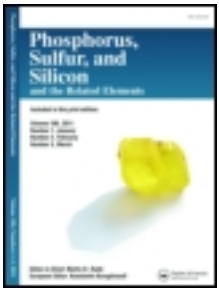

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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF SOME NEW MISCELLANEOUS S-TRIAZOLES

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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF SOME NEW MISCELLANEOUS S-TRIAZOLES

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The reaction of aryloxyacetic acid with thiocarbohydrazide under condition of fusion gave the corresponding s-triazole derivatives **2a-c**. The dicyano derivatives **3, 4** were obtained via reaction of compound **2c** with [bis(methylsulfanyl)methylidine]malononitrile and/or ethoxymethylenemalononitrile. Interaction of compound **2c** with bromomalononitrile yielded the corresponding triazolothiadiazine derivative **5**. In addition reaction of compound **2c** with phenyl isothiocyanate furnished triazolothiadiazole derivative **6**. Fusion of arylaminoacetic acids **8, 9** with thiocarbohydrazide afforded s-triazole derivatives **10, 11**, respectively. The reaction of benzylthioacetic acid **12** with thiocarbohydrazide yielded the triazole derivative **13**. When cyanoacetic acid **14** was reacted with thiocarbohydrazide the pyrazolotriazole derivative **16** was obtained. Some of the obtained compounds showed remarkable antifungal activity comparable to the fungicide Mycostatine.

Keywords: Triazoles; triazolothiadiazines; triazolothiadiazoles and antifungal activity

1. INTRODUCTION

s-Triazole derivatives are reported to exhibit broad spectrum biological activity such as antibacterial [1,2], antifungal [3], insecticidal [4] and anticancer [5,6] activities. In addition certain 1,3,4-thiadiazole, thiadiazine derivatives are reported to exhibit a wide range of biological properties such as antibacterial [7], antifungal [8] and hypocholesterolemic activities

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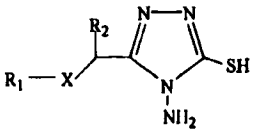
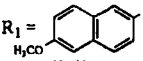
[9]. Recently, we synthesized a number of s-triazoles having methylene [10], a symmetric carbon atom [11], sulfonamide and carboxamide [12] moieties in general formula **Ia-d** which were evaluated for their antifungal activity and some of them exhibited remarkable activity. In continuation of our work it deemed of interest to design and synthesis of certain s-triazole structure containing ether, amino and sulfide groups **Ie-i** in order to study their structure activity relationshipe and hoping that the new sulfur compounds might show significant biological properties.



I

Ia; R_1 =  ; $R_2 = CH_3$; X = zero

Ib, R_1 =  SH; R_2 = H; X = CH_2

Ic; $R_1 = C_6H_3$ - 2Cl; 2,5; R_2 = H; X = SO_2NH

Id; $R_1 = C_6H_4$ - Cl-o; R_2 = H; X = CONH

Ie; $R_1 = C_6H_4$-CH_3 - o; R_2 = H; X = O

If; $R_1 = C_6H_4$-CH_3 - m; R_2 = H; X = O

Ig; $R_1 = C_6H_4$-CH_3 - p; R_2 = H; X = NH

Ih; $R_1 = C_6H_4$-Cl -p; R_2 = H; X = NH

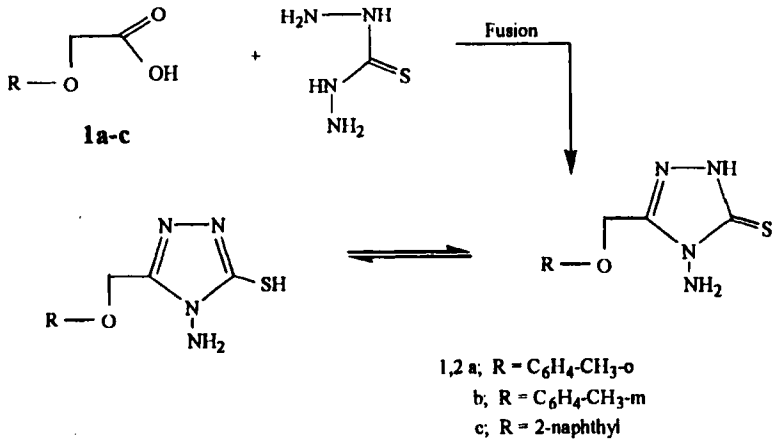
Ii; $R_1 = C_6H_5$-CH_2; R_2 = H; X = S

2. INVESTIGATIONS, RESULTS AND DISCUSSION

2.1. Chemistry

To realize the synthesis of the target antifungal compounds. The following Schemes were adopted. Fusion of aryloxyacetic acids **1a-c** with thiocarbohydrazide afforded 4-amino-5-mercapto-3-aryloxymethyl-s-triazoles **2a-c**, respectively (Scheme 1).

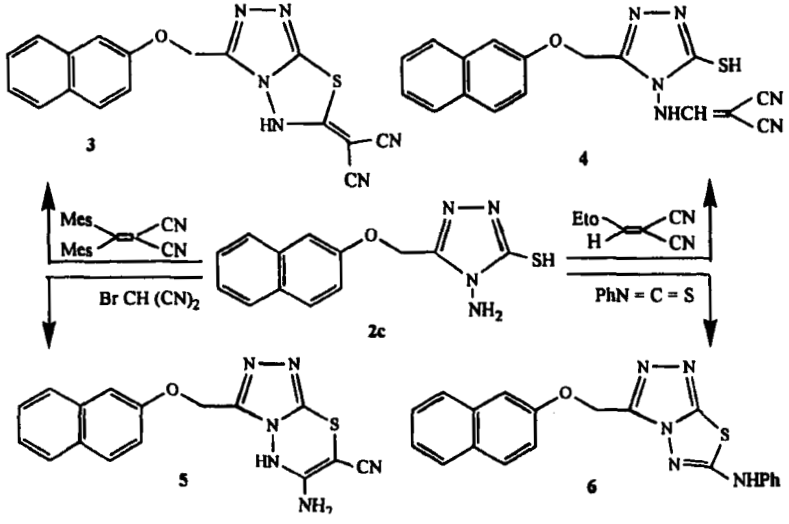
IR spectrum of compound **2a** showed bands at 3220, 3209 cm^{-1} (NH_2), 2930 cm^{-1} (CH aliph.), 1645 cm^{-1} (C=N). ^{1}H-NMR spectrum of (**2b** in DMSO-d_6) revealed signals at 2.3 (s, 3H, CH_3), 4.9 (s, 2H, OCH_2), 5.6 (s, 2H, NH_2), 6.8–7.4 (m, 4H, Ar-H). 4-Amino-5-mercapto-3-(2-naphthyloxymethyl)-s-triazole [13] **2c** was used as strategic starting material for the synthesis of a new series of biologically active heterocyclic compounds. Thus, interaction of compound **2c** with [bis(methyl-sulfanyl)methylidine]malononitrile afforded the dicyano derivative **3**



SCHEME 1

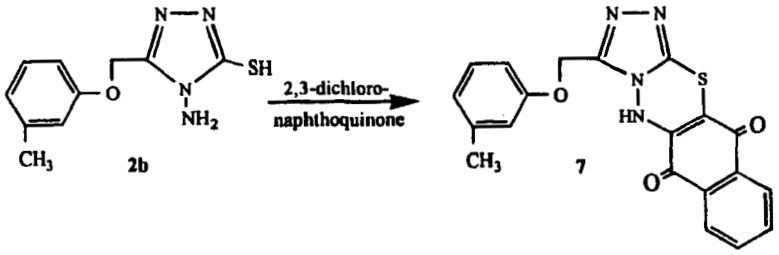
(Scheme 2). Also, the dicyano derivative **4** was obtained through reaction of compound **2c** with ethoxymethylenemalononitrile. IR spectrum of compound **3** revealed bands at 3172 cm^{-1} (NH), 2925 cm^{-1} (CH aliph.), 2210 cm^{-1} (C≡N), 1627 cm^{-1} (C=N). Mass spectrum of compound **3** showed a molecular ion peak m/z 346 (M^+, 0.12%), 144 (100%), 312 (0.81%), 271 (9.47%), 202 (7.95%), 169 (5.50%), 115 (56.64%), 69 (3.38%). IR spectrum of compound **4** revealed bands at 3303 cm^{-1} (NH), 2927 cm^{-1} (CH aliph.), 2200, 2210 cm^{-1}(2C≡N), 1625 cm^{-1} (C=N). Interaction of compound **2c** with bromomalononitrile furnished the corresponding triazolothiadiazine derivative **5**. IR spectrum of compound **5** exhibited bands at 3400, 3380 cm^{-1} (NH_2, NH), 2220 cm^{-1} (C≡N), 1590 cm^{-1} (C=N). Mass spectrum of compound **5** showed a molecular ion peak m/z 336 (M^+, 31.37%), 182 (100%), 311 (72.55%), 243 (68.63%), 145 (62.75%), 103 (64.71%), 65 (76.47%).

On the other hand reaction of compound **2c** with phenyl isothiocyanate gave the corresponding 6-anilinotriazolothiadiazole derivative **6**. IR spectrum of compound **6** revealed bands at 3300 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2900 cm^{-1} (CH aliph.), 1600 cm^{-1} (C=N). ^{1}H-NMR spectrum of **6** exhibited signals at 5.2 (s, 2H, OCH_2), 7.2–7.8 (m, 12H, Ar-H), 10.1 (s, 1H, NH).



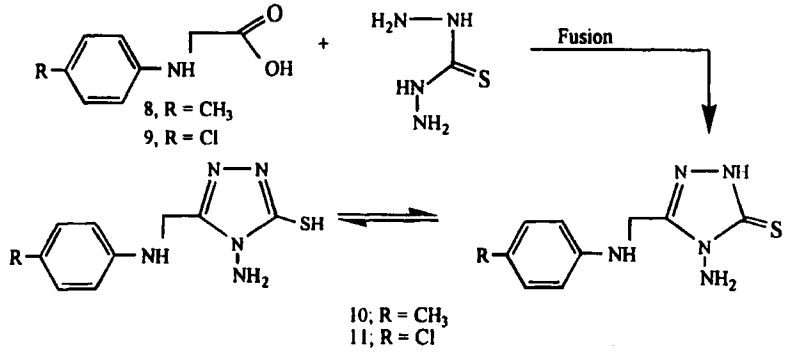
SCHEME 2

Interaction of 4-amino-5-mercapto-3-(3--tolyloxymethyl)-s-triazole **2b** with 2,3-dichloronaphthoquinone effected cyclization to furnish triazolothiadiazine derivative **7** through elimination of two moles of HCl (Scheme 3). IR spectrum of compound **7** revealed bands at 3150 cm^{-1} (NH), 3100 cm^{-1} (CH arom.), 2970 cm^{-1} (CH aliph.), 1680, 1660 cm^{-1} (2C=O). Mass spectrum of compound **7** revealed a molecular ion peak m/z at 390 (M^+, 2.41%), with a base peak at 55 (100%) and other significant peaks at 366 (9.37%), 307 (29.99%), 281 (8.30%), 207 (18.21%), 149 (62.25%), 105 (44.44%), 76 (42.70%).



SCHEME 3

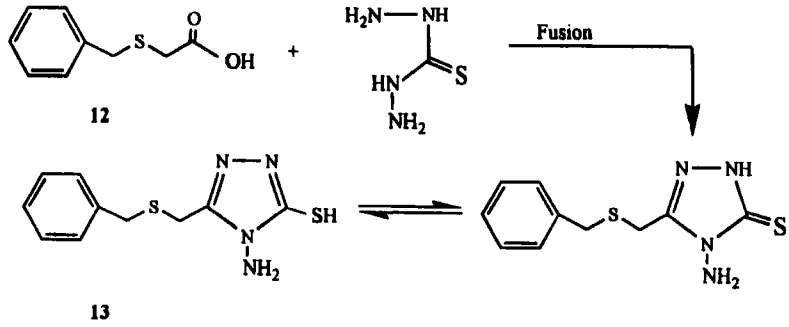
Fusion of the arylaminoacetic acids **8** and **9** with thiocarbohydrazide afforded the corresponding s-triazole derivatives **10** and **11**, respectively (Scheme 4). ^{1}H-NMR spectrum of (**10** in DMSO-d_6) exhibited signals at 2.4 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 6.2 (s, 2H, NH_2), 6.6–7.5 (m, 4H, Ar-H), 8.3 (s, 1H, NH-CH_2), 12.3 (s, 1H, NH-triazole). ^{1}H-NMR spectrum of (**11** in DMSO-d_6) showed signals at 4.4 (s, 2H, CH_2), 5.7 (s, 2H, NH_2), 6.0–7.3 (m, 4H, Ar-H), 12.1 (s, 1H, NH-CH_2), 13.5 (s, 1H, NH triazole). Mass spectrum of compound **11** revealed a molecular ion peak m/z at 255 (M^+, 68.45%), with a base peak at 63 (100%) and other significant peaks appeared at 192 (19.21%), 160 (39.01%), 128 (53.31%), 96 (23.58%) and 73 (22.32%).



SCHEME 4

The reaction of benzylthioacetic acid **12** with thiocarbohydrazide under condition of fusion furnished the corresponding 4-amino-5-mercapto-3-benzylthiomethyl-s-triazole **13** (Scheme 5). ^{1}H-NMR spectrum of compound **13** exhibited signals at 3.6, 3.8 (2s, 4H, CH_2-S-CH_2), 5.5 (s, 2H, NH_2), 7.2–7.4 (m, 5H, Ar-H), 13.6 (br, 1H, NH-triazole). Mass spectrum of compound **13** revealed a molecular ion peak m/z 252 (M^+, 94.01%), 63 (100%), 192 (23.74%), 160 (54.50%), 128 (64.09%), 96 (24.45%).

When cyanoacetic acid **14** was reacted with thiocarbohydrazide, the pyrazolotriazole **16** was obtained through the intermediate cyanomethyl-s-triazole **15** (Scheme 6). This was confirmed on the basis of elemental analysis and spectral data. IR spectrum showed the absence of carbonitrile group (C≡N) and presence of bands at 3288, 3200 cm^{-1}

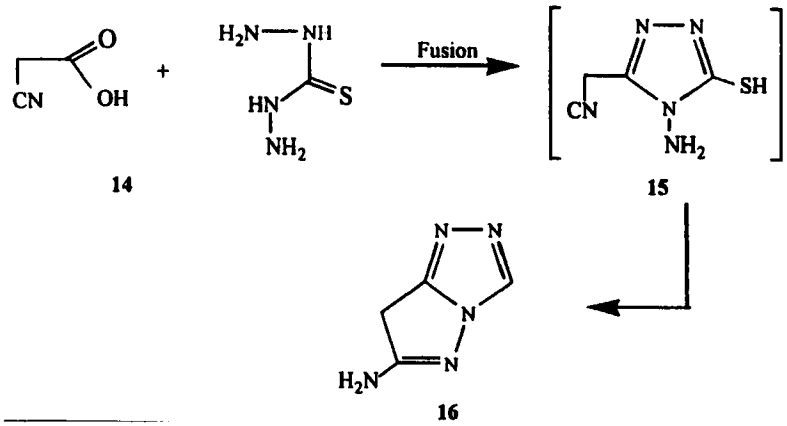


12

13

SCHEME 5

(NH_2), 3100 cm^{-1} (CH arom.), 1614 cm^{-1} (C=N). Mass spectrum of compound **16** revealed a molecular ion peak m/z 155 (M^+, 20.73%), 60 (100%), 156 (M^++1, 20.65%), 157 (M^++2, 9.62%), 115 (64.25%), 83 (58.30%), 69 (63.44%).



14

15

16

SCHEME 6

2.2. Antifungal activity

Most of the newly synthesized compounds were screened for their antifungal activity against four species of fungi, namely, *Aspergillus ochraceus*

Wilhelm (AUCC-230), *Penicilium chrysogenum* Thom (AUCC-530), *Aspergillus flavus* Link (AUCC-164) and *Candida albicans* (Robim) Berkho (AUCC-1720), using a cup plate agar difusion method [14]. The fungi cultures were maintained on Czapek's Dox agar medium. The tested compounds were dissolved in N,N-dimethylformamide (DMF) to get a solution of 1 mg/ml concentration. The inhibition zones were measured in (mm) at the end of an incubation period of 48 hr. at 28°C. Dimethylformamide showed no inhibition zones. Mycostatine was used as a reference to evaluate the potency of the tested compounds. The minimal inhibitory concentration (MIC) of the active compounds were measured using two fold serial dilution method [15].

TABLE I Characterization data of newly synthesized compounds

Compd. No.	*M. P °C*	*Yield %*	*Mol.-formula (Mol. wt)*	*Analyses Required/(Found) %*		
				C	*H*	*N*
2a	215–217	72	$C_{10}H_{12}N_4OS$ (236)	50.84 (51.10)	5.08 (5.20)	23.72 (23.40)
2b	205–207	75	$C_{10}H_{12}N_4OS$ (236)	50.84 (50.50)	5.08 (4.80)	23.72 (24.00)
3	> 300	77	$C_{17}H_{10}N_6OS$ (346)	58.95 (59.20)	2.89 (2.60)	24.27 (24.60)
4	225–227	70	$C_{17}H_{12}N_6OS$ (348)	58.62 (58.40)	3.44 (3.10)	24.13 (24.40)
5	260–262	65	$C_{16}H_{12}N_6OS$ (336)	57.14 (57.40)	3.57 (3.20)	25.0 (25.20)
6	240–242	78	$C_{20}H_{15}N_5OS$ (373)	64.34 (64.60)	4.02 (4.30)	18.76 (18.50)
7	> 300	76	$C_{20}H_{14}N_4O_3S$ (390)	61.53 (61.30)	3.58 (3.80)	14.35 (14.10)
10	203–205	81	$C_{10}H_{13}N_5S$ (235)	51.06 (50.80)	5.53 (5.20)	29.78 (29.50)
11	206–208	83	$C_9H_{10}N_5SCl$ (255.5)	42.27 (42.50)	3.91 (3.60)	27.39 (27.10)
13	213–215	68	$C_{10}H_{12}N_4S_2$ (252)	47.61 (47.20)	4.76 (4.90)	22.22 (22.50)
16	258–260	80	$C_4H_5N_5S$ (155)	30.96 (31.30)	3.22 (3.50)	45.16 (45.40)

TABLE II Antifungal activity of some newly synthesized compounds (inhibition zones, mm)

mpd .No	*Aspergillus ochraceus Wilhelm (AUCC-230)*	*Penicillium chrysogenum Thom (AUCC-530)*	*Aspergillus flavus Link (AUCC-164)*	*Candida albicans (Ro Berkho (AUCC-172*
2b	24	36	20	35
2c	22	38	24	36
10	20	35	20	34
11	34	20	34	20
13	32	38	34	22
14	34	36	35	24
ne	30 µg/ml	36	40	38	40

ctured by Bristol-Myers Squibb, Giza, Egypt.

The results are illustrated in Table (II). The antifungal activity of some of the synthesized compounds showed that triazoles containing either aryloxymethyl moieties **2b, 2c**, or 4-tolylamino moiety **10** were found to be the most active compounds against *Penicillium chrysogenum* and *Candida albicans* (MIC values were, 50–100 μg/ml), while triazole containing 4-chloroanilino moiety **11** exhibited higher activity against *Aspergillus ochraceus* and *Aspergillus flavus* (MIC value 50 μg/ml). On the other hand triazoles having either benzylthiomethyl moieties **13** or pyrazole moieties **16** revealed high activity against *Aspergillus ochraceus*, *Penicillium chrysogenum*, and *Aspergillus flavus*, (MIC values were 50–75 μg/ml). These results indicate that the biologically active compounds 2**b, 2c, 10, 11, 13** and **16** are nearly active as the standard fungicide Mycostatine (MIC 30 μg/ml).

3. EXPERIMENTAL

3.1. Apparatus and methods

All m.p., s are uncorrected. Elemental analyses were carried out at the microanalytical laboratories of the Faculty of Science, Cairo University. The IR spectra (KRr) were measured on a Shimadzu IR 110 spectrophotometer, ^{1}H-NMR spectra were obtained on a BRUKER proton NMR-Avance 300 (300 MHz), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard. Mass spectra were run on HP Model MS-5988.

3.2. Synthesis of 4-amino-5-mercapto-3-(2-or3-tolyloxymethyl)-s-triazoles (2a, b)

A mixture of thiocarbohydrazide (0.01 mol) and aryloxyacetic acid (0.01 mol) was fused at 180°C in an oil bath for 15 min. After cooling the reaction mixture was triturated with ethanol to give **2a, b**, respectively.

3.3. Synthesis of 6-dicyanoethylidene-5H-3-(2-naphthyloxymethy)-s-triazolo[3,4-b]thiadiazole (3)

A mixture of **2c** (0.01 mol), [bis(methylsulfanyl)methylidene]-malononitrile (0.01 mol) in dimethylformamide (20 ml) containing triethylamine

(0.01 mol) was refluxed for 10 hr. The obtained solid was recrystallized from ethanol to give **3**.

3.4. Synthesis of 4-aminomethylenemalononitrile-1H-5-thioxo-3-(2-naphthyloxymethyl)-s-triazole (4)

A mixture of **2c** (0.01 mol), ethoxymethylenemalononitrile (0.01 mol) in dimethylformamide (20 ml) containing triethylamine (0.01 mol) was refluxed for 10 hr. The obtained solid was recrystallized from ethanol to give **4**.

3.5. Synthesis of 6-amino-7-cyano-3-(2-naphthyloxymethyl)-s-triazolo-[3,4-b] [1,3,4]thiadiazine (5)

A mixture of **2c** (0.01 mol), bromomalononitrile (0.01 mol) and potassium hydroxide (0.01 mol) in ethanol (50 ml) was refluxed for 1 hr. The solid obtained was collected and recrystallized from ethanol to give **5**.

3.6. Synthesis of 6-anilino-3-(2-naphthyloxymethyl)-s-triazolo [3,4-b]-thiadiazole (6)

A solution of **2c** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in dry pyridine (20 ml) was refluxed until the evolution of H_2S has ceased (12 hr.). The reaction mixture was poured into ice cold water (100 ml). The product was filtered off, dried and recrystallized from ethanol to give **6**.

3.7. Synthesis of 3-(3-tolyloxymethyl)-6,11-dioxo(naphtho-[5,6:2,3] [1,3,4]thiadiazino[2,3-c]-s-triazole (7)

A mixture of **2b** (0.01 mol) and 2,3-dichloronaphthoquinone (0.01 mol) in dimethylformamide (20 ml) containing (0.01 mol) triethylamine was refluxed for 12 hr. The obtained solid was recrystallized from ethanol to give **7**.

3.8. Synthesis of 4-amino-5-mercapto-3-(4-arylamino)-s-triazoles (10), (11)

A mixture of thiocarbohydrazide (0.01 mol), and arylaminoacetic acid (0.01 mol) was fused in an oil bath at 180°C for 15 min. After cooling the reaction mixture was triturated with ethanol to give **10, 11**, respectively.

3.9. Synthesis of 4-amino-5-mercapto-3-benzylthiomethyl-s-triazole (13)

A mixture of thiocarbohydrazide (0.01 mol) and benzylthioacetic acid (0.01 mol) was fused at 180°C in an oil bath for 15 min. After cooling the reaction mixture was triturated with ethanol to give **13.**

3.10. Synthesis of 4-amino-7-mercapto-3H-pyrazolo[3,4-b]-s-triazole (16)

A mixture of thiocarbohydrazide (0.01 mol) and cyanoacetic acid **14** (0.01 mol) was fused at 180°C in an oil bath for 15 min. After cooling the reaction mixture was triturated with ethanol to give **16.**

Acknowledgements

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