



SYNTHESIS AND SCREENING OF SOME DIHYDROPYRIMIDINE DERIVATIVES AS ANTIMICROBIAL AGENTS

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Article Received on: 17/07/12 Revised on: 20/08/12 Approved for publication: 02/09/12

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ABSTRACT

The wide applications of pyrimidine fused heterocyclic compounds prompted us to synthesize a new series of dihydropyrimidine derivatives through Biginelli reaction. The synthesized compounds were characterized by IR and ¹H-NMR analysis. The titled compounds were evaluated for antibacterial activity against selected gram positive and gram negative bacteriae. Also the antifungal activity of the compounds was evaluated. The novel derivatives were found to have significant activity against the microorganisms.

Key words: Pyrimidines, anhydrides, biginelli reaction, antibacterial, antifungal

INTRODUCTION

Fused pyrimidine heterocyclic compound are well known for their diverse biological activities as anticancer, antimicrobial, antihypertensive, antimycobacterial, antiviral agents¹⁻⁵. Dihydropyrimidinones, the products of the Biginelli reaction, are widely used in the pharmaceutical industry as calcium channel blockers and alpha-1 antagonists. The presence of a pyrimidine base in thymine, cytosine and uracil, the essential building blocks of nucleic acids, DNA and RNA is one of the possible reasons for their activities. Pyrimidine ring is found in vitamins like riboflavin, thiamine and folic acid. Pyrimidine nucleus is also present in barbituric acid and its several derivatives which are used as hypnotics. The biological significance of the pyrimidine derivatives has promoted us to synthesize some new substituted dihydropyrimidines, and evaluate them for their antimicrobial activity.

MATERIALS AND METHODS

All the solvents and reagents were of laboratory grade. The melting points of the titled compounds were determined by open capillary method and were uncorrected. The purity of the compounds was checked by thin layer chromatography. The infrared analysis was carried out by JASCO 4100 FT IR using KBr pellet disc technique⁶. ¹H-NMR was recorded on a Bruker 500MHz spectrometer using tetramethylsilane as standard⁷. The chemical shifts were recorded in parts per million (ppm).

Synthesis of biginelli compound:

A mixture of 0.15mole of thiourea, 0.1mole of ethylacetoacetate and 0.1mole of benzaldehyde were dissolved in 25ml of ethanol along with 3 drops of conc.HCl and refluxed for one and half an hour. The reaction mixture was then poured into 100ml ice cold water with stirring and left overnight at room temperature, filtered and dried. The products were recrystallised using ethanol. Similar procedure was followed for other substituted aldehydes.

Synthesis of carbonylhydrazide derivative [H1-H3]

A mixture of 0.1mole of biginelli compound and 0.1mole of hydrazine hydrate were dissolved in 20ml of ethanol along with 4 drops of conc.H₂SO₄ and refluxed for 3 hrs. The

reaction mixture was then evaporated to obtain a residue which was further recrystallised from ethanol.

Synthesis of substituted dihydro pyrimidine derivatives [A1-A3]

About 0.5gm of hydrazido product and 0.5gm of maleic anhydride, 5ml of glacial acetic acid were refluxed for one hour. The reaction mixture was then poured into ice cold water in a beaker, filtered and dried. The precipitate was then recrystallised from ethanol.

A-1: Yield: 73.57%, M.P. 165°C, Rf: 0.82, IR (cm⁻¹): 1593.25 (C=C stretch), 1655.94 (C=O stretch), 1279.81 (C-N stretch), 2812.31 (CH₃ stretch), ¹H NMR (δppm): 2.50 (s, 3H, CH₃), 9.67 (s, 1H, NH), 12.53 (s, 1H, NH), 7.69 (s, 1H, CONH), 6.62-7.05 (m, 10H, ArH)

A-2: Yield: 73.57%, M.P. 155°C, Rf: 0.55, IR (cm⁻¹): 1573.97 (C=C stretch), 1644.37 (C=O stretch), 1274.98 (C-N stretch), 2956.01 (OH stretch), 1126.47 (C-O-C stretch), ¹H NMR (δppm): 2.50(s,3H,CH₃), 9.35(s,1H,OH), 9.58(s,1H,NH), 3.80(s,1H,OCH₃), 10.68(s,1H,NH), 7.52 (s,1H,CONH), 7.01– 7.18 (s,8H,ArH)

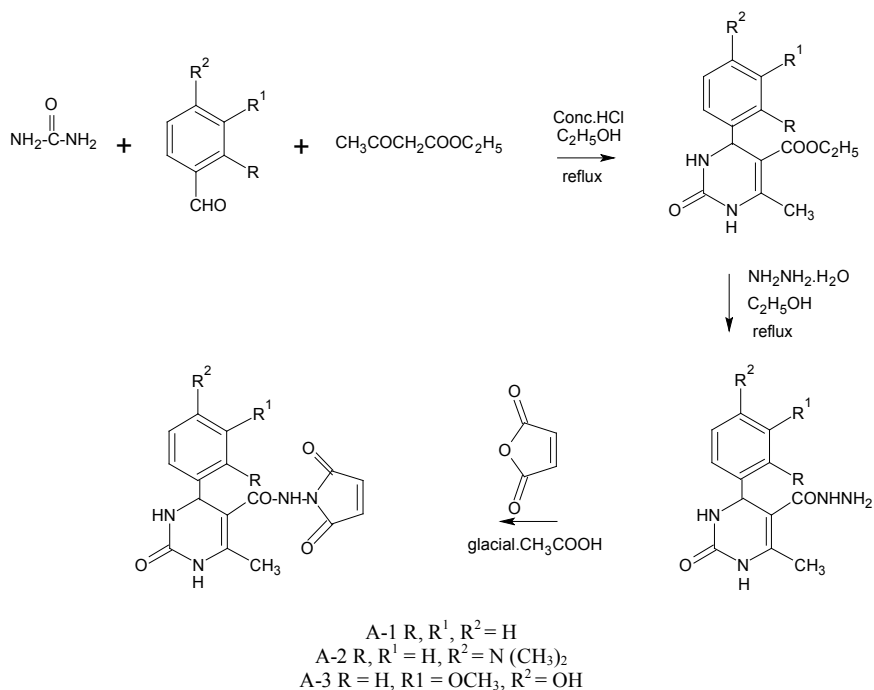
A-3: Yield: 73.57%, M.P. 170°C, Rf: 0.85, IR (cm⁻¹): 1593.25(C=C stretch), 1656.91 (C=O stretch), 1279.81 (C-N stretch), 1371.43 (C-H stretch), ¹H NMR (δppm): 2.50(s,3H,CH₃), 3.25(s,6H,N(CH₃)₂), 10.32 (s,1H,NH), 12.68 (s,1H,NH), 7.72 (s,1H,CONH), 7.11– 7.19 (s,9H,ArH)

ANTIMICROBIAL SCREENING

The titled compounds were screened for antimicrobial activity⁸ by disc diffusion method against the microorganisms such as *Bacillus subtilis*, *Staphylococcus albus*, *Staphylococcus aureus*, *Micrococcus luteus*, *Salmonella paratyphi*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Candida albicans* and *Aspergillus parasiticus*. All the compounds exhibited significant activity against *Salmonella paratyphi* and *Escherichia coli* and highly significant activity against the fungal organisms. Ciprofloxacin 10µg/ml capacity disc were used as positive reference standard for antibacterial activity. Cotrimazole 10µg/ml capacity was used as positive reference standard for antifungal activity.

TABLE NO.: 1 ANTIMICROBIAL ACTIVITY OF THE TITLED COMPOUNDS

Microorganisms	Zone of Inhibition(mm)			
	A-1	A-2	A-3	Standard
<i>Bacillus subtilis</i>	10	9	11	36
<i>Staphylococcus albus</i>	11	10	13	31
<i>Staphylococcus aureus</i>	11	14	16	44
<i>Micrococcus luteus</i>	12	13	18	34
<i>Salmonella paratyphi</i>	17	16	18	21
<i>Escherichia coli</i>	9	11	14	24
<i>Pseudomonas aeruginosa</i>	16	15	13	35
<i>Klebsiella pneumoniae</i>	11	12	18	33
<i>Candida albicans</i>	17	17	16	21
<i>Aspergillus parasitis</i>	13	17	18	22



RESULTS AND DISCUSSION

The present study deals with the synthesis of newer dihydropyrimidine derivatives through Biginelli reaction. The structures of the titled compounds were confirmed by melting point, thin layer chromatography, infra red analysis and NMR analysis. Finally the compounds were screened for antibacterial and antifungal activity against microorganisms such as *Bacillus subtilis*, *Staphylococcus albus*, *Staphylococcus aureus*, *Micrococcus luteus*, *Salmonella paratyphi*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Candida albicans* and *Aspergillus parasiticus*. All the compounds were found to exhibit highly significant activity against the bacteriae *Salmonella paratyphi*, *Escherichia coli* and the fungal organisms *Candida albicans* and *Aspergillus parasiticus* due to the incorporation of maleic anhydride moiety on the pyrimidine ring.

CONCLUSION

Substituted dihydropyrimidine derivatives were synthesized and screened for their antimicrobial activity. The synthesized compounds were found to have a significant antibacterial activity and a more pronounced antifungal activity. The present work details on the broad spectrum of antibacterial

and antifungal activity in comparison with a standard antibiotic. It will be worthwhile to investigate the effect of titled compounds on other biological activities which can broaden the therapeutic utility for the compounds synthesized, that will form part of a future study on titled compounds.

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Source of support: Nil, Conflict of interest: None Declared