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Research Article

Synthesis and evaluation of dialkyl-4-substituted-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives as anticonvulsive agents

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ABSTRACT

A series of symmetrical dialkyl-4-substituted-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives were prepared by the classical Hantzsch method. This method involved in the condensation of aromatic aldehyde, alkylacetoacetate and ammonia in methanol. The structure of all the twelve synthesized 1,4-dihydropyridne derivatives was confirmed by the IR, H^1NMR, and MASS spectra. All the synthesized compounds were screened for the anticonvulsant activity by using Maximal electroshock (MES) and Pentylenetetrazole (PTZ) induced models. Compounds 3F and 3L exhibited significant anticonvulsant activity in MES and PTZ induced seizure in rats.

Keywords: 1, 4-dihydropyridine; Hantzsch method; Maximal electroshock method; Pentylenetetrazole induced Method

INTRODUCTION

Epilepsy is common chronic neurological disorder characterized by seizures and approximately 1% of the world wide population was affected, the incidence of seizures were highest in the children's at the age of below 10 years and becomes decline, but it appears again at the age of 50 years with development of strokes, brain tumors or Alzheimer's disease (Herfindal et al., 2001). The recent analytical studies reported that the rate of epilepsy in India was at 5.59 per 1000 populations, and there were no statistically different rates between men and women or urban or rural residence (Shashikant et al., 2010). There are considerable evidences that calcium is an important factor for the induction of epilepsy. Specifically, different seizure-inducing agents or procedures cause a rapid intraneuronal influx of calcium ions, which is causally related to the subsequent epileptic activity (Subudhi et al., 2009). Calcium channel blockers (1, 4-dihydropyridines) are reported to be effective against the whole range of convulsive procedures including electroshock and pentylenetetrazole induced seizures (Shafiee et al., 2004). Previously, it was demonstrated that the dihydropyridine calcium channel blockers are effective anticonvulsant candidates in experimental seizures (Meyer et al., 1987; Palmer et al., 1993).

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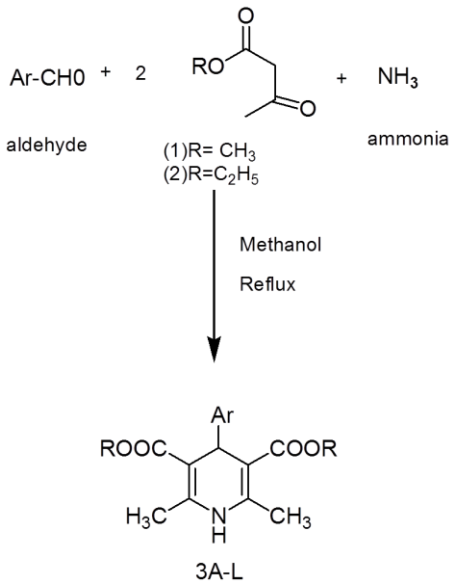
Some of the derivatives i.e. A, B, G, J and K were reported previously as L-type Ca^{2+} channel antagonists (Chang et al., 2010). In view of these facts, we made an attempt to find the influence of spacer groups between 4-aryl and 1, 4-dihydropyridine ring system and the effect on anticonvulsant activity. We have synthesized dialkyl-4-substituted-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives and their evaluation for anticonvulsant activity by pentylenetetrazole induced and maximal electroshock method.

MATERIALS & METHODS

Chemistry

Aldehydes and esters were procured from Sigma-Aldrich and Merck chemicals. All other chemicals are of AR grade. Purity of the samples was monitored by TLC analysis using Precoated aluminium plates (Merck), coated with Silica Gel (Kieselgel 60) with F_{254} indicator. Melting points were determined in open capillaries using Analab melting point apparatus and were uncorrected. IR spectra were recorded as KBr diluted pellets on a Jasco FTIR (FTIR-4100) Spectrophotometer. ^{1}H NMR spectra were carried out on Jeol-400 MHz NMR Spectrophotometer (JNM-400) using TMS as internal reference. Chemical shifts (δ values are given in parts per million (ppm) using $CDCl_3$ as solvent coupling constants (J) in Hz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet.

Accurate masses were obtained on LCMS (schimadzu) APCI modelLC-2010 EV. Elemental analyses were performed on Perkin Elmer 2400 C, H, N elemental analyser.



Scheme: 1 Synthesis of dialkyl-4-substituted-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives (3A-3L)

General method for preparation of dialkyl-4-substituted-2,6-dimethyl-1,4-dihydropyridne-3,5-dicarboxylate (A-L)

A mixture of aldehyde (0.01mole) and alkylacetoacetate (0.03mole) was dissolved in methanol (20ml), treated with ammonia (25%, 0.02 mole), and it was refluxed for 8-24 hrs, the completion of the reaction can be monitored by using the TLC plates coated with silica gel (MP-chloroform: ethanol-9.5:0.5) and evaporated the reaction mixture to separate solid (Francesca et al., 2009). The obtained solid was dried and recrystallised with methanol to obtain the purified compounds. The physical data was included in table 1 and the anaalytical data was discussed in experimental part.

EXPERIMENTAL

***Preparation of dimethyl-4-phenyl-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3A)**

0.01mole of benzaldehyde and 0.03mol of methylacetoacetate (3) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 8 hrs. Mp 157^{o}C; yield: 75 %; IR (KBr, ν_{max},cm^{-1}): 3342 (NH str), 3016 (Ar C-H str), 1648 (C=C str), 1700 (C=Ostr). H^{1}NMR (MeOD,400MHz) δ ppm: 2.315 (s,CH_3 at C-2&C-6, 6H), 3.626 (s,OCH_3 at C-3&5, 6H), 4.842 (s, CH at C-4, 1H), 4.963 (s, NH, 1H), 7.22-7.184 (m,C_6H_5, 5H). MASS: m/e: 301(M^+). Anal. Calcd (%) for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65; O, 21.24. Found: C, 67.62; H, 6.2; N, 4.39; O, 20.98.

***Preparation of dimethyl-4-(2-nitropheny)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3B)**

0.01mole of 2-nitrobenzaldehyde and 0.03mol of methylacetoacetate (3) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 12 hrs. Mp 170^{o}C; yield: 78 %; IR (KBr, ν_{max}, cm^{-1}): 3339 (NH str), 2930 (Ar C-H str), 1698 (C=O str). H^{1}NMR (MeoD,400MHz) δ ppm: 2.65 (s,CH_3 at C-2&6, 6H), 3.726 (s,OCH_3 at C-3&5,6H),4.942 (s, CH at C-4,1H), 5.163 (s, NH, 1H), 7.194-7.25 (m,C_6H_4,4H). MASS: m/e: 346(M^+). Anal. Calcd (%) for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09; O, 27.72. Found: C, 58.92; H, 5.19; N, 8.01; O, 27.69.

***Preparation of dimethyl-4(benzyl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3C)**

0.01mole of phenylacetaldehyde and 0.03mol of methylacetoacetate (3) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 24 hrs. Mp 180^{o}C; yield: 74 %; IR (KBr, ν_{max},cm^{-1}): 3328 (NHstr), 2783.43 (Ar C-Hstr), 1673 (C=Ostr).H^{1}NMR (MeOD,400MHz) δ ppm: 1.32 (s, CH_3 at C-3&5, 6H), 1.7 (s, CH_3 at C-2&6), 2.59 (d, CH_2 of $CH_2C_6H_5$,2H), 3.52 (t, CH at C-4, 1H), 7.21-7.0 (m, C_6H_5, 5H). MASS Spectra: m/e: 315 (M^+). Anal. Calcd (%) for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44; O, 20.29. Found: C, 68.43; H, 6.68; N, 4.32; O, 20.18.

***Preparation of dimethyl-4(phenethyl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3D)**

0.01mole of 3-phenylpropionaldehyde and 0.03mol of methylacetoacetate (3) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 12 hrs. Mp 120^{o}C; yield: 77 %; IR (KBr, ν_{max},cm^{-1}): 3404 (NHstr), 2893.53 (Ar C-Hstr), 1643 (C=Ostr). H^{1}NMR (MeOD, 400MHz) δ ppm: 1.15 (s, CH_3 at C-3&5, 6H), 1.46 (s,CH_3,C-2&6, 6H), 1.518 (t,CH_2 of $CH_2CH_2C_6H_5$, 2H), 2.161 (s,CH_2 of $CH_2CH_2C_6H_5$, 2H), 3.209 (t, CH at C-4, 1H), 4.747 (s, NH, 1H), 7.2 -6.96 (m, C6H5, 5H). MASS Spectra: m/e: 329 (M^+). Anal. Calcd (%) for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; O, 19.43. Found: C, 69.12; H, 6.98; N, 4.20; O, 19.38.

***Praparation of dimethyl-4-(styryl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3E)**

0.01mole of cinnamaldehyde and 0.03mol of methylacetoacetate (3) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 12 hrs. Mp 140^{0}c; yield: 75%; IR (KBr, ν_{max},cm^{-1}): 3242 (NH str), 3026 (ArC-H str), 1668 (C=C str), 1670 (C=O str). H^{1}NMR (MeOD,400MHz) δppm: 2.51 (s, CH_3 at C-2&6, 6H), 3.52 (s, OCH_3 at C-3&5, 6H), 4.742 (s, CH at C_4,1H), 5.873 (s,NH,1H), 6.07-6.2 (dd, CH=CH,1H), 6.5-6.6 (d, CH=CH,1H), 7.32-7.24 (m,5H,C_6H_5). MASS: m/e: 327 (M^+), 326(M-H)$^+$.Anal. Calcd (%) for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; O, 19.55. Found: C, 69.69; H, 6.42; N, 4.19; O, 19.49.

***Preparation of dimethyl-4(2-nitrostyryl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3F)**

0.01mole of 4-nitrocinnamaldehyde and 0.03mol of methylacetoacetate (3) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 24 hrs. Mp 179^{O}c; yield: 76%; IR (KBr,

Table 1: Physical data of the synthesized compounds 3A-3L

S. No.	Compound	R	Ar	M.F
1	3A	CH_3	C_6H_5-	$C_{17}H_{18}NO_4$
2	3B	CH_3	2-$NO_2C_6H_4$-	$C_{17}H_{17}N_2O_6$
3	3C	CH_3	$CH_2C_6H_5$-	$C_{18}H_{20}NO_4$
4	3D	CH_3	$C_6H_5CH_2CH_2$-	$C_{19}H_{22}NO_4$
5	3E	CH_3	C_6H_5CH=CH-	$C_{19}H_{22}NO_4$
6	3F	CH_3	4-NO_2C6H5CH=CH-	$C_{19}H_{19}N_2O_6$
7	3G	C_2H_5	C_6H_5-	$C_{21}H_{26}NO_4$
8	3H	C_2H_5	2$NO_2C_6H_5$	$C_{19}H_{22}NO_4$
9	3I	C_2H_5	$C_6H_5CH_2$-	$C_{20}H_{24}NO_4$
10	3J	C_2H_5	$C_6H_5CH_2CH_2$-	$C_{18}H_{20}NO_4$
11	3K	C_2H_5	C_6H_5CH=CH-	$C_{21}H_{23}N_2O_6$
12	3L	C_2H_5	4-NO_2C6H5CH=CH-	$C_{21}H_{23}N_2O_6$

Table 2: The anticonvulsant activity of synthesized compounds by MES method

Treatment groups	Time of decrease in hind limb extension in sec	Seizure inhibition (%)
Control	17±0.38	--
Phenytoin	5.1±1.06*	70
Compound 3A	6±0.26*	65
Compound 3B	5±0.92*	70
Compound 3C	12.3±0.02 ^{ns}	28
Compound 3D	10.3±1.02^{ns}	39
Compound 3E	4.9 ±0.78*	70
Compound 3F	4.1 ±0.29*	76
Compound 3G	6±0.1*	65
Compound 3H	4.3±3.53*	75
Compound 3I	10.3±0.98 ^{ns}	39
Compound 3J	8.2±1.09*	52
Compound 3K	4.2±0.19*	75
Compound 3L	4.0±0.12*	76

All value expressed as mean ±SD; One way Anova followed by dunnet's post test. *p<0.001 vs Control group, ns – Non Significant

ν_{max},cm^{-1}): 3392(NHstr), 2986 (Ar C-Hstr), 1688 (C=Cstr), 1679 (C=Ostr). H^1NMR(MeOD, 400MHz) δppm: 2.115 (s,CH_3,6H), 3.426 (s,OCH_3;6H), 4.542 (s, H-C_4,1H), 5.687 (s,NH,1H), 7.72-7.54 (m,4H,C_6H4), 6.27 &6.59 (s, CH=CH,2H). MASS: m/e: 372 (M^+). Anal. Calcd (%) for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52; O, 25.78. Found: C, 61.98; H, 5.35; N, 7.48; O, 25.65.

***Preparation of diethyl -4-phenyl-2, 6-dimethyl-1, 4-dihydropyrinde-3, 5-dicarboxylate* (3G)**

0.01mole of benzaldehyde and 0.03mol of ethylacetoacetate (4) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 8 hrs. Mp 150^{0}C; yield: 76; IR (KBr, ν_{max},cm^{-1}): 3264 (NHstr), 3091 (ArC-Hstr), 1690 (C=Ostr). H^1NMR (MeOD,400MHz) δppm: 1.5 (t, CH_3 at C-3&5, 6H),1.98 (s,CH_3 at C-2 & C-6, 6H), 4.02-4.12 (q,OCH2 at C-3&5, 4H), 4.34 (s, CH at C_4,1H), 5.7 (s, NH, 1H), 7.36-7.21 (m, C_6H_5, 5H). MASS Spectra: m/e: 329(M^+). Anal. Calcd (%) for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; O, 19.43. Found: C, 69.21; H, 6.90; N, 4.16; O, 19.12.

***Preparation of diethyl-4-(2-nitropheny)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3H)**

0.01mole of 2-nitrobenzaldehyde and 0.03mol of ethylacetoacetate (4) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 12 hrs. Mp 165^{o}C; yield: 70; IR (KBr, ν_{max},cm^{-1}): 3296 (NH str), 3012 (Ar C-H str), 1654 (C=Ostr), 1400 (N-O asym str). H^1NMR (MeOD, 400MHz) δppm: 1.98-2.21(t,CH_3 at C-3&5, 6H), 2.31 (s,CH_3 at C-2&C-6, 6H), 3.6 (s, CH at C-4,1H), 4.12-4.09 (q,OCH_2 at C-3&5, 4H), 5.86 (s, NH,1H), 7.38-7.25 (m,4H,C_6H_4). MASS Spectra: m/e: 374(M^+). Anal. Calcd (%) for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48; O, 25.64. Found: C, 60.91; H, 5.23; N, 7.41; O, 25.23.

***Preparation of diethyl-4(benzyl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3I)**

0.01mole of phenylacetaldehyde and 0.03mol of ethylacetoacetate (4) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 24 hrs.Mp 150^{o}C; yield: 76 %; IR (KBr, ν_{max},cm^{-1}): 3339 (NHstr), 2893.53 (Ar C-Hstr), 1683 (C=O

str). H^1NMR (MeOD,400MHz) δ ppm: 1.362 (t,CH_3 at C-3&5,6H), 1.754 (s, CH_3 at C-2&6, 6H), 2.518(s, CH_2 of $CH_2C_6H_5$ 2H), 3.429 (t, CH at C_4, 1H), 5.747 (s, NH, 1H), 4.233 (q,OCH_2 at C-3&5, 4H), 7.32 -7.15 (m, C_6H_5, 5H). MASS Spectra: m/e: 343 (M^+). Anal. Calcd (%) for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08; O, 18.64. Found: C, 69.89; H, 7.31; N, 4.05; O, 18.58.

***Preparation of diethyl-4(phenethyl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3J)**

0.01mole of 3-phenylpropionaldehyde and 0.03mol of ethylacetoacetate (4) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 12 hrs. Mp 110°C; yield: 77 %; IR (KBr, v_{max},cm^{-1}): 3344 (NH str), 3093.53 (Ar C-H str), 1693 (C=O str). H^1NMR (MeOD,400MHz) δ ppm: 1.15 (t, CH_3 at C-3&5, 6H), 1.46 (s,CH_3,C-2&6, 6H), 1.518 (t,CH_2 of $CH_2CH_2C_6H_5$, 2H), 2.161 (s,CH_2 of $CH_2CH_2C_6H_5$, 2H), 3.209 (t, CH at C-4, 1H), 4.03(q,OCH_2 at C-3&5, 4H), 4.747 (s, NH, 1H), 7.2 -6.96 (m, C6H5, 5H). MASS Spectra: m/e: 357 (M^+), 356(M-H)$^{+\cdot}$ Anal. Calcd (%) for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92; O, 17.90. Found: C, 70.53; H, 7.58; N, 3.89; O, 17.83.

***Prepration of diethyl-4-(styryl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3K)**

0.01mole of cinnamaldehyde and 0.03mol of ethylacetoacetate (4) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 12 hrs. Mp 180°C; yield: 78 %; IR (KBr, v_{max},cm^{-1}): 3335.29(NHstr), 2983.11(Ar C-H str), 1691 (C=O str), 1691(C=C str). H^1NMR (MeOD,400MHz) δ ppm: 1.18-1.65 (t,CH_3 at C-3&5, 6H), 1.2(s,CH_3 at C-2&6, 6H), 3.201(s, CH at C_4,1H), 4.2-4.5 (q, OCH_2 at C-3&5, 4H), 4.735 (s,NH,1H), 6.052 &6.092(brd,CH=CH, 2H), 7.134-7.093 (m, C_6H_5,5H). MASS Spectra: m/e: 355.3(M^+). Anal. Calcd (%) for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94; O, 18.01. Found: C, 70.92; H, 7.02; N, 3.73; O, 17.90.

***Preparation of diethyl-4(2-nitrostyryl)-2, 6-dimethyl-1, 4-dihydropyridne-3, 5-dicarboxylate* (3L)**

0.01mole of 4-nitrocinnamaldehyde and 0.03mol of ethylacetoacetate (4) was dissolved in 20ml of methanol, treated with 25%, 0.02 mole of ammonia and it was refluxed for 24 hrs. Mp 170°C; yield: 78 %; IR (KBr, v_{max},cm^{-1}): 3329.89 (NH str), 2973.91 (ArC-Hstr), 1681 (C=Ostr), 1684 (C=C str). H^1NMR (MeOD,400MHz) δ ppm: 1.85 (t,CH_3 at C-3&5, 6H), 1.59 (s,CH_3 at C-2&6,6H), 4.201 (s, CH at C_4, 1H), 5.25 (s, NH, 1H), 4.84 (q,OCH_2 atC-3&5, 4H), 6.15(dd, CH=CH of styryl, 1H) &6.88 (d, CH=CH of styryl, 1H), 7.93-7.782 (m,C_6H_4,4H). MASS Spectra: m/e: 400(M^+). Anal. Calcd (%) for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00; O, 23.97. Found: C, 62.92; H, 6.01; N, 6.89; O, 23.23.

Table 3: Anti convulsant activity of synthetic compounds against PTZ induced seizure

Treatment groups	Latency period for seizure in sec	Number of animals died / used	Mortality rate in percentage
Control	76 ± 0.02	6/6	100%
Diazepam	160 ± 1.06**	1/6	86
Compound 3A	159 ± 0.24**	3/6	50
Compound 3B	110 ± 3.01^{ns}	2/6	33.3
Compound 3C	221 ± 2.09***	2/6	33.3
Compound 3D	300 ± 0.0***	0/6	100
Compound 3E	300 ± 0.0***	0/6	100
Compound 3F	0 ± 0.0***	0/6	100
Compound 3G	143 ± 2.324**	3/6	50
Compound 3H	0 ± 0.0***	0/6	100
Compound 3I	239 ± 0.78***	2/6	33.3
Compound 3J	300 ± 0.0***	1/6	16.6
Compound 3K	300 ± 0.0***	0/6	100
Compound 3L	300 ± 0.0***	0/6	100

All value expressed as mean ±SD; Oneway Anova followed by dunnet's post test. ***p<0.001 vs Control group, **p<0.01 vs control group, ns – Non Significant

Pharmacology

Maximal electric shock method (MES mothod)

Male wistar rats of weight 150-200gms were selected and constant room temperature was maintained 22±05°C, with proper food and water for 1 week and 6 rats were used for each dose of each compound, saline was used as a control, phenytoin 30mg/kg body weight was used and the test compounds of dose 30mg/kg body weight were used by dissolving in absolute ethanol. The test solutions were injected through intraperitonial route, after an hour of injection maximal electroshock (Inco Electroconvulsiometer model# 100-3) of 150 mA current for 0.2 seconds administered through ear electrodes to induce convulsions in the control and drug treated animals and the severity of convulsion was assessed by measuring the duration of hind limb extension. (Table-2) (B. B. Subudhi et al., 2009)

Pentylenetetrazole (PTZ) induced seizures in rat:

The Wistar albino rats were selected two weeks prior to conducting the experiment by injecting the pentylenetetrazole in a dose of 80 mg/kg subcutaneously in the scruff of neck. Only those rat which showed clonic convulsions within 5 minutes during preliminary examination were chosen for the present study. After 45 minutes of the drug treatment, PTZ (80 mg/kg subcutaneously) was given in the scruff of neck. Animals were observed for latency for clonic convulsions, and 24 hour mortality. Absence of clonic convulsions in drug treated groups was taken as criteria for anticonvulsant activity. (Table-3) (Jolanta Obniska et al., 2010)

Statistical analysis

Results were analyzed by one way analysis of variance (ANOVA) and all values of the synthesized compounds are expressed as mean ± SD. P value of less than 0.05 was considered to be significant.

RESULTS AND DISCUSSION

All the derivatives 3A-3L were synthesized in a step by classical Hantzsch method, involved in the reaction of aldehyde, alkylacetoacetate and amine condensation followed by the elimination of 3 moles of water molecules (Francesca et al., 2009). Some of the derivatives i.e. A, B, G, J and K were reported previously as L-type Ca^{2+} channel antagonists (Chang et al., 2010). The spectroscopic data of the derivatives were analysed and compared with the previously reported. All the compounds 3A-3L were evaluated for anticonvulsant activity by pentylenetetrazole (PTZ) induced and maximal electroshock (MES) induced models. All the compounds showed the significant activity ($p<0.001$ vs control) against PTZ induced seizures except 3B. Compound 3D, 3F and 3L showed the increased latency periods with maximum protection against mortality. Other compounds were exhibited medium latency periods and all the compounds were more significant than diazepam except 3A, 3B and 3G.

In the MES method, all the compounds showed the significant activity except 3C, 3D and 3I. Compounds 3F,3H,3K and 3L showed significant inhibition against electro shock induced convulsion. Of all the compounds, 3B, 3E, 3F, 3H, 3K and 3L exhibited lower limb extension periods and increased protection against electroshock induced seizures which was comparable to standard phenytoin.

The above results gave the information that, phenyl substitution at 4^{th} position and 3^{rd} and 5^{th} dialkyl substitutions of the 1,4-dihydropyridine ring system may help to exhibit the anticonvulsant activity and 2-nitro substitution on the phenyl ring present in the derivatives 3B and 3H increased the inhibitory activity (Fisher et al., **1993;** Ramesh et al., **1987**). Replacement of phenyl group with other aryl substitutions like benzyl, phenethyl, styryl and 4-nitrostyryl groups dramatically increased the seizure inhibitory activity. Ethyl substitution at 3^{rd} and 5^{th} positions present in the compounds 3G-3L showed the significant protection than the methyl group present in the compounds 3A-3F. Introduction of the spacer group like methyl and ethyl groups between 4-phenyl and 1,4-dihydropyridine ring system was decreased the anticonvulsant activity. The vinyl molecule was exhibited the better anticonvulsant activity than the 3A and 3G.

CONCLUSION

The present study revealed that, the compounds 3F and 3L as most significant derivatives and further the spacer groups may not influenced the anticonvulsant activity. The results of this present research may be helpful for the researchers to develop potent anticonvulsant drugs in further study.

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