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Microwave assisted synthesis and antibacterial activity of benzyl piperazine with pyrimidine and isoindolinedione

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ABSTRACT

1-(4-(4-benzylpiperazin-1-yl)phenyl) ethan one on condensation with aryl aldehydes afforded 1-(4-(4-benzylpiperazin-1-yl)phenyl)-3-phenylprop-2-en-1-one **(1a-e)** in good yields which underwent cyclization with guanidine hydrochloride **(2)** furnished 4-(4-(4-benzylpiperazin-1-yl)phenyl)-6-substituted phenyl pyrimidin-2-amine **(3a-e)**. The treatment of compound **(3a-e)** with phthalic anhydride **(4)** in the presence of catalytically amount of DMF under microwave irradiation yielded 2-(4-(4-(4-benzylpiperazin-1-yl)phenyl)-6-substituted phenyl pyrimidin-2-yl)isoindoline-1,3-dione **(5a-e)**. All 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

Phthalic anhydride;
Benzyl piperazine with pyrimidine and isoindolinedione;
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. Phthalimide derivatives constitute an important class of compounds possessing diverse type of biological properties including antimicrobial[10], antimalatial[10], antihypertensive[11,12], and antiviral[12] activity. Therefore, it was envisaged that chemical entities with both 4-(4-(4-benzylpiperazin-1-yl)phenyl)-6-substituted phenyl pyrimidin-2-amine and phthalic anhydride might result of 2-(4-(4-(4-benzylpiperazin-1-yl)phenyl)-6-substituted phenyl pyrimidin-2-yl)isoindoline-1,3-dione **(5a-e)** with interesting biological activity.

Microwave (MW) activation as non-conventional energy source has become a very popular and useful technology in synthetic organic chemistry[13-16] 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[13,14]. 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

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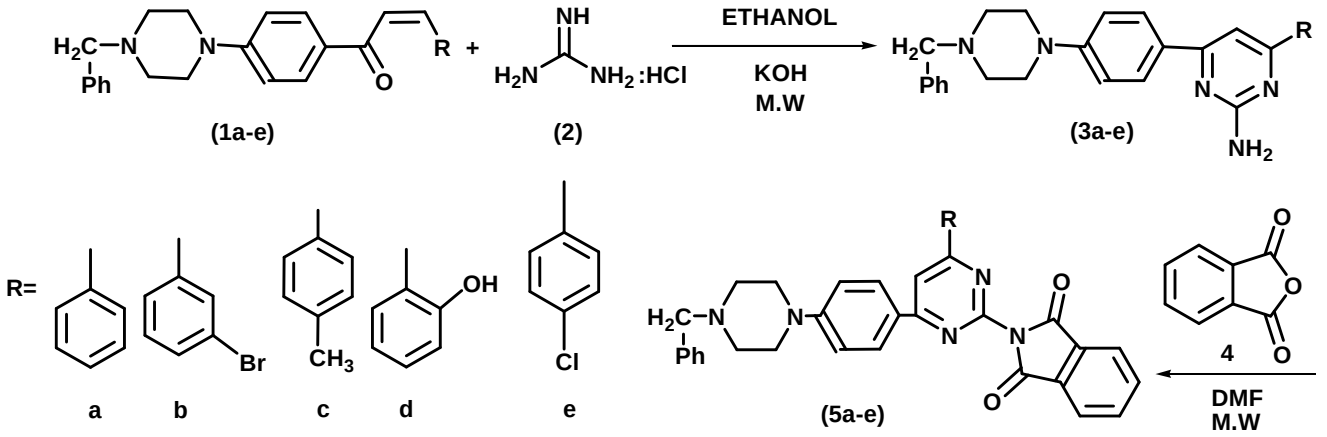
determined on a Cintex melting point apparatus and are uncorrected. The ^{1}H NMR were recorded in the indicated solvent on a Varian 500 MHz and 200 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a a Jeol JMS 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 1-(4-(4-benzylpiperazin-1-yl)phenyl)-3-substituted aryl prop-2-en-1-one (1a-e)

A mixture of 1-(4-(4-benzylpiperazin-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 ethanol **(1a-e)** (Scheme 1).

General procedure for the preparation of 4-(4-(4-benzylpiperazin-1-yl)phenyl)-6-substituted phenyl-pyrimidin-2-amine (3a-e)

A mixture of 1-(4-(4-benzylpiperazin-1-yl)phenyl)-3-substituted aryl prop-2-en-1-one **(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 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 1). The chemical, spectral data and biological data of the compounds **(3a-e)** are in TABLES 1,2,3 and 4.



Scheme 1 : Synthesis of 2-(4-(4-(4-benzylpiperazin-1-yl)phenyl)-6-substituted phenyl pyrimidin-2-yl)isoindoline-1,3-dione

General procedure for the preparation of 2-(4-(4-(4-benzylpiperazin-1-yl) phenyl)-6- substituted phenyl-pyrimidin-2-yl)isoindoline-1,3-dione (5a-e)

A mixture of 4-(4-(4-benzylpiperazin-1-yl)phenyl)-6- substituted phenylpyrimidin-2-amine **(3a-e)**, (0.01 mole), phthalic anhydride (4, 0.01 mole) and DMF

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

Comp.	M. Formula	m.p (°C)	Yield (%)
3a	$C_{27}H_{27}N_5$	141	72
3b	$C_{27}H_{26}BrN_5$	115	68
3c	$C_{28}H_{29}N_5$	111	75
3d	$C_{27}H_{27}N_5O$	132	62
3e	$C_{35}H_{31}N_5$	125	85
5a	$C_{35}H_{29}N_5O_2$	145	76
5b	$C_{35}H_{28}BrN_5O_2$	130	80
5c	$C_{36}H_{31}N_5O_2$	126	71
5d	$C_{36}H_{29}N_5O_3$	140	65
5e	$C_{43}H_{33}N_5O_2$	138	78

Elemental analyses for C,H,N are within ± 0.4% of the theoretical values.

***Solvent for crystallization: Ethyl acetate: Methanol (3a-e) and Methanol for (5a-e).**

(drops) was subjected to microwave irradiation at 600W for 6 min. After completion of the reaction as indicated by T.L.C. 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 by recrystallization 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 2 : Spectral data of the compounds (3a-e) and (5a-e)

Compd.	^{1}HNMR (DMSO-d_6, ppm)
3a	2.6(2H,s,-CH_2), 2.7(4H,m,2x CH_2), 3.6(4H,m,2xCH_2), 3.99(2H,brs,-NH_2), 7.60 (1H, s, C-5-H), 6.58-7.83 (14H, m, Ar-H)
3b	2.6(2H,s,-CH_2), 2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_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 (12H, m, Ar-H)
3c	2.37(3H,s,-CH_3), 2.6(2H,s,-CH_2), 2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_2), 3.74 (2H,brs,-NH_2), 7.56 (1H, s, C-5-H), 6.52- 8.11 (13H, m, Ar-H)
3d	2.6(2H,s,-CH_2), 2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_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 (13H, m, Ar-H)
3e	2.6(2H,s,-CH_2),2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_2), 4.14 (2H,brs,-NH_2), 7.2 (1H, s, C-5-H), 6.75- 8.69 (18H, m, Ar-H)
5a	2.6(2H,s,-CH_2), 2.7(4H,m,2x CH_2), 3.6 (4H,m,2x CH_2), 7.60 (1H, s, C-5-H), 6.58- 7.83 (18H, m, Ar-H)
5b	2.6(2H,s,-CH_2), 2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_2), 6.6(1H,s,C-2-H),8.4 (1H, s, C-5-H), 6.9- 8.2 (16H, m, Ar-H)
5c	2.37(3H,s,-CH_3), 2.6(2H,s,-CH_2),2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_2),7.56 (1H, s, C-5-H), 6.52-8.11 (17H, m, Ar-H)
5d	2.6(2H,s,-CH_2), 2.7 (4H,m,2x CH_2), 3.6(4H,m,2x CH_2), 6.37(1H,s,C-2-OH),7.48 (1H, s, C-5-H), 6.73- 8.11 (17H, m, Ar-H)
5e	2.6(2H,s,-CH_2), 2.7 (4H,m,2xCH_2), 3.6(4H,m,2xCH$_2$), 7.2 (1H, s, C-5-H), 6.75- 8.69 (22H, m, Ar-H)

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

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

Compd.	IR (KBr, cm^{-1})
3a	1575 (C=C), 1610(C=N), 3194,3431(-NH_2)
3b	1565 (C=C), 1602(C=N), 3194, 3431(-NH_2)
3c	1575 (C=C), 1608(C=N), 3194, 3431(-NH_2)
3d	1612 (C=C), 3194, 3431(-NH_2)
3e	1567 (C=C), 1604(C=N), 3194,3431(-NH_2)
5a	1575 (C=C), 1610(C=N), 1721,1786 (C=O)
5b	1565 (C=C), 1602(C=N), 1721,1787 (C=O)
5c	1575 (C=C), 1608(C=N), 1721,1786 (C=O)
5d	1612(C=N), 1720,1786 (C=O)
5e	1567 (C=C), 1604(C=N), 1721,1787 (C=O)

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:

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

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

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. **(3b)**, **(3e)** and **(3c)** showed good activity against towards all the bacteria. Compound **(3a)** was not growth inhibitory for many organisms. **(5a)**, **(5c)** and **(5d)** were potent against all the bacteria compared to other compounds in the seires. Compound **(5b)** did not show good activity against the organisms. 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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