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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 , Spectral Studies

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ABSTRACT

A highly efficient environment-friendly one-pot synthesis of Dimethyl-2,6-dimethyl-4-[3-phenyl-1H-pyrazol-4-yl]-1,4-dihydropyridine-3,5-dicarboxylate, Diethyl-2,6-dimethyl-4-[3-phenyl-1H-pyrazol-4-yl]-1,4-dihydropyridine-3,5-dicarboxylate, Dimethyl-2,6-dimethyl-4-(3-[4-chlorophenyl]-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate, Diethyl-2,6-dimethyl-4-(3-[4-chlorophenyl]-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate were prepared successfully from defferent pyrazole aldehydes using ammonium acetate and β-keto ester or 1,3-diketone in presence of acetic acid gave good yields.

Introduction

In recent decades, multicomponent reactions (MCR's) have gained wide applicability in the field of synthetic organic chemistry as they increase the efficiency of the reaction and decrease the number of laboratory operations along with quantities of solvent and chemicals used. These methods also considerably reduce the reaction time and facilitate the yield of products than the normal multiple step methods. One-pot, four-component synthesis of symmetrically substituted 1,4-dihydropyridines were first reported by Arthur Hantzsch in 1882 [1]. Hantzsch 1,4-dihydropyridines (1,4-DHPs) and their derivatives are an important class of bioactive molecules in the pharmaceutical field [2]. They possess antiinflammatory, anti-microbial [3], anti-oxidant, antiulcer activities [4]. DHPs are commercially used as calcium channel blockers for the treatment of cardiovascular diseases, including hypertension [5]. Recently, the synthesis of DHPs with respect to Multidrug Resistance (MDR) reversal in tumor cell gave a new dimension to their applications [6,7]. In addition,1,4-DHP class of compounds are excellent starting synthons for development of antitubercular agents [8,9]. Oxidative aromatization reactions of DHPs are taking place in biological systems in presence of certain enzymes. The nitrogen heterocycles thus prepared by Hantzsch method are of great importance because of their role in biological systems. They have been served as model compounds for the NAD-NAPH biological redox systems [10e12]. Recently, antibiotic-resistant microbes are making their inexorable march and medicinal chemists have now realized that the discovery of more powerful antibiotics is not the only answer to this threat. But, a real need exists in searching a novel antimicrobial that expresses antimicrobial properties, possibly acting through mechanisms different from those of existing drugs. In this context, it is very essential to successfully develop novel, efficient antimicrobial agents with clinically unexploited mode of action. Further, pyrazole derivatives have showed significant biological activities, such as anti-microbial [13], analgesic [14], anti-inflammatory [15] and, anticancer [16]. This gave a great impetus to the search for potential pharmacologically active drugs carrying pyrazole substituents. Keeping in view of this and in continuation of our search on biologically potent molecules [17e21], we hereby report the synthesis of some new 1,4-dihydropyridine derivatives containing pyrazole nucleus. These compounds were evaluated for their antimicrobial and antioxidant properties.

Experimental .

Chemicals and Reagents

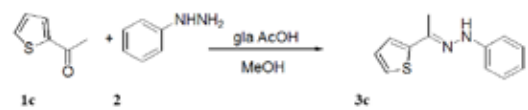
The tested derivatives were prepared at the Department of Chemistry, University college of Science, Osmania University. Phenyl hydrazine and acetophenone for the synthesis was obtained from Sigma–Aldrich Ltd. India. For the antimicrobial assay, all solutions were prepared in distilled, sterile water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

1.3 Synthesis of thiophene pyrazole aldehyde:

1.3.1 Synthesis of schiffs base:

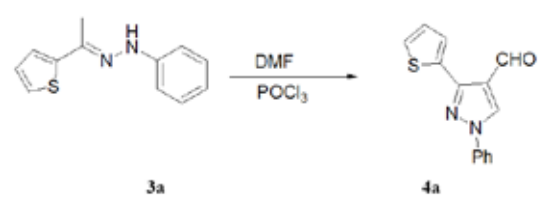
Glacial acetic acid (1 ml) and phenylhydrazine (**2**) (20 mmol) were added to a solution of acetothiophene **(1c)** (24 mmol) in 90 ml of ethanol. Then, the reaction mixture was refluxed for 1 h. The precipitate was filtered and recrystallized with ethanol (92%).

Scheme: 3.3



1.3.2 Vilsmeier–Haack reaction:

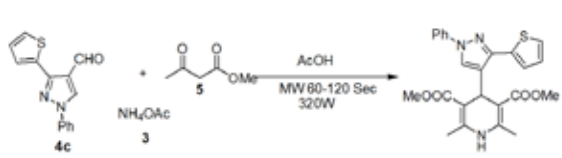
Dimethylformamide (35.3 mmol) and $POCl_3$ (35.3 mmol) were previous separately cooled at 0 °C before being stirred at such temperature. A solution of **3c** (11.76 mmol) in DMF (3 ml) was added dropwise to the reaction mixture which was, then warmed to r.t stirred over night. The mixture was basified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



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

To a solution of Thiophene pyrazole aldehyde **(4c)** (5mmol), methyl acetoacetate (10 mmol) and ammonium acetate (5 mmol) was added 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: 4.5



4. 4-[3-(4-Bromo-phenyl)-1phenyl-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yield (443 mg, 93%) as a pale yellow solid, mp 149-150 °C; In the IR spectrum (KBr, cm^{-1}) of exhibited characteristics of

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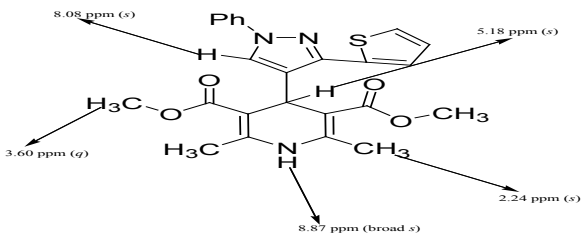
N-H, carbonyl, ester and aromatic carbons: 3320, 3013, 2972, 1693, 1596, 1305, 1032.

^{1}H NMR (400 MHz, DMSO-d_6): 2.24 (s, 6H,Me), 3.60 (s, 6H, CO_2Me), 5.18 (s,1H, pyridine CH), 7.26 (t, J 8.0 Hz, 1H, Ph), 7.40 (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), 8.08 (s, 1H, pyrazole CH), 8.87 (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.

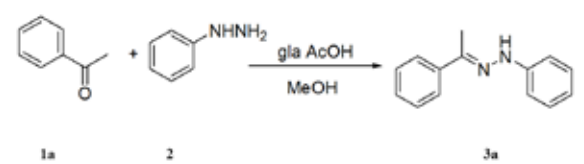


1.1 Synthesis of Simple pyrazole aldehyde:

1.1.1 Synthesis of schiffs base:

Glacial acetic acid (1 ml) and phenylhydrazine (**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%).

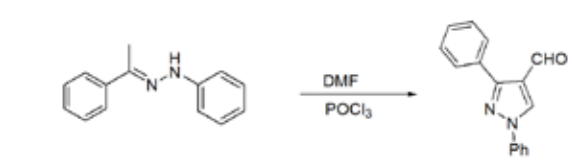
Scheme: 3.1



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 dropwise 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%.



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

A mixure of simple pyrazole aldehyde **(4a)** (5mmol), ethyl 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, ^{1}H and ^{13}C NMR.

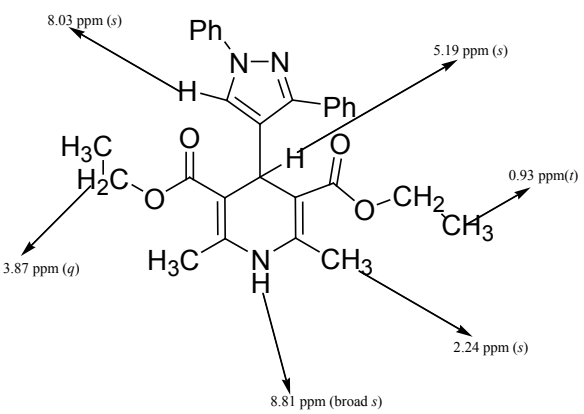
Scheme: 4.2

4-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester: Yield (352 mg, 89%) as a pale yellow solid, mp 216-218 °C;

In the IR spectrum (KBr, cm^{-1}) of exhibited characteristics of N-H, carbonyl, ester and aromatic carbons: 3325, 3261, 3081, 2950, 1672, 1300, 1145, 1022.

^{1}H NMR (400 MHz, DMSO-d_6): 0.93 (t, J 7.7 Hz, 6H, CO_2CH_2Me), 2.24 (s, 6H, Me), 3.81 (q, 2H, CO_2CH_2Me), 5.19 (s, 1H, pyridine CH), 7.29 (s, 1H, Ph), 7.39 (t, J 7.7 Hz, 2H, Ph), 7.81 (t, J 7.6 Hz, 1H, Ph), 7.93 (d, J 7.7 Hz, 2H, Ph), 8.03 (s, 1H, pyrazole H), 8.81 (brs, 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: 14.5, 18.7, 28.7, 59.3, 103.2, 125.9, 127.9, 128.3, 128.6, 132.0, 138.1, 141.2, 145.4, 167.6.



Acknowledgments

The project work embodied in this thesis has been carried out in the Department of Chemistry, Osmania university, Hyderabad, under the supervision of **Prof.V.Prabhakar Reddy,** Department of Chemistry, Osmania university, Hyderabad.

Conclusion

In conclusion, we have developed an easy and efficient method to prepare a variety of 2-amino-4-phenyl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives from the reaction of different aryl aldehydes, dimedone, malononitrile and ammonium acetate in the presence of catalytic amount of MTSA at 60 ◦C under solvent-free conditions and produced the corresponding products in good to excellent yields. Also the catalyst could be successfully recovered and recycled at least for four runs without significant loss in activity. The one-pot nature and the use of reusable and an eco-friendly catalyst make it an inter-

esting alternative to multi-step approaches.

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