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Research Paper

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Evaluation of Antimicrobial Activity and Efficient Synthesis of 3, 4-Dihydropyrimidin-2-(1H)-One by Using Cobalt Chloride Doped Polyaniline Composite (PANI-Co) As Catalyst

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ABSTRACT:

The present study aimed to use a method for the synthesis of some 3, 4 -dihydropyrimidin-2-(1H) - ones by using Cobalt Chloride Doped Polyaniline Composite (Co- PANI-) as Catalyst. The study tried to study the Biginelli reaction can be performed without solvent and with new catalyst or not. To find the effectiveness of the catalyst (Co- PANI), we described a novel protocol for the efficient synthesis of some 3, 4-dihydropyrimidin-2- (1H) -one using aldehydes, alkyl acetoacetate, and urea or thiourea at 80°C under solvent-free conditions by Cobalt Chloride Doped Polyaniline Composite (Co-PANI) as Catalyst. This catalyst is efficient due to its high yields, use in mild conditions, ecofriendly, environmentally friendly, cost effective and reusable. The synthesized compounds were characterized by spectroscopic technique. The synthesized compounds were evaluated for antimicrobial activity. The results showed that these compounds show a remarkable biological activity against all the tested bacteria. We have demonstrated a novel method for the synthesis of substituted dihydropyrimidinones catalyzed by Cobalt Chloride Doped Polyaniline Composite (Co-PANI) as Catalyst.

Keywords: Cobalt Chloride Doped Polyaniline composite (Co-PANI), DHPMs, antimicrobial activities, Biginelli reaction, MIC.

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1. Introduction

The Italian chemist Pietro Biginelli in 1893 attempt was made to synthesize Dihydropyrimidinones (DHPMs) through multicomponent reactions [1] Biginelli reaction is multi-component reactions (MCR) used for the synthesis of dihydropyrimidinones/thiones. The 3,4- dihydropyrimidin-2 (1H) ones / thiones (DHPMs) reported that they exhibit the antimicrobial activity of various drugs such as anti-bacterial, anti-viral, as anti- hypertensive effects as calcium channel modulators and Multi-drug resistance reversal [2- 7]. Biginelli reaction minimum yield of product [8]. In the recent year researcher tried to develop the new method to improve the yield of the product by using the different catalyst and reaction conditions. i.e. the use of bismuth(III) nitrate [9], $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ [10], $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ [11], RuCl_3 [12], Glutamic acid [13], ZrCl_4 [14], silica sulfuric acid [15], thiamine hydrochloride [16], L-(+)-tartaric acid-dimethylurea [17], polyvinylsulfonic acid [18],

imidazole-1-yl-acetic acid [19], $[\text{Al}(\text{H}_2\text{O})_6](\text{BF}_4)_3$ [20], $p\text{-TsOH} \cdot \text{H}_2\text{O}$ [21], H_3BO_3 [22], $\text{HClO}_4\text{-SiO}_2$ [23], $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ [24], mesoporous silica catalyst, chlorosulfonic acids [25], triphenyl phosphine [26], Al-plated MCM-41 [27], $(\text{NH}_4)_2\text{CO}_3$ [28], $\text{CrCl}_3 \cdot 7\text{H}_2\text{O}$ [29], CaCl_2 [30], γ -

aminobutyric acid [31], $\text{SiO}_2\text{-H}_2\text{SO}_4$ [32], $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ [33], alumina- supported trifluoromethane sulfonic acid [34], chloro- trimethyl silane [35], NaCl [36], $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ [37], and other reagents have been found to be effective.

However, some of these methods are expensive and harmful to the environment and gives low yields, incompatibility with other functional groups and isolation of product is difficult. Therefore, there is need to develop the low cost, ecofriendly catalyst for the synthesis of 3, 4- Dihydropyrimidin - 2-(1H)-one.

The 3, 4- Dihydropyrimidin - 2-(1H)-one Biginelli compounds [38] has increased the scope in medicinal chemistry. The dihydropyrimidinones exhibit wide range of biological activities such as antibacterial, antiviral, antitumor, and anti-inflammatory actions [39]. Due to its biological activities scientist attracts towards synthetic and biological evaluation of the Biginelli compounds.

The much work is carried out related with the synthetic methodology and biological evaluations of these compounds. The synthesis of industrially important and other nitrogenous biologically active compounds has long been a significant branch of organic synthesis [40-43].

In the present work we have synthesize the some 3, 4- Dihydropyrimidin - 2-(1H)-one by using Cobalt Chloride Doped Polyaniline Composite (Co-PANI) as Catalyst and study their antimicrobial activity of these compounds.

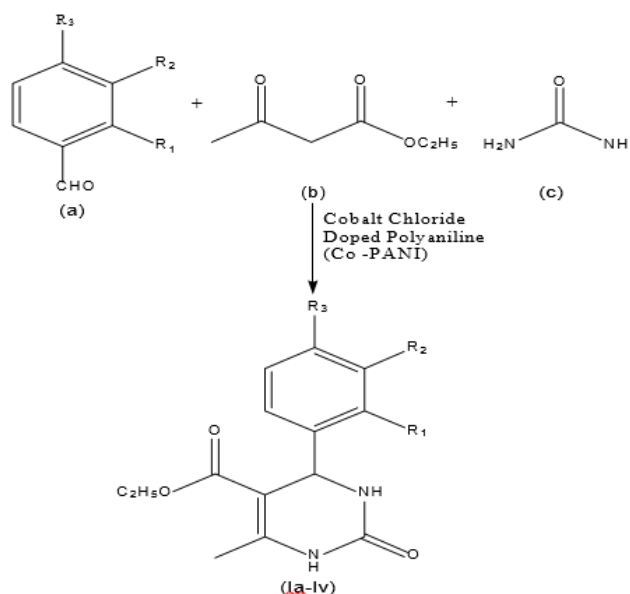


Fig: 1- General Scheme for the synthesis of Biginelli compounds using Cobalt Chloride Doped Polyaniline Composite (PANI-Co) as Catalyst

Experimental

Material:

All chemicals supplied by the Merck (Extra pure) Chemical Companies and used were without further purification. IR spectra were recorded on a Perkin-Elmer 1640 FT-IR instrument. The ^1H - and ^{13}C -NMR spectra were recorded on a Bruker DPX-300 NMR machine. Unless otherwise specified, CDCl_3 was used as solvent. Mass spectra were recorded with a Bruker Daltonic Data Analysis 2.0 spectrometer.

Preparation Co-PANI Composite as a Catalyst:

The Cobalt Chloride Doped Polyaniline (PANI-Co) composite as Catalyst was prepared by the chemical doping method. The polyaniline was synthesized by the chemical oxidation method at low temperature (0 to 3°C). Ammonium Persulphate and Hydrochloric Acid used as a oxidizing agent as received without further purification. 10 ml Aniline was first dissolve in 2 M 100 ml

Hydrochloric Acid (HCl) (Merk). Then this solution is kept in the ice bath below 5°C temperature. Ammonium Persulphate solution (Usually 10%) was added to the above solution with constant stirring. This polymerization process were completed within the three to four hours and the finally the green color polyaniline was formed. It is washed with the hot dilute HCl and dried it in the oven for 24 Hours.

An appropriate amount of the Cobalt Chloride 0.1 M was dissolve in polyaniline (PANI) solution. Doping of cobalt was done by the chemical doping method. For uniform distribution of cobalt to form the Cobalt Chloride Doped Polyaniline (PANI-Co) composite stirring was continued for 2 hours. PANI-Co composite was formed and confirmed by the instrumental technique and used as the effective catalyst.

General procedure of synthetic 3,4-dihydropyrimidin-2(1H)-one:

A mixture of aromatic aldehyde (1 mmol), 1,3-dicarbonyl compounds (1 mmol), urea or thiourea (1.5 mmol) was prepared. After that we added Cobalt Chloride Doped Polyaniline (PANI-Co) composite (3 mol %) as catalyst. The mixture was dissolved in 2mL of absolute

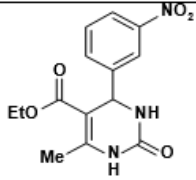
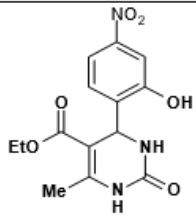
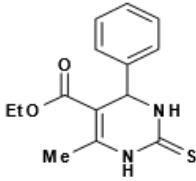
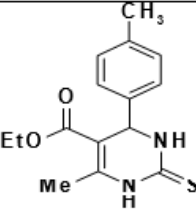
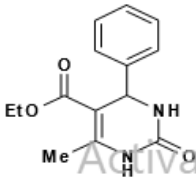
ethanol. The mixture was refluxed for suitable time and the progress of the reaction was monitored by TLC. After completion of the reaction the catalyst was recovered by filtration, the filtrate was evaporated and the solid was then washed with cold water. Recrystallize the product with ethanol we got the pure 3,4-dihydropyrimidin-2(1H)-one.

Following DHPMs were synthesized:

Reaction conditions: Aldehyde = 10 mmol, urea/thiourea=15 mmol, β -keto-ester =10 mmol, Catalyst = 20 wt. % with respect to aldehyde, Solvent free, Temp. = 25⁰C by using the Cobalt Chloride Doped Polyaniline (PANI-Co) composite (3 mol %) as catalyst. All compounds are well characterized by spectroscopic techniques.

Table: 1- List of the biologically evaluated compounds

Compound Code	Name of the Compound	Structural Formulae
Ia	Ethyl 1,2,3,4-tetrahydro-4-(2-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate	
Ib	Ethyl 4-(2-chloro-4-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate	
Ic	Ethyl 4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate	
Id	Ethyl 4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate	
Ie	Ethyl 1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate	

If.	Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxylate	
Ig.	Ethyl 1,2,3,4-tetrahydro-4-(2-hydroxy-4-nitrophenyl)-6-methyl-2-oxopyrimidine-5-carboxylate	
Ih.	Ethyl 1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (Ih).	
Ii.	Ethyl 1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-p-tolylpyrimidine-5-carboxylate	
Ij.	Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate	

2. Result and discussion:

The antimicrobial activity of Biginelli compounds DHPMs i. e. Ia to Ij was assessed against the test organisms *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, *Bacillus Subtilis*, *Pseudomonas aeruginosa*, *Bacillus megatherium*, *Salmonella typhi*, *Shigella dysenteriae*, *Klebsiella Pneumoniae* and *Proteus mirabilis*. All bacterial species used in present investigation are known human pathogens.

The MIC values were determined by serial dilution method. The comparative study of MIC values of the compounds is given in Table-2.

The results of sensitivity of various pathogens towards the synthesized Biginelli compounds were tested. The results of sensitivity of pathogens towards the synthesized DHPMs (Ia to Ij) are shown.

For convenience, the compounds were graded as ---

- Highly active : With MIC values > 3 to 12.5 µg/ml
- Moderately active : With MIC values > 25 to µg/ml
- Poorly active : With MIC values > 100 – 200 µg/ml

Most of the Biginelli compounds shows moderate activity with MIC values in the range > 3 to 200 µg/ml towards Gram positive and Gram negative micro-organisms.

Table: 2- Comparative study of MIC values of DHPMs against micro-organisms.

Compounds → Microbes↓	Ia	Ib	Ic	Id	Ie	If	Ig	Ih	Ii	Ij
<i>Staphylococcus aureus</i>	12.5	100	3.0	100	6.2	25	50	12.5	100	6.2
<i>Escherichia coli</i>	12.5	50	>3.0	25	6.2	12.5	50	6.2	50	100
<i>Proteus vulgaris</i>	25	100	>3.0	25	>3.0	12.5	6.2	6.2	50	100
<i>Bacillus Subtilis</i>	3.0	25	6.2	25	>3.0	25	100	12.5	100	6.2
<i>Pseudomonas aeruginosa</i>	25	25	6.2	50	6.2	6.2	12.5	50	25	3.0
<i>Bacillus megatherium</i>	12.5	100	6.2	50	6.2	50	100	6.2	50	100
<i>Salmonella typhi</i>	100	50	3.0	25	3.0	50	100	3.0	25	3.0
<i>Shigella dysenteriae</i>	50	25	3.0	12.5	>3.0	25	50	50	25	50
<i>Klebsiella Pneumoniae</i>	25	100	>3.0	25	3.0	12.5	25	12.5	100	6.2
<i>Proteus mirabilis</i>	12.5	25	>3.0	50	6.2	25	50	50	25	3.0

Compounds Ib, and Id were less active towards all the pathogens excepting *Pseudomonas aeruginosa* and *Proteus vulgaris* respectively. Compounds Ig were less active with respect to antimicrobial activity towards used pathogens. The compound Ia, Ic, Ie and If is exceptionally sensitive towards *S. dysenteriae*.

3. Conclusion

The Biginelli compounds were found to have considerable antimicrobial activity towards all the pathogenic bacteria Ia. Whereas in case of compounds Ib, and Id the results were exceptionally appreciable towards the micro-organisms *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Shigella dysenteriae*, *Bacillus subtilis*, *Bacillus megatherium*, *Proteus vulgaris* and *Bacillus subtilis*, *Shigella dysenteriae*.

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