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Preparation and Biological Evaluation of Novel Pyrimidines from Novel Chalcones

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ABSTRACT

Pyrimidines are the parent substances of a large group of heterocyclic compounds and play a vital role in many biological processes, as found in nucleic acids, several vitamins, coenzymes, purines and possess therapeutic activities like antimicrobial, anti-inflammatory, anticancer, antiviral, antitubercular and antimalarial activities. In the present study an attempt is made to synthesize pyrimidines from novel chalcones which provide an easy route of synthesis and chalcones themselves possess antimicrobial activity. All these compounds were characterized by means of their IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds were evaluated for antimicrobial activity by cup plate method.

Key words: Pyrimidines, Chalcones, Synthesis, Antimicrobial activity, Cup plate method.

INTRODUCTION

Chalcones and pyrimidines were reported to possess various biological activities. In the present communication we report the synthesis of novel chalcones[1-11] following claisen-schmidt condensation using 3-acetylpyridine with either aromatic or heteroaromatic aldehydes (2_{a-f}) in the presence of alkali. The resulting chalcones (3_{a-f}) after purification and characterization by physical and spectral methods have been successfully converted into novel substituted pyrimidines[12-19] 4_{a-f}) by reaction with guanidine hydrochloride. The structures of the various synthesized compounds were assigned on the basis of elemental analyses, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds were screened for their antimicrobial activity[20-22] and the results were reported.

MATERIAL AND METHODS

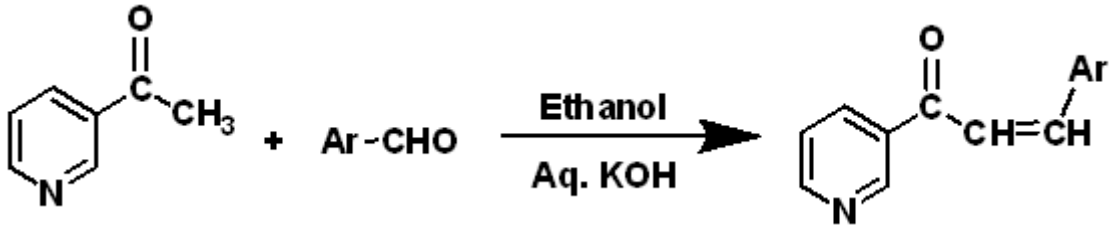
Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in the indicated solvent on Bruker AMX 400 MHz spectrophotometer using TMS as an

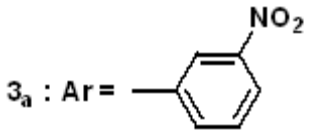
internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer BXF1 spectrophotometer. Microanalyses were performed on carlo Ebra 1108 element analyzer and were within the ± 0.5% of the theoretical values. Column chromatography was performed on silica gel (Merck, 100-200 mesh).

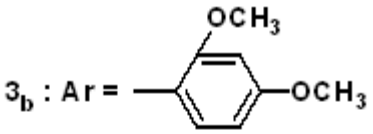
General procedure for the synthesis of novel chalcones

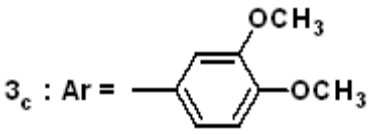
Equimolar quantity (0.001mol) of 3-acetylpyridine and respective aldehydes were mixed and dissolved in minimum amount of alcohol. To this, 40 % aqueous potassium hydroxide solution (15 ml) was added slowly and mixed occasionally for 24 hrs, at room temperature. Completion of the reaction was identified by TLC using Silica gel-G. After completion of the reaction, the reaction mixture was poured into crushed ice, if necessary acidified with dil.HCl. The solid separated was filtered and dried. It was purified by column chromatography on silica gel (100-200 #, Merck), using ethylacetate and hexane mixture (1:1) as mobile phase.

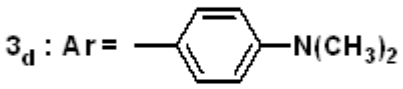
Reaction

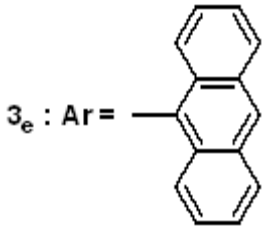


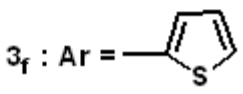












1-(3'- pyridyl)-3-(3''-nitrophenyl)-2-propen-1-one (3_a)

Yield 87%; mp 178 °C; Relative molecular mass 254; IR (KBr) 1690 (C=O), 1610 (HC = CH), 1590 (C =N); ^{1}H-NMR 7.50 (1H, d, J=17 Hz , -CO-CH=), 7.86 (1H, d, J=17 Hz, =CH-Ar), 7.65-9.20 (8H, Ar-H).Anal.calcd for $C_{10}H_{10}N_2O_3$: C, 64.56; H, 3.93; N, 11.02. Found: C, 64.57; H, 3.95; N, 11.04.

1-(3'- pyridyl)-3-(2'', 4"-dimethoxyphenyl)-2-propen-1-one (3_b)

Yield 86%; mp 156 °C; Relative molecular mass 269; IR (KBr) 1690 (C =O), 1618 (HC =CH), 1596 (C =N); ^{1}H-NMR 3.90 (6H, s, 2 x OCH_3), 7.50 (1H, d, J=17 Hz, - CO- CH =), 8.07 (1H, d, J=17 Hz, = CH- Ar), 6.50-9.20 (8H, Ar- H). Anal.calcd for $C_{16}H_{15}NO_3$: C, 71.37; H, 5.57; N, 5.20. Found: C, 71.39; H, 5.55; N, 5.19.

1-(3'-pyridyl)-3-(3'', 4"-dimethoxyphenyl)-2-propen-1-one (3_c)

Yield 75%; mp 138 °C; Relative molecular mass 269; IR (KBr) 1684 (C=O), 1610 (CH=CH), 1590 (C=N), 1210 (C-O-C); ^{1}H-NMR 3.90 (6H, s, 2 x OCH_3), 7.01 (1H, d, J=17 Hz , -CO-CH=), 7.38 (1H, d, J=17 Hz, =CH- Ar), 6.85-8.70 (7H, Ar-H) Anal.calcd for $C_{16}H_{15}NO_3$: C, 71.37; H, 5.57; N, 6.28. Found: C, 71.38; H, 5.59; N, 6.26.

1-(3'-pyridyl)-3-(4''-N, N-dimethylaminophenyl)-2-propen-1-one (3_d)

Yield 95%; mp 144 °C; Relative molecular mass 252; IR (KBr) 1696 (C=O), 1620 (CH=CH), 1586 (C=N), 1180 (-N-$(CH_3)_2$); ^{1}H-NMR 3.05 (6H, s, N Me_2), 6.69 (1H, d, J=17 Hz , -CO-CH=), 7.10 (1H, d, J=17 Hz , =CH - Ar), 7.25 – 8.73 (8H, Ar-H). Anal.calcd for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.17; H, 6.32; N, 11.10.

1-(3'-pyridyl)-3-(9''-anthracenyl)-2-propen-1-one (3_e)

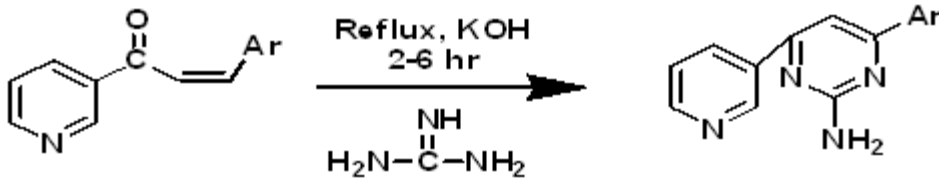
Yield 95%; mp 78 °C; Relative molecular mass 309; IR (KBr) 1695 (C =O), 1610 (HC =CH), 1592 (C = N), 1528 (C=C); ^{1}H-NMR 7.46 (1H, d, J=17 Hz , =CH-Ar), 7.24 (1H, d, J=17 Hz, -CO-CH=), 7.2 - 8.94 (13H, Ar-H). Anal.calcd for $C_{22}H_{15}NO$: C, 90.10; H, 5.11; N, 4.77. Found: C, 90.09; H, 5.13; N, 4.75.

1-(3'-pyridyl)-3-(2''-thienyl)-2-propen-1-one (3_f)

Yield 96%; mp 162 °C; Relative molecular mass 215; IR (KBr) 1696 (C=O), 1620 (CH=CH), 1590 (C=N), 650 (C-S); ^{1}H-NMR 7.07 (1H, d, J=17 Hz, -CO-CH=), 7.39 (1H, d, =CH -Ar), 7.20-8.73 (7H, Ar-H). Anal.calcd for $C_{12}H_9NOS$: C, 66.97; H, 4.18; N, 6.51. Found: C, 64.99; H, 4.16; N, 6.50.

General procedure for the synthesis of pyrimidines

A mixture of chalcones (obtained by the above method) of 3-acetylpyridine (0.001 mol) and guanidine hydrochloride (0.001 mol) in absolute ethanol (10 ml) were refluxed on a water bath for 6 hours. The solvent was completely evaporated and the residue was poured into ice cold water, the precipitated solid was collected by filtration and crystallized from a suitable solvent to give the desired substituted pyrimidine.



(3_{a-f}) (4_{a-f})

2-amino-4-(3'- pyridyl)-6-(3"-nitrophenyl) pyrimidine (4_a)

Yield 72%; mp 265-269 °C; Relative molecular mass 293; IR (KBr) 3342 (NH_2), 1642 (C=N), 1586 (C=C), 1358 (C-N); ^{1}H-NMR 7.20 (1H, s, C-5-H), 5.52 (2H, s, C-2- NH_2), 7.40-8.70 (8H, Ar-H). Anal.calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.75; N, 23.89. Found: C, 61.45; H, 3.79; N, 23.91.

2-amino-4-(3'-pyridyl)-6-(2", 4"-dimethoxyphenyl) pyrimidine (4_b)

Yield 65%; mp 238-242 °C; Relative molecular mass 308; IR (KBr) 3316 (NH_2), 1680 (C=N), 1570 (C=C), 1340 (C-N), 1210 (C-O-C); ^{1}H-

NMR 7.36 (1H, s, C-5-H), 5.52 (2H, s, C-2-NH_2), 7.26-8.60 (7H, Ar-H). Anal.calcd for $C_{17}H_{16}N_4O_2$: C, 65.59; H, 5.14; N, 18.00. Found: C, 65.60; H, 5.13; N, 18.01.

2-amino-4-(3'- pyridyl)-6-(3", 4"-dimethoxy phenyl) pyrimidine (4_c)

Yield 75%; mp 285-289 ^{0}C; Relative molecular mass 311; IR (KBr) 3340 (NH_2), 1632 (C=N), 1579 (C=C), 1356 (C-N), 1208 (C-O-C); ^{1}H-NMR 7.30 (1H, s, C-5-H), 5.58 (2H, s, C-2-NH_2), 3.95 (6H, 2 x OCH_3), 6.90 – 8.69 (7H, Ar-H). Anal.calcd for $C_{17}H_{16}N_4O_2$: C, 65.59; H, 5.14; N, 18.00. Found: C, 65.57; H, 5.12; N, 18.02.

Table 1: Antibacterial activity

Compound No	Zone of inhibition (in mm) Quantity in µg/ml									
	B. subtilis		*B. pumilis*		*S. aureus*		*E. coli*		*P. vulgaris*	
	50	100	50	100	50	100	50	100	50	100
3_a	13	22	12	20	13	19	14	20	14	20
3_b	15	23	13	22	15	21	17	23	16	24
3_c	16	22	15	23	17	20	18	24	17	25
3_d	10	18	10	17	09	15	13	18	12	19
3_e	11	17	10	16	08	16	12	19	10	19
3_f	10	17	10	17	08	15	12	18	10	17
4_a	13	18	15	19	15	18	17	19	15	17
4_b	10	18	10	17	16	18	17	19	12	14
4_c	11	13	11	18	13	16	16	18	13	15
4_d	08	12	11	13	14	16	15	19	10	12
4_e	09	13	12	15	11	15	16	19	16	18
4_f	10	14	12	16	12	15	15	19	15	17
Ampicillin	20	25	19	27	19	24	22	28	21	30

Table 2: Antifungal activity

Compound No	Zone of inhibition (in mm) Quantity in µg/ml					
	A. niger		*C. albicans*		*R. oryzae*	
	0.05ml	0.1ml	0.05ml	0.1ml	0.05ml	0.1ml
3_a	16	22	17	22	15	23
3_b	13	16	13	19	10	19
3_c	13	17	12	19	10	18
3_d	15	19	15	21	12	20
3_e	13	17	11	20	10	18
3_f	11	15	12	18	12	19
4_a	14	18	15	18	13	19
4_b	10	13	13	16	10	15
4_c	10	14	13	16	11	16
4_d	10	13	12	16	10	14
4_e	13	17	14	17	12	18
4_f	12	16	14	17	11	17
Fluconazole	25	28	24	29	22	28

2-amino-4-(3'-pyridyl)-6-(4"-dimethylaminophenyl) pyrimidine (4_d)

Yield 72%; mp 265-269 ^{0}C; Relative molecular mass 266; IR (KBr) 3342 (NH_2), 1642 (C=N), 1586 (C=C), 1358 (C-N), 1108 (-N-$(CH_3)_2$); ^{1}H -NMR 7.30 (1H, s, C-5-H), 5.30 (2H, s, C-2-NH_2), 3.10 (6H, -N-$(CH_3)_2$) -6.80– 9.10 (8H, Ar-H). Anal.calcd for $C_{17}H_{17}N_5$: C, 70.10; H, 5.84; N, 24.05. Found: C, 70.06; H, 5.82; N, 24.02.

2-amino-4-(3'-pyridyl)-6-(9"-anthracenyl) pyrimidine (4_e)

Yield 75%; mp 295-299 ^{0}C; Relative molecular mass 348; IR (KBr) 3340 (NH_2),1640 (C=N), 1580 (C=C), 1358 (C-N); ^{1}H-NMR 7.30 (1H, s, C-5-H), 5.60 (2H, s, C-2-NH_2), 7.10-8.75 (13H, Ar-H). Anal.calcd for $C_{23}H_{16}N_4$: C, 79.31; H, 4.59; N, 16.09. Found: C, 79.28; H, 4.56; N, 16.10.

2-amino-4-(3'- pyridyl)-6-(2"-thienyl) pyrimidine (4_f)

Yield 62%; mp 208-212 ^{0}C; Relative molecular mass 254; IR (KBr) 3308 (NH_2), 1632 (C=N), 1579 (C=C), 1358 (C-N), ^{1}H-NMR 7.20 (1H, s, C-5-H), 5.30 (2H, s, C-2-NH_2), 7.10 – 8.80 (7H, Ar-H). Anal.calcd for $C_{13}H_{10}SN_4$: C, 61.41; H, 3.93; N, 22.04. Found: C, 61.38; H, 3.90; N, 22.01.

Antimicrobial activity

The antibacterial activity of synthesized chalcones and their pyrimidine derivatives was conducted against three Gram-positive bacteria viz., *Bacillus pumilis, Bacillus subtilis* and *Staphylococcus aureus* and two Gram-negative bacteria viz., *Escherichia coli, Proteus vulgaris* by using cup plate method. Preparation of nutrient broth, subculture, agar medium and peptone water was done as per standard procedure. Each test compound (5 mg) was dissolved in dimethylsulfoxide (5 ml) to give a concentration of 1000 mg/ml. All the compounds and the standard were tested at 50 µg (0.05 ml) and 100 µg (0.1 ml) dose levels and DMSO used as a control. Ampicillin as standard drug was also prepared at a concentration of 1000 mg/ml in sterilized distilled water.

All the compounds which were screened for antibacterial activity, also screened for their antifungal activity. The fungi employed for screening were *Aspergillus niger, Rhizopus oryzae* and *Candida albicans*. Fluconazole was employed as standard to compare the results. The test organisms were sub-cultured using potato-dextrose-agar (PDA) medium.

Each test compound (5mg) was dissolved in dimethylsulfoxide (5ml) to give a concentration of 1000 µg/ml. Fluconazole solution was also prepared at a concentration of 1000 mg/ml in sterilized distilled water. All the compounds and the standard were tested at 50 µg (0.05 ml) and 100 µg (0.1 ml) dose levels and DMSO used as a control.

RESULTS AND DISCUSSION

The screening results reveal that all the synthesized novel compounds showed significant antimicrobial activity. Among all the synthesized novel pyrimidine compounds, the novel pyrimidine with 3-nitro substitution (4_e) exhibited the effective antibacterial and antifungal activities. The standard drugs used were Ampicillin and Fluconazole for antibacterial and antifungal activity respectively.

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