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# Synthesis, Characterization and Antimicrobial Activities of Some New Oxazolo Pyrimidine Derivatives

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## ABSTRACT

Some new thiozolo pyrimidine derivatives have been synthesized. The products tested for their antibacterial activity against Gram (+)ve and Gram (-)ve bacteria. The structures of derivatives were established on the basis of their elemental analysis, IR, NMR and Mass Spectral data.

**Keywords:** Oxazolo Pyrimidine, Antibacterial Activity, Antifungal Activities, Biginelli Reaction

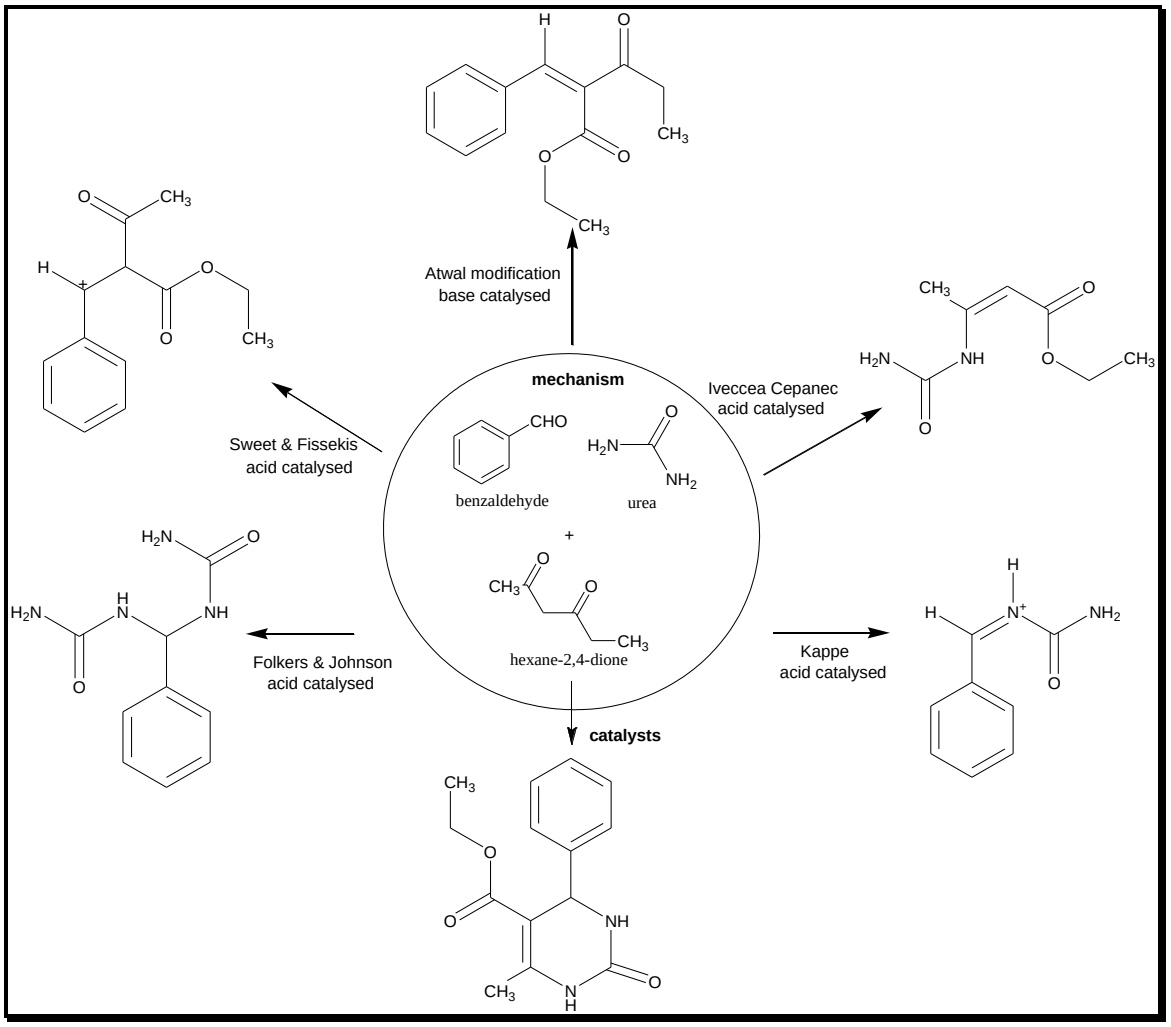
## I. INTRODUCTION

Research programs for the discovery of new drugs and for improving the evolution criteria are under way in many laboratories. In addition knowledge of specific constituents of the mycobacterium cell and their biochemical roles has advanced considerably in the recent years. Also, recent improvements in the knowledge of the mechanism of action of available drugs and the biochemical mechanism of resistance to them may be used as a basis for design new and better drugs to care the mycobacterium diseases.

Pyrimidine is an important class of natural and non natural products, many of them exhibit useful biological activities and clinic applications. In living organisms substituted purines and pyrimidines occur widely. Pyrimidines are most active classes of compounds possessing wide spectrum of biological activities like in vitro activity against unrelated DNA and RNA, diuretic, antitumor, anti-HIV, and cardiovascular. In addition to this various analogs of pyrimidines[1] have been found to possess antibacterial[2-8], antifungal[9-12], antileishmanial[13], anti-inflammatory[14-15], analgesic[16], antihypertensive[17-18], antipyretic[19], antiviral[20-22], antidiabetic[23], anti-allergic[24], anticonvulsan[25], antioxidant[26-27], antihistaminic[28], herbicidal[29], anticancer activities[30-33], etc.

### Biginelli reaction

Biginelli scaffold was shown to be of great value from a pharmaceutical point of view, because of this importance investigations were very fast. Italian chemist Pietro Biginelli reported this reaction for the first time which is taken as the birth of this reaction. The most attractive part for this motif is biological activity and asymmetric synthesis of compounds which will be discussed in separate sections. It is pertinent to mention here that modification of the Biginelli reaction has widely been used in recent years, since it involves two steps.




**Experimental:**

**A. Preparation of ethyl 4-(4-chlorophenyl)-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 mole , mono/di/tri/ substituted benzaldehyde-(4-chlorobenzaldehyde) (0.1 mole ), and urea (0.1 mole ) 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 67 % with MP $230^0$ C.

**B. Preparation of ethyl (2*Z*)-2-(Aryl) -5-(4-chlorophenyl)-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-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.005 mole ), benzaldehyde (0.05 mole ), chloro aceticacid (0.05 mole ), sodium acetate (0.05 mole ), 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 MP $211^0$ C, Yield 59 %.

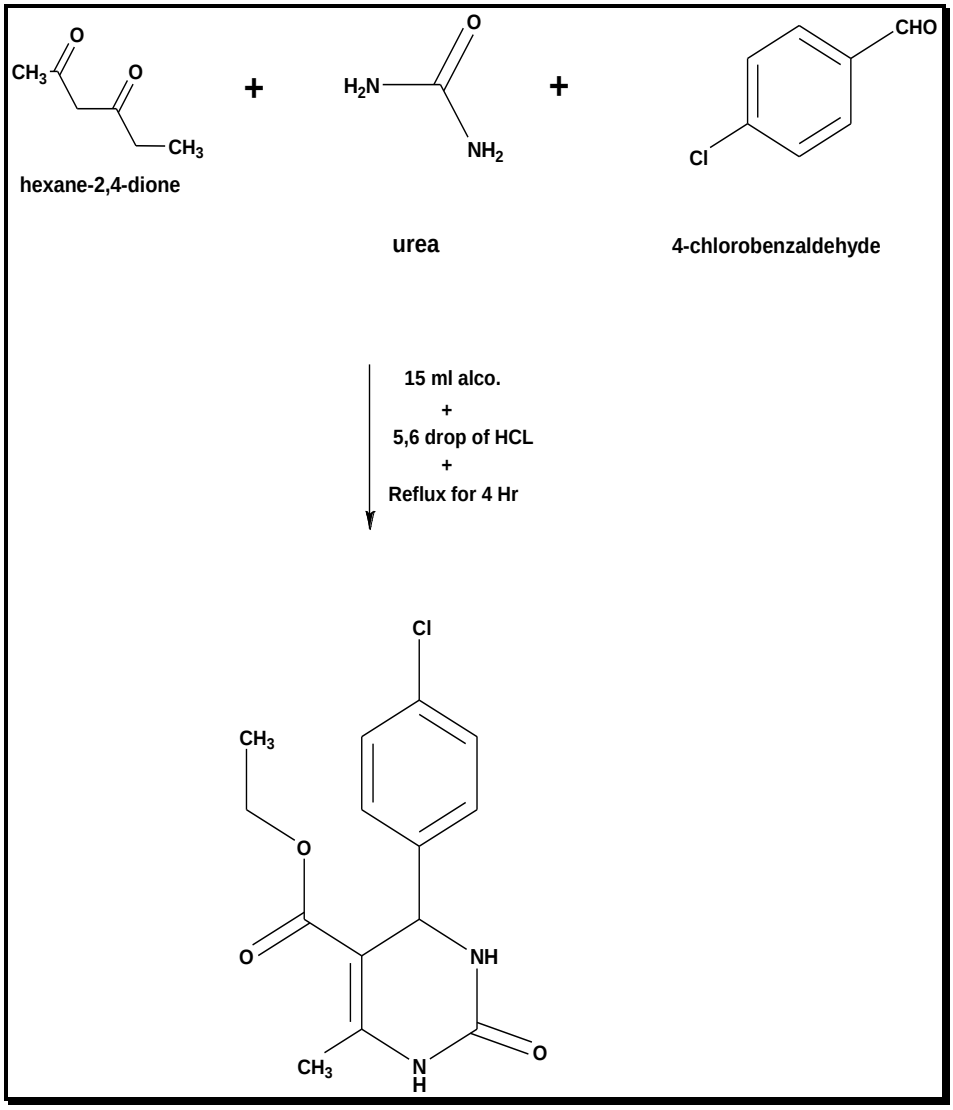
The purity of compounds was routinely checked on TLC aluminum sheet silica gel 60 $F_{245}$ (E. Merck) using

benzene-methanol (4.5:0.5 v/v) or benzene-ccl4–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 mole ecules. We have undertaken to investigate the role of functional groups on mole ecular geometry, conformation and generation of supramole ecular assemblies in the solid state. Furthermore the synthesized derivatives have also been evaluated for their antibacterial, antiinfective activity by Broth Dilution method.

## II. REACTION WORK

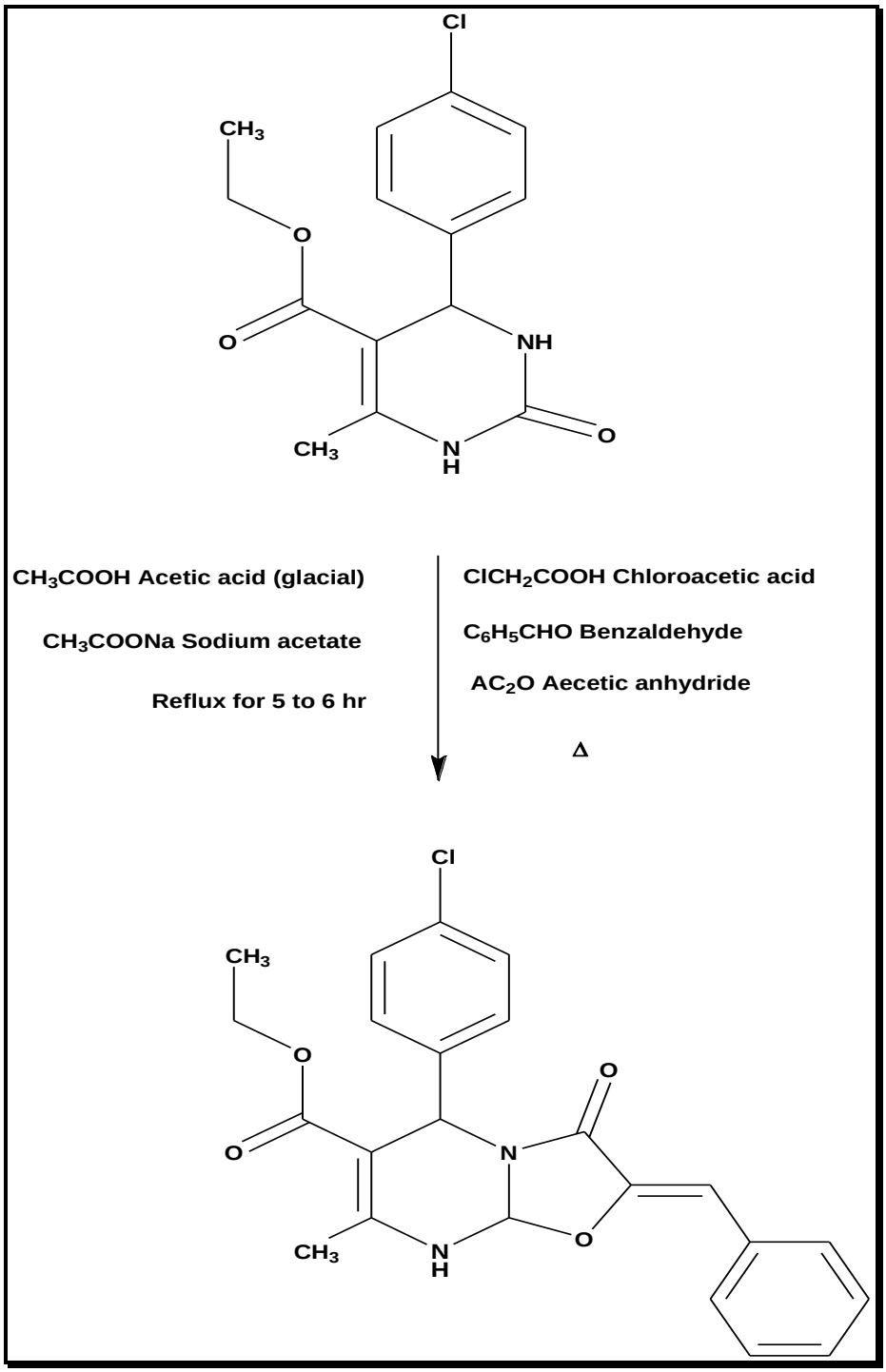
**Reaction–1:** Preparations of ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:




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

Reaction – 2 :

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

Table 1

| Sr No. | Code No. | -Ar | MOLE ECULAR FORMULA | M. P. °C | YIELD ( % ) | % OF CARBON FOUND | % OF CARBON REQD. | % OF NITROGEN FOUND | % OF NITROGEN REQD. | MOLE ECUR WEIGHT |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CLO 1 | $-C_6H_5$ | $C_{23}H_{21}ClN_2O_3S$ | 211°C | 59% | 65.00 | 65.02 | 6.55 | 6.59 | 424.87 |
| 2 | CLO 2 | $-4-OCH_3-C_6H_4$ | $C_{24}H_{23}ClN_2O_4S$ | 207°C | 58% | 63.35 | 63.37 | 6.12 | 6.16 | 454.90 |
| 3 | CLO 3 | $-2,4-(CL)_2-C_6H_3$ | $C_{23}H_{19}Cl_3N_2O_3S$ | 173°C | 61% | 55.90 | 55.95 | 5.63 | 5.67 | 493.76 |
| 4 | CLO 4 | $-4-CH_3-C_6H_4$ | $C_{24}H_{23}ClN_2O_3S$ | 197°C | 59% | 65.62 | 65.68 | 6.35 | 6.38 | 438.90 |
| 5 | CLO 5 | $-4-F-C_6H_4$ | $C_{23}H_{20}ClFN_2O_3S$ | 204°C | 67% | 62.35 | 62.38 | 6.30 | 6.33 | 442.86 |
| 6 | CLO 6 | $-4-Br-C_6H_4$ | $C_{23}H_{20}BrClN_2O_3S$ | 205°C | 59% | 54.81 | 54.84 | 5.50 | 5.56 | 503.77 |
| 7 | CLO 7 | $-4-Cl-C_6H_4$ | $C_{23}H_{20}Cl_2N_2O_3S$ | 203°C | 53% | 60.11 | 60.14 | 6.05 | 6.10 | 459.32 |
| 8 | CLO 8 | $-3-OH-C_6H_4$ | $C_{23}H_{21}ClN_2O_4S$ | 172°C | 68% | 62.59 | 62.66 | 6.32 | 6.35 | 440.87 |
| 9 | CLO 9 | $-4-OH-C_6H_4$ | $C_{23}H_{21}ClN_2O_4S$ | 200°C | 69% | 62.62 | 62.66 | 6.30 | 6.35 | 440.87 |
| 10 | CLO 10 | $-3-OCH_3-4-OH-C_6H_3$ | $C_{24}H_{23}ClN_2O_5S$ | 201°C | 54% | 61.18 | 61.21 | 5.94 | 5.95 | 470.90 |
| 11 | CLO 11 | $-2-NO_2-C_6H_4$ | $C_{23}H_{20}ClN_3O_5S$ | 170°C | 62% | 58.72 | 58.79 | 8.91 | 8.94 | 469.87 |
| 12 | CLO 12 | $-C_4H_3O$ | $C_{21}H_{19}ClN_2O_4S$ | 209°C | 64% | 60.76 | 60.80 | 6.72 | 6.75 | 414.83 |
| 13 | CLO 13 | $-3-NO_2-C_6H_4$ | $C_{23}H_{20}ClN_3O_5S$ | 212°C | 59% | 58.76 | 58.79 | 8.91 | 8.94 | 469.87 |
| 14 | CLO 14 | $-4-NO_2-C_6H_4$ | $C_{23}H_{20}ClN_3O_5S$ | 193°C | 64% | 58.73 | 58.79 | 8.89 | 8.94 | 469.87 |

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

**Table 2**

| 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 | CLO1 | -$C_6H_5$ | 250 | 200 | 250 | 250 |
| 2 | CLO2 | -4-$OCH_3$-$C_6H_4$ | 200 | 250 | 200 | 200 |
| 3 | CLO3 | -2,4-$(CL)_2$-$C_6H_3$ | 100 | 250 | 250 | 100 |
| 4 | CLO4 | -4-$CH_3$-$C_6H_4$ | 200 | 200 | 500 | 500 |
| 5 | CLO5 | -4-F-$C_6H_4$ | 250 | 62.5 | 200 | 250 |
| 6 | CLO6 | -4-Br-$C_6H_4$ | 200 | 200 | 250 | 200 |
| 7 | CLO7 | -4-Cl-$C_6H_4$ | 62.5 | 250 | 200 | 250 |
| 8 | CLO8 | -3-OH-$C_6H_4$ | 125 | 50 | 125 | 250 |
| 9 | CLO9 | -4-OH-$C_6H_4$ | 200 | 200 | 125 | 62.5 |
| 10 | CLO10 | -3-$OCH_3$-4-OH-$C_6H_3$ | 100 | 62.5 | 250 | 250 |
| 11 | CLO11 | -2-$NO_2$-$C_6H_4$ | 50 | 200 | 250 | 125 |
| 12 | CLO12 | -$C_4H_3O$ | 125 | 200 | 500 | 50 |
| 13 | CLO13 | -3-$NO_2$-$C_6H_4$ | 250 | 62.5 | 62.5 | 200 |
| 14 | CLO14 | -4-$NO_2$-$C_6H_4$ | 200 | 62.5 | 50 | 100 |
| 15 | Gentamycin | | 0.05 | 1 | 0.25 | 0.5 |
| 16 | Ampicillin | | 100 | -- | 250 | 100 |
| 17 | Chloramphenicol | | 50 | 50 | 50 | 50 |
| 18 | Ciprofloxacin | | 25 | 25 | 50 | 50 |
| 19 | Norfloxacin | | 10 | 10 | 10 | 10 |

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

**Table 3**

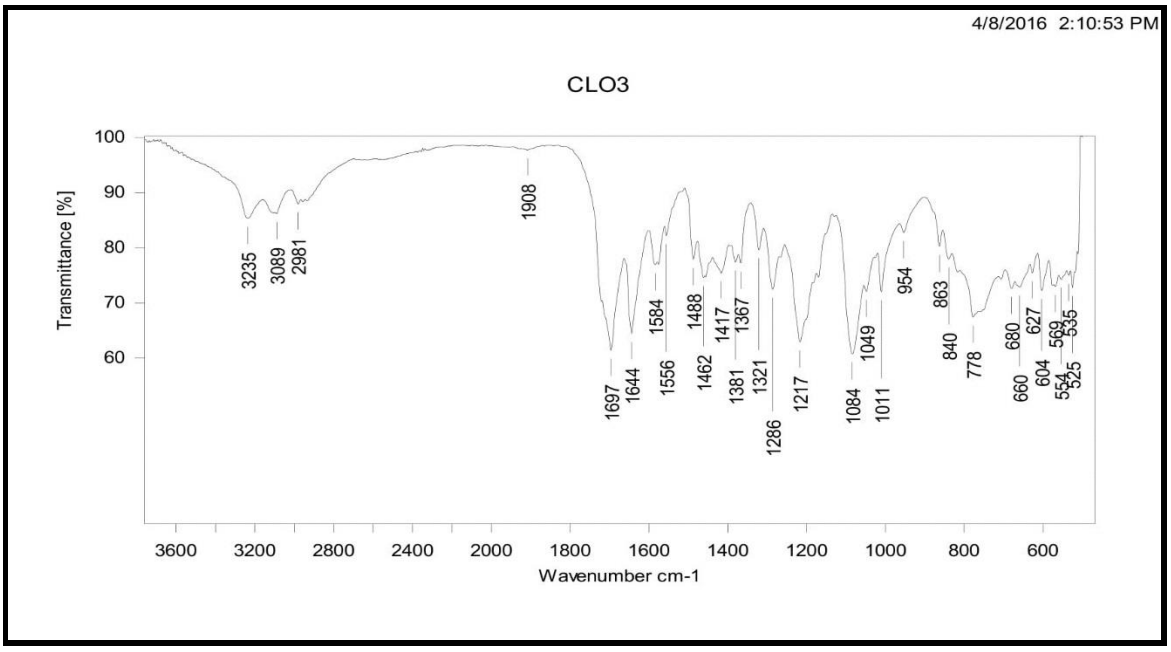
| MINIMAL FUNGICIDAL CONCENTRATIONS (MFC) in µg/mL | | | | | |
|---|---|---|---|---|---|
| | | | Fungus | | |
| | | | *C.albicans* | *A.nigar* | *A.clavatus* |
| Sr No. | Code No | -Ar | MTCC 227 | MTCC 282 | MTCC 1323 |
| 1 | CLO1 | -$C_6H_5$ | 1000 | 500 | 1000 |

| | | | | | |
|---|---|---|---|---|---|
| 2 | CLO2 | -4-$OCH_3$-$C_6H_4$ | 100 | 125 | 200 |
| 3 | CLO3 | -2,4-$(CL)_2$-$C_6H_3$ | 500 | >1000 | 500 |
| 4 | CLO4 | -4-$CH_3$-$C_6H_4$ | 250 | 100 | 125 |
| 5 | CLO5 | -4-F-$C_6H_4$ | 500 | 1000 | 500 |
| 6 | CLO6 | -4-Br-$C_6H_4$ | 250 | >1000 | >1000 |
| 7 | CLO7 | -4-Cl-$C_6H_4$ | 100 | 500 | 500 |
| 8 | CLO8 | -3-OH-$C_6H_4$ | 50 | 125 | 200 |
| 9 | CLO9 | -4-OH-$C_6H_4$ | 250 | 500 | 62.5 |
| 10 | CLO10 | -3-$OCH_3$-4-OH-$C_6H_3$ | 62.5 | 100 | 125 |
| 11 | CLO11 | -2-$NO_2$-$C_6H_4$ | 200 | 62.5 | 50 |
| 12 | CLO12 | -$C_4H_3O$ | 125 | 50 | 125 |
| 13 | CLO13 | -3-$NO_2$-$C_6H_4$ | 500 | 125 | 500 |
| 14 | CLO14 | -4-$NO_2$-$C_6H_4$ | 100 | 250 | 62.5 |
| 15 | Nystatin | | 100 | 100 | 100 |
| 16 | Greseofulvin | | 500 | 100 | 100 |

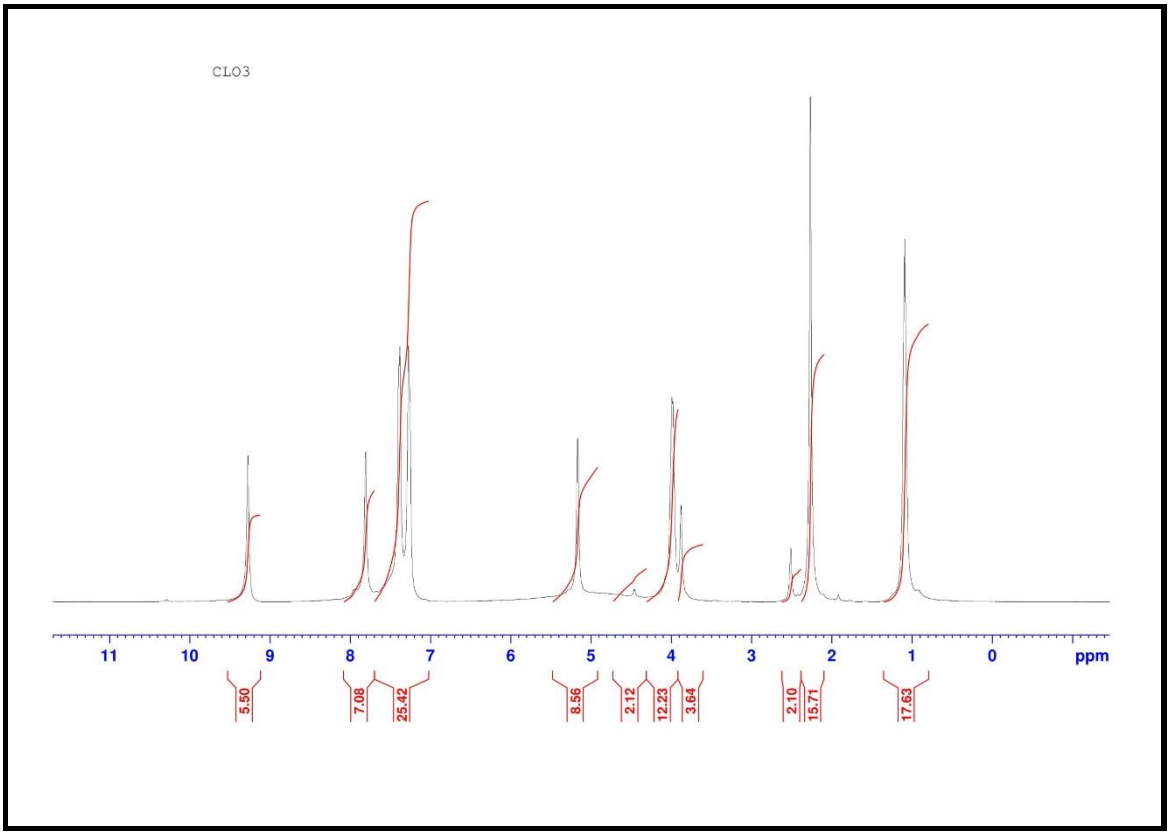
**Characterization of ethyl (2*Z*)-2-(2,4-dichlorobenzylidine)-5-(4-chlorophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-6-carboxylate (ClO3):**

**Table 4**

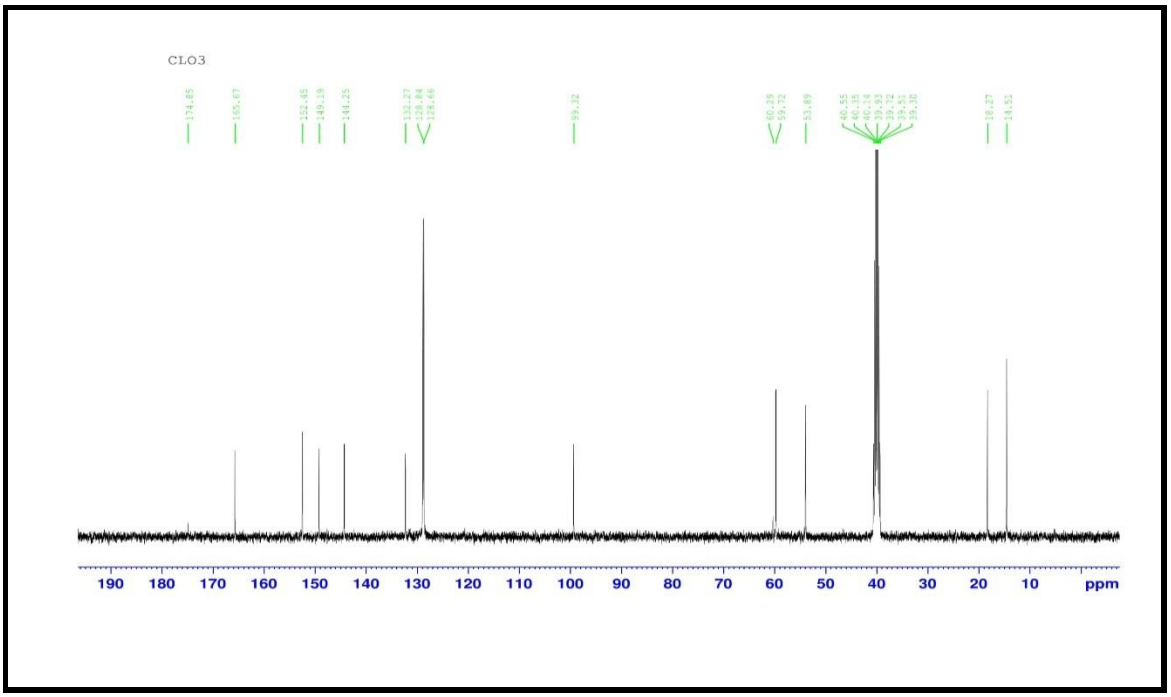
| IR Spectra | NMR Spectra | | GCMS |
|---|---|---|---|
| IR region between 400 to 4000 $cm^{-1}$ | 1H NMR (CDCl3) δ(ppm) | 13C NMR(CDCl3) δ(ppm) | Fragmentation of mass spectra (m/z) |
| 3255 (>NH medium, pyrimidine ring) | 1.0 (3H, t, ethyl CH3) | 14.51, 18.27 | 491 (M-2) |
| | 2.0 (3H, s, C6-CH3) | 39.30, 40.55 | 492 (M-1) |
| 3089 (-C-H str., aromatic) | 5.01 (2H, q, OCH2) | 53.89, 60.29 | 493 (M+) |
| 2981 (-$CH_3$ str.) | 4.9 (1H, s) | 99.32 | 494 (M+1) |
| 1697 (>C=O ester str.) | 5.20 (1H, s) | 128.66 | 495 (M++2) |
| 1644 (cyclic -C=O) | 6.86 (1H, s, NH, D2O exchangeable) | 132.27 | |
| 1584, 1556 (-C=N and aromatic -C=C) | 7.1-8.0 (7H, overlapping signals of Ar-H) | 144.25 | |
| 1462 (>CH medium, aromatic ring) | 9.35 (1H, s, NH) | 149.19 | |
| 1084 (-C=O (-NH) str., aromatic system) | | 152.45 | |
| 778 (-C-Cl str., aromatic) | | 165.67 | |
| 680 (str., di-substituted aromatic) | | 174.85 | |



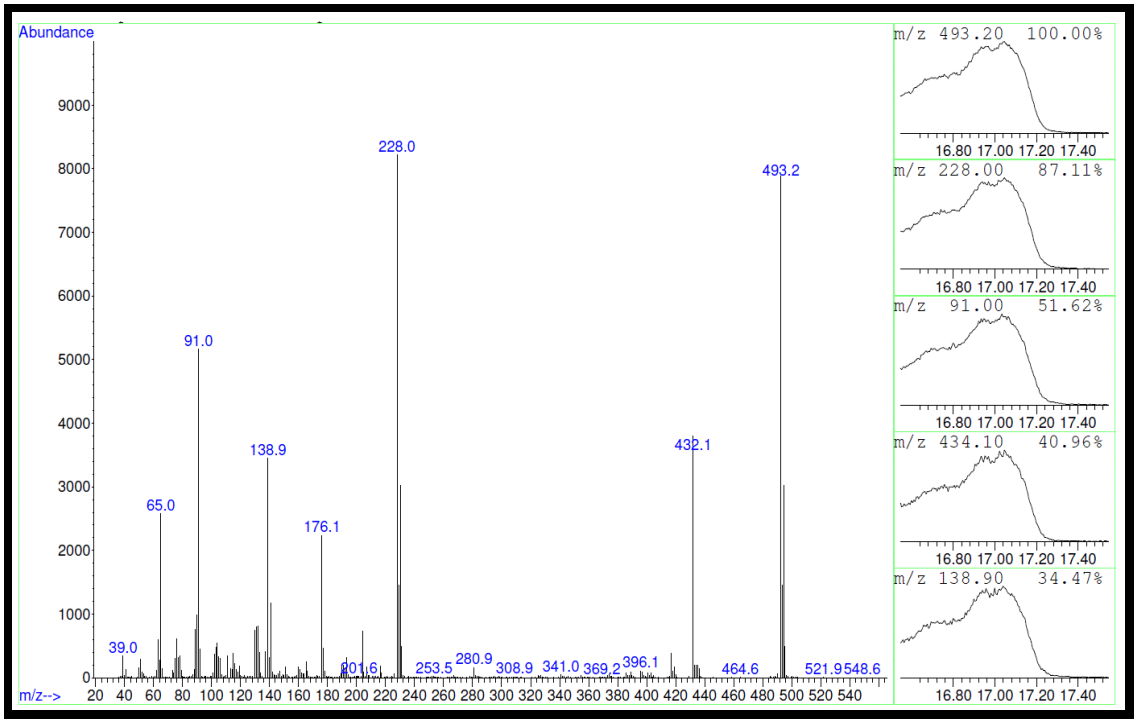

IR Spectra




1H NMR




13C NMR




GCMS

## III. ACKNOWLEDGEMENT

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