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# Synthesis, Characterization and Antimicrobial Study of a Novel Compound by Biginelli Reaction

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## Abstract
Ethyl-4-Methyl-2-Oxo-6 (2, 3, 4-trimethoxyphenyl) hexahydropyrimidine-5-carboxylate was synthesized by Biginelli reaction by using Ethyl Acetoacetate, 2, 3, 4-Trimethoxy benzaldehyde as aromatic aldehyde with urea. We have developed an efficient procedure for conducting the three-component reaction at fairly low temperatures. We have analysed the structural features of the synthesised compounds based on $^1$H NMR spectra and IR spectroscopy. The antibacterial activity of the synthesised compound against MDR *P.aeruginosa* was evaluated as described by CLSI standards. The newly synthesised compound was screened for their antibacterial activity and antifungal activity against test pathogen and the size of zone of inhibition was 12 mm at 50µg/ml and the relative inhibitory zone of inhibition was calculated as 71%. The synthesised compound exhibits potent antifungal activity.

**Keywords**
Biginelli reaction, antibacterial activity, antifungal activity

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## INTRODUCTION
From the literature survey, it is evidenced that, biological and chemical field of Pyrimidines plays a vital role in the life process[1]. Multicomponent reactions in which three or more reactants are combined in a single vessel to generate new molecules that contain portions of each reactant undoubtedly maintain great importance in organic and medicinal chemistry due to the synthetic efficiency and molecular diversity required in the discovery of new lead compounds, in particularly Biginelli compounds. The Biginelli compounds[2] due to their biological importance has rendered their effectiveness as calcium channel blockers and other properties[3-5]. Biginelli compounds and their derivatives is increasing tremendously because of their therapeutic and pharmacological properties and also because of interesting biological activities of several marine alkaloids which contain the dihydropyrimidine nucleus [6-9]. The efficiency of a Biginelli reaction as economic and ecological way has been proved by performing the multicomponent reactions under solventless conditions by using heterogeneous catalysts. The Biginelli reaction has been preferred due to the

fundamental synthetic reactions under heterogeneous catalysis on the basis continuous investigation in the research[10]. Synthesis of this heterocyclic nucleus is more importance. The simple procedure involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions at high temperature[11]. In substituted aromatic and aliphatic aldehydes, the Biginelli's reaction gives low yields. It has raised to develop new multistep procedures that produce high in the multicomponent synthesis[12].

**EXPERIMENTAL AND PROCEDURE**

In the present study, the chemicals and reagents use are all of commercial products. The liquids and solids were purified by usual methods of distillation and crystallization. By using Gallenkamp melting point apparatus, melting points were determined and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrum BX 1 and NMR on a Brucker 400 MHz spectrometer using TMS as an internal reference.

A mixture of 40 mmol of 2,3,4-Trimethoxy benzaldehyde, 40 mmol Ethyl aceto acetate, 45 mmol urea or thiourea and catalytic amount (a few drops of the liquid acid or a few crystals (ranging from 5-100 mg of the mono- or dicarboxylic acid as mentioned) in 10 mL of ethanol was heated under reflux for a few hours. The reaction was monitored by TLC. After cooling the reaction mixture was diluted with 100 mL of water, kept for a few hours, the precipitates were filtered off, washed with water and dried. A portion was recrystallized from ethanol to give the expected dihydropyrimidone (or thione). Some reactions were carried out by fusion on a hot plate (solventless condition) and the contents were dissolved in ethanol and purified as usual. All the products of the reactions were compared with the authentic samples prepared by the literature methods and were found to be identical in all respects.

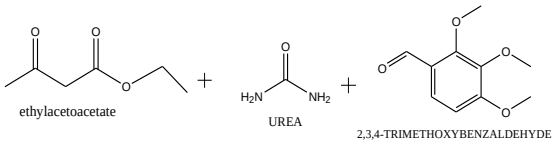
Antimicrobial activity of synthesized compound was evaluated against *MDR Pseudomonas aeruginosa, E.coli* and *Staphylococcus aureus* by the disc diffusion method as per National committee for Clinical Laboratory Standards (NCCLS). Approximately $10^7$ CFU of each organism were inoculated in on Muller-Hinton agar (MHA) plates and then 50 µg of solution was added to disc and placed over the agar surface and amikacin used as positive control.

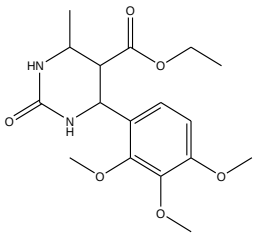
The reaction of aldehyde, ethyl acetoacetate and urea under different reaction conditions is depicted in the following scheme.

**RESULTS AND DISCUSSION**

In this study, Ethyl-4-Methyl-2-Oxo-6(2,3,4-trimethoxyphenyl) hexahydropyrimidine-5-carboxylate has been synthesized and their antibacterial and antimicrobial activities were evaluated. The synthetic procedure for preparation of title compounds is given below**.** The structures of the compounds were confirmed by spectral methods IR, $^1$H NMR, MS and elemental analysis.

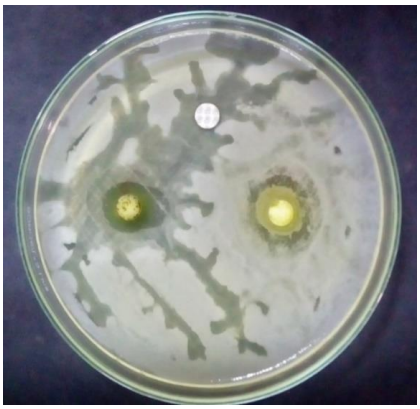
In IR spectra, some significant stretching bands due to N-H, C=O and C=N were observed at 3345-3198, 1688-1665 and 1345-1222 $cm^{-1}$ respectively. In 1H NMR spectra, the signal due three hydrogen of $OCH_2CH_3$ protons appeared at 1.0-1.2 ppm as triplet and two hydrogen of $OCH_2CH_3$ appeared at 4.1 ppm as quartet. The 1,4-dihydropyrimidine N-H, 6-$CH_3$, Ar-$OCH_3$ and Ar-$CH_3$ protons were observed at 8.6-10.1, 2.3-2.9, 3.7-3.8 and 2.3-2.4 ppm respectively. All the aromatic protons were observed in the expected regions. Mass spectra of compounds showed $(M+1)^+$ and $(M+2)^+$ peaks in agreement with their molecular formula.



ethyl 4-methyl-2-oxo-6-(2,3,4-trimethoxyphenyl)hexahydropyrimidine-5-carboxylate

All the test pathogens were highly sensitive to the tested compound at 100 µg and were moderately sensitive at 25 µg g. Potent antibacterial activity was observed at 100 µg and the zone of inhibition was 20±0.28mm against *P.aeruginosa* and 16.±1.12 mm against methicilin resistant *S.aureus* (MRSA) followed by 19±0.002 mm against *E.coli.* This increased antimicrobial activity of the complexes as compared to the amikacin is probably due to the fact that chelation increases the lipophilicity of compound[12] (Akkasali et al., 2009)



**Antibacterial activity of the synthesised compound**

| Microorganism | Zone of inhibition (mm) | |
|---|---|---|
| | Compound | Standard |
| *Staphyloccoccus aureus* | 12 | 42 |
| *Bacilus Subtilis* | 10 | 36 |
| *Pseudomonas aeruginosa* | 20 | 34 |
| *Escherichia Coli* | 19 | 24 |
| *Aspergillus parasitis* | 13 | 22 |
| *Candida albicans* | 15 | 21 |

## CONCLUSION

The compound was synthesised and screened for antibacterial and antifungal studies. It has found that, the compound has significant antibacterial activity and antifungal activity. This research can extend to investigate the effect of newly compounds on various biological activities which can strengthen the therapeutic applications to the human utility.

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