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Synthesis and biological evaluation of some new 3-[2′-methyl-6′-monosubstituted quinazolinon-4′-(3′H)-onyl]-2-substituted aryl-4-thiazolidinones as anticonvulsant agents

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Abstract : A new series of thiazolidin-4-one derivatives were synthesised by reaction of 3-amino-2-methyl-6-monosubstituted quinazolin-4(3H)-ones (1a-1b) with various substituted aldehydes and thioglycolic acid in presence of acetic acid in toluene. The structures of these compounds have been established by elemental (C,H,N) and spectral (IR, H-NMR, and Mass) analysis. The synthesised compounds were screened in vivo ,for their acute toxicity and anticonvulsant activity in MES and PTZ models. Almost all compounds have shown promising anticonvulsant activity. Compound 3k was the most potent compound of this series.

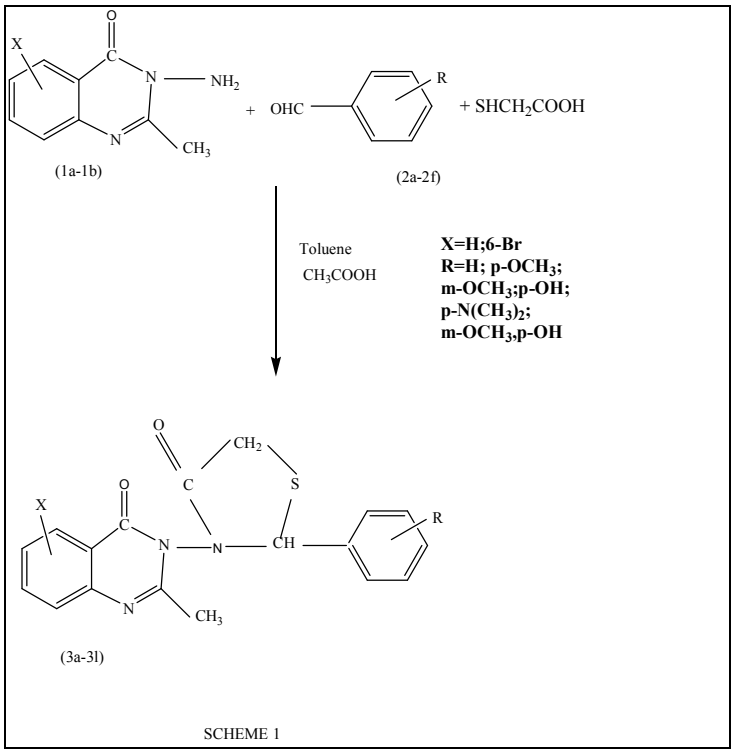
Key words : Quinazolinonyl-4-thiazolidinones, anticonvulsant activity, acute toxicity.

Introduction :

Sulphur containing heterocycles have been under investigation for a long time because of their medicinal properties (1). Among these type of molecules, 4- thiazolidinones have been shown to have various important biological activities especially anticonvulsant (2-6). In the same way quinazolinone is an another nitrogen containing heterocyclic compound and belongs to the privileged structure in modern medicinal chemistry. It is also interesting to note from chemical literature that quinazolinone derivatives were also found to possess wide spectrum of anticonvulsant activity (7-12). The aforementioned compounds have inspired us to attach substituted quinazolinone to the 4- thiazolidinone and the combination of two privileged structures in one molecule leads to drug like molecule which possess better anticonvulsant activity with lower toxicity.

Chemistry :

The structures of the compounds is depicted in scheme– 1. 3-Amino-2-methyl-6-monosubstituted quinazolin-4(3H)-ones (1a-1b) were treated with various substituted aldehydes and thioglycolic acid in presence of acetic acid in toluene to afford compounds (3a-3l).



SCHEME 1

Pharmacological Activities

Anticonvulsant activity

Maximum electroshock seizure (MES) test

This test was performed according to the method of Tomen et al (13). The group of ten rats were treated with test drugs (50mg/kg i.p.) / phenytoin sodium (30mg/kg i.p.). After 1h they were subjected to a shock of 150 mA by convulsiometer through ear electrodes for 0.2s and the presence or absence of extensor response was noted. Animals in which extensor response was abolished were taken as protected rats.

Pentylenetetrazole (PTZ) induced test

This test was performed by following the method oh Fischer (14) .The rats were injectewd with pentylenetetrazole in dose of 70mg/kg subcutaneously in scruff of neck. After 2-4 min. Of PTZ injection animals developed sequence of excitement, myclonic jerks, clonic seizures, one or more maximum tonic seizures. Animals exihibiting these seizure pattern were selected. Standard drug used in this model was sodium valproate (80mg/kg i.p.) and was injected 60 min. prior to PTZ challenge.

All the newly synthesised compounds were studied for their anticonvulsant activity at a dose of 50mg/kg i.p. in maximal electroshock and pentylenetetrazole induced seizures respectively. All the newly synthesised compounds have shown anticonvulsant activity in both the models (ranging from 50-90% and 40-80% in MES and PTZ models respectively). The anticonvulsant activity of all the compounds are reported in Table 2. Compound 5d was found to possess potent anticonvulsant activity it was studied three graded doses (12.5, 25and50mg/kg i. P.).

Table 2: Pharmacological data of compounds (3a- 3e), (4a-4e) and (5a-5e)

Compounds	Acute toxicity ALD_{50} (mg/kg i.p.)	Anticonvusant activity		
		Dose (mg/kg i.p.)	MES	PTZ
3a	>1000	50	60^{**}	60^{**}
3b	>1000	50	70^{**}	60^{**}
3c	>1000	50	70^{**}	70^{**}
3d	>1000	50	80^{***}	70^{**}

3e	>1000	50	80***	80***
3f	>1000	50	70**	80***
3g	>1000	50	60***	70**
3h	>1000	50	80***	70**
3i	>1000	50	80***	80***
3j	>1000	50	70**	60**
3k	>1000	50 25 12.5	90*** 60** 30	80*** 40 30
3i	>1000	50	80***	70**
Phenytoin sodium		30	80***	
Sodium Valproate	>1000	80		80***
Propylene glycol		20ml	0	0
*p < 0.05, **p < 0.01, ***p < o.001.				

Acute toxicity study

The compounds were investigated for their ALD_{50} which was estimated by following the method of Smith (15).

Experimental

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H. N, were within + 0.05 % of the theoretical value. IR spectra (KBr) are recorded on Bachmann Acculab-spectrophotometer.[1] H NMR spectra were recorded by Bruker WM 400 FT instrument using $CDCI_3$ as solvent and tetramethylsilicane (TMS) as internal reference standard . All chemical shift (d) are in ppm. The purities of the compounds were checked by thin layer chromatography (TLC) on silica gel-G plates of 0.5 mm thickness. The elemental analysis of the compounds were performed on Heracus Carlo Erba 1108 analyser.

Preparation of 3-[2'-methyl-6'-monosubstituted quinazolinon-4'-(3'H)-onyl]-2-substituted aryl-4-thiazolidinones (3a-3l) :

The starting compounds 3-amino-2-methyl-6-monosubstituted quinazolin-4(3H)-ones (1a-1b) were prepared by literature methao (16) .A mixture of corresponding 3-amino-2-methyl-6-mono -substituted quinazolinon-4(3H)-ones (1a-1b) (0.1 mol) and acetic acid heated(10 drops) in toluene (30 ml) was heated at 110^0C witha Dean- Stark trap for 3h. Afterward the thioglycolic acid (0.2mol) was added and the mixture was washed with a standard solution of $NaHCO_3$ (90 ml), driedwith $MgSO_4$ and concentrated to give the products. When necessary compounds were washed with a hot solution of hexane : ethyl acetate (9:1) and recrystallised with appropriate solvents to furnish the pure products.

3-[2'-methyl- quinazolinon-4'-(3'H)-onyl]-2-benzyl-4-thiazolidinones as anticonvulsant agents (3a) :

Yield 56% ; Mp 188^0C ; IR (KBr , cm^{-1}) : 2900 (CH_2), 1750 (C=O of thiolactam moiety), 1720 (C=O of quinazolinone ring), 1635 (C=N), 690 (C-S-C) ; ^{1} H-NMR ($CDCL_3$) : d 8.25-7.15 (m, 9H,Ar-H), 6.10 (s,1H, CH-Ar), 3.65 (s, 2H, CH_2 of thialactam moiety), 2.39 (s, 3H,CH_3), (ppm) ; MS : $[M]^+$ M/Z 337.

Various other compounds (3b-3l) were synthesised similarly. Their physical and analytical data are given in table 1.

Table 1: Physical and analytical data of compounds (3a-3e), (4a-4e) and (5a-5e)

Compd.	X	R	M.P. (^{0}C)	Yield (%)	Recryst. solvent	Mol.For. (MolWt)	Elemental Analysis (%)		
							C (calcd ; found)	H (calcd; Found)	N (calcd; found)
3a	H	H	188	56	methanol	$C_{18}H_{15}N_3O_2S$ (337)	64.09 ; 64.11	4.45 ; 4.48	12.46 ; 12.50
3b	H	p-OCH_3	192	61	acetone	$C_{19}H_{17}N_3O_3S$ (367)	61.12 ; 61.09	4.63 ; 4.60	11.44 ; 11.48
3c	H	m-OCH_3	175	62	ethanol	$C_{19}H_{17}N_3O_3S$ (367)	61.12 ; 61.13	4.63 ; 4.65	11.44 ; 11.41
3d	H	p-OH	185	59	benzene	$C_{18}H_{15}N_3O_3S$ (353)	61.18 ; 61.21	4.81 ; 4.77	11.89 ; 11.92
3e	H	p-$N(CH_3)_2$	201	58	methanol	$C_{20}H_{20}N_4O_2S$ (380)	63.15 ; 63.18	5.26 ; 5.28	14.73 ; 14.69
3f	H	m-OCH_3, p-OH	210	60	ethanol	$C_{19}H_{17}N_3O_4S$ (383)	59.53 ; 59.55	4.43 ; 4.45	10.96 ; 10.93
3g	Br	H	187	62	methanol	$C_{18}H_{14}N_3O_2S$ Br (416)	51.92 ; 51.89	3.36 ; 3.32	10.09 ; 10.11
3h	Br	p-OCH_3	204	65	benzene	$C_{19}H_{16}N_3O_3S$ Br (446)	51.12 ; 51.15	3.58 ; 3.60	9.41 ; 9.38
3i	Br	m-OCH_3	180	56	methanol	$C_{19}H_{16}N_3O_3S$ Br (446)	51.12 ; 51.50	3.58 ; 3.61	9.41 ; 9.44
3j	Br	p-OH	195	59	ethanol	$C_{18}H_{14}N_3O_3S$ Br (432)	50.00 ; 50.03	3.24 ; 3.22	9.72 ; 9.75
3K	Br	p-$N(CH_3)_2$	210	57	ethanol	$C_{20}H_{19}N_4O_2S$ Br (459)	52.28 ; 52.31	4.13 ; 4.11	12.20 ; 12.18
3i	Br	m-OCH_3, p-OH	215	56	acetone	$C_{19}H_{16}N_3O_4S$ Br (462)	49.35 ; 49.33	3.46 ; 3.42	9.09 ; 9.11

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