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Microwave Assisted Synthesis and Pharmacological Screening of Novel 6-Methyl-2-oxo-4-substituted 5-(5-Phenyl-1,3,4-oxadiazole-2-yl)-1,2,3, 4-tetrahydropyrimidines

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A simple and efficient method has been developed for the synthesis of various 1,3,4-oxadiazole derivatives prepared from DHPM using microwave irradiation technique. The series of 1,3,4-oxadiazole-2-yl-1,2,3,4-tetrahydropyrimidine-2(1*H*)-one derivatives synthesized, were structurally confirmed by analytical and spectral data and evaluated for there lipoxygenase inhibitory and antibacterial activities. The results showed that this skeletal framework exhibited marked potency as lipoxigenase inhibition and antibacterial agents. The most active lipoxigenase inhibitor and antibacterial agent was 6-methyl-2-oxo-4-(*p*-nitrophenyl)-5-(5-phenyl-1,3,4-oxadiazole-2-yl)-1,2,3,4-tetrahydropyrimidine.

Key Words: DHPM, 1,3,4-Oxadiazole, Lipoxygenase.

INTRODUCTION

One of the greatest triumphs of modern medicine has been the introduction of a rational system of antimicrobial therapy to combat infectious disease. More recently, appropriately functionalized DHPMs have been emerged as orally active calcium channel blocker[1], antimicrobial, antibacterial agents[2]. A large number of medicines which have been discovered belong to a class of heterocyclic containing nitrogen, oxygen and sulphur. Biological activity of these heterocyclic compounds has helped the medicinal chemist to plan, organize and improve newer approaches towards the discovery of new drugs. In view of the general observation that pharmacological activity is invariably associated with a large variety of heterocyclic compounds, the investigation of some heterocyclic such as substituted 1,3,4-oxadiazole, has been undertaken[3-5]. Derivatives of these compounds are reported to possess a wide spectrum of biological properties which include antibacterial, anticancer, antiinflammatory, antihypertensive, analgesic and antifungal activities[6-8]. Leukotrines derived from lipoxygenase also play an important role in the initiation of inflammation and pain along with prostaglandins. Literature reveals that conversion of hydrazide group into corresponding 1,3,4-oxadiazole, which show some antiinflammatory and cyclooxygenase inhibitory activity of parent drug but also induced lipoxygenase inhibition[9]. Thus it is conceivable to develop a series of oxadiazole by microwave assisted synthesis approach with the aim of investigating their antibacterial and Lipoxigenase inhibitory activity.

EXPERIMENTAL

Melting points of synthesized compounds were determined with open capillary tube on a Chemtek (Variable heater) melting point apparatus and were uncorrected. IR spectra (KBr disc) were recorded on FTIR-8400s Shimadzu system. Proton magnetic resonance spectra (HNMR) were recorded on bruker AC-300F NMR spectrometer (300 MHz) using DMSO-d_6 as solvent and tetramethyl silane (TMS) as internal standard. Mass spectrum was recorded on Jeol SX 102/DA-600 mass spectrometer/data system using Argon/Xenon (6 Kv, 10 mA) as FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature using *m*-nitro benzyl alcohol (NBA) matrix. All the compounds were routinely checked by TLC on silica gel G plates using acetone/benzene (9:1, v/v) solvent system and developed plates were visualized by UV light.

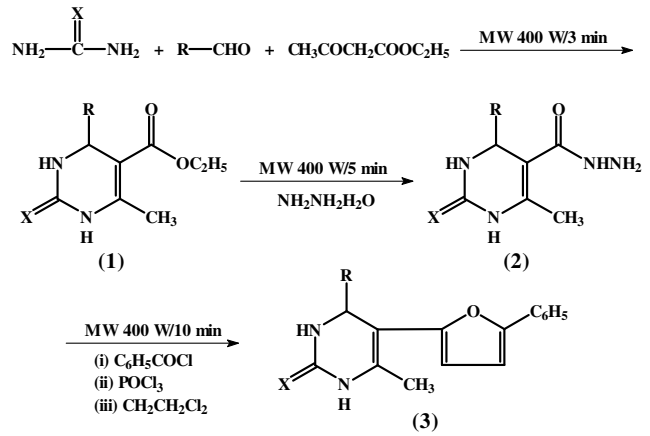
In present investigations, NSAIDS required were obtained from respective manufacturers and enzymes used for lipoxygenase inhibitoy activity were obtained as gift samples from Sigma chemicals Co. USA. The microwave assisted synthesis were carried out using a Synthos 300 monomode oven monitored manually and temperature maintained at a constant value (140 °C) within the power modulation of 1400 W. Stirring was provided manually in intervals. While reactions were performed in open glass vessels within a ramp time of 10 s to 2 min. All reagents were obtained from Merk Chemicals Limited. Solvents used were of analytical grade and, when necessary, were purified and dried by standard methods.

General procedure

Synthesis of ethyl-6-methyl-2-oxo-4-substituted phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1): To a mixture of urea (0.15 mol), substituted aldehyde (0.10 mol) and ethylacetoacetate (0.10 mol) in ethanol (75 mL), few drops of concentrated hydrochloric acid was added. The reaction mixture was taken in round-bottom flask placed in a microwave oven and irradiated at 400 W for 3 min and the solvent was removed by vacuum distillation. The reaction mixture was poured into ice water (100 mL) with stirring and left overnight at room temperature. The solid product was filtered, dried and recrystallized from ethanol to afford ethyl-6-methyl-2-oxo-4-substituted phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1.1-1.8). The reaction was monitored by using TLC and IR data. m.p. 112-116 ºC, IR (KBr, ν_{max}, cm^{-1}): 1645 (amide C=O), 1714 (ester C=O), 3246 (-NH). ^{1}H NMR (DMSO-d_6): δ 1.07 (t, 3H, CH_3-ester); 2.25 (s, 3H, dihydropyridyl-CH_3); 3.93 (q, 2H, CH_2-ester); 5.15 (d, 1H, dihydropyridyl-CH); 7.2-7.5 (m, 4H, Ar-H) 7.7 (s, 1H, 3-NH); 9.25 (s, 1H, 1-NH), mass (FAB): 237(M^+,12 %), 189 (base peak 100 %).

Synthesis of 6-methyl-2-oxo-4-substituted phenyl-1,2,3,4- tetrahydropyrimidine-5-carbohydrazide (2): To a hot solution (0.01 mol) of compound **1** in ethanol (150 mL), was added hydrazine hydrate (99 %, 0.015 mol). The reaction mixture was taken in round-bottom flask placed in a microwave oven and irradiated at 400 W for 5 min and the solvent was removed by vacuum distillation. The solvent was removed to possible extent by distillation and the product thus separated was filtered and purified by recrystallization from ethanol to get a colourless crystalline solid. The reaction was monitored by using TLC and IR data. m.p. 132-137 ºC, IR (KBr, ν_{max}, cm^{-1}): 1647 (amide C=O), 3247 (-NH). ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H, dihydropyridyl -CH_3); 4.0 (s, 2H, NH_2); 5.1 (d, 1H, -NH); 7.22-7.5 (m, 4H, Ar-H); 7.77 (s, 2H, 3-NH/CH); 9.25 (s, 1H, 1-NH), mass (FAB): 251 (M^+, 9 %), 186 (base peak 100 %).

Synthesis of 6-methyl-2-oxo-4-substituted 5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1,2,3,4-tetrahydropyrimidine-2(1*H*)-one (3a-h): To a solution of benzoyl chloride (0.01 mol) in dichloroethane (10 mL) and compound **2** (0.01 mol), phosphorous oxychloride (5 mL) was added and content were irradiated at 400 W for 10 min. Excess of solvent and $POCl_3$ were distilled at reduced pressure. Reaction mass was cooled and poured into ice, left overnight (**Scheme-I**). The product was obtained by filtration and purified by recrystallization using ethanol. The reaction was monitored by using TLC and IR data. m.p. 198-202 ºC, IR (KBr, ν_{max}, cm^{-1}): 1689 (amide C=O), 1026 (C-O-C), 1603 and 1582 (C=N). ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 6H, CH_3-N-CH_3); 2.1 (s, 3H, -CH_3); 2.65 (s, 1H, -CH); 7.43-7.47 (d, 4H, Ar-H, attached with dihydropyrimidine); 7.55 (s, 1H, 1NH); 7.57 (s, 1H, 1NH); 7.95-8.15 (d, 5H, Ar-H, attached with oxadiazoles); mass (FAB): 305 (M^+,15 %), 188 (base peak 100 %). Anal. (%) calcd. for $C_{14}H_{16}N_2O_3$: C, 64.36; H, 8.35; N, 16.18; Found: C, 64.31; H, 7.99; N, 16.12.

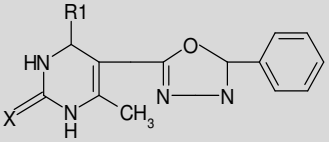


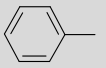
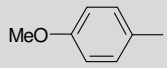
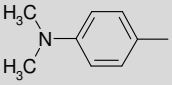
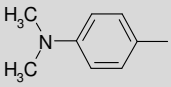
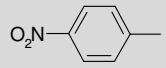
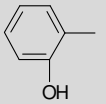
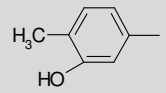
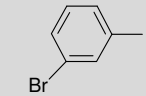
Scheme-I

RESULTS AND DISCUSSION

Synthesis of 6-methyl-2-oxo-4-substituted 5-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidine by microwave assisted approach is found highly efficient to produced moderate in excellent yield (Table-1). The reaction occurred remarkably fast, under mild condition using inexpensive reagents and microwave oven as the irradiation source. 6-Methyl-2-oxo-4-nitro-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidine, emerge as the most active antibacterial agent and also shown maximum inhibition of 52, 39 and 43 %, respectively at 0.25 mM concentration.

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS



Compd.	R1	X	Yield (%)	m.p. (ºC)	m.f.
3a		O	72	198-202	$C_{14}H_{16}N_2O_3$
3b		O	78	114-116	$C_{15}H_{18}N_2O_4$
3c		O	71	113-115	$C_{16}H_{21}N_3O_3$
3d		S	69	115-117	$C_{16}H_{21}N_3O_2S$
3e		O	72	119-121	$C_{14}H_{15}N_3O_5$
3f		O	64	112-114	$C_{14}H_{16}N_2O_4$
3g		O	68	130-132	$C_{15}H_{18}N_2O_5$
3h		O	71	126-128	$C_{14}H_{15}N_2O_3Br$

Lipoxygenase inhibitory activity: The lipoxidase activity was determined by the measurements of spectral absorbance of the conjugated hydroperoxidase produced by lipoxidase catalysis. The lipoxygenase inhibitory activity was determined by *in vitro* method. A direct spectrophotometric assay employing increase in absorbance at 234 nm as a function of time where soyabean lipoxidase as a representative of 5-lipoxygenase enzyme and linoleic acid as the substrate were used. All the derivatives were tested and found to exhibit lipoxygenase inhibition with **3e**, **3g** and **3h** showing maximum inhibition of 52, 39 and 43 %, respectively at 0.25 mM concentration (Fig. 1).

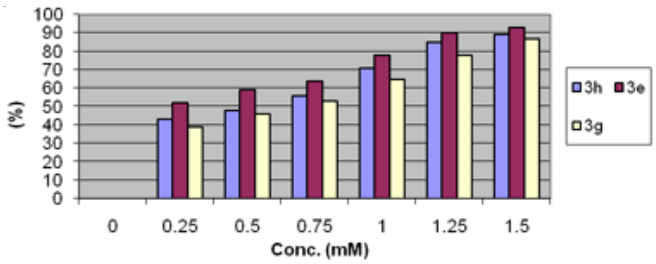


Fig. 1. Lipoxygenase inhibitory activity of synthesized compounds **3e**, **3g**, **3h**

Antibacterial activity: The synthesized compounds are screened for antibacterial activity by cup plate method. For this activity two species were selected, *Staphylococcus aureus* for gram positive and *Eschellia coli* for gram negative activities respectively using DMF as a control. The results of the synthesized compounds were compared with standard drugs as shown in (Table-2). Compounds **3e**, **3g**, **3h** showed promising antibacterial activity against gram +ve (*Staphylococcus aureus*) and **3b**, **3e**, **3g**,**3h** showed promising antibacterial activity against gram-ve (*E. coli*), compared to standard drugs procaine penicillin and streptomycin respectively.

It is suggested that this work will be useful for further studies in terms of structure activity relationship (SAR) to improve the biological and pharmacological properties of these compounds.

TABLE-2
ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compd.	Mean zone inhibition (mm)			
	Staphylococcus aureus (+ve)		*Escherichia coli* (-ve)	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
Procaine penicillin	24	24	-	-
Streptomycin	-	-	20	22
3a	07	10	10	12
3b	08	12	13	14
3c	08	13	09	13
3d	08	10	08	10
3e	13	14	11	12
3f	07	11	08	12
3g	14	15	11	14
3h	10	12	12	14

Note: < 9 mm resistant, 10-14 mm intermediate, < 14 mm susceptible

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