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SYNTHESIS AND FUNGITOXICITY OF SOME NEW HETEROCYCLIC COMPOUNDS

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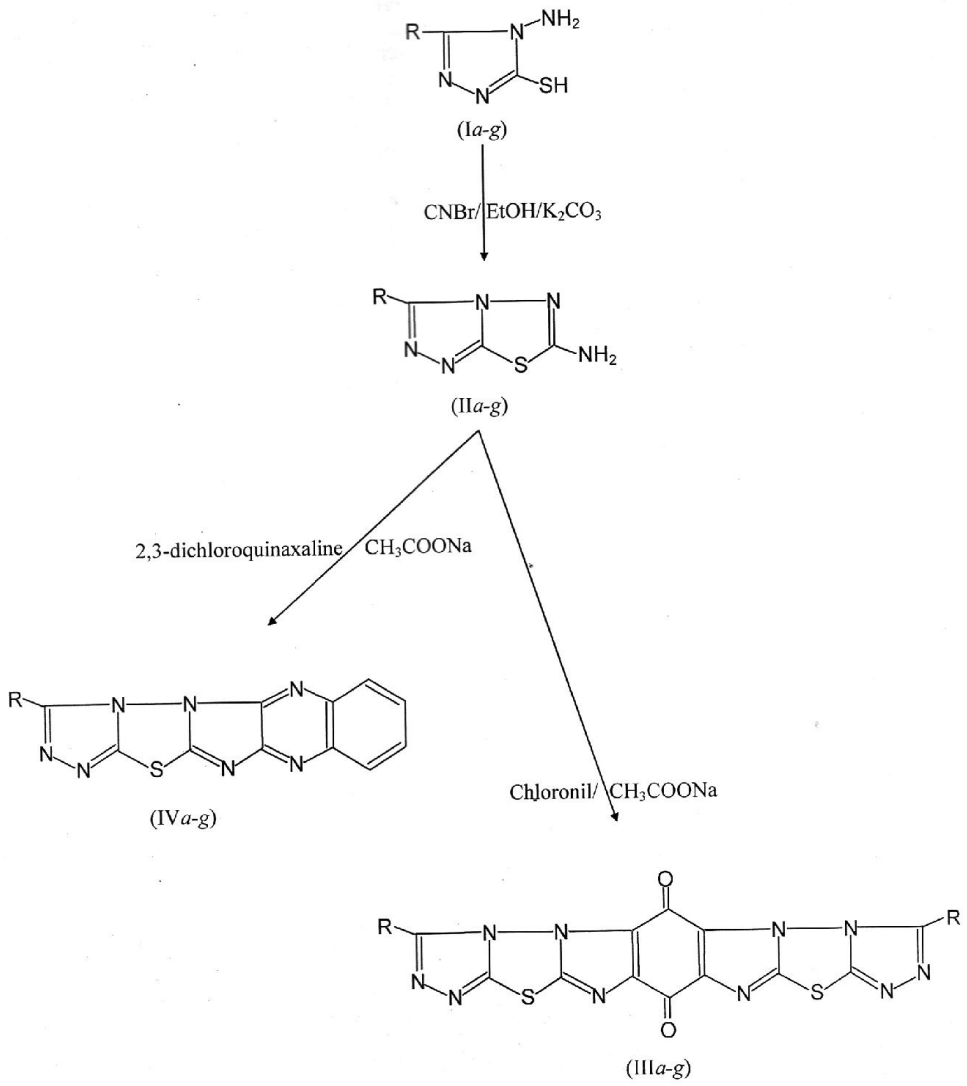
3-Aryl-s-triazolo-[3, 4-b]-1-3, 4-thiadiazolo [3, 2-b] imidazo [4, 5-b] quinoxalines (III*a-g*) and 3, 9-diaryl-6-14-dioxo-bis-(s-triazolo-[3, 4-b]-1, 3, 4-thiadiazolo [3, 2-b] imidazolo [4, 5-b] cyclohexane]-5a, 6a-diene) (IV*a-g*) have been synthesized from 3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles (II*a-g*), which is obtained from starting materials 3-aryl-4-amino-5-mercapto-s-triazoles (I*a-g*). Following the method of Reid and Heindel [1]. All the synthesized fourteen compounds [III*a-g*] & [IV*a-g*] were characterized by their molecular formula, elemental analysis I.R. and ^{1}HNMR spectral data. Fungicidal activity of the synthesized compounds was evaluated against *Phytophthora infestans* and *Aspergillus niger*. Fungicidal screening data correlated with the structural features of the tested compounds.

KEYWORDS: Triazoles, Dithane M-45, *Phytophthora infestans* and *Aspergillus niger*.

INTRODUCTION

Nitrogen containing heterocyclic compounds are present in all the living beings performing important biological functions. Nitrogenous heterocyclic compounds occurred widely in roast food and drugs and possess different pharmacological properties due to oxidation of nitrogen in molecules [2]. s-Triazole nucleus is associated with broad spectrum of pesticidal activity like fungicides [3, 4], bactericides [5, 6], herbicides [7, 8], insecticides [9, 10] etc. Similarly 1, 3, 4-thiadiazole nucleus also possesses a large number of biological activities like fungicidal [11, 12], insecticidal [13, 14] herbicidal [15, 16]. In association quanoxaline derivatives show medicinal properties [17, 18]. Keeping the above observation in view the compound (III*a-g*) and (IV*a-g*) have been synthesized with the hope that fusion of the biolabile 1, 3, 4-triazole and 1, 3, 4-thiadiazole with quinoxalline nuclei might result in the fungicides of enhance potency. The reaction sequence leading to the formation of title compounds is given in the Scheme-I and fungicidal screening data are given in the experimental section.



R : a = C_6H_5, b = 2-C_6H_4Cl; c = 2-$C_6H_4CH_3$; d = 2-$C_6H_4OCH_3$
e = 4-C_6H_4Cl; f = 4-$C_6H_4CH_3$; g = 4-$C_6H_4OCH_3$

Scheme-I

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. The IR Spectra in KBr were recorded either on Perkin-Elmer 157 or Hitachi 295 Infrared spectrophotometer. ^{1}HNMR spectra were recorded on a EM 360L (60 MHz) NMR spectrometer in $DMSOd_6$ with TMS as internal reference. Chemical shifts are expressed in δ ppm.

3-Aryl-4-amino-5-mercapto-s-triazoles (I*a-g*).

3-Aryl-4-amino-5-mercapto-s-triazoles were prepared in excellent yield following the method of Reid and Heindel [1] following seven mercapto triazoles were prepared which well agreed with their analytical data already reported in litrature.

(a) 3-(phenyl)-4-amino-5-mercapto-1,2,4-triazoles; M.P. 243°C, yield 50%

(b) 3-(2-chlorophenyl)-4-amino-5-mercapto-1, 2, 4-triazoles; M.P. 239°C, yield 53%

(c) 3-(2-methylphenyl)-4-amino-5-mercapto-1, 2, 4-triazoles; M.P. 240°C, yield 51%

(d) 3-(2-methoxyphenyl)-4-amino-5-mercapto-1, 2, 4-triazoles; M.P. 243°C, yield 50%

(e) 3-(4-Chlorophenyl)-4-amino-5-mercapto-1, 2, 4-triazoles; M.P. 241°C, yield 53%

(f) 3-(4-methylphenyl)-4-amino-5-mercapto-1, 2, 4-triazoles; M.P. 244°C, yield 52%

(g) 3-(4-methoxyphenyl)-4-amino-5-mercapto-1, 2, 4-triazoles; M.P. 245°C, yield 54%

6-Amino-3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles (II*a-g*).

A mixture of 3-aryl-4-amino-5-mercapto-s-triazole 5.0 gm (0.022 mol) and cyanogen bromide 2.31 gm (0.022 mol) in ethanol (150 ml) was heated under reflux on a water-bath for 6 hour concentrated to one fourth of its original volume and neutralized with saturated aqueous solution of K_2CO_3. The white precipitate thus obtained, was filtered and crystallized from ethanol to give colourless shiny crystals.

6-amino-3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles thus synthesized in 55-60% yield of theory and recrystallized from ethanol which are given in Table-1 with their characterization data of M.P. yield, molecular formula, elemental analysis, IR and ^{1}H-NMR spectra of the representative compounds.

Table 1. Characterization data of 6-amino-3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazoles.

Compd. No.	R	Yield (%)	M.P. (^{0}C)	Molecular Formula	Analysis Found (Calcd)%		
					C	N	S
a	C_6H_5	58	239	$C_9H_7N_5S$	49.76 (49.75)	32.25 (32.27)	14.74 (14.75)
b	2-C_6H_4Cl	56	241	$C_9H_6N_5SCl$	43.02 (43.05)	27.88 (27.87)	12.74 (12.72)
c*	2-$C_6H_4CH_3$	55	243	$C_{10}H_9N_5S$	51.94 (51.92)	30.30 (30.29)	13.85 (13.87)
d	2-$C_6H_4OCH_3$	59	244	$C_{10}H_9N_5SO$	48.58 (48.59)	28.34 (28.33)	12.95 (12.94)
e	4-C_6H_4Cl	58	242	$C_9H_6N_5SCl$	43.02 (43.01)	27.88 (27.89)	12.74 (12.75)
f	4-$C_6H_4CH_3$	56	244	$C_{10}H_9N_5S$	51.94 (51.95)	30.30 (30.33)	13.85 (13.84)
g	4-$C_6H_4OCH_3$	60	245	$C_{10}H_9N_5SO$	48.58 (48.61)	28.34 (28.36)	12.95 (12.97)

* IR(KBr) : 835 (1,4-disubstituted benzene ring), 1520 (C-N stretching), 1615 (cyclic C=N), 3140, 3310 (N-H stretching) cm^{-1}

^{1}H-NMR (DMSO-d_6) δ : 2.40 (3H, s, CH_3), 5.25-(2H, br, s, NH_2), 7.00-7.80 (4H, m, Ar-H)

3, 9-Diaryl-6, 14-dioxo-bis-(s-triazolo-[3, 4-b]-1, 3, 4-thiadiazolo [3, 2-b] imidazolo [4, 5-b] cyclohexane]-5a, 6a-diene) (III*a-g*).

A solution of 6-amino-3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazole 0.03 gm (0.00128 ml) in acetic acid (25 ml) was added to a solution of chloronil 0.147 gm (0.0006 mol) and

anhydrous sodium acetate 0.093 gm (0.0012 mol) in acetic acid (25 ml). The reaction mixture was heated under reflux for 3 hour. The mixture acquired reddish colouration and a red coloured solid started separating after about 15-20 min. cooled and filtered the solid separated, washed through with water in order to remove sodium acetate, then with mix ethanol and finally recrystallized from acetic acid to give red coloured crystals.

Similarly other 3, 9-diaryl-6, 14-dioxo-bis-(s-triazolo [3, 4-b)-1, 3, 4-thiadiazolo [3, 2-b] [imidazolo [4, 5-b] cyclohexan]-5a, 6a-diene) thus synthesized in 54-60% yield of theory and recrystallized from ethanol which are recorded in Table-2 with their characterization data of M.P., Yield, molecular formula, elemental analysis, IR and ^{1}H-NMR spectra of the representative compounds.

Table 2. Characterization data of 3, 9-diaryl-6, 14-dioxo-bis-(s-triazolo-[3, 4-b]-1, 3, 4-thiadiazolo [3, 2-b] imidazolo [4, 5-b] cyclohexane]-5a, 6a-diene)

Compd. No.	R	Yield (%)	M.P. (°C)	Molecular Formula	Analysis Found (Calcd)%		
					C	N	S
a	C_6H_5	58	243	$C_{25}H_{13}N_{10}S_2O_2$	54.64 (54.61)	23.56 (23.57)	10.77 (10.79)
b	2-C_6H_4Cl	57	244	$C_{25}H_{11}N_{10}S_2O_2Cl_2$	48.62 (48.61)	22.69 (22.70)	10.37 (10.40)
c**	2-$C_6H_4CH_3$	56	246	$C_{26}H_{14}N_{10}S_2O_2$	55.51 (55.50)	24.91 (24.94)	11.38 (11.39)
d	2-$C_6H_4OCH_3$	55	247	$C_{26}H_{14}N_{10}S_2O_4$	52.22 (52.50)	23.56 (23.59)	10.77 (10.78)
e	4-C_6H_4Cl	54	245	$C_{25}H_{11}N_{10}S_2O_2Cl_2$	48.62 (48.65)	22.69 (22.67)	10.37 (10.35)
f	4-$C_6H_4CH_3$	50	247	$C_{26}H_{14}N_{10}S_2O_2$	55.51 (55.53)	24.91 (24.89)	11.38 (11.35)
g*	4-$C_6H_4OCH_3$	56	248	$C_{26}H_{14}N_{10}S_2O_4$	52.52 (52.55)	23.56 (23.55)	10.77 (10.76)

* IR (KBr) : 840 (1, 4-disubstituted benzene ring), 1525 (C-N stretching), 1615 (cyclic C=N), 1650 (C=O), 3045, (aromatic C-H stretching) cm^{-1}

^{1}H-NMR(DMSO-d_6) δ : 3.81 (6H, s, two-OCH_3), 7.06-7.90 (8H, m, Ar-H)

** IR (KBr) : 845 (1, 4-disubstituted benzene ring), 1530 (C-N stretching), 1620 (cyclic C=N), 1645 (C=O), 3040, (aromatic C-H stretching) cm^{-1}

^{1}H-NMR(DMSO-d_6) δ : 2.40 (6H, s, two-OCH_3), 7.01-7.99 (8H, m, Ar-H)

3-Aryl-s-triazolo-[3,4-b]-1,3,4-thiadiazolo [3,2-b] imidazo [4,5-b] quinoxalines (IV*a-g*)

A solution of 6-amino-3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazole 0.5 gm (0.002 mol) 2, 3-dichloroquinoxaline 0.398 gm (0.002 mol) and anhydrous sodium acetate 0.328 gm. (0.004 mol) in ethanol (25 ml) was heated under reflux for 6 hour. The reaction mixture was concentrated, cooled and poured into cold water. A yellow precipitate thus obtained, was filtered off, dried and recrystallized from methanol to give yellow coloured crystals.

Similarly all the 3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazolo-[3, 2-b]-imidazo [4, 5-b]-quinoxaline thus synthesized in 56-60% yield of theory and recrystallized from ethanol which are given in Table-3 with their characterization data of M.P., Yield, Molecular formulae, elemental analysis, IR and ^{1}H-NHR spectra of the representative compounds are given.

Table 3. Characterization data of 3-aryl-s-triazolo-[3, 4-b]-1, 3, 4-thiadiazolo [3, 2-b] imidazo [4, 5-b] quinoxalines.

Compd. No.	R	Yield (%)	M.P. (^{0}C)	Molecular Formula	Analysis Found (Calcd)%		
					C	N	S
a	C_6H_5	58	86	$C_{17}H_9N_7S$	59.47 (59.49)	28.57 (28.55)	09.32 (09.31)
b	2-C_6H_4Cl	59	82	$C_{17}H_8N_7SCl$	54.11 (54.14)	25.99 (25.98)	08.48 (08.49)
c	2-$C_6H_4CH_3$	57	84	$C_{18}H_{11}N_7S$	60.50 (60.51)	27.45 (27.42)	08.96 (08.97)
d	2-$C_6H_4OCH_3$	58	85	$C_{18}H_{11}N_7OS$	57.90 (57.93)	26.27 (26.26)	08.57 (08.95)
e	4-C_6H_4Cl	56	83	$C_{17}H_8N_7SCl$	54.11 (54.10)	25.45 (27.97)	08.48 (08.45)
f**	4-$C_6H_4CH_3$	55	83	$C_{28}H_{11}N_7S$	60.50 (60.49)	27.45 (27.47)	08.96 (08.95)
g*	4-$C_6H_4OCH_3$	60	86	$C_{18}H_{11}N_7OS$	57.90 (57.88)	26.27 (26.28)	08.57 (08.55)

* IR (KBr) : 760, 825 (1, 2 and 1, 4-disubstituted benzene ring),
1525 (C-N stretching), 1615 (cyclic C=N),
3020, 3035, (aromatic C-H stretching) cm^{-1}
^{1}H-NMR(DMSO-d_6) δ : 3.80 (3H, s, OCH_3), 7.03-7.94(8H, m, Ar-H)

** IR (KBr) : 765, 830 (1, 2 and 1, 4-disubstituted benzene ring),
1525 (C-N stretching), 1615 (cyclic C=N),
3025, 3045, (aromatic C-H stretching) cm^{-1}
^{1}H-NMR(DMSO-d_6) δ : 2.40 (3H, s, CH_3), 7.00-7.99 (8H, m, Ar-H)

FUNGICIDAL ACTIVITY : The fungicidal activity of such fourteen compounds (III*a-g*) & (IV*a-g*) were evaluated against *Phytophthora infestans* and *Aspergillus niger* at 1000, 100 & 10 ppm concentration following the Agar Plate Technique [19] and the results are summarized in Table-4.

Results and discussion

It is evident from the result of the antifungal activities (Table-4) clearly indicates that all the compounds (III*a-g*) & (IV*a-g*) significantly inhibited more than 68% mycelial growth of both the test fungi *i.e*. *Phytophthora infestans* and *Aspergillus niger* at 1000 ppm concentration but their activity decreased considerable at lower concentration (100 and 10 ppm) of these the most active compounds (III*a*) and (IV*a*) exhibited fungicidal action almost equivalent to that of **Dithane M-45** at 1000 ppm concentration and inhibited 24-48% growth of both the fungal species even at 100 ppm concentrations.

Conclusions

The comparison of antifungal activity of the title compounds shows that (IV*a-g*) are less active then compound (III*a-g*). The over all results are not so encouraging as one would except from the combined performance of the fused boilable nuclei *i.e*. 1,3,4-thiadiazole with

1, 2, 4-triazole and imidazole. This might be attributed to the partial saturation in the triazole and thiadiazole nucleus, resulting in the less of planarity of the thiadiazole and 1, 2, 4-triazole ring system. It is however noteworthy that the introduction of chloro and methoxy group in the phenyl moiety of these compounds tend to argument and the fungitoxicity and that the introduction of chloro group is more effective than that of 4-methoxy group. Fungicidal activity varied marginally with the fungal species. The screening data (Table-4) clearly indicates that there was significant alteration in the fungitoxicity with the change of the toxophoric group. For example introduction of chloro groups in the aryl moiety of these compounds tends to augment the fungitoxicity. The fungal activity varied but marginally with the fungal species.

Table-4. Fungicidal screening data of Imidazo [2, 1-b]-1, 3, 4-thiadiazolo [2, 3-c]-s-triazole, s-triazolo [3, 4-b]-1, 3, 4-thiadiazolo [3, 2-b] imidazo [4, 5-b] quinoxaline and bis-(s-triazolo [3, 4-b]-1, 3, 4-thiadiazolo [3,2-b] [imidazo [4, 5-b] cyclohexane]-5a, 6a-diene (III*a-g*) and (IV*a-g*).

Compd. No.	Average % inhibition against.					
	Phytophthora infestans at			Aspergillus niger at		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
IIIa	99	56	48	98	54	46
b	79	40	32	79	38	30
c	72	38	29	71	36	26
d	89	44	33	87	41	29
e	97	52	44	95	51	39
f	77	39	30	76	37	31
g	70	38	27	70	36	25
IVa	98	53	44	97	54	42
b	76	40	28	75	40	31
c	69	35	24	68	36	26
d	84	42	34	85	43	33
e	95	51	39	93	49	37
f	72	38	30	73	39	31
g	75	40	32	74	39	29
Dithane M-45	100	81	68	100	80	67

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