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MICROWAVE ASSISTED SYNTHESIS AND EVALUATION OF ANTICONVULSANT ACTIVITY OF SOME 1, 4-DIHYDROPYRIDINE DERIVATIVES

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Keywords:

Thiadiazole, Dihydropyridines, Chloramine -T, Anticonvulsant

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ABSTRACT: In the view of an extensive literature survey that revealed the anticonvulsant profile of 1,4-dihydropyridines and 1,3,4-Thiadiazole, we have coupled these two moieties with the aim of achieving an enhanced anticonvulsant effect. In present investigation some of ethyl-1-((5-amino-1, 3, 4-thiadiazol-2-yl) methyl)-5-ethyl-2, 6-dimethyl-4-substituted phenyl-1, 4-dihydro-pyridine-3-carboxylate derivatives are synthesized through four steps. A greener approach is employed by using Chloramine-T as an efficient and safer oxidative catalyst for the synthesis of Thiadiazole and the use of the Microwave technique for accelerating the chemical reactions. The structures of the newly synthesized compounds were confirmed on the basis of IR, ^{1}H-NMR, and Mass analyses. An acute toxicity study was done to determine LD_{50} of the newly synthesized compounds. Some of the synthesized compounds were evaluated for their anticonvulsant effect by PTZ induced convulsions method. Statistical testing was done by one-way ANOVA followed by Dunnett's test. The compounds F123 and showed the highest percentage of protection against convulsions at the dose of 15 mg/kg among the evaluated compounds compared to control.

INTRODUCTION: Epilepsy is the most prevalent neurological disorder affecting 1-2% of the world's population. Despite the availability of the conventional AEDs and the development of several new anticonvulsants, the treatments of epilepsy still remain inadequate since the loss of effectiveness (resistance) occurs after prolonged drug exposure [1, 2]. There is an ever-increasing need for research into newer molecules with lesser toxicities and side effects for treating epileptic seizures. 1,4-dihydropyridines and 1,3,4-thiadizoles are hydrophobic molecules possessing preliminary CNS properties [3, 4].

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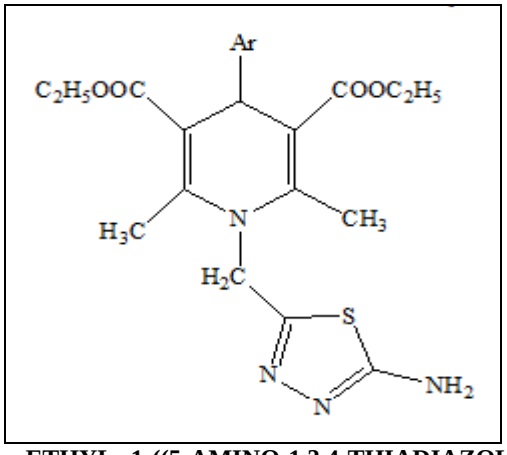


FIG. 1: ETHYL 1-((5-AMINO-1,3,4-THIADIAZOL-2-YL) METHYL)-2,6-DIMETHYL-4-SUBSTITUTED ARYL-1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLATES. Where, Ar =*p*-F-C_6H_5, *p*-Chromon-2yl, *p*-CH=CH-C_6H_5, *p*-OMe-C_6H_5, C_6H_5, o-Cl-C_6H_5, C_4H_3O-, *p*-NO_2-C_6H_5, *p*-OH-C_6H_5, *p*-Cl-C_6H_5

Hence, the coupling of these moieties is done in the present investigation with the hope of achieving enhanced anticonvulsant activity with the

objectives, *viz*. Synthesis of molecules containing both heterocycles *viz*. 1,3,4-thiadiazole and 1,4-dihydropyridine as shown in **Fig. 1**, Purification and Characterization of the synthesized compounds by IR, ^{1}H-NMR and Mass analyses and Pharmacological evaluation of the synthesized compounds for their anticonvulsant activity.

MATERIALS AND METHODS:

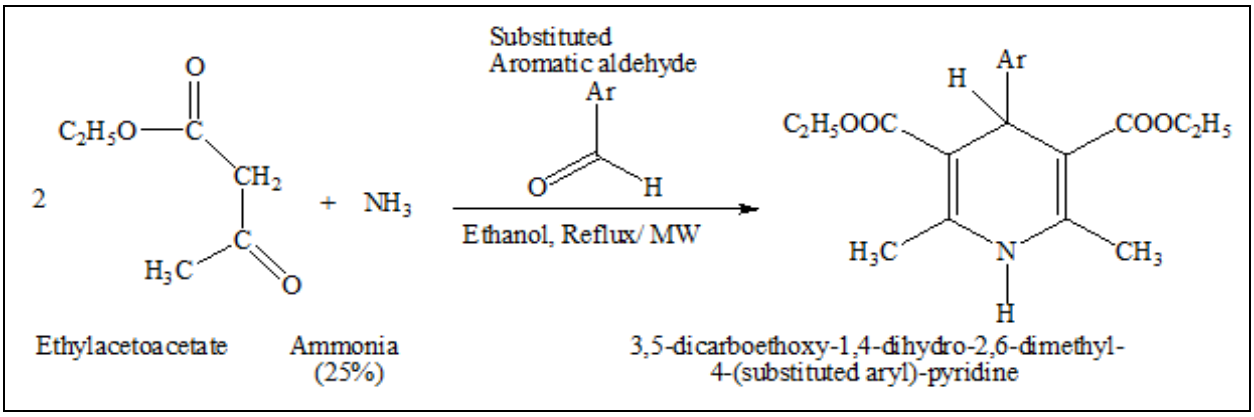
Reagents and Chemicals: All the chemicals were of laboratory reagent grade and were obtained from Thomas Baker, Sigma-Aldrich. Melting points were taken in one end sealed glass capillary using liquid paraffin in Thiele's tube and were uncorrected (Omega scientific industries). Analytical thin-layer chromatography was performed on 60F254 precoated silica gel plates (Merck) to establish the identity of reactants and products monitored in-between reactions as well at the end for completion of the reaction. The spots were visualized in UV chamber or by iodine vapors in an enclosed chamber. The solvent systems used for Thin-Layer Chromatography were,

(A: Chloroform: Methanol, 7:3), (B: Toluene: methanol, 4:3), (C: Acetone: methanol, 6:4), (D: n-Hexane: ethyl acetate, 6:4)

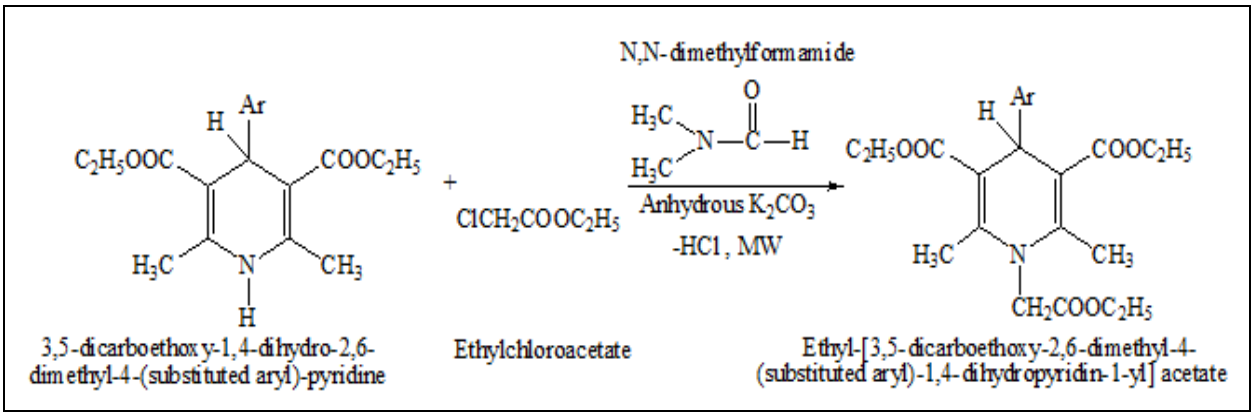
Instruments: Infra-Red spectra of compounds were recorded on DRS on a shimadzu1000 FTIR spectrometer in the range of 4000-200 cm^{-1}. Proton (^{1}H) Nuclear Magnetic Resonance Spectra of compounds were recorded on Bruker Avance II 400 NMR Spectrophotometer using DMSO as a solvent at SAIF, Punjab University, Chandigarh. Mass spectra of compounds were recorded on WATERS, Q-TOF MICROMASS (LC-MS) at SAIF, Punjab University, Chandigarh. All microwave reactions [5] were carried on 'Catalyst System' CATA 2R- Scientific Microwave Synthesizer with power setting from P-1 to H (700 W).

Synthetic Scheme:

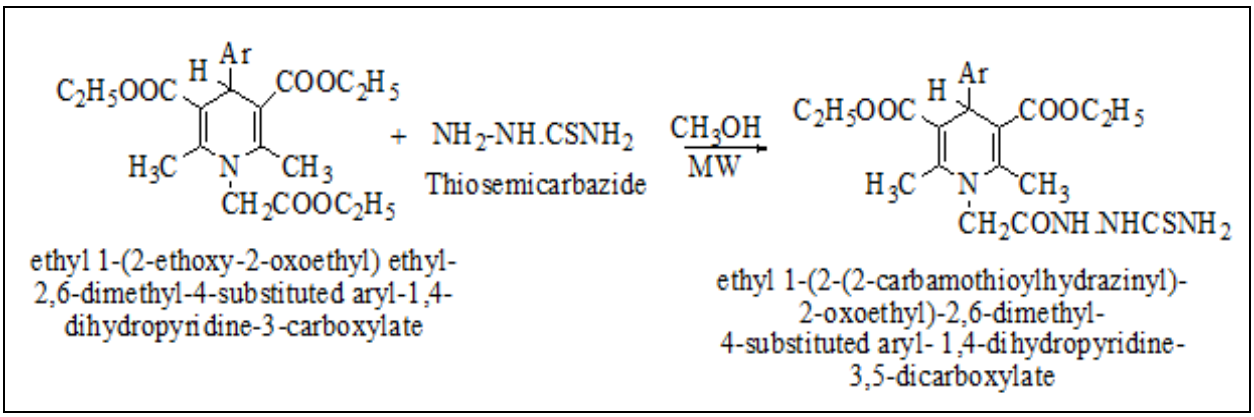
Step I: Synthesis of 3, 5-dicarboethoxy-1, 4-dihydro-2, 6-dimethyl-4-(substituted aryl)-pyridine.



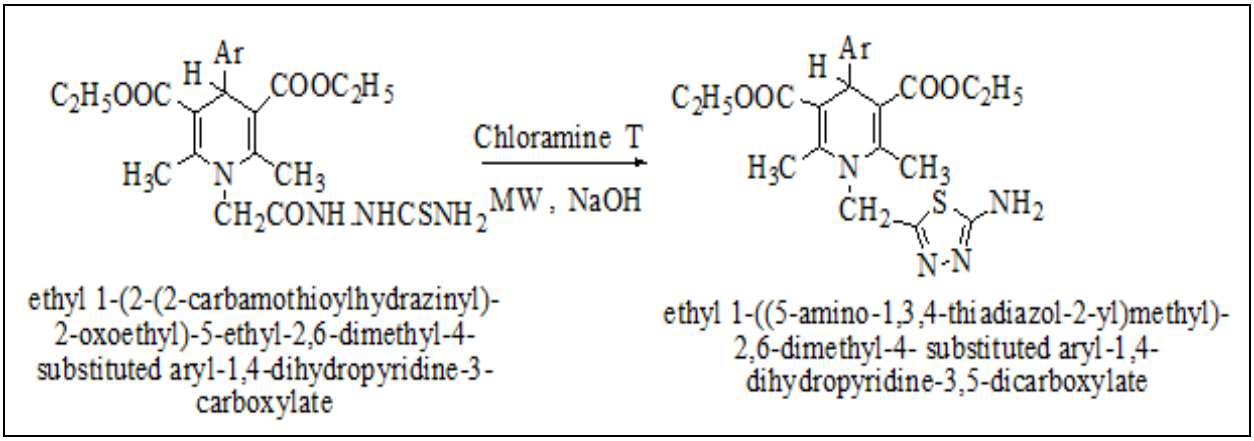
Step II: Synthesis of Ethyl-[3,5-dicarboethoxy-2,6-dimethyl-4- (substituted aryl) -1,4-dihydro -pyridin-1-yl] acetate



Step III: Synthesis of ethyl 1-(2-(2-carbamothioylhydrazinyl)-2-oxoethyl)-2, 6-dimethyl-4-substituted aryl-1, 4-dihydropyridine-3,5-dicarboxylate



Step IV: Synthesis of ethyl 1-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2,6-dimethyl-4-substituted aryl-1,4-dihydropyridine-3,5-dicarboxylate



Step I: Synthesis of 3, 5-dicarboethoxy-1, 4-dihydro-2, 6-dimethyl-4-(substituted aryl)-pyridine: [6, 7] A mixture of Ethylacetoacetate 5.2 g (5.02 mL, 0.04 mol), substituted aromatic aldehyde (0.02 mol) and conc. Ammonia (1.6 mL) in ethanol (12 mL) was irradiated under microwaves at 350 W for 10-20 min. To the resulting mixture, warm water (10 mL) was added and then allowed to cool in a refrigerator. It was extracted with two 10 mL portions of Chloroform, the combined Chloroform extract was dried with anhydrous Sodium sulphate. Dried Chloroform extract was allowed to evaporate and the solid product was collected, air-dried and recrystallized from ethanol. The purity of the product was checked by TLC.

Step II: Synthesis of Ethyl-[3,5-dicarboethoxy-2,6-dimethyl-4- (substituted aryl) -1,4-dihydro-pyridin-1-yl] acetate: A mixture of equimolar quantities (0.01 mol) of 3,5-dicarboethoxy-1,4-dihydro-2,6-dimethyl-4-(substituted aryl)-pyridine, Ethylchloroacetate, and anhydrous Potassium carbonate insufficient N,N-dimethylformamide was irradiated under microwaves for 15-20 min at 560 W. Reaction mixture was cooled to room temperature, poured into 50 g of crushed ice and stirred vigorously. Solid thus obtained was filtered, air-dried, and recrystallized from Ethanol. Purity of the product was checked by TLC.

Step III: Synthesis of ethyl 1-(2-(2-carbamothioylhydrazinyl)-2-oxoethyl)-2,6-dimethyl-4-substituted aryl-1, 4-dihydropyridine-3,5-dicarboxylate: A mixture of Ethyl-[3,5-dicarboethoxy-2,6-dimethyl-4- (substituted aryl) -1,4-dihydro-pyridin-1-yl] acetate (0.15 mol) and thiosemicarbazide (0.15 mol) was ground in a mortar for uniform mixing using sufficient methanol. The mixture was kept inside a microwave oven operating at 350W for 15-30 min. The completion of the reaction was checked by TLC. The product was recrystallized from ethanol.

Step IV: Synthesis of ethyl 1-((5-amino-1,3,4-thiadiazol-2-yl)methyl)-2,6-dimethyl-4-substituted aryl-1,4-dihydropyridine-3,5-dicarboxylate: The mixture of ethyl 1-(2-(2-carbamothioylhydrazinyl)-2-oxoethyl)-2, 6-dimethyl-4-substituted aryl-1, 4-dihydropyridine-3,5-dicarboxylate (0.010mol) and Chloramine-T (0.02mol) irradiated under micro-wave at 455W for 15-30 min., cooled to room temperature, then crushed ice was added and Treated with 10% NaOH to obtain the solid which was filtered and washed with water. The completion of the reaction was checked by TLC. The product was recrystallized from ethanol.

Pharmacological Evaluation:

Acute Toxicity Studies of Synthesized Compounds: OECD guidelines (no. 425) were followed foracute toxicity studies. Acute oral toxicity in mice was carried out for determining median Lethal Dose (LD_{50}).

Anticonvulsant Activity of Synthesized Compounds: [8, 9]

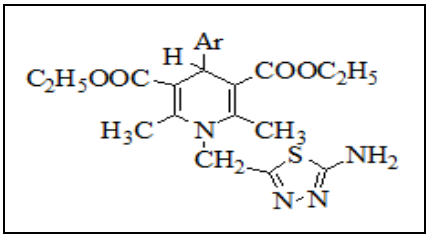
Animals: Swiss Albino mice of male/female sex, weighing 18-25gm were used for the study. The animals were purchased from National Institute of Biosciences, A/P: Dhangawadi, Bhor, Pune, India. Animals were housed in different groups consisting of Six animals in each group, in plastic cages under good hygienic conditions in registered animal house of MET's Institute of Pharmacy, Nashik (Registration no. 1344/ac/08/CPCSEA). Bedding of rice husk was replaced twice in a week so as to maintain good hygienic conditions. An ambient temperature of 25±1 ºC, the relative humidity of 45-55% and 12 h light: 12 h dark cycles were maintained in the animal house. The animals had free access to water and a standard pelleted diet except during experimentation, food and water was withheld. All the experiments were conducted according to the guidelines of the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environments and Forests, Government of India with their procedures and protocols reviewed and approved by the Institutional Animal Ethical Committee (IAEC), constituted under CPCSEA.

Preparation of Doses: Pentylenetetrazole in distilled water (Dose: 80 mg/kg, i.p.), Diazepam in distilled water (Dose: 2 mg/kg, i.p.), The test compounds at Dose I (90 mg/kg) and Dose II (135 mg/kg) in DMSO.

Procedure: The animals were divided into twelve groups of six animals each. One group is used for studying the effects of Pentylenetetrazole alone (Control), and the other for studying the protective effects of Diazepam (Standard). The remaining ten groups were used for studying the effects of synthesized compounds. Pentylenetetrazole (PTZ) (80 mg/kg, body weight) was administered intraperitoneally to induce convulsions in control, and the onset of convulsions and percentage protection was noted. PTZ (80 mg/kg, i.p.) was administered half an hour after the administration of Diazepam and the test compounds. In the case of Diazepam-treated animals, either delay or complete abolition of convulsions was noted. The test group animals were observed for the onset of convulsions and percentage of protection. The Diazepam treated and test animals were observed following PTZ injection up to half an hour for Increase in latency (onset time) to induce convulsions and percentage of protection. Readings of the test compounds are compared with control.

RESULTS AND DISCUSSION: The title compounds were synthesized by microwave method using Chloramine-T as an oxidizing agent. The completion of all the reactions was monitored by TLC. Physicochemical properties, microwave reaction conditions, and percentage yield of synthesized compounds are shown in **Table 1**.

TABLE 1: PHYSICOCHEMICAL PROPERTIES OFETHYL1-((5-AMINO-1, 3, 4-THIADIAZOL-2-YL) METHYL)-5-ETHYL-2, 6-DIMETHYL-4-(SUBSTITUTED ARYL)-1, 4-DIHYDROPYRIDINE-3-CARBOXYLATE



S. no.	Compound code	Ar	Microwave method				R_f value	Solvent system
			Melting point (°C)	power Watt	Time (min)	Yield (%)		
1	AN 123	*p*-OMe-C_6H_4-	308-310	455	15	82	0.53	A
2	BZ 01	C_6H_5-	250-252	455	20	78	0.65	B
3	Cl 01	*o*-Cl-C_6H_4-	180-182	455	25	62	0.46	A
4	PCl123	*p*-Cl-C_6H_4-	164-166	455	20	58	0.41	A
5	Fur 123	C_4H_3O-	170-172	455	30	64	0.81	B
6	N 01	*p*-NO_2-C_6H_4-	214-216	455	15	57	0.56	D
7	OH 01	*p*-OH-C_6H_4-	260-262	455	15	77	0.48	A
8	CH=CH01	-(CH=CH)-C_6H_4	190-192	455	30	87	0.52	D
9	Chr 01	*p*-(Chromon-2yl)	230-232	455	25	54	0.78	D
10	F 123	*p*-F-C_6H_4-	198-200	455	30	69	0.42	A

The structures of the compounds were confirmed on the basis of IR, ^{1}H NMR, and Mass analyses.

Ethyl-1-{(5-amino-1, 3, 4-thiadiazol-2yl) methyl} -4-(4-fluorophenyl)-2, 6-dimethyl-1, 4-dihydro-pyridine-3, 5-carboxylate(F123): IR(KBr) (cm^{-1}) 2964 (C─H), 1404 C─H def (─CH_3), 848 C─H def (OOP) (Disubstituted, *para),* 1247Asym 1035 Sym (C─O─C), 1737 (C═O) Ester, 3313 (N─H), 1651 (N─H def), 1348 (C─N), 754 (C-S), 1404 (C-F), 1H NMR (DMSO-d6, 400MHz, δ ppm)7.44 (d, 2H Aromatic ─CH), 7.36 (d, 2H, Aromatic ─CH), 4.53 (s, 1H, Methine─CH), 1.82 (s, 6H,─2CH_3), 3.38 (s, 2H, Methylene─CH_2), 4.20(t,4H, methylene), 1.30(t, 6H, methyl), 4.70(s, 2H, NH_2), MS, m/z (%) 460 (M+).

Ethyl-1-{(5-amino-1, 3, 4-thiadiazol-2yl) methyl} -4-(4-chlorophenyl)-2, 6-dimethyl-1, 4-dihydro-pyridine-3, 5-carboxylate (PCl123): IR(KBr) (cm^{-1}) 2870 (C─H), 1382 (C─H def), 829 (C─H def (OOP)), 1253 Asym (C─O─C), 1737 (C═O), 1276 (C─O), 1031 (N-N), 734 (C-S), 2696 (N-H), 1097 (C─Cl), 1H NMR (DMSO-d6, 400MHz, δ ppm) 7.11-8.25 (d, 4H Aromatic ─CH), 7.36 (d, 2H, Aromatic ─CH), 3.53 (s, 1H, Methine─CH), 1.72 (s, 6H,─2CH_3), 3.48 (s, 2H, Methylene ─CH_2), 4.19 (t,4H, methylene), 1.29 (t, 6H, methyl), 4.00(s, 2H, NH_2), MS, m/z (%) 477 (M+).

Ethyl-1-{(5-amino-1, 3, 4-thiadiazol-2yl) methyl} 2, 6-dimethyl-4-styrl-1, 4-dihydro -pyridine-3, 5-carboxylate ((CH=CH)01): IR(KBr) (cm^{-1}) 2848 (C─H),1448 (C─H def) (─CH_3), 3024 (C-H) styryl, 1597,1473 (C═C)styryl, 798 (C─H def) (OOP), 1246 Asym (C─O─C), 1035 Sym (C─O─C), 1651 (N─H def), 1278 (C─N), 1035 (N-N), 750 (C-S), 2249 (N-H), 1H NMR (DMSO-d6, 400MHz, δ ppm) 7.30-8.1 (d, 6H, aromatic), 6.25 (d, 1H, styryl), 6.10 (d, 1H, styryl), 3.80 (s, 1H, methane ─CH), 1.75(s, 6H, ─2CH_3), 3.41(s, 2H, Methylene ─CH_2), 4.25 (t, 4H, methylene), 1.19 (t, 6H, methyl), 4.93(s, 2H, NH_2), MS, m/z (%) 468 (M^+).

Ethyl-1-{(5-amino-1, 3, 4-thiadiazol-2yl) methyl} -4-(furan-2-yl)-2, 6-dimethyl-1, 4-dihydropyri-dine-3, 5-carboxylate (fur123): IR(KBr) (cm^{-1}) 2850 (C─H), 1446(C─H def), 754 (monosubsti-tution, aromatic), 1066 (C─O─C ether), 1762 (C═O), 1298(C─O), 1035(N-N), 754 (C-S), 3302 (N-H), 1645 (N-H def),1H NMR (DMSO-d6, 400MHz, δ ppm) 6-7.2 (d, 3H, furan), 4.70 (s, 1H, methane ─CH), 1.85 (s, 6H, ─2CH_3), 3.75 (s, 2H, Methylene ─CH_2), 4.22 (t, 4H, methylene), 1.31 (t, 6H, methyl), 4.3(s, 2H, NH_2), MS, m/z (%) 432 (M^+).

Ethyl-1-{(5-amino-1, 3, 4-thiadiazol-2yl) methyl} -4-(4-methoxyphenyl)-2, 6-dimethyl-1, 4-dihydro-pyridine-3, 5-carboxylate (AN123): IR (KBr) (cm^{-1}) 2845 (C─H), 1448 (C─H def), 798 (Disubstitution, para), 1246 (Asym C─O─C ether), 1037 (SymC─O─C ether) 1761 (C═O), 1300 (C─O), 1037 (N-N), 748 (C-S), 3334 (N-H), 1541 (N-H def). 1H NMR (DMSO-d6, 400MHz, δ ppm) 6.60-7 (d, 4H, aromatic), 3.65 (s, 3H, OCH_3), 4.40 (s, 1H, methine ─CH), 1.79 (s, 6H,─2CH_3), 3.50 (s, 2H, Methylene ─CH_2), 4.15 (t, 4H, methylene), 1.38 (t, 6H, methyl), 4.1(s, 2H, NH_2), MS, m/z (%) 472 (M+).

Pharmacological Evaluation of the Synthesized Compounds: Acute toxicity study was done for determining LD_{50}. The LD_{50} was found to be 845.6 mg/Kg; therefore the two doses were selected for the anticonvulsant evaluation of the compounds, *i.e.,* Dose I: 90 (~1/10 of LD_{50}) and Dose II: 135 mg/kg (~1.5 times of the dose I).

The Anticonvulsant activity of some synthesized compounds was evaluated in mice using PTZ induced convulsions method. The results are shown in **Table 2.**

The graphical comparison of the latency to induce convulsion in minutes at both the doses selected for the test compounds along with the control (PTZ, 80 mg/kg) is shown in **Fig. 2.**

TABLE 2: ANTICONVULSANT EFFECT OF SOMEETHYL-1-((5-AMINO-1, 3, 4-THIADIAZOL-2-YL) METHYL)-5-ETHYL-2, 6-DIMETHYL-4-(SUBSTITUTED ARYL)-1, 4-DIHYDROPYRIDINE-3-CARBOXYLATE DERIVATIVES IN MICE USING PTZ INDUCED CONVULSIONS METHOD

S. no.	Code	Ar	Dose (mg/Kg, i.p.)	Latency to induce convulsions (min)	% Protection
1	PTZ (Control)	Pentylenetetrazole	80	2.02±0.05	0
2	Diazepam	7-chloro-5-phenyl-2,3-dihydrobenzodiazepine-2-one	2	-	100
3	F123	p-FC_6H_4-	90	2.23±0.49^{NS}	20
			135	3.64±0.11**	80
4	PCl 123	p-ClC_6H_4-	90	2.63±0.33 ^{NS}	20
			135	3.63±0.14**	40
5	AN 123	p-$OCH_3C_6H_4$-	90	3.98±0.21**	60
			135	4.04±0.17**	60
6	Fur 123	C_4H_3O-	90	3.08±0.07*	40
			135	3.66±0.14**	80

N=6, in each group; *: P < 0.05; **: P <0.01; NS: Non- significant; One Way ANOVA followed by Dunnett's test. Values expressed as Mean ± SEM

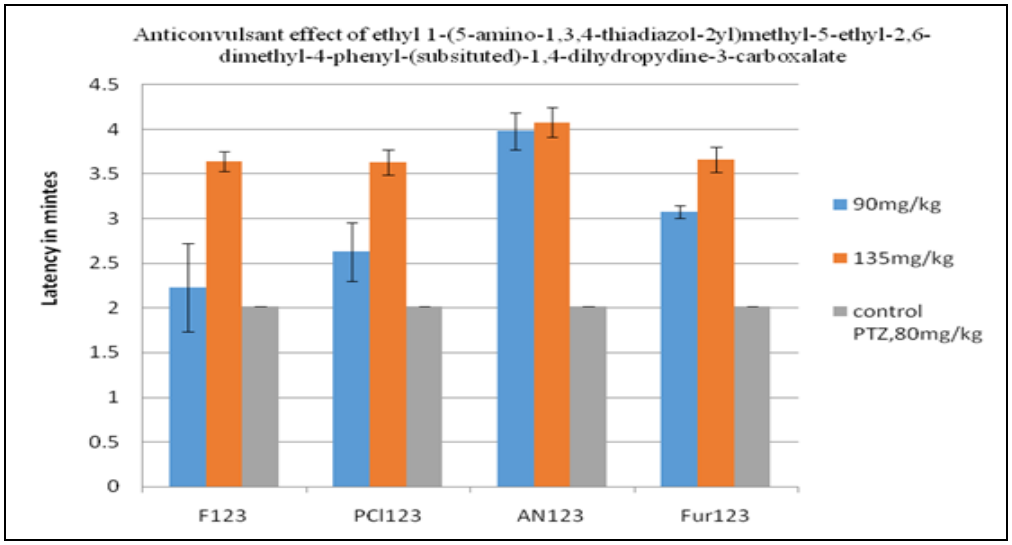


FIG. 2: COMPARISON OF LATENCY TO INDUCE CONVULSIONS OF SOME ETHYL-1-((5-AMINO-1, 3, 4-THIADIAZOL-2-YL) METHYL)-5-ETHYL-2, 6-DIMETHYL-4-(SUBSTITUTED ARYL)-1, 4-DIHYDROPYRIDINE--3-CARBOXYLATES IN MICE USING PTZ INDUCED CONVULSIONS

CONCLUSION: In the present investigation, the 1, 4-dihydropyridines were coupled to 1, 3, 4-Thiadiazoles with the aim of achieving the enhanced anticonvulsant effect. The synthesis of novel compounds comprised of four steps; firstly the Hantzsch dihydropyridines were prepared, then their esters were prepared and then their corresponding hydrazides were prepared from which the final compoundsethyl1-((5-amino-1, 3, 4-thiadiazol-2-yl) methyl)-5-ethyl-2, 6-dimethyl-4-phenyl- 1, 4- dihydropyridine- 3- carboxylate were synthesized. The microwave technique is rapid and efficient, resulting in reduced reaction times and increased yields compared to the conventional technique. The synthesized compounds were confirmed on the basis of IR, ^{1}H-NMR, and Mass analyses. An acute toxicity study was done to determine the LD_{50} of the newly synthesized compounds. Some of the synthesized compounds were evaluated for their anticonvulsant effect by PTZ induced convulsions method. Statistical testing was done by one-way ANOVA followed by Dunnett's test. Based on the present investigation following conclusions are outlined:

- The use of Microwave technology in synthesis resulted in drastically reduced reaction times and increased yields.
- The pharmacological evaluation of the compounds showed increase in latency (onset time) to induce convulsions, a decrease in the number of convulsions, and an increase in latency of death compared to control.
- The compounds F123 and AN123 showed the highest percentage of protection (80%) at the dose of 135 mg/kg among the evaluated compounds compared to control.
- The analysis of structural features revealed that the substitution of methoxy group, fluoro group enhanced the anticonvulsant potential of the synthesized compounds.

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CONFLICTS OF INTEREST: The authors have no conflict to declare.

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