits exceeds the restraints imposed by inhibitory mechanisms [21]. Ionotropic glutamate receptors of the AMPA and NMDA are the primary mediators of excitation in the CNS [22] and are critical to seizure generation and spread [23]. Less is known about the role of kainate receptors (KARs). KARs are also ionotropic glutamate receptors which share 40% homology with AMPA receptors and 20% homology with NMDA receptors [24] KARs are responsible for a portion of glutamate-mediated excitation like AMPA and NMDA receptors at some synapses, inducing those in limbic regions relevant to epilepsy [25]. Axonal kainate can affect axonal excitability leading to ectopic action potentials [26]. Agonist, kainic acid, is a powerful convulsant, kainate antagonists would be expected to have antiepileptic effects [27]. Literature evidence suggests that KARs are widely distributed in the CNS; represent a major target through which the convulsant kainate induces seizures and status epilepticus [28]. Various studies in brain regions have demonstrated that KARs contribute to postsynaptic excitation of principal neurons [29-32] and interneurons [33,34] and also act presynaptically to modulate GABA [35] and glutamate [36] release. Some authors reported that seizure protection can be achieved through inhibition of KARs [37], whereas others have proposed that activation of these receptors is a promising antiepileptic strategy [38]. A selective, noncompetitive allosteric AMPA-receptor antagonist, perampanel, was approved for adjunctive epilepsy treatment [39,40] and topiramate was approved to act at AMPA/KARs at high concentrations [41]. Glutamate receptor inhibitors (GRIs) are structurally diverse group of compounds binds to the glutamate receptor and interacts with a specific allosteric non-substrate binding pocket site. GRIs non-competitively inhibits glutamate receptor, blocks its mechanism and makes it unable to bind glutamate. 4(3H)-quinazolinones are one of the most frequently encountered heterocycles in medicinal chemistry reported having diverse pharmacological activities. A literature survey disclosed

RESULTS

Compounds 3C (d-4), 3B (d-4), and 3A (d-4) were observed to be most feasible to act against glutamate receptor for anticonvulsant activity.

CONCLUSIONS

The results obtained revealed that numbers of novel quinazolinone semicarbazone derivatives are effective in chemical to induce (chemo shock) model and showing good anticonvulsant activity.

Keywords: Quinazolinone, Semicarbazones, Strychnine, Thiosemicarbazide, 4-aminopyridine, Anticonvulsant activity, Chemo shock. © 2017 The Authors. Published by Innovare Academy Pvt.Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10i4.16876

ABSTRACT

Objective: This work is designed at finding new structure leads with potential anticonvulsant activities of 4(3H)-quinazolinone pharmacophore scaffold.

Methods: A new series of 4(3H)-quinazolinone pharmacophore was designed with substituted moieties possesses different electronic environment in the hope of developing potent and safe new effective compounds. In such fashion, in this paper, we report the synthesis and anticonvulsant activity (Chemo shock) of N-1(substituted-N-4)[(4-oxo-3-phenyl-3, 4-dihydro-quinazoline-2-ylmethyl) semicarbazones 3A-d (1-7), 3B-d (1-7), 3C-d (1-7), their chemical structure were characterized using IR, 1H-NMR, and elemental analysis techniques. Their anticonvulsant activity was evaluated using chemicals strychnine, thiosemicarbazide and 4-aminopyridine induced seizure models at a dose of 30, 100, 300 mg/kg unto 2 hrs tests in mice. The rotarod assay was performed in mice to evaluate the neurotoxicity of the compounds.

RESULTS: Compounds 3C (d-4), 3B (d-4), and 3A (d-4) were observed to best feasible to act against glutamate receptor for anticonvulsant activity.

Conclusions: The results obtained revealed that numbers of novel quinazolinone semicarbazone derivatives are effective in chemical to induce (chemo shock) model and showing good anticonvulsant activity.

Keywords: Quinazolinone, Semicarbazones, Strychnine, Thiosemicarbazide, 4-aminopyridine, Anticonvulsant activity, Chemo shock.
that the presence of a substituted aromatic ring at position 3 is the necessary requirement for the anticonvulsant activities of compounds such as methaqualone, etataqualone, mecloqualone, and alfemazine. Methaqualone was an important compound in the field of synthetic anticonvulsant, possessed quinazoline core which was responsible for its activity [42]. Literature survey revealed that the semicarbazones have documented consistent advances in the design of novel anticonvulsant agents [43,44] and the structure-activity relations (SAR) from accumulated semicarbazone anti-epileptics indicate that compounds providing handle for (a) aryl binding site with a hydrophobic group, (b) hydrogen bonding domain, (c) lone pair of electrons, and (d) moieties for hydrophobic interaction are favorable for the activity. The aim of this study, therefore, to synthesize new series of quinazoline semicarbazone derivatives with the purpose of considering their possible anticonvulsant activity by chemo shock method.

**METHODS**

**Experimental**

Melting points were determined in open capillary tubes and are uncorrected. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) using silica gel G as a stationary phase and visualized by iodine vapors. Solvent system was chloroform:methanol (9:1). Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer, and the values found within ±0.4% of the theoretical values. "H NMR spectra were recorded on DPX-300 H NMR spectrometer and BRUKER-400 Ultra shieldTM spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. The IR spectra were recorded in KBr pellets on BIO-RAD FTS, IR spectrophotometer. All the chemicals and solvents used were procured from Merck (India), S. D. Fine Chemicals (India) & Rankem (India).

**General procedure for synthesis of compounds 3A-d (1-7), 3B-d (1-7), 3C-d (1-7) derivatives**

Compounds 3A-d (1-7), 3B-d (1-7), 3C-d (1-7), were synthesized as describe in Schemes 1 and 2. The N-chloroanthranilic acid analog 2 was obtained by reacting anthranilic acid (1.45 mmol) with sodium hypochlorite in tetrahydrofuran at 0-5°C. Analogue 2 (4.59 mmol) was further refluxed with substituted anilines (5.51 mmol) in the presence of phosphorous oxychloride in tetrahydrofuran for 1 h to yield 2-chloromethyl-3-sustituted aryl-3H-quinazolin-4-one 3A, 3B, 3C, 3 derivatives Scheme 1. Compounds 3A, 3B, 3C were converted to corresponding amines derivatives 3A-a, 3B-a, 3C-a by reaction with ammonia which was further reacted with sodium cyanate in the presence of catalytic amount of glacial acetic acid to produce urea derivatives 3A-b, 3B-b, 3C-b as per previously known urea preparation method [45-47]. Different substituted semicarbazides 3A-c, 3B-c, 3C-c were obtained by condensation of these urea derivatives with hydrazine hydrate in ethanol under basic condition. The semicarbazone 3A-d (1-7), 3B-d (1-7), 3C-d (1-7), derivatives were prepared by reaction of the appropriate aryl/cycloalkyl aldehyde or ketone listed in Table 1 with the corresponding semicarbazide in glacial acetic acid Scheme 2. Final compounds were washed with brine solution and treated with Na2SO4. TLC was performed throughout the reactions to optimize the reactions for purity and completion. The physical data for the newly synthesized compounds are presented in Table 2. The formation of the title compounds was confirmed by its IR and "H NMR spectral studies.

Characterization of N-1 substituted-N-4-[4-oxo-3-phenyl-3,4-dihydro-quinazoline-2-yl]methyl semicarbazones derivatives are as follows:

**Scheme 1** Preparation procedure of different aromatic amine derivative of N-chloroanthranilic acid

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
& \quad \text{NaHCO}_3 \\
& \quad \text{CICH}_2\text{COCl} \\
& \quad \text{N-chloroacetyl anthranilic acid} \\
& \quad \text{POC}_3 \text{Cl} \\
& \quad \text{N-chloroethyl derivatives} \\
& \quad \text{A. X} = \text{-H} \\
& \quad \text{B. X} = \text{-Cl} \\
& \quad \text{C. X} = \text{-NO}_2
\end{align*}
\]
Scheme 2: Preparation procedure of quinazolinone semicarbazone derivatives

N-1[4(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylmethyl)semicarbazone 3A(d-1) IR (KBr, cm⁻¹) 3383 (Ar-H), 1693 (C=O), 1671 (C=C), 1706 (C=O), 3366 (N-H), 1674 (C-N str of NHN=C); 1H NMR (300 MHz, CDCl₃, ppm, δ): 6.78 (m, 4H, Ar-H), 7.55 (m, 5H, ArH), 2.95 (s, 2H, CH₂) 4.50 (s, 1H, NH), 11.29 (s, 1H, CONH); anal. Calcd for: C₉H₇ClNO₂ (445.13) (%): Found = C (63.52) H (4.67) N (16.10).

N-1[4(3-(4-chlorophenyl)-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)methyl]semicarbazone 3A(d-2) IR (KBr, cm⁻¹) 3385 (Ar-H), 1694 (C=O), 1671 (C=N), 1544 (C=C), 1710 (C=O), 3356 (N-H), 1483 (N-O), 1674 (C=N str of NHN=C); 1H NMR (300 MHz, CDCl₃, ppm, δ): 6.37 (m, 4H, Ar-H), 7.48 (m, 5H, ArH), 2.95 (s, 2H, CH₂) 4.52 (s, 1H, NH), 11.30 (s, 1H, CONH); anal. Calcd for: C₁₀H₇ClNO₂ (440.11) (%): Found = C (58.70) H (3.88) N (17.10) calculated = C (58.72) H (3.90) N (17.12).

N-1[4(3-(4-chlorophenyl)-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)methyl]semicarbazone 3A(d-3) IR (KBr, cm⁻¹) 3386 (Ar-H), 1694 (C=O), 1671 (C=N), 1542 (C=C), 1710 (C=O), 3354 (N-H), 1480 (N-O), 1673 (C=N str of NHN=C); 1H NMR (300 MHz, CDCl₃, ppm, δ): 6.50 (m, 4H, Ar-H), 7.49 (m, 5H, ArH), 2.95 (s, 2H, CH₂) 4.53 (s, 1H, NH), 11.29 (s, 1H, CONH); anal. Calcd for: C₁₀H₇ClNO₂ (436.11) (%): Found = C (58.68) H (3.87) N (17.02) calculated = C (58.72) H (3.90) N (17.12).
Table 1: Different aryl/cycloalkyl aldehyde or ketone used in the preparation of quinazolinone semicarbazone derivatives 3A-d (1-7), 3B-d (1-7), 3C-d (1-7)

| Serial number | Compound ID | X     | R        | R1        |
|---------------|-------------|-------|----------|-----------|
| 1             | 3A-d-1      | -H    | -H       | -C,H,Cl   |
| 2             | 3A-d-2      | -H    | -CH₃     | -C,H₁     |
| 3             | 3A-d-3      | -H    | -CH₃     | -C,H,NO₂  |
| 4             | 3A-d-4      | -H    | -H       |           |
| 5             | 3A-d-5      | -H    | -H       |           |
| 6             | 3A-d-6      | -H    | -H       |           |
| 7             | 3A-d-7      | -H    | -C,H₁    | -C,H₁     |
| 8             | 3B-d-1      | -Cl   | -H       | -C,H,Cl   |
| 9             | 3B-d-2      | -Cl   | -CH₃     | -C,H₁     |
| 10            | 3B-d-3      | -Cl   | -CH₃     | -C,H,NO₂  |
| 11            | 3B-d-4      | -Cl   | -H       |           |
| 12            | 3B-d-5      | -Cl   | -H       |           |
| 13            | 3B-d-6      | -Cl   | -H       |           |
| 14            | 3B-d-7      | -Cl   | -C,H₁    | -C,H₁     |
| 15            | 3C-d-1      | -NO₂  | -H       | -C,H,Cl   |
| 16            | 3C-d-2      | -NO₂  | -CH₃     | -C,H₁     |
| 17            | 3C-d-3      | -NO₂  | -CH₃     | -C,H,NO₂  |
| 18            | 3C-d-4      | -NO₂  | -H       |           |
| 19            | 3C-d-5      | -NO₂  | -H       |           |
| 20            | 3C-d-6      | -NO₂  | -C,H₁    | -C,H₁     |
| 21            | 3C-d-7      | -NO₂  | -C,H₁    | -C,H₁     |

For: CₓHᵧClₓNₓOₓ (421.09) (%): Found = C (59.72) H (3.80) N (16.57) calculated = C (59.79) H (3.82) N (16.60).

N-[[3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]methyl]-semicarbazone 3B(d-7) IR (KBr, cm⁻¹) 3373 (Ar-H), 1655 (C=C), 1608 (C=N), 1559 (C=C), 1709 (C=O), 3557 (N-H), 1669 (C=N str of NHN=C), 1674 (C=H str of CONH), 1725 (C=O), 3357 (N-H), 1669 (C=N str of NHN=C) ppm, δ: 6.71 (m, 4H, Ar-H), 7.24 (m, 5H, ArH), 2.75 (s, 2H, CH₂), 4.54 (s, 1H, NH), 11.35 (s, 1H, CONH), analyzed. Calculated for: CₓHᵧClₓNₓOₓ (507.14) (%): Found = C (57.90) H (3.60) N (17.59) calculated = C (57.93) H (3.59) N (17.62).

N-[[3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]methyl]-semicarbazone 3C(d-1) IR (KBr, cm⁻¹) 3382 (Ar-H), 1686 (C=C), 1608 (C=N), 1552 (C=C), 1725 (C=O), 3360 (N-H), 1091 (Ar-Cl), 1674 (C=N str of NHN=C) ppm, δ: 6.71 (m, 4H, Ar-H), 7.24 (m, 5H, ArH), 2.75 (s, 2H, CH₂), 4.54 (s, 1H, NH), 11.35 (s, 1H, CONH), analyzed. Calculated for: CₓHᵧClₓNₓOₓ (476.01) (%): Found = C (57.90) H (3.60) N (17.59) calculated = C (57.93) H (3.59) N (17.62).

N-[[3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]methyl]-semicarbazone 3C(d-2) IR (KBr, cm⁻¹) 3382 (Ar-H), 1693 (C=C), 1608 (C=N), 1563 (C=C), 1715 (C=O), 3360 (N-H), 1674 (C=N str of NHN=C) ppm, δ: 6.71 (m, 4H, Ar-H), 7.24 (m, 5H, ArH), 2.75 (s, 2H, CH₂), 4.54 (s, 1H, NH), 11.35 (s, 1H, CONH), analyzed. Calculated for: CₓHᵧClₓNₓOₓ (507.14) (%): Found = C (59.72) H (3.80) N (16.57) calculated = C (59.79) H (3.82) N (16.60).
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Table 2: Physical properties of the final synthesized quinazolinone semicarbazone derivatives

| Compound ID | Molecular formula | Log p | Melting point (°C) | Yield (%) |
|-------------|-------------------|-------|-------------------|-----------|
| 3A-d-1      | C₃H₆ClN₂O₂      | 3.11  | 266-268           | 74        |
| 3A-d-2      | C₃H₆N₂O₂        | 3.33  | 272-274           | 70        |
| 3A-d-3      | C₃H₆N₂O₂        | 3     | 275-277           | 72        |
| 3A-d-4      | C₃H₆N₂O₂        | 3.66  | 282-284           | 64        |
| 3A-d-5      | C₃H₆N₂O₂        | 3.22  | 284-286           | 69        |
| 3A-d-6      | C₃H₆N₂O₂        | 2.89  | 290-292           | 68        |
| 3A-d-7      | C₃H₆N₂O₂        | 3.88  | 287-289           | 71        |
| 3B-d-1      | C₃H₆ClN₂O₂      | 3     | >300              | 78        |
| 3B-d-2      | C₃H₆ClN₂O₂      | 3.22  | >300              | 82        |
| 3B-d-3      | C₃H₆ClN₂O₂      | 2.89  | >300              | 70        |
| 3B-d-4      | C₃H₆ClN₂O₂      | 3.44  | >300              | 65        |
| 3B-d-5      | C₃H₆ClN₂O₂      | 3.11  | 298-300           | 75        |
| 3B-d-6      | C₃H₆ClN₂O₂      | 2.78  | >300              | 80        |
| 3B-d-7      | C₃H₆ClN₂O₂      | 3.77  | >300              | 85        |
| 3C-d-1      | C₃H₆ClN₂O₂      | 2.78  | 295-297           | 86        |
| 3C-d-2      | C₃H₆N₂O₂        | 3     | 255-257           | 56        |
| 3C-d-3      | C₃H₆N₂O₂        | 2.67  | 225-227           | 50        |
| 3C-d-4      | C₃H₆N₂O₂        | 3.22  | 260-262           | 72        |
| 3C-d-5      | C₃H₆N₂O₂        | 2.89  | >300              | 65        |
| 3C-d-6      | C₃H₆N₂O₂        | 2.56  | >300              | 62        |
| 3C-d-7      | C₃H₆N₂O₂        | 3.55  | >300              | 80        |

¹H NMR (300 MHz, CDCl₃, ppm, δ): 6.83 (m, 4H, Ar-H), 7.54 (m, 5H, ArH), 2.68 (s, 2H, CH₂), 1.40 (s, 3H, CONH), 11.35 (s, 1H, CONH). Calculated for C₁₆H₁₈N₄O₂ (465.15): Found = C (63.11) H (4.40) N (18.44) calculated = C (63.15) H (4.42) N (18.41).

N-(3-[4-nitrophenyl]-4-oxo-3, 4-dihydroquinazolin-2-yl) methyl semicarbazide 3A-d-5 IR (KBr, cm⁻¹) 3383 (Ar-H), 1699 (C=O), 1619 (C=O), 1554 (C=O), 1720 (C=O), 1358 (N=O), 1488 (N=O). Calculated for C₁₆H₁₈N₄O₂ (465.15): Found = C (63.11) H (4.40) N (18.44) calculated = C (63.15) H (4.42) N (18.41).

Anticonvulsant screening

Animals

Albino mice of either sex weighing between 25-30 g were used in this study. All albino mice employed in this study is approved by the Institutional Animal Ethics Committee of NBRI, Lucknow and carried out as per CPCSEA guidelines. The animals were kept in large spacious hygienic cages during the course of the experimental period. The animals had free access to standard commercial diet and water ad libitum and were kept in rooms maintained at 22±1°C with 12 hrs light-dark cycle. The animals were divided into three groups of 10 animals each: Group I: Control group (distilled water treated), Group II: Test group (were dissolved in polyethylene glycol-400 and 30, 100, 300 mg/kg i.p doses), Group III: Standard group, on reference drug (diazepam 10 mg/kg i.p. phenytoin 30 mg/kg i.p.). All the drugs were administered 30 minutes before the administration of strychnine (1 mg/kg, i.p.) thiosemicarbazide (20 mg/kg, s.c) and 4-aminopyridine (13.3 mg/kg, s.c). The anticonvulsant screening of the final compounds was done according to the protocols of the anticonvulsant drug development program [48].

Procedure

Strychnine induced model

Mice of either sex with a weight of 25-30 g were treated with the test compounds or the standards (e.g., diazepam 10 mg/kg i.p) by an oral or intraperitoneal administration. Controls received the vehicle only. 30 minutes prior treatment with a subcutaneous dose of 1 mg/kg strychnine, test compounds in doses 30, 100, 300 mg/kg i.p. was injected. The occurrence of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1 hr, 2 hrs and 4 hrs, respectively [49].

Thiosemicarbazide induced model

Mice of either sex with a weight of 25-30 g were treated with the test compounds or the standard (e.g., diazepam 10 mg/kg i.p.) by the oral or intraperitoneal administration. Controls received the vehicle only. 30 minutes prior treatment with a subcutaneous dose of 20 mg/kg thiosemicarbazide, test compounds in doses 30, 100, 300 mg/kg i.p. was injected. The occurrence of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1 hr, 2 hrs and 4 hrs, respectively [50].

4-aminopyridine induced model

Mice of either sex weighing 25-30 g will allow acclimatizing with free access to food and water for a 24-hr period before testing. Test drugs will administer at a dose of 30, 100, 300 mg/kg body weight intraperitoneally (i.p). 30 minutes prior to subcutaneous injection of 4-aminopyridine at a dose of 13.3 mg/kg. Controls treated with 4-aminopyridine only exhibit characteristic behavioral signs, such as hyperreactivity, trembling, intermitted forelimb/hindlimb clonic followed by hind limb extension, tonic seizures, and death. The standard drug phenytoin at a dose of 30mg/kg body weight was taken for comparison [51].
Neurotoxicity (NT) screening
The activity of the drugs interfering with motor coordination was checked by the rotarod test. The mice will train to stay on an accelerating rotarod that rotates at 6 revolutions per minute. Trained animals were given ip injection of the test compounds in doses of 30, 100, 300 mg/kg. The rod diameter was 3.2 cm. NT indicated by the inability of the animal to maintain equilibrium on the rotarod for at least 1 minute in each of three trials. The dose, at which the animals were unable to grasp the rotarod, will determine. All the results were reported in Table 3.

RESULTS AND DISCUSSIONS
Chemistry
A series of new quinazolinone derivatives 3A-d (1-7), 3B-d (1-7), and 3C-d (1-7) have been synthesized using appropriate routes. All newly synthesized compounds were characterized on the basis of their m.p, Rf value (data are shown in Table 2). Fourier transform infrared, ^1H^ NMR, and elemental analysis. From the structural investigation, IR spectra showed the stretching frequency range between 1580 and 1620/cm, which showed the presence of imine linkage and also the absence of -NH peak for the synthesized quinazolinone semicarbazone derivatives. Dependent substitution of double bonded nitrogen group of imine C=N could be the reason for the characteristic absorption close to the carbonyl C=O of amide (1632-1685 cm^-1) or C=C of alkenes (1600-1680/cm) double bond stretching region. ^1H^-NMR spectra give a characteristic proton resonance shifts for all the synthesized quinazolinone semicarbazone derivatives, which ensured the existence of aromatic, amine, amide, and imine protons. Almost all the synthesized analog showed potent anticonvulsive activity.

Design
The conformational analysis of the older generation clinically active anticonvulsants such as phenytoin, phenobarbitalone, carbamazepine, lamotrigine, rufinamide, and remacemide led to the proposal of a general model for anticonvulsant activity comprising of two aromatic rings or they are equivalent in a favored orientation and the third region containing a hydrogen bond-forming functional groups in terms of interaction at the binding site as proposed by Dimmock et al. [43]. All the synthesized compounds comprise these essential pharmacophoric requirements that are important for good anticonvulsant activity.

Pharmacology
Quinazolinone heterocycles are the attractive scaffold as anticonvulsant agents as well as various CNS activities [52,53]. We have designed a novel quinazolinone semicarbazones. In the pharmacological study, we have investigated anticonvulsant activity as well as the NT. All the synthesized compounds were screened for their anticonvulsant activity using various chemical induced convulsion models using strychnine, thiosemicarbazide and 4-aminopyridine to induce convulsion, diazepam and phenytoin were used as the standard drug at the dose of 30, 100, 300 mg/kg b.w. anticonvulsant activity and NT data for the semicarbazones of quinazolinone derivatives 3A-d (1-7), 3B-d (1-7), 3C-d (1-7) are given in Table 3, and most of the compounds showed mild to moderate anticonvulsant activity. The analogs 3A-d-5, 3B-d-5, and 3C-d-5 were active at 30 mg/kg and 100 mg/kg only at 0.5 h and 1 h, indicating that they have the rapid onset of action and shorter duration of action and were exhibit moderate anticonvulsant activity. The compounds 3A-d-4, 3B-d-4, 3C-d-4 were observed to be most active for anticonvulsant activity. All the compounds showed activity against chemo shock method pinpointing their capability to prevent seizure spread.

SAR
It also showed that a substituted aromatic ring in position 3 is significant for anticonvulsant activity. Various N-[1-substituted-N-[4-(4-oxo-3-phenyl-3, 4-dihydro-quinazoline-2-ylmethyl) semicarbazones derivatives 3A-d (1-7), 3B-d (1-7), 3C-d (1-7) were synthesized to establish the pharmacophoric substituents, responsible for the activity.

Table 3: Anticonvulsant evaluation and neurotoxicity screenings of new quinazolinone semicarbazone derivatives 3A-d (1-7), 3B-d (1-7), 3C-d (1-7) in the strychnine, thiosemicarbazide, 4-aminopyridine induce model after intraperitoneal injection in mice

| Compound ID | Time to peak effect | Strychnine induced convulsion | Thiosemicarbazide induced convulsion | 4-amino pyridine induced convulsion | Neurotoxicity screen |
|-------------|-----------------|-----------------------------|-------------------------------------|-----------------------------------|----------------------|
|             | 0.5 h | 1 h | 2 h | 0.5 h | 1 h | 2 h | 0.5 h | 1 h | 2 h | 0.5 h | 4 h |
| Controls    |       |     |     |       |     |     |       |     |     |       |     |
| 3A-d-1      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3A-d-2      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3A-d-3      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3A-d-4      | 300   | 100 | 100 | 300   | 100 | 30  | 100   | 30  | -   | 300   | 300 |
| 3A-d-5      | 30    | 100 | -   | 30    | 100 | -   | 30    | 30  | -   | 30    | 30  |
| 3A-d-6      | 30    | 30  | -   | -     | -   | -   | -     | -   | -   | 30    | 30  |
| 3A-d-7      | 30    | -   | -   | -     | -   | -   | -     | -   | -   | 30    | -   |
| 3B-d-1      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3B-d-2      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3B-d-3      | 30    | -   | -   | -     | -   | -   | -     | -   | -   | 30    | -   |
| 3B-d-4      | 300   | 100 | 100 | 300   | 100 | 30  | 100   | 30  | -   | 300   | 300 |
| 3B-d-5      | 30    | 30  | -   | 30    | 30  | -   | 30    | 30  | -   | 30    | 30  |
| 3B-d-6      | 30    | -   | -   | -     | -   | -   | -     | -   | -   | 30    | -   |
| 3B-d-7      | 30    | -   | -   | -     | -   | -   | -     | -   | -   | 30    | -   |
| 3C-d-1      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3C-d-2      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3C-d-3      | 30    | -   | -   | 30    | -   | -   | 30    | -   | -   | 30    | -   |
| 3C-d-4      | 300   | 100 | 100 | 300   | 100 | 30  | 100   | 30  | 30  | 300   | 300 |
| 3C-d-5      | 100   | 30  | -   | 100   | 30  | -   | 30    | 30  | -   | 30    | 30  |
| 3C-d-6      | 30    | 30  | -   | 30    | 30  | -   | 30    | 30  | -   | 30    | 30  |
| 3C-d-7      | 30    | -   | -   | -     | -   | -   | -     | -   | -   | 30    | -   |
| Diazepam (mg/kg) | 10 | 10 | 10 | 10 | 10 | 10 | - | - | - | - | - |
| Phenytoin (mg/kg) | 30 | 30 | 30 | 30 | 30 | 30 | - | - | - | - | - |

n=10, test compounds were suspended in polyethylene glycol and doses of 30, 100, 300 mg/kg were administered through intraperitoneal (I.p.) injection in mice. The figures in the table indicate the dose in mg/kg at which bioactivity was observed in a majority of the animals. The dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg). In neurotoxicity screen the figure indicate the dose at which no neurotoxicity was observed and the dash (-) indicates compounds was not tested.
The aryl/cyclohexyl ring acts as a lipophilic domain, C=O group acts as electron donor, NH groups act as hydrogen bonding domain, and the aryl substituent acts as the distal hydrophobic center,Fig 1. Thus, it may be stated that compounds 3A-d-1 (1-7), 3B-d (1-7), 3C-d (1-7) fulfill the essential pharmacophoric requirements for anticonvulsant activity. Compounds 3A-d-5, 3B-d-5, 3C-d-5 displayed moderate and compounds 3A-d-4, 3B-d-4, 3C-d-4 most protection in chemo shock models study and supported the pharmacophoric character of cyclohexyl moiety for anticonvulsant activity. This observation supports the fact that substitution on the aryl ring by halogen led to a number of semicarbazones with low ED₅₀ value and high protective index value. This observation also indicated the role of electronic factors affecting anticonvulsant activity.

CONCLUSION

In this paper, we have attempted to design and synthesized novel quinazolinone derivatives that exhibit anticonvulsant activity. The results obtained revealed that numbers of novel quinazolinone derivatives effective in chemical induce (chemo shock) model, compounds 3A-d-4, 3B-d-4, 3C-d-4 showed the most active while 3A-d-5, 3B-d-5, 3C-d-5 moderate activity and remaining compounds showed mild activity. This study provides the broad-spectrum anticonvulsant activity of substituted quinazolinone semicarbazones that are comparatively higher or equipotent to the currently available drugs in the comparison tests. Overall, the synthesized compounds emerged as more active and less neurotoxic derivatives.

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