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Microwave assisted synthesis and antibacterial activity of 2-(4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-yl) isoindoline-1, 3-diones

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ABSTRACT

1-(4-(piperidin-1-yl) phenyl) ethanone **(3)** has been synthesized by the reaction of piperidine **(1)** with 4-chloro acetophenone **(2)** in the presence of dry acetone under microwave irradiation. 1-(4-(piperidin-1-yl) phenyl) ethanone **(3)** on condensation with aryl aldehydes **(4a-e)** afforded 3-phenyl-1-(4-(piperidin-1-yl) aryl substituted) prop-2-en-1-one **(5a-e)** in good yields which underwent cyclization with guanidine hydrochloride **(6)** furnished 4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-amine **(7 a-e)**. The treatment of compound **(7a-e)** with phthalic anhydride **(8)** in the presence of catalytical amount of DMF under microwave irradiation yielded 2-(4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-yl) isoindoline-1,3-diones **(9a-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

4-Phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-amine;
2-(4-Phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-yl) isoindoline-1, 3-diones;
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], antimalarial[10], antihypertensive[11,12], and antiviral[12] activity. Therefore, it was envisaged that chemical entities with both 4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-amine and phthalimide might result of 2-(4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-yl) isoindoline-1,3-diones **(9a-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 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 procedure 1-(4-(piperidin-1-yl)phenyl)ethanone (3)

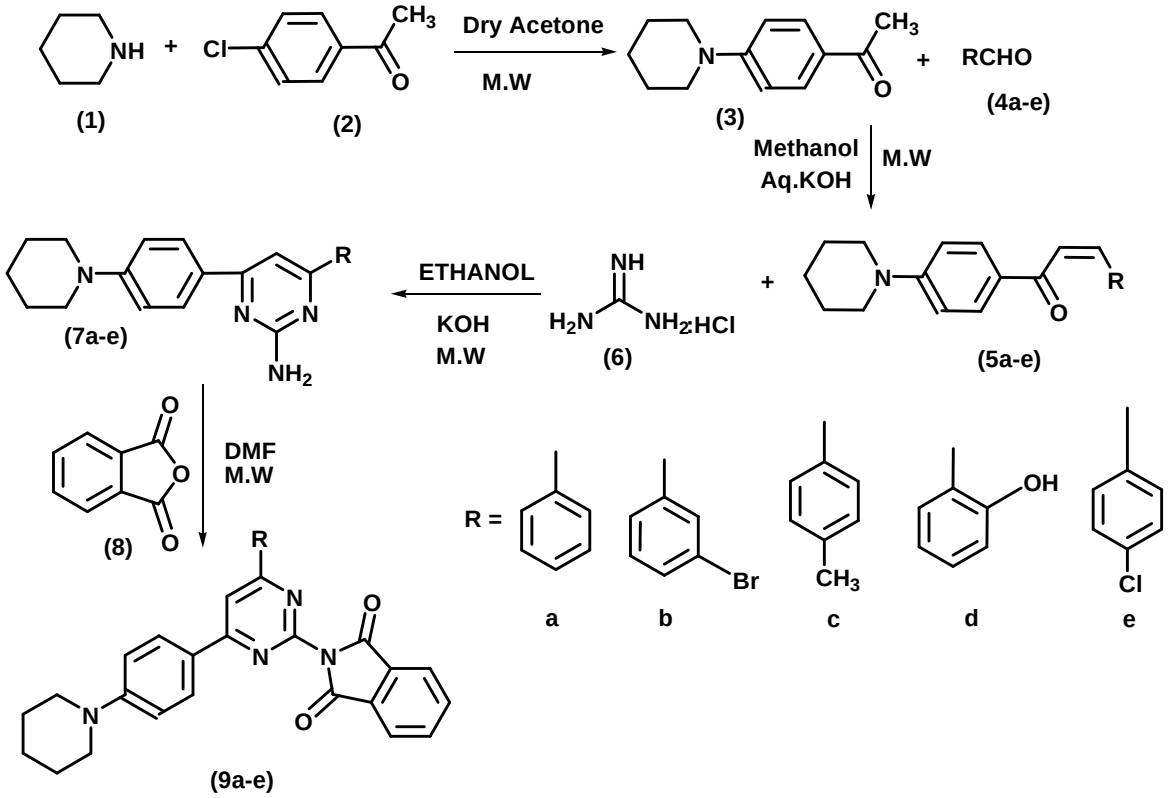
A mixture of piperidine (1, 0.01 mole), 4-chloro acetophenone (2, 0.01 mole) and dry acetone (10ml) was subjected to microwave irradiation at 600W for 5 min. After completion of the reaction as indicated by T.L.C. The reaction mixture was cooled to room temperature. The separated solid was filtered and purified by recrystallization ethanol to afforded **(3)** (Scheme 1).

General procedure for the preparation of 3-phenyl-1-(4-(piperidin-1-yl) aryl substituted) prop-2-en-1-one (5a-e)

A mixture of 1-(4-(piperidin-1-yl)phenyl)ethanone **(3)**, (0.01 mole), aryl aldehydes **(4a-e)**, (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 **(5a-e)** (Scheme 1). The chemical, spectral data and biological data of the compounds **(7a-e)** are in TABLE 1, 2, 3 and 4.

General procedure for the preparation of 4-phenyl-6-(4-(piperidin-1-yl)aryl substituted) pyrimidin-2-amine (7a-e)

A mixture of 3-phenyl-1-(4-(piperidin-1-yl) aryl substituted) prop-2-en-1-one **(5a-e)**, (0.01mole) and



Scheme 1 : Synthesis of 2-(4-phenyl-6-(4-(piperidin-1-yl) aryl substituted)pyrimidin-2-yl)isoindoline-1,3-diones

guanidine hydrochloride (6, 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 **(7a-e)** are in TABLE 1, 2, 3 and 4.

TABLE 1 : Characterization data of compounds (5a-e), (7a-e) and (9a-e)

Comp.	M. Formula	m.p (°C)	Yield (%)
5a	$C_{20}H_{20}NO$	112	85
5b	$C_{20}H_{20}BrNO$	1 05	73
5c	$C_{21}H_{23}NO$	122	68
5d	$C_{20}H_{21}NO_2$	116	79
5e	$C_{25}H_{28}NO$	127	82
7a	$C_{21}H_{22}N_4$	143	85
7b	$C_{21}H_{21}BrN_4$	112	62
7c	$C_{22}H_{24}N_4$	109	76
7d	$C_{21}H_{22}N_4O$	135	68
7e	$C_{29}H_{26}N_4$	122	72
9a	$C_{29}H_{24}N_4O_2$	130	78
9b	$C_{29}H_{23}BrN_4O$	120	65
9c	$C_{30}H_{26}N_4O_2$	128	72
9d	$C_{29}H_{24}N_4O_3$	142	80
9e	$C_{37}H_{28}N_4O_2$	136	78

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).**

General procedure for the preparation of 2-(4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-yl)isoindoline-1,3-diones (9a-e)

A mixture of 4-phenyl-6-(4-(piperidin-1-yl) aryl substituted) pyrimidin-2-amine **(7a-e)**, (0.01 mole), phthalic anhydride (8, 0.01 mole) and DMF (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 completed 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 **(9a-e)** (Scheme 1). The chemical, spectral data and biological data of the compounds **(7a-e)** are in TABLE 1, 2, 3 and 4.

TABLE 2 : Spectral data of the compounds (5a-e), (7a-e) and (9a-e)

Compd.	^{1}HNMR (DMSO-d_6, ppm) ($CDCl_3$)(δ ppm)
5a	1.8(6H,m,3x-CH_2); 3.1 (4H,t,2xCH_2); 7.20(1H,d,CH); 7.26(1H,d,CH), 6.9-7.8(9H,Ar-H)
5b	1.8(6H,m,3x-CH_2);3.1(4H,t,2xCH_2);7.20(1H,d,CH); 7.26(1H,d,CH),6.9-7.8(8H,Ar-H)
5c	1.8(6H,m,3x-CH_2); 2.37(3H,s,-CH_3); 3.1(4H,t,2xCH_2) ;7.20 (1H,d,CH),7.26(1H,d,CH)
5d	1.8(6H,m,3x-CH_2); 3.1(4H,t,2xCH_2) ;6.37(1H,s,C-2-OH),7.20 (1H,d,CH),7.26(1H,d,CH);6.9-7.8(8H,m,Ar-H)
5e	1.8(6H,m,3x-CH_2); 3.1(4H,t,2xCH_2) ;7.20 (1H,d,CH),7.26(1H,d,CH); 6.9-7.8(8H,m,Ar-H)
7a	1.8(6H,m,3x-CH_2); 3.1(4H,t,2xCH_2) ;3.99(2H,brs,-NH_2)7.6 (1H,s,C-5-H),; 6.58-7.83(8H,m,Ar-H)
7b	1.8(6H,m,3x-CH_2);3.1(4H,t,2xCH_2);4.26(2H,brs,-MH_2);6.6(1H,s, C-2-H);8.4 (1H,s,C-5-H),; 6.9- 8.2(7H,m,Ar-H), 7.83(8H,m,Ar-H)
7c	1.8(6H,m,3x-CH_2); 2.37(3H,s,-CH_3); 3.1(4H,t,2xCH_2) ; 3.74(2H,brs,-NH_2); 7.56(1H,s,C-5-H),6.52-8.11(8H,m,Ar-H)
7d	1.8(6H,m,3x-CH_2); 3.1(4H,t,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),
7e	1.8(6H,m,3x-CH_2); 3.1(4H,t,2xCH_2),4.14(2H,brs,-NH_2) 7.2(1H,s,C-5-H), 6.75-8.69(13H,m,Ar-H)
9a	1.8 (6H,m,3xCH_2); 3.1(4H,t,2xCH_2); 7.6(1H,s,C-5-H); 6.58-7.83(13H,m,Ar-H)
9b	1.8 (6H,m,3xCH_2); 3.1(4H,t,2xCH_2); 6.6(1H,s,C-2-H), 8.4 (1H,s,C-5-H); 6.9-8.2(11H,m,Ar-H)
9c	1.8 (6H,m,3xCH_2); 2.37(3H,s,-CH_3), 3.1(4H,t,2xCH_2); 7.56 (1H,s,C-5-H), 6.52-8.11(12H,m,Ar- H)
9d	1.8 (6H,m,3xCH_2); 3.1(4H,t,2xCH_2); 6.37(1H,s,C-2-OH),7.48 (1H,s,C-5-H), 6.73-8.11(12H,m,Ar- H)
9e	1.8 (6H,m,3xCH_2); 3.1(4H,t,2xCH_2); 7.2 (1H,s,C-5-H), 6.75-8.69 (17H,m, Ar- H)

S, singlet; d, doublet ; dd, doublet of doublets; m, multiplet.
***Solvent for ^{1}HNMR : DMSO-d_6 for (5a-e) and (7a-e) ; $CDCl_3$ for (9a-e).**

TABLE 3 : Spectral data of the compounds (5a-e), (7a-e) and (9a-e)

Compd.	IR (KBr, cm^{-1})
5a	1575(C = C);1602(C = N); 3194,3431 (-NH_2)
5b	536(C-Br);1564(C = C);1598(C = N); 3194,3431(-NH_2)
5c	1575 (C = C);1603(C = N); 3194,3431 (-NH_2)
5d	1572 (C = N); 3194, 3431 (-NH_2)
5e	1567(C = C);1602 (C = N); 3194,3431 (-NH_2)
7a	3431,3194 (-NH_2), 1610(C = N),1575(C = C)
7b	3431,3194 (-NH_2), 1602 (C = N), 1565(C = C)
7c	3431,3194 (-NH_2), 1608(C = N),1575(C = C)
7d	3431,3194 (-NH_2), 1612(C = N)
7e	3431,3194 (-NH_2), 1604 (C = N), 1567 (C = C)
9a	1786,1721 (C = O), 1610(C = N), 1575(C = C)
9b	1787,1721 (C = O), 1602(C = N),1565(C = C)
9c	1786,1721 (C = O), 1608 (C = N), 1575(C = C)
9d	1786,1720 (C = O), 1612(C = N)
9e	1787,1721 (C = O), 1604 (C = N), 1567(C = C)

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 (5a-e), (7a-e) and (9a-e)

Compound	Inhibition zone in mm at 100µg/ml concentration.			
	Staphylococcus Aureus	E.coli	Salmonella typhi	B.subtilis
5a	12	12	---	8
5b	17	13	12	9
5c	11	10	10	7
5d	15	11	---	7
5e	---	---	8	8
7a	9	8	8	6
7b	13	10	9	10
7c	---	5	---	6
7d	18	4	7	12
7e	8	---	4	10
9a	7	12	8	---
9b	10	13	---	11
9c	15	6	13	15
9d	4	12	8	11
9e	13	10	9	10
Standard 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. **(7d)** and **(5b)** were as good as the standard drug chloramphenicol towards *S.aureus*. Similarly, **(9b)** and **(9d)** were effective against *E.coli* while **(5e)** and **(7e)** were not growth inhibitory. **(5b)** and **(9c)** were effective against *S.typhi* but most derivatives did not show good inhibitory activity against this bacterium. Compound **(9c)** was the most potent for inhibition of *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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REFERENCES

[1] J.Mattew, A.V.Subba Rao, S.Rambhav; Curr.Sci., **53(11)**, 576-7 **(1984)**.
[2] T.Yamakawa, H.Kagechika, E.Kawachi, Y.Hashimoto, K.Shedo; J.Med.Chem., **33(5)**, 1430-7 **(1990)**.
[3] S.Isida, A.Matsuda, Y.Kawamura, K.Yamanaka; Chromatography (Tokyo), **8**, 146-51 **(1960)**.
[4] M.B.Hogale, N.P.Dhore, A.R.Shelar, P.K.Pawar; Orient.J.Chem., **2**, 55-7 **(1986)**.
[5] V.K.Ahluwalia, L.Nayal, N.Kalia, S.Bala, A.K.Tahim; Indian J.Chem., **26B(4)**, 384-6 **(1987)**.
[6] A.K.Bhat, R.P.Bhamana, M.R.Patel, R.A.Bellare, C.V.Deliwala; Indian J.Chem., **10(7)**, 694-8 **(1972)**.
[7] H.Ishitsuka, Y.T.Ninomiya, C.Ohsawa, M.Fujiu, Y.Suhara; Antimicrob.Agents Chem.-Other. **22(4)**, 617-21 **(1982)**.
[8] Y.Ninomiya, N.Shimma, H.Ishitsuka; Antiviral Res., **13(2)**, 61-74 **(1990)**.
[9] Sk.A.Rahaman, Y.Rajendra Pasad, Phani Kumar, Bharath Kumar; Saudi Pharmaceutical Journal, **17(3)**, July **(2009)**.
[10] S.Bhawani Singh, M.Deepika, K.B.Lalith, G.L.Talesera; Indian J.Chem., **43B**, 1306 **(2004)**.
[11] B.M.Khadikar, S.D.Samant; Indian J.Chem., **32B**, 1137 **(1993)**.
[12] V.K.Pandey, T.Sarah, T.Zehra, R.Raghubir, M.Dixit, M.N.Joshi, S.K.Bajpai; Indian J.Chem., **43B**, 180 **(2004)**.
[13] S.Caddick; Tetrahedron, **51**, 10403 **(1995)**.
[14] A.Loupy, A.Petit, J.Hamelin, F.Texier-Boullet, P.Jacquault, D.Mathe; Syntheisis, 1213 **(1998)**.
[15] R.S.Varma; Green Chem., **1**, 43 **(1993)**.
[16] P.Lidstorm, J.Tierney, B.Wathey, J.Westman; Tetrahedron, **57**, 9225 **(2001)**.