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Research Article

Synthesis, Preliminary Anticonvulsant (Electro-Shock) and Acute Oral Toxicity Screening of Substituted-3-Acetyl-2-(substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(substitutedphenyl)propan-1-one

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ABSTRACT

The current research aimed to synthesize a novel series of 5-substituted mannich bases using the substitution at 5th position at which the hydrogen atom was replaced by two different substituents, p-nitroacetophenone and p-chloroacetophenone having significant anticonvulsant activity. A novel series of substituted-3-acetyl-2-(substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(substitutedphenyl)propan-1-one (6a-6t) were synthesized and evaluated for pharmacological activity. A total of 20 compounds, were synthesized by conventional methods and the purity of synthesized compounds were confirmed by melting point and thin layer chromatography (TLC) analysis. Fourier transform infrared (FTIR), proton nuclear magnetic resonance (^{1}H-NMR), mass and elemental analysis characterized the structures of lead compounds. All the novel synthesized compounds (6a-6t) were preliminarily screened by anticonvulsant activity by maximum electroshock induced seizure against phenytoin as a standard drug at a 30 mg/kg dose. In the results of the spectral study, all the compounds showed characteristic peaks in FTIR and ^{1}H-NMR spectroscopy. Compounds containing chlorine moiety show [M+2]+ peak in mass spectrum. In this study all the novel synthesized compounds showed significant anticonvulsant activity. The most significant synthesized compound 3-acetyl-2-(3-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6e) found as a primary class of anticonvulsants that have shown practically identical anticonvulsant action with uniquely lower neurotoxicity. Further, the preliminary safety profile of the most potent significant compound (6e) was screened for 'acute oral toxicity' as per organisation for economic co-operation and development (OECD) guidelines, in total fourteen days of observation the normal behavior of animals suggest that compound (6e) was safe and non-toxic in nature. This study suggested further modification and improvement in the field of anticonvulsants drug development.

Introduction

Epilepsy is a broadly communal series of neurological conditions affecting millions of individuals worldwide. It's mostly distributed and spread with a greater chance, especially in infants and aged individuals. Currently, genomic technology is revealing the multi-cellular genetic configuration of epilepsy types, generating a paradigm shift.[1] Epilepsy is multi-complex cellular neurological manifestation and a study of genetic predisposition but not a single expression phenomenon with etiology.[2] The current study has resulted in a newer classification of epileptic manifestations (fits) and diverse epilepsy. Antiepileptic therapy might overcome seizures in up to two-thirds of all persons but does not alter prolonged prognosis[3,4] Nitrogen and sulfur-containing heterocyclic

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compounds play an important role in various fields of the pharmaceutical drug industry.[5] Heterocyclic chemistry includes at least half of all research in the field of organic chemistry worldwide. Specific configurations of heterocyclic compounds build the basic skeleton for numerous pharmaceutical, veterinary and agrochemical agents. In recent ten years, heterocyclic molecules got special attention due to their efficient uses in medicinal chemistry.[6] 1,5-Benzothiazepine derivatives play a significant function of the development and discovery of new drugs, due to their wide range of biological effects, i.e., antifeedants,[7] cardiovascular,[4] antimicrobial,[5] antifungal,[8] calcium antagonist,[9] central nervous system depressant,[10] anti-platelet aggregation,[11] anti-human immunodeficiency virus,[12] bradykinin receptor antagonist,[13] anti-inflammatory[14] and anti-psychotic agents.[15] Traditionally, small heterocyclic molecules have been a reliable source for the discovery of novel medicinal agents.[16,17]

From previous studies, it was shown that anticonvulsant properties containing compounds follow the Lipinski's rule of five, a good absorption and permeability of the central nervous system CNS is likely if: molecular weight is ≤ 500, oil/water distribution coefficient (LogP) is ≤ 5 (all the existing antiepileptic drugs has logP in the range of 1.3–2.8), hydrogen bond donors ≤ 5 (expressed as the sum of OHs and NHs), hydrogen bond acceptor ≤ 10 (expressed as the sum of Ns and Os) and number of rotatable bonds ≤ 10. Successfully strategy by the literature data supports substitution in 1,5-Benzothiazepine at 3 and 5 positions, yielding a compound with clinical benefit for new antiepileptic drugs.[18,19] Former experimental data investigation unfolded different compounds generated by ring system substitution at various positions.

The current research was aimed to synthesize a novel series of 5-Substituted mannich bases by the substitution at 5th position at which hydrogen atom was replaced by two different substituents, *p*-nitroacetophenone and *p*-chloroacetophenone having significant anticonvulsant activity. All the novel substituted synthesized derivatives has been confirmed by elemental and spectroscopic analysis, the final compounds substituted-3-Acetyl-2-(substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(substitutedphenyl)propan-1-one (6a-6t) preliminary screening for anticonvulsant agent by Maximal electroshock seizures (MES) method.[20] Rota rod study also evaluated for neurotoxicity.[21] In context to confirmation of safety profile, acute oral toxicity studies as per OCED guidelines.[22]

Nowadays epilepsy is a serious neurological disorder that affects around 50 million people worldwide. Almost 30% of epileptic patients suffer from pharmacoresistance, which is associated with social isolation, dependent behavior, low marriage rates, unemployment, psychological issues and reduced quality of life. In the current scenario, the problem is that the larger number of antiepileptic drugs available in the market but they have many side effects, limited route of drug administration and limited efficacy. So, development of new antiepileptic derivatives or modification in existed 1, 5-Benzothiazepine compound is necessary.

Materials and Methods

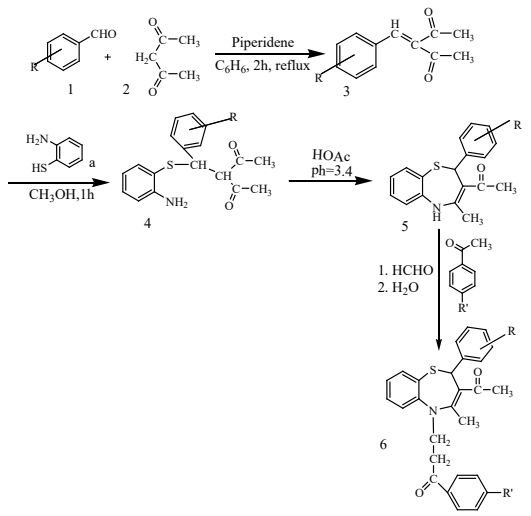
All the solvents and reagents used for the synthesis of novel compounds were purchased from S.D. Fine Chemicals and E. Merck. The melting point ranges of all the novel synthesized compounds were determined by the open tube capillary method[23] by melting point test apparatus (Medicraft Pharmaceutical Pvt. Ltd.). The final product and intermediate product of chemical reactions was monitored by TLC in which mobile phase used chloroform: methanol (9:1). A chemical structure of novel synthesized compounds was confirmed by Infra-red spectrometer on perkin-elmer FTIR-8400S (made by SHIMADZU, Japan) in which KBr pressed pellet techniques were used. Proton Nuclear Magnetic Resonance (NMR) spectra on Bruker DRX300 in DMSO-d6 at 300 MHz (TMS as an internal standard used) and Molecular mass characterized by Micro mass quarto electrospray ionisation mass spectrometry (ESI-MS) by ESI technique. Elemental analysis characterized by Carlo Erba EA 1108. The oil/water distribution coefficient is determined by using octanol phosphate buffer solution and calculating log *p-value* by Chem-draw Ultra 8 software.

General Procedure for Synthesis of Substituted-3-acetyl-2-(substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(substitutedphenyl) propan-1-one (6a-6t)

Piperidine and 2, 4-pentadione were dissolved in benzene containing a round bottom flask, then substituted benzaldehyde added dropwise drop at a room temperature, refluxing the reaction mixture for two hrs with continuous stirring. Cool the reaction mixture and then the organic layer is washed by 10% sodium carbonate solution. The product is collected and reacts with *o*-Aminothiophenol with continuous stirring for about one hrs. After completing the chemical reaction, collect the solid product and wash it with methanol and water. The methanol-containing solid product treated acetic acid until pH reaches four with continuous stirring for about 12 hours. The solid product obtained by reaction mixture was collected and then washed and recrystallized with methanol. Mannich bases (6a-6t) are obtained by reacting the compound (5) with two different substituents *p*-nitroacetophenone and *p*-chloroacetophenone in the presence of formaldehyde and refluxing the mixture for about 3 hours (Table 1).

Determination of Partition Coefficient (log P)

The determination of oil/water distribution coefficient/ partition coefficient (log P) of substituted-3-acetyl-2-(substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-



Scheme 1: Synthesis of Substituted-3-acetyl-2-(substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(substitutedphenyl) propan-1-one (6a-6t)

5(2H)-yl)-1-(substitutedphenyl)propan-1-one (6a-6t) using octanol and phosphate buffer by flask shake method and C log P calculated with the help of Chem. Draw ultra 8 version software.

Where, R = H, *o*-Cl, *m*-Cl, *p*-Cl, *o*-NO_2, *m*-NO_2, *p*-NO_2, *O*-OCH_3, *m*-OCH_3, *p*-OCH_3. R' = Cl, NO_2.

Spectral Analysis

3-Acetyl-2-phenyl-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chloro phenyl)propan-1-one (6a*)* FTIR (KBr) n, cm^{-1}: 3072 (Ar. C-H_{str}), 2977 (Ali. C-H_{str}), 1688 (C=O_{str}), 1618 (Ar. C=C$_{str}$), 1272 (Ar. C-N_{str}), 1182 (Al. C-N_{str}), 824 (Ar. C-Cl_{str}), 726 (C-H *p*-disub. benzene), 648 (C-S_{str}); ^{1}H NMR, δ ppm: 1.840 (s, 3H, CH_3), 2.294 (s, 3H, CH_3), 2.893-2.943 (m, 4H, CH_2), 6.128 (s, 1H, Ar-H), 7.280-7.408 (m, 12H, Ar-H); MS (m/z): 363 $[M+1]^+$, 364 $[M+2]^+$; Elemental analysis: C, 70.25, H, 5.65, N, 3.26, S, 6.87, Cl, 7.21 %.

3-Acetyl-2-phenyl-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-nitro phenyl)propan-1-one (6b*)* FTIR (KBr) n, cm^{-1}: 3075 (Ar. C-H_{str}), 2925 (Ali. C-H_{str}), 1687 (C=O_{str}), 1623 (Ar. C=C$_{str}$), 1421 (N-Ostr), 1325 (Ar. C-N_{str}), 1180 (Al. C-N_{str}), 806 (C-H *p*-disub. benzene), 701 (C-S_{str}); ^{1}H NMR, δ ppm: 1.322 (s, 3H, CH_3), 2.142 (s, 3H, CH_3), 2.854-2.925 (m, 4H, CH_2), 6.219 (s, 1H, Ar-H), 7.569-7.893 (m, 12H, Ar-H); MS (m/z): 473 $[M+1]^+$; Elemental analysis: C, 67.34 , H, 4.65, N, 5.23, S, 5.74 %.

3-Acetyl-2-(4-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-chloro phenyl)propan-1-one (6c) FTIR (KBr) n, cm^{-1}: 3080 (Ar. C-H_{str}), 2958 (Ali. C-H_{str}), 1685 (C=O_{str}), 1602 (Ar. C=C$_{str}$), 1326 (Ar. C-N_{str}), 1180 (Al. C-N_{str}), 852 (Ar. C-Cl_{str}), 812 (C-H *p*-disub. benzene), 703 (C-S_{str});^{1}H NMR, δ ppm: 1.309 (s, 3H, CH_3), 2.029 (s, 3H, CH_3), 2.821-2.993(m, 4H, CH_2), 6.229 (s, 1H, Ar-H), 7.722-7.941 (m, 12H, Ar-H); MS (m/z): 497 $[M+1]^+$, 498 $[M+2]^+$; Elemental analysis: C, 65.34, H, 4.34, N, 3.45, S, 5.74, Cl, 13.87 %.

3-Acetyl-2-(4-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-nitro phenyl)propan-1-one (6d) FTIR (KBr) n, cm^{-1}: 3078 (Ar. C-H_{str}), 2939 (Ali. C-H_{str}), 1674 (C=O_{str}), 1592 (Ar. C=C$_{str}$), 1419 (N-Ostr), 1313 (Ar.

Table 1: Physicochemical data of synthesized compounds (6a-6t)

Compound	R	R'	Molecular formula	Log P value	CLog P value	Melting Point (°C)	*R_f value	Yield (%)
6a	H	Cl	$C_{27}H_{24}ClNO_2S$	3.12	3.75	82–83	0.87	43
6b	H	NO_2	$C_{27}H_{24}N_2O_4S$	0.76	1.87	77	0.93	41
6c	4-Cl	Cl	$C_{27}H_{23}Cl_2NO_2S$	3.68	3.47	78–79	0.96	36
6d	4-Cl	NO_2	$C_{27}H_{23}ClN_2O_4S$	0.65	1.58	88–89	0.81	43
6e	3-Cl	Cl	$C_{27}H_{23}Cl_2NO_2S$	3.48	3.47	83–84	0.74	84
6f	3-Cl	NO_2	$C_{27}H_{23}ClN_2O_4S$	0.54	1.23	79–80	0.54	75
6g	2-Cl	Cl	$C_{27}H_{23}Cl_2NO_2S$	5.68	7.47	86–87	0.61	63
6h	2-Cl	NO_2	$C_{27}H_{23}ClN_2O_4S$	0.75	1.69	109–110	0.86	40
6i	4-NO_2	Cl	$C_{27}H_{23}ClN_2O_4S$	0.49	1.83	98–99	0.36	55
6j	4-NO_2	NO_2	$C_{27}H_{23}N_3O_6S$	0.89	1.45	76–77	0.53	49
6k	3-NO_2	Cl	$C_{27}H_{23}ClN_2O_4S$	1.02	1.53	84–85	0.38	71
6l	3-NO_2	NO_2	$C_{27}H_{23}N_3O_6S$	0.93	1.47	73	0.93	64
6m	2-NO_2	Cl	$C_{27}H_{23}ClN_2O_4S$	0.93	1.72	89–90	0.42	52
6n	2-NO_2	NO_2	$C_{27}H_{23}N_3O_6S$	0.94	1.21	76–77	0.64	67
6o	4-OCH_3	Cl	$C_{28}H_{26}ClNO_3S$	3.21	3.67	142–143	0.75	60
6p	4-OCH_3	NO_2	$C_{28}H_{26}N_2O_5S$	1.43	1.79	156	0.78	73
6q	3-OCH_3	Cl	$C_{28}H_{26}ClNO_3S$	3.00	3.67	162–163	0.67	62
6r	3-OCH_3	NO_2	$C_{28}H_{26}N_2O_5S$	1.24	1.73	148–149	0.84	42
6s	2-OCH_3	Cl	$C_{28}H_{26}ClNO_3S$	3.53	3.97	167–168	0.52	76
6t	2-OCH_3	NO_2	$C_{28}H_{26}N_2O_5S$	1.06	1.89	153–154	0.47	62

*Mobile phase: Chloroform: Methanol (9:1)

Table 2: Anticonvulsant evaluation after 0.5 hrs administration of compounds (6a-6t) using MES model

Compound No.	*Doses (mg/kg)*	*Time (sec) in various phases of convulsion after 0.5 hrs*				*Recovery/ Death*	*Neurotoxicity screen*
		Flexion (Mean ± SEM)	*Extensor (Mean ± SEM)*	*Clonus (Mean ± SEM)*	*Stupor (Mean ± SEM)*		
	30	4.43 ± 0.34***	7.67 ± 0.44***	15.66 ± 0.21***	116.13 ± 0.64***	Recovery	Absent
6a	100	3.59 ± 0.28**	9.28 ± 0.07***	10.48 ± 0.92***	48.50 ± 1.40***	Recovery	Absent
	300	5.09 ± 0.30***	11.3 ± 0.47***	35.97 ± 0.94***	119.48 ± 0.68***	Recovery	Absent
	30	5.14 ± 0.80^{ns}	16.35 ± 0.73^{ns}	18.67 ± 0.98***	120.05 ± 1.73**	Recovery	Absent
6b	100	3.46 ± 0.39**	23.26 ± 0.63***	33.05 ± 0.47**	55.02 ± 0.31**	Recovery	Absent
	300	6.35 ± 0.59**	25.20 ± 0.50***	36.81 ± 0.88*	120.62 ± 0.60**	Recovery	Absent
	30	4.04 ± 0.22**	6.47 ± 0.36***	9.06 ± 0.24***	47.02 ± 0.28***	Recovery	Absent
6c	100	2.44 ± 0.17***	4.47 ± 0.09***	8.40 ± 0.05***	46.22 ± 0.24***	Recovery	Absent
	300	4.19 ± 0.20***	18.21 ± 0.84***	34.01 ± 0.51***	113.87 ± 0.18***	Recovery	Absent
	30	8.41 ± 0.41^{ns}	23.75 ± 0.31**	40.87 ± 1.00**	193.48 ± 0.85**	Recovery	Absent
6d	100	9.23 ± 0.29**	11.14 ± 0.20^{ns}	20.74 ± 0.50***	61.39 ± 0.47***	Recovery	Absent
	300	4.85 ± 0.72**	22.71 ± 0.40***	34.51 ± 0.82***	113.99 ± 0.43**	Recovery	Absent
	30	3.46 ± 0.34***	4.87 ± 0.17***	8.78 ± 0.18***	44.07 ± 0.62***	Recovery	Absent
6e	100	2.84 ± 0.35***	3.09 ± 0.18***	8.32 ± 0.43***	45.06 ± 1.19***	Recovery	Absent
	300	3.17 ± 0.30***	7.9 ± 0.18***	18.84 ± 0.15***	114.74 ± 0.72***	Recovery	Absent
	30	8.28 ± 0.44^{ns}	22.73 ± 0.67**	41.03 ± 0.85**	193.48 ± 0.96**	Recovery	Absent
6f	100	5.35 ± 0.33**	10.41 ± 0.58***	44.81 ± 0.55**	52.40 ± 0.39**	Recovery	Absent
	300	10.75 ± 0.22**	20.82 ± 0.25	35.39 ± 0.50**	114.54 ± 0.30**	Recovery	Absent
	30	2.83 ± 0.36***	3.73 ± 0.18***	7.79 ± 0.32***	40.15 ± 0.37***	Recovery	Absent
6g	100	3.05 ± 0.17***	5.13 ± 0.24***	9.01 ± 0.19***	45.48 ± 0.50***	Recovery	Absent
	300	4.07 ± 0.23**	20.435 ± 0.29**	35.13 ± 0.42**	119.34 ± 0.45**	Recovery	Absent
	30	7.42 ± 0.21ns	22.18 ± 0.27^{ns}	39.07 ± 0.09**	191.48 ± 0.47*	Recovery	Absent
6h	100	5.98 ± 0.40**	10.13 ± 0.32***	42.74 ± 0.69*	165.63 ± 0.72**	Recovery	Absent
	300	10.27 ± 0.32*	21.66 ± 0.28*	35.76 ± 0.37**	120.18 ± 0.63***	Recovery	Absent
	30	8.27 ± 0.44*	23.58 ± 0.28^{ns}	40.35 ± 0.81*	193.01 ± 0.43*	Recovery	Absent
6i	100	8.37 ± 0.35**	23.73 ± 0.28^{ns}	40.75 ± 1.04*	190.67 ± 0.70*	Recovery	Absent
	300	7.46 ± 0.28**	21.70 ± 0.67*	37.24 ± 0.51*	188.54 ± 0.75**	Recovery	Absent
	30	8.86 ± 0.31^{ns}	27.12 ± 0.91^{ns}	41.29 ± 0.71*	196.19 ± 1.64*	Recovery	Absent
6j	100	9.26 ± 0.49*	26.07 ± 0.56*	41.31 ± 0.77*	193.45 ± 1.17*	Recovery	Absent
	300	7.70 ± 0.38*	23.27 ± 0.56*	37.21 ± 0.44*	189.64 ± 0.39*	Recovery	Absent
	30	7.63 ± 0.40**	20.74 ± 0.50*	37.95 ± 0.34**	168.31 ± 0.56**	Recovery	Absent
6k	100	6.84 ± 0.20**	21.16 ± 0.51***	35.38 ± 0.45**	164.85 ± 0.77**	Recovery	Absent
	300	7.43 ± 0.48**	22.58 ± 0.33**	39.20 ± 0.43**	188.63 ± 0.64***	Recovery	Absent
	30	8.30 ± 0.18*	23.18 ± 0.59^{ns}	39.66 ± 0.30*	171.57 ± 0.53*	Recovery	Absent
6l	100	7.85 ± 0.43**	21.98 ± 0.74**	37.52 ± 0.78**	170.11 ± 0.55**	Recovery	Absent
	300	7.86 ± 0.39**	23.19 ± 0.64*	41.61 ± 0.82*	189.83 ± 0.91*	Recovery	Absent
	30	9.50 ± 0.46**	23.67 ± 0.31**	45.08 ± 0.67^{ns}	195.22 ± 0.76**	Recovery	Absent
6m	100	9.16 ± 0.39**	23.10 ± 0.32**	43.38 ± 0.45**	193.88 ± 0.61**	Recovery	Absent
	300	8.26 ± 0.44**	23.02 ± 0.39**	38.34 ± 0.50**	193.57 ± 0.56**	Recovery	Absent
	30	10.99 ± 0.21**	24.89 ± 0.20^{ns}	45.39 ± 0.45	198.69 ± 0.73**	Recovery	Absent
6n	100	9.59 ± 0.22**	24.62 ± 0.45^{ns}	44.32 ± 0.33**	195.01 ± 0.50**	Recovery	Absent
	300	8.85 ± 0.19**	22.79 ± 0.55**	40.31 ± 0.54***	193.61 ± 0.25**	Recovery	Absent

	30	6.40 ± 0.20***	24.12 ± 0.17***	26.39 ± 0.79***	127.34 ± 0.92**	Recovery	Absent
6o	100	5.01 ± 0.31***	7.72 ± 0.52***	17.63 ± 0.24***	51.59 ± 0.50***	Recovery	Absent
	300	6.59 ± 0.44***	11.47 ± 0.85***	36.13 ± 0.91**	127.21 ± 0.88***	Recovery	Absent
	30	7.15 ± 0.22*	24.37 ± 0.58^{ns}	25.55 ± 0.42**	126.01 ± 0.39**	Recovery	Absent
6p	100	8.66 ± 0.22*	22.97 ± 0.30*	43.56 ± 0.84*	194.25 ± 0.24*	Recovery	Absent
	300	7.25 ± 0.46**	24.83 ± 0.35*	36.49 ± 0.56**	129.89 ± 0.87**	Recovery	Absent
	30	6.08 ± 0.41**	22.81 ± 0.81*	19.61 ± 0.27***	123.59 ± 0.90^{ns}	Recovery	Absent
6q	100	4.47 ± 0.34**	8.77 ± 0.55***	12.99 ± 0.34***	52.20 ± 0.22***	Recovery	Absent
	300	6.18 ± 0.25***	10.54 ± 0.75***	40.57 ± 0.77*	128.96 ± 0.97***	Recovery	Absent
	30	6.67 ± 0.15**	23.97 ± 0.84**	19.91 ± 0.42***	124.56 ± 0.83**	Recovery	Absent
6r	100	5.62 ± 0.17**	22.04 ± 0.45**	22.02 ± 0.50**	120.99 ± 0.56**	Recovery	Absent
	300	6.49 ± 0.42**	24.37 ± 0.61***	41.77 ± 0.99**	129.61 ± 0.36**	Recovery	Absent
	30	5.52 ± 0.27***	21.01 ± 0.51**	17.17 ± 0.36***	118.19 ± 0.95^{ns}	Recovery	Absent
6s	100	3.13 ± 0.22***	5.87 ± 0.25***	9.45 ± 0.18***	48.96 ± 0.42***	Recovery	Absent
	300	5.76 ± 0.19***	9.80 ± 0.21***	39.25 ± 0.37***	125.91 ± 0.71***	Recovery	Absent
	30	6.6 ± 0.32**	21.23 ± 0.31**	18.31 ± 0.31**	119.24 ± 0.81**	Recovery	Absent
6t	100	6.35 ± 0.49**	21.88 ± 0.58**	22.67 ± 0.61*	121.52 ± 0.22**	Recovery	Absent
	300	6.85 ± 0.53**	23.63 ± 0.41**	40.47 ± 0.56**	126.60 ± 0.68**	Recovery	Absent
Control	30% v/v PEG400	4.74 ± 0.23	15.12 ± 0.12	23.5 ± 0.38	110.80 ± 0.66	Recovery	Absent
Phenytoin	30	2.47 ± 0.04***	3.50 ± 0.08***	7.69 ± 0.17***	42.32 ± 0.19***	Recovery	Absent

N = 6, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3: Anticonvulsant evaluation after 4 hours administration of compounds (6a-6t) using Manufacturing execution systems (MES) model

Compound No.	*Doses (mg/kg)*	*Time (sec) in various phases of convulsion after 4 hours*				*Recovery/Death*	*Neurotox^{i}city screen*
		Flexion (Mean ± SEM)	*Extensor (Mean ± SEM)*	*Clonus (Mean ± SEM)*	*Stupor (Mean ± SEM)*		
	30	4.20 ± 0.24**	7.67 ± 0.44***	15.66 ± 0.21***	114.97 ± 0.96***	Recovery	Absent
6a	100	3.47 ± 0.25***	8.91 ± 0.20***	9.83 ± 0.55***	46.66 ± 0.60***	Recovery	Absent
	300	4.94 ± 0.20*	10.29 ± 0.30***	35.47 ± 0.48***	119.48 ± 0.68***	Recovery	Absent
	30	4.47 ± 0.41**	15.95 ± 0.57^{ns}	18.32 ± 0.91*	118.38 ± 0.48**	Recovery	Absent
6b	100	3.27 ± 0.31***	21.78 ± 0.89**	32.35 ± 0.54***	54.84 ± 0.32***	Recovery	Absent
	300	6.01 ± 0.58**	24.60 ± 0.48**	36.33 ± 0.92**	120.62 ± 0.60**	Recovery	Absent
	30	3.80 ± 0.22**	5.87 ± 0.28***	8.63 ± 0.33***	46.26 ± 0.54***	Recovery	Absent
6c	100	2.30 ± 0.45***	4.10 ± 0.20***	8.06 ± 0.32***	46.22 ± 0.24***	Recovery	Absent
	300	3.73 ± 0.32**	14.89 ± 0.80***	33.01 ± 0.59***	113.87 ± 0.18***	Recovery	Absent
	30	8.27 ± 0.44**	23.93 ± 0.28*	39.60 ± 0.20***	193.34 ± 0.84**	Recovery	Absent
6d	100	8.54 ± 0.31**	11.23 ± 0.19**	21.26 ± 0.46*	61.39 ± 0.47**	Recovery	Absent
	300	4.18 ± 0.32*	22.16 ± 0.51**	33.88 ± 0.50***	113.99 ± 0.5**	Recovery	Absent
	30	3.32 ± 0.29***	4.29 ± 0.23***	8.61 ± 0.17***	43.48 ± 0.27***	Recovery	Absent
6e	100	2.69 ± 0.25***	3.01 ± 0.19***	7.97 ± 0.39***	43.9 ± 0.62***	Recovery	Absent
	300	3.02 ± 0.33**	7.3 ± 0.24***	18.49 ± 0.28***	114.74 ± 0.72***	Recovery	Absent
	30	7.81 ± 0.21**	23.11 ± 0.44***	41.38 ± 0.78**	193.16 ± 0.73**	Recovery	Absent
6f	100	5.07 ± 0.30*	11.51 ± 0.30***	44.16 ± 0.63**	52.40 ± 0.39**	Recovery	Absent
	300	10.85 ± 0.25**	20.43 ± 0.29***	35.27 ± 0.41**	114.54 ± 0.30**	Recovery	Absent

	30	2.68 ± 0.36***	3.62 ± 0.14***	6.99 ± 0.39***	38.79 ± 0.76***	Recovery	Absent
6g	100	2.94 ± 0.16***	4.85 ± 0.20***	8.48 ± 0.29***	45.48 ± 0.50***	Recovery	Absent
	300	3.82 ± 0.19**	19.62 ± 0.47***	34.56 ± 0.32***	119.34 ± 0.45***	Recovery	Absent
	30	7.71 ± 0.21*	21.73 ± 0.35*	39.59 ± 0.60**	191.83 ± 0.42*	Recovery	Absent
6h	100	5.53 ± 0.31**	9.63 ± 0.33***	42.31 ± 0.69**	165.65 ± 0.72*	Recovery	Absent
	300	9.45 ± 0.32*	21.65 ± 0.17*	35.76 ± 0.37**	120.18 ± 0.63**	Recovery	Absent
	30	7.61 ± 0.32***	10.84 ± 0.18***	38.74 ± 0.68**	192.48 ± 0.64**	Recovery	Absent
6i	100	8.90 ± 0.47**	24.03 ± 0.25***	42.12 ± 0.66**	190.66 ± 0.70^{ns}	Recovery	Absent
	300	7.71 ± 0.28***	22.54 ± 0.84***	37.82 ± 0.61**	189.20 ± 0.36***	Recovery	Absent
	30	6.69 ± 0.82***	10.21 ± 0.44***	41.08 ± 0.67**	193.47 ± 0.63**	Recovery	Absent
6j	100	8.93 ± 0.47***	25.56 ± 0.44**	40.95 ± 0.76***	192.45 ± 0.63***	Recovery	Absent
	300	7.36 ± 0.22***	22.96 ± 0.73***	38.03 ± 0.63***	188.89 ± 0.69***	Recovery	Absent
	30	8.27 ± 0.17***	12.35 ± 0.83**	39.09 ± 0.64***	169.16 ± 0.88**	Recovery	Absent
6k	100	7.78 ± 0.55***	21.6 ± 0.56***	37.66 ± 0.81**	164.85 ± 0.77**	Recovery	Absent
	300	8.41 ± 0.45***	22.93 ± 0.46***	41.62 ± 0.91***	188.63 ± 0.64***	Recovery	Absent
	30	7.74 ± 0.37**	23.58 ± 0.28^{ns}	38.19 ± 0.91***	170.35 ± 0.68***	Recovery	Absent
6l	100	7.52 ± 0.50**	19.95 ± 0.79**	37.71 ± 0.79***	170.11 ± 0.55***	Recovery	Absent
	300	7.35 ± 0.36**	22.67 ± 0.62**	41.14 ± 0.74**	190.16 ± 0.85**	Recovery	Absent
	30	8.87 ± 0.18***	11.05 ± 0.30***	44.29 ± 0.27***	166.84 ± 0.40***	Recovery	Absent
6m	100	9.74 ± 0.44**	23.46 ± 0.36***	43.70 ± 0.47***	193.88 ± 0.61**	Recovery	Absent
	300	8.84 ± 0.40***	23.68 ± 0.28***	38.95 ± 0.89*	193.57 ± 0.56***	Recovery	Absent
	30	10.76 ± 0.17**	17.15 ± 0.41**	44.88 ± 0.53**	196.68 ± 0.95**	Recovery	Absent
6n	100	9.42 ± 0.32**	24.45 ± 0.43*	44.45 ± 0.28**	195.01 ± 0.50**	Recovery	Absent
	300	8.99 ± 0.19**	23.13 ± 0.47**	39.79 ± 0.68**	193.61 ± 0.25**	Recovery	Absent
	30	6.07 ± 0.17***	22.60 ± 0.86**	25.09 ± 0.70***	127.00 ± 0.91**	Recovery	Absent
6o	100	4.74 ± 0.27***	7.06 ± 0.48***	17.30 ± 0.26***	51.59 ± 0.50***	Recovery	Absent
	300	6.25 ± 0.26***	11.47 ± 0.42***	35.11 ± 0.36***	128.77 ± 0.55***	Recovery	Absent
	30	6.77 ± 0.29**	23.41 ± 0.39*	25.00 ± 0.30**	125.20 ± 0.34**	Recovery	Absent
6p	100	8.20 ± 0.35*	22.71 ± 0.04*	42.37 ± 0.06**	194.25 ± 0.24**	Recovery	Absent
	300	6.44 ± 0.29**	24.38 ± 0.40^{ns}	35.71 ± 0.41**	132.50 ± 0.60**	Recovery	Absent
	30	5.82 ± 0.35**	21.27 ± 0.94***	19.08 ± 0.62*	121.91 ± 0.81***	Recovery	Absent
6q	100	4.21 ± 0.32^{ns}	8.22 ± 0.35***	12.26 ± 0.42***	52.20 ± 0.22***	Recovery	Absent
	300	5.92 ± 0.15***	10.6 ± 0.61***	38.64 ± 0.49***	128.53 ± 0.95***	Recovery	Absent
	30	6.36 ± 0.40**	22.68 ± 0.83**	19.30 ± 0.37*	123.49 ± 0.96***	Recovery	Absent
6r	100	5.56 ± 0.13***	20.93 ± 0.40***	21.11 ± 0.11***	120.99 ± 0.56***	Recovery	Absent
	300	5.63 ± 0.12***	22.91 ± 0.81***	40.43 ± 0.98**	129.61 ± 0.36**	Recovery	Absent
	30	5.14 ± 0.29*	20.73 ± 0.43***	16.86 ± 0.31*	117.19 ± 0.45***	Recovery	Absent
6s	100	2.95 ± 0.23***	5.71 ± 0.25***	9.00 ± 0.17***	48.96 ± 0.42***	Recovery	Absent
	300	5.57 ± 0.17**	9.48 ± 0.30***	37.55 ± 0.78***	126.13 ± 0.71***	Recovery	Absent
	30	6.20 ± 0.15**	20.99 ± 0.30**	17.76 ± 0.27**	118.17 ± 0.34**	Recovery	Absent
6t	100	5.62 ± 0.17**	20.28 ± 0.60**	21.81 ± 0.40*	121.52 ± 0.22**	Recovery	Absent
	300	6.85 ± 0.53*	23.63 ± 0.41**	40.47 ± 0.56***	126.60 ± 0.68**	Recovery	Absent
Control	30% v/v PEG400	4.53 ± 0.10	15.67 ± 0.18	20.56 ± 0.31	109.08 ± 0.61	Recovery	Absent
Phenytoin	30	1.57 ± 0.11***	3.19 ± 0.13***	7.20 ± 0.20***	37.63 ± 0.30***	Recovery	Absent

N = 6, *p < 0.05, **p < 0.01, ***p < 0.001

Table 4: Oral acute toxicity and gross behavioral studies of synthesized compound (6e)

S. No.	*Response*	*Animals*	
		Prior to treatment	*Later to treatment*
1.	Skin colour	Normal	Normal
2.	Pain response	Normal	Normal
3.	Grooming	Absent	Absent
4.	Food intake	Normal	Normal
5.	Alertness	Normal	Normal
6.	Righting reflux	Normal	Normal
7.	Corneal reflex	Present	Present
8.	Tremors	Absent	Absent
9.	Pupils	Normal	Normal
10.	Convulsion	Absent	Absent
11.	Urination	Normal	Normal
12.	Sleep	Normal	Normal
13.	Diarrhoea	Absent	Absent
14.	Torch response	Normal	Normal
15.	Lethargy	Absent	Absent
16.	Water intake	Normal	Normal
17.	Salivation	Normal	Normal
18.	Coma	Absent	Absent
19.	Gripping	Normal	Normal
20.	Mortality	Not applicable	Nil
21.	Touch response	Normal	Normal

C-N_{str}), 1174 (Al. C-N_{str}), 844 (Ar. C-Cl_{str}), 813 (C-H *p*-disub. benzene), 678 (C-S_{str}); ^{1}H NMR, δ ppm: 1.542 (s, 3H, CH_3), 2.119 (s, 3H, CH_3), 2.880-2.933 (m, 4H, CH_2), 6.293 (s, 1H, Ar-H), 7.370-7.580 (m, 12H, Ar-H); MS (m/z): 508 $[M+1]^+$, 509 $[M+2]^+$; Elemental analysis: C, 63.85, H, 4.65, N, 5.23, S, 5.86, Cl, 6.34 %.

3-Acetyl-2-(3-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6e) FTIR (KBr) n, cm^{-1}: 3082 (Ar. C-H_{str}), 2977 (Ali. C-H_{str}), 1809 (C=O_{str}), 1604 (Ar. C=C_{str}), 1284 (Ar. C-N_{str}), 1174 (Al. C-N_{str}), 833 (C-H *p*-disub. benzene), 754 (C-H *m*-disub. benzene), 644 (C-S_{str}), 603 (Ar. C-Cl_{str}); ^{1}H NMR, δ ppm: 1.329 (s, 3H, CH_3), 2.089 (s, 3H, CH_3), 2.821-2.983 (m, 4H, CH_2), 6.239 (s, 1H, Ar-H), 7.740-7.961 (m, 12H, Ar-H); MS (m/z): 497 $[M+1]^+$, 498 $[M+2]^+$; Elemental analysis: C, 64.64, H, 4.24, N, 2.48, S, 5.67, Cl, 13.***27*** %.

3-Acetyl-2-(3-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6f) FTIR (KBr) n, cm^{-1}: 3078 (Ar. C-H_{str}), 2939 (Ali. C-H_{str}), 1674 (C=O_{str}), 1592 (Ar. C=C_{str}), 1419 (N-Ostr), 1313 (Ar. C-N_{str}), 1174 (Al. C-N_{str}), 844 (C-H *p*-disub. benzene), 813 (C-H *m*-disub. benzene), 761 (Ar. C-Cl str), 678 (C-S_{str}), 603 (Ar. C-Cl_{str}); ^{1}H NMR, δ ppm: 1.312 (s, 3H, CH_3), 2.129 (s, 3H, CH_3), 2.820-2.933 (m, 4H, CH_2), 6.292 (s, 1H, Ar-H), 7.372-7.580 (m, 12H, Ar-H); MS (m/z): 508 $[M+1]^+$, 509 $[M+2]^+$; Elemental analysis: C, 64.12, H, 4.65, N, 4.27, S, 5.42, Cl 5.67 %.

3-Acetyl-2-(2-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6g) FTIR (KBr) n, cm^{-1}: 3068 (Ar. C-H_{str}), 2975 (Ali. C-H_{str}), 1679 (C=O_{str}), 1608 (Ar. C=C_{str}), 1286 (Ar. C-N_{str}), 1116 (Al. C-N_{str}), 835 (C-H *p*-disub. benzene), 754 (C-H *m*-disub. benzene), 603 (C-S_{str}), 540 (Ar. C-Cl_{str}); ^{1}H NMR, δ ppm: 1.229 (s, 3H, CH_3), 2.029 (s, 3H, CH_3), 2.831-2.993 (m, 4H, CH_2), 6.329 (s, 1H, Ar-H), 7.720-7.941 (m, 12H, Ar-H); MS (m/z): 497 $[M+1]^+$, 498 $[M+2]^+$; Elemental analysis: C, 64.56, H, 4.28, N, 2.67, S, 5.41, Cl, 13.28 %.

3-Acetyl-2-(2-chlorophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6h) FTIR (KBr) n, cm^{-1}: 3051 (Ar. C-H_{str}), 2935 (Ali. C-H_{str}), 1677 (C=O_{str}), 1585 (Ar. C=C_{str}), 1419 (N-Ostr), 1315 (Ar. C-N_{str}), 1174 (Al. C-N_{str}), 846 (C-H *p*-disub. benzene), 761 (C-H *o*-disub. benzene), 678 (Ar. C-Cl_{str}), 632 (C-S_{str}); ^{1}H NMR, δ ppm: 1.603(s, 3H, CH_3), 2.214 (s, 3H, CH_3), 2.626-2.732 (m, 4H, CH_2), 6.224 (s, 1H, Ar-H), 7.674-7.727 (m, 12H, Ar-H); MS (m/z): 508 $[M+1]^+$, 509 $[M+2]^+$; Elemental analysis: C, 32.15, H, 2.43, N, 2.21, S, 3.63, Cl, 3.39 %.

3-Acetyl-2-(4-nitrophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6i) FTIR (KBr) n, cm^{-1}: 3089 (Ar. C-H_{str}), 2970 (Ali. C-H_{str}), 1685 (C=O_{str}), 1598 (Ar. C=C_{str}), 1363 (N-Ostr), 1299 (Ar. C-N_{str}), 1145 (Al. C-N_{str}), 790 (C-H *p*-disub. benzene), 730 (Ar. C-Cl_{str}), 686 (C-S_{str}); ^{1}H NMR, δ ppm: 1.322 (s, 3H, CH_3), 2.132 (s, 3H, CH_3), 2.700-2.792 (m, 4H, CH_2), 6.690 (s, 1H, Ar-H), 7.220-7.339 (m, 12H, Ar-H); MS (m/z): 508 $[M+1]^+$, 509 $[M+2]^+$; Elemental analysis: C, 62.53, H, 4.85, N, 5.23, S, 7.12, Cl, 5.21 %.

3-Acetyl-2-(4-nitrophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6j) FTIR (KBr) n, cm^{-1}: 3099 (Ar. C-H_{str}), 2925 (Ali. C-H_{str}), 1789 (C=O_{str}), 1687 (Ar. C=C_{str}), 1325 (N-Ostr), 1292 (Ar. C-N_{str}), 1180 (Al. C-N_{str}), 933 (C-H *p*-disub. benzene), 806 (C-S_{str}); ^{1}H NMR, δ ppm: 1.820 (s, 3H, CH_3), 2.326-2.442 (m, 4H, CH_2), 3.143 (s, 3H, CH_3), 6.802 (s, 1H, Ar-H), 7.702-7.827 (m, 12H, Ar-H); MS (m/z): 518 $[M+1]^+$; Elemental analysis: C, 62.66, H, 4.42, N, 8.21, S, 6.16 %.

3-Acetyl-2-(3-nitrophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6k) FTIR (KBr) n, cm^{-1}: 3049 (Ar. C-H_{str}), 2968 (Ali. C-H_{str}), 1772 (C=O_{str}), 1610 (Ar. C=C_{str}), 1446 (N-Ostr), 1332 (Ar. C-N_{str}), 1226 (Al. C-N_{str}), 921 (C-H *p*-disub. benzene), 854 (C-H *m*-disub. benzene), 738 (C-S_{str}), 572 (Ar. C-Clstr); ^{1}H NMR, δ ppm: 1.123 (s, 3H, CH_3), 1.716-1.841 (m, 4H, CH_2), 2.503 (s, 3H, CH_3), 6.202 (s, 1H, Ar-H), 7.102-7.227 (m, 12H, Ar-H); MS (m/z): 508 $[M+1]^+$, 509 $[M+2]^+$; Elemental analysis: C, 64.87, H, 4.32, N, 4.86, S, 5.24, Cl, 5.77 %.

3-Acetyl-2-(3-nitrophenyl)-4-methylbenzo[b][1,4] thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6l) FTIR (KBr) n, cm^{-1}: 3056 (Ar. C-H_{str}), 2995 (Ali. C-H_{str}), 1760 (C=O_{str}), 1620 (Ar. C=C_{str}), 1377 (N-Ostr), 1271 (Ar. C-N_{str}), 1209 (Al. C-N_{str}), 840 (C-H *p*-disub. benzene), 738 (C-H *m*-disub. benzene), 619 (C-S_{str}); ^{1}H NMR, δ ppm:

1.120 (s, 3H, CH_3), 1.726-1.842 (m, 4H, CH_2), 2.543 (s, 3H, CH_3), 6.202 (s, 1H, Ar-H), 7.102-7.227 (m, 12H, Ar-H); MS (m/z): 518 $[M+1]^+$; Elemental analysis: C,61.58, H, 4.37, N, 7.34, S, 5.14 %.

3-Acetyl-2-(2-nitrophenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6m) FTIR (KBr) n, cm^{-1}: 3049 (Ar. C-H_{str}), 2968 (Ali. C-H_{str}), 1772 (C=O_{str}), 1610 (Ar. C=C_{str}), 1446 (N-Ostr), 1332 (Ar. C-N_{str}), 1226 (Al. C-N_{str}), 834 (C-H *p*-disub. benzene), 738 (C-H *o*-disub. benzene), 691 (C-S_{str}), 572 (Ar. C-Clstr); ^1H NMR, δ ppm: 1.623 (s, 3H, CH_3), 2.244 (s, 3H, CH_3), 2.623-2.732 (m, 4H, CH_2), 6.223 (s, 1H, Ar-H), 7.634-7.723 (m, 12H, Ar-H); MS (m/z): 508 $[M+1]^+$, 509 $[M+2]^+$; Elemental analysis: C, 64.56, H, 3.54, N, 4.67, S, 5.63, Cl, 5.42 %.

3-Acetyl-2-(2-nitrophenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6n) FTIR (KBr) n, cm^{-1}: 3072 (Ar. C-H_{str}), 2995 (Ali. C-H_{str}), 1675 (C=O_{str}), 1625 (Ar. C=C_{str}), 1483 (N-Ostr), 1313 (Ar. C-N_{str}), 1186 (Al. C-N_{str}), 840 (C-H *p*-disub. benzene), 752 (C-H *o*-disub. benzene), 628 (C-S_{str}); ^1H NMR, δ ppm: 1.250 (s, 3H, CH_3), 1.650 (s, 3H, CH_3), 2.476-2.563 (m, 4H, CH_2), 6.323 (s, 1H, Ar-H), 7.363-7.459 (m, 12H, Ar-H); MS (m/z): 518 $[M+1]^+$; Elemental analysis: C, 58.32, H, 3.74, N, 7.62, S, 7.18 %.

3-Acetyl-2-(4-methoxyphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6o) FTIR (KBr) n, cm^{-1}: 3081 (Ar. C-H_{str}), 2964 (Ali. C-H_{str}), 1680 (C=O_{str}), 1614 (Ar. C=C_{str}), 1359 (Ar. C-N_{str}), 1274 (Al. C-N_{str}), 1190 (C-O-Cstr), 829 (C-H *p*-disub. benzene), 700 (C-S_{str}); ^1H NMR, δ ppm: 1.201 (s, 3H, CH_3), 2.480 (s, 3H, CH_3), 2.708-2.724 (m, 4H, CH_2), 3.702 (s, 3H, OCH_3), 6.281 (s, 1H, Ar-H), 7.712-7.828 (m, 12H, Ar-H); MS (m/z): 493 $[M+1]^+$, 494 $[M+2]^+$; Elemental analysis: C, 64.21, H, 4.64, N, 2.84, S, 6.23, Cl, 6.42 %.

3-Acetyl-2-(4-methoxyphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6p) FTIR (KBr) n, cm^{-1}: 3047 (Ar. C-H_{str}), 2835 (Ali. C-H_{str}), 1733 (C=O_{str}), 1608 (Ar. C=C_{str}), 1448 (N-Ostr), 1326 (Ar. C-N_{str}), 1232 (Al. C-N_{str}), 1143 (C-O-Cstr), 850 (C-H *p*-disub. benzene), 719 (C-S_{str});^1H NMR, δ ppm: 1.275 (s, 3H, CH_3), 1.704-1.871 (m, 4H, CH_2), 3.307 (s, 3H, CH_3), 3.706 (s, 3H, OCH_3), 6.223 (s, 1H, Ar-H), 7.304-7.457 (m, 12H, Ar-H); MS (m/z): 503 $[M+1]^+$; Elemental analysis: C, 64.32, H, 4.24, N, 6.76, S, 5.23 %.

3-Acetyl-2-(3-methoxyphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6q) FTIR (KBr) n, cm^{-1}: 3062 (Ar. C-H_{str}), 2898 (Ali. C-H_{str}), 1687 (C=O_{str}), 1610 (Ar. C=C_{str}), 1313 (Ar. C-N_{str}), 1190 (C-O-Cstr), 1125 (Al. C-N_{str}), 812 (Ar. C-Clstr), 734 (C-H *p*-disub. benzene), 705 (C-H *m*-disub. benzene), 642 (C-S_{str}); ^1H NMR, δ ppm: 1.204 (s, 3H, CH_3), 2.325(s, 3H, CH_3), 2.800-2.957 (m, 4H, CH_2), 3.704 (s, 3H, OCH_3), 6.428 (s, 1H, Ar-H), 7.260-7.399 (m, 12H, Ar-H); MS (m/z): 492 $[M+1]^+$, 493 $[M+2]^+$; Elemental analysis: C, 65.23, H, 4.21, N, 2.74, S, 5.62, Cl, 6.52 %.

3-Acetyl-2-(3-methoxyphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6r) FTIR (KBr) n, cm^{-1}: 3040 (Ar. C-H_{str}), 2881 (Ali. C-H_{str}), 1675 (C=O_{str}), 1618 (Ar. C=C_{str}), 1467 (N-Ostr), 1313 (Ar. C-N_{str}), 1186 (C-O-Cstr), 1110 (Al. C-N_{str}), 820 (C-H *p*-disub. benzene), 734 (C-H *m*-disub. benzene), 642 (C-S_{str}); ^1H NMR, δ ppm: 1.234 (s, 3H, CH_3), 2.385 (s, 3H, CH_3), 2.820-2.950 (m, 4H, CH_2), 3.754 (s, 3H, OCH_3), 6.427 (s, 1H, Ar-H), 7.663-7.795 (m, 12H, Ar-H); MS (m/z): 503 $[M+1]^+$; Elemental analysis: C, 64.16, H, 5.12, N, 4.86, S, 6.32 %.

3-Acetyl-2-(2-methoxyphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6s) FTIR (KBr) n, cm^{-1}: 3080 (Ar. C-H_{str}), 2958 (Ali. C-H_{str}), 1685 (C=O_{str}), 1602 (Ar. C=C_{str}), 1326 (Ar. C-N_{str}), 1180 (Al. C-N_{str}), 1105 (C-O-Cstr), 852 (C-H *p*-disub. benzene), 802 (Ar. C-Clstr), 715 (C-H *o*-disub. benzene), 685 (C-S_{str}); 1.262 (s, 3H, CH_3), 2.438 (s, 3H, CH_3), 2.721-2.824 (m, 4H, CH_2), 3.781 (s, 3H, OCH_3), 6.224 (s, 1H, Ar-H), 7.321-7.432 (m, 12H, Ar-H); MS (m/z): 493 $[M+1]^+$, 494 $[M+2]^+$; Elemental analysis: C, 64.53, H, 4.23, N, 2.76, S, 5.32, Cl, 6.17 %.

3-Acetyl-2-(2-methoxyphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-nitrophenyl)propan-1-one (6t) FTIR (KBr) n, cm^{-1}: 3072 (Ar. C-H_{str}), 2995 (Ali. C-H_{str}), 1675 (C=O_{str}), 1625 (Ar. C=C_{str}), 1593 (Ar. C-N_{str}), 1483 (N-Ostr), 1313 (Al. C-N_{str}), 1110 (C-O-Cstr), 910 (Ar. C-Clstr), 815 (C-H *p*-disub. benzene), 752 (C-H *o*-disub. benzene), 628 (C-S_{str}); ^1H NMR, δ ppm: 1.168 (s, 3H, CH_3), 2.358 (s, 3H, CH_3), 2.588-2.684 (m, 4H, CH_2), 3.781 (s, 3H, OCH_3), 6.184 (s, 1H, Ar-H), 7.224-7.352 (m, 12H, Ar-H); MS (m/z): 503 $[M+1]^+$; Elemental analysis: C, 64.27, H, 5.75, N, 5.43, S, 6.28 %.

Pharmacology

Animals and Environment Condition

Swiss albino mice weighing (20 ± 25gm) of either sex will be procured from the Laboratory Animal Facility, Central Drug Research Institute, Lucknow. They will be kept in an animal house in a well cross-ventilated room at 25 ± 2°C, and with relative humidity 44–56%, light and dark cycles of 10 and 14 hours respectively for one week before and during the experiments. Animals will be provided with a standard rodent pellet diet (Bharat Ansh Scientific Industries) and food will be withdrawn 18–24 hours before the experiment, water will be allowed *ad libitum.* All studies will be performed in accordance with the guide for the care and use of laboratory animals, as adopted and promulgated by the Institutional Animal Care Committee, CPCSEA, India (Reg. No. 1957/PO/Re/S/17CPCSEA).

Anticonvulsant activity [24-27]

The albino mice were divided into three groups (n = 6). Control group (Received 30% v/v PEG400 aqueous solution). Synthesized compounds (6a-6t) i.e. treated

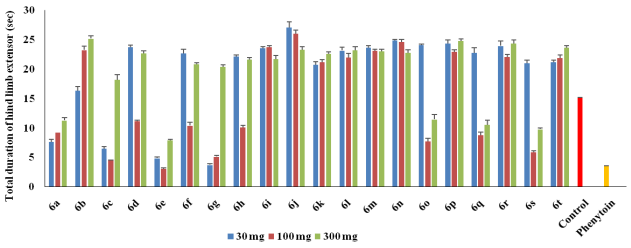


Fig. 1: Graphical representation of anticonvulsant evaluation after 0.5 hours administration of compounds (6a-6t) using MES model.

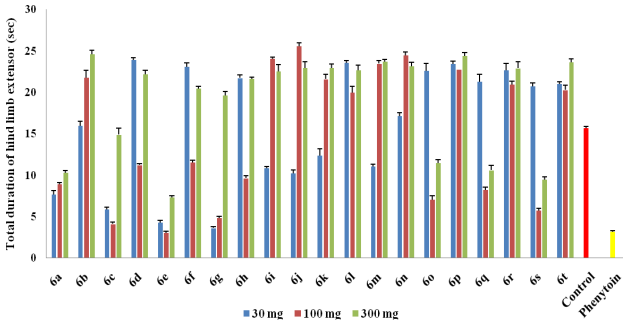


Fig. 2: Graphical representation of anticonvulsant evaluation after 4 hours administration of compounds (6a-6t) using MES model.

groups (Received 30, 100 and 300 mg/kg in 30% v/v PEG400 aqueous solution doses i.p. route). Standard group (Received Phenytoin 30 mg/kg in 30% v/v PEG400 aqueous solution).

Maximal Electroshock Seizures (MES) [25-28]

All the novel synthesized compounds (6a-6t) preliminary screen for anticonvulsant activity by maximal electroshock seizures method. In mice, seizures were elicited with a 60 Hz alternating current of 150 mA intensity; apply current on the upper eye lid for 0.2 second. After intraperitoneal administration of test compounds (6a-6t) at doses of 30, 100 and 300 mg/kg in 30% v/v PEG400 aqueous solution, the pharmacological response was evaluated at two time intervals 0.5 and 4 hours. Different phases of seizures (a) tonic flexion (b) tonic extensor (c) clonic convulsion (d) stupor (e) recovery/death were observed in all groups of animals. The animals of the control and standard groups undergo the same procedure mentioned above. The observation of the after electroshock showed reduced time or abolished extensor phase are represented in Tables 2 and 3.

Neurotoxicity Studies[28]

Motor impairment confirmation done in albino mice by using the Rota rod apparatus (Medicraft Pharma. Pvt. Ltd). Prior to conducting the experiment every experimental animal was trained to stay on accelerating rota rod at 10 rpm. At 30 minutes after the administration of synthesized novel compounds (6a-6t) the animals were screened for neurotoxicity on a knurled rotating rod and mice failing to hold the rod for one minute at least in each of three trials were potentially experiencing neurotoxicity.

Oral Acute Toxicity Studies of Potent Compound[29-30]

The animals were divided into two groups (n=6); Group I: Control group (Received vehicle 30% v/v PEG 400 in distilled water through oral route). Group II: Test group (Received single dose 2000 mg/kg in 30% v/v PEG 400 in distilled water through oral route). Once the test drug was administered, the food and water supply was restricted for about 2 hours. Clinical signs and symptoms for initially 24 hours with special courtesy given starting 4 hours and daily subsequently 14 days after the test drug administration. Moreover, as per OECD guidelines, factors like righting reflux, gripping, pupils, pain response, tremors, convulsion, skin color, corneal reflex, salivation, torch response, water intake, food intake, sleep, diarrhea, grooming, urination, alertness, lethargy, touch response, coma and mortality were observed.

Statistical Analysis

All the values are represented in the form of mean ± standard error mean (SEM) and these all values analyzed by ANOVA then multiple comparison tests apply by dunnett's test.[28] All the statistical analysis were analyzed and collect the data by using graph pad prism 5 version software.

Results And Discussion

Chemistry

A novel series of Substituted-3-acetyl-2 (substitutedphenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(substitutedphenyl)propan-1-one (6a-6t) were synthesized in satisfactory yield (36–84%). The physicochemical properties on the basis of Log P, Clog P, m.p. R_f and % yield of synthesized compounds are shown in Tabl-1. The chemical structures of lead compounds were characterized by spectroscopic (FTIR, ^{1}H-NMR, MASS) and elemental methods.

Anticonvulsant Screening

The anticonvulsant activity of synthesized compounds is carried out under the Antiepileptic Drug Development (ADD) Program. The screening of the anticonvulsant activity of all the novel compounds (6a-6t) was performed by Maximal electroshock seizure (MES) method in albino mice of either sex. In the primary MES screening, mostly compounds exhibit potent activity at 30 and 100 mg/kg dose without neurotoxin in nature except compounds 6b, 6d, 6f, 6h, 6i, 6j, 6k, 6l, 6m, 6n, 6p, 6r and 6t. Mostly nitro substituted synthesized derivative produced neurotoxicity at a maximum dose 300 mg/kg. The compound 3-Acetyl-2-(3-chlorophenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6e) has shown protection against MES induced seizures at dose of 30 mg/kg after 0.5 hours of administration and

continued protection against seizures at the same dose after 4 hrs also. It signified that a compound (**6e)** has rapid onset and long duration of anticonvulsant activity at a lower dose and the result is comparable with the standard drug, Phenytoin. In a neurotoxicity study, most of the compounds did not show any neurotoxicity at 0.5 and 4 hours except the nitro group containing functional group. The nitro substituted compounds showed poor or less activity due to low log P. From the above results it was found that the chloro derivatives exhibit better activity and the *m*-substituted derivative was found to possess more significant activity, alteration at *m*-position affect the activity. All the nitro substituted compounds showed poor activity due to low CNS penetration. The introduction of the chloro group in ring proved to enhance the anticonvulsant activity. The graphical representation of data is shown in Figs 1 and 2.

Oral Acute Toxicity

The most potent significant compound 3-Acetyl-2-(3-chlorophenyl)-4-methylbenzo[b][1,4]thiazepin-5(2H)-yl)-1-(4-chlorophenyl)propan-1-one (6e) with its dose 2000 mg/kg administered to test animals, total fourteen days observation normal behavior of animals that suggest the compound (6e) safe and non toxic nature up to dose 2000 mg/kg. Compound (6e) is found as a pharmacophore molecule for further modification and improvement in the field of anticonvulsants drug development. The observations of behavioral studies are represented in Table 4.

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