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Synthesis, Antimicrobial Activity and Characterization of Some Novel Thiozolo Pyrimidine Derivatives

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ABSTRACT

Thirteen new thiozolo pyrimidine derivatives have been synthesized from Biginelli reaction. The structures of derivatives were established on the basis of their elemental analysis, IR, NMR and Mass Spectral data. The title compounds have been tested for antibacterial and antifungal activities against different strains of bacteria.

Keywords : Thiozolo Pyrimidine, Antibacterial Activity, Antifungal Activities, Biginelli Reaction

I. INTRODUCTION

HETEROCYCLIC FIVE AND SIX MEMBERED COMPOUNDS

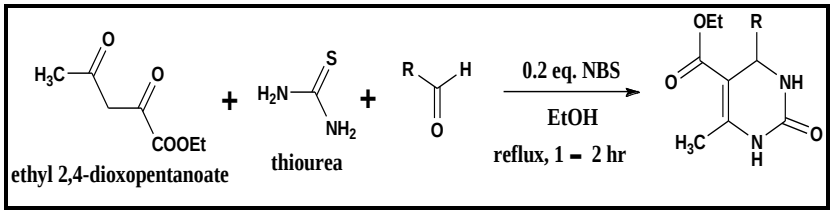
When nitrogen and oxygen can be included in the rings, they are called Heterocyclic compounds. The Hetero means that more than one kind of element is included within the ring and Cyclic indicates that there is at least one ring present in the compound. A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements, members of its rings. Heterocyclic chemistry is the branch of chemistry. It makes do synthesis, properties and applications of these heterocycles. Heterocyclic compounds may be inorganic or organic. Most contain at least one carbon in their structure.

Oxoimidazolines have been reported to exhibit antibacterial[1,2], antifungal[3], and antimicrobial activities[4-7]. Imidazolinones have also been reported to possess fungicidal[8,9], herbicidal[9], and vasodilator activities[10].

Recently we have prepared pyrimidine derivatives and reported their antibacterial and antifungal activities[11-13]. All role of heterocyclic compounds derivatives in certain biological importance prompted us to synthesize newly compounds for their antimicrobial activity.

Biginelli reaction:

Biginelli reaction is a three component reaction between an aldehyde, ß-ketoester and thiourea substances. It is a rapid and facile synthesis of dihydropyrimidones. In pharmaceutical it is very interesting compound.



This reaction was developed by Pietro Biginelli in 1891. The reaction can catalyze by acids. Several solid-phase protocols utilizing different linker attachments have been published.

USES:

- Substituted thioureas are useful in catalysis in organic synthesis that was called thiourea organocatalysis[47-52].
- Production of flame retardant resins and vulcanization accelerators produced in industrial by thiourea derivatives.
- Thiourea is used to tone silver-gelatin photographic prints, also used as an auxiliary agent in diazo paper, light-sensitive photocopy paper and all kind of copy paper.

Reaction procedure:

Reaction: 1

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

A mixture of Ethyl aceto acetate (0.01 mole), 3-nitrobenzaldehyde (0.01 mole) and thiourea (0.01 mole) with ethanol (20 mL) in 250 mL RBF was refluxed for 6 h in concentrated catalic HCl (5 to 6 drop). The reaction mixture was poured in crushed ice and product was isolated and re-crystallized from ethanol: DMF. MP is 195^0 C, Yield 71 %.

Reaction: 2

Preparation of ethyl (2*Z*)-2-(benzylidene)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS1)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-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: $C_{23}H_{21}N_3O_5S$, DMF MP 237^{0}C Yield 58%.

Preparation of ethyl (2*Z*)-2-(4-methoxybenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS2)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-methoxybenzaldehyde (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: $C_{24}H_{23}N_3O_6S$, DMF MP 240^{0}C Yield 59%.

Preparation of ethyl (2*Z*)-2-(2,4-dichlorobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS3)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 2,4-dichlorobenzaldehyde (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: $C_{23}H_{19}Cl_2N_3O_5S$, DMF MP 170^{0}C Yield 54%.

Preparation of ethyl (2*Z*)-2-(4-methylbenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS4)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-methylbenzaldehyde (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: $C_{24}H_{23}N_3O_5S$, DMF MP 221^{0}C Yield 53%.

Preparation of ethyl (2*Z*)-2-(4-fluorobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS5)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-fluorobenzaldehyde (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: $C_{23}H_{20}FN_3O_5S$, DMF MP 256^{0}C Yield 65%.

Preparation of ethyl (2*Z*)-2-(4-bromobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS6)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-bromobenzaldehyde (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: $C_{23}H_{20}BrN_3O_5S$, DMF MP 260^{0}C Yield 68%.

Preparation of ethyl (2*Z*)-2-(4-chlorobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS7)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-chlorobenzaldehyde (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: $C_{23}H_{20}ClN_3O_5S$, DMF MP 276^{0}C Yield 61%.

Preparation of ethyl (2*Z*)-2-(3-hydroxybenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS8)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 3-hydroxybenzaldehyde (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: $C_{23}H_{21}N_3O_6S$, DMF MP 219^{0}C Yield 54%.

Preparation of ethyl (2*Z*)-2-(4-hydroxybenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS9)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-hydroxybenzaldehyde (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: $C_{23}H_{21}N_3O_6S$, DMF MP 265^{0}C Yield 50%.

Preparation of ethyl (2*Z*)-2-(4-hydroxy-3-methoxybenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS10)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-hydroxy-3-methoxybenzaldehyde (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: $C_{24}H_{23}N_3O_7S$, DMF MP 248^{0}C Yield 52%.

Preparation of ethyl (2*Z*)-2-(2-nitrobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS11)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 2-nitrobenzaldehyde (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: $C_{23}H_{20}N_4O_7S$, DMF MP 244^{0}C Yield 65%.

Preparation of ethyl (2*Z*)-2-(3-nitrobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS13)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 3-nitrobenzaldehyde (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: $C_{23}H_{20}N_4O_7S$, DMF MP 255^{0}C Yield 51%.

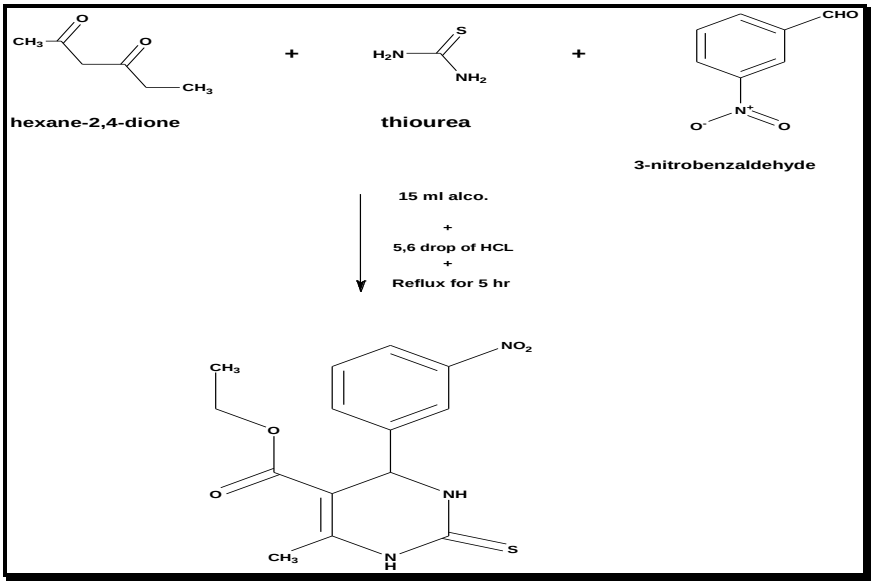
Preparation of ethyl (2*Z*)-2-(4-nitrobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS14)

A mixture of ethyl 4-(3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mole), 4-nitrobenzaldehyde (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: $C_{23}H_{20}N_4O_7S$, DMF MP 183^{0}C Yield 58%.

The progress and purity of the reaction and compounds were routinely checked on TLC aluminum sheet silica gel 60 F_{245} (E.Merck) using benzene-methanol (2.25:0.25 v/v) or benzene-Carbon tetrachloride–methanol (1.25:1.0:0.25 v/v) as irrigate and was developed in an iodine chamber. The purity of compounds was checked by taking its melting point by melting measurement. Their data was recorded and measure under antiinfective, antimicrobial drugs.

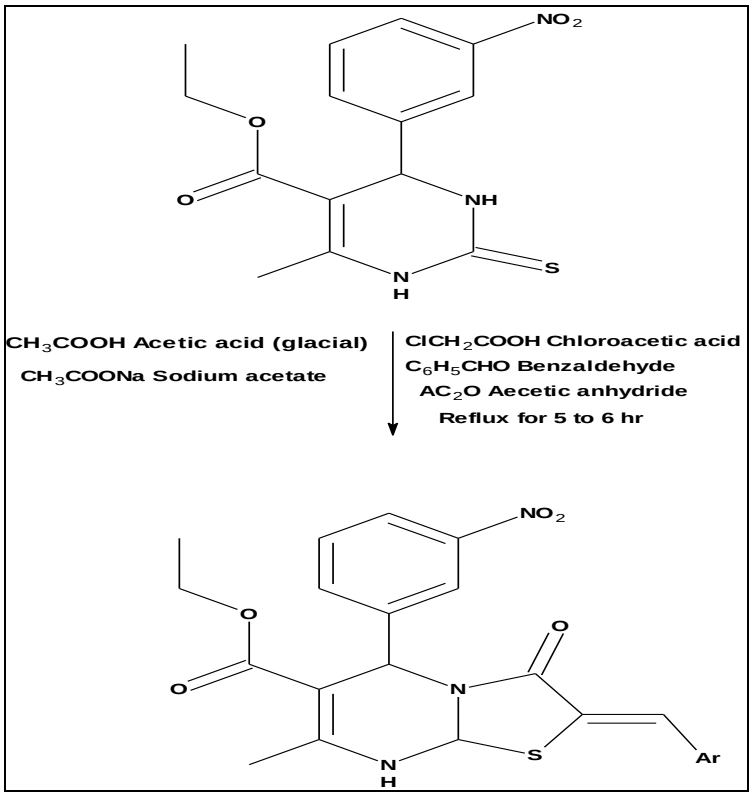
Reaction:

a) Preparation of ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:



ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

b) Preparation of ethyl (2*Z*)-2-(Aryl)-7-methyl-5-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate:



ethyl (2*Z*)-2-(Aryl)-7-methyl-5-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate

Where Ar = Different aryl group

Physical Experimental data :

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

Table 1

Sr No.	Code No	-Ar	MOLECULAR FORMULA	MP °C	YIELD (%)	% OF CARBON FOUND	% OF CARBON REQD.	% OF NITROGEN FOUND	% OF NITROGEN REQD.	MOLECULAR WEIGHT
1	NS1	-C_6H_5	$C_{23}H_{21}N_3O_5S$	237°C	58%	61.17	61.18	9.30	9.31	451.19
2	NS2	-4-OCH_3-C_6H_4	$C_{24}H_{23}N_3O_6S$	240°C	59%	59.85	59.86	8.71	8.73	481.52
3	NS3	-2,4-$(CL)_2$-C_6H_3	$C_{23}H_{19}Cl_2N_3O_5S$	170°C	54%	53.05	53.08	8.05	8.07	520.38
4	NS4	-4-CH_3-C_6H_4	$C_{24}H_{23}N_3O_5S$	221°C	53%	61.90	61.92	9.00	9.03	465.52

5	NS5	-4-F-C_6H_4	$C_{23}H_{20}FN_3O_5S$	256^{0}C	65%	58.81	58.84	8.92	8.95	469.48
6	NS6	-4-Br-C_6H_4	$C_{23}H_{20}BrN_3O_5S$	260^{0}C	68%	52.01	52.08	7.90	7.92	530.39
7	NS7	-4-Cl-C_6H_4	$C_{23}H_{20}ClN_3O_5S$	276^{0}C	61%	56.81	56.85	8.62	8.65	485.94
8	NS8	-3-OH-C_6H_4	$C_{23}H_{21}N_3O_6S$	219^{0}C	54%	59.02	59.09	8.90	8.99	467.49
9	NS9	-4-OH-C_6H_4	$C_{23}H_{21}N_3O_6S$	265^{0}C	50%	58.98	59.09	8.90	8.99	467.49
10	NS10	-3-OCH_3-4-OH-C_6H_3	$C_{24}H_{23}N_3O_7S$	248^{0}C	52%	57.92	57.94	8.40	8.45	497.52
11	NS11	-2-NO_2-C_6H_4	$C_{23}H_{20}N_4O_7S$	244^{0}C	65%	55.61	55.64	11.25	11.28	496.49
12	NS13	-3-NO_2-C_6H_4	$C_{23}H_{20}N_4O_7S$	255^{0}C	51%	55.63	55.64	11.26	11.28	496.49
13	NS14	-4-NO_2-C_6H_4	$C_{23}H_{20}N_4O_7S$	183^{0}C	58%	55.60	55.64	11.22	11.28	496.49

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

Table 2

MINIMAL BACTERIAL CONCENTRATIONS (MBC) in µg/mL						
			Gram negative bacteria		**Gram positive bacteria**	
Sr No.	**Code No**	**-Ar**	***E.coli*** MTCC 443	***P.aeruginosa*** MTCC 1688	***S.aureus*** MTCC 96	***S.pyogenus*** MTCC 442
1	NS1	-C_6H_5	250	50	500	500
2	NS2	-4-OCH_3-C_6H_4	200	250	200	200
3	NS3	-2,4-$(CL)_2$-C_6H_3	62.5	200	500	500
4	NS4	-4-CH_3-C_6H_4	200	250	205	250
5	NS5	-4-F-C_6H_4	100	200	250	250
6	NS6	-4-Br-C_6H_4	100	100	125	200
7	NS7	-4-Cl-C_6H_4	250	100	200	250

8	NS8	-3-OH-C_6H_4	200	200	500	250
9	NS9	-4-OH-C_6H_4	200	50	500	500
10	NS10	-3-OCH_3-4-OH-C_6H_3	100	62.5	250	250
11	NS11	-2-NO_2-C_6H_4	200	200	250	50
12	NS13	-3-NO_2-C_6H_4	125	200	62.5	100
13	NS14	-4-NO_2-C_6H_4	250	250	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

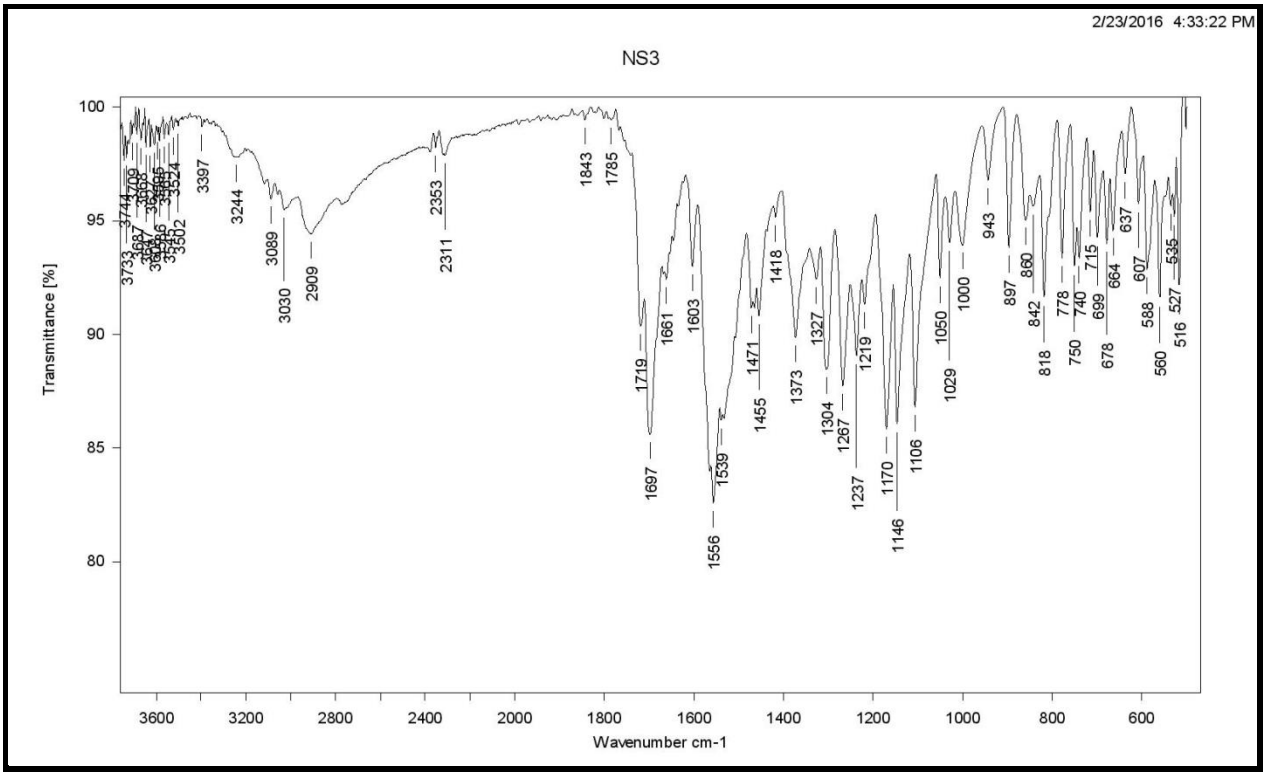
Antifungal activity of ethyl (2*Z*)-2-(Aryl)-7-methyl-5-(3-nitrophenyl)-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate:

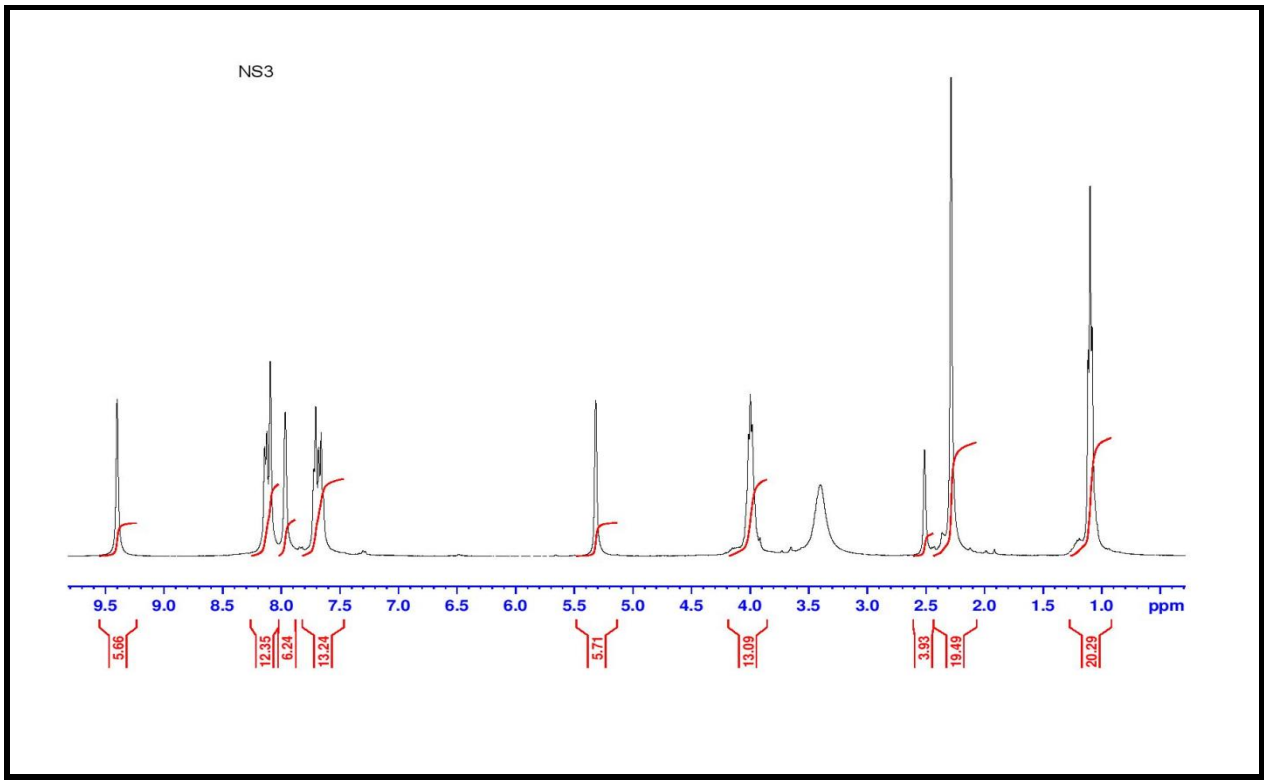
Table 3

MINIMAL FUNGICIDAL CONCENTRATIONS (MFC) in µg/mL					
Sr No.	**Code No**	**-Ar**	**Fungus**		
			C.albicans	*A.nigar*	*A.clavatus*
			MTCC 227	MTCC 282	MTCC 1323
1	NS1	-C_6H_5	125	100	125
2	NS2	-4-OCH_3-C_6H_4	50	100	100
3	NS3	-2,4-$(CL)_2$-C_6H_3	500	125	50
4	NS4	-4-CH_3-C_6H_4	500	>1000	>1000
5	NS5	-4-F-C_6H_4	100	500	500
6	NS6	-4-Br-C_6H_4	1000	>1000	>1000
7	NS7	-4-Cl-C_6H_4	1000	500	500
8	NS8	-3-OH-C_6H_4	100	1000	100
9	NS9	-4-OH-C_6H_4	1000	200	200
10	NS10	-3-OCH_3-4-OH-C_6H_3	200	100	125
11	NS11	-2-NO_2-C_6H_4	100	200	50
12	NS13	-3-NO_2-C_6H_4	1000	100	100
13	NS14	-4-NO_2-C_6H_4	100	125	1000
14	Nystatin		100	100	100
15	Greseofulvin		500	100	100

Characterization of ethyl (2*Z*)-2-(2,4-dichlorobenzylidine)-5-(3-nitrophenyl)-7-methyl-3-oxo-2,3,8,8a-tetrahydro-5*H*-[1,3]thiozolo[3,2-*a*]pyrimidine-6-carboxylate: (NS3)

This compound was obtained as a solid.
IR (KBr): νmax (cm–1), 3397 (N-H), 2909 (C-H), 2311 (N-C-S), 1719 (C=O ester), 1697 (cyclic C=O), 1539 (C=N and aromatic C=C), 1146 (C-O), 1556, 1373 (N-O), 778, 750 (C-Cl), 678 (aromatic). 1H-NMR (400 MHz, DMSO-d6): δ ppm, 1.0 (3H, t, ethyl CH3), 1.90 (3H, s, C6-CH3), 2.51 (2H, q, OCH2), 3.50 (1H, s), 3.70 (1H, s), 4.20 (s br, 1H, NH, D2O exchangeable), 7.49-8.40 (7H, overlapping signals of Ar-H), 9.71 (1H, s, NH). 13C-NMR (100 MHz, DMSO-*d*6): δ ppm, 14.47, 18.32, 39.46, 40.58, 59.85, 98.78, 121.47, 122.80, 133.50, 147.46, 165.54. LCMS: *m/z* = 520 (M+), 522 (M++2), 524 (M++4).

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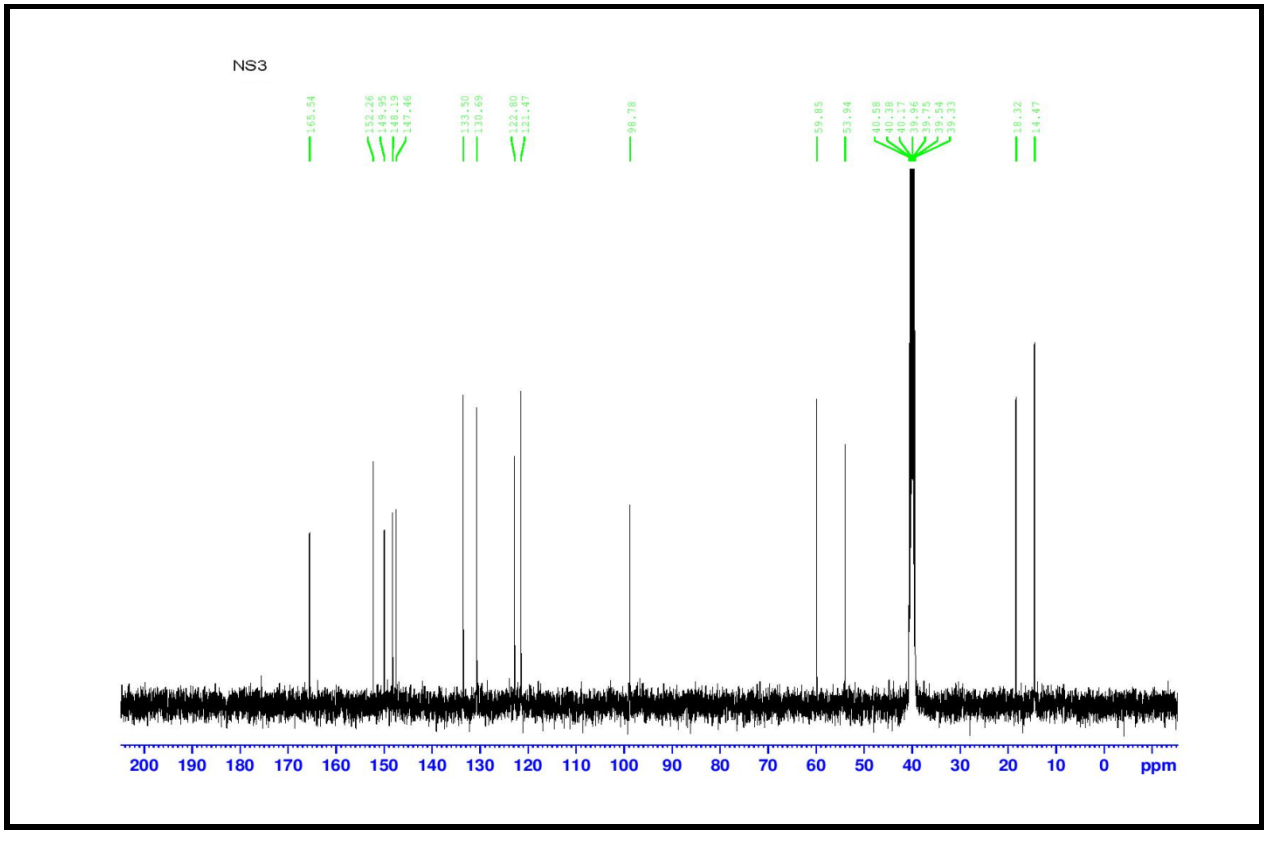
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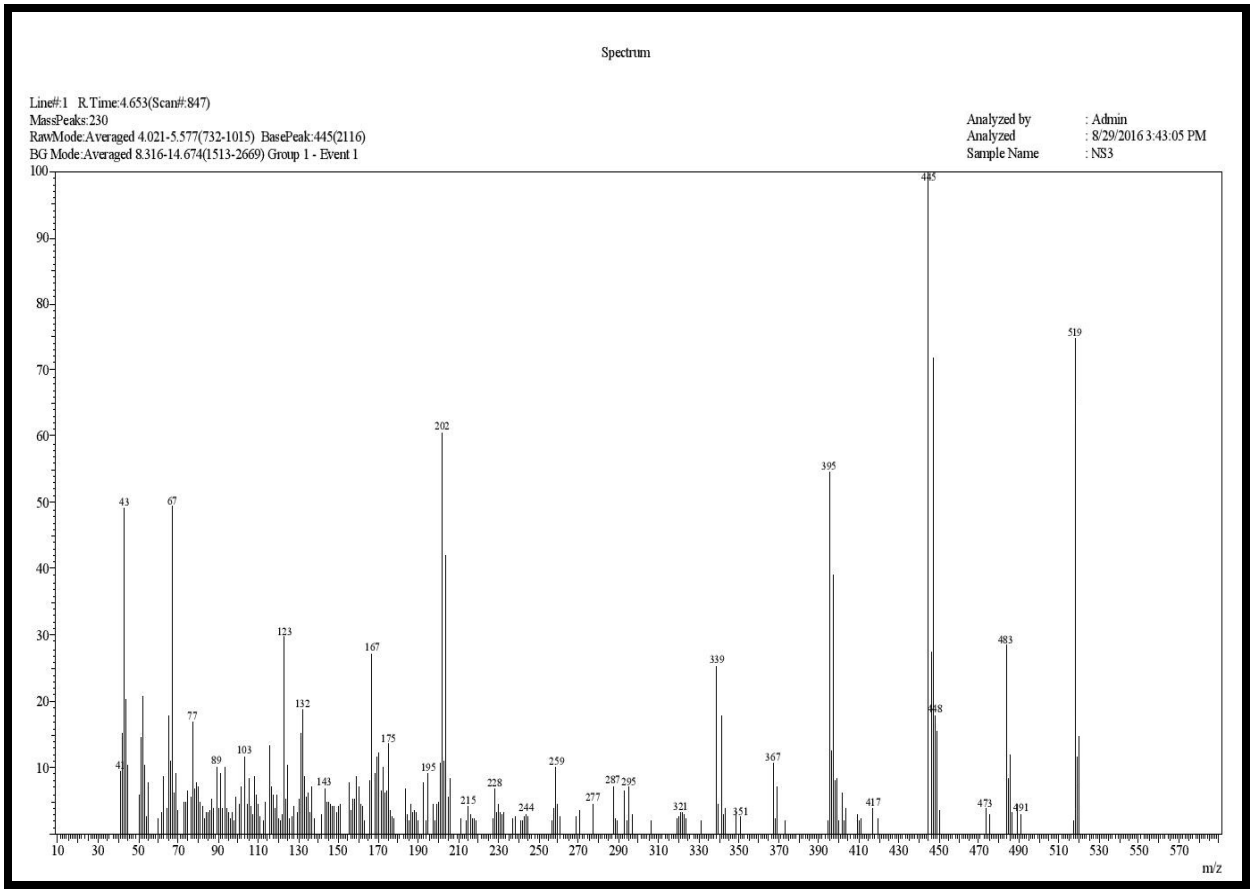

II. ACKNOWLEDGEMENT

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III. REFERENCES

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