"Efficient Synthesis and Antimicrobial Potential of N-Mannich Bases of 3, 4- Dihydropyrimidin-2-(1H)-ones Catalyzed by Cobalt Chloride Doped Polyaniline Composite"

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Abstract:

This study explores a novel, eco-friendly protocol for synthesizing N-Mannich bases of 3,4-dihydropyrimidin-2(1H)-ones using cobalt chloride doped polyaniline composite (Co-PANI) as a catalyst under solvent-free conditions. Employing the Biginelli reaction with aldehydes, alkyl acetoacetate, and urea or thiourea at 80°C, we demonstrate that Co-PANI catalysis yields high efficiency, mild reaction conditions, and excellent reusability, making it a cost-effective and environmentally benign option. The synthesized compounds were structurally characterized through spectroscopic techniques, and their antimicrobial efficacy was evaluated. Results indicate that these compounds exhibit significant activity against various bacterial strains. This method highlights the potential of Co-PANI as an effective, reusable catalyst, advancing sustainable practices in organic synthesis and offering promising antimicrobial applications for dihydropyrimidinones.

Keywords: N-Mannich Bases of DHPMs, biological activities, Biginelli reaction, MIC.

Introduction:

Pharmaceutical industries have shown a strong interest in multicomponent reactions, green chemistry approaches, and solvent-free synthesis methods for producing complex drugs. These methodologies are essential for exploring the molecular diversity involved in complex reactions, particularly with heterocyclic compounds [1-6]. Among these, the Biginelli synthesis stands out as a valuable multicomponent reaction in organic and medicinal chemistry, enabling the efficient production of multifunctional compounds, such as 3,4-dihydropyrimidin-2(1H)-ones and related heterocycles [7].

Over the past few decades, Biginelli compounds, including 3,4-dihydropyrimidine-2(1H)-ones, have been recognized for their diverse biological activities. They have demonstrated potential as anti-inflammatory agents, HIV inhibitors, analgesics, anticancer agents, antihypertensive drugs, neuropeptide Y (NPY) antagonists, calcium channel blockers, and α-1a-antagonists [8-9]. However, the Biginelli reaction often suffers from low yields. To address this, recent studies have explored various catalytic methods, including the use of zeolites, to improve efficiency and yield in Biginelli syntheses. [10], natural catalyst, glutamic acid [11] CuCl2·2H2O[18], [12], Al(NO3)3·9H2O[13], silica sulfuric acid [14], ZrCl4 [15], 3·OEt2 [16], various Lewis acids [17], [18], [19], N-sulfonic acid poly(4-vinylpyridinium)chloride [20]. CAN [21], molecular I2 [22], PPh3 [23], Dowex [24], baker's yeast [25], triflates [26], [27], [28], covalently anchored sulfonic acid on silica [29], TiO2-CNTs [30], DBSA [31], LaCl3-graphite [32], heteropolyacids [33], ammonium carbonate [34], l-proline [35], TCCA [36], and silica-bonded N-propyl sulfamic acid [37].

Many existing methods for synthesizing N-Mannich Bases of 3,4-dihydropyrimidin-2(1H)-one are expensive, environmentally harmful, yield low product quantities, lack compatibility with other functional groups, and make product isolation challenging. Consequently, there is a need for a low-cost, eco-friendly catalyst for the synthesis of N-Mannich Bases of 3,4-dihydropyrimidin-2(1H)-one.

Biginelli compounds, specifically N-Mannich Bases of 3,4-dihydropyrimidin-2(1H)-ones [38], have expanded the scope of medicinal chemistry due to their wide range of biological activities, including antibacterial, antiviral, antitumor, and anti-inflammatory effects [39]. The significant biological potential of these compounds has spurred scientific interest in both their synthesis and biological evaluation.

Substantial research has been conducted on the synthetic methodologies and biological assessments of these compounds. Synthesizing nitrogenous biologically active compounds, especially those with industrial relevance, remains a crucial area in organic synthesis [40-42].

In this study, we synthesized N-Mannich Bases of 3,4-dihydropyrimidin-2(1H)-one derivatives using cobalt chloride doped polyaniline composite (Co-PANI) as a catalyst and evaluated the antimicrobial activity of these compounds.

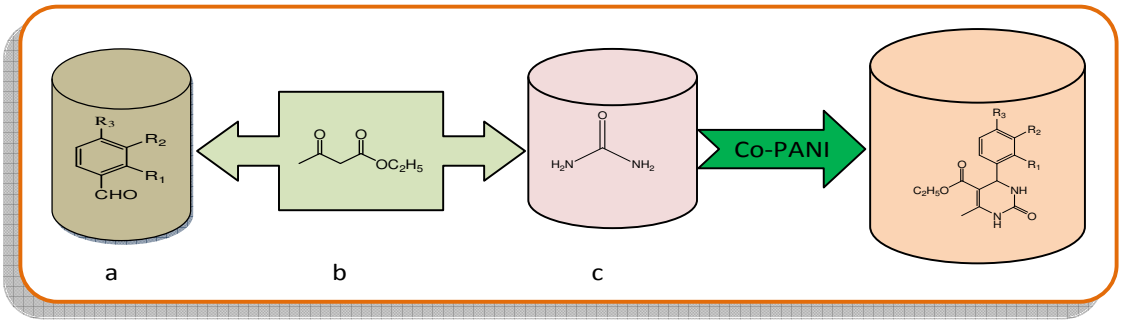

Fig: 1- General Scheme for the synthesis of Biginelli compounds (BCa to BCi) using Cobalt Chloride Doped Polyaniline Composite (PANI-Co) as Catalyst

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 13C-NMR spectra were recorded on a Bruker DPX-300 NMR machine. Unless otherwise specified, CDCl3 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 oxidization method at low temperature (0 to 3^{0c}). 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 ^{0c} 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 N-Mannich Bases of 3,4-dihydropyrimidin-2(1H)-one:

In typical synthesis of N-Mannich Bases of of 3,4-dihydropyrimidin-2(1h)-ones, mixture of the DHPMS, Formaldehyde (0.4 Mole) will be added under stirring. The reaction Mixture will be stir at room temperature for some time to complete the reaction of formaldehyde and to yield the methylol derivative of DHPM. To this solution the solution of Secondary amine diethylamine (0.2 Mole) will be added dropwise. After that we added Cobalt Chloride Doped Polyaniline (Co-PANI) (3mol %) as catalyst and reflux for half an hour. The reaction mixture will be poured into cold water. Finally it will be dried and will be purified by recrystallization from chloroform to give N-Mannich Bases of of 3,4-dihydropyrimidin-2(1h)-ones.

After completion of reaction the catalyst was filtered off by using ethanol and washed with acetone and ether successively and reused for next cycle. The crude products obtained were recrystallised by using chloroform.

The melting points of all the synthesize compounds were recorded in precision digital melting point apparatus, Model MP-D and are uncorrected.

Table : 1 Synthesis of N-Mannich Bases of 3,4-dihydropyrimidin-2(1H)-one by using Co-PANI as a Catalyst

Product	R1	R2	R3	% Yield	Melting point
BCa	-H	–H	-OMe	80	255^0 C
BCb	-OMe	–H	-Cl	81	239^0 C
BCc	–H	–H	-Cl	89	235^0C
BCd	-Cl	–H	–H	78	232^0C
BCe	-OH	–H	–H	77	230^0C
BCf	–H	$–NO_2$	–H	80	237^0C
BCg	- NO_2,	-H	-H	82	238^0C
BCh	-H	-H	-H	83	231^0C
BCi	-H	-H	$-CH_3$	88	255^0C

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

Compound	*S. aureus*	E. coli	*P. aeruginosa*	*B. megatherium*	*S. typhi*	*S. dysentariae*	*K. Pneumoniae*
BCa	50	100	100	50	25	50	50
BCb	6.2	6.2	25	12.5	25	50	50
BCc	50	50	50	100	50	25	25
BCd	25	25	12.5	50	50	25	50
BCe	100	100	50	100	3	12.5	25
BCf	25	25	50	25	12.5	>3	12.5
BCg	3	3	>3	6.2	3	3	6.2
BCh	100	50	100	25	100	100	25
BCi	6.2	6.2	6.2	3	6.2	6.2	12.5

Result and discussion:

The compounds BC_g and BC_i possess highest activity with the MIC values 3 to 6.2 µg/ml. towards all the test micro-organisms (See Table -2). Compounds BC_a, BC_b, and BC_c were less active towards all the pathogens, whereas the compound BC_b is exceptionally active towards *Staphylococcus aureus* with MIC value 6.2.

The compounds Bc_d, BC_e, and BC_f were less active with respect to antimicrobial activity towards used pathogen excepting *Proteus vulgaris, Bacillus megatherium and Salmonella typhi* respectively.

The compounds BC_h, were less active towards used micro-organisms.Thus the micro-organisms *Bacillus subtilis* and *Proteus mirabilis* were comparatively highly resistive towards all the synthesized compounds excepting BC_g and BC_i

Also from the Table–2, it can be conclude that, the supplementary drug Codeine was found synergistic with the combination of compounds BC_g, and BC_i.

The results were exceptionally appreciable towards the pathogens *S. aureus, E.coli., P.vulgaris, P.aeruginosa, B.megatherium, S.typhi, S.dysentariae* and *K.pneumoniae*.

Conclusion:

The present study demonstrates that among the synthesized compounds, BCg and BCi exhibit the most potent antimicrobial activity, with MIC values ranging from 3 to 6.2 μg/ml against all tested microorganisms. In contrast, compounds BCa, BCb, and BCc showed relatively lower activity, although BCb displayed notable efficacy against Staphylococcus aureus. Compounds Bcd, BCe, and BCf showed selective activity against Proteus vulgaris, Bacillus megatherium, and Salmonella typhi, respectively, while compound BCh was largely ineffective. Notably, Bacillus subtilis and Proteus mirabilis emerged as the most resistant strains, except when treated with BCg and BCi. Additionally, the combination of these two compounds with codeine indicated a synergistic effect, further enhancing their antimicrobial potential. These findings suggest that BCg and BCi, particularly in combination with codeine, could serve as promising candidates for further development in antimicrobial therapy.

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