IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# One Pot Multicomponent Synthesis Of 1,4-DHP Derivatives By Using Hantzsch Reaction

**Ashwin U. Rahangdale[1], D. P. Kawade[2], Aniqua T. S. Sheikh[3], Anirudh S. Mishra[4]**

Department of pharmaceutical chemistry, Priyadarshini J.L College of pharmacy, Nagpur, Maharashtra, India.

**Abstract**

Dihydropyridine derivatives were synthesized via a unique, environment friendly, and highly effective one-pot multicomponent process, which produced a good to wonderful yield. An important class of low molecular weight heterocyclic scaffolds is represented by 1, 4-dihydropyridines and their derivatives. The Hantzsch pyridine synthesis was completed quickly at room temperature in solvent-free condition using various 1,3-diones and the same starting ingredient aldehyde derivatives such as 5-bromothiophene-2-carboxaldehyde and ammonium acetate in the presence of the catalyst ceric ammonium nitrate (CAN). Interestingly, we discovered that just one of the compounds had excellent antifungal activity against Candida albicans when compared to griseofulvin, while all the compounds were assessed for their in vitro antibacterial and antifungal activities. Every chemical has had its cytotoxicity evaluated using cell lines from breast tumours.

**Keywords:** one-pot multicomponent, Heterocyclic scaffolds, 1, 4-dihydropyridines, ceric ammonium nitrate, Hantzsch reaction.

## Introduction

First described by Arthur Hantzsch in the 19th century, the Hantzsch synthesis is a commonly used 3CR for the direct synthesis of derivatives of 1,4-dihydropyridine (DHPs) (1882). Many DHPs are well known for their biological activity as calcium channel blockers, while they also exhibit a wide range of additional pharmacological properties that have been identified for multiple DHPs, such as antidiabetic, bronchodilator, anticancer, and HIV protease inhibitors [1,2,3]. Remarkably, due to the similarity between DHPs and the natural product enzyme co-factors NAD(P)H and their oxidized forms NAD(P), the Hantzsch adducts, also called Hantzsch esters, have been demonstrated to have a significant potential as hydride (or hydrogen) transfer reagents [4,5]. These reactions have multiple asymmetric variants of the H-transfer mechanism, each with improved enantioselectivities.

The Hantzsch MCR's sensitivity is affected by a number of variables, including the presence or absence of a solvent, catalyzed or non-catalyzed versions, substituent effects on the reagents, reaction time, temperature, and the presence of an acid or base [6,7,8,9]. As a result, alternative compounds have been developed rather than the Hantzsch ester after adverse reactions were discovered and thoroughly documented under more favorable conditions. With varied new active functional groups in their primary skeleton, a number of therapeutically significant medications, including amlodipine, felodipine, isradipine, nicodipine, and nifedipine, entered the market. Lately, numerous initiatives have been made to enhance the Hantzsch reaction

by various alternative methods [10]. But in the last ten to fifteen years, the majority of these reactions have been described with new trends as one-pot multicomponent reactions (MCRs) [11,12].

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Over the past ten years, there has been a growing interest in the synthesis of thiazolo pyridine, a nitrogen-containing heterocyclic aromatic chemical, due to its numerous applications in pyrotechnics, propellants, explosives, and chemotherapy, among other fields [15]. Due to the synthetic and biological significance of triazolo pyridine and its fused aromatic heterocyclic derivatives in several heterocyclic aromatic compound areas, there has been a significant focus on their chemistry in the present day. An antiviral medication containing thiazolo pyridine's nucleus has been developed to stop the spread of malignant tumor cells. Thiazolopyridine's nucleus is one of the most important heterocyclic aromatic compounds and the building block of numerous natural products and pharmaceuticals. The phenomenon where substitution of a pyridine ring with a thiazolo leads to derivatives [16,17].

Promastigote and amastigote forms have been tested against a range of 1,4-dihydropyridine (DHP) compounds that have been produced. Comparing the compounds to the reference medication, amphotericin B, all displayed increased activity. But compared to the reference medication glucantime, they showed less activity. Under low nanomolar and low micromolar concentrations, these substances exhibited outstanding anti-promastigote and anti-amastigote properties [18].

**Physicochemical characteristics of pyridine**

- **Formula:** $C_5H_5N$
- **Molar mass:** 81.12 g/mol
- **IUPAC Name:** Azabenzene, Azine
- **Appearance:** Colourless to pale yellow crystals or oily liquid
- **Density:** 1.1-1.2 g/cm³
- **Boiling point:** 210-220°C
- **Solubility:** In alcohol, ether and miscible with water
- **Melting point:** 175-180°C
- **Log P:** 0.5-2.5

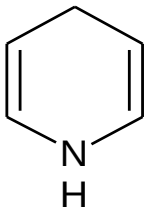



**Fig.1. 1,4-Dihydropyridine**

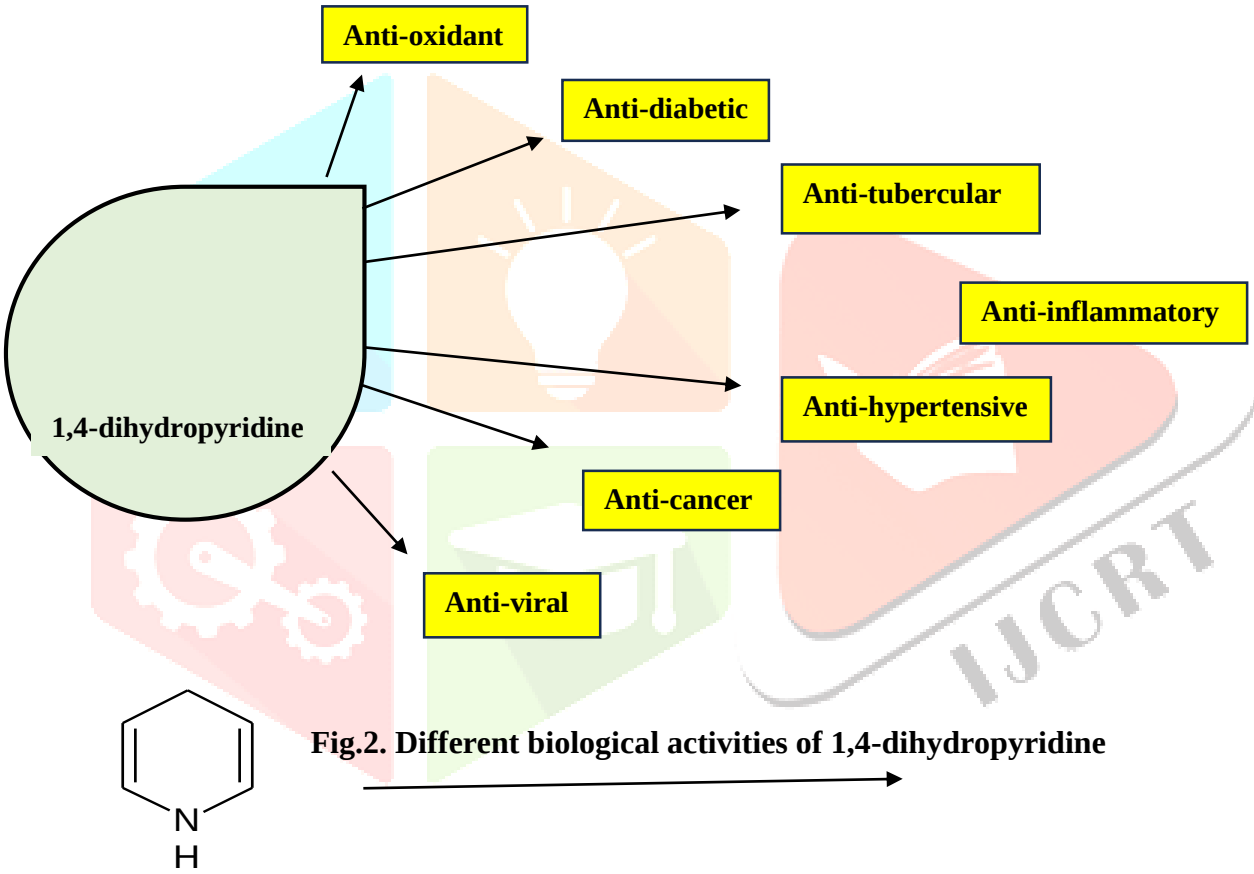
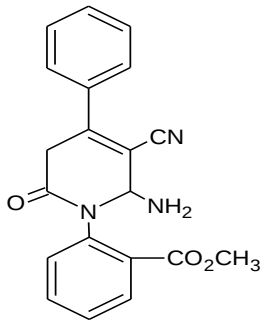
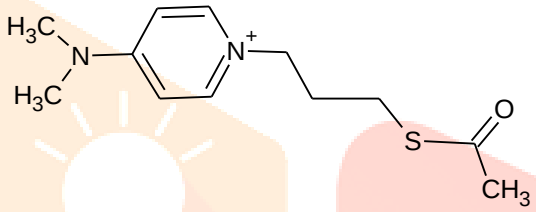
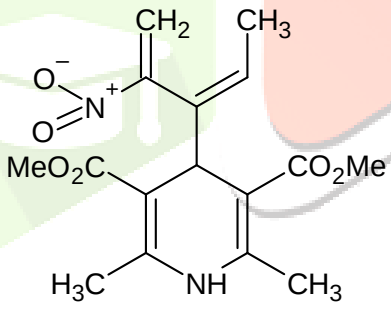


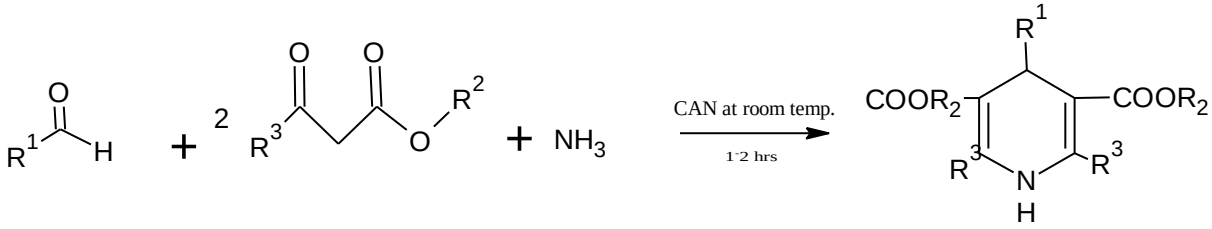

**Fig.2. Different biological activities of 1,4-dihydropyridine**

**Table.1. Literature Review**

| Sr. no. | Author | Derivatives | Biological activity |
|---|---|---|---|
| **1.** | M.H. Helal a,b, S.A. El-Awdan c, M.A. Salem a,d, T.A. Abd-elaziz a, Y.A. Moahamed a, A.A. El-Sherif |  methyl 2-(6-amino-5-cyano-2-oxo-4-phenyl-3,6-dihydropyridin-1(2*H*)-yl)benzoate | **Anticancer activity** |
| **2.** | Anwar A., Khalid S., Perveen S., Ahmed S., Siddiqui R., Khan N.A., Shah M.R. |  4-(dimethylamino)pyridinepropylthioacetate | **Antimicrobial activity** |
| **3.** | Marudai Balasubramanian |  dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate | **Antihypertensive activity** |

## Material & methods

**Scheme:** Synthetic pathway for the synthesis of 1,4-dihydropyridinr derivatives.



**Substituted Aldehyde** **β-diketone** **Ammonia** **Substituted 1,4-dihydropyridine**

**Synthetic Procedure**

5-Bromothiophene-2-carboxyaldehyde (1.91 g, 0.01 mol), ammonia (0.77 g, 0.01 mol), different 1,3-diones (1–2.5 g, 0.01/0.02 mol) and CAN (0.28 g, 0.5 mmol) were added to a 100 ml round bottom flask. The mixture was stirred well for 1–2.5 h at room temperature, then the product was poured out and the mixture became solid. The progress of the reaction was monitored by TLC. The product was washed with water and then treated with n-hexane to remove impurities; after drying, the crude brown/yellow product was recrystallized using ethanol followed by charcoal treatment.

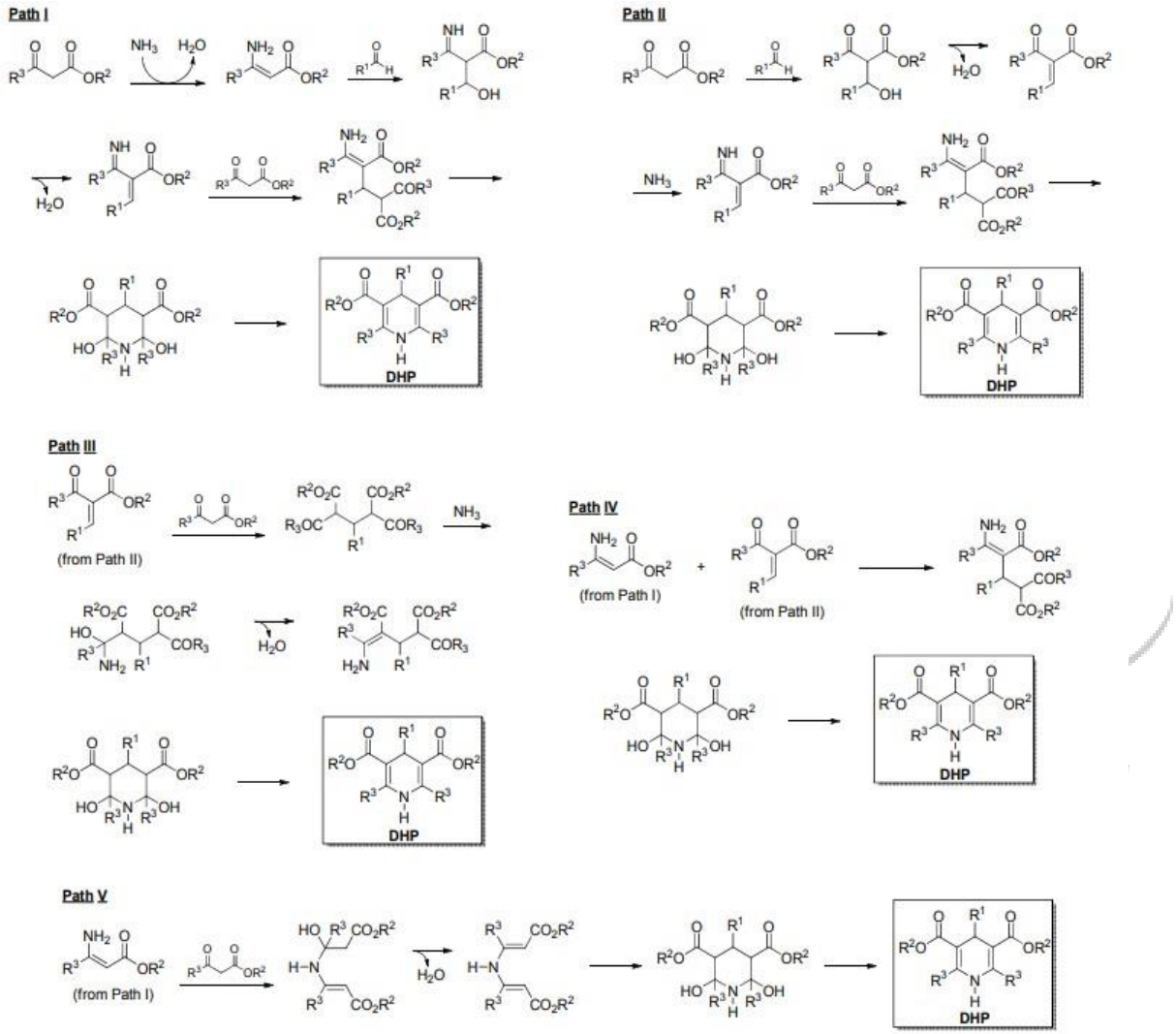



**Fig.3.** Mechanism of action for Hantzsch multicomponent reaction.

## Conclusion

According to the literature survey, Hantzsch reaction is a well-organized solvent-free green procedure for the multicomponent synthesis of dihydropyridine derivatives using the catalyst CAN. Solvent-free procedure is more efficient than the conventional method. The advantages of the Hantzsch pyridine synthesis are shorter reaction times, simplicity of the reaction, good product yield and easy workup procedures with regard to the build-up to the reaction, which is economical and easy, with CAN being a powerful catalyst for the many organic syntheses. The cytotoxicity of all the compounds has been assessed against breast tumour cell lines (BT-549), but no activity was found.

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