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MICROWAVE ASSISTED DIRECT RAPID AND EFFICIENT SYNTHESIS OF SOME NOVEL DIHYDROPYRIMIDINES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

One pot three-component Biginelli reaction of aromatic aldehyde, β-keto amide and urea/thiourea has been carried out under microwave irradiation and by conventional method. All the prepared compounds were characterized by their spectral (IR, NMR, Mass) data and screened for their antimicrobial activity.

Key words : Biginelli reaction, Dihydropyrimidinones, Dihydropyrimidinethiones, Antimicrobial activity.

INTRODUCTION

Dihydropyrimidine is the most important member in all the diazines. The chemistry of pyrimidines and their derivatives has been studied for over a century due to the association of these systems with a variety of biological properties. Since 1980's, a number of publications and patents are published for the activity of DHPM derivatives which indicates that the interest on the subject is tremendously increased[1–3]. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial and antiinflammatory activities has been described to these partly reduced pyrimidine derivatives[4]. Recently, appropriately functionalized DHPMs have emerged as orally active antihypertensive agents[5–7] or $\alpha 1_a$ adrenoceptor-selective antagonists[8, 9]. Mayer et al.[10–12] have recently identified the structurally rather simple DHPM (monastrol) as a novel cell-permeable molecule. Monastrol is the only cell-permeable molecule currently known to specifically inhibit mitotic kinesin Eg5 and can therefore be considered as a leader for the

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development of new anticancer drugs. Looking to these multifold properties exhibited by them, We are reporting here the synthesis and biological activities of some novel dihydropyrimidinones and dihydropyrimidinethiones in the hope that they may possess potential biological activitities.

Conventional methods for synthesizing dihydropyrimidines utilizes aromatic aldehyde, β Keto ester and urea or thiourea in the presence of acidic catalyst. Although, several methods are reported for the synthesis of dihydropyrimidines in literature, We report herewith the direct and rapid method for the synthesis of dihydropyrimidines under microwave irradiation as well as conventional method.

The structures of the synthesized compounds were assigned based on elemental analysis, IR, ^{1}H NMR and Mass spectral data. All newly synthesized compounds have been screened for their *in vitro* antimicrobial activity.

EXPERIMENTAL

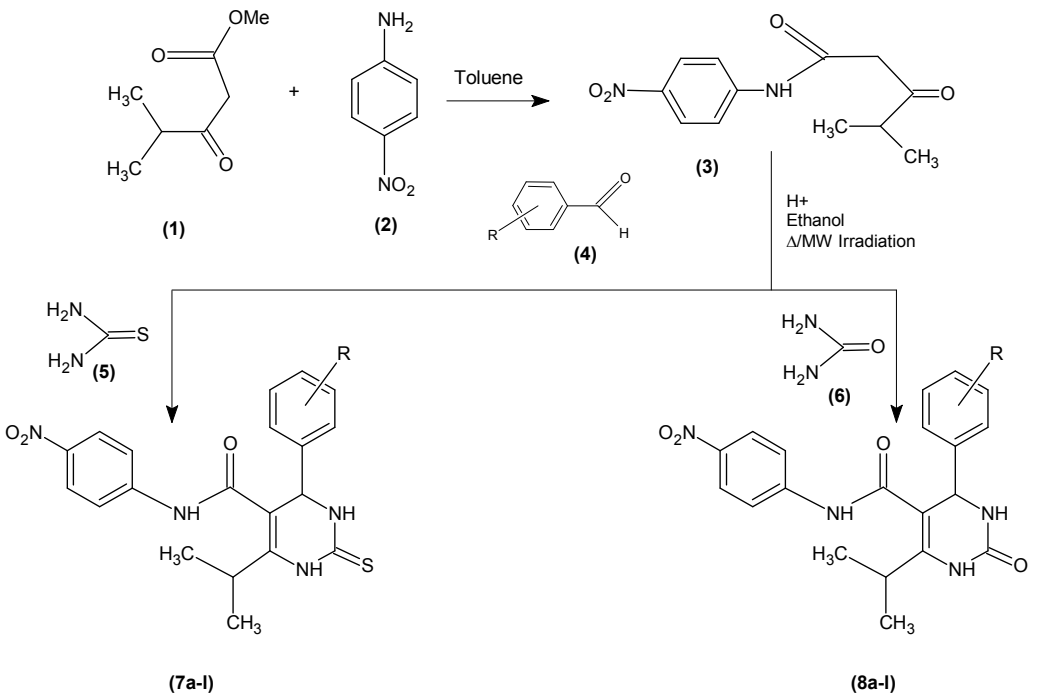
Melting points were determined in open capillary and are uncorrected. Thin layer chromatography using silica gel G (E. Merck) plates was used to monitor the reactions and purity of the synthesized compounds. All the products have been characterized by elemental analysis, IR, ^{1}H NMR and mass spectral study. IR spectra were recorded on Shimadzu FTIR-8400 spectrophotometer in KBr disc and noteworthy absorption levels (cm^{-1}) are listed. ^{1}H NMR spectra were recorded on Brucker spectrometer (300 MHz) using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer, Elemental analysis were performed on a Carlo Erba EA 1108 elemental analyzer.

General procedure for preparation of 4-methyl-N-(p-nitrophenyl)-3-oxo-pentanamide (3)

A mixture of methyl-4-methyl-3-oxopentanoate **(1)** (0.01 mol) and p-nitroaniline **(2)** (0.01 mol) in toluene was refluxed for 12 hrs with continuous removal of low boiling methanol azeotropically by Dean and Stark. After completion of reaction, the reaction mixture was cooled to room temperature and washed with dil. HCl and then with water. Toluene was distilled out under vacuum. The resulting residue was crystallized from n-hexane.

General procedure for preparation of 4-aryl-6-isopropyl-5-[N-(p-nitrophenyl) aminocarbonyl]-3, 4-dihydropyrimidine-2(1H)-thiones (7a-l)

A mixture of thiourea **(5)** (0.01 mol), aromatic aldehyde **(4)** (0.01 mol) and 4-methyl-N-(p-nitrophenyl)-3-oxo-pentanamide **(3)** (0.01 mol) in 15 mL of ethanol containing few drops of concentrated hydrochloric acid was refluxed on water bath till reaction is completed. The solution was allowed to stand for 12 hrs. at room temperature and separated title compounds were filtered off, washed with hot ethanol and recrystallized from dioxane.



Scheme

General procedure for preparation of 4-aryl-6-isopropyl-5-[N-(p-nitrophenyl) aminocarbonyl]-3, 4-dihydropyrimidine-2(1H)-ones (8a-l)

A mixture of urea **(6)** (0.01 mol), aromatic aldehyde **(4)** (0.01 mol) and 4-methyl-N-(p-nitrophenyl)-3-oxo-pentanamide **(3)** (0.01 mol) in 15 mL of ethanol containing few drops of concentrated hydrochloric acid was refluxed on water bath till reaction is completed. The solution was allowed to stand for 12 hrs at room temperature and separated title compounds were filtered off, washed with hot ethanol and recrystallized from dioxane.

General procedure for preparation of (7a-l)/(8a-l) under microwave irradiation

A mixture of thiourea/urea (0.01 mol), aromatic aldehyde **(4)** (0.01 mol) and 4-methyl-N-(p-nitrophenyl)-3-oxo-pentanamide **(3)** (0.01 mol) in 15 mL of ethanol containing few drops of concentrated hydrochloric acid was well stirred in 50 mL beaker and placed into the microwave oven for irradiation for the appropriate time. After the completion of reaction by monitoring on TLC, the reaction mixture was allowed to stand for some time and separated solid mass was filtered and washed with hot ethanol. The pure title compounds were isolated and recrystallized from dioxane.

Spectroscopic data

IR spectrum (KBr) of **(7h)** showed absorption frequencies (cm^{-1}) at : 1381 (isopropyl), 1301 (C = S), 3399 (N-H pyrimidine), 1661 (C = O), 1334 (NO_2), 1209 (Ar-O-C)

Mass spectrum of the compound **(7h)** recorded its molecular ion at m/z 426, 396, 383, 366, 289**,** 261, 245, 230, 219, 202, 137, 121, 178 and 177

^{1}H NMR **(7a)** (DMSO-d6+$CDCl_3$) : 1.57 (d, 6H), 3.84 (m, 1H), 5.6 (s, 1H), 7.13 (d, J=8.4Hz, 2H), 7.23 (d, J=8.5Hz, 2H), 7.33 (d, J=7.9Hz, 2H), 7.40 (d, J=8.5Hz, 1H), 7.58 (d, J=8.01Hz, 2H), 8.4 (s, 1H), 8.63 (s, 1H), 8.75 (d, 1H)

IR spectrum (KBr) of **(8h)** showed absorption frequencies (cm^{-1}) at : 1389 (isopropyl), 1698 (C=O pyrimidine), 3410 (N-H pyrimidine), 3343 (N-H amide), 1660 (C=O), 1332 (NO_2), 1210 (Ar-O-C)

Mass spectrum of the compound **(8a)** recorded its molecular ion at m/z 363, 336, 303, 275, 260, 243, 215, 199, 173, 164, 106, 90, 77.

^{1}H NMR **(8j)** (DMSO-d6+$CDCl_3$) : 1.45 (d, 6H), 3.84 (m, 1H), 4.8 (s, 1H), 7.13 (d, J=8.85Hz, 2H), 7.19 (d, J=8.61Hz, 2H), 7.24 (d, J=8.95Hz, 2H), 7.59 (d, J=9.1Hz, 2H), 8.88 (d, 1H), 9.05(s, 1H), 9.89 (s, 1H)

Twenty four novel compounds were synthesized following this procedure. The physical data of these compounds are presented in Table 1.The physical data, yield details and biological activity of novel dihydropyrimidinethiones **(7a-l)** and dihydropyrimidinones **(8a-j)** are presented in Tables 1 and 2, respectively.

Table 1

Compound	Substituent (R)	M. P. (°C)	Yield (%)		Molecular formula	Antimicrobial activity				
			Conventional method	Microwave method		*B. coccus*	*S. aureus*	*Aerogenes*	*P. aeruginosa*	*A. niger*
7a	H	247	47	62	$C_{20}H_{20}N_4O_3S$	12	15	14	16	14
7b	4-Cl	233	45	52	$C_{20}H_{19}ClN_4O_3S$	14	11	13	15	16
7c	2-Cl	241	50	59	$C_{20}H_{19}ClN_4O_3S$	11	7	9	8	10
7d	4-F	267	47	54	$C_{20}H_{19}FN_4O_3S$	18	15	17	17	19
7e	4-OH, 3-OCH_3	244	55	60	$C_{21}H_{22}N_4O_5S$	16	13	12	16	14
7f	2-OH	251	52	63	$C_{20}H_{20}N_4O_4S$	18	18	21	19	20
7g	4-CH_3	259	35	50	$C_{21}H_{22}N_4O_3S$	12	13	8	10	15
7h	4-OCH_3	242	39	57	$C_{21}H_{22}N_4O_4S$	6	9	11	8	14
7i	3, 4-$(OCH_3)_2$	235	45	60	$C_{21}H_{24}N_4O_5S$	13	11	14	16	15
7j	4-NO_2	274	42	52	$C_{20}H_{19}N_5O_5S$	12	16	12	14	18
7k	3-NO_2	255	44	48	$C_{20}H_{19}N_5O_5S$	12	17	14	14	17
7l	3-OC_6H_5	260	48	53	$C_{26}H_{24}N_4O_4S$	10	12	17	15	19
		Amoxicillin				25	25	20	22	0
		Benzoylpenicillin				18	19	21	21	0
		Ciprofloxacin				20	15	22	16	0
		Erythromycin				22	21	19	23	0
		Griseofulvin				0	0	0	0	26

Table 2

Compound	Substituent (R)	M. P. (°C)	Yield (%)		Molecular formula	Antimicrobial activity				
			Conventional method	Microwave method		B. coccus	S. aureus	Aerogenes	P. aeruginosa	A. Niger
8a	H	247	45	61	$C_{20}H_{20}N_4O_4$	10	12	17	15	16
8b	4-Cl	233	41	50	$C_{20}H_{19}ClN_4O_4$	12	14	18	16	17
8c	2-Cl	241	48	55	$C_{20}H_{19}ClN_4O_4$	15	17	11	13	18
8d	4-F	267	47	55	$C_{20}H_{19}FN_4O_4$	14	15	17	18	21
8e	4-OH, 3-OCH_3	244	51	57	$C_{21}H_{22}N_4O_6$	16	12	13	11	17
8f	2-OH	251	37	49	$C_{20}H_{20}N_4O_5$	17	15	18	14	18
8g	4-CH_3	259	36	61	$C_{21}H_{22}N_4O_4$	9	10	11	13	20
8h	4-OCH_3	242	47	61	$C_{21}H_{22}N_4O_5$	10	8	13	14	18
8i	3, 4-$(OCH_3)_2$	235	39	60	$C_{21}H_{24}N_4O_6$	16	16	12	16	14
8j	4-NO_2	274	41	42	$C_{20}H_{19}N_5O_6$	13	15	14	12	18
8k	3-NO_2	255	34	45	$C_{20}H_{19}N_5O_6$	10	13	15	12	17
8l	3-OC_6H_5	260	35	55	$C_{26}H_{24}N_4O_5$	11	10	9	10	16
		Amoxicillin				25	25	20	22	0
		Benzoylpenicillin				18	19	21	21	0
		Ciprofloxacin				20	15	22	16	0
		Erythromycin				22	21	19	23	0
		Griseofulvin				0	0	0	0	26

Biological activity

Antibacterial and antifungal activity by cup plate agar diffusion method[13]

All the compounds have been evaluated for their *in vitro* biological assay like antibacterial activity towards *Gram-positive* bacteria viz., *Bacillus coccus, Staphylococcus aureus* and gram-negative bacteria viz., *Pseudomonas aeruginosa, Aerogenes* and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg. The biological activities of synthesized compounds were compared with standard drugs viz., amoxicillin,

benzyl penicillin, ciprofloxacin, erythromycin and antifungal activity was compared with griseofulvin.

RESULTS AND DISCUSSION

The concept of microwave induced organic reactions activation has been utilized for rapid and efficient synthesis of a series of new Biginelli compounds. The dihydropyrimidine thiones **(7a-l)** as well as dihydropyrimidinones **(8a-l)** have been synthesized by the acid catalyzed condensation of aromatic aldehydes **(4)** with 4-methyl-N-(p-nitrophenyl)-3-oxo-pentanamide **(3)** and urea/ thiourea **(6)/(5)** in open borosilicate glass vessels using ethanol as energy transfer medium **(Scheme)**. In order to study the possible existence of a specific microwave effect as compared with the conventional heating mode, We have studied reactions both under microwave irradiation and by the thermal method, but in the latter case, lower yield was observed even after heating for 10 h, which indicates that the effect of microwave irradiation is not purely thermal. Short reaction times along with enhanced yields and easy work up are the main advantages observed.

It has been observed from the antimicrobial activity data that all compounds were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. However, the maximum activity was observed in compounds bearing R = o-hydroxyphenyl, p-fluorophenyl substituents against *B. coccus*. The significant activity was observed in compounds bearing R = o-hydroxyphenyl, m-nitrophenyl against *S. aureus.* The maximum activity was displayed by the compounds bearing R = o-hydroxyphenyl, p-fluorophenyl against *Aerogenes*. In the case of *P. seudomonas* all the compounds were least active except R = o-hydroxyphenyl, p-fluorophenyl. The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds bearing R = o-hydroxyphenyl, p-fluorophenyl against *A. niger*. The antibacterial activity was compared with standard drug viz. amoxicillin, benzoyl penicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. griseofulvin.

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