Available Online at www.ijpscr.info
International Journal of Pharmaceutical Sciences and Clinical Research 2021; 1(3):356-364

RESEARCH ARTICLE

The Antiepileptic Effect of Synthesized Derivatives of Quinazoline-4(3H)-One

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Received: 10-05-2021; Revised: 15-06-2021; Accepted: 12-07-2021

ABSTRACT

The objective of the paper was to design and synthesize new derivatives of ((E)-3-(5-((substituted phenylamino) methyl)-1,3,4-thiadiazol-2-yl)-2styrylquinazolin-4(3H)-one and evaluated for their anticonvulsant potential. Materials and Methods: Various syntheses of (E)-3-(5-(substituted aminomethyl)- 1,3,4-thiadiazol-2-yl)-2-styrylquinazolin-4(3H)-one derivatives have been synthesized by reacting 2-substituted benzoxazin-4-one with (E)-2-(4-Substituted styryl)-4H-benzo[d] [1,3]oxazin-4-one. All synthesized compounds have been characterized by the infrared, 1H-NMR, and mass spectral analysis. Proposed compounds have been evaluated for anticonvulsant potential by subcutaneous pentylenetetrazole and maximal electroshock seizure model and compared with the reference drug phenytoin and carbamazepine. Neurotoxicity study of the synthesized compounds was also performed. Results and Discussion: The anticonvulsant evaluation of synthesized compound QNM-1, QNM-2, QNM-4, QNM-6, QNM-9, QNM-11, QNM-13, and QNM-15 has shown seizure protection at 100 mg/kg dose after 30 min and 4 h, so they have good onset of action as quickly reach brain and have prolonged action reveal that compound metabolized slowly, whereas compounds QNM-7, QNM-8, and QNM-12 were moderate active and reveal that their high concentration is required to cross blood–brain barrier. Compounds QNM-3, QNM-5, QNM-10, and QNM-14 were less active. Compounds having chlorine, bromine, fluorine, and nitro in the phenyl moiety have shown good activity when attached to para group but the addition of meta and ortho group of the same may provide least active compounds and in last fluorine compounds have shown comparative less active compounds. Conclusion: The pharmacological evaluation suggests that eight synthesized compounds have shown promising anticonvulsant potential and bulkier compounds can easily penetrate BBB to exert their effect.

Keywords: Anticonvulsant, Carbamazepine, Maximal electroshock seizure, Neurotoxicity, Phenytoin

INTRODUCTION

Therapeutic science has stays a remarkable situation among science and biology.[1] Medicinal science assumes a critical part in the improvement of new particles, their ID, and interpretative connect with their successful activity at the atomic level just as construction movement connections, meant the connection between synthetic structure[2] and pharmacological action of the compounds.[3] An enormous number of heterocyclic compound are additionally utilized clinically, for instance, penicillin, cephalosporin, morphine, nicotine, and 5-fluorouracil.[4] Heterocyclic mixtures can be aliphatic or sweet smelling in character, contingent on the electronic constitution.[5] Epilepsy is a central nervous system (CNS) malfunction that drives either to summed up hyperactivity including basically all pieces of the mind or hyperactivity of just a bit of the brain.[6] It has been assessed that satisfactory control of

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seizures could not be gotten in up to 20% of the patients with epilepsy utilizing the original of antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, sodium valproate, and diazepam).[7] The spasms of roughly 25% of epileptics are enough constrained by current clinically accessible medications. The current medication treatment is joined by various incidental effects including languor, ataxia, gastrointestinal unsettling influences, gingival hyperplasia, and megaloblastic weakness. The action of mixtures relies on the replacement and little changes in position just as particle may ruin or modify their pharmacological impact. This alteration might be their position, substitution of electron pulling out bunch just as expansion of new iota may modify their pharmacological action.[8] Slight change at some point totally switches the activity of the compound, as for the situation, when the terminal methyl gathering of 5-(1-methyl amyl)-5-ethyl barbituric corrosive is drawn one carbon particle closer the core to structures 5-(1,3-dimethyl butyl)-5-ethyl barbituric corrosive changed over tranquilizers mesmerizing movement toward anticonvulsant.[9] 2-methyl-3-o-tolyl; 4(3H)-quinazolinone is a powerful mesmerizing specialist and other 4(3H)- quinazolinone and its subordinates have been accounted for to show pain relieving, sedative, antibacterial, anticancer, anticonvulsant, antihypertensive, mitigating, hostile to tuberculosis,[10] anticonvulsant,[11] and antioxidant,[12] diuretic, muscle relaxant, calming, against hepatitis-A virus,[13] and sedative properties. The majority of the medications utilized in the crude arrangement of medication were from the regular sources, for instance, morphine, quinine, digitalis, ergot, and atropine were gotten from plant sources and their helpful employments. The previous decade has seen a constant interest in the advancement of anticonvulsant drugs. Writing overview uncovered that the presence of subbed fragrant ring at third position and methyl/phenyl bunch at second situation of 4(3H)-quinazolinone is vital prerequisite for the CNS gloom and anticonvulsant action. This speculation urges us to fabricate the alteration of quinazolinone at the second and third positions. The target of the papers was to configuration, incorporate, and assessment of combined mixtures for anticonvulsant potential.

MATERIALS AND METHODS

2-chloroacetyl chloride, thiosemicarbazide, and formaldehyde were purchased from Sigma-Aldrich. New Delhi. Substituted anilines (Aniline, p-fluoro aniline, o-fluoroaniline, p-chloroaniline, o-chloroaniline, m-chloro aniline, m-bromo aniline, p-bromo aniline, and p-nitro aniline) were purchased from HiMedia. Acetic anhydride, di-methyl formamide, glacial acetic acid substituted, and benzaldehyde (benzaldehyde, p-fluorobenzaldehyde, p-Bromobenzaldehyde, and p-Tolualdehyde) were purchased from chemical drug house, New Delhi, India. The chemical used for experimental work was synthetic grade. The melting points of the synthesized compounds were determined in open glass capillaries. Infrared (IR) spectra were recorded on ALPHA (Bruker) Fourier transform IR spectrometer. Elemental analysis was performed and found values were within 0.4% of theoretical values. 13C-NMR spectra were recorded on Bruker Avance 400 spectrophotometer at 400 MHz, 5 mm multi-nuclear inverse probe head, low- and high-temperature facility, and HRMAS accessory. Mass spectra were recorded using Mass Spectrometers Jeol SX-102 (FAB) by ESI.

Chemistry

The synthesis of (E)-3-(5-(substitutedaminomethyl)-1,3,4-thiadiazol-2-yl)-2-styrylquinazolin-4(3H)-one is accompanied in Figure 1.

The present synthesis comprises

1. Synthesis of 1,3,4-thiadiazole
2. Synthesis of (E)-3-(5-(((4-Substitutedphenyl) amino)methyl)-1,3,4-thiadiazol-2-yl)-2-styrylquinazolin-4(3H)-one.

Synthesis-I

Synthesis of 1,3,4-thiadiazole

Step 1: Synthesis of 5-(chloromethyl)-1,3,4-thiadiazol-2-amine

In that reaction, substituted aminothiadiazole[3] was prepared by the conventional method by the following procedure: In this reaction, 2-chloroacetyl chloride[2] (0.1 M) and thiosemicarbazide[1] (0.1 M) were mixed and

refluxed with conc. sulfuric acid for 2½ h. When the reaction is completed, reaction mixture was cooled in ice bath and neutralize with ammonia solution (2.5%).[14] The reaction was monitored by the thin-layer chromatography (TLC) method. The solid product thus obtained was filtration and recrystallized using 75% ethanol. The product is characterized by 1H-NMR (6.99 ppm N-H; 4.62 ppm CH2) and ultraviolet (UV) spectral analysis. The compounds were shown peak at 280 nm by UV spectroscopic analysis.

Step 2: Synthesis of 5-(substituted-amino methyl)-1,3,4-thiadiazol-2-amine

In that reaction, 5-(chloromethyl)-1,3,4-thiadiazol-2-amine[3] (0.1 M) was taken in round-bottom flask and formaldehyde was dissolved in methanol (3.0 ml) and then was added drop wise with continuous stirring. The resulting mixture was stirred during ½ h to complete the mixing. To this reaction mixture, methanol solution of aniline/p-fluoro, aniline/o-fluoro, aniline/p-chloro, aniline/o-chloro, aniline/m-chloro, aniline/m-bromo aniline/p-bromo, and aniline/p-nitro aniline (0.1 M)[4] was mixed and reflux for 2 h at 65–70°C.[15] Then, after reaction mixture was cool at room temperature and solution poured in cold water. The solidification of compounds arises and obtained solid was filtered and washed with hot distilled water. The obtained solid product was air dried for further synthesis. Obtained compound N-((5-amino-1,3,4-thiadiazol-2-yl)methyl)nitramide [Figure 2][5] was characterized by IR, 1H-NMR and was found consistent with an expected structure. The IR data of 3270.5 (N-H str.); 3082.5 (Ar. C-H); 1515.3 (C=N str.); 642.5 (C-S str.); and 1466.9 (N=O asym. str.) confirm the compound N-((5-amino-1,3,4-thiadiazol-2-yl)methyl) nitramide. This compounds further confirmed by the 1H-NMR (167 C2-1,3,4-thiadiazole, 56 ppm CH2-NH). TLC has been performed each and every steps to confirm the completion of the reaction.

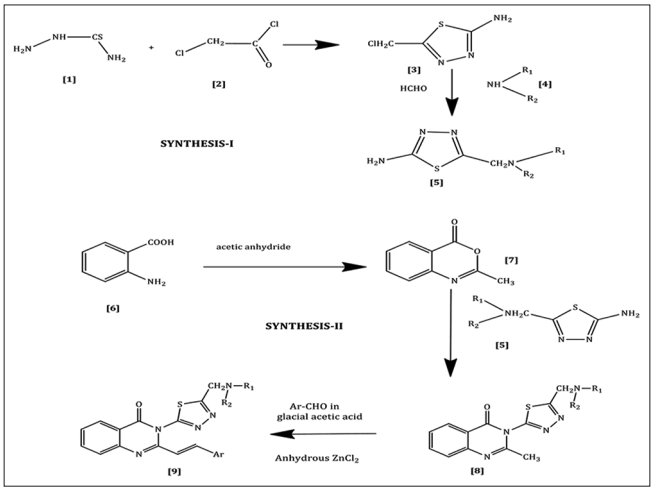


Figure 1: Schematic representation of synthesis-I and scheme-II

Synthesis-II

Synthesis of (E)-3-(5-(((4-Substitutedphenyl)amino) methyl)-1,3,4-thiadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

Step 1: Synthesis of 2-methyl-4H-benzo[d][1,3] oxazin- 4-one[16]

In this reaction, anthranilic acid[6] (0.01 M) was refluxed under anhydrous condition for 4 h using acetic anhydride as a solvent. The remaining unreacted acetic anhydride was distilled off to get product N-acetyl anthranilic acid. Then, N-acetyl anthranilic acid was further refluxed with acetic anhydride, under anhydrous condition for 4 h to obtain the solid mass of 2-methyl benzoxazin-4-one.[7] The products were dried and recrystallized from petroleum ether. The reaction was monitored by the TLC for the completion of the reaction. The compounds 7 (2-methyl benzoxazine-4- one) were characterized by 1H-NMR spectra (7.09–8.128 (δppm)=m, 4H (Ar); 2.511(δ ppm)=s, 3H, CH3). The 2-methyl benzoxazine-4-one was also confirmed by the IR analysis, IR peak shows at

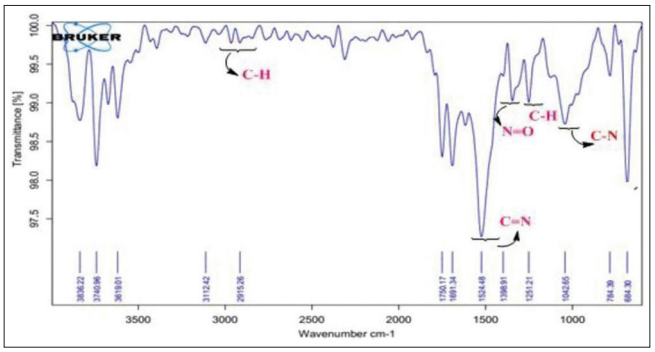


Figure 2: N-((5-amino-1,3,4-thiadiazol-2-yl)methyl) nitramide

N-H str. (primary amine 3580 cm−1), and Ar-CH (3200 cm−1) [Figure 3].

Step 2: Synthesis of 3-(5-((Substitutedamino) methyl)-1,3,4-thiadiazol-2-yl)-2 methylquina zolin-4(3H)-one

In that reaction, 2-methyl-4H-benzo[d][1,3] oxazin-4-one[7] (0.1 M) and obtained compounds[5] (0.1 M) were suspended in glacial acetic acid and refluxed for 4 h. After completion of reaction, the reaction mixture was cooled at room temperature and then it was poured into crushed ice and kept overnight in the refrigerator.[14] The obtained solid product[8] was filtered, washed with cold water, and recrystallized from hot ethanol (75%). The synthesis was monitored by the TLC for the completion of the reaction.

Step 3: Synthesis of (E)-3-(5-(((4-Substitutedphenyl) amino)methyl)-1,3,4-thiadiazol-2-yl)-2- styrylquinazolin-4(3H)-one

In that reaction, equimolar quantity of compound[8] (0.2 M) was taken in round-bottom flask, benzaldehyde and substituted benzaldehyde (p-fluorobenzaldehyde; p-Bromobenzaldehyde/p-Tolualdehyde) were dissolved in glacial acetic acid (0.2 M) and refluxed at 130–140°C for 2 h by the addition of anhydrous zinc chloride (0.1 g). After, reaction completion, mixture was washed with cold water to dissolve unreacted zinc chloride. The obtained solid residue after filtration was washed with cold ethanol.[17] The purification of the synthesized compounds[9] was done by dissolving the compounds in minimum quantity of dimethylformamide (DMF) and then added this solution to distilled water. This synthesis was monitored by the TLC to confirm the completion of the reaction.

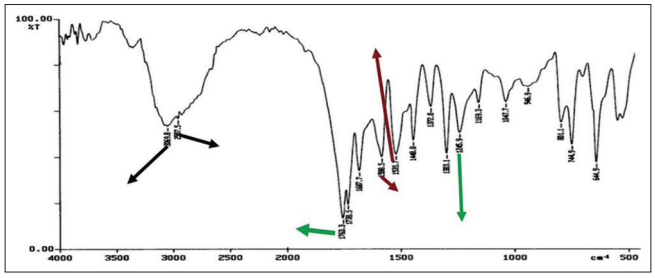


Figure 3: Infrared spectra of 2-methyl benzoxazinone

Pharmacological evaluation of synthesized compounds

Anticonvulsant evaluation of (E)-3-(5-(substitutedaminomethyl)-1,3,4-thiadiazol-2-yl)-2-styryl quinazolin-4(3H)-one was done by the anticonvulsant drug development program protocol. The profile of anticonvulsant activity was established after injection by the i.p. maximal electroshock seizure (MES) pattern test.[18] Anticonvulsant potential of synthesized compounds has been evaluated by two methods, that is, maximal electroshock (MES)and subcutaneous pentylenetetrazole seizures (scPTZ) methods. 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.[19]

Study Protocol

Healthy young Swiss albino mice weighing between 20 and 30 g were used. Before the administration of the test samples, standard and control, the mice were first tested by giving current of 50 mA for 0.2 s using electro convulsometer. Those animals which showed characteristic course of convulsions were selected for experiment. The selected animals were divided into three groups of six animals each. After 1 h of the administration of the standard drug (phenytoin) and the test samples, the electric shock was induced. The different phases of convulsions, that is, tonic flexion, tonic extensor, clonic convulsion, stupor, and recovery time or death were observed. The time (seconds) spent by the animals in each phase was recorded. The percentage protection provided by the standard and test samples was calculated. The scPTZ test was performed by administering PTZ dissolved in 0.9% NaCl solution in posterior midline of the animals. A minimal time of 30 min consequent to administration of PTZ was used for seizure detection. Protection was referred to as the failure to observe an episode of clonic convulsions of least 5 s duration during this time period.

Experimental

Swiss albino mice of either sex (30–40 g) were used as experimental animals for anticonvulsant

and neurotoxic activities. Animals were kept in wire mesh cages in a restricted access room for 1 week before the experiments. The animals were fed with standard laboratory pellets and purified water *ad libitum*. Before the experiments, animals were fasted for 12 h. At 12 days, wash period was allowed before start of next study. All the test compounds were suspended in 30% aqueous polyethylene glycol 400. In each of the experiment, a control group was made which received the vehicle (30% PEG-400). All the experiments were carried out according to protocols approved by the Institutional Animal Ethical Committee, INSTITUT NAME (Committee registration number CPCSEA/./YEAR/01 and Letter reference number is Animal ethical committee/ IAEC/YEAR/01 dated.../.../.2020).

Determination of NT

The test is used to evaluate whether any drug is interfering with established anticonvulsant activity. In 1957, Dunham and Miya suggested that the skeletal muscle relaxation induced by a test compound can be evaluated by testing the ability of Swiss albino mice to remain on a revolving rod. Many investigators have subsequently sued this forced motor activity. The dose that impairs, the ability of 50% of the Swiss albino mice to remain on the revolving rod is considered as the end point.

Method Employed for NT Evaluation

The method as adopted by Dunham and Miya was used. The Swiss albino mice were trained to stay an accelerating rotarod of diameter 3.2 cm rotating of a speed of 6 revolutions per minute. Only those animals showing ability to remain on the revolving rod for at least 1 min were selected for the test. These trained Swiss albino mice were divided into group of six animals each and were given test compounds by intraperitoneal route in doses of 30, 100, and 300 mg/kg. Thirty minutes after intraperitoneal administration, Swiss albino mice were placed on the rotating rod. The dose which indicated the inability of the animal to remain on the rod for at least 1 min in each of three trials was taken as the neurotoxic dose.

Methods Employed for Anticonvulsant Evaluation

For the anticonvulsant evaluation of synthesized compounds, two methods were selected, that is, MES and scPTZ seizure methods. Compounds affording protection in MES test usually prove to be useful in treating generalized tonic–clonic and complex partial seizures, that is, generalized tonic–clonic seizure (grand mal epilepsy), while those showing activity in scPTZ test usually are of value in absence seizure (petit mal epilepsy).

Maximal Electroshock Method

Albino Swiss albino mice were used for this experiment. Food was withdrawn 12–15 h before the commencement of the experiments, while water was withdrawn immediately before the experiment. Maximum seizures were induced by applications of electrical current across the brain through corneal electrodes primed with normal saline (0.9% NaCl). The stimulus parameters were 50 mA AC in a pulse of 60 Hz for 0.2 s. After applying shock, Swiss albino mice were observed for the type of convulsion produced and the hind limb extensor response was taken as the end point.[20] Animals showing positive hind limb extensor response were used for testing drug substance. The animals were divided into groups of six animals each. The test compounds were suspended in 30% v/v aqueous polyethylene glycol 400 in concentrations so that the total volume injected to animals do not exceed 0.01 ml/g. Animals were administered intraperitoneally the test compound in 30, 100, and 300 mg/kg. After 30 min and 4 h of drug administration, electrical shock was given through corneal electrodes. Disappearance of the hind limb extensor component of convulsion if any was used as positive criteria.[21]

scPTZ Method

Swiss albino mice of either sex were divided in groups of six animals each. The test compounds were administrated i.p. to all animals in a group in dose of 30, 100, and 300 mg/kg. Pentylenetetrazole

(85 mg/kg) was injected subcutaneously, 30 min and 4 h after the administration of the drugs. The absence or presence of an episode of clonic convulsion was taken as the end point. Standard drugs used for both the above studies were phenytoin and carbamazepine. The absence of tonic spasms in the observed time period indicates a compounds ability to abolish the effect of pentylenetetrazole on seizure threshold.[22]

RESULTS

Spectral Analysis

A total of 15 compounds were synthesized. The structures of the synthesized compounds (QNM-1 to QNM-15) were characterized by IR, 13C-NMR spectra, and mass spectroscopy. The IR spectra of the synthesized compounds showed characteristic absorption band between 1680 and 1700 cm^{-1} due to C=O str. (quinazolinone ring); between 1600 and 1650 cm^{-1} due to C=C str. (vinyl group); between 1520 and 1560 cm^{-1} due to C=N str. (1,3,4-thiadiazole and quinazolinone ring), between 1210 and 1250 due to C-N str. of quinazolinone ring; between 550 and 780 cm^{-1} due to C-S str. (1,3,4-thiadiazole ring); 1090 cm^{-1} due to Ar-Cl str.; and between 400 and 500 cm^{-1} due to aryl C-Cl in chloro containing compounds and 3163.3 C-H str. (Aromatic ring). In 13C-NMR spectra of the synthesized compounds, C-2 and C-4 of quinazolinone were observed between 160–165 and 167–168 (δ, ppm), respectively, C-11 and C-5, C-6, C-7, C-8, C-9, C-10, C-12, C-13, C-14 and C18, C16, C15 and C17, C16 of quinazolinone were observed between 112–115 and 122.1–147.8 (δ, ppm), respectively. Methyl carbons were observed at 21.3 ppm. In addition, peaks at δ 77.0 ppm for CDCl3 (solvent) and at δ 39.0 ppm for dimethyl sulfoxide-d6 (solvent) were also observed in respective cases. Elemental analysis of all synthesized compound was within the ±0.4% of the theoretical values. Generation of dense sooty flame and formation of oily layer after nitration of the compounds confirmed the presence of aromatic ring in all the synthesized compounds. In the FAB mass spectra, two prominent peaks were observed. TLC has been executed for the monitored of reaction and purity of the synthesized compounds using silica gel G in various solvent systems such as hexane/ethanol (95%)/chloroform/benzene, and iodine chamber has been used for the visualization and in some cases UV chamber used. All these characterization parameters showed that the structure of the synthesized compounds was near to expected.

NT 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. NT 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. The data are presented in Table 1.

Anticonvulsant Activity of Synthesized Compounds

Maximal electroshock method

Only 11 compounds were shown protection against MES convulsion at dose level used in the study. Compounds QNM-1, QNM-2, QNM-4, QNM-6, QNM-9, QNM-11, QNM-13, and QNM-15 have shown the effect 30 min after administration of 30 mg/kg of the drug [Table 1]. From the point of view of potency, these drugs can be claimed to be better as comparable to phenytoin and carbamazepine, but failed to show the effect after 4 h of administration. These 11 compounds showed quick onset of action. It is highlighted that the presence of electron rich atom/group attached at the para position of the aryl ring showed increased potency in the MES screen.

Table 1: Anticonvulsant effect of the synthesized compounds (QNM-1–QNM-15)

QNM-1	30	100
QNM-2	30	-
QNM-4	100	100
QNM-6	30	100
QNM-9	30	100
QNM-11	100	-
QNM-13	30	100
QNM-15	100	300

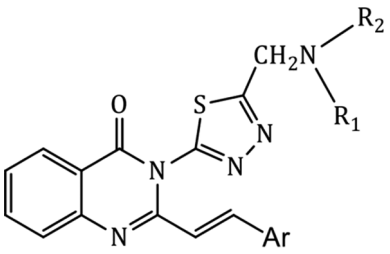
All the synthesized compounds were active in MES screen for a long duration of time (after 4 h)

scPTZ method

In the ScPTZ model, only six compounds, that is, QNM-3, QNM-4, QNM-7, QNM-10, QNM-13, and QNM-15 have showed protection of the convulsions but that too at the dose level of 300 mg/kg. Out of these compounds, all other compounds, that is, QNM-1, QNM-2, QNM-5, QNM-6, QNM-8, QNM-9, QNM-12, and QNM-14 have failed to protect the convulsion after 4 h of administration of the drugs [Table 1]

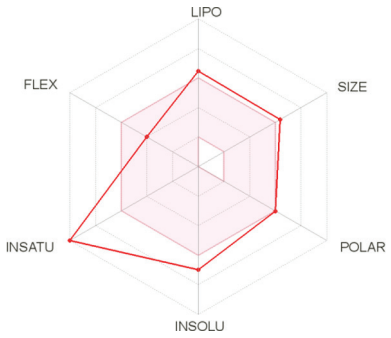
DISCUSSION

MES test screening includes in different period of seizure, intensifies QNM-1, QNM-2, QNM-4, QNM-6, QNM-9, QNM-11, QNM-13, and QNM-15 were discovered generally dynamic at anticonvulsant screening when contrasted and phenytoin (standard medication). Out of the multitude of mixtures QNM-7, QNM-8, and QNM-12 has shown medium movement while rest of the mixtures QNM-3, QNM-5, QNM-10, and QNM-14 were discovered dormant or least dynamic. Mixtures QNM-6, QNM-9, and QNM-11 have shown expansive degree of movement, which is favorable when contrasted with phenytoin. QNM-6 and QNM-11 have shown the practically comparative movement as contrast with phenytoin. Consequently, we can say that these could impede MES subsequently proposing that these could be useful in clonic–tonic (fantastic mal) seizures. The anticonvulsant assessment of blended compound QNM-1, QNM-2, QNM-4, QNM-6, QNM-9, QNM-11, QNM-13, and QNM-15 has shown seizure security at 100 mg/kg portion after 30 min and 4 h, so they have great beginning of activity as fast arrive at cerebrum and have delayed activity uncover that compound processed gradually, while compounds QNM-5, QNM-8, and QNM-14 were fairly less dynamic and uncover that their high fixation is needed to cross blood-mind obstruction.



S. No.	Code No.	Ar	R1	R2	Minimum active dose (mg/kg)*				*Neurotoxicity Dose (mg/kg)	
					Maximal electroshock seizure test		scPTZ test			
					0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
	QNM-1	-C6H5	-C6H5	H	30	100	-	-	-	-
	QNM-2	-C6H5	-C6H5Cl (p)	H	30	-	-	-	-	-
	QNM-3	-C6H5	-C6H5Cl (o)	H	-	300	300	-	-	100
	QNM-4	-C6H5	-C6H5Cl (m)	H	100	100	-	300	-	-
	QNM-5	-C6H5	-C6H5F (o)	H	-	-	-	-	300	-
	QNM-6	-C6H5	-C6H5Br (p)	H	30	100	-	-	-	-
	QNM-7	-C6H5Br	-C6H5Br (p)	H	-	300	300	-	-	-
	QNM-8	-C6H5Br	-C6H5F (p)	H	-	-	-	-	100	-
	QNM-9	-C6H5Br	-C6H5NO2 (p)	H	30	100	-	-	-	-
	QNM-10	-C6H5F	-C6H5F (o)	H	-	300	300	-	100	300
	QNM-11	-C6H5F	-C6H5F (p)	H	100	-	-	-	300	-
	QNM-12	-C6H5F	-C6H5NO2 (p)	H	-	300	-	-	-	-
	QNM-13	-C6H5CH3	-C6H5Cl (p)	H	30	100	-	300	-	-
	QNM-14	-C6H5CH3	-C6H5F	H	-	-	-	-	100	-
	QNM-15	-C6H5CH3	-C6H5Br	H	100	300	300	-	300	-
Phenytoin					30	30	-	-	100	100
Carbamazepine					30	100	100	300	100	300

*Dose in mg/kg at which bioactivity was observed in majority of the animals. The (−) sign indicates absence of protection of convulsion at the maximum dose administered, that is, 300 mg/kg.



Physicochemical properties	
Formula	$C_{24}H_{15}BrN_6O_2S$
Molecular weight	531.38 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	27
Fraction Csp3	0.00
Num. rotatable bonds	6
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar refractivity	138.58
TPSA	130.37 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.44
Log $P_{o/w}$ (XLOGP3)	5.78
Log $P_{o/w}$ (WLOGP)	5.43
Log $P_{o/w}$ (MLOGP)	3.88
Log $P_{o/w}$ (SILICOS-IT)	5.56
Consensus Log $P_{o/w}$	5.02
Water solubility	
Log *S* (ESOL)	−6.97
Solubility	5.73e-05 mg/ml ; 1.08e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	−8.29
Solubility	2.74e-06 mg/ml; 5.17e-09 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	−9.22
Solubility	3.23e-07 mg/ml; 6.08e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	−5.44 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal chemistry	
PAINS	0 alert
Brenk	0 alert
Lead likeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.78

(Contd...)

Mixtures QNM-5, QNM-8, and QNM-14 were less dynamic; this might be because of the presence of bromine bunch at ortho position and fluorine bunches at para and meta position at phenyl ring. In different cases, the replacement of C6H5CH3 and -C6H5F bunch joined to 2-position in 4(3H)-benzoxazin-4-one may lessen the movement. After assessment of least dynamic portion of the integrated mixtures in anticonvulsant action, we further chosen 100 mg/kg body weight portion to notice the impact of mixtures on various periods of spasm.

CONCLUSION

This study concluded that these synthesized compounds have potential anticonvulsant activity and other pharmacological activity also prompted. Bulkier compounds are more lipophilic and can cross blood–brain barrier to exert their effect on CNS. The present study explored that substitution of 4(3H)-quinazolinone at the second and third H position of 4(3H)-quinazolinone leads to the development of new chemical entities with potent

sedative-hypnotic as compared to anticonvulsant activity.

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