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

R. SURENDRRA KUMAR, A. IDHAYADHULLA, A. JAMAL ABDUL NASSER*, S. KAVIMANI1 AND S. INDUMATHY1
P. G. and Research Department of Chemistry, Jamal Mohamed College, Tiruchirappalli - 620 020, 1Department of Pharmacology, Mother Theresa Post Graduate and Research Institute of Health Science, Puducherry – 605 006, India

Kumar, et al.: Anticonvulsant Activity of New Series of 1,4-Dihydropyridine Derivatives

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]. Thiosemicarbazone 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 ¹H NMR and ¹³CNMR 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.

Synthesis of diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (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.

**Address for correspondence
E-mail: jamal_abdulchem@ymail.com**
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-H str of CH₃), 1755 (C = O, ester), 802 (Ar-H). ¹H NMR (DMSO-d₆): δ 8.25 (s, 1H, NH of pyridine ring), 7.33-7.27 (m, 5H, Ph-ring), 4.70 (s, 1H, C₆-H), 4.22 (q, 4H, C₂-OCH₂CH₃ and C₅-OCH₂CH₃), 2.28 (s, 6H, C₆-CH₃ and C₆-H), 1.32 (t, 6H, C₆-OCH₂CH₃ and C₆-OCH₂CH₃). Elemental analysis calculated for C₁₉H₂₂N₂O₆: C 69.24, H 7.07, N 19.41. 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 str), 3074 (Ar-H), 2942 (C-H str of CH₃), 1741 (C = O, ester), 837 (C-Cl), 787 (Ar-H). ¹H NMR (DMSO-d₆): δ 8.31 (s, 1H, NH of pyridine ring), 7.36-7.19 (dd, 4H, Ph-ring), 4.76 (s, 1H, C₆-H), 4.18 (q, 4H, C₂-OCH₂CH₃ and C₅-OCH₂CH₃), 2.21 (s, 6H, C₂-CH₃ and C₂-CH₃), 1.34 (t, 6H, C₂-OCH₂CH₃ and C₆-OCH₂CH₃). Elemental analysis calculated for C₁₉H₂₂ClNO₆: 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 CH₃), 1764 (C = O, ester), 1447 (C-OH), 814 (Ar-H). ¹H NMR (DMSO-d₆): 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, C₆-H), 4.28 (q, 4H, C₂-OCH₂CH₃ and C₅-OCH₂CH₂), 2.12 (s, 6H, C₂-CH₃ and C₂-CH₃), 1.28 (t, 6H, C₂-OCH₂CH₃ and C₂-OCH₂CH₃). Elemental analysis calculated for C₁₉H₂₂O₇N: C 69.07, H 6.71, N 4.06. Found: C 69.03, H 6.75, N 4.01.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1e):

Yield (72%), mp: 197, IR (KBr, cm⁻¹): ν: 3352 (N-H str), 3026 (Ar-H), 2961 (C-H str of CH₃), 1742 (C = O, ester), 823 (Ar-H). ¹H NMR (DMSO-d₆): δ 8.21 (s, 1H, NH of pyridine ring), 6.86-7.17 (dd, 4H, Ph-ring), 4.69 (s, 1H, C₆-H), 4.23 (q, 4H, C₂-OCH₂CH₃ and C₂-OCH₂CH₃), 3.84 (s, 3H, -OCH₃), 2.23 (s, 6H, C₂-CH₃ and C₂-CH₃), 1.30 (t, 6H, C₂-OCH₂CH₃ and C₂-OCH₂CH₃). Elemental analysis calculated for C₂₁H₂₅NO₇: 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-H str of CH₃), 1761 (C = O, ester), 808 (Ar-H). ¹H NMR (DMSO-d₆): δ 8.37 (s, 1H, NH of pyridine ring), 7.28-7.21 (dd, 4H, Ph-ring), 4.70 (s, 2H, C₂-H), 4.22 (q, 4H, C₂-OCH₂CH₃ and C₂-OCH₂CH₃), 3.12 (s, 6H, -N(CH₃)), 2.28 (s, 6H, C₂-CH₃ and C₂-CH₃), 1.32 (t, 6H, C₂-OCH₂CH₃ and C₂-OCH₂CH₃). Elemental analysis calculated for C₂₆H₃₂N₂O₇: 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-diy]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 (NH₂), 3192 (NHC = O), 3037 (Ar-H), 1721 (C = O), 1263 (C = S), 1095 (N-C-N), 811 (Ar-H). ¹H NMR (CDCl₃): δ 9.64 (s, 2H, NH₂), 8.46 (s, 1H, NH of pyridine ring), 8.12 (d, 1H, C₂ CONH and C₂ CONH), 7.22 (s, 5H, Ph-ring), 6.14-6.32 (d, 2H, furyl ring), 5.15 (s, 2H, C₆-H), 2.33 (s, 6H, C₂-CH₃ and C₂-CH₃), 2.14 (d, 1H, -NHCS). ¹³C NMR (CDCl₃): 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-CH₃ 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 C₁₇H₁₂₂N₂O₅S₂: 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]dicarboxyl}dihydrazinecarbothioamide (2b): Yield (53%), mp: 192, IR (KBr, cm⁻¹): ν: 3372 (NH), 3200 (NH-C=O), 3218 (NH₂), 3034 (Ar-H), 1718 (C=O), 1260 (C=S), 1091 (N-C=N), 808 (Ar-H).

1H NMR (CDCl₃): δ = 9.62 (s, 2H, NH₂), 8.43 (s, 1H, NH of pyridine ring), 8.09 (d, 1H, C₆=CONH and C₅=CONH), 7.39-7.22 (m, 5H, Ph-ring), 5.17 (s, 2H, C₂-H), 2.37 (s, 6H, C₆-CH₃ and C₆-CH₂), 2.12 (d, 1H, -NHCS). ¹³C NMR (CDCl₃): δ 131.3, 128.5, 130.9, 141.8 (4C in furyl ring), 166.2 (3,5 C=O), 181.7 (3,5 C=S), 149.9 (2,6 C in pyridine ring), 34.6 (4C in pyridine ring), 19.7 (2,6-CH₃ in pyridine ring). MS (m/z, relative abundance, %): 420.20 (M⁺+1, 20.1), 319.28, 185.2, 157.21, 81.11. Elemental analysis calculated for C₁₇H₁₂₁N₂O₅S₂: 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]dicarboxyl}dihydrazinecarbothioamide (2c): Yield (76%), mp: 195, IR (KBr, cm⁻¹): ν: 3342 (NH), 3218 (NH₂), 3041 (Ar-H), 1530 (C=NO₂), 1272 (C=S), 1710 (C=O), 1091 (N-C=N), 801 (Ar-H).

1H NMR (CDCl₃): δ 9.77 (s, 2H, NH₂), 8.60 (bs, 1H, NH of pyridine ring), 8.15 (d, 1H, C₆-CONH and C₅-CONH), 7.42-7.18 (m, 5H, Ph-ring), 5.17 (s, 2H, C₂-H), 2.31 (s, 6H, C₆-CH₃ and C₆-CH₂), 2.08 (d, 1H, -NHCS). ¹³C NMR (CDCl₃): 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-CH₃ 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 C₁₇H₁₂₁N₂O₄S₂: C 43.96, H 4.34, N 24.12, S 13.81. Found: C 43.91, H 4.38, N 24.17, S 15.87.

2,2’-{{4-(4-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl}dicarboxyl}dihydrazinecarbothioamide(2e): Yield (76%), mp: 192, IR (KBr, cm⁻¹): ν: 3342 (NH), 3218 (NH₂), 3041 (Ar-H), 1530 (C=NO₂), 1272 (C=S), 1710 (C=O), 1091 (N-C=N), 801 (Ar-H).

1H NMR (CDCl₃): δ 9.77 (s, 2H, NH₂), 8.60 (bs, 1H, NH of pyridine ring), 8.15 (d, 1H, C₆-CONH and C₅-CONH), 7.42-7.18 (m, 5H, Ph-ring), 5.17 (s, 2H, C₂-H), 2.31 (s, 6H, C₆-CH₃ and C₆-CH₂), 2.08 (d, 1H, -NHCS). ¹³C NMR (CDCl₃): 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-CH₃ 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 C₁₇H₁₂₁N₂O₄S₂: C 43.96, H 4.34, N 24.12, S 13.81. Found: C 43.91, H 4.38, N 24.17, S 15.87.
185.26, 157.21. Elemental analysis calculated for 
C_{19}H_{23}N_{5}O_{5}S: 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]dicarboxonyl} dihydrazinecarbothioamide(2g):

Yield (61%), mp: 205, IR (KBr, cm^{-1}) ν: 3321 (NH), 3211 (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), 8.52 (s, 1H, NH of pyridine ring), 8.03 (d, 1H, C_5-CONH and C_5-C=CONH), 6.62-7.07 (m, 4H, Ph-ring), 5.13 (s, 2H,C_6), 2.07 (d, 1H, -NHCS), 3.06 (s, 1H, -N(CH_3)_2) 2.19 (s, 6H, C_6-CH_3 and C_6-CH_3).

13C 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_{23}N_{5}O_{5}S: C 49.33, H 5.69, 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 pentamethylenetetrazole 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 pentamethylenetetrazole dissolved in physiological saline. Convulsions reports are presented in [Table 1].

Assay group:

A solution of the compound being tested in physiological saline was intraperitoneally administered after 15 min a time that was considered sufficient for complete absorption, that same dose of pentamethylenetetrazole 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.

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-substituted phenyl-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-diyldicarbonyldihydrazinecarbothioamide (2a-g) by hydrazinolysis method\textsuperscript{[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 \(\delta 8.11\) to 8.41, attributable to NH protons present in 1,4-dihydropyridine ring, and another important singlet at \(\delta 4.67\) 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 \(\delta 8.41\) - 8.64 attributable to NH protons, present in the 1,4-dihydropyridinering. The NHCS and NH\(_2\) groups showed a singlet at \(\delta 2.02\)–2.12 and 9.14–9.82, respectively. The \(^1\)C NMR spectrum of compounds (2a-g) showed peaks at \(\delta 163.1\)-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)](image-url)
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.

ACKNOWLEDGMENTS

We wish to thank for state Government of Tamil Nadu, India. They are providing state government fellowship for financial support. We sincerely thank, Principal of Jamal Mohamed College, for providing Laboratory facilities.

REFERENCES

1. Gaudio AC, Korolkovas A, Takahata Y. Quantitative structure relationships for 1,4-DHP calcium channel. J Pharm Sci 1994;83:1110-5.
2. Schleifer KJ. Stereoselective characterization of the 1,4-dihydropyridine binding site at L-type calcium channels in the resting state and the opened inactivated state. J Med Chem 1999;42:2204-11.
3. Visentin S, Amiel P, Frittero R, Boschi D, Roussel C, Giusta L, et al. Synthesis and Voltage-Clamp Studies of Methyl 1,4-dihydro-2,6-dimethyl-5-nitro-4-(benzofurazanyl)pyridine-3-carboxylate Racemates and Enantiomers and of their Benzoferoxanyl Analogues. J Med Chem 1999;42:1422-7.
4. Jiang JL, Li AH, Jang SY, Chang L, Melman N, Moro S, et al. Chiral Resolution and Stereo specificity of 6-Phenyl-4-phenylethyl-1,4-dihydropyridines as Selective Adenosine Receptor Antagonists. J Med Chem 1999;42:3055-65.
5. Godfraid T, Miller R, Wibo M. Calcium antagonism and calcium entry Blockade. Pharmocol Rev 1986;38:321-416.
6. Khadilkar B, Borkar S. Silica gel supported ferric nitrate a convenient oxidizing reagent. Synth Commun 1998;28:207-12.
7. Schnell B, Krenn W, Faber K, Kappe CO. Synthesis and reactions of Biginelli compounds part 23. Chemoenzymatic synthesis of enantionmecallypur 4-aryl, 3,4-dihydropyrimdin-2(1H)-ones. J Chem Soc Perkin Trans 2000;24:4382-9.
8. Sabitha G, Reddy GS, Reddy CS. A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature. Tetrahedron Lett 2003;44:1129-31.
9. Stout DM, Meyers Al. Recent Advances in the Chemistry of Dihydropyridines. Chem Rev 1982;82:223-43.
10. Ji SJ, Jiang ZQ, Lu J, Loh TP. Facile ionic liquids-promoted one-pot synthesis of polyhydroquinoline derivatives under solvent free conditions. Synlett 2004;5:831-35.
11. Suarez M, Ochoa E, Verdecia Y. A joint experimental and theoretical structural study of novel substituted 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines. Tetrahedron 1999;55:875-84.
12. Tu S, Wei Q, Ma H. The synthesis of novel substituted 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines without solvent under microwave irradiation. Synth Commun 2001;31:2657-61.
13. Pattan SR, Raval VB, Venkatramana N, Khade AB, Butle SR, Jadhav SG, et al. Synthesis and evaluation of some 1,4-dihydropyridine and their derivatives as antihypertensive agents. Indian J Chem 2007;46B:698-701.
14. Suresh T, Swamy SK, Reddy VM. Synthesis and bronchodilatory activity of new 4-aryl-3,5-bis(2-chlorophenyl)-carbamoyl-2,6-dimethyl-1,4-dihydropyridines and their 1-substituted analogues. Indian J Chem 2007;46B:115-21.
15. Bhavik D, Sureja D, Naliapara Y, Shah A, Saxena AK. Synthesis and QSAR Studies of 4-Substituted phenyl-2,6-dimethyl-3,5-bis-N-(substitutedphenyl) carbamoyl-1,4-dihydropyridines as potential antitubercular agents. Bioorg Med Chem 2001;9:1993-8.
16. Amimi M, Navidpour L, Shafee A. Synthesis and antitubercular Activity of new N,N-diaryl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydropyridines.
17. Nandi AK, Chaudhri S, Mazumdah SK, Ghosh S. Effect of chlorine substitution on the structure and activity of 4-phenylthiosemicarbazide: Crystal and molecular structure of 4-(4-chlorophenyl)thiosemicarbazide J Chem Soc Perkin Trans 2 1984;11:1729-33.

18. Ali MA, Chowdhary MA, Naziruddin M. Four- and five-coordinate copper(II) complexes containing mixed ligands. Polyhedron 1984;3:595-8.

19. Scovill JP, Klayman DL, Franchino CF. 2-Acetylpipridine thiosemicarbazones. 4. Complexes with transition metals as antimalarial and antileukemic agents. J Med Chem 1982;25:1261-4.

20. Bindu P, Kurup MR, Satyakeerty TR. Epr cyclic voltammetric and biological activities of copper(II) complexes of salicylaldehyde N(4)-substituted thiosemicarbazone and heterocyclic bases. Polyhedron 1999;18:321-31.

21. Krall RJ, Penny JK, White BG, Kupferberg HJ, Swinyard EA. Antiepileptic drug development II anticonvulsant drug screening. Epilepsia 1978;19:409-28.

22. Poter RJ, Cereghino JJ, Gladding GD, Hessie BJ, Kupferberg HJ, Scoville B, et al. Antiepileptic Drug Development Program. Cleve Clin Q 1984;51:293-9.

23. Srivastava SK, Srivastava S, Srivastava SD. Synthesis of new 1,2,4-triazolo-thiadiazoles and 2-oxoazetidines as antimicrobial, anticonvulsant and antiinflammatory agents. Indian J Chem 2002;41B:2357-63.

24. Ojha S, Ameta U, Dhakar N, Talesara GL. Synthesis and characterization of some alkoxyphthalimide derivatives of benzotriazolylthiadiazoles and benzotriazolylthiazolidinones. Indian J Chem 2007;46B:860-5.

25. Hadizadeh F, Shaficee A, Kazemi R, Mohammadi M. Synthesis of 4-(1-Phenylmethyl-5-imidazolyl)-1,4-dihydropyridines as calcium channel Antagonists. Indian J Chem 2002;41B:2679-82.

Accepted 13 November 2010
Revised 22 October 2010
Received 22 February 2010
Indian J. Pharm. Sci., 2010, 72 (6): 719-725