Chemotherapeutic Agents. IX. Synthesis and Pesticidal Activities of Bis[4-aryl/alkyl-1,2,4-triazoline-5-thione-3-yl]alkanes and 1-Aryl/alkyl-3-[4-(4-aryl/alkyl-1,2,4-triazoline-5-thione-3-yl)phenyl]thiourea and Related Compounds

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Various bis[4-aryl/alkyl-1,2,4-triazoline-5-thione-3-yl]alkanes (**3**) were prepared from base cyclization of bis thiosemicarbazide **2** and transformed into sulphides by reaction with different alkyl halides in alkaline medium. These compounds were further oxidised to sulphones **5** with acidic potassium permanganate. 1-Aryl-3-[4-(4-aryl/alkyl-1,2,4-triazoline-3-thione-5-yl)phenyl]thioureas (**8**) were prepared in two steps from *p*-aminophenylhydrazide (**6**) and aryl/alkylisothiocyanates. Alkylation of **8** with different alkyl halides yielded exclusively sulphides **9**. Some sulphides **12** and Mannich bases **13** from 5-(*p*-fluorophenyl)-1,3,4-oxadiazol-2-thione (**11**) were also prepared to evaluate their pesticidal activities. All the prepared compounds were screened for pesticidal activities but none of them exhibited any significant activity.

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As a part of our research program to develop new potential pesticidal agents, triazoles from bis hydrazide **1** and *p*-aminophenylhydrazide (**6**) were synthesized. The therapeutic importance of 1,2,4-triazoles as antibacterial [1-3], antifungal [4] and insecticidal [5] agents is well documented. Recently Dobosz [6] has synthesized and reported the antitubercular activity of thiosemicarbazido-1,2,4-triazole **I** and bis 1,2,4-triazole **II**. Both compounds possess the active pharmacophore $\begin{matrix}HN\\HN\end{matrix}>C=S$ either in isolated or cyclic systems.

Taking structural features into consideration it was thought worthwhile to prepare compounds analogous to **I** and **II** with slight modifications in bridge length and point of attachment at triazole rings.

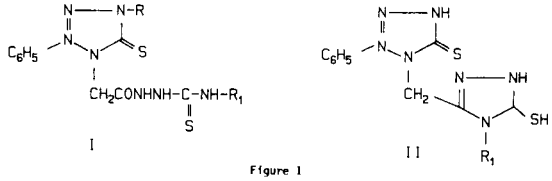
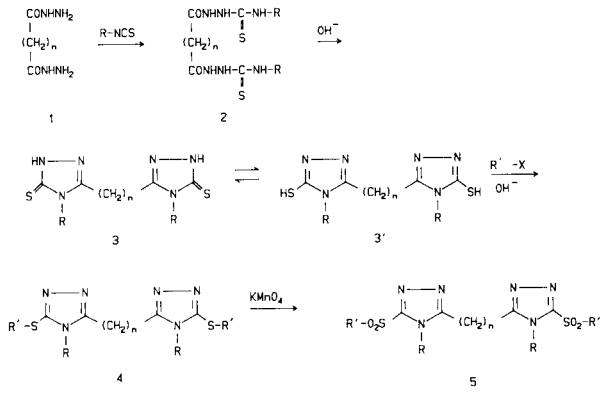


Figure 1

Bis-[4-aryl/alkyl-1,2,4-triazolin-5-thion-3-yl]alkanes **3** were prepared from bis hydrazide **1** in two steps. Initially, hydrazides **1** were converted into bis thiosemicarbazide by reaction with aryl/alkylisothiocyanate in boiling ethanol. Base cyclization of the resulting thiosemicarbazides **2** provided bistriazoles **3**, which were alkylated with different alkyl halides to bis[4-aryl/alkyl-5-alkylthio-1,2,4-triazol-3-yl]alkanes **4** in alkaline medium. The sulphides **4** were oxidised to the corresponding bis[4-aryl/alkyl-5-alkylsul-

Scheme 1



Scheme 2

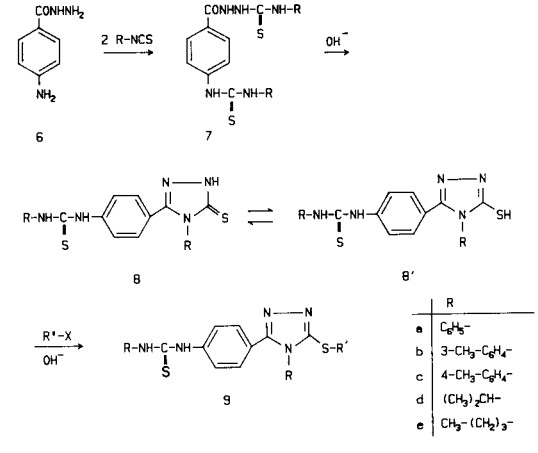
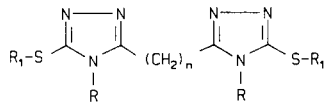


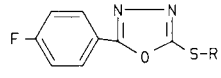
Table 1



Bis[4-alkyl/aryl-3-alkylthio-1,2,4-triazol-5-yl]alkanes **3,4**

Compound		R	R'	MP	Molecular Formula	M+	Elemental Analysis (%) Calcd.			Found		
No.	n			°C			C	H	N	C	H	N
1	0	CH_3-	H-	>300	$C_6H_8N_6S_2$	228	31.58	3.51	36.84	31.83	3.68	36.52
2	0	C_2H_5-	H-	>300	$C_8H_{12}N_6S_2$	256	37.50	4.69	32.81	37.81	4.23	33.23
3	0	C_2H_5-	CH_3-	168	$C_{10}H_{16}N_6S_2$	284	42.25	5.63	29.58	42.53	5.78	30.01
4	1	C_2H_5-	H-	280	$C_9H_{14}N_6S_2$	270	40.00	5.19	31.11	40.25	5.25	31.53
5	1	C_2H_5-	CH_3-	151	$C_{11}H_{18}N_6S_2$	298	44.30	6.04	28.19	44.45	6.32	28.47
6	1	$(CH_3)_2CH$-	2,4-$(NO_2)_2C_6H_3$-	190	$C_{25}H_{22}N_{10}O_8S_2$	630	43.81	3.49	22.22	44.23	3.68	22.52
7	1	$(CH_3)_2CH$-	$C_6H_5CH_2$-	135	$C_{25}H_{30}N_6S_2$	478	62.76	6.28	17.57	62.81	6.35	17.63
8	2	C_2H_5-	H-	>300	$C_{10}H_{16}N_6S_2$	284	42.25	5.63	29.58	42.38	5.75	29.25
9	2	C_2H_5-	CH_3-	152	$C_{12}H_{20}N_6S_2$	312	46.15	6.41	26.92	46.32	6.51	26.73
10	2	C_2H_5-	$C_6H_5CH_2$-	144	$C_{24}H_{28}N_6S_2$	464	62.07	6.03	18.10	62.35	6.31	18.43
11	2	3-FC_6H_4-	H-	>300	$C_{18}H_{14}F_2N_6S_2$	416	51.92	3.37	20.19	52.06	3.53	20.55
12	2	3-FC_6H_4-	CH_3-	192	$C_{20}H_{18}F_2N_6S_2$	444	54.05	4.05	18.92	54.38	4.51	18.78
13	2	3-FC_6H_4-	$C_6H_5CH_2$-	173	$C_{32}H_{26}F_2N_6S_2$	596	64.43	4.36	14.09	64.73	4.21	14.38
14	2	3-FC_6H_4-	3,4$Cl_2C_6H_3CH_2$-	217	$C_{32}H_{22}Cl_4F_2N_6S_2$	734	52.32	3.00	11.44	52.56	3.23	11.78
15	2	3-$CH_3C_6H_4$-	CH_3-	220	$C_{22}H_{24}N_6S_2$	436	60.55	5.50	19.27	60.72	5.38	19.57
16	2	3-$CH_3C_6H_4$-	CH_2=CH-CH_2-	190	$C_{26}H_{28}N_6S_2$	488	63.93	5.74	17.21	63.58	5.35	17.59
17	2	3-$CH_3C_6H_4$-	$CH_3(CH_2)_4$-	165	$C_{30}H_{40}N_6S_2$	548	65.69	7.30	15.33	65.32	7.56	15.45
18	2	3-$CH_3C_6H_4$-	$C_6H_5CH_2$-	215	$C_{34}H_{32}N_6S_2$	588	69.39	5.44	14.29	69.46	5.32	14.53
19	2	3-$CH_3C_6H_4$-	2,4-$(NO_2)_2C_6H_3$-	255	$C_{32}H_{24}N_{10}O_8S_2$	740	51.89	3.24	18.92	52.18	3.56	19.27
20	4	$(CH_3)_2CH$-	CH_3-	170	$C_{16}H_{28}N_6S_2$	368	52.17	7.61	22.83	52.37	7.32	22.69
21	4	3-$CH_3C_6H_4$-	CH_3-	170	$C_{24}H_{28}N_6S_2$	464	62.07	6.03	18.10	62.23	6.31	18.39
22	4	3-$CH_3C_6H_4$-	CH_2=CH-CH_2-	145	$C_{28}H_{32}N_6S_2$	516	65.12	6.20	16.28	65.45	6.38	16.53
23	4	3-$CH_3C_6H_4$-	$CH_3(CH_2)_4$-	190	$C_{32}H_{44}N_6S_2$	576	66.67	7.63	14.58	66.82	7.58	14.32
24	4	3-$CH_3C_6H_4$-	$C_6H_5CH_2$-	165	$C_{36}H_{36}N_6S_2$	616	70.13	5.84	13.64	70.27	5.39	13.75

Table 2



2-Aralkylthio-5-(*p*-fluorophenyl)-1,3,4-oxadiazoles **12**

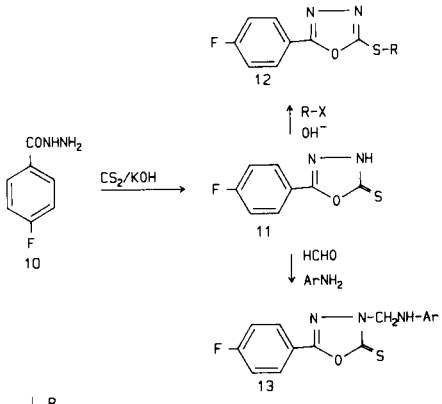
Compound No.	R	MP °C	Molecular Formula	Elemental Analysis (%) Calcd. C	H	N	Found C	H	N
12a	4-$NO_2C_6H_4CH_2$-	144	$C_{15}H_{10}FN_3O_3S$	54.38	3.02	12.69	54.22	3.12	13.16
12b	2-$NO_2C_6H_4CH_2$-	152	$C_{15}H_{10}FN_3O_3S$	54.38	3.02	12.69	54.12	3.28	13.09
12c	2,4-$(NO_2)_2C_6H_3$-	188	$C_{14}H_7FN_4O_5S$	46.41	1.97	15.47	46.08	1.94	15.42
12d	4-$ClC_6H_4CH_2$-	128	$C_{15}H_{10}ClFN_2OS$	56.16	8.74	8.74	56.01	8.73	8.38

phonyl-1,2,4-triazol-3-yl]alkanes **5** with potassium permanganate.

1-Aryl/alkyl-3-[4-(4-aryl/alkyl-1,2,4-triazoline-5-thion-3-yl)phenyl]thioureas **8** were prepared by intramolecular cyclocondensation of thiosemicarbazides **7**, which were obtained by the reaction of *p*-aminophenylhydrazide (**6**) with aryl/alkylisothiocyanate. The thiones **8** were transformed into sulphides **9** by reaction with equimolar quantities of alkyl halides in 4% alcoholic sodium hydroxide.

5-(*p*-Fluorophenyl)-1,3,4-oxadiazol-2-thione (**11**) was syn-

Scheme 3



	R
a	4-$NO_2C_6H_4CH_2$-
b	2-$NO_2C_6H_4CH_2$-
c	2,4-$(NO_2)_2C_6H_3CH_2$-
d	4-$ClC_6H_4CH_2$-

thesized by the procedure reported earlier [7-9] and transformed into 5-(*p*-fluorophenyl)-2-aralkylthio-1,3,4-oxadiazoles **12** by reaction with different alkyl halides on **10** in DMF using potassium carbonate as a base. The ir spectrum of 2-(*p*-nitrobenzylthio)-5-(*p*-fluorophenyl)-1,3,4-oxadiazole (**12a**) showed peaks at 1520 and 1340 cm^{-1} due to *sym* and *asym* stretching vibrations of the NO_2 group. The peak at 1590 cm^{-1} was assigned for CH-bending vibrations. Finally, 3-trifluoromethylphenylaminomethyl-5-(*p*-fluorophenyl)-1,3,4-oxadiazole-2-thione (**13**) was obtained by reaction of **12** with formaldehyde and 3-trifluoromethylaniline.

All the compounds were screened for antifungal, antiviral and antibacterial activities but none of them exhibited any significant activities.

EXPERIMENTAL

Melting points were determined in an open capillary on a Thomas-Hoover apparatus and are uncorrected. The ir and mass spectra of the compounds were recorded on a Perkin Elmer spectrometer 157 and Jeol JMs D-300 spectrometer respectively. The nmr spectra were recorded on a Perkin Elmer R-32 spectrometer in deuteriochloroform using TMS as internal standard.

Bis(4-aryl/alkyl-5-thio-1,2,4-triazol-3-yl)alkanes **3**.

These compounds were synthesized by base cyclization of bis(4-aryl/alkyl thiosemicarbazido)alkanes (**2**) as described earlier [10].

Bis(4-aryl/alkyl-5-alkylthio-1,2,4-triazol-3-yl)alkanes **4**.

A solution of bis(4-aryl/alkyl-5-thio-1,2,4-triazol-3-yl)alkane in 8% aqueous sodium hydroxide was treated with two equivalents of alkyl halide and stirred for 2-3 hours at room temperature. During this period, the precipitate obtained was filtered, washed with water and crystallized from a suitable solvent.

Compounds thus prepared are listed in Table 1 with their relevant data.

Bis(4-phenyl-5-benzylsulphonyl-1,2,4-triazol-3-yl)octane (**5**).

A solution of bis[4-phenyl-5-benzylthio-1,2,4-triazol-3-yl]octane (0.5 g) in glacial acetic acid (5 ml) was treated dropwise with 3% aqueous potassium permanganate under stirring till the violet colour persisted. The precipitate obtained was filtered, washed with water and crystallized from acetic acid, mp 135°, yield 45%; ^1H nmr (deuteriochloroform): δ 2.51 (t, 2 CH_2), 1.2-1.7 (m, 6 CH_2), 3.49 (s, S-CH_2), 7.21-7.51 (m, Ar-H).

Anal. Calcd. for $C_{38}H_{40}N_6O_4S_2$: C, 64.41; H, 5.65; N, 11.86. Found: C, 64.81; H, 5.25; N, 11.94.

1-(4-Phenylthioureido)benzoyl-4-phenylthiosemicarbazide (**7a**).

A mixture of *p*-aminophenylhydrazide (1.5 g) and phenyl isothiocyanate (2.8 g) was refluxed in ethanol for 2 hours. During this period, the precipitate obtained was filtered and crystallized from water-DMF, yield 78%, mp 200°; ms: m/z = 421 (M^+).

Anal. Calcd. for $C_{21}H_{19}N_5OS_2$: C, 59.86; H, 4.51; N, 16.63. Found: C, 60.12; H, 4.38; N, 16.35.

1-(4-[*m*-Tolyl]thioureido)benzoyl-4-(*m*-tolyl)thiosemicarbazide (**7b**).

This compound was prepared from **6** and *m*-tolyl isothiocyanate as described above, yield 75%, mp 180-185°.

Anal. Calcd. for $C_{23}H_{23}N_5OS_2$: C, 61.47; H, 4.68; N, 15.59. Found: C, 61.76; H, 4.78; N, 15.99.

1-(4-[*p*-Tolyl]thioureido)benzoyl-4-(*p*-tolyl)thiosemicarbazide (**7c**).

The compound was obtained by the reaction of **6** with *p*-tolyl isothiocyanate in 80% yield as described in the preceding experiment, mp 175°; ms: m/z = 449 (M^+).

Anal. Calcd. for $C_{23}H_{23}N_5OS_2$: C, 61.47; H, 4.68; N, 15.39. Found: C, 61.72; H, 4.38; N, 15.79.

1-Phenyl-3-[4-(4-phenyl-1,2,4-triazoline-5-thion-3-yl)phenyl]thiourea (**8a**).

A solution of **7a** (1 g) in aqueous sodium hydroxide (50%, 10 ml) was refluxed for 3 hours, cooled and filtered. The filtrate was neutralized with dilute hydrochloric acid and the precipitate was filtered. The crude product was crystallized with DMF-water, yield 75%, mp 190-195°; ms: m/z = 403 (M^+).

Anal. Calcd. for $C_{21}H_{17}N_5S_2$: C, 62.53; H, 4.22; N, 16.62. Found: C, 62.78; H, 4.38; N, 16.85.

1-(*m*-Tolyl)-3[4-(4-(*m*-tolyl)-1,2,4-triazoline-5-thion-3-yl)phenyl]thiourea (**8b**).

The title compound was prepared by refluxing **7b** (1 g) in 5% aqueous sodium hydroxide for 3 hours and isolated as described above, yield 67%, mp 210°; ms: m/z = 431 (M^+).

Anal. Calcd. for $C_{23}H_{21}N_5S_2$: C, 64.04; H, 4.87; N, 16.24. Found: C, 64.35; H, 5.12; N, 16.38.

1-(*p*-Tolyl)-3-[4-(4-(*p*-tolyl)-1,2,4-triazoline-5-thion-3-yl)phenyl]thiourea (**8c**).

Compound **8c** was obtained by refluxing a solution of **7c** (1 g) in aqueous sodium hydroxide (10 ml, 5%) as described above, yield 80%, mp 228°; ms: m/z = 431 (M^+).

Anal. Calcd. for $C_{23}H_{21}N_5S_2$: C, 64.04; H, 4.87; N, 16.24. Found: C, 64.40; H, 4.75; N, 16.64.

1-Isopropyl-3-[4-(4-isopropyl-1,2,4-triazoline-5-thion-3-yl)phenyl]-thiourea (**8d**).

A mixture of *p*-aminophenylhydrazide (1.5 g) and isopropyl isothiocyanate (2.0 g) in ethanolic sodium hydroxide (5%, 15 ml) was refluxed for 5 hours, cooled and filtered. The filtrate was neutralized with acetic acid. The white precipitate thus obtained was filtered, washed with water and finally crystallized from water-DMF, yield 60%, mp 210-215°.

Anal. Calcd. for $C_{15}H_{21}N_5S_2$: C, 53.73; H, 6.27; N, 20.90. Found: C, 53.85; H, 5.92; N, 21.15.

1-(*n*-Butyl)-3-[4-(4-(*n*-butyl)-1,2,4-triazoline-5-thion-3-yl)phenyl]-thiourea (**8e**).

This substance was prepared from **6** (1.5 g) and *n*-butyl isothiocyanate (2.4 g) as described in the preceding experiment, yield 55%, mp 180°; ms: m/z = 363 (M^+).

Anal. Calcd. for $C_{17}H_{25}N_5S_2$: C, 56.20; H, 6.89; N, 19.28. Found: C, 56.35; H, 6.56; N, 19.58.

1-Phenyl-3[4-(5-benzylthio-4-phenyl-1,2,4-triazol-3-yl)phenyl]thiourea (**9**).

A solution of **8a** (0.8 g) in ethanolic sodium hydroxide (6 ml) was stirred with benzyl chloride (0.26 g) for 5 hours. After adding excess water to the reaction mixture, the precipitate was filtered, washed with water and finally crystallized from DMF-water, mp 170°; ms: m/z = 493 (M^+).

Anal. Calcd. for $C_{28}H_{23}N_5S_2$: C, 68.15; H, 4.66; N, 14.20. Found: C, 68.36; H, 4.92; N, 14.38.

2-(*p*-Nitrobenzylthio)-5-(*p*-fluorophenyl)-1,3,4-oxadiazole (**12a**).

An equimolar mixture of **10** and *p*-nitrobenzyl bromide in DMF was stirred with anhydrous potassium carbonate for 2-3 hours at room temperature. The precipitate obtained after dilution with water was filtered off, washed with water and crystallized from DMF-water, yield 20%.

Other compounds prepared similarly are presented in Table 2 with their relevant data.

3-Trifluoromethylphenylaminomethyl-5-(*p*-fluorophenyl)-1,3,4-oxadiazole-2-thione (**13**).

An alcoholic solution of **11** (0.5 g) was treated with an equimolar amount of 3-trifluoromethylaniline (0.42 g) and formaldehyde (0.3 g, 38%) at 0°. After 2 hours a white precipitate separated, which was filtered and crystallized from acetone, mp 142°.

Anal. Calcd. for $C_{16}H_{11}N_3F_4OS$: C, 52.03; H, 2.98; N, 11.44. Found: C, 52.31; H, 3.22; N, 11.27.

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