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Microwave assisted synthesis and antibacterial activity of some piperidine containing pyrimidine imines and thiazolidinones

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ABSTRACT

1-(4-(4-piperidin-1-yl)phenyl)ethanone on condensation with aryl aldehydes afforded 1-(4-(4-piperidin-1-yl)phenyl)-3-substituted phenylprop-2-en-1-one **(1a-e)** in good yields which underwent cyclization with guanidine hydrochloride **(2)** furnished 4-phenyl-6-(4-(piperidin-1-yl) substituted phenyl)pyrimidin-2-amine **(3a-e)** followed by condensation of **(3a-e)** with benzaldehyde **(4)** yielded N-benzylidene-4-phenyl-6-(4-(piperidin-1-yl) substituted phenyl)pyrimidin-2-amine **(5a-e)**. The cyclo condensation of compound **(5a-e)** with mercapto acetic acid **(6)** gave 2-phenyl-3-(4-phenyl-6-(4-(piperidin-1-yl)substituted phenyl)pyrimidine-2-yl)thiazolidin-4-one **(7a-e)** in appreciable yields. All the reactions have been carried out under microwave irradiation. The structures of the above synthesized new compounds were established by spectral data. All the new compounds have been screened for their antibacterial activity.

KEYWORDS

Chalcones;
Pyrimidines;
Imines;
Thiazolidinones;
Microwave irradiation;
Antibacterial activity.

INTRODUCTION

Pyrimidines are important class of heterocyclic compounds which possess wider range of pharmacological activities such as anticancer[1,2], antibacterial[3], anti-inflammatory[4], antiviral[5], antitubercular[6], antihypertensive[7] and anticonvulsant[8], antihistamic[9] activity. It is an established fact that thiazolidinones and imines show potent antitubercular[10], antimicrobial[11], anticancer[12], antiviral[13], antifungal[13,14], and antibacterial[13,14] activities which are precursors for thiazolidinones[15,16]. Due to the activities associated with imines and thiazolidinones an attempt was made to generate novel potent antibacterial imines **(5a-e)** and thiazolidinones **(7a-e)** from amine moiety **(3a-e)**. Microwave (MW) activation as non-conventional energy source has become a very popular and useful technology in synthetic organic chemistry[17-20] Recently organic transformations accelerated under microwave irradiation conditions gained wide popularity due to many practical advantages associated with experimental simplicity, short reaction time, enhanced reaction rates, high yields and environment-friendly reaction conditions[17,18]. Herein is reported a practical and efficient method for the synthesis of some novel pyrimidines and thiazolidinones under microwave irradiation. All the new compounds were characterized by their elemental analyses and their spectral data.

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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 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}). Irradiation was carried out in a domestic microwave over (LG MG 556 P,2450 MHz).

General procedure for the preparation of chalcone derivatives (1a-e)

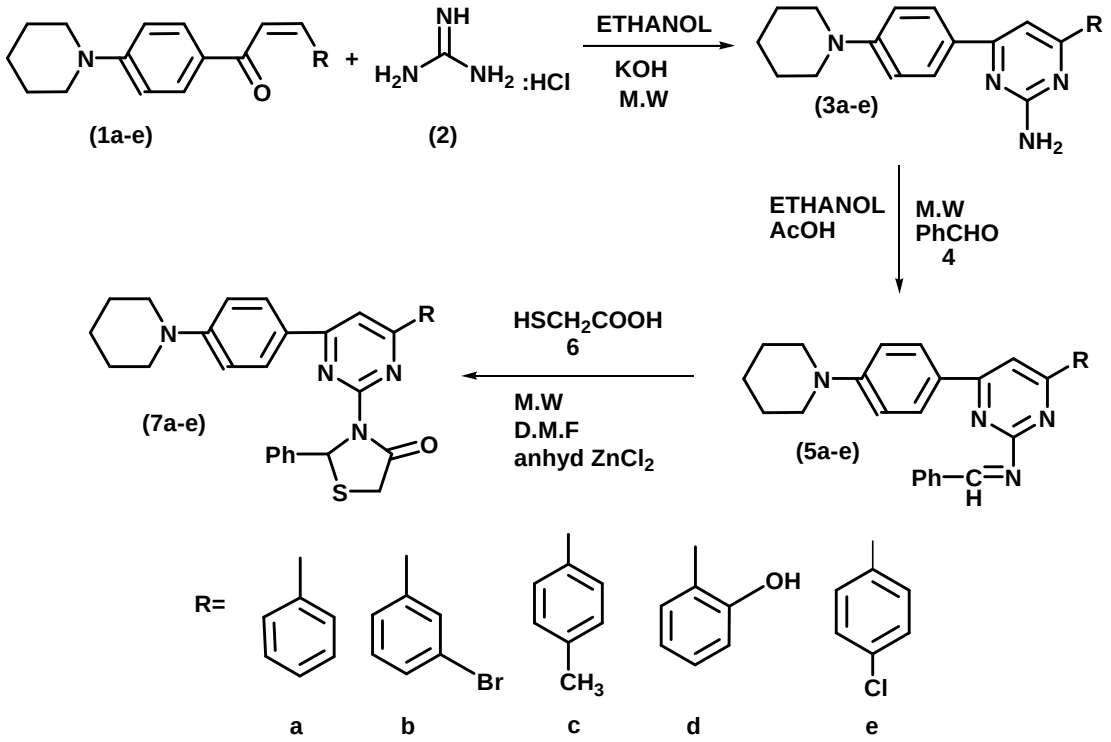
A mixture of 1-(4-(4-piperidin-1-yl) phenyl)-ethanone (0.01 mole), aryl aldehydes (0.01 mole), an aqueous solution of 10% KOH (10ml) and methanol (20ml) was subjected to microwave irradiation at 600W for 5 min. After completion of the reaction as indicated by T.L.C. The reaction mixture was cooled to 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 1)

General procedure for the preparation of pyrimidines (3a-e)

A mixture of appropriate Chalcones **(1a-e)**, (0.01mole) and guanidine hydrochloride **(2)**, (0.01 mole) and alcoholic KOH (10ml) was subjected to microwave irradiation at 600W for 6 min. After completion of the reaction as indicated by T.L.C. The solvent was completed 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 1). The chemical, spectral data and biological data of the compounds **(3a-e)** are in TABLES 1, 2, 3 and 4.

General procedure for the preparation of imines (5a-e)

A mixture of compound **(3a-e)**, (0.01mol),



Scheme 1 : Synthesis of 2-phenyl-3-(4-phenyl-6-(4-(piperidin-1-yl) substituted phenyl)pyrimidine-2-yl)thiazolidin-4-one (7a-e)

benzaldehyde **(4)**, (0.01mol), few drops of acetic acid and ethanol was subjected to microwave irradiation at 600W for 5 min. After completion of the reaction as indicated by T.L.C. The solvent was completed 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 1). The chemical, spectral data and biological data of the compounds **(5a-e)** are in TABLES 1, 2, 3 and 4.

TABLE 1 : Characterization data of compounds (3a-e), (5a-e) and (7a-e)

Comp.	M. Formula	m.p (°C)	Yield (%)
3a	$C_{21}H_{22}N_4$	142	82
3b	$C_{21}H_{21}BrN_4$	115	65
3c	$C_{22}H_{24}N_4$	102	80
3d	$C_{21}H_{22}N_4O$	128	78
3e	$C_{29}H_{26}N_4$	122	68
5a	$C_{28}H_{26}N_4$	191	62
5b	$C_{28}H_{25}BrN_4$	194	69
5c	$C_{29}H_{28}N_4$	181	64
5d	$C_{28}H_{26}N_4O$	202	67
5e	$C_{36}H_{30}N_4$	205	58
7a	$C_{30}H_{28}N_4OS$	218	60
7b	$C_{30}H_{27}BrN_4OS$	215	62
7c	$C_{31}H_{30}N_4OS$	192	57
7d	$C_{30}H_{28}N_4O_2S$	218	55
7e	$C_{38}H_{32}N_4OS$	223	89

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 thiazolidinones (7a-e)

A mixture of compound **(5a-e)**, (0.01 mole) and thioglycolic acid **(6)**, (0.02mole), anhydrous zinc chloride (0.001mole) and DMF (2ml) was subjected to microwave irradiation at 600W for 5 min. After completion of the reaction as indicated by T.L.C. The solvent was completed 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, 2, 3 and 4.

Antibacterial activity

In vitro screening of newly prepared compounds

TABLE 2 : Spectral data of the compounds (3a-e), (5a-e) and (7a-e)

Compd.	^{1}HNMR (DMSO-d_6, ppm)
3a	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 3.99(2H, brs,-NH_2), 7.60(1H,s, C-5-H), 6.58- 7.83(9H, m,Ar-H)
3b	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_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	1.8(6H,m,3XCH_2), 2.37(3H,s,-CH_3), 3.1(4H,m,2XCH_2), 3.74 (2H, brs, -NH_2), 7.56 (1H,s,C-5-H), 6.52- 8.11 (8H, m,Ar-H)
3d	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_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, m,Ar-H)
3e	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 4.14 (2H, brs,-NH_2),7.2 (1H,s,C-5- H), 6.75- 8.69 (13H, m,Ar-H)
5a	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 7.60(1H,s,C-5-H), 6.58-7.83(14H, m,Ar-H), 8.59(1H,s,-N=CH)
5b	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_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	1.8(6H,m,3XCH_2), 2.37(3H,s,-CH_3), 3.1(4H,m,2XCH_2), 7.56 (1H,s,C-5-H), 6.52- 8.11 (13H, m,Ar-H), 8.59(1H,s,-N=CH)
5d	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 6.37(1H,s,C-2-OH), 7.48 (1H,s,C-5- H), 6.52-8.11 (8H, m,Ar-H),8.58(1H,s,-N=CH),
5e	1.8 (6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 7.2 (1H,s,C-5-H),8.59(1H,s,- N=CH), 6.75-8.69 (18H, m,Ar-H)
7a	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 3.46(2H,s,CH_2-S),5.95(1H,s,-N-CH- S) 7.60(1H,s,C-5-H), 6.58- 7.83(14H, m,Ar-H)
7b	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 3.46(2H,s,CH_2S), 5.95(1H,s,-N-CH- S), 6.6(1H,s,C-2-H), 8.4(1H,s,C-5-H), 6.9-8.2 (12H, m,Ar-H)
7c	1.8(6H,m,3XCH_2), 2.37(3H,s,-CH_3), 3.1(4H,m,2XCH_2), 3.46 (2H, s, CH_2), 5.95(1H,s,-N-CH-S), 2.37(3H,s,-CH_3), 7.56 (1H,s,C-5-H), 6.52- 8.11 (13H, m,Ar-H)
7d	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 3.46 (2H,s,CH_2.S), 5.95(1H,s,-N- CH-S), 6.37(1H,s,C-2-OH), 7.48 (1H,s,C-5-H), 6.73-8.11 (13H, m,Ar-H)
7e	1.8(6H,m,3XCH_2), 3.1(4H,m,2XCH_2), 3.46(2H,s,CH_2-S), 5.95(1H,s,-N- CH-S), 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.

TABLE 3 : Spectral data of the compounds (3a-e), (5a-e) and (7a-e)

Compd.	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	1575(C=C), 3194, 3431(-NH_2)
3e	1567(C=C), 1602(C=N),3194,3431(-NH_2)
5a	1575(C=C), 1602(C=N),2900 (-CH)
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	696(C-S-C),1567(C=C), 1602(C=N), 1765(C=O), 2922(C-H of CH_2)
7b	536(C-Br), 696(C-S-C), 1564(C=C), 1598(C=N), 1765(C=O), 2922(C-H of CH_2)
7c	696(C-S-C),1575(C=C), 1603(C=N), 1765(C=O), 2922(C-H of CH_2)
7d	696(C-S-C),1575(C=C), 1765(C=O), 2922(C-H of CH_2)
7e	696(C-S-C),1567(C=C),1602(C=N), 1765(C=O),2922(C-H of CH_2)

TABLE 4 : Antibacterial screening data of the compounds (3a-e), (5a-e) and (7a-e)

Compound	Staphylococcus aureus	Klebsiella pneumoniae	Bacillus cereus	Pseudomon as putida	Salmonella paratyphi A	Salmonella paratyphi B
3a	6	4	8	3	2	2
3b	13	8	10	12	8	5
3c	11	12	6	12	13	14
3d	16	8	18	5	6	8
3e	4	8	8	10	9	12
5 a	8	12	14	8	4	6
5 b	12	8	6	4	-	5
5 c	6	3	4	6	10	8
5 d	8	12	7	5	5	5
5 e	8	11	4	8	8	6
7 a	9	10	12	8	8	12
7 b	10	6	2	2	3	1
7 c	2	3	3	4	1	3
7 d	4	6	6	2	3	4
7 e	4	8	10	7	6	8
Chloramphenicol	18	15	18	12	20	19

for antibacterial activity was screened through agar-cup method. The bacterial species used were *S.aureus*, *E.coli*, *S.typhi*, *B.cereus*, *Pseudomonas putida* and *Klebsiella pneumoniae*. 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. **(3d)**, **(3b)** and **(3c)** were more effective against *S.aureus*. Compound **(3c)** was effective against all the bacteria under investigation. Compounds **(3d)** was the most potent for inhibition of *B.cereus.* Compound **(5a)** was effective against *S.typhi* but most derivatives did not show good inhibitory activity against this bacterium. Compounds of the **(7a-e)** series did not show much activity against all the bacteria. 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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