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Synthesis and Characterizations of ethyl(2Z)-2-(Aryl)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate Derivatives as Biological and Antifungal Active Agents

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ABSTRACT

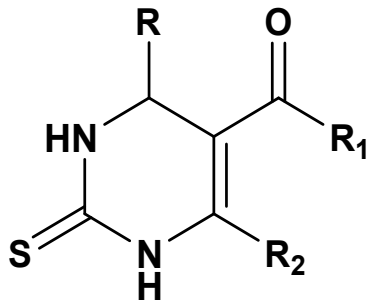
The aim of this study was to synthesize several pyrimidine derivatives. Pyrimidine nucleus was synthesized by Biginelli reaction in past. (1) At first stage reaction the pyrimidine derivative synthesized by reaction between EAA (ethylacetoacetate), substituted benzaldehyde, and thiourea. (2) At second stage reaction give excellent yield of ethyl(2Z)-2-(Aryl)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5H-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives (1-13) synthesized by using first reaction derivative, chloro acetic acid, sodium acetate, acetic anhydride, glacial acetic acid with various substituted benzaldehyde. They are characterized by elemental analyses like IR spectra, NMR spectra and GCMS. The products have been tested for their antibacterial and antifungal activity against gram (+) positive and gram (-) negative bacteria.

Keywords: 2,3,8,8 a-tetrahydro, Pyrimidine, Biginelli reaction, Antibacterial activity, Antifungal activity.

I. INTRODUCTION

Medicinal chemistry has several armlets of chemistry and biology. However, incumbent it concerns with the rubric of mechanisms of function and action of drugs. It establishes association between structure and activity in reaction. In chemistry mechanisms and reaction we can link biodynamic behavior with chemical reactivity and physical properties and fundamental information. Now a days 1,2,3,4-tetrahydropyrimidine (compound-1) and Biginelli compounds have received vital attention owing their diverse range of biological properties.

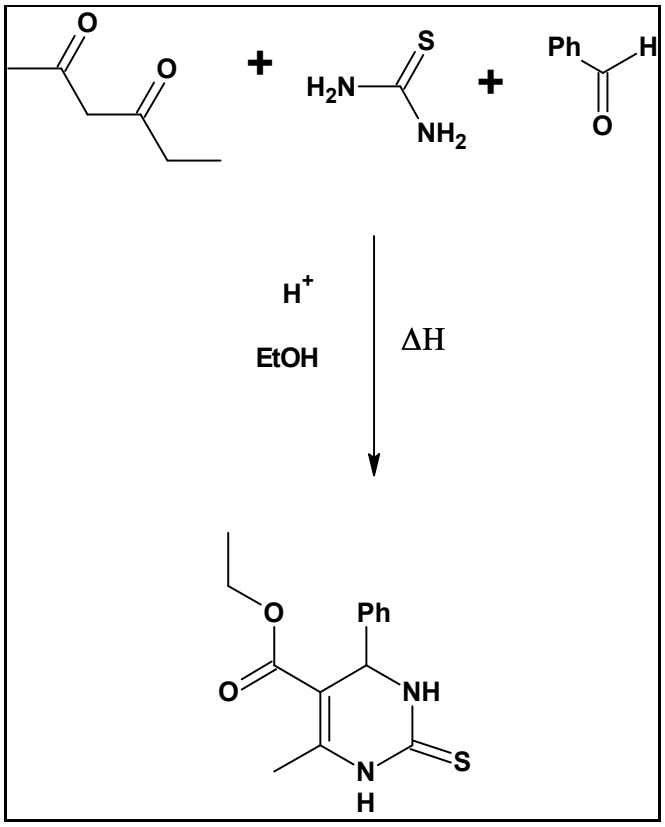
Pyrimidine derivatives are possessed several interacted functional groups in Biginelli compounds which determines also great biological activity in organic chemistry. They are also calcium channel blockers [1] and great synthetic potential [2]. Biginelli reaction has been enchanting the range of organic chemists all over the world in recent year. Biologically, substituted tetrahydropyrimidines are an important class of biologically active molecules. The Biginelli reaction is a multiple component chemical reaction, in which 3,4-dihydropyrimidinin-2-ones obtain from an aryl aldehyde, ethyl acetoacetate and thiourea. Pietro Biginelli was synthesized his derivatives in 1891 [3-5].



Compound-1
(Where R, R_1, R_2 = different groups)

Biginelli reaction is called a multiple component chemical reaction. In that reaction 3,4-dihydropyrimidin-2(1H)-ones is obtain by ethylacetoacetate, an aryl aldehyde and thiourea [6] reactants. That is named for the Italian chemist Pietro Biginelli. This reaction was carried out by Pietro Biginelli in 1893. In these reaction Bronsted acids

and/or by Lewis acids such as boron trifluorides [7] are used as a catalyst. Many different linker combinations have been published in several solid-phase [8].



Syntheses of thiazolo [9-14] Pyrimidines are used as a potential for pharmaceutical application. So our work is concerned with the study of the effects of structural modification on the biological activities of the target compounds. And conformed their structure by characterization data like IR, NMR and MASS.

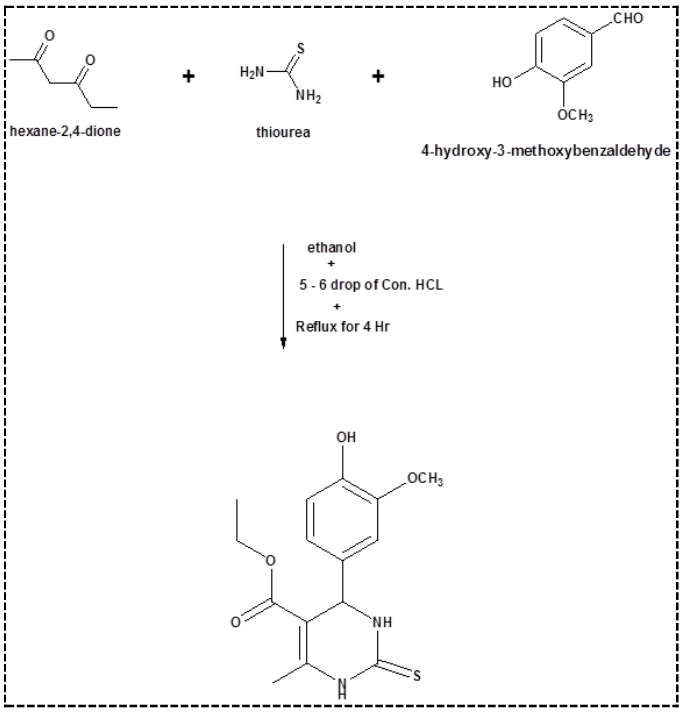
II. METHODS AND MATERIAL

Method:

Step: 1

Preparation of ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:

A mixture of 4-hydroxy-3-methoxy benzaldehyde-vanillin (0.1 mol), EAA (0.1 mol), thiourea (0.1 mol) and 20 ml ethanol filled in 250 ml of RBF. Then reflux for 4-5 hr in presence of concentrated (HCl) hydrochloric acid as catalyst. The reaction completion was monitored through thin layer chromatography and a content of the reaction mixture was poured in crushed ice-cold water. Product was isolated, filtered, dried and recrystallized from ethanol to obtain the pure compounds. The yield was 60 % with m.p 218^0 C.



Ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

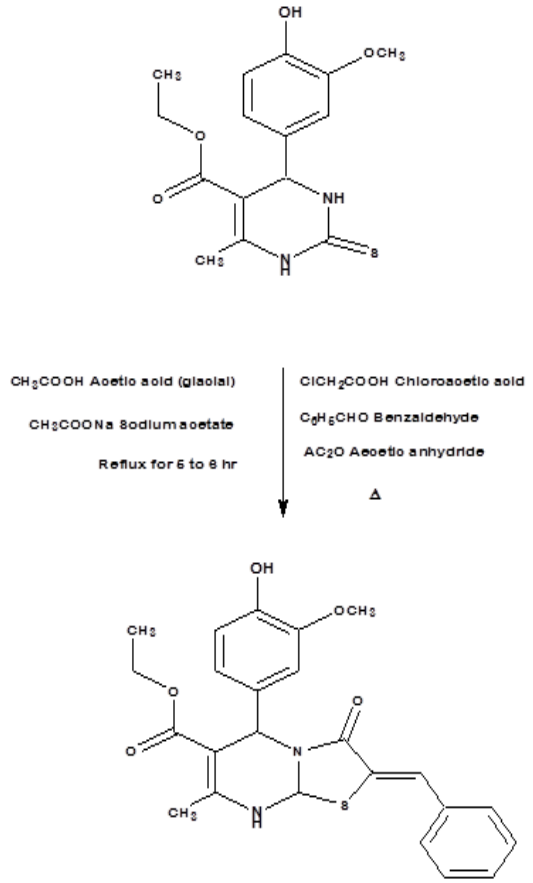
Step: 2

Preparation of ethyl(2*Z*)-2-(Aryl)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate:

A mixture of ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.005 mol), substituted benzaldehyde (0.05 mol), chloroacetic acid (0.05 mol), sodium acetate (0.05 mol), acetic anhydride (0.05 mol) and 10 ml glacial acetic acid taken in 250 ml of RBF. Reflux this mixture for 5 to 6 hr. Moiety was obtained by pours this solution in to ice containing water. Derivative recrystallized by ethanol:DMF m.p 218^0 C, Yield 56 %.

The purity of ethyl(2*Z*)-2-benzylidene-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2 *a*]pyrimidine-6-carboxylate-(1) compound was routinely checked on TLC aluminum sheet silica gel 60 F_{245} (E. Merck) using benzene-

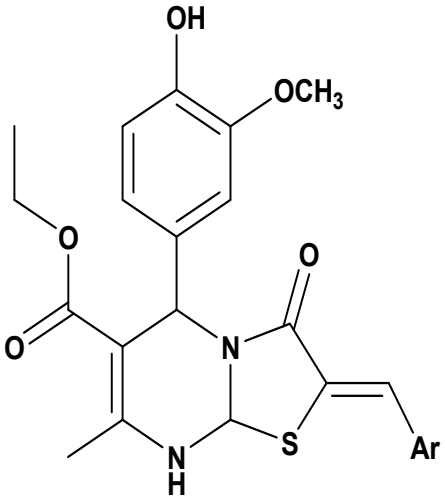
methanol (4.5:0.5 v/v) or benzene-CCl_4–methanol (2.5:2.0:0.5 v/v) as irrigate and was developed in an iodine chamber. Other derivative (2-13) compounds of the series were prepared by using similar method.



ethyl(2*Z*)-2-benzylidene-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate-(1)

Physical constants:

Physical constants of ethyl (2*Z*)-2-(Aryl)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate:



Where Ar = Different aryl group

Sr No.	-Ar	MOLECULAR FORMULA	M. P. ^{O}C	YIELD (%)	% OF CARBON		% OF NITROGEN		MOL. WEIGHT
					FOUND	REQD.	FOUND	REQD.	
1	-C_6H_5	$C_{24}H_{24}N_2O_5S$	218-220^{0}C	56%	63.68	63.70	6.15	6.19	452.52
2	-4-OCH_3-C_6H_4	$C_{25}H_{26}N_2O_6S$	189-190^{0}C	58%	62.21	62.23	5.79	5.81	482.54
3	-2,4-$(CL)_2$-C_6H_3	$C_{24}H_{22}Cl_2N_2O_5S$	208-210^{0}C	59%	55.25	55.28	5.36	5.37	521.41
4	-4-CH_3-C_6H_4	$C_{25}H_{26}N_2O_5S$	192-195^{0}C	62%	64.34	64.36	5.98	6.00	466.54
5	-4-F-C_6H_4	$C_{24}H_{23}FN_2O_5S$	183-186^{0}C	54%	61.21	61.26	5.91	5.95	470.51
6	-4-Br-C_6H_4	$C_{24}H_{23}BrN_2O_5S$	168-170^{0}C	59%	54.20	54.24	5.53	5.27	531.41
7	-4-Cl-C_6H_4	$C_{24}H_{23}ClN_2O_5S$	180-181^{0}C	53%	59.15	59.19	5.74	5.75	486.96
8	-3-OH-C_6H_4	$C_{24}H_{24}N_2O_6S$	198-199^{0}C	61%	61.49	61.52	5.96	5.98	468.52
9	-4-OH-C_6H_4	$C_{24}H_{24}N_2O_6S$	221-223^{0}C	68%	61.51	61.52	5.94	5.98	486.52
10	-3-OCH_3-4-OH-C_6H_3	$C_{25}H_{26}N_2O_7S$	173-175^{0}C	54%	60.21	60.23	5.61	5.62	498.54
11	-2-NO_2-C_6H_4	$C_{24}H_{23}N_3O_7S$	235-236^{0}C	50%	57.90	57.94	8.40	8.45	497.52
12	-3-NO_2-C_6H_4	$C_{24}H_{23}N_3O_7S$	225-227^{0}C	58%	57.91	57.94	8.42	8.45	497.52
13	-4-NO_2-C_6H_4	$C_{24}H_{23}N_3O_7S$	176-179^{0}C	53%	57.89	57.94	8.40	8.45	497.52

III. RESULTS AND DISCUSSION

Experimental section:

All starting material, reagents and solvents are commercially available and were used after further purification in methanol. All melting points were taken in paraffin bath and are uncorrected. IR spectra were recorded on BRUKER ALPHA-E spectrometer [15]. 1H NMR were recorded on BRUKER 400MHz spectrometer. Chemical shift (δ) are reported in part per million (ppm) relative to traces of $CDCl_3$ [16]. Mass spectra were recorded on SHIMADZU QP-2010. Reaction progress was checked by TLC by keeping the plates in iodine vapor or UV lamp.

The IR, NMR spectrum and MASS of ethyl(2*Z*)-2-benzylidene-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (1) and other derivatives (2-13) was recorded.

Derivative (1): **IR** (KBr): νmax (cm−1), 3123 (>NH), 2980 (CO-NH), 2782 (CH_3 str.), 1736 (C=O and aromatic C=C), 1591 (C=S (-NH) str.), 1432 (>CH), 1122 (>C=S), 1020 (C-Cl), 794, 757, 677 (str., tri-substituted aromatic).
1H-NMR (400 MHz): δ ppm, 1.95 (t, 3H, J = 7 Hz, ester -CH_3), 2.13 (s, 6H, Ar-CH_3), 2.31 (s, H, -CH), 3.95 (q, 2H, J = 7.12 Hz ester-CH_2), 4.20 (d, H, -CH), 7.20-7.56 (m, 9H, Ar-H), 8.96 (d, H, -NH), 9.90 (s, H, -OH).
13C NMR ($CDCl_3$) δ (ppm): 13.80 (ester CH_3), 20.81 (CH_3), 22.47 (CH_3), 56.00 (ester CH_2), 60.11 (CH), 108.75, 116.56, 119.35, 122.20, 127.60, 129.19, 129.52, 130.18, 131.09, 131.74, 137.74, 139.49, 165.91, 164.82 (C=O).
GCMS: Fragmentation of mass spectra m/z: 452.2 (M^+), 453 (M+1), 455 (M+3).

Biological Activity

Antibacterial and Antifungal activity

The synthesized compounds were screened for their *in-vitro* antimicrobial activity against *Escherichia Coli* (Gram negative), *Staphylococcus Aureus (*Gram negative*), Staphylococcus aureus (*Gram positive*), Streptococcus Pyogenes* (Gram positive) and antifungal activity against *Candida albicans, Aspergillus niger* and *Aspergillus clavatus* by measuring in MBC and in MFC method in µg/mL. The synthesized compounds were compared with standard antibacterial drugs Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin and antifungal drugs Nystatin and Greseofulvin. Antibacterial and antifungal activity was carried out by broth dilution method at concentrations of 1000, 500, 250, 200, 125, 100, 62.5 [17] µg/mL respectively.

Product Code	Minimal Bactericidal Concentration (MBC) in µg/mL				Minimal Fungicidal Concentration (MFC) in µg/mL		
	Gram negative bacteria		Gram positive bacteria		Fungus		
	E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenus*	*C.albicans*	*A.nigar*	*A.clavatus*
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323
1	100	100	125	62.5	250	200	250
2	500	200	200	250	200	1000	1000
3	250	250	100	62.5	500	1000	1000
4	200	100	125	100	250	250	200
5	100	200	125	62.5	200	200	500
6	125	100	62.5	100	250	250	200
7	200	200	100	100	>1000	>1000	>1000
8	125	62.5	125	200	250	200	>1000
9	200	100	125	62.5	250	500	200
10	125	200	62.5	100	500	200	>1000
11	200	62.5	200	100	500	250	200
12	125	200	100	100	>1000	500	>1000
13	100	100	125	62.5	500	250	>1000

Gentamycin	0.05	1	0.25	0.5	--	--	--
Ampicillin	100	--	250	100	--	--	--
Chloramphenicol	50	50	50	50	--	--	--
Ciprofloxacin	25	25	50	50	--	--	--
Norfloxacin	10	10	10	10	--	--	---
Nystatin	--	--	--	--	100	100	100
Greseofulvin	--	--	--	--	500	100	100

IV. DISCUSSION

Many derivatives of thiozolo pyrimidines are synthesized in research laboratory. Now a day there are many important uses of them like anti-bacterial and antiinfective activity. This thesis consists of the overall comparison of the compound synthesized in my research work. Out of them Pyrimidine derivatives possesses remarkable pharmaceutical importance.

V. ACKNOWLEDGEMENT

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