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

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ABSTRACT

Pyrimidine plays a significant role among other heterocycles. Pyrimidine nucleus was synthesized by Biginelli reaction. The purpose of this study was to synthesize several oxazolo derivative compounds (1-13) and evaluate them for their antibacterial activity. The structures of all title compounds have been confirmed on the basis of their analytical, IR spectral data. The title compounds have been tested for antibacterial and antifungal activities against different strains of bacteria.

Keywords: Oxazolo Pyrimidine, Antibacterial activity, antifungal activities, Biginelli reaction

I. INTRODUCTION

The synthesis and antimicrobial activity of condensed pyrimidine derivatives have been reported. Oxazolo [3,2-*a*] pyrimidine derivatives are the bioisosteric analogues of purine and pyrimidine. They are also potentially bioactive molecules in organic chemistry. In synthesis work many derivatives with different substitution patterns display interesting pharmacological activities. Heterocyclic pyrimidines are 5 and 6-membered heterocyclic ring compounds composed of nitrogen and carbon. The base of DNA and RNA are recognized pyrimidines. The origin of the term Pyrimidine dates back to 1884, when Pinner introduced the term from a combination of the words pyridine and amidine [1].

Many derivatives with different substitutional patterns display interesting antimicrobial [2] and pharmacological activities. Oxazolo pyrimidines have hypoglycemic and antidiabetic activities. Since 1848, the first primary synthesis from aliphatic fragments was carried out by Frank Land then a many distinct primary synthetic method has been synthesized and published [3-5]. It is also possible to prepare many heterocycles derivatives from other heterocycles like pyrole [6], imidazole [7], isooxazoles and oxazoles [8], pyridines [9-12], pyrazines [13], tetrahydropyrimidines [14], oxazines and thiazines by various reaction processes.

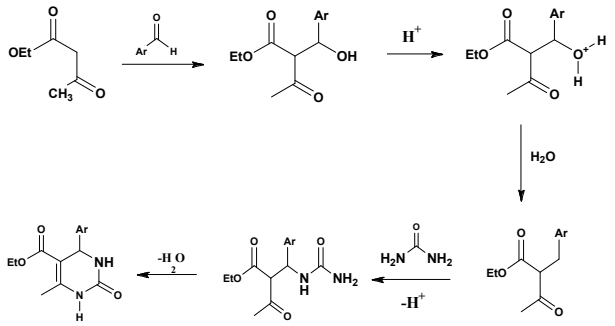
Oxazolo pyrimidines have antifungal, antimalerial, antitumor, anticancer and antiinfactive activities [15-17]. Pyrimidine derivatives play a vital role in synthetic organic chemistry. Mainly their wide range of biological activities recognised as calcium channel blockers. Most of derivatives of pyrimidine [18-20] which are synthesized have significant biological and antifungal activity [21-23].

II. METHODS AND MATERIAL

Biginelli Reaction:

In 1983, a simple and direct producing compound method, first reported by Biginelli. It involves a three Component, one-pot condensation of an aldehyde, β–ketoester and urea. This has led to the development of multi-step strategies. That produce overall higher yield. Its name was coming from Italian chemist Pietro Biginelli. It is a series of bimolecular reaction and

compounds.

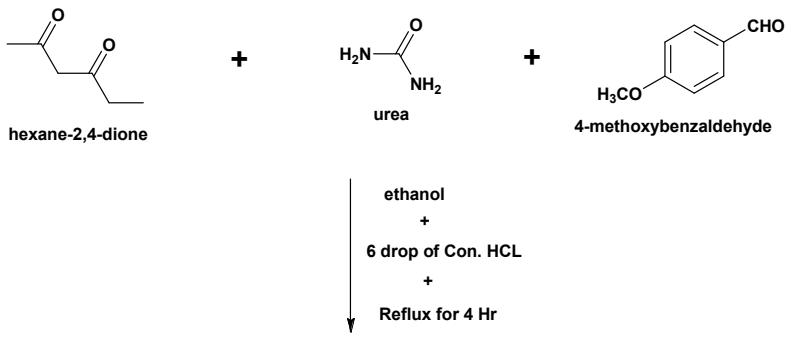


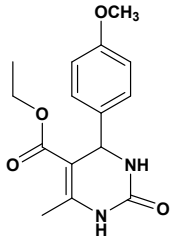
This mechanism is superseded by one by Kappe in 1997

Reaction 1:

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

A mixture of Hexane-2,4-dione (0.01 mole), benzaldehyde (0.01 mole) and urea (0.01 mole) in ethanol (20 ml) was refluxed for 5 h. The reaction mixture was poured in crushed ice and product was isolated and re-crystallized from ethanol. 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.





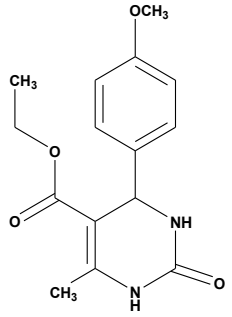
Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

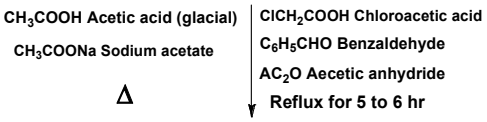
Reaction 2

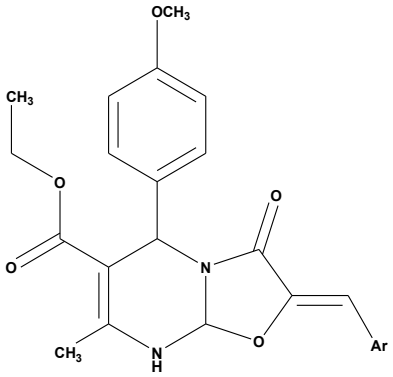
Preparation of (2*Z*)-ethyl-2-(Aryl)-3,5,8,8a-tetrahydro-5-(4-methoxyphenyl)-7-methyl-3-oxo-2H-oxazolo[3,2-*a*]pyrimidine-6-carboxylate:

A mixture of ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(0.01 mole), substituted benzaldehyde (0.01 mole), chloro aceticacid (0.01 mole), 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 207^{0}C Yield 56%.

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.





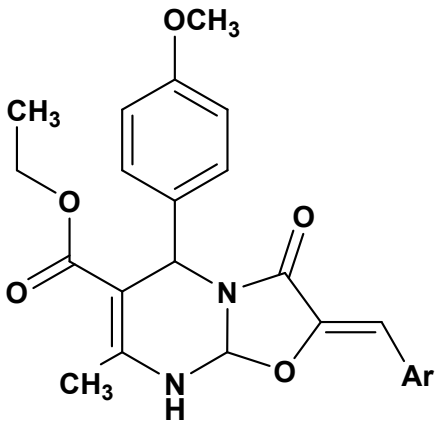


(2*Z*)-ethyl-2-(Aryl)-3,5,8,8a-tetrahydro-5-(4-methoxyphenyl)-7-methyl-3-oxo-2H-oxazolo [3,2-*a*]pyrimidine-6-carboxylate

Where Ar = Different aryl group

III. RESULTS AND DISCUSSION

Physical constants Table 1



Sr No.	-Ar	MOLECULAR FORMULA	M. P. ^{O}C	YIELD (%)	% OF CARBON		% OF NITROGEN		MOL. WEIGHT
					FOUND	REQD.	FOUND	REQD.	
1	$-C_6H_5$	$C_{24}H_{24}N_2O_5$	207^0C	56%	68.50	68.56	6.61	6.66	420.45
2	$-4-OCH_3-C_6H_4$	$C_{25}H_{26}N_2O_6$	210^0C	58%	66.62	66.65	6.19	6.22	450.48
3	$-2,4-(CL)_2-C_6H_3$	$C_{24}H_{22}Cl_2N_2O_5$	205^0C	68%	58.89	58.91	5.68	5.72	489.34
4	$-4-CH_3-C_6H_4$	$C_{25}H_{26}N_2O_5$	194^0C	64%	69.10	69.11	6.40	6.45	434.48
5	$-4-F-C_6H_4$	$C_{24}H_{23}FN_2O_5$	198^0C	70%	65.68	65.74	6.31	6.39	438.44
6	$-4-Br-C_6H_4$	$C_{24}H_{23}BrN_2O_5$	209^0C	65%	57.70	57.73	5.59	5.61	499.35
7	$-4-Cl-C_6H_4$	$C_{24}H_{23}ClN_2O_5$	196^0C	62%	63.30	63.37	6.10	6.16	454.90
8	$-3-OH-C_6H_4$	$C_{24}H_{24}N_2O_6$	200^0C	64%	66.00	66.04	6.40	6.42	436.45
9	$-4-OH-C_6H_4$	$C_{24}H_{24}N_2O_6$	198^0C	63%	66.00	66.04	6,40	6.42	436.45
10	$-3-OCH_3-4-OH-C_6H_3$	$C_{25}H_{26}N_2O_7$	212^0C	58%	64.32	64.37	6.00	6.01	466.48
11	$-2-NO_2-C_6H_4$	$C_{24}H_{23}N_3O_7$	199^0C	59%	61.88	61.93	9.01	9.03	465.45
12	$-C_4H_3O$	$C_{22}H_{22}N_2O_6$	210^0C	62%	64.29	64.38	6.79	6.83	410.41
13	$-3-NO_2-C_6H_4$	$C_{24}H_{23}N_3O_7$	202^0C	69%	61.88	61.93	9.00	9.03	465.45

Experimental

Melting points of (2*Z*)-ethyl-2-(benzylidene)-3,5,8,8a-tetrahydro-5-(4-methoxyphenyl)-7-methyl-3-oxo-2H-oxazolo[3,2-*a*]pyrimidine-6-carboxylate and other derivatives (1-13) were determined in open glass capillaries in a paraffin bath. The IR spectrum of derivatives was recorded on a BRUKER FT-IR spectrophotometer. NMR spectra were recorded in 400 MHz BRUKER instrument.

IR (KBr): νmax (cm−1), 3234 (>NH), 2929 (CO-NH), 2834 (CH_3 str.), 1721 (C=O and aromatic C=C), 1583 (C=S (-NH) str.), 1366 (>CH), 1217, 1174 (>C=S), 1030 (C-Cl), 778,762 (str., tri-substituted aromatic). 1H-NMR (400 MHz): δ ppm, 1.31 (t, 3H, J = 7 Hz, ester -CH_3), 2.17 (s, 6H, Ar-CH3), 2.42 (s, H, -CH), 3.43 (q, 2H, J = 7.12 Hz ester-CH_2), 3.83 (s, H, -OCH_3), 4.05 (d, H, -CH), 6.97-7.32 (m, 9H, Ar-H), 8.21 (d, H, -NH). 13C NMR (CDCl3) δ (ppm): 14.56, 18.22, 39.35, 40.19, 55.51, 100.05, 114.16, 137.53, 148.47, 152.65, 165.85 (C=O). GCMS: Fragmentation of mass spectra m/z: 420.43 (M^+), 421 (M+1), 422 (M+).

IV. 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). Antifungal activity also screened for their *in-vitro* against *Candida albicans, Aspergillus niger* and *Aspergillus clavatus* by measuring in MBC and in MFC method in µg/mL. Antibacterial and antifungal activity was carried out by broth dilution method at concentrations of 1000, 500, 250, 200, 125, 100, 62.5 [24] µg/mL respectively.

Table 2:

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	62.5	100	200	250	250	200	250
2	250	500	100	100	200	>1000	>1000

3	250	200	100	200	500	>1000	>1000
4	62.5	100	200	200	200	500	500
5	62.5	100	125	200	250	200	250
6	100	125	100	125	500	1000	1000
7	250	250	125	200	250	>1000	>1000
8	200	62.5	100	125	200	250	250
9	62.5	200	200	100	500	1000	1000
10	250	250	62.5	125	250	200	250
11	250	200	100	125	>1000	500	>1000
12	250	62.5	200	200	200	250	>1000
13	200	200	200	100	250	200	500
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

V. CONCLUSION

Now a day there are many important uses of them like antimicrobial and anti-infective activity. This work consists of the overall comparison of the compound synthesized in my research work. Out of them Pyrimidine derivatives possesses remarkable pharmaceutical importance and biological activities.

VI. ACKNOWLEDGEMENT

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