Studies in The Synthesis of Betti's Products Rhodanine as Pharmacological Activities and Potential Fungicides.

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Abstract: **Studies in the title of work investigated and synthesized by the 2-Thio-4-Keto-Thiazolidene condensed with Betti's products or cyano-ethylated aromatic aldehydi, Betti's reaction was carried out with 5-Arylidene-2-Thio-4-Keto-Thiazolidine which contains sulphur as their fungicidal activity. Applicability of rhodanine derivatives is as chemotherapeutic value. In recent work to condensed rhodanine with some aldehyde obtained good yield and investigate their analytical application and their fungicidal activity of new synthesized rhodanine.**

- **(i) Arylamino-methylation of 5-Arylidene Rhodanines, formation of substituted rhodanine.**
- **(ii) Condensation of primary aromatic amine with 5-Arylidene Rhodanines formation of Thiazolidinones derivatives of rhodanine.**
- **(iii) Condensation of Malonanilic acid hydrazide with 5-Arylidene rhodanine, formation of Substituted malonanilic thiazolidones derivatives of rhodanine.**
- **(iv) Condensation of diamino-diphenyl sulphone with -5- arylidene rhodanine.**

In the present Investigation it was thought worthwhile to synthesis some condensation products of 5-arylidene rhodanine for testing their antifungal activity.

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INTRODUCTION

Fungicidal activities of Betti's products Rhodanine, Quinolinols and Arylidene in a large variety of these compounds has been found to the Therapeutic value. Previously fungal infection was regarded as an uncommon disease.

Now in recent years fungal infections are worldwide in nature and are systemic as well as local and rural or remote area of all ages. The well-known fungal diseases are candidiasis, dermatomycosis, mycosis and tineaversi colour. Organic compounds with rhodanine and quinoline moiety are of much interest to research worker's in the field of synthetic analytical and pharmacological activities.

A large number of hydrazide, hydrazone's have shown significant ameobicidal activities. Many remedies have been used against infections and research still continues which would lead one to conclude that the ideal topical antifungal agent has not yet been found.

The Betti's products 2-thio-4-Keto thiazolidenes, 8-quinolinols and lactones have been found to be effective as antifungal activities.

2-Thio-4-Keto-Thiozolidine, known as rhodanine, is an important five membered heterocyclic compound which possesses a reactive methylene group at position five sulphur containing compounds are known for their pharmacological activities, antimicrobial activity has been found to be associated with thiazolidenone and Arylidene rhodanines are also used for analytical applications.

In recent work of Thesis further investigation of related compounds synthesized in laboratory and found anti-fungicidal activities. It is intended to persure the present work along the following lines.

First phase of the work proposed in synthesis or preparation of some 2- mercapto-4- keto-thiazolidene and its derivatives to condensed some newly synthesized aromatic aldehyde to assess their analytical and fungicidal activity.

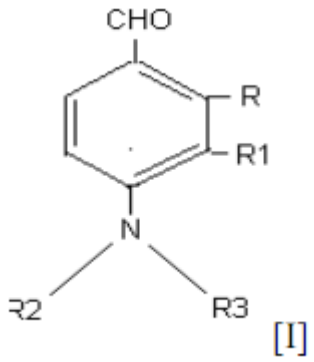
SYNTHESIZED RHODANINE

The pharmaceutical industry started to show great interest for the preparation of newly Betti's products.

Fungicidal activities of Betti's products rhodanine, and quinolinols derivatives or aromatic aldehyde in a large variety of these compounds has been found to the therapeutic value.

The Betti's products 2-Thio-4-Keto-thiazolidene and cyano ethyl aromatic aldehyde. With condensed and formation of some Betti's products.

Substituted rhodanine are well known for their analytical application 5-Arylidene rhodanine and p-dimethylamino benzylidene rhodanine is among the more important analytical reagents for the detection of metals and their fungicidal activity of newly synthesized rhodanine derivatives with following aldehyde.



[I]

(i) $R = R_1 = H$

(ii) $R = CH_3$, $R_1 = H$

(iii) $R = OCH_3$, $R_1 = H$

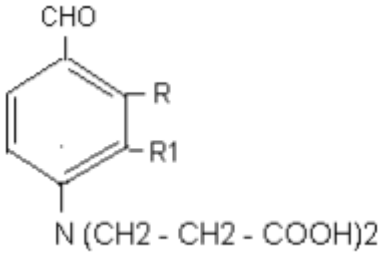
(iv) $R = OC_2H_5 = R_1 = H$

(v) $R = H$ $R_1 = I$, Br

(vi) $R_2 = R_3 =$ $- CH_2 - CH_2 - CN$

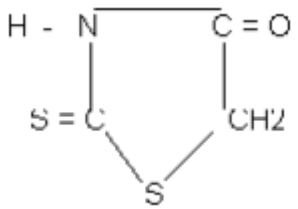
(vii) $CH_2 - CH_2 - Cl$

(viii) $CH_2 - CH_2 - COOH$



In the present Investigation p-dimethylamino benzaldehyde and five newly synthesized aldehyde have been condensed with rhodanine in presence of glacial acetic acid and freshly fused sodium acetate and newly 5-arylidene rhodanine have been obtained and investigated antifungal activity of 5-(4-NN-BIS-2-carboxy ethylamino-2-methyl Benzylidene) rhodanine.

Chemistry of rhodanine :- Due to presence of reactive methylene group at position five and replaceable hydrogen atom at position three, it has been thought to synthesized some new derivatives for studying their fungicidal activity.

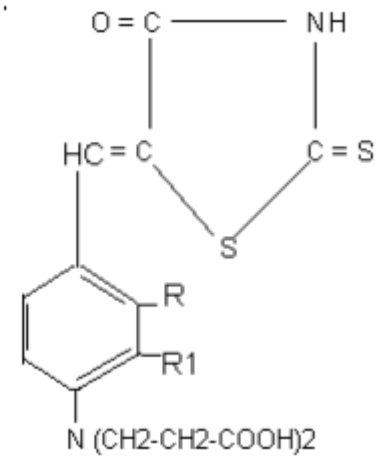


1- Arylamino-methylation of 5-Arylidene Rhodanine.

The reaction of 5-arylidene rhodanine with primary aromatic amine and formaldehyde in presence of ethanol is known as arylamino methylation.

The Newly synthesized 5-(4-NN-bis -2'-carboxy ethylamino-2-methyl-benzylidene) rohdanine (R=CH3, R'=H) has been condensed with formaldehyde and ten aromatic primary amine under the reaction condition of mannich. Ten arylamino methylated rhodanines of the type 3-(□ - substituted aniline methyl) -5- (4-NN – BIS –2' – carboxy – ethylamino -2- methyl – Benzylidene) rhodanine. Compounds were tested for Their antifungal activity against CURVULARIA LUNATE and HELMINTHOSPORIUM ORYZAE following the disc diffusion and Hanging drop method and tested antifungal activity of aniline-methylated rhodanine has been found to be most effective against fungi and show good fungicidal activity of compounds (IV,V,VI.VII, VIII).

The Fungicidal activity of these compounds has given in table.



Antifungal activity of 5-Arylidene Rhodanines

S. No.	R	R1	Antifungal activity			
			C.Lunata		H.Oryzae	
			Germination %	Lengtn Tube	Germination %	Lengtn Tube

1	P-Dimethyl amino benzaldehyde		50	32	10	180
	H					
2		H	65	75	20	220
	CH3					
3		H	80	90	60	240
	O-CH3					
4		H	90	240	90	300
	O-C2H5					
5		H	60	200	80	310
	H					
6		I	80	270	90	350
	Chloromycetin Water-ethanol (9:1 v/v)		95	320	95	400

All the Products No. 1 to 6 Table were screened in VITRO Against Curvularia Lunate and Helmenthosporium oryzae by disc diffusion and hanging drop methods. Table No.1 show fungicidal activity quite comparable to commercial fungicide chloromy cetin.

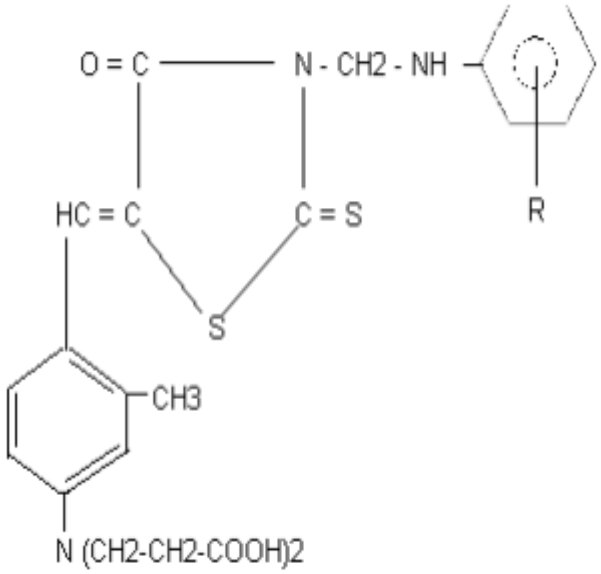
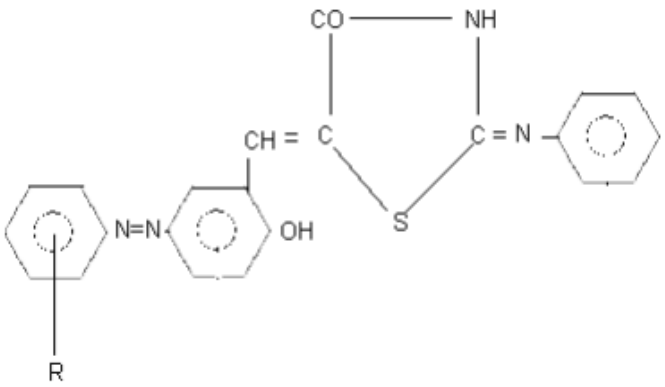


TABLE-1-B

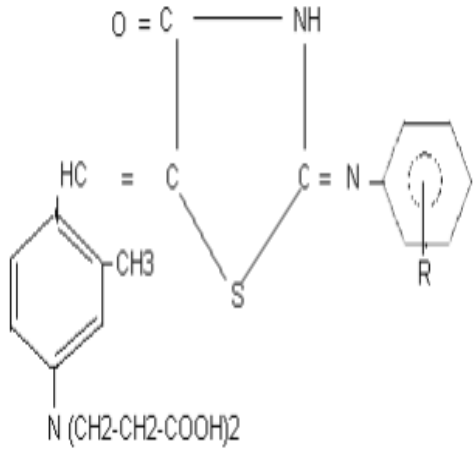
S. No.	R.	Fungicidal activity			
		C.Lunata		H.Oryzae	
		Germination %	Lengtn Tube	Germination %	Lengtn Tube
1	H	30	50	40	61
2	O-CH3	65.	71	49	90
3	M-CH3	75	148	75	150
4	p-CH3	80	175	80	190
5	O-CH3	85	190	90	200

2- condensation of primary aromatic amines with 5-arylidene rhodanine.

The reaction of aromatic amines with rhodanine was performed first of all by grancher [12] recently bux and shukla [15] have synthesized a series of such products and found anti-amoebical activity.



In the present investigation ten primary aromatic amines have been condensed with 5-arylidene-rhodanine (r=ch_3 r'=h) by the procedure as recomonded by bux and shukla [15] new products of rhodanine derivatives have been obtained. 2-(imino-substituted-phenyl) – 5 - (4-nn-bis-2'carboxy ethyl-amino-2-methyl benzylidene) 4-thiazolidinones.

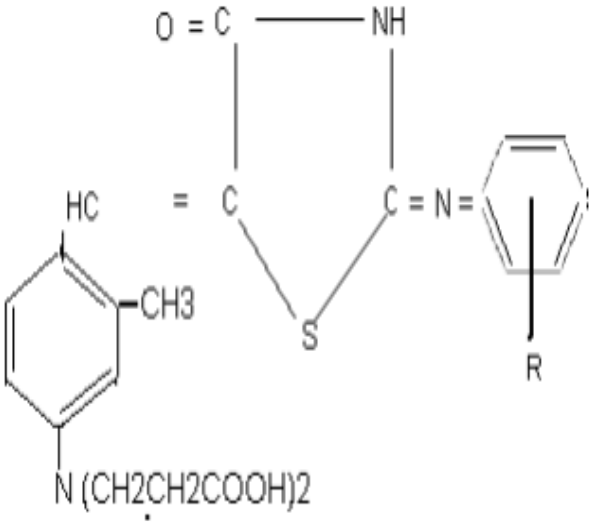


R=H, CH3 (O, m., p) Cl (O.m. p)

-OCH_3 (O.m.p.)

Table no.02

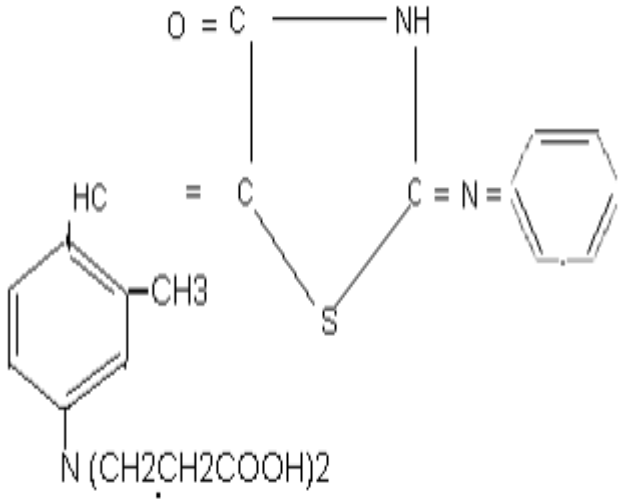
2-9imino-substituted-phenyl)-5-(-4-nn-bis-2'-carboxy ethyl amino -2-methyl-benzylidene)-4-thiazolidinones



S.No.	R	COLOUR	M.P.O C	YIELD %	MOLECULAR FORMULA	% OF N		% OF S	
						FOUND	CALCD	FOUND	CALCD
1.	H	Red	217	50	$C_{23}H_{23}N_3O_5S$	9.00	9.27	6.88	7.06
2.	o-CH_3	Brown	201	59	$C_{24}H_{25}N_3O_5S$	8.78	8.99	6.53	6.85
3.	m-CH_3	Reddish violet	231	52	$C_{24}H_{25}N_3O_5S$	8.78	8.99	6.53	6.85
4.	p-CH_3	Reddish brown	211	61	$C_{24}H_{25}N_3O_5S$	8.58	8.99	6.33	6.85
5.	o-OCH_3	Reddish orange	209	58	$C_{24}H_{25}N_3O_6S$	8.32	8.69	6.32	6.62
6.	m-OCH_3	Deep brown	227	65	$C_{24}H_{25}N_3O_6S$	8.42	8.69	6.12	6.62
7.	p-OCH_3	Brownish red	203	57	$C_{24}H_{25}N_3O_6S$	8.15	8.69	6.40	6.62
8.	o-Cl	Reddish pink	217	63	$C_{23}H_{22}N_3O_5SCl$	8.21	8.61	6.23	6.56
9.	m-Cl	Red	207	65	$C_{23}H_{22}N_3O_5SCl$	8.15	8.61	6.13	6.56
10.	p-Cl	Deep red	235	53	$C_{23}H_{22}N_3O_5SCl$	8.31	8.61	6.40	6.56

Table no.03

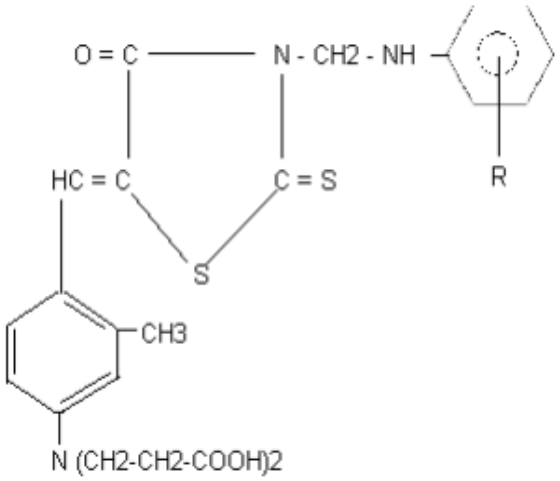
I.r.absorption frequencies of -2-(iminophenyl)-5-(-4nn-bis-2'-carboxy ethyl amino-2-methyl-benzylidene)-4-thiazolidinone



S.No.	BOND/GROUP	ABSORPTION	BAND

		BAND (cm^{-1})	INTENSITY
1	C=O (In five membered	1010	Strong
2	ring)	1620	Sharp and strong
3	NH (Stretching)	1650	Medium
4	C=H (Imino group	2965	Strong
5	stretching)	1720	Strong
6	-CH3(Stretching)	1110	Sharp and strong
	-COOH (Stretching)		
	C=S (Stretching)		

Table No.04
ANTIFUNGAL ACTIVITY OF

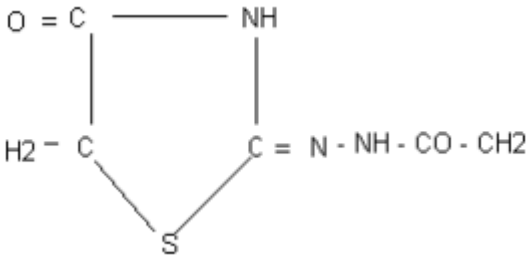


S.No.	R.	FUNGICIDAL ACTIVITY			
		C.Lunate		H.Oryzae	
		Germination %	Germ tube length(μ)	Germination %	Germ tube length(μ)
1.	H	30	50	40	61
2.	o-CH_3	65	71	49	92
3.	m-CH_3	77	150	80	165
4.	p-CH_3	80	200	85	210
5.	o-OCH_3	88	180	90	200
6.	m-OCH_3	88.5	230	89	185
7.	p-OCH_3	91	251	95.1	248
8.	o-Cl	90	190	94	340
9.	m-Cl	87.5	240	91	201
10.	p-Cl	90	290	94.4	360
	CHLOROMYCETIN Water,etoH(9:IV/V)	95	320	91.5	395

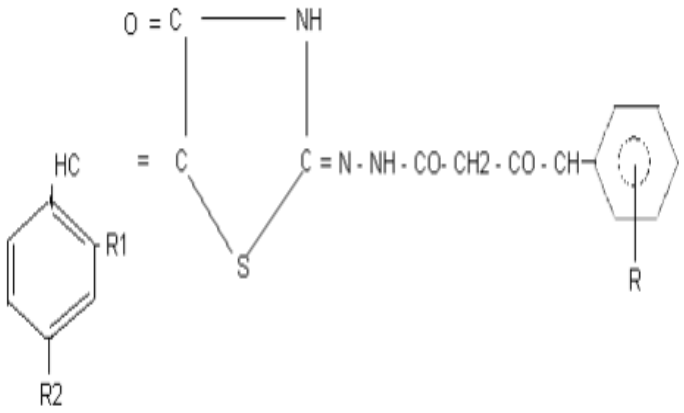
All this compound table no.04 were tested for their fungicidal activity against curvularia lunate and helminthosporium oryzae. Chloro and methoxy group at position 4 in benzene nucleus increase the toxicity to both the species of fungi.

(3) condensation of malonilic acid hydrazides with 5-arylidene rhodanines.

Reaction of phenyl hydrazine with rhodanine has been studied by grancher[12] . The reaction of semicarbazide with rhodanine in aqueous solution (alcoholic) presence of barium carbonate, rhodanine derivatives of semicarbazide are obtained in good yield.



In the present investigation it was thought worthwhile to synthesized some new rhodanine derivatives by the condensation of malonanilic acid hydrazide and 5-arylidene rhodanine in presence of barium carbonates in ethanol medium on water bath products of 2 (substituted malonanilic acid hydrazide) 5-(4-nn-bis -2'- carboxy ethyl – amino 2-methyl – benzylidene) 4-thiazolidinones.



R = H.Cl (O.M.P.)

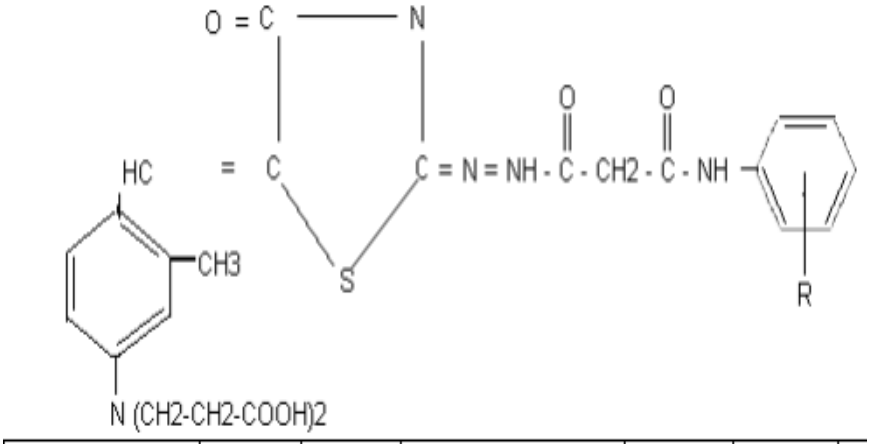
R1 = CH3

R2 = N (CH2 - CH2 - COOH)2

Funglcidal activity of all the campounds table no.05 there tested for their antifungal activity against same fungi in table no.05

Table no.05

2-(substituted malonanilic acid hydrazido)-5-(-4-nn-bis-2'-carboxy ethyl amino-2-methyl-benzylidene)-4-thiazolidinones



S.No.	R	COLOUR	MP.0C	YIELD %	Molecular formula	% of N		% of S	
						FOUND	CALCD	FOUND	CALCD
1.	H	Yellowish red	181	61.0	$C_{26}H_{27}N_5O_7S$	12.35	12.65	5.67	5.78
2.	o-CH_3	Pinkish red	192	51.0	$C_{27}H_{29}N_5O_7S$	12.15	12.34	5.34	5.64
3.	m-CH_3	Reddish brown	201	53.0	$C_{27}H_{29}N_5O_7S$	12.20	12.34	5.41	5.64
4.	p-CH_3	Reddish Orange	162	62.0	$C_{27}H_{29}N_5O_7S$	12.12	13.34	5.28	5.64
5.	o-OCH_3	Greenish red	181	59.5	$C_{27}H_{29}N_5O_8S$	11.80	12.00	5.28	5.48
6.	m-OCH_3	Pink	175	58.0	$C_{27}H_{29}N_5O_8S$	11.98	12.00	5.21	5.48
7.	p-OCH_3	Yellowish red	180	51.5	$C_{27}H_{29}N_5O_8S$	11.82	12.00	5.22	5.48
8.	o-Cl	Reddish violet	165	48.0	$C_{26}H_{26}N_5O_7SCl$	11.78	11.91	5.21	5.44
9.	m-Cl	Pink	171	57.0	$C_{26}H_{26}N_5O_7SCl$	11.72	11.91	5.27	5.44
10.	p-Cl	Dark red	203	49.0	$C_{26}H_{26}N_5O_7SCl$	11.60	11.91	5.11	5.44

FUNGICIDAL ACTIVITY:-

All the compounds (table no.5) were tested for their antifungal activity against curvularia lunate and helminthosporum oryzae by the disc diffusion and hanging drop method.

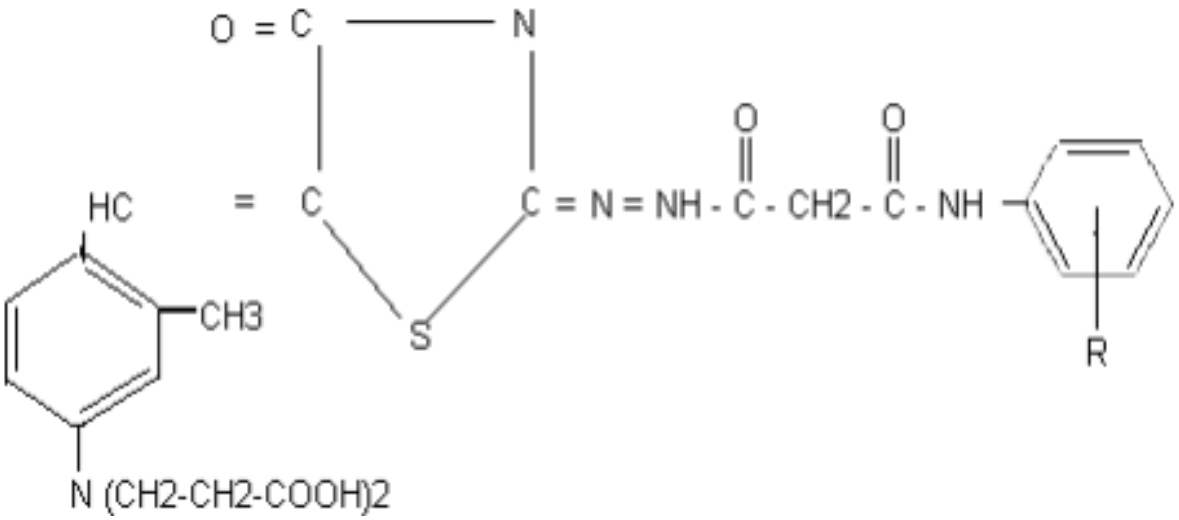
The result has been compared with commercial fungicide chloromycetin.

The highest fungicidal activity has been showed by the compound.

The result of fungicidal activity has been recorded in table no.5

Table no.06

Antifungal activity of 2-(substituted malonanilic acid hydrazido)-5-(4-nn-bis-2'-carboxy ethyl amino-2- methyl-benzylidene)-4-thiazolidinones

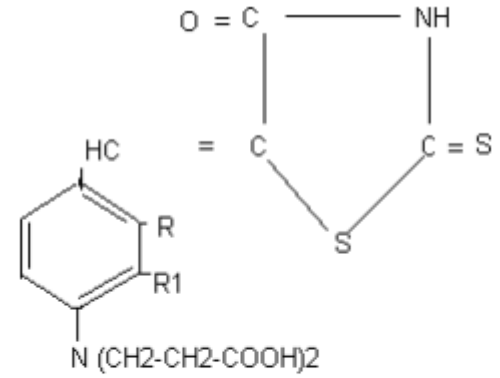


(4) Condeusation of p-p' Di-amino – Diphenyl sulphone with 5-Arylidene rhodanines.

In the present investigation it was thought worthwhile to synthesize some condensation products of dapsone with 5-arylidene rhodanine for testing their antifungal activity.

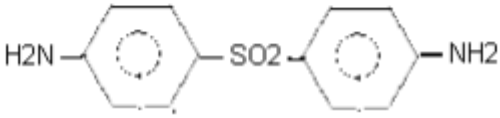
In the present study 5-arylidene rhodanine have been condensed with. Dapsone in an oil bath at 180^0 – 200^0c adopting the procedure of Bux and Shukla[15] and six New products of 4-4-BIS-Amino-5(p-di-methyl amino benzylidene rhodanine diphenyl sulphone) were obtained.

All the New synthesized compounds were tested for their fungicidal activity against Curvularia Lunate and Helminthosporium oryzae.



R = H, CH_3, OCH_3, OC_2H_5

R1= H.I.Cl.



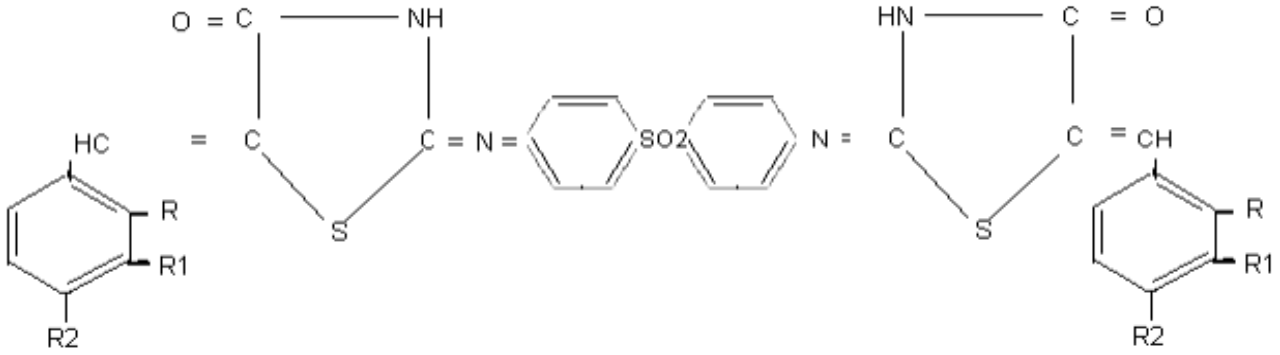
FUNGICIDAL ACTIVITY :-

The fungitoxicity data obtained indicate that all the compounds table no.7 are promising fungicides. The activities vary from strong to moderates on both the fungal species. All the compounds table 7 were tested for their fungicidal activity against curvularia lunat and helminthosporium oryzae by the disc diffusion and hanging drop methad. Synthesised new campound show highest fungicidal activity .

The results have been compared with commercial fungicide chloromycetine fungicidal data of these compounds are recorded in table no.7 (a)

Table no.07

Condensation products of 5-arylidene-rhodanines and dapsone



S. No.	R=R'	R1= R'1	R2=R'2	COLOUR	M.P. oC	YIELD %	MOLECULAR FORMULA	N%		S%	
								FUND	CALCD	FOUND	CALCD
1.	H	H	$N(CH_3)_2$	Deep red	210	41	$C_{38}H_{32}N_8S_3O_4$	12.03	11.83	13.75	13.34
2.	H	H	$N(CH_2CH_2COOH)_2$	Reddish	219	55	$C_{44}H_{40}N_8O_{12}S_3$	8.93	8.62	10.21	10.
3.	CH3	H		brown	217	35	$C_{48}H_{44}N_8O_{12}S_3$	8.67	8.35	9.92	9.58
4.	OCH3	H	$N(CH_2CH_2COOH)_2$	Pinkish red	227	37	$C_{48}H_{44}N_8O_{14}S_3$	8.4	8.12	9.6	9.4
5.	OC2H5	H		Reddish brown	199	67	$C_{48}H_{48}N_8O_{14}S_3$	8.17	7.98	9.33	9.12
6.	H	I	$N(CH_2CH_2COOH)_2$	Reddish violet	231	26	$C_{44}H_{38}N_8O_{12}S_3\ I_2$	7.03	6.99	8.04	7.88
			$N(CH_2CH_2COOH)_2$	Purple red							
			$N(CH_2CH_2COOH)_2$								

Table no.07

Condensation products of 5-arylidene-rhodanines and dapsone

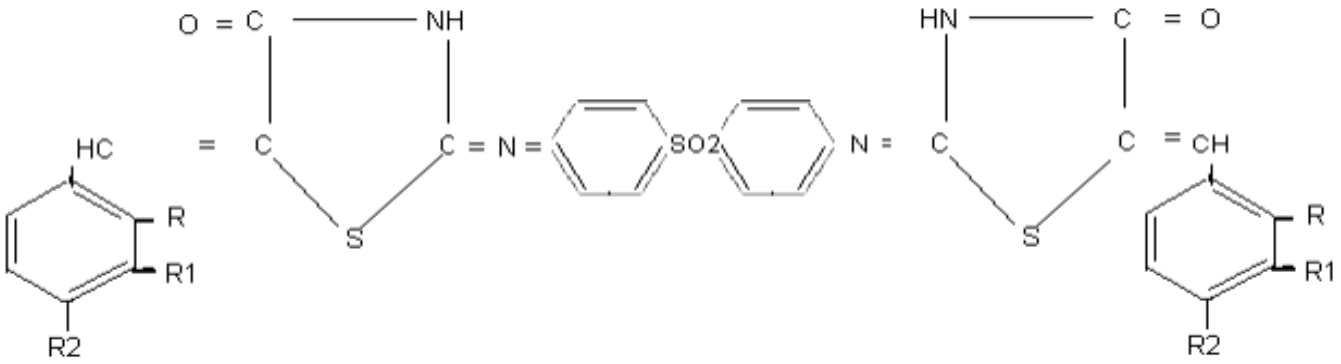


Table no. 7(a) Fungicidal activity of the products

S.No.	R=R'	R1=R'1	R2=R'2	FUNGICIDAL ACTIVITY			
				C.Lunata germination	Tube Length	H.ORYZAE germination	Tube Length
1.	H	H	$N(CH_3)_2$	50	131	60	160
2.	H	H	$N(CH_2CH_2COOH)_2$	61	201	71	191
3.	CH3	H	$N(CH_2CH_2COOH)_2$	67	240	75	340
4.	OCH3	H	$N(CH_2CH_2COOH)_2$	90	230	86	280
5.	OC2H5	H	$N(CH_2CH_2COOH)_2$	92	228	90	380
6.	H	I	$N(CH_2CH_2COOH)_2$	95	314	95	390
			CHLOROMYCETIN (Water – Ethanol 9.1 V/v				

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