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RESEARCH ARTICLE

Synthesis and Antimicrobial Activity of Some Novel Chalcones of 3-Acetyl Pyridine and their Pyrimidine Derivatives

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Abstract: Chalcones afford a facile route of access to many of the heterocyclic systems containing oxygen and nitrogen. An attempt is therefore made to synthesize chalcones from 3-acetylpyridine by reaction with either aromatic or heteroaromatic aldehyde using Claisen-Schmidt condensation. The resulting chalcones after purification and characterization by physical and spectral methods have been successfully converted into substituted pyrimidines by reaction with guanidine hydrochloride. 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 activities by cup plate method.

Keywords: Chalcones, Synthesis, Antimicrobial activity

Introduction

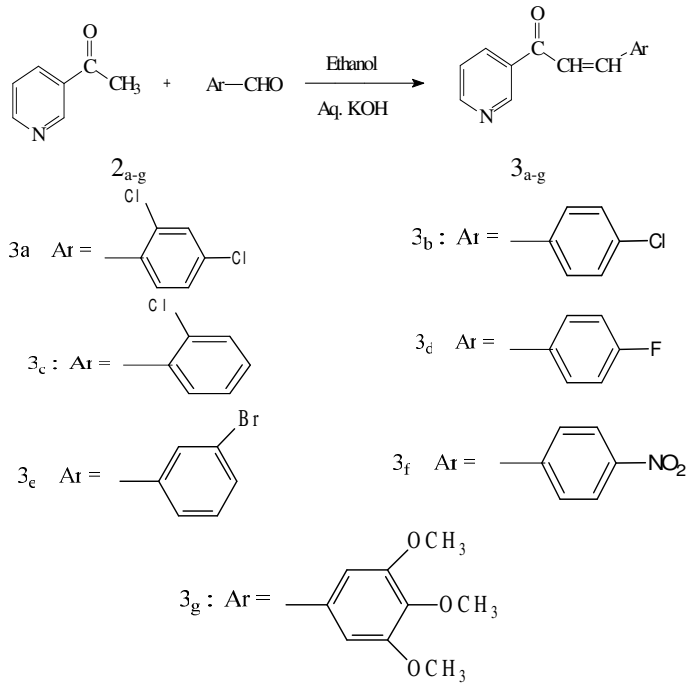
Chalcones either natural or synthetic and their heterocyclics are known to exhibit various biological activities. They have been reported to possess antioxidant, antimicrobial, antileishmanial, anti-inflammatory, antitumour and antibacterial activity. The presence of a reactive, unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent on the rings. In the present communication we report the reaction of 3-acetylpyridine with different aromatic aldehydes (**2**$_{\mathbf{a-g}}$) to form chalcones[1-13] (**3**$_{\mathbf{a-g}}$) in the presence of alkali. The resulting chalcones after purification and characterization by physical and spectral methods have been successfully converted into substituted pyrimidines[14-19] (**4**$_{\mathbf{a-g}}$) 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[20-21].

Experimental

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 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 h, at room temperature. Completion of the reaction was identified by TLC using Silica gel-G. After completion of the reaction (Scheme 1), 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.



Scheme 1

*1-(3'- Pyridyl)-3-(2'',4''-dichlorophenyl)-2-propen-1-one (**3$_a$**)*

Yield 82%; mp 155; Relative molecular mass 277; IR (KBr) 1673 (C=O), 1607 (HC = CH), 1584 (C =N), 1096 (C – Cl); ^{1}H NMR 7.47 (1H, d, J=17 Hz , =CH-Ar), 7.2 (1H, d, J=17 Hz, -CO-CH=), 7.57 – 8.76 (7H, Ar-H).Anal.calcd for $C_{14}H_9Cl_2NO$: C, 60.64; H, 3.25; N, 5.05. Found: C, 60.62; H, 3.23; N, 5.06.

*1-(3'- Pyridyl)-3-(4''-chlorophenyl)-2-propen-1-one (**3$_b$**)*

Yield 82%; mp 167; Relative molecular mass 243; IR (KBr) 1672 (C =O), 1610 (HC =CH), 1596 (C =N), 1090 (C- Cl); ^{1}H NMR 7.41 (1H, d, J=17 Hz, - CO- CH =), 7.70 (1H, d, J=17 Hz, = CH- Ar), 7.1 – 8.7 (8H, Ar- H). Anal.calcd for $C_{14}H_{10}ClNO$: C, 69.13; H, 4.11; N, 5.76. Found: C, 69.12; H, 4.13; N, 5.74.

*1-(3'-Pyridyl)-3-(2''-chlorophenyl)-2-propen-1-one (**3$_c$**)*

Yield 78%; mp 96; Relative molecular mass 244; IR (KBr) 1690 (C=O), 1626 (CH=CH), 1580 (C=N), 1086 (C-Cl); ^{1}H NMR 7.26 (1H, d, J=17 Hz, -CO-CH=), 7.42 (1H, d, J=17 Hz, =CH- Ar), 7.49– 8.74 (8H, Ar-H) Anal.calcd for $C_{14}H_{10}ClNO$: C, 69.13; H, 4.10; N, 5.76. Found: C, 69.10; H, 4.09; N, 5.77.

*1-(3'-Pyridyl)-3-(4''-fluorophenyl)-2-propen-1-one (**3$_d$**)*

Yield 90%; mp 90; Relative molecular mass 226; IR (KBr) 1680 (C=O), 1610 (CH=CH), 1584 (C=N), 1110 (C-F); ^{1}H NMR 7.26 (1H, d, J=17 Hz, -CO-CH=), 7.47 (1H, d, J=17 Hz, =CH - Ar), 7.08 – 8.74 (8H, Ar-H). Anal.calcd for $C_{14}H_{10}FNO$: C, 74.33; H, 4.42; N, 6.19. Found: C, 74.30; H, 4.40; N, 6.17.

*1-(3'-Pyridyl)-3-(3''-bromophenyl)-2-propen-1-one (**3$_e$**)*

Yield 92%; mp 140; Relative molecular mass 288; IR (KBr) 1680 (C =O), 1610 (HC =CH), 1580 (C = N), 1170 (C- Br); ^{1}H NMR 6.67 (1H, d, J=17 Hz, -CO-CH=), 7.3 (1H, d, J=17 Hz, =CH-Ar), 6.99 – 8.76 (8H, Ar-H). Anal.calcd for $C_{14}H_{10}BrNO$: C, 58.33; H, 3.47; N, 4.86. Found: C, 58.34; H, 3.48; N, 4.84.

*1-(3'-Pyridyl)-3-(4''-nitrophenyl)-2-propen-1-one (**3$_f$**)*

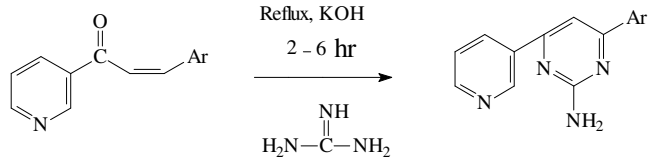
Yield 86%; mp 156; Relative molecular mass 254; IR (KBr) 1690 (C=O), 1618 (CH=CH), 1596 (C=N), 1520 (N=O, asymmetric), 1340 (N=O, symmetric); ^{1}H NMR 7.20 (1H, d, J=17 Hz, -CO-CH=), 7.45 (1H, d, J=17 Hz, =CH -Ar), 7.4 -8.53 (8H, Ar-H). Anal.calcd for $C_{14}H_{10}N_2O_3$: C, 66.56; H, 3.93; N, 11.02. Found: C, 64.54; H, 3.92; N, 11.00.

*1-(3'-Pyridyl)-3-(3'', 4'', 5''-trimethoxyphenyl)-2-propen-1-one (**3$_g$**)*

Yield 78%; mp 115; Relative molecular mass 299; IR (KBr) 1690 (C = O), 1610 (HC =CH), 1585 (C = N), 1210 (C- O - C); ^{1}H NMR 3.95 (9H, 3xOCH_3), 7.20 (1H,d, J=17 Hz, -CO-CH =), 7.26 (1H, d, J=17 Hz, =CH-Ar) 7.20 – 7.28 (6H, Ar - H). Anal.calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.68; N, 4.68. Found: C, 68.20; H, 5.66; N, 4.67.

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$_{a-g}$**) (**4$_{a-g}$**)

*2-Amino-4-(3'- pyridyl)-6-(2",4"-dichlorophenyl) pyrimidine (**4**$_a$)*

Yield 65%; mp 238-242 ^{0}C; Relative molecular mass 317; IR (KBr) 3316(NH_2), 1680(C=N), 1570 (C=C), 1340 (C-N),1050 (C-Cl); ^{1}H NMR 7.20 (1H, s, C-5-H), 5.23 (2H, s, C-2- NH_2), 7.40-8.80 (7H, Ar-H). Anal.calcd for $C_{15}H_{10}Cl_2N_4$: C, 56.78; H, 3.15; N, 17.66. Found: C, 56.76; H, 3.12; N, 17.64.

*2-Amino-4-(3'-pyridyl)-6-(4"-chlorophenyl) pyrimidine (**4**$_b$)*

Yield 56%; mp 232-236 ^{0}C; Relative molecular mass 282; IR (KBr) 3338 (NH_2), 1670 (C=N), 1580 (C=C), 1348 (C-N), 1050 (C-Cl); ^{1}H NMR 7.25 (1H, s, C-5-H), 5.27 (2H, s, C-2-NH_2), 6.98 - 8.71 (8H, Ar-H). Anal.calcd for $C_{15}H_{11}ClN_4$: C, 63.82; H, 3.89; N, 19.85. Found: C, 63.80; H, 3.88; N, 19.80.

*2-Amino-4-(3'- pyridyl)-6-(2"-chlorophenyl) pyrimidine (**4**$_c$)*

Yield 68%; mp152-126 ^{0}C; Relative molecular mass 282; IR (KBr) 3312 (NH_2), 1690 (C=N), 1567 (C=C), 1368 (C-N), 1034 (C-Cl); ^{1}H NMR 7.30 (1H, s, C-5-H), 5.25 (2H, s, C-2-NH_2), 6.90 – 8.7 (8H, Ar-H). Anal.calcd for $C_{15}H_{11}ClN_4$: C, 63.82; H, 3.89; N, 19.85. Found: C, 63.80; H, 3.87; N, 19.82.

*2-Amino-4-(3'-pyridyl)-6-(4"-fluorophenyl) pyrimidine (**4**$_d$)*

Yield 55%; mp 114-118 ^{0}C; Relative molecular mass 266; IR (KBr) 3336 (NH_2), 1682 (C=N), 1568 (C=C), 1365 (C-N), 1086 (C-F); ^{1}H NMR 7.30 (1H, s, C-5-H), 5.20 (2H, s, C-2-NH_2), 6.9 0– 8.75 (8H, Ar-H). Anal.calcd for $C_{15}H_{11}FN_4$: C, 67.66; H, 4.13; N, 21.05. Found: C, 67.64; H, 4.10; N, 21.03.

2-Amino-4-(3'-pyridyl)-6-(3"-bromophenyl) pyrimidine (4_e):

Yield 72%; mp 253-257 ^{0}C; Relative molecular mass 327; IR (KBr) 3340 (NH_2),1660 (C=N), 1540 (C=C), 1358 (C-N), 1020 (C-Br); ^{1}H NMR 7.20 (1H, s, C-5-H), 5.30 (2H, s, C-2-NH_2), 6.50-8.3 (8H, Ar-H). Anal.calcd for $C_{15}H_{11}BrN_4$: C, 55.04; H, 3.36; N, 17.12. Found: C, 55.05; H, 3.38; N, 17.10.

*2-Amino-4-(3'- pyridyl)-6-(3"-nitrophenyl) pyrimidine (**4**$_f$)*

Yield 72%; mp 265-269 ^{0}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-(3",4",5"-trimethoxyphenyl) pyrimidine (**4**$_g$)*

Yield 62%; mp 285-289 ^{0}C; Relative molecular mass 338; IR (KBr) 3335 (-NH_2), 1681 (C=N),1567 (C=C), 1358 (C-N), 1202(O-CH_3); ^{1}H NMR 7.30 (1H, s, C-5-H), 5.30 (2H, s, C-2-NH_2), 3.85 (9H, 3x OCH), 6.54 - 8.8 (6H, Ar-H). Anal.calcd for $C_{18}H_{18}N_4O_3$: C, 63.90; H, 5.34; N, 16.56. Found: C, 63.88; H, 5.30; N, 16.58.

Results and Discussion

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 µg/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 µg/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 (5 mg) was dissolved in dimethylsulfoxide (5 mL) to give a concentration of 1000 µg/mL. Fluconazole solution was also prepared at a concentration of 1000 µg/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.

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*	
	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL
3_a	08	15	08	13	07	10	09	13	08	11
3_b	09	17	08	15	08	14	10	15	11	16
3_c	10	18	09	17	09	16	11	17	11	17
3_d	11	19	10	18	10	17	12	18	12	18
3_e	07	14	08	13	06	10	09	12	08	11
3_f	12	20	11	19	11	18	13	19	13	19
3_g	17	22	16	23	17	21	18	24	18	26
4_a	17	20	18	21	16	17	19	21	18	20
4_b	16	20	18	21	17	19	18	21	16	17
4_c	15	19	17	20	17	19	19	23	16	18
4_d	18	21	17	21	17	19	20	21	18	20
4_e	14	19	16	20	15	18	17	19	15	17
4_f	13	18	15	19	15	18	17	19	15	17
4_g	09	15	12	14	15	17	16	20	11	13
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*	
	0.05 mL	0.1 mL	0.05 mL	0.1 mL	0.05 mL	0.1 mL
3_a	21	27	19	26	19	27
3_b	18	24	19	24	17	25
3_c	19	25	19	24	17	25
3_d	17	23	18	23	16	24
3_e	20	26	19	25	18	26
3_f	16	21	16	21	14	23
3_g	11	15	10	17	08	14
4_a	17	21	18	22	16	22

Contd…

4_b	16	20	18	21	15	21
4_c	16	20	18	20	15	21
4_d	18	22	17	21	17	22
4_e	15	19	16	19	14	20
4_f	14	18	15	18	13	19
4_g	09	11	11	14	08	12
Fluconazole	22	28	20	27	20	29

Conclusion

The screening results reveal that **3_{a-g}** showed significant antibacterial activity. In particular compound **3_g** having electron releasing substituent *i.e.,* trimethoxy group showed moderate to considerable antibacterial activity against all the organisms employed at a conc. of 1000 μg/mL (0.1 mL) dose level. In comparison to pyrimidines (**4_{a-g}**) synthesized using chalcone (**3_{a-g}**) showed better antibacterial activity than chalcones. In particular pyrimidine containing fluorine (**4_d**) substituent present at *para* position on phenyl ring enhanced the antibacterial activity.

From the results it is evident that chalcones with electron withdrawing (**3_a**) substituent showed better antifungal activity than other chalcones. The standard drugs used were ampicillin and fluconazole for antibacterial and antifungal activity respectively.

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