Research Article

DESIGN, SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF NOVEL *N* 1-[2-(SUBSTITUTED PHENYL)-4-OXO-1, 3-THIAZOLAN-3-YL]-2, 2-DIPHENYLACETAMIDES

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ABSTRACT

The current therapy of epilepsy is associated with a number of side effects including sedation and hypnosis. Newer improved molecules are needed with lesser side effects and with improved physical properties. In view of these facts, a series of novel *N* 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l) and hydrazones (IVa-l) were synthesized by treating diphenyl acetic acid with abs. ethanol in presence of conc. H_2SO_4 to give Diphenyl ester (I), which was treated with hydrazine hydrate to give corresponding hydrazide (II). The hydrazide was then treated with different arylaldehydes to give the corresponding hydrazones (IVa-l) and then treated with thioglycolic acid to obtained novel *N* 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l).The structures of the synthesized compounds were confirmed on the basis of their elemental analysis and spectral data (IR, ^{1}H-NMR and MS). The *N* 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l) and hydrazones (IVa-l) were screened for their anticonvulsant activity and neurotoxicity by maximal electroshock seizure (MES) method and rotarod method respectively. The compounds Vb, Ve, IVb, IVd and IVh were found to be most active in MES test; whereas Vc, IVb and IVd successfully passed the rotorod test without any sign of neurological deficit.

Keywords: 4-Thiazolidinone, Hydrazone, Anticonvulsant Screening, Neurotoxicity Screening.

INTRODUCTION

Epilepsy, a common chronic neurological disorder that is characterized by recurrent unprovoked seizures, inflicts more than 60 million people worldwide according to epidemiological studies[1,2]. Every year approximately 2, 50, 000 new cases are added to this figure. It is roughly estimated that 28-30% of patients are resistant to the available medical therapies. Despite the development of several new anticonvulsants the treatment of epilepsy remains still inadequate, and the patients suffer from a lot of specific problems like neurotoxicity, depression and other CNS related diseases. Moreover many antiepileptic drugs have serious side effects and lifelong medication may be required. Therefore, it is essential to search for newer chemical entities for the treatment of epilepsy[3-6].

In recent years, the chemistry of 4-Thiazolidinone and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. Heterocycles bearing a symmetrical 4-Thiazolidinone moiety are reported to show a broad spectrum of pharmacological properties such as antimicrobial, anticancer, antitubercular, anti-inflammatory, analgesic, neurotoxity and anticonvulsant activities[7-10]. Derivatives of 4-Thiazolidinone and 1, 3, 4-thiadiazole condensed nucleus system (triazolothiadiazoles) found to have diverse pharmacological activities such as fungicidal, bactericidal, insecticidal, herbicidal, anticancer, antiinflammatory and CNS stimulant properties. They also find application as dyes, lubricants and analytical reagents[11-15].

Literature survey reveals that *N* 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides have not been paid much attention for their anticonvulsant properties and neurotoxity activity. Hence, the present studies were undertaken to study the anticonvulsant and neurotoxity potential of fused 4-Thiazolidinone. In this paper, we report the synthesis, anticonvulsant and neurotoxicity study of a series of *N* 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l).

MATERIALS AND METHODS

Experimental procedure

The melting points were determined in open glass capillary tubes using Kjedahl flask containing liquid paraffin and are uncorrected. Thin layer chromatography (TLC) was carried out using Silica gel G (Merck). Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer and the values were found within ±0.4% of the theoretical values. The FT-IR Spectra were recorded in KBr pellets on (BIO-RAD FTS), FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on DPX-300 NMR spectrometer and BRUKER-400 Ultra Shield™ spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS). The physical constants and spectral data of the synthesized compounds are presented in **Table 1** and **Table 2** respectively.

Table 1: Physical constants of the titled compounds **(IVa-l, Va-l)**

Compound	R	Mol. Formula[a]	Mol. Wt.	Log P[b]	M.p (°C)[c]	Yield (%)	Rf[d]-value	% N found[e] (calculated)
IVa	4-Cl	$C_{21}H_{17}ClN_2O$	348.83	0.71	180	83	0.75	20.88 (20.86)
IVb	2,4-$(Cl)_2$	$C_{21}H_{16}Cl_2N_2O$	383.27	1.68	185	70	0.66	15.25 (15.26)
IVc	4-F	$C_{21}H_{17}FN_2O$	332.37	0.80	198	85	0.58	15.21 (15.24)
IVd	2-OCH_3	$C_{22}H_{20}N_2O_2$	344.41	1.19	184	65	0.56	15.17 (15.20)
IVe	3-NO_2	$C_{21}H_{17}N_3O_3$	359.38	0.55	230	80	0.60	14.35 (14.38)
IVf	4-NO_2	$C_{21}H_{17}N_3O_3$	359.38	0.47	196	73	0.76	20.22 (20.25)
IVg	2-OH	$C_{21}H_{18}N_2O_2$	330.38	1.43	190	75	0.64	16.10 (16.12)
IVh	4-OH	$C_{21}H_{18}N_2O_2$	330.38	1.10	250	76	0.72	19.67 (19.69)
IVi	4-OCH_2COOH	$C_{23}H_{20}N_2O_4$	388.42	1.11	250	82	0.81	14.61 (14.64)
IVj	4-OH-3-OCH_3	$C_{22}H_{20}N_2O_3$	360.41	1.09	200	60	0.34	14.53 (14.56)
IVk	4-OH-3-OC_2H_5	$C_{23}H_{22}N_2O_3$	374.44	1.98	180	81	0.46	14.62 (14.63)
IVl	3,4-$(OCH_3)_2$	$C_{23}H_{22}N_2O_3$	374.44	1.17	196	80	0.63	13.53 (13.56)
Va	4-Cl	$C_{23}H_{19}ClN_2O_2S$	422.92	1.87	205	72	0.66	19.38 (19.40)
Vb	2,4-$(Cl)_2$	$C_{23}H_{18}Cl_2N_2O_2S$	457.37	1.10	206	70	0.73	15.37 (15.39)
Vc	4-F	$C_{23}H_{19}FN_2O_2S$	406.47	1.06	210	74	0.46	15.37 (15.38)
Vd	2-OCH_3	$C_{24}H_{22}N_2O_3S$	418.51	0.55	188	60	0.67	20.20 20.23)
Ve	3-NO_2	$C_{23}H_{19}N_3O_4S$	433.48	0.76	195	75	0.56	15.26 (15.24)
Vf	4-NO_2	$C_{23}H_{19}N_3O_4S$	433.48	1.71	190	70	0.78	15.21 (15.23)
Vg	2-OH	$C_{23}H_{20}N_2O_3S$	404.48	0.60	210	82	0.56	15.23 (15.25)
Vh	4-OH	$C_{23}H_{20}N_2O_3S$	404.48	0.82	205	68	0.70	15.90 (15.92)
Vi	4-OCH_2COOH	$C_{25}H_{22}N_2O_5S$	462.52	1.20	215	65	0.86	14.98(14.99)
Vj	4-OH-3-OCH_3	$C_{24}H_{22}N_2O_4S$	434.51	0.98	210	73	0.65	16,02(16.04)
Vk	4-OH-3-OC_2H_5	$C_{25}H_{24}N_2O_4S$	448.53	1.04	215	75	0.73	15.43(15.45)
Vl	3,4-$(OCH_3)_2$	$C_{25}H_{24}N_2O_4S$	448.53	1.57	198	80	0.76	17.65(17.68)

[a]Solvent of crystallization-Ethanol, [b]Log P was calculated by using absorbance data, Chloroform/ Phosphate buffer at 28°C, [c]Melting point of the compounds, [d]Solvent system- Toluene:Ethyl acetate : Formic acid (5:4:1). [e]Elemental analysis for C, H, N were within ±0.4% of the theoretical value.

Synthesis of aryl acid ethyl esters (II) and their hydrazides (III)

These compounds were obtained from different aryl/aroyl acids (**1**) by the method reported in the literature[16].

Synthesis of different arylaldehydes derivative of hydrazone (IVa-l).

A mixture of hydrazide **(II)** (0.005 mol) and different substituted arylaldehydes (0.005 mol) was taken in absolute ethanol (15ml) and refluxed for 2-3 hrs on cooling a solid mass separated out that was filtered and then recrystalized from ethanol[17,18].

Synthesis Of Different Derivatives Of *N* 1-[2-(Substituted Phenyl)-4-Oxo-1, 3-Thiazolan-3-yl]-2, 2-Diphenylacetamides (IVa-l).

In a round bottom flask the compound **(IVa-l)** (0.002mol) in dioxane (50ml) was taken and thioglycolic acid (0.002mol) was added to it and the mixture was refluxed for 8-10 hrs at 120°C.The reaction mixture was concentrated on crushed ice and neutralized with 2% sodium bicarbonate solution, solid mass that separated out was filtered and recrystallized from ethanol[19,20].

BIOLOGICAL EVALUATION

Anticonvulsant Screening: The anticonvulsant screening of the final compounds was done according to the protocols of National Institute of Neurological Disorders and Stroke, NIH (USA).

Maximal Electroshock Seizure Test (MES): The compounds were screened for their anticonvulsant activity by electroshock seizure method[21,22]. Supra-maximal electroshock of current intensity of 50 mA, 60Hz for 0.2 sec. duration was applied to mice, with the doses of test compounds 30, 100, 300 mg/Kg. The abolition of the hind limb tonic extensor spasm was recorded as anticonvulsant activity as shown in **Table 3**.

Neurotoxicity Screening (NT): The minimal motor impairment was measured in mice by the rotorod test[23,24]. The mice (20-25 gm) were trained to stay on an accelerating rotorod that rotates at 10 rotations/min. and its diameter was 3.2 cm. Only those mice were taken for the test which can stay on the revolving rod for at least one minute. Trained animals were injected i.p. with the test compounds at doses of 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibration on the rod for at least one minute as shown in **Table 3**.

Table 2: Spectral data of the compounds **(IVa-l, Va-l)**

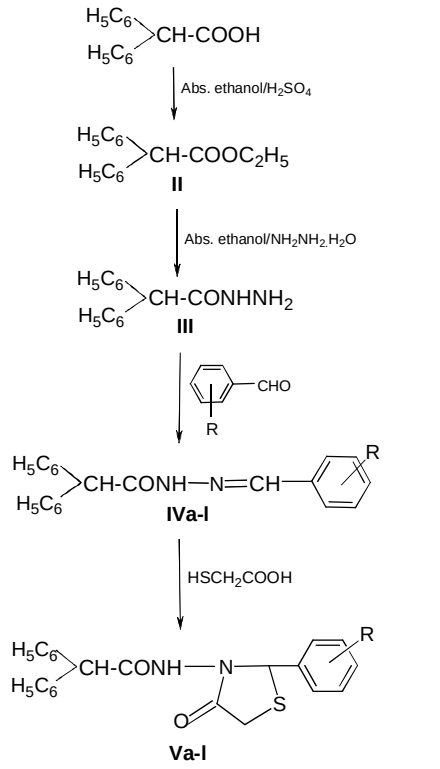
Compound	IR (KBr), cm^{-1}	^{1}HNMR (DMSO-d_6), δ (ppm)†
IVa	3317 (NH_2), 3068 (CH), 2596 (SH), 1590 (C=N).	3.98 (s, 2H, CH_2), 5.65 (s, 2H, NH_2), 7.08-7.31 (m, 5H, phenyl) 13.82 (br s, SH).
IVb	3350 (NH_2), 3010 (CH), 2550 (SH), 1605 (C=N).	2.99 (s, 2H, CH_2), 5.50 (s, 2H, NH_2), 7.50-6.98 (m, 5H, phenyl) 12.82 (br s, SH).
IVc	3293 (NH_2), 3071 (CH), 2608 (SH), 1605 (C=N).	5.11 (s, 2H, OCH_2), 5.72 (s, 2H, NH_2), 7.11-7.36 (m, 5H, phenyl) 13.91 (br s, SH).
IVd	3310 (NH_2), 3085 (CH), 2603 (SH), 1598 (C=N).	4.98 (s, 1H, OH), 5.58 (s, 2H, NH_2), 7.03-7.37 (m, 5H, phenyl) 13.87 (br s, SH).
IVe	3034 (CH), 1740 (C=O) 1630 (C=N), 1489 (C-N), 721 (C-S-C).	3.92 & 4.33 (s, each, 2 x CH_2), 7.09-7.78 (m, 10H, Ar H), 8.31 (s, 1H, CONH).
IVf	3060 (CH), 1636 (C=N), 1489 (C-N), 721 (C-S-C), 545 (C-Br).	4.31 (s, 2H, CH_2), 7.13 - 7.73 (m, 9H, Ar-H).
IVg	3044 (CH), 1590 (C=N), 1489 (C-N), 716 (C-S-C), 541 (C-Br).	3.96 (s, 2H, CH_2), 7.17 - 7.72 (m, 9H, Ar H).
IVh	3051 (CH), 1581 (C=N), 1476 (C-N), 721 (C-S-C), 568 (C-Br).	4.49 (s, 2H, CH_2), 7.20 - 7.44 (m, 5H, phenyl), 7.88 - 7.96 (m, 4H, *p*-disubstituted phenyl).
IVi	3034 (CH), 1747 (C=O), 1590 (C=N), 1469 (C-N), 716 (C-S-C).	3.94 (s, 2H, CH_2), 7.13 - 7.81 (m, 14H, Ar H).
IVj	3380 (NH, indole), 3028 (CH), 1608 (C=N), 1490 (C-N), 743 (C-S-C).	4.41 & 4.50 (s, each, 2 x CH_2), 6.75 - 7.47 (complex m, 10H, Ar-H), 8.58 (s, 1H, NH).
IVk	3047 (CH), 1592 (C=N), 1461 (C-N), 718 (C-S-C).	4.44 & 4.98 (s, 2 x CH_2), 7.35 - 8.16 (complex m, 12H, Ar-H).
IVl	3309 (NH), 3033 (CH), 1697 (C=O), 1583 (C=N), 1474 (C-N), 723 (C-S-C).	4.31 (s, 2H, CH_2), 5.10 (s, 2H, OCH_2), 6.85 - 7.43 (m, 10H, Ar H), 8.33 (s, 1H, CONH).
Va	2990 (CH), 1597 (C=N), 1485 (C-N), 690 (C-S-C), 543 (C-Br).	5.64 (s, 2H, OCH_2), 7.04 (t, 1H, H-4, *o*-disubstituted phenyl), 7.19 (d, 2H, H-5,6, *o*-disubstituted phenyl), 7.39 (t, 2H, H-2,6, phenyl), 7.68 (m, 2H, H-4, phenyl + H-3, *o*-disubstituted phenyl), 7.98 (d, 2H, H-3,5, phenyl).
Vb	3028 (CH), 1609 (C=N), 1479 (C-N), 709 (C-S-C), 550 (C-Br).	5.12 (s, 2H, OCH_2), 6.83 - 7.46 (m, 9H, Ar H).
Vc	3037 (CH), 1615 (C=N), 1486 (C-N), 716 (C-S-C), 544 (C-Br).	5.10 (s, 2H, OCH_2), 6.81 - 7.49 (m, 9H, Ar H).
Vd	3080 (CH), 1747 (C=O), 1655 (C=N), 1466 (C-N), 692 (C-S-C).	5.65 (s, 2H, OCH_2), 7.02 - 7.85 (complex m, 14H, Ar-H).
Ve	3373 (NH, indole), 3016 (CH), 1614 (C=N), 1456 (C-N), 706 (C-S-C).	4.56 (s, 2H, CH_2), 5.29 (s, 2H, OCH_2), 6.97 - 7.53 (m, 10H, Ar-H), 8.63 (s, 1H, NH).
Vf	3024 (CH), 1598 (C=N), 1450 (C-N), 698 (C-S-C).	4.56 (s, 2H, CH_2), 5.29 (s, 2H, OCH_2), 7.06 - 7.56 (m, 12H, Ar-H).
Vg	3052 (CH), 1753 (C=O), 1608 (C=N), 1467 (C-N), 701 (C-S-C).	3.08 & 3.85 (s, each, 2 x CH_2), 5.14 (s, 2H, OCH_2), 6.40 - 7.36 (m, 10H, Ar-H).
Vh	3652 (OH), 3054 (CH), 1606 (C=N), 1482 (C-N), 707 (C-S-C).	3.08 (s, 2H, CH_2), 4.86 (s, 1H, OH), 6.92 - 8.13 (m, 9H, Ar H), 8.31 (s, 1H, CONH).
Vi	3695 (OH), 3029 (CH), 1598 (C=N), 1489 (C-N), 689 (C-S-C), 571 (C-Br).	4.95 (s, 1H, OH), 6.94 - 8.18 (m, 8H, Ar-H).
Vj	3657 (OH), 3005 (CH), 1607 (C=N), 1473 (C-N), 693 (C-S-C), 589 (C-Br).	4.95 (s, 1H, OH), 6.86 - 7.95 (m, 8H, Ar-H).
Vk	3690 (OH), 3023 (CH), 1585 (C=N), 1457 (C-N), 688(C-S-C), 572 (C-Br).	4.94 (s, 1H, OH), 6.83 - 7.86 (m, 8H, Ar-H).
Vl	3660 (OH), 3011 (CH), 1589 (C=N), 1475 (C-N), 701 (C-S-C).	4.03 (s, 2H, CH_2), 4.91 (s, 1H, OH), 7.11 - 8.14 (m, 11H, Ar H).

†s = singlet; d = doublet; t = triplet; m = multiplet; br = broad; Ar H = aromatic protons.

Table 3: Anticonvulsant and Neurotoxicity screening of the title compounds **(IVa-l, Va-l)**

Compound	R	MES screen[a]		Neurotoxicity screen[a]	
		0.5h	4h	0.5h	4h
IVa	4-Cl	100	300	300	--
IVb	2,4-$(Cl)_2$	30	300	--	300
IVc	4-F	30	300	--	--
IVd	2-OCH_3	100	300	300	--
IVe	3-NO_2	100	300	--	300
IVf	4-NO_2	--	300	300	300
IVg	2-OH	30	300	300	--
IVh	4-OH	100	300	300	300
IVi	4-OCH_2COOH	100	300	--	300
IVj	4-OH-3-OCH_3	30	300	--	300
IVk	4-OH-3-OC_2H_5	30	300	--	--
IVl	3,4-$(OCH_3)_2$	100	300	300	--
Va	4-Cl	--	--	--	300
Vb	2,4-$(Cl)_2$	100	--	--	--
Vc	4-F	100	300	300	--
Vd	2-OCH_3	100	300	--	--
Ve	3-NO_2	30	300	300	300
Vf	4-NO_2	30	300	300	300
Vg	2-OH	100	300	--	--
Vh	4-OH	100	300	--	--
Vi	4-OCH_2COOH	100	--	300	--
Vj	4-OH-3-OCH_3	100	300	--	300
Vk	4-OH-3-OC_2H_5	--	300	300	--
Vl	3,4-$(OCH_3)_2$	100	-	-	300

[a]Doses of 30, 100 and 300 mg/kg were administered. The figures in the table indicate the minimum dose where by bioactivity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 hrs after injections were given. The dash (--) indicates an absence of activity at maximum dose administered (300 mg/kg). [b]Data from references (21,22, 23 and 24)



Scheme 1.Protocol for synthesis of the title compounds **(IV a-l, IVa-l)**

Log p determination

The dependence of biological activity in the set of congeneric agents or lipophilic character has been shown in many types of drug action in particular, the reports by Lien and co-workers indicated that the anticonvulsant activity of different types of compounds were correlated with lipophilicity. However it has been observed that the maximum potency of the drugs which act on the central nervous system (CNS) is obtained with congeners having an optimum lipophilicity (log Po) near 2. In this study, we attempted to correlate the anticonvulsant activity of the 3,6-disubstituted-[1,2,4]-triazolo-[3,4-*b*][1,3,4]-thiadiazoles with the calculated log P value, CLOGP . The experimental log P values of the compounds were determined using chloroform phosphate buffer method[25-27].

RESULTS AND DISCUSSION

In preliminary screening, the test compounds were dissolved in propylene glycol -400 and administered, each an i.p. injection at three dose levels (30, 100 and 300 mg/kg) in albino mice (Swiss strain) and the activity was examined after 0.5 and 4 h intervals against maximal electroshock-induced seizure (MES) threshold test. The anticonvulsant and neurotoxicity data of the compounds and standard drugs are presented in **Table 3**. The compounds that exhibited most potent anti-MES activity included **IVb, IVc, IVg, IVj, IVk**, **Ve** and **Vf** which have activity comparable with phenytoin and carbamazepine. Minimal motor impairment was measured by rotorod test. The compounds **IVc, IVk, Vb , Vd,** and **Vg** successfully passed the rotorod test without any sign of neurological deficit whereas the compounds **IVa, IVd, IVf, IVg, IVh, IVl, Vc, Ve, Vf** and **Vh** exhibited neurological deficit at dose of 300 mg/kg i.p.

The compounds **IVb, IVg, IVk, Va, Vf** and **Vr** were found to be more lipophilic having potent anticonvulsant activity. The other compounds **IVd, IVh, IVi, IVj, IVl, Vb** and **Vc** were also lipophilic having same potency. The compounds **IVa, IVc, IVe, IVf, Vd, Ve** and **Vg** are less lipophilic and are less active in MES test.

CONCLUSION

In conclusion, the present study reveals the anticonvulsant and neurotoxity potential of fused 4-thiazolidinone derivatives. The results indicated that electron withdrawal group in position 2 and 4 [disubstituted phenyl-4-oxo-1,3-thiazolan-3-yl]-2,2-diphenyl acetamides was essential for the activity. Thus a number of novel *N* 1-[2-(substituted phenyl)-4-oxo-1,3-thiazolan-3-yl]-2,2-diphenyl acetamides derivatives exhibited anticonvulsant Screening and Neurotoxicity Screening by using MES test and Rotarod respectivily. Some compounds like **IVb, IVg, IVk, , IVm, Vf** and **Vh** showed more lipophilic character and were more active. The compounds **IVa, IVd, IVh, IVi, IVj, IVl, Vb, Vc** and **Vd** were also lipophilic but were less active in MES test. Some of the above mentioned compounds have shown higher degree of protection and obviously may have future commitment.

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