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Anticonvulsant activity of some Novel N-(4'oxo-2'-(Aryl/ Heteryl Substituted) Thiazolidin-3'-yl)-3-Carboxamido-2H-Chromen-2-ones

Indulatha VN*, Gopal N[1], Jayakar B[2]

* Dept. Pharmaceutical Chemistry, Periyar College of Pharmaceutical Sciences, Tiruchirapalli, Tamilnadu, India.
[1] MAHSA University College, Kuala Lumpur, Malaysia.
[2] Vinayaka Missions College of Pharmacy, Salem, Tamilnadu.

ABSTRACT

Novel N-[4'-oxo-2'-(substituted phenyl)-thiazolidin-3'-yl]-3-carboxamido-2H-chromen-2-one (IV $_{a\text{-}b,\ d,\ f,\ h\text{-}m}$) were synthesized and evaluated for their anticonvulsant activity. After i.p injection at doses of 100 mg/kg body weight, all the synthesized new derivatives were examined by the Maximal Electro Shock induced seizures (MES) model in mice. All the compounds reduce the time of the tonic extensor phase at dose of 100 mg/kg (bw) and all were statistically significant at different ($p<0.05$) from the control group. Compound IV-m showed very low protection of 41.13%, IV-j showed 63.83% protection and the remaining compounds showed 43-58% protection, indicative of these compounds ability to prevent seizure spread at the dose level of 100 mg/kg (bw) when compared to the standard drug Diazepam, which showed 85.82% protection at the dose of 4 mg/kg (bw).

Keywords: Coumarin, Thiazolidinones, Anticonvulsant activity, Maximal Electro Shock method, Benzylidene derivatives

Corresponding author
Email: indhumpharm@yahoo.co.in

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INTRODUCTION

Electro shock induced seizure is a common model of epileptic seizure and has been used to screen the antiepileptic drugs. The Maximal Electro Shock (MES) is a model for generalized tonic clonic seizures. It is highly reproducible with consisted end points. The behavioral and electrographic seizures generated in this model are consistent with the human disorder. Moreover, this model identifies those compounds which prevent seizure spread. Abolition of the hind limb tonic extensor component indicates the test compounds ability to inhibit Maximal Electro Shock induced seizure spread. Generally it is considered that the compounds which prevent seizure spread (active in the MES test), can lower seizure threshold at the same time and thus, those compounds would have pro-convulsant activity property along with to prevent generalized tonic seizures [1].

Coumarin and their derivatives were an important class of heterocyclic compounds and presenting a wide range of bioactivities [2]. Among the most important literature studied are anti tumor, anticoagulant, antitubercular, CNS depressant activity, antimicrobial activity, Respiratory stimulant, diuretic and spermatogenic activity. Coumarinyl thiazolidinones and their derivatives are shown to have potent CNS activities such as anticonvulsant and CNS depressant activity. A literature survey revealed that the presence of a substituted hetero aromatic ring at the position of 2 are a necessary requirement for central nervous system (CNS) depression and anticonvulsant activities [3]. Synthesized hybrid molecule of thiazolidin coumarinyl -2 ones comprises two fragments coumarinyl -2 ones and thiazolidinones, whose derivatives have been found to exhibit significant anticonvulsant properties [4].

MATERIALS AND METHODS

CHEMISTRY:

All the reagents / chemicals / solvents of laboratory grade used were obtained from Merck (India), SD Fine and CDH Laboratories. The solvents were purified by distillation before their use. The solvent systems used for Thin Layer Chromatography were given in the experimental procedure. Silica Gel G used for TLC was CDH brand. Iodine chamber and UV lamps were used for visualization of TLC spots. Whatmann filter paper (No. 1, England) was used for filtration (vacuum or ordinary). Melting points of all the compounds were recorded in liquid paraffin bath in open capillary tubes and are uncorrected.

SYNTHESIS:

Newly synthesized compounds were attempted to prepare a compound to possess anticonvulsant activity. According to the literature, shows that the presence of substituted ring at the position 3 and a keto group at position 2 may exhibit the potent CNS depression and anticonvulsive property [5].

These reported compounds were designed and synthesized for testing CNS property of coumarin moiety. In this work, the third position of the coumarin nucleus was substituted with carboxamido derivatives to verify the moderation in the CNS activity. N-(substituted aryl / heteryl)-3-carbohydrazide-2H-chromen-2-ones (III $_{a\text{-}d,\ f,\ h\text{-}m}$) is cyclised to get N-(4'oxo-2'-(substituted aryl/heteryl thiazolidin-2-one)-3-carboxamido-2H-chromen-2-one (IV $_{a\text{-}b,\ d,\ f,\ h\text{-}m}$) comprises these two fragments, whose derivatives have been found to show increase or decrease in their anticonvulsant activity. They were most potent when compared with Diazepam in MES test.

Synthesis of 3-(carbethoxy)-chromen-(2H)-one (I)

To an equimolar mixture of salicylaldehyde and diethyl maloanate in 25ml of absolute ethanol, 0.5ml of piperidine & 0.02ml of glacial acetic acid were added and refluxed for 2 hrs. Then the reaction mixture was cooled to room temperature and poured into ice cold water. The solid separated out was filtered and washed with ice cold aq. 50 % ethanol and crystallized by ethanol to give TLC Pure compound.

Synthesis of 3-(carbohydrazide)-chromen-(2H)-one (II)

To a solution of I (0.1mol) in ethanol (25 ml) was added hydrazine hydrate (0.12 mol). The reaction mixture was refluxed for 3 hrs, cooled to room temperature. A product, which separated out was filtered and it was crystallized with Methanol to give colorless crystalline TLC pure compound II.

Synthesis of N-Substituted benzylidene-2H-chromen-2-one-3-carbohydrazide:

General Procedure (III): A mixture of II (0.01mol) and substituted aromatic aldehydes (0.01mol) was dissolved in ethanol (25ml) and refluxed for 4 hrs. The reaction mixture was cooled to room temperature and poured onto crushed ice. A product which separated was filtered and washed with water and it is air dried. It was crystallized form suitable solvents to give TLC pure crystals. Following the above procedure, compounds III ($_{a\text{-}c,\ d,\ f,\ h\text{-}m}$) was synthesized.

Synthesis of N-(4-Substituted thiazolidin-2-one)-2H-chromen-2-one-3-carboxamide:

General Procedure (IV) : A mixture of II (0.01 mol) and thioglycolic acid (0.02 mol) in presence of aluminium trichloride (0.05 gm) was refluxed for 5 hrs in an oil bath at oil bath. The reaction mixture was cooled and triturated with 10% sodium carbonate solution. A solid mass, which separated out was filtered and washed several time with water. It was air dried and crystallized from ethanol to yield TLC pure compounds IV ($_{a\text{-}b,\ d,\ f,\ h\text{-}m}$).

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Table 1: Physical data of Newly synthesized N-[4'-Oxo-2'-(Substituted Aryl / Heteryl)-Thiazolidin-3'-Yl]-3-Carboxamido-2H-Chromen-2-one Derivatives (IV $_{a-b, d, f, h-m}$)

S. No.	Compound code	R/R'	R1	R2	R3	Melting Point (°C)	R_f Value	% Yield	Elemental analysis (Calculated)					
									C	H	N	O	S	Cl
1.	IV-a	Aryl	Cl	-	-	221-223	0.6666	69.34	62.74	3.95	7.32	8.36	8.38	9.26
2.	IV-b	Aryl	-	-	OCH_3	141-143	0.6393	73.98	66.65	4.79	7.4	12.68	8.47	-
3.	IV-c	Aryl	OH	-	-	291-293	0.5892	90.76	65.92	4.43	7.69	13.17	8.80	-
4.	IV-d	Aryl	-	-	-	282-284	0.4828	83.86	68.94	4.63	8.04	9.18	9.20	-
5.	IV-f	Aryl	-	OCH_3	OH	286-287	0.5344	82.20	63.94	4.60	7.1	16.22	8.13	-
6.	IV-h	Aryl	-	-	$N(CH_3)_2$	274-276	0.5600	94.03	67.50	5.41	10.73	8.17	8.19	-
7.	IV-i	Aryl	-	-	OH	298-300	0.5000	78.60	65.92	4.43	7.69	13.17	8.80	-
8.	IV-j	Aryl	NO_2	-	-	221-223	0.4745	83.49	61.06	3.84	10.68	16.27	8.15	-
9.	IV-k	Aryl	-	-	Cl	231-233	0.5849	71.29	62.74	3.95	7.32	8.36	8.38	9.26
10.	IV-l	Furfuryl	-	-	-	192-194	0.3958	85.97	63.89	4.17	8.28	14.18	9.48	-
11.	IV-m	Aryl	-	OH	-	211-213	0.4561	71.39	65.92	4.43	7.69	13.17	8.80	-

ANTICONVULSANT ACTIVITY:

Animals: The study was carried out on Swiss albino mice (either sex) weighting between 25 - 30 gm housed in propylene cages. The mice were grouped and maintained under standard laboratory conditions with natural light dark cycle. They were fed on standard diet and water ad libitum. Mice were acclimatized to their environment for a week prior to experimentation.

Test compounds, their doses and routes of administration: The drug used as standard was Diazepam in a dose of 4 mg/kg (bw). The dose of test compounds were 100 mg/kg (bw) for III $_{a-c, d, f, h-m}$, IV $_{a-b, d, f, h-m}$. The standard and test compounds were administered intraperitoneally in the form of 0.5 % CMC.

Experimental Procedure: Measurement of the seizure threshold for each animal was determined by Maximal Electroshock (MES) Method. The animals were divided in groups of six each and standard drug was injected to one group, the control group of animals was given only 0.5% CMC suspension and the remaining groups were administered different test compounds. After a gap of 30 min of administration of test compounds, all the groups of mice were given electroshock via ear electrodes (forceps style) using an electro convulsiometer. The electroshock consisted of a single train of pulse with a current of 42mA was applied through the ear clip electrodes for duration of about 0.2 sec. The time spent by the animal in tonic extensor phase is considered as the parameter for anticonvulsant activity. A reduction of complete abolition of tonic extensor phase is considered as anticonvulsant property of a drug. [6]

Statistical data: The values were expressed as Mean ±SEM. The statistical analysis was carried out by one way Analysis of Variance (ANOVA) followed by Dunnett's test. $P < 0.05$ was considered significant.

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RESULTS AND DISCUSSION

The synthesis of the title compounds N-[4'- oxo - 2' - (substituted aryl/ heteryl) - thiazolidin-3'-yl] – 3 - carboxamido- 2H-chromen-2-ones (IV $_{a\text{-}b,\ d,\ f,\ h\text{-}m}$) carried out as depicted in scheme –I, reaction of N-(substituted aryl / heteryl)-3-carbohydrazide)- chromen -2H ones (III $_{a\text{-}c,\ d,\ f,\ h\text{-}m}$). In this work, the newly synthesized compounds were tested for their anticonvulsant activity, which was comparable to that of diazepam as a standard drug. As a result, these compounds are potential with different pharmacophore groups was applied to prepared from N-(substituted aryl / heteryl)-3-carbohydrazide-2H-chromen-2-ones (III $_{a\text{-}d,\ f,\ h\text{-}m}$)., in order to further study the effect of these moieties on the anticonvulsant activity, they were prepared from coumarin -3 carbohydrazide and condensed with thioglycolic acid in presence of triethylamine in dimethyl formamide under reflux for 6 hrs to get N-[4'- oxo - 2' - (substituted aryl/ heteryl) - thiazolidin-3'-yl] – 3 - carboxamido- 2H-chromen-2-ones (IV $_{a\text{-}b,\ d,\ f,\ h\text{-}m}$). The structures of these newly synthesized were established through spectroscopic analysis (UV, IR and ^{1}HNMR) as well as Mass spectral bands. The IR spectra shows the presence of NH, C=O (Lactone) in the range of 3000-3500 and 1600-1710 respectively. While the ^{1}HNMR spectra showed the disappearance of signals corresponding to the methyl carbon proton and the presence of NH proton signals that disappeared on deuterium exchange. From these findings it was concluded that the formation of coumarinyl hydrazones. Appearance of lactonised carbonyl group of coumarin was not destructed and formation of thiazolidinones ring was confirmed. The mass spectrum of IV-d exhibited the molecular ion peak at m/z 369.

Table 2: Anticonvulsant Activity of N-(Substituted Benzylidene)-3-Carbohydrazide-2H-Chromen-2-One (III $_{a\text{-}c,\ d,\ f,\ h\text{-}m}$) & N-[4'-Oxo-2'-(Substituted Aryl / Heteryl)-Thiazolidin-3'-Yl]-3-Carboxamido-2H-Chromen-2-One Derivatives (IV $_{a\text{-}b,\ d,\ f,\ h\text{-}m}$)

Compound No	Tonic extensor phase time (sec)		Compound No	Tonic extensor phase time (sec)	
	Mean ± S.D.	% inhibition		Mean ± S.D.	% inhibition
III $_{a}$	9.5 ± 1.05*	59.57*	**IV $_{a}$**	10 ± 0.89*	57.45*
III $_{b}$	12. 7± 0.82	46.10	**IV $_{b}$**	12.0 ± 1.10	48.94
III $_{d}$	11.3 ± 1.03*	51.77*	**IV $_{d}$**	9.7 ± 1.03*	58.87*
III $_{f}$	11.20 ± 1.17*	52.48*	**IV $_{f}$**	9.8 ± 0.75	58.16
III $_{h}$	13.2 ± 0.75	43.97	**IV $_{h}$**	11.0 ± 0.63	53.19
III $_{i}$	11.3 ± 0.82	51.77	**IV $_{i}$**	10.3 ± 0.82*	56.03*
III $_{j}$	13.3 ± 1.21*	43.26*	**IV $_{j}$**	8.5 ± 0.55*	63.83*
III $_{k}$	14.0 ± 0.89	40.43	**IV $_{k}$**	13.2 ± 0.75	43.97
III $_{l}$	12.5 ± 0.84*	46.81*	**IV $_{l}$**	11,7 ± 1.03	50.35
III $_{m}$	11.5 ± 1.05*	51.06*	**IV $_{m}$**	13.8 ± 0.75*	41.13*
Control	23.5 ± 1.05	-	**Control**	23.5 ± 1.05	-
Diazepam	3.3 ± 0.82*	85.82*	**Diazepam**	3.3 ± 0.82*	85.82*

* P <0.05 * P<0.001

Statistically significant from control group (using Dunnett'test as post hoc test).

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SCHEME

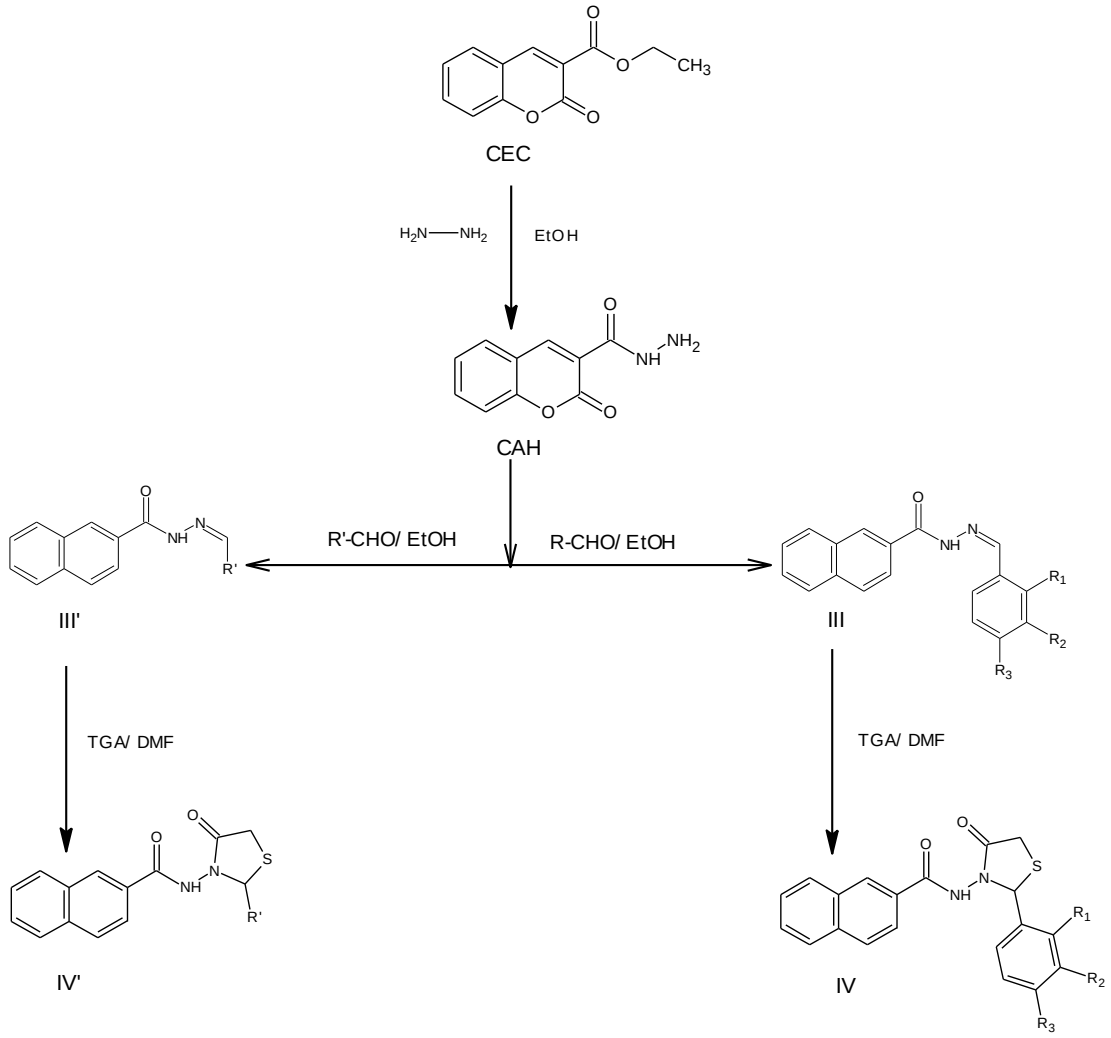

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Table 3: Graphical representation of Anticonvulsant Activity of N-(Substituted Benzylidene)-3-Carbohydrazide-2H-Chromen-2-One (III $_{a\text{-}c,\ d,\ f,\ h\text{-}\ h\text{-}m}$)

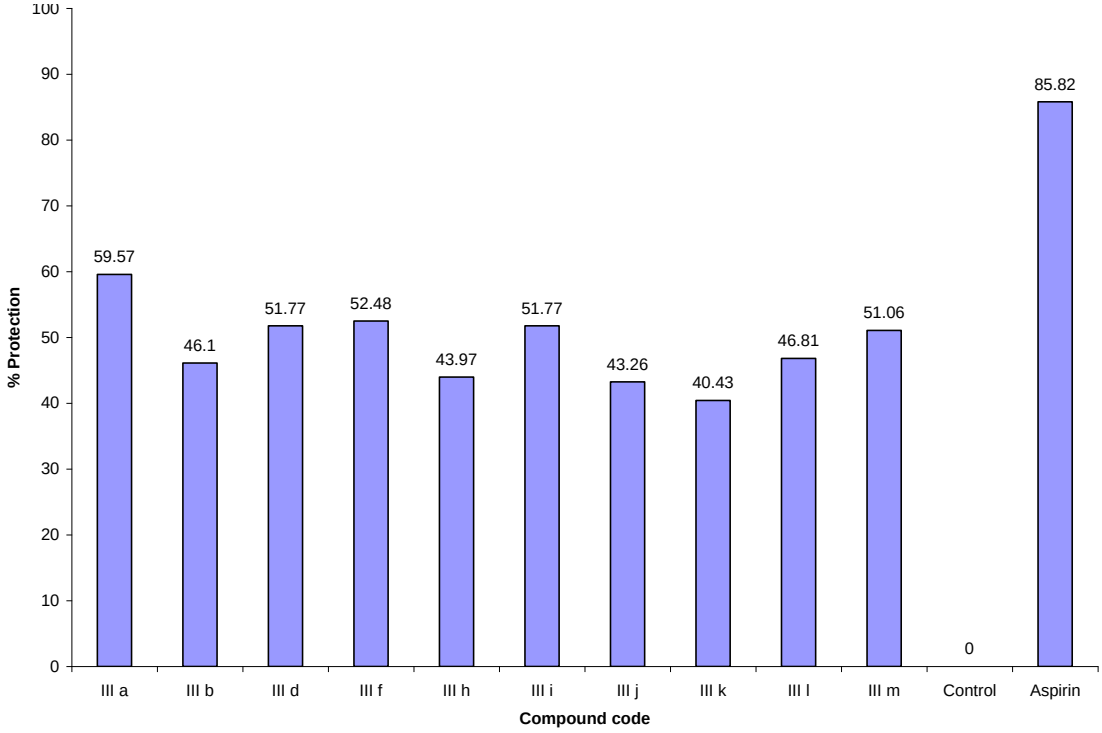
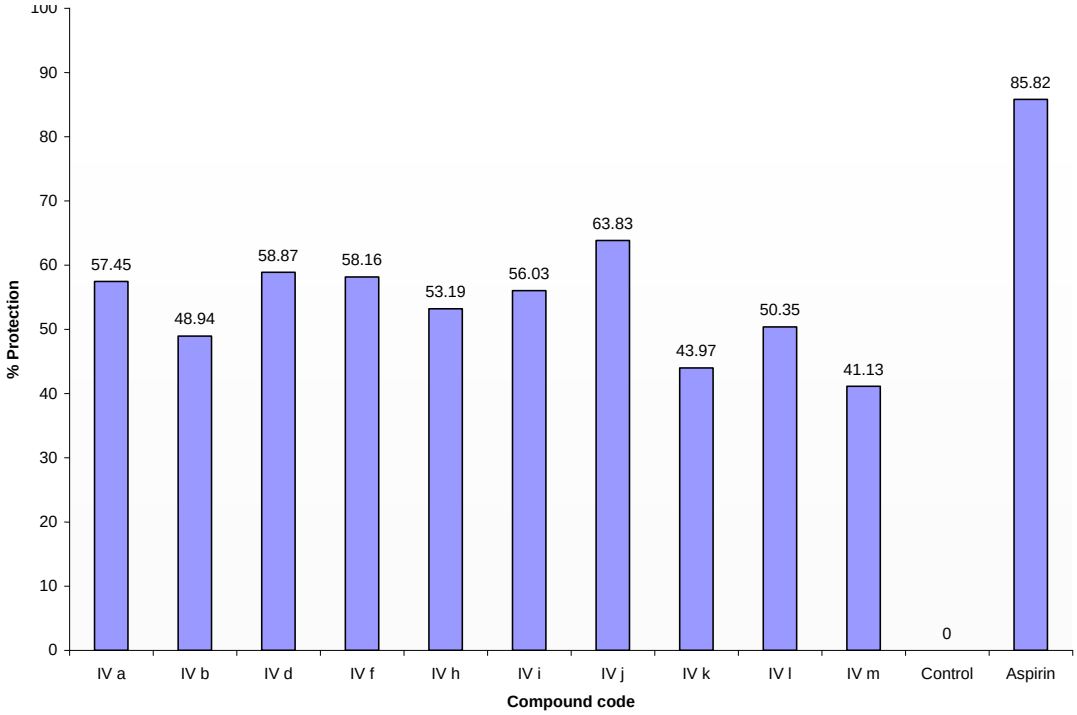


Table 4: Graphical representation of Anticonvulsant Activity of N-[4'-Oxo-2'-(Substituted Aryl / Heteryl)-Thiazolidin-3'-Yl]-3-Carboxamido-2H-Chromen-2-One Derivatives (IV $_{a\text{-}b,\ d,\ f,\ h\text{-}m}$)



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