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ANTIFUNGAL SCREENING AND OXIDATION BEHAVIOR OF SOME MICROWAVE ASSISTED BENZOTHIAZINE DRUGS

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ABSTRACT

Some azole and azine series compounds are ubiquitous components both of physiologically active products and of important pharmaceuticals, among them the 4H-1,4-benzothiazine nucleus, known to chemists as azine, is the parent member of a broad spectrum of nitrogen heterocyclic biochemicals commonly found in nature, some of these are highly effective anti-cancer agent, blocking carcinogenic substance, before they reach their cellular targets and eliminating DNA damage in cell nuclei. It may turn out to be a good tranquilizers, anti-inflammatory, antivirals, antibacterial, antimalarial and anti-fungal.

4H-1,4-benzothiazines are nitrogen and sulphur containing heterocyclic compounds, which are analogous to phenothiazines and possess similar structural specificity the presence of a fold along N-S axis, which is important factor for imparting a wide spectrum of pharmacological and biological activities. The molecule has an –(CH=CH)- group replacing phenylene group -(C_6H_4)- from the phenothiazines.

Structural resemblance to these two compounds and their pharmacological and industrial applications have stimulated our interest to construct microwave induced fused benzothiazines libraries on solid phase to find novel hit compounds towards multiple biological targets and better medicinal agents. During the past decades azine series have been developed via substitution patterns, but their oxidation behavior has not yet very popular. So keeping in mind all the industrial and medicinal applications. Our interest to extend studies of benzothiazines with 30% hydrogen-peroxide in glacial acetic acid to study the oxidation of benzothiazines to their sulphones, with a hope to obtain new compounds for therapeutic testing and better medicinal agents. The purity of the synthesized compounds was checked by thin-layer chromatography. Their biological activities along with the physical studies have been done to continue the new research area.

Key words: Benzothiazines, Anticancer agents, Antiviral, Antifungal, Phenothiazines, Pharmacological activity, Medicinal agents.

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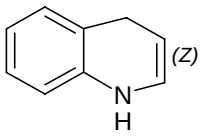
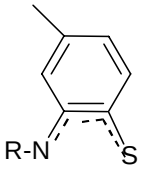
INTRODUCTION

Some nitrogen heterocyclic biochemicals of 4H-1,4-benzothiazines series are analogous to phenothiazines, which can therapeutically use for the treatment of psychotic patents, compounds itself and their sulphones possessing a broad spectrum of anticancer activity, antiponastic and antimalarial activity due to the presence of a fold along N-S axis. Which is an important factor for imparting a wide spectrum of pharmacological and biological activities to benzothiazines[1,2].



4H-1,4-benzothiazene



Fold along N-S axis

The benzothiazines differ from the phenothiazines only in having an ethylene linkage instead of O-phenylene skeleton (-C_6H_4-). Survey of literature reveals that sulphones of phenothiazine derivatives have been studied and characterized, but oxidation behavior of 4H-1,4-benzothiazine is not studied well. The oxidation of sulphide linkage in 4H-1,4-benzothiazines[3] to S-S dioxide leads to an interesting class of heterocyclic sulphones not only from medicinal and industrial[4,5] point of view, but also from structural point of view. These compounds are recognized as pharmacophores have received great attention in drug – discovery and lead optimization[6]. They have been used as anti inflammatory, diuretics, tranquilizer, anti malarials and fungicides[7-9].

There are some other articles of benzothiazine drugs, which deals with their synthesis, used in therapy[10], as indicators[11], dyes[12], heat stabilizers[13], effect against cancer and in treatment of neuropsychatric disorders. Based on above findings and in continuation of our research work on the synthesis of nitrogen heterocyclic derivatives of biological interest, in this paper derivatives of 4H-1,4-benzothiazines were prepared by microwave assisted reactions and converted into their corresponding sulphones to understand the oxidation behavior of benzothiazines and to investigate the changes in spectral analysis caused by the oxidation behavior , which was useful to establish the structure and geometry .

Methodology

Melting points were determine in open glass capillaries and were uncorrected. Thin layer on silica gel “G” coated glass plates using benzene-ethanol (8:2) as eluent was used for monitoring the progress.

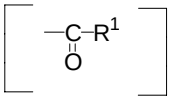
Microwave assisted reactions were carried out in a household MW oven with inverter technology (generating fixed frequency through the required time) for realistic control operating at 1000 W generating 2450 MHZ frequency. The apparatus was modified for favorer applications magnetic stirrer and external reflux condenser.

IR spectra were obtained as KBr discs in range 400-4000 cm^{-1} on Perkin Elmer spectrophotometer at CDRI Lucknow. ^1H NMR spectra were recorded at CDRI Lucknow using $CDCl_3$ as reference. ESR spectra of the compound were recorded at liquid nitrogen temperature in the X-band region at IIT, Mumbai. X-band spectrometer equipped with 100 KHz field modulations. Tetracynoethylene (TCNE) was used as standard.

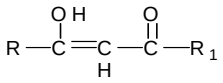
Prepration of substituted 4H-1,4-benzothiazines

In the present work, a number of unknown ring substituted 4H-1,4-benzothiazines have been synthesized by the condensation and oxidative cyclisation of 2-amino-3-methyl-5-nitrobenzenethiol and various active methylene compounds (β-diketones/β-ketoesters) in DMSO.

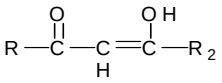
Under the experimental condition, 2-aminobenzenethiol is readily oxidized to bis-2-(aminophenyl) disulphide. The reaction proceeds through the formation of an intermediate enaminoketone. Due to high reactivity of α-position of enaminoketone towards nucleophilic attack, it cyclises to 4H-1,4-benzothiazines (V) by the scission of S-S bond. β-diketones/β-ketoesters exhibit keto-enol tautomerism and two enolic forms are possible namely (III) and (IV). Hence there is a possibility for the formation of two types of benzothiazine (V) and (VIII), but only benzothiazine (V) is obtained. Mass spectral investigations show that the benzothiazine obtained contain carbonyl linkage as –



which suggest the existence of tautomer (III) under experimental condition (employing dimethyl sulphoxide a polar solvent) resulting in the formation of benzothiazines (V) instead of (VIII) via the formation of an intermediate (IV).



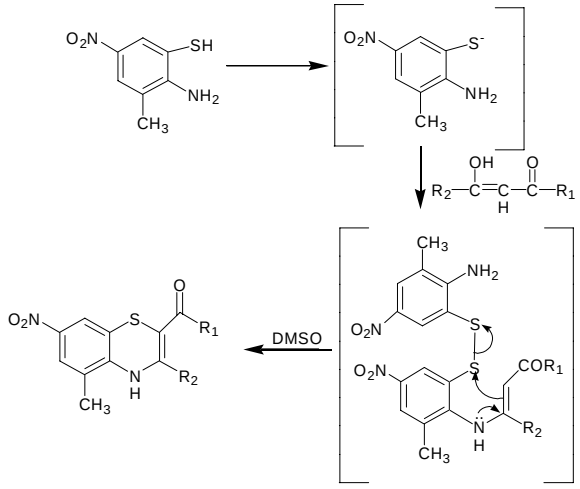
III



V I

Substituted benzyolacetones (III) used for the preparation of 4H-1,4-benzothiazine

have been synthesized by Claisen-condensation of ethylacetate with substituted acetophenone (**Scheme 1**).



Scheme 1

Following reactive methylene compounds were used for the synthesis of various 4H-1,4-benzothiazines.

(a) Methyl acetoacetate

(b) Acetyl acetone

(c) Benzyol acetone

(d) 4-Chloro benzyol acetone

(e) 4-Methyl benzyol acetone

(f) 4-Methoxy benzyol acetone

In the present work, the 4H-1,4-benzothiazines synthesized are –

(a) Methyl-3,5-dimethyl-7-nitro-4H-1,4-benzothiazine-2-carboxylate

(b) 2-acetyl-3,5-dimethyl-7-nitro-4H-1,4-benzothiazine

(c) 2-benzyol-3,5-dimethyl-7-nitro-4H-1,4-benzothiazine

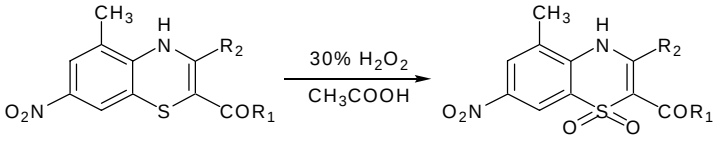
(d) 2-(4-chlorobenzyol)-3,5-dimethyl-7-nitro-4H-1,4-benzothiazine

(e) 2-(4-methylbenzyol)-3,5-dimethyl-7-nitro-4H-1,4-benzothiazine

(f) 2-(4-methoxybenzyol)-3,5-dimethyl-7nitro-4H-1,4-benzothiazine

Prepration of substituted 4H-1,4-benzothiazine sulphones

30% H_2O_2 (5 mL) was added to a solution of substituted H-1,4-benzothiazine (0.01 mol) in glacial acetic acid (20 mL) and refluxed for 15 minutes. Colour of the solution turns yellow, heating was stopped and another lot of H_2O_2 (5 mL) was added. The reaction mixture was again refluxed for 3-4 hrs. The excess of the solvent removed by distillation under reduced pressure and the solution was poured in a beaker containing ice cold water.



Scheme 2

The yellow residue obtained was filtered and crystallized from ethanol. The physical data are recorded in Table 3.

Synthesized 4H-1,4-benzothiazinesulphones are –

(a) Methyl-3,5-dimethyl-7-nitro-4H-1,4-benzothiazinesulpho-ne-2-carboxylate

(b) 2-acetyl-3,5-dimethyl-7-nitro-4H-1,4-benzothiazinesulph-one-2-carboxylate

(c) 2-benzyol-3,5-dimethyl-7-nitro-4H-1,4-benzothiazinesulp-hone-2-carboxylate

(d) 2-(4-chlorobenzyol)-3,5-dimethyl-7-nitro-4H-1,4-benzoth-iazinesulphone-2-carboxylate

(e) 2-(4-methylbenzyol)-3,5-dimethyl-7-nitro-4H-1,4-benzothiazinesulphone-2-carboxylate

(f) 2-(4-methoxybenzyol)-3,5-dimethyl-7-nitro-4H-1,4-benzothiazinesulphone-2-carboxylate

IR Spectral studies

A sharp band in the region of 1675-1600 cm^{-1} due to C=O stretching vibrations. A sharp peak near about 3385-3255 cm^{-1} is found due to the N-H stretching vibrations. In all the benzothiazines asymmetric and symmetric vibrations of $–NO_2$ group assigned to the region of 1590-1510 cm^{-1} and 1360-1320 cm^{-1}, respectively. C-H deformation vibration of

the CH_3 group are found in the range of 1485-1420 cm^{-1} and 1400-1330 cm^{-1}. In the compound (comp. D) C-Cl stretching vibration is found at 770 cm^{-1} and in the compound (G,H) the C-O-C asymmetric and symmetric vibration are found at 1265-1250 cm^{-1} and 1025-1020 cm^{-1}.

NMR Spectral studies

The ^1H NMR spectra of benzothiazines have been examined in DMSO and compared on the basis of chemical shifts, spin –spin interaction and their effect on substitution. A persual of Table 6 shows that a singlet is observed at δ 9.32-8.83 due to the assignment of –N-H proton, another singlet in the region δ 4.14-2.14 is found due to presence of CH_3 protons in the C_2position. A multiplet is observed in the region of δ 7.88-6.30 showing the presence of aromatic proton.

In the region δ 2.95-1.90 a weak singlet assigned to the CH_3 proton at C_3 position, besides this an broadened singlet in the same region at δ 2.49-1.95 due to the presence of CH_3 proton at C_5 position.

The shifting of signals towards the higher frequency region in corresponding sulphones conform the oxidation of the 4H-1,4-benzothiazine through sulphide linkage to S-S dioxide. Only in compound-3, due to the presence of $–C_6H_5$ group, the singlet of C_5 position becomes weaker, similarly in all the last three compound, the presence of an aromatic ring at C_5 position decreased the δ value.

Anti-fungal studies[14]

The general laboratory techniques followed in the course of this investigation are as suggested by Booth and Hawksworth.

Test organism

Test organism used in the present investigation was isolated form it's natural habitat (plants, debris), after isolation it was purified and characterized, then identified, which are *Alternaria-Alternata* and *Aspergillus niger*, earlier used for the antifungal studies of phenylthioureas and 2-aminobenzothiazones. Serial dilution method was used as same as previous research Testing[15-19].

Agar plate technique was used to check the antifungal study of 4H-1,4-benzothiazines and their corresponding sulphones, 2 mL and 5 mL sample solution of concentration 103 ppm and 104 ppm of substituted 4H-1,4-benzothioazines and their

corresponding sulphones in 40% methanol-benzene solvent was specially transferred into sterile petri-plates. Into these plates 20 mL of PDA (media) was poured and mixed with compound solution by rotating the petri-plates in clock-wise and anticlock-wise direction and was allowed to solidify. To evaporate the solvent, the Petri-plates were kept at 60^{o}C for two hrs.

After the solidification of the above medium and evaporation of solvent, single hypha/spore of test organism was specially transferred in the center of the Petri-plates. The above plates were wrapped in polyethene sheets and put in incubator at 30 ± 1^{o}C for 72 hrs, i.e., for 3 days. After the period of incubation, the plates were observed for the growth of fungus for different concentration of the benzothiazines and benzothiazine- sulphones used in the present study. The growth of fungus was measured by recording the total area of fungal colony. The data were statistically analyzed according to the following formula:

$$\% \text{ Inhibition} = \left(\frac{C - T}{C}\right) \times 100$$

where C = Diameter of fungal colony in control plate after 72 hrs

T = Diameter of fungal colony in test plate after 72 hr

The anti-fungal activities of 4H-1,4-benzothiazines and their sulphones have been screened against *Alternaria-Alternata* and *Aspergillum niger* at 100 ppm, 1000 ppm and 10000 ppm, using 2 mL and 5 mL of these solutions by agar-plate technique 40.

A vision of Table 9 and 10 reveals that all the sulphones show higher activity than pure 4H-1,4-benzoazines, Table 7 and 8 suggesting that sulphones are more powerful anti fungal agents, nitrogen and sulphur containing compounds are able to enhance the performance of 4H-1,4-benzothiazoles. The enhanced activity of newly synthesized sulphones as compare to those of the benzothiazines could possible be explained on the basis of presence of donor atoms 'N' and 'S', as well as the structural compatibility with molecular nature of the toxic moiety. A perusal of Table 7 to 10 unfurls a very interesting pattern of % inhibition with increasing concentration. For all the benzothiazines and their corresponding sulphones,on increasing the concentration from 100 ppm to 1000 ppm, the % inhibition increases but on increasing the concentration from 1000 ppm to 10000 ppm , there has been unexpected decrease in % inhibition for all the systems. The comparative order could be summarized as –

$$\% \text{ Inhibition} = 100 \text{ ppm} < 1000 \text{ ppm} > 10000 \text{ ppm}$$

Table 1: Physical data of substituted 4H-1,4-benzothiazines (A-F)

S. No.	R_1	m.p. (^oC)	Yeild	Mol. formula	% C Found (Cal.)	% N Found (Cal.)	% H Found (Cal.)	% S Found (Cal.)
A	$-CH_3$	137	65	$C_{12}H_{12}N_2SO_3$	54.51 (54.54)	10.57 (10.6)	4.50 (4.54)	12.10 (12.12)
B	$-OCH_3$	147	60	$C_{12}H_{12}N_2SO_4$	51.39 (51.42)	9.97 (10.0)	4.26 (4.28)	11.40 (11.42)
C	$-C_6H_5$	172	50	$C_{17}H_{14}N_2SO_3$	62.54 (62.57)	8.56 (8.58)	4.26 (4.29)	9.79 (9.81)
D	$-C_6H_4Cl$ (p)	187	47	$C_{17}H_{13}N_2SO_3Cl$	56.55 (56.58)	7.74 (7.76)	3.57 (3.60)	8.85 (8.87)
E	$-C_6H_4CH_3$ (p)	162	54	$C_{18}H_{16}N_2SO_3$	63.50 (63.52)	8.20 (8.23)	4.67 (4.70)	9.39 (9.41)
F	$-C_6H_4$ $-OCH_3$ (p)	179	42	$C_{18}H_{16}N_2SO_4$	60.64 (60.67)	7.82 (7.86)	4.46 (4.49)	8.96 (8.98)

Table 2: Physical data of substituted 4H-1,4-benzothiazinesulphones (G to L)

S. No.	R_1	m.p (^oC)	Yield	Mol. formula	% C Found (Cal.)	% N Found (Cal.)	% H Found (Cal.)	% S Found (Cal.)
G	$-CH_3$	199	67	$C_{12}H_{12}N_2SO_5$	48.60 (48.64)	9.42 (9.45)	4.01 (4.05)	10.80 (10.81)
H	$-OCH_3$	192	63	$C_{12}H_{12}N_2SO_6$	46.13 (46.15)	8.94 (8.97)	3.80 (3.84)	10.22 (10.25)
I	$-C_6H_5$	201	65	$C_{17}H_{14}N_2SO_5$	56.94 (56.97)	&.80 (7.82)	3.90 (3.91)	8.90 (8.92)
J	$-C_6H_4Cl$ (p)	225	55	$C_{17}H_{13}N_2SO_5Cl$	51.95 (51.97)	7.12 (7.13)	3.30 (3.31)	8.13 (8.15)
K	$-C_6H_4CH_3$ (p)	195	72	$C_{18}H_{16}N_2SO_5$	52.04 (52.06)	7.50 (7.52)	4.27 (4.30)	8.57 (8.60)
L	$-C_6H_4$ OCH_3 (p)	238	54	$C_{18}H_{16}N_2SO_6$	55.61 (55.67)	7.18 (7.21)	4.10 (4.12)	8.21 (8.24)

Table 3: IR Spectral data of substituted 4H-1,4-benzothiazines (A to F) (in cm^{-1})

S. No.	R_1	A	B	C	D	E	F
A	$-CH_3$	3255	1532 1330	1675	1460 1355	----	----
B	$-OCH_3$	3280	1590 1345	1630	1475 1350	----	----
C.	$-C_6H_5$	3285	1560 1320	1600	1480 1360	----	----
D	$-C_6H_4Cl(p)$	3345	1510 1330	1640	1420 1330	770	----
E	$-C_6H_4CH_3(p)$	3385	1570 1330	1650	1455 1375	----	----
F	$-C_6H_4OCH_3(p)$	3310	1535 1360	1630	1485 1400	----	1250 1020

A = N-H stretching vibrations, B = Asymmetric and symmetric vibration of NO_2 group,
C = C=O Stretching vibration, D = C-H deformation vibration of $–CH_3$ group,
E = C-Cl Stretching vibration, F = C-O-C asymmetric and symmetric vibrations

Table 4: IR Spectral data of substituted 4H-1,4-benzothiazinesulphones (G to L) (in cm^{-1})

S. No.	$-R_1$	A	B	C
G	$-CH_3$	3255 (3280)	1675 (1710)	1040 (1075)
H	$-OCH_3$	3280 (3360)	1630 (1695)	1050 (1090)
I	$-C_6H_5$	3285 (3420)	1620 (1700)	1060 (1040)
J	$-C_6H_4Cl(p)$	3315 (3410)	1640 (1680)	1050 (1070)
K	$-C_6H_4CH_3(p)$	3355 (3385)	1650 (1710)	1055 (1085)
L	$-C_6H_4OCH_3(p)$	3310 (3350)	1630 (1650)	1030 (1060)

A = N-H stretching vibrations, B = C=O stretching vibrations, C = C-S asymmetric and symmetric vibrations

Table 5: NMR Spectral data of substituted 4H-1,4-benzothiazines (A to F)

S. No.	R_1	Solvent	St. Peak		
			δ value	Signal	Observation
A	$-CH_3$	DMSO-d_6	8.85	1 singlet	N-H Proton
			7.29-6.37	2 multiplet	Aromatic protons
			3.87	3 singlet	CH_3 protons of $COCH_3$ at C_2
			2.51	3 singlet	CH_3 protons at C_3
			2.44	3 singlet	CH_3 protons at C_5
B	$-OCH_3$	DMSO-d_6	8.83	1 singlet	N-H Proton
			7.24-6.48	2 multiplet	Aromatic protons
			4.14	3 singlet	CH_3 protons of $COCH_3$ at C_2
			2.49	3 singlet	CH_3 protons at C_3
			2.42	3 singlet	CH_3 protons at C_5
C	$-C_6H_5$	DMSO-d_6	9.11	1 singlet	N-H proton
			7.46-6.70	7 multiplet	Aromatic protons
			2.64	3 singlet	CH_3 protons at C_3
			1.96	3 singlet	CH_3 protons at C_5
D	$-C_6H_4Cl$ (p)	DMSO-d_6	9.24	1 singlet	N-H proton
			7.60-6.71	7 multiplet	Aromatic protons
			2.74	3 singlet	CH_3 protons at C_3
			1.74	3 singlet	CH_3 protons at C_5
E	$-C_6H_4CH_3$ (p)	DMSO-d_6	9.02	1 singlet	N-H Proton
			7.16-6.50	2 multiplet	Aromatic protons
			4.46	3 singlet	CH_3 protons at p-position of benzoyl side chain at C_2
			2.92	3 singlet	CH_3 protons at C_3
			2.13	3 singlet	CH_3 protons at C_5
F	$-C_6H_4OCH_3$ (p)	DMSO-d_6	9.24	1 singlet	N-H Proton
			7.62-6.73	2 multiplet	Aromatic protons
			3.73	3 singlet	CH_3 protons at p-position of benzoyl side chain at C_2
			2.74	3 singlet	CH_3 protons at C_3
			1.94	3 singlet	CH_3 protons at C_5

Table 6: Characteristic vibrations of the sulphonyl group in 1H-1,4-benzothiazine-sulphones (in cm^{-1})

S. No.	R_1	$\nu_{1sym.}(SO_2)$		$\nu_2(SO_2)$		$\nu_{3asym.}(SO_2)$	
		KBr	CCl_4	KBr	CCl_4	KBr	CCl_4
G	$-CH_3$	1165	-	555	535	1360	1365
		1145	-	520	515	1315	-
		1135	-	-	-	1295	-
		1125	-	-	-	-	-
H	$-OCH_3$	1155	-	535	555	1370	1365
		1140	-	515	530	1320	-
		1135	-	-	-	1290	-
		1130	-	-	-	-	-
I	$-C_6H_5$	1155	-	545	543	1365	1360
		1140	-	520	530	1315	-
		1130	-	-		1285	-
		1135	-	-		-	-
J	$-C_6H_4Cl$ (p)	1150	-	545	525	1350	1360
		1165	-	530	525	1320	-
		1135	-	-	-	1280	-
		1145	-	-	-	-	-
K	$-C_6H_4CH_3$ (p)	1165	-	540	555	1360	1345
		1160	-	515	525	1345	-
		1145	-	-	-	1275	-
		1125	-	-	-	-	-
L	$-C_6H_4OCH_3$ (p)	1150	-	540	550	1365	1355
		1145	-	520	530	1325	-
		1130	-	-	-	1275	-
		1120	-	-	-	-	-

Table 7: % Inhibition for 4H-1,4-benzothiazines (A to F) against *Alternaria-Alternata*

S. No.	Compound R_1	100 ppm		1000 ppm		10,000 ppm	
		2-mL	5-mL	2-mL	5-mL	2-mL	5-mL
A	$-CH_3$	80.2	82.4	85.0	90.0	68.3	49.3
B	$-OCH_3$	82.1	89.5	90.0	92.4	61.0	48.3
C	$-C_6H_5$	83.0	85.1	86.3	90.1	56.0	39.0
D	$-C_6H_4Cl$(p)	86.0	87.9	97.0	98.2	64.0	66.2
	(CSB) CH_3	89.2	90.0	92.4	94.8	88.2	86.8
E	$-C_6H_4CH_3$(p)	82.0	83.0	87.2	89.3	67.8	68.0
	(CSB) OCH_3	91.4	95.2	94.0	96.2	87.4	85.0
F	$-C_6H_4OCH_3$(p)	83.1	85.2	91.2	90.7	55.0	57.2
	(CSB) C_6H_5	91.8	95.8	95.6	96.8	84.4	84.8

Table 8: % Inhibition for 4H-1,4-benzothiazines (A to F) against *Aspergillus Niger*

S. No.	Compound R_1	100 ppm		1000 ppm		10,000 ppm	
		2-mL	5-mL	2-mL	5-mL	2-mL	5-mL
A	$-CH_3$	60.7	63.14	64.17	67.20	59.12	50.17
	(CSB) CH_3	68.8	72.2	70.2	75.8	65.0	58.8
B	$-OCH_3$	67.11	65.18	68.12	69.15	58.1	54.1
	(CSB) OCH_3	75.2	78.8	77.8	79.0	68.8	63.4
C	$-C_6H_5$	69.14	70.13	71.1	73.14	51.12	57.0
	(CSB) C_6H_5	77.7	79.8	80.0	84.4	72.0	76.8
D	$-C_6H_4Cl$(p)	70.12	72.17	68.12	69.15	58.19	54.12
E	$-C_6H_4CH_3$(p)	69.18	70.02	67.11	68.0	54.14	56.0
F	$-C_6H_4OCH_3$(p)	63.0	67.2	65.21	63.2	52.73	54.0

Table 9: % Inhibition for 4H-1,4-benzothiazinesulphones (G to L against *Alternaria-Alternate*

S. No.	Compound R_1	100 ppm		1000 ppm		10,000 ppm	
		2-mL	5-mL	2-mL	5-mL	2-mL	5-mL
G	$-CH_3$	82.4	84.4	86.0	92.0	69.4	57.3
H	$-OCH_3$	84.2	89.9	92.0	93.5	64.0	53.0
I	$-C_6H_5$	84.0	87.2	87.4	92.1	57.0	44.0
J	$-C_6H_4Cl$(p)	89.8	92.7	98.0	99.5	65.0	69.0
K	$-C_6H_4CH_3$(p)	85.0	89.7	89.2	90.4	66.0	68.2
L	$-C_6H_4OCH_3$(p)	84.1	90.2	92.2	94.7	58.0	59.2

Table 10: % Inhibition for 4H-1,4-benzothiazinesulphones (G to L) against *Aspergillus Niger*

S. No.	Compound R_1	100 ppm		1000 ppm		10,000 ppm	
		2-mL	5-mL	2-mL	5-mL	2-mL	5-mL
G	$-CH_3$	68.2	69.2	69.7	70.0	60.2	54.2
H	$-OCH_3$	69.7	66.15	70.2	67.2	60.0	55.0
I	$-C_6H_5$	70.14	69.13	72.12	70.14	59.0	57.8
J	$-C_6H_4Cl$(p)	71.0	72.8	72.2	74.8	61.0	63.0
K	$-C_6H_4CH_3$(p)	79.8	80.2	80.5	82.2	68.0	68.9
L	$-C_6H_4OCH_3$(p)	74.2	76.2	76.0	77.8	66.8	68.2

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