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DESIGN, SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL SUBSTITUTED PHENYTOIN DERIVATIVES

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ABSTRACT

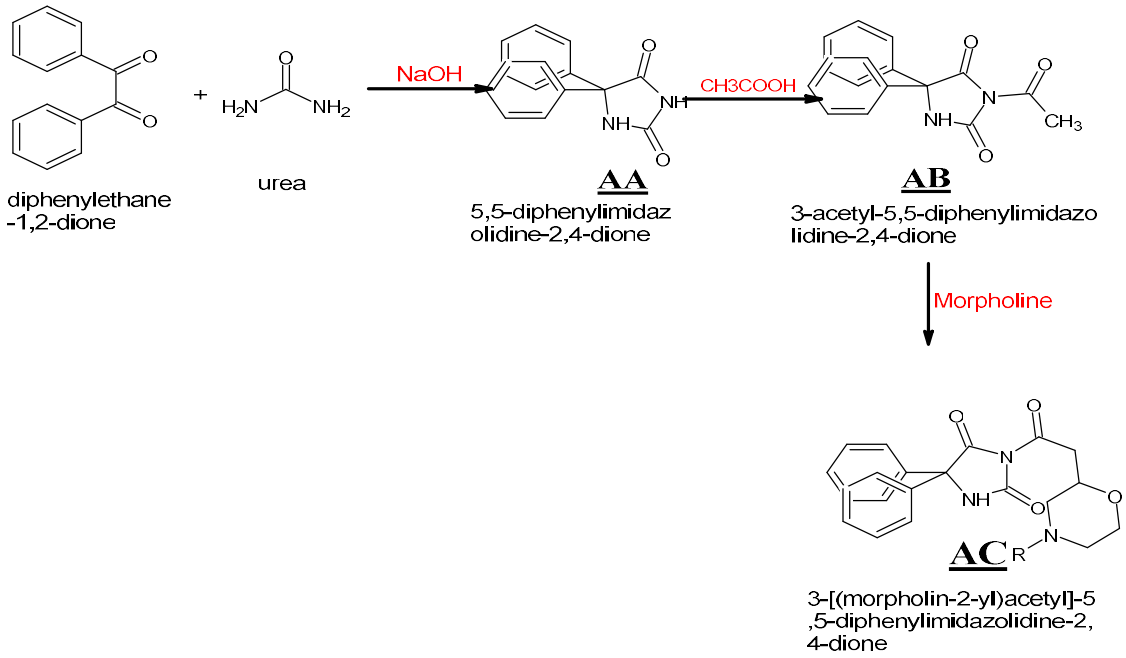
There is an increasing prevalence of epileptic patients throughout the world and new compounds are necessary to overcome this. While the current available treatment causes abnormal body movement, loss of coordination and confusion, etc. this has led to a demand for more affordable, more effective methods for epileptic patients. Aim of this research is too focused on finding alternative medicinal remedies with significant anticonvulsant activity as well as low adverse effects. This study synthesized, characterized, and evaluated anti-convulsant properties of synthetic Hydantoin hybrid of 5, 5-Diphenylimidazolidione-2, 4-dione derivatives. Hybrid between phenytoin and 1-Oxa-4-azacyclohexane Tetrahydro-1, 4-oxazine Diethylene oximide were synthesized and tested for anticonvulsant activity. **MATERIAL AND METHODS:** Preliminary anticonvulsant activity was performed using subcutaneous phentylenetetrazole (scPTZ) screens in Wistar rats. Standard dose of phenytoin is 100mg/kg is used in this model and dose of PTZ is 85mg/kg is used. **RESULT:** Among synthesized compounds the anticonvulsant activity are shown by AA, AC, AC1, AC6 and AC7 having the highest protection (80%) in the scPTZ test at a dose of 85mg/kg whereas the

compound AC (step-III) product shows promising anticonvulsant effect in the PTZ model. **CONCLUSION:** Derivatives developed in this study provide new classes of anti-convulsant effect, and further optimization like bioavailability and lowering the side effect as much as possible can be performed using this information.

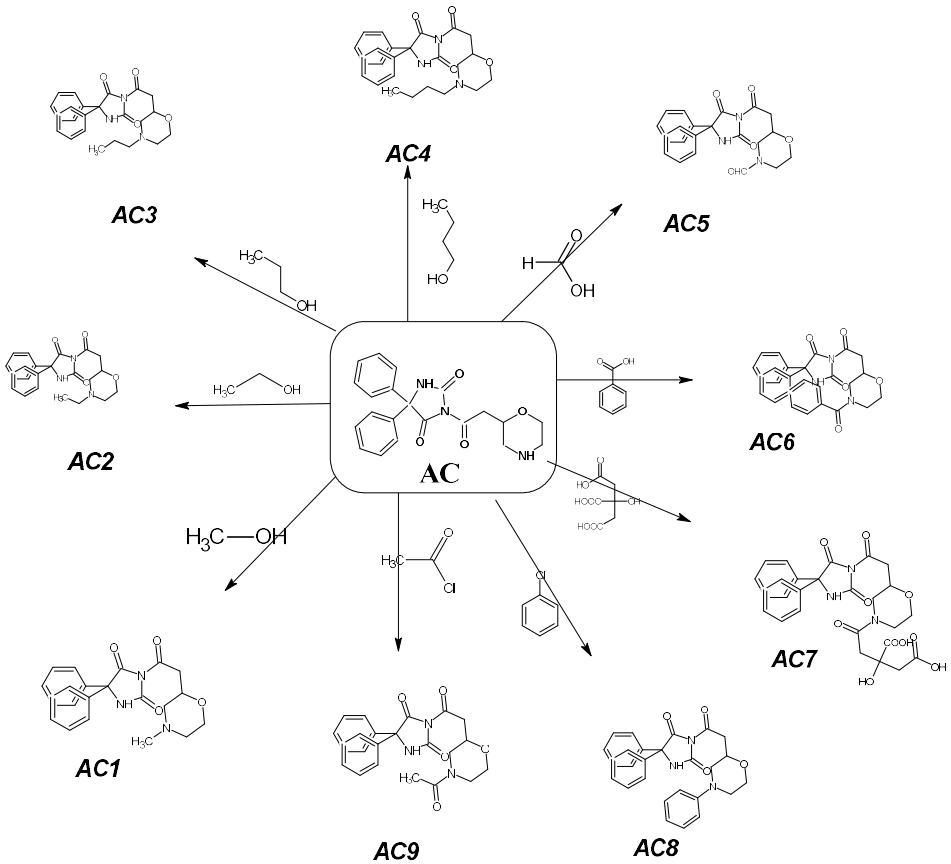
Keywords: 5, 5-Diphenylimidazolidione-2, 4-dione, In-vivo study, scPTZ, Anti-convulsant, Morpholine

INTRODUCTION:

Epilepsy is the most common, serious and neurodegenerative disease with the affection of 65 million people worldwide. People having epilepsy suffer from head trauma, parenteral injuries, misunderstanding and discrimination. As stress of living with epilepsy may lead to loss of autonomy for activities of daily living **[1]**. It is neurological disorder and characterized by the periodic and unpredictable occurrence of seizures which are caused by the discontinuous discharge of cerebral neurons. There is significant advances had been made in the epilepsy research, currently available medications have been associated with severe side effects that are ranges from minimal brain impairment to the death from hepatic failure **[2]**. The shortage of understanding and complexness of the mechanism of action definitely affects the event of latest candidates as potential Anti-Epileptic medicine (AEDs) through mechanism-driven styles. So, the look of a brand new anticonvulsant depends on form similarities as basic descriptors of process drug discovery to model and also the correct understanding of the protein-ligand interactions **[3]**. Hydantoin moiety demonstrates anticonvulsant, analgesic, antibacterial, anti-inflammatory, antitumor activities **[4]**. More than 300 compounds have been synthesized and tested for anticonvulsant evaluation of drugs. Representative Imidazolidine like thiosemicarbazide, 1, 3, 4-oxadiazole, 1, 3, 4-thiadiazole or 1, 2, 4-triazole, benzhydrol, chlorobenzhydrol. The purpose of the present work is to study the synthesis of derivatives of 5, 5-Diphenylimidazolidine-2, 4-Dione as a potential two benzyl rings and one imidazolidine ring. The morpholine moiety was introduced in the structure to increase the anticonvulsant activity as well as to minimize the side effects of the convulsions **[5]**.



Scheme 1: Synthesis of 3-[(morpholin-2-yl) acetyl]-5, 5-diphenylimidazolidine-2, 4-Dione



Scheme 1.1: Synthesis of derivatives (AC1-AC9) from 3-[(morpholin-2-yl) acetyl]-5, 5-diphenylimidazolidine-2, 4-Dione

MATERIALS AND METHODS:

Here all chemicals and reagents utilized were of a business contingency of laboratory grade obtained from Sigma-Aldrich and Merck and have been used without further detoxification.

EXPERIMENTAL CHEMISTRY:

Tile compounds AA, AB, AC and AC1 to AC9 have been synthesized as per scheme 1 and 5,5-Diphenylimidazolidine-2,4-dione (AA) 1 (2 mol) was reacted with glacial acetic acid (GAA) 1 ml it gives (AB), Acetylation reaction takes place as Acetyl group work as a bridge between Phenytoin and morpholine ring. Heat the reaction mixture of AA and AB at about 80-100 ºC for 2 & ½ hoursIt gives of 3-[(Morpholine-2-yl)] Acetyl-5,5-Diphenylimidazolidine-2,4-Dione.(AC). This further heating with different reactant leads to synthesis of derivatives AC1 to AC9. AC1 to AC4 gives 4-Alkyl-Morpholine-3-Acetyl]-5, 5-Diphenylimidazolidine-2, 4-Dione. While AC5 gives [Morpholine-4-carbaldehyde-3-Acetyl]-5,5-Diphenylimidazolidine-2,4-Dione, AC6 gives (Morpholin-4-yl)(phenyl)methanone-3-Acetyl]-5,5-Diphenylimidazolidine-2,4-Dione, AC7 gives (2-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl] butanedioicacid-5,5-Diphenylimidazolidine-2,4-Dione, AC8 gives4-Phenyl[(morpholin-2-yl)acetyl] 5,5diphenylimidazolidine-2,4-dione, AC9 gives 1-(morpholin-4-yl)ethan-1-one]-5,5-diphenylimidazolidine-2,4-dione. All the synthesized compounds were recrystallized using petroleum ether. Characterization of both intermediates and final compounds were analyzed by various physiochemical techniques and spectral techniques. The melting points of final compounds were on melting point apparatus (Omkar instruments). The success of the derived reaction and the purity of final compounds were recorded by thin layer chromatography using silica gel G plates. The FTIR spectra were recorded using Shimadzu-FTIR-8400Sspectrophotometer the KBr pellet process. The ^{1}HNMR was reported in the BRUKER SPECT PROBHD Z119470_0152 NMR spectrometer using DMSO as a solvent. Mass spectra were recorded onBRUKER IMPACT HD II (HRMS) mass spectrometer $(M+1)^{+}$. The elementary analysis (C, H, and N) was determined using ACD Chemsketcher. The C, H, N values for the compounds were found to be in the range of ±0.4 percent. The physiochemical and spectral characterization data for the final compounds AA to AC9 were provided in **Table 1 and Table 2**.

PHARMACOLOGICAL EVALUATION:

All of the experimental treatments were carried out in compliance with CPCSEA guidelines **[8]** and licensed by the foundation's proposal no. 1942/PO/Re/S/17/CPCSEA/2022/02/01

ANIMALS:

Swiss albino mice weighing between 18-25 gm used for oral toxicity and Wistar rats weighing 130-250 gm. used for biological evaluation in order to acclimatize them at laboratory levels, the animals were kept to individual cages for a week. They were given free access to water and food **[6]**.

ANTICONVULSANT ACTIVITY:

Final compounds AA, AB, AC, AC1, AC3, AC6, AC7, AC9 were assessed for anticonvulsant activity that and subcutaneous pentylenetetrazole (scPTZ) models.

Table 1: Physico-chemical characterization data for final compounds (AA-AC9)

Comp. Code	R	Mol. Formula	Mol. Wt.	M. P. (ºC)	% Yield
AA	-	C15H12N2O2	294.30	305 ºC	86.59
AB	-COCH3	C17H14N2O3	379.40	319 ºC	47.45
AC	-ONC4H9	C21H20N3O4	393.43	310 ºC	58.20
AC1	-CH3	C22H23N3O4	407.46	320 ºC	86.20
AC2	-CH2CH3	C23H25N3O4	421.48	308 ºC	77.41
AC3	-CH2CH2CH3	C24H27N3O4	435.51	293 ºC	84.90
AC4	-CH2CH2CH2CH3	C25H29N3O4	407.41	314 ºC	77.41
AC5	-CHO	C22H21N3O5	483.51	317 ºC	60.86
AC6	-COC6H5	C28H25N3O5	553.51	314 ºC	74.76
AC7	-C6H8O6	C27H27N3O10	455.50	310 ºC	67.56
AC8	-C6H5	C27H25N3O4	421.44	290 ºC	74.72
AC9	-COCH3	C23H23N3O5	294.30	318 ºC	65

Table 2: Spectral Characterization data of the final compounds (AA-AC9)

Comp. Code	IR (KBr, cm-1)	1H NMR (DMSO, δ in ppm)	Mass (*m/e*) [M+1]+	Elemental Analysis
AA	3074 (C-H Stretch (Aromatic) 2793 (C-H Stretch (Aliphatic) 1696 (C=C Stretch (Aromatic) 1186 (C-C Stretch (Aromatic) 3476(N-H Stretch (Aromatic)	7.411 (s, 1H, ArH), 7.408 (s, 1H, ArH), 7.400 (s, 1H,ArH),7.397 (s, 1H, ArH), 7.391 (s, 1H, ArH), 7.386(s, 1H, ArH), 7.362 (s, 1H, ArH), 7.357 (s, 1H, ArH), 7.347 (s, 1H, ArH), 7.344 (s, 1H, ArH), 7.338 (s, 1H, ArH) 7.334 (s, 1HArH)3.773 (ArNH), 3.776 (ArNH)	251.462	C (71.42%) H(4.79%) N (11.10%) O (12.68%)
AB	3098(C-H Stretch (Aromatic) 1672 (C=C Stretch (Aromatic) 1270(C-C Stretch (Aromatic) 3476(N-H Stretch (Aromatic) 1725 (C=O Ketone) 2918 (R-O-R` Aromatic Stretch)	7.398 (s, 1H ArH), 7.391 (s, 1H ArH),7.386 (s, 1H ArH),7.384(s,1HArH),7.364(s, 1H ArH),7.360 (s,1H ArH),7.355(s,1H,ArH),7.350(s,1H,ArH), 7.349(s,1H,ArH),11.089 (s,ArNH), 2.519 (s, - CH3)	-	C (69.38%) H(4.79%) N (9.52%) O (16.31%)

AC	**3074 (C-H Stretch (Aromatic) 2793 (C-H Stretch (Aliphatic) 1696 (C=C Stretch (Aromatic) 1186 (C-C Stretch (Aromatic) 3476(N-H Stretch (Aromatic)**	**7.415 (s, 1H ArH), 7.411(s, 1H ArH), 7.408 (s, 1H ArH), 7.400 (s, 1H ArH),7.398 (s, 1H ArH),7.391 (s, 1H ArH), 7.386 (s, 1H ArH), 7.360 (s, 1H ArH), 7.355 (s, 1H ArH),7.349(s, 1H ArH), 7.346(s, 1H ArH),7.338(s, 1H ArH),7.334(s, 1H ArH),7.331(s, 1H ArH),7.067(s, 1H ArH), 10.298 (s, ArNH), 10.288 (s, ArNH)**	**378.8653**	**C (66.66%) H(5.33%) N (11.10%) O (16.91%)**
AC1	**1696 (C=C stretching), 1712 (C=O stretching), 1695 (C-N stretching), 1317 (C-C stretching), 1346 (Aromatic C-N stretching), 3483 (N-H Stretching (3º Amide), 1340 (C-H stretching), 3074 (C-H stretch Aliphatic).**	**9.305 (s, 1H, ArH), 7.737-7.398(s,4H, ArH), 7.360-7.057 (s, 6H, ArH), 10.298 (s, ArNH), 10.288, (s, ArNH) 2.670 (-CH3)**	**392.1586.**	**C (67.16%) H(5.89%) N (10.68%) O (16.27%)**
AC2	**1725(C=C stretching), 1725 (C=O stretching), 1340(C-N stretching), 1132 (C-C stretching), 647(N-H wagging), 3468 (N-H Stretching (3º Amide), 1340 (C-H stretching), 3275 (C-H stretch Aliphatic).**	**-**	**-**	**C (67.80%) H(6.18%) N (10.31%) O (15.71%)**
AC3	**1695(C=C stretching), 1725 (C=O stretching), 1340(C-N stretching), 1132 (C-C stretching), 647(N-H wagging), 3468 (N-H Stretching (3º Amide), 1340 (C-H stretching), 3275 (C-H stretch Aliphatic).**	**-**	**-**	**C (68.39%) H(6.46%) N (9.97%) O (15.18%)**
AC4	**1602(C=C stretching), 1702 (C=O stretching), 1263(C-N stretching), 1085(C-C stretching), 631(N-H wagging), 3498 (N-H Stretching (3º Amide), 3082(C-H stretching Aromatic), 2997 (C-H stretch Aliphatic).**	**-**	**-**	**C (68.95%) H(6.71%) N (9.65%) O (14.69%)**
AC5	**1601(C=C stretching), 1725 (C=O stretching), 1342(C-N stretching), 1000(C-C stretching), 647(N-H wagging), 3300 (N-H Stretching (3º Amide), 3082(C-H stretching Aromatic), 3000 (C-H stretch Aliphatic).**	**7.736-7.337 (s, 10H ArH), 7.334-7.025 (s, 8H ArH) 3.323 (s, 1NH ArNH) 2.515-2.494 (s, -CH3)**	**-**	**C (64.86%) H(5.20%) N (10.31%) O (19.64%)**
AC6	**1600.63 (C=C stretching), 1725 (C=O stretching), 1342(C-N stretching), 1000(C-C stretching), 770 (N-H wagging), 3400.85 (N-H Stretching (3ºAmide), 3082(C-H stretching Aromatic), 3000.63 (C-H stretch Aliphatic).**	**-**	**-**	**C (71.19%) H(5.53%) N (9.22%) O (14.05%)**
AC7	**1679 (C=C stretching), 1725 (C=O stretching), 1332 (C-N stretching), 1000(C-C stretching), 585(N-H wagging), 3400.85 (N-H Stretching (3ºAmide), 3082(C-H stretching Aromatic), 3000.63 (C-H stretch Aliphatic).**	**7.737-7.348 (s, 10H ArH) 7.342-7.025 (s, 10H ArH) 3.325 (s, -CH3) 9.304 (ArNH)**	**-**	**C (58.59%) H(4.92%) N (7.59%) O (28.98%)**
AC8	**1600 (C=C stretching), 1764 (C=O stretching), 1342 (C-N stretching), 1000.87 (C-C stretching), 770 (N-H wagging), 3100.97 (N-H Stretching (3ºAmide), 3082(C-H stretching Aromatic), 2800.13 (C-H stretch Aliphatic).**	**-**	**-**	**C (71.19%) H(5.53%) N (9.22%) O (14.05%)**
AC9	**1600 (C=C stretching), 1600.63 (C=O stretching), 1266.04 (C-N stretching), 1200.47 (C-C stretching), 778.136 (N-H wagging), 3206.08 (N-H Stretching (3ºAmide), 3000.69 (C-H stretching Aromatic), 2519 (C-H stretch Aliphatic).**	**-**	**-**	**C (65.55%) H(5.50%) N (9.97%) O (7.78%)**

Table 3: Preliminary anticonvulsant screening data of final compounds AA-AC9 in scPTZ model					
Compounds	Doses (mg/kg)	Onset of Convulsions (sec)	Duration of Convulsions (sec)	Avg. % Protection	Recovery/Death
AA	50	93±0.11	148±0.77	78%	Recovery
	100	104±0.52*	52±0.36*	88%	
	200	122±0.23*	26±0.14*	102%	
AB	50	84±0.41	119±0.96	70%	Recovery
	100	98±0.63	90±0.44	83%	
	200	114±0.31*	46±0.32*	96%	
AC	50	86±0.32	183±0.63	72%	Recovery
	100	100±0.21*	103±0.22	84%	
	200	117±0.32*	41±0.24*	106%	
AC1	50	82±0.85	139±0.87	69%	Recovery
	100	91±0.12	89±0.52	76%	
	200	107±0.32*	53±0.44	90%	
AC2	50	81±0.12	119±0.48	68%	Recovery
	100	90±0.41	80±0.55	76%	
	200	106±0.47*	66±0.96	88%	
AC3	50	63±0.63	163±0.41	53%	Recovery
	100	79±0.41	101±0.33	66%	
	200	96±0.22	63±0.47	80%	
AC4	50	58±0.52	142±0.48	49%	Recovery
	100	70±0.12	99±0.63	59%	
	200	88±0.85	73±0.74	74%	
AC5	50	69±0.11	150±0.55	58%	Recovery
	100	78±0.78	91±0.92	66%	
	200	96±0.52	52±0.34	81%	
AC6	50	72±0.63	148±0.63	61%	Recovery
	100	85±0.74	84±0.41	72%	
	200	107±0.63*	50±0.22	89%	
AC7	50	65±0.11	165±0.87	55%	Recovery
	100	80±0.52	89±0.11	68%	
	200	101±0.74*	39±0.22	85%	
AC8	50	70±0.96	172±0.63	59%	Recovery
	100	75±0.14	105±0.41	63%	
	200	99±0.85	38±0.21	83%	
AC9	50	58±0.33	187±0.15	49%	Recovery
	100	75±0.87	104±0.32	64%	
	200	105±0.36*	46±0.22*	88%	
Std. Phenytoin	100	119±0.41**	11±0.32**	100	Recovery

Values are expressed mean ± SEM (n=6). Values are statistically significant at *P and more significant at **P Vs. control using one way ANOVA followed by Dunnet's test.

scPTZMODEL

The animals were categorized into six groups consisting six animals in each group. Testing, controlled, standard, lower dose, Middle dose and higher dose. The synthesized substance were diluted into the DMSO and delivered orally to animals. After 30 min, the animals were treated subcutaneously with a convulsive dosage of PTZ (85mg/ kg). Phenytoin (100mg/kg) was used as a reference compound. Upon administration of PTZ observations were made 60 min. The findings of the scPTZ model for the synthesized compounds AA-AC9 are displayed in **Table 3 [7]**.

RESULT AND DISCUSSION:

Chemistry:

The synthesis of the title compounds AA-

AC9 (XII) wasperformed according to the reaction sequence describedin **Scheme 1**. FTIR, ^{1}H NMR and HRMS and basic research examined the intermediates and the final products. The spectral data obtained were found to be in keeping with the synthesized compound structures.

Anticonvulsant Activity:

Subcutaneous pentylenetetrazole test:

Table 3 describes the onset of action of each synthesized compound, duration of convulsion and the percent protection safety. At a lower dose of 50mg / kg displayed 49%-78%, at middle dose of 100mg/kg displayed 59% to 88% percentage protection and at higher dose of 200mg/kg percentage protection displayed 74% to 106%. The onset of action of synthesized compounds and the duration of convulsion were given in **Table 3**. The compounds AA, AB, AC, AC1, AC2, AC6, AC7, AC9 showed prominent activity compared to that of standard phenytoin drug. All the observations like onset of action, duration of convulsion and the percentage protection were given in **Table 3**. The **Figure 1 and Figure 2** shows the comparison of activity shown by different compounds in the form of onset of action and the percent protection of the compounds.

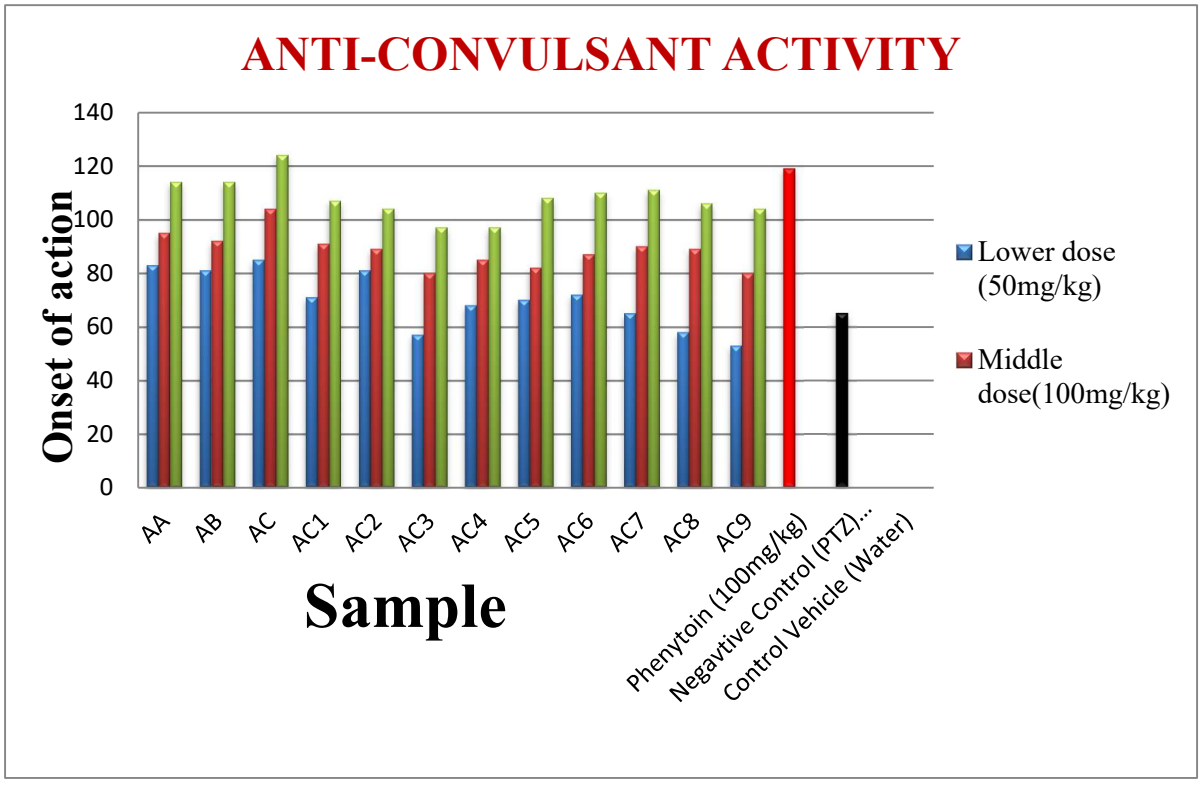


Figure 1: Comparison of onset of action final compounds at different doses in scPTZ model

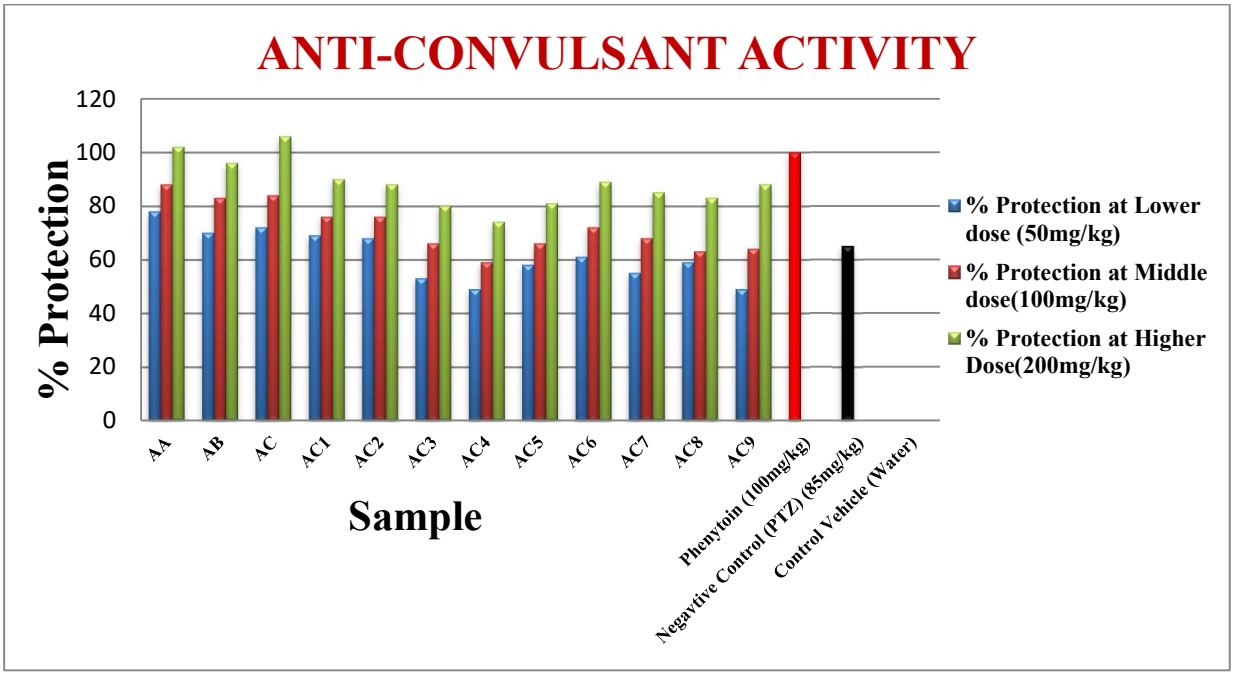


Figure 2: Comparison of % Protection of final compounds at different doses in scPTZ model

CONCLUSION:

In the present synthetic work a sequence or series of 5, 5-Diphenylimidazolidine-2, 4-Dione and the derivatives of 3-[(Morpholine-2-yl)] Acetyl-5, 5-Diphenylimidazolidine-2, 4-Dione. AC compound tested for anticonvulsant behavior using scPTZ model. The compounds show strong anticonvulsant action. Synthesized compounds like AA, AB, AC and AC1 showed strong anticonvulsant action percent protection (102%, 96%, 106%, and 90% respectively). Total synthesized compounds showed moderate to good anticonvulsant activity.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVATIONS

CNS: Central Nervous System; **AED's:** Anti-epileptic Drugs; **scPTZ:** Subcutaneous Pentylene Tetrazole; **FTIR:** Fourier Transform Infra-Red spectroscopy; **NMR:** Nuclear Magnetic Resonance; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **DMSO:** Dimethylsulphoxide; **IAEC:** Institutional animal ethical committee; **%:** Percentage; **Mol. Wt.:** Molecular weight; **Mol. Formula:** Molecular Formula; **IR:**

InfraRed spectroscopy; **M. P.:** Melting Point; **TLC:** Thin Layer Chromatography.

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