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Synthesis, Antimicrobial Assessment of Chalcones and their Pyrimidine Derivatives

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

The aim of the study was to transform chalcones synthesized to their respective pyrimidine derivatives which was successful. The synthesized compounds were subjected to antimicrobial assay against bacteria and fungi organisms screened, however sample ZB had inhibitory effect against bacterial strains. Sample ZB is active against *S. aureus* and *E. coli* with an MIC of 5 and 1 mg/mL with a zone of inhibition 11 and 23 mm respectively. When compared to sample B had activity against *E. coli* with a minimum inhibitory concentration of 0.1 mg/mL and zone of inhibition of 20 mm. Modification of 4-(2-hydroxyphenyl)-6-(2,3,4-trimethoxyphenyl)pyrimidin-2-one to pyrimidin-2-one increases spectrum of activity against gram positive bacterial *S. aureus*. Sample A inhibits *B. subtilis* and *P. marneffei* with an MIC of 10 mg/mL with a zone of inhibition of 14 mm and 20 mm respectively. Transformation of Sample A to 2-aminopyrimidine drastically abolish the antibacterial and antifungal effect. Sample ZA is inactive against bacteria and fungi organisms,

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when compared to ZB which inhibits *S. aureus* and *E. coli*. The spectral analysis revealed that the samples are in line with literature and had a melting point (100-103^{o}C and 115-117^{o}C) for sample ZA and ZB respectively. The starting materials had a melting point (55-57^{o}C and 95-100^{o}C) for Sample A and B respectively.

Keywords: Chalcones; pyrimidine; antimicrobial; spectroscopy; heterocyclic compounds.

1. INTRODUCTION

Heterocyclic compounds are known to play important role in the management of various diseases and such compounds include; celecoxib (anti-inflammatory) carbamazepine, phenobarbitone (anticonvulsants), diazepam (hypnotic and sedative), 5-Fluorouracil (anticancer), glipizide (antidiabetic), sulphadoxine, pyrimethamine, metronidazole (antiprotozoan), Losartan and amlodipine (antihypertensive), trifluridine, idoxuridine, stavudineand zidovudine (antiviral) sulphadiazine and trimethoprim (antibacterial), fluconazole (antifungal), pesticides and herbicides (paraquat), These compounds are lifesaving agents and could play important role in our daily lives [1-11]. Pyrimidine is a useful scaffold for various medicinal agents with broad spectrum of biological activities. The aim of the study was to synthesize pyrimidine and pyrimidone analogues, from simple precursor and to determine the antimicrobial effect against bacteria and fungi organisms.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Guanidine (Sigma Aldrich), Urea (J.T Baker), 1,3-diphenyl-2-propen-1-one, 1(2'-Hydroxyphenyl)-3(2,3,4-trimethoxyphenyl)-2-propen-1-one, sodium carbonate, ethylacetate (JHD), petroleum spirit (Sigma Aldrich), DMSO (JHD), Fluconazole 200 mg, Ofloxacin 200 mg (Diamond Remedies, India).

2.2 Materials

Muller Hinton Agar, Sabourand Agar, TLC plate (Merck).

2.3 Instrument/Apparatus

Gallenkamp Melting Point Apparatus, FTIR (Agilent Cary 630), NMR Agilent 400 MHz, UV Lamp Autoclave, Incubator.

2.4 Microorganism

Staphylococcus aureus (NCTC6571), *Bacillus subtilis* (NCTC8236) *Escherichia coli* (ATCC25922) *Pseudomonas aeruginosa* (ATCC 10145), *Trichophyton mentagrophytes, Aspergillus niger, Candida albican and Penicilium marneffei* (Clinical isolates).

2.5 Chemistry

The synthesis of Chalcones were based on the Claisen Schmidt condensation reaction of an aromatic aldehyde and acetophenone or their derivatives in presence of a base to form α,β-unsaturated ketone. These were further reacted with urea or guanidine to form pyrimidine derivatives.

2.6 Synthesis of 1,3-Diphenyl-2-Propen-1-One and Derivatives (A-B)

Equivalent of 0.198 M benzaldehyde and acetophenone and their substituted derivatives in 25 mL of ethanol were mixed in 250 mL flat bottom flask and immersed in an ice-bath and stirred using magnetic stirrer until 0^{o}C temperature was ascertained by the thermometer and 50 mL of cold 10% of potassium hydroxide was added in a drop-wise manner using burette with continuous stirring. At the end of the addition it was allowed to stir for 30 minutes and kept in a refrigerator 7 days. The mixture was neutralized with 10% acetic acid at 0^{o}C and the precipitate filtered under suction and the crystals washed using cold water and recrystalised in methylated spirit, filtered, air dried, weighed and melting point determined to give A-B.

2.7 Synthesis of 4,6-Diphenyl-2-Aminopyrimidine (ZA)

Equivalent of 0.009 M 1,3-diphenyl-2-propen-1-one and guanidine carbonate were reacted in presence of sodium carbonate in a flat bottom flask. The mixture was refluxed at 100^{o}C for 12

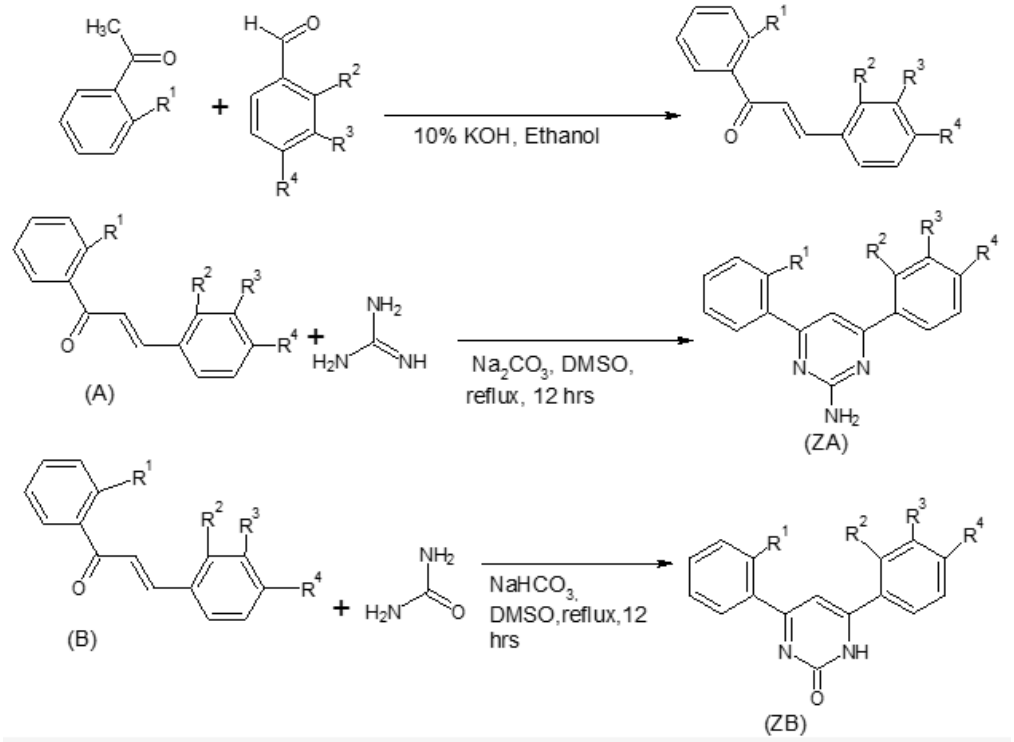
hrs and progress of reaction was monitored using TLC. The reaction mixture was allowed to cool and 300 mL of cold water was added, precipitates were collected under suction and recrystalized in hot water: methanol (1:1), filtered, dried and melting point determined to obtain sample (4,6-diphenyl-2-aminopyrimidine).

2.8 Synthesis of 4-(2-hydroxyphenyl)-6-(2,3,4-trimethoxyphenyl)Pyrimidin-2-one (ZB)

Equivalent of 0.016 M 2,3,4-trimethoxy-2'-hydroxychalcone and urea and the reaction was catalyzed using equivalent molar ratio of $NaHCO_3$ in 25 mL of DMSO flat bottom flask, refluxed for 12 hrs and progress of reaction monitored using TLC, The reaction mixture was allowed to cool and 100 mL of cold water was added, precipitates collected and recrystalized in methanol, dried and melting point determined.

2.9 Antimicrobial Assay

From the pure overnight culture of bacterial used, the colonies were harvested and diluted in a sterile saline of 0.9% NaCl, 100 fold dilution approximately $1x10^8$ CFU and Turbidity was compared to 0.5 Mcfarland standard suspensions. This protocol was carried for both the fungal and bacterial species. About 1 mL of various suspensions of the microbial organisms was transferred to the petri dishes containing Muller Hinton Agar and Sabourand dextrose Agar for the assay of samples against bacteria and fungi organism respectively. This was done at a temperature of 40-45^{o}C and it was swirled to ensure uniform distribution of the organism. Wells were made using a cork borer (10 mm). The samples were screened at 10, 5, 1, and 0.1 mg/mL stock concentration. The wells were filled with the samples and allowed to stand for 30 minutes on the bench, the bacterial samples were incubated at 27-30^{o}C for 18-24 hours while the fungi samples were kept on the bench for 48 hours and zone of inhibition were recorded [12].



Sample	R^1	R^2	R^3	R^4
A	H	H	H	H
B	-OH	$-OCH_3$	$-OCH_3$	$-OCH_3$
ZA	H	H	H	H
ZB	-OH	$-OCH_3$	$-OCH_3$	$-OCH_3$

Fig. 1. Synthesis of 1,3-diphenyl-2-propen-1-one (A-B) and derivatives (ZA-B)

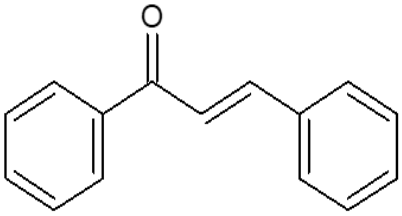
3. RESULTS AND DISCUSSION

3.1 Antibacterial Effect

The samples were assessed against bacteria and fungi organisms. Sample A had an inhibitory effect against fungi organism; *P. Marneffei,* while Sample B, ZA and ZB were inactive against fungi strains. Sample B, and ZB were active against *S. aureus* and *E. coli*. All the samples assessed were inactive against *P. aeruginosa.*

3.2 Spectroscopic Analysis

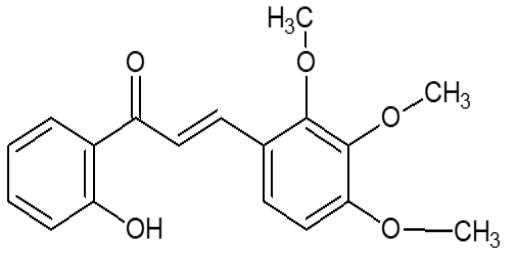
3.2.1 1,3-Diphenyl-2-propen-1-one (A)



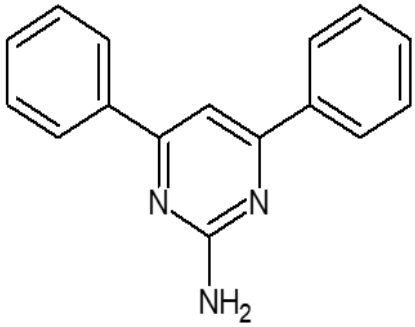
Yield (72.79%), mp (55-57^{o}C), IR(KBr)), 3313.60, 3235.33-3157.06 (C-H stretch of Aromatic group), 3022.87-3060.14 (=C-H stretch in 2-propene), (2810.41-2970.68), 1658.66 (C=O), 1073.47. ^{1}H-NMR ($CDCl_3$, δ ppm) 7.4-8.1 (Ar-H), ^{13}C-NMR ($CDCl_3$, δ ppm), 190.78 (C=O), 145 (O=C-C=) 138.45, 135.13, 133.07(C=CH), 130.82, 129.22, 128.89, 128.83, 128.82, 128.79, 128.73, 128.70, 128.67, 122.32 (Ar-C).

3.2.2 2,3,4 -Trimethoxy-2'-hydroxychalcone (B)

Yield (90.13 %), mp (95-100^{o}C), (IR, KBr,cm^{-1}) 3346 (OH), 3080 (=C-H), 1682 (C=O)^{1}H-NMR ($CDCl_3$, δ ppm), 13.08 (1H, OH), 6.41-8.17 (Ar-H), 3.8 (9H, OCH3), ^{13}C-NMR ($CDCl_3$, δ ppm), 194.16 (C=O), 163.69 (Ar-C), 155.33 (Ar-C),153.27, 143.44,141.06, 136.05, 129.77, 120.43, 118.86, 118.57, 117.71, 111.86, 109.11, 56.72, 56.39, 56.32(-OCH_3).

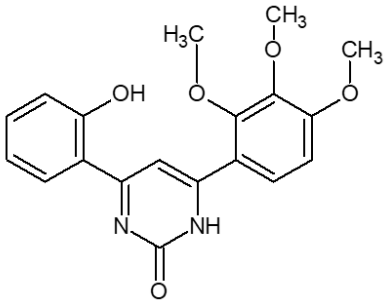


3.2.34,6-diphenylpyrimidin-2-amine (ZA)



Yield (90.39%), melting point (100-103^{o}C), (IR KBr,cm^{-1}), 3100, (=C-H, Ar-H), 3348 (NH_2) , ^{1}H NMR($CDCl_3$, δ ppm), 8.0(m, Ar-H) 6.8-7.9 (m,Ar-H), for aromatic protons, 5.7 (2H, -NH_2, s), ^{13}C-NMR ($CDCl_3$, δ ppm), 166.51 (Ar-C), 163.99 (Ar-C)138.05, 129.29. 129.05, 129.05, 128.46, 127.99, 127.42, 127.42, 126.98, 104.52 (Ar-C).

3.2.4 4-(2-hydroxyphenyl)-6-(2,3,4-trimethoxyphenyl)pyrimidin-2-one (ZB)



Yield (55.85 %), melting point (115-117^{o}C), IR (Kbr (cm^{-1}) 3256 (NH), 3347 (Ar-OH) 1682 (C=O), ^{1}H-NMR ($CDCl_3$, δ ppm) 13.0 (1H, OH), 6.4-8.2 (7H, m Ar-H), 3.8 (9H, s, OCH_3), ^{13}C-NMR ($CDCl_3$, δ ppm), 194.16 ppm, (C=O), 163.71, 155.0, 153.0, 143.0, 141.07, 136.16, 136.36, 129.77, 127.20, 121.60, 120.46, 118.0 (Ar-C) and 56.72, 56.39, 56.32 (3C, -OCH_3).

3.3 Discussion

The synthesis yielded about (55-90.39 %) and sample ZA had a melting point of 100-103^{o}C while ZB had a melting point of 115-117^{o}C. The spectral data are in agreement as reported in literature assignment of pyrimidine analogues [13-18]. However, 4-(2-hydroxyphenyl)-6-(2,3,4-trimethoxyphenyl)pyrimidin-2-one inhibited *S. aureus and E. coli*. These compounds had no inhibitory effect against fungi strains. Sample ZB

Table 1. Antibacterial effect of chalcones and their pyrimidine derivatives

Samples	Concentration mg/mL/Zone of Inhibition															
	S. aureus				***E. coli***				***B. subtilis***				***P. aeruginosa***			
	10	5	1	0.1	10	5	1	0.1	10	5	1	0.1	10	5	1	0.1
A	-	-	-	-	-	-	-	-	14	-	-	-	-	-	-	-
B	-	-	-	-	32	28	25	20	-	-	-	-	-	-	-	-
ZA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ZB	20	11	-	-	30	25	23	-	-	-	-	-	-	-	-	-
Ofx (60 ug)	25	-	-	-	22	-	-	-	28	-	-	-	26	-	-	-

Table 2. Antifungal effect of chalcones and their pyrimidine derivatives

Samples	Concentration mg/mL/Zone of Inhibition															
	Tm				**Ca**				**An**				**Pm**			
	10	5	1	0.1	10	5	1	0.1	10	5	1	0.1	10	5	1	0.1
A	-	-	-	-	-	-	-	-	-	-	-	-	20	-	-	-
B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ZA	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ZB	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
FLU 2 mg/ml	22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Keys; - *(no inhibition of growth)*, Tm = *Trichophyton mentagrophytes, Ca = Candida albican; An = Aspergillus niger, Pm Penicilium marneffei*

is active against *S. aureus* and *E. coli* with an MIC of 5 and 1 mg/mL with a zone of inhibition11 and 23 mm respectively. When compared to sample B had activity against *E. coli* with a minimum inhibitory concentration of 0.1 mg/mL and zone of inhibition of 20 mm. Modification of 4-(2-hydroxyphenyl)-6-(2,3,4-trimethoxyphenyl) pyrimidin-2-one to pyrimidin-2-one increases spectrum of activity against gram positive bacterial *S. aureus*. Sample A inhibits *B. subtilis* and *P. marneffei* with an MIC of 10 mg/mL with a zone of inhibition of 14 mm and 20 mm respectively. Transformation of Sample A to 2-aminopyrimidine drastically abolish the antibacterial and antifungal effect. Sample ZA is inactive against bacteria and fungi organisms, when compared to ZB which inhibits *S. aureus* and *E. coli*. Although, 2,4-diaminopyrimidine analogue trimethoprim and sulphadiazine are used as an antibacterial agent [8]. These further showed that structural transformation of chalcone to pyrimidine led to the conversion of the α,β-unsaturated ketone which is the pharmacophore responsible for antibacterial activities [11-14].

4. CONCLUSION

The synthesis of 2-aminopyrimidine and pyrimidin-2-one was successful using chalcone as a useful intermediate as shown by the result of the spectral analysis. The 2-aminopyrimidine was inactive against bacteria and fungi organisms assessed while the 2-pyrimidone analogue displayed antibacterial activity against *S. aureus* and *E. coli*, inactive against bacterial strains *P. aeruginosa.*

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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