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Synthesis of Some New Substituted Quinazolin-4-*3H*-Ones as Potent Anticonvulsant Agents

Neha Garg, Trilok Chandra, S. Lata, K. K. Saxena and Ashok Kumar*

Medicinal Chemistry Division, Department of Pharmacology, LLRM Medical College, Meerut-250004 (U.P.), India

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Abstract. A new series of 3-(4-(2-(6,8-dibromo-3-(substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl) hydrazinyl)thiazol-2-yl)-2-phenylthiazolidin-4-ones were synthesized and their structures were elucidated on the basis of elemental analyses and spectroscopic studies (IR, ^{1}H-NMR). All the synthesized compounds **1-32** were screened for their anticonvulsant activity at a dose of 30 mg/kg. The compound **31** was found to be the most potent compound of this series showing 90% protection against MES.

Keywords: benzylidenoquinazolinones, thiazolylquinazolinones, thiazolidinoylquinazolinone, anticonvulsant activity, toxicity

Introduction

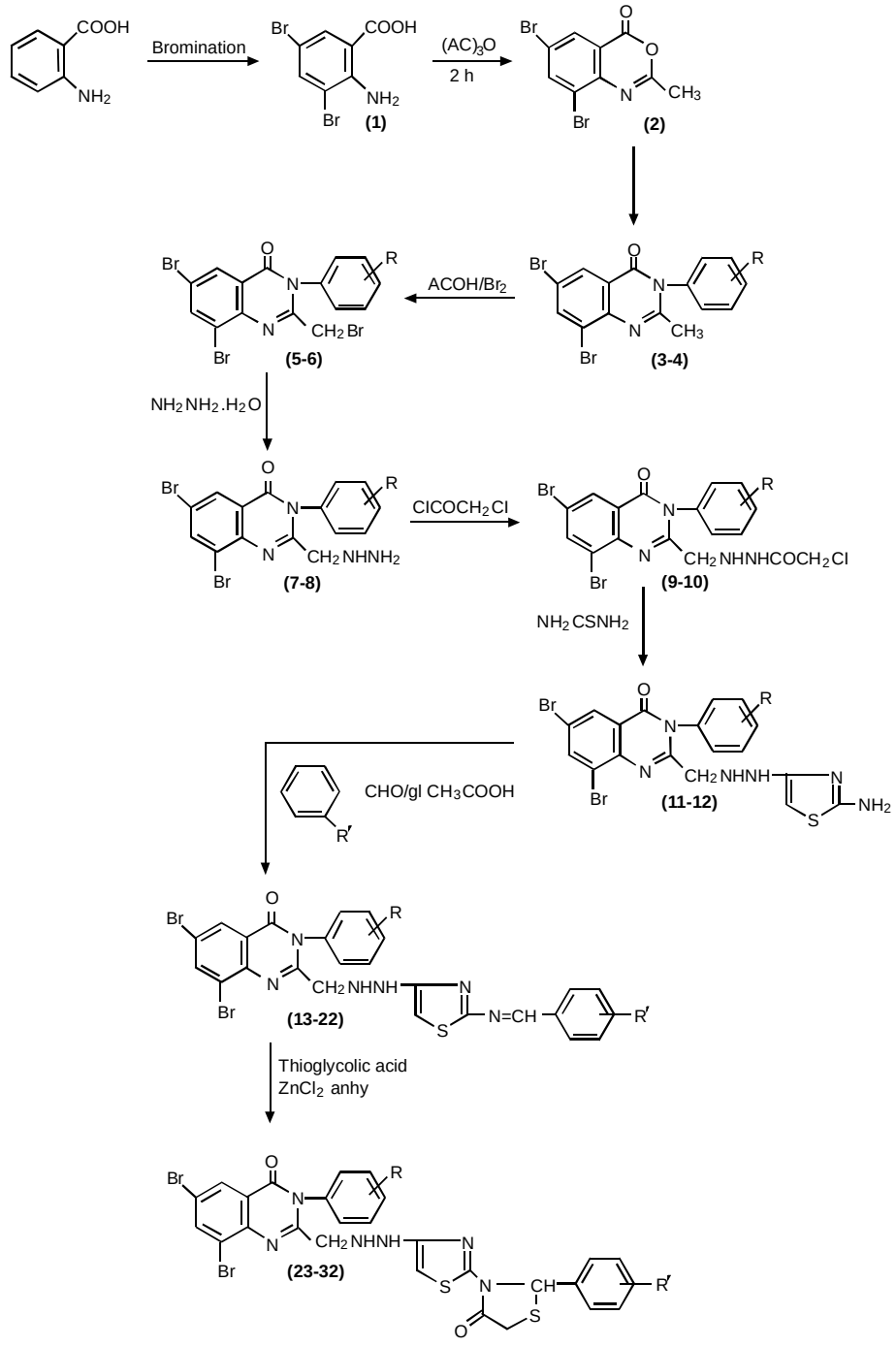
Quinazolinone derivatives have evoked considerable attention in recent years as these are endowed with a range of pharmaceutical activities. 3H-quinazoline-4-one represents a useful nucleus for preparation of some new anticonvulsant agents, since quinazolines exhibited interesting pharmacological properties like anticonvulsant activity (Georgey *et al.*, 2008; Guan *et al.*, 2007; El-Helby and Wahab, 2003; Zappala *et al.*, 2003) and anti-inflammatory activity (Alagarsamy *et al.*, 2006). Thiazoles and thiazolidinones having different heterocyclic nuclei were found to possess anticonvulsant activity (Shekarchi *et al.*, 2005; Arachana *et al.*, 2003; 2002). In the present study, a new series of 3-(4-(2-(6,8-dibromo-3-(substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl) methyl)hydrazinyl)thiazol-2-yl)-2-phenylthiazolidin-4-ones were synthesized and structures of these compounds were elucidated on the basis of elemental analyses and spectroscopic studies (IR, ^{1}H-NMR). All the synthesized compounds **1-32** were screened for their anticonvulsant activity at a dose of 30 mg/kg.

Materials and Methods

Compound **1** (3,5 dibromoanthranitic acid) synthesized according to the method of Wheeler and Oates (1910) and its reaction with acetic anhydride (Bogert and Seli, 1907) yielded compound **2** (6, 8-dibromo-2-methyl-*4H*-benzoxazin-4-one). Reaction of the latter with *P*-hydroxy amline furnished compounds 3-4. Bromination of 6, 8-dibromo-3(substitute diphenyl)-2-methylquinazolin-4 (*3H*)-ones i.e., compounds **3-4** yielded 6,8-dibromo-2-bromomethyl- 3-(substituted phenyl) quinazolin-4(*3H*)-ones i.e., compounds **5-6**. These brominated products on treatment with 99% hydrazine hydrate afforded 6,8-dibromo-2-hydrazinylmethyl-3-(substituted phenyl) quinazolin-4-(*3H*)-ones i.e., compounds **7-8**, which on reaction with chloroacetylchloride gave 2-chloro-(6,8-dibromo-3-(substituted phenyl)-4-oxo-3, 4-dihydroquinazolin-2-yl) methyl) acetohydride compounds **9-10;** these were converted to thiazole congeners i.e., 2-(2'-aminothiazol-4'-yl) hydrazinyl) methyl)-6,8-dibromo-3-(substituted phenyl) quinazolin-4(*3H*)-ones (compounds **11-12**) by the reaction of thiourea. The compounds **11-12** reacted with different aromatic aldehydes to give 2-(2'-(benzylideneamino-thiazol-4'-yl) hydrazinyl)-6, 8-dibromo-3-(substituted phenyl) quinazolin-4(*3H*)-ones (compounds **13-22**). Substituted benzylidene congeners **13-22** were cyclized on reacting with thioglycolic acid in the presence of a pinch anhydrous $ZnCl_2$ to yield 3-(4-(2-(6, 8-dibromo-3-(substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)hydrazinyl)thiazol-2-yl)-2-phenyl thiazolidin-4-ones (compounds **23-32**).

The melting points of compounds were determined in open capillaries and are uncorrected. Homogeneity of the synthesized compounds was routinely checked by thin layer chromatography on silica gel-G plates. The eluent was a mixture of different polar and nonpolar solvents in different proportions and spots were located in iodine chamber. The IR spectra were recorded on Bruker IFS-66 V FT IR (ν_{max} in cm^{-1}). The ^{1}H NMR spectra were recorded by Brucker DRX-400 FT NMR instrument using $CDCl_3$ and DMSO-d_6 as solvent and tetramethyl silane (TMS) as internal reference standard. All chemical shift (δ) values were recorded in ppm. Elemental analysis (CHN) of these newly synthesized

*Author for correspondence; E-mail: rajputak@gmail.com



Scheme

compounds were performed on a Carlo Erba-1108 elemental analyzer.

Synthesis of 3,5-dibromoanthranilic acid (1). It was prepared according to the method of Wheeler and Oates (1910). Bromine (0.8 mol) in acetic acid (20 ml) was added dropwise to the solution of anthranilic acid (0.4 mol) in absolute ethanol (60 ml).The solid product thus crystallized out was washed with hot water and dried. It was recrystallized from methanol to afford compound **1**, m.p. 219 °C (reported m.p. 218 °C).

Synthesis of 6,8-dibromo-2-methyl-*4H*-benzoxazin-4-one (2). It was prepared according to the method of Bogert and Seli (1907). A mixture of compound **1** (3,5-dibromoanthranilic acid, 0.01 mol) and acetic anhydride (0.02 mol) were refluxed

for 2-3 h with constant stirring. The excess of acetic anhydride was distilled off on cooling a solid separated out which was filtered, washed with petroleum ether (60-80 ºC) and dried to give compound **2**, m.p. 182 °C (reported m.p. 184 °C).

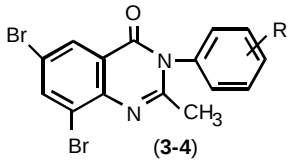
Synthesis of 6,8-dibromo 3-(*p*-hydroxyphenyl)-2-methyl-quinazolin-4(*3H*)-one (3). A mixture of compound **2** (0.2 mol) and *p*-hydroxy aniline (0.2 mol) was heated on free flame for 10-20 min in conical flask. After the disappearance of water droplets in conical flask, it was kept at room temperature. On cooling a jelly like mass was obtained which was dissolved in methanol, refluxed and poured into water. The solid thus obtained was filtered, dried and finally recrystallized from ethanol to give compound **3**, m.p. 202 °C; yield 62%; molecular formula $C_{15}H_{10}N_2O_2Br_2$; IR(KBr)ν_{max} cm^{-1}: 610 (C-Br), 1635 (C=N), 1550 (C=C of aromatic ring), 1720 (C=O of quinazolin ring), 1734 (OH): ^{1}H-NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 7.25-7.90 (m, 6H, Ar-H), 9.30 (s, 1H, Ar-OH exchangeable). Compound **4** was prepared by employing the aforementioned method. Physical and analytical data are shown in Table Ia.

Synthesis of 6,8-dibromo-2-bromomethyl-3-(*p*-hydroxyphenyl) quinazolin-4(*3H*)-one (5). Bromine (0.4 mol) in acetic acid (20 ml) was added drop wise to the solution of compound **3** (0.2 mol) in acetic acid (50 ml).The reaction mixture was poured onto crushed ice then left overnight at room temperature. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from ethanol to afford compound **5**, m.p. 214 °C; yield 70%; molecular formula $C_{15}H_9N_2O_2Br_3$; IR(KBr) ν_{max} cm^{-1}: 608 (C-Br), 1550 (C=C of aromatic ring), 1632 (C=N), 1715 (C=O of quinazolin ring), 3425 (OH); ^{1}HNMR ($CDCl_3$): δ 2.75 (s, 2H, CH_2), 7.20-7.85 (m, 6H, Ar-H), 9.86 (s, 1H, Ar-OH exchangeable). The compound **6** was prepared by employing the aforementioned method. Physical and analytical data are shown in Table Ia.

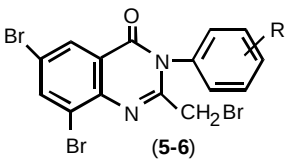
Synthesis of 6,8-dibromo-2–hydrazinylmethyl-3-(*p*-hydroxyphenyl)quinazolin-4(*3H*)-one (7). A mixture of compound **5** (0.1 mol) and hydrazine hydrate (99%) (0.2 mol) in methanol was refluxed for 10 h the excess of solvent was distilled off and the reaction mixture was poured onto ice. The solid thus obtained was filtered, washed with water, dried and recrystallized from methanol to afford compound **7**, m.p. 222 ºC; yield 64%; molecular formula $C_{15}H_{12}N_4O_2Br_2$; IR(KBr)ν_{max} cm^{-1}: 610 (C-Br),1270 (N-N), 1300 (C-N), 1550 (C=C of aromatic ring),1720 (C=O of quinazolin ring), 1620 (C=N), 3425 (OH), 3300 (NH, NH_2): ^{1}H-NMR ($CDCl_3$: δ 2.64 (s, 2H, CH_2N), 6.45 (s, 2H, -NH_2 exchangeable with D_2O), 7.22-7.82 (m, 6H, Ar-H), 9.42 (s, 1H, $NHCH_2$), 9.85 (s,1H, Ar-OH exchangeable). The compound **8** was prepared by employing the afore mentioned method and their physical and analytical data are shown in Table Ia.

Synthesis of 2-chloro-(6,8-dibromo--3-(*p*-hydroxyphenyl) -4-oxo-3, 4-dihydro quinazolin -2-yl) methyl) acetohydride (9). To the solution of compound **7** (0.01 mol) in dry benzene chloroacetylchloride (0.02 mol) was added gradually with stirring under cool condition. The reaction mixture was further stirred for another 2 h at room temperature and then refluxed for 4 h. Benzene was removed by distillation, to yield

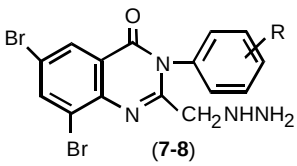
Table Ia. Physical and analytical data of compounds (**3-10**).



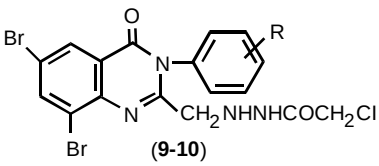
(**3-4**)



(**5-6**)



(**7-8**)



(**9-10**)

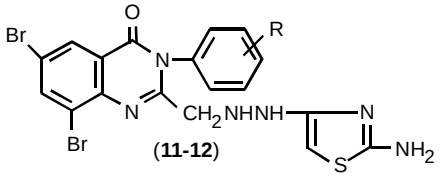
Comp. No.	R	R'	M.P. (ºC)	Yield	Recrystalization solvent	Molecular formula	Elemental analysis					
							%C		% H		%N	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
3	-4OH	-	202	62	Ethanol	$C_{15}H_{10}N_2O_2Br_2$	43.90	43.95	2.43	2.55	6.82	6.94
4	-2Cl	-	196	63	Methanol	$C_{15}H_9N_2OBr_2Cl$	42.00	42.08	2.10	2.01	6.53	6.63
5	-4OH	-	214	70	Ethanol	$C_{15}H_9N_2O_2Br_3$	36.80	36.76	1.84	1.94	5.73	5.48
6	-2Cl	-	210	72	Benzene	$C_{15}H_8N_2OBr_3Cl$	35.46	35.51	1.57	1.50	5.51	5.68
7	-4OH	-	222	64	Methanol	$C_{15}H_{12}N_4O_2Br_2$	40.90	40.84	2.72	2.80	12.72	12.52
8	-2Cl	-	220	62	Acetone	$C_{15}H_{11}N_4OBr_2Cl$	39.25	39.22	2.39	2.46	12.21	12.32
9	-4OH	-	240	70	Methanol	$C_{17}H_{13}N_4O_3Br_2Cl$	39.57	39.64	2.32	2.28	10.86	10.95
10	-2Cl	-	230	71	Ethanol	$C_{17}H_{12}N_4O_2Br_2Cl_2$	38.20	38.28	2.05	2.15	10.34	10.30

the product, which was finally recrystallized from methanol to afford compound **9**, m.p. 242 ºC ; yield 70%; molecular formula $C_{17}H_{13}N_4O_3Br_2Cl$; IR(KBr)ν_{max} cm^{-1}: 610 (C-Br), 760 (C-Cl), 1270 (N-N), 1320 (C-N), 1550 (C=C of aromatic ring), 1715 (C=O of quinazolin ring), 1618 (C=N), 3480 (OH), 3320 (N-H), 2956 (C-H aliphatic), 3055 (C-H aromatic), 3480 (OH); ^{1}H-NMR ($CDCl_3$): δ 2.60 (s, 2H, CH_2), (s, 2H,-CH_2Cl), 7.25-7.80 (m, 6H, Ar-H), 7.86 (brs, 2H, $NHNH_2$), 9.85 (s, 1H, Ar-OH exchangeable). The compound **10** was prepared by employing the afore mentioned method and their physical and analytical data are shown in Table Ia.

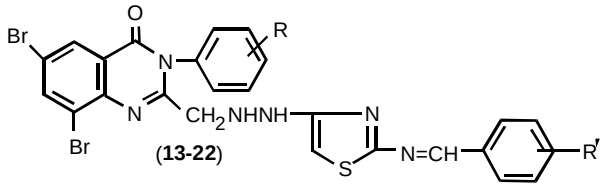
Synthesis of 2–(2'-aminothiazol-4'-yl)hydrazinyl)methyl)-6,8-dibromo-3-(*p*-hydroxy phenyl)quinazolin-4(*3H*)-one (11). A mixture of compound **9** (0.02 mol), thiourea (0.02 mol) and acetone (60 ml) was refluxed for 12 h. The completion of reaction was monitored by TLC. It was then concentrated and cooled, where upon the solid separated out. It was filtered and then recrystallized from methanol. The solid thus obtained was washed with 2% saturated sodium carbonate solution and water to liberate the base, completely dried and recrystallized from ethanol to afford compound **11**, m.p. 250ºC; yield 68%; molecular formula $C_{18}H_{14}N_6O_2SBr_2$; IR(KBr)ν_{max} cm^{-1}: 612 (C-Br), 690 (C-S-C), 1270 (N-N), 1220 (C-N), 1580 (C=C of aromatic ring), 1715 (C=O of quinazolin ring), 1616 (C=N), 3485 (OH) ,3390 (N-H); ^{1}H-NMR ($CDCl_3$): δ 2.55 (s, 2H, CH_2 NH), 6.40 (s, 2H, -NH_2 exchangeable with D_2O), 7.25-7.84 (m, 7H, Ar-H), 7.89 (bs, 2H, $NHNH_2$), 10.00 (s, 1H, Ar-OH exchangeable). The compound **12** was prepared by employing the afore mentioned method and their physical and analytical data are shown in Table Ib.

Synthesis of 2-(2'-(benzylideneamino-thiazol-4'-yl) hydrazinyl)-6,8-dibromo-3-(*p*-hydroxyphenyl) quinazolin-4 (*3H*) -one (13).To the solution of compound **11** (0.01 mole) in methanol (80 ml), benzaldehyde (0.01 mol) with few drops of glacial acetic acid was added and then reaction mixture was refluxed for 10 h; completion of the reaction was monitored by TLC. After distillation of excess of solvent; the reaction mixture was cooled, diluted with cold water and filtered. The solid thus obtained was recrystallized from ethanol to furnish compound **13**, m.p. 260 ºC; yield 58%; molecular formula $C_{25}H_{18}N_6O_2SBr_2$; IR(KBr)ν_{max} cm^{-1}: 608 (C-Br), 690 (C-S-C), 1270 (N-N), 1219 (C-N), 1575 (C=C of aromatic ring), 1717 (C=O of quinazolin ring), 1620 (C=N), 3382 (N-H), 3485 (OH); ^{1}H-NMR ($CDCl_3$): δ 2.56 (s, 2H, -CH_2NH), 7.05-7.90 (m, 12H, Ar-H), 7.85 (bs, 2H, NHNH exchangeable with D_2O), 4.62 (s, 1H, CH, Ar), 10.04 (s, 1H, Ar-OH exchangeable). The compounds **14-22** were prepared by employing the aforementioned method and their physical and analytical data are shown in Table Ib.

Table Ib. Physical and analytical data of compounds (**11-22**).



(**11-12**)



(**13-22**)

Comp. No.	R	R'	M.P. (ºC)	Yield	Recrystalization solvent	Molecular formula	Elemental analysis					
							%C		% H		%N	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
11	-4OH	-	250	68	Ethanol	$C_{18}H_{14}N_6O_2SBr_2$	40.14	40.10	2.60	2.74	15.61	15.69
12	-2Cl	-	240	74	Acetone	$C_{18}H_{13}N_6OSBr_2Cl$	38.81	38.84	2.33	2.35	15.09	15.29
13	-4OH	-H	260	58	Ethanol	$C_{25}H_{18}N_6O_2SBr_2$	47.92	47.84	2.87	2.67	13.41	13.31
14	-4OH	-4OH	270	59	Benzene	$C_{25}H_{18}N_6O_3SBr_2$	46.72	46.76	2.80	3.10	13.08	13.19
15	-4OH	-4OCH_3	265	61	Methanol	$C_{26}H_{20}N_6O_4SBr_2$	47.56	47.64	3.04	3.16	12.80	12.95
16	-4OH	-3OCH_3, -4-OH	240	73	Ethanol	$C_{26}H_{20}N_6O_4SBr_2$	46.42	46.36	2.97	2.90	12.50	12.89
17	-4OH	-4$N(CH_3)_2$	258	71	Acetone	$C_{27}H_{23}N_7O_2SBr_2$	48.43	48.33	3.43	3.54	11.26	11.25
18	-2Cl	-H	250	69	Methanol	$C_{27}H_{17}N_6OSBr_2Cl$	48.46	48.66	2.54	2.45	12.56	12.50
19	-2Cl	-4OH	255	62	Methanol	$C_{25}H_{17}N_6O_2SBr_2Cl$	45.42	45.30	2.57	2.48	12.71	12.61
20	-2Cl	-4OCH_3	272	66	Benzene	$C_{26}H_{19}N_6O_2SBr_2Cl$	46.25	46.35	2.81	2.95	12.45	12.58
21	-2Cl	-3OCH_3, -4-OH	275	63	Acetone	$C_{26}H_{19}N_6O_3SBr_2Cl$	45.18	45.38	2.75	2.87	12.16	12.00
22	-2Cl	-4$N(CH_3)_2$	262	74	Ethanol	$C_{27}H_{22}N_7OSBr_2Cl$	47.12	47.24	3.20	3.15	14.25	14.38

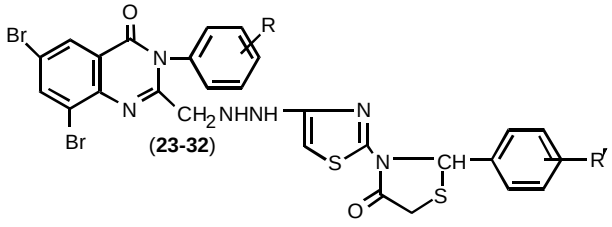
Synthesis of 3-(4-(2-(6,8-dibromo-3-(*p*-hydroxyphenyl)-4-oxo-3,4-dihydro quinazolin-2-yl) methyl) hydrazinyl) thiazol-2-yl)-2-phenylthiazolidin-4-one (23). A mixture of compound **13** (0.01 mol), thioglycolic acid (0.01 mol) and anhydrous $ZnCl_2$ (2 gm) in absolute ethanol was refluxed for 10 h. The progress and completion of reaction was checked by TLC. After refluxing, excess of solvent was distilled off and the residue was poured in cold water, filtered, dried and finally the product was recrystallized from benzene to furnish compound **23**, m.p. 268 ºC; yield 60%; molecular formula $C_{27}H_{20}N_6O_3S_2Br_2$; IR(KBr)$\nu_{max}$ cm^{-1}: 610 (C-Br), 682 (C-S-C), 1217 (C-N), 1574 (C=C of aromatic ring), 1740 (C=O of quinazolin ring), 1622 (C=N), 3370 (N-H), 3515 (OH). ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 2H,-CH_2NH), 4.05 (s, 2H, -CH_2 of thiazolidinone ring), 7.07-7.10 (m, 12H, Ar-H), 7.94 (bs, 2H, NHNH exchangeable with D_2O), 4.60 (s, 1H, CH-Ar), 10.08 (s, 1H, Ar-OH exchangeable). The compounds **24-32** were prepared by employing the afore mentioned method and their physical and analytical data are shown in Table Ic.

Anticonvulsant activity. The anticonvulsant activity was performed according the method of Toman *et al.* (1946) on Charles foster rats of either sex weighing, between 90-150 g. Rats were divided into groups of ten animals each. The rats were treated with different doses of test drugs or phenytoin sodium 30 mg/kg i.p., After one hour, they were subjected to a shock of 150 m.A by convulsiometer through ear electrodes for 2 sec and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats. The compounds were also investigated for their acute toxicity ALD_{50} in mice by following the method of Smith (1960).

Results and Discussion

Newly synthesized compounds were evaluated for anticonvulsant activity at a dose of 30 mg/kg i.p., and have shown varying degrees (10% to 90%) of anticonvulsant activity. The characteristic feature of this series is the presence of a five membered thiazole ring at second position of quinazolin moieties which was further substituted with imino arylidenyl or imino substituted arylidenyl group at the second position of five membered thiazole ring. The compounds **3-12** exhibited 10% to 50 % of anticonvulsant activity and compounds **13-22** exhibited 50% to 80% anticonvulsant activity. It was observed that compound **13** and **18** with substituted phenyl group, exhibited 50% and 60% activity, while compounds **16** and **21** with substituted 3-methoxy-4-hydroxyphenyl ring, exhibited 70% and 80% protection against seizures, respectively. Considering the potentiality of the compound **21**, it was studied in detail at three graded doses 7.5, 15, 30 mg/kg i.p., it showed equipotent activity to phenytoin sodium 80%. Compounds **14**, **15**, **17**, **19**, **20** and **22** with substituted 4-hydroxyphenyl ring compounds **14** and **19**; 4-methoxy-phenyl ring compound, **15** and **20** and 4-N, N-dimethyl-phenyl ring compounds **17** and **22** exhibited 60%, 70%, 70%, 70%, 60% and

Table Ic. Physical and analytical data of compounds (**23-32**)



(**23-32**)

Comp. No.	R	R'	M.P. (ºC)	Yield	Recrystalization solvent	Molecular formula	Elemental analysis					
							%C		% H		%N	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
23	-4OH	-H	268	60	Benzene	$C_{27}H_{20}N_6O_3S_2Br_2$	46.28	46.34	2.85	2.80	12.00	12.06
24	-4OH	-4OH	275	54	Acetone	$C_{27}H_{20}N_6O_4S_2Br_2$	45.25	45.20	2.79	2.85	11.73	11.68
25	-4OH	-4OCH_3	272	58	Methanol	$C_{28}H_{22}N_6O_4S_2Br_2$	46.02	46.12	3.01	3.08	11.50	11.55
26	-4OH	-3OCH_3, -4-OH	250	70	Methanol	$C_{28}H_{22}N_6O_5S_2Br_2$	45.04	45.09	2.94	3.05	11.26	11.22
27	-4OH	-4$N(CH_3)_2$	265	69	Ethanol	$C_{29}H_{25}N_7O_3S_2Br_2$	46.83	46.89	3.36	3.30	13.18	13.12
28	-2Cl	-H	242	65	Acetone	$C_{27}H_{19}N_6O_2S_2Br_2$ Cl	45.09	45.12	2.64	2.60	11.69	11.64
29	-2Cl	-4OH	263	60	Methanol	$C_{27}H_{19}N_6O_3S_2Br_2Cl$	44.11	44.28	2.58	2.64	11.43	11.33
30	-2Cl	-4OCH_3	280	63	Methanol	$C_{28}H_{21}N_6O_3S_2Br_2Cl$	4.88	44.66	2.80	2.84	11.22	11.28
31	-2Cl	-3OCH_3, -4-OH	265	60	Ethanol	$C_{28}H_{21}N_6O_4S_2Br_2Cl$	43.95	43.99	2.74	2.70	10.98	10.95
32	-2Cl	-4$N(CH_3)_2$	270	70	Acetone	$C_{29}H_{24}N_7O_2S_2Br_2Cl$	45.69	45.62	3.15	3.10	12.86	12.82

Table 2. Anticonvulsant activity of compound (**1-32**)

Comp. No.	R	R'	Anticonvulsant activity (SMES)[c] Dose (mg/kg i.p.)	No. of animals exhibiting convulsions	Seizure protection (%)	ALD_{50} (mg/kg i.p.)
	P.G.[a]		2 ml	10	0	
	Phenytoin sodium[b]		30	2	80***	
1						
2						
3	-4-OH	-	30	9	10	>1000
4	-2-Cl	-	30	8	20	>1000
5	-4-OH	-	30	8	20	>1000
6	-2-Cl	-	30	8	20	>1000
7	-4-OH	-	30	8	20	>1000
8	-2-Cl	-	30	7	30	>1000
9	-4-OH	-	30	7	30	>1000
10	-2-Cl	-	30	6	40**	>1000
11	-4-OH	-	30	6	40**	>1000
12	-2-Cl	-	30	5	50**	>1000
13	-4-OH	-	30	5	50**	>1000
14	-4-OH	-4-OH	30	4	60**	>1000
15	-4-OH	$-4\text{-}OCH_3$	30	3	70**	>1000
16	-4-OH	$3\text{-}OCH_3$,-4-OH	30	3	70**	>1000
17	-4-OH	$-4N(CH_3)_2$	30	4	60**	>1000
18	-2-Cl	-H	30	4	60**	>1000
19	-2-Cl	-4-OH	30	3	70**	>1000
20	-2-Cl	$-4\text{-}OCH_3$	30	3	70**	>1000
			7.5	9	10	
21	-2-Cl	$3\text{-}OCH_3$,-4-OH	15	6	40**	>1000
			30	2	80***	
22	2-Cl	$-4N(CH_3)_2$	30	3	70**	>1000
23	-4-OH	-H	30	4	60**	>1000
24	-4-OH	-4-OH	30	2	80***	>1000
25	-4-OH	$3\text{-}OCH_3$	30	3	70**	>1000
26	-4-OH	$3\text{-}OCH_3$, 4-OH	30	2	80***	>1000
27	-4-OH	$-4N(CH_3)_2$	30	3	70**	>1000
28	-2-Cl	-H	30	3	70**	>1000
29	-2-Cl	-4-OH	30	2	80***	>1000
30	-2-Cl	$-4\text{-}OCH_3$	30	3	70**	>1000
			7.5	8	20	
31	-2-Cl	$3\text{-}OCH_3$,4-OH	15	5	50**	>2000
			30	1	90***	
32	-2-Cl	$-4N(CH_3)_2$	30	2	80***	>1000

* = P < 0.05, ** = P< 0.01, *** = P < 0.001; [a] = P.G.- propylene glycol standard for control; [b] = phenytoin sodium, reference standard for anticonvu-lsant activity; [c] = supramaximal electroshock seizure pattern test

70% inhibition of seizures, respectively. Furthermore, compounds **23-32** of this series were characterized by the presence of thiazolidinone ring in addition to thiazole ring. The compounds **26** and **31** with substituted 3-methoxy-4-hydroxyphenyl ring have shown 80% and 90% activity, respectively, against seizures. Considering the potentiality of compound **31** i.e. 3-(4-(2-(6,8-dibromo-3- (*p*-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)hydrazinyl) thiazol-2-yl)-2-phenylthiazolidin-4-one, it was further studied in detail at three graded doses 7.5, 15, 30 mg/kg, i.p., for its anticonvulsant activity and showed most potent activity. The results shows better activity than the standard drug. Table 2 show the results of compounds **1-32** and standard drug phenytoin sodium. Compounds **23** and **28** with substituted phenyl ring at the second position of thiazolidinone ring showed 60% and 70% protection, respectively, whereas compounds **24** and **29** having 4-hydroxyphenyl group showed the same degree of protection i.e, 80% against MES test. Compounds having 4-methoxyphenyl ring i.e., compounds **25** and **30** have also shown remarkable protection of 70% each. Compounds **22** and **32** with substituted 4-N, N-dimethylphenyl ring exhibited 70% and 80% inhibition of seizures, respectively. The newly synthesized compounds were also tested for approximate lethal dose ALD_{50} and were found to exhibit a higher value of ALD_{50} i.e., more than 1000 mg/kg, i.p., except compound **31** which exhibited ALD_{50} of more than 2000 (maximum dose tested) thus indicating the safer nature of these compounds. It can be concluded that cyclisation of substituted imino arylidenyl compounds **13-22** into thiazolidinones **23-32** has no remarkable effect on anticonvulsant activity except compound **31** which is the most active compound of this series.

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