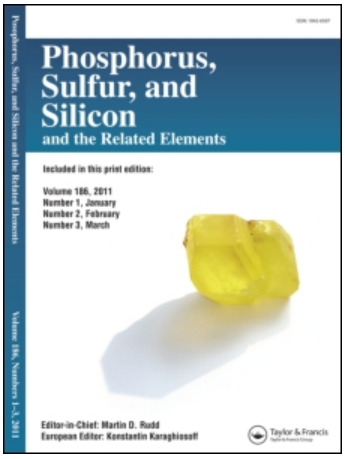

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SYNTHESIS AND REACTIONS OF N-CHLOROMETHYL-1,2,4-TRIAZOLES WITH SULFUR AND OXYGEN NUCLEOPHILES

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SYNTHESIS AND REACTIONS OF N-CHLOROMETHYL-1,2,4-TRIAZOLES WITH SULFUR AND OXYGEN NUCLEOPHILES

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2-Chloromethyl-1,2,4-triazole-3-thione derivatives (**1** and **2**) were synthesized through the hydroxymethyl derivatives, and reacted with alkyl, aryl and heteroaryl thiols to give the corresponding sulfides (**3–15**). Compounds **1** and **2** were reacted with sodium alkoxides and phenoxide affording the corresponding ethers (**19–24**). Transformation of C=S to C=O has been achieved by the action of mercuric acetate. Condensation of compounds **1** and **2** with hydrazine, phenylhydrazine and hydroxylamine yielded bicyclic condensation products **27–32**. Activity of the newly synthesized compounds against different kinds of fungi has been investigated in vitro.

Key words: 2-Chloromethyl-1,2,4-triazole-3-thione; thiols; alkoxides.

INTRODUCTION

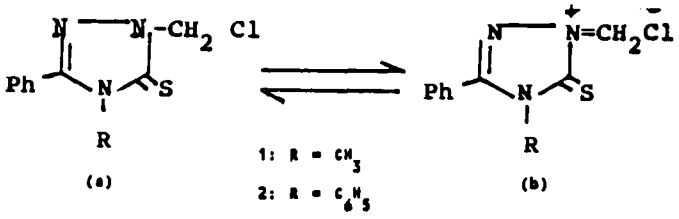
The s-triazole derivatives have found extensive investigations in recent years due to their useful application in different areas of biological activity[1–5] and as industrial intermediates.[6,7] Some derivatives have tuberculotherapeutic,[1] antifungal,[2] anti-inflammatory[3] and antibacterial activity.[4] Other derivatives show diuretic and natriuretic activity.[5]

The present work emphasized the synthesis of new s-triazole derivatives and testing of their antifungal activity against different kinds of fungi.

For this purpose 2-chloromethyl-4-methyl-5-phenyl-1,2,4-triazole-3-thione (**1**) and 2-chloromethyl-4,5-diphenyl-1,2,4-triazole-3-thione (**2**) were chosen as suitable starting materials.

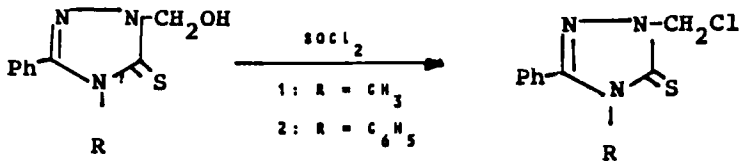
RESULTS AND DISCUSSION

The free bases of compounds **1** and **2** are stable enough to be handled, unlike the N-chloromethyl derivatives of more basic azoles. The electron withdrawing ability of the adjacent C=S group is thought to be responsible for the stability of the covalent form (**a**) relative to the ionic form (**b**).[8,9]



† To whom the correspondence should be addressed.

Compounds **1** and **2** were prepared from the corresponding hydroxymethyl derivatives[10-12] by the action of neat thionyl chloride at room temperature in 80% to 75% yields, respectively. Their structure was confirmed on the basis of their elemental and spectral analyses.



The IR spectrum (KBr, Cm^{-1}) of compounds **1** and **2** revealed the absence of the absorption bands corresponding to the hydroxyl group while exhibiting characteristic absorption bands corresponding to C—Cl at [780 (**1**) and 790 (**2**)], C=S at 1100 (**1**, **2**) and C=N at [1600 (**1**), 1590 (**2**)]. The ^{1}HNMR spectrum ($CDCl_3$, δ) of compound **1** showed characteristic signals corresponding to 5 H aromatic (7.39, s), 2 H aliphatic N—CH_2—Cl (6.3, s) and 3 H aliphatic N—CH_3 (3.98, s). The ^{1}HNMR spectrum ($CDCl_3$, δ) of compound **2** showed signals corresponding to 10 H aromatic (7.68–7.2, m) and 2 H aliphatic N—CH_2—Cl (6.17, s).

Compounds **1** and **2** were allowed to react with alkyl, aryl and heteroaryl thiols in presence of sodium ethoxide to give the corresponding sulfides **3–15** (Table I). The structure of these sulfides was proved by elemental analyses, IR and ^{1}HNMR spectra. The IR spectra (KBr, Cm^{-1}) of the resulted sulfides showed the absence of the absorption bands of C=S, C=N- and C—H groups (Table II). The ^{1}HNMR showed characteristic signals according to the proposed structures (Table III).

Different procedures have been developed for C=S → C=O transformation, especially by the action of soft borderline electrophiles.[13] Recently, it has been found that mercuric acetate has the ability to effect such transformation.[10] It was of interest to study its effect on the newly synthesized sulfides with 2-thiocarbonyl group at the 3-position, where transformation to their oxygen synthons (**16–18**) took place at moderate yields (Scheme 1). The IR spectra of the oxygen analogues showed the absence of C=S absorption bands while exhibiting characteristic C=O absorption at 1700, 1700 and 1710 cm^{-1}, respectively.

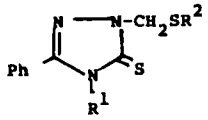
Compounds **1** and **2** were allowed to react with sodium alkoxides and phenoxide to give the corresponding ethers (**19–24**, Table IV). The IR spectra (KBr, Cm^{-1}) of these ethers showed the absence of the absorption band corresponding to C—Cl, while exhibiting absorption bands corresponding to C—O—C grouping (Table V). Again, C=S → C=O transformation for these compounds has been effected (**25**, **26**) by the action of mercuric acetate in boiling methanol (Scheme 1).

The IR (KBr) of compounds **25** and **26** showed the absence of the C=S absorption band while exhibiting characteristic C=O absorption at 1700 and 1710 Cm^{-1}, respectively.

Condensation of compounds **1** and **2** with ammonia derivatives, namely hydrazine, phenylhydrazine, and hydroxylamine in refluxing xylene, afforded the bicyclic condensation products (**27–32**), (Scheme 2). The IR spectra and ^{1}HNMR spectra of these compounds confirm the proposed structures.

TABLE I

2-(Alkyl, aryl or heteroaryl) thiomethyl-4,5-disubstituted-3-thiones (3–15)



Compd No.	R^1	R^2	m.p. °C	yield %	Found/Calculated C%	H%	N%
3	C_6H_5	n-propyl	130	50	63.14 63.34	5.54 5.57	12.12 12.32
4	CH_3	isopropyl	135	29	55.72 55.90	6.03 6.09	15.00 15.05
5	C_6H_5	isopropyl	150	60	63.04 63.34	5.51 5.57	12.19 12.32
6	CH_3	cyclohexyl	100	65	60.00 60.18	6.49 6.58	13.00 13.16
7	C_6H_5	cyclohexyl	159	70	66.00 66.14	6.00 6.03	11.08 11.02
8	CH_3	p-chlorophenyl	115	45	54.90 55.25	4.00 4.02	12.00 12.08
9	C_6H_5	p-chlorophenyl	162	59	61.05 61.54	3.87 3.91	10.00 10.25
10	CH_3	pyridyl	105	60	56.81 57.12	4.40 4.45	17.70 17.83
11	C_6H_5	pyridyl	145	63	63.70 63.83	4.20 4.25	14.59 14.89
12	CH_3	2-benzoxazolyl	135	65	57.60 57.62	3.90 3.95	15.81 15.81
13	C_6H_5	2-benzoxazolyl	190	73	63.06 63.46	4.00 3.84	13.38 13.46
14	CH_3	2-benzothiazolyl	100	70	55.00 55.13	3.58 3.70	15.00 15.13
15	C_6H_5	2-benzothiazolyl	165	66	61.00 61.11	3.50 3.70	12.70 12.96

TABLE II

IR spectral data of compounds 3–15 (KBr., Cm^{-1}

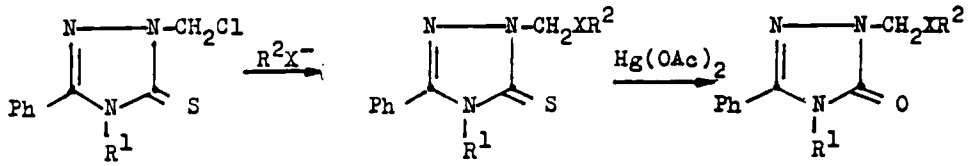
Compound No.	C-S-C	C=S	C=N	C-H
3	690 s	1090 w	1600 m	3030-2930 br
4	689 m	1180 s	1550 s	3040-2900 w
5	690 s	1160 w	1600 m	2920 m
6	688 s	1180 s	1560 s	2840-2820 s
7	690 s	1100 w	1590 m	2920 s
8	690 s	1100 s	1560 m	2980 w
9	690 m	1100 w	1590 w	3030-2920 w
10	680 m	1120 s	1580 s	3000 m
11	720 s	1150 s	1590 m	3020 w
12	700 s	1130 s	1580 s	3000 w
13	700 s	1120 w	1600 w	3030-2960 br
14	700 m	1170 m	1600 m	3000 w
15	690 w	1100 w	1590 m	3050 w

TABLE III

^1H NMR Chemical shifts of compounds 3–15, ($CDCl_3$, δ ppm)

Comp. No.	aromatic protons(m)	$N-CH_2-S$ (s)	$N-CH_3$ (s)	Other Chem. shifts
3	7.78-7.2 (10 H)	5.5	---	3.1-2.8 (t,SCH_2-C) 2.01 (m,C-CH_2-C) 1.37-0.8(t,CH_3)
4	7.8-7.25 (5 H)	5.5	3.7	3.4-3.1(m,S-CH,1H), 1.3(d,6H,isopropyl
5	7.77-7.15 (10 H)	5.5	——	3.3-3.0(m,S-CH,1H), 1.35(d,6H,isopropyl
6	7.7 (s,5 H)	5.5	3.71	2-1.1 (m,11H) cyclohexyl
7	7.68-7.28(10 H)	5.6	---	2.08-1.1(m,11 H) cyclohexyl
8	7.78-7.28(9 H)	5.7	3.7	
9	7.8 -7.2 (14 H)	5.81	---	
10	8.69-8.49(d,1 H; N-CH) 7.69-6.99(8 H)	6.21	3.7	
11	8.75-8.59(d,1 H; N-CH) 7.69-7 (13 H)	6.3	---	
12	7.89-7.3 (9 H)	6.3	3.7	
13	7.7-7.25 (14 H)	6.3	——	
14	7.79-7.39(9 H)	6.3	3.7	
15	7.7-7.22 (14 H)	6.4	---	

s : singlet; d : doublet m : multiplet



1,2 3-15 and 19-24 16-18 and 25,26

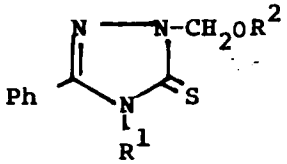
3 - 18 : X = S 19 - 26 : X = O

Compound No.		
R^1: $-CH_3$	R^1: $-C_6H_5$	R^2
1	2	-
-	3	n-propyl
4	5	isopropyl
6	7,16	cyclohexyl
8	9	p-chlorophenyl
10,17	11	2-pyridyl
12	13	2-benzoxazolyl
14,18	15	2-benzothiazolyl
19	20	methyl
21	22	ethyl
23	24-26	phenyl

Scheme 1

TABLE IV

2-Alkoxy (phenoxy)-methyl-4,5-disubstituted 1,2,4-triazol-3-thiones (19-24)



Comp. No.	R^1	R^2	m.p. °C	yield %	Found/Calculated C%	H%	N%
19	CH_3	CH_3	32	51	55.67	5.43	17.42
					56.17	5.53	17.87
20	C_6H_5	CH_3	150	49	64.15	5.00	14.00
					64.65	5.05	14.14
21	CH_3	C_2H_5	30	55	57.33	6.00	16.46

TABLE IV (*Continued*)

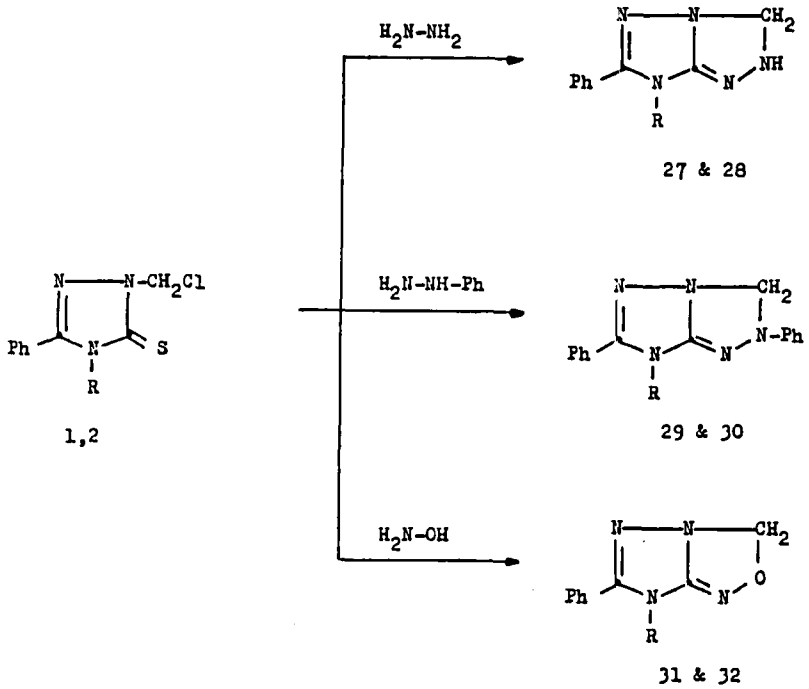
					57.83	6.02	16.86
22	C_6H_5	C_2H_5	207	57	65.09	5.39	13.21
					65.59	5.46	13.50
23	CH_3	C_6H_5	116	40	64.14	5.01	13.90
					64.64	5.05	14.14
24	C_6H_5	C_6H_5	150	70	70.00	4.60	11.31
					70.19	4.73	11.70

TABLE V

The IR spectral data of compounds 19--24

Comp.No.	C=S	C-O-C	C=N	C-H
19	1120 m	1150 w	1590 w	3030-2900 m
20	1110 m	1150 m	1590 w	3020-2900 w
21	1150 w	1150 m	1620 m	3030-2900 m
22	1160 w	1150 w	1600 m	3050-2900 w
23	1140 s	1150 m	1600 s	3030-3000 w
24	1100 s	1150 m	1630 s	3030 m

m : medium; s : strong; w : weak



1, 27, 29, and 31 : R = $-CH_3$

2, 28, 30 and 32 : R = $-C_6H_5$

Scheme 2

The majority of the new synthesized compounds were screened in vitro against different kinds of fungi namely: Aspergillus flavus, Microsporum canis, *M.*cookei Trichyphyton rubrum, Candida albicans and Histoplasma capsulatum (Table VII).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin Elmer 137 spectrophotometer ^{1}HNMR were recorded at 60 MHz on a Varian A-60 spectrometer. TMS was used as internal reference. All compounds were checked for their purity on silica gel TLC plates. Elemental analyses were done by the microanalytical laboratory, Cairo University, Egypt. All the analyses are in accordance with the proposed structures.

2-Chloromethyl-4-methyl-5-phenyl-1,2,4-triazole-3-thione (**1**): Thionyl chloride (20 ml) was added to 2-hydroxymethyl-4-methyl-5-phenyl-1,2,4-triazole-3-thione[10-12] (5 g, 20 mmol) and kept at room temperature for 15 hrs. The thionyl chloride was vacuum distilled and the residual product was crystallized from chloroform/petroleum ether to give compound **1** in 80% yield, m.p. 91–92°C

Analysis	C%	H%	N%	Cl%
Found	49.82	4.01	17.41	14.45
Cal.	50.10	4.17	17.53	14.82

2-Chloromethyl-4,5-diphenyl-1,2,4-triazole-3-thione (**2**): By following the procedure described above for compound (**1**). The product was crystallized from chloroform/pet. ether, m.p. 160°C, yield 75%.

Analysis	C%	H%	N%	Cl%
Found	59.29	3.59	13.52	11.34
Cal.	59.70	3.98	13.93	11.77

2-(Alkyl, aryl or hetroaryl) thiomethyl-4,5-disubstituted-1,2,4-triazole-3-thiones (**3–15**); *General Procedure*: The thiol (10 mmol) was added to sodium ethoxide (10 mmol) in 25 ml of ethanol, then compound **1** or **2** was added portionwise over about 10 minutes and allowed to warm and be stirred overnight. The reaction mixture was concentrated, cooled and filtered. The precipitate was crystallized from ethanol to give the corresponding sulphide (Tables I, II and III).

2-Substituted thiomethyl-4,5-disubstituted-1,2,4-triazol-3-ones (**16–18**); *General Procedure*: Mercuric acetate (1 mmol) was added to a solution of the 3-thione derivative (7, 10, or 14; 1 mmol in 100 ml of methanol) and refluxed for 10 hr, then filtered while hot. The solvent was concentrated, cooled and filtered. The solid product was recrystallized from methanol: yield 50–60% of the oxygen analogue. **16**: 2-cyclohexylthiomethyl-4-methyl-5-phenyl-1,2,4-triazol-3-one, m.p. 170°C. Its ^{1}HNMR ($CDCl_3$, δ) showed absorption bands at 7.6–7.09 (m, 10 H aromatic), 5.5 (s, N—CH_2—S) and at 2.3—1.2 (m, cyclohexyl 11 H). **17**: pyridinothiomethyl-4-methyl-5-phenyl-1,2,4-triazol-3-one: m.p., 155°C. **18**: 2-(benzothiazol-2-yl) thiomethyl-4-methyl-5-phenyl-1,2,4-triazol-3-one: m.p., 85°C. Its ^{1}HNMR ($CDCl_3$, δ) showed absorption bands at 7.91–7.01 (m, 9 H aromatic), 3.71 (s, 3 H, N—CH_3) and 6.3 (s, 2 H, N—CH_2—S).

TABLE VI

^{1}HNMR chemical shifts of compounds **19**, **20**, **22** and **24**. ($CDCl_3$, δ)

Comp.No.	aromatic H (m)	N-CH_3 (S)	N-CH_2-O (S)
19	7.7(s,5H)	3.6	3.4
20	7.78-7.28(10H)	---	3.8
23	7.67-6.95(10H)	3.65	---
24	7.68-7.28(15H)	---	---

2-Alkoxymethyl-4,5-disubstituted-1,2,4-triazol-3-thiones (**19–22**); *General Procedure*: To a solution of sodium alkoxide of (5 mmol) in 25 ml of its corresponding alcohol, was added (5 mmol) of Compound **1** or **2** and the mixture was refluxed for 8 hrs. The solvent was removed under reduced pressure. The residue was dissolved in ether and washed thoroughly with water.

The ethereal layer was dried using anh. $MgSO_4$, then evaporated under reduced pressure. The residue was crystallized from the appropriate solvent (Tables IV, V and VI).

2-Phenoxymethyl-4,5-disubstituted-1,2,4-triazole-3-thiones (**23, 24**); *General Procedure*: To a solution of sodium ethoxide in 10 ml (5 mmol) of ethanol was added (5 mmol) phenol, and the mixture was heated at 50°C for 10 min., then 5 mmol of compound **1** or **2** was added to the reaction mixture and refluxed while stirring for 5 hrs., cooled and filtered. The precipitate was washed with water, dried and crystallized from ethanol (Tables IV, V and VI).

4,5-Disubstituted-2-phenoxymethyl-1,2,4-triazol-3-ones (**25, 26**); *General Procedure*: To a solution of the 3-thione derivative **23** or **24** (1 mmol in 100 ml of methanol) was added mercuric acetate, (1 mmol), the mixture was refluxed for 7 hrs and then treated according to the procedure described before (for compounds **16–18**). 25: 4-Methyl-5-phenyl-2-phenoxymethyl-1,2,4-triazol-3-one; m.p. 34°C, 40% yield (crystallized from methanol). An ^{1}HNMR ($CDCl_3$, δ) showed absorption band at 7.8–7.4 (m, 10 H aromatic), 5.95 (s, 2 H, N—CH_2—O) and at 3.8 (s, 3 H, N—CH_3). **26**: 4,5-Diphenyl-2-phenoxymethyl-2,4-triazol-3-one; m.p. 170°C (from methanol), 60% yield. ^{1}HNMR ($CDCl_3$, δ) showed signals at 7.7–7 (m, 15 H aromatic) and at 5.91 (s, 2 H, N—CH_2—O).

TABLE VII

Antifungal activity of some 1,2,4-triazole derivatives

Comp.No.	Pathogenic Fungi					
	1	2	3	4	5	6
4	+++	+	++	++	-	+
5	-	++	+	++	-	++
6	++	++	+	++	+	+
7	++	--	++	+	+	-
8	+	+	-	++	++	+
9	-	-	++	+	++	++
10	-	+	-	++	++	++
11	+	-	-	+	+	--
12	-	+	-	+	-	--
13	+++	+	+++	++	+	+
14	-	++	+	+	+	+
15	+	+	++	++	++	++
20	++	++	+	++	++	+
22	-	+	+	+	+	++
23	-	++	+	+	++	+
24	-	-	+	-	++	++
27	-	+	+	+	++	++
28	+	-	-	+	++	-
29	-	+	-	+	-	-
30	-	-	-	+	+	+
31	-	+	-	+	-	-
32	+	+	-	+	-	-

- : no effect, no clear zone; + : weak, ≥ 2 mm in diameter;
++ : moderate, 2-5 mm in diameter; +++: strong, ≤ 5 mm in diameter

1- Aspergillus flavus , 2- Microsporum canis,
3- M.cookei 4- Trichophyton rubrum,
5- Candida albicans, 6- Histoplasma capsulatum,

4-Methyl-3-phenyl-6,7-dihydro-s-triazolo [4,3-b]-1,2,4-triazole (**27**): A solution of 1 (5 mmol) in 100 ml of benzene was added to 5 mmol of hydrazine hydrate and 5 mmol of triethylamine. The reaction mixture was stirred 2 hrs. at room temperature. The solvent was distilled then 30 ml of xylene was added and the mixture was refluxed for about 24 hrs. until hydrogen sulfide decreased, cooled and filtered. The precipitated product was crystallized from benzene/pet. ether (40–60), m.p. 190°C, 65% yield. The IR spectra (KBr, Cm^{-1}) showed signals at 1600 m (C=N), 2920 m (C—H stretching) and at 3080 w (NH) ^1H NMR ($CDCl_3$, δ) showed signals at 7.3–7.72 (m, 5 H arom.), at 3.5 (s, 3 H, N—CH_3) and at 5.8 (s, 2 H, —N—CH_2—N).

3,4-Diphenyl-6,7-dihydro-s-triazolo-[4,3-b]-1,2,4-triazole (**28**): Compound **2** was used following the same procedure described above for compound **27** m.p. 220°C (from ethanol), 81% yield. The IR spectra (KBr, Cm^{-1}) showed signals at 1590 S (C=N), 2910 w (C—H st.) and at 3060 m (NH). The ^{1}HNMR ($CDCl_3$, δ) showed absorption bands at 7.78–7.28 (m, 10 H aromatic) and at 5.9 (s, 2 H, N—CH_2—N).

3,6-Diphenyl-4-methyl-6,7-dihydro-s-triazolo[4,3-b]-1,2,4-triazol (**29**): A solution of 1 (5 mmol) in 100 ml of benzene was added to phenylhydrazine hydrochloride (5 mmol) and (10 mmol) triethylamine; then the procedure described above for hydrazinc hydrate was followed, m.p. 130°C (from ethanol), 70% yield. The IR (KBr, Cm^{-1}) showed absorption at 1600 w (C=N), 3000–2940 s (C—H st.). ^1H NMR ($CDCl_3$, δ) showed signals at 7.3–7.4 (m, 10 H, arom.), at 3.45 (s, 3 H, N—CH_3) and at 5.8 (s, 2 H, N—CH_2—N).

The same procedure was used using compound **2** instead of **1** to prepare 3,4,6-triphenyl-6,7-dihydro-s-triazolo-[4,3-b]-1,2,4-triazole (30); m.p. 200°C (from pet. ether 60–80), 80% yield. The IR (KBr, Cm^{-1}) showed bands at 1590 w (C=N) and at 2910 w (C—H st.). The ^{1}HNMR ($CDCl_3$, δ) showed signals at 7.4–7 (m, 15 H aromatic) and at 5.55 (s, N—CH_2—N).

4-Methyl-3-phenyl-7 H-1,2,4-oxadiazolo-[4,3-b]-1,2,4-triazole (**31**): A solution of 1 (5 mmol) in 40 ml of benzene was added to hydroxylamine hydrochloride (5 mmol) and (10 mmol) triethylamine and then the same procedure was used as for compound **27**, m.p. 225°C (from ethanol), 60% yield. The IR (KBr, Cm^{-1}) showed bands at 1600 w (C=N) and at 3030–2940 m (C—H st.). The ^{1}HNMR ($CDCl_3$, δ) showed absorption bands at 7.65–7 (m, 5 H aromatic), 3.43 (s, 3 H, N—CH_3) and at 5.89 (s, 2 H, N—CH_2—O).

The same procedure way was applied using compound **2** to prepare: 3,4-Diphenyl-(7 H)-1,2,4-oxadiazolo [4,3-b]-1,2,4-triazole (32): m.p. 235°C (from ethanol), 77% yield. The IR (KBr, Cm^{-1}) showed bands at 1600 m (C=N) and at 2980–2940 s (C—H st.). ^1H NMR ($CDCl_3$, δ) showed signals at 7.2–7.67 (m, 10 H, arom.) and at 5.82 (s. 2 H, N—CH_2—O).

Antifungal Screening: Petri dishes (9 Cm) were prepared, each having 10 ml of suitable medium (Czapek's agar or Sabouraud's agar). Plates were inoculated each with 0.1 ml of a suspension of one of the tested organisms 7 mm. Filter paper discs (1 cm in diameter) were saturated with the tested compound (10% concentration), and transferred immediately to the surface of each plate. Each plate contained 4 discs. The plates were incubated at 25°C ± 1°C for 10 days (Table VII).

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