International Journal of Scientific Research in Chemistry (IJSRCH)
© 2019 IJSRCH | Volume 4 | Issue 1 | ISSN : 2456-8457

Synthesis and Characterizations of Oxazolo Thiazolo Pyrimidine Derivatives as Biological Active and Antiinfective Agents

S. N. Chadotra, B. B. Baldaniya
Department of Chemistry, M. G. Science institute, Navarangpura, Ahmedabad, Gujarat, India

ABSTRACT

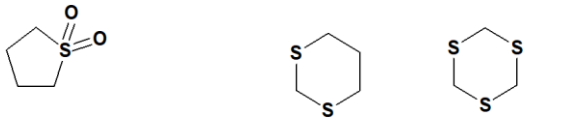
Pyrimidines are those molecules that make our life possible being the building blocks of DNA and RNA. Pyrimidine plays a significant role among other heterocycles. Literature survey reveals that partially reduced pyridine and Pyrimidine derivatives are known to have antihypertensive property. Pyrimidine nucleus was synthesized by Biginelli reaction. The aim of this study was to synthesize and introduce many title compound evaluate them for their antibacterial and antifungal activity. The structures of all title compounds have been confirmed on the basis of their analytical, IR and NMR spectral data. The title compounds have been tested for antibacterial activities against different strains of bacteria.

Keywords : Oxazolo Pyrimidine**,** Antibacterial Activity, Biginelli Reaction.

I. INTRODUCTION

A cyclic compound which is a Heterocyclic ring structure that has atoms of at least two different elements. Those elements are members of its ring or rings. Heterocyclic chemistry is the branch of organic chemistry which deals with applications, synthesis, and properties of these heterocyclic ring structure. Majority of drugs, most biomass like cellulose, nucleic acids and many synthetic dynes are included in heterocyclic chemistry.

Heterocyclic compound may be inorganic or organic, containing at least one or two carbon. Organic chemistry referred when atoms are neither carbon nor hydrogen as heteroatom. Hantzsch-Widman nomenclature recommends for naming heterocyclic compounds.



tetrahydrothiophene 1,1-dioxide Sulfolane | 1,3-dithiane | 1,3,5-trithiane

Organic chemistry has its own descent in the study of natural products. This still remains the most important role in our life and whole world. Many organic compounds occur naturally. Their functions are often of fundamental importance to living organisms.

In the past decades, the pyrimidine and their derivatives have attracted increasing interest in the realms of natural and synthetic organic chemistry because of their diverse therapeutic and pharmacological properties. These non-planner heterocyclic compounds have medicinal importance for further modification in the heterocyclic frame work. In medicinal there are not a single paper is published on the anticancer screening of compounds.

Pyrimidines are among those molecules that make life possible being the building blocks of DNA and RNA. Several analogs of pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. Fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reaction in susceptible patients and are found to be more potent and less likely to produce side effects and hence are being widely used[1]. There are several other important groups of pyrimidines with medicinal uses.

II. METHODS AND MATERIAL

RECENT DEVELOPMENTS IN THE AREA:

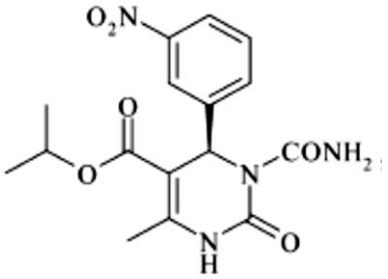
The determination of structure of a molecule provides two fold benefits-it helps to modify the drug and also to synthesize a new drug as the changes in the structure are accompanied with change in the biological activity. The crystal structure studies of these series compounds are important. The new synthesis organic molecules and its biologically activity, characterizations include crystal structure determination of various organic.

Molecules by X-ray crystallographic technique are well known. The crystal structures of large variety of organic compounds are determined and large numbers of research papers are published every year in the International Journals such as Acta Crystallographica, journal of Medicinal chemistry, journal of Heterocycle, European journal of medicinal chemistry, journal of American chemical society, analytical science, molecules, Zeitscrift Fur Kristallographie, Journal of Applied Crystallography, Journal of Molecular Structure etc.

A broad range of biological effects and reactivity, including antibacterial activities have been ascribed to Biginelli compounds. One such compound is Monastrol, which has been shown to be a cell-permeable molecule that blocks a normal bipolar spindle assembly in mammalian cells and, therefore, causes cell cycle arrest. Research in this field is in progress for the development of Monastrol as an anti-cancer drug.

BEGINELLI REACTION:

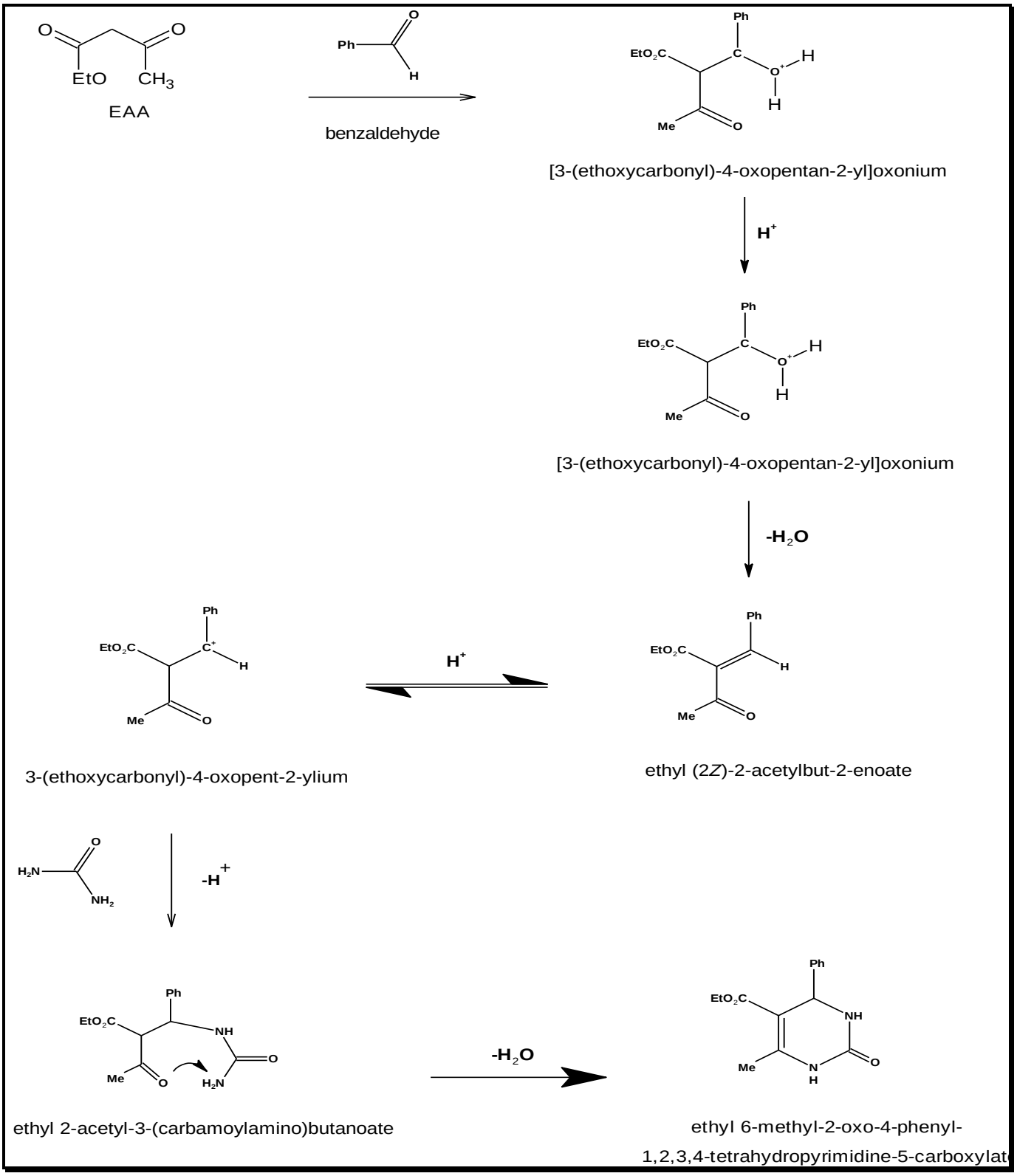
A simple and direct method, first reported by Biginelli in 1893, involves a three Component, one-pot condensation of an aldehyde, a β–ketoester and urea or thiourea Under strongly acidic condition. This has lead to the development of multi step Strategies that produce overall higher yield, but lack of the simplicity of the Biginelli synthesis. As a result, many improved procedures for the preparation of given product. The **Biginelli reaction**[2-3] is a chemical reaction that makes 3,4-dihydropyrimidin-2(1*H*)-ones from ethyl acetoacetate[4-5] , an aryl aldehyde similar to benzaldehyde , and urea . So that's why it is named for the Italian-chemist Pietro Biginelli. The synthesis of pyrimidines and Thiazolopyrimidine are published large in number in above International Journals every year[6-10]. The result of the three-component reaction was a new product that was correctly characterized as a ethyl 4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (THPM)[11]. They have emerged as integral backbones of several calcium channel blockers[12-14] **Fig 1**.



(*R*)-SQ 32926

Fig:1

Reaction Mechanism :



This mechanism is superseded by one by Kappe in 1997

III. RESULTS AND DISCUSSION

Experimental:

Preparation:

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

A 250 ml RBF was filled with a mixture of EAA(ethylacetoacetate)- 0.1 mol, mono/di/tri/ substituted benzaldehyde-(4-hydroxy-3-methoxy benzaldehyde-veniline) (0.1 mol), and urea (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 66 % with m.p 227^0 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-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate:

A mixture of ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.005 mol), 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 162^0 C, Yield 54 %.

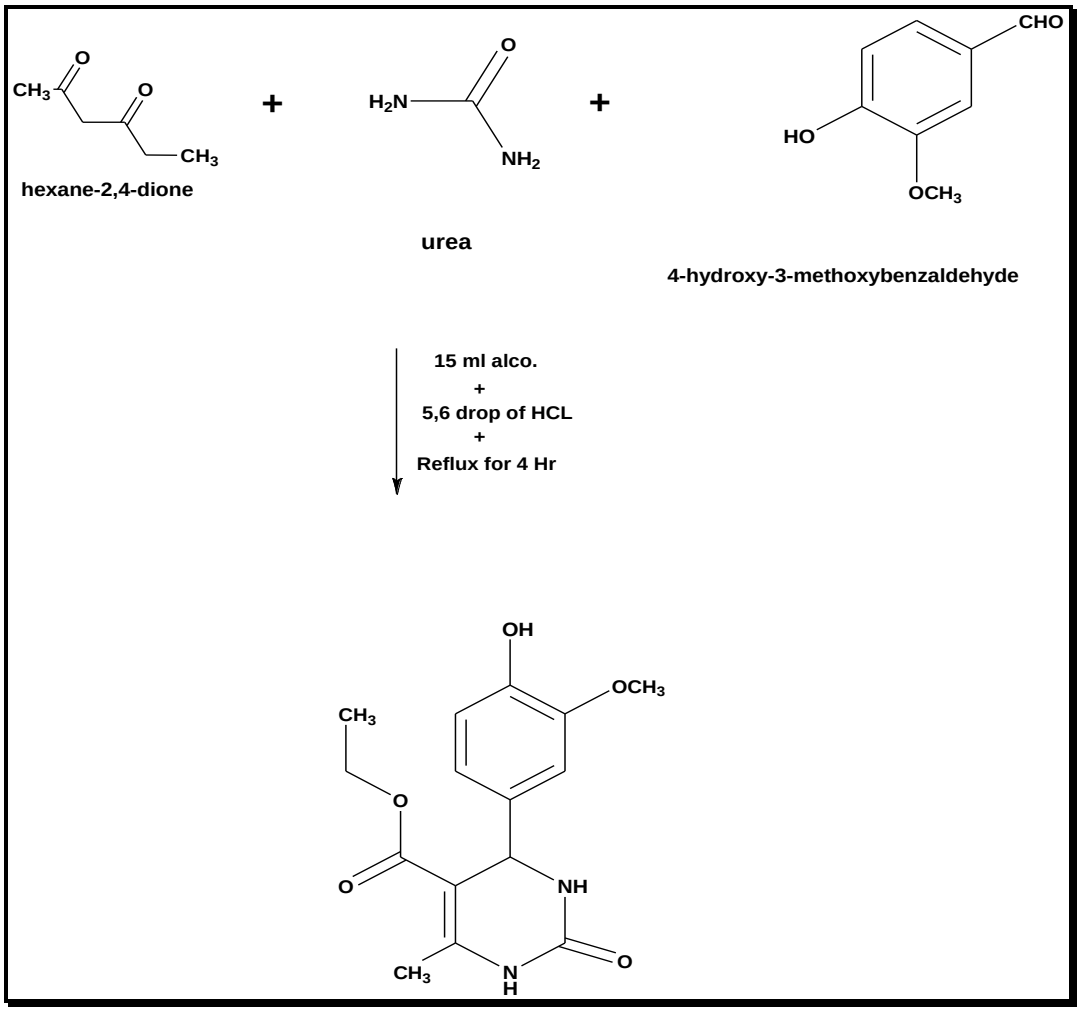
The purity of compounds was routinely checked on TLC aluminum sheet silica gel 60 F_{245} (E. Merck) using benzene-methanol (4.5:0.5 v/v) or benzene-ccl_4–methanol (2.5:2.0:0.5 v/v) as irrigate and was developed in an iodine chamber.

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 :

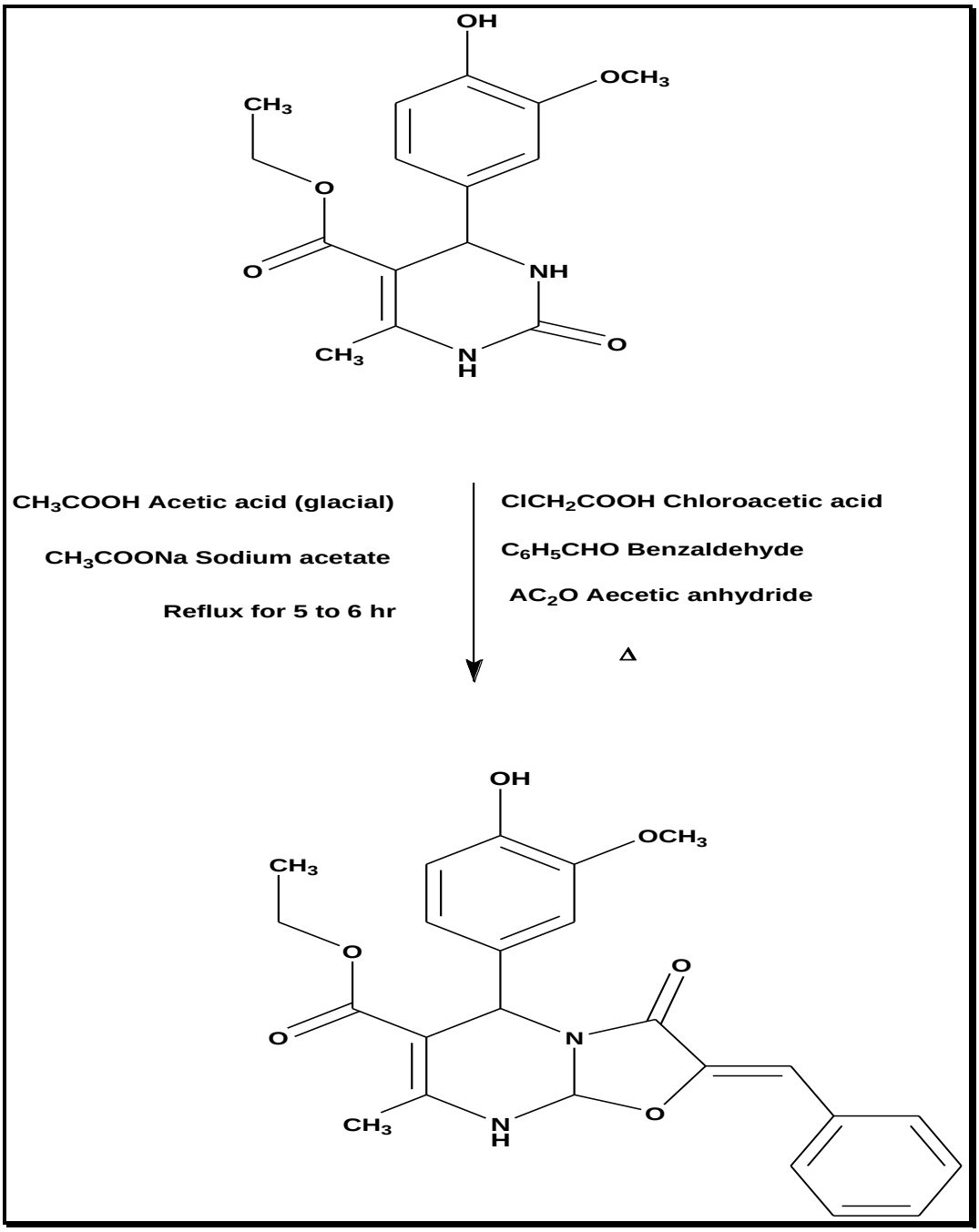
Preparations of ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:



ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Reaction – 2 :

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

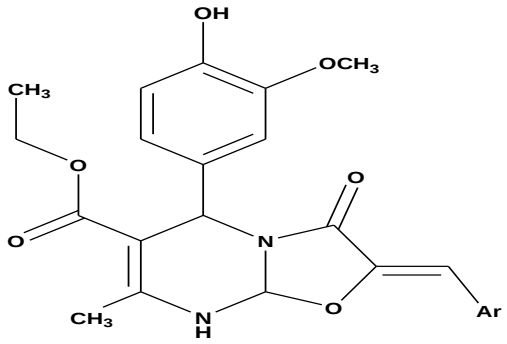


ethyl (2*Z*)-2-benzylidene-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate

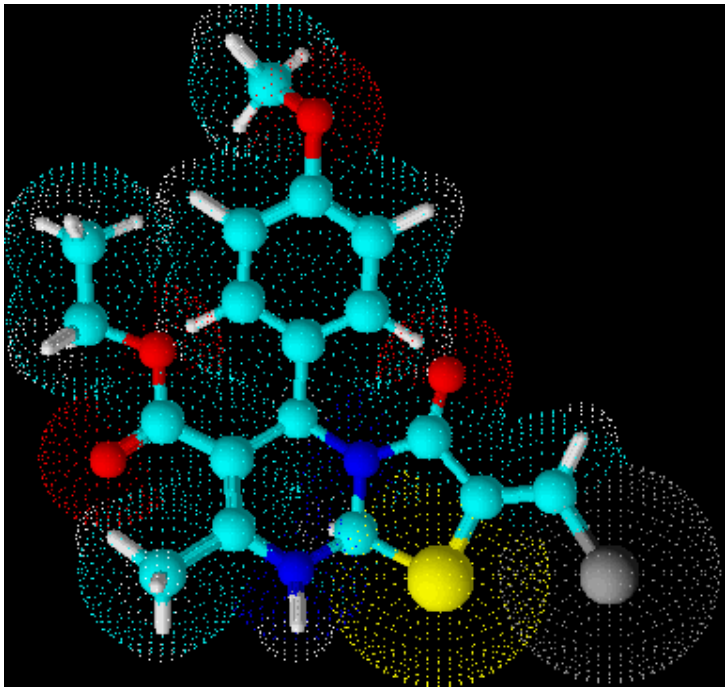
Where Ar = Different aryl group

Physical Experimental data :

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]oxazolo[3,2-*a*]pyrimidine-6-carboxylate:



Sr No.	Code No.	-Ar	MOLECULAR FORMULA	M. P. ^{O}C	YIELD (%)	% OF CARBON FOUND	% OF CARBON REQD.	% OF NITROGEN FOUND	% OF NITROGEN REQD.	MOLECULAR WEIGHT
1	VO1	$-C_6H_5$	$C_{24}H_{24}N_2O_6$	162^0C	54%	66.01	66.04	6.40	6.42	436.45
2	VO2	$-4-OCH_3-C_6H_4$	$C_{25}H_{26}N_2O_7$	178^0C	59%	64.34	64.37	5.98	6.01	466.48
3	VO3	$-2,4-(CL)_2-C_6H_3$	$C_{24}H_{22}Cl_2N_2O_6$	160^0C	64%	57.01	57.04	5.51	5.54	505.34
4	VO4	$-4-CH_3-C_6H_4$	$C_{25}H_{26}N_2O_6$	158^0C	59%	66.62	66.65	6.20	6.22	450.48
5	VO5	$-4-F-C_6H_4$	$C_{24}H_{23}FN_2O_6$	176^0C	58%	63.40	63.43	6.14	6.16	454.44
6	VO6	$-4-Br-C_6H_4$	$C_{24}H_{23}BrN_2O_6$	164^0C	56%	55.91	55.93	5.41	5.44	515.35
7	VO7	$-4-Cl-C_6H_4$	$C_{24}H_{23}ClN_2O_6$	225^0C	53%	61.20	61.21	5.90	5.95	470.90
8	VO8	$-3-OH-C_6H_4$	$C_{24}H_{24}N_2O_7$	205^0C	52%	63.69	63.71	6.14	6.19	452.45
9	VO9	$-4-OH-C_6H_4$	$C_{24}H_{24}N_2O_7$	240^0C	54%	63.67	63.71	6.17	6.19	452.45
10	VO10	$-3-OCH_3-4-OH-C_6H_3$	$C_{25}H_{26}N_2O_8$	230^0C	68%	62.20	62.23	5.80	5.81	482.48
11	VO11	$-2-NO_2-C_6H_4$	$C_{24}H_{23}N_3O_8$	195^0C	55%	59.81	59.87	8.68	8.73	481.45
12	VO13	$-3-NO_2-C_6H_4$	$C_{24}H_{23}N_3O_8$	222^0C	57%	59.86	59.87	8.72	8.73	481.45
13	VO14	$-4-NO_2-C_6H_4$	$C_{24}H_{23}N_3O_8$	212^0C	65%	59.85	59.87	8.70	8.73	481.45



3d view of compound

Antibacterial activity

Antibacterial activity is taken by broth dilution method. Concentrations of 1000,500, 200, 100, 50, 25, 12.5 µg/ml respectively in shown table. Antibacterial activity showed 0.25, 0.05, 0.5 and 1 µg/mL MBC against *E. coli, S. aureus, E. pyogenes and P. aeruginosa* respectively.

Antibacterial activity of ethyl (2*Z*)-2-(Aryl)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[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	VO1	-C_6H_5	250	200	125	500
2	VO2	-4-OCH_3-C_6H_4	50	250	125	200
3	VO3	-2,4-$(CL)_2$-C_6H_3	62.5	200	500	62.5
4	VO4	-4-CH_3-C_6H_4	250	62.5	100	125
5	VO5	-4-F-C_6H_4	100	200	250	250
6	VO6	-4-Br-C_6H_4	50	62.5	100	200
7	VO7	-4-Cl-C_6H_4	250	250	125	250
8	VO8	-3-OH-C_6H_4	200	200	62.5	250
9	VO9	-4-OH-C_6H_4	250	200	100	62.5

10	VO10	-3-OCH_3-4-OH-C_6H_3	500	250	200	200
11	VO11	-2-NO_2-C_6H_4	200	200	250	62.5
12	VO13	-3-NO_2-C_6H_4	125	200	62.5	100
13	VO14	-4-NO_2-C_6H_4	250	125	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

Antifungal activity:

"K. Nystatin" used as a standard drug for antifungal activity, which showed 100 µg/mL MFC against fungi, that used in antifungal activity. Same coumpounds are tested for antifungal activity against C. albicans A. niger and A. clavatus. Concentrations is 1000, 500, 200, 100, 50, 25, 12.5 µg/ml respectively taken.

Antifungal activity of ethyl (2*Z*)-2-(Aryl)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[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	VO1	-C_6H_5	125	200	100
2	VO2	-4-OCH_3-C_6H_4	250	62.5	200
3	VO3	-2,4-$(CL)_2$-C_6H_3	250	50	125
4	VO4	-4-CH_3-C_6H_4	500	1000	>1000
5	VO5	-4-F-C_6H_4	500	250	>1000
6	VO6	-4-Br-C_6H_4	62.5	250	50
7	VO7	-4-Cl-C_6H_4	125	100	200
8	VO8	-3-OH-C_6H_4	200	62.5	125
9	VO9	-4-OH-C_6H_4	500	>1000	1000
10	VO10	-3-OCH_3-4-OH-C_6H_3	250	500	500
11	VO11	-2-NO_2-C_6H_4	100	125	200
12	VO13	-3-NO_2-C_6H_4	250	50	62.5
13	VO14	-4-NO_2-C_6H_4	200	50	100
14	Nystatin		100	100	100
15	Greseofulvin		500	100	100

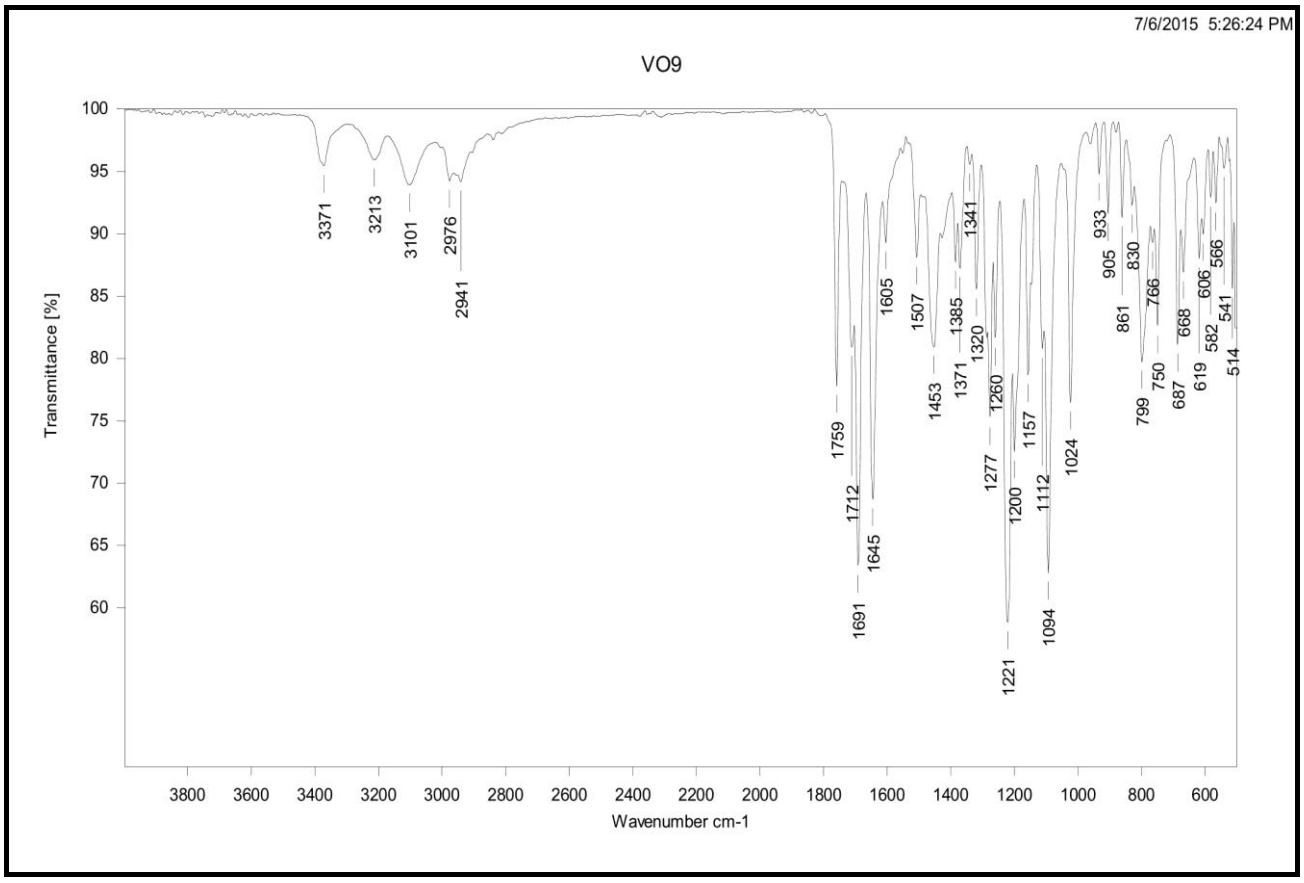
Experimental:

Melting points of derivatives were determined in open glass capillaries in a paraffin bath. The 1H-NMR spectrum of compound verified on the basis of their chemical shifts, multiplicities, and coupling constants. Two singlets appeared at δ 5.95 ppm and δ 8.79 ppm was due to the proton present in the pyrimidine and pyrazole ring respectively. A triplet appeared at δ 1.09 ppm and quartet at δ 3.99 ppm indicate the presence of methyl and methylene protons of the ester chain. Benzylidene proton appeared as a singlet at δ 7.48 ppm. Two singlets observed at δ 2.23 ppm and δ 2.31 ppm indicated the presence of two methyl group present in the structure. In the IR spectrum, the sharp absorption band appeared at 1,653 cm–1 was due to carbonyl group of the ester and other sharp band appeared at 1,614 cm–1 was due to the cyclic carbonyl group. LCMS and 13C-NMR spectrum was in complete agreement with the title compound.

The IR spectrum of [1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate and other derivatives (in KBr pellets) was recorded on a BRUKER FT-IR spectrophotometer.

Characterization of ethyl (2*Z*)-2-(4-hydroxybenzylidine)-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate (VO9):

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)
3371 (>NH medium, pyrimidine ring)	1.2 (3H, t, ethyl CH3)	14.60, 18.29	450 (M-2)
3101, 2976 (-O-H str.)	1.9 (3H, s, C6-CH3)	20.84, 39.97	451 (M-1)
3213 (-C-H str., aromatic)	5.34 (1H, s, OH)	39.99, 40.20	452 (M+)
2941 (-CH_3 str.)	4.01 (2H, q, OCH2)	54.12, 99.42	453 (M+1)
1759 (>C=O ester str.)	3.73 (6H, s, C6-OCH3)	111.44	454 (M++2)
1699, 1616 (cyclic -C=O)	2.49 (3H, s)	118.23	
1507 (-C=N and aromatic -C=C)	5.1 (1H, s)	138.23	
1453 (>CH medium, aromatic ring)	5.40 (1H, s)	138.84	
1112 (-C=O (-NH) str., aromatic system)	6.66 (1H, s, NH, D2O exchangeable)	149.12	
742 (str., tri-substituted aromatic)	6.90-7.98 (7H, overlapping signals of Ar-H)	152.61	
652 (str., di-substituted aromatic)	9.40 (1H, s, NH)	169.04	



The progress of the reaction and 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.

IV.CONCLUSION

Many derivatives of 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 4-hydroxy-3-methoxyphenyl oxazolo pyrimidine derivatives. Out of them -4-OCH_3-C_6H_4, -2,4-$(CL)_2$-C_6H_3 and -4-Br-C_6H_4 were optimum against *P.aeruginosa* gram negative bacteria. -4-CH_3-C_6H_4 and -4-Br-C_6H_4 were optimum against *S.aureus* and -2,4-$(CL)_2$-C_6H_3, -3-OH-C_6H_4, -2-NO_2-C_6H_4, -3-NO_2-C_6H_4 and -4-NO_2-C_6H_4 were optimum against *S.aureus* and *S.pyogenus* gram positive bacteria.
- Result of antifungal activity of 4-hydroxy-3-methoxyphenyl oxazolo pyrimidine derivatives showed that compounds 4-Br-C_6H_4 showed exquisite activity against *C.albicans.* -4-OCH_3-C_6H_4, -2,4-$(CL)_2$-C_6H_3, -3-OH-C_6H_4, -3-NO_2-C_6H_4 and -4-NO_2-C_6H_4 showed exquisite activity against *A.nigar.* 4-Br-C_6H_4 and -3-NO_2-C_6H_4 showed exquisite activity against *A.clavatus*. -C_6H_5, -4-OCH_3-C_6H_4, -2,4-$(CL)_2$-C_6H_3, -4-F-C_6H_4, -4-Br-C_6H_4, -4-Cl-C_6H_4, -3-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

We are thankful to our principal of M. G. Science Institute, Ahmedabad and the Ahmadabad Education Society for facilitating us a well-equipped research laboratory and library. We are also thankful to the North America Institute of Pharmaceutical Technology, Toronto for NMR data collection and Microcare laboratory & tuberculosis research centre, Surat for biological activity. For Mass data collection we are thankful to Saurastra University, Rajkot.

VI. REFERENCES

[1]. G. C. Rovnyak, S. D. Kimbali, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Hedberg, M. Malley, J. P. McCarthy, R. Zhang and S. Moorland, J. Med. Chem.,1995, 38, 119.

[2]. M. Zamadar(a); D. Aebisher; A. Greer "Singlet Oxygen Delivery Though the Porous Cap of a Hollow-Core Fiber Optic Device" J. Phys. Chem. B 2009.

[3]. Biginelli, P. *Ber.* 1891, *24*, 1317 & 2962.

[4]. Kappe, C. O. *Tetrahedron* 1993, *49*, 6937-6963. (Review)

[5]. Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* 1998, *63*, 3453-3457.

[6]. Wipf, P.; Cunningham, A. *Tetrahedron Lett.* 1995, *36*, 7819-7822.

[7]. M. Zamadar(a); A. Greer "Singlet Oxygen as an Reagent in Organic Synthesis" In Handbook of Synthetic Photochemistry; Albini, A., Fagnoni, M., Eds.; Wiley-VCH: Weinheim (in press).

A. Castillo;(a); A. Greer "Theoretical Studies of a Singlet Oxygen-Releasing Dioxapaddlane (1,4-Diicosa naphthalene-1,4-endoperoxide)" *Struct. Chem.* 2009*, 30,* 399-407.

[8]. M. L. Raber; A. Castillo;(a); A. Greer; C. A. Townsend "A Conserved Lysine in beta-Lactam Synthetase Assists Ring Cyclization: Implications for Clavam and Carbapenem Biosynthesis" ChemBioChem 2009 (submitted).

[9]. E. M. Greer; D. Aebisher; A. Greer; R. Bentley "Computational Studies of the Tropone Natural Products, Thiotropocin, Tropodithietic acid, and Troposulfenin. Significance of Thiocarbonyl-enol Tautomerism" J. Org. Chem. 2008, 73, 280-283.

[10]. Greer and J. F. Liebman "Paradigms and Paradoxes: Energetics of the Oxidative Cleavage of Azo Compounds" *Struct. Chem.* **2008**, *19*, 817-818.

[11]. M. M Jotani and B. B. Baldaniya, Acta Cryst., 2006, E62, o5871-o5873.

[12]. M. M Jotani and B. B. Baldaniya, Acta Cryst., 2007, E63, o1937-o1939.

[13]. N. C. Desai,M. T. Chhabaria, Amit Dodiya, Ajit M. Bhavsar, B. B. Baldaniya, Synthesis, characterization, anticancer activity, and QSAR-studies of some new tetrahydropyrimidines, Med Chem Res, 2011,20:1331–1339.

Cite this article as :

S. N. Chadotra, B. B. Baldaniya, "Synthesis and Characterizations of Oxazolo Thiazolo Pyrimidine Derivatives as Biological Active and Antiinfective Agents", International Journal of Scientific Research in Chemistry (IJSRCH), ISSN : 2456-8457, Volume 4 Issue 1, pp. 17-28, January-February 2019. URL : http://ijsrch.com/IJSRCH19416