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SYNTHESIS OF SOME NOVEL 2-SUBSTITUTED IMINO-7-SUBSTITUTED PHENYL-3, 7-DIHYDRO-2H-[1, 3] THIAZOLO [5, 4-E] - THIAZIN-5-AMINE AS ANTIFUNGAL ACTIVITY

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ABSTRACT: The condensation of 2-imino-5 substituted benzylidene-4-thiazolidinone (1) with thiourea (2) in the presence of glacial acetic acid to gives 2-substituted imino-7-substituted phenyl-3,7-dihydro-2H-[1,3] thiazolo [5,4-e]-thiazin-5-amine (3). The antifungal activities of the compounds (3a-h) were tested against *A.niger* and *A. flavus*. The growth of both fungi *A. niger* and *A. flavus* are inhibited to some extent by all the synthesized compounds. Hence all are antifungal agents.

Keywords: Thiazole, Thiazole derivatives, Substituted Thiazine derivatives, Antifungal activity

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INTRODUCTION: Heterocyclic compounds comprise the major family of organic compounds. These are enormously essential with a wide range of synthetic, pharmaceutical, and industrial applications and are famous for their biological activities. There is an extensive spectrum of biological activities shown by many compounds containing five-membered heterocyclic rings in their structure. The high therapeutic properties of these heterocycles have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. These heterocyclic compounds have broadened the scope in remedying various dispositions in clinical medicines. Thiazoles have been reported to show pharmacological activities [1].

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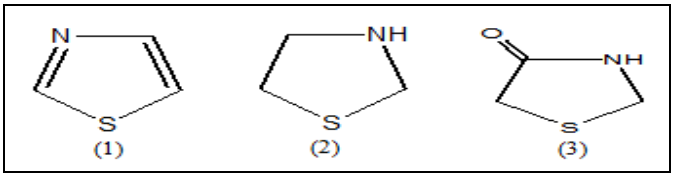
Thiazole (1) is a well known heterocyclic compound with two heteroatoms, sulfur, and nitrogen at position 1 and 3. The tetrahydro derivatives of thiazole are known as thiazolidine (2), and oxo-derivative of thiazolidine is called thiazolidinone (3). Thiazolidinone is an important compound of this group.



Thiazoles represent an important class of heterocyclic compounds. The thiazole derivatives are widely used in the field of medicine, industry and agriculture. The derivatives of thiazole have been reported as fungicides [2-3], Pesticides [4], insecticides [5], antibacterial [6-7], anti-inflammatory [8], anticonvulsant [9], antitubercular [10], antiviral [11], and anticancer [12]. An attempt is to synthesize some novel 2-substituted imino-7-substituted phenyl - 3, 7-dihydro-2H-[1, 3] thiazolo [5, 4-e] - thiazin-5-

amine. The synthesized compounds (3) have been screened for antifungal activity against *A. niger* and *A. flavus.*

MATERIALS AND METHODS: Melting points were taken in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on Perkin-Elmer-720 spectrophotometer. The ^1H NMR spectra were recorded in $CDCl_3$ on Varian A-60 D. spectrophotometer. The chemical shifts are recorded in ppm downfield from TMS, which are used as an internal standard.

2-substituted imino-7-substituted phenyl-3, 7-dihydro-2H-[1, 3] thiazolo [5, 4-e] - thiazin-5-amine (3a-h) (General Method).

A 0.05 mol of 2-substituted imino-5-benzylidene-4-thiazolidinone and 0.05 mol thiourea was dissolved in 100 ml of glacial acetic acid by refluxing for 5 hours, it was allowed to cool and the solid obtained was filtered. The crude products were pressed firmly and recrystallized from ethanol: water. The physical data of all the synthesized compounds are given in **Table 1.**

TABLE 1: PHYSICAL DATA OF ALL THE SYNTHESIZED COMPOUNDS

Comp. no	R	X	M.P.(^{0}C)	Yield (%)	Molecular formula	Elemental Analysis			IR υcm^{-1}	^1H NMR ($CDCl_3$)
						C	H	N		
3a	H	H	189	65	$C_{11}H_{10}N_4S_2$	50.38	3.81	21.37	3390(NH), 760 (C-S), 1680 (C=N), 3080 (Ar-CH)	7.19-8.25 (m,5H,Ar-H), 5.71 (s,4H,NH),2.81 (s,1H,CH)
3b	H	p-OMe	177	62	$C_{12}H_{12}N_4S_2O$	49.31	4.10	19.18	3380 (NH), 780 (C-S), 1673 (C=N), 3075 (Ar-CH), 1250 (C-OCH_3)	7.20-8.24 (m,4H,Ar-H), 5.461 (s,4H,NH), 2.69 (s,1H,CH), 3.53 (s,3H,OCH_3)
3c	H	p-$N(Me)_2$	162	64	$C_{13}H_{15}N_5S_2$	51.14	4.91	22.95	3383 (NH), 778 (C-S), 3079 (Ar-CH)	7.22-8.26 (m,4H,Ar-H), 5.61 (s,4H,NH), 2.7 (s,1H,CH), 3.79 (s.6H,NMe_2)
3d	H	p-NO_2	159	73	$C_{11}H_9N_5S_2O_2$	42.99	2.93	22.80	3370 (NH), 775 (C-S), 3101 (Ar-CH), 1470 (C-NO_2)	7.26-8.35 (m,4H,Ar-H),5.48 (s,4H,NH),2.75(s,1H,CH)
3e	Ph	H	197	72	$C_{17}H_{14}N_4S_2$	60.35	4.14	16.56	3365 (NH), 770 (C-S), 3098 (Ar-CH)	7.23-8.36 (m,16H,Ar-H),5.52 (s,3H,NH),2.68(s,1H,CH)
3f	Ph	p-OMe	186	66	$C_{18}H_{16}N_4S_2O$	58.69	4.34	15.21	3349 (NH), 772 (C-S), 3083 (Ar-CH), 1265 (C-OCH_3)	7.25-8.37 (m,9H,Ar-H),5.56 (s,3H,NH),2.73(s,1H,CH) , 3.53 (s,3H.OCH_3)
3g	Ph	p-$N(Me)_2$	178	64	$C_{19}H_{19}N_5S_2$	59.84	4.98	18.37	3384 (NH), 762 (C-S), 3075 (Ar-CH)	7.24-8.31 (m,9H,Ar-H),5.47 (s,3H,NH),2.67(s,1H,CH) , 3.7 (s,6H,N-Me_2)
3h	Ph	p-NO_2	164	71	$C_{17}H_{13}N_5S_2O_2$	53.26	3.39	18.27	3382 (NH), 765 (C-S), 3062 (Ar-CH), 1435 (C-NO_2)	7.27-8.35 (m,9H,Ar-H),5.54 (s,3H,NH),2.72 (s,1H,CH)

Antifungal Activity: The compounds (3a-h) were screened for their antifungal activity against *A. niger* and *A. flavus* by known method [13] at the three concentrations *viz*. 1000, 100 and 10 ppm. The screening data of compounds are listed in **Table 2**. Results were compared with commercial fungicide miconazole tested under similar conditions.

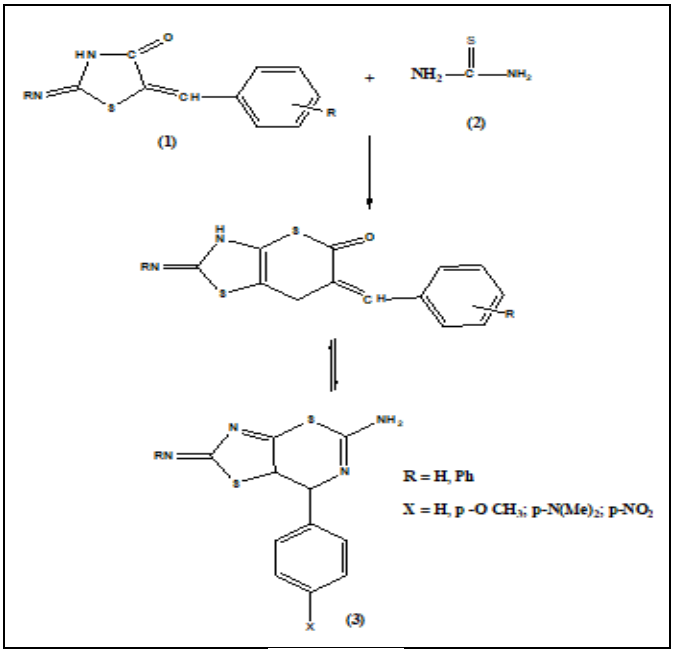
The percentage inhibition has been calculated by the formula

$$\% \text{ inhibition} = (C-T) \times 100/C$$

Where C and T are a diameter (in mm) of fungus colony in control and treated plates respectively.

TABLE 2: SCREENING DATA OF COMPOUNDS

Comp. no.	R	X	*A. niger* Concentration (ppm) used			*A. flavus* Concentration (ppm) used		
			1000	100	10	1000	100	10
3a	H	H	69.7	53.2	35.7	67.2	56.5	32.1
3b	H	p-OMe	67.9	51.8	36.3	68.3	56.8	33.2
3c	H	p-$N(Me)_2$	66.5	53.8	35.4	67.1	56.3	32.0
3d	H	p-NO_2	73.2	57.6	39.0	70.0	57.1	34.8
3e	Ph	H	67.1	56.5	32.0	64.3	50.1	32.8
3f	Ph	p-OMe	67.2	53.5	34.0	65.9	52.3	34.2
3g	Ph	p-$N(Me)_2$	65.8	51.4	32.1	64.7	52.1	33.8
3h	Ph	p-NO_2	70.8	57.3	36.7	72.3	53.4	34.6



SCHEME 1

RESULT AND DISCUSSIONS: It is observed from the antifungal screening data that most of the compounds have significant toxicity at 1000 ppm, but their toxicity decreases upon dilution **Table 2**. The antifungal activity of the compounds is due to the presence of biolabile groups N=C-S, and N-N=C present in the nuclei of the compound and slight variation in their antifungal activity is due to OCH_3, N-$(Me)_2$ and NO_2 group attached with benzene nucleus. All the synthesized compounds show antifungal activity against *A. niger* and *A. flavus*.

CONCLUSION: The growth of both fungi *A. niger* and *A. flavus* are inhibited to some extent by all the synthesized compounds. The compounds having a p-nitro group in each set of derivatives are more active. The compounds having p-nitrophenyl and p-methoxy phenyl groups in thiazinopyrazole enhanced the fungicidal activity against both the test fungi *A. niger* and *A. flavus.*

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CONFLICT OF INTEREST: Nil

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