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SYNTHESIS AND EVALUATION OF NEW 2-(SUBSTITUTED PHENYL)-3-[5'-(2'-OXO-2*H*-CHROMEN-3'-YL)-1,3,4-OXADIAZOL-2-YL]-1,3-THIAZOLIDIN-4-ONES AS ANTICONVULSANTS

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ABSTRACT
A series of 2-(substituted phenyl)-3-[5'-(2''-oxo-2*H*-chromen-3'-yl)-1,3,4-oxadiazol-2-yl]-1,3-thiazolidin-4-ones 4-16 were synthesized in good yield and evaluated for their possible anticonvulsant and neurotoxic study. All the synthesized compounds were in good agreement with elemental and spectral data. Majority of the compounds were active in MES test. All the compounds were less neurotoxic than the standard drug phenytoin.

Key words: *Chromene; Oxadiazole; Thiazolidinones; MES test; Neurotoxicity.*

INTRODUCTION
Many compounds bearing five-membered heterocyclic rings such as triazoles, oxadiazoles, thiadiazoles have been synthesized and evaluated for their anticonvulsant activities.[1-3] In our previous work, we reported that benzothiazole, sulphonamide and coumarin derivatives had considerable anticonvulsant activity.[4-7] The present work was focused on the synthesis and anticonvulsant screening of new 2-(substituted phenyl)-3-[5'-(2''-oxo-2*H*-chromen-3'-yl)-1,3,4-oxadiazol-2-yl]-1,3-thiazolidin-4-ones.

According to the proposed pharmacophoric requirements for anticonvulsant action (i) aryl binding site with a hydrophobic group; (ii) hydrogen bonding domain exemplified by the presence of the (-NHCO-) grouping; (iii) two electron donor system; (iv) distal hydrophobic binding site whose size determines the type of activity,[8] we have designed and synthesized the titled compounds **4-16**. The lipophilic aryl ring was replaced with coumarin ring, a versatile heterocyclic molecule; hydrogen accepter domain was represented by thiazolidinone moiety (Fig. 1). Interestingly these compounds have shown appreciable anticonvulsant activity. The three dimensional optimized structure of the titled compounds is depicted in (Fig. 2).

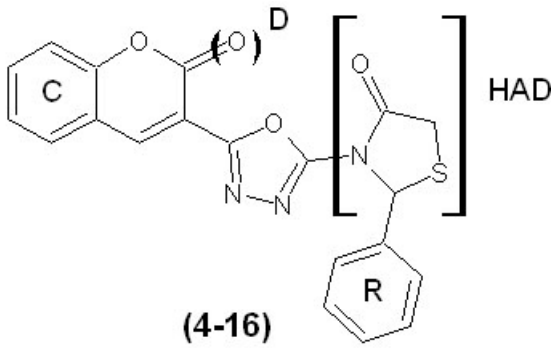

Figure 1. Proposed elements for anticonvulsant activity in basic structure of compounds. (R) Hydrophobic domain, (HAD) hydrogen acceptor domain, (D) electron donor moiety and (C) Distal aryl ring.

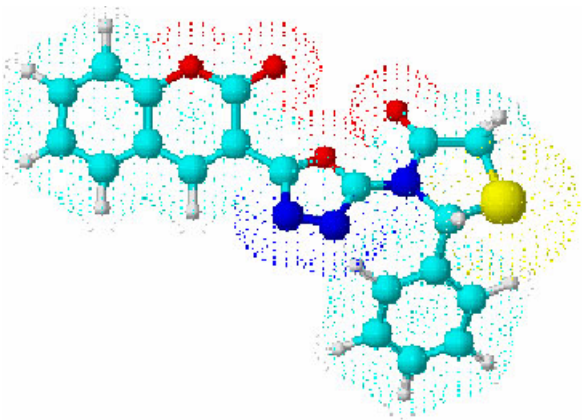

Figure 2. Three-dimensional optimized general structure of 2-(substituted phenyl)-3-[5-(2-oxo-2H-chromen-3-yl)-1,3,4-oxadiazol-2-yl]-1,3-thiazolidin-4-ones (4-16)

EXPERIMENTAL
Chemistry
Melting points were determined in open capillary tubes and are uncorrected. Elemental data of C, H and N were within ± 0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Bruker model DRX 300 NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on BIO-RAD FTS 135 spectrometer using KBr pellet.

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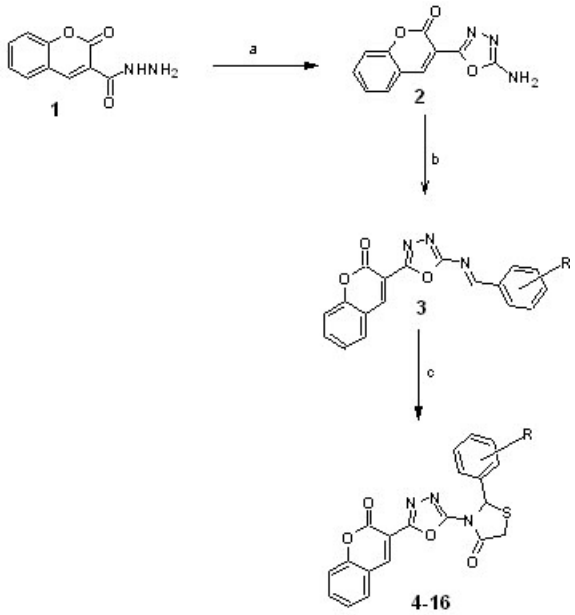
TLC was carried out using silica gel G. All the chemicals and solvents used were obtained from Merck.

Synthesis of target compounds **4-16** was performed according to (Scheme 1).



R= Cl, F, NO_2, OH, CH_3, OCH_3, $N(CH_3)_2$

Scheme 1. *Reagents and conditions: (a) Cyanogen bromide; (b) Substituted benzaldehyde/glacial acetic acid; (c) Mercapto acetic acid/Anhy. $ZnCl_2$*

2-Oxo-2*H*-chromene-3-carbohydrazide (1): The starting compound 2-oxo-2*H*-chromene-3-carbohydrazide was prepared as described previously.[9]

3-(5'-Amino-1,3,4-oxadiazol-2'-yl)-2*H*-chromen-2-one (2): To an ethanolic solution of 2-oxo-2*H*-chromene-3-carbohydrazide (**1**, 2.18 g, 0.01 mol), cyanogen bromide (1.06 g, 0.01 mol) was added. The reaction mixture was warmed at 55-60 °C for 90 min. The resulting solution was cooled and neutralized by sodium bicarbonate ($NaHCO_3$) solution. The solid 3-(5-amino-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one was filtered out. FT-IR (KBr) cm^{-1}: 3000 (C-H) str., 1622 (C=O, coumarin) str.; 1600 (C=C) str., 1275 (C-O) str.; ^{1}H NMR (DMSO-d_6) d ppm: 6.99-7.39 (m, 4H, Ar-H), 8.71 (s, 1H, Ar-H, H-4), 5.38 (s, 2H, NH_2).

3-(5-{[(1*E*)-(substituted phenyl) methylene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones (3): Compound 3-(5-amino-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one (**2**, 2.44 g, 0.01 mol), substituted benzaldehydes (0.01 mol) and glacial acetic acid (2 mL) were refluxed in 1,4-dioxan (40 mL) for 8 h. The solvent was distilled off at reduced pressure. The product 3-(5-{[(1*E*)-(substituted phenyl) methylene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one was obtained by pouring the reaction mixture in ice-cold water. It was recrystallized from ethanol. FT-IR (KBr) cm^{-1}: 3000 (C-H) str., 1580 (N=C) str.; 1669 (C=O, coumarin) str.; 1348 (C-N) str., 1268 (C-O) str.; 1527 (C=C) str.; ^{1}H NMR (DMSO-d_6) d ppm: 6.96-8.74 (m, 8H, *J* = 10 Hz, Ar-H), 8.31 (s, 1H, Ar-H, H-4), 8.33 (s, 1H, N=CH-Ar).

2-(Substituted phenyl)-3-[5'-(2''-oxo-2*H*-chromen-3'-yl)-1,3,4-oxadiazol-2-yl]-1,3-thiazolidin-4-ones (4-16): Compound 3-(5-{[(1*E*)-(substituted phenyl) methylene] amino}-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one (**3**, 0.01 mol) and mercaptoacetic acid (0.9 g, 0.01 mol) were refluxed in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxan (25 mL) for 12 h. The reaction mixture was then cooled and poured onto crushed ice. The product 2-(substituted phenyl)-3-[5'-(2''-oxo-2*H*-chromen-3'-yl)-1,3,4-oxadiazol-2-yl]-1,3-thiazolidin-4-ones separated out was filtered, dried and crystallized from ethanol. FT-IR (KBr) cm $^{-1}$: 3000 (C-H) str., 1594 (N=C) str., 1680 (C=O, coumarin) str.; 1600 (C=C) str. , 1350 (C-N) str. , 1272 (C-O) str.; ^{1}H NMR (DMSO-d_6) d ppm: 3.62 (s, 2H, b-thialactam ring); 7.0-8.32 (m, 8H, Ar-H), 8.83 (s, 1H, Ar-H, H-4), 8.39 (s, 1H, -CH-Ar).

Analytical and spectral data of all the synthesized compounds were in good agreement with the composition of synthesized compounds. The data of physicochemical properties of all the compounds are given in (Table 1).

Table 1. *Physical data of compounds (**4-16**)*

Compd.	R	M.p (°C)	Yield (%)	Molecular formula[a]	R_f[b]	R_M[c]	% N Found (Calc.)
4	3-NO_2	178	60	$C_{20}H_{13}N_5O_5S$	0.73	-0.13	12.88(12.83)
5	3,4-$(OCH_3)_2$	170	55	$C_{22}H_{19}N_3O_5S$	0.75	-0.12	9.33(9.30)
6	4-OH	300(d*)	62	$C_{20}H_{15}N_3O_5S$	0.60	-0.22	10.34(10.31)
7	2-OH	175	65	$C_{20}H_{15}N_3O_5S$	0.50	-0.3	10.27(10.31)
8	2-NO_2	210	68	$C_{20}H_{13}N_5O_5S$	0.74	-0.13	12.78(12.83)
9	3-OH	150	64	$C_{20}H_{15}N_3O_5S$	0.52	-0.28	10.30(10.31)
10	4-$N(CH_3)_2$	180	60	$C_{22}H_{20}N_4O_4S$	0.57	-0.24	12.84(12.89)
11	4-F	200	58	$C_{20}H_{12}FN_3O_4S$	0.64	-0.19	10.22(10.26)
12	4-OCH_3	170	67	$C_{21}H_{15}N_3O_5S$	0.7	-0.15	10.00(9.97)
13	2-Cl	300(d*)	70	$C_{20}H_{12}ClN_3O_4S$	0.8	-0.09	9.83(9.86)
14	3-Cl	250	58	$C_{20}H_{12}ClN_3O_4S$	0.82	-0.08	9.89(9.86)
15	4-Cl	280	65	$C_{20}H_{12}ClN_3O_4S$	0.83	-0.08	9.85(9.86)
16	H	210	70	$C_{20}H_{13}N_3O_4S$	0.68	-0.16	10.77(10.73)

[a]Elemental analysis for C, H, N and S were within □ 0.4% and □ 0.3% respectively of the theoretical values.
[b]Eluents used in TLC were Toluene: Ethyl acetate: Formic acid (5:4:1) for compounds.
[c] R_M = log (1-1/R_f).

Anticonvulsant activity

The anticonvulsant activity of the synthesized compounds was determined by evaluation of the ability of the compounds to protect mice convulsions induced by electroshock and neurotoxicity by rotorod method as routine model.[10-11] Male albino mice (Swiss, 18-25 g) were used as experimental animals. The test compounds were suspended in polyethylene glycol (PEG).

MES-Maximal electroshock seizure Test

Maximal electroshock seizures were elicited with a 60 cycle altering current of 50 mA intensity (5-7 times that necessary to elicit minimal electroshock seizures) delivered for 0.25 s via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animal protected/ number of animals tested. Initial anticonvulsant activity and neurotoxicity data for titled compounds are reported in (Table 2).

Table 2. *Anticonvulsant and neurotoxicity results of the titled compounds (**4-16**)*

Compd.	Intraperitonial injection in mice[a]			
	MES screen		Toxicity screen	
	0.5 h	4 h	0.5 h	4 h
4	100	300	300	-
5	300	300	300	-
6	300	300	300	-
7	100	300	300	300
8	30	100	300	-
9	100	300	300	300
10	300	300	300	300
11	100	300	300	300
12	30	100	300	100
13	30	100	300	100
14	30	100	300	300
15	30	100	300	300
16	300	300	300	300
Phenytoin[b]	30	30	100	100
Carbamazepine[b]	30	100	100	300
Phenobarbital[b]	100	30	100	300

[a] Doses of 30, 100 and 300 mg/kg were administered. The figure in the table indicates the minimum dose whereby bioactivity was demonstrated in half or more of the animals. The animals were examined 0.5 and 4 h after administration. The (-) indicates an absence of activity at maximum dose administered (300 mg/kg).[b] Data from references.[14-16]

NT-Neurotoxicity: The rotorod test was used to evaluate neurotoxicity. The animal was placed on a 3.2 cm diameter knurled rod rotating at 6 rpm. Normal mice can remain on a rod rotating at this speed indefinitely. Neurological toxicity is defined as the failure of the animal to remain on the rod for 1 min.

RESULTS AND DISCUSSION

The synthesized titled compounds **4-16** were initially screened at 30, 100 and 300 mg/kg intraperitoneally in mice for anticonvulsant activity. All the compounds were active in MES test at a dose of 300 mg/kg indicative of their ability to protect the seizure spread. At a dose of 30 mg/kg, the compounds that showed protection in half or more tested mice were **8, 12, 13, 14** and **15** after 0.5 h. These compounds also showed protection against MES test after 4 h but at higher dose of 100 mg/kg. At a dose of 100 mg/kg, the compounds that showed protection were **4, 7, 9** and **11** after 0.5 h. These compounds also showed protection against MES test after 4 h but at a higher dose of 300 mg/kg. Compounds, which showed protection against MES test at 300 mg/kg after 0.5 h and 4 h, were **5, 10** and **16.**

In neurotoxicity screening, the compounds **4, 5, 6** and **8** were devoid of toxicity after 4 h interval. All the compounds showed neurotoxicity at a higher dose of 300 mg/kg after 0.5 h time interval. The compounds **12** and **13**, showed neurotoxicity at a dose of 100 mg/kg after 4 h.

The compounds, which contained substituents, like NO_2, Cl and OCH_3 at distal phenyl ring showed potent activity against MES test. The compounds with substituents like OH and F at distal phenyl ring showed moderate activity against MES test. The compounds with substituents like $N(CH_3)_2$, 3,4-$(OCH_3)_2$ and H showed protection against MES test but at higher dose of 300 mg/kg. The thiazolidinone moiety, which contains S-CH_2, increases the lipophilicity of the compounds.

Lipophilicity determination

The dependence of biological activity of congeneric agents on lipophilic character has been shown in many types of drug action. The anticonvulsant activity of different types of compounds was reported to be correlated with lipophilicity[12]. The experimental log *P* values were determined using octanol-water method[13] for compounds, which showed significant protection. The compound **12** and **13** had log *P* value of 1.0 and 1.65 respectively, which were near to optimum log *P* value of ± 2. Among the compounds showing anticonvulsant activity, compounds with more lipophilic substitutions like OCH_3, NO_2 and Cl group in distal aryl ring are more active. Basic structure of the compounds fulfilled all the pharmacophoric structural requirements.

CONCLUSION

In conclusion, results confirmed the pharmacophoric model elements are necessary for anticonvulsant activity. Substitutions with OCH_3, Cl and NO_2 group at distal aryl ring showed significant MES activity as compared to other substituents with bigger hydrophobic domain.

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