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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anticonvulsant activity of novel quinazolin-4(3*H*)-one derived pyrazole analogs

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Abstract Eighteen novel 6,8-(dibromo/unsubstituted)-2-(methyl/phenyl)-3-(4-(5-(substitutedphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)phenyl)-quinazolin-4(3*H*)-ones **4a**–**4r** were designed and synthesized in good yield. Antiepileptic screening of the title compounds was performed using MES and scPTZ seizures tests while the neurotoxicity was determined by rotorod test. In the preliminary screening, compounds **4d**, **4e**, **4p**, **4q**, and **4r** were found active in MES model, while **4a**, **4d**, **4f**, **4m**, and **4p** showed significant antiepileptic activity in scPTZ model. Further, all these eight compounds were administered to rats and compounds **4e**, **4p**, and **4q** showed better activity than Phenytoin in oral route. Among these compounds **4p** revealed protection in MES after i.p. administration at a dose of 30 mg/kg (0.5 h) and 100 mg/kg (4 h). The compound **4p** also provided protection in the scPTZ at a dose of 100 mg/kg (0.5 h) and 300 mg/kg (4 h).

Keywords Quniazoline · Pyrazole · Epilepsy · In vivo studies · Neurotoxicity

Introduction

Epilepsy is a common neurological disorder, affecting a large section of population (45–100 million people) worldwide (Bell and Sander, 2002). Based on the main molecular mechanism of action currently used antiepileptic drugs (AEDs), can be broadly classified into four major categories as mentioned follow: (a) enhancement of GABA-mediated inhibition or other effect on the GABA system, (b) modulation of voltage-dependent Na^+ and/or Ca^{2+} channels, (c) modulation of synaptic release and (d) inhibition of synaptic excitation mediated by ionotropic glutamate receptors (Pollard and French, 2006). Currently, a significant group of patients are resistant to the available AEDs, hence there is a need for improved agents for the treatment of seizure disorders. Polytherapy with AEDs is necessary in clinical practice because of the limited efficacy of monotherapy. The long established AEDs control seizures in 50 % of patients developing partial seizures and in 60–70 % of those developing generalized seizures (Lopes Lima, 2000; Berk *et al*., 2001; Duncan, 2002). Moreover, many AEDs have serious side effects such as ataxia, drowsiness, gingival hyperplasia, gastrointestinal disturbances, and megaloblastic anemia (Spear, 2001). Toxicity, intolerance, and lack of efficacy are the limitations of the current AEDs. All of these have stimulated intensive research on novel AEDs. The complex mechanism of action of most of the AEDs and the insufficient information on the cellular mechanism of epilepsy in human makes it difficult to use rational methodologies in the field of drug discovery. Thus based on the existence of different pharmacophores that were established through the analysis of structural characteristics of clinically effective drugs, as well as other antiepileptic compounds design of new AEDs are needed (Karakurt *et al*., 2010; Deng *et al*., 2010; Alam *et al*., 2010). It is well documented from the literatures (Estrada and Pena, 2000; Bruno-Blanch *et al*., 2003), that one of the important core fragments is defined by the presence of (i) hydrogen donor/acceptor unit (HAD),

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(ii) one electron donor atom (D), and (iii) a hydrophobic domain (A) (aryl ring substituted/unsubstituted). This common template is found in the structures of well-established first generation AEDs such as phenytoin/carbamazepine or in the second generation AEDs or among the newest drugs (e.g., 8 felbamate) and the drugs in clinical trial (Fig. 1). For the development of novel therapeutics based on the pharmacophore model much efforts devoted in the recent years resulted in the availability of several newer AEDs, such as lamotrigine, levetiracetam, pregabalin, stiripentol, tiagabine, topiramate, and zonisamide (Stefan and Feuerstein, 2007). Therefore, the search for new AEDs continues to be an active area of investigation in medicinal chemistry.

The chemistry of quinazoline compounds has been the subject of considerable interest due to their wide spectrum of biological activity as many, such as anticonvulsant (Kumar *et al*., 2011), anti-cancer (Abdel Gawad *et al*., 2010), anti-tubercular (Pattan *et al*., 2006), anti-viral (Dinakaran *et al*., 2003), anti-microbial (Mohamed *et al*., 2010), anti-helmintic (Shukla and Shukla, 1989), analgesic and anti-inflammatory activity (Alagarsamy *et al*., 2005). Quinazolin-4(3*H*)-one represents a good template for preparation of some new anticonvulsant agents since such a heterocyclic system possess the required pharmacophoric moiety. In the arsenal of anticonvulsant agents, recently pyrazole derivatives have constituted a vital part and its worth has been proved by the progressive findings in the literature. The anticonvulsant action of pyrazole moiety is ascribed to its unique properties of being a two-electron donor system and ability to act as a constrained pharmacophore at the receptor site (Abdel-Aziz *et al*., 2009; Ozdemir *et al*., 2007, 2008).

Our preceding research on quinazolin-4(3*H*)-one derivative as anticonvulsant agents driven us to continue synthesizing newer derivatives in which intended to associate quinazolin-4(3*H*)-one nucleus to the pyrazole moiety. Association of the two active pharmacophores is expected to wield synergistic effects to the resulting molecule. Based on these findings, we have designed to synthesize a series of 6,8-(dibromo/unsubstituted)-2-(methyl/phenyl)-3-(4-(5-(substituted phenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)phenyl)-quinazolin-4(3*H*)-ones as potent anticonvulsant agents.

Results and discussion

The reaction sequence leading to the synthesis of titled compounds **4a**–**4r** is outlined in Scheme 1. The synthesis of 6,8-(dibromo/unsubstituted)-2-(methyl/phenyl)-4*H*-benzo-[1,3]-oxazin-4-one **1a**–**1c** involved a simple acetylation/benzoylation of anthranilic acid/3,5-dibromo anthranilic acid followed by ring closure reaction. In the subsequent step, 4-(6,8-(dibromo/unsubstituted)-2-(methyl/phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid **2a**–**2c** were synthesized through simple reaction by treating compounds **1a**–**1c** with *p*-amino benzoic acid with the elimination of water molecule. On treating with thionyl chloride followed by hydrazine hydrate, compounds **2a**–**2c** gets converted to its respective hydrazide derivatives **3a**–**3c**. In the last step, the compounds **4a**–**4r** were synthesized by a ring closure reaction, in which a different chalcones (α,β-unsaturated carbonyl compound) and hydrazide derivative of quinazoline analog **3a**–**3c** were reacted. TLC was performed throughout the reactions to optimize the reactions for purity and completion.

The structures of the synthesized compounds were confirmed by elemental analysis and spectral (IR, ^{1}H-NMR, and Mass) data. Formation of the benzoxazine ring in compound **1a/1b/1c** was confirmed by the presence of absorption peak at 1,706–1,751 and 1,038–1,055 cm^{-1} in IR due to the presence of C=O and C–O–C stretching, respectively. The formations of compound **2a/2b/2c** were confirmed by the appearance of broad peak in between 2,817 and 2,864 cm^{-1} in IR corresponds to O–H stretching of COOH and appearance of singlet between δ 9.84 and 10.01 ppm for single protons in its ^{1}H-NMR spectra which might be assigned to COOH group. The conversion of hydrazide **3a/3b/3c** from carboxylic acid **2a/2b/2c** can be recognized by strong absorption peak around 3,350 cm^{-1} in IR due to N–H stretching and appearance of singlet in its ^{1}H-NMR spectra between δ 3.47 and 3.71 ppm for two protons which might be assigned to NH_2 of hydrazide group. The presence of –NH in hydrazide was confirmed by appearance of singlet for single proton in ^{1}H-NMR spectra between δ 8.35 and 8.45 ppm. The IR spectrum of title compound **4e** showed sharp absorption peaks at 3,581 cm^{-1} corresponding to O–H stretching vibration. The multiple weak absorption peaks at 3,142 cm^{-1} corresponds to Ar–H stretching vibration. The strong absorption at 1,748 cm^{-1} is due to the C=O stretching vibration and the moderate intensity absorption at 1,634 cm^{-1} corresponds to a C=N stretching vibration. The weak absorption at 1,618 cm^{-1} arises due to C=C stretching. The absorption at 1,063 cm^{-1} is due to the C–O stretching vibration in C–O–C. Its ^{1}H-NMR spectrum showed a singlet at δ 2.43 ppm due to the presence of CH_3 at C_2 of quinazolinone. Appearance of double doublet between δ 3.16–3.19 and 3.68–3.71 ppm corresponds to C_4–H_1 and C_4–H_2 of pyrazole, respectively. The presence of double doublet between δ 5.54 and 5.58 ppm confirms the presence of single proton in C_5 of pyrazole. A singlet appeared in ^{1}H-NMR at δ 5.72 ppm confirms the presence of hydroxyl group. A group of signals appeared between δ 7.32 and 8.59 ppm corresponds to Ar–H protons. Further, mass spectrum confirmed their purity and molecular weight.

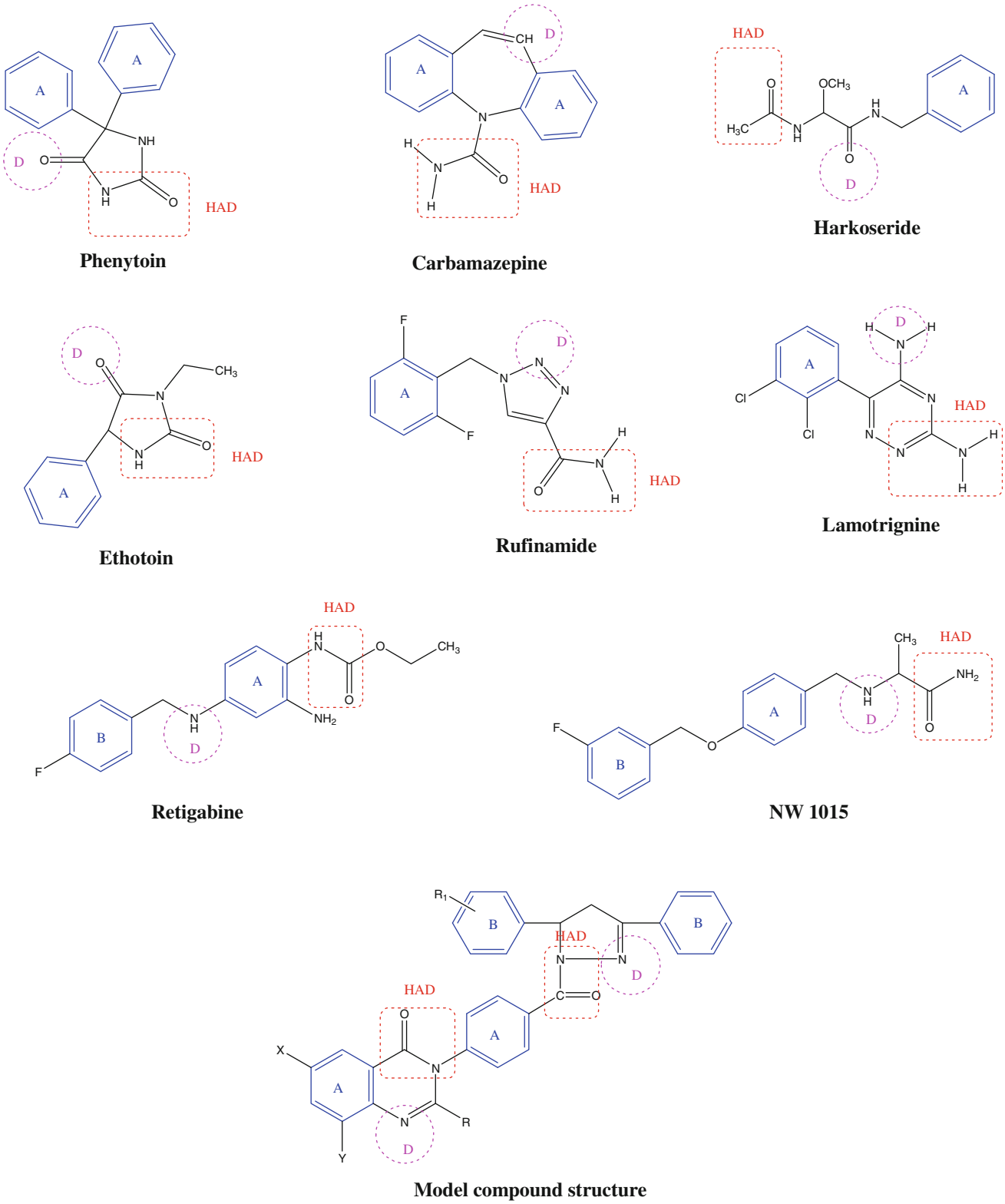
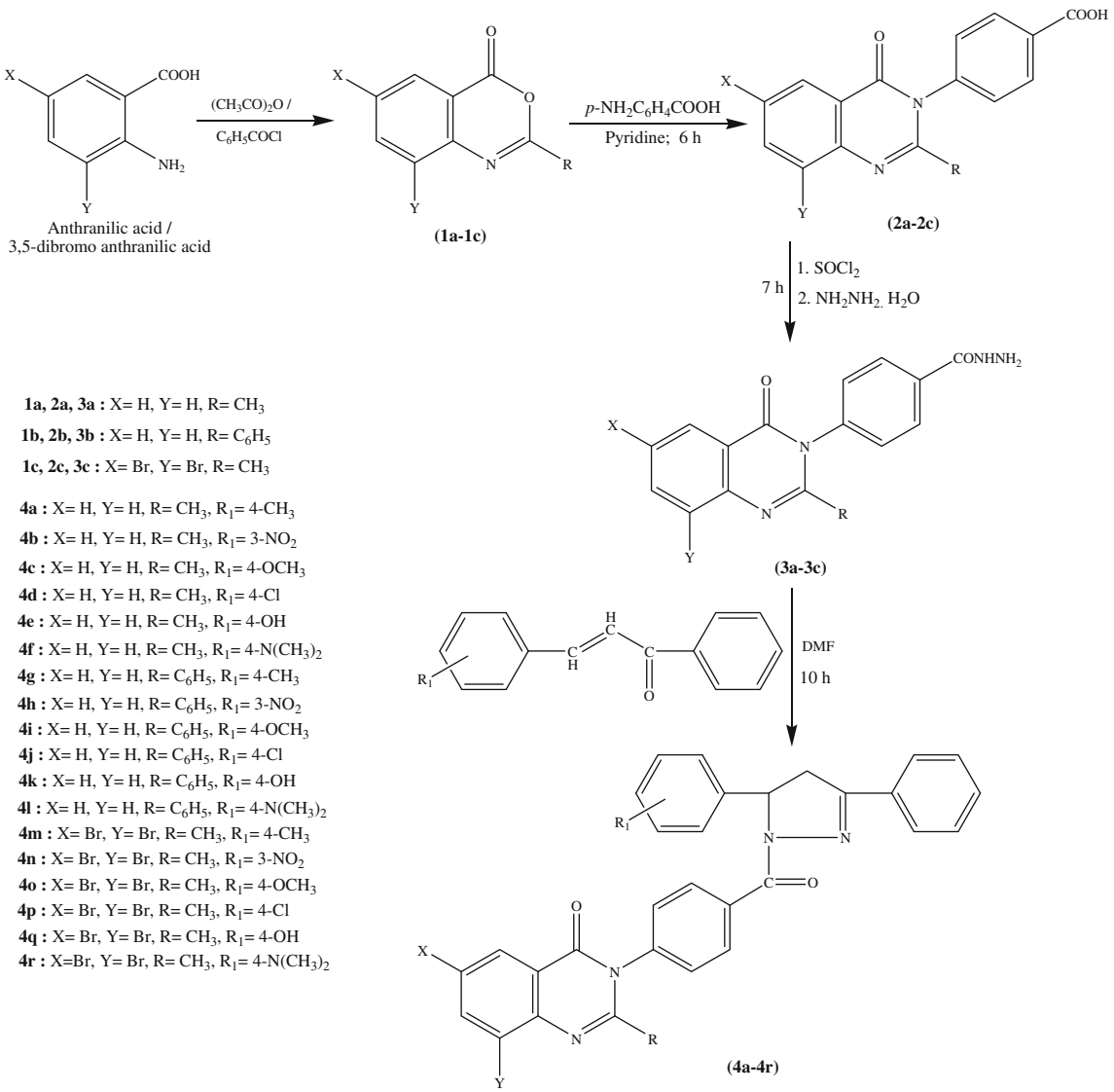


Fig. 1 Pharmacophoric pattern of well-known antiepileptics and model compound with its vital structuralfeatures: *A* hydrophobicarylringsystem, *HAD* hydrogen bond acceptor/donor domain, *D* electron donor moiety, and *B* distal aryl ring



Scheme 1 Synthetic protocols of intermediate and target compounds **4a–4r**

For the identification of antiepileptic activity in mice, test compounds were administered i.p. and challenged by maximal electroshock seizure test (MES) and subcutaneous pentylenetetrazole (scPTZ) test. Compounds found to be active in these seizure challenges are generally regarded to be significantly useful candidates in treatment of partial, generalized, and even absence seizures. The data regarding the antiepileptic screening of all the compounds are reported in Table 1.

Out of several tested compounds, four compounds **4d**, **4e**, **4p**, **4q**, and **4r** were found to be significantly active in the electroshock investigation as they showed protection at the lowest dose of 30 mg/kg after 0.5 h. But at higher doses (100 mg/kg) these compounds continued to show the activity after 4.0 h except **4e**, which needs 300 mg/kg indicating the rapid onset as well as long duration of action of these compounds. The promising activity of the compounds may be attributed to the substitutions at the hydrophobic domain. These compounds contain electron donating groups at the para position of the distal aryl ring. In general, it was observed that the para-substituted derivatives exhibited better activity than meta-substituted derivatives. This may be because of the fact that the para-substituted derivatives are better fitted into the receptor site. After 0.5 h, at 100 mg/kg compounds **4a**, **4c**, **4f**, **4j**, **4k**, **4m**, and **4o** were showed protection indicating the ability of these compounds to protect from seizures at relatively lower dose. These compounds except **4c** and **4k** were also active after 4.0 h at 300 mg/kg dose.

Most of the compounds exhibited moderate to good antiepileptic activity in the scPTZ screening. Compounds that revealed protection in the scPTZ test, indicating the

ability of substance to increasing seizure threshold, at a dose of ≤100 mg/kg after 0.5 h included **4a**, **4d**, **4f**, **4m**, and **4p**. The above results were comparable to results obtained for ethosuximide which is recognized as reference antiepileptic for this screen. Among all tested compounds, **4m** was found to be remarkably active at a dose between 30 and 100 mg/kg after 0.5 h, as it continued to show activity after 4.0 h at 300 mg/kg dose. Except **4g** and **4l** rest of compounds **4b**, **4c**, **4e**, **4h**–**4k**, **4n**–**4o**, **4q**, and **4r** were active at 300 mg/kg either after 0.5 or 4.0 h. It was observed that in this method, the most active compound has substitution at aryl ring of quinazolinone by electron releasing group resulted in increased antiepileptic activity.

Table 1 Antiepileptic activity and neurotoxicity of compounds **4a**–**4r** administered intraperitoneally to mice

Compounds	MES[a] screening		scPTZ[b] screening		NT[c] screening	
	0.5 h[d]	4.0 h[d]	0.5 h[d]	4.0 h[d]	0.5 h[d]	4.0 h[d]
4a	100	300	100	300	–	–
4b	–	–	–	300	ND	ND
4c	100	–	300	–	–	300
4d	30	100	100	300	300	–
4e	30	300	300	300	100	300
4f	100	300	100	300	–	–
4g	300	–	–	–	ND	ND
4h	–	–	300	–	ND	ND
4i	–	300	–	300	ND	ND
4j	100	300	300	–	–	300
4k	100	–	–	300	–	–
4l	–	300	–	–	ND	ND
4m	100	300	>30[e]	300	–	300
4n	–	–	–	300	ND	ND
4o	100	300	300	–	300	300
4p	30	100	100	300	–	–
4q	30	100	300	300	300	–
4r	30	100	300	–	300	300
Phenytoin[f]	30	30	–	–	100	100
Ethosuximide[g]	–	–	100	300	–	–

The sign – (ndash) represents the absence of activity at maximum dose administered (300 mg/kg)

ND not determined

[a] Maximal electroshock test (administered intraperitoneally to mice at doses ranging from 30 to 300 mg/kg)

[b] Subcutaneous pentylenetetrazole test (administered intraperitoneally to mice at doses ranging from 30 to 300 mg/kg)

[c] Neurotoxicity (administered intraperitoneally to mice at doses ranging from 30 to 300 mg/kg)

[d] Time of test after drug administration

[e] scPTZ activity >30 means that the compound showed activity between 30 and 100 mg/kg

[f] Reference drug, data for phenytoin Ref. (Yogeeswari *et al*., 2005)

[g] Reference drug, data for ethosuximide ref (Rajak *et al*., 2009)

Many compounds that are **4a**, **4c**–**4h**, **4j**, **4k**, **4m**, and **4o**–**4r** were showed activity in either MES or scPTZ model at any one of the tested dose after 0.5 h. The study reveals that 83 % of the compounds that is **4a**, **4c**–**4g**, **4i**–**4m**, and **4o**–**4r** were shown activity in MES screening, whereas in scPTZ test except **4g** and **4l**, rest of 89 % of the compounds were active at any one of the tested dose. These reports revealed that maximum of compounds possessed some scPTZ selectivity.

Neurotoxicity study was evaluated by rotorod test in mice. The study revealed that most of the candidate compounds exhibited neurotoxicity at doses higher than widely prescribed drugs phenytoin or carbamazepine. But while evaluating an antiepileptic compounds, separation between antiepileptic and neurotoxic dose is desirable. All the compounds evaluated for their neurotoxicity study except **4b**, **4g**, **4h**, **4i**, **4l**, and **4n**, due to their poor response in antiepileptic activity. In neurotoxic study at 100 mg/kg dose **4e** was found to be neurotoxic. Compounds **4c**, **4d**, **4j**, **4m**, **4o**, **4q**, and **4r** were showed neurotoxicity at 300 mg/kg, while all other compounds **4a**, **4f**, **4k**, and **4p** were not found to be neurotoxic at maximum administered dose.

Ability to inhibit epilepsy when given by the oral route is a valuable property of candidate antiepilepsy. This screen discloses the time of onset, the approximate time of peak effect (TPE) and the duration of antiepileptic activity or neurotoxicity. We identified eight compounds **4a**, **4d**, **4e**, **4f**, **4m**, **4p**, **4q**, and **4r** from the initial screen that were further evaluated for oral availability using the MES acute seizure model and neurotoxicity in rats at a dose of 30 mg/kg. The results obtained are presented in Table 2.

From these data, it was observed that the most active compounds are **4e**, **4p**, and **4q** which protected 100 % (4/4)

Table 2 Antiepileptic activity and toxicity of compounds **4d**, **4e**, **4m**, **4p**, and **4q** administered orally (30 mg/kg) to rats

Compounds	MES[a]					TOX[b]
	0.25 h[c]	0.5 h[c]	1 h[c]	2 h[c]	4 h[c]	
4a	1/4	2/4	2/4	3/4	3/4	0/4 (–)[d]
4d	1/4	2/4	2/4	3/4	3/4	0/4 (–)[d]
4e	1/4	2/4	2/4	4/4	4/4	0/4 (–)[d]
4f	0/4	0/4	0/4	1/4	2/4	0/4 (–)[d]
4m	1/4	2/4	2/4	3/4	3/4	0/4 (–)[d]
4p	1/4	2/4	2/4	4/4	4/4	0/4 (–)[d]
4q	1/4	2/4	2/4	4/4	4/4	0/4 (–)[d]
4r	0/4	2/4	1/4	0/4	0/4	0/4 (–)[d]
Phenytoin[e]	1/4	4/4	3/4	3/4	3/4	0/4 (–)[d]

[a] Maximal electroshock test (dose of 30 mg/kg was administrated. The data indicate: number of rats protected/number of rats tested)

[b] Neurotoxicity (number of rats protected/number of rats tested)

[c] Time after drug administration

[d] (–) No neurotoxicity at dose tested

[e] Reference drug, data for phenytoin ref (Yogeeswari *et al*., 2005)

of rats at time points 2 and 4 h, 50 % (2/4) at 0.5 and 1 h and 25 % (1/4) at 0.25 h. These molecules were more active and showed longer duration of satisfactory action than phenytoin. While, compounds **4a**, **4d**, and **4m** were found moderately effective in rat MES oral screen and protected only 75 % (3/4) of rats at time points 2 and 4 h, 50 % (2/4) at 0.5 and 1 h, and 25 % (1/4) at 0.25 h. Rest of tested compounds **4f** and **4r** were less effective and it protected only 50 % (2/4) of tested animals at the time point 0.5 h (**4r**) or 4 h (**4f**) and 25 % (1/4) at 1 h (**4r**) and 2 h (**4f**). All derivatives tested were non-neurotoxic when given orally. The in vivo data in rats confirmed absorption of compounds from gastrointestinal tract and also their penetration to central nervous system. The inhibition of electrically induced seizures that is characteristic for phenytoin and phenytoin-like drugs may indicate the influence of compound on voltage depended Na^+ channels as the most plausible mechanism of antiepileptic action.

On correlating the structures of the sample candidate with their biological activity, it has been observed that, out of eighteen tested compounds **4a**–**4r**, eight compounds **4a**, **4d**, **4e**, **4f**, **4m**, **4p**, **4q**, and **4r** exhibited better activity in MES and/scPTZ test. All the above-mentioned compounds were all 2-methyl quinazolinone derivative. The nature of substituted group on C_2 of quinazoline ring appeared to greatly influence the antiepileptic activity; the 2-methyl derivative **4a**–**4f** and **4m**–**4r** exhibited higher antiepileptic activity than the 2-phenyl derivative **4g**–**4l**. At the same 2-methyl derivative, the compound with electron donating substitution at distal aryl ring **4a**, **4c**–**4f**, **4m**, and **4o**–**4r** exhibited higher antiepileptic activity than the compound with electron withdrawing substitution **4b** and **4n**. Among electron donating groups *p*-Cl, *p*-OH, and *p*-CH_3 substituted compounds **4a**, **4d**–**4e**, **4m**, and **4p**–**4q** exhibited better activity. Moreover, *p*-OCH_3 and *p*-$N(CH_3)_2$ substituted compounds **4c**, **4f**, **4o**, and **4r** had slightly decrease antiepileptic activity. However, the *m*-NO_2 derivative **4b** and **4n** did not exhibit significant antiepileptic activity. The increases in antiepileptic activity of test compounds with 2-methyl quinazolinone derivatives may be attributed due to the presence of extra one electron releasing group on quinazolinone ring (which is absent in 2-phenyl derivatives) which might be accountable for additional bonding with the binding site.

In summary, majority of clinically active AEDs possess a nitrogen hetero atomic system with one or more phenyl rings, at least one carbonyl group and hydrogen donor/acceptor unit. Remembering the above fact we have designed and synthesized eighteen title compounds. The structure of the title compounds **4a**–**4r** satisfied all the pharmacophoric structural requirements that is, the presence of quinazolin-4(3*H*)-one moiety as hydrophobic portion, N as electron donor system, the presence of carbonyl group and another hydrophobic distal aryl ring responsible for controlling the pharmacokinetic properties of the antiepileptic. All eighteen title compounds were screened for their antiepileptic activity by MES and scPTZ model along with its neurotoxicity. In this series, generally compounds possessing 2-methyl quinazolinone ring exhibited significant antiepileptic activity in comparison to 2-phenyl quinazolinone ring. Among the screened compounds **4d**, **4e**, **4p**, **4q**, and **4r** were exhibited significant activity in MES screening, while compound **4a**, **4d**, **4f**, **4m**, and **4p** showed significant antiepileptic activity in scPTZ model. These eight compounds **4a**, **4d**, **4e**, **4f**, **4m**, **4p**, **4q**, and **4r** were selected for oral administration in rats at 30 mg/kg dose. Compounds **4e**, **4p**, and **4q** exhibited better antiepileptic activity in oral dose than standard drug phenytoin. The most active one was 6,8-dibromo-3-(4-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)phenyl)-2-methylquinazolin-4-(3*H*)-one **4p** that revealed protection in the electrically induced seizures at a dose of 30 and 100 mg/kg (i.p.) after 0.5 and 4 h, respectively. This molecule also provided protection in the scPTZ at a dose of 100 and 300 mg/kg after 0.5 and 4 h, respectively. Thus, the compound **4p** emerged out as the lead molecule with a wide spectrum of antiepileptic activity without any neurotoxicity.

Experimental

General

The chemicals and reagents used were obtained from various chemical units Qualigens, E. Merck India Ltd., CDH, and SD Fine Chem. These solvents used were of LR grade and purified before their use. The silica gel G used for analytical chromatography (TLC) was obtained from E. Merck India Ltd. Solvent systems were used ethyl acetate:hexane:formic acid (4:4:2). All the melting points (m.p.) were taken in open glass capillary and are uncorrected. ^{1}H-NMR spectra were taken on a Bruker ultra shield (300 MHz) NMR spectrometer in $CDCl_3$ using tetramethylsilane [$(CH_3)_4Si$] as internal standard. Chemical shift (δ) are expressed in ppm. Mass spectra were obtained on a JEOL-SX-102 instrument using electron impact ionization. All the IR spectra were recorded in KBr pellets on a Jasco FT-IR 410 spectrometer. Elemental analysis was performed on a Perkin Elmer model 240c analyzer and were within ±0.4 % of the theoretical values.

*Synthesis of 6,8-(dibromo/unsubstituted)-bromo-2-(methyl/phenyl)-4H-benzo-(1,3)-oxazin-4-one (**1a–1c**)*

For the synthesis of 2-methyl derivative, a mixture of anthranilic acid/3,5-dibromo anthranilic acid 1.37/2.94 g

(0.01 mol) and acetic anhydride 10.2 ml (0.1 mol) was refluxed on gentle flame for 1 h (4 h for dibromo derivatives) (Alagarsamy *et al*., 2002, 2003). The excess of acetic anhydride was distilled off under reduced pressure and the residue was dissolved in petroleum ether and kept aside for 1 h. The light brown solid **1a/1c** which obtained was filtered and dried.

To a solution of anthranilic acid 13.7 g (0.1 mol) dissolved in pyridine (60 ml), benzoyl chloride 28 g (0.2 mol) was added to synthesize 2-phenyl derivative. The mixture was stirred for 30 min followed by treatment with 5 % $NaHCO_3$ (15 ml). The solid **1b** obtained was recrystallized from ethanol.

2-Methyl-4H-benzo[d][1,3]oxazin-4-one ***(1a)*** Yield = 71 %; m.p. 182 °C; IR (KBr) cm^{-1}: 3096 (Ar C–H_{Str}), 2882 (CH_3 C–H_{Str}), 1712 (cyclic C=O_{str}), 1636 (C=N_{str}), 1600 (C=C_{str}), 1055 (cyclic C–O–C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.38 (s, 3H, CH_3), 6.92–7.40 (m, 4H, Ar–H); MS (*m/z*): 161 [M^+]; Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.16; H, 4.40; N, 8.66.

2-Phenyl-4H-benzo[d][1,3]oxazin-4-one ***(1b)*** Yield = 80 %; m.p. 120 °C; IR (KBr) cm^{-1}: 3077 (Ar C–H_{Str}), 1751 (cyclic C=O_{str}), 1625 (C=N_{str}), 1616 (C=C_{str}), 1038 (cyclic C–O–C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 6.95–7.78 (m, 9H, Ar–H); MS (*m/z*): 223 [M^+]; Anal. Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.42; H, 4.05; N, 6.29.

6,8-Dibromo-4H-benzo[d][1,3]oxazin-4-one ***(1c)*** Yield = 74 %; m.p. 175 °C; IR (KBr) cm^{-1}: 3060 (Ar C–H_{Str}), 2938 (CH_3 C–H_{Str}), 1706 (cyclic C=O_{str}), 1623 (C=N_{str}), 1609 (C=C_{str}), 1047 (cyclic C–O–C_{str}), 576 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.43 (s, 3H, CH_3), 7.78 (s, 1H, C_7–H of quinazoline), 8.07 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 321 [M+2]; Anal. Calcd for $C_9H_5Br_2NO_2$: C, 33.89; H, 1.58; N, 4.39. Found: C, 34.01; H, 1.59; N, 4.41.

Synthesis of 4-[6,8-(dibromo/unsubstituted)-4-oxo-2-(methyl/phenyl)quinazolin-3(4H)-yl]benzoic acid ***(2a–2c)***

4*H*-benzo[d](1,3)-oxazin-4-one **1a/1b/1c** 1.61/2.23/3.19 g (0.01 mol) and *p*-amino benzoic acid 1.37 g (0.01 mol) were dissolved in 50 ml of anhydrous pyridine and heated on sand bath for 6 h. The resulting solution was cooled in ice bath and treated with 100 ml of 1 N hydrochloric acid. The product separated **2a/2b/2c** was filtered, washed with water and crystallized from ethanol.

4-(2-Methyl-4-oxoquinazolin-3(4H)-yl)benzoic acid ***(2a)*** Yield = 75 %; m.p. 218 °C; IR (KBr) cm^{-1}: 3083 (Ar C–H_{Str}), 2911 (CH_3 C–H_{Str}), 2817 (COOH), 1735 (cyclic C=O_{str}), 1628 (C=N_{str}), 1615 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.55 (s, 3H, CH_3), 6.80–7.82 (m, 8H, Ar–H), 9.97 (s, 1H, COOH); MS (*m/z*): 280 [M^+]; Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.71; H, 4.30; N, 10.02.

4-(4-Oxo-2-phenylquinazolin-3(4H)-yl)benzoic acid ***(2b)*** Yield = 70 %; m.p. 148 °C; IR (KBr) cm^{-1}: 3091 (Ar C–H_{Str}), 2864 (COOH), 1743 (cyclic C=O_{str}), 1619 (C=N_{str}), 1608 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 6.76–7.63 (m, 13H, Ar–H), 10.01 (s, 1H, COOH); MS (*m/z*): 342 [M^+]; Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18. Found: C, 73.55; H, 4.13; N, 8.15.

4-(6,8-Dibromo-2-methyl-4-oxoquinazolin-3(4H)-yl)benzoic acid ***(2c)*** Yield = 72 %; m.p. 204 °C; IR (KBr) cm^{-1}: 3079 (Ar C–H_{Str}), 2926 (CH_3 C–H_{Str}), 2842 (COOH), 1718 (cyclic C=O_{str}), 1644 (C=N_{str}), 1625 (C=C_{str}), 558 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3H, CH_3), 6.89–7.46 (m, 4H, Ar–H), 7.55 (s, 1H, C_7–H of quinazoline), 7.89 (s, 1H, C_5–H of quinazoline), 9.84 (s, 1H, COOH); MS (*m/z*): 440 [M+2]; Anal. Calcd for $C_{16}H_{10}Br_2N_2O_3$: C, 43.87; H, 2.30; N, 6.39. Found: C, 43.77; H, 2.29; N, 6.41.

Synthesis of 4-[6,8-(dibromo/unsubstituted)-4-oxo-2-(methyl/phenyl)quinazolin-3(4H)-yl]benzohydrazide ***(3a–3c)***

To 4-[6,8-(dibromo/unsubstituted)-4-oxo-2-(methyl/phenyl) quinazolin-3(4*H*)-yl]benzoicacid **2a/2b/2c** 2.80/3.42/4.38 g (0.01 mol), thionyl chloride 1.78 g (0.015 mol) was added and refluxed for 1 h. Then the excess of thionyl chloride was distilled off and the reaction mixture was cooled in ice bath. The product formed was immediately used for next step.

To the above product 40 ml of ethanol was added. To this solution 95 % hydrazine hydrate 1 g (0.02 mol) was slowly added with stirring. Then the mixture was refluxed for 6 h followed by removal of excess solvent under reduced pressure and resultant solution was poured in ice cold water. The product separated **3a/3b/3c** was filtered and recrystallised from ethanol.

4-(2-Methyl-4-oxoquinazolin-3(4H)-yl)benzohydrazide ***(3a)*** Yield = 76 %; m.p. 233 °C; IR (KBr) cm^{-1}: 3351 (NH_{str}), 3108 (Ar C–H_{Str}), 2905 (CH_3 C–H_{Str}), 1740 (cyclic C=O_{str}), 1637 (C=N_{str}), 1618 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.29 (s, 3H, CH_3), 5.54 (s, 2H, $–NH_2$), 6.83–8.05 (m, 8H, Ar–H), 8.48 (s, 1H, NH of hydrazide); MS (*m/z*): 294 [M^+]; Anal. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.43; H, 4.77; N, 18.98.

4-(4-Oxo-2-phenylquinazolin-3(4H)-yl)benzohydrazide ***(3b)*** Yield = 70 %; m.p. 180 °C; IR (KBr) cm^{-1}: 3378 (NH_{str}), 3085 (Ar C–H_{Str}), 1726 (cyclic C=O_{str}), 1613 (C=N_{str}), 1605 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 5.71 (s, 2H, –NH_2), 6.97–7.92 (m, 13H, Ar–H), 8.35 (s, 1H, NH of hydrazide); MS (*m/z*): 356 [M^+]; Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.85; H, 4.54; N, 15.66.

4-(6,8-Dibromo-2-methyl-4-oxoquinazolin-3(4H)-yl)benzohydrazide ***(3c)*** Yield = 73 %; m.p. 247 °C; IR (KBr) cm^{-1}: 3365 (NH_{str}), 3097 (Ar C–H_{Str}), 2892 (CH_3 C–H_{Str}), 1739 (cyclic C=O_{str}), 1621 (C=N_{str}), 1609 (C=C_{str}), 570 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.34 (s, 3H, CH_3), 5.47 (s, 2H, –NH_2), 6.85–7.69 (m, 4H, Ar–H), 7.71 (s, 1H, C_7–H of quinazoline), 8.08 (s, 1H, C_5–H of quinazoline), 8.42 (s, 1H, NH of hydrazide); MS (*m/z*): 454 [M+2]; Anal. Calcd for $C_{16}H_{12}Br_2N_4O_2$: C, 42.51; H, 2.68; N, 12.39. Found: C, 42.43; H, 2.67; N, 12.35.

Synthesis of 6,8-(dibromo/unsubstituted)-2-(methyl/phenyl)-3-(4-(5-(substituted phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) phenyl)-quinazolin-4(3H)-one ***(4a–4r)***

Different aromatic chalcones were prepared according to the reported method (Kini and Gandhi, 2008). Various aromatic chalcone (0.005 mol) was added to the 4-[6,8-(dibromo/unsubstituted)-4-oxo-2-(methyl/phenyl)quinazolin-3(4*H*)-yl]benzo hydrazide **3a/3b/3c** 1.47/1.78/2.26 g (0.005 mol) in 100-ml round bottom flask containing 25 ml of *N*,*N*-dimethyl formamide. The above mixture was refluxed at 120–140 °C for a period of 10 h. Then the reaction mixture was cooled, poured into a beaker containing ice cold water and kept aside for 24 h. The obtained product **4a**–**4r** was separated by filtration, dried over the filter paper and recrystallised using ethanol.

2-Methyl-3-(4-(3-phenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl) quinazolin-4(3H)-one ***(4a)*** Yield = 76 %; m.p. 190–192 °C; R_f 0.78; IR (KBr) cm^{-1}: 3115 (Ar C–H_{Str}), 2928 (CH_3 C–H_{Str}), 1744 (cyclic C=O_{str}), 1631 (C=N_{str}), 1609 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.19 (s, 3H, CH_3 of quinazoline), 2.70 (s, 3H, Ar–CH_3), 3.14–3.16 (dd, J = 5.8 Hz, 1H, C_4–H_1 of pyrazole), 3.70–3.74 (dd, J = 5.6 Hz, 1H, C_4–H_2 of pyrazole), 5.51–5.54 (dd, J = 6.0 Hz, 1H, C_5–H of pyrazole), 7.25–8.46 (m, 17H, Ar–H); MS (*m/z*): 498 [M^+]; Anal. Calcd for $C_{32}H_{26}N_4O_2$: C, 77.09; H, 5.26; N, 11.24. Found: C, 76.94; H, 5.28; N, 11.21.

2-Methyl-3-(4-(5-(3-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) phenyl)quinazolin-4(3H)-one ***(4b)*** Yield = 81 %; m.p. 231–233 °C; R_f 0.70; IR (KBr) cm^{-1}: 3131 (Ar C–H_{Str}), 2945 (CH_3 C–H_{Str}), 1728 (cyclic C=O_{str}), 1619 (C=N_{str}), 1603 (C=C_{str}), 1534 and 1313 (C–NO_2); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3H, CH_3 of quinazoline), 3.09–3.13 (dd, J = 5.2 Hz, 1H, C_4–H_1 of pyrazole), 3.76–3.80 (dd, J = 5.4 Hz, 1H, C_4–H_2 of pyrazole), 5.56–5.59 (dd, J = 5.6 Hz, 1H, C_5–H of pyrazole), 7.13–8.37 (m, 17H, Ar–H); MS (*m/z*): 529 [M^+]; Anal. Calcd for $C_{31}H_{23}N_5O_4$: C, 70.31; H, 4.38; N, 13.23. Found: C, 70.19; H, 4.40; N, 13.18.

3-(4-(5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-methylquinazolin-4(3H)-one ***(4c)*** Yield = 78 %; m.p. 223–225 °C; R_f 0.83; IR (KBr) cm^{-1}: 3156 (Ar C–H_{Str}), 2932 (CH_3 C–H_{Str}), 1725 (cyclic C=O_{str}), 1643 (C=N_{str}), 1621 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.15 (s, 3H, CH_3 of quinazoline), 3.17–3.20 (dd, J = 6.0 Hz, 1H, C_4–H_1 of pyrazole), 3.62–3.66 (dd, J = 5.2 Hz, 1H, C_4–H_2 of pyrazole), 3.73 (s, 3H, –OCH_3), 5.48–5.53 (dd, J = 5.8 Hz, 1H, C_5–H of pyrazole), 7.47–8.50 (m, 17H, Ar–H); MS (*m/z*): 514 [M^+]; Anal. Calcd for $C_{32}H_{26}N_4O_3$: C, 74.69; H, 5.09; N, 10.89. Found: C, 74.86; H, 5.07; N, 10.86.

3-(4-(5-(4-Chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-methylquinazolin-4(3H)-one ***(4d)*** Yield = 75 %; m.p. 196–198 °C; R_f 0.65; IR (KBr) cm^{-1}: 3119 (Ar C–H_{Str}), 2923 (CH_3 C–H_{Str}), 1737 (cyclic C=O_{str}), 1625 (C=N_{str}), 1614 (C=C_{str}), 852 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.72 (s, 3H, CH_3 of quinazoline), 3.06–3.11 (dd, J = 5.2 Hz, 1H, C_4–H_1 of pyrazole), 3.75–3.78 (dd, J = 5.8 Hz, 1H, C_4–H_2 of pyrazole), 5.57–5.60 (dd, J = 5.6 Hz, 1H, C_5–H of pyrazole), 7.19–8.26 (m, 17H, Ar–H); MS (*m/z*): 520 [M+2]; Anal. Calcd for $C_{31}H_{23}ClN_4O_2$: C, 71.74; H, 4.47; N, 10.80. Found: C, 71.92; H, 4.49; N, 10.77.

3-(4-(5-(4-Hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-methylquinazolin-4(3H)-one ***(4e)*** Yield = 74 %; m.p. 255–257 °C; R_f 0.89; IR (KBr) cm^{-1}: 3581 (OH_{str}), 3142 (Ar C–H_{Str}), 2950 (CH_3 C–H_{Str}), 1748 (cyclic C=O_{str}), 1634 (C=N_{str}), 1618 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.43 (s, 3H, CH_3 of quinazoline), 3.16–3.19 (dd, J = 6.0 Hz, 1H, C_4–H_1 of pyrazole), 3.68–3.71 (dd, J = 5.6 Hz, 1H, C_4–H_2 of pyrazole), 5.54–5.58 (dd, J = 5.4 Hz, 1H, C_5–H of pyrazole), 5.72 (s, 1H, OH), 7.32–8.59 (m, 17H, Ar–H); MS (*m/z*): 500 [M^+]; Anal. Calcd for $C_{31}H_{24}N_4O_3$: C, 74.38; H, 4.83; N, 11.19. Found: C, 74.49; H, 4.85; N, 11.16.

3-(4-(5-(4-(Dimethylamino)phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) phenyl)-2-methylquinazolin-4(3H)-one ***(4f)*** Yield = 82 %; m.p. 237–239 °C; R_f 0.80; IR

(KBr) cm^{-1}: 3136 (Ar C–H_{Str}), 2931 (CH_3 C–H_{Str}), 1723 (cyclic C=O_{str}), 1648 (C=N_{str}), 1622 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.24 (s, 3H, CH_3 of quinazoline), 2.87 (s, 6H, –$N(CH_3)_2$), 3.07–3.14 (dd, $J = 5.4$ Hz, 1H, C_4–H_1 of pyrazole), 3.65–3.72 (dd, $J = 5.8$ Hz, 1H, C_4–H_2 of pyrazole), 5.49–5.55 (dd, $J = 6.0$ Hz, 1H, C_5–H of pyrazole), 7.16–8.35 (m, 17H, Ar–H); MS (*m/z*): 527 [M^+]; Anal. Calcd for $C_{33}H_{29}N_5O_2$: C, 75.12; H, 5.54; N, 13.27. Found: C, 75.26; H, 5.52; N, 13.22.

*2-Phenyl-3-(4-(3-phenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl) quinazolin-4(3H)-one (**4g**)* Yield = 79 %; m.p. 199–201 °C; R_f 0.68; IR (KBr) cm^{-1}: 3127 (Ar C–H_{Str}), 2941 (CH_3 C–H_{Str}), 1745 (cyclic C=O_{str}), 1628 (C=N_{str}), 1613 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.53 (s, 3H, Ar–CH_3), 3.18–3.21 (dd, $J = 6.2$ Hz, 1H, C_4–H_1 of pyrazole), 3.77–3.80 (dd, $J = 5.6$ Hz, 1H, C_4–H_2 of pyrazole), 5.55–5.60 (dd, $J = 5.2$ Hz, 1H, C_5–H of pyrazole), 7.30–8.54 (m, 22H, Ar–H); MS (*m/z*): 560 [M^+]; Anal. Calcd for $C_{37}H_{28}N_4O_2$: C, 79.27; H, 5.03; N, 9.99. Found: C, 79.13; H, 5.05; N, 9.96.

*3-(4-(5-(3-Nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-phenylquinazolin-4(3H)-one (**4h**)* Yield = 75 %; m.p. 244–246 °C; R_f 0.87; IR (KBr) cm^{-1}: 3145 (Ar C–H_{Str}), 1722 (cyclic C=O_{str}), 1646 (C=N_{str}), 1629 (C=C_{str}), 1522 and 1319 (C–NO_2); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.11–3.17 (dd, $J = 5.4$ Hz, 1H, C_4–H_1 of pyrazole), 3.71–3.75 (dd, $J = 5.2$ Hz, 1H, C_4–H_2 of pyrazole), 5.53–5.57 (dd, $J = 5.8$ Hz, 1H, C_5–H of pyrazole), 7.25–8.46 (m, 22H, Ar–H); MS (*m/z*): 591 [M^+]; Anal. Calcd for $C_{36}H_{25}N_5O_4$: C, 73.09; H, 4.26; N, 11.84. Found: C, 73.26; H, 4.27; N, 11.80.

*3-(4-(5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-phenylquinazolin-4(3H)-one (**4i**)* Yield = 80 %; m.p. 235–237 °C; R_f 0.76; IR (KBr) cm^{-1}: 3109 (Ar C–H_{Str}), 1743 (cyclic C=O_{str}), 1635 (C=N_{str}), 1616 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.19–3.23 (dd, $J = 6.0$ Hz, 1H, C_4–H_1 of pyrazole), 3.69–3.74 (dd, $J = 5.4$ Hz, 1H, C_4–H_2 of pyrazole), 3.81 (s, 3H, –OCH_3), 5.50–5.55 (dd, $J = 5.2$ Hz, 1H, C_5–H of pyrazole), 7.15–8.34 (m, 22H, Ar–H); MS (*m/z*): 576 [M^+]; Anal. Calcd for $C_{37}H_{28}N_4O_3$: C, 77.07; H, 4.89; N, 9.72. Found: C, 76.96; H, 4.95; N, 9.75.

*3-(4-(5-(4-Chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-phenylquinazolin-4(3H)-one (**4j**)* Yield = 73 %; m.p. 210–212 °C; R_f 0.72; IR (KBr) cm^{-1}: 3124 (Ar C–H_{Str}), 1731 (cyclic C=O_{str}), 1617 (C=N_{str}), 1609 (C=C_{str}), 868 (C–Cl); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.09–3.15 (dd, $J = 6.2$ Hz, 1H, C_4–H_1 of pyrazole), 3.73–3.79 (dd, $J = 5.6$ Hz, 1H, C_4–H_2 of pyrazole), 5.54–5.59 (dd, $J = 5.8$ Hz, 1H, C_5–H of pyrazole), 7.21–8.47 (m, 22H, Ar–H); MS (*m/z*): 582 [M+2]; Anal. Calcd for $C_{36}H_{25}ClN_4O_2$: C, 74.41; H, 4.34; N, 9.64. Found: C, 74.57; H, 4.36; N, 9.60.

*3-(4-(5-(4-Hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-phenylquinazolin-4(3H)-one (**4k**)* Yield = 78 %; m.p. 263–265 °C; R_f 0.81; IR (KBr) cm^{-1}: 3524 (OH_{str}), 3118 (Ar C–H_{Str}), 1726 (cyclic C=O_{str}), 1632 (C=N_{str}), 1615 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.18–3.24 (dd, $J = 5.8$ Hz, 1H, C_4–H_1 of pyrazole), 3.70–3.76 (dd, $J = 5.2$ Hz, 1H, C_4–H_2 of pyrazole), 5.56–5.61 (dd, $J = 5.6$ Hz, 1H, C_5–H of pyrazole), 5.85 (s, 1H, OH), 7.22–8.55 (m, 22H, Ar–H); MS (*m/z*): 562 [M^+]; Anal. Calcd for $C_{36}H_{26}N_4O_3$: C, 76.85; H, 4.66; N, 9.96. Found: C, 77.01; H, 4.65; N, 9.93.

*3-(4-(5-(4-(Dimethylamino)phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) phenyl)-2-phenylquinazolin-4(3H)-one (**4l**)* Yield = 72 %; m.p. 258–260 °C; R_f 0.75; IR (KBr) cm^{-1}: 3133 (Ar C–H_{Str}), 2926 (CH_3 C–H_{Str}), 1749 (cyclic C=O_{str}), 1624 (C=N_{str}), 1602 (C=C_{str}); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.83 (s, 6H, –$N(CH_3)_2$), 3.10–3.15 (dd, $J = 5.4$ Hz, 1H, C_4–H_1 of pyrazole), 3.68–3.77 (dd, $J = 5.8$ Hz, 1H, C_4–H_2 of pyrazole), 5.52–5.58 (dd, $J = 6.0$ Hz, 1H, C_5–H of pyrazole), 7.29–8.48 (m, 22H, Ar–H); MS (*m/z*): 589 [M^+]; Anal. Calcd for $C_{38}H_{31}N_5O_2$: C, 77.40; H, 5.30; N, 11.88. Found: C, 77.56; H, 5.28; N, 11.84.

*6,8-Dibromo-2-methyl-3-(4-(3-phenyl-5-p-tolyl-4,5-dihydro-1H-pyrazole-1-carbonyl) phenyl)quinazolin-4(3H)-one (**4m**)* Yield = 74 %; m.p. 206–208 °C; R_f 0.90; IR (KBr) cm^{-1}: 3095 (Ar C–H_{Str}), 2921 (CH_3 C–H_{Str}), 1738 (cyclic C=O_{str}), 1623 (C=N_{str}), 1612 (C=C_{str}), 574 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.45 (s, 3H, CH_3 of quinazoline), 2.66 (s, 3H, Ar–CH_3), 3.22–3.24 (dd, $J = 6.0$ Hz, 1H, C_4–H_1 of pyrazole), 3.66–3.72 (dd, $J = 5.2$ Hz, 1H, C_4–H_2 of pyrazole), 5.49–5.53 (dd, $J = 5.6$ Hz, 1H, C_5–H of pyrazole), 7.05–8.16 (m, 13H, Ar–H), 8.32 (s, 1H, C_7–H of quinazoline), 8.50 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 658 [M+2]; Anal. Calcd for $C_{32}H_{24}Br_2N_4O_2$: C, 58.56; H, 3.69; N, 8.54. Found: C, 58.74; H, 3.68; N, 8.57.

*6,8-Dibromo-2-methyl-3-(4-(5-(3-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)quinazolin-4(3H)-one (**4n**)* Yield = 77 %; m.p. 250–252 °C; R_f 0.62; IR (KBr) cm^{-1}: 3138 (Ar C–H_{Str}), 2952 (CH_3 C–H_{Str}), 1746 (cyclic C=O_{str}), 1645 (C=N_{str}), 1623 (C=C_{str}), 1541 and 1324 (C–NO_2), 559 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ

ppm): 2.18 (s, 3H, CH_3 of quinazoline), 3.18–3.21 (dd, $J = 5.6$ Hz, 1H, C_4–H_1 of pyrazole), 3.74–3.78 (dd, $J = 5.8$ Hz, 1H, C_4–H_2 of pyrazole), 5.56–5.61 (dd, $J = 5.4$ Hz, 1H, C_5–H of pyrazole), 7.21–8.07 (m, 13H, Ar–H), 8.20 (s, 1H, C_7–H of quinazoline), 8.47 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 689 [M+2]; Anal. Calcd for $C_{31}H_{21}Br_2N_5O_4$: C, 54.17; H, 3.08; N, 10.19. Found: C, 54.30; H, 3.07; N, 10.17.

*6,8-Dibromo-3-(4-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2methylquinazolin-4(3H)-one (**4o**)* Yield = 73 %; m.p. 239–241 °C; R_f 0.77; IR (KBr) cm^{-1}: 3146 (Ar C–H_{Str}), 2938 (CH_3 C–H_{Str}), 1721 (cyclic C=O_{str}), 1615 (C=N_{str}), 1607 (C=C_{str}), 572 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.34 (s, 3H, CH_3 of quinazoline), 3.07–3.12 (dd, $J = 5.4$ Hz, 1H, C_4–H_1 of pyrazole), 3.65–3.69 (dd, $J = 5.2$ Hz, 1H, C_4–H_2 of pyrazole), 3.85 (s, 3H, –OCH_3), 5.52–5.57 (dd, $J = 5.8$ Hz, 1H, C_5–H of pyrazole), 7.17–8.25 (m, 13H, Ar–H), 8.46 (s, 1H, C_7–H of quinazoline), 8.59 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 674 [M+2]; Anal. Calcd for $C_{32}H_{24}Br_2N_4O_3$: C, 57.16; H, 3.60; N, 8.33. Found: C, 57.32; H, 3.61; N, 8.31.

*6,8-Dibromo-3-(4-(5-(4-chlorophenyl)3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) phenyl)-2-methylquinazolin-4(3H)-one (**4p**)* Yield = 71 %; m.p. 227–229 °C; R_f 0.84; IR (KBr) cm^{-1}: 3123 (Ar C–H_{Str}), 2947 (CH_3 C–H_{Str}), 1734 (cyclic C=O_{str}), 1639 (C=N_{str}), 1605 (C=C_{str}), 859 (C–Cl), 566 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.52 (s, 3H, CH_3 of quinazoline), 3.15–3.19 (dd, $J = 5.2$ Hz, 1H, C_4–H_1 of pyrazole), 3.61–3.67 (dd, $J = 6.0$ Hz, 1H, C_4–H_2 of pyrazole), 5.47–5.50 (dd, $J = 5.4$ Hz, 1H, C_5–H of pyrazole), 7.03–7.96 (m, 13H, Ar–H), 8.13 (s, 1H, C_7–H of quinazoline), 8.36 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 678 [M+2]; Anal. Calcd for $C_{31}H_{21}Br_2ClN_4O_2$: C, 55.01; H, 3.13; N, 8.28. Found: C, 54.90; H, 3.14; N, 8.31.

*6,8-Dibromo-3-(4-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-methylquinazolin-4(3H)-one (**4q**)* Yield = 76 %; m.p. 281–283 °C; R_f 0.69; IR (KBr) cm^{-1}: 3540 (OH_{str}), 3091 (Ar C–H_{Str}), 2919 (CH_3 C–H_{Str}), 1745 (cyclic C=O_{str}), 1644 (C=N_{str}), 1627 (C=C_{str}), 553 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.26 (s, 3H, CH_3 of quinazoline), 3.21–3.24 (dd, $J = 5.8$ Hz, 1H, C_4–H_1 of pyrazole), 3.77–3.81 (dd, $J = 5.2$ Hz, 1H, C_4–H_2 of pyrazole), 5.58–5.61 (dd, $J = 5.6$ Hz, 1H, C_5–H of pyrazole), 5.79 (s, 1H, –OH), 7.16–8.03 (m, 13H, Ar–H), 8.18 (s, 1H, C_7–H of quinazoline), 8.41 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 660 [M+2]; Anal. Calcd for $C_{31}H_{22}Br_2N_4O_3$: C, 56.56; H, 3.37; N, 8.51. Found: C, 56.70; H, 3.36; N, 8.49.

*6,8-Dibromo-3-(4-(5-(4-(dimethylamino)phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)phenyl)-2-methylquinazolin-4(3H)-one (**4r**)* Yield = 75 %; m.p. 275–277 °C; R_f 0.71; IR (KBr) cm^{-1}: 3117 (Ar C–H_{Str}), 2958 (CH_3 C–H_{Str}), 1725 (cyclic C=O_{str}), 1623 (C=N_{str}), 1611 (C=C_{str}), 562 (C–Br); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.49 (s, 3H, CH_3 of quinazoline), 2.82 (s, 6H, –$N(CH_3)_2$), 3.10–3.16 (dd, $J = 5.2$ Hz, 1H, C_4–H_1 of pyrazole), 3.69–3.73 (dd, $J = 5.4$ Hz, 1H, C_4–H_2 of pyrazole), 5.50–5.56 (dd, $J = 6.2$ Hz, 1H, C_5–H of pyrazole), 7.09–8.17 (m, 13H, Ar–H), 8.35 (s, 1H, C_7–H of quinazoline), 8.64 (s, 1H, C_5–H of quinazoline); MS (*m/z*): 687 [M+2]; Anal. Calcd for $C_{33}H_{27}Br_2N_5O_2$: C, 57.83; H, 3.97; N, 10.22. Found: C, 57.98; H, 3.95; N, 10.19.

Pharmacology

All the synthesized compounds were evaluated for their antiepileptic effects using male albino mice (Swiss 18–25 g) and rat (Wistar 100–150 g). The primary qualitative evaluations were performed in mice involved two epilepsy tests (MES and scPTZ). Acute neurological toxicity induced by the compounds in mice was assessed through standardized rotorod test. In the initial screening, candidate compounds were screened for their antiepileptic potential through MES and scPTZ models in mice at a dose level of 30, 100, and 300 mg/kg by intraperitoneal (i.p.) route and the groups of mice are tested at different time points (i.e., 0.5 and 4 h) post administration of the test candidate. It is generally acknowledged that the MES model, which uses an electrical stimulus, induces generalized tonic–clonic seizures. Through electrical induction, it is used to help recognize those compounds which prevent seizure spread. The scPTZ is a model where the myoclonic seizures induced by chemical induction. It helps in identifying those compounds that might act by increasing seizure threshold. Each group consisted of six animals. The animals were maintained in colony cages at 25 ± 2 °C, relative humidity of 45–55 %, under a 12 h light and dark cycle; were fed standard animal feed (Olfert *et al*., 1993). All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

Antiepileptic activity

The maximal electroshock test (MES)

The MES is a model for generalized tonic–clonic seizures and provides a hint of a compound's ability to stop seizure spread when all neuronal circuits in the brain are maximally active. These seizures are extremely reproducible and are electro physiologically reliable with human

seizures. For the MES, a drop of anesthetic and electrolyte solution (tetracaine hydrochloride (0.5 %) in saline (0.9 %)) was applied to the eyes of individual animal before to placement of the corneal electrodes. The electrical stimulus in the MES test was 50 mA, 60 Hz, for mice and 150 mA, 60 Hz, for rats delivered for 0.2 s by an apparatus similar to previously reported method (Woodbury and Davenport, 1952; White *et al*., 1995). Abolition of the hindleg tonic extensor component of the seizure was used as the endpoint. Mice are initially tested with different doses of 30, 100, and 300 mg/kg of test compound given by i.p. injection at various intervals while rats are initially screened at a fixed dose of 30 mg/kg given by oral route.

The subcutaneous pentylenetetrazole seizure test (scPTZ)

Subcutaneous injection of the convulsant pentylenetetrazole produces clonic seizures in laboratory animals. The scPTZ test detects the ability of test compounds to raise the seizure threshold of an animal and thus protect it from exhibiting a clonic seizure. Animals are pretreated with various doses of the test compound given by i.p. injection. The dose of pentylenetetrazole which induce convulsions in 97 % of animals (CD_{97} 85 mg/kg mice) is injected into a loose fold of skin in the midline of the neck. The animals are placed in isolation cages to minimize stress (Swinyard *et al*., 1961) and observed for the next 30 min for the presence or absence of a seizure. An episode of clonic spasms, ~3–5 s, of the fore and/or hindlimbs, jaws, or vibrissae is taken as the endpoint. Animals which do not meet this criterion are considered protected.

Acute toxicity-minimal motor impairment

To assess a compound's undesirable side effects (toxicity), animals are monitored for overt signs of impaired neurological or muscular function. In mice, the rotorod (Dunham and Miya, 1957) procedure is used to disclose minimal muscular (MMI) or neurological impairment (MNI). When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal can maintain its equilibrium for long periods of time. The animal is considered toxic if it falls off this rotating rod three times during a 1 min period. In addition to MMI, animals may exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of placing response, and changes in muscle tone.

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