



SYNTHESIS AND ANTICONVULSANT EVALUATION OF *N*-(5-(4-SUBSTITUTEDPHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-3-YLAMINO)-2-*O*-TOLYLQUINAZOLIN-4(3*H*)-ONESDERIVATIVES

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ABSTRACT

Epilepsy is a most common central nervous system disorder, it concern with the sudden electric discharge and characterized by recurrent seizures due to neurological, environmental and social consequences, also may be genetic or non-genetic. Drug resistance and ADE's side effects are common; therefore a search for novel antiepileptic drugs with higher efficiency & less toxicity still continues to be an area of investigation. A series of *N*-(5-(4-substituted phenyl)-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-*o*-tolylquinazolin-4(3*H*)-oneweredesign and synthesized. All target compounds evaluated for their anticonvulsant activity using maximal electroshock seizure (MES) & subcutaneous pentylene tetrazole (scPTZ) models. The structures of the synthesized compounds were confirmed by spectral data and elemental analysis. The compounds were also tested for their neurotoxicity using rotarod apparatus. All the compounds showed significant anticonvulsant & neurotoxic activities. *N*-(5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-*o*-tolylquinazolin-4(3*H*)-one (**QZ5**) was found to be the most active compound in MES (percentage protection = 78.53 at 150 mg/kg) & scPTZ (percentage protection = 82.89 at 75 mg/kg) models and was found to be non-neurotoxic.

INTRODUCTION

Epilepsy is a most common central nervous system disorder, illustrating sudden electric discharge and characterized by recurrent seizures due to neurological, environmental and social consequences. It also may be genetic or non-genetic. 50 million people of the world are suffering from epilepsy¹. 0.5% epileptic population are in India². More than

two year younger children and more than 65 older adults suffer from the risk factors of epilepsy. It's all due to the delayed recognition of seizures, inadequate treatment, accidental brain damage, social consequences etc. Uncontrolled epilepsy is associated with excess mortality³, cognitive and behavioural dysfunctions⁴, and social and educational disadvantage⁵.

Anti-epileptic drugs (AED's) are the most common regimen approved by world health organisation. Enormous AEDs, belonging to different classes, are used nowadays to treat epilepsy including phenytoin, carbamazepine, valproic acid, topiramate, Gabapentin, Felbamate, Levetiracetam, etc.⁶ A large number of epileptic people have satisfactory improvements with AED's but it reflects limitations like insufficient seizure control, unpredictability of effect and its loss, poor efficacy, inadequate information about the drug receptors etc. and the most common drawback is the risk of drug resistance. Long-term outcome studies and randomized trials 7–10 suggest that fewer than 50% of patients could become seizure-free on the first AED⁷. An alternative drug (substitution) is Unavoidable when the patient develops intolerable adverse *i.e.* drowsiness, ataxia, gastrointestinal disturbance, megaloblastic anaemia and hirsutism^{8,9}. Anti-epileptics with higher efficacy and without any side effects is the most common search area in medicinal chemistry.

In recent research of area nitrogen containing heterocyclic compounds have a great significance due to their effectiveness and a large number of medicinal molecules had been developed with their higher efficacy towards the treatment¹⁰. Quinazoline is a fused heterocyclic molecule of benzene and pyrimidine having two nitrogen atoms at first and second positions. It possesses diverse biological activities including anticancer¹¹⁻¹², anti-tumor¹³, antibacterial¹⁴, antifungal¹⁵, antiviral¹⁶, anti-inflammatory¹⁷, antidepressant¹⁸, anticonvulsant¹⁹ etc. The clinically existing quinazoline derived molecules include prazosin, gefitinib, erlotinib, tetrodotoxin, alfuzosin etc.²⁰ Methaqualone, a quinazoline containing compound, was firstly discovered as sedative hypnotic. Methaqualone inspired the researchers to emphasize on the quinazoline nucleus for the synthesis of novel anti-epileptic drug molecules through different

substitution at different positions. Second and third position of the quinazoline are responsible for their anticonvulsant actions²¹. Additionally four pharmacophoric features *i.e.* a hydrophobic aryl ring, an electron donor group, a hydrogen bond acceptor group & a hydrophobic-hydrophilic ring, are also supposed important for enhancing their efficacies²².

The present work aimed to design and synthesize quinazoline derivatives by modification at second & third. All the derivatives were evaluated for anticonvulsant activity through MES²³ (Maximal electroshock seizures) and scPTZ²⁴ (Subcutaneous pentylenetetrazole) models. Derivatives were also assessed for their neurotoxicity by rota rod test²⁵. The design and synthetic approach for the quinazoline derivatives were as represented in Figure 1.

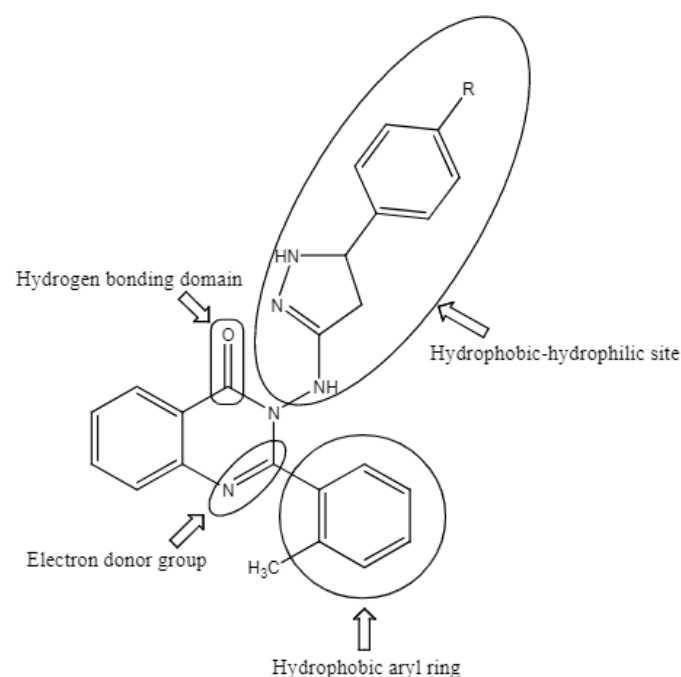
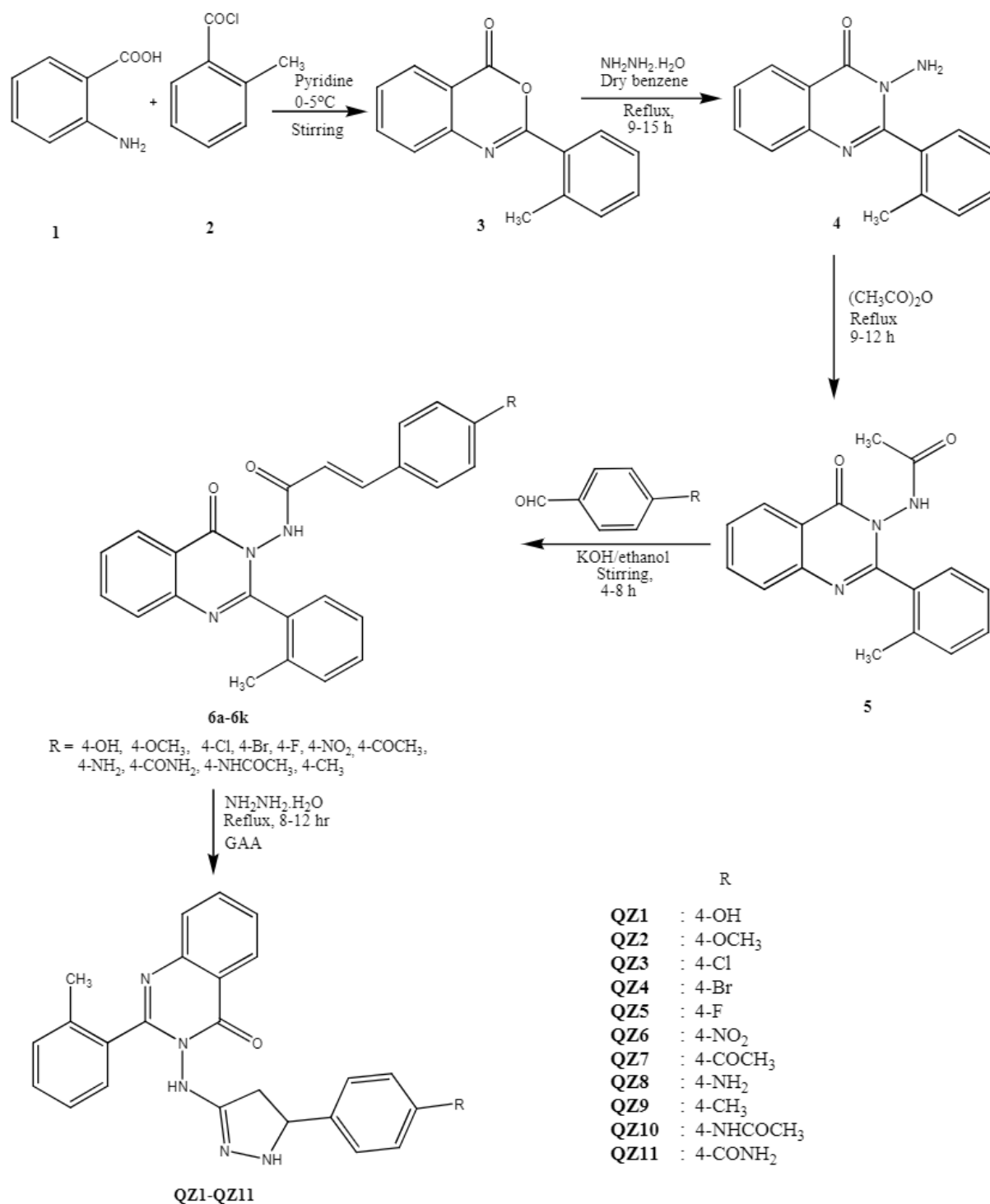


Figure 1. A graphical representation of *N*-(5-(4-substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-*o*-tolylquinazolin-4(3*H*)-one derivatives including their pharmacophoric features necessary for anticonvulsant activity



Scheme 1. Synthesis of *N*-(substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one derivatives

MATERIAL AND METHOD

All the chemicals & reagents used were of commercial quality of laboratory grade obtained from Sigma-Aldrich & Merck and were used without further purification.

Experimental Chemistry

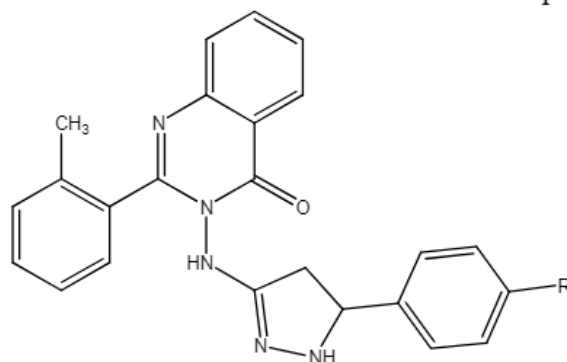
The title compounds **QZ1** – **QZ11** were synthesized according to the Scheme 1. 2-Aminobenzoic acid **1** (0.1 mol) was reacted with 4-methoxy benzoyl chloride **2** (0.2 mol) in presence of pyridine at a temperature of 0-5°C to produce the first intermediate 2-(4-methoxy phenyl)-4*H*-benz-[1,3]-oxazin-4-ones (**3**) which on further reaction with hydrazine hydrate (0.01 mol) led to the formation of next intermediate 3-amino-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one

(4). Reaction of compound **4** (0.01 mol) with acetic anhydride (0.01 mol) in presence of hydrated sodium acetate & HCl resulted in the formation of the N-[2-(4-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl]acetamide (**5**). Compound **5** on further reaction with appropriately substituted benzaldehydes led to the synthesis of compounds **6a-6k** which on further cyclization with hydrazine hydrate (0.01 mol) yielded the corresponding final compounds **QZ1 – QZ11**.

Characterization of all the intermediates & final compounds was carried out by various physicochemical & spectral techniques. The melting point of all the final compounds was recorded on digital melting point apparatus (Kshitij Innovation) using one end open capillary tubes and are uncorrected. The progress of the reaction and the purity of intermediates

& final compounds was confirmed by the thin layer chromatography using silica gel G plates. FTIR spectra was recorded on SHIMADZU IR affinity spectrophotometer using KBr pellet method. The ^1H NMR was recorded on a BRUKER FOURIER 300 HD spectrophotometer using CDCl_3 as a solvent. TMS was used as the internal standard. Mass spectra was recorded on a Varian 1200L mass spectrometer. The data was expressed as $(\text{M}+1)^+$ values. Elemental analysis (C, H, N) was determined using a Carlo-Erba 1160 elemental analyzer. The C, H, N values for the compounds were found to be in the range of $\pm 0.4\%$. The physicochemical & spectral characterization data of the final compounds **QZ1 – QZ11** were as presented in Table 1 and Table 2 respectively.

Table 1. Physicochemical characterization data of final compounds **QZ1 – QZ11**



QZ1 – QZ11

Comp. Code.	R	Mol. Formula	Mol. Wt.	M. P. ($^{\circ}\text{C}$)	% Yield
QZ1	-OH	$\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_2$	411.46	219-222	56.34
QZ2	-OCH ₃	$\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_2$	425.48	185-190	65.45
QZ3	-Cl	$\text{C}_{24}\text{H}_{20}\text{ClN}_5\text{O}$	429.9	199-203	76.65
QZ4	-Br	$\text{C}_{24}\text{H}_{20}\text{BrN}_5\text{O}$	474.35	178-182	54.12
QZ5	-F	$\text{C}_{24}\text{H}_{20}\text{FN}_5\text{O}$	413.45	189-193	76.98
QZ6	-NO ₂	$\text{C}_{24}\text{H}_{20}\text{N}_6\text{O}_3$	440.45	210-215	64.38
QZ7	-COCH ₃	$\text{C}_{26}\text{H}_{23}\text{N}_5\text{O}_2$	437.49	198-202	58.21
QZ8	-NH ₂	$\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}$	410.47	193-195	50.32
QZ9	-CH ₃	$\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}$	409.48	196-199	56.97
QZ10	-NHCOCH ₃	$\text{C}_{26}\text{H}_{24}\text{N}_6\text{O}_2$	452.51	187-190	62.54
QZ11	-CONH ₂	$\text{C}_{25}\text{H}_{22}\text{N}_6\text{O}_2$	438.48	176-179	60.23

Table 2. Spectral characterization data of the final compounds **QZ1 – QZ11**

Comp. Code	IR (KBr, cm ⁻¹)	¹ H NMR (CDCl ₃ , δ in ppm)	Mass (m/e) [M+1] ⁺	Elemental analysis	
				Calculated	Observed
QZ1	3550 (-OH str), 3410 (-NH str), 3100 (C-H str), 2920 (C-H str) 2917 (Asym Str. -CH ₃), 2860 (C-H str), 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend), 1310 (-OH bend), 1250 (C-N str)	6.68-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 5.0 (s, 1H O-H) 2.35 (s, 3H, C-H).	412.17	C (70.06%) H (5.14%) N (17.02%) O (7.78%)	C (69.46%) H (5.13%) N (17.53%) O (7.62%)
QZ2	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 2820 (-OCH ₃ str) 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend), 1250 (C-N str).	6.72-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 3.73 (s, 3H, C-H), 2.35 (m, 3H, C-H)	426.19	C (70.57%) H (5.45%) N (16.46%) O (7.52%)	C (71.05%) H (5.12%) N (16.53%) O (7.32%)
QZ3	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend), 1250 (C-N str), 800 (-Cl)	6.72-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (m, 3H, C-H)	430.14	C (67.05%) H (4.69%) Cl (8.25%) N (16.29%) O (3.72%)	C (67.27%) H (4.25%) Cl (8.15%) N (16.34%) O (3.65%)
QZ4	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend), 1250 (C-N str), 1020 (-Br).	6.72-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (m, 3H, C-H)	-	C (60.77%) H (4.25%) N (14.76%) O (3.37%) Br (16.84%)	C (60.82%) H (4.12%) N (14.63%) O (3.27%) Br (17.01%)
QZ5	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend), 1250 (C-N str), 1150 (-F).	6.72-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (m, 3H, C-H)	-	C (69.72%) H (4.88%) F (4.60%) N (16.94%) O (3.87%)	C (69.35%) H (4.87%) F (4.07%) N (16.56%) O (3.43%)
QZ6	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 1690 (C=O str), 1660 (C=C str), 1550 (-NO ₂ str) 1516 (C-C str), 1470(C-H bend), 1250 (C-N str)	6.72-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (m, 3H, C-H)	441.16	C (65.45%) H (4.58%) N (19.08%) O (10.90%)	C (65.38%) H (4.28%) N (19.21%) O (10.34%)

QZ7	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 2820 (-OCH ₃ str) 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend),1250 (C-N str)	7.09-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.55 (m, 3H, C-H), 2.35 (m, 3H, C-H)	-	C (71.38%) H (5.30%) N (16.01%) O (7.31%)	C (71.92%) H (5.09%) N (16.32%) O (7.06%)
QZ8	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 2820 (-OCH ₃ str) 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend),1250 (C-N str)	6.41-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (m, 3H, C-H), 4.0 (d, 2H, N-H)	-	C (70.23%) H (5.40%) N (20.47%) O (3.90%)	C (70.34%) H (5.00%) N (20.54%) O (3.34%)
QZ9	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 2820 (-OCH ₃ str) 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend),1250 (C-N str)	7.0-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (m, 3H, C-H), 2.0 (s, 1H, N-H)	410.19	C (73.33%) H (5.66%) N (17.10%) O (3.91%)	C (73.23%) H (5.54%) N (17.99%) O (3.03%)
QZ10	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 2820 (-OCH ₃ str) 1690 (C=O str), 1660 (C=C str), 1516 (C-C str), 1470(C-H bend),1250 (C-N str)	7.09-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (s, 3H, C-H), 8.0 (s, 1H, N-H), 2.02 (m, 3H, C-H)	-	C (69.01%) H (5.35%) N (18.57%) O (7.07%)	C (69.87%) H (5.75%) N (18.55%) O (7.56%)
QZ11	3410 (-NH str), 3050 (C-H str), 2920 (C-H str) 2917 (Asym Str), 2860 (C-H str), 2820 (-OCH ₃ str) 1690 (C=O str), 1660(C=C str), 1516 (C-C str), 1470(C-H bend),1250 (C-N str)	7.09-7.9 (m, 4H, ArH), 7.0 (s, 1H, N-H), 2.35 (s, 3H, C-H), 6.0 (d, 2H, N-H),	439.18	C (68.48%) H (5.06%) N (19.17%) O (7.30%)	C (68.95%) H (5.43%) N (19.35%) O (7.96%)

PHARMACOLOGICAL EVALUATION

All the experimental procedures were accomplished according to CPCSEA guidelines and approved by IAEC of the Institute (1205/c/08/CPCSEA).

Animals

Swiss albino mice weighing about 18-25 g were used in the entire study. The animals were housed in individual cages for one week to acclimatize them at the laboratory

conditions. They were allowed free access to water and food.

Anticonvulsant activity

The final compounds **QZ1** – **QZ11** were evaluated for the anticonvulsant activity using maximal electroshock seizure (MES) and subcutaneous pentylene tetrazole (scPTZ) model.

MES

The animals were divided into three groups consisting of 6 animals each viz. test, control and standard. All the test compounds were dissolved in 1% CMC

solution and administered intraperitoneally to the animals at three doses of 25 mg/kg, 75 mg/kg & 150 mg/kg; 30 minutes prior to delivery of seizures. Phenytoin (25 mg/kg) was used as a reference compound. Control animals were given 0.9% saline solution. Mice were treated with an electroshock of 50 mA for 0.2 s by means of electroconvulsimeter through a pair of ear clip electrodes & the latency of the seizures was recorded. The results of the MES test for **QZ1** – **QZ11** were as is presented in Table 3.

scPTZ model

The experimental animals were divided into different groups, initially manipulated and treated in the similar fashion as depicted in MES method. After 30 min, the animals were subcutaneously injected with the convulsive dose of PTZ (60 mg/kg). Sodium valproate (200 mg/kg) was used as a reference compound. Observations were made 60 min after the administration of PTZ. The results of the scPTZ model for the synthesized compounds **QZ1** – **QZ11** is expressed in Table 4.

ED₅₀ was measured by the curve plotted between log dose and probit values. Percentage protection in MES and scPTZ model was calculated by using following equation:

$$\% \text{ protection} = [1 - (T_1/T_2) * 100]$$

T₁ = preconvulsion time in control

T₂ = Preconvulsion time in test

Table 3. Preliminary anticonvulsant screening data of final compounds **QZ1** – **QZ11** in MES model

Comp Code	Dose (mg/kg)	Onset convulsion threshold (Mean± SEM)	% Protection	ED ₅₀ value
QZ1	25	3.45±0.45	35.65	158.4
	75	6.42±0.32	65.42	
	150	10.26±0.25	78.36	
QZ2	25	8.12±0.33	72.66	133.4
	75	3.76±0.12	40.96	

	150	10.35±0.25	78.55	
QZ3	25	6.46±0.65	65.63	108.4
	75	6.87±0.42	67.69	
QZ4	150	8.12±0.36	72.66	150
	25	7.43±0.54	70.12	
	75	6.9±0.76	67.83	
QZ5	150	9.56±0.16	76.78	158.4
	25	8.76±0.43	74.66	
	75	7.94±0.32	72.04	
QZ6	150	10.34±0.27	78.53	65.12
	25	2.98±0.65	25.50	
	75	8.32±0.43	73.32	
QZ7	150	4.92±0.21	54.88	76.32
	25	3.72±0.43	40.32	
	75	7.77±0.32	71.43	
QZ8	150	8.26±0.19	73.12	56.43
	25	5.76±0.20	61.46	
	75	6.23±0.31	64.37	
QZ9	150	7.11±0.21	68.78	87.56
	25	3.46±0.12	35.84	
	75	5.01±0.73	55.69	
QZ10	150	5.21±0.25	57.39	120.34
	25	2.53±0.39	12.25	
	75	4.56±0.41	51.32	
QZ11	150	8.35±0.22	73.41	94.34
	25	9.21±0.27	75.90	
	75	3.45±0.14	35.65	
Pheny toin (Std.)	150	7.21±0.65	69.21	-
	25	12.23±0.33	81.85	

All values expressed the mean ± SEM (n = 6)

Table 4. Preliminary anticonvulsant screening data of final compounds **QZ1** – **QZ11** in scPTZ model

Comp . Code	Dose (mg/kg)	Onset clonic convulsion threshold (Mean± SEM)	% Prote ction	ED ₅₀ value
QZ1	25	50.03±0.65	74.82	44.66
	75	35.32±0.14	64.33	
	150	46.82±0.27	73.09	
QZ2	25	20.23±0.43	37.72	11.94
	75	56.56±0.27	77.72	
	150	30.76±0.63	59.04	
QZ3	25	47.52±0.12	73.48	11.94
	75	50.85±0.28	75.22	

	150	38.43±0.53	67.21	
QZ4	25	58.32±0.41	78.40	
	75	64.65±0.78	80.51	
	150	72.21±0.11	82.55	44.67
QZ5	25	61.35±0.52	79.46	
	75	73.63±0.32	82.89	
	150	72.85±0.53	82.70	39.63
QZ6	25	33.65±0.32	62.56	
	75	26.64±0.12	52.70	130.6
	150	44.76±0.28	71.85	2
QZ7	25	60.43±0.63	79.15	
	75	43.32±0.42	70.91	
	150	47.65±0.56	73.56	63.39
QZ8	25	69.64±0.28	81.91	
	75	70.01±0.48	82.00	
	150	39.64±0.73	68.21	33.96
QZ9	25	30.23±0.32	58.32	
	75	49.65±0.12	74.62	
	150	40.83±0.53	69.14	75.76
QZ10	25	39.64±0.24	68.21	
	75	86.64±0.43	85.46	
	150	22.35±0.13	43.62	87.34
QZ11	25	59.23±0.64	78.73	
	75	27.34±0.35	53.91	
	150	43.45±0.43	71.00	45.28
Sodium valproate	200	140.3±0.46	91.02	-

Neurotoxicity screening

The compounds were assessed for minimal motor impairment using rotarod apparatus. The animals were trained to stay on accelerating rotarod (rod diameter: 3.2 cm) revolving at a speed of 6 rpm. The trained animals were given an *i. p.* injection of the test compounds (dose: 150 mg/kg). Neurotoxicity was indicated by the ability of the animals to maintain equilibrium on the rod for at least one minute in each of the three successive trials. The animals were tested at four time intervals *viz.* 0.5 h, 1 h, 2 h & 4 h. The observations were as tabulated in table 5.

Table 5. Neurotoxicity screening data for the final compounds **QZ1 – QZ11**

Comp. Code	0.5 h	1 h	2 h	4 h
QZ1	0/4	0/4	0/4	1/4

QZ2	0/4	0/4	1/4	0/4
QZ3	0/4	0/4	0/4	0/4
QZ4	0/4	0/4	0/4	0/4
QZ5	0/4	0/4	0/4	0/4
QZ6	0/4	0/4	0/4	0/4
QZ7	0/4	0/4	1/4	2/4
QZ8	0/4	0/4	0/4	0/4
QZ9	0/4	0/4	1/4	1/4
QZ10	0/4	0/4	1/4	2/4
QZ11	0/4	0/4	1/4	2/4
Phenytoin	0/4	0/4	0/4	0/4

The data indicates number of animals toxic/total number of animals used

RESULTS AND DISCUSSION

Chemistry

The synthesis of the title compounds **QZ1 – QZ11** was carried out as per the reaction sequence illustrated in Scheme 1. The intermediates & final compounds were analysed by FTIR, ¹H NMR, mass spectrometry and elemental analysis. The spectral data obtained was found to be in accordance with the structures of the synthesized compounds.

Anticonvulsant activity

MES test

The preliminary MES screening results was expressed in the form of percentage protection and as presented in Table 3. All compounds were possessed anticonvulsant activity at different doses at 25 mg/kg, 75mg/kg and 150mg/kg. The compounds **QZ2**, **QZ5**, **QZ11** & **QZ4** showed more than 70% protection whereas compounds **QZ1**, **QZ6**, **QZ7** & **QZ9** showed less than 50% protection and the compound **QZ10** showed least percentage protection (< 25%) at a dose 25 mg/kg. At a dose of 75 mg/kg, compound **QZ6**, **QZ7** & **QZ5** showed more than 70% protection whereas

compounds **QZ2**, **QZ9** & **QZ11** showed less than 50% protection and all other compounds showed percentage protection in between 50% - 70%. All compounds at a dose of 150 mg/kg showed percentage protection in between 50% - 70%

whereas **QZ3**, **QZ4**, **QZ5** revealed >75% protection. The comparison of onset convulsion threshold & percentage protection of the synthesized compounds were as illustrated in Figure 2 & 3 respectively.

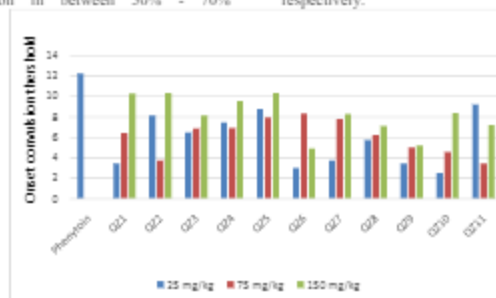


Figure 2. Comparison of onset convulsion threshold of final compounds at different doses in MES model

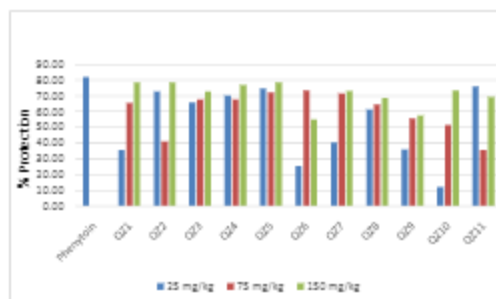


Figure 3. Comparison of percentage protection of final compounds at different doses in MES model

scPTZ test

The preliminary scPTZ screening results expressed in the form of percentage protection were as presented in Table 4. At a dose 25 mg/kg, all compounds showed percentage protection above 50% except **QZ2** (37.72%) Further, all compounds revealed a percentage protection of more than 60% at a dose of

75 mg/kg except compounds **QZ6** & **QZ11** which showed < 50% protection. Whereas, at a dose of 150 mg/kg, all compounds revealed > 60% except compounds **QZ2** & **QZ10** showed < 50% protections. The comparison of clonic convulsion threshold and percentage protection of the final compounds were as illustrated in Figure 4 & 5 respectively.

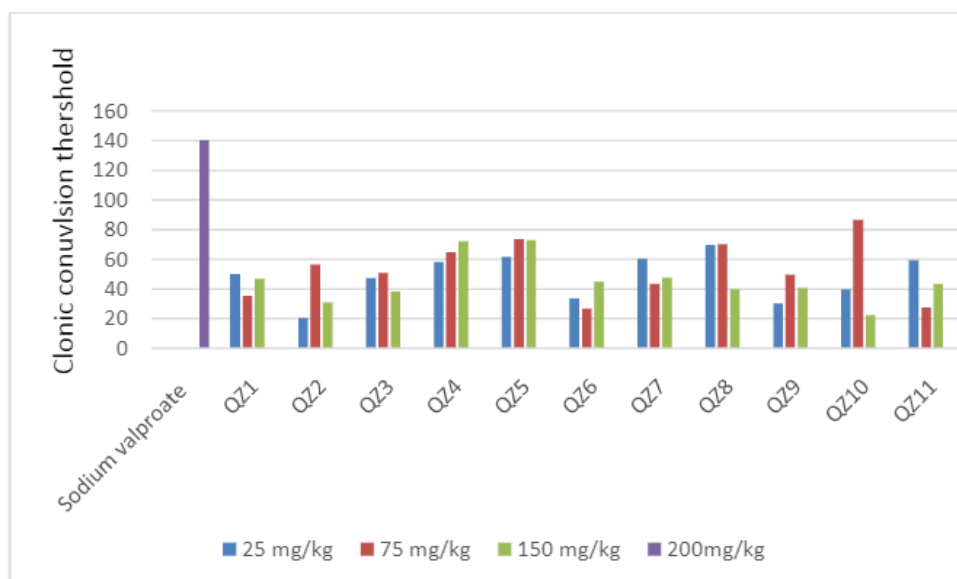


Figure 4. Comparison of clonic convulsion threshold of all synthesized compounds at different doses in scPTZ model

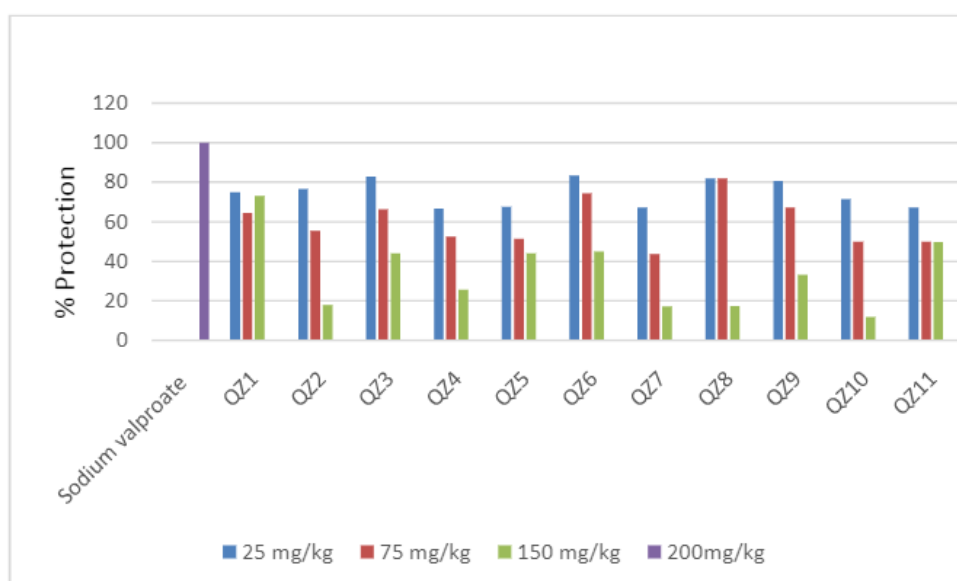


Figure 5. Comparison of percentage protection of final compounds at different doses in scPTZ model

Neurotoxicity screening

The results of neurotoxicity screening were as expressed in Table 5. None of the compounds were found to be neurotoxic up to 1 h except compounds **QZ9&QZ10** (25% neurotoxic). Mild toxicity (25%) was exhibited by Compounds **QZ2, QZ7, QZ9, QZ10 & QZ11** at 2 h. Compound **QZ1, QZ9, QZ7, QZ10 & QZ11** exhibited 25-50% toxicity at 4 h. Compounds **QZ3, QZ4, QZ5, QZ6&QZ8** were found to be non-neurotoxic at all the time intervals tested upto 4 h.

CONCLUSION

We report the synthesis of a series *N*-(5-(4-substitutedphenyl)-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-*o*-tolylquinazolin-4(3*H*)-ones evaluated for anticonvulsant activity using MES & scPTZ models. Neurotoxicity screening was assessed by rotarod apparatus. The compounds showed significant anticonvulsant activity. Among the synthesized compounds *N*-(5-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-*o*-tolylquinazolin-4(3*H*)-one, **QZ5** was found to be the most active in both MES (percentage protection = 78.53

at 150 mg/kg) & scPTZ (percentage protection = 82.89 at 75 mg/kg) models and was found to be non-neurotoxic. Thus results suggested that such quinazolines could be a promising scaffold for the discovery of novel anticonvulsants.

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