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Study of 1,4 Dihydropyridine derivative for Antifungal Activity

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Abstract

1,4 Dihydropyridines are very versatile compounds and have very important role as therapeutic agents. The 1, 4 Dihydropyridines (1,4 DHPs) are well known as calcium channel blocker and their use in treatment of cardiovascular diseases is very common. These compounds are also known to have antimicrobial activities. The 1,4 DHPs are N-heterocyclic compounds represent very important framework for agricultural and pharmaceutical industries. These are also known to have antibacterial and antifungal activities. Hence, the substituted 1,4- Dihydropyridine derivate was synthesized in presence of tetra butyl ammonium bromide catalyst and evaluated for its antifungal activity.

Keywords: Ammonium acetate, 4-chloro Benzaldehyde, ethylene glycol, antifungal, Agar nutrient

Introduction

Dihydropyridine are known to have very important role in biological activity. The most important biological activity associated with 1,4 Dihydropyridine is to target L-type calcium channel with highest calcium antagonistic properties. They are used in treatment of cardiovascular disease and hypertension [1, 2]. The clinical and experimental studies reveals that substituted dihydropyridines are able to reduce the risk of developing neurodegenerative diseases and can work as antioxidants, Neuroprotective and cardio protective agents [3, 4]. Interest in 1,4-dihydropyridines also relates to nicotinamide adenine dinucleotide (NADH), a coenzyme, and its unique ability to reduce many functional groups in biological systems. The development of new drugs for the treatment of multi drug resistant tuberculosis (MDR TB) is the top priority area of most of the developing countries in the world today. It was reported that the dihydropyridines also have resistance reversal properties and antitubercular activities [5, 6]. Further, 1,4-dihydropyridines serve as NADH mimics and this enzyme has great significance for developing new anti-TB drugs as it is involved in biosynthesis of mycobacterial cell wall polymers with others ACP reductase, enoyl-ACP reductase in presence of Mn^{2+} . One of the well-established TB drug Isoniazid (INH) with pyridine nucleus, has been known to affect mycobacterial fatty acid biosynthesis as a mimic of NADH. Therefore study of 1,4 dihydropyridines is an important research area for the medicinal chemist.

Dihydropyridine nucleus is very common in many drugs like Vasodilator, bronchodilator, anti-atherosclerotic, antitumor, antidiabetic and hepatoprotective agents [7, 8]. These are known to act as neuroprotectants anti-platelet aggregators. Dihydropyridines are also very important in the treatment of Alzheimer's disease and used as anti-ischemic agents [9-11]. It is interesting to note that an enzyme Nicotinamide Adenine Dinucleotide (NADH) is also related to 1,4 Dihydropyridine nucleus. This co-enzyme play very important role in biological system. Within cardiovascular system calcium is involved in the activation of cardiac cells, the genesis of the action potential, the coupling electrical activation to myocardial contraction of vascular smooth muscle. Thus the multidimensional and multifunctional effects of 1,4-DHPs were explained by its structural variations scaffolds with appropriate substituent, capable of interacting with different receptors and ion channels. During the last decade, interest has arisen to neurotropic effects of different 1,4-DHPs and these are able to penetrate the blood-brain barrier and reduce the risk of developing neuro-degenerative diseases. In addition to this role of 1,4-DHPs as insecticides like Isradipine are found to be beneficial for the Alzheimer's disease treatment strategy [12, 13]. Antibiotics have a killing effect on wide range of microbes. The range of bacteria or other microorganisms that is affected by a certain antibiotic is expressed as its spectrum of action.

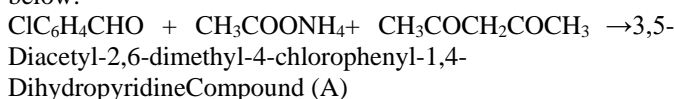
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Therefore in continuation of my work on dihydropyridines, it was thought to synthesize substituted 1,4 Dihydropyridine derivative to investigate its pharmacological importance. Since such compounds are known to have potent antibacterial activity against gram-negative bacteria and high antifungal activity against *Candida albicans* [14, 15], thus its antifungal activity was investigated in this present study.

Dihydropyridine derivatives have been synthesized by several methods. Generally three component reaction between an aldehyde, nitrogen containing compound and beta diketo compounds are used to prepare 1,4 Dihydropyridines. One of the oldest method is Hantzsch synthesis in which many researchers have done modifications to make the method more effective, less toxic and to increase the yields. Thus looking into the pharmacological importance of this class of compounds the present study involves synthesis of substituted 1,4-Dihydropyridine and its bioevaluation.

Material and Methods

Many earlier reported methods for the synthesis of 1,4 dihydropyridines involve modified Hantzsch synthesis using catalysts [16-19]. In the present work 1,4-Dihydropyridine derivative (3,5-Diacetyl-2,6-dimethyl-4-chlorophenyl-1,4-Dihydropyridine) has been synthesized by the reaction of aromatic aldehyde i.e. 4-chlorobenzaldehyde, ammonium acetate and acetyl acetone in presence of ecofriendly solvent ethylene glycol. For this first to the magnetically stirred slurry of 4 Å molecular sieve in ethylene glycol, Acetyl Acetone and Ammonium Acetate was added at room temperature, the reaction mixture was then heated and followed by addition of 4-chlorobenzaldehyde and tetra butyl ammonium bromide (TBAB) as a phase transfer catalyst and stirring continued till the 4-chloro benzaldehyde was disappeared. The completion of reaction was checked by thin layer chromatography and after 2.5 hrs the reaction mixture was poured into the cold water and the crude product obtained was then filtered and dissolved in suitable solvent. Anhydrous Sodium sulphate was then added to absorb the moisture and filtered. The crude product obtained was dried and weighed. The product obtained was purified by column chromatography and characterized by elemental analysis and spectroscopy. The reaction involved in synthesis of compound (A) was given below:



Antimicrobial Activity

Synthesized compound (A) was evaluated for its Antimicrobial activity. 200 mg /ml (in DMSO) dilution was prepared.

Microorganism used

Fresh culture of following fungi were used in the study:

1. *Aspergillus Niger*
2. *Aspergillus tereus*
3. *Aspergillus japonicus*
4. *Penicillium chrysogenum*

Antimicrobial Assay

The agar well diffusion method was used. One ml of diluted inoculum (10⁵CFU/ml) of test organism was mixed on Sabraud's agar media for fungus, shaken and pour in sterilized Petri plates. The wells of 8 mm diameter were punched into the agar medium. To each well 200mg/ml

compound was added and allowed to diffuse, each compound was tested against each organism in triplicate set.

The antimicrobial activities were then tested for each compound and recorded as diameter of the zone inhibited in mm by our test compound (A). Antifungal activity against the fungus: *Aspergillus Niger*, *Aspergillus tereus*, *Penicillium chrysogenum*, *Aspergillus japonicus* is given in table 1.

Table 1: The Antifungal activity of compound (A)

S. No.	Test organisms	Concentration of compound (A)	Zone of inhibition in (mm)
1.	<i>Aspergillus niger</i>	200mg/ml	15 mm
2.	<i>Aspergillus tereus</i>	200mg/ml	14 mm
3.	<i>Penicillium chrysogenum</i>	200mg/ml	22 mm
4.	<i>Aspergillus japonicus</i>	200mg/ml	20 mm

Results and Discussions

The synthesised compound A, ie 3,5-Diacetyl-2,6-dimethyl-4-chlorophenyl-1,4-Dihydropyridine was evaluated for antifungal activity. The fungal strains used as organisms are *Aspergillus niger*, *Aspergillus tereus*, *Aspergillus japonicus* and *Penicillium chrysogenum*. The compound was dissolved in DMSO and 200mg/ml concentration was made and inoculated to the test organism, after 72 hours a portion of fungal colony was killed by the test sample and this was appeared as clear zone around the test compound (A). This zone was measured in mm scale and the result obtained are 15 mm (*Aspergillus niger*), 14 mm (*Aspergillus tereus*), 20 mm (*Aspergillus japonicus*) and 22mm (*Penicillium chrysogenum*) as given in above table 1.

Conclusion

The synthesized compound (A) 3,5-Diacetyl-2,6-dimethyl-4-chlorophenyl-1,4-Dihydropyridine was synthesized in quantitative yield and it was evaluated for antifungal activity. The maximum inhibition was observed against *Penicillium chrysogenum*.

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