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Synthesis and characterizations of ethyl (2Z)-2-(Aryl)-5-(4-fluorophenyl)-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 (2*Z*)-2-(Aryl)-5-(4-fluorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives, 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.

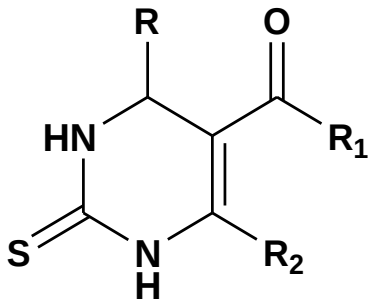
Keywords : 2,3,8,8a-Tetrahydro, Pyrimidine, Biginelli Reaction, Antibacterial Activity, Antifungal Activity.

I. INTRODUCTION

In medicines most often drugs are organic compounds, which are divided into the broad class of small organic molecules like Atorvastatin, fluticasone, and Biologics like erythropoietin, insulin glargine. In medicinal research focusing on small organic molecules encompasses synthetic organic chemistry, aspects of natural productions and computational with chemical biology with structural biology, together aiming at the discovery and development of new therapeutic agents.

For disease or deficiency medicine either externally or internally for curing in drug medicinal field. In synthesis discovery, development, identification and interpretation of molecule is carried out which is synthesized. Thus we can identify, studied, synthesized and produce metabolic products of drug and it's derivate and compounds. Medicinal chemistry involves isolation characterization and synthesis of compounds that can be used in medicine and drug for prevention, treatment and cure of diseases. So medicinal chemistry involves and provides chemical basis for the interdisciplinary.

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].

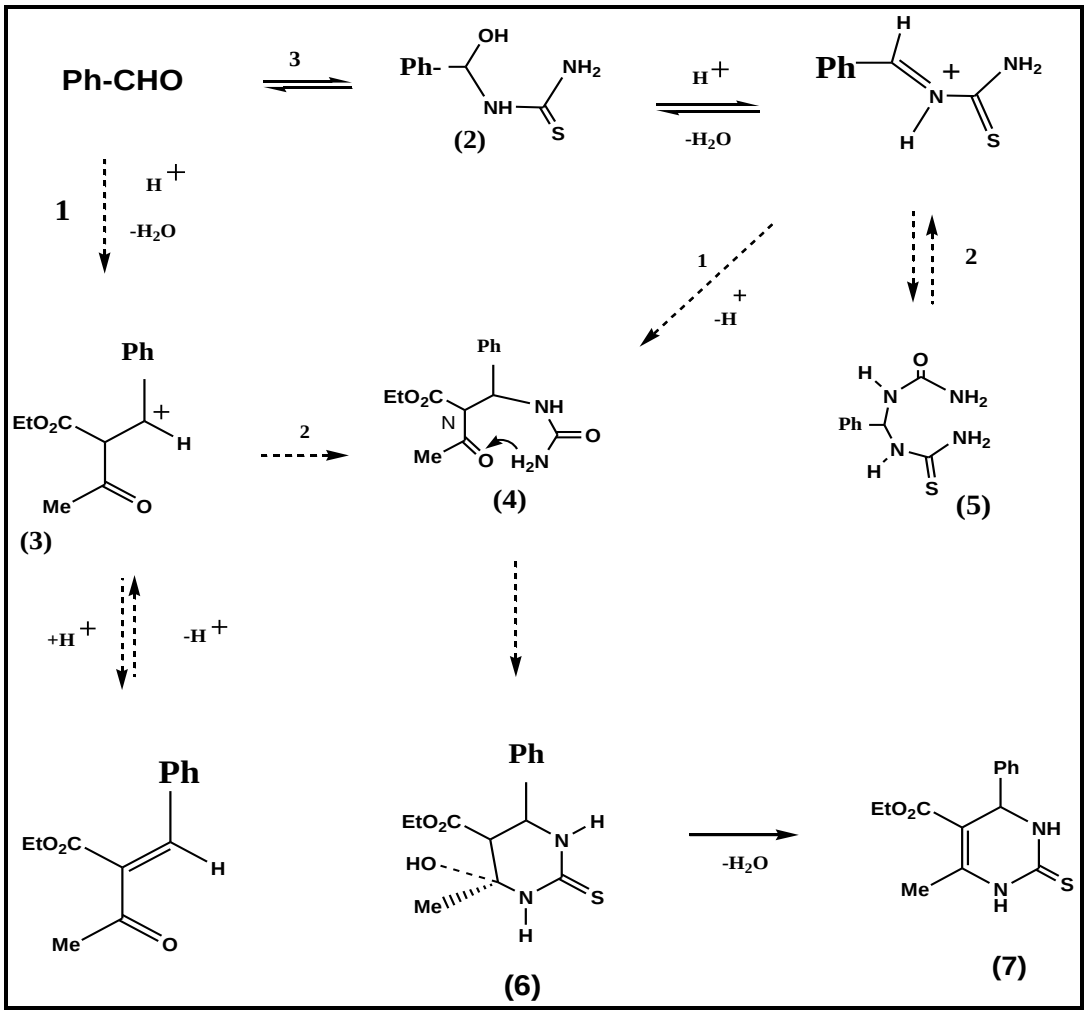


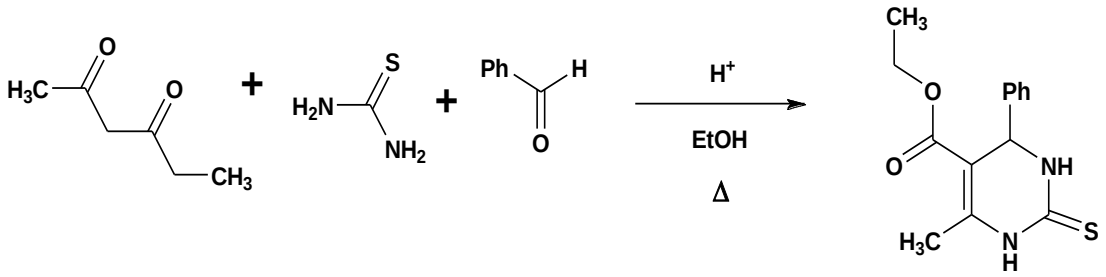
Compound-1
(Where R, R_1, R_2 = different groups)

The mechanism of the Biginelli reaction:

The Biginelli reaction is a one-pot three component reaction between a β-keto ester, aryl aldehyde and thiourea to produced pyrimidine derivatives. The reaction was taken under acidic conditions. With protonation of the aldehyde by the acid start this reaction and then followed by attack of the amine from thiourea. The enol form of the β-keto ester attacked on the intermediate. Proton transfer steps, release of water are result in the final pyrimidine product.

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

Experimental:

Preparation:

A. **Preparation of ethyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate**:

A 250 ml RBF was filled with a mixture of EAA(ethylacetoacetate)- 0.1 mol, substituted benzaldehyde-(4-fluorobenzaldehyde) (0.1 mol), and thiourea (0.1 mol) were refluxed in 15-20 ml of ethanol for 4-5 hr in presence of concentrated (HCl) hydrochloric acid as catalyst. The reaction completion was monitored through thin layer chromatography and contents 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 69 % with m.p 222^0 C.

The purity of compounds 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.

B. **Preparation of ethyl (2*Z*)-2-(Aryl)-5-(4-fluorophenyl)-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-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.005 mol), mono/di/tri substituted benzaldehyde (0.05 mol), chloro aceticacid (0.05 mol), sodium acetate (0.05 mol), acetic anhydride (5 ml) in glacial acetic acid (10 ml) in 250 ml RBF was refluxed for 5 to 6 hr. The reaction completion was monitored through thin layer chromatography and contents 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. DMF m.p 180^0 C, Yield 65 %.

The purity of compounds 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.

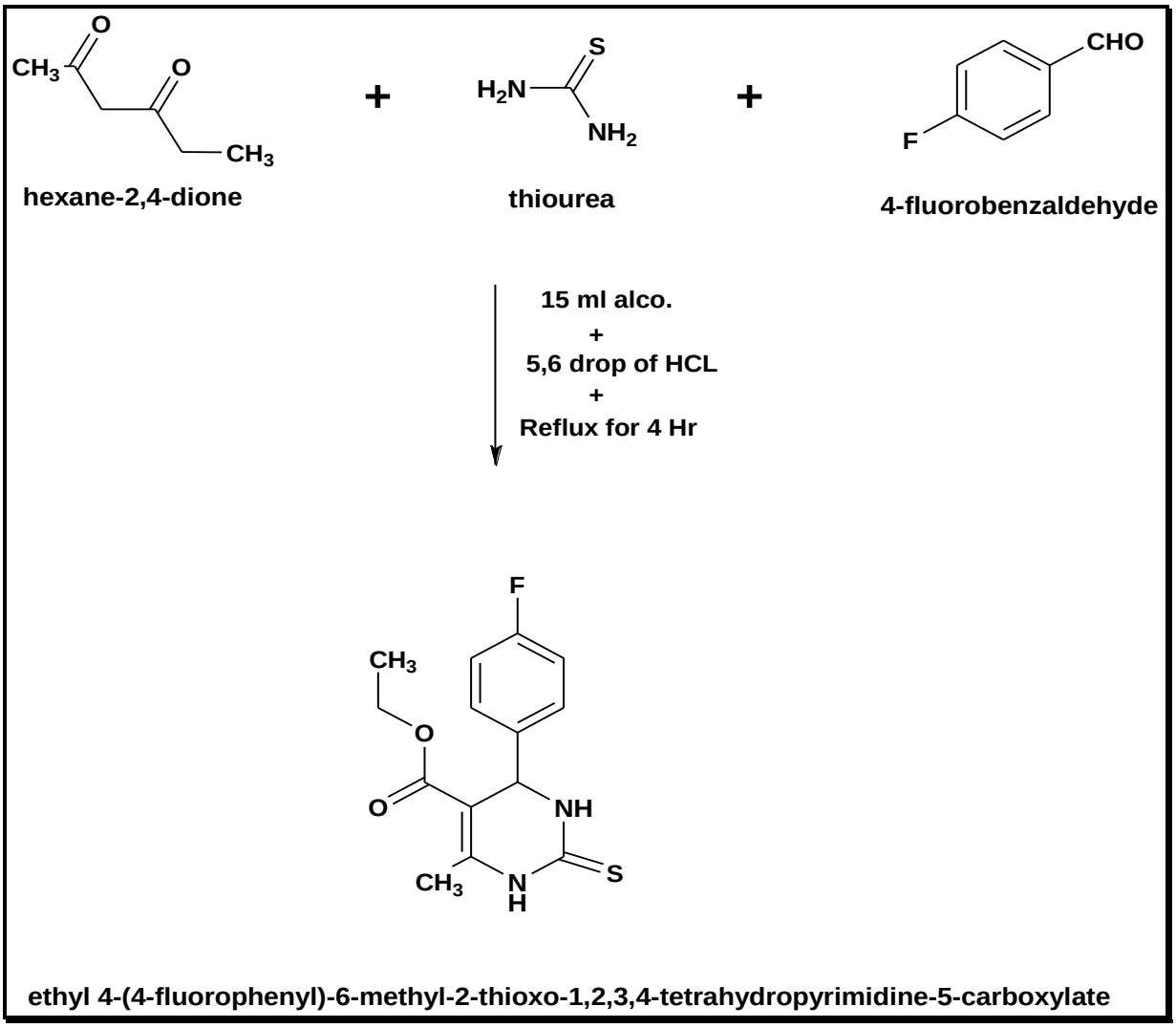
Other derivative compounds of the series were prepared by using similar method. The purity of these derivatives were analyzed through melting point measurements. In view of tremendous application of these compounds, we have prepared a library of molecules. We have undertaken to investigate the role of functional groups on molecular geometry,

conformation and generation of supramolecular assemblies in the solid state. Furthermore the synthesized derivatives have also been evaluated for their antibacterial, antiinfective activity by Broth Dilution method.

Reaction work:

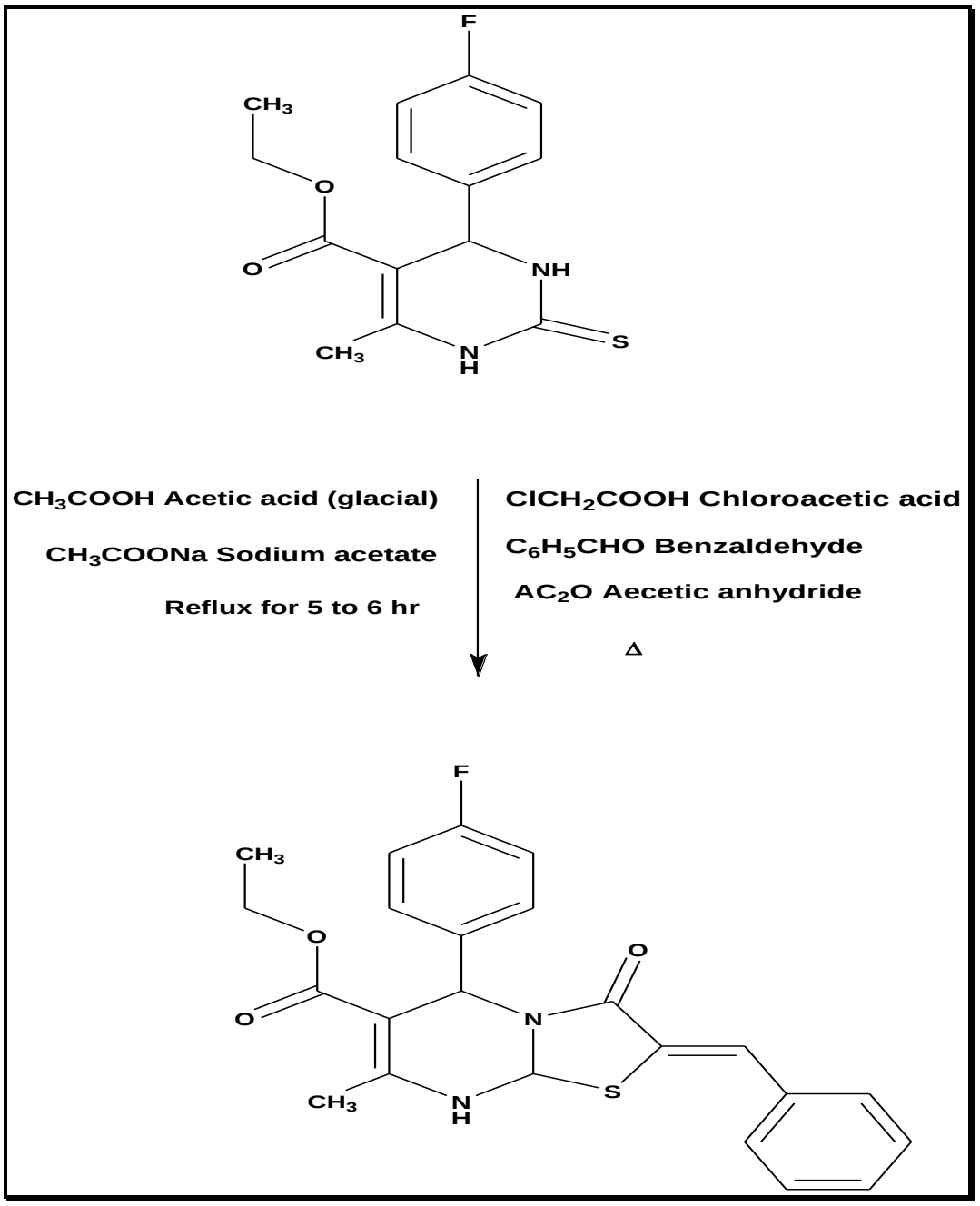
Reaction – 1 :

Preparations of ethyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate



Reaction – 2 :

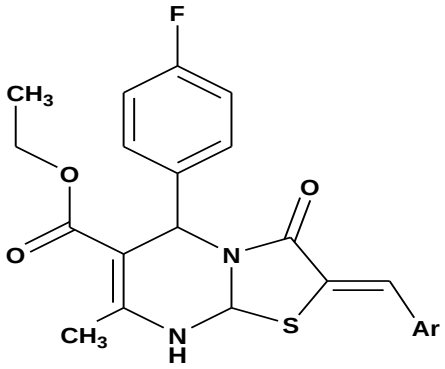
Preparations of ethyl (2*Z*)-2-(Aryl)-5-(4-fluorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate:



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

Physical Experimental data :

Physical constants of ethyl (2*Z*)-2-(Aryl)-5-(4-fluorophenyl)-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

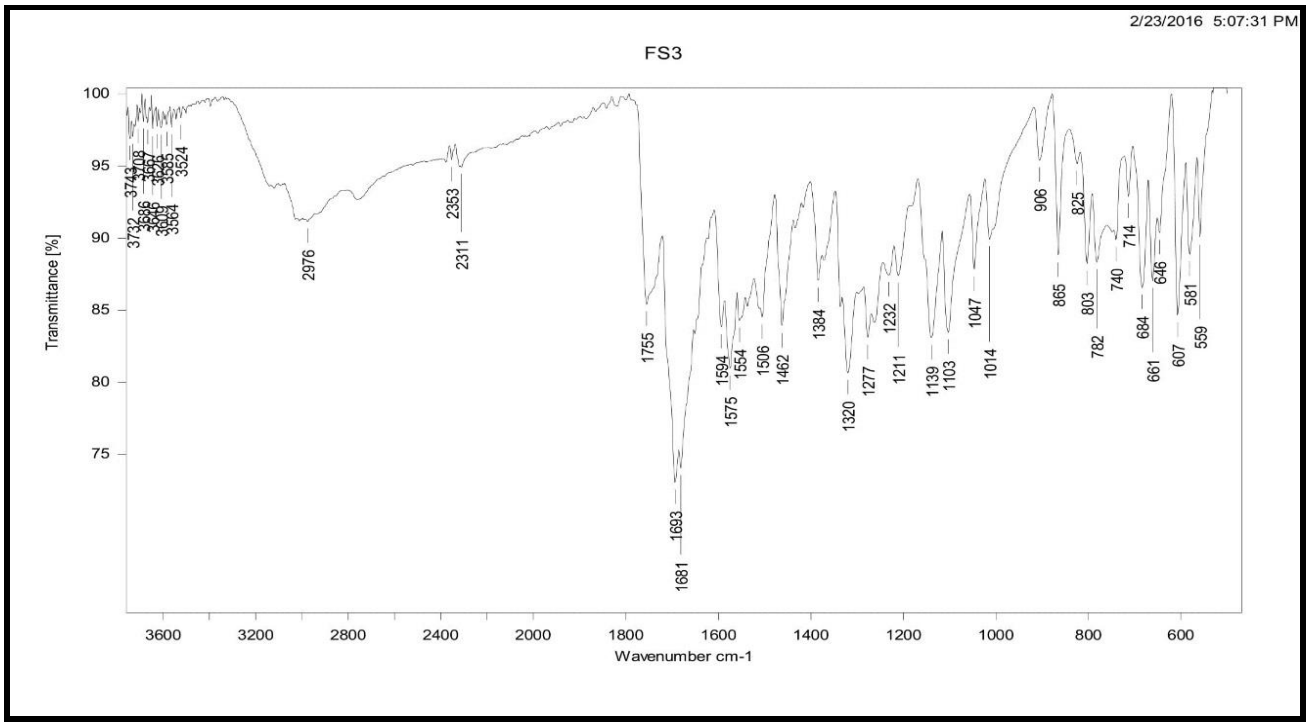
Sr No.	Code No	-Ar	MOLECULAR FORMULA	M. P. ^{O}C	YIELD (%)	% OF CARBON		% OF NITROGEN		MOLECULAR WEIGHT
						FOUND	REQD.	FOUND	REQD.	
1	FS1	-C_6H_5	$C_{23}H_{21}FN_2O_3S$	180-182^{0}C	65%	65.03	65.08	60.58	6.60	424.48
2	FS2	-4-OCH_3-C_6H_4	$C_{24}H_{23}FN_2O_4S$	202^{0}C	64%	63.40	63.42	6.12	6.16	454.51
3	FS3	-2,4-$(CL)_2$-C_6H_3	$C_{23}H_{19}Cl_2FN_2O_3S$	186^{0}C	62%	55.94	55.99	5.64	5.68	493.37
4	FS4	-4-CH_3-C_6H_4	$C_{24}H_{23}FN_2O_3S$	176-179^{0}C	59%	65.71	65.73	6.34	6.39	438.51
5	FS5	-4-F-C_6H_4	$C_{23}H_{20}F_2N_2O_3S$	256^{0}C	61%	62.40	62.43	6.30	6.33	442.47
6	FS6	-4-Br-C_6H_4	$C_{23}H_{20}BrFN_2O_3S$	206^{0}C	53%	54.85	54.88	5.51	5.57	503.38
7	FS7	-4-Cl-C_6H_4	$C_{23}H_{20}ClFN_2O_3S$	210^{0}C	64%	60.18	60.19	6.6	6.10	458.93
8	FS8	-3-OH-C_6H_4	$C_{23}H_{21}FN_2O_4S$	238^{0}C	68%	62.69	62.71	6.32	6.36	440.48
9	FS9	-4-OH-C_6H_4	$C_{23}H_{21}FN_2O_4S$	216^{0}C	70%	62.69	62.71	6.31	6.36	440.48
10	FS10	-3-OCH_3-4-OH-C_6H_3	$C_{24}H_{23}FN_2O_5S$	198-200^{0}C	64%	61.24	61.26	5.94	5.95	470.51
11	FS11	-2-NO_2-C_6H_4	$C_{23}H_{20}FN_3O_5S$	168-170^{0}C	58%	58.80	58.84	8.85	8.95	469.48
12	FS13	-3-NO_2-C_6H_4	$C_{23}H_{20}FN_3O_5S$	240^{0}C	71%	58.80	58.84	8.91	8.95	469.48
13	FS14	-4-NO_2-C_6H_4	$C_{23}H_{20}FN_3O_5S$	233^{0}C	69%	58.70	58.84	8.94	8.95	469.48

III. RESULTS AND DISCUSSION

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 $CDCl_3$ [16,17]. 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 [1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate and other derivatives was recorded.

Table 1: Characterization of ethyl (2*Z*)-2-(2,4-dichlorobenzylidine)-5-(4-fluorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (FS3):

IR Spectra	NMR Spectra		GCMS
IR region between 400 to 4000 cm^{-1}	1H NMR (CDCl3) δ(ppm)	13C NMR(CDCl3) δ(ppm)	Fragmentation of mass spectra (m/z)
3524 (>NH medium, pyrimidine ring)	1.030 (3H, t, ethyl CH3)	21.55	491 (M-2)
2976 (-C-H str., aromatic)	1.7 (3H, s, C6-CH3)	39.36, 39.99	492 (M-1)
1755 (>C=O ester str.)	3.4 (2H, q, OCH2)	40.61	493 (M+)
1681 (cyclic -C=O)	4.1 (1H, s)	116.82	494 (M+1)
1575 (-C=N and aromatic -C=C)	4.3 (1H, s)	128.65	495 (M++2)
1554 (-C=S (-NH) str., aromatic system)	6.4 (1H, s, NH, D2O exchangeable)	130.12	
1462 (>CH medium, aromatic ring)	7.05-7.9 (7H, overlapping signals of Ar-H)	131.82	
782, 740 (-C-Cl str., aromatic)	9.7 (1H, s, NH)	134.88	
684 (str., tri-substituted aromatic)		167.52	
661 (str., di-substituted aromatic)		175.68	
		180.07	



Biological activity:

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

MINIMAL BACTERIAL CONCENTRATIONS (MBC) in µg/ml						
			Gram negative bacteria		Gram positive bacteria	
			E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenus*
Sr No.	Code No	-Ar	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
1	FS1	-C_6H_5	250	200	100	100
2	FS2	-4-OCH_3-C_6H_4	125	200	250	500
3	FS3	-2,4-$(CL)_2$-C_6H_3	250	200	100	250
4	FS4	-4-CH_3-C_6H_4	500	200	125	200
5	FS5	-4-F-C_6H_4	100	200	250	250
6	FS6	-4-Br-C_6H_4	250	250	100	200
7	FS7	-4-Cl-C_6H_4	500	500	200	62.5
8	FS8	-3-OH-C_6H_4	100	200	100	250
9	FS9	-4-OH-C_6H_4	200	62.5	62.5	500
10	FS10	-3-OCH_3-4-OH-C_6H_3	100	62.5	100	250
11	FS11	-2-NO_2-C_6H_4	200	62.5	250	62.5
12	FS13	-3-NO_2-C_6H_4	125	100	62.5	100
13	FS14	-4-NO_2-C_6H_4	250	250	62.5	200
14	Gentamycin		0.05	1	0.25	0.5
15	Ampicillin		100	--	250	100
16	Chloramphenicol		50	50	50	50
17	Ciprofloxacin		25	25	50	50
18	Norfloxacin		10	10	10	10

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

MINIMAL FUNGICIDAL CONCENTRATIONS (MFC) in µg/ml					
			Fungus		
			C.albicans	*A.nigar*	*A.clavatus*
Sr No.	Code No	-Ar	MTCC 227	MTCC 282	MTCC 1323
1	FS1	-C_6H_5	100	62.5	125
2	FS2	-4-OCH_3-C_6H_4	500	1000	1000
3	FS3	-2,4-$(CL)_2$-C_6H_3	250	500	500
4	FS4	-4-CH_3-C_6H_4	250	>1000	>1000

5	FS5	-4-F-C_6H_4	125	125	62.5
6	FS6	-4-Br-C_6H_4	500	200	62.5
7	FS7	-4-Cl-C_6H_4	1000	250	200
8	FS8	-3-OH-C_6H_4	50	100	500
9	FS9	-4-OH-C_6H_4	62.5	200	200
10	FS10	-3-OCH_3-4-OH-C_6H_3	200	62.5	100
11	FS11	-2-NO_2-C_6H_4	100	200	125
12	FS13	-3-NO_2-C_6H_4	200	100	50
13	FS14	-4-NO_2-C_6H_4	62.5	50	125
14	Nystatin		100	100	100
15	Greseofulvin		500	100	100

IV. CONCLUSION

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.

- This section is shows antibacterial activity with 4-fluorophenyl tetrahydro thiazolo pyrimidine derivatives. Out of them -4-OH-C_6H_4, -3-OCH_3-4-OH-C_6H_3 and -2-NO_2-C_6H_4 were lofty active against gram negative bacteria *E.coli* and *P.aeruginosa*. -4-Cl-C_6H_4, -4-OH-C_6H_4, -2-NO_2-C_6H_4, -3-NO_2-C_6H_4, -4-NO_2-C_6H_4 were lofty against gram positive bacteria *S.aureus and S.pyogenus.*
- This section is shows antifungal activity with 4-fluorophenyl tetrahydro thiazolo pyrimidine derivatives. Antifungal activity results showed that compounds -3-OH-C_6H_4, -4-OH-C_6H_4 and -4-NO_2-C_6H_4 showed excellent activity against *C.albicans.* -C_6H_5, -3-OCH_3-4-OH-C_6H_3 and -4-NO_2-C_6H_4 showed excellent activity against *A.nigar.* -4-F-C_6H_4, -4-Br-C_6H_4 and -3-NO_2-C_6H_4 showed excellent activity against *A.clavatus*. -C_6H_5, -2,4-$(CL)_2$-C_6H_3, -4-CH_3-C_6H_4, -4-F-C_6H_4, -4-Cl-C_6H_4, -3-OH-C_6H_4, -4-OH-C_6H_4, -3-OCH_3-4-OH-C_6H_3, -2-NO_2-C_6H_4, -3-NO_2-C_6H_4 and -4-NO_2-C_6H_4 showed good activity against *C.albicans, A.nigar* and *A.clavatus.*

V. ACKNOWLEDGEMENT

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