Synthesis and pharmacological studies of new derivatives of dimethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

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A new series of 1,4-dihydropyridine derivatives 1b-14b has been prepared by incorporation of an amino unit. Aminomethylene group is attached to the aryl ring at C4 of the 1,4-dihydropyridine ring. The hydrochlorides of the compounds are tested for their biological activity.

The research on 1,4-dihydropyridine systems is of current interest due to their valuable activity as calcium antagonists. Effect of substitution on the 1,4-dihydropyridine ring on biological activity has been widely studied in the process of determining structure-activity relationships.

The above reactions were condensed under Hantzsch conditions to give various 1,4-dihydropyridine derivatives (Path-1). The same compounds were prepared by another route (Path-2) by the Mannich reaction of the 1,4-dihydropyridine derivative of vanillin 1c with various amines (Scheme 1).

**Note**

**Experimental Section**

**Method A**

4-Hydroxy-3-methoxy-5-(4-phenyl-1-piperazino)methylbenzaldehyde 1a. Phenylpiperazine (9.72 g, 0.06 mole), paraformaldehyde (1.8 g, 0.06 mole) were taken in a 250 mL flask. To this MeOH (100 mL) was added and the mixture refluxed on a steam-bath for 30 min. Vanillin (9.12 g, 0.06 mole) dissolved in MeOH (30 mL) was added slowly over a period of 10 min to the above mixture and was then refluxed on a steam-bath for 36 hr. On cooling, solid was obtained which was recrystallized from a mixture of CHCl3/petroleum ether. Carrying out the reaction for lesser time gave lower yields of the product. IR (KBr): 3452 (O-H stretching), 3074 (aromatic C-H stretching), 2940 (aliphatic C-H stretching), 2828 and 2741 (aldehyde C-H stretching), 1674 (C=O stretching), 1587 and 1487 (aromatic C-C stretching), 1326 and 1144 (C-O stretching), 761 and 692 due to out-of-plane C-H deformation indicating a monosubstituted benzene ring; 1H NMR (CDCl3): δ 2.8 (t, 4H, piperazine ring protons), 3.26 (t, 4H, piperazine ring protons), 3.88 (s, 2H, methylene group protons), 3.95 (s, 3H, methoxy group protons), 6.8-6.95 (m, 3H, protons on the phenyl ring at the positions ortho and para to the piperazine ring N), 7.2 (d, 1H, J = 1.83 Hz, vanillin ring proton, one para to the methoxy group), 7.28 (dt, 2H, Jortho = 7.32 Hz, Jpara = 6.40 Hz, Jmeta = 2.32 Hz, protons on the phenyl ring at the positions meta to the piperazine ring N), 7.37 (d, 1H, J = 1.83 Hz, vanillin ring proton, one ortho to the methoxy group), 9.8 (s, 1H, aldehyde proton).

Compounds 2a-7a were prepared similarly. The characterization data of 1a-7a are given in Table I.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[4-hydroxy-3-methoxy-5-(4-phenyl-1-piperazino)methyl]-phenyl-3,5-pyridinedicarboxylate 1b. A mixture of 1a (1.63 g, 5 mmoles), methyl 3-aminoacetoacetate (0.58 g, 5 mmoles) and methyl acetoacetate (0.58 g, 5 mmoles) was refluxed in EtOH (40 mL) in the dark for 30 hr.

**Table I**
No solid appeared on cooling. The mixture was concentrated, scratched with a glass rod and cooled overnight. The solid appeared which was recrystallized from a mixture of CHCl₃/petroleum ether.  

**Method B**  
Dimethyl 1,4-dihydro-2,6-dimethyl-4-[4-hydroxy-3-methoxy-5-(4-phenyl-1-piperazino)methyl]-phenyl-3,5-pyridinedicarboxylate.  
Vanillin (7.60 g, 50 mmoles), methyl acetacetate (5.8 g, 50 mmoles) and methyl 3-aminocrotonate (5.8 g, 50 mmoles) were refluxed in EtOH (40 mL) in the dark for 6 hr. On cooling, the solid appeared which was filtered and washed with cold MeOH. The solid was dried to yield 11.1g (64%) of the product, m.p. 231-32°C. 

**Scheme I**  
Dimethyl 1,4-dihydro-2,6-dimethyl-4-[4-hydroxy-3-methoxy-5-(4-phenyl-1-piperazino)methyl]-phenyl-3,5-pyridinedicarboxylate. Compound (1.74 g, 5 mmoles), phenylpiperazine (0.81 g, 5 mmoles) and paraformaldehyde (0.15 g, 5 mmoles) were refluxed in MeOH (10 mL) in the dark for 10 hr. On cooling, the solid appeared which was recrystallized from a mixture of CHCl₃/petroleum ether. IR (KBr): 3511 (O-H stretching), 3326 (N-H stretching), 3010 (aromatic C-H stretching), 2987 and 2947 (aliphatic C-H str). 1682 (C=O stretching), 1217 and 1121 (C-O stretching). 757 and 691 due to out of plane C-H deformation indicating a monosubstituted benzene ring.
Compounds 2b-14b were prepared similarly. The characterization data of 1b-14b are given in Table II. The hydrochlorides of all the 1,4-dihydropyridine derivatives were prepared by passing HCl gas with cooling through the alcoholic solutions of the compounds, followed by concentration.

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<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Found (%) (Calc.)</th>
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\(^{1} {H} NMR (CDCl_{3}): \delta 1.23 (t, 6H, -COOCH_{2}CH_{3}), 2.34 (s, 2H, 2,6-dimethyl groups' protons), 2.71 (t, 4H, piperazine ring protons), 3.23 (t, 4H, piperazine ring protons), 3.70 (s, 2H, methylene group protons), 3.82 (s, 3H, -OCH_{3}), 4.0-4.2 (m, 4H, -COOCCH_{2}CH_{3}), 4.90 (s, 1H, pyridyl, H-4), 5.22 (s, 1H, H-11), 6.50 (d, 1H, J = 6.5 Hz, vanillin ring proton, one para to the methoxy group), 6.78 (d, 1H, J = 8.3 Hz, vanillin ring proton, one ortho to the methoxy group), 6.85-6.92 (m, 3H, protons on the phenyl ring at the positions ortho and para to the piperazine ring N). 7.27 (g, 2H, J_{ortho} = 7.32 Hz, J_{meta} = 8.79 Hz, protons on the phenyl ring at the positions meta to the piperazine ring N).
Pharmacology

The compounds prepared were tested for the negative inotropic and chronotropic effects on the frog heart and for the smooth muscle relaxation effect on the guinea pig tenia coli (cf. Table III) as per the methods mentioned by Hegde and Rao.\textsuperscript{31,32} The solutions of the hydrochlorides of the compounds were prepared in water in different concentrations. A $10^{-4}$ M stock solution of Nifedipine was prepared in alcohol, and subsequent dilutions were done with water.

Statistical Analysis - Contractile force developed at each dose level was expressed as mean ± s.d. Differences between the mean values were analyzed for statistical significance using the students t-test. A probability level of $p < 0.05$ was considered to be indicative of significance.

Results and Discussion

The tested compounds showed negative chronotropic and inotropic effect on the isolated frog heart and relaxed the K$^+$ depolarized contracted tenia coli. Although the concentrations required to produce these effects are higher than that of nifedipine, the compounds are expected to produce greater activity in vivo due to their expected higher bioavailability.

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