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Synthesis and Antibacterial Activity of Some Novel Pyrimidines and Piperidinyl Acetamides

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1-[4-(4-Benzylpiperidin-1-yl)phenyl]ethanone on condensation with aryl aldehydes afforded 1-[4-(4-benzylpiperidin-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-benzylpiperidin-1-yl)phenyl]-6-substituted phenyl pyrimidin-2-amine (**3a-e**) followed by reaction with chloroacetyl chloride (**4**) in the presence of triethyl amine yielded N-4-[4-(4-benzylpiperidin-1-yl)phenyl]-6-substituted phenyl pyrimidin-2-yl)-2-chloroacetamide (**5a-e**). The compound N-4-(4-(4-benzylpiperidin-1-yl) phenyl)-6-substituted phenyl pyrimidin-2-yl)-2-(piperidin-1-yl)acetamide (**7a-e**) has been prepared by treatment of piperdine, dry acetone and anhydrous potassium carbonate. The structures of the above synthesized new compounds were established by spectral data. All the new compounds have been screened for their antibacterial activity.

Key Words: Chalcones, Pyrimidines, Piperidinyl acetamides, 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. 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], anticonvulsant[8] and antihistamic[9] activities. 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 present work described the synthesis of chloro acetamide and piperidinyl acetamides. Herein is reported a practical and efficient method for the synthesis of some novel pyrimidines and piperidinyl acetamides. All the new compounds were characterized by their elemental analyses and their spectral data.

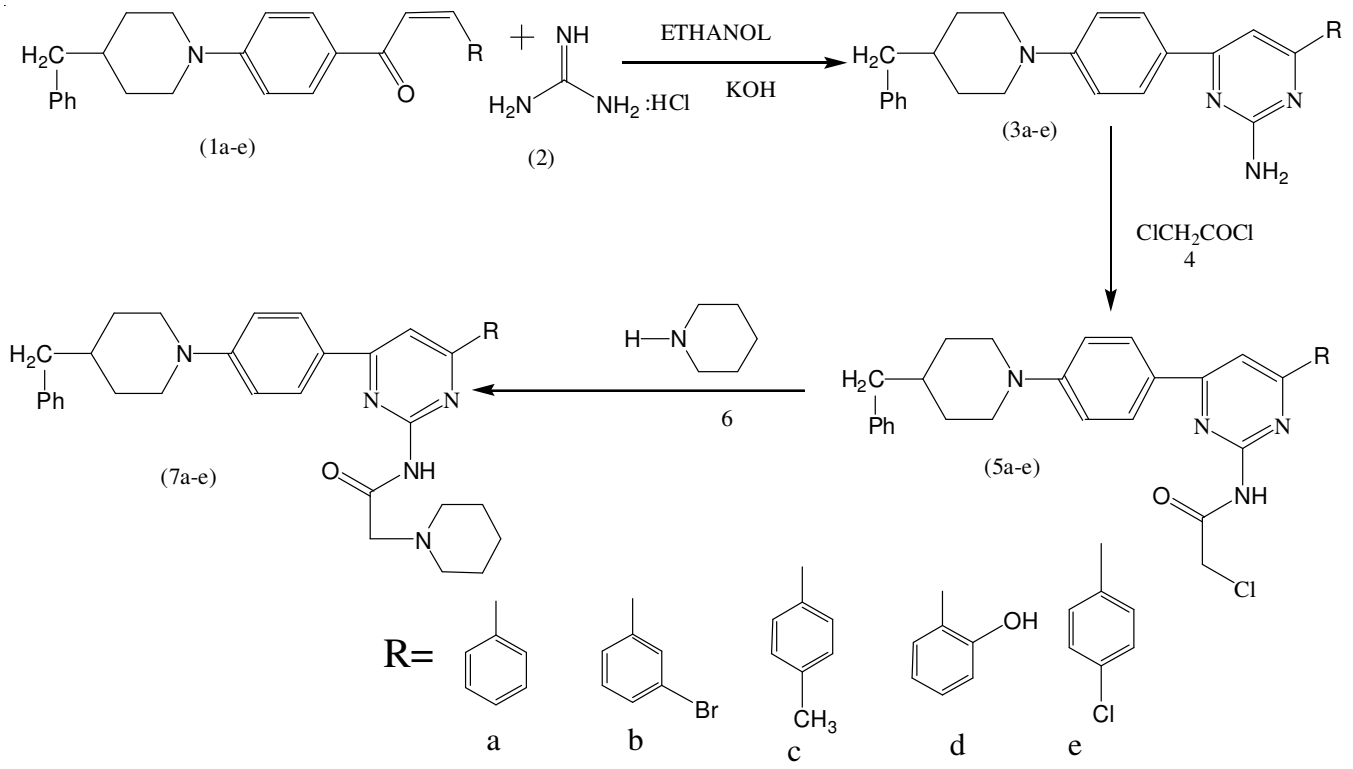
EXPERIMENTAL

Chemicals and solvents were reagent grade and used without further purification. Melting points were determined on a Cintex melting point apparatus and are uncorrected. The ^{1}H NMR were recorded in the indicated solvent on a Varian 500 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}). Irradiation was carried out in a domestic microwave oven (LG MG 556 P, 2450 MHz).

General procedure for the preparation of chalcone derivatives (1a-e): A mixture of 1-[4-(4-benzylpiperidin-1-yl)phenyl]ethanone (0.01 mol), aryl aldehydes (0.01 mol), an aqueous solution of 10 % KOH (10 mL) and methanol (20 mL) was refluxed for 8 h. 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 afford (**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.

General procedure for the preparation of N-4-(4-(4-benzylpiperidin-1-yl)phenyl)-6-substituted phenyl



Scheme-I: Synthesis of N-4-(4-(4-benzylpiperidin-1-yl)phenyl)-6-substituted phenyl pyrimidin-2-yl)-2-(piperidin-1-yl) acetamide

pyrimidin-2-yl)-2-chloroacetamide (5a-e): A mixture of (**3a-e**, 0.01 mol), chloroacetyl chloride (**4**, 0.01 mol), dichloromethane (20 mL) and triethyl amine (3 mL) was heated at 65 ºC for 4 hrs. After completion of the reaction as indicated by TLC. The precipitated solid was collected by filtration (**Scheme-I**). The chemical, spectral data and biological data of the compounds (**5a-e**) are in Tables 1-4.

General procedure for the preparation of N-4-(4-(4-benzylpiperidin-1-yl) phenyl)-6-substituted phenyl pyrimidin-2-yl)-2-(piperidin-1-yl) acetamide (7 a-e): A mixture of (**5a-e**, 0.01 mol), piperidine (**6**, 0.01 mol), acetone (20 mL) and powdered potassium carbonate (0.01 mol) was

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

Compound	m.f.	m.p. (ºC)	Yield (%)
3a	$C_{28}H_{28}N_4$	128	74
3b	$C_{28}H_{27}BrN_4$	122	70
3c	$C_{29}H_{30}N_4$	131	80
3d	$C_{28}H_{28}N_4$	135	68
3e	$C_{36}H_{32}N_4$	118	83
5a	$C_{30}H_{29}ClN_4O$	102	67
5b	$C_{30}H_{28}BrClN_4O$	98	68
5c	$C_{31}H_{31}ClN_4O$	111	63
5d	$C_{30}H_{29}ClN_4O$	115	61
5e	$C_{38}H_{33}ClN_4O$	108	72
7a	$C_{35}H_{39}N_5O$	141	74
7b	$C_{35}H_{38}BrN_5O$	135	68
7c	$C_{36}H_{41}N_5O$	128	64
7d	$C_{35}H_{39}N_5O$	133	73
7e	$C_{43}H_{43}N_5O$	124	62

Elemental analyses for C, H, N are within ± 0.4 % of the theoretical values. *Solvent for crystallization: ethanol for (**5a-e**); ethylacetate: methanol (7a-e) and methanol for (**9a-e**).

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

Comp.	^{1}H NMR (DMSO-d_6, ppm) ($CDCl_3$) (δ ppm)
3a	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2); 3.99 (2H, brs, -NH_2), 5.1 (1H, m, -CH-), 7.6 (1H, s, C-5-H); 6.58-7.83 (14H, m, Ar-H)
3b	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2); 4.26 (2H, brs, -NH_2); 5.1 (1H, m, -CH-), 6.6 (1H, s, C-2-H); 8.4 (1H, s, C-5-H), 6.9-8.2 (13H, m, Ar-H)
3c	1.8 (4H, m, 2x-CH_2); 2.37 (3H, s, -CH_3); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2); 3.74 (2H, brs, -NH_2); 5.1 (1H, m, -CH-), 7.56 (1H, s, C-5-H), 6.52-8.11 (13H, m, Ar-H)
3d	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2), 3.93 (2H, brs, -NH_2); 5.1 (1H, m, -CH-), 6.37 (1H, s, C-2-OH); 7.48 (1H, s, C-5-H); 6.73-8.11 (13H, m, Ar-H)
3e	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2), 4.14 (2H, brs, -NH_2), 5.1 (1H, m, -CH-), 7.2 (1H, s, C-5-H), 6.75-8.69 (13H, m, Ar-H)
5a	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2); 4.3 (2H, s, -CH-Cl), 5.1 (1H, m, -CH-), 7.6 (1H, s, C-5-H); 6.58-7.83 (14H, m, Ar-H), 8.2 (1H, brs, -NH-)
5b	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2); 4.3 (2H, s, -CH-Cl), 5.1 (1H, m, -CH-), 6.6 (1H, s, C-2-H); 8.4 (1H, s, C-5-H), 6.9-8.2 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)
5c	1.8 (4H, m, 2x-CH_2); 2.37 (3H, s, -CH_3); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2); 4.3 (2H, s, -CH-Cl), 5.1 (1H, m, -CH-), 7.56 (1H, s, C-5-H), 6.52-8.11 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)
5d	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2), 4.3 (2H, s, -CH-Cl), 5.1 (1H, m, -CH-), 6.37 (1H, s, C-2-OH); 7.48 (1H, s, C-5-H); 6.73-8.11 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)
5e	1.8 (4H, m, 2x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (4H, t, 2xCH_2), 4.3 (2H, s, -CH-Cl), 5.1 (1H, m, -CH-), 7.2 (1H, s, C-5-H), 6.75-8.69 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)

7a	1.8 (10H, m, 5x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (8H, t, 4xCH_2); 3.5 (2H, s, -CH_2-N-), 5.1 (1H, m, -CH-), 7.6 (1H, s, C-5-H); 6.58-7.83 (14H, m, Ar-H), 8.2 (1H, brs, -NH-)
7b	1.8 (10H, m, 5x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (8H, t, 4xCH_2); 3.5 (2H, s, -CH_2-N-), 5.1 (1H, m, -CH-), 6.6 (1H, s, C-2-H); 8.4 (1H, s, C-5-H), 6.9-8.2 (13H, m, Ar-H), 8.2 (1H, brs, -NH-).
7c	1.8 (10H, m, 5x-CH_2); 2.37 (3H, s, -CH_3); 2.6 (2H, d, CH_2-Ar), 3.1 (8H, t, 4xCH_2); 3.5 (2H, s, -CH_2-N-), 5.1 (1H, m, -CH-), 7.56 (1H, s, C-5-H), 6.52-8.11 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)
7d	1.8 (10H, m, 5x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (8H, t, 4xCH_2), 3.5 (2H, s, -CH_2-N-), 5.1 (1H, m, -CH-), 6.37 (1H, s, C-2-OH); 7.48 (1H, s, C-5-H); 6.73-8.11 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)
7e	1.8 (10H, m, 5x-CH_2); 2.6 (2H, d, CH_2-Ar), 3.1 (8H, t, 4xCH_2), 3.5 (2H, s, -CH_2-N-), 5.1 (1H, m, -CH-), 7.2 (1H, s, C-5-H), 6.75-8.69 (13H, m, Ar-H), 8.2 (1H, brs, -NH-)

*Solvent for ^{1}H NMR: DMSO-d_6 for (**5a-e**) and (**7a-e**); $CDCl_3$ for (**9a-e**).

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

Compound	IR (KBr, ν_{max}, cm^{-1})
3a	1610 (C=N), 1575 (C=C), 3431, 3194 (-NH_2)
3b	1602 (C=N), 1565 (C=C), 3431, 3194 (-NH_2)
3c	1608 (C=N), 1575 (C=C), 3431, 3194 (-NH_2)
3d	1612 (C=N), 3431, 3194 (-NH_2)
3e	1604 (C=N), 1567 (C=C), 3431, 3194 (-NH_2)
5a	720 (C-Cl), 1610 (C=N), 1575 (C=C), 1680 (C=O)
5b	720 (C-Cl), 1602 (C=N), 1565 (C=C), 1680 (C=O)
5c	720 (C-Cl), 1608 (C=N), 1575 (C=C), 1680 (C=O)
5d	720 (C-Cl), 1612 (C=N), 1680 (C=O)
5e	720 (C-Cl), 1604 (C=N), 1567 (C=C, 1680 (C=O)
7a	1610 (C=N), 1575 (C=C), 1680 (C=O)
7b	1602 (C=N), 1565 (C=C), 1680 (C=O)
7c	1608 (C=N), 1575 (C=C), 1680 (C=O)
7d	1612 (C=N), 1680 (C=O)
7e	1604 (C=N), 1567 (C=C), 1680 (C=O)

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

Comp.	Inhibition zone in mm at 100 µg/mL concentration			
	S. aureus	*E. coli*	*S. typhi*	*B. subtilis*
3a	8	5	7	–
3b	10	8	3	9
3c	–	5	8	3
3d	14	11	–	7
3e	14	10	9	3
5a	4	–	–	5
5b	5	12	7	12
5c	7	–	–	10
5d	10	14	5	11
5e	8	–	–	10
7a	4	8	5	7
7b	5	7	6	–
7c	10	–	3	5
7d	14	13	5	10
7e	12	9	9	8
Standard chloramphenicol	19	23	24	18

refluxed for 4 h. After completion of the reaction as indicated by TLC. The solvent was completely evapourated and the residue was poured into ice cold water. The precipitated solid was collected by filtration (**Scheme-I**). The chemical, spectral data and biological data of the compounds (**7a-e**) are in Tables 1-4.

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 depicted in the Table-4 given below.

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. **5d** and **5e** were effective against *S. aureus*, *E. coli* while **5c** was not growth inhibitory. **7b** and **7d** were also showed good inhibitory activity against the organisms tested. Compound **9d** was the most potent for inhibition of *S. aureus* and *E. coli*. From the above study, it may be concluded that it is worthwhile to pursue further investigations by manipulating these novel pyrimidines.

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