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Synthesis of Some New Alkyl Triazolyl Sulphides, Bis-Triazolyl Disulphides, Bis-Triazolyl Ethylene Disulphides and Triazolyl Aryl Dithiocarbamates as Antifungal Agents

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Several new alkyl triazolyl sulphides (1–12), bis-triazolyl disulphides (13–18), bis-triazolyl ethylene disulphides (19–24) and triazolyl aryl dithiocarbamates (25–48) have been prepared. Most of the compounds have been screened for their antifungal activity against two fungi, *viz. Aspergillus niger* and *Helminthosporium oryzae* and found to be antifungal. Based on the screening data, possible structure-activity relationship has been discussed.

INTRODUCTION

It is well known that mercapto (—SH) group is an important toxophore especially for pesticidal activity[1]. Several heterocyclic sulphides are reported to display antitubercular[2] and antifungal[3] activities. Further, a comparison of biocidal activity of mercapto compounds and their disulphides showed that the latter were relatively more active[4] than parent mercapto compounds. Similarly, dithiocarbamates possess —N—C=S system, which is an essential structural feature responsible for biocidal activities[5,6]. Keeping these facts in view and in continuation of our ongoing research for new antifungal agents[7], the title compounds have been prepared.

Alkyl-(3-aryloxymethyl/aryl-4-aryl-1,2,4-triazol-5-yl) sulphides (1–12) were prepared by refluxing a mixture of 3-aryloxymethyl/aryl-4-aryl-5-mercapto-1,2,4-triazoles and alkyl bromide in presence of fused sodium acetate. Oxidation of 3-aryloxymethyl/aryl-4-aryl-5-mercapto-1,2,4-triazoles by bromine afforded bis-(3-aryloxymethyl/aryl-4-aryl-1,2,4-triazol-5-yl)-disulphides (13–18). Bis-triazolyl ethylene disulphides (19–24) were prepared by refluxing a mixture of requisite triazoles, ethylene dibromide and fused sodium acetate. The condensation of aryl isothiocyanate to 3-aryloxymethyl/aryl-4-aryl-5-mercapto-1,2,4-triazoles in pyridine yielded the corresponding triazolyl aryl dithiocarbamates (25–41) (Scheme 1).

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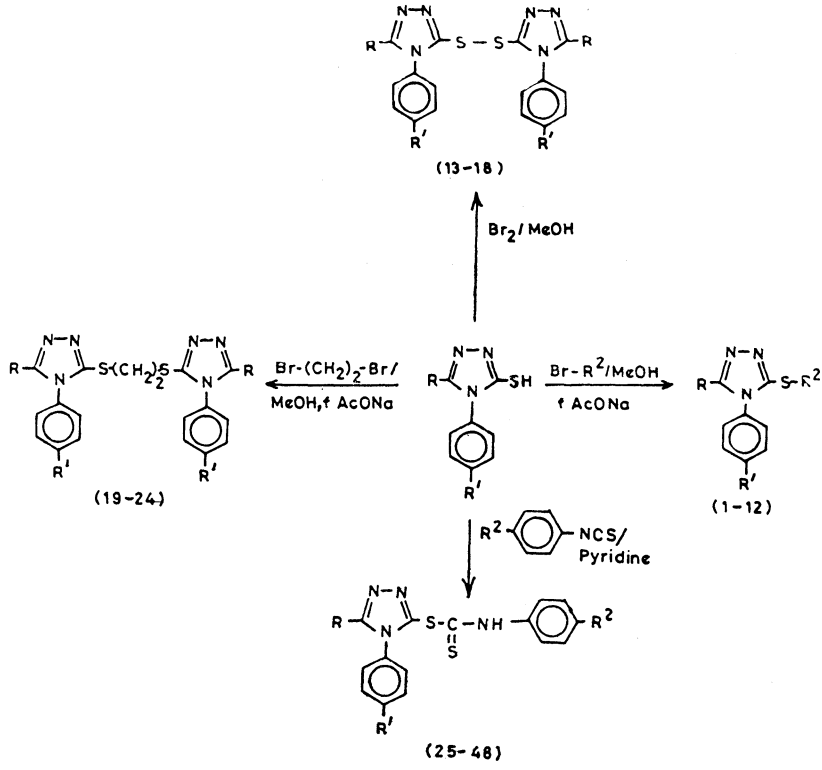

SCHEME-1

Structures of all the compounds were characterised by elemental and spectral data.

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer-710 spectrophotometer in nujol. The completion of reaction and purity of the synthesized compounds were checked by TLC.

Alkyl-(3-aryloxymethyl/aryl-4-aryl-1,2,4-triazol-5-yl) sulphides (1–12)

To a methanolic solution (25 ml) of 3-aryloxymethyl/aryl-4-aryl-5-mercapto-1,2,4-triazole[7] (0.01 M), fused sodium acetate (2.00 g) and an alkyl bromide (0.01 M) were added. The resulting mixture was gently refluxed for 4 hrs. It was cooled and then poured into water. The solid separating out was filtered, washed and recrystallised from aqueous ethanol to yield 1 54.57%, m.pt. 96°C (Found N, 12.29; S, 9.36. $C_{19}H_{21}N_3OS$ requires N, 12.39; S, 9.44%); ν_{max} 1580 (C=N), 1380 (C—CH_3), 1020 and 1240 (=C—O—C) and 760 cm^{-1} (=C—S—C).

The compounds thus prepared are given in Table 1 along with their characterisation data.

Bis-(3-aryloxymethyl/aryl-4-aryl-1,2,4-trizol-5-yl) disulphides (13-18)

To an ice-cold methanolic solution (25 ml) of 3-aryloxymethyl/aryl-4-aryl-5-mercapto-1,2,4-triazole[7] (0.01 m), a cold methanolic solution of bromine (0.005 M) was added dropwise with swirling. It was kept as such for 2 hrs and then evaporated. The residue thus obtained was washed with water, dilute sodium hydroxide, again with water and then recrystallised from aqueousethanol to yield **13** 64.52%, m.pt. 48°C(Found: N, 13.43; S, 10.21. $C_{34}H_{32}N_6O_2S_2$ requires N, 13.55; S, 10,32%); ν_{max} 1600 (C=N). 1360 (C—CH_3) and 1020 and 1250 cm^{-1} (=C—O—C).

The compounds thus prepared are given in Table 2 along with their characterisation data.

Bis-(3-aryloxymethyl/aryl-4-aryl-1,2,4-triazol-5-yl)-ethylene disulphides (19-24)

A methanolic solution (25 ml) of 3-aryloxymethyl/aryl-4-aryl-5-mercapto-1,2,4-triazole[7] (0.01 M), ethylene dibromide (0.005 M) and fused sodium acetate (2.00 g) was refluxed gently for 4 hrs. It was cooled and then poured into water. The solid separating out was filtered, washed and recrystallised from aqueous ethanol to yield **19** 66.36%, m.pt. 153°C (Found: N, 12.84; S, 10.00, $C_{36}H_{36}N_6O_2S_2$ requires N, 12.96; S, 9.88%); ν_{max} 1580 (C=N), 1400 (S—CH_2), 1380 (C—CH_3) and 1220 and 1240 cm^{-1} (=C—O—C).

The compounds thus prepared are given in Table 3 along with their characterisation data.

(3-Aryloxymethyl/aryl-4-aryl-1,2,4-triazol-5-yl)-aryl dithiocarbamates (25-48)

A solution of 3-aryloxymethyl/aryl-5-mercapto-1,2,4-triazole[7] (0.01 M) and an aryl isothiocyanate (0.01 M) in pyridine (10 ml) was refluxed for 6 hrs. It was cooled, poured into water and filtered. The residue thus obtained was washed with ether and recrystallised from aqueous ethanol to yield **25** 52.47%, m.pt. 190°C (Found: N, 12.49; S, 14.23. $C_{22}H_{18}N_4OS_2$ requires N, 15.56; S, 14.35%); ν_{max} 3200 (NH), 1540 (C=N), 1360 (C—CH_3), 1040–1240 (=C—O—C) and 1100 cm^{-1} (C=S).

The compounds thus prepared are given in Table 4 along with their characterisation data.

ANTIFUNGAL SCREENING

Thirty six compounds have been screened for their antifungal activity by agar growth technique[4] against two fungi, viz. *A. niger* and *H. oryzae*.

TABLE 1

CHARACTERISATION DATA OF ALKYL-(3-ARYLOXYMETHYL/ARYL-4-ARYL-1,2,4-TRIAZOL-5-YL) SULPHIDES

Compound No.	R	R^1	R^2	% Yield	M. Pt. °C	Molecular formula	% Found/(Calcd) N	% Found/(Calcd) S
1	$2,3\text{-}(CH_3)_2C_6H_3OCH_2-$	H–	CH_3CH_2-	54.6	96	$C_{19}H_{21}N_3OS$	12.29 (12.39)	9.36 (9.44)
2	$2,3\text{-}(CH_3)_2C_6H_3OCH_2-$	H–	$CH_3CH_2CH_2-$	78.2	67	$C_{10}H_{23}N_3OS$	11.80 (11.90)	9.13 (9.06)
3	$2,3\text{-}(CH_3)_2C_6H_3OCH_2-$	H–	$CH_3CH_2CH_2CH_2-$	58.3	47	$C_{21}H_{25}N_3OS$	11.31 (11.44)	8.62 (8.72)
4	$3,4\text{-}(CH_3)_2C_6H_3OCH_2-$	H–	CH_3CH_2-	55.2	91	$C_{19}H_{21}N_3OS$	12.28 (12.39)	9.37 (9.44)
5	$3,4\text{-}(CH_3)_2C_6H_3OCH_2-$	H–	$CH_3CH_2CH_2-$	75.1	62	$C_{20}H_{23}N_3OS$	11.78 (11.90)	8.95 (9.06)
6	$3,4\text{-}(CH_3)_2C_6H_3OCH_2-$	H–	$CH_3CH_2CH_2CH_2-$	60.8	43	$C_{21}H_{25}N_3OS$	11.33 (11.44)	8.83 (8.72)
7	$4\text{-}CH_3O.C_6H_4-$	H–	CH_3CH_2-	81.0	87	$C_{17}H_{17}N_3OS$	13.38 (13.50)	10.20 (10.29)
8	$4\text{-}CH_3O.C_6H_4-$	H–	$CH_3CH_2CH_2-$	81.5	127	$C_{18}H_{19}N_3OS$	12.80 (12.92)	9.93 (9.85)
9	$4\text{-}CH_3O.C_6H_4-$	H–	$CH_3CH_2CH_2CH_2-$	77.6	113	$C_{19}H_{21}N_3OS$	12.25 (12.39)	9.32 (9.44)
10	$4\text{-}OH.C_6H_4-$	H–	CH_3CH_2-	81.8	169	$C_{16}H_{15}N_3OS$	14.02 (14.14)	10.89 (10.77)
11	$4\text{-}OH.C_6H_4-$	H–	$CH_3CH_2CH_2-$	79.4	97	$C_{17}H_{17}N_3OS$	13.38 (13.50)	10·18 (10.29)
12	$4\text{-}OH.C_6H_4-$	H–	$CH_3CH_2CH_2CH_2-$	69.2	244	$C_{18}H_{19}N_3OS$	12.81 (12.92)	9.74 (9.85)

TABLE 2

CHARACTERISATION DATA OF BIS-(3-ARYLOXYMETHYL/ARYL-4-ARYL-1,2,4-TRIAZOL-5-YL)-DISULPHIDES

Compd. No.	R	R^1	% Yield	M.Pt. °C	Molecular formula	% Found/(Calcd.) N	S
13	2,3-$(CH_3)_2C_6H_3OCH_2$–	H–	64.5	48	$C_{34}H_{32}N_6O_2S_2$	13.43 (13.55)	10.21 (10.32)
14	3,4-$(CH_3)_2C_6H_3OCH_2$–	H–	62.9	42	$C_{34}H_{32}N_6O_2S_2$	13.44 (13.55)	10.41 (10.32)
15	α-$C_{10}H_7OCH_2$–	H–	75.3	119	$C_{38}H_{28}N_6O_2S_2$	12.52 (12.65)	9.73 (9.64)
16	4-$CH_3O.C_6H_4$–	H–	62.1	157	$C_{30}H_{24}N_6O_2S_2$	14.75 (14.89)	11.23 (11.35)
17	4-$OH.C_6H_4$–	H–	62.7	215	$C_{28}H_{20}N_6O_2S_2$	15.56 (15.67)	11.82 (11.94)
18	4-$OH.C_6H_4$–	Cl–	56.9	155	$C_{28}H_{18}Cl_2N_6O_2S_2$	13.76 (13.88)	10.47 (10.58)

TABLE 3

CHARACTERISATION DATA OF BIS-(3-ARYLOXYMETHYL/ARYL-4-ARYL-1,2,4-TRIAZOL-5-YL)-ETHYLENE DISULPHIDES

Compd. No.	R	R^1	% Yield	M.Pt. °C	Molecular formula	% Found/(Calcd.) N	S
19	2,3-$(CH_3)_2C_6H_3OCH_2$–	H–	66.4	153	$C_{36}H_{36}N_6O_2S_2$	12.84 (12.96)	10.00 (9.88)
20	3,4-$(CH_3)_2C_6H_3OCH_2$–	H–	64.2	139	$C_{36}H_{36}N_6O_2S_2$	12.83 (12.96)	9.78 (9.88)
21	α-$C_{10}H_7OCH_2$–	H–	67.1	185	$C_{40}H_{32}N_6O_2S_2$	12.03 (12.14)	9.14 (9.25)
22	4-$CH_3O.C_6H_4$–	H–	55.7	230	$C_{32}H_{58}N_6O_2S_2$	14.07 (14.19)	10.69 (10.81)
23	4-$OH.C_6H_4$–	H–	56.0	>360	$C_{30}H_{24}N_6O_2S_2$	14.77 (14.89)	11.22 (11.35)
24	4-$OH.C_6H_4$–	Cl–	67.0	265	$C_{30}H_{22}Cl_2N_6O_2S_2$	13.15 (13.27)	10.21 (10.11)

TABLE 4

CHARACTERISATION DATA OF (3-ARYLOXYMETHYL/ARYL-4-ARYL-1,2,4-TRIAZOL-5-YL)-ARYL DITHIOCARBAMATES

Compd. No.	R	R^1	R^2	% Yield	M.Pt. °C	Molecular formula	% Found/(Calcd.) N	S
25	2,3-$(CH_3)_2C_6H_3OCH_2$–	H–	H–	52.5	190	$C_{24}H_{22}N_4OS_2$	12.49 (12.56)	14.23 (14.35)
26	2,3-$(CH_3)_2C_6H_3OCH_2$–	H–	Cl–	50.8	197	$C_{24}H_{21}ClN_4OS_2$	11.54 (11.65)	13.21 (13.32)
27	2.3-$(CH_3)_2C_6H_3OCH_2$–	H–	C_2H_5O–	50.4	188	$C_{26}H_{26}N_4O_2S_2$	11.32 (11.43)	13.17 (13.06)
28	2,3-$(CH_3)_2C_6H_3OCH_2$–	Cl–	H–	51.0	159	$C_{24}H_{21}ClN_4OS_2$	11.55 (11.65)	13.22 (13.32)
29	2,3-$(CH_3)_2C_6H_3OCH_2$–	Cl–	Cl–	51.5	157	$C_{24}H_{20}Cl_2N_4OS_2$	10.75 (10.87)	12.50 (12.43)
30	2,3-$(CH_3)_2C_6H_3OCH_2$–	Cl–	C_2H_5O–	50.9	144	$C_{26}H_{25}ClN_4O_2S_2$	10.55 (10.68)	12.07 (12.20)
31	3,4-$(CH_3)_2C_6H_3OCH_2$–	H–	H–	54.9	157	$C_{24}H_{22}N_4OS_2$	12.48 (12.56)	14.46 (14.35)
32	3,4-$(CH_3)_2C_6H_3OCH_2$–	H–	Cl–	53.3	160	$C_{24}H_{21}ClN_4OS_2$	11.55 (11.65)	13.22 (13.32)
33	3,4-$(CH_3)_2C_6H_3OCH_2$–	H–	C_2H_5O–	54.1	145	$C_{26}H_{26}N_4O_2S_2$	11.33 (11.43)	13.14 (13.06)
34	3,4-$(CH_3)_2C_6H_3OCH_2$–	Cl–	H–	52.9	140	$C_{24}H_{21}ClN_4OS_2$	11.54 (11.65)	13.21 (33.32)
35	3,4-$(CH_3)_2C_6H_3OCH_2$–	Cl–	Cl–	64.0	150	$C_{24}H_{20}Cl_2N_4OS_2$	10.74 (10.87)	12.31 (12.43)
36	3,4-$(CH_3)_2C_6H_3OCH_2$–	Cl–	C_2H_5O–	52.4	130	$C_{26}H_{25}ClN_4O_2S_2$	10.56 (10.68)	12.08 (12.20)

Table 4 (contd.)

Compd. No.	R	R^1	R^2	% Yield	M.pt. °C	Molecular formula	% Found/(Calcd.) N	% Found/(Calcd.) S
37	4-$CH_3O.C_6H_4$–	H–	H–	63.4	195	$C_{22}H_{18}N_4OS_2$	13.29 (13.39)	15.20 (15.31)
38	4-$CH_3O.C_6H_4$–	H–	Cl–	52.4	157	$C_{22}H_{17}ClN_4OS_2$	12.26 (12.38)	14.03 (14.14)
39	4-$CH_3O.C_6H_4$–	H–	C_2H_5O–	62.3	147	$C_{24}H_{22}N_4O_2S_2$	12.02 (12.12)	13.96 (13.85)
40	4-$CH_3O.C_6H_4$-	Cl–	H–	65.6	188	$C_{22}H_{17}ClN_4OS_2$	12.28 (12.38)	14.25 (14.14)
41	4-$CH_3O.C_6H_4$–	Cl–	Cl–	74.5	180	$C_{22}H_{16}Cl_2N_4OS_2$	11.41 (11.50)	13.03 (13.14)
42	4-$CH_3O.C_6H_4$–	Cl–	C_2H_5O–	77.5	204	$C_{24}H_{21}ClN_4O_2S_2$	11.17 (11.28)	12.74 (12.89)
43	4-$OH.C_6H_4$–	H–	H–	62.9	272	$C_{21}H_{16}N_4OS_2$	13.74 (13.86)	15.72 (15.84)
44	4-$OH.C_6H_4$–	H–	Cl–	53.6	266	$C_{21}H_{15}ClN_4OS_2$	12.63 (12.77)	14.46 (14.59)
45	4-$OH.C_6H_4$–	H–	C_2H_5O–	59.2	260	$C_{23}H_{20}N_4O_2S_2$	12.38 (12.50)	14.40 (14.29)
46	4-$OH.C_6H_4$–	Cl–	H–	55.2	289	$C_{21}H_{15}ClN_4OS_2$	12.65 (12.77)	14.70 (14.59)
47	4-$OH.C_6H_4$–	Cl–	Cl–	55.6	283	$C_{21}H_{14}Cl_2N_4OS_2$	11.69 (11.84)	13.40 (13.53)
48	4-$OH.C_6H_4$–	Cl–	C_2H_5O–	59.1	249	$C_{23}H_{19}ClN_4O_2S_2$	11.50 (11.61)	13.15 (13.26)

The fungus was planted in agar growth media mixed with test compounds. The diameter of the fungus colony was measured at three different concentrations, viz. 1000, 100 and 10 ppm. The inhibition of the fungus growth was determined as the difference in growth between the control plate and those treated with the test compound. The activity of the test compounds was compared with commercial fungicide Carbendazim under similar conditions. The number of replications in each case was three. The percentage inhibition was calculated as:

$$\text{Percentage inhibition} = \frac{(C - T)}{C} \times 100$$

C = diameter of fungus colony (in mm) in the control plate after 96 hrs.

T = diameter of fungus colony (in mm) in the treated plate after 96 hrs.

RESULTS AND DISCUSSION

The results show* that all the compounds under investigation were fairly toxic against both the fungi at 1000 ppm, but their toxicity decreased markedly on dilution at 1000 ppm and 100 ppm. They were, however. more toxic against *H. oryzae* than *A. niger*. Dithiocarbamates displayed good level of toxicity than other compounds screened. Further, alkyl sulphides, bis-triazolyl disulphides and bis-triazolyl ethylene disulphides displayed nearly the same level of fungitoxicity and they showed better toxicity than their parent triazoles[7]. Compounds 30 and 36 were found to be more fungitoxic against both the fungi and the toxicity displayed by them was quite comparable with commercial fungicide, carbendazim at 1000 ppm. In general, the aryloxy derivatives were more potent than aryl derivatives and compounds with methoxy and/or chlorine groups displayed better fungitoxicity.

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