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Synthesis, preliminary anticonvulsant and toxicity screening of substituted 3-(Dimethyl/Diethylamino)-{1-[4-methyl-2-substitutedphenyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one

V. K. Chaudhari
Mahatma Gandhi Institute of Pharmacy, Lucknow-227101, Uttar Pradesh, India
Corresponding author email: vikashk464@gmail.com

D. Pathak
Rajiv Academy for Pharmacy, Mathura-281001, Uttar Pradesh, India

Z. Hussain
Mahatma Gandhi Institute of Pharmacy, Lucknow-227101, Uttar Pradesh, India

***Abstract*---**Background; 1,5-benzothiazepine moiety is a very important pharmacophore bioactive compound that exhibits different biological activities. By the literature review the basic structure requirements for anticonvulsant activity contains molecular weight less than 500, Oil/water distribution coefficient is less than 5, Hydrogen bond donors more than 5 and Hydrogen bond acceptor more than 10. Aim of study: Aim of the study is to synthesize a novel series of 1,5-benzothiazepine nucleus containing Mannich bases which retained anticonvulsant biological activities with less toxic effect. Materials & methods: We synthesized successfully various substituted 3-(Dimethyl/Diethylamino)-{1-[4-Methyl-2 substitutedphenyl-2,5-dihydro-1,5 benzothiazepin-3-yl]}propan-1-one (6a-6t). Completion of chemical reaction was monitored by thin layer chromatography on silica gel G coated plates and final compounds were purified by recrystallisation with methanol. The chemical structure of synthesized compounds confirmed by chromatographi, electro analytical and physiochemical analysis. Results & discussion: All the novel synthesized compounds screened by anticonvulsant activity by maximum electroshock induced seizure against Phenytoin as standard. All the synthesized compounds showed significant anticonvulsant activity. The most potent significant compound was found 3-(Dimethylamino)-{1-[3-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6e). Further, preliminary

safety profile of most potent significant compound 6e was evaluated by acute oral toxicity and neurotoxicity testing.

***Keywords*---**Acute toxicity, Anticonvulsant, Neurotoxicity, Mannich bases.

Introduction

Drug design is a very essential tool for discovery and development of new pharmacophore compounds (Jeyaprakash et al., 2009). The benzothiazepine are the class of compound having benzodiazepine type nucleus the only difference between then is of sulphur atom in place of "N" atom in heterocyclic ring system (Gulhan et al., 2004)).

1,5-Benzothiazepin derivatives are important class of compounds due to wide spectrum of biological activities such as antifeedants (Reddy et al.,1993), cardiovascular (Minako et al., 1998), antimicrobial (Saini et al., 2008), antifungal (Afzal et al., 2021), CNS depressant (Falco et al., 2006), antiplatelet aggregation (Genton et al.,1977), bradykinin receptor antagonist (Ivorra et al., 1992), anti-inflammatory Muriel et al., 1999) and antipsychotic agents (Panda et al., 2008).

Notably, the world health organization reports epilepsy as one of the long-standing diseases, infecting human being (Ameta et al., 2013). Seizures may be varying from the time lapses of attention or muscle jerk to severe and prolonged convulsion. They may also vary in frequency of time, from less than one year to several per day (Pandeya et al., 2003, Raja et al., 2003).

In present time acquired conspicuous significance due to their wide biological activities (Ansari et al., 2008). Accumulative literature data supports the notion of substitution of 3 and 5 positions, yielding a compound with clinical benefit. Former experimental data investigation unfolded different compounds generated by ring system substitution at various positions. Notably, we considered the compounds having substitution primarily at the position 3 and 5. The side chain substitution at position 3 and at position 5 the H atom gets substituted by varying suitable group. The novel substituted synthesize derivatives has been confirmed by elemental and spectroscopic analysis, the final synthesized compounds (6a-6t) preliminary screen for anticonvulsant agent by MES model. Rota rod study also evaluated for neurotoxicity. Hence to ascertain and establish the safety for its application, acute toxicity studies as per OCED guidelines 420.

Materials and Methods

The melting points of all synthesized compounds were determined by open capillary tube method. The final product and intermediate product of chemical reaction was monitor by thin layer chromatography using chloroform: methanol (9:1) as a mobile phase. Infra-red were identified on perkin-elmer FTIR-8400S spectrometer (SHIMADZU, Japan) by pressed pellet technique. ^{1}H-NMR spectra on Bruker DRX300 in DMSO-d6 at 300MHz using TMS as an internal standard and Molecular mass characterized by Micromass quarto ESI-MS under ESI

technique. Elemental analysis characterized by Carlo Erba EA 1108. Oil/water distribution coefficient determined using octanol phosphate buffer solution and C log P value calculated on Chem-Draw Ultra 8 software. All the solvents & reagents used were obtained by Qualigens® Fine chemical.

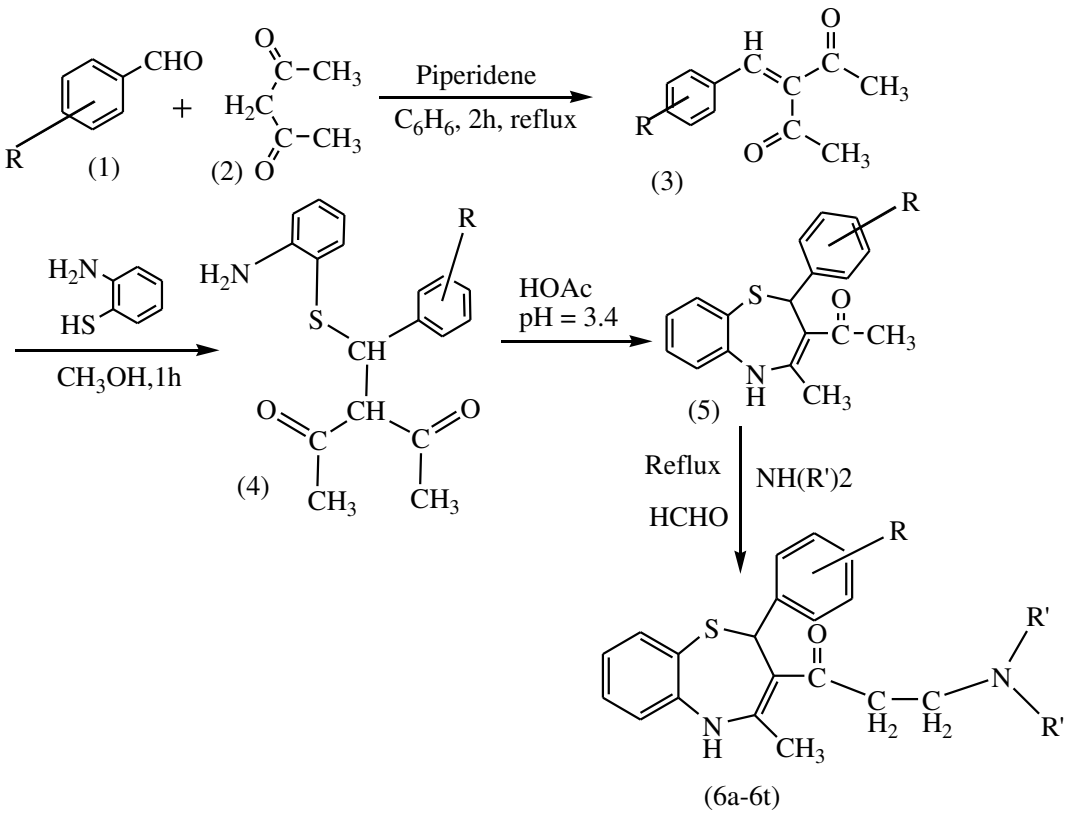
General procedure for synthesis of substituted 3-(Dimethyl/Diethylamino)-{1-[4-Methyl-2-substitutedphenyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6a-6t)

Piperidine and 2, 4-Pentadione dissolved in benzene then at room temperature substituted benzaldehyde added drop wise drop at a room temperature. The chemical reaction mixture reflux for 2 hrs with continuous stirring. The reaction mixture containing compound cool and then organic layer washed with aq. 10% Na_2CO_3. Collect the product and then react with *o*-aminothiophenol with continuous stirring for about 60 minutes. After completion of reaction collect the solid product and wash with H_2O and CH_3OH.

The solid product containing methanol treated with acetic acid solution until pH reaches four with continuous steering for about 12 hrs. The solid product obtain by reaction mixture was collected then it washed and recrystallized with methanol solvent. Mannich bases (6a-t) obtained by reacting compound (5) with two different substituent's diethyl amine and dimethyl amine with HCHO (formaldehyde) for about 3 hrs.

Determination of partition coefficient (log P)

The determination of Oil/water distribution coefficient/Partition coefficient of substituted 1,5-Benzothiazepine **(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.



(6a-6t)

Scheme: Synthetic route of Mannich bases (6a-6t)

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

Compound	R	R'	Molecular formula	Log P value	CLog P value	Melting Point (°C)	*R_f value	Yield (%)
6a	H	CH_3	$C_{21}H_{24}N_2OS$	2.68	3.01	78	0.69	47
6b	H	C_2H_5	$C_{23}H_{28}N_2OS$	3.35	3.78	83-84	0.63	44
6c	4-Cl	CH_3	$C_{21}H_{23}ClN_2OS$	3.23	3.95	100-102	0.84	37
6d	4-Cl	C_2H_5	$C_{23}H_{27}ClN_2OS$	3.91	3.67	75-77	0.82	41
6e	3-Cl	CH_3	$C_{21}H_{23}ClN_2OS$	3.23	3.25	65-66	0.72	53
6f	3-Cl	C_2H_5	$C_{23}H_{27}ClN_2OS$	3.91	3.96	70-71	0.45	67
6g	2-Cl	CH_3	$C_{21}H_{23}ClN_2OS$	3.23	3.94	80-81	0.85	37
6h	2-Cl	C_2H_5	$C_{23}H_{27}ClN_2OS$	3.91	3.76	109-110	0.92	39
6i	4-NO_2	CH_3	$C_{21}H_{23}N_3O_3S$	0.89	1.24	90-92	0.65	40
6j	4-NO_2	C_2H_5	$C_{23}H_{27}N_3O_3S$	0.68	1.84	97-98	0.39	36
6k	3-NO_2	CH_3	$C_{21}H_{23}N_3O_3S$	1.23	1.69	76-77	0.74	43
6l	3-NO_2	C_2H_5	$C_{23}H_{27}N_3O_3S$	0.96	1.68	82-83	0.65	42
6m	2-NO_2	CH_3	$C_{21}H_{23}N_3O_3S$	0.92	1.92	73-74	0.52	56
6n	2-NO_2	C_2H_5	$C_{23}H_{27}N_3O_3S$	1.38	2.48	78-79	0.75	38
6o	4-OCH_3	CH_3	$C_{22}H_{26}N_2O_2S$	2.55	2.85	94-95	0.68	60

6p	4-OCH_3	C_2H_5	$C_{24}H_{30}N_2O_2S$	3.23	3.59	99-100	0.54	62
6q	3-OCH_3	CH_3	$C_{22}H_{26}N_2O_2S$	2.55	2.84	152-153	0.77	48
6r	3-OCH_3	C_2H_5	$C_{24}H_{30}N_2O_2S$	3.23	3.95	190-191	0.65	54
6s	2-OCH_3	CH_3	$C_{22}H_{26}N_2O_2S$	2.55	2.84	65-66	0.48	57
6t	2-OCH_3	C_2H_5	$C_{24}H_{30}N_2O_2S$	3.23	3.86	86-87	0.61	64

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

Pharmacology

Animal and environment condition

Swiss albino mice weighing (20–25g) of either sex will be procured from the National Laboratory Animal Centre (NLAC), Central Drug Research Institute, Lucknow. They will be kept in departmental animal house in well cross-ventilated room at 25±2°C, and relative humidity 44–56%, light and dark cycles of 10 and 14 hrs. respectively for 1 week before and during the experiments. Animals will be provided with standard rodent pellet diet (Amrut, India) and the food will be withdrawn 18-24 hrs. before the experiment though, water will be allowed ad-labium. 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.). All the chemicals used will be used analytical grade from standard companies and water represents the double distilled water.

Anticonvulsant activity

The animals were divided in into three groups of six animals each: Group I: Control group (Received 30% v/v PEG400 aq. Solution). Group II: Test group (Received 30, 100 & 300 mg/kg in 30% v/v PEG400 doses through *i.p.* route). Group III: Standard (Received Phenytoin (30 mg/kg) in 30% v/v PEG400).

Experimental model

Maximal electroshock seizures (MES)

Seizures were elicited with a 60 Hz alternating current of 150 mA intensity in mice. The current was applied on the upper eye lid for 0.2 second. After *i.p.* administration of the compounds, the activities were evaluated at two time intervals 0.5 hrs and 4 hrs. Different phases of seizures (a) tonic flexion (b) tonic extensor (c) clonic convulsion (d) stupor (e) recovery or death was observed in each group of animals. The animals of the control and standard groups undergo the same procedure that mentioned above procedure (Kulkarni, 2011). The observation of data after electroshock showed reduced time or abolish extensor phase are represented in table 2 and 3.

Neurotoxicity studies

Motor impairment confirmation done in rats by employing rota rod apparatus. Prior conducting the experiment every experimental animal was trained to stay on accelerating rota rod upto 10 rpm. After the administration of test drug the animals were tested for neurotoxicity on a knurled rotating rod and rats failing to hold rod for 1 minute at least in each of 3 trials were potentially experiencing neurotoxicity (Kulkarni, 2011).

Oral acute toxicity studies

The animals were divided in into two groups of 6 animals each: Group I: Control group (Received double distilled water through oral route). Group II: Test group (Received single dose of 2000mg/kg in 30% v/v PEG400 through oral route). Once test drug was administered, the food and water supply was restricted for about 2 hrs. We notice that clinical sign and symptoms for initially 24 hrs with special courtesy given starting 4 hrs duration and daily subsequently 14 days after the test drug administration. Factors like righting reflux, gripping, pupils, pain response, tremors, convulsion, skin colour, corneal reflex, salivation, torch response, water intake, food intake, sleep, diarrhoea, grooming, urination, alertness, lethargy, touch response, coma and mortality were observed accordance of OECD guidelines 420 (OECD, 2000, Jonsson et al., 2013, Ali et al., 2014). The observation of results represented in Table 4.

Statistical analysis

All the values represented in the form of Mean ± SEM and these all values analyzed by ANOVA then multiple comparison tests apply by dunnett's. All the statistical analysis was analyzed by using graph pad prism 5 version software (Kulkarni, 2011).

Results and Discussion

Chemistry

A series of novel substituted 1,5-Benzothiazepine (6a-6t) were synthesized in satisfactory yield (40-80%) The physicochemical properties of synthesized compounds are described in table 1. All final derivatives structures were characterized by elemental and spectroscopic methods.

Compounds Detail

3-(Dimethylamino)-{1-[4-methyl-2-phenyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6a) FTIR (KBr) ν, cm^{-1}): 3365 ($N\text{-}H_{str}$), 3051 (Ar. $C\text{-}H_{str}$), 2935 (Ali. $C\text{-}H_{str}$), 1677 ($C{=}O_{str}$), 1630 (Ar. $C{\cdots}C_{str}$), 1315 (Ar. $C\text{-}N_{str}$), 1174 (Al. $C\text{-}N_{str}$), 678 ($C\text{-}S_{str}$); ^1H NMR, δ ppm: 1.196-1.395 (m, 9H, CH_3), 2.752-2.853 (m, 4H, CH_2), 4.502 (s, 1H, N-H, D_2O exchange), 5.200 (s, 1H, CH), 6.904-6.983 (m, 4H, Ar-H), 7.259-7.285 (m, 5H, Ar-H); MS (m/z): 253 $[M+1]^+$; Elemental analysis: C, 71.55, H, 6.86, N, 7.95, S, 9.10 %.

3-(Diethylamino)-{1-[4-methyl-2-phenyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6b) FTIR (KBr) ν, cm^{-1}): 3350 (N-H_{str}), 3056 (Ar. C-H_{str}), 2995 (Ali. C-H_{str}), 1760 (C=O_{str}), 1620 (Ar. C⋯C$_{str}$), 1271 (Ar. C-N_{str}), 1209 (Al. C-N_{str}), 619 (C-S_{str}); ^{1}H NMR, δ ppm: 1.625-1.798 (m, 6H, CH_3), 2.101 (s, 3H, CH_3), 2.410-2.505 (t, 2H, CH_2), 2.735-2.979 (m, 4H, CH_2), 3.001-3.181 (t, 2H, CH_2), 6.181 (s, 1H, Ar-H), 7.232-7.505 (m, 9H, Ar-H), 8.124 (s, 1H, N-H, D_2O exchange); MS (m/z): 381 $[M+1]^+$; Elemental analysis: C, 72.59, H, 7.42, N, 7.36, S, 8.43 %.

3-(Dimethylamino)-{1-[4-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6c) FTIR (KBr) ν, cm^{-1}): 3370 (N-H_{str}), 3075 (Ar. C-H_{str}), 2925 (Ali. C-H_{str}), 1687 (C=O_{str}), 1623 (Ar. C⋯C$_{str}$), 1325 (Ar. C-N_{str}), 1180 (Al. C-N_{str}), 1033 (Ar. C-Cl_{str}), 806 (C-H *p*-disub. benzene), 700 (C-S_{str}); ^{1}H NMR, δ ppm: 2.130-2.179 (m, 6H, CH_3), 2.505 (s, 3H, CH_3), 2.754-2.884 (t, 2H, CH_2), 2.949-3.120 (t, 2H, CH_2), 6.178 (s, 1H, Ar-H), 7.358-7.408 (m, 8H, Ar-H), 9.253 (s, 1H, N-H, D_2O exchange); MS (m/z): 387 $[M+1]^+$; 388 $[M+2]^+$; Elemental analysis: C, 65.18, H, 5.99, N, 7.24, S, 8.29, Cl, 9.16 %.

3-(Diethylamino)-{1-[4-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6d) FTIR (KBr) ν, cm^{-1}): 3362 (N-H_{str}), 3071 (Ar. C-H_{str}), 2952 (Ali. C-H_{str}), 1683 (C=O_{str}), 1602 (Ar. C⋯C$_{str}$), 1317 (Ar. C-N_{str}), 1182 (Al. C-N_{str}), 1095 (Ar. C-Cl_{str}), 835 (C-H *p*-disub. benzene), 603 (C-S_{str}); ^{1}H NMR, δ ppm: 1.407-1.476 (m, 6H, CH_3), 2.104-2.278 (t, 2H, CH_2), 2.304 (s, 3H, CH_3), 2.754-2.778 (m, 4H, CH_2), 3.309-3.397 (t, 2H, CH_2), 6.376 (s, 1H, Ar-H), 7.356-7.503 (m, 8H, Ar-H), 9.256 (s, 1H, N-H, D_2O exchange); MS (m/z): 415 $[M+1]^+$; 416 $[M+2]^+$; Elemental analysis: C, 66.57, H, 6.56, N, 6.75, S, 7.73, Cl, 8.54 %.

3-(Dimethylamino)-{1-[3-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6e) FTIR (KBr) ν, cm^{-1}): 3419 (N-H_{str}), 2996 (Ar. C-H_{str}), 2909 (Ali. C-H_{str}), 1799 (C=O_{str}), 1674 (Ar. C⋯C$_{str}$), 1313 (Ar. C-N_{str}), 1174 (Al. C-N_{str}), 1074 (Ar. C-Cl_{str}), 756 (C-H *m*-disub. benzene), 678 (C-S_{str}); ^{1}H NMR, δ ppm: 1.423-1.483 (m, 6H, CH_3), 2.142 (s, 3H, CH_3), 2.410-2.427 (t, 2H, CH_2), 2.616-2.665 (t, 2H, CH_2), 6.213 (s, 1H, Ar-H), 7.680-7.727 (m, 8H, Ar-H), 8.427 (s, 1H, N-H, D_2O exchange); MS (m/z): 387 $[M+1]^+$; 388 $[M+2]^+$; Elemental analysis: C, 65.18, H, 5.99, N, 7.24, S, 8.29, Cl, 9.16 %.

3-(Diethylamino)-{1-[3-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6f) FTIR (KBr) ν, cm^{-1}): 3371 (N-H_{str}), 3054 (Ar. C-H_{str}), 2933 (Ali. C-H_{str}), 1739 (C=O_{str}), 1606 (Ar. C⋯C$_{str}$), 1353 (Ar. C-N_{str}), 1280 (Al. C-N_{str}), 1041 (Ar. C-Cl_{str}), 742 (C-H *m*-disub. benzene), 686 (C-S_{str}); ^{1}H NMR, δ ppm: 1.543-1.582 (m, 4H, CH_2), 1.923-1.997 (m, 6H, CH_3), 2.354-2.383 (t, 2H, CH_2), 2.715-2.733 (t, 2H, CH_2), 3.376 (s, 3H, CH_3), 6.320 (s, 1H, Ar-H), 7.672-7.685 (m, 8H, Ar-H), 8.685 (s, 1H, N-H, D_2O exchange); MS (m/z): 415 $[M+1]^+$; 416 $[M+2]^+$; Elemental analysis: C, 66.57, H, 6.56, N, 6.75, S, 7.73, Cl, 8.54 %.

3-(Dimethylamino)-{1-[2-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6g) FTIR (KBr) ν, cm^{-1}): 3380 (N-H_{str}), 3049 (Ar. C-H_{str}), 2910 (Ali. C-H_{str}), 1772 (C=O_{str}), 1610 (Ar. C⋯C$_{str}$), 1332 (Ar. C-N_{str}), 1226 (Al. C-N_{str}), 1092 (Ar. C-Cl_{str}), 738 (C-H *o*-disub. benzene), 691 (C-S_{str}); ^{1}H

NMR, δ ppm: 1.663-1.670 (m, 6H, CH_3), 2.214 (s, 3H, CH_3), 2.418-2.426 (t, 2H, CH_2), 2.626-2.641 (t, 2H, CH_2), 6.214 (s, 1H, Ar-H), 7.670-7.717 (m, 8H, Ar-H), 8.413 (s, 1H, N-H, D_2O exchange); MS (m/z): 387 $[M+1]^+$; 388 $[M+2]^+$; Elemental analysis: C, 65.18, H, 5.99, N, 7.24, S, 8.29, Cl, 9.16 %.

3-(Diethylamino)-{1-[2-chlorophenyl-4-methyl-2, 5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6h) FTIR (KBr) ν, cm^{-1}): 3361 (N-H_{str}), 3040 (Ar. C-H_{str}), 2881 (Ali. C-H_{str}), 1675 (C=O_{str}), 1618 (Ar. C=C$_{str}$), 1313 (Ar. C-N_{str}), 1186 (Al. C-N_{str}), 1110 (Ar. C-Cl_{str}), 734 (C-H *o*-disub. benzene), 642 (C-S_{str});); ^1H NMR, δ ppm: 1.267-1.353 (m, 6H, CH_3), 1.923-1.986 (m, 4H, CH_2), 2.224-2.256 (t, 2H, CH_2), 2.825-2.867 (t, 2H, CH_2), 3.404 (s, 3H, CH_3), 6.112 (s, 1H, Ar-H), 7.123-7.267 (m, 8H, Ar-H), 8.557 (s, 1H, N-H, D_2O exchange); MS (m/z): 415 $[M+1]^+$; 416 $[M+2]^+$; Elemental analysis: C, 66.57, H, 6.56, N, 6.75, S, 7.73, Cl, 8.54 %.

3-(Dimethylamino)-{1-[4-nitrophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6i) FTIR (KBr) ν, cm^{-1}): 3259 (N-H_{str}), 3117 (Ar. C-H_{str}), 2939 (Ali. C-H_{str}), 1693 (C=O_{str}), 1637 (Ar. C=C$_{str}$), 1496 (N-O str.), 1319 (Ar. C-N_{str}), 1072 (Al. C-N_{str}), 840 (C-H *p*-disub. benzene), 684 (C-S_{str}); ^1H NMR, δ ppm: 1.134 (m, 6H, CH_3), 2.213-2.234 (t, 2H, CH_2), 2.826-2.867 (t, 2H, CH_2), 2.513 (s, 3H, CH_3), 5.853 (s, 1H, Ar-H), 7.156-7.252 (m, 8H, Ar-H), 8.142 (s, 1H, N-H, D_2O exchange); MS (m/z): 398 $[M+1]^+$; Elemental analysis: C, 63.45, H, 5.83, N, 10.57, S, 8.07 %.

3-(Diethylamino)-{1-[4-nitrophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6j) FTIR (KBr) ν, cm^{-1}): 3269 (N-H_{str}), 3060 (Ar. C-H_{str}), 2904 (Ali. C-H_{str}), 1779 (C=O_{str}), 1619 (Ar. C=C$_{str}$), 1473 (N-O str.), 1380 (Ar. C-N_{str}), 1238 (Al. C-N_{str}), 838 (C-H *p*-disub. benzene), 690 (C-S_{str}); ^1H NMR, δ ppm: 1.243-1.264 (m, 6H, CH_3), 1.723-1.732 (m, 4H,CH_2), 2.415-2.443 (t, 2H, CH_2), 2.627-2.652 (t, 2H, CH_2), 3.372 (s, 3H, CH_3), 6.523 (s, 1H, Ar-H), 7.225-7.387 (m, 8H, Ar-H), 8.382 (s, 1H, N-H, D_2O exchange); MS (m/z): 426 $[M+1]^+$; Elemental analysis: C, 64.92, H, 6.40, N, 9.87, S, 7.54 %.

3-(Dimethylamino)-{1-[3-nitrophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6k) FTIR (KBr) ν, cm^{-1}): 3294 (N-H_{str}), 3124 (Ar. C-H_{str}), 2848 (Ali. C-H_{str}), 1750 (C=O_{str}), 1614 (Ar. C=C$_{str}$), 1492 (N-O str.), 1307 (Ar. C-N_{str}), 1246 (Al. C-N_{str}), 651 (C-H *m*-disub. benzene), 604 (C-S_{str}); ^1H NMR, δ ppm: 1.877 (m, 6H, CH_3), 2.417-2.453 (t, 2H,CH_2), 2.624-2.659 (t, 2H, CH_2), 3.374 (s, 3H, CH_3), 6.378 (s, 1H, Ar-H), 7.264-7.421 (m, 8H, Ar-H), 8.215 (s, 1H, N-H, D_2O exchange); MS (m/z): 398 $[M+1]^+$; Elemental analysis: C, 63.45, H, 5.83, N, 10.57, S, 8.07 %.

3-(Diethylamino)-{1-[3-nitrophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6l) FTIR (KBr) ν, cm^{-1}): 3320 (N-H_{str}), 3134 (Ar. C-H_{str}), 2947 (Ali. C-H_{str}), 1550 (C=O_{str}), 1608 (Ar. C=C$_{str}$), 1346 (N-O str.), 1296 (Ar. C-N_{str}), 1180 (Al. C-N_{str}), 690 (C-H *m*-disub. benzene), 626 (C-S_{str}); ^1H NMR, δ ppm: 1.192-1.242 (m, 6H, CH_3), 1.792-1.842 (m, 4H,CH_2), 2.229-2.296 (t, 2H, CH_2), 2.823-2.876 (t, 2H, CH_2), 2.503 (s, 3H, CH_3), 6.202 (s, 1H, Ar-H), 7.123-7.227 (m, 8H, Ar-H), 8.382 (s, 1H, N-H, D_2O exchange); MS (m/z): 426 $[M+1]^+$; Elemental analysis: C, 64.92, H, 6.40, N, 9.87, S, 7.54 %.

3-(Dimethylamino)-{1-[2-nitrophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6m) FTIR (KBr) ν, cm^{-1}): 3417 (N-H_{str}), 3052 (Ar. C-H_{str}), 2936 (Ali. C-H_{str}), 1799 (C=O_{str}), 1691 (Ar. C⋯C$_{str}$), 1419 (N-O str.), 1315 (Ar. C-N_{str}), 1175 (Al. C-N_{str}), 761 (C-H *o*-disub. benzene), 679 (C-S_{str}); ^{1}H NMR, δ ppm: 1.418 (m, 6H, CH_3), 2.288 (s, 3H, CH_3), 2.417-2.434 (t, 2H,CH_2), 2.558-2.596 (t, 2H, CH_2), 6.321 (s, 1H, Ar-H), 7.251-7.365 (m, 8H, Ar-H), 8.339 (s, 1H, N-H, D_2O exchange); MS (m/*z*): 398 $[M+1]^+$; Elemental analysis: C, 63.45, H, 5.83, N, 10.57, S, 8.07 %.

3-(Diethylamino)-{1-[2-nitrophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6n) FTIR (KBr) ν, cm^{-1}): 3359 (N-H_{str}), 3063 (Ar. C-H_{str}), 2893 (Ali. C-H_{str}), 1661 (C=O_{str}), 1593 (Ar. C⋯C$_{str}$), 1469 (N-O str.), 1303 (Ar. C-N_{str}), 1176 (Al. C-N_{str}), 742 (C-H *o*-disub. benzene), 657 (C-S_{str}); ^{1}H NMR, δ ppm: 1.252-1.342 (m, 6H, CH_3), 1.731-1.842 (m, 4H,CH_2), 2.229-2.296 (t, 2H, CH_2), 2.503 (s, 3H, CH_3), 2.823-2.876 (t, 2H, CH_2), 6.202 (s, 1H, Ar-H), 7.431-7.552 (m, 8H, Ar-H), 8.152 (s, 1H, N-H, D_2O exchange); MS (m/*z*): 426 $[M+1]^+$; Elemental analysis: C, 64.92, H, 6.40, N, 9.87, S, 7.54 %.

3-(Dimethylamino)-{1-[4-methoxyphenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6o) FTIR (KBr) ν, cm^{-1}): 3353 (N-H_{str}), 3109 (Ar. C-H_{str}), 2933 (Ali. C-H_{str}), 1761 (C=O_{str}), 1595 (Ar. C⋯C$_{str}$), 1352 (Ar. C-N_{str}), 1157 (C-O-C_{str}), 1026 (Al. C-N_{str}), 831 (C-H *p*-disub. benzene), 692 (C-S_{str}); ^{1}H NMR, δ ppm: 1.211-1.283 (m, 6H, CH_3), 2.484 (s, 3H, CH_3), 2.610-2.634 (t, 2H,CH_2), 2.712-2.724 (t, 2H, CH_2), 3.712 (s, 3H, OCH_3), 6.211 (s, 1H, Ar-H), 7.712-7.788 (m, 8H, Ar-H), 8.224 (s, 1H, N-H, D_2O exchange); MS (m/*z*): 383 $[M+1]^+$; Elemental analysis: C, 69.08, H, 6.85, N, 7.32, S, 8.38 %.

3-(Diethylamino)-{1-[4-methoxyphenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6p) FTIR (KBr) ν, cm^{-1}): 3425 (N-H_{str}), 3092 (Ar. C-H_{str}), 2935 (Ali. C-H_{str}), 1744 (C=O_{str}), 1650 (Ar. C⋯C$_{str}$), 1350 (Ar. C-N_{str}), 1282 (C-O-C_{str}), 1166 (Al. C-N_{str}), 831 (C-H *p*-disub. benzene), 748 (C-S_{str}); ^{1}H NMR, δ ppm: 1.252-1.332 (m, 6H, CH_3), 1,917-1.987 (m, 4H, CH_2), 2.214-2.239 (t, 2H,CH_2), 2.826-2.897 (t, 2H, CH_2), 3.252 (s, 3H, CH_3), 3.732 (s, 3H, OCH_3), 5.832 (s, 1H, Ar-H), 7.561-7.622 (m, 8H, Ar-H), 8.252 (s, 1H, N-H, D_2O exchange); MS (m/*z*): 411 $[M+1]^+$; Elemental analysis: C, 70.21, H, 7.36, N, 6.82, S, 7.81 %.

3-(Dimethylamino)-{1-[3-methoxyphenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6q) FTIR (KBr) ν, cm^{-1}): 3365 (N-H_{str}), 3051 (Ar. C-H_{str}), 2935 (Ali. C-H_{str}), 1677 (C=O_{str}), 1630 (Ar. C⋯C$_{str}$), 1315 (Ar. C-N_{str}), 1174 (C-O-C_{str}), 1091 (Al. C-N_{str}), 678 (C-H *m*-disub. benzene), 632 (C-S_{str}); ^{1}H NMR, δ ppm: 1.196-1.395 (m, 9H, CH_3), 2.752-2.853 (m, 4H,CH_2), 3.740 (s, 3H, OCH_3), 4.502 (s, 1H, N-H, D_2O exchange); 5.200 (s, 1H, Ar-H), 6.904-6.983 (m, 4H, Ar-H), 7.259-7.285 (m, 4H, Ar-H), MS (m/*z*): 383 $[M+1]^+$; Elemental analysis: C, 69.08, H, 6.85, N, 7.32, S, 8.38 %.

3-(Diethylamino)-{1-[3-methoxyphenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6r) FTIR (KBr) ν, cm^{-1}): 3380 (N-H_{str}), 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 (C-O-C_{str}), 1037 (Al. C-N_{str}), 812 (C-H *m*-disub. benzene), 703 (C-S_{str}); ^{1}H

NMR, δ ppm: 1.245-1.315 (m, 6H, CH_3), 1.714-1.871 (m, 4H,CH_2), 2.350-2.357 (t, 2H, CH_2), 2.600-2.670 (t, 2H, CH_2), 3.367 (s, 3H, CH_3), 3.716 (s, 3H, OCH_3), 6.220 (s, 1H, Ar-H), 7.334-7.457 (m, 8H, Ar-H), 8.150 (s, 1H, N-H, D_2O exchange); MS (m/z): 411 $[M+1]^+$; Elemental analysis: C, 70.21, H, 7.36, N, 6.82, S, 7.81 %.

3-(Dimethylamino)-{1-[2-methoxyphenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6s) FTIR (KBr) ν, cm^{-1}): 3425 (N-H_{str}), 3142 (Ar. C-H_{str}), 2995 (Ali. C-H_{str}), 1802 (C=O_{str}), 1623 (Ar. C⋯C$_{str}$), 1352 (Ar. C-N_{str}), 1164 (C-O-C_{str}), 1053 (Al. C-N_{str}), 750 (C-H *o*-disub. benzene), 671 (C-S_{str}); ^1H NMR, δ ppm: 1.128-1.216 (m, 6H, CH_3), 2.413-2.464 (t, 2H, CH_2), 2.558-2.571 (t, 2H, CH_2), 2.358 (s, 3H, CH_3), 3.721 (s, 3H, OCH_3), 6.114 (s, 1H, Ar-H), 7.264-7.356 (m, 8H, Ar-H), 8.278 (s, 1H, N-H, D_2O exchange); MS (m/z): 383 $[M+1]^+$; Elemental analysis: C, 69.08, H, 6.85, N, 7.32, S, 8.38 %.

3-(Diethylamino)-{1-[2-methoxyphenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (6t) FTIR (KBr) ν, cm^{-1}): 3344 (N-H_{str}), 3134 (Ar. C-H_{str}), 2947 (Ali. C-H_{str}), 1750 (C=O_{str}), 1608 (Ar. C⋯C$_{str}$), 1346 (Ar. C-N_{str}), 1180 (C-O-C_{str}), 1064 (Al. C-N_{str}), 769 (C-H *o*-disub. benzene), 690 (C-S_{str}); ^1H NMR, δ ppm: 1.103-1.290 (m, 6H, CH_3), 1.834-1.929 (m, 4H, CH_2), 2.457-2.486 (t, 2H, CH_2), 2.625-2.655 (t, 2H, CH_2), 3.788 (s, 3H, OCH_3), 4.143 (s, 3H, CH_3), 6.172 (s, 1H, Ar-H), 7.222-7.321 (m, 8H, Ar-H), 8.331 (s, 1H, N-H, D_2O exchange); MS (m/z): 411 $[M+1]^+$; Elemental analysis: C, 70.21, H, 7.36, N, 6.82, S, 7.81 %.

Anticonvulsant screening

The primarily screening of the anticonvulsant, all derivatives of synthesized novel Mannich bases found that protection against MES which exhibit the significant good ability of these derivatives to stop seizures. Mostly compounds exhibit potent activity at 30 & 100 mg/kg dose without neurotoxin in nature except compounds **6i, 6j, 6m and 6n.** Mostly the synthesized derivative produced neurotoxicity at a maximum dose 300 mg/kg. The dose range between 30-100 mg/kg was tested for knowing therapeutic phenomena. The most significant 3-(Dimethylamino)-{1-[3-chlorophenyl-4-methyl-2,5-dihydro-1,5-benzothiazepin-3-yl]}propan-1-one (**6e)** showed maximum potency at 300 mg/kg with low toxicity from varying ranges of doses. Compounds **6i, 6j 6k, 6l, 6m** and **6n** (nitro substituted) showed poor or less activity due to low log P.

Considering above results it became certain that the derivatives of chloro showed best activity and ortho substituted derivative possess more significant activity, while para position alteration affect their activity. On the contrary the nitro substituted derivative exhibit poor CNS penetrating ability and hence low activity. On the other hand chloro group insertion in ring system increases their antiepileptic activity.

Oral acute toxicity

The novel most significant synthesized compound **6e** with its dose 2000 mg/kg administered to test animals no harmful effect on their social reactions and watched for fourteen days time period regularly. All test group animals shown not any poisonous/deadly impact during the acute toxicity study. My current

investigation shows that the administration of test compound up to 2000 mg/kg didn't any indication of harmfulness toxicity or mortality in animals at the time of experimental period.

Conclusion

A series of novel substituted Mannich bases (6a-6t) synthesized successfully and primarily biological screening done by MES model for antiepileptic activity. The best significant synthesized compound **6e** found as a primary class of anticonvulsants that have shown practically identical anticonvulsant action with uniquely lower neurotoxicity. Acute toxicity study as per OECD guidelines compound **6e** found that non toxic nature. Total fourteen days observation normal behavior of animals that suggest the all novel compounds (6a-6t) safe and innocuous nature up to dose 2000 mg/kg. Compound **6e** found as a pharmacophore molecule for further modification and improvement in field of anticonvulsants drug development.

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 hr				Recovery/Death	Neurotoxicity screen
		Flexion (Mean±SEM)	Extensor (Mean±SEM)	Clonus (Mean±SEM)	Stupor (Mean±SEM)		
6a	30	3.83±0.12*	16.77±0.38*	15.32±0.25***	116.64±0.42**	Recovery	Absent
	100	2.93±0.15**	14.01±0.16**	8.81±0.35***	47.38±0.42***	Recovery	Absent
	300	4.84±0.18	24.42±0.37***	35.34±0.37***	119.12±0.40***	Recovery	Absent
6b	30	3.81±0.42*	17.40±0.40*	16.35±0.73***	116.96±0.90**	Recovery	Absent
	100	2.75±0.18**	13.40±0.24**	9.42±0.25***	47.58±0.56***	Recovery	Absent
	300	5.49±0.37	25.20±0.50***	35.21±0.54***	120.07±0.53***	Recovery	Absent
6c	30	3.79±0.23*	6.16±0.45***	8.72±0.38***	46.87±0.40***	Recovery	Absent
	100	2.24±0.04***	4.21±0.23***	8.17±0.20***	46.15±0.25***	Recovery	Absent
	300	3.81±0.18*	21.94±0.38***	33.26±0.41***	113.19±0.27*	Recovery	Absent
6d	30	4.24±0.29*	6.93±0.46***	9.23±0.29***	48.02±0.65***	Recovery	Absent
	100	2.70±0.29**	4.86±0.21***	8.79±0.20***	46.87±0.34***	Recovery	Absent
	300	4.29±0.37^{ns}	22.71±0.40***	33.62±0.36***	113.99±0.43*	Recovery	Absent
6e	30	3.11±0.29**	3.46±0.12***	8.29±0.34***	43.40±0.28***	Recovery	Absent
	100	2.30±0.8***	2.85±0.13***	7.68±0.31***	44.42±1.12***	Recovery	Absent
	300	2.82±0.21**	10.12±0.20***	18.41±0.14***	113.45±0.36*	Recovery	Absent
6f	30	4.07±0.18*	3.96±0.23***	8.63±0.45***	44.82±0.52***	Recovery	Absent
	100	2.82±0.26**	3.44±0.25***	8.61±0.30***	46.05±1.21***	Recovery	Absent
	300	3.53±0.32*	10.75±0.22***	18.84±0.24***	114.11±0.21*	Recovery	Absent
6g	30	2.47±0.34**	4.36±0.24***	7.54±0.32***	39.41±0.73***	Recovery	Absent
	100	2.93±0.18**	5.04±0.25***	8.94±0.18***	45.20±0.52***	Recovery	Absent
	300	3.90±0.27	20.82±0.25***	34.87±0.25***	118.87±0.17***	Recovery	Absent
6h	30	2.96±0.32**	4.78±0.25***	8.16±0.27***	40.74±0.52***	Recovery	Absent
	100	3.43±0.27**	5.49±0.32***	9.53±0.36***	46.15±0.61***	Recovery	Absent
	300	4.44±0.27 ^{ns}	21.59±0.31***	35.40±0.40***	119.49±0.31***	Recovery	Absent
6i	30	7.87±0.19***	23.25±0.32***	39.71±0.26***	192.69±0.74***	Recovery	Absent
	100	8.27±0.37***	23.73±0.28***	39.58±0.76***	190.17±0.63***	Recovery	Absent
	300	6.96±0.10***	21.19±0.41***	36.87±0.47***	189.07±0.38***	Recovery	Absent
6j	30	8.44±0.22***	24.57±0.32***	40.53±0.50***	194.55±0.93***	Recovery	Absent
	100	8.63±0.39***	24.51±0.28***	40.06±0.61***	190.91±0.64***	Recovery	Absent
	300	7.11±0.11***	21.71±0.43***	37.68±0.45***	189.69±0.36***	Recovery	Absent
6k	30	6.94±0.45**	20.02±0.47***	37.05±0.37***	167.09±0.69***	Recovery	Absent
	100	6.76±0.17**	20.23±0.52***	13.24±0.68***	164.38±0.92***	Recovery	Absent
	300	6.75±0.20**	22.58±0.33***	39.20±0.43***	188.63±0.64***	Recovery	Absent
6l	30	8.21±0.19***	21.29±0.71***	38.81±0.61***	169.59±1.21***	Recovery	Absent

	100	7.28±0.36**	20.95±0.26**	36.52±0.52***	164.87±0.80***	Recovery	Absent
	300	7.44±0.29***	23.54±0.38***	40.17±0.51***	189.51±0.78***	Recovery	Absent
6m	30	9.25±0.31***	23.53±0.28***	43.89±0.30***	195.91±0.72***	Recovery	Absent
	100	8.34±0.27***	22.62±0.31***	42.90±0.23***	193.32±0.33***	Recovery	Absent
	300	7.75±0.22***	22.53±0.38***	38.76±0.57***	192.93±0.20***	Recovery	Absent
6n	30	10.42±0.34***	24.21±0.44***	44.63±0.26***	197.95±0.85***	Recovery	Absent
	100	8.90±0.24***	23.48±0.37***	43.44±0.32***	194.2±0.48***	Recovery	Absent
	300	8.27±0.28***	23.34±0.51***	39.74±0.45***	193.58±0.26***	Recovery	Absent
6o	30	6.17±0.26*	23.76±0.11***	25.88±0.25**	124.14±0.90***	Recovery	Absent
	100	3.96±0.19**	13.69±0.37**	16.67±0.38***	51.05±0.59***	Recovery	Absent
	300	5.92±0.14*	24.00±0.19***	35.36±0.36***	128.81±0.56***	Recovery	Absent
6p	30	6.96±0.24**	24.52±0.50***	25.24±0.36*	126.32±0.53***	Recovery	Absent
	100	4.62±0.33**	14.55±0.62**	17.65±0.26***	52.61±0.32***	Recovery	Absent
	300	6.52±0.27**	24.68±0.33***	35.85±0.40***	129.91±0.87***	Recovery	Absent
6q	30	5.42±0.42*	22.41±0.85***	18.97±0.21***	121.53±0.38***	Recovery	Absent
	100	4.47±0.34**	13.47±0.38**	12.79±0.34***	52.10±0.23***	Recovery	Absent
	300	5.85±0.21*	23.06±0.40***	40.06±0.50***	127.97±0.62***	Recovery	Absent
6r	30	6.17±0.39*	24.07±0.84***	19.73±0.42***	123.54±0.76***	Recovery	Absent
	100	5.07±0.27**	14.39±0.25**	13.60±0.29***	52.91±0.35***	Recovery	Absent
	300	6.18±0.25**	23.93±0.63***	40.97±0.71***	128.94±0.62***	Recovery	Absent
6s	30	5.24±0.27 ns	19.46±0.45**	16.58±0.37***	116.58±0.29***	Recovery	Absent
	100	3.13±0.22***	5.87±0.25***	9.45±0.18***	48.96±0.42***	Recovery	Absent
	300	5.72±0.22*	22.56±0.33***	38.86±0.23***	125.57±0.63***	Recovery	Absent
6t	30	5.98±0.44*	20.32±0.46***	17.63±0.36***	118.39±0.56***	Recovery	Absent
	100	3.63±0.12**	6.52±0.32***	10.11±0.41***	50.34±0.77***	Recovery	Absent
	300	6.52±0.44*	23.49±0.46***	39.85±0.49***	126.32±0.48***	Recovery	Absent
Control	30% v/v PEG400	4.80±0.36	15.70±0.45	23.73±0.61	111.47±0.85	Recovery	Absent
Phenytoin	30	2.49±0.05***	3.54±0.07***	7.69±0.28***	42.56±0.30***	Recovery	Absent

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

Table 3: Anticonvulsant evaluation after 4 hr administration of compounds (6a-6t) using MES model

Compound No.	Doses (mg/kg)	Time (sec) in various phases of convulsion after 4 hr				Recovery/Death	Neurotoxicity screen
		Flexion (Mean±SEM)	Extensor (Mean±SEM)	Clonus (Mean±SEM)	Stupor (Mean±SEM)		
6a	30	2.79±0.19***	14.87±0.49*	13.43±0.36***	114.35±0.81**	Recovery	Absent
	100	2.82±0.18***	3.97±0.22***	8.23±0.23***	42.63±0.50***	Recovery	Absent
	300	5.74±0.42**	24.94±0.28***	35.63±0.40***	118.37±0.37***	Recovery	Absent
6b	30	3.21±0.15***	14.34±0.45*	13.18±0.31***	112.57±0.88*	Recovery	Absent
	100	4.6±0.47*	5.55±0.46***	9.37±0.32***	44.28±0.67***	Recovery	Absent
	300	6.26±0.38**	25.30±0.50***	36.46±0.46***	119.12±0.31***	Recovery	Absent
6c	30	2.35±0.03***	4.89±0.23***	7.46±0.38***	43.65±0.63***	Recovery	Absent
	100	2.84±0.32***	3.96±0.31***	8.39±0.27***	46.20±0.89***	Recovery	Absent
	300	5.50±0.23**	22.94±0.22***	33.66±0.07***	115.18±0.40***	Recovery	Absent
6d	30	2.74±0.25***	5.25±0.36***	7.48±0.28***	43.37±0.77***	Recovery	Absent
	100	4.66±0.57*	5.19±0.40***	10.09±0.35***	47.95±0.59***	Recovery	Absent
	300	5.08±0.35*	23.64±0.38***	34.34±0.46***	116.02±0.52***	Recovery	Absent
6e	30	1.55±0.12***	2.67±0.06***	7.01±0.19***	36.29±0.66***	Recovery	Absent
	100	2.09±0.19***	3.35±0.20***	7.46±0.32***	41.66±0.40***	Recovery	Absent
	300	3.10±0.26***	12.91±0.29***	20.25±0.39*	118.84±0.33***	Recovery	Absent
6f	30	2.25±0.40***	3.11±0.29***	7.65±0.23***	36.83±0.39***	Recovery	Absent
	100	3.32±0.37**	4.98±0.45***	8.75±0.31***	43.95±0.52***	Recovery	Absent
	300	3.62±0.36**	13.39±0.40***	20.89±0.14*	119.63±0.48***	Recovery	Absent
6g	30	1.82±0.17***	3.14±0.32***	7.02±0.48***	40.47±0.82***	Recovery	Absent
	100	2.39±0.30***	4.40±0.38***	7.47±0.30***	44.13±0.33***	Recovery	Absent
	300	3.83±0.32*	20.60±0.23***	36.01±0.23***	120.44±0.27***	Recovery	Absent
6h	30	2.87±0.50**	4.02±0.45***	7.64±0.33***	42.35±0.41***	Recovery	Absent
	100	4.28±0.45*	5.66±0.44***	8.42±0.36***	46.35±0.63***	Recovery	Absent

	300	4.23±0.29*	21.26±0.31***	36.45±0.19***	121.32±0.59***	Recovery	Absent
6i	30	6.31±0.24***	21.31±0.33***	37.53±0.45***	188.54±0.59***	Recovery	Absent
	100	6.90±0.36***	22.49±0.53***	38.13±0.36***	189.35±0.65***	Recovery	Absent
	300	7.18±0.23***	17.05±0.29**	37.23±0.40***	187.85±0.44***	Recovery	Absent
6j	30	6.90±0.19***	22.35±0.37***	38.6±0.50***	189.25±0.85***	Recovery	Absent
	100	7.98±0.37***	24.16±0.42***	39.23±0.52***	190.29±0.31***	Recovery	Absent
	300	7.69±0.26***	17.57±0.38**	37.80±0.33***	189.00±0.47***	Recovery	Absent
6k	30	5.30±0.17*	17.57±0.42**	33.94±0.67***	162.77±0.76***	Recovery	Absent
	100	6.06±0.22**	20.21±0.60***	35.10±0.78***	163.21±0.71***	Recovery	Absent
	300	5.99±0.26**	21.88±0.27***	37.69±0.31***	187.12±0.40***	Recovery	Absent
6l	30	6.04±0.42**	19.14±0.60**	34.91±0.16***	165.18±0.83***	Recovery	Absent
	100	6.86±0.36***	21.86±0.99***	35.95±0.37***	164.87±0.04***	Recovery	Absent
	300	6.74±0.25***	23.18±0.35***	38.44±0.27***	188.32±0.70***	Recovery	Absent
6m	30	7.41±0.32***	21.42±0.31***	41.58±0.36***	191.82±0.69***	Recovery	Absent
	100	7.46±0.49***	21.53±0.53***	42.43±0.36***	192.30±0.72***	Recovery	Absent
	300	8.16±0.30***	18.74±0.17***	38.18±0.40***	188.72±0.38***	Recovery	Absent
6n	30	8.29±0.40***	22.43±0.62***	42.63±0.31***	193.41±0.64***	Recovery	Absent
	100	8.98±0.55***	24.12±0.54***	43.56±0.19***	194.06±0.52***	Recovery	Absent
	300	8.82±0.21***	18.99±0.13***	38.90±0.48***	189.65±0.45***	Recovery	Absent
6o	30	4.75±0.21*	21.16±0.28***	19.97±0.48*	120.14±0.78***	Recovery	Absent
	100	3.92±0.40*	5.46±0.34***	11.87±0.47***	49.98±0.81***	Recovery	Absent
	300	5.47±0.18**	23.63±0.21***	34.31±0.13***	126.70±0.42***	Recovery	Absent
6p	30	5.37±0.34*	21.56±0.47***	20.46±0.29***	121.19±0.17***	Recovery	Absent
	100	5.22±0.40*	6.86±0.16***	12.99±0.67***	51.83±0.65***	Recovery	Absent
	300	5.80±0.27**	24.12±0.40***	34.65±0.28***	127.79±0.51***	Recovery	Absent
6q	30	3.81±0.17**	18.72±0.29***	16.97±0.46**	118.56±0.72***	Recovery	Absent
	100	3.31±0.23**	4.83±0.14***	7.17±0.56***	47.83±0.61***	Recovery	Absent
	300	5.72±0.27**	22.70±0.25***	39.56±0.51***	127.11±0.77***	Recovery	Absent
6r	30	4.27±0.18*	19.49±0.35***	17.67±0.39***	119.50±0.56***	Recovery	Absent
	100	5.12±0.40*	5.70±0.32***	8.26±0.41***	48.00±0.67***	Recovery	Absent
	300	6.46±0.30***	23.11±0.36***	40.25±0.42***	127.56±0.71***	Recovery	Absent
6s	30	3.95±0.33*	17.25±0.27**	14.4±0.28***	113.65±0.64**	Recovery	Absent
	100	2.07±0.19***	4.25±0.13***	8.09±0.36***	43.95±0.53***	Recovery	Absent
	300	5.47±0.33**	22.23±0.42***	38.50±0.42***	124.74±0.36***	Recovery	Absent
6t	30	4.68±0.34*	17.84±0.45**	15.54±0.34***	115.20±0.36***	Recovery	Absent
	100	3.09±0.29**	4.70±0.17***	8.50±0.37***	44.94±0.33***	Recovery	Absent
	300	6.07±0.29**	23.06±0.31***	38.89±0.38***	125.80±0.54***	Recovery	Absent
Control	30% v/v PEG400	4.66±0.17	15.49±0.31	20.38±0.60	109.00±0.88	Recovery	Absent
Phenytoin	30	1.95±0.35***	3.03±0.23***	7.32±0.16***	36.68±0.86***	Recovery	Absent

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

Table 4: Effect of compound 6e for acute toxicity study

S.N.	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

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