A Convenient One-Pot Synthesis and Antimicrobial Activity of Pyrimido[1,2-*b*][1,2,4,5]tetrazines

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The synthesis of the hitherto unreported 3-amino-2,3-dihydro-6-phenyl-2-thioxo-4(1*H*)-pyrimidine **2** and 3-amino-2-methylthio-6-phenyl-4(3*H*)-pyrimidinone **3** is described. Reactions of hydrazonoyl halides **1** with either **2** or **3** afforded 6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones **6**. The latter products were screened for their antifungal and antibacterial properties. The mechanism of the studied reactions is discussed.

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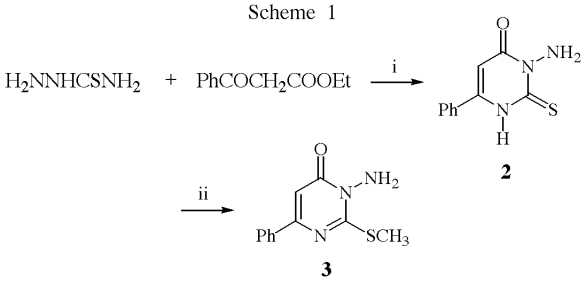
Introduction.

Recently, we have shown that reactions of hydrazonoyl halides **1** with heterocyclic thiones, having a thiourea residue in their structure, provide direct, efficient and regioselective routes for synthesis of various azoloazole derivatives [1-4]. In continuation of such studies in this area, we felt it would be interesting to extend our investigations to reactions of **1** with heterocyclic systems having a thiosemicarbazide residue in their structures such as 3-amino-2,3-dihydro-6-phenyl-2-thioxo-4(1*H*)-pyrimidinone **2** in an attempt to develop a new simple strategy for synthesis of functionalized pyrimido[1,2-*b*][1,2,4,5]tetrazines. At present, the synthesis of the latter ring system from 3-amino-6-substituted-2-thiouracils comprises three steps *viz*. (i) conversion of the latter into the respective 2-methylthio derivatives, (ii) hydrazinolysis of such 2-methylthiouracils to get 3-amino-2-hydrazino-4(3*H*)-pyrimidinones and (iii) condensation of the latter with one carbon cyclizing reagents such as *ortho* esters, dimethylformamide dimethylacetal, or dimethoxymethyl acetate in glacial acetic acid to get the respective pyrimido[1,2-*b*]-[1,2,4,5]tetrazines [5]. The interest in the latter derivatives is due to the recent finding that derivatives of such ring system were reported to be strong inhibitors of human cytomegalovirus protease [6]. In the present paper, we wish to report the synthesis of both **2** and **3**, which have been unreported hitherto, and the results of the study of their reactions with **1**. In addition, the results of screening of the products, namely pyrimido[1,2-*b*][1,2,4,5]tetrazines **6a-i**, isolated from the studied reactions, for their potential antifungal and antibacterial properties are reported.

Results and Discussion.

The required starting materials namely 3-amino-6-phenyl-2-thiouracil **2** and its 2-methylthio derivative **3** have not been reported hitherto. They were prepared in this work as depicted in Scheme 1. Thus, reaction of thiosemicarbazide with ethyl benzoylacetate in ethanol in the presence of sodium ethoxide yielded the 2-thiouracil derivative **2**. Methylation of the latter with methyl iodide in ethanol in the presence of sodium ethoxide afforded the 2-methylthio derivative **3** in 74% yield. The structures of both **2** and **3** were evidenced by their spectra (mass, IR, ^{1}H NMR) and microanalyses. For example, their IR spectra reveal the NH_2 and CO bands in the regions 3300-3100 and 1680-1650 cm^{-1}. The ^{1}H NMR spectrum of **2** shows, in addition to the aromatic proton multiplet, three characteristic signals at δ 4.72, 6.14 and 11.00 assignable to NH_2, ring C5-H and NH protons, respectively. The ^{1}H NMR spectrum of **3** shows the presence of the S-CH_3, NH_2 and C5-H protons as three singlets at δ 3.13, 5.72 and 6.71, respectively.

Scheme 1



Reagents: i, EtONa/EtOH; ii, EtONa/EtOH/CH_3I

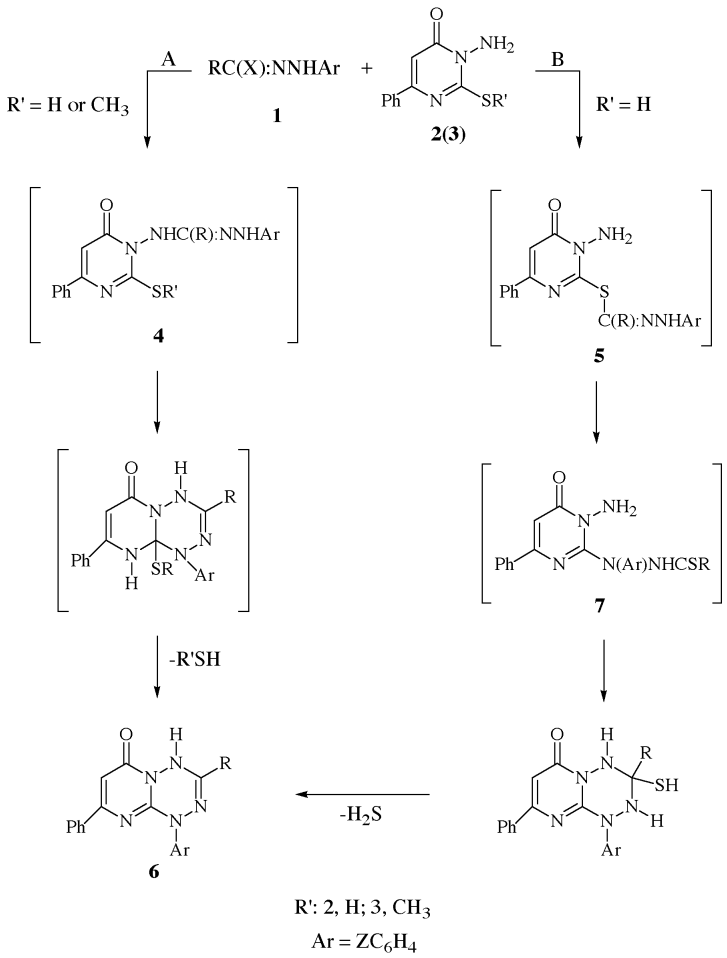
Refluxing of **1** with **2** in ethanol in the presence of triethylamine until hydrogen sulfide ceased to evolve and working up the reaction mixture gave, in each case, one product as evidenced by tlc analysis. At first, it was anticipated that such reactions would yield the respective pyrimido[4,3-*b*][1,3,4]thiadiazine derivatives by analogy to the reactions of **1** with 2-aminothiophenols which were reported to give benzothiadiazine derivatives [7]. Surprisingly, however, the products isolated from the reactions of **1a-i** with **2** were found to be free of sulfur. All such products display in their IR spectra absorption bands in the regions 3260-3200 and 1700-1670 cm^{-1} due to the NH and C=O groups, respectively. Their ^{1}H NMR spectra, while they show a common characteristic singlet signal in the region δ 8.9-9.4 assignable to the NH proton, they reveal the absence of N-NH_2 proton signal present in the spectrum of **2** at δ 4.72. Their mass spectra show, in addition to the expected molecular ions, peaks at m/z corresponding to [M^+ - R] , [M^+ - RC(NH):NNHAr], [M^+ -RC(:N)NH),

[ArN] and [Ar] fragments (see Experimental). On the basis of these spectral characteristics together with their microanalytical data, the products isolated from the reactions of **2** with **1a-i** were assigned the pyrimido[1,2-*b*][1,2,4,5]tetrazine structures **6a-i**, respectively (Scheme 2). Such structure assignment was substantiated by ^{13}C nmr spectra. For example, the ^{13}C nmr spectrum of **6c** in $CDCl_3$ reveals, as expected, fifteen signals at δ 24.2, 103.5, 123.9, 126.8, 126.9, 128.6, 128.7, 130.9, 135.5, 139.7, 143.2, 143.6, 157.1, 160.1, 189.2.

To account for the formation of **6**, the two possible pathways A and B depicted in Scheme 2 were considered. Thus, it is suggested that reactions of **1** with **2** or **3** presumably proceed through initial formation of the respective hydrazidine derivatives **4** which subsequently undergo cyclization with concurrent elimination of hydrogen sulfide to give **6** (Route-A). The formation of **4** is analogous to the reactions of **1** with hydrazines which were reported to give the corresponding hydrazidines [8]. Alternatively, reaction of **1** with **2** may start with the formation of the thiohydrazonate esters **5** which undergo *in situ* Smiles rearrangement [9,10] under the reaction conditions employed to afford the corresponding thiohydrazides **7**. Then the thiohydrazides **7** undergo cyclization as soon as they are formed with concurrent elimination of hydrogen sulfide to give **6** as the end products (Route B, Scheme 2). All attempts to isolate any of the aforementioned intermediates **4, 5** and **7** were unsuccessful, however. Presumably, such intermediates are converted under the employed reaction conditions to the final products **6** as soon as they are formed.

To distinguish between these two alternative pathways, the reactions of **1a-i** each with 3-amino-2-methylthio-6-phenyl-4(3*H*)-one derivative **3** were investigated. Thus, refluxing a mixture of **1** and **3** in pyridine afforded, in each case, one product whose ^1H NMR spectrum showed the

Scheme 2



R/Z/X: **a**, EtOCO/H/Cl; **b**, PhNHCO/H/Cl; **c**, CH_3CO/H/Cl; **d**, PhCO/H/Br; **e**, 2-Naphthoyl/H/Br; **f**, 2-Thenoyl/4-Me/Br; **g**, Ph/H/Cl; **h**, PhCH=CH/H/Cl; **i**, CH_3/4-NO_2/Br.

absence of both the methylthio and amino proton signals present at δ 3.13 and 5.72, respectively in the spectrum of the respective 3-amino-2-methylthiopyrimidinone **3**. Instead, the spectra of the products isolated revealed in each case, a characteristic NH proton singlet signal in the region δ 9.0 - 9.4. Furthermore, such products proved identical in all respects (m.p., mixed m.p., IR) with those obtained above from **1** and **2**. As compound **3** cannot form thiohydrazonates with **1**, it is not unreasonable to conclude that route-A in Scheme 2 seems to be the most plausible mechanism for the studied reactions of **1** with **3** leading to **6**.

In conclusion, the foregoing results indicate collectively that the studied reactions of **1** with either 3-amino-6-phenyl-2-thioxopyrimidin-4(1*H*)-one **2** or 3-amino-2-methylthio-6-phenylpyrimidin-4(3*H*)-one **3** provide easy access to pyrimido[1,2-*b*][1,2,4,5]tetrazine derivatives **6**. The latter compounds represent important extensions in the chemistry of ring-fused 4*H*-1,2,4,5-tetrazines. The availability of the 4-nitrogen atom for further substitution offers the potential for novel biologically active materials or dyestuffs.

Antimicrobial Activity.

The compounds **6a-i** were tested for their antimicrobial activities using four fungi species namely *Rhizopus spp.* **RS**, *Aspergillus fumigatus* **AF**, *Syncephalastrum racemosum* **SR** and *Candida spp.* **CS**. Also, five bacteria species namely *Pseudomonas aeruginosa* **PA**, *Proteus vulgaris* **PV**, *Bacillussubtilis* **BS**, *Escherichia coli* **EC** and *Salmonella spp.* **SS** were tested. The organisms were tested against the activity of solutions of concentration of 1.0 μg/ml of each compound and using inhibition zone diameter in cm (IZD) as criterion for the antimicrobial activity. The fungicide Terbinafin and the bactericide Chloramphenicol were used as references to evaluate the potency of the tested compounds under the same conditions. The results are depicted in Table 1.

The results revealed that compound **6b** exhibited the highest degree of inhibition against all tested organisms. Furthermore, while the data showed that all other compounds **6c-f,h,i** are active against the two species **PA** and **PV**, they exhibit no inhibition of the two bacteria species **EC** and **SS** and the fungi species **SR**. Compounds **6a** and **6g** showed activity only against the two micro-organisms **PA** and **PV**. However, the activities of the tested compounds are much less than that of the standard antifungal and antibacterial agents used.

EXPERIMENTAL

All melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 200 spectrometer in deuterated chloroform with tetramethylsilane (TMS) as an internal standard. IR spectra were determined with a Fourier Transform and Pye Unicam Infrared spectrophotometer using a potassium bromide wafer. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at an ionizing potential of 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of Cairo University, Giza, Egypt.

The biological evaluations of the products **6a-i** were carried out at The Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt. The hydrazonoyl halides **1a-i** were prepared by following the procedures reported earlier [11-17].

3-Amino-2,3-dihydro-6-phenyl-2-thioxo-4(1*H*)pyrimidinone (**2**).

To an ethanolic sodium ethoxide solution, prepared from sodium metal (4.6 g, 0.2 mol) and absolute ethanol (100 ml), were added thiosemicarbazide (9.1 g, 0.1 mole) and ethyl benzoylacetate (19.2 g, 0.1 mole) with stirring. The reaction mixture was refluxed for 4 hours and then cooled. The solid that

Table 1

Antimicrobial Activity of the Products **6a-I** [a]

Compound No.	Micro-organism/IZD (cm)								
	RS	**AF**	**SR**	**CS**	**PA**	**PV**	**BS**	**EC**	**SS**
6a	0	0	0	0	1.2	1.3	1.4	0	0
6b	1.9	2.0	1.8	1.9	1.8	2.0	1.8	1.5	1.4
6c	0	1.1	0	1.4	1.2	1.2	0	0	0
6d	1.3	1.7	0	1.2	1.2	1.2	1.5	0	0
6e	1.3	1.5	0	1.2	1.1	1.4	1.4	0	0
6f	0	0	0	1.3	1.3	1.3	1.3	0	0
6g	0	0	0	0	1.2	1.2	0	0	0
6h	0	0	0	1.3	1.1	1.2	1.4	0	0
6i	0	1.4	0	1.3	1.3	1.3	1.2	0	0
TE [b]	4.7	5.0	3.6	3.0	3.6				
CA [c]						2.6	2.6	2.8	2.4

[a] 50 ml of solution whose concentration 1.0 μg/ml was tested; [b] Terbinafin; [c] Chloramphenicol.

precipitated was isolated by filtration and was dissolved in water (100 ml). The resulting solution was acidified with acetic acid, and crystallized from ethanol to give pure **2**: Yield 15 %, m.p. 238-40 °C, IR: ν (cm^{-1}) 3286, 3132 (NH_2), 1658 (CO); ^1H NMR: δ 4.72 (s, 2H), 6.14 (s, 1H), 7.49 - 7.67 (m, 5H), 11.0 (s, 1H); MS m/z (%) 220 (14), 219 (100), 191 (9), 188 (19), 146 (44), 129 (10), 117 (8), 103 (27), 77 (31).

Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54.9; H, 4.2; N, 19.0 %.

3-Amino-6-phenyl-2-methylthio-4(3*H*)-pyrimidinone (**3**).

To an ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g, 0.01 mol) and absolute ethanol (100 ml), was added compound **2** (2.19 g, 0.01 mole) with stirring. To the resulting solution was added methyl iodide (1.42 g, 0.01 mol), and the mixture was refluxed on a water bath for 1 hour and then left at room temperature overnight. The precipitated solid was collected by filtration and crystallized from ethanol to give pure **3**: Yield 74 %, m.p. 176°C, ir: ν (cm^{-1}) 3302, 3201 (NH_2), 1680 (CO); ^1H nmr: δ 3.13 (s, 3H), 5.72 (s, 2H), 6.71 (s, 1H), 7.44 - 8.03 (m, 5H); MS m/z (%) 234 (74), 233 (79), 217 (100), 204 (69), 192 (37), 160 (17), 129 (39), 119 (43), 116 (35), 102 (68), 89 (41), 77 (90).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.8; H, 4.7; N, 18.0 %.

1,3-Disubstituted-8-phenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-ones (**6**).

To a mixture of equimolecular quantities of the appropriate hydrazonoyl halide **1** and 2-thiouracil derivative **2** (0.005 mole each) in absolute ethanol (40 ml) was added triethylamine (0.7 ml, 0.005 mole). The resulting mixture was refluxed until hydrogen sulfide ceased to evolve (4 - 6 hours) and then cooled. The solid that precipitated upon cooling was isolated by filtration, washed with water, dried and finally crystallized from ethanol to give the respective pure pyrimidotetrazine derivative **6** in 45-67% yield.

Alternatively, the latter products **6** were also prepared as follows. A mixture of equimolar quantities of the 2-methylthio derivative **3** and the appropriate hydrazonoyl halide **1** (5 mmol each) were refluxed in pyridine for 10 hours and cooled. The cold reaction mixture was then poured onto ice-cold hydrochloric acid with stirring. The solid that precipitated was collected, washed with water and finally crystallized from ethanol to give the corresponding pyrimidotetrazines **6** which were found identical in all respects with that obtained above from **1** and **2**. The various pyrimido[1,2-*b*][1,2,4,5]tetrazines **6a-i** that were prepared, together with their physical constants, are listed subsequently.

Ethyl(1,8-diphenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one)-3-carboxylate (**6a**).

Compound **6a** was obtained in 45 % Yield; m.p. 138-140 °C (EtOH); IR: ν (cm^{-1}) 3286, 1720, 1681 cm^{-1}; ^1H NMR: δ 1.41 (t, 3H), 4.44 (q, 2H), 6.65 (s, 1H), 7.27-7.70 (m, 10H), 9.03 (s, 1H); MS m/z (%) 376 (M^+, 79), 348 (10), 303 (7), 262 (6), 248 (22), 247 (19), 171 (9), 145 (14), 129 (9), 116 (8), 103 (15), 91 (6), 77 (100).

Anal. Calcd. for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66. Found: C, 63.7; H, 4.7; N, 18.6 %.

N-Phenyl-(1,8-diphenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one)-3-carboxamide (**6b**).

Compound **6b** was obtained in 42% yield; m.p. 200-202 °C (EtOH); IR: ν (cm^{-1}) 3217, 1700, 1660 (cm^{-1}); ^1H NMR: δ 6.64 (s, 1H), 7.34-7.70 (m, 15H), 8.6 (s, 1H), 9.4 (s, 1H); MS m/z (%) 422 (M^+, 88), 357 (17), 302 (38), 262 (16), 247 (12), 171 (9), 145 (9), 105 (23), 91 (12), 77 (100).

Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89. Found: C, 67.4; H, 4.1; N, 19.9 %.

3-Acetyl-1,8-diphenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one (**6c**).

Compound **6c** was obtained in 66% yield; m.p. 214-216 °C (EtOH); IR: ν (cm^{-1}) 3217, 1700, 1666; ^1H NMR: δ 2.54 (s, 3H), 6.64 (s, 1H), 7.34-7.71 (m, 10H), 9.09 (s, 1H); MS m/z (%) 345 (M^+, 89), 302 (100), 262 (10), 171 (11), 145 (8), 129 (13), 103 (28), 91 (9), 77 (69).

Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.1; H, 4.6; N, 20.0 %.

3-Benzoyl-1,8-diphenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one (**6d**).

Compound **6d** was obtained in 35% yield; m.p. 224-226 °C (EtOH); IR: ν (cm^{-1}) 3247, 1674, 1650; ^1H NMR: δ 6.70 (s, 1H), 7.25-8.26 (m, 15H), 9.42 (s, 1H); MS m/z (%) 407 (M^+, 34), 302 (3), 262 (1), 171 (2), 145 (4), 105 (100), 91 (3), 77 (58).

Anal. Calcd. for $C_{24}H_{17}N_5O_2$: C, 70.75; H, 4.21; N, 17.19. Found: C, 70.0; H, 4.2; N, 17.3 %.

3-(2-Naphthoyl)-1,8-diphenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]-tetrazin-6-one (**6e**).

Compound **6e** was obtained in 50% yield; m.p. 232-234°C (EtOH); IR: ν (cm^{-1}) 3294, 1681, 1650; ^1H NMR: δ 6.70 (s, 1H), 7.34-8.94 (m, 17H), 9.48 (s, 1H); MS m/z (%) 458 (M^+, 42), 302 (3), 262 (3), 171 (2), 155 (100), 127(69), 103 (4), 91 (3), 77 (34).

Anal. Calcd. for $C_{28}H_{19}N_5O_2$: C, 73.51; H, 4.19; N, 15.31. Found: C, 73.1; H, 4.2; N, 15.1 %.

3-(2-Thenoyl)-1-(4-methylphenyl)-8-phenyl-6*H*-pyrimido-[1,2-*b*][1,2,4,5]tetrazin-6-one (**6f**).

Compound **6f** was obtained in 52% yield; m.p. 228-230 °C (EtOH); IR: ν (cm^{-1}) 3232, 1689, 1670; ^1H NMR: δ 2.45 (s, 3H), 6.66 (s, 1H), 7.25-8.3 (m, 12H), 9.49 (s, 1H); MS m/z (%) 427 (M^+, 30), 316 (7), 261 (26), 171 (3), 129 (3), 111 (100), 105 (2), 91 (24), 77 (6).

Anal. Calcd. for $C_{23}H_{17}N_5O_2S$: C, 64.62; H, 4.01; N, 16.38. Found: C, 64.9; H, 4.1; N, 16.4 %.

1,3,8-Triphenyl-6*H*-pyrimido[1,2-*b*][1,2,4,5]tetrazin-6-one (**6g**).

Compound **6g** was obtained in 50% yield; m.p. 200-202 °C (EtOH); IR: ν (cm^{-1}) 3201, 1681; ^1H NMR: δ 6.66 (s, 1H), 7.25-7.87 (m, 15H), 9.00 (s, 1H); MS m/z (%) 379 (M^+, 86), 262 (3), 247 (8), 220 (3), 171 (6), 117 (3), 105 (27), 91 (5), 77 (100).

Anal. Calcd. for $C_{23}H_{17}N_5O$: C, 72.81; H, 4.52; N, 18.48. Found: C, 73.0; H, 4.4; N, 18.1 %.

1,8-Diphenyl-3-(2-phenylethenyl)-6*H*-pyrimido[1,2-*b*][1,2,4,5]-tetrazin-6-one (**6h**).

Comound **6h** was obtained in 54% yield; m.p. 250-251°C (EtOH); IR: ν (cm^{-1}) 3209, 1674; ^1H NMR: ν 6.65 (s, 1H), 6.70 (d, 1H), 6.76 (d, 1H), 7.15-7.77 (m, 15H), 8.80 (s, 1H); MS m/z (%) 405 (M^+, 100), 314 (3), 302 (2), 262 (3), 247 (7), 220 (3), 171 (6), 145 (6), 129 (14), 105 (23), 91 (5), 77 (87).

Anal. Calcd. for $C_{25}H_{19}N_5O$: C, 74.06; H, 4.72 ; N, 17.27. Found: C, 73.9; H, 4.7; N, 17.2%.

3-Methyl-1-(4-nitrophenyl)-8-phenyl-6*H*-pyrimido[1,2-*b*]-[1,2,4,5]tetrazin-6-one (**6i**).

Compound **6i** was obtained in 58% yield ; m.p. > 300 °C (EtOH); IR: ν (cm^{-1}) 3193, 1651; MS m/z (%) 362 (M^+, 100), 347 (2), 293 (10), 266 (3), 247 (4), 171 (11), 169 (4), 136 (4), 122 (40), 116 (8), 105 (4), 90 (4), 77 (14).

Anal. Calcd. for $C_{18}H_{14}N_6O_3$: C, 59.67; H, 3.89; N, 23.19. Found: C, 60.1; H, 4.1; N, 23.4 %.

Antimicrobial Assay.

Cultures of four fungi species namely *Rhizopus spp*. **RS**, *Aspergillus fumigatus* **AF**, *Syncephalastrum racemosum* **SR** and *Candida spp*. **CS** as well as five bacteria species namely *Pseudomonas aeruginosa* **PA**, *Proteus vulgaris* **PV**, *Bacillussubtilis* **BS**, *Escherichia coli* **EC** and *Salmonella spp*. **SS** were used to investigate the antimicrobial activity of the compounds **6a-i**. The antimicrobial activity was assayed biologically using diffusion plate technique. The latter technique was carried out by pouring a spore suspension of the fungal species (one ml of sterile water contains approximately 10^8 conidia) or spreading bacterial suspension over a solidified malt agar medium. The layer is allowed to set for 30 minutes. A solution of the test compound **6** (1.0 μg/ml) was placed onto sterile 5 mm filter paper discs and allowed to dry, then the discs were placed on the centre of the malt agar plate and incubated at optimum incubation temperature 28 ± 2 °C. Test organism growth may be affected by the inhibitory action of the test compound, so a clear zone around the disc appears as an indication of the inhibition of test organism growth. The size of the clearing zone is proportional to the inhibitory action of the compound **6**. The fungicide Terbinafin and the bactericide Chloramphenicol were used as standards under the same conditions. Measurements were considered after 72 hours for fungi and 24 hours for bacteria. The results are summarized in Table 1.

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