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Synthesis and Anticonvulsant activity of Thiazolidinone derivatives

Velmurugan. V* ,Leelavathi. N, Kalvikkarasi S,

Shanmuga Priya S, Vijey Aanandhi M.

**School Of Pharmaceutical Sciences, VISTAS,
Department of pharmaceutical chemistry, Vels University, Chennai,
Tamilnadu-600117,India.**

Corres.author: muruganvel75 @yahoo.co.in

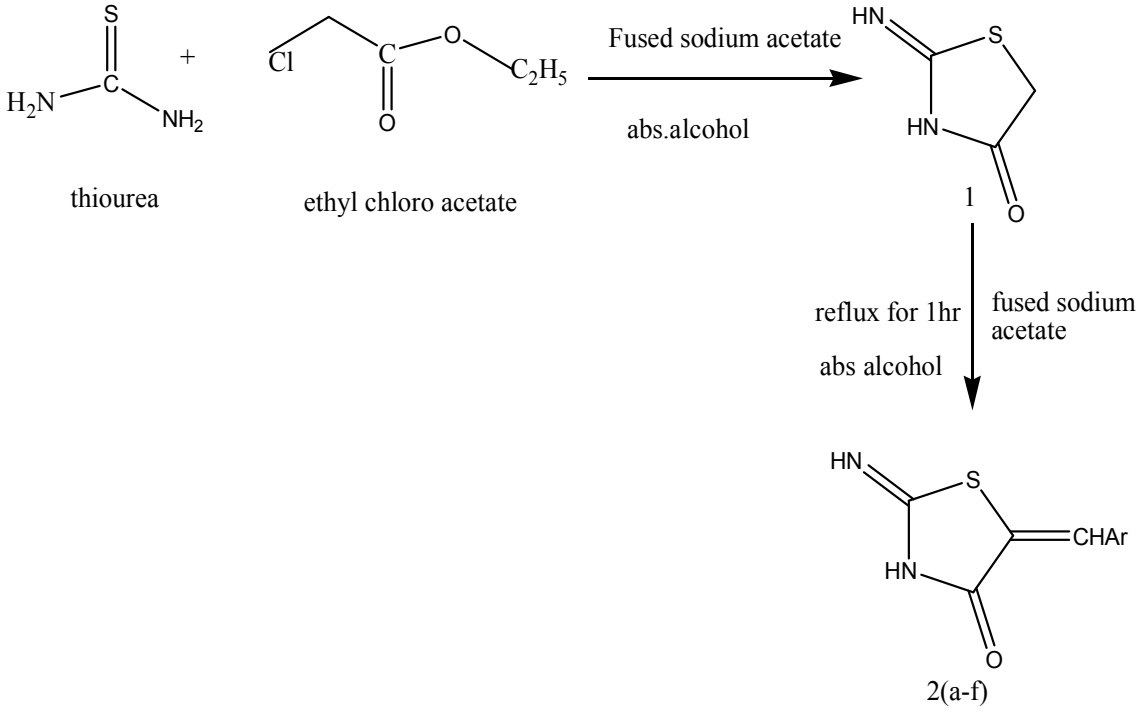
Abstract: The present study was undertaken to investigate the anticonvulsant activity of thiazolidinone derivatives using maximal electroshock-induced seizure (MES) in mice.Thiazolidinone derivatives were synthesized from thiourea. Compounds 2a to 2f were synthesized and characterized TLC, elemental analysis, IR and ^{1}H.NMR spectroscopy. The pharmacological effects were noted for myoclonic flexion, extension, clonus, stupor and mortality. Similarly for standard values were noted. Mice were divided to six groups. Suspensions of compounds/standard (100mg/kg) in 2% CMC in saline was administered i.p. the untreated group is administered with vehicle. Drop of 0.9% saline is installed in each eye group prior to application of electrodes. Mice was subjected to shock and failure to extended limbs to an angle greater than 90º is defined as protection All the compounds were evaluated for their anticonvulsant activity by maximal electroshock seizure (MES) method.
Keywords: Thiazolidinone, Anticonvulsant, maximal electroshock.

Introduction[1-3]

Thiazole is structurally related to thiophene, thiazole was first described by Hantzcs and Weber in 1887. Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. It gives out different derivatives with all different types of biological activities**.** Thiazolidinones in the presence of various reagents undergo different types of reactions to yield other heterocyclic compounds. Eg. Thiazole, benzimidazole, thiopyrano-thiazolone, benzodiazepine, triazoles, benzothiophenes. Thiazolidinone derivatives are prepared by reacting thiourea with ethyl chloroacetate in the presence of absolute alcohol and fused sodium acetate and the obtained product was treated with aromatic Aldehydes in the presence of suitable agents.

Literature review reveals that thiazolidinone derivatives exhibit diverse pharmacological activities like anti-inflammatory, analgesic, antiviral, antimicrobial, antimycobacterial, anti-fungal activities. Based on the above observation it is worthwhile to prepare newer compounds of thiazolidinone derivatives for their anticonvulsant activity. A convulsant is a drug which induces convulsions and for epileptic seizures the opposite if an anti convulsant. These drugs generally act as stimulants at low doses. Most convulsants are antagonists at either GABA or glycine receptors or ionotropic glutamine receptors agonists. Some drugs may cause convulsions as a side effect at high doses. In view of the varied biological and pharmacological application we have synthesized some new thiazolidinone derivatives (2a-2f).

Scheme



Experimental[1-15]

Melting points were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer using KBr disc method. ^{1}HNMR spectra were recorded on ^{1}H FT-NMR spectrometer in DMSO. The compounds were analyzed for elemental analysis and the percentages of elements were found to be very near that of the calculated values. Physical data were recorded in table-1 and spectral data in table-2.

Synthesis of 2-imino-1,3-thiazolan-4-one(1)

The thiourea (1m mol) was dissolved in 25ml absolute alcohol and fused sodium acetate (1m mol) and ethyl chloroacetate was added to the above mixture and refluxed for an hour. The reaction mixture was transferred into a beaker and cooled in an ice bath. The obtained precipitate was filtered, washed and dried. The product was recrystallised.

Synthesis of 2-imino-5-(Z)-arylmethylidene-1, 3-thiazolan-4-one (2a-2f)

A mixture of aromatic aldehyde (1m mol), 2-imino-1,3-thiazolan-4-one(1m mol) was dissolved in 15ml absolute alcohol and fused sodium acetate (1m mol) was added and refluxed for an hour. The reaction mixture was transferred into a beaker and cooled in an ice bath. The precipitate obtained was filtered, washed and dried. The product was recrystallised.

Anti convulsant activity:

All the animal experiment protocols of this project are approved by the Institutional Animal Ethics Committee (XII/VELS/PCHEM/43/2000/ CPCSEA/ IAEC/11.03.11) of School of pharmaceutical sciences, Vels University. Chennai, Tamil Nadu. India.

Table No.1: Physical parameters and elemental analysis of synthesized compounds

Compound	Mol. Formula	Mol.wt	M.P°C	Rf	Yield%	Elemental analysis(calculated)		
						%C	%H	%N
2a	$C_{10}H_9N_3O_3S$	251. 26	139-143	0.5	75	47.8	3.6	16.73
2b	$C_{10}H_9BrN_2OS$	285.16	128-130	0.32	82	42.11	3.18	9.83
2c	$C_{10}H_{10}N_2O_2S$	222.26	172-175	0.53	68	54.04	4.54	12.61
2d	$C_{10}H_{10}N_2O_2S$	222.26	164-168	0.66	77	54.04	4.54	12.61
2e	$C_{10}H_9ClN_2OS$	240.71	162-165	0.72	65	49.9	3.77	11.65
2f	$C_{12}H_{12}N_2OS$	232.30	170-175	0.37	64	62.05	5.21	12.07

MES test:

The synthesized compounds were subjected to anticonvulsant activity by maximal electroshock method. The pharmacological effects were noted for myoclonic flexion, extension, clonus, stupor and mortality. Similarly for standard values were noted. Mice will be divided into different groups with 6 in each group. Suspensions of compounds/std (100mg/kg) in 2%CMC in saline will be administered i.p. The untreated group is administered with the vehicle. Drop of 0.9%saline is installed in each eye prior to application of electrodes. Mice will be subjected to shock and failure to extend limbs to an angle greater than 90˚is defined as protection. The results were given in (table-3).

Results and Discussion

MES induced tonic seizures can be prevented either by drugs that inhibit voltage dependant Na+ channels such as Phenytoin, Valproate, Felbamate and Lamotrigine or by drugs that block glutaminergic excitation mediated by the n-methyl-D-aspartate (NMDA) receptor, such as Felbmate. The thiazolidinone derivatives were synthesized and screened for anti convulsant activity. All the synthesized compounds were characterized by TLC, elemental analysis, melting point, IR and ^{1}H NMR. Analysis indicated by the symbols of the elements is very close to the theoretical values. The compounds were evaluated for their anticonvulsant activity by maximal electroshock method. Some of the compounds showed more activity than the standard and some are equally active to standard drug Phenytoin.

The IUPAC names of the synthesized compounds were-

2a-5-(2-nitrobenzyl)-2-iminothiazolidin-4-one
2b-5-(4-bromobenzyl)-2-iminothiazolidin-4-one
2c-5-(2-hydroxybenzyl)-2-iminothiazolidin-4-one
2d-2-imino-5-(phenoxymethyl)thiazolidin-4-one
2e-5-(4-chlorobenzyl)-2-iminothiazolidin-4-one
2f-5-cinnamyl-2-iminothiazolidin-4-one.

Table No.2: Spectral analysis of synthesised compounds

Compound	IR(KBr) (cm^{-1})	^{1}H NMR(DMSO)δ in ppm
2a	2922,1704,1620,1574,1532,1347, 1271,1135,1045,871	1.8(s,H),3.34(d,2H),3.86(s,H),7.34(t,4H),8(s,H)
2b	3346,2256,1944,1696,1614,1473,1411, 1211,1085,884,832,575541,525	1.5(s,H),2.5(d,2H),3.59(d,2H),7.01(d,4H)
2c	3382,3180,3065,2682,2254,1620,1500, 1461,1413,1134,816	3.5(d,2H),6.9(d,4H),8(s,H)
2d	2760,2272,1954,1836,1655,1193,888,839,695	8(s,H),7.3(t,5H)6.4(d,2H),3.5(s,H),2.9(d,2H)
2e	3179,2921,2254,1697,1620,1576,1501,1414, 1167,1134,1091,830,762,700,641	8(s,H),7.0(d,4H)6.4(d,2H),3.8(s,H),3.5(d,2H)
2f	1659,1623,1576,1451,1337,1307, 1187,1128,1048,816,749,688	8(s,H),6.7(t,5H)4.2(d,2H),3.9(s,H)

Table No.3: Anticonvulsant activity of synthesized compounds by MES method

S.No	Compounds	Flexion in sec	Extension in sec	Clonus in sec	Stupor in sec	Mortality (%)
1	2a	3±0.2	8±0.5***	22±0.6***	25±0.4***	0
2	2b	3±0.4	7±0.4***	19±0.4***	23±0.5***	0
3	2c	2±0.5	8±0.2***	23±0.3*	20±0.2***	0
4	2d	3±0.3	9±0.4***	22±0.5***	26±0.4***	0
5	2e	2±0.2	7±0.3***	18±0.2***	28±0.3***	0
6	2f	3±0.3	6±0.4***	23±0.4*	31±0.3^{ns}	0
7	Control	3±0.2	18±0.6	25±0.4	32±0.7	0
8	Phenytoin	4±0.3	12±0.3***	24±0.6^{ns}	30±0.4*	0

All the values are expressed as mean±SEM (n=6), $^{*}p<0.05$, $^{***}p<0.001$vs control
(One-way ANOVA followed by Dunnett's test)

The anti convulsant activities of all the synthesized compounds were screened by MES method. The results are tabulated in table 3 and were given as mean± SEM values. The mean ± values of all the synthesized compounds were significant when compared to mean ± SEM of control. The SEM values were calculated by one way ANNOVA method followed by Dunnet multiple comparison test using a computer program. Generally, any compound which reduces or abolishes the extension stage of convulsion was considered 2a, 2b, 2c reduce the extension stage convulsion compared to the control. The compounds posses' activity against convulsion.

Conclusion

Based on the literature review some of the thiazolidinone derivatives were synthesized. The synthesis was done in two step process. The physio-chemical properties of all the synthesized compounds like melting point, percentage yield were observed. The Rf values were also calculated by observing the thin-layer chromatography plates and the values were recorded.

Out of the synthesized six compounds, compound 2a-5-(2-nitrobenzyl)-2-iminothiazolidin-4-oneposses good anti convulsant activity showing good response in flexion, extension, clonus and stupor when compared to compound 2b-5-(4-bromobenzyl)-2-iminothia zolidin-4-one, compound 2c-5-(2-hydroxy benzyl)-2-iminothiazolidin-4-one. These compounds have shown better activity when compared to control and less activity compared to standard drug phenytoin.

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