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SHORT COMMUNICATION

NEUROPHARMACOLOGICAL AND TOXICITY STUDY OF NEWLY PREPARED *N*-[5-(3-CHLORO-4-FLUOROPHENYL)-1,3,4-THIADIAZOL-2-YL]-2-SUBSTITUTED ACETAMIDES

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Abstract: Various *N*-(5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-substituted acetamides were synthesized starting from 3-chloro-4-fluorobenzaldehyde. Structures of the compounds were confirmed on the basis of spectral data. The compounds were evaluated for their anticonvulsant activity. Neurotoxicity and hepatotoxicity studies were also performed. Interestingly, out of ten compounds, three compounds (**VIb, VIe** and **VIg**) were found to be effective at a dose of 30 mg/kg. Compounds **VIb** and **VIe** showed slight neurotoxicity whereas **VIg** was found to be free from any neural impairment. Out of the six compounds examined for hepatotoxicity only compound **VIc** showed an elevated alkaline phosphatase value with $p < 0.01$.

Keywords: acetamide, acetazolamide, anticonvulsant activity, neurotoxicity, hepatoxicity

Epilepsy is a central nervous system (CNS) disorder characterized by paroxysmal cerebral dysrythmia, manifesting itself as brief episodes (seizures) of loss or disturbances of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena (1). Approximately 1-2% people in all nations and of all races are affected by epileptic disorder (2, 3). The prevalence of epilepsy and other seizure disorders in Saudi population were estimated approximately 0.65% (4). Over 30% epileptics do not have seizure control even with the best available medications (5).

Thus, the search for newer antiepileptic agents with more selectivity and lower toxicity continues to be an area of investigation in medicinal chemistry (6). In the effort to get the potent antiepileptic agents, several five and six membered heterocyclic compounds were synthesized and had shown considerable anticonvulsant activities (7, 8).

Acetazolamide and methazolamide are well known antiepileptic drugs with 1,3,4-thiadiazole moiety incorporated into acetamide group. Moreover, literature sources have proven that other derivatives of 1,3,4-thiadiazole are also potent anticonvulsant agents (9, 10). Attaching substituted acetamides with 1,3,4-thiadiazole is expected to increase the antiepileptic activity by producing the synergistic effect. Many antiepileptic drugs have been discovered on the basis of structural similarities (11).

The structural similarities between title compounds and acetazolamide (or methazolamide) along with some recently reported antiepileptic agents (12-14) prompted me to design and synthesize several *N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-substituted acetamides for antiepileptic screenings. Interestingly, these compounds were found to have appreciable anticonvulsant activity with lower neuro- and hepatotoxicity.

EXPERIMENTAL

Chemistry

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker model DRX 300 NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on BIO-RAD FTS 135 spectrometer using KBr pellets. TLC was carried out using silica gel G as stationary phase and toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v) as mobile phase for all the obtained compounds. All the chemicals and solvents used were obtained from Merck. All kits used in the present study were the products of Biodiagnostic Co.

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(Egypt), Biosystems Co. (Spain) and Randox Laboratories (U. K.).

Synthesis of (*E*)-*N*-(3-chloro-4-fluorobenzylidene) hydrazinecarbothioamide (III)

To a mixture of equimolar amount of 3-chloro-4-fluorobenzaldehyde (0.01 mol) and thiosemicarbazide (0.01 mol) in absolute ethanol (25 mL), 2-3 drops of acetic acid were added and content of the flask was refluxed for 2.0 h. After completion of the reaction monitored by TLC, the content of the flask was reduced to half by destillation and left overnight for crystallization. The crystalline mass obtained was filtered off, washed with water, dried, and recrystallized from ethanol.

Synthesis of 5-(3-chloro-4-fluorophenyl)-1, 3, 4-thiadiazol-2-amine (IV)

Thiosemicarbazone (**III**, 0.005 mol) obtained above was suspended in 300 mL distilled water in a 1000 mL beaker. Ferric chloride (0.15 mol) in 300 mL distilled water was added to it. The reaction mixture was stirred for one hour at 80-90°C and filtered while hot. A mixture of citric acid (0.11 mol) and sodium citrate (0.05 mol) was added to the filtrate and stirring was continued for 15 min. After cooling the whole solution, it was taken in a bigger vessel (to account for the increase in volume) and neutralized with 10% aqueous ammonia. The precipitate which separated out was filtered and recrystallized from 25% aqueous ethanol to give pure product.

Synthesis of the title compounds (VIa-j)

To a mixture of compound **V** (0.003 mol) and various substituted amine (0.003 mol) in 20 mL of absolute ethanol, 1 mL of triethylamine (TEA) was added and the whole was refluxed for 12–15 h. After completion of the reaction, content of the flask was reduced to half by distillation and left overnight. The crystalline mass obtained was filtered off, washed with water, dried, and recrystallized from ethanol to give the title compounds (**VIa-j**).

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(methylamino)acetamide (VIa)**

Yield 65%, m.p. 128°C, R_f 0.63, *C* Log P 2.69; IR (KBr, cm^{-1}): 3323 (NH), 2897 (CH), 1556 (C=O), 1489 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.91 (s, 1H), 7.59-7.61 (d, 1H, *J* = 8.0 Hz), 6.53-6.41 (dd, 1H, *J* = 7.8, *J* = 2.3 Hz), 6.01 (bs, 1H, NHC=O, D_2O-exchangeable), 4.12 (s, 2H, CH_2), 2.26 (s, 3H, NH-CH_3), 0.97 (s, H, NH); ESI-MS m/z 300.74.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(cyclohexylamino)acetamide (VIb)**

Yield 61%, m.p. 140°C, R_f 0.77, *C* Log P 4.66; IR (KBr, cm^{-1}): 3326 (NH), 2885 (CH), 1568 (C=O), 1475 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.79 (s, 1H), 7.45-7.47 (d, 1H, *J* = 7.6 Hz), 6.55-6.39 (dd, 1H, *J* = 8.1, *J* = 2.6 Hz), 6.14 (bs, 1H, NHC=O, D_2O-exchangeable), 4.15 (s, 2H, CH_2), 1.57 (m, 11H, cyclohexyl), 0.88 (s, 1H, NH); ESI-MS m/z 368.09.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(phenylamino)acetamide(VIc)**

Yield 59%, m.p. 119°C, R_f 0.73, *C* Log P 4.18; IR (KBr, cm^{-1}): 3341 (NH), 2908 (CH), 1596 (C=O), 1481 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.95 (s, 1H), 7.61-7.63 (d, 1H, *J* = 8.0 Hz), 7.33-7.01 (dd, 1H, *J* = 8.3, *J* = 2.5 Hz), 6.95-6.54 (m, 5H, phenyl), 6.23 (bs, 1H, NHC=O, D_2O-exchangeable), 4.61 (bs, 1H, NH-phen., D_2O-exchangeable), 4.32(s, 2H, CH_2); ESI-MS m/z 362.04.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(p-tolylamino)acetamide (VId)**

Yield 70%, m.p. 133°C, R_f 0.69, *C* Log P 4.64; IR (KBr, cm^{-1}): 3337 (NH), 2898 (CH), 1578 (C=O), 1475 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.81 (s, 1H), 7.58-7.60 (d, 1H, *J* = 8.2 Hz), 7.54-7.40 (dd, 1H, *J* = 7.0, *J* = 2.1 Hz), 6.91-6.50 (m, 4H, phenyl), 6.11 (bs, 1H, NHC=O, D_2O-exchangeable), 4.47 (bs, 1H, NH-phen., D_2O-exchangeable), 4.08 (s, 2H, CH_2), 2.26 (s, 3H, CH_3-phen.); ESI-MS m/z 376.06.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(4-chlorophenylamino)acetamide (VIe)**

Yield 63%, m.p. 129°C, R_f 0.57, *C* Log P 4.97; IR (KBr, cm^{-1}): 3378 (NH), 2928 (CH), 1585 (C=O), 1488 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.88 (s, 1H), 7.78-7.80 (d, 1H, *J* = 7.8 Hz), 7.65-7.51 (dd, 1H, *J* = 7.6, *J* = 2.2 Hz), 6.98-6.25 (m, 4H, phenyl), 6.13 (bs, 1H, NHC=O, D_2O-exchangeable), 4.86 (bs, 1H, NH-phen., D_2O-exchangeable), 4.16 (s, 2H, CH_2); ESI-MS m/z 396.00.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(4-fluorophenylamino)acetamide (VIf)**

Yield 75%, m.p. 127°C, R_f 0.88, *C* Log P 4.63; IR (KBr, cm^{-1}): 3381 (NH), 2934 (CH), 1589 (C=O), 1491 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.93 (s, 1H), 7.81-7.83 (d, 1H, *J* = 8.0 Hz), 7.69-7.50 (dd, 1H, *J* = 7.3, *J* = 1.9 Hz), 7.08-6.32 (m, 4H, phenyl), 6.18 (bs, 1H, NHC=O, D_2O-exchangeable), 4.93 (bs, 1H, NH-phen., D_2O-exchangeable), 4.21 (s, 2H, CH_2); ESI-MS m/z 380.03.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(4-methoxyphenylamino)acetamide (VIg)**

Yield 67%, m.p. 138°C, R_f 0.83, *C* Log P 4.00, IR (KBr, cm^{-1}): 3345 (NH), 2906 (CH), 1552 (C=O), 1466 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.72 (s, 1H), 7.65-7.63 (d, 1H, *J* = 7.5 Hz), 7.54-7.33 (dd, 1H, *J* = 7.9, *J* = 2.4 Hz), 6.98-6.79 (m, 4H, phenyl), 6.12 (bs, 1H, NHC=O, D_2O-exchangeable), 4.61 (bs, 1H, NH-phen., D_2O-exchangeable), 4.17 (s, 2H, CH_2), 3.39 (s, 3H, -OCH_3); ESI-MS m/z 392.05.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(piperidin-1-yl)acetamide (VIh)**

Yield 72%, m.p. 115°C, R_f 0.93, *C* Log P 3.24; IR (KBr, cm^{-1}): 3328 (NH), 2879 (CH), 1541 (C=O), 1452 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.61 (s, 1H), 7.24-7.22 (d, 1H, *J* = 7.7 Hz), 6.43-6.20 (dd, 1H, *J* = 7.4, *J* = 2.05 Hz), 6.08 (bs, 1H, NHC=O, D_2O-exchangeable), 4.15 (s, 2H, CH_2), 2.88-2.72 (m, 5H, piper.), 2.52-2.38 (m, 4H, piper.), 1.88 (s, 1H, NH); ESI-MS m/z 354.07.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-morpholinoacetamide (VIi)**

Yield 55%, m.p. 122°C, R_f 0.86, *C* Log P 1.69; IR (KBr, cm^{-1}): 3336 (NH), 2883 (CH), 1556 (C=O), 1478 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.72 (s, 1H), 7.31-7.29 (d, 1H, *J* = 7.8 Hz), 6.49-6.25 (dd, 1H, *J* = 7.6, *J* = 2.2 Hz), 6.15 (bs, 1H, NHC=O, D_2O-exchangeable), 4.19 (s, 2H, CH_2), 3.97 (s, H, NH), 2.95-2.81 (m, 4H, morph.), 2.63-2.33 (m, 4H, morph.); ESI-MS m/z 356.05.

***N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]-2-(4-methylpiperazin-1-yl)acetamide (VIj)**

Yield 79%, m.p. 130°C, R_f 0.65, *C* Log P 2.12; IR (KBr, cm^{-1}): 3331 (NH), 2878 (CH), 1549 (C=O), 1475 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 7.69 (s, 1H), 7.28-7.26 (d, 1H, *J* = 7.6 Hz), 6.41-6.17 (dd, 1H, *J* = 7.5, *J* = 2.3 Hz), 6.10 (bs, 1H, NHC=O, D_2O-exchangeable), 4.13 (s, 2H, CH_2), 3.86 (s, H, NH), 2.75-2.28 (m, 8H, piperazine), 1.86 (s, 3H, CH_3); ESI-MS m/z 369.08.

Pharmacology

Anticonvulsant activity

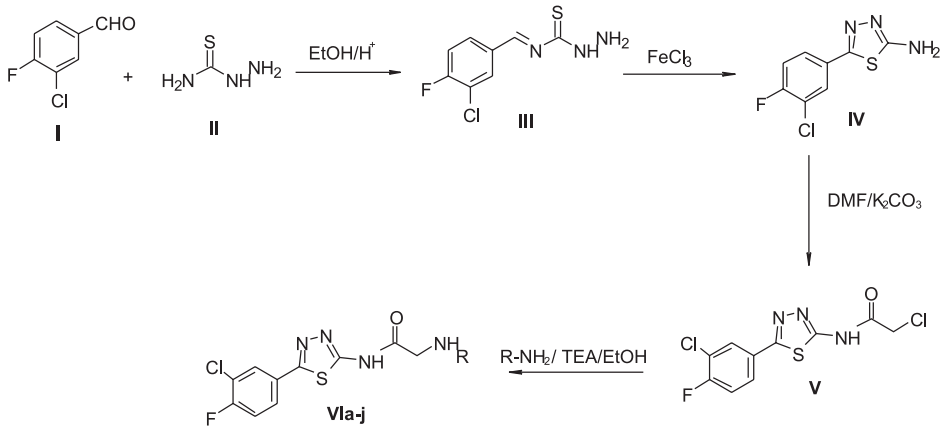
The investigations were conducted on Swiss albino mice of either sex (25-30 g). Food and water were withdrawn prior to the experiments. All the compounds (**VIa-j**) were dissolved in propylene glycol. Initially, all compounds were administered *i.p.* at doses of 30, 100, 300 mg/kg to mice. Activity was established using the MES and scPTZ tests according to the protocol (15, 16) by Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institute of Health, Bethesda, MD, USA.

Maximal electroshock seizure (MES) test

Mice were prescreened 24 h before the testing of the title compounds (**VIa-j**) by delivering maximal electroshock 50 mA; 60 Hz and 0.2 s duration by means of corneal electrodes.. A drop of 0.9% sodium chloride was instilled in each eye prior to the application of electrodes in order to prevent death of the animal. Abolition of hind limb tonic extensor component of the seizure in half or more of the animals is defined as protection.

Subcutaneous pentylenetetrazol test (*sc*PTZ)

The *sc*PTZ test utilized a dose of pentylenetetrazol 70 mg/kg. This produced clonic seizures lasting for a period of at least 5 s. The test compounds were administered at the three graded doses i.e., 30, 100 and 300 mg/kg, *i.p.* At the anticipated



Scheme 1. Synthetic route of the title compounds (**VIa-j**)

time, the convulsant was administered subcutaneously. Animals were observed over a 30 min period. Absence of clonic spasm in half or more of the animals in the observed time period indicated a compound's ability to abolish the effect of pentylenetetrazol on seizure threshold.

Neurotoxicity studies

Rotorod test

The minimal motor impairment was measured in mice by the rotorod test (17). The mice were trained to stay on an accelerating rotorod of diameter 3.2 cm that rotates at 10 rpm. Trained animals were given *i.p.* injection of the test compounds in doses of 30, 100 and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least one minute in each of the three trials.

Ethanol potentiation test

Mice were treated with the test compound and 1 h later with ethanol 2.5 g/kg *i.p*. This dose of ethanol did not induce lateral position in the control animals. The number of animals that were in the lateral position after receiving ethanol in each group was determined (18).

Hepatotoxicity

Liver enzyme estimation

Adult male albino rats (150-175 g) of Wistar strain were used to find out the toxic effects, if any, of the synthesized compounds on liver. The biochemical parameters such as serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) were estimated by the Reitman and Frankel's method (19) while alkaline phosphatase (ALP) was measured by using King's method (20).

RESULTS AND DISCUSSION

Chemistry

The compounds (**VIa-j**) were synthesized according to the route shown in Scheme 1. The synthesis of (*E*)-*N*-(3-chloro-4-fluorobenzylidene) hydrazine carbothioamide (**III**) was involved in a reaction between 3-chloro-4-fluorobenzaldehyde and thiosemicarbazide in the presence of ethanol and acetic acid. In the second step, cyclization of compound (**III**) takes place in the presence of ferric chloride resulting in 1,3,4-thiadiazole synthesis. Synthesis of 2-chloro-*N*-[5-(3-chloro-4-fluorophenyl)-1,3,4-thiadiazol-2-yl]acetamide (**V**) was performed by adding chloroacetyl chloride to a mixture of substituted 1,3,4-thiadiazole (compound **IV**). Similarly, the title compounds (**VIa-j**) were synthesized by reacting compound (**V**) with various substituted phenyl/cyclohexyl/amines in the presence of triethylamine (TEA). The outline of the reactions is shown in Scheme 1. All the synthesized compounds were well characterized by elemental analysis and spectroscopic data. The elemental analyses results for C, H and N were found within ± 0.4% of the theoretical value. In

Table 1. Anticonvulsant and neurotoxicity data of compounds (**VIa-j**).

Compound	MES		scPTZ		Neurotoxicity		Ethanol potentiation
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	
VIa	300	300	X	X	X	X	X
VIb	30	100	300	(–)	300	(–)	300
VIc	100	100	100	300	300	(–)	(–)
VId	100	300	(–)	(–)	(–)	(–)	300
VIe	30	100	100	300	300	300	(–)
VIf	100	300	(–)	300	(–)	(–)	(–)
VIg	30	300	(–)	300	(–)	(–)	(–)
VIh	300	300	X	X	X	X	X
VIi	(–)	(–)	X	X	X	X	X
VIj	300	300	X	X	X	X	X
Phenytoin	30	30	(-)	(-)	100	100	X

Dose of 30, 100 and 300 mg/kg were administered *i.p*. The figures indicate the minimum dose whereby bioactivity was demonstrated in half or more mice. The (-) indicates an absence of activity at maximum dose administered (300 mg/kg). The (X) indicates not tested.

Table 2. Enzyme estimation of the most active compounds.

Compound	ALP (KA unit/dL) (Mean ± SEM)	SGOT (IU/L) (Mean ± SEM)	SGPT (IU/L) (Mean ± SEM)
VIb	30.43 ± 1.62	43.37 ± 2.04	45.54 ± 1.23
VIc	38.79 ± 0.98**	36.89 ± 1.05	40.94 ± 0.96
VId	31.97 ± 1.06	48.21 ± 1.71	51.27 ± 1.98
VIe	26.31 ± 1.17	37.21 ± 1.37	44.67 ± 1.40
VIf	24.97 ± 1.81	50.37 ± 2.01	51.99 ± 1.05
VIg	36.07 ± 1.59	54.28 ± 1.89	57.51 ± 1.91
Control	23.5 ± 1.70	29.57 ± 1.65	33.20 ± 0.85

The concentrations of SGPT and SGOT are expressed in international unit per liter whereas for alkaline phosphatase, the concentration is expressed as KA unit per deciliter. Number of animals tested (n = 6). Significantly different from control **$p < 0.01$. The mean ± SEM values were calculated using ANOVA followed by Dunnett's multiple comparison test.

the IR spectra, absorption bands for N-H, C-H, C=O and C=C were found in the region of 3381-3323, 3934-2878, 1596-1541 and 1491-1452 cm^{-1}, respectively. The ^{1}H NMR spectra showed three distinct aromatic zones of multiplet at δ values 6.65-7.93 ppm. A broad singlet was assigned for N-H attached with 1,3,4-thiadiazole.

Anticonvulsant activity

Anticonvulsant evaluation of compounds (**VIa-j**) in mice utilizing MES and scPTZ models are summarized in Table 1 together with the neurotoxicity data. Among the tested compounds of the series, **VIb, VIe** and **VIg** exhibited fifty percent or more protection at a dose of 30 mg/kg after 0.5 h and have shown activity comparable to phenytoin. Out of these three compounds, **VIb** and **VIe** were also active after 4 h at a dose of 100 mg/kg body mass. This shows the rapid onset and long duration of action of these compounds at a comparatively low dose. Compounds **VIc, VId** and **VIf** showed protection at a dose of 100 mg/kg body mass after 0.5 h. These compounds were also active after 4 h but at a higher dose, 300 mg/kg body mass, except compound **VIc** which was active after 4 h at the same dose i.e., 100 mg/kg body mass. This shows the ability of these compounds to prevent spreading of seizures. Compound **VIi** is devoid of activity in MES test whereas the rest of the compounds have very low activity.

Only those compounds were chosen for chemoshock activity utilizing scPTZ animal model that showed the highest to moderate activity against MES test. Therefore, compounds **VIb**, **VIc**, **VId**, **VIe**, **VIf** and **VIg** were subjected to scPTZ test. Compounds **VIc** and **VIe** showed significant activity while compounds **VIb**, **VId**, **VIf** and **VIg** exhibited low or no activity.

The undesired side effect i.e., neurotoxicity of highly and moderately active compounds were evaluated by conducting the rotorod and ethanol potentiation tests and the results are expressed in Table 1. Three compounds **VIb**, **VIe** and **VIg** that exhibited encouraging anti-MES activity were found safe or to possess very low neurotoxicity. Two anticonvusant active compounds, **VIb** and **VId** showed very low motor impairment in ethanol potentiation tests. The other active compounds successfully passed the rotorod and ethanol potentiation test.

Compounds **VIb**, **VIc**, **VId**, **VIe**, **VIf** and **VIg** were selected for the liver enzyme analysis as these compounds were found potent in anticonvulsion tests. Exposure to high concentrations of these compounds (300 mg/kg) may result in its accumulation in the liver and, in turn, to alterations in the liver function. Transaminases (SGOT and SGPT) are intracellular enzymes, released into the circulation after damage and necrosis of hepatocytes. Alkaline phosphatase (ALP) is a membrane-bound enzyme related to the transport of various metabolites and is considered a sensitive biomarker for liver disease. Liver enzyme estimation of the above mentioned compounds was carried out and the results are shown in Table 2. Results are expressed in international unit per liter (as the mean ± SEM) for SGOT and SGPT and KA unit per deciliter for alkaline phosphatase, with six animals in each group whereas **$p < 0.01$ is significantly different from control. It was observed that all the values were comparable to the control and the changes seen, were not significant except in case of compound **VIc** that showed an elevated alkaline phosphatase value ($p < 0.01$). Hence it can be concluded that except compound **VIc**, the other tested compounds do not possess any adverse affect on liver or bone tissues.

The *C* log P data for all the title compounds (**VIa-j**) were calculated using ACD lab version 8.0. A majority of the compounds i.e., **VIa**, **VIb**, **VIc**, **VId**, **VIe**, **VIf**, **VIg**, **VIh**, and **VIj** have *C* Log *P* value above 2 except compound **VIi** which has *C* Log P value 1.69. It was suggested in the literature that a *C* Log P value of at least 2.0 is required for a drug to cross the blood brain barrier (21, 22). The *C* Log P data were in agreement with the aforementioned hypothesis (except compound **VIg**) and it was observed that those compounds which had C Log P values above 2 exhibited significant anticonvulsant activity.

In structure activity relationship, it was noticed that one of the major contributing factors which regulate the anticonvulsant activity was the different substitutions in the aromatic ring, and particularly halogen substitutions (**VIe** and **VIf**) showed an increase in the potency in MES screen**.** Furthermore, the presence of a bulkier electron donating methoxy group at para position of the phenyl ring i.e., compound **VIg**, exhibited a paradoxical result with the lipophilicity hypothesis. An increase in anticonvulsant activity was observed in methoxy derivative (compound **VIg)**, even though methoxy derivative was less lipophilic than the methyl (compound **VId)** and the unsubstituted (compound **VIc)** derivatives of phenyl ring. The same lipophilic hypothesis may be applied for highly active compound **VIb** (30 mg/kg) which contains cyclohexyl group. Replacing carbon atom from cyclohexyl ring with any heteroatom caused a decrease in activity as observed in compounds **VIh**, **VIi** and **VIj**.

In conclusion, it can be said that the present series of acetamide derivatives display an encouraging anticonvulsant activity with lower neuro- and hepatotoxicity. These compounds can be considered as lead molecules for future investigations.

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