Synthesis and Characterizations of Ethyl (2z) - 2 - (aryl) - 5 - (4-
 methoxyphenyl)- 7 -methyl - 3 - oxo-2, 3, 8, 8a-tetrahydro-5h- [1,3]
thiozo [3,2-a] pyrimidine-6-carboxylate as Biological Active Agents

J. S. Makwana, Dr. B. B. Baldaniya*
Chemistry Department, M G Science Institute, Navarangpura, Ahmedabad, Gujarat, India

ABSTRACT

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 purpose of this study was to synthesize several title compounds (2a-2k) 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 activities against different strains of bacteria.

Keywords : Thiozolo Pyrimidine, Antibacterial Activity, Biginelli Reaction

I. INTRODUCTION

Medicinal chemistry is introduced as principles of chemistry and biology. It is also give knowledge which leads to the introduction of new therapeutic agents. Pyrimidines are those molecules that make our life possible being the building blocks of DNA and RNA. Also there are some thiouracil derivatives and compounds, which produce adverse reaction in susceptible patients are being widely used1. There are many other vital groups of pyrimidines with medicinal uses11.

In the past decades, the pyrimidines have attracted increasing interest in the realms of natural organic chemistry because of their diverse therapeutic and pharmacological properties. These non-planer heterocyclic compounds have emerged as the integral backbones of calcium channel modulators, antihypertensive agents, α1a- adrenergic receptor antagonists, neuropeptide Y (NPY) antagonist, hepatitis B virus replication inhibitors, several marine derived natural products such as Crambine, Betzelladine β (potent hivgp-120 CD4 inhibitors)11. Pilomycalin alkaloids have been reported to contain dhpms and thpms moiety12.

Several analogs of pyrimidines have been used with the synthesis and functioning of nucleic acids e.g. Fluorouracil, which is used in cancer treatment, cancer antibiotic and cancer drugs9-10. 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-cancer15 drug.

II. METHODS AND MATERIAL

1. Biginelli Reaction

A simple and direct producing compound 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 is a reaction that creates 3,4-dihydropyrimidin-2(1H)-ones2-3-4-5, an aryl aldehyde ,
and urea or thiourea. Its name was coming from Italian chemist Pietro Biginelli.

**Reaction Mechanism:**

The reaction mechanism of the Biginelli reaction is a series of bimolecular reactions and compounds. The aldol condensation of ethylacetooxacetate and the aryl aldehyde. The nucleophilic addition of urea. It gives the intermediate, which immediately dehydrates to give the desired product.

\[
\text{OEt} \quad \text{O} \quad \text{O} \quad \text{OEt} \quad \text{O} \quad \text{Ar} \quad \text{H} \\
\text{OEt} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{Ar} \quad \text{OEt} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{Ar} \quad \text{NH} \quad \text{2} \quad \text{H} \quad \text{2O} \\
\text{OEt} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{Ar} \quad \text{OEt} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{Ar} \quad \text{OEt} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{Ar} \quad \text{NH} \quad \text{2} \quad \text{H} \quad \text{2O} \\
\]

This mechanism is superseded by one by Kappe in 1997.

**Section – 1:**

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

**Reaction 1:**

\[
\text{HCO} \quad \text{C} \quad \text{O} \quad \text{CH} \quad + \quad \text{H}_{2} \text{N} \quad \text{NH}_{2} \quad + \quad \text{CH}_{3} \text{COCH}_{2} \text{CHO} \\
\text{15 ml alco.} \\
\text{6.6 drop of HCL} \\
\text{Reflux for 4 hr} \\
\]

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

**Reaction 2:**

\[
\text{CH}_{3} \quad \text{COOH} \quad \text{Acetic acid (glacial)} \quad \text{ClCH}_{2} \text{COOH} \quad \text{Chloroacetic acid} \\
\text{CH}_{3} \text{COONa} \quad \text{Sodium acetate} \quad \text{C}_{6} \text{H}_{5} \text{CHO} \quad \text{Benzaldehyde} \\
\text{AC}_{2} \text{O} \quad \text{Acetic anhydride} \quad \Delta \\
\text{Reflux for 5 to 6 hr} \\
\]

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

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

A mixture of Ethyl aceto acetate (0.01 mole), benzaldehyde (0.01 mole) and thiourea (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 68%

The progress of the reaction and the purity of compounds was routinely checked on TLC aluminum sheet silica gel 60 F_{254} (E.Merck) using benzene-methanol (4.5:0.5 v/v) or benzene-clc4-methanol (2.5:2.0:0.5 v/v) as irrigate and was developed in an iodine chamber.

Table 2 : Antibacterial and Antifungal Activities
Antibacterial Activity

Antibacterial activity is taken by broth dilution method. Concentrations of 1000, 500, 200, 100, 50, 25, and 12.5 µg/ml respectively in shown table. The standard drug used in the present study is “Gentamycin” for evaluating antibacterial activity which 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 compounds 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

Experimental:

Melting points of Ethyl (2Z)-2-(Aryl)-5-(4-methoxyphenyl)-7-methyl-3-oxo-2,3,8a-tetrahydro-5H-[1,3]thiazolo[3,2-α]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. A triplet appeared at δ 2.18 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 7.48-7.80 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. Two singlets appeared at δ 5.95 ppm and δ 8.51 ppm was due to the proton present in the pyrimidine and pyrazole ring respectively.

The IR spectrum of Ethyl (2Z)-2-(Aryl)-5-(4-methoxyphenyl)-7-methyl-3-oxo-2,3,8a-tetrahydro-5H-[1,3]thiazolo[3,2-α]pyrimidine-6-carboxylate (in KBr pellets) was recorded on a BRUKER FT-IR spectrophotometer.

**Figure 1. 3d view of compound**
IV. ACKNOWLEDGEMENT

We are thankful to the principal of M. G. Science Institute, Ahmadabad to providing research facilities, IR data collection and North America Institute of Pharmaceutical Technology, Toronto for NMR data collection.

V. REFERENCES