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Synthesis of Condensed and Uncondensed Tetrazolo[1,5-*b*][1,2,4]triazines as Potential Antimicrobial Agents

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Summary. Reactions of two cyclic amidrazones, the 6-methyl and 6-phenyl derivatives of 7-hydrazinotetrazolo[1,5-*b*][1,2,4]triazines with mono- and dicarbonyl compounds afforded various heterocyclic systems. Thus, acetic acid, benzoyl chloride, or ethyl chloroformate reacted with the former cyclic amidrazones to yield the corresponding [1,2,4]triazolo[4,3-*d*]tetrazolo[1,5-*b*][1,2,4]triazines. With pyruvic acid or ethyl pyruvate the corresponding hydrazone derivatives were obtained, which then cyclized to tetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-*c*][1,2,4]triazines. The 9,10-dioxotetrazolotriazinotriazine structures were synthesized by condensative cyclization of the cyclic amidrazones with diethyl oxalate, whereas the reaction of these amidrazones with acetylacetone or ethyl acetoacetate furnished pyrazolyltetrazolo[1,5-*b*][1,2,4]triazines through the isolable hydrazone intermediates. Some of the representative members of the prepared compounds were screened for antimicrobial activity.

Keywords. Cyclic amidrazones; Hydrazones; Tetrazolotriazine heterocycles; Antimicrobial activity.

Introduction

Various reviews dealing with the synthesis of condensed 1,2,4-triazines have been published [1–3]. The 1,2,4-triazine moiety plays a vital role in many biological activities including antiviral [4], antihypertensive [4, 5], blood-platelet aggregation inhibitory [5, 6], analgesic [7], and antibacterial properties [8, 9] as well as some of new anti-HIV and anticancer agents [10]. In continuation of our extensive program on the synthesis of condensed tetrazolo heterocycles [11–16] using different reagents, we describe in this article the synthesis of some compounds having various heterocyclic rings condensed or uncondensed to tetrazolo[1,5-*b*][1,2,4]triazines in anticipation of expected interesting antimicrobial agents.

Results and Discussion

Reaction of 7-hydrazino-6-methyltetrazolo[1,5-*b*][1,2,4]triazine (**1a**) or 7-hydrazino-6-phenyltetrazolo[1,5-*b*][1,2,4]triazine (**1b**) with excess of acetic acid yielded the corresponding 9-methyl[1,2,4]triazolo[4,3-*d*]tetrazolo[1,5-*b*][1,2,4]triazines **2a** and **2b**. Similarly, benzoyl chloride reacted with each of cyclic amidrazone **1a** and **1b** to provide the corresponding 9-phenyl-congeners **3a** and **3b**. None of the possible intermediates of the aforementioned reactions was isolated. On the other hand, heating the hydrazines **1a** or **1b** with an excess of ethyl chloroformate in pyridine gave products, which showed neither ester-carbonyl absorption nor ethyl group signals in the ^{1}H NMR spectra. The products showed NH and CON absorptions and were, consequently, assigned the structure of [1,2,4]triazolo[4,3-*d*]tetrazolo[1,5-*b*][1,2,4]triazin-9(8*H*)-ones **4a** and **4b**.

Condensation of **1a** or **1b** with pyruvic acid either at ambient temperature or heating at 100°C resulted in the corresponding hydrazones **5a** and **5b**, which possessed IR absorptions characteristic of

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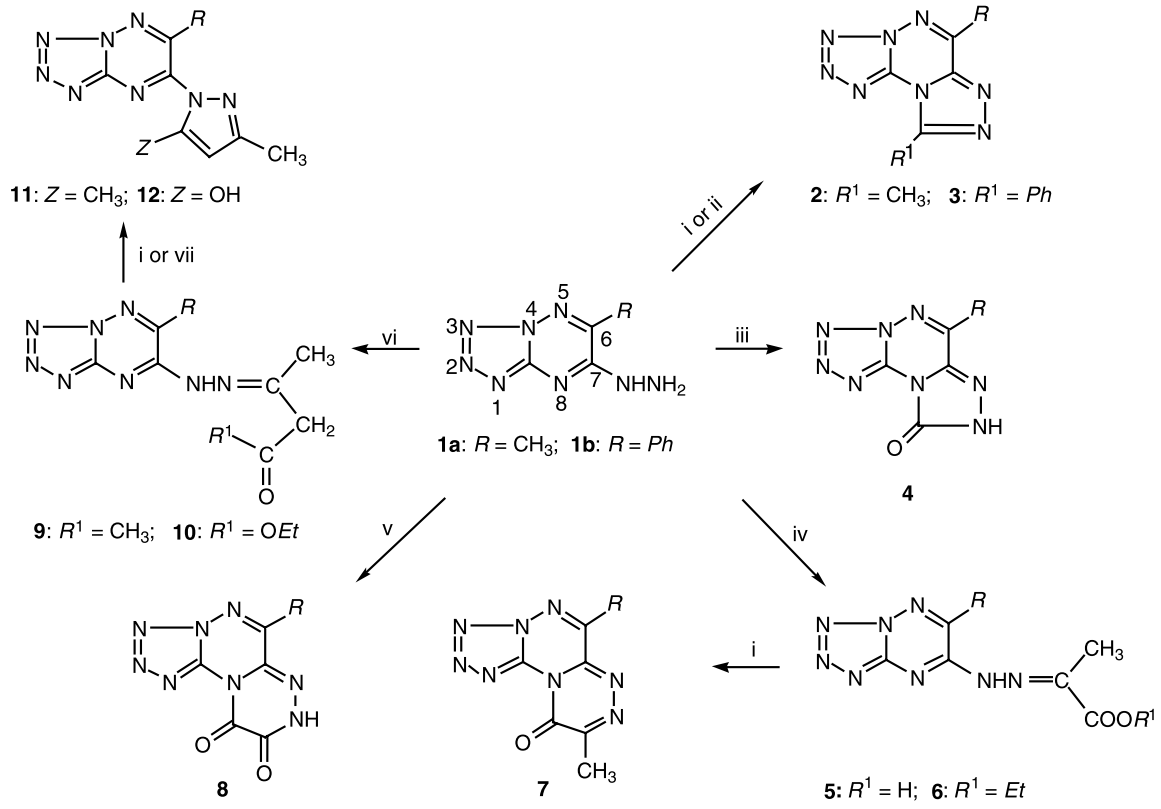

i, CH_3COOH; ii, *Ph*COCl; iii, ClCOO*Et*; iv, $CH_3COCOOR^1$; v, $(COOEt)_2$; vi, $CH_3COCH_2COR^1$; vii, NaO*Et*

Scheme 1

OH, NH, and COOH groups. Ethyl pyruvate also reacted with the hydrazines **1a** and **1b** to furnish the corresponding hydrazones **6a** and **6b**. ^{1}H NMR spectra of the latter contained the triplet and quartet patterns of signals characteristic of the ethyl group. Acid-induced heterocyclization of **5a** or **6a** by heating in acetic acid gave one and the same product, which displayed the disappearance of the OH and NH absorptions but showed a CON absorption in the IR region. The ^{1}H NMR spectrum of this cyclization product revealed no ethyl group pattern. These data together with the correct elemental analysis are compatible with the 6,9-dimethyltetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-*c*][1,2,4]triazin-10(9*H*)-one structure (**7a**). Similarly, both hydrazones **5b** and **6b** were cyclized to 9-methyl-6-phenyl derivative **7b**.

Condensative cyclization of **1a** and **1b** with equimolar amounts of diethyl oxalate afforded the corresponding tetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-*c*][1,2,4]triazine-9,10(8*H*)-diones **8a** and **8b**. Assignment of these structures and exclusion of possible intermediate hydrazido structures was established by correct elemental analysis as well as the absence of the triplet-quartet pattern of ^{1}H NMR signals characteristic of an ethyl group.

Condensation of the hydrazines **1a** or **1b** with acetylacetone at 100°C yielded the corresponding hydrazone derivatives **9a** and **9b** which showed IR absorptions characteristic of NH and C=O. ^{1}H NMR spectra of these products revealed the presence of NH (exchangeable), methylene, and methyl group signals. Heating **9a** or **9b** with acetic acid resulted in their cyclization to the 7-(3,5-dimethylpyrazol-1-yl)tetrazolo[1,5-*b*][1,2,4]triazine systems **11a** and **11b** which revealed only a C=N absorption and lacked NH and C=O absorptions characteristic of the parent hydrazone, and a pyrazolyl CH proton signal in their ^{1}H NMR spectra.

Likewise, condensation of ethyl acetoacetate with **1a** or **1b** caused formation of the hydrazone intermediates **10a** and **10b**, which underwent base catalyzed cyclization upon heating with sodium ethoxide to provide either the 1,2,4-triazolo (**2a** and **2b**) or pyrazolyl (**12a** and **12b**) derivatives through the elimination of an ethyl acetate or an ethyl alcohol molecule. Thus, the evidences of the cyclization of

Table 1. Minimal inhibitory concentration ($MIC/\mu g\,cm^{-3}$) of selected compounds

Comp. No.	*S. aureus*	*E. coli*	*C. albicans*
2b	100	>200	100
4a	>200	100	25
7b	50	50	100
8b	100	100	12.5
12a	50	50	25
Ampicillin	12.5	25	–
Clotrimazole	–	–	12.5

the hydrazones **10a** and **10b** are: (a) the melting point and thin layer chromotography of the obtained cyclization products are not similar to the structures **2a** and **2b**, and (b) spectroscopic data of these products showed OH and lacked any amide absorption bands in the IR region; the ^{1}H NMR exhibited OH (exchangeable) and pyrazolyl CH proton signals. Accordingly, the products were decisively assigned as the 7-(5-hydroxy-3-methylpyrazol-1-yl)tetrazolo[1,5-*b*][1,2,4]triazine derivatives **12a** and **12b**, and the formation of 1,2,4-triazolo structures **2a** and **2b** could be excluded thereby. This is in accordance with previous reports [17, 18], but contradicts another one [19] on the reaction of ethyl acetoacetate with different cyclic amidrazones.

Compounds **2b**, **4a**, **7b**, **8b**, and **12a** were screened [20] for *in vitro* activities against *Gram*-positive (*Staphylococcus aureus*) and *Gram*-negative bacteria (*Escherichia coli*) in addition to a fungus (*Candida albicans*). The minimal inhibitory concentration ($MIC/\mu g\,cm^{-3}$) [21] is displayed in Table 1 showing that **7b** and **12a** exhibit an antimicrobial activity against *S. aureus* (25%) and *E. coli* (50%) comparable to that of ampicillin. Furthermore, **8b** possessed an antimycotic activity against *C. albicans* comparable to that of clotrimazole, while **4a** and **12a** were 50% of that of clotrimazole.

In conclusion, it seems that the results obtained in the present work demonstrate the scope for the utility of 7-hydrazino-6-methyl (phenyl) tetrazolo[1,5-*b*][1,2,4]triazines as synthons for the construction of condensed and uncondensed heterocyclic systems by various reagents.

Experimental

Melting points were determined in capillary tubes in a MEL-TEMP II melting apparatus. The IR spectra were recorded on a Perkin-Elmer FT Paragon 1000 and Pye-Unicam SP-300 spectrometers. ^{1}H NMR spectra were scanned on a Varian Mercury VXR-3000 spectrometer using *TMS* as an internal standard. MS were recorded on a Shimadzu GCMS-Q 1000EX mass spectrometer at 70 eV. Microanalyses were performed by the Microanalytical Unit, Cairo University, Egypt, their results agreed with the calculated values. Cyclic amidrazones **1a** and **1b** were synthesized from 1,5-diaminotetrazole and α-ketoacids [13] followed by reaction with P_2S_5 and N_2H_4 (mp **1a** = 190°C; **1b** = 175°C).

*Synthesis of **2a** and **2b** (General Procedure)*
A solution of 3 mmol **1a** or **1b** in 10 cm^3 glacial acetic acid was boiled under reflux for 1 h and the solvent was evaporated *in vacuo*. The obtained residue was crystallized from methanol.

6,9-Dimethyl[1,2,4]triazolo[4,3-d]tetrazolo[1,5-b][1,2,4]triazine (**2a**, $C_6H_6N_8$)
Yield 0.42 g (74%); mp 210°C; IR: $\bar{\nu} = 1615$ (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.56$, 2.35 (2s, 2CH_3) ppm; MS: m/z (%) = 190 (M^+, 13).

9-Methyl-6-phenyl[1,2,4]triazolo[4,3-d]tetrazolo[1,5-b][1,2,4] triazine (**2b**, $C_{11}H_8N_8$)
Yield 0.51 g (66%); mp 235°C; IR: $\bar{\nu} = 1625$ (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 7.65$–7.20 (m, 5*Ar*H), 2.30 (s, CH_3) ppm; MS: m/z (%) = 252 (M^+, 24).

*Synthesis of **3a** and **3b** (General Procedure)*
A mixture of 3 mmol **1a** or **1b** in 2 cm^3 pyridine and 5 cm^3 benzoyl chloride was heated under reflux for 3 h. The reaction mixture was cooled at room temperature and poured onto ice-H_2O and then extracted with $CHCl_3$ (3×15 cm^3). The $CHCl_3$ extract was washed with 10% aqueous $NaHCO_3$ solution and H_2O, dried (Na_2SO_4), and evaporated. The obtained residue was crystallized from methanol.

6-Methyl-9-phenyl[1,2,4]triazolo[4,3-d]tetrazolo[1,5-b][1,2,4] triazine (**3a**, $C_{11}H_8N_8$)
Yield 0.45 g (59%); mp 220°C; IR: $\bar{\nu} = 1630$ (C=N) cm^{-1}; MS: m/z (%) = 252 (M^+, 25).

6,9-Diphenyl[1,2,4]triazolo[4,3-d]tetrazolo[1,5-b][1,2,4]triazine (**3b**, $C_{16}H_{10}N_8$)
Yield 0.62 g (65%); mp 240°C; IR: $\bar{\nu} = 1620$ (C=N) cm^{-1}; MS: m/z (%) = 315 (M^++1, 17.2).

*Synthesis of **4a** and **4b** (General Procedure)*
A suspension of 3 mmol **1a** or **1b** in 2 cm^3 pyridine was treated with 5 cm^3 ethyl chloroformate and the mixture was heated under reflux for 4 h. The reaction mixture was poured onto ice-water and the product which separated was filtered off, washed with water, and crystallized from methanol.

6-Methyl[1,2,4]triazolo[4,3-d]tetrazolo[1,5-b][1,2,4]triazin-9-(8H)-one (**4a**, $C_5H_4N_8O$)
Yield 0.44 g (76%); mp 200°C; IR: $\bar{\nu} = 3300$ (NH), 1680 (CON), 1625 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 11.80$ (s, NH, exchangeable), 2.31 (s, CH_3) ppm.

6-Phenyl-1,2,4-triazolo[4,3-d]tetrazolo[1,5-b][1,2,4]triazin-9-(8H)-one (**4b**, $C_{10}H_6N_8O$)
Yield 0.53 g (68%); mp 220°C; IR: $\bar{\nu} = 3400$ (NH), 1695 (CON), 1640 (C=N) cm^{-1}; MS: m/z (%) = 255 (M^++1, 9), 254 (M^+, 28).

*Synthesis of **5a** and **5b** or **6a** and **6b** (General Procedure)*
To a solution of 3 mmol **1a** or **1b** in 10 cm^3 methanol, 3 mmol pyruvic acid or ethyl pyruvate were added and the mixture was kept at ambient temperature for 24 h or heated at reflux for 1 h. The product which separated was filtered off, washed with ether, and crystallized from methanol.

Pyruvic acid {6-methyltetrazolo[1,5-b][1,2,4]triazin-7-yl}hydrazone (**5a**, $C_7H_8N_8O_2$)
Yield 0.56 g (76%); mp 170°C; IR: $\bar{\nu} = 3450$ (OH), 3220 (NH), 1710 (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 12.50$ (s, OH, exchangeable), 11.85 (s, NH, exchangeable), 2.50, 2.20 (2s, 2 CH_3) ppm; MS: m/z (%) = 236 (M^+, 30).

Pyruvic acid {6-phenyltetrazolo[1,5-b][1,2,4]triazin-7-yl}hydrazone (**5b**, $C_{12}H_{10}N_8O_2$)
Yield 0.71 g (77%); mp 165°C; IR: $\bar{\nu} = 3390$ (OH), 3190 (NH), 1720 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 12.90$ (s, OH, exchangeable), 12.10 (s, NH, exchangeable), 7.60–7.10 (m, 5 *Ar*H), 2.25 (s, CH_3) ppm.

Ethyl pyruvate {6-methyltetrazolo[1,5-b][1,2,4]triazin-7-yl} hydrazone (**6a**, $C_9H_{12}N_8O_2$)
Yield 0.84 g (74%); mp 175°C; IR: $\bar{\nu} = 3210$ (NH), 1730 (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 11.50$ (s, NH, exchangeable), 3.90 (q, CH_2), 2.60, 2.42 (2s, 2 CH_3), 1.42 (t, CH_3) ppm.

Ethyl pyruvate {6-phenyltetrazolo[1,5-b][1,2,4]triazin-7-yl} hydrazone (**6b**, $C_{14}H_{14}N_8O_2$)
Yield 0.71 g (71%); mp 160°C; IR: $\bar{\nu} = 3200$ (NH), 1720 (C=O), 1620 (C=N) cm^{-1}; MS: m/z (%) = 326 (M^+, 14).

6,9-Dimethyltetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-c][1,2,4]triazin-10(9H)-one (**7a**, $C_7H_6N_8O$)
A mixture of 2 mmol **5a** or **6a** and 10 cm^3 acetic acid was heated under reflux for 2 h and then evaporated to dryness. The obtained residue was crystallized from methanol. Yield 0.31 g (67%); mp 210°C; IR: $\bar{\nu} = 1680$ (CON), 1620 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.60$ (s, 2 CH_3) ppm; MS: m/z (%) = 218 (M^+, 12).

9-Methyl-6-phenyltetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-c][1,2,4] triazin-10(9H)-one (**7b**, $C_{12}H_8N_8O$)
This was similarly prepared from 2 mmol **5b** or **6b** and 10 cm^3 acetic acid; yield 0.41 g (62%); mp 225°C; IR: $\bar{\nu} = 1690$ (CON), 1620 (C=N) cm^{-1}; MS: m/z (%) = 281 (M^++1, 20), 280 (M^+, 2.7).

6-Metyltetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-c][1,2,4]-triazine-9,10(8H)-dione (**8a**, $C_6H_4N_8O_2$)
A mixture of 3 mmol **1a** and 3 mmol diethyl oxalate was heated for 1 h at 100°C. After attaining room temperature, the mixture was triturated with methanol and the product, which separated, was filtered off and crystallized from methanol; yield 0.42 g (64%); mp 240°C; IR: $\bar{\nu} = 3320$ (NH), 1690, 1650 (CON), 1595 (C=N) cm^{-1}; MS: m/z (%) = 220 (M^+, 16).

6-Phenyltetrazolo[1′,5′:2,3][1,2,4]triazino[5,4-c][1,2,4]triazine-9,10(8H)-dione (**8b**, $C_{11}H_6N_8O_2$)
It was similarly prepared from 3 mmol **1b** and 3 mmol diethyl oxalate; yield 0.52 g (60%); mp 250°C; IR: $\bar{\nu} = 3330$ (NH), 1700, 1680 (CON), 1600 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 12.10$ (s, NH, exchangeable), 7.20–7.50 (m, 5 *Ar*H) ppm; MS: m/z (%) = 282 (M^+, 20).

*Synthesis of **9a** and **9b** or **10a** and **10b** (General Procedure)*
A solution of 3 mmol **1a** or **1b** in 10 cm^3 methanol was added to 3 mmol acetylacetone or ethyl acetoacetate and the mixture was heated at reflux for 2 h. The separated product was filtered off, washed with ether, and crystallized from methanol.

Acetylacetone {6-methyltetrazolo[1,5-b][1,2,4]triazin-7-yl} hydrazone (**9a**, $C_9H_{12}N_8O$)
Yield 0.54 g (72%); mp 180°C; IR: $\bar{\nu} = 3335$ (NH), 1700 (C=O), 1625 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 11.92$ (s, NH, exchangeable), 4.10 (s, CH_2), 2.55, 2.35, 2.15 (3s, 3 CH_3) ppm.

Acetylacetone {6-phenyltetrazolo[1,5-b][1,2,4]triazin-7-yl} hydrazone (**9b**, $C_{14}H_{14}N_8O$)
Yield 0.61 g (64%); mp 190°C; IR: $\bar{\nu} = 3300$ (NH), 1710 (C=O), 1630 (C=N) cm^{-1}; MS: m/z (%) = 310 (M^+, 12.6).

Ethyl acetoacetate {6-methyltetrazolo[1,5-b][1,2,4]triazin-7-yl} hydrazone (**10a**, $C_{10}H_{14}N_8O_2$)
Yield 0.51 g (61%); mp 155°C; IR: $\bar{\nu} = 3290$ (NH), 1730 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 12.10$ (s, NH, exchangeable), 4.25 (q, CH_2), 3.95 (s, CH_2), 2.50, 2.20 (**2s**, 2 CH_3), 1.30 (t, CH_3) ppm; MS: m/z (%) = 278 (M^+, 6).

Ethyl acetoacetate {6-phenyltetrazolo[1,5-b][1,2,4]triazin-7-yl} hydrazone (**10b**, $C_{15}H_{16}N_8O_2$)
Yield 0.75 g (72%); mp 170°C; IR: $\bar{\nu} = 3300$ (NH), 1720 (C=O), 1635 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 11.94$ (s, NH, exchangeable), 7.70–7.20 (m, 5 *Ar*H), 4.10 (q, CH_2), 3.90 (s, CH_2), 2.35 (s, CH_3), 1.20 (t, CH_3) ppm; MS: m/z (%) = 341 (M^++1, 17), 340 (M^+, 22).

7-(3,5-Dimethylpyrazol-1-yl)-6-methyltetrazolo[1,5-b][1,2,4] triazine (**11a**, $C_9H_{10}N_8$)
A solution of 2 mmol **9a** in 10 cm^3 acetic acid was boiled under reflux for 2 h and then evaporated to dryness under reduced pressure. The obtained residue was crystallized from methanol; yield 0.31 g (67%); mp 200°C; IR: $\bar{\nu} = 1620$ (C=N)

cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 5.30$ (s, pyrazolyl CH), 2.52, 2.30, 2.25 (3s, 3 CH_3) ppm; MS: m/z (%) = 230 (M^+, 8).

7-(3,5-Dimethylpyrazol-1-yl)-6-phenyltetrazolo[1,5-b][1,2,4] triazine (**11b**, $C_{14}H_{12}N_8$)

The title compound was prepared from 2 mmol **9b** and 10 cm^3 acetic acid as described for the preparation of **11a**; yield 0.43 g (65%); mp 230°C; IR: $\bar{\nu} = 1635$ (C=N) cm^{-1}; MS: m/z (%) = 292 (M^+, 14).

7-(5-Hydroxy-3-methylpyrazol-1-yl)-6-methyltetrazolo[1,5-b] [1,2,4]triazine (**12a**, $C_8H_8N_8O$)

A solution of 2 mmol **10a** in 15 cm^3 freshly prepared 0.1 *M* sodium ethoxide solution was heated under reflux for 2 h. The resulting solution was neutralized with acetic acid and product which separated was filtered off and crystallized from methanol; yield 0.24 g (57%); mp 190°C; IR: $\bar{\nu} = 3390$ (OH), 1610 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 12.30$ (s, OH, exchangeable), 5.60 (s, pyrazolyl CH), 2.60, 2.35 (2s, 2 CH_3) ppm.

7-(5-Hydroxy-3-methylpyrazol-1-yl)-6-phenyltetrazolo[1,5-b] [1,2,4]triazine (**12b**, $C_{13}H_{10}N_8O$)

It was similarly prepared from 2 mmol **10b** and 15 cm^3 sodium ethoxide solution (0.1 *M*); yield 0.41 g (67%); mp 205°C; IR: $\bar{\nu} = 3400$ (OH), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 11.95$ (s, OH, exchangeable), 7.80–7.20 (m, 5 *Ar*H), 5.93 (s, pyrazolyl CH), 2.40 (s, CH_3) ppm; MS: m/z (%) = 294 (M^+, 17).

Antimicrobial Screening

Solutions of the test compounds, ampicillin trihydrate and clotrimazole were prepared in *DMSO* at a concentration of 1600 $\mu g/cm^3$. Twofold dilutions of the compounds were prepared (800, 400, ..., 6.25 g/cm^3). The microorganism suspensions at 10^6 Colony Forming Unit/cm^3 (*CFU*/cm^3) concentration were inoculated to the corresponding wells. Plates were incubated at 36°C for 24 to 48 h. The incubation chamber was kept sufficiently humid. At the end of the incubation period, the minimal inhibitory concentrations (*MIC*) were determined. Controls with *DMSO* and uninoculated media were also investigated.

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