Synthesis and Anticonvulsant Activity of a New Series of 1,4-Dihydropyridine Derivatives

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A series of 1,4-dihydropyridine derivatives (1a–g) were prepared from three compounds condensation of Hantzsch synthesis. A new series of 2,2'-{[4-(aryl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide (2a-g) were prepared from compounds diethyl 4-(aryl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-g) reacted with thiosemicarbazide to give the corresponding compounds (2a-g) by hydrazinolysis method. The synthesized compounds were confirmed by IR, ¹HNMR, ¹³CNMR, mass spectral and elemental analyses. The newly synthesized compounds (2a-g) were screened for anticonvulsant activity against in swiss albino rat. The test was evaluated by maximal electrode induced convulsion method. Synthesized compounds were used two (50 and 100 mg/kg) concentrations. Compounds (1a-g) were inactive while compounds (2a-g) have moderate anti-convulsant activity compared with standard phenytoin drug. The compound 2,2'-{[4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide (2a) has highly active compared with other compound (2b-2g).

Key words: 1,4-dihydropyridine, anticonvulsant activity, condensation, thiosemicarbazide

1,4-dihydropyridine derivatives are of interest because of their potential biological activity such as antihypertensive[1-4], antiinflammatory[5] and antiischemic activities[6] and also as calcium channel modulators of the nifedipine type[7]. Several methods have been described for the synthesis of 1,4-dihydropyridine[8-12]. Recently, some new 3,5-substituted 1,4-dihydropyridine derivatives were synthesized which exhibit pharmacological activities[13-16]. Thosemicarbazone also has significant biological activities such as antitumour, fungicide, bactereocide, antiinflammatory, and antiviral activities[17-20]. Keeping these observations in mind, the present study worked on the synthesis of a new series of 1,4-dihydropyridine derivatives and screened their level of anticonvulsant activity.

MATERIALS AND METHODS

Melting points were recorded in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on a FT - IR Shimadzu 8201pc (4000-400 cm^{-1}) and ^{1}H NMR and ^{13}CNMR were recorded on a Broker DRX-300 MHz. Mass spectra (EI) were obtained on a Joel JMS D-300 spectrometer operating at 70eV. Elemental analyses (C, H, N, and S) were undertaken using an Elementer analyser model vario EL III. The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

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Synthesis of diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxy late (1a):
A reaction mixture was made up of ethyl acetoacetate (2 mol), furualdehyde (1 mol) and ammonium hydroxide (1 mol) in methanol (20 ml). It was then heated and refluxed for 4 h. The obtained solid was filtered off, the solid was washed with water and recrystallized using absolute ethanol. The above procedure was followed for the synthesis of compounds (1b–g). Yield 75%, mp: 158**,** IR (KBr, cm^{-1}) ν: 3349 (N-H str), 3030 (Ar-H), 2940 (C-H str of CH_3), 1745 (C=O, ester), 812 (Ar-H). ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H, NH of pyridine ring), 6.27-6.10 (d, 3H, furylring), 4.72 (s, 2H, C_4-H), 4.20 (q, 4H, C_3-OC$\underline{H}_2$CH$_3$ and C_5-OC$\underline{H}_2$CH$_3$), 2.31 (s, 6H, C_2-C$\underline{H}_3$ and C_6-C$\underline{H}_3$), 1.34 (t, 6H, C_2-OCH$_2$C$\underline{H}_3$ and C_6-OCH2C$\underline{H}_3$). Elemental analysis calculated for $C_{17}H_{12}NO_5$: C 63.94, H 6.63, N 4.39. Found: C 63.98, H 6.67, N 4.35.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(1b):
Yield 66%, mp: 253, IR (KBr, cm^{-1}) ν: 3350 (N-H str), 3034 (Ar-H), 2953 (C-Hstr of CH_3), 1755 (C=O, ester), 802 (Ar-H). ^{1}H NMR (DMSO-d_6): δ 8.25 (s, 1H, NH of pyridine ring), 7.33-7.27 (m, 5H, Ph-ring), 4.70 (s, 1H, C_4-H), 4.22 (q, 4H, C_3-OC$\underline{H}_2$$CH_3$ and C5-OC$\underline{H}_2$$CH_3$), 2.28 (s, 6H, C_2-CH_3 and C_6-CH_3), 1.32 (t, 6H, C_2-OCH_2C$\underline{H}_3$ and C6-OCH2C$\underline{H}_3$). Elemental analysis calculated for $C_{19}H_{23}NO_4$: C 69.28, H 7.04, N 19.43. Found: C 69.24, H 7.07, N 19.41.

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1c):
Yield 57%, mp: 240, IR(KBr, cm $^{-1}$) ν: 3332 (N-H sYield 57%, mp: 240, IR (KBr, cm^{-1}) ν: 3332 (N-H str), 3074 (Ar-H), 2942 (C-Hstr of CH_3), 1741 (C=O, ester), 837 (C-Cl), 787 (Ar-H). ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 1H, NH of pyridine ring), 7.36-7.19 (dd, 4H, Ph-ring), 4.76 (s, 1H, C_4-H), 4.18 (q, 4H, C_3-OC$\underline{H}_2$$CH_3$ and C_5-OC$\underline{H}_2$$CH_3$), 2.21 (s, 6H, C_2-CH_3 and C_6-CH_3), 1.34 (t, 6H, C_2-OCH_2C$\underline{H}_3$ and C6-OCH2C$\underline{H}_3$). Elemental analysis calculated for $C_{19}H_{22}ClNO_4$: C 62.72, H 6.09, N 3.85. Found: C 62.75, H 6.07, N 3.81.

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1d):
Yield 56%, mp: 240, IR (KBr, cm^{-1}) ν: 3342 (N-H str), 3024 (Ar-H), 2922 (C-H str of CH_3), 1764 (C=O, ester), 1447 (C-OH), 814 (Ar-H). ^{1}H NMR (DMSO-d_6) : δ 9.47 (s, 1H, C-OH), 8.41 (s, 1H, NH of pyridine ring), 7.34-7.07 (dd , 4H, Ph-ring), 4.67 (s, 1H, C_4-H), 4.28 (q, 4H, C_3-OC$\underline{H}_2$$CH_3$ and C5-OC$\underline{H}$2CH_3), 2.12 (s, 6H, C_2-CH_3 and C_6-CH_3), 1.28 (t, 6H, C_2-OCH2C$\underline{H}_3$ and C_6-OCH_2C$\underline{H}_3$). Elemental analysis calculated for $C_{19}H_{23}NO_5$: C 69.07, H 6.71, N 4.06. Found: C 69.O3, H 6.75, N 4.01.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1e):
Yield (69%), mp: 197, IR (KBr, cm^{-1}) ν: 3354 (N-H str), 3037 (Ar-H), 2973 (C-H str of CH_3), 1762 (C=O, ester), 1536 (C-NO_2), 812 (Ar-H). ^{1}HNMR (DMSO-d_6) : δ 7.13-7.47 (dd , 4H, Ph-ring), 8.11 (s, 1H, NH of pyridine ring), 4.79 (s,1H,C_4-H), 4.25 (q, 4H, C_3-OC$\underline{H}_2$$CH_3$ and C_5-OC$\underline{H}_2$$CH_3$), 2.31 (s, 6H, C_2-CH_3 and C_6-CH_3), 1.37 (t, 6H, C_2-OCH_2C$\underline{H}_3$ and C_6-OCH_2C$\underline{H}_3$). Elemental analysis calculated for $C_{19}H_{22}N_2O_6$: C 60.95, H 7.48, N 7.48. Found: C 60.91, H 7.42, N 7.41.

Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(1f):
Yield (72%), mp: 197, IR (KBr, cm^{-1}) ν: 3352 (N-H str), 3026 (Ar-H), 2961 (C-H str of CH_3), 1742 (C=O, ester), 823 (Ar-H). ^{1}H NMR (DMSO-d_6): δ 8.21 (s, 1H, NH of pyridine ring), 6.86-7.17 (dd, 4H, Ph-ring), 4.69 (s, 1H, C_4-H), 4.23 (q, 4H, C_3-OC$\underline{H}_2$$CH_3$ and C_5-OC$\underline{H}_2$$CH_3$), 3.84 (s, 3H, -O$CH_3$), 2.23 (s, 6H, C_2-CH_3 and C_6-CH_3), 1.30 (t, 6H, C_2-OCH_2C$\underline{H}_3$ and C_6-OCH_2C$\underline{H}_3$). Elemental analysis calculated for. $C_{20}H_{25}NO_5$: C 66.83, H 7.01, N 3.90. Found: C 66.87, H 7.07, N 3.97.

Diethyl 4-(4-(dimethylamino)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1g):
Yield (56%), mp: 227, IR (KBr, cm^{-1}) ν: 3348 (N-H str), 3027 (Ar-H), 2956 (C-Hstr of CH_3), 1761 (C=O, ester), 808 (Ar-H)**.** ^{1}H NMR (DMSO-d_6): δ 8.37 (s, 1H, NH of pyridine ring), 7.28-7.21 (dd, 4H, Ph-ring), 4.70 (s, 2H, C_4-H), 4.22 (q, 4H, C_3-OC$\underline{H}_2$$CH_3$ and C_5-OC$\underline{H}_2$$CH_3$), 3.12 (s, 6H, -N$(CH_3)_2$), 2.28 (s, 6H, C_2-CH_3 and C_6-CH_3), 1.32 (t, 6H, C_2-OCH_2C$\underline{H}_3$ and C_6-OCH_2C$\underline{H}_3$). Elemental analysis calculated for $C_{19}H_{23}NO_4$: C 67.72, H 7.58 ,N 7.52. Found: C 67.77, H 7.52, N 7.55.

Synthesis of 2,2'-{[4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide (2a):
A reaction mixture was made up of compound (1a) (0.1 mol), thiosemicarbazide dissolved in ethanol (30 ml) and a few drops DMSO. It was then heated under reflux for 10 h. The obtained solid was allowed to cool and then poured in to crushed ice. The solid was collected by filtration, washed with water and recrystallised using ethanol. The above procedure was followed for the synthesis of compounds (2b–g). Yield (70%). mp:197

IR (KBr, cm^{-1}) ν: 3370 (NH), 3221 (NH_2), 3192 (NHC=O), 3037(ArH), 1721 (C=O), 1263 (C=S), 1095 (N-C-N), 811 (Ar-H). ^{1}H NMR ($CDCl_3$): δ 9.64 (s, 2H, NH_2), 8.46 (s, 1H, NH of pyridine ring), 8.12 (d, 1H, C_3- CON$\underline{H}$ and C_5- CON$\underline{H}$), 7.22 (s, 5H, Ph-ring), 6.14-6.32 (d, 2H, furyl ring), 5.15 (s, 2H, C_4-H), 2.33 (s, 6H, C_2-CH_3 and C_6-CH_3), 2.14 (d, 1H, -NHCS). ^{13}C NMR ($CDCl_3$): δ 111.8, 108.3, 143.2, 152.8 (4C in furyl ring), 105.3 (3,5 C in pyridine ring), 166.2 (3,5 C=O), 182.1 (3,5 C=S), 148.9 (2,6-C in pyridine ring), 35.3 (4C in pyridine ring), 18.2 (2,6-CH_3 in pyridine ring). MS (*m/z,* relative abundance, %): 410 (M^{+}+1, 30.2), 291.30, 161.27, 175.22, 147.12, 81.11. Elemental analysis calculated for $C_{17}H_{21}N_7O_2S_2$: C 48.67, H 5.50, N 23.37, S 15.29. Found: C 48.64, H 5.57, N 23.31, S 15.34.

2,2'-[(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-diyl)dicarbonyl]dihydrazinecarbothioamide (2b): Yield (53%), mp: 192, IR (KBr, cm^{-1}) ν: 3372 (NH), 3200 (NH-C=O), 3218 (NH_2), 3034 (Ar-H), 1718 (C=O), 1260 (C=S), 1091 (N-C-N); 808 (Ar-H). ^{1}H NMR ($CDCl_3$): δ= 9.62 (s, 2H, NH_2), 8.43 (s, 1H, NH of pyridine ring), 8.09 (d, 1H, C_3-CON<u>H</u> and C_5-CON<u>H</u>), 7.39-7.22 (m, 5H, Ph-ring), 5.17 (s, 2H, C_4-H), 2.37 (s, 6H, C_2-CH_3 and C_6-CH_3), 2.12 (d, 1H, -NHCS) . ^{13}CNMR ($CDCl_3$): δ= 131.3, 128.5, 130.9, 141.8 (4C in furyl ring), 106.8 (3,5 C in pyridine ring), 164.6 (3,5 C=O), 182.8 (3,5 C=S), 147.9 (2,6-C in pyridine ring), 34.6 (4C in pyridine ring), 18.9 (2,6-CH_3 in pyridine ring). MS (*m/z,* relative abundance, %) : 420.20 (M^{+}+1, 20.1), 301.34, 241.28, 185.2, 157.21, 81.11. Elemental analysis calculated for $C_{17}H_{21}N_7O_2S_2$: C 48.67, H 5.50, N 23.37, S 15.29. Found: C 48.64, H 5.55, N 23.33,S 15.33.

2,2'-{[4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide (2c): Yield (68%), mp: 194, IR(KBr, cm^{-1}) ν: 3325 (NH), 3231 (NH_2), 3198 (NH-C=O), 3024 (Ar-H), 1707 (C=O), 1265 (C=S), 1097 (N-C-N), 827 (C-Cl). ^{1}HNMR ($CDCl_3$): δ 9.41 (s, 2H, NH_2), 8.41 (bs, 1H, NH of pyridine ring), 8.11 (d, 1H, C_3 - CON<u>H</u> and C_5- CON<u>H</u>), 7.38- 7.14 (m, 5H, Ph-ring), 5.10 (s, 2H, C_4-H), 2.45 (s, 6H, C_2-CH_3 and C_6-CH_3), 2.08 (d, 1H, -NHCS). ^{13}C NMR ($CDCl_3$): δ 128.7, 108.3, 143.2, 152.8 (4C in furyl ring), 105.3 (3,5 C in pyridine ring), 166.2 (3,5 C=O), 182.1 (3,5 C=S), 148.9 (2,6-C in pyridine ring), 39.3 (4C in pyridine ring), 18.2 (2,6-CH_3 in pyridine ring). MS (*m/z,* relative abundance, %) : 454.12 (M^{+}+1, 12.3), 335.78, 275.73, 219.70, 157.21, 81.11. Elemental analysis calculated for $C_{17}H_{20}ClN_7O_2S_2$: C 44.98, H 4.40, N 21.60, S14.14. Found: C 44.94, H 4.44, N 21.64, S14.18.

2,2'-{[4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl}dihydrazinecarbothioamide(2d): Yield (74%), mp: 201, IR (KBr, cm^{-1}) ν: 3342 (NH), 3220 (NH_2), 3192 (NH-C=O), 3028 (Ar-H), 1717 (C=O), 1472 (C-OH), 1242 (C=S), 1091 (N-C-N). ^{1}H NMR($CDCl_3$): δ 9.71 (s, 2H, NH_2), 9.41 (s, 1H, OH), 8.64 (bs, 1H, NH of pyridine ring), 8.01 (d, 1H, C_3-CON<u>H</u> and C_5-CON<u>H</u>), 7.33-7.27 (m, 5H, Ph-ring), 5.11 (s, 2H, C_4-H), 2.25 (s, 6H, C_2-CH_3 and C_6-CH_3), 2.02 (d, 1H, -NHCS). ^{13}C NMR ($CDCl_3$): δ 155.8, 137.1, 130.3, 114.2 (4C in furyl ring), 102.9 (3,5 C in pyridine ring), 164.9 (3,5 C=O), 184.6 (3,5 C=S), 148.1 (2,6-C in pyridine ring), 43.8 (4C in pyridine ring), 19.2 (2,6-CH_3 in pyridine ring). MS (*m/z,* relative abundance, %): 435.52 (M^{+}+1, 27.2), 257.28, 201.26, 173.21, 157.21, 81.11. Elemental analysis calculated for $C_{17}H_{21}N_7O_2S_2$: C 46.88, H 22.51, N 4.86, S 14.72. Found: C 46.84, H 22.54, N 4.84, S 14.76.

2,2'-{[4-(4-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicerbonyl} dihydrazinecarbothioamide (2e): Yield (76%), mp: 195, IR (KBr, cm^{-1}) ν: 3310 (NH), 3241 (NH_2), 3218 (NH-C=O), 3041 (Ar-H), 1530 (C-NO_2), 1272 (C=S), 1710 (C=O), 1091 (N-C-N). ^{1}H NMR ($CDCl_3$): δ 9.77 (s, 2H, NH_2), 8.60 (bs, 1H, NH of pyridine ring), 8.15 (d, 1H, C_3-CON<u>H</u> and C_5-CON<u>H</u>), 7.42-7.18 (m, 5H, Ph-ring), 5.17 (s, 2H, C_4-H), 2.31 (s, 6H, C_2-CH_3 and C_6-CH_3), 2.08 (d, 1H, -NHCS). ^{13}C NMR ($CDCl_3$): δ 143.2, 123.7, 126.7 (4C in furyl ring), 102.9 (3,5 C in pyridine ring), 164.9 (3,5 C=O), 181.9 (3,5 C=S), 149.9 (2,6 C in pyridine ring), 44.5 (4C in pyridine ring), 19.7 (2,6-CH_3 in pyridine ring). MS (*m/z,* relative abundance %): 465.52 (M^{+}+1, 12.78), 346.34, 286.20, 258.23, 230.21, 202.20, 81.11. Elemental analysis calculated for $C_{17}H_{20}N_8O_4S_2$: C43.96, H4.34, N24.12, S13.81. Found: C43.91, H4.38, N24.17, S15.87.

2,2'-{[4-(4-methoxyhenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide(2f): Yield (66%), mp: 210, IR (KBr, cm^{-1}) ν: 3323 (NH), 3251 (NH-C=O), 3231 (NH_2), 3034 (Ar-H), 1717 (C=O), 1251 (C=S), 1091 (N-C-N), 801 (Ar-H). ^{1}H NMR(DMSO-d_6): δ 9.82 (s, 2H, NH_2), 8.57 (bs, 1H, NH of pyridine ring), 8.05 (d, 1H, C_3-CON<u>H</u> and C_5-CON<u>H</u>), 7.33-7.27 (m, 5H, Ph-ring), 5.21 (s, 2H, C_4-H), 3.81 (s, 3H, -OCH_3), 2.10 (d, 1H, -NHCS), 2.25 (s, 6H, C_2-C<u>H_3</u> and C_6-C<u>H_3</u>). ^{13}C NMR ($CDCl_3$): δ 111.8, 108.3,143.2, 152.8 (4C in furyl ring), 105.3 (3,5 C in pyridine ring), 166.2 (3,5 C=O), 181.7 (3,5 C=S), 147.7 (2,6-C in pyridine ring), 44.7 (4C in pyridine ring), 18.8 (2,6-CH_3 in pyridine ring), 55.9 (-OCH_3). MS (*m/z,* relative abundance, %): 450.21 (M^{+}+1, 29.12), 331.36, 271.31, 243.25, 215.29, 185.26, 157.21. Elemental analysis calculated for $C_{18}H_{23}N_7O_3S_2$: C 48.09, H 5.16, N 21.81, S 14.27. Found: C 48.08, H 5.19, N 21.83, S,14.25.

2,2'-{[4-(4-dimethylnitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothioamide(2g):
Yield (61%), mp: 205, IR (KBr, cm^{-1}) ν: 3321 (NH), 3211 (NH_2), 3118 (NH-C=O), 3021 (Ar-H), 1712 (C=O), 1248 (C=S), 1091 (N-C-N), 808 (Ar-H). ^1H NMR (DMSO-d_6): δ 9.66 (s, 2H, NH_2), 8.52 (s, 1H, NH of pyridine ring), 8.03 (d, 1H, C_3-CON<u>H</u> and C_5-CON<u>H</u>), 6.62-7.07 (m, 4H, Ph-ring), 5.13 (s, 2H,C_4-H), 2.07 (d, 1H, -NHCS), 3.06 (s, 1H, -$N(CH_3)_2$) 2.19 (s, 6H, C_2-CH_3 and C_6-CH_3). ^{13}C NMR ($CDCl_3$): δ 112.8, 134.8, 128.3, 148.2, 152.8 (4C in furyl ring), 106.3 (3,5 C in pyridine ring), 165.2 (3,5 C=O), 181.1 (3,5 C=S), 147.9 (2,6-C in pyridine ring), 39.3 (4C in pyridine ring), 40.8 ($N(CH_3)_2$, 46.5 (4C in pyridine ring), 18.2 (2,6-CH_3 in pyridine ring). MS (*m/z,* relative abundance, %) : 463.22 (M^++1, 16.24), 432.56, 344.41, 284.35, 256.29, 213.23, 199.24, 185.26. Elemental analysis calculated for $C_{19}H_{26}N_8O_2S_2$: C 49.33, H 5.67, N 24.22, S 13.86. Found: C 49.34, H 5.69, N 24.24, S 13.84.

Anticonvulsant activity:
Anticonvulsant activity method described in the anticonvulsant drug development (ADD) program protocol[21,22]. Compounds (2a-g) were screened for their anticonvulsant activity against the pentyleneteterzole induced convulsions. The Swiss albino-rats are weighing 150 g divided into 9 groups containing 5 animals in each group, the test compounds are dissolved in DMSO and doses at (50 and 100 mg/kg). Normal saline solution was intraperitoneally administered, followed 15 min later by an intravenous 48.7 mg dose of pentamethylenetrazole dissolved in physiological saline. Convulsions reports are presented in [Table 1].

Assay group:
A solution of the compound being tested in physiological saline was intrapertioneally administered after 15 min a time that was considered sufficient for complete absorption, that same dose of pentamethyleneteterzole was administered.

Reference group:
Phenytoin (50 mg/kg) was dissolved in physiological saline. After 15 min the same dose of pentamethylenetetrazole was applied. The test was evaluated by maximal electrode induced convulsion method. The maximal electroshock seizure (MES) convulsions electroshock is applied through the corneal electrodes.

TABLE 1: EFFECT OF COMPOUNDS (2A-G) ON THE DURATION OF CONVULSIONS

C. No	Dose (mg/Kg)	Duration of convulsion (s)	Percentage of activity (%)
Normal saline	-	63.6	0
2a	50	14.2*	78
	100	10.4*	84
2b	50	18.2*	71
	100	14.0*	77
2c	50	20.0*	68
	100	13.4*	78
2d	50	19.2*	69
	100	12.8*	79
2e	50	16.0*	74
	100	12.5*	80
2f	50	19.0*	70
	100	16.0*	74
2g	50	19.2*	69
	100	15.1*	76
Phenytoin	50	1.7*	98

*$P > 0.001$ Vs Control, The compounds (2a-g) shows marked anticoagulant activity and have significant P value. Formula for calculating the percentage of the activity: (Control duration of convulsions/test duration of convulsions/ Control duration of convulsions)×100

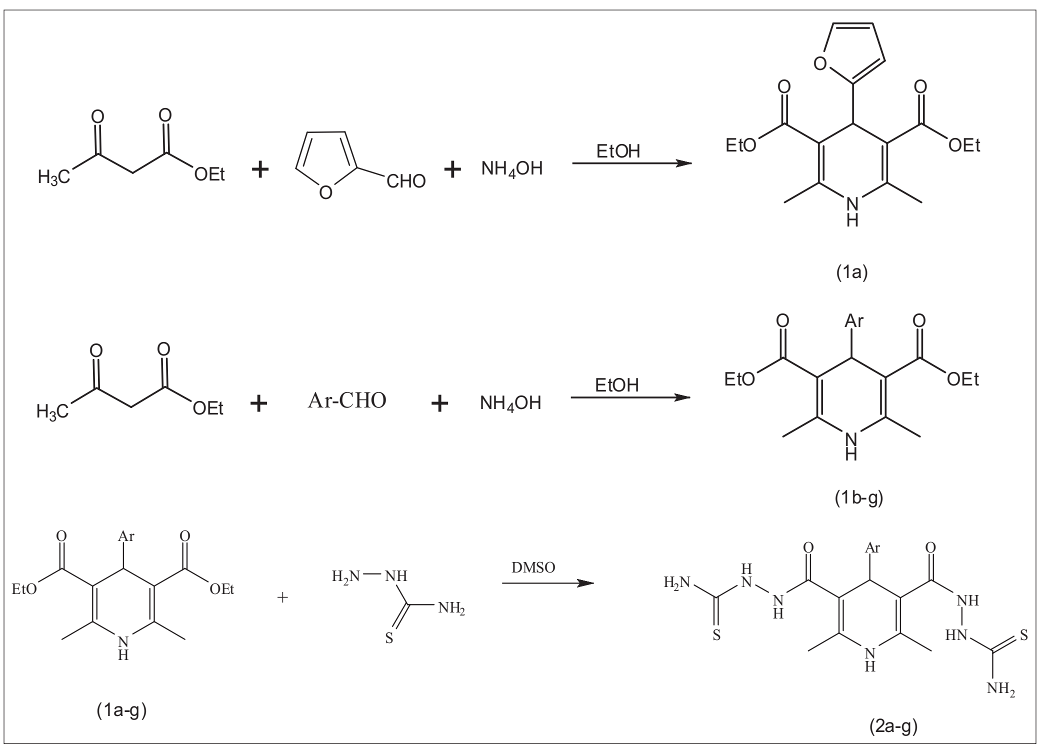
TABLE 2: PHYSICAL CONSTANTS OF SYNTHESIZED COMPOUNDS

Compounds	Ar	Yield %	mp(°)
1a	-Furan	75	158
1b	-Ph	66	253
1c	4-ClC_6H_4	57	240
1d	4-OHC_6H_4	56	246
1e	4-$NO_2C_6H_4$	69	197
1f	4-$CH_3OC_6H_4$	72	188
1g	4-$(CH_3)_2N$-C_6H_4	56	227
2a	-Furan	70	197
2b	Ph	53	192
2c	4-ClC_6H_4	68	194
2d	4-OHC_6H_4	74	201
2e	4-$NO_2C_6H_4$	76	195
2f	4-$CH_3OC_6H_4$	66	210
2g	4-$(CH_3)_2N$-C_6H_4	61	205

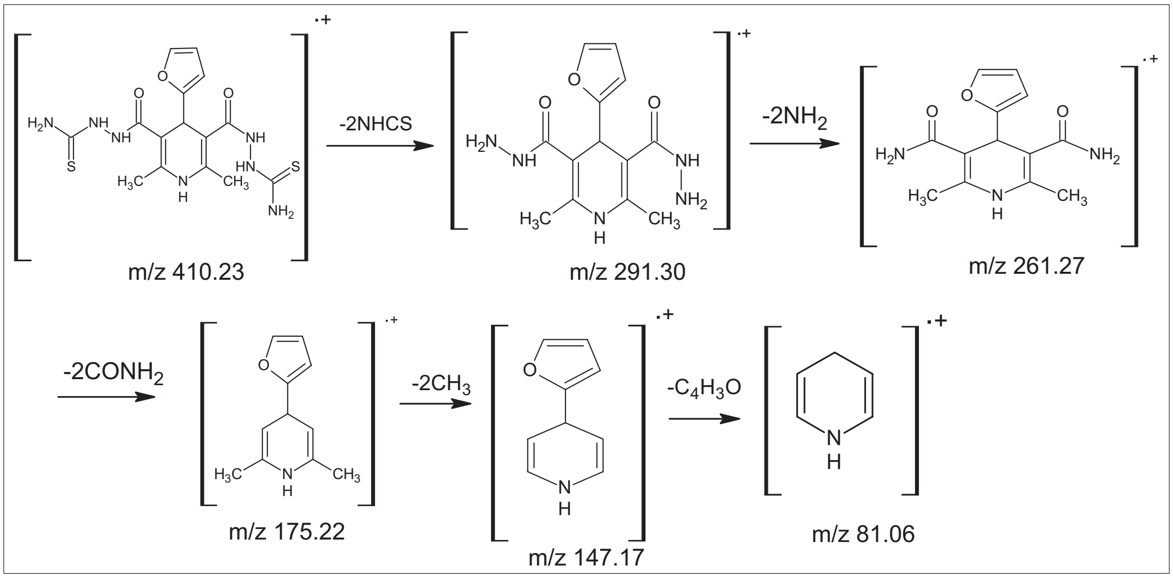
RESULTS AND DISCUSSION

A series diethyl 2,6-dimethyl-4-substituted phenyl-1,4-dihydropyridine-3,5-dicarboxylate derivatives (1a-g) were prepared as base by following the method previously described literature[23]. 2,6-dimethyl-

4-substitutedphenyl-1,4-dihydropyridine-3,5-dicarboxylate (1a-g) reacted with thiosemicarbazide to give 2,2'-{[4-(4-substituted aromatic alcohols)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]dicarbonyl} dihydrazinecarbothio amide (2a-g) by hydrazinolysis method[24,25] (Scheme 1). The Physical constants and percentage yields of all compounds are summarized in Table 2. The IR spectrum of the compounds (1a-g) showed an absorption band at 3332 to 3354 cm^{-1} due to the NH stretching, and another absorption band at 1741-1764 cm^{-1} due to the carbonyl group present in the ester function. The compound 1b showed an absorption band for the Cl-C group at 837 cm^{-1} and compound 1c showed an absorption band for the OH-C group at 1447 cm^{-1}, the compound 1d showed an absorption bands at 1536 cm^{-1} corresponding to (NO_2–C). The ^{1}H NMR spectrum of compound (1a-g), showed a singlet at δ 8.11 to 8.41, attributable to NH protons present in 1,4-dihydropyridine ring, and another important singlet at δ 4.67 to 4.79 which was attributable to the 4-CH present in the 1,4-dihydropyridine ring. The IR spectrum of compounds (2a-g), showed an absorption band at 3320 to 3372 cm^{-1} due to NH group present in the 1,4-dihydropyridine ring and, another absorption band at 3118- 3198 cm^{-1} which is due to the NH-C=O stretch. An absorption band for C=S group was observed at 1245 to 1272 cm^{-1}. The ^{1}HNMR spectrum of (2a-g) showed a singlet at δ 8.41 - 8.64 attributable to NH protons, present in the 1,4-dihydropyridinering. The NHCS and NH_2 groups showed a singlet at δ 2.02–2.12 and 9.14–9.82, respectively. The ^{13}C NMR spectrum of compounds (2a-g) showed peaks at δ 163.1-166.2, corresponding to the 3,5- position of CONH in the pyridine ring, 181.1–184.6 corresponding to the 3,5-position of CS in the pyridine ring, 34.6–46.5 corresponding to 4- position of carbon in the pyridine ring and 18.2-19.7 corresponding to the 2,6- position of CH_3 in the pyridine ring, respectively. The mass spectrum of compound (2a) showed that the molecular ion peak at m/z 410.23 and base peak of the compound m/z 261.25. The mass spectral fragmentation of compound (2a) showed the Scheme 2. Fig. 1 indicates that effect of compounds (2a-g) on the duration of convulsions. Compounds (1a-g) were inactive at the doses tested while compounds (2a-g) have significant activity at 100 mg/kg concentration. The effect of compounds (2a-g) on neuronal excitability as measured by their influence on the percentage of animals affected by convulsions is shown in Table 1. The compound (2a) had highly active compared with other compounds (2b-g) at both doses (50 and 100 mg / kg). Since a dose of 150 mg/kg caused no signs of toxicity during the 24 h following its administration to a group of animals, this can be beneficial for further studies. The



Scheme 1: Synthesis of new series of 1,4-dihydropyridine derivatives (1a-g) and (2a-g)



Scheme 2: Mass spectral fragmentation of compound (2a)

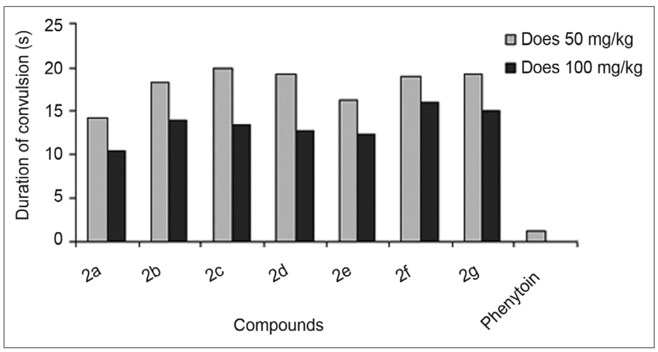


Fig. 1: Comparison of duration of convulsion with test compounds. Compound (2a-g) was used two does at 50 (■) and 100 (■) (mg/kg), whereas, phenytoin was used as a standard.

compound (2a) has highly active due to the presence of furan ring in 4-position of 1,4-dihydropyridine ring. Pharmacological and further preclinical investigations are currently underway.

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