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Research Article

Synthesis of Newer Quinazolin-4(3H)-onyl Thiazolidinones as Potent Anticonvulsant Agents

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Abstract: 2-[3'- Aminoacetyl amino-2'-methyl-6-monosubstituted quinazolin-4'(3'H)-onyl-imino]-4-thiazolidinones 5-6 were synthesised by cyclisation of 1-[3'-Aminoacetyl-2'-methyl-6'-monosubstituted quinazolin-4'(3'H)-onyl]-thiosemicarbazide 3-4 . 7-18 were synthesised by condensation of various substituted aldehydes at the 5th position of thiazolidinones 5-6. The newly synthesised compounds showed anticonvulsant activity ranging from 50%-90% (seizure protection). Compound 18, 2-[3'-aminoacetyl amino-2'-methyl-6'-bromosubstituted quinazolin-4'(3')-onyl imino]-5-methyl-(*p*-N,N-dimethyl benzyl) -4-thiazolidinone showed maximum activity being more potent than the reference drug phenytoin sodium.

Keywords: Quinazolin-4(3H)-onyl thiazolidinone derivatives, anticonvulsant activity, mouse, rat, synthesis

INTRODUCTION

Quinazolinone [1-6] substituted by different heterocyclic moieties at 3rd position of this heterocyclic system have been reported to exhibit anticonvulsant property. Several of these three-heterocyclic substituted quinazolinones show a high level of protection against maximal electroshock [MES] induced convulsions in animal models. Moreover, thiazolidinone [7-12] derivatives substituted by different heterocyclic moieties have been reported to exhibit anticonvulsant activity. However, these compounds have not been in clinical use as they possess either less activity or more side effects.

Incorporating thiazolidinone moiety at 3rd position of quinazolinone nucleus might be thought to yield more potent anticonvulsant compounds as substituted moiety is itself anticonvulsant and substitution at 3rd position further results in protection against convulsions. Thus, the substitution by these moieties may be synergistic. The present project is therefore, aimed at synthesizing such compounds.

MATERIAL AND METHODS

Chemistry

All melting points were uncorrected. The purity of the compounds was checked by TLC on silica gel-G. Plates and spots were located by iodine. IR spectra were recorded on Beckman-Acculab-10-spectrophotometer (ν_{max} in cm^{-1}). ^{1}H-NMR spectra was recorded on a Bruker 300-FT instrument.

The compounds 3-18 (see table 5) were tested both for their anticonvulsant activity and acute toxicity. Phenytoin sodium was used as reference drug for anticonvulsant activity.

Synthesis

2-[3'- Aminoacetyl amino-2'-methyl-6-monosubstituted quinazolin-4'(3'H)-onyl-imino]-4-thiazolidinones 5-6 and 2-[3'-aminoacetyl amino-2'-methyl-6'-monosubstituted quinazolin-4'(3')-onyl-imino]-5-methyl-(substituted aryl) -4-thiazolidinones 7-18 were synthesised according to the synthetic pathway shown in scheme 1.

Reaction of ethyl chloroacetate with 2-methyl-6-monosubstituted quinazolin-4(3H)- ones yielded 3-(aminoethylethanoato)-2-methyl-6-monosubstituted quinazolin-4(3H)-ones 1-2, which on reaction with thiosemicarbazide afforded the corresponding 1-[3'-aminoacetyl-2'-methyl-6'-monosubstituted quinazolin-4'(3'H)-onyl]-thiosemicarbazide 3-4. Reaction of 3-4 with bromoacetic acid will afford 2-[3'-aminoacetylamino-2'methyl-6'-monosubstituted quinazolin- 4'(3'H)-onyl-imino]-4-thiazolidinones 5-6. When compounds 5-6 were condensed with various aromatic aldehydes , corresponding 2-[3'-aminoacetyl amino-2'-methyl-6'-monosubstituted quinazolin-4'(3')-onyl- imino]-5-methyl-(substituted aryl) -4-thiazolidinones 7-18 were formed.

Synthesis of 3- aminoethylethanoato-2-methyl-6-monosubstituted quinazolin-4(3H)-ones (1-2) (Table 1)

A mixture of 2-methyl-6-monosubstituted quinazolin-4(3H)-ones (0.1 mol) ethyl chloroacetate (0.1mol) and anhydrous K_2CO_3 (8.0 g),were refluxed

for 24 h. After refluxing, the excess of solvent was distilled off with the help of a distillation assembly.The reaction mixtures were cooled, filtered with the help of a filteration pump washed with water and recrystallised from appropriate solvents. The physical and analytical data of compounds are given in Table 1. Compound 1: 1H-NMR ($CDCl_3$) *d* 9.60(ss, 1H, $NHCH_3$), 7.90-7.25 (m, 4H, Ar-H), 4.38 (d, 2H, $NHCH_2$), 4.10 (q,2H, J=7Hz, $COOCH_2CH_3$), 2.30 (s, 3H, CH_3), 1.20(t, 3H, J=7Hz, $COOCH_2CH_3$) (ppm); IR (cm^{-1}, KBr): 3250(NH), 2840(CH_2), 1740(C=O of ester), 1550(C=C of aromatic ring).

Synthesis of 1-[3'-aminoacetyl-2'-methyl-6'-monosubstitutedquinazolin-4'(3'H)-onyl]-thiosemicarbazide(3-4)(table 2)

A solution of **3**- aminoethylethanoato-2-methyl-6-monosubstituted quinazolin-4(3H)-ones **1-2** (o.075 mol) and thiosemicarbazide (0.075 mol) in methanol (dry 50 ml) were refluxed on a steam bath for about 15 h. The excess of the solvent was distilled off with the help of distillation assembly and the viscous masses were poured into ice-cold water, filtered with the help of a filteration pum and recrystallised from appropriate solvents. The physical and analytical data of the compounds are given in Table 2. Compound **3**: ^{1}H-NMR ($CDCl_3$) *d* 9.40(brs, 1H, $NHCH_2$), 8.65(m, 4H, $NHNHCS\text{-}NH_2$), 8.15-7.10(m, 4H, Ar-H), 4.40(d, 2H, $NHCH_2$), 2.30(s, 3H,CH_3) (ppm); IR (cm^{-1}, KBr); 3400(NH, NH_2), 2853(CH_2),1710(C=O of amides), 1130(=C=S).

Synthesis of 2-[3'-aminoacetylamino-2'methyl-6'-monosubstituted quinazolin- 4'(3'H)-onyl-imino]-4-thiazolidinones (5-6) (Table 3)

Bromoacetic acid (0.01 mol) was added to 1-[3'-aminoacetyl-2'-methyl-6 -monosubstituted-quinazolin-4'(3'H)-onyl]-thiosemicarbazide**s** (0.01 mol) in methanol and the reaction mixture was refluxed for 8 h. The reaction mixture was poured into ice-cold water. The separated solid was filtered, washed with water and recrystallised from appropriate solvents. The physical and analytical data of the compounds are given in Table 3. Compound **5**: 1H-NMR ($CDCl_3$ *d* 9.45(brs, 1H, $NHCH_2$), 8.10-7.10(m, 4H, Ar-H), 4.22(d, 2H, $NHCH_2$), 2.26(s, 3H, CH_3), 9.25(ss, 1H, NHCO), 3.68(s, 2H, CH_2 of thialactam ring), 10.34(s, 1H, NH) (ppm); IR (cm^{-1}, KBr); 3410(NH), 1745(C=O of thialactam moiety), 1720(C=O of quinazolon ring), 1632(C=N), 690(C-S-C).

Synthesis of 2-[3'-aminoacetyl amino-2'-methyl-6'-monosubstituted quinazolin-4'(3')-onyl- imino]-5-methyl-(substituted aryl) -4-thiazolidinones (7-18) (Table 4)

A mixture of compounds **5-6** (2.5 mol) was condensed with various aromatic aldehydes (2.5 mol) in presence of a few drops of glacial acetic acid in methyl alcohol for 8 h. The excess of solvent was distilled off and the residue thus obtained were recrystallised from appropriate solvents. The Physical and analytical data of the compounds are given in Table 4. Compound **7**: ^{1}H-NMR ($CDCl_3$) *d* 9.40(brs, 1H, $NHCH_2$), 8.25-7.15(m, 9H, Ar-H), 4.20(d, 2H, $NHCH_2$), 2.39(s, 3H, CH_3), 9.20(ss, 1H, NHCO), 10.28(s, 1H, NH), 6.10(s, 1H, CH-Ar).

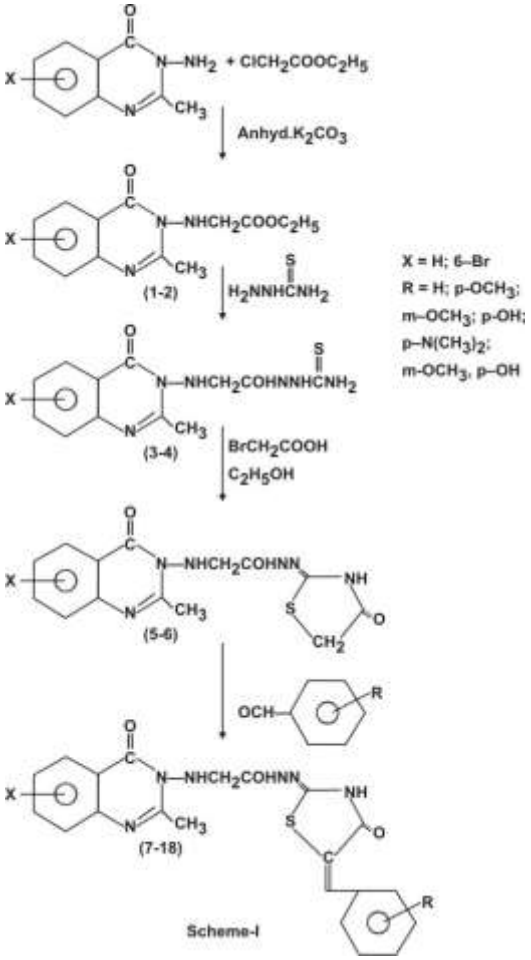

Fig-1: Synthesis Scheme-I

Pharmacology

The test compounds were suspended in propylene glycol and administered intraperitoneally (i.p.). The experiments were performed on albino rats of Charles foster of either sex of 60-90 days weighing 80-120 g and on mice 90-120 days and weighing 20-25 g. Pregnancy was excluded. A total of 60 rats and 30 mice were used in groups of 10 rats respectively 10 mice/group. The rats and mice were maintained at the following conditions: 37$\pm$ 1^0 C, 70$\pm$5 % relative humidity, 12h light/dark cycle. Food and water were freely available up to the times of tests. The study protocol was approved by the ethical committee of Lala Lajpat Rai Memorial Medical College.

Acute toxicity in mice

All the compounds were investigated for their acute toxicity (ALD_{50}) in mice by following the procedure of Smith [13].

Anticonvulsant activity

Maximal electroshock seizure (MES) test

T he MES test was performed by following the method of Tomen et al. [14]. Rats of either sex weighing 90-120 g were divided into groups of ten animals each. The test drugs and phenytoin sodium as reference drug were administered i.p. in rats. After 1 h, they were subjected to a shock of 150 mA using a convulsiometer through ear electrodes for 0.2s and the presence or absence of extensor response was noted. Animals in which the extensor response was abolished were taken as protected rats.

RESULTS

Acute toxicity in mice

All the compounds of the present series showed ALD_{50} >1000 mg/kg i.p., thus indicating a good safety margin. However, compound 18 exhibited an ALD_{50} >2000mg/kg i.p.

Anti-convulsant avtivity in rat

In MES test, out of 16 compounds, compounds 12, 14, 15, 17 and 18 were found to be most active with 80%, 80%, 80%, 80% and 90% inhibition of seizures, respectively. The results are shown in Table 5.

Table-1: Physical properties of 3-(aminoethylethanaoto)-2-methyl-6-monosubstituted quinazolin-4(3H)-ones 1-2.

Comp - ound	X	M.P . (^{0}C)	Cryst. solvent	Yield (%)	Calcd. (found) %			Molecular Formula
					C	H	N	
1	H	44	methanol	65	59.77(59.79)	5.74(5.72)	16.09(16.11)	$C_{13}H_{15}N_3O_3$
2	6-Br	203	ethanol	58	45.88(45.90)	4.11(4.09)	12.35(12.33)	$C_{13}H_{14}N_3O_3Br$

Table-2: Physical properties of 1-[3'-aminoacetyl-2'-methyl-6'-monosubstituted quinazolin-4'(3'H)-onyl]-thiosemicarbazide 3-4 .

Compoun d	X	M.P. (^{0}C)	Cryst. solvent	Yield (%)	Calcd. (found) %			Molecular Formula
					C	H	N	
3	H	84	methanol	66	47.05(47.02)	4.57(4.60)	27.45(27.46)	$C_{12}H_{14}N_6O_2S$
4	6-Br	190	methanol	70	37.40(37.38)	3.37(3.41)	21.81(21.79)	$C_{12}H_{13}N_6O_2SBr$

Table-3: Physical properties of 2-[3'-aminoacetylamino-2'methyl-6'-monosubstituted quinazolin- 4'(3'H)-onyl-imino]-4-thiazolidinones 5-6.

Comp - ound	X	M.P . (^{0}C)	Cryst. solvent	Yield (%)	Calcd. (found) %			Molecular Formula
					C	H	N	
5	H	125	ethanol	70	48.55(48.58)	4.04(4.03)	24.27(24.30)	$C_{14}H_{14}N_6O_3S$
6	6-Br	160	ethanol	80	39.52(39.57)	3.05(3.06)	19.76(19.78)	$C_{14}H_{13}N_6O_3SBr$

Table-4: physical properties of 2-[3'-aminoacetyl amino-2'-methyl-6'-monosubstituted quinazolin-4'(3')-onyl-imino]-5-methyl-(substituted aryl) -4-thiazolidinones 7-18.

com pd	X	R	M.p (^{0}C)	Cryst. solvent	Yield (%)	Calcd. (found) %			Molecular Formula
						C	H	N	
7	H	H	116	ethanol	75	58.06(58.04)	4.14(4.13)	19.35(19.33)	$C_{21}H_{18}N_6O_3S$
8	H	p-OCH_3	190	methan-ol	70	56.89(56.91)	4.31(4.28)	18.10(18.08)	$C_{22}H_{20}N_6O_4S$
9	H	m-OCH_3	175	aceto-ne	62	56.89(56.88)	4.31(4.34)	18.10(18.13)	$C_{22}H_{20}N_60_4S$
10	H	p-OH	185	ethanol	65	56.00(56.01)	4.00(4.02)	18.66(18.70)	$C_{21}H_{18}N_6O_4S$
11	H	p-N (CH_3)	205	acetone	62	57.86(57.88)	4.82(4.80)	20.54(20.53)	$C_{23}H_{23}N_7O_3S$
12	H	m-OCH_3, p-OH	220	ethanol	70	54.88(54.90)	4.36(4.39)	17.46(17.42)	$C_{22}H_{21}N_6O_5S$
13	Br	H	240	ethanol	68	49.12(49.09)	3.31(3.29)	16.37(16.35)	$C_{21}H_{17}N_6O_3SBr$
14	Br	p-OCH_3	210	toluene	60	48.61(48.59)	3.49(3.51)	15.46(15.45)	$C_{22}H_{19}N_6O_4SBr$
15	Br	m-OCH_3	180	methanol	62	48.61(48.62)	3.49(3.47)	15.46(15.42)	$C_{22}H_{19}N_6O_4SBr$
16	Br	p-OH	160	acetone	74	47.63(47.60)	3.21(3.19)	15.87(15.91)	$C_{21}H_{17}N_6O_4SBr$
17	Br	p-N (CH_3)	235	ethanol	72	49.64(49.69)	3.95(3.92)	17.62(17.60)	$C_{23}H_{22}N_7O_3SBr$
18	Br	m-OCH_3, p-OH	250	methanol	68	47.14(47.11)	3.57(3.60)	15.00(15.02)	$C_{22}H_{20}N_6O_5SBr$

Table-5: Pharmacological data of compounds (3-18)

Compounds	Acute toxicity ALD_{50} (mg/kg i.p.)	Anticonvusant activity	
		Dose (mg/kg i.p.)	% Inhibition of seizures
3	>1000	100	50**
4	>1000	100	60**
5	>1000	100	60**
6	>1000	100	70**
7	>1000	100	70**
8	>1000	100	70**
9	>1000	100	70**
10	>1000	100	60**
11	>1000	100	70**
12	>1000	25 50 100	30 40** 80***
13	>1000	100	70**
14	>1000	100	80***
15	>1000	100	80***
16	>1000	100	70**
17	>1000	100	80***
18	>2000	25 50 100	30 50* 90***
Phenytoin sodium		30	80***
Propylene glycol		20ml	0

*p < 0.05, **p < 0.01, ***p < o.001.

DISCUSSION

All the newly synthesised compounds were studied for their anticonvulsant activity. The Compounds were screened for their anticonvulsant activity against maximal electroshock induced seizures at a dose of 100mg/kg i.p., and were found to exhibit substantive anticonvulsant activity ranging from 50% to 90%. The characteristic feature of this series is the incorporation of quinazolinone and thiazolidinone moieties into a single molecular framework. While evaluating the anticonvulsant activity, it was observed that compounds having bromo group at 6^{th} position of quinazolinonyl moiety were found to be more potent than those without bromo group i.e. compounds 4 and 6 having 60% and 70% activity more active than compounds 3 and 5 with 50% and 60% inhibition of seizures. Further, the next step compounds substituted with different aldehydes at the 5^{th} position of the thiazolidinone ring also elicited remarkable anticonvulsant activity upto 90%. All the compounds 7-18 of this step exhibited potent anticonvulsant activity 70% to 90%. However compound 18 (having *p*-N, N-dimethylbenzyl group at the 5^{th} position of thiazolidinonyl moiety) have shown most potent activity of 90% against MES test which is more potent than standard drug phenytoin sodium (8-0%) and hence it was studied at three graded doses of 25mg/kg i.p., 50mg/kg i.p., 100mg/kg i.p. and showed 30%, 50%, 90% inhibition of seizures respectively. The newly synthesised 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 18 which exhibited ALD_{50} of more than 2000 mg/kg i.p. (maximum dose tested) thus indicating the safer nature of these compounds.

REFERENCES

1. Zayed, M. F. (2014). New fluorinated quinazolinone derivatives as anticonvulsant agents. *Journal of Taibah University Medical Sciences*, *9*(2), 104-109.
2. Kadi, A. A., El-Azab, A. S., Alafeefy, A. M., & Abdel-Hamide, S. G. (2009). Synthesis and biological screening of some new substituted 2-Mercapto-4-(3H)-quinazolinone analogs as anticonvulsant agents.
3. Saravanan, G., Alagarsamy, V., & Prakash, C. R. (2012). Design, synthesis and anticonvulsant activities of novel 1-(substituted/unsubstituted benzylidene)-4-(4-(6, 8-dibromo-2-(methyl/phenyl)-4-oxoquinazolin-3 (4H)-yl) phenyl) semicarbazide derivatives. *Bioorganic & medicinal chemistry letters*, *22*(9), 3072-3078.
4. El-Azab, A. S., Abdel-Hamide, S. G., Sayed-Ahmed, M. M., Hassan, G. S., El-Hadiyah, T. M., Al-Shabanah, O. A., ... & El-Subbagh, H. I. (2013). Novel 4 (3H)-quinazolinone analogs: synthesis and

anticonvulsant activity. *Medicinal Chemistry Research*, *22*(6), 2815-2827.

5. Ilangovan, P., Ganguly, S., Pandi, V., & Stables, J. P. (2010). Design and synthesis of novel quinazolinone derivatives as broad spectrum anticonvulsants. *Der Pharmacia Lettre*, *2*(1), 13-21.
6. El-Helby, A. G., & Wahab, M. H. (2003). Design and synthesis of some new derivatives of 3H-quinazolin-4-one with promising anticonvulsant activity. *Acta pharmaceutica (Zagreb, Croatia)*, *53*(2), 127-138.
7. Shiradkar, M. R., Ghodake, M., Bothara, K. G., Bhandari, S. V., Nikalje, A., Akula, K. C., ... & Burangeb, P. J. (2007). Synthesis and anticonvulsant activity of clubbed thiazolidinone–barbituric acid and thiazolidinone–triazole derivatives. *Arkivoc*, *14*, 58-74.
8. Biradar, J. S., & Manjunath, S. Y. (2004). Synthesis and biological activities of novel 2-(5'-substituted-3'-phenylindole-2'-yl)-1, 3, 4-oxadiazino [5, 6-b] indole and 3-(5'-substituted-3'-phenylindole-2'-amido) spiro-(indol-3, 2-thiazolidine)-2, 4-diones. *Indian journal of chemistry. Sect. B: Organic chemistry, including medical chemistry*, *43*(2), 389-392.
9. Bhaumik, A., Chandra, M. A. Saha, S., Mastanaiah, J., Visalakshi, T. (2014). Synthesis, characterization and evaluation of anticonvulsant activity of some novel 4-thiazolidinone derivatives. Sch. Acad. J. Pharm, 3,128-132.
10. Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & medicinal chemistry*, *20*(11), 3378-3395.
11. Ergenc, N., & Capan, G. (1994). Synthesis and anticonvulsant activity of new 4-thiazolidone and 4-thiazoline derivatives. *Farmaco (Societa chimica italiana: 1989)*, *49*(6), 449-451.
12. Agarwal, A., Lata, S., Saxena, K. K., Srivastava, V. K., & Kumar, A. (2006). Synthesis and anticonvulsant activity of some potential thiazolidinonyl 2-oxo/thiobarbituric acids. *European journal of medicinal chemistry*, *41*(10), 1223-1229.
13. Smith, W. G. (1961). 1 Pharmacological Screening Tests. *Progress in medicinal chemistry*, *1*, 1-33.
14. Toman, J. E., Swinyard, E. A., & Goodman, L. S. (1946). Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. *Journal of neurophysiology*, *9*(3), 231-239.