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Synthesis and Antibacterial Activity of Some Pyrimidines Containing β-Lactams

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1-[4-(4-Methylpiperazin-1-yl)phenyl]ethanone on condensation with aryl aldehydes afforded 1-[4-(4-methylpiperazin-1-yl)phenyl]-3-substituted phenyl prop-2-en-1-one (**1a-e**) in good yields, which underwent cyclization with guanidine hydrochloride (**2**) furnished 4-[4-(4-methylpiperazin-1-yl) phenyl]-6-substituted phenyl pyrimidin-2-amine (**3a-e**) followed by condensation of (**3a-e**) with benzaldehyde (4) yielded N-benzylidene-4-[4-(4-methylpiperazin-1-yl) phenyl]-6-substituted phenyl pyrimidin-2-amine (**5a-e**). The cyclo condensation of compound (**5a-e**) with chloro acetyl chloride (**6**) in presence of triethylamine gave 3-chloro-1-[4-(4-(4-methylpiperazin-1-yl) phenyl]-6-substituted phenyl pyrimidin-2-yl)-4-phenylazetidin-2-one (**7a-e**). The structures of these pyrimidines were established by spectral data. All the new compounds have been screened for their antibacterial activity.

Key Words: Chalcones, Pyrimidines, Imines, β-Lactams, Antibacterial activity.

INTRODUCTION

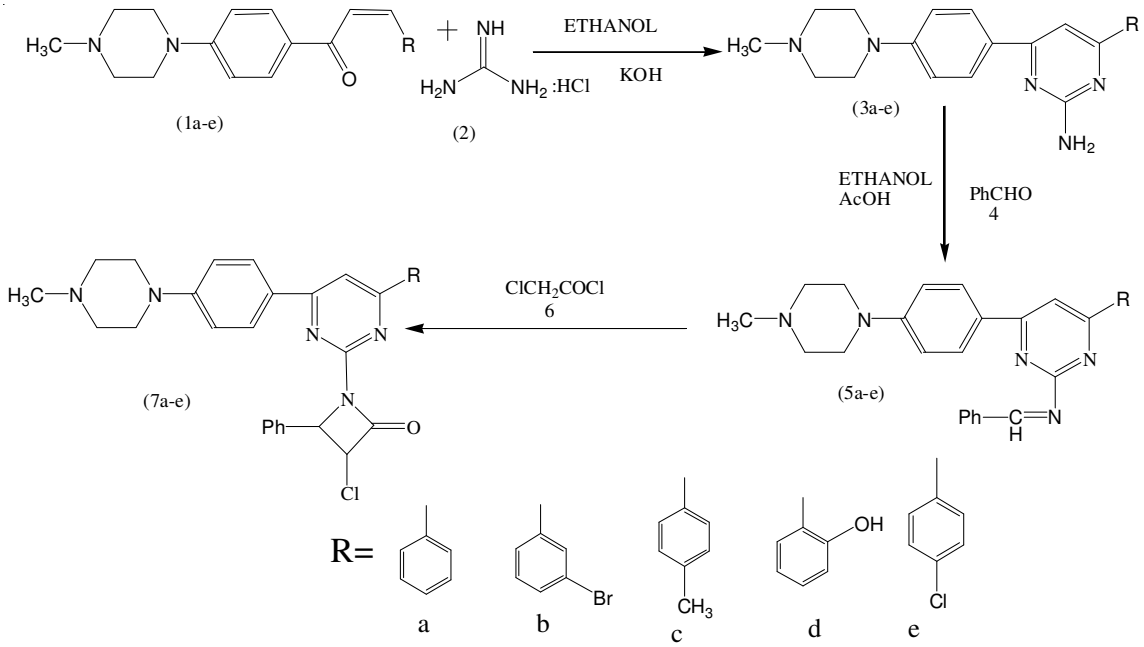
The synthesis and pharmacological activity of condensed pyrimidine derivatives have been reported. To prepare new pyrimidine derivatives we used chalcone as a starting material. Chalcones are 1,3-diary-l-2-propene-1-ones. Pyrimidines are important class of heterocyclic compounds, which possess wider range of pharmacological activities such as anticancer[1,2], antibacterial[3], antiinflammatory[4], antiviral[5], antitubercular[6], antihypertensive[7] and anticonvulsant[8], antihistamic[9] activity. It is an established fact that imines show potent antitubercular[10], antimicrobial[11], anticancer[12], antiviral[13], antifungal[13,14], and antibacterial[13,14] activities. The synthesis of azitidinone[15] from aminopyridine have been reported earliar. Herein is reported a practical and efficient method for the synthesis of some novel pyrimidines and azitidinone. All the new compounds were characterized by their elemental analyses and their spectral data.

EXPERIMENTAL

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a cintex m.p. apparatus and are uncorrected. The ^{1}H NMR were recorded in the indicated solvent on a Varian 500 MHz and 200 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Brucher-IFS-66 FT-IR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E. Merk Kieselgel 60 F_{254}).

General procedure for the preparation of chalcone derivatives (1a-e): A mixture of 1-[4-(4-methylpiperazin-1-yl)phenyl]ethanone (0.01 mole), aryl aldehydes (0.01 mol), an aqueous solution of 10 % KOH (10 mL) and methanol (20 mL) was refluxed for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and poured into crushed ice and then acidified with hydrochloric acid. The separated solid was filtered and purified by recrystallization from ethyl acetate and methanol (7:3) to afforded (**1a-e**) (**Scheme-I**).

General procedure for the preparation of pyrimidines (3 a-e): A mixture of appropriate chalcones (**1a-e**, 0.01 mol) and guanidine hydrochloride (**2**) (0.01 mol) and alcoholic KOH (10 mL) was heated to reflux for 5 h. After completion of the reaction as indicated by TLC, the solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration. The solid thus obtained was purified on silica gel column using ethyl acetate and methanol mixture (8:2) solvent system (**Scheme-I**). The chemical, spectral data and biological data of the compounds (**3a-e**) are presented in Tables 1-4.



Scheme-I. Synthesis of 3-chloro-1-(4-(4(4-methylpiperazin-1-yl) phenyl)-6-substituted phenyl pyrimidin-2-yl)-4-phenylazetidin-2-one (**7a-e**)

General procedure for the preparation of imines (5a-e) : A mixture of compound (**3a-e**, 0.01 mol), benzaldehyde (**4**) (0.01 mol), few drops of acetic acid and ethanol was heated at 65 ºC for 4 h. After completion of the reaction as indicated by TLC, the solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration. The solid thus obtained was crystallized from methanol (**5a-e**) (**Scheme-I**). The chemical, spectral data and biological data of the compounds (**5a-e**) are given in Tables 1-4.

TABLE-1
CHARACTERIZATION DATA OF COMPOUNDS
(**3a-e**), (**5a-e**) AND (**7a-e**)

Comp.	m.f.	m.p. (ºC)	Yield (%)
3a	$C_{21}H_{23}N_5$	140	75
3b	$C_{21}H_{22}N_5Br$	112	69
3c	$C_{22}H_{25}N_5$	135	82
3d	$C_{21}H_{23}N_5$	142	72
3e	$C_{29}H_{27}N_5$	122	77
5a	$C_{28}H_{27}N_5$	187	67
5b	$C_{28}H_{27}N_5Br$	192	69
5c	$C_{29}H_{29}N_5$	182	64
5d	$C_{28}H_{27}N_5$	202	62
5e	$C_{36}H_{31}N_5$	210	71
7a	$C_{30}H_{28}N_5OCl$	210	67
7b	$C_{30}H_{28}N_5OBrCl$	215	62
7c	$C_{31}H_{30}N_5OCl$	201	60
7d	$C_{30}H_{28}N_5OCl$	221	68
7e	$C_{38}H_{32}N_5OCl$	218	65

Elemental analyses for C, H, N are within ± 0.4 % of the theoretical values. *Solvent for crystallization: Ethyl acetate: Methanol for (**3a-e**); Methanol for (**5a-e**) and (**7a-e**).

General procedure for the preparation of azetidin-2-ones (7a-e): A mixture of compound (**5a-e**, 0.01 mol), choloroacetyl chloride (**6**) (0.02 mol), toluene (20 mL) and tri ethylamine (0.02 mol) were refluxed for 8 h. After completion of the reaction as indicated by TLC, the solvent was completely

TABLE-2
SPECTRAL DATA OF THE COMPOUNDS
(**3a-e**), (**5a-e**) AND (**7a-e**)

Comp.	^{1}H NMR (DMSO-d_6, ppm)
3a	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4X CH_2), 3.99 (2H, brs,-NH_2), 7.60 (1H, s, C-5-H), 6.58-7.83 (9H, m, Ar-H)
3b	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 4.26 (2H, brs,-NH_2), 6.6 (1H, s, C-2-H), 8.4 (1H, s, C-5-H), 6.9 – 8.2 (7H, m, Ar-H).
3c	2.2 (3H, s, -CH_3), 2.37 (3H, s, -CH_3), 2.5-2.8 (8H, m, 4XCH_2), 3.74 (2H, brs, -NH_2), 7.56 (1H, s, C-5-H), 6.52-8.11 (8H, m, Ar-H).
3d	2.3 (3H, s, CH_3), 2.5-2.99 (8H, m, 4XCH_2), 3.93 (2H, brs,-NH_2), 6.37 (1H, s, C-2- OH), 7.48 (1H, s, C-5-H), 6.73-8.11 (8H, s, Ar-H).
3e	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 4.14 (2H, brs,-NH_2), 7.2 (1H, s, C-5-H), 6.75- 8.69 (13H, m-Ar-H).
5a	2.3 (3H, s, CH_3) 2.5-2.8 (8H, m, 4XCH_2), 7.60 (1H, s, C-5-H), 6.58-7.83 (14H, m, Ar-H), 8.59 (1H, s, -N=CH).
5b	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 6.6 (1H, s, C-2-H), 8.4 (1H, s, C-5-H), 6.9 – 8.2 (12H, m, Ar-H), 8.59 (1H, s, -N=CH).
5c	2.2 (3H, s, -CH_3), 2.37 (3H, s, -CH_3), 2.5-2.8 (8H, m, 4XCH_2), 7.56 (1H, s, C-5-H), 6.52-8.11 (13H, m, Ar-H), 8.59 (1H, s, -N=CH).
5d	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 6.37(1H, s, C-2-OH), 7.48 (1H, s, C-5-H), 6.73-8.11 (13H, s, Ar), 8.59 (1H, s, -N=CH).
5e	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 7.2 (1H, s, C-5-H), 6.75- 8.69(18H, m-Ar-H), 8.59 (1H, s, -N=CH).
7a	2.3 (3H, s, CH_3) 2.5-2.8 (8H, m, 4XCH_2), 5.1 (1H, d, -CH-N), 5.5 (1H, d, -CH-Cl), 7.60 (1H, s, C-5-H), 6.58-7.83 (14H, m, Ar-H).
7b	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 5.1 (1H, d, -CH-N), 5.5 (1H, d, -CH-Cl), 6.6 (1H, s, C-2-H), 8.4 (1H, s, C-5-H), 6.9–8.2 (12H, m, Ar-H).
7c	2.2 (3H, s, -CH_3), 2.37 (3H, s, -CH_3), 2.5-2.8 (8H, m, 4XCH_2), 5.1 (1H, d, -CH-N), 5.5 (1H, d, -CH-Cl), 7.56 (1H, s, C-5-H), 6.52-8.11 (13H, m, Ar-H).
7d	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 5.1 (1H, d, -CH-N), 5.5 (1H, d, -CH-Cl), 6.37 (1H, s, C-2-OH), 7.48 (1H, s, C-5-H), 6.73-8.11 (13H, s, Ar-H).
7e	2.3 (3H, s, CH_3), 2.5-2.8 (8H, m, 4XCH_2), 5.1 (1H, d, -CH-N), 5.5 (1H, d, -CH-Cl), 7.2 (1H, s, C-5-H), 6.75-8.69 (18H, m-Ar-H).

S: singlet; d: doublet ; dd: doublet of doublets; m: multiplet.

evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration. The solid thus obtained was crystallized from methanol (**7a-e**) (**Scheme-1**). The chemical, spectral data and biological data of the compounds (**7a-e**) are in Tables 1-4.

TABLE-3
SPECTRAL DATA OF THE COMPOUNDS (**3a-e**), (**5a-e**) AND (**7a-e**)

Comp.	IR (KBr, cm^{-1})
3a	1575 (C=C);1602 (C=N); 3194, 3431 (-NH_2)
3b	536 (C-Br); 1564 (C=C); 1598 (C=N); 3194, 3431 (-NH_2)
3c	1575 (C=C); 1603 (C=N); 3194, 3431 (-NH_2)
3d	1572 (C=N); 3194, 3431 (-NH_2)
3e	1567 (C=C);1602 (C=N); 3194, 3431 (-NH_2)
5a	1575 (C=C); 1602 (C=N); 2900 (C-H)
5b	536 (C-Br); 1564 (C=C); 1598 (C=N); 2900(C-H)
5c	1575 (C=C); 1603 (C=N); 2900 (C-H)
5d	1572 (C=N); 2900 (C-H)
5e	1567 (C=C); 1602 (C=N); 2900(C-H)
7a	1575 (C=C); 1602 (C=N); 1610 (C=O), 2900 (C-H)
7b	536 (C-Br); 1564 (C=C); 1598 (C=N); 1610 (C=O), 2900 (C-H)
7c	1575 (C=C); 1603 (C=N); 1610 (C=O), 2900 (C-H)
7d	1572 (C=N); 1610 (C=O), 2900 (C-H)
7e	1567 (C=C); 1602 (C=N); 1610 (C=O), 2900 (C-H)

Antibacterial activity: *In vitro* screening of newly prepared compounds for antibacterial activity was screened through agar-cup method. The bacterial species used were *S. aureus*, *E.coli*, *S. typhi* and *B. subtilis*. The results are given in Table-4.

TABLE-4
ANTIBACTERIAL SCREENING DATA OF THE COMPOUNDS (**3a-e**), (**5a-e**) AND (**7a-e**)

Compound	Inhibition zone in mm at 100µg/mL concentration			
	Staphylococcus aureus	*E. coli*	*Salmonella typhi*	*B. Subtilis*
3a	06	08	6	12
3b	10	7	6	5
3c	4	9	8	5
3d	3	7	4	9
3e	–	–	8	8
5 a	6	5	8	5
5 b	–	6	12	6
5 c	4	5	8	4
5d	10	3	4	6
5 e	5	2	–	8
7a	2	6	3	9
7b	3	10	7	–
7c	10	–	12	10
7d	4	12	5	13
7e	9	9	–	12
Chloramphenicol	19	23	24	18

RESULTS AND DISCUSSION

Perusal of the above Table-4 reveals that the derivatives were growth inhibitory towards all the bacteria. In the synthesized compounds some compounds showed moderate to good activity while some were found to be inactive. **5a** and **5b** showed good activity. **7b** was effective against *S.typhi* but most derivatives did not show good inhibitory activity against this bacterium. Compounds **9d** and **9e** were potent against *E. coli*, *B. subtilis*. From the above study, it may be concluded that it is worthwhile to pursue further investigating by manipulating these novel pyrimidines.

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