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Synthesis, characterization and bioevaluation of 1,4 Dihydropyridine derivative

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Abstract
1,4 Dihydropyridine is a very feasible heterocyclic ring with various substituents at different positions. Many drugs are known to have Dihydropyridine nucleus like Vasodialator, bronchiodialator, anti-atherosclerotic, antitumar, antidiabetic and hepatoprotective agents. Dihydropyridine is a multifunctional compound and a lead molecule in the area of drug discovery. They are known to have resistant reversal property and the most important biological activity associated with 1,4 Dihydropyridine are calcium channel blocker so they are used in treatment of cardiovascular diseases. Further such compounds are also known to have antimicrobial activities as antibacterial and antifungal agents. Therefore the studies was carried out to synthesize the substituted 1, 4- Dihydropyridine derivate and to see the effect of compound against gram positive and gram negative bacteria. Its antibacterial activity was investigated under present study.

Keywords: 4-chloro benzaldehyde, ammonium acetate, antibacterial, ethylene glycol

Introduction
Dihydropyridine (DHP) is a six membered heterocyclic ring containing N at 1 position. This class of compounds have very important role in biological activity. It is very feasible at 4 position for substitution. It has been found that dihydropyridine ring is very important for its biological activity. The most common biological activity associated with 1,4 Dihydropyridine are calcium channel blocker and their use in treatment of cardiovascular disease and hypertension [1, 2]. Dihydropyridine nucules is very common in many other drugs like antihypertensive, antianginal, bronchodilator, antitumar, antidiabetic and hepatoprotective agents [3-5]. These are also known to act as neuroprotectants anti-platelet aggregators. Some 1,4 Dihydropyridines (DHPs) are reported as antioxidants, antitubercular and known to have drug reversal property [6-9]. DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure. The resemblance of 1,4-dihydropyridines with nicotinamide adenine dinucleotide (NADH), a coenzyme involved in hydrogen transfer reactions in biological processes to reduce many functional groups in biological systems attracts the attention of medicinal chemists working in the area of drug discovery. Many researchers have been reported the therapeutic importance of 1,4 dihydropyridine derivatives and many existing drugs contain its nucleus as basic scaffolds for their biological activity. For the study of antimicrobial activity the role of antibiotics against the various bacterial strains is important. Antibiotics are low-molecular weight substances that are produced as secondary metabolites by certain groups of microorganisms, especially Streptomyces, Bacillus, and a few molds (Penicillium and Cephalosporium) that are inhabitants of soils. Antibiotics may have a cidal (killing) effect or a static (inhibitory) effect on a range of microbes. The range of bacteria or other microorganisms that is affected by a certain antibiotic is expressed as its spectrum of action. Therefore, 1,4 Dihydropyridine derivatives have been synthesized for their pharmocological importance. These are new class of compounds reported to have very potent antibacterial activity against gram-negative bacteria and high antifungal activity against *Candida albicans*. Such compounds have been investigated for various other bacteria like *Staphylococcus epidermis* and found to have binding interaction with its protein. Hence, the scientific community found the 1,4, Dihydropyridine derivatives a new class of compounds as antibacterial and antifungal agents [10-12].

Review of Literature
Since the first report of the Hantzsch synthesis for 1,4-dihydropyridines a number of strategies have been developed for their synthesis due to their important biochemistry and biological

activities. The prominent biological activities associated with 1,4-dihydropyridines are as Ca^{++} channel blockers and their role as drugs for the treatment of cardiovascular diseases and hypertension [13, 14]. Some drugs have dihydropyridine nucleus such as, nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris. Nislodipine is a also potent vasodilator and nimodipine exhibits selectivity for cerebral vasculature [15]. These molecules are also known to have antihypertensive, antidiabetic, antitumor, anti-inflammatory, analgesic and antitubercular activities, Many of the existing drugs or molecules in clinical trials possess this dihydropyridine skeleton as shown in Figure 1. Further, pyridine a heterocyclic nucleus played a pivotal role in the development of different medicinal agents. After considering the success of noble insecticides belonging to group neoticotinoids [16, 17] like imidacloprid and nicotine noble derivative of pyridine have been developed and used as insecticide agents. It is seem that pyridine congeners are associated with different biological properties like pesticidal, insecticidal and fungicidal activity [18-19].

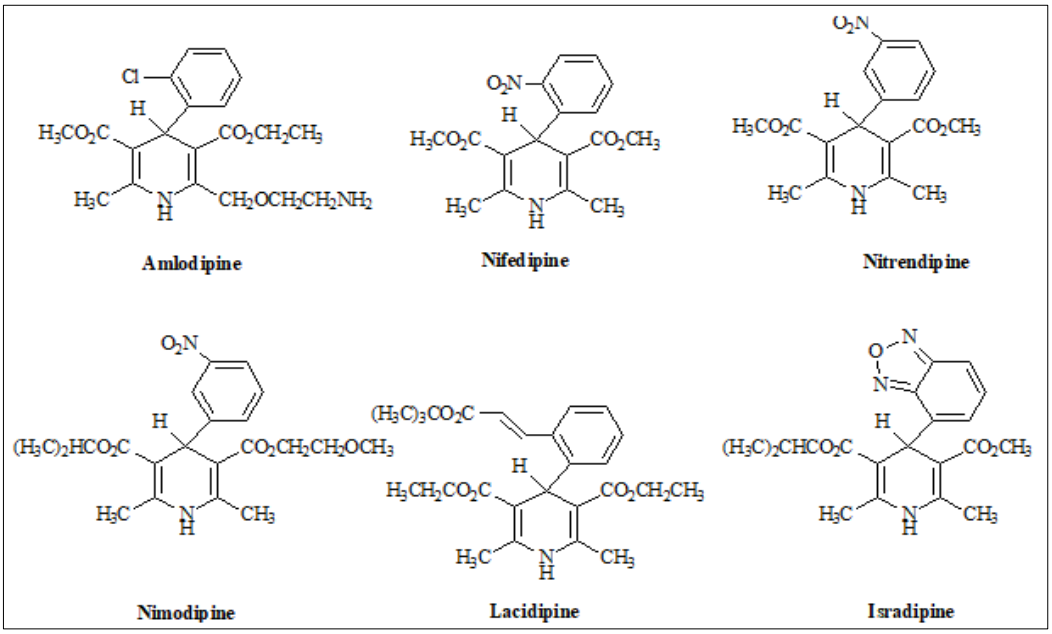

Fig 1: Dihydropyridines based drugs or candidate drugs

Dihydropyridines, in general, have been synthesized by several methods including Hantzsch ester synthesis; reduction of pyridines and pyridinium salts; nucleophilic addditions to pyridines or pyridinium salts; synthesis via rearrangements, fragmentations and cycloadditions; and insertion reactions and using catalysts like TBAHS [20-23].

Alternative strategies for the synthesis involving different catalysts and conditions are known but some of them suffer from one or more drawbacks like low yields, use of costly reagents and drastic reaction conditions. The method for the synthesis of glycosyl dihydropyridines was reported earlier but required a very high temperature and DMF as solvent with 48 hrs refluxing, and the yields were not high in every reaction. Some other methods encountered use of catalyst and solvent less approach for the synthesis of 1,4-dihydropyridines [24, 27]. Some DHPs showed activity against the bacteria like *Staphylococcus epidermis* and found to have binding interaction with its protein [28]. Hence, the scientific community found the 1,4, Dihydropyridine derivatives a new class of compounds as antibacterial and antifungal agents. In continuation of our earlier work on dihydropyridines, it was thought to synthesize 1,4 Dihydropyridine derivatives for its biological activity against various strains of bacteria.

Aim of Study

1, 4-Dihydropyridines (1, 4-DHPs) are very important class of compounds in the field of drugs and pharmaceuticals. Interest in 1,4-dihydropyridines is due to nicotinamide adenine dinucleotide (NADH), a coenzyme, with unique ability to reduce various functional groups in biological systems. In the view of its pharmacological importance in this present study substituted 1,4-Dihydropyridine derivative was synthesized and its characterization and bioevaluation was done to explore the importance of this class of molecules.

Material and Methods

In the present work, 1, 4 Dihydropyridine derivatives has been synthesized by an efficient method. One mole of 4-chlorobenzaldehyde on reaction with two mole of β-keto compound, acetylacetone and one mole of ammonium acetate in the presence of eco friendly solvent ethylene glycol underwent condensation reaction and led to the formation of 1,4 dihydropyridine (compound) in quantitative yield. In above method 4 A˚ molecular sieves play very important role to carry out the reaction in forward direction by simultaneous absorption of water released during the condensation reaction. To the magnetically stirred slurry of 4A° molecular sieve (400mg) in ethylene glycol (20 ml), Acetyl Acetone (4,39 ml,42.6 mmol) and Ammonium Acetate (1.645gm,) was added at room temperature, the reaction mixture was heated followed by addition of 4-choloro benzaldehyde (3 gm, 21.3 mmol) and tetra butyl ammonium bromide (TBAB) as a phase transfer catalyst (500mg) and stirring continued till the 4-chloro benzaldehyde was disappeared. After 2.5 hrs the reaction was completed. The reaction mixture was then poured into the cold water, and the obtained product was filtered and dissolved in suitable solvent (chloroform) and anhydrous sodium. Sulphate (Na_2SO_4) was then added to

absorb the moisture and filtered. The crude product obtained after evaporation of solvent under reduced pressure and weighed. The product obtained was purified by column chromatography. The reaction involved in synthesis of compound was given in Figure 2 below.

$ClC_6H_4CHO + CH_3COONH_4 + CH_3COCH_2COCH_3 \rightarrow$ 3,5-Diacetyl-2,6-dimethyl-4-chlorophenyl-1,4-Dihydropyridine (compound)

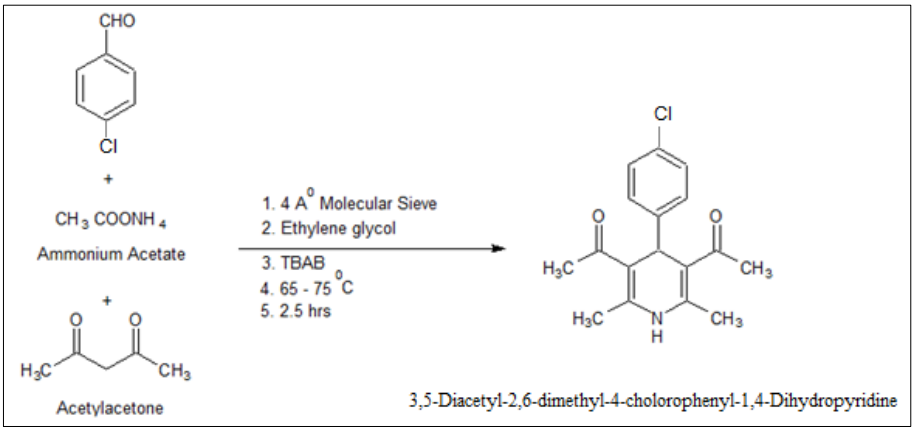

Fig 2: Synthesized Compound (3,5-Diacetyl-2,6-dimethyl-4-chlorophenyl-1,4-Dihydropyridine)

Antimicrobial Activity

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

Microorganism used

Fresh culture of following bacteria were used in the study:

Bacterial Strains

1. *E. coli*
2. *Staphylococcus aurous*
3. *Proteus mirabilis*
4. *Bacillus cereus*

Antimicrobial Assay

Bioevaluation of the compound has been carried out by using agar well diffusion method. One ml of diluted innoculums (105CFU/ml) of test organism was mixed on the Muller Hinton agar media (for bacteria) and Sabraud's agar (for fungus), shaked and pour in sterilized Petri plates. The wells of 8mm 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 plate were then incubated aerobically 37 °C for the bacteria stains for 24 hrs and at 27 °C for fungi for 72 hrs.

The antimicrobial activities were then tested for each compound and recorded as diameter of the zone inhibited in mm by our test compound. Antimicrobial activity against the bacteria: *Bacillus cereus*, Staphylococcus *aureus*, *Proteus*, *E. coli* are given in table 1.

Table 1: The Antibacterial activity of compound

S. No.	Bacterial species	Gm strain	Concentration	Inhibition zone (mm)
1.	*Bacillus cereus*	Gram positive	200 mg/ml	18 mm
2.	*Staphylococcus aureus*	Gram positive	200 mg/ml	19 mm
3.	*Proteus mirabilis*	Gram negative	200 mg/ml	-
4.	*Escherichia coli*	Gram negative	200 mg/ml	15 mm

Results and Discussions

The compound was screened against two gram positive i.e. Staphylococcus *aureus* and Proteus mirabilis and two gram negative bacterial strains i.e. Escherichia *coli* and Bacillus *cereus.* The compound was dissolved in DMSO (Dimethyl sulfoxide) and a concentration of 200 mg/ml was made and added to the petri plate of each strain. The activity result of compound against above mentioned strains is given above table 1. It was shown by 18 mm, 19 mm and 15 mm against Bacillus cereus, Staphylococcus aureus and Escherichia coli respectively.

Conclusion

The synthesized compound i.e. (3,5-Diacetyl-2,6-dimethyl-4-phenyl-1,4-Dihydropyridine) was synthesized in quantitative yield and it was evaluated for antibacterial activity. The maximum inhibition was noticed against the bacterium *Staphylococcus aureus*.

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