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

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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 introduse many title compound (1a -1m) 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

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.

"DRUG DESIGN" requires the knowledge of the structure of a drug molecule as well as that of receptor molecule involved in drug receptor interaction. The structure of a molecule is responsible for its biological activities as the small change in the structure.

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.

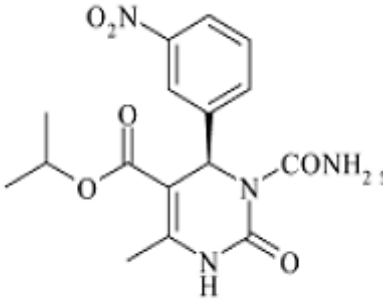
The new synthesis organic molecules and its biologically activity, characterizations include crystal structure determination of various organic.

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:

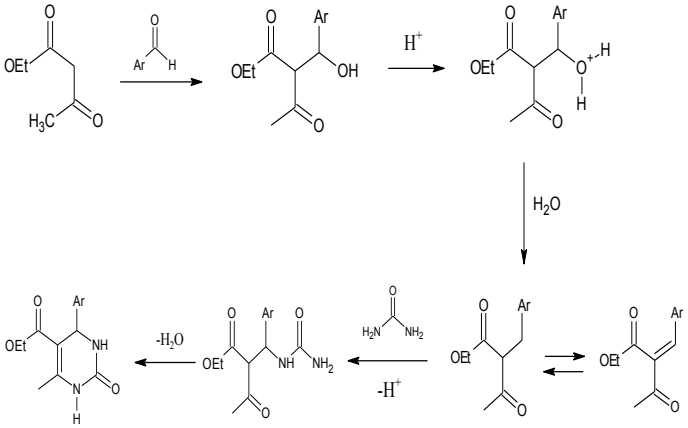
A simple and direct method, first reported by Biginelli in 1893, involves a three Component, one-pot condensation of an aldehyde, a β–ketoester and urea or thiourea Under strongly acidic condition. This has lead to the development of multi-step Strategies that produce overall higher yield, but lack of 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[10-6]. 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

Figure1.

Reaction Mechanism:

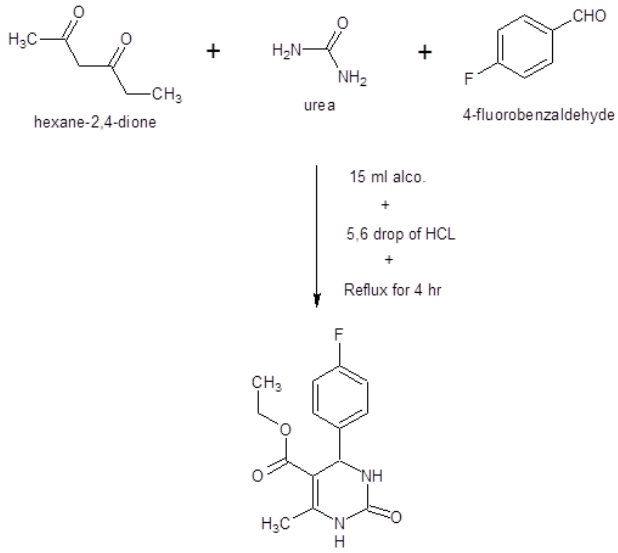


This mechanism is superseded by one by Kappe in 1997

Section -1:

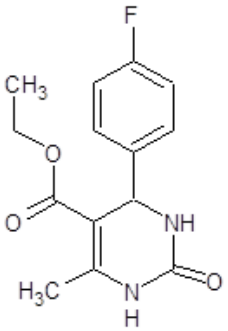
Preparations of ethyl (2*Z*)-2-(Aryl)-5-(4-fluorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate:

Reaction 1:



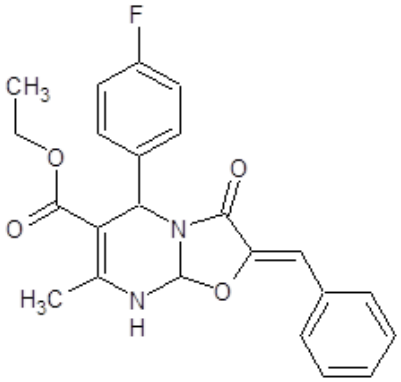
Ethyl4-(4-fluoroyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Reaction 2:



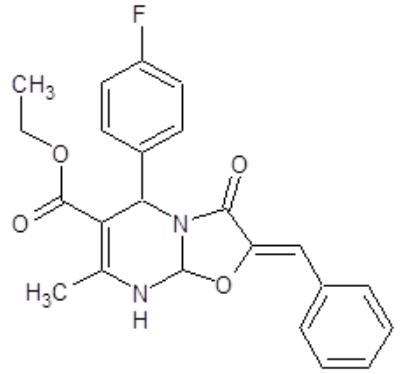
Ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

CH_3COOH Acetic acid (glacial) | $ClCH_2COOH$ Chloroacetic acid
CH_3COONa Sodium acetate | C_6H_5CHO Benzaldehyde
Δ | AC_2O Aecetic anhydride
Reflux for 5 to 6 hr



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

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



Sr No.	-Ar	MOLECULAR FORMULA	M. P. ^{O}C	YIELD (%)	% OF CARBON		% OF NITROGEN		Mol. Wt
					FOUND	REQD.	FOUND	REQD.	
1a	$-C_6H_5$	$C_{23}H_{21}FN_2O_3S$	169^0C	56%	65.03	65.08	60.58	6.60	424.48
1b	$-4-OCH_3-C_6H_4$	$C_{24}H_{23}FN_2O_4S$	163^0C	64%	63.40	63.42	6.12	6.16	454.51
1c	$-2,4-(CL)_2-C_6H_3$	$C_{23}H_{19}Cl_2FN_2O_3S$	162^0C	62%	55.94	55.99	5.64	5.68	493.37
1d	$-4-CH_3-C_6H_4$	$C_{24}H_{23}FN_2O_3S$	156^0C	59%	65.71	65.73	6.34	6.39	438.51
1e	$-4-F-C_6H_4$	$C_{23}H_{20}F_2N_2O_3S$	171^0C	61%	62.40	62.43	6.30	6.33	442.47
1f	$-4-Br-C_6H_4$	$C_{23}H_{20}BrFN_2O_3S$	158^0C	53%	54.85	54.88	5.51	5.57	503.38
1g	$-4-Cl-C_6H_4$	$C_{23}H_{20}ClFN_2O_3S$	166^0C	64%	60.18	60.19	6.6	6.10	458.93
1h	$-3-OH-C_6H_4$	$C_{23}H_{21}FN_2O_4S$	170^0C	68%	62.69	62.71	6.32	6.36	440.48
1i	$-4-OH-C_6H_4$	$C_{23}H_{21}FN_2O_4S$	167^0C	70%	62.69	62.71	6.31	6.36	440.48
1j	$-3-OCH_3-4-OH-C_6H_3$	$C_{24}H_{23}FN_2O_5S$	179^0C	64%	61.24	61.26	5.94	5.95	470.51
1k	$-2-NO_2-C_6H_4$	$C_{23}H_{20}FN_3O_5S$	160^0C	53%	58.81	58.84	8.90	8.95	469.48
1l	$-3-NO_2-C_6H_4$	$C_{23}H_{20}FN_3O_5S$	190^0C	71%	58.80	58.84	8.91	8.95	469.48
1m	$-4-NO_2-C_6H_4$	$C_{23}H_{20}FN_3O_5S$	152^0C	66%	58.79	58.84	8.93	8.95	469.48

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

A mixture of Ethyl aceto acetate (0.01 mole), benzaldehyde (0.01 mole) and urea (0.01 mole) in ethanol (20 ml) was refluxed for 6 h. The reaction mixture was poured in crushed ice and product was isolated and re-crystallized from ethanol: DMF .Yield 78% 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.

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

A mixture of ethyl 4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), benzaldehyde (0.01 mole),chloroaceticacid,sodium acetate (0.01 mole), acetic anhydride (0.01 mole) in acetic acid (20 ml) was refluxed for 5 to 6 hr. The reaction mixture was poured in crushed ice and product was isolated and re-crystallized from ethanol: DMF m.p 170^0C Yield 58%

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.

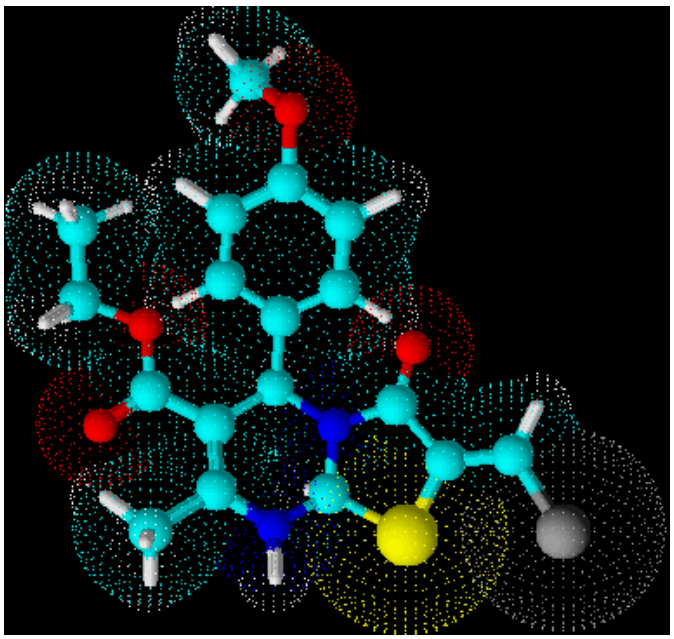


Figure 2. 3d view of compound

Table 2: Antibacterial and Antifungal Activities

SR NO.	Minimal bactericidal concentration (MBC) in µg/ml				Minimal fungicidal concentration (MFC) in µg/ml		
	E.coli	*P.aeru ginosa*	*S.aureus*	*S.pyogenus*	*C.albicans*	*A.nigar*	*A.clavatus*
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
	- 443	-1688	-96	- 442	-227	-282	-1323
1a	200	500	1000	500	500	500	500
1b	50	100	1000	1000	500	500	500
1c	200	500	1000	1000	1000	1000	1000
1d	100	50	500	250	500	500	500
1e	100	1000	500	500	500	500	200
1f	100	100	1000	500	1000	1000	1000
1g	100	250	500	500	500	500	500
1h	100	200	1000	1000	1000	1000	1000
1i	50	500	500	1000	500	500	500
1j	50	100	1000	500	1000	500	500
1k	200	250	1000	1000	500	500	500
1l	200	100	1000	1000	1000	1000	1000
1m	100	500	500	1000	1000	1000	1000

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.

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.

III. RESULTS AND DISCUSSION

Melting points of Ethyl (2*Z*)-2-(benzylidene)-5-(4-fluorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate and other 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 Ethyl (2*Z*)-2-(benzylidene)-5-(4-fluorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-

[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate(1a) and other derivatives (in KBr pellets) was recorded on a BRUKER FT-IR spectrophotometer.
IR (KBr): νmax (cm−1), 3402 (>NH), 3111 (C-H), 1714 (C=O ester), 1552 (C=N and aromatic C=C) , 1159 (C-O), 756 (C-Cl), 698,754 (str., tri-substituted aromatic).

1H-NMR (400 MHz, DMSO-d6): δ ppm, 1.09 (t, 3H, *J* = 7 Hz, ester-CH3), 3.99 (q, 2H, *J* = 7.12 Hz ester-CH2), 2.31 (s, 3H, CH3), 2.23 (s, 3H, Ar-CH3), 5.95 (s, 1H, pyrimidine-CH), 7.48 (s, 1H, CH), 7.11–8.02 (m, 12H, Ar-H), 8.79 (s, 1H, pyrazole CH).

13C-NMR (100 MHz, DMSO-*d*6): δ ppm, 13.88 (ester CH3), 20.67 (CH3), 22.47 (CH3), 54.72 (ester CH2), 60.14 (CH), 108.75, 115.56, 119.35, 119.42, 122.24, 127.38, 127.69, 128.32, 128.71, 129.21, 129.58, 130.08, 131.13, 131.75, 131.79, 131.88, 137.47, 138.00, 138.49, 150.97, 151.01, 155.14, 163.91,164.82 (C=O).

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.

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