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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and evaluation of new hybrid pharmacophore quinazolino-tetrazoles as anticonvulsant strategy

Sachin Malik · Suroor A. Khan

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Abstract The anticonvulsant study of 25 newly synthesized quinazolin-4(3*H*)-one substituted 1*H* and 2*H*-tetrazoles (**6a–6d**, **7a–7b**, **8a–8i**, **8a′–8i′**) was executed. The study employing the maximal electroshock and subcutaneous pentylenetetrazole (scPTZ) screens, the 'gold standards' in the preliminary anticonvulsant breakthrough and the neurotoxicity study applying the rotorod test unveiled a triad of compounds **6c**, **7b** and **8i′** as the looms amongst the compendium of synthesized compounds. The quantification data of these compounds following oral administration in rats showcased **7b** to endorse a remarkable position in the MES screen with a protective indice (PI) of >39.67 and **6c** in the scPTZ delineating a PI > 3.10, respectively. All the potent compounds were destitute of toxicity.

Keywords Quinazolin-4(3*H*)-one · Tetrazoles · Anticonvulsant activity · Hepatic toxicity

Introduction

Epilepsy is a major neurological condition that strikes all populations (Hauser *et al.*, 1991) represented by paroxysmal cerebral dysrhythmia, manifested as brief episodes (seizures) of loss or disturbance of consciousness, often followed by convulsions (Fisher *et al.*, 2005). The past decades have endorsed many approaches in the evolution of new strategies for the treatment of epilepsy, mainly focused in the prevention of seizures. The antiepileptic drugs (AEDs) presently employed provides adequate seizure control in a substantial number of the patients (Bell and Sander, 2002; Lopes Lima, 2000; Perucca, 2002; Berk *et al.*, 2001). In spite of the prominent therapeutic arsenal of old and new AEDs, unfortunately it is estimated that up to 30 % of affected population are still immune to available medication (Holmes, 2007; Perucca *et al.*, 2007; Smith *et al.*, 2007). Moreover, many AEDs have grievous side effects, such as ataxia, drowsiness, gingival hyperplasia, gastrointestinal disturbances, along with dose-related toxicity and peculiar adverse effects that wander in harshness from minimal brain impairment and megaloblastic anaemia to death from aplastic anaemia or hepatic failure (Spear, 2001; Brown and Holmes, 2001; Kramer, 2001). These confinements with conventional antiepileptic drugs necessitate the need for the development of more efficacious and safer antiepileptic drugs.

One of the most frequently encountered heterocycles in medicinal chemistry is 4(3*H*)-quinazolinones, which posses various pharmacological activities like antifungal (Tiwari *et al.*, 2007), antibacterial (Grover and Kini, 2006), antitumor (Cao *et al.*, 2005), anti-inflammatory (Giri *et al.*, 2009), anticonvulsant (El-Helby and AbdelWahab 2003; Kadi *et al.*, 2006; Jatav *et al.*, 2008), analgesic (VanZyl, 2001; Kumar *et al.*, 2003) and antitubercular (Mohamed *et al.*, 2004; Mohamed *et al.*, 2005). A literature sight exposed that the presence of a substituted aromatic ring at position 3 and a methyl group at position 2 on quinazolin-4(3*H*)-one nucleus is an essential requirement for CNS depressant and antiepileptic activities (El-Azab and ElTahir, 2012; El-Azab *et al.*, 2011). Quinazolin-4(3*H*)-one constitutes a good template for the preparation of some new anticonvulsant agents, since such a heterocyclic system has the required pharmacophoric moiety. Methaqualone, a crucial landmark in the area of synthetic anticonvulsants owned quinazoline core responsible for its

S. Malik · S. A. Khan (✉)
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062, India
e-mail: sakhanpchem@gmail.com

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activity (Gujral *et al.*, 1957). Its 3-(2-chlorophenyl)-2-methyl-4(3*H*)-quinazolinone analogue (Mecloqualone) was found to possess marked anticonvulsant action, 1.5 times more potent than phenytoin sodium (DPH) against electroshock induced convulsions and 10 times more potent than Troxidone against pentylenetetrazol induced seizures (Bhaduri *et al.*, 1964; Salimath *et al.*, 1956). Interestingly, a series of 3-substituted quinazolinones structurally related to methaqualone showed good protection against maximal electroshock and subcutaneous Metrazol induced seizures (Wolfe *et al.*, 1990; Aziza, 1997).

Similarly, tetrazoles belong to the privileged heterocyclic scaffolds, in the modern medicinal chemistry as they have a wide range of biological activities admitting anticonvulsant (Sun *et al.*, 2010a, b; Alhano *et al.*, 2006), antitubercular (Chitra *et al.*, 2011), antiemetic (Armour *et al.*, 1996), antiamoebic (Wani *et al.*, 2012), antihistaminic (Pellicciari *et al.*, 1999), antihypertensive (Nicolai *et al.*, 1995) and antidepressant activities (Deng *et al.*, 2010; Wang *et al.*, 2009; Beghi *et al.*, 2004). The tetrazole nuclei in YKP3089 a novel compound with broad-spectrum anticonvulsant activity under clinical development (Phase II studies) at SK Life Science having good tolerability, possibility of once daily dosing and broad spectrum activity in animal models of epilepsy has focused considerable interest (Bialer *et al.*, 2010).

Tetrazoles generally do not exhibit pharmacological activity, however, many of its derivatives possess interesting biological activities due to metabolically stable surrogates for carboxylic acids, and offer a more favourable pharmacokinetic profile due to their lipophilic spacer property (Butler, 1996; Juby *et al.*, 1968; Chiu *et al.*, 1989; Furkawa *et al.*, 1982; Koldobskii and Kharbash, 2003; O'Neill *et al.*, 1998; Liljebris *et al.*, 2002; MDDR database, 2001). Tetrazoles exhibit a planar structure. Hansch showed that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylate, an important factor in allowing the molecule to pass through cell membranes (Peters *et al.*, 2001; Kubo *et al.*, 1993). Hydrogen bonding capability of tetrazolic anions with receptor recognition sites is a key interaction for enhanced binding affinity (Holland and Pereira, 1967).

Moreover, all the designed compounds comprised of the four pharmacophoric elements that are necessary for good anticonvulsant activity suggested by Pandeya *et al.* as manifested in many currently used antiepileptic drugs. These are hydrophobic domain, hydrogen bonding domain, electron donor moiety and distal hydrophobic domain (Pandeya *et al.*, 2000).

In view of these points, it was thought worthwhile to prepare a new hybrid that clubbed both quinazolin-4(3*H*)-one and substituted tetrazoles (Fig. 1), having high lipid solubility in hope of developing new potent and safer compounds. Herein, a new series of methaqualone analogue comprising alkoxy tetrazole with carbonyl, sulfonyl, aryl, alkyl pyridinyl moieties were designed, synthesized and evaluated for anticonvulsant activity.

Results and discussion

Chemistry

Present study was undertaken to synthesize some novel quinazol-4(3*H*)-one embedded tetrazole with aromatic and heteroaromatic nuclei derivatives, and to investigate their probable anticonvulsant effect. Target compounds were obtained in five-step reaction process, outlined in Scheme 1 and 2. 8-hydroxy-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (3) first key intermediate was obtained by the reaction of 3-hydroxyanthranilic acid with acetic anhydride followed by treatment with *o*-toludine in anhydrous pyridine to afford 8-acetyloxy-2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone (2), which was subjected to catalytic hydrolysis by the reaction with potassium carbonate in methanol to give compound (3). Alkylation of the 8-hydroxy-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (3) with chloroacetonitrile under basic conditions gave the nitriles i.e. 2-(2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yloxy)acetonitrile (4) in good yield. The tetrazole moiety was prepared by heating the nitrile with sodium azide in DMF in presence of triethyl ammonium chloride. The proposed mechanism involves a nucleophilic attack of azide ion on the carbon of the nitrile group, followed by ring closure of the imino azide to form the tetrazole ring. The tetrazole ring in 8-((1*H*-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (5) was established by direct [2 + 3] cycloaddition of azide with nitrile derivative (4). Subsequent acylation and alkylation was performed with different benzoyl chloride, benzenesulfonyl chloride and benzyl chloride derivatives under basic conditions to afford designed compounds. 8-((2-benzoyl-substituted-2*H*-tetrazol-5-yl)-methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**6a–6d**) was prepared with different benzoyl chloride under basic conditions, until odour of acid chloride disappeared. Similar process was followed for synthesis of 2-methyl-8-((2-(phenyl substituted-sulfonyl)-2*H*-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**7a**, **7b**) using different benzenesulfonyl chloride derivatives under more basic conditions than benzyl chlorides. In both acylation process electrophiles attack the N-2 position of tetrazole and form 2,5-disubstituted tetrazoles, which is confirmed from the thermal decomposition to form Huigen product. Tetrazole rings are readily converted into the *N*-benzyl derivatives at room temperature, using 1.5 equivalents of benzyl chloride in triethylamine and acetonitrile, to form regioisomeric mixture of 1,5-disubstituted tetrazoles (**8a′–8i′**) and 2,5-disubstituted tetrazoles (**8a–8i**), which are separated by column chromatography in varied yields.

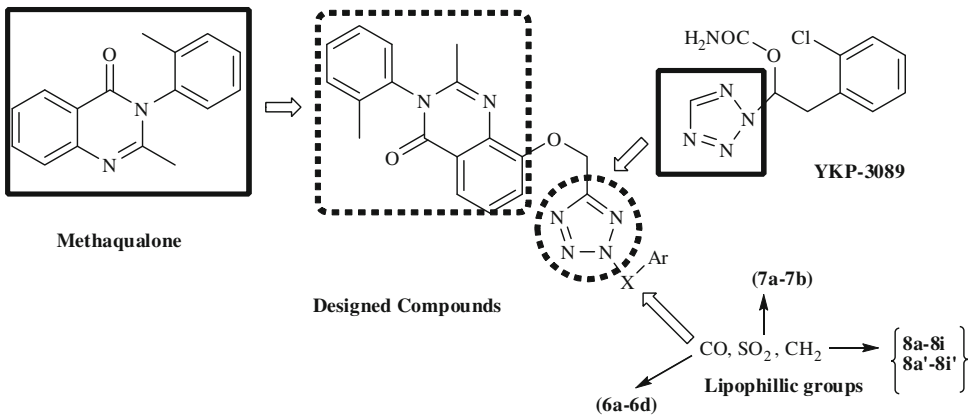
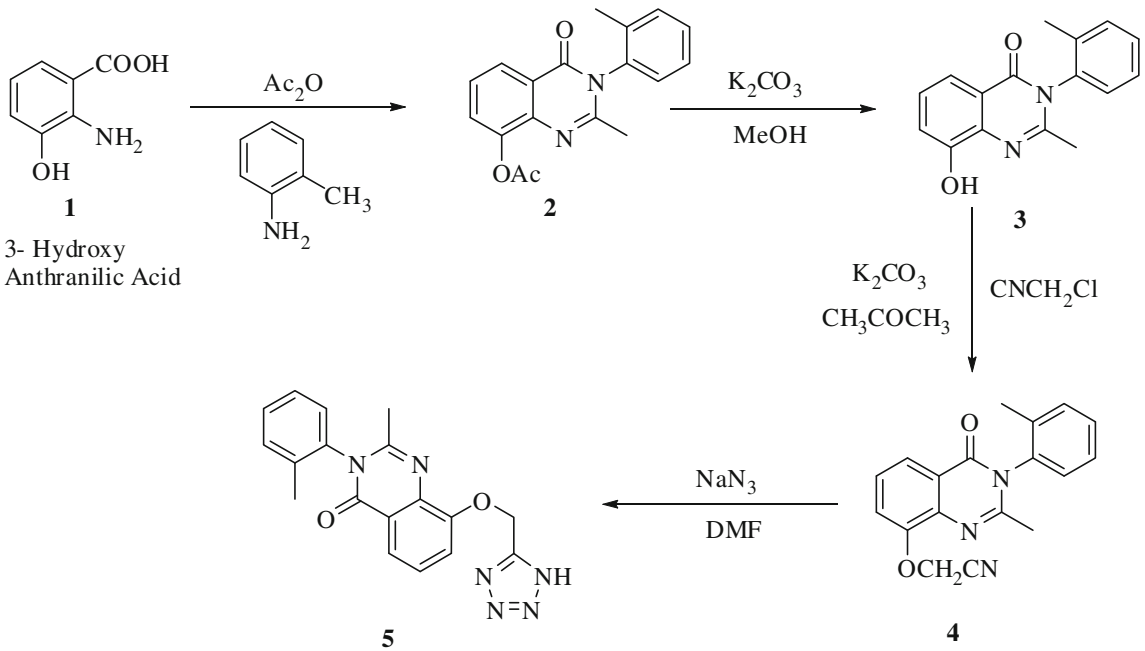
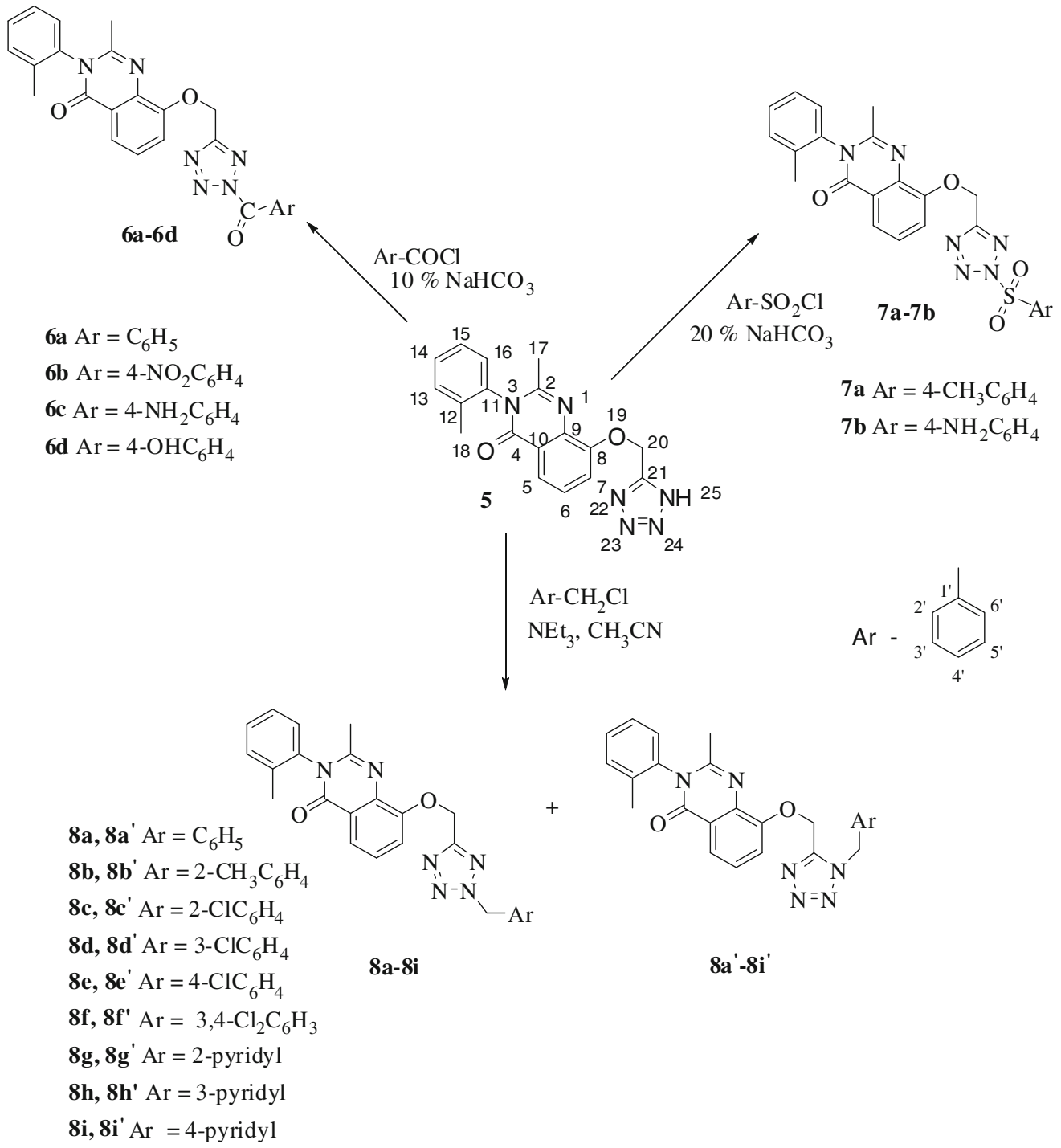


Fig. 1 Structure of biologically active anticonvulsant agents and rationally designed template for targeted compound (**6a–6d**, **7a–7b**, **8a–8i**, **8a′–8i′**)

The most common nucleophile type reactions at the tetrazole nitrogens arise from the acidity of the ring N–H bond. The tetrazolic acids form stable anions when treated with bases, and are more reactive than neutral tetrazoles towards alkylating agents. The product is a mixture of 1N and 2N-alkyl isomers (Scheme 3), the relative proportions of which depend upon the conditions of the alkylation, the steric requirements of the alkylating agent and the influence of the 5-substituent. The regioisomers can be distinguished with a high reliability and generally they can be isolated in good yields by simple chromatography on silica gel. In N-disubstituted tetrazoles series, the more polar 1,5-disubstituted form (high dipole moment) usually has a higher melting point or boiling point than the corresponding 2,5-disubstituted isomer (lower dipole moment). Furthermore, ^{1}H NMR studies studies of disubstituted tetrazoles have shown that protons of CH_2 group bonded to N_1 of 1,5-disubstituted tetrazoles are more shielded than the corresponding protons of 2,5-disubstituted tetrazoles. Moreover, their ^{13}C NMR spectra have shown that the tetrazole-C_5 carbon atom of 1,5-disubstituted tetrazoles is more shielded than the tallying carbon of the 2,5-disubstituted tetrazoles (May and Abell, 2001; Bethel *et al.*, 1999; Byard and Herbert, 1999). Based on these accounted observations, compounds **8a′–8i′** was assigned as 1,5-disubstituted tetrazoles since its ^{1}H NMR spectrum displayed signals for N–CH_2 protons between δ 5.25–5.50 ppm, while its ^{13}C NMR spectrum displayed C_5 resonance at around δ 150 ppm. Meanwhile compounds **8a–8i** was designated as 2,5-disubstituted tetrazoles as evidenced from its ^{1}H NMR that exhibited signals for N–CH_2 protons between δ 5.85–6.20 ppm, whereas, its ^{13}C NMR spectrum showed signals for tetrazole-C_5 atom at around δ 160 ppm. The physical and elemental analyses data for titled compounds are summarized in Table 1. Moreover, the structures of all the



Scheme 1 Synthetic scheme for the key intermediate 8-((1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**5**)

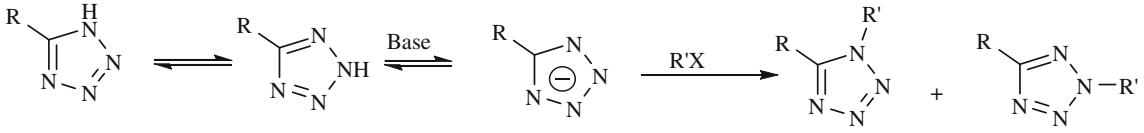


Scheme 2 Synthesis of the final compounds (**6a–6d**, **7a–7b**, **8a–8i**, **8a′–8i′**)

synthesized compounds are established from its IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis.

Pharmacology

The newly synthesized compounds were evaluated for anticonvulsant screening based on the NIH anticonvulsant drug development (ADD) program protocol (Rogawski and Loscher, 2004). The pre-clinical Phase I evaluation was executed using the two 'gold standards' (White, 2003) anticonvulsant models namely the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test. Neurotoxicity of the active compounds was ascertained using the minimal motor impairment-Rotorod



Scheme 3 Alkylation to tetrazoles to form a mixture of 1,5 and 2,5-disubstituted tetrazoles

test. The MES test is linked with the electrical induction of the seizure, whereas PTZ test involves a chemical induction to generate the convulsion. The test compounds were administered intraperitoneally (i.p.) into the mice at the doses of 30, 100 and 300 mg/kg in the MES screen, whereas 100 and 300 mg/kg in the scPTZ screen. Phenytoin was picked out as standard drug in the MES and minimal motor impairment test, whereas ethosuximide was selected for the scPTZ screening. The evaluation was carried out at two time intervals of 0.5 and 4.0 h, respectively.

The MES test for generalized tonic–clonic seizure evaluation keyed out some clinical candidates that forbade seizure spread. Amongst the plethora of the synthesized compounds, four compounds **6a**, **6c**, **7b** and **8i′**, exhibited significantly active profile against the electrically induced seizures at a dose of 30 mg/kg at 0.5 h duration. Compound **7b** upheld at the same dose after 4.0 h, whereas, **6a**, **6c** and **8i′** were active at a higher dose of 100 mg/kg, rendering rapid onset and shorter duration of action of the triad at the lower dose. The compounds **5**, **6d**, **8g** and **8h′** revealed protection at the dose level of 100 mg/kg at 0.5 h. At 4.0 h compound **5** persisted to show anti-MES protection at the same dose, whereas, compounds **6d** and **8h′** indicated to prevent the seizure spread at a higher dose of 300 mg/kg. The compound **8g**, **8g′**, **8h** and **8i** with rapid onset provided in cessation of activity at 4.0 h duration. The remaining compounds showed anticonvulsant activity at the maximum administered dose of 300 mg/kg at 0.5 h with loss in activity at 4.0 h, except compound **7a** that retained its similar profile at the latter reported time (Table 2).

The compounds portraying better anticonvulsant profile in the MES screen were further challenged by chemically induction of seizures in the scPTZ test. The compounds **5**, **6c**, **6d**, **7b** and **8i′** raised the seizure threshold at a dose of 100 mg/kg after 0.5 h interval. Interestingly, **6c** depicted activity at the same dose at 4.0 h as well marking it as the most efficient compound of the series. The compounds **7b** and **8i′** rendered anti-scPTZ action at a higher dose of 300 mg/kg equating the effect of the reference drug ethosuximide. The compounds **5** and **6d** ensued in cessation of activity at 4.0 h duration. The compounds **6a**, **8g**, **8g′**, **8h**, **8h′** and **8i** established protection against the scPTZ induced convulsions at the maximum dose of 300 mg/kg after 0.5 h leading to loss in activity at 4.0 h, except **8g′** and **8h′** that preserved its activity at 300 mg/kg after 4.0 h (Table 2).

The minimal motor impairment was performed using rotorod test in the compounds exhibiting protectivity against MES and scPTZ induced convulsions. The compound **6a**, **6c**, **7b**, **8i** and **8i′** were found to be devoid of any neurotoxicity even at the maximum dose, thereby, considering it to be much safer than the standard drug phenytoin. Compound **6d**, **8g** and **8h** gave equivalent neurotoxicity profile compared to phenytoin at 0.5 h, but the increase in the magnitude of dose indicated a decrease in toxicity after 4.0 h duration, suggesting it to be less toxic than the standard drug after prolonged absorption. The compound **5**, **8g′** and **8h′** had minimal motor impairment dose equivalent to the standard drug phenytoin (Table 2).

In accord to the Anticonvulsant Screening Project (ASP) disposition, the upshots of the prelude anticonvulsant screening in mice, compounds **6c**, **7b** and **8i′** were selected for canvassing their anticonvulsant effect (MES and scPTZ screen) after oral administration into rats at a dose of 30 and 50 mg/kg, respectively as the ability to inhibit epilepsy by oral route is a valuable property for development as drug candidate. The outcomes are arrayed in Table 3 and Table 4.

The data illustrated one peak of 100 % protection at 0.5 h like phenytoin and succeeded by 50 % at 0.25, 1, 2 and 4 h for **7b** proposing it to be the most active of the series, thereby, retaining the anticonvulsant potential after prolonged interval in MES screen. The accompanying compound **6c** attained a maximum of 75 % protection at 0.5 h, followed by a decrease up to 25 % after prolonged administration. The orally dosed compound **8i′** achieved merely 50 % protection in MES test an hour after administration. Likewise, the scPTZ study of **8i′** analyzed a peak of 50 % protection at 0.5 and 1 h, compared to 25 % at 2 h and no protection at 4 h, respectively. It remarked **8i′** to have slow absorption, but rapid metabolism against PTZ induced seizures. The compounds **6c** and **7b** were represented by retarded absorption, and merely 25 % protection at 2 h against oral induction in scPTZ test with the continuance of 25 % protection for **6c**, and an increase to 50 % for **7b** after 4 h duration.

The MES protection graph of the compounds **6c**, **7b** and **8i′** after oral administration is revelatory of the fact of delayed but sustained absorption of these compounds after prolonged duration of time. The scPTZ oral administration protection indices binned **8i′** as promising candidate having comparable activity to the standard drug ethosuximide.

Table 1 Physicochemical data of synthesized compounds (**4**, **5**, **6a–6d**, **7a–7b**, **8a–8i**, **8a′–8i′**)

Compd. no.	Mol. formula (Mol. weight)	Yield[a] (%)	M.p. (°C)	Elemental analyses[b]		
				Calculated/found (%)		
				C	H	N
4	$C_{18}H_{15}N_3O_2$	71.55	105–108	70.81	4.95	13.76
	(305.33)			70.82	4.92	13.77
5	$C_{18}H_{16}N_6O_2$	55.45	260–265	62.06	4.63	24.12
	(348.36)			62.01	4.42	24.10
6a	$C_{25}H_{20}N_6O_3$	75.88	95–98	66.36	4.46	18.57
	(452.46)			66.34	4.48	18.55
6b	$C_{25}H_{19}N_7O_5$	66.66	80–84	60.36	3.85	19.71
	(497.46)			60.33	3.88	19.72
6c	$C_{25}H_{21}N_7O_3$	70.35	220–224	64.23	4.53	20.97
	(467.48)			64.20	4.55	20.95
6d	$C_{25}H_{20}N_6O_4$	64.45	167–170	64.10	4.30	17.94
	(468.46)			64.07	4.33	17.93
7a	$C_{25}H_{22}N_6O_4S$	72.20	180–182	59.75	4.41	16.72
	(502.54)			59.77	4.38	16.70
7b	$C_{24}H_{21}N_7O_4S$	82.25	242–246	57.25	4.20	19.47
	(503.53)			57.22	4.22	19.45
8a/8a′	$C_{25}H_{22}N_6O_2$	56.66/	108–110/	68.48	5.06	19.17
	(438.48)	28.55	132–134	68.49	5.04	19.19
8b/8b′	$C_{26}H_{24}N_6O_2$	48.80	150–155/	69.01	5.35	18.57
	(452.51)	30.50	190–192	68.98	5.36	18.57
8c/8c′	$C_{25}H_{21}ClN_6O_2$	40.85	155–158	63.49	4.48	17.77
	(472.93)	32.25	220–223	63.48	4.50	17.76
8d/8d′	$C_{25}H_{21}ClN_6O_2$	38.70	180–182	63.49	4.48	17.77
	(472.93)	25.45	215–216	63.50	4.47	17.80
8e/8e′	$C_{25}H_{21}ClN_6O_2$	52.48	200–204	63.49	4.48	17.77
	(472.93)	32.40	235–238	63.49	4.47	17.76
8f/8f′	$C_{25}H_{20}Cl_2N_6O_2$	45.20	170–172	59.18	3.97	16.56
	(507.37)	22.50	204–210	59.20	3.96	16.60
8g/8g′	$C_{23}H_{18}N_7O_2$	42.20	160–163	65.09	4.27	23.10
	(424.43)	26.60	210–212	65.11	4.25	23.14
8h/8h′	$C_{23}H_{18}N_7O_2$	35.80	192–195	65.09	4.27	23.10
	(424.43)	25.58	226–229	65.12	4.25	23.07
8i/8i′	$C_{23}H_{18}N_7O_2$	60.30	220–222	65.09	4.27	23.10
	(424.43)	32.20	252–256	65.08	4.26	23.08

[a] Solvent for recrystallization

[b] Elemental analyses for C, H and N were within ±0.4 % of the theoretical values

The phase II quantitative estimation in the MES and scPTZ screen for the orally administered rats was established through the investigation of the median effective dose (ED_{50}) and median toxic dose (TD_{50}) at the antecedently gauged time of peak effect (TPE). An insight of the quantification data of MES screen plied compound **7b** more potent than phenytoin, as manifested from its protective indice (TD_{50}/ED_{50}) of >39.67. In the scPTZ attainments equalizing, the effect of standard drug ethosuximide (PI > 3.0), **6c** fended against the chemically induced seizures thereby making a remarkable decrease in the ED_{50} to 10.90 mg/kg and TD_{50} >150 mg/kg, ensuing in a comparable of protection index of >3.10. However, **8i′** depicted a protective window lesser than that of phenytoin and ethosuximide chosen as reference drugs in the MES and scPTZ screen, respectively (Table 5).

The barren from major limitation of hepatotoxicity in anticonvulsant drugs was provided through the estimation of serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) after chronic administration of **6c**, **7b** and **8i′** to rats for 2 weeks. The candidates did not figure any significant increase up to

Table 2 Pharmacological screening (Phase I) of the synthesized compounds

Compd.	Intraperitoneal injection in mice[a]					
	MES[b]		scPTZ[c]		NT[d]	
	0.5 h	4 h	0.5 h	4 h	0.5	4 h
5	100	100	100	–	100	100
6a	30	100	300	–	300	300
6b	300	–	X	X	X	X
6c	30	100	100	100	300	300
6d	100	300	100	–	100	300
7a	300	300	X	X	X	X
7b	30	30	100	300	300	300
8a	300	–	X	X	X	X
8a′	300	–	X	X	X	X
8b	300	–	X	X	X	X
8b′	300	–	X	X	X	X
8c	300	–	X	X	X	X
8c′	300	–	X	X	X	X
8d	300	–	X	X	X	X
8d′	300	–	X	X	X	X
8e	300	–	X	X	X	X
8e′	300	–	X	X	X	X
8f	300	–	X	X	X	X
8f′	300	–	X	X	X	X
8g	100	–	300	–	100	300
8g′	100	–	300	300	100	100
8h	100	–	300	–	100	300
8h′	100	300	300	300	100	100
8i	100	–	300	–	300	300
8i′	30	100	100	300	300	300
Phenytoin[e]	30	30	–	–	100	100
Ethosuximide[e]	–	–	100	300	–	–

Negative control group received 0.9 % saline (10 mL/kg) which showed zero % protection

[a] Number of animal used = 4, Doses of 30, 100 and 300 mg/kg were administered. The figure in the table indicates the minimum dose whereby, bioactivity was demonstrated in half or more of the mice. The animals were examined at 0.5 and 4 h. A (–) dash indicates the absence of anticonvulsant activity and neurotoxicity at the maximum dose administered (300 mg/kg). X indicates the compound not tested against anticonvulsant activity and neurotoxicity

[b] Maximal electroshock test

[c] Subcutaneous pentylenetetrazole test

[d] Neurotoxicity screening-rotorod test

[e] Reference drugs, data for phenytoin and ethosuximide were used as positive control, Ref. (Thirumurugan *et al.*, 2006)

Table 3 Evaluation of selected compounds in MES test after oral administration (30 mg/kg) to rats

Compd.	Oral administration to rats[a] (h)				
	0.25	0.5	1.0	2.0	4.0
6c	1	3	2	1	1
7b	2	4	2	2	2
8i′	0	1	2	1	1
Phenytoin[b]	1	4	3	3	3

[a] Figure indicate the number of rats out of four which are protected

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

Table 4 Evaluation of selected compounds scPTZ test after oral administration (50 mg/kg) to rats

Compd.	Oral administration to rats[a] (h)				
	0.25	0.5	1.0	2.0	4.0
6c	0	0	0	1	1
7b	0	0	0	1	2
8i′	0	2	2	1	0
Ethosuximide[b]	0	2	1	1	0

[a] Figure indicate the number of rats out of four which are protected

[b] Reference drug, data for ethosuximide Ref. (Thirumurugan *et al.*, 2006)

95 % level of significance for these enzymes compared to the control as well as the standard drug phenytoin Table 6.

The in vivo data in rats supported 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 suggest the influence of compound on voltage depended Na^+ channels, as the most credible mechanism of antiepileptic action, and provide more insights for the anticonvulsant effects of these new analogues against convulsant-induced seizures, which will be considered extensively in our future study.

Table 5 Quantification studies (Phase II) of selected compounds in rats after oral administration

Compd.	TPE (h)[a]	MES ED_{50} [b] (mg/kg)	scPTZ ED_{50} [b] (mg/kg)	NT TD_{50} [c] (mg/kg)	PI[d]
6c	2	10.90 (8.72–25.90)	48.35 (40.50–100.20)	>150	>13.76 (MES) >3.10 (scPTZ)
7b	4	4.93 (3.80–7.40)	72.30 (45.60–90.80)	195.57 (163.36–210.55)	>39.67 (MES) >2.71 (scPTZ)
8i′	1	12.90 (10.72–25.10)	>100	>200	>15.51 (MES) >2 (scPTZ)
Phenytoin[e]	1	28.1 (27.7–35.20)	>500	>1000	>35.58 (MES)
Ethosuximide[f]	2	>500	167.0 (116.0–237.0)	>500	>3.0 (scPTZ)

[a] Time to peak effect

[b] ED_{50}—median effective dose required to assure anticonvulsant protection in 50 % animals

[c] TD_{50}—median toxic dose eliciting minimal neurological toxicity in 50 % animals

[d] PI—protective index (TD_{50}/ED_{50})

[e] Reference drug, data for phenytoin, Ref. (Porter *et al.*, 1984)

[f] Reference drug, data for ethosuximide, Ref. (White *et al.*, 2002)

Table 6 Effect of selected compounds on serum levels of liver transaminases in rats

Compd.[a]	SGPT[b,e] (units/mL)	SGOT[c,e] (units/mL)
Control[d]	46.2 ± 5.20	73.2 ± 5.96
6c	44.6 ± 4.32	64.8 ± 5.25
7b	43.3 ± 4.70	70.2 ± 4.70
8i′	45.1 ± 6.20	73.1 ± 5.75
Phenytoin	52.6 ± 3.48	84.1 ± 6.50

Reference drug, phenytoin tested at 25 mg/kg oral for 14 days

[a] The compounds were tested at a dose of 30 mg/kg oral for 14 days

[b] Denotes serum glutamate oxaloacetate transaminase

[c] Denotes serum glutamate pyruvate transaminase

[d] Control animals (six rats) were treated with 0.5 % methylcellulose for 14 days

[e] Each value represents the mean ± SEM of six rats, not significant from the control value at $p < 0.05$ (student's t test)

Conclusion

The jibing of the chemical structure and the ascertained biological activity of the probed compound, it was observed that from the inventory of 25 examined compounds, **6c**, **7b** and **8i′** proved to be of clinical significance. The quinazolinone nuclei dissembled as the mainstay for the persuading the anticonvulsant activity. The introduction of the benzyloxy tetrazole moiety as the core fragment synergized the activity. The presence of the free carbonyl (**6a–6d**) and sulphonyl group (**7a–8b**) attributed to the amplification of the anticonvulsant stimulus. Moreover, it is clear that that good anticonvulsant activity was confined to compounds containing free oxygen functionality. The ameliorating amino fragment at the para position of the benzene moiety in the favored compounds **6c** and **7b** auspicated the substituent effect of the synthesized compounds. Whilst, the substitution of electron donating and electron withdrawing groups did not ascribed to anticonvulsant potentiating effect in the 2,5-substituted **8a–8f** and 1,5-substituted **8a′–8f′**, the majorly role was played by the heterocyclic pyridinyl moiety colligated through the alkyl linkage to the tetrazole nuclei. Moreover, the 4-pyridinyl analogue **8i′** accounted for owing the substantial anticonvulsant potential than the congeners of the group.

Experimental

Chemistry

All reagents were used as purchased from commercial suppliers like Merck India Ltd., S.D Fine Chemicals, Sigma Aldrich and Qualigens and were used without purification. The purity and homogeneity of the compounds were assessed by the thin-layer chromatography (TLC) performed on Merck silica gel 60 F_{254} aluminum sheets. Melting points were determined in one end open capillary tubes on Buchi 530 melting point apparatus and are uncorrected. Elemental data of C, H, and N were within ±0.4 % of the theoretical value as determined by Perkin Elmer Model 240 analyzer. The Infrared Spectra of compounds were recorded on Perkin Elmer Spectrum BX-II Spectrophotometer using KBr pellets are represented by the following abbreviations: *s* (strong), *m* (medium), *w* (weak) and *br* (broad) absorption bands. ^{1}H NMR and ^{13}C NMR spectra of DMSO-d_6/$CDCl_3$ solutions were, respectively, recorded at 400 MHz with Bruker model DRX 400 NMR Spectrometer using TMS [$(CH_3)_4Si$] as

internal standard. Signal multiplicities are represented by the following abbreviations: s (singlet), br s (broad singlet), d (doublet), t (triplet), and m (multiplet). Chemical shifts are reported in δ values (ppm) relative to TMS $\delta = 0$. The Mass Spectra was recorded on a Waters Micro-mass ZQ 2000 Spectrophotometer. The structures were confirmed by both spectral (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analyses.

2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yl acetate (**2**)

The synthesis of 2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yl acetate (**2**) was carried out according to reported procedure (El-Azab *et al.*, 2011). Yield 83.50 %; m.p.: 130–132 °C; IR (KBr) υ_{max} (cm^{-1}): 3120, 3100 (*s*, Ar C–H_{str}), 2830 (*s*, CH_3, C–H_{str}), 1740 (*s*, Ar C=O_{str}), 1720 (*s*, cyclic C=O_{str}), 1522 (*w*, C=N_{str}), 1445 (*w*, Ar C=C_{str}), 1220, 1055 (*s*, C–O_{str}); ^{1}H NMR (δ) $CDCl_3$: 2.08 (s, 3H), 2.10 (s, 3H), 2.30 (s, 3H), 7.05 (d, 1H, $J = 7.5$ Hz), 7.25–7.45 (m, 3H), 7.52 (d, 1H, $J = 8.2$. Hz), 7.68 (d, 1H, $J = 7.5$ Hz), 8.15 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (δ) $CDCl_3$: 17.5 (C-18), 20.4 (OCO<u>CH_3</u>), 25.8 (C-17), 121.1 (C-10), 122.4 (C-5), 124.5 (C-6), 126.6 (C-16), 127.5 (C-7), 127.8 (C-14 and C-15), 131.3 (C-13), 134.5 (C-12), 136.6 (C-11), 141.5 (C-8), 146.7 (C-9), 155.4 (C-2), 161.1 (C-4), 168.8 (O<u>CO</u>CH_3); MS (*m*/*z*): 309.45 ($M^+ + 1$).

8-hydroxy-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**3**)

The synthesis of 2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yl acetate (**3**) was carried out according to reported procedure (El-Azab *et al.*, 2011). Yield 73.25 %; m.p.: 160–165 °C; IR (KBr) υ_{max} (cm^{-1}): 3540 (*s*, O–H_{str}), 3150, 3120 (*s*, Ar C–H_{str}), 2850 (*s*, CH_3, C–H_{str}), 1710 (*s*, cyclic C=O_{str}), 1525 (*w*, C=N_{str}), 1460, 1445 (*w*, Ar C=C_{str}); ^{1}H NMR (δ) $CDCl_3$: 2.15 (s, 3H), 2.32 (s, 3H), 7.10 (d, 1H, $J = 7.0$ Hz), 7.25–7.40 (m, 3H), 7.62 (d, 1H, $J = 7.5$ Hz), 7.70 (d, 1H, $J = 7.5$ Hz), 8.10 (d, 1H, $J = 7.5$ Hz), 11.20 (br s, 1H, OH); ^{13}C NMR (δ) $CDCl_3$: 17.1 (C-18), 25.5 (C-17), 121.5 (C-10), 121.8 (C-5), 125.1 (C-6), 126.4 (C-16), 127.1 (C-7), 128.4 (C-14 and C-15), 131.5 (C-13), 135.1 (C-12), 137.1 (C-11), 145.5 (C-9), 150.1 (C-8), 154.4 (C-2), 160.5 (C-4); MS (*m*/*z*): 267.35 ($M^+ + 1$).

2-(2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yloxy)acetonitrile (**4**)

A mixture of 8-hydroxy-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**3**) (585.2 mg, 2.2 mmol) and K_2CO_3 (615 mg, 4.5 mmol) in acetone (60 mL) was stirred at room temperature for 30 min. Chloroacetonitrile (423 µL, 6.7 mmol) was slowly added and stirring was continued for 18 h at 50 °C. After cooling, the reaction mixture was filtered and evaporated rendering colourless crystals of 2-(2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yloxy) acetonitrile (4). IR (KBr) υ_{max} (cm^{-1}): 3050, 3040 (*s*, Ar C–H_{str}), 2229 (*s*, C$\equiv$$N_{str}$), 1680 (*s*, cyclic C=$O_{str}$), 1523 (*w*, C=$N_{str}$), 1454, 1433 (*w*, Ar C=C_{str}), 1291 (*s*, C–O_{str}); ^{1}H NMR (δ) $CDCl_3$: 2.21 (s, 3H, CH_3 of quinazoline), 2.35 (s, 3H, Ar–CH_3), 4.90 (s, 2H, OCH_2), 6.95 (d, 1H, $J = 7.0$ Hz), 7.20–7.45 (m, 3H), 7.55 (d, 1H, $J = 7.0$ Hz), 7.70 (d, 1H, $J = 7.5$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) $CDCl_3$: 18.2 (C-18), 24.5 (C-17), 54.5 (O<u>CH_2</u>CN), 115.7 (OCH_2<u>CN</u>), 121.5 (C-10), 122.8 (C-5), 124.6 (C-6), 126.5 (C-16), 127.3 (C-7), 129.2 (C-14 and C-15), 132.5 (C-13), 134.3 (C-12), 136.6 (C-11), 146.5 (C-9), 152.2 (C-8), 155.2 (C-2), 162.4(C-4); MS (*m*/*z*): 306.11 ($M^+ + 1$).

8-((1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**5**)

A mixture of 2-(2-methyl-4-oxo-3-*o*-tolyl-3,4-dihydroquinazolin-8-yloxy)acetonitrile (**4**) (428.4 mg, 1.40 mmol) and sodium azide (194 mg, 2.99 mmol) in dry DMF (10 mL) was stirred in a sealed flask at 80 °C for 4 days. The reaction mixture was concentrated under reduced pressure, H_2O added (10 mL) and acidified to pH 3 with 2 M HCl. The aqueous phase was extracted with Et_2O and the organic phase washed with aqueous saturated $CaCl_2$. After drying, evaporation and column chromatography [toluene–EtOAc–AcOH (24:24:2)] followed by recrystallization (EtOAc–light petroleum) gave **5** as colourless crystals. IR (KBr) υ_{max} (cm^{-1}): 3115, 3097 (*s*, Ar C–H_{str}), 2929 (*s*, CH_3, C–H_{str}), 2700–2500 (*br m*, N–H_{str}), 1724 (*s*, cyclic C=O_{str}), 1623 (*w*, C=N_{str}), 1550 (*w*, N=N–N_{str}, tetrazole), 1450, 1440 (*w*, Ar C=C_{str}), 1250 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.19 (s, 3H, CH_3 of quinazoline), 2.70 (s, 3H, Ar-CH_3), 4.60 (s, 2H, OCH_2), 7.05 (d, 1H, $J = 8.0$ Hz), 7.20–7.55 (m, 3H), 7.75 (d, 1H, $J = 8.0$ Hz), 7.90 (d, 1H, $J = 8.5$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz), 12.80 (br s, NH of tetrazole, D_2O exchangeable); ^{13}C NMR (δ) $CDCl_3$: 17.6 (C-18), 23.8 (C-17), 68.8 (C-20), 120.9 (C-10), 122.4 (C-5), 125.6 (C-6), 126.4 (C-16), 127.2 (C-7), 128.4 (C-14 and C-15), 133.1 (C-13), 135.1 (C-12), 138.2 (C-11), 145.5 (C-9), 150.2 (C-8), 154.4 (C-21), 156.2 (C-2), 162.5 (C-4); MS (*m*/*z*): 349.20 ($M^+ + 1$).

General procedure for the synthesis of compounds (**6a-6d**)

8-((1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**5**) (543.7 mg, 1.5 mmol) (**5**) was processed with substituted benzoyl chloride [**6a/6b/6c/6d** 210.5 (0.25 mL)/278/233.3/234(0.32 mL) mg, 1.5 mmol] in 10 mL of 10 % sodium bicarbonate solution. The mixture was shaken vigorously until the odour of aromatic acid chloride had

disappeared. The solids separated out and were filtered and dried. Recrystallization of the dried compounds from aqueous ethanol yielded compounds **6a**–**6d**.

8-((2-benzoyl-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**6a**)

IR (KBr) υ_{max} (cm^{-1}): 3145, 3120 (*s*, Ar C–H_{str}), 2950 (*s*, CH_3, C–H_{str}), 1730 (*s*, cyclic C=O_{str}), 1650 (*s*, Ar C=O_{str}), 1610 (*w*, C=N_{str}), 1510 (*w*, N=N–N_{str}, tetrazole), 1420 (*w*, Ar C=C_{str}), 1210 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.15 (s, 3H, CH_3 of quinazoline), 2.45 (s, 3H, Ar–CH_3), 4.50 (s, 2H, OCH_2), 7.0 (d, 1H, $J = 7.0$ Hz), 7.20–7.55 (m, 6H), 7.65 (d, 2H), 7.70 (d, 1H, $J = 7.0$ Hz), 8.0 (d, 1H, $J = 7.5$ Hz), 8.30 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.2 (C-18), 24.3 (C-17), 68.5 (C-20), 120.8 (C-10), 122.7 (C-5), 125.1 (C-6), 126.2 (C-16), 127.1 (C-7), 128.7 (C-14 and C-15), 129.7 (C-3′ and C-5′), 130.4 (C-1′), 130.8 (C-2′ and C-6′), 133.2 (C-13), 134.2 (C-4′), 135.1 (C-12), 136.6 (C-11), 143.8 (C-9), 152.1 (C-8), 154.3 (C-2), 161.6 (C-21), 162.2 (C-4), 169.3 (C=O of benzoyl); MS (*m*/*z*): 453.33 ($M^+ + 1$).

2-methyl-8-((2-(4-nitrobenzoyl)-2H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**6b**)

IR (KBr) υ_{max} (cm^{-1}): 3156, 3100 (*s*, Ar C–H_{str}), 2932 (*s*, CH_3, C–H_{str}), 1760 (*s*, cyclic C=O_{str}), 1680 (*s*, Ar C=O_{str}), 1600 (*w*, C=N_{str}), 1526, 1339 (*s*, asymmetric and symmetric NO_2 $_{str}$), 1490 (*w*, N=N–N_{str}, tetrazole), 1420, 1400 (*w*, Ar C=C_{str}), 1215 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.25 (s, 3H, CH_3 of quinazoline), 2.55 (s, 3H, Ar–CH_3), 4.66 (s, 2H, OCH_2), 7.10 (d, 1H, $J = 7.5$ Hz), 7.20–7.65 (m, 3H), 7.80 (d, 1H, $J = 7.5$ Hz), 7.90 (d, 1H, $J = 7.0$ Hz), 8.30 (d, 1H, $J = 8.0$ Hz), 8.35 (d, 2H, $J = 12.0$ Hz), 8.43 (d, 2H, $J = 12.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 18.5 (C-18), 26.1 (C-17), 69.3 (C-20), 120.7 (C-10), 121.8 (C-5), 125.2 (C-6), 126.4 (C-16), 126.7 (C-3′ and C-5′), 127.1 (C-7), 128.2 (C-2′ and C-6′), 128.6 (C-14 and C-15), 130.4 (C-4′), 131.9 (C-13), 133.2 (C-12), 135.5 (C-11), 136.4 (C-1′), 142.3 (C-9), 151.5 (C-8), 153.3 (C-2), 160.6 (C-21), 161.2 (C-4), 170.3 (C=O of benzoyl); MS (*m*/*z*): 498.21 ($M^+ + 1$).

8-((2-(4-aminobenzoyl)-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**6c**)

IR (KBr) υ_{max} (cm^{-1}): 3365 (*s*, N–H_{str}), 3150, 3100 (*s*, Ar C–H_{str}), 2890 (*s*, CH_3, C–H_{str}), 1750 (*s*, cyclic C=O_{str}), 1695 (*s*, Ar C=O_{str}), 1610 (*w*, C=N_{str}), 1550 (*w*, N=N–N_{str}, tetrazole), 1440 (*w*, Ar C=C_{str}), 1220 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.20 (s, 3H, CH_3 of quinazoline), 2.55 (s, 3H, Ar–CH_3), 4.30 (s, 2H, OCH_2), 4.80 (s, 2H, NH_2, D_2O exchangeable), 6.77 (d, 2H, $J = 10$ Hz), 7.0 (d, 1H, $J = 7.5$ Hz), 7.20 (d, 2H, $J = 10$ Hz), 7.30-7.65 (m, 3H), 7.70 (d, 1H, $J = 7.5$ Hz), 7.90 (d, 1H, $J = 8.0$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.8 (C-18), 23.5 (C-17), 69.9 (C-20), 116.2 (C-3′ and C-5′), 121.1 (C-10), 122.3 (C-5), 124.9 (C-6), 125.6 (C-16), 127.1 (C-7), 127.5 (C-2′ and C-6′), 129.4 (C-14 and C-15), 130.2 (C-1′), 131.4 (C-13), 133.2 (C-12), 135.5 (C-11), 140.4 (C-9), 150.5 (C-8), 152.6 (C-4′), 154.2 (C-2), 161.1 (C-21), 163.5 (C-4), 170.5 (C=O of benzoyl); MS (*m*/*z*): 468.54 ($M^+ + 1$).

8-((2-(4-hydroxybenzoyl)-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**6d**)

IR (KBr) υ_{max} (cm^{-1}): 3580 (*s*, O–H_{str}), 3150, 3120 (*s*, Ar C–H_{str}), 2870 (*s*, CH_3, C–H_{str}),1900–1600 (*w*, overtones, Ar C–H_{str}), 1750 (*s*, cyclic C=O_{str}), 1685 (*s*, Ar C=O_{str}), 1620 (*w*, C=N_{str}), 1510 (*w*, N=N–N_{str}, tetrazole), 1460 (*w*, Ar C=C_{str}), 1210 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.30 (s, 3H, CH_3 of quinazoline), 2.50 (s, 3H, Ar–CH_3), 4.44 (s, 2H, OCH_2), 7.10 (d, 1H, $J = 7.5$ Hz), 7.20 (d, 2H, $J = 8.2$ Hz), 7.30–7.65 (m, 3H), 7.78 (d, 1H, $J = 7.5$ Hz), 7.85 (d, 1H, $J = 7.5$ Hz), 7.95 (d, 2H, $J = 8.2$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz), 11.02 (br s, 1H, OH); ^{13}C NMR (δ) DMSO-d_6 : 18.8 (C-18), 26.2 (C-17), 67.9 (C-20), 119.2 (C-3′ and C-5′), 121.7 (C-10), 122.4 (C-5), 123.8 (C-6), 125.5 (C-16), 126.9 (C-7), 128.1 (C-1′), 129.6 (C-14 and C-15), 130.5 (C-2′ and C-6′), 131.7 (C-13), 134.2 (C-12), 136.2 (C-11), 145.2 (C-9), 152.2 (C-8), 154.1 (C-4′), 156.5 (C-2), 160.5 (C-21), 162.8 (C-4), 169.6 (C=O of benzoyl); MS (*m*/*z*): 469.24 ($M^+ + 1$).

General procedure for the synthesis of compounds (**7a**, **7b**)

8-((1*H*-tetrazol-5-yl)methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (543.7 mg, 1.5 mmol) (**5**) was treated with substituted benzenesulfonyl chloride (**7a/7b** 285.9/287.4 mg, 1.5 mmol) in 10 mL of 20 % sodium bicarbonate solution. The mixture was shaken vigorously until the odour of aromatic acid chloride had disappeared. The solids separated out and were filtered and dried. Recrystallization of the dried compounds from aqueous ethanol yielded compounds **7a**, **7b**.

2-methyl-3-*o*-tolyl-8-((2-tosyl-2H-tetrazol-5-yl) methoxy) quinazolin-4(3*H*)-one (**7a**)

IR (KBr) υ_{max} (cm^{-1}): 3145, 3120 (*s*, Ar C–H_{str}), 2930 (*s*, CH_3, C–H_{str}), 1950–1600 (*w*, overtones, Ar C–H_{str}), 1720 (*s*, cyclic C=O_{str}), 1600 (*w*, C=N_{str}), 1470 (*w*, N=N–N_{str}, tetrazole), 1440 (*w*, Ar C=C_{str}), 1297, 1151 (*s*, asymmetric and symmetric SO_{2str}), 1205 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.25 (s, 3H, CH_3 of quinazoline), 2.45 (s, 3H, Ar–CH_3),

2.65 (s, 3H, Ar–CH_3), 4.55 (s, 2H, OCH_2), 6.90 (d, 1H, $J = 7.5$ Hz), 7.10–7.40 (m, 3H), 7.35 (d, 2H, $J = 8.5$ Hz), 7.50 (d, 2H, $J = 7.5$ Hz), 7.78 (d, 1H, $J = 7.5$ Hz), 7.90 (d, 1H, $J = 8.0$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 18.4 (C-18), 22.3 (4′-$\underline{CH_3}C_6H_4$), 24.6 (C-17), 65.2 (C-20), 121.4 (C-10), 122.5 (C-5), 125.2 (C-6), 126.6 (C-16), 127.5 (C-7), 128.2 (C-2′ and C-6′), 129.2 (C-14 and C-15), 130.5 (C-3′ and C-5′), 131.2 (C-13), 133.2 (C-12), 135.1 (C-11), 136.6 (C-1′), 138.2 (C-4′), 142.2 (C-9), 151.1 (C-8), 153.6 (C-2), 160.6 (C-21), 164.2 (C-4); MS (*m/z*): 503.42 ($M^+ + 1$).

8-((2-(4-aminophenylsulfonyl)-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**7b**)

IR (KBr) υ_{max} (cm^{-1}): 3415 (*s*, N–H_{str}), 3150, 3110 (*s*, Ar C–H_{str}), 2800 (*s*, CH_3, C–H_{str}), 1730 (*s*, cyclic C=O_{str}), 1610 (*w*, C=N_{str}), 1520 (*w*, N=N–N_{str}, tetrazole), 1440, 1430 (*w*, Ar C=C_{str}), 1285, 1120 (*s*, asymmetric and symmetric SO_{2str}), 1205 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.15 (s, 3H, CH_3 of quinazoline), 2.45 (s, 3H, Ar–CH_3), 4.30 (s, 2H, OCH_2), 4.54 (s, 2H, NH_2, D_2O exchangeable), 6.70 (d, 2H, $J = 10$ Hz), 7.0 (d, 1H, $J = 7.0$ Hz), 7.25 (d, 2H, $J = 10$ Hz), 7.30–7.55 (m, 3H), 7.80 (d, 1H, $J = 7.0$ Hz), 7.98 (d, 1H, $J = 8.0$ Hz), 8.25 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.8 (C-18), 23.5 (C-17), 69.9 (C-20), 116.2 (C-3′ and C-5′), 121.1 (C-10), 122.3 (C-5), 124.9 (C-6), 125.8 (C-16), 127.4 (C-7), 129.4 (C-14 and C-15), 130.2 (C-2′ and C-6′), 131.4 (C-13), 131.7 (C-12), 135.5 (C-11), 137.6 (C-1′), 142.5 (C-9), 150.5 (C-8), 152.6 (C-4′), 154.2 (C-2), 161.1 (C-21), 163.5 (C-4); MS (*m/z*): 504.44 ($M^+ + 1$).

General procedure for the synthesis of compounds (**8a**–**8i**, **8a′**–**8i′**)

To an oven-dried, round-bottomed flask under dry atmosphere were added 8-((1*H*-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (543.7 mg, 1.5 mmol) (**5**) and substituted aromatic and heteroaromatic methyl chloride [**8a**–**8a′**(189.8 mg)/**8b**–**8b′**(210.9 mg)/(**8c**–**8c′**)–(**8e**–**8e′**) (241.5 mg)/**8f**–**8f′**(293.2 mg)/(**8g**–**8g′**)–(**8i**–**8i′**) (191.3 mg), 1.5 mmol]. The flask was sealed with a rubber septum. Anhydrous acetonitrile (10 mL) was added via syringe to form white slurry. Triethylamine (0.32 mL, 230 mg, 2.3 mmol) was added via syringe, and the mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC (silica gel/1:1 ethyl acetate:hexane; 2,5-disubstituted product (**8a**–**8i**) R_f—0.4, 1,5-disubstituted product (**8a′**–**8i′**) R_f—0.3). Brine (15 mL) was added to quench the reaction and the mixture was transferred to a separatory funnel and then extracted with ethyl acetate. The combined organic extracts were dried over sodium sulphate, filtered and concentrated. The regioisomeric disubstituted tetrazoles were separated by column chromatography (TLC conditions) to give 1,5-disubstitued tetrazole as a white fluffy powder and 2,5-disubstituted tetrazole as white crystalline solid. Both were recrystallized from ethyl acetate/hexane.

8-((2-benzyl-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8a**)

IR (KBr) υ_{max} (cm^{-1}): 3154, 3100 (*w*, Ar C–H_{str}), 2920 (*s*, CH_3, C–H_{str}), 1695 (*s*, cyclic C=O_{str}), 1620 (*w*, C=N_{str}), 1525 (*w*, N=N–N_{str}, tetrazole), 1440, 1420 (*w*, Ar C=C_{str}), 1215 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.20 (s, 3H, CH_3 of quinazoline), 2.35 (s, 3H, Ar–CH_3), 4.32 (s, 2H, OCH_2), 6.15 (s, 2H, N–CH_2), 7.10 (d, 1H, $J = 7.0$ Hz), 7.20-7.55 (m, 6H), 7.70 (d, 1H, $J = 7.0$ Hz), 7.85 (d, 2H), 8.10 (d, 1H, $J = 7.5$ Hz), 8.30 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.8 (C-18), 23.6 (C-17), 56.8 (–$\underline{CH_2}$ of benzyl), 70.8 (C-20), 120.8 (C-10), 121.2 (C-5), 124.5 (C-6), 125.3 (C-4′)126.4 (C-16), 126.8 (C-2′ and C-6′), 127.5 (C-7), 128.5 (C-3′ and C-5′), 129.5 (C-14 and C-15), 131.3 (C-13), 134.4 (C-12), 134.8 (C-1′), 136.5 (C-11), 145.5 (C-9), 150.8 (C-8), 153.2 (C-2), 161.1 (C-21), 163.2 (C-4); MS (*m/z*): 439.50 ($M^+ + 1$).

8-((1-benzyl-1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8a′**)

IR (KBr) υ_{max} (cm^{-1}): 3100 (*w*, Ar C–H_{str}), 2950 (*s*, CH_3, C–H_{str}), 1680 (*s*, cyclic C=O_{str}), 1610 (*w*, C=N_{str}), 1515 (*w*, N=N–N_{str}, tetrazole), 1420 (*w*, Ar C=C_{str}), 1230 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.11 (s, 3H, CH_3 of quinazoline), 2.40 (s, 3H, Ar–CH_3), 4.55 (s, 2H, OCH_2), 5.50 (s, 2H, N–CH_2), 7.20 (d, 1H, $J = 7.5$ Hz), 7.25-7.55 (m, 6H), 7.65 (d, 1H, $J = 7.5$ Hz), 7.80 (d, 2H), 8.0 (d, 1H, $J = 8.0$ Hz), 8.25 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 18.5 (C-18), 24.1(C-17), 50.5 (–$\underline{CH_2}$ of benzyl), 66.8 (C-20), 120.5 (C-10), 121.2 (C-5), 123.4 (C-6), 125.5 (C-4′), 126.2 (C-16), 126.9 (C-2′ and C-6′), 127.1 (C-7), 128.1 (C-3′ and C-5′), 129.2 (C-14 and C-15), 130.4 (C-13), 133.4 (C-12), 134.4 (C-1′), 136.2 (C-11), 142.7 (C-9), 151.2 (C-8), 152.2 (C-21), 153.6 (C-2), 161.5 (C-4); MS (*m/z*): 439.25 ($M^+ + 1$).

2-methyl-8-((2-(2-methylbenzyl)-2H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**8b**)

IR (KBr) υ_{max} (cm^{-1}): 3140, 3100 (*s*, Ar C–H_{str}), 2930 (*s*, CH_3, C–H_{str}), 1950–1600 (*w*, overtones, Ar C–H_{str}), 1680 (*s*, cyclic C=O_{str}), 1620 (*w*, C=N_{str}), 1475 (*w*, N=N–N_{str}, tetrazole), 1445 (*w*, Ar C=C_{str}), 1205 (*s*, C–O_{str}), 746 (*w*, Phenyl C–H_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.25 (s, 3H, CH_3 of quinazoline), 2.30 (s, 3H, Ar–CH_3), 2.50 (s, 3H, Ar–CH_3), 4.65 (s, 2H, OCH_2), 6.20 (s, 2H, N–CH_2), 6.95 (d, 1H, $J = 7.0$ Hz), 7.10-7.40 (m, 5H), 7.60 (d, 2H,

$J = 7.8$ Hz), 7.78 (d, 1H, $J = 7.0$ Hz), 7.90 (d, 1H, $J = 8.0$ Hz), 8.20 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.5 (C-18), 20.5 (2-$\underline{CH_3}C_6H_4$), 24.7 (C-17) 56.2 (C-20), 73.1 (–$\underline{CH_2}$ of benzyl), 120.2 (C-10), 121.4 (C-5), 123.8 (C-2′), 124.6 (C-6), 125.9 (C-5′), 126.8 (C-16), 127.5 (C-7), 128.3 (C-14 and C-15), 129.1 (C-3′), 130.3 (C-4′), 131.3 (C-6′), 131.5 (C-13), 133.2 (C-12), 135.6 (C-11), 137.6 (C-1′), 144.4 (C-9), 149.8 (C-8), 152.2 (C-2), 160.2 (C-21), 162.5 (C-4); MS (*m/z*): 453.33 ($M^+ + 1$).

2-methyl-8-((1-(2-methylbenzyl)-1H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**8b′**)

IR (KBr) υ_{max} (cm^{-1}): 3150, 3120 (*s*, Ar C–H_{str}), 2900 (*s*, CH_3, C–H_{str}), 1900–1600 (*w*, overtones, Ar C–H_{str}), 1640 (*s*, cyclic C=O_{str}), 1610 (*w*, C=N_{str}), 1510 (*w*, N=N–N_{str}, tetrazole), 1445, 1414 (*w*, Ar C=C_{str}), 1220 (*s*, C–O_{str}), 740 (*w*, Phenyl C–H_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.15 (s, 3H, CH_3 of quinazoline), 2.25 (s, 3H, Ar–CH_3), 2.64 (s, 3H, Ar–CH_3), 4.60 (s, 2H, OCH_2), 5.40 (s, 2H, N–CH_2), 7.15 (d, 1H, $J = 7.5$ Hz), 7.25–7.45 (m, 5H), 7.65 (d, 2H, $J = 8.1$ Hz), 7.78 (d, 1H, $J = 7.5$ Hz), 7.84 (d, 1H, $J = 8.5$ Hz), 8.22 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.2 (C-18), 21.1 (2-$\underline{CH_3}C_6H_4$), 24.2 (C-17), 51.4 (C-20), 66.1 (–$\underline{CH_2}$ of benzyl), 120.5 (C-10), 121.1 (C-5), 123.5 (C-2′), 124.4 (C-6), 125.9 (C-5′), 126.6 (C-16), 127.1 (C-7), 128.6 (C-14 and C-15), 129.1 (C-3′), 130.5 (C-4′), 131.3 (C-6′), 131.8 (C-13), 133.4 (C-12), 135.3 (C-11), 137.2 (C-1′), 145.4 (C-9), 150.2 (C-8), 152.2 (C-21), 153.5 (C-2), 162.6 (C-4); MS (*m/z*): 453.32 ($M^+ + 1$).

8-((2-(2-chlorobenzyl)-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8c**)

IR (KBr) υ_{max} (cm^{-1}): 3142, 3115 (*s*, Ar C–H_{str}), 2950 (*s*, CH_3, C–H_{str}), 1748 (*s*, cyclic C=O_{str}), 1634 (*w*, C=N_{str}), 1555 (*w*, N=N–N_{str}, tetrazole), 1200 (*s*, C–O_{str}), 746 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.22 (s, 3H, CH_3 of quinazoline), 2.44 (s, 3H, Ar–CH_3), 4.65 (s, 2H, OCH_2), 5.90 (s, 2H, N–CH_2), 7.15 (d, 1H, $J = 7.5$ Hz), 7.10-7.55 (m, 5H), 7.70 (d, 1H, $J = 7.5$ Hz), 7.80 (d, 2H, $J = 8.2$ Hz), 7.90 (d, 1H, $J = 8.5$ Hz), 8.10 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 18.6 (C-18), 25.2 (C-17), 57.3 (C-21), 70.7 (–$\underline{CH_2}$ of benzyl), 121.2 (C-10), 122.5 (C-5), 124.4 (C-6), 124.7 (C-2′), 126.3 (C-16), 127.3 (C-7), 127.5 (C-5′), 127.9 (C-14 and C-15), 129.8 (C-4′), 131.3 (C-13), 131.7 (C-3′), 132.5 (C-6′), 133.4 (C-1′), 134.6 (C-12), 135.5 (C-11), 144.2 (C-9), 148.8 (C-8), 152.2 (C-2), 158.8 (C-21), 162.5 (C-4); MS (*m/z*): 473.55 ($M^+ + 1$ for ^{35}Cl), 474.80 ($M^+ + 1$ for ^{37}Cl).

8-((1-(2-chlorobenzyl)-1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8c′**)

IR (KBr) υ_{max} (cm^{-1}): 3119 (*s*, Ar C–H_{str}), 2925 (*s*, CH_3, C–H_{str}), 1737 (*s*, cyclic C=O_{str}), 1625 (*w*, C=N_{str}), 1550 (*w*, N=N–N_{str}, tetrazole), 1205 (*s*, C–O_{str}), 740 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.25 (s, 3H, CH_3 of quinazoline), 2.35 (s, 3H, Ar–CH_3), 4.40 (s, 2H, OCH_2), 5.30 (s, 2H, N–CH_2), 7.10 (d, 1H, $J = 7.0$ Hz), 7.10–7.55 (m, 5H), 7.70 (d, 1H, $J = 7.0$ Hz), 7.84 (d, 2H, $J = 7.8$ Hz), 7.90 (d, 1H, $J = 8.5$ Hz), 8.15 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.6 (C-18), 24.2 (C-17), 51.3 (C-20), 66.7 (-$\underline{CH_2}$of benzyl), 120.8 (C-10), 122.4 (C-5), 124.5 (C-6), 124.5 (C-2′), 126.4 (C-16), 127.2 (C-7), 127.5 (C-5′), 128.3 (C-14 and C-15), 130.2 (C-4′) 131.4 (C-3′), 131.6 (C-13), 132.5 (C-6′), 132.9 (C-1′), 134.5 (C-12), 135.5 (C-11), 143.2 (C-9), 148.8 (C-8), 152.2 (C-21), 154.4 (C-2), 160.8 (C-4); MS (*m/z*): 473.50 ($M^+ + 1$ for ^{35}Cl), 474.85 ($M^+ + 1$ for ^{37}Cl).

8-((2-(3-chlorobenzyl)-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8d**)

IR (KBr) υ_{max} (cm^{-1}): 3096 (*s*, Ar C–H_{str}), 2885 (*s*, CH_3, C–H_{str}), 1712 (*s*, cyclic C=O_{str}), 1636 (*w*, C=N_{str}), 1525 (*w*, N=N–N_{str}, tetrazole), 1210 (*s*, C–O_{str}), 820 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.10 (s, 3H, CH_3 of quinazoline), 2.34 (s, 3H, Ar–CH_3), 4.53 (s, 2H, OCH_2), 5.95 (s, 2H, N–CH_2), 7.05 (d, 1H, $J = 7.5$ Hz), 7.10–7.45 (m, 4H), 7.50 (d, 1H, $J = 7.5$ Hz), 7.63 (s, 1H), 7.82 (d, 2H, $J = 7.8$ Hz), 7.91 (d, 1H, $J = 8.0$ Hz), 8.18 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 18.5 (C-18), 25.1 (C-17), 57.2 (C-20), 72.2 (–$\underline{CH_2}$ of benzyl), 120.5 (C-10), 122.4 (C-5), 124.5 (C-6), 125.2 (C-4′), 126.2 (C-16), 127.0 (C-7), 127.2 (C-6′), 128.8 (C-14 and C-15), 129.2 (C-2′), 129.8 (C-5′), 131.1 (C-13), 132.3 (C-1′), 134.6 (C-3′), 134.9 (C-12), 136.5 (C-11), 142.5 (C-9), 149.4 (C-8), 153.3 (C-2), 160.5 (C-21), 161.5 (C-4); MS (*m/z*): 473.85 ($M^+ + 1$ for ^{35}Cl), 474.95 ($M^+ + 1$ for ^{37}Cl).

8-((1-(3-chlorobenzyl)-1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8d′**)

IR (KBr) υ_{max} (cm^{-1}): 3060 (*s*, Ar C–H_{str}), 2935 (*s*, CH_3, C–H_{str}), 1702 (*s*, cyclic C=O_{str}), 1626 (*w*, C=N_{str}), 1515 (*w*, N=N–N_{str}, tetrazole), 1205 (*s*, C–O_{str}), 822 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.12 (s, 3H, CH_3 of quinazoline), 2.32 (s, 3H, Ar–CH_3), 4.52 (s, 2H, OCH_2), 5.40 (s, 2H, N–CH_2), 7.08 (d, 1H, $J = 7.5$ Hz), 7.10–7.45 (m, 4H), 7.53 (d, 1H, $J = 7.5$ Hz), 7.65 (s, 1H), 7.81(d, 2H, $J = 8.2$ Hz), 7.90 (d, 1H, $J = 8.0$ Hz), 8.10 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.5 (C-18), 24.5 (C-17), 49.2 (C-20), 68.5 (–$\underline{CH_2}$ of benzyl), 120.8 (C-10), 122.6 (C-5),

124.1 (C-6), 125.8 (C-4′), 126.8 (C-16), 127.1 (C-6′), 127.6 (C-7), 128.4 (C-14 and C-15), 129.5 (C-2′), 129.7 (C-5′), 131.4 (C-13), 132.5 (C-1′), 134.4 (C-12), 135.1 (C-3′), 136.2 (C-11), 143.5 (C-9), 148.6 (C-8), 150.0 (C-21), 152.5 (C-2), 163.4 (C-4); MS (*m/z*): 473.65 ($M^+ + 1$ for ^{35}Cl), 474.75 ($M^+ + 1$ for ^{37}Cl).

8-((2-(4-chlorobenzyl)-2H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8e**)

IR (KBr) υ_{max} (cm^{-1}): 3133 (*s*, Ar C–H_{str}), 2927 (*s*, CH_3, C–H_{str}), 1749 (*s*, cyclic C=O_{str}), 1624 (*w*, C=N_{str}), 1530 (*w*, N=N–N_{str}, tetrazole), 1195 (*s*, C–O_{str}), 846 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.14 (s, 3H, CH_3 of quinazoline), 2.45 (s, 3H, Ar–CH_3), 4.60 (s, 2H, OCH_2), 6.12 (s, 2H, N–CH_2), 7.10 (d, 1H, $J = 7.5$ Hz), 7.10–7.45 (m, 3H), 7.66 (d, 1H, $J = 7.5$ Hz), 7.70 (d, 2H, $J = 8.8$ Hz), 7.95 (d, 1H, $J = 8.0$ Hz), 8.10 (d, 2H, $J = 8.8$ Hz), 8.18 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 16.9 (C-18), 22.8 (C-17), 57.1 (C-20), 71.6 (–$\underline{CH_2}$ of benzyl), 121.4 (C-10), 122.5 (C-5), 124.5 (C-6), 126.6 (C-16), 127.6 (C-7), 128.1 (C-14 and C-15), 128.5 (C-3′ and C-5′), 130.0 (C-2′ and C-6′), 131.5 (C-4′), 132.2 (C-13), 133.5 (C-12), 134.6 (C-1′), 135.5 (C-11), 145.5 (C-9), 150.5 (C-8), 152.2 (C-2), 161.1 (C-21), 162.5 (C-4); MS (*m/z*): 473.90 ($M^+ + 1$ for ^{35}Cl), 475.10 ($M^+ + 1$ for ^{37}Cl).

8-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl) methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8e′**)

IR (KBr) υ_{max} (cm^{-1}): 3138 (*s*, Ar C–H_{str}), 2957 (*s*, CH_3, C–H_{str}), 1746 (*s*, cyclic C=O_{str}), 1645 (*w*, C=N_{str}), 1510 (*w*, N=N–N_{str}, tetrazole), 1232 (*s*, C–O_{str}), 852 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.24 (s, 3H, CH_3 of quinazoline), 2.46 (s, 3H, Ar–CH_3), 4.68 (s, 2H, OCH_2), 5.50 (s, 2H, N–CH_2), 7.10 (d, 1H, $J = 7.5$ Hz), 7.10-7.45 (m, 3H), 7.60 (d, 1H, $J = 7.5$ Hz), 7.72 (d, 2H, $J = 8.8$ Hz), 7.92 (d, 1H, $J = 8.0$ Hz), 8.05 (d, 2H, $J = 8.8$ Hz), 8.15 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.8 (C-18), 22.5 (C-17), 51.5 (C-20), 68.6 (–$\underline{CH_2}$ of benzyl), 120.8 (C-10), 122.2 (C-5), 124.5 (C-6), 126.6 (C-16), 127.5 (C-7), 128.2 (C-14 and C-15), 128.5 (C-3′ and C-5′), 130.1 (C-2′ and C-6′), 131.5 (C-4′), 131.9 (C-13), 133.8 (C-12), 134.6 (C-1′), 135.7 (C-11), 142.5 (C-9), 149.6 (C-8), 150.2 (C-21), 153.6 (C-2), 160.8 (C-4); MS (*m/z*): 473.70 ($M^+ + 1$ for ^{35}Cl), 474.45 ($M^+ + 1$ for ^{37}Cl).

8-((2-(3,4-dichlorobenzyl)-2H-tetrazol-5-yl)methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*) one (**8f**)

IR (KBr) υ_{max} (cm^{-1}): 3127 (*s*, Ar C–H_{str}), 2947 (*s*, CH_3, C–H_{str}), 1745 (*s*, cyclic C=O_{str}), 1628 (*w*, C=N_{str}), 1553 (*w*, N=N–N_{str}, tetrazole), 1215 (*s*, C–O_{str}), 846, 825 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.19 (s, 3H, CH_3 of quinazoline), 2.38 (s, 3H, Ar–CH_3), 4.70 (s, 2H, OCH_2), 5.95 (s, 2H, N–CH_2), 7.05 (d, 1H, $J = 7.0$ Hz), 7.15 (d, 1H, $J = 7.8$ Hz), 7.18-7.55 (m, 3H), 7.62 (d, 1H, $J = 7.0$ Hz), 7.78 (s, 2H), 7.95 (d, 1H, $J = 8.0$ Hz), 8.10 (d, 1H, $J = 7.8$ Hz), 8.15 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.5 (C-18), 24.2 (C-17), 55.8 (C-20), 70.5 (–$\underline{CH_2}$ of benzyl), 121.2 (C-10), 122.5 (C-5), 124.4 (C-6), 126.5 (C-16), 127.0 (C-7), 127.9 (C-14 and C-15), 128.5 (C-6′), 129.2 (C-4′), 130.0 (C-2′), 130.5 (C-5′), 130.8 (C-13), 132.5 (C-3′), 134.6 (C-12), 135.1 (C-1′), 136.5 (C-11), 145.5 (C-9), 151.6 (C-8), 153.3 (C-2), 160.0 (C-21), 162.6 (C-4); MS (*m/z*): 473.25 ($M^+ + 1$ for $^{35,35}Cl$), 474.95 ($M^+ + 1$ for $^{35,37}Cl$), 476.33 ($M^+ + 1$ for $^{37,37}Cl$).

8-((1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl)methoxy)-2-methyl-3-*o*-tolylquinazolin-4(3*H*)-one (**8f′**)

IR (KBr) υ_{max} (cm^{-1}): 3107 (*s*, Ar C–H_{str}), 2942 (*s*, CH_3, C–H_{str}), 1725 (*s*, cyclic C=O_{str}), 1625 (*w*, C=N_{str}), 1523 (*w*, N=N–N_{str}, tetrazole), 1211 (*s*, C–O_{str}), 848, 824 (*w*, Ar C–Cl); ^{1}H NMR (δ) DMSO-d_6 : 2.16 (s, 3H, CH_3 of quinazoline), 2.40 (s, 3H, Ar–CH_3), 4.52 (s, 2H, OCH_2), 5.35 (s, 2H, N–CH_2), 7.04 (d, 1H, $J = 7.0$ Hz), 7.14 (d, 1H, $J = 7.8$ Hz), 7.18-7.55 (m, 3H), 7.60 (d, 1H, $J = 7.0$ Hz), 7.75 (s, 2H), 7.95 (d, 1H, $J = 8.5$ Hz), 8.15 (d, 1H, $J = 7.8$ Hz), 8.25 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.1 (C-18), 25.2 (C-17), 50.5 (C-20), 67.5 (–$\underline{CH_2}$ of benzyl), 120.9 (C-10), 122.2 (C-5), 124.5 (C-6), 126.5 (C-16), 127.4 (C-7), 128.2 (C-6′), 128.7 (C-14 and C-15), 129.5 (C-4′), 130.2 (C-2′), 130.5 (C-5′), 131.2 (C-13), 132.5 (C-3′), 133.9 (C-12), 135.4 (C-1′), 136.3 (C-11), 144.5 (C-9), 150.2 (C-20), 151.3 (C-8), 154.0 (C-2), 161.5 (C-4); MS (*m/z*): 473.35 ($M^+ + 1$ for $^{35,35}Cl$), 474.88 ($M^+ + 1$ for $^{35,37}Cl$), 476.20 ($M^+ + 1$ for $^{37,37}Cl$).

2-methyl-8-((2-(pyridin-2-ylmethyl)-2H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**8g**)

IR (KBr) υ_{max} (cm^{-1}): 3097, 3092 (*s*, Ar C–H_{str}), 2920 (*s*, CH_3, C–H_{str}), 1744 (*s*, cyclic C=O_{str}), 1620 (*w*, C=N_{str}), 1510 (*w*, N=N–N_{str}, tetrazole), 1450 (*w*, Ar C=C_{str}), 1250 (*s*, C–O_{str}), 796, 744 (*s*, pyridine); ^{1}H NMR (δ) DMSO-d_6 : 2.19 (s, 3H, CH_3 of quinazoline), 2.50 (s, 3H, Ar–CH_3), 4.58 (s, 2H, OCH_2), 6.00 (s, 2H, N–CH_2), 7.05 (d, 1H, $J = 8.0$ Hz), 7.20–7.55 (m, 3H), 7.65 (d, 1H, $J = 8.0$ Hz), 7.90 (d, 1H, $J = 8.5$ Hz), 8.05 (t, 2H, $J = 7.7, 4.8, 1.7$ Hz), 8.10 (d, 1H, $J = 8.0$ Hz), 8.21 (d, 1H, $J = 7.8$ Hz), 8.65 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.5 (C-18), 23.5 (C-17), 57.2 (C-20), 72.2 (–$\underline{CH_2}$ of pyridin-2-yl methyl)), 121.2 (C-10), 122.4 (C-5), 122.7 (C-4′), 124.6 (C-6), 125.6 (C-5′), 126.5 (C-16), 127.5 (C-7), 128.9 (C-14 and C-15), 131.5 (C-13), 134.4 (C-12), 136.5 (C-11), 137.5

(C-6′), 143.3 (C-1′), 146.2 (C-9), 148.6 (C-3′), 150.5 (C-8), 152.5 (C-2), 160.0 (C-21), 162.5 (C-4); MS (*m*/*z*): 425.50 ($M^+ + 1$).

2-methyl-8-((1-(pyridin-2-ylmethyl)-1H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**8g′**)

IR (KBr) υ_{max} (cm^{-1}): 3079 (*s*, Ar C–H_{str}), 2938 (*s*, CH_3, C–H_{str}), 1704 (*s*, cyclic C=O_{str}), 1623 (*w*, C=N_{str}), 1528 (*w*, N=N–N_{str}, tetrazole), 1460 (*w*, Ar C=C_{str}), 1208 (*s*, C–O_{str}), 786, 742 (*s*, pyridine); ^{1}H NMR (δ) DMSO-d_6 : 2.24 (s, 3H, CH_3 of quinazoline), 2.56 (s, 3H, Ar–CH_3), 4.54 (s, 2H, OCH_2), 5.33 (s, 2H, N–CH_2), 7.02 (d, 1H, $J = 8.0$ Hz), 7.20–7.55 (m, 3H), 7.60 (d, 1H, $J = 8.0$ Hz), 7.88 (d, 1H, $J = 8.5$ Hz), 8.08 (t, 2H, $J = 7.7, 4.8, 1.3$ Hz), 8.15 (d, 1H, $J = 8.5$ Hz), 8.25 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 4.5$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.2 (C-18), 23.8 (C-17), 52.2 (C-20), 69.5 (–$\underline{CH_2}$ of pyridin-2-yl methyl), 120.9 (C-10), 122.5 (C-5), 122.7 (C-4′), 124.6 (C-6), 125.5 (C-5′), 126.5 (C-16), 127.8 (C-7), 128.2 (C-14 and C-15), 131.3 (C-13), 134.6 (C-12), 135.8 (C-11), 137.7 (C-6′), 142.5 (C-1′), 144.4 (C-9), 148.9 (C-3′), 150.0 (C-8), 152.5 (C-21), 154.2 (C-2), 161.4 (C-4); MS (*m*/*z*): 425.24 ($M^+ + 1$).

2-methyl-8-((2-(pyridin-3-ylmethyl)-2H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*) one (**8h**)

IR (KBr) υ_{max} (cm^{-1}): 3095, 3086 (*s*, Ar C–H_{str}), 2920 (*s*, CH_3, C–H_{str}), 1704 (*s*, cyclic C=O_{str}), 1635 (*w*, C=N_{str}), 1528 (*w*, N=N–N_{str}, tetrazole), 1480 (*w*, Ar C=C_{str}), 1220 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.10 (s, 3H, CH_3 of quinazoline), 2.36 (s, 3H, Ar–CH_3), 4.68 (s, 2H, OCH_2), 6.10 (s, 2H, N–CH_2), 7.05 (d, 1H, $J = 7.0$ Hz), 7.20–7.45 (m, 3H), 7.60 (d, 1H, $J = 7.0$ Hz), 7.77 (t, 1H, $J = 7.9, 4.9$ Hz), 7.90 (d, 1H, $J = 8.5$ Hz), 8.10 (d, 1H, $J = 8.0$ Hz), 8.35 (d, 1H, $J = 7.9$ Hz), 8.45 (d, 1H, $J = 4.9$ Hz), 8.75 (s, 1H); ^{13}C NMR (δ) DMSO-d_6 : 18.5 (C-18), 24.5 (C-17), 57.6 (C-20), 70.8 (–$\underline{CH_2}$ of pyridin-3-yl methyl), 121.2 (C-10), 121.8 (C-1′), 122.5 (C-5), 124.4 (C-6), 126.4 (C-5′), 127.0 (C-16), 127.5 (C-7), 129.6 (C-14 and C-15), 131.2 (C-6′), 131.8 (C-13), 135.0 (C-12), 135.8 (C-11), 145.5 (C-9), 147.6 (C-2′), 150.0 (C-4′), 152.5 (C-8), 157.4 (C-2), 160.4 (C-21), 163.6 (C-4); MS (*m*/*z*): 425.10 ($M^+ + 1$).

2-methyl-8-((1-(pyridin-3-ylmethyl)-1H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*) one (**8h′**)

IR (KBr) υ_{max} (cm^{-1}): 3108 (*s*, Ar C–H_{str}), 2926 (*s*, CH_3, C–H_{str}), 1714 (*s*, cyclic C=O_{str}), 1644 (*w*, C=N_{str}), 1521(*w*, N=N–N_{str}, tetrazole), 1485 (*w*, Ar C=C_{str}), 1195 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.20 (s, 3H, CH_3 of quinazoline), 2.35 (s, 3H, Ar–CH_3), 4.78 (s, 2H, OCH_2), 5.42 (s, 2H, N–CH_2), 7.02 (d, 1H, $J = 7.0$ Hz), 7.20-7.45 (m, 3H), 7.55 (d, 1H, $J = 7.0$ Hz), 7.75 (t, 1H, $J = 7.8, 4.9$ Hz), 7.85 (d, 1H, $J = 8.0$ Hz), 8.15 (d, 1H, $J = 8.0$ Hz), 8.30 (d, 1H, $J = 7.8$ Hz), 8.55 (d, 1H, $J = 4.8$ Hz), 8.68 (s, 1H); ^{13}C NMR (δ) DMSO-d_6 : 17.5 (C-18), 23.6 (C-17), 51.5 (C-20), 68.8 (–$\underline{CH_2}$ of pyridin-3-yl methyl), 120.8 (C-10), 121.5 (C-1′), 122.8 (C-5), 124.0 (C-5′), 124.6 (C-6), 126.2 (C-16), 127.2 (C-7), 129.7 (C-14 and C-15), 131.5 (C-6′), 132.4 (C-13), 135.0 (C-12), 135.7 (C-11), 144.5 (C-9), 146.6 (C-2′), 150.3 (C-4′), 152.2 (C-21), 152.8 (C-8), 156.6 (C-2), 162.6 (C-4); MS (*m*/*z*): 425.25 ($M^+ + 1$).

2-methyl-8-((2-(pyridin-4-ylmethyl)-2H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*) one (**8i**)

IR (KBr) υ_{max} (cm^{-1}): 3188 (*s*, Ar C–H_{str}), 2950 (*s*, CH_3, C–H_{str}), 1705 (*s*, cyclic C=O_{str}), 1640 (*w*, C=N_{str}), 1520 (*w*, N=N–N_{str}, tetrazole), 1202 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.20 (s, 3H, CH_3 of quinazoline), 2.51 (s, 3H, Ar–CH_3), 4.53 (s, 2H, OCH_2), 5.85 (s, 2H, N–CH_2), 7.10 (d, 1H, $J = 7.0$ Hz), 7.10-7.45 (m, 3H), 7.55 (d, 1H, $J = 7.0$ Hz), 7.78 (d, 2H, $J = 6.0$ Hz), 7.92 (d, 1H, $J = 8.0$ Hz), 8.15 (d, 1H, $J = 8.0$ Hz), 8.45 (d, 2H, $J = 6.0$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.3 (C-18), 24.4 (C-17), 55.5 (C-20), 73.5 (–$\underline{CH_2}$ of pyridin-4-yl methyl), 120.6 (C-2′), 121.3 (C-10), 122.5 (C-5), 124.7 (C-6), 126.6 (C-16), 127.5 (C-7), 127.8 (C-14 and C-15), 130.8 (C-13), 134.4 (C-12), 136.6 (C-11), 138.5 (C-1′), 146.5 (C-9), 148.5 (C-3′), 150.0 (C-8), 152.5 (C-2), 159.6 (C-21), 164.0 (C-4); MS (*m*/*z*): 425.11 ($M^+ + 1$).

2-methyl-8-((1-(pyridin-4-ylmethyl)-1H-tetrazol-5-yl) methoxy)-3-*o*-tolylquinazolin-4(3*H*)-one (**8i′**)

IR (KBr) υ_{max} (cm^{-1}): 3120, 3055 (*s*, Ar C–H_{str}), 2910 (*s*, CH_3, C–H_{str}), 1725 (*s*, cyclic C=O_{str}), 1635 (*w*, C=N_{str}), 1545 (*w*, N=N–N_{str}, tetrazole), 1230 (*s*, C–O_{str}); ^{1}H NMR (δ) DMSO-d_6 : 2.22 (s, 3H, CH_3 of quinazoline), 2.37 (s, 3H, Ar–CH_3), 4.59 (s, 2H, OCH_2), 5.25 (s, 2H, N–CH_2), 7.05 (d, 1H, $J = 7.5$ Hz), 7.10–7.40 (m, 3H), 7.55 (d, 1H, $J = 7.5$ Hz), 7.80 (d, 2H, $J = 6.5$ Hz), 7.90 (d, 1H, $J = 8.0$ Hz), 8.25 (d, 1H, $J = 8.0$ Hz), 8.40 (d, 2H, $J = 6.5$ Hz); ^{13}C NMR (δ) DMSO-d_6 : 17.5 (C-18), 23.4 (C-17), 50.5 (C-20), 68.6 (–$\underline{CH_2}$ of pyridin-4-yl methyl), 120.8 (C-2′), 121.5 (C-10), 122.2 (C-5), 124.0 (C-6), 125.8 (C-16), 127.0 (C-7), 127.6 (C-14 and C-15), 131.5 (C-13), 133.3 (C-12), 135.6 (C-11), 138.8 (C-1′), 145.5 (C-9), 147.7 (C-3′), 150.6 (C-8), 151.5 (C-21), 152.7 (C-2), 160.6 (C-4); MS (*m*/*z*): 425.30 ($M^+ + 1$).

Pharmacology

Albino Rat (Wistar, 150–200 g), Albino mice (Swiss, 25–30 g) were used in groups as experimental animals. The test compounds and standard drug were suspended in Tween 80 (1 %) or in a 0.5 % methyl cellulose-water

mixture and administered intraperitoneally. Animals were housed in wire-mesh cages under the laboratory conditions (26 ± 2 °C), 12–12 h light/dark. Animals were allowed to acclimatize with free access to food and water for a 24 h period before testing. All the experimental protocols were carried out with the permission of the Institutional Animal Ethics Committee (IAEC). Animals were obtained from the Central Animal House Facility (173/CPCSEA, 28 Jan., 2000), Jamia Hamdard, New Delhi, India.

Maximal electroshock test (MES)

In the MES screen, an electrical stimulus of 0.2 s in duration (50 mA in mice and 150 mA in rat at 60 Hz) is delivered via corneal electrodes primed with an electrolyte solution containing an anaesthetic agent (Krall *et al.*, 1978).

Subcutaneous pentylenetetrazole seizure test (scPTZ)

This screen utilizes a dose of pentylenetetrazole (85 mg/kg in mice and 70 mg/kg in rats) that produces clonic seizures lasting for a period of at least 5 s in 97 % (CD_{97}) of animals tested. At the anticipated time of testing, the convulsant is administered subcutaneously. All the compounds were injected intraperitoneally into mice at the dose levels of 30, 100 and 300 mg/kg, with anticonvulsant activity and neurotoxicity assessment at 0.5 and 4 h after administration.

Selected derivatives were administrated orally into rats using four animals at a fixed dose of 30 (MES test) and 50 mg/kg (scPTZ test). This screen discloses the time of onset, the approximate time of peak effect (TPE) and the duration of anticonvulsant activity. For both doses the motor impairment was studied in parallel. Rats were tested at five time periods ranging from one quarter to 4 h post substance administration (Clark *et al.*, 1984).

Neurological toxicity (NT)

Neurological toxicity induced by a compound was detected in mice using standardized rotorod test. Untreated control mice or rats, when placed on the rod, can maintain their equilibrium for a prolonged time period. The acute motor impairment can be demonstrated by the inability of the animal to maintain equilibrium for a given time (1 min) (Dunham and Miya, 1957).

Quantification studies

The quantitative determination of ED_{50} and TD_{50} values was performed at previously estimated time of peak effect after oral administration into rats. Groups of eight rats received various doses of the compound until at least three points were established in the range of 10–90 % seizure protection or minimal neurotoxicity. From the plot of the data obtained, the respective ED_{50} and TD_{50} values, 95 % confidence intervals, slope of the regression line and standard error of the slope were calculated by means of a computer program (Litchfield and Wilcoxon, 1949).

Hepatotoxicity studies

The animals were divided into groups of six, and the control group received a basal diet and vehicle. Other groups were administered the test drug in a dose of 30 mg/kg/day oral (in PEG 400 or 2 % methylcellulose) for 14 days. After the specified period, each animal was anaesthetized by anaesthetic ether, and blood was collected by cardiac puncture to assess the transaminase activity. The in vitro determination of transaminase activity was carried out according to the 2,4-dinitrophenyl hydrazine method using SPAN diagnostic reagent kits (Nydick *et al.*, 1955; Reitman and Frankel, 1957).

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References

Alhano C, Cupello A, Mainardi P, Scarrone S, Favale E (2006) Successful treatment of epilepsy with serotonin reuptake inhibitors: proposed mechanism. Neurochem Res 31:509–514

Armour DR, Congreve M, Evans M, Guntrip S, Hubbard T, Kay C, Middlemiss D et al (1996) Tetrazole NK1 receptor antagonists: the identification of an exceptionally potent orally active antiemetic compound. Bioorg Med Chem Lett 6:1015–1020

Aziza MA (1997) Synthesis and anticovulsant testing of some new 2-phenyl-6-iodo-3-substituted-4-(3*H*)-quinazolinone derivatives. Az J Pharm Sci 19:129–135

Beghi E, Roncolato M, Visona G (2004) Depression and altered quality of life in women with epilepsy of childbearing age. Epilepsia 45:64–70

Bell GS, Sander JW (2002) The epidemiology of epilepsy: the size of the problem. Seizure 11(Suppl. A):306–314

Berk M, Segal J, Janet L, Vorster M (2001) Emerging options in the treatment of bipolar disorders. Drugs 61:1407–1414

Bethel PA, Hill MS, Mahon MF, Molloy KC (1999) Reactions of organo tin tetrazoles: synthesis of functionalised poly-tetrazoles. J Chem Soc Perkin Trans 1:3507–3514

Bhaduri AP, Khanna NM, Dhar ML (1964) Potential anticonvulsants synthesis of 2,3-disubstituted-4-quinazolinones and quinazolino-4-thiones. Ind J Chem 2:159–161

Bialer M, Johannessen SI, Levyd RH, Peruccae E, Tomsonf T, White HS (2010) Progress report on new antiepileptic drugs: a summary of the Tenth Eilat Conference (EILAT X). Epilepsy Res 92:89–124

Brown TR, Holmes GL (2001) Epilepsy. N Eng J Med 344:1145–1151

Butler RN (1996) Comprehensive heterocyclic chemistry II. Pergamon Press, Oxford

Byard SJ, Herbert JM (1999) Preparation and NMR spectroscopic studies of the glucuronides of irbesartan. Tetrahedron 55:5931–5936

Cao SL, Feng YP, Jiang YY, Liu SY, Ding GY, Li RT (2005) Synthesis and in vitro antitumor activity of 4(3*H*)-quinazolinone derivatives with dithiocarbamate side chains. Bioorg Med Chem Lett 15:1915–1917

Chitra S, Paul N, Muthusubramanian S, Manisankar P, Yogeeswari P, Sriram D (2011) Synthesis of 3-heteroarylthioquinoline derivatives and their in vitro antituberculosis and cytotoxicity studies. Eur J Med Chem 46:4897–4903

Chiu AT, Duncia JV, McCall DE, Wong PC Jr, Price WA, Thoolen MJMC, Carini DJ, Johnson AL, Timmermans PBWM (1989) Nonpeptide angiotensin II receptor antagonists. III. structure–function studies. J Pharmacol Exp Ther 250:867–874

Clark CR, Wells MJM, Sansom RT, Norris GN, Dockens RC, Ravis WR (1984) Anticonvulsant activity of some 4-aminobenzamides. J Med Chem 27:779–782

Deng XQ, Wei CX, Song MX, Chai KY, Sun ZG, Quan ZS (2010) Synthesis and studies on anticonvulsant and antidepressant activities of 5-alkoxy-tetrazolo [1, 5-a]quinolines. Bull Korean Chem Soc 31:447–452

Dunham NW, Miya TA (1957) A note on a simple apparatus for detecting neurological deficit in rats and mice. J Am Pharm Asso Sci 46:208–209

El-Azab AS, ElTahir KEH (2012) Synthesis and anticonvulsant evaluation of some new 2, 3, 8-trisubstituted-4(3*H*)-quinazoline derivatives. Bioorg Med Chem Lett 22:327–333

El-Azab AS, ElTahir KEH, Attia MS (2011) Synthesis and anticonvulsant evaluation of some novel 4(3*H*)-quinazolinones. Monatsh Chem 142:837–848

El-Helby AGHA, AbdelWahab MH (2003) Design and synthesis of some new derivatives of 3*H*-quinazolin-4-one with promising anticonvulsant activity. Acta Pharma 53:127–138

Fisher R, Boas WVE, Blume W, Elger C, Genton P, Lee P, Engel J (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46:470–472

Furkawa Y, Kishimoto S, Nishikawa K, Takeda Chem Industries Ltd (1982) Hypotensive imidazole derivatives. US Patent 4 340:598

Giri RS, Thaker HM, Giordano T, Williams J, Rogers D, Sudersanam V, Vasu KK (2009) Design, synthesis and characterization of novel 2-(2, 4-disubstituted-thiazole-5-yl)-3-aryl-3*H*-quinazoline-4-one derivatives as inhibitors of NF-κB and AP-1 mediated transcription activation and as potential anti-inflammatory agents. Eur J Med Chem 44:2184–2189

Grover G, Kini SG (2006) Synthesis and evaluation of new quinazoline derivatives of nalidixic acid as potential antibacterial and antifungal agents. Eur J Med Chem 41:256–262

Gujral ML, Sareen KN, Kohli RP (1957) Evaluation of anticonvulsant activity of 2, 3-disubstituted quinazolines: a new class of anticonvulsant drugs. Ind J Med Res 45:207–211

Hauser WA, Annegers JF, Kurland LT (1991) The prevalence of epilepsy in Rochester, Minnesota. Epilepsia 32:429–445

Holland GF, Pereira J (1967) Heterocyclic tetrazoles, a new class of lipolysis inhibitors. J Med Chem 10:149–154

Holmes GL (2007) Animal model studies application to human patients. Neurology 69:S28–S32

Jatav V, Mishra P, Kashaw S, Stables JP (2008) CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1, 3, 4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones. Eur J Med Chem 43(9):1945–1954

Juby PF, Hudyma TW, Brown M (1968) Preparation and antiinflammatory properties of some 5-(2-anilinophenyl) tetrazoles. J Med Chem 11:111–117

Kadi AA, El-Azab AS, Alafeefy AM, Abdel-Hamide SG (2006) Synthesis and biological screening of some new substituted 2-mercapto-4(3*H*)quinazolinone analogues as anticonvulsant agents. Az J Pharm Sci 34:147–158

Koldobskii GI, Kharbash RB (2003) 2-Substituted and 2, 5-disubstituted tetrazoles. Russ J Org Chem 39:453–470

Krall RL, Penry JK, White BG, Kupferberg HJ, Swinyard EA (1978) Antiepileptic drug development: II. Anticonvulsant drug screening. Epilepsia 19:409–428

Kramer G (2001) Epilepsy in the elderly: some clinical and pharmacotherapeutic aspects. Epilepsia 42(Suppl. 3):55–59

Kubo K, Kohara Y, Imamiya E, Sugiura Y, Inada Y, Furukawa Y, Nishikawa K, Naka T (1993) Nonpeptide angiotensin II receptor antagonists: synthesis and biological activity of benzimidazolecarboxylic acids. J Med Chem 36:2182–2195

Kumar A, Sharma S, Bajaj AK, Sharma S, Panwar H, Singh N, Srivastava VK (2003) Some new 2, 3, 6-trisubstituted quinazolinones as potent anti-inflammatory, analgesic and COX-II inhibitors. Bioorg Med Chem 11:5293–5299

Liljebris C, Larsen SD, Ogg D, Palazuk BJ, Bleasdale JE (2002) Investigation of potential bioisosteric replacements for the carboxyl groups of peptidomimetic inhibitors of protein tyrosine phosphatase 1B: identification of a tetrazole-containing inhibitor with cellular activity. J Med Chem 45:1785–1798

Litchfield JT, Wilcoxon FA (1949) A simplified method of evaluating dose-effect experiments. J Pharmacol Exp Ther 96:99–113

Lopes Lima JM (2000) The new drugs and strategies to manage epilepsy. Curr Pharm Design 6:873–878

May BCH, Abell AD (2001) The synthesis and crystal structure of alpha-keto tetrazole-based dipeptide mimics. Tetrahedron Lett 42:5641–5644

Mohamed MS, Ibrahim MK, Alafeefy AM, Abdel-Hamide SG (2004) Synthesis of certain new 6-iodoquinazolines as potential antitubercular agents. J Applied Sci 4(2):302–307

Mohamed MS, Ibrahim MK, Alafeefy AM, Abdel-Hamide SG (2005) Synthesis of certain new 6-iodoquinazolines as potential antitubercular agents. Int J Pharmacol 1(3):261–265

Nicolai E, Cure G, Goyard J, Kirchner M, Teulonl JM, Versignyz A et al (1995) Synthesis and angiotensin II receptor antagonist activity of C-linked pyrimidine derivatives. Eur J Med Chem 30:365–375

Nydick I, Wrobelewski F, Ladue JS (1955) Evidence for increased serum glutamic oxalacetic transaminase (SGOT) activity following graded myocardial infarcts in dogs. Circulation 22:161–163

O'Neill MJ, Bond A, Ornstein PL, Ward MA, Hicks CA, Hoo K, Bleakman D, Lodge D (1998) Decahydroisoquinolines: novel competitive AMPA/kainate antagonists with neuroprotective effects in global cerebral ischaemia. Neuropharmacol 37:1211–1222

Pandeya SN, Yogeeswari P, Stables JP (2000) Synthesis and anticonvulsant activity of 4-bromophenyl substituted aryl semicarbazones. Eur J Med Chem 35:879–886

Pellicciari R, Giacomo BD, Coletta D, Natalini B, Ni MH (1999) A new synthesis of carboxyterfenadine (fexofenadine) and its bioisosteric tetrazole analogs. Farmaco 54:600–610

Perucca E (2002) Marketed new antiepileptic drugs: are they better than old-generation agents? Ther Drug Monit 24:74–80

Perucca E, French J, Bialer M (2007) Development of new antiepileptic drugs: challenges, incentives, and recent advances. Lancet Neurol 6:793–804

Peters L, Frohlich R, Boyd ASF, Kraft A (2001) Noncovalent interactions between tetrazole and an *N*,*N*′-diethyl-substituted benzamidine. J Org Chem 66:3291–3298

Porter RJ, Cereghino JJ, Gladding GD, Hessie BJ, Kupferberg HJ, Scoville B, White BG (1984) Antiepileptic drug development program. Cleve Clin Q 51:293–305

Reitman S, Frankel S (1957) A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am J Clin Pathol 28:56–58

Rogawski MA, Loscher W (2004) The neurobiology of antiepileptic drugs. Nat Rev Neurosci 5:553–564

Salimath SR, Patel R, Shah NM (1956) Synthesis of 6-halogenated 2, 3-disubstituted-4-quinazolinones III. J Ind Chem Soc 33: 140–146

Smith M, Wilcox KS, White HS (2007) Discovery of antiepileptic drugs. Neurotherapeutics 4:12–17

Spear BB (2001) Pharmacogenetics and antiepileptic drug. Epilepsia 42:31–34

Sun XY, Wei CX, Deng XQ, Sun ZG, Quan ZS (2010a) Evaluation of the anticonvulsant activity of 6-(4-chlorophenyoxy)-tetrazolo[5, 1-a]phthalazine in various experimental seizure models in mice. Pharmacol Rep 62:273–277

Sun XY, Wei CX, Deng XQ, Sun ZG, Quan ZS (2010b) Synthesis and primary anticonvulsant activity evaluation of 6-alkyoxyl-tetrazolo [5, 1-a]phthalazine derivatives. Arzneimittelforschung 60:289–292

Thirumurugan R, Sriram D, Saxena A, Stables JP, Yogeeswari P (2006) 2,4-Dimethoxyphenyl semicarbazones with anticonvulsant activity against three animal models of seizure: synthesis and pharmacological evaluation. Bioorg Med Chem 14: 3106–3112

Tiwari AK, Singh VK, Bajpai A, Shukla G, Singh S, Mishra AK (2007) Synthesis and biological properties of 4-(3*H*)-quinazolone derivatives. Eur J Med Chem 42:1234–1238

VanZyl EFA (2001) Survey of reported synthesis of methaqualone and some positional and structural isomers. Forensic Sci Int 122:142–149

Wang HJ, Wei CX, Deng XQ, Li FN, Quan ZS (2009) Synthesis and evaluation on anticonvulsant and antidepressant activities of 5-alkoxy-tetrazolo[1, 5-a]quinazolines. Arch Pharm Chem Life Sci 342:671–675

Wani MY, Bhat AR, Azam A, Choi L, Athar F (2012) Probing the antiamoebic and cytotoxicity potency of novel tetrazole and triazine derivatives. Eur J Med Chem 48:313–320

White HS (2003) Pre-clinical development of antiepileptic drugs: past, future and directions. Epilepsia 44:2–8

White HS, Woodhead JH, Wilcox KS, Stables JP, Kupferberg HJ, Wolf HH (2002) Antiepileptic drugs. Lippincott, Philadelphia, pp 43–44

Wolfe JF, Rathman TL, Sleevi MC, Campbell JA, Greenwood TD (1990) Synthesis and anticonvulsant activity of some new 2-substituted 3-aryl-4(3*H*)-quinazolinones. J Med Chem 33(1): 161–166

MDDR Database (2001) A simple search of the MDDR database (6/01) provided 173 1-alkylated and 151 2-alkylated 5-C-tetrazoles and 147 1-alkylated and 33 2-alkylated5-heterotetrazoles. http://accelrys.com/products/databases/synthesis/

Yogeeswari P, Sriram D, Thirumurugan R, Raghavendran JV, Sudhan K, Pavana RK, Stables JP (2005) Discovery of *N*-(2, 6-Dimethylphenyl)-substituted semicarbazones as anticonvulsants: hybrid pharmacophore-based design. J Med Chem 48:6202–6211