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Research Paper

# Synthesis, Characterization, Docking Studies And Bio-Efficacy Evaluation of Novel 1,4-Dihydropyridine Derivatives

Chemistry

KEYWORDS : 1,4-Dihydropyridine Derivatives , Antimicrobial Studies , Spectral Studies

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## ABSTRACT

*In the present study two new series of Hantzsch 1,4-dihydropyridine derivatives (1,4-DHPs) containing substituted pyrazole moiety (5a and 5c ) were synthesized by the reaction of pyrazole aldehyde with 1,3-dicarbonylcompounds (ethylacetoacetate and methylacetoacetate) and ammonium acetate. The newly synthesized compounds were characterized by IR, NMR, study and also by C, H, N analyses. New compounds were screened for their antimicrobial activity by paper disc method.*

**Introduction**

In recent years, multicomponent reactions (MCRs)[1] have attracted much attention and frequently used to synthesize highly functionalized molecules in a single flask operation. In addition, MCRs in water have been shown to be a powerful tool for developing libraries of medicinal scaffolds as well as for the requirements of green chemistry because of its cheapness, easy availability and benign character.[2] In continuation of our ongoing research work employing water as a solvent in the multicomponent organic transformation,[3] we have found that the Hantzsch reaction can be designed very smoothly in the presence of water, tuning the polarity by ethyl lactate in the presence of visible light. 1,4-Dihydropyridines (DHPs) are an important class of N-heterocyclic scaffolds of low molecular weight in medicinal field, providing important ligands for biological receptors.[4] These compounds, although described for the first time by Arthur Hantzsch in 1882[5] by successive structural modifications involving additions, reductions and condensations mainly in the 1,2 and 6-positions of the dihydropyridine ring, its unique structural features have recently been recognized as vital drugs in the treatment of angina pectoris,[6] Many DHPs are already commercial products such as: amlodipine, felodipine, isradipine, lacidipine, nicardipine, nitrendipine, nifedipine and nemadipine B, of which nitrendipine and nemadipine B exhibit potent calcium channel blocking activities. These molecules have gained therapeutic success due to the efficient binding to the active site of the receptors of calcium channels. [8] Their pharmacological properties include neuro and radio protective effects,[9,10] anti-inflammatory[11], HIV protease inhibition and in the treatment of Alzheimer's disease,[12] anti-microbial,[13,14] bronchodilator, antitumor, anti-inflammatory, antiulcer activities,[15] antidiabetic agents, antioxidants,[16,17] antitubercular agents,[18,19] neuroprotectants.[20] Pyrazolyl 1,4-DHP derivatives have showed potential biological activities including anti-inflammatory, calcium channel activity, including control of arthropod pests, and also pyrazolylpyridine ligands exhibit efficient lanthanide sensors.[21-24] Therefore, the synthesis of pyrazolyl 1,4-DHPs has become of interest to synthetic chemists and biologists. Several groups have reported the synthesis of 1,4-DHPs with $I_2$,[25] TMSCl/NaI,[26] $InCl_3$,[27] $Yb(OTf)_3$,[28] $FeCl_3$,[29] $SiO_2$/ $NaHSO_4$,[30] CAN,[31] $Al_2O_3$,[32] $Mg(ClO_4)_2$,[33] TCT,[34] PTSA,[35] and $SiO_2$esulfonic acid[36] promote these type of reactions. Although some of these reactions are performed under mild conditions,most of them require a long period for completion, expensive materials, tedious work-up, the formation of side products, and give only modest yields of the products. Therefore, development and introduction of a convenient, cost effective, milder and efficient method for the pyrazolyl 1,4-DHPs is of practical importance and is still in demand. Recently, the nanocatalyst has received considerable attention as efficient catalyst for various reactions that is MgO NT is an efficient, cost effective and recyclable catalyst for the synthesis of biological important pyrazolyl 1,4-DHP derivatives. Due to the unique molecular structure, certain Hantzsch dihydropyridines are considered as imitates of the biological redox system NAD/NADH$^+$ and have emerged as hydrogen transfer agents in biomimetic reductions[37] and also as photoactive materials.[38] A variety of methods have been emerged to achieve the synthesis of this dihydro pyridine nucleus. Most of the methods[39–54] reported previously have focused on the modification and the optimization of the process parameters of the Hantzsch reaction to minimize reaction time and maximize reaction conversion to achieve the desired 1,4-DHP in high purity. These methodologies are generally based on the usage of ionic liquids, metal/metal-free catalysts, microwave and ultrasound irradiation.[55] Ananthakrishnan et al.[56]

Microwave-assisted synthesis has revolutionized many processes in recent years as a valuable alternative to the use of conductive heating for accelerating transformations in synthetic organic chemistry [57], colloidal science [58], natural product chemistry [59], medicinal chemistry [60], solid-phase peptide synthesis [61] and in the biosciences [62]. Despite the many advantages of this heating method, and the introduction of a wide range of instrumentation [57], the scale up of microwave mediated reactions still poses a number of challenges, in particular as a result of a lack of uniform heating [63]. Scale-up using batch methodologies in open reaction vessels can give excellent yields but might not be appropriate for certain volatile or toxic reagents whereas continuous flow processing, providing the reaction mixture is homogeneous,

**Experimental**

**Chemicals and Reagents**

The tested derivatives were prepared at the Department of Chemistry, University college of Science, Osmania University. Phenyl hydrazine and acetophenone for the synthesis was obtained from Sigma–Aldrich Ltd. India. For the antimicrobial assay, all solutions were prepared in distilled, sterile water on the day of the experiment, 1,4-DHP was dissolved in DMSO (dimethyl sulphoxide, Sigma–Aldrich Ltd. Steinheim,India), Ampicillin for antimicrobial studies was purchased from local pharmaceuticals.

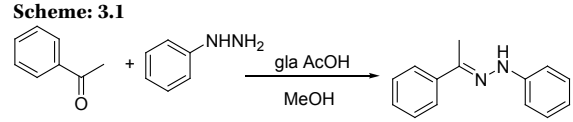
**Results and discussion**

**1.1 Synthesis of Simple pyrazole aldehyde:**

**1.1.1 Synthesis of schiffs base:**

Glacial acetic acid (1 ml) and phenyl hydrazine (**2**) (20 mmol) were added to a solution of acetophenone **(1a)** (24 mmol) in 90 ml of ethanol. Then, the reaction mixture was refluxed for 1 h. The precipitate was filtered and recrystallized with ethanol (92%).

**Scheme: 3.1**




**1a** **2** **3a**

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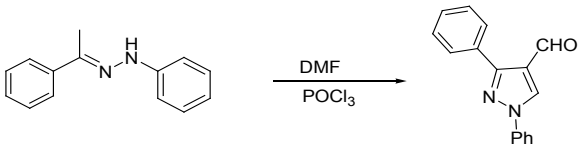
**1.1.2 Vilsmeier–Haack reaction:**

Dimethylformamide (35.3 mmol) and $POCl_3$ (35.3 mmol) were previous separately cooled at 0°c before being stirred at such temperature. A solution of **3a** (11.76 mmol) in DMF (3 ml) was added drop wise to the reaction mixture which was, then warmed to r.t stirred over night. The mixture was basified with a cool saturated NaOH solution. The precipitate was filtered, washed with water and recrystallized from ethanol, yield 95%.

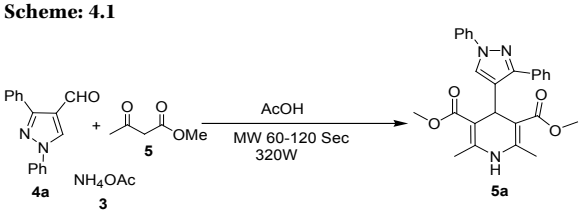



**3a** **4a**

**4.1 Synthesis of 4-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester:**

A mixture of simple pyrazole aldehyde **(4a)** (5 mmol), methyl acetoacetate (10 mmol), ammonium acetate (10 mmol) and catalytical amount of acetic acid without solvent in a beaker kept at the center of the microwave oven (320 W) and irradiated for a period of 10 sec. After every irradiation (10 s), the beaker was removed from the microwave oven and stirred the reaction mixture. The completion of the reaction was checked by TLC (ethylacetate:hexane, 8:2). The total period of microwave irradiation was in the range of 60-120 s. The reaction mixture was then extracted with ethylacetate, organic layer washed with water and dried over anhydrous $Na_2SO_4$. Organic solvent was evaporated under reduced pressure and solid compound, which was crystallized from absolute ethanol is identified as 1,4- DHPs in excellent yield. The obtained products were confirmed by FT-IR, $^1H$ and $^{13}C$ NMR and elemental analysis.

**Scheme: 4.1**

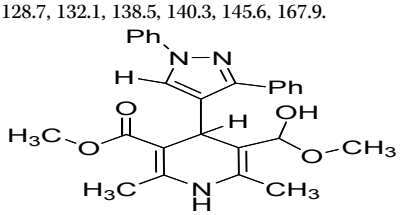



**4-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester:** Yield (337 mg, 92%) as a yellow solid, mp 196-198 °C;

In the IR spectrum (KBr, $cm^{-1}$) of exhibited characteristics of N-H, carbonyl, ester and aromatic carbons: 3323, 3264, 3083, 2930, 1685, 1625, 1495, 1311, 1021.

$^1H$ NMR (400 MHz, DMSO-$d_6$): 2.18 (s, 6H, Me), 3.14 (s, 6H, $CO_2Me$), 5.02 (s, 1H, pyridine CH), 7.21 (s, 1H, pyrazole CH), 7.33 (t, J 7.6 Hz, 2H, Ph), 7.44 (t, J 7.6 Hz, 1H, Ph), 7.68 (d, J 7.6 Hz, 2H, Ph), 8.83 (s, 1H, pyridine NH), 12.59 (brs, 1H, pyrazole NH).

In the $^{13}C$ NMR (100 MHz, DMSO-$d_6$) spectrum (ppm) showed the presence of thirteen signals attributed carbons. The signals resonated downfield at δ: 18.5, 28.7, 31.2, 99.8, 102.8, 127.6, 128.3, 128.7, 132.1, 138.5, 140.3, 145.6, 167.9.

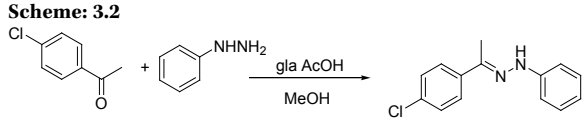


**1.2 Synthesis of 4-Chloro pyrazole aldehyde:**

**1.2.1 Synthesis of schiffs base:**

Glacial acetic acid (1 ml) and phenyl hydrazine (**2**) (20 mmol) were added to a solution of acetophenone **(1b)** (24 mmol) in 90 ml of ethanol. Then, the reaction mixture was refluxed for 1 h. The precipitate was filtered and recrystallized with ethanol (92%).

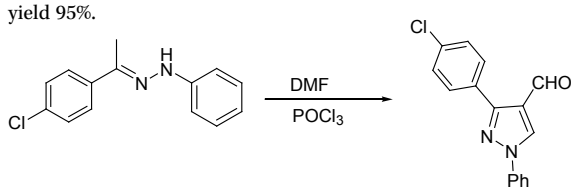
**Scheme: 3.2**




**1b** **2** **3b**

**1.2.2 Vilsmeier–Haack reaction:**

Dimethylformamide (35.3 mmol) and $POCl_3$ (35.3 mmol) were previous separately cooled at 0 °C before being stirred at such temperature. A solution of **3b** (11.76 mmol) in DMF (3 ml) was added drop wise to the reaction mixture which was, then warmed to r.t stirred over night. The mixture was basified with a cool saturated NaOH solution. The precipitate was filtered, strongly washed with water and recrystallized from ethanol, yield 95%.

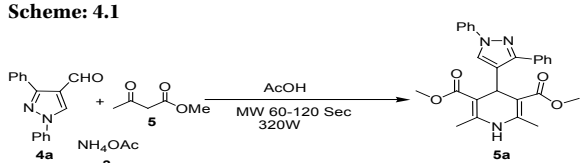



**3b** **4b**

**4.1 Synthesis of 4-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5- dicarboxylic acid dimethyl ester:**

A mixture of simple pyrazole aldehyde **(4a)** (5 mmol), methyl acetoacetate (10 mmol), ammonium acetate (10 mmol) and catalytical amount of acetic acid without solvent in a beaker kept at the center of the microwave oven (320 W) and irradiated for a period of 10 sec. After every irradiation (10 s), the beaker was removed from the microwave oven and stirred the reaction mixture. The completion of the reaction was checked by TLC (ethylacetate:hexane, 8:2). The total period of microwave irradiation was in the range of 60-120 s. The reaction mixture was then extracted with ethylacetate, organic layer washed with water and dried over anhydrous $Na_2SO_4$. Organic solvent was evaporated under reduced pressure and solid compound, which was crystallized from absolute ethanol is identified as 1,4- DHPs in excellent yield. The obtained products were confirmed by FT-IR, $^1H$ and $^{13}C$ NMR and elemental analysis.

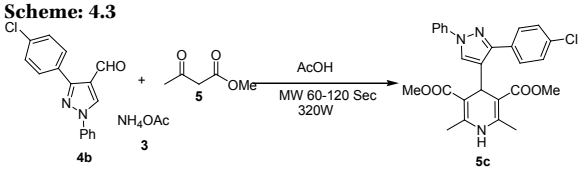
**Scheme: 4.1**




**4.3 Synthesis of 4-[3-(4-Chloro-phenyl)-1phenyl-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester:**

A solution of 4-Chloro pyrazole aldehyde **(4b)** (5mmol), methyl acetoacetate (10 mmol) and ammonium acetate (5 mmol) by the addition of a catalytic amount of glacial acetic acid and the reaction was kept in microwave. After completion of the reaction (TLC monitoring), ice-cold water was added to the reaction mixture and the precipitate was filtered. The products were recrystallized from ethanol. The obtained products were confirmed by FT-IR, $^1H$ and $^{13}C$ NMR.

**Scheme: 4.3**

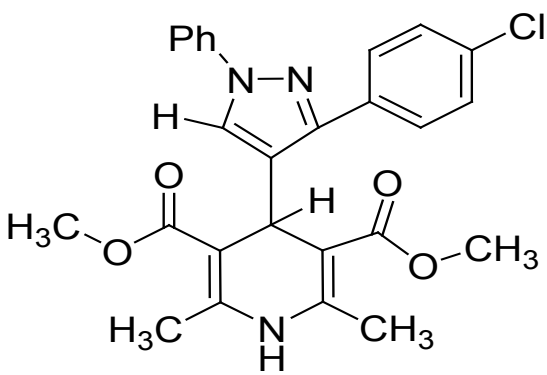



**4. Dimethyl 2,6-dimethyl-4-(3-[4-chlorophenyl]-1-phenyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4g):** Yield (443 mg, 93%) as a pale yellow solid, mp 149-150 °C;

In the IR spectrum (KBr, $cm^{-1}$) of exhibited characteristics of N-H, carbonyl, ester and aromatic carbons: 3320, 3013, 2972, 1693, 1596, 1305, 1032.

$^1H$ NMR (400 MHz, DMSO-$d_6$): 2.19 (s, 6H,Me), 3.85 (s, 6H, $CO_2Me$), 5.18 (s,1H, pyridine CH), 7.27 (t, J 8.0 Hz, 1H, Ph), 7.45 (t, J 8.0 Hz, 2H, Ph), 7.56 (d, J 8.1 Hz, 2H, Ph), 7.83 (q, J 8.1 Hz, 4H, Ph), 8.06 (s, 1H, pyrazole CH), 8.85 (s, 1H, pyridine NH).

In the $^{13}C$ NMR (100 MHz, DMSO-$d_6$) spectrum (ppm) showed the presence of thirteen signals attributed carbons. The signals resonated downfield at δ: 18.7, 29.3, 50.7, 102.3, 118.6, 126.6, 128.3, 128.6, 129.9, 130.2, 130.5, 132.6, 133.9, 139.8, 145.9, 148.9, 167.7.




**Antimicrobial Studies**

The antibacterial activity of compound 1 and 4 shows effect of concentration on Staphylococcus aureus with Ampicilin as a positive control and DMSO as a negative control. Inhibition zone data from **Table 2**, indicate that four compound showed considerable activity against Staphylococcus aureus and Escherichia coli at 1 mg/ml and 0.5 mg/ml concentrations. DMSO control showed a negligible activity and Ampicilin shows positive activity as compared with the compounds. Compound 4 showed the highest activity24 mm, 19 mm against Escherichia coli at the concentrations of 1 mg/ml and 0.5 mg/ml. The same compound also showed an activity of 21 mm, 16mm inhibition against *B. subtilis*. The compounds 1, 2 and 3 showed less activity against these bacteria than the four's compound. It is evident from our results that all four compounds possess antibacterial activity.

**Table 1 : Antibacterial Activities**

| compounds | Zone of inhibition (26-28 mm) | | | | | |
|---|---|---|---|---|---|---|
| | E. coli | | B. subtilis | | S. aureus | |
| | 0.05mL | 0.10mL | 0.05mL | 0.10mL | 0.05mL | 0.10mL |
| 1 | 10 | 21 | 10 | 21 | 12 | 19 |
| 2 | 12 | 16 | 15 | 24 | 15 | 20 |
| 3 | 10 | 23 | 13 | 22 | 14 | 15 |
| 4 | 19 | 24 | 16 | 21 | 14 | 17 |

**Docking simulations**

Molecular docking studies were carried out to determine the binding mode between compound and the protein (pdb code: 2HVP). This was used as templates for the docking studies. The aim was to study the nucleobase sequence selectivity by computer simulation. The relative orientation, interaction, Hydrogen bond and Vander Waals in the docked compound determined from the results of the docking study were analyzed using the graphical program Silver Visualizer 1.1. The views table 2 and fig 1, shows the different modes in which the compounds1 and 2 intercalated into the 2HPV protein.

**Table 2: Hydrogen bonding interactions, Bond lengths and Dock scores of 2HPV prptien with 1 and 2 compounds.**

| com-pounds | H –Bond Donor-Ac-ceptor | Bond Length (Å) | Vander Waals interactions | Bond Length (Å) | Gold Score |
|---|---|---|---|---|---|
| Com-pound 1 | N18-HIS488:ND1 | 2.816 | C20-HIS488:CB | 2.742 | -50.946 |
| | N18-HIS488:NE2 | 2.941 | C28-HIS488:ND1 | 2.056 | |
| | O11-ALA312:N | 3.059 | C32-LEU489:CG | 1.762 | |
| | | | C29-ASP313:N | 2.731 | |
| | | | N19-HIS488:ND1 | 1.762 | |
| | | | | | |
| Com-pound 2 | O1-ASP484:OD2 | 2.110 | C31-LYS481:O | 2.225 | -30.209 |
| | O14-ASP484:OD2 | 2.723 | C32-LYS481:C | 2.182 | |
| | O13-THR311:OG1 | 2.813 | C33-THR:485:OG1 | 2.195 | |
| | | | C35-ALA312:N | 2.597 | |

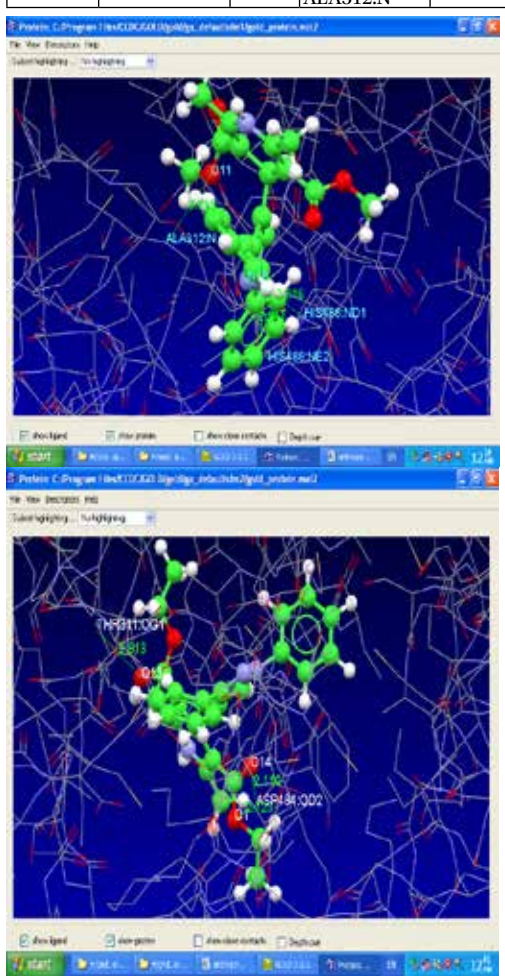


**Fig. 1. Interaction between compounds and 2HPV protein. Compounds 1&2 shown in Green color**

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**CONCLUSION**

In summary, the present method is very simple, mild and efficient for the synthesis of 1,4-DHPs. In addition, this protocol has advantages in terms of short reaction time, solvent-free reaction, high yield, easy work-up and eco-friendly. We believe that this method is a useful addition to the present methodology for the synthesis of 1,4-DHPs.

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