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## DESIGN, SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF SOME AZOLE DERIVATIVES

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**Abstract:** Three new 1,3,4-oxadiazole, 1,3-thiazolidine and 1,2,4-triazole derivatives were obtained starting from furan-2-carbohydrazide. Then, 1,2,4-triazole compound was converted to the corresponding Mannich bases using several secondary amines including piperidine, piperazine, morpholine or thiomorpholine moiety. The synthesis of 5-(furan-2-yl)-4-[[[(4-methoxyphenyl)methylidene]amino]-4*H*-1,2,4-triazole-3-thiol (**XIII**) was performed starting from furan-2-carbohydrazide by three steps. The structures of the synthesized compounds were well characterized by elemental analyses, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectral studies. Newly synthesized compounds were screened for their antimicrobial activities and some of them displayed activity against the tested microorganisms.

**Keywords:** furan-2-carbohydrazide, 1,2,4-triazole, Mannich base, Schiff base, antimicrobial activity

Research and development of potent and effective antimicrobial agents represent one of the most important advances in therapeutics; the main aim of these efforts is not only control the serious infections, but also prevention and treatment of some infectious complications of other therapeutic modalities such as cancer chemotherapy and surgery. Over the past century, the decline in mortality and increase in life expectancy in North America and Europe is at least partially due to the discovery of new effective antibiotics (1, 2).

Over the past two decades, triazole derivatives attracted continued interest in the medicinal field owing to their varied biological activities such as antibacterial (3-7), fungicidal (8, 9), anti-inflammatory (10, 11), antihypertensive (12, 13), herbicidal (14, 15), antiviral (16), antagonistic (17) and antitumoral (18-24).

Triazoles were reported to exhibit stable properties to acidic and basic hydrolysis and also reductive-oxidative conditions. Favorable properties and enhanced biological activities of triazole nucleus were attributed to its dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions. This moiety is also known as relatively resistant to metabolic degradation.

Tazobactam, a  $\beta$ -lactamase inhibitor antibiotic, is the best known example of triazole containing structures (Fig. 1) (25-27). Other triazole containing drugs, itraconazole, fluconazole and posaconazole constitute an important class of antifungal agents having greater antifungal potency, lower toxicity, and a wider antifungal spectrum activity than the older imidazoles (28) (Fig. 1).

Among the important pharmacophores responsible for antimicrobial activity, the triazole scaffold is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antimicrobial agents. It was reported that the primary structural requirement for the antimicrobial azole class is a weakly basic imidazole or triazole ring bonded by a nitrogen-carbon linkage to the rest of the structure (1).

Piperazine and morpholine constitute other heterocyclic moieties important for antimicrobial activity. Several compounds that contain a piperazine or morpholine nucleus with antimicrobial activity have been synthesized; some of them contain an azole ring as well. For instance, while eperzolid, which is a member of the oxazolidinone class of antibacterial agents, consists of morpholine and oxazolidinone rings linked each other *via* a fluo-

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rophenylene linkage, another antibacterial, linezolid, contains a piperazine ring instead of morpholine (29). Piperacillin is an important example of extended spectrum  $\beta$ -lactam antibiotic containing a piperazine nucleus (Fig. 2).

Multicomponent reactions have been considered as a major part of synthetic organic chemistry with advantages ranging from lower reaction times and temperatures to higher yields. The amino alkylation of aromatic compounds by Mannich reaction has been reported to have a considerable importance for designing efficient bioactive molecules. Some Mannich bases derived from 1,2,4-triazoles carrying a methyl piperazine or morpholine ring have been described as possessing protozoicidal, antimicrobial or anticancer activities (30-35).

Despite the existence of a number of antimicrobial agents used for the treatment of infectious diseases, the misuse and overuse of them resulted in clinically resistant strains of fungi and bacteria. Due to this reason, it is crucial development of new class of antibiotics having different mechanisms of action than the existing ones.

As a part of our continuing study on the synthesis of biologically active compounds and on the basis of the fact that more efficacious antibacterial compounds can be designed by joining two or more biologically active heterocyclic systems together in a single molecular framework (36), this paper presents the synthesis of new triazole derivatives carrying two or more heterocyclic rings as hybrid molecules possessing antimicrobial activity.

## EXPERIMENTAL

### Synthesis

All the chemicals were purchased from Fluka Chemie AG Buchs (Switzerland). Melting points of the synthesized compounds were determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminium sheets. The mobile phase was ethyl acetate and detection was made using UV light. IR spectra were recorded for potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer.

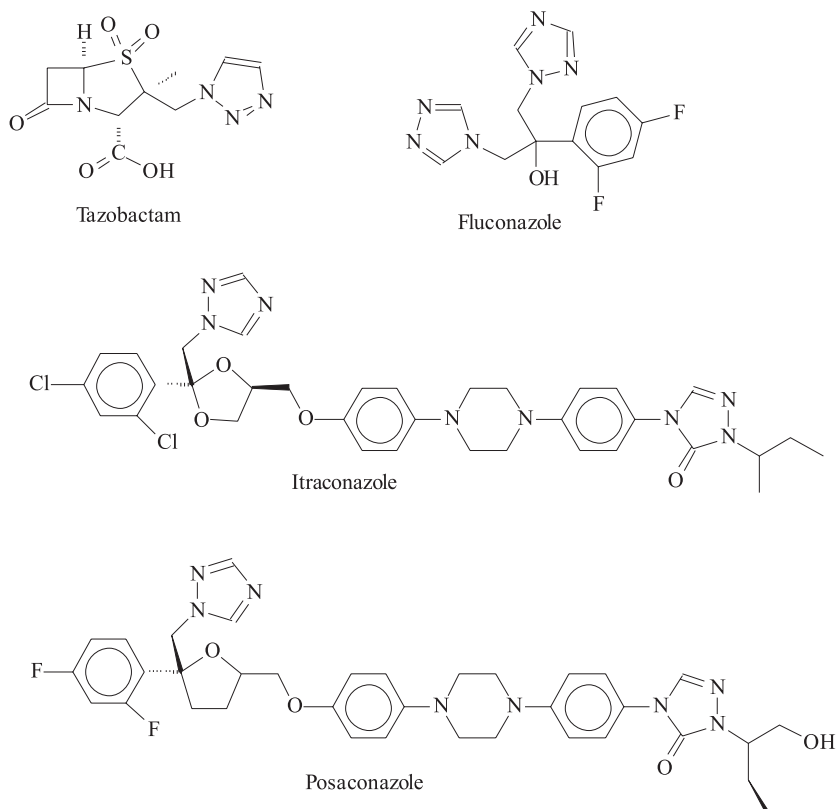


Figure 1. Triazole drugs

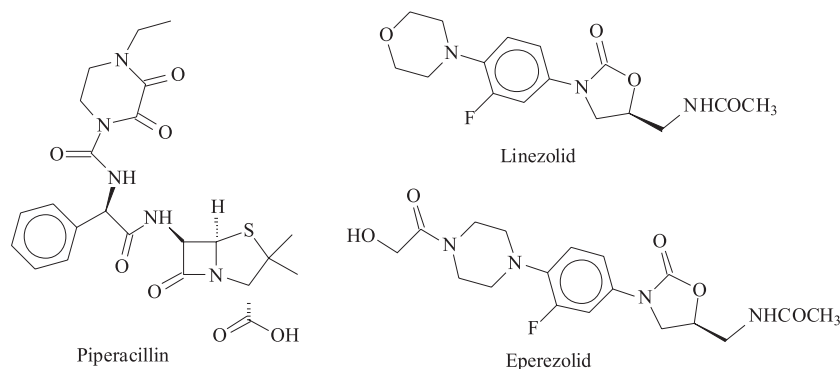


Figure 2. Some compounds with antimicrobial activity that contain piperazine or morpholine nucleus

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Bruker Avance II 400 MHz NMR spectrometer (chemical shift in ppm downfield from TMS as an internal reference). The elemental analysis was performed on a Costech Elemental Combustion System CHNS-O elemental analyzer. The mass spectra were obtained at a Quattro LC-MS (70 eV) instrument.

#### *N*-Benzyl-2-(furan-2-ylcarbonyl)hydrazinecarbothioamide (II)

A mixture of furan-2-carbohydrazide (10 mmol) and benzylisothiocyanate was allowed to reflux in ethanol for 4 h. On cooling it overnight in cold, a solid was obtained. This crude product was filtered off and recrystallized from ethanol to afford the desired compound **II**. Yield: 81%, m.p.: 196°C. IR (KBr,  $\text{cm}^{-1}$ ): 3309 (2NH), 3236 (NH), 1677 (C=O), 1563 (C=S).  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 4.68 (s, 2H,  $\text{CH}_2$ ), 6.63 (s, 1H, ArH), 7.19–7.28 (m, 6H, ArH), 7.87 (s, 1H, ArH), 8.67 (s, 1H, NH), 9.43 (s, 1H, NH), 10.32 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 47.35 ( $\text{CH}_2$ ), arom C: [112.57 (CH), 115.49 (CH), 127.25 (CH), 127.74 (CH), 128.26 (2CH), 128.68 (CH), 146.32 (CH), 140.18 (C), 146.99 (C)], 168.30 (C=O), 182.81 (C=S). MS:  $m/z$  (%): 105.84 (56), 126.67 (51), 166.76 (38), 184.84 (31), 190.72 (30), 196.91 (25), 241.89 (28), 275.85 ( $[\text{M}]^+$ , 21), 282.98 (43), 298.00 ( $[\text{M} + \text{Na}]^+$ , 43), 313.88 ( $[\text{M} - 1 + \text{K}]^+$ , 100), 383.41 (86). Analysis: calcd. for  $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ : 56.71 C, 4.76 H, 15.26 N, 11.65 S%; found: 56.82 C, 4.75 H, 15.15 N, 11.27 S%.

#### *N*-Benzyl-5-(furan-2-yl)-1,3,4-oxadiazol-2-amine (III)

4-Chlorophenacylbromide (10 mmol) and dried sodium acetate (50 mmol) were added to the

solution of compound **II** (10 mmol) in ethanol and the reaction mixture was refluxed for 12 h. Then, the reaction mixture was cooled to room temperature and the salt was separated by filtration. After evaporating the solvent under reduced pressure, an oily product appeared. On treating it with water, a solid was obtained. This crude product was recrystallized from ethyl acetate to afford the desired compound **III**. Yield 25%, m.p.: 180–182°C. IR (KBr,  $\text{cm}^{-1}$ ): 3221 (NH), 1629 (C=O).  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 4.42 (s, 2H,  $\text{CH}_2$ ), 6.67–6.70 (dd, 1H, ArH,  $J = 2.8, 2.6$  Hz), 7.01 (d, 1H, ArH,  $J = 3.4$  Hz), 7.24–7.37 (m, 5H, ArH), 7.90 (d, 1H, ArH,  $J = 0.8$  Hz), 8.45 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 46.74 ( $\text{CH}_2$ ), arom C: [112.19 (CH), 112.87 (CH), 127.86 (CH), 128.04 (2CH), 129.07 (2CH), 139.27 (C), 139.85 (C), 146.19 (CH), 151.71 (C), 163.71 (C)]. MS:  $m/z$  (%): 242.25 ( $[\text{M} + 1]^+$ , 100). Analysis: calcd. for  $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2$ : 64.72 C, 4.60 H, 17.42 N%; found: 64.94 C, 4.47 H, 17.10 N%.

#### *N'*-(3-Benzyl-4-oxo-1,3-thiazolidin-2-ylidene)furan-2-carbohydrazide (IV)

Ethyl bromoacetate (10 mmol) and dried sodium acetate (50 mmol) were added to the solution of compound **II** (10 mmol) in ethanol and the reaction mixture was refluxed for 12 h. Then, the reaction mixture was cooled to room temperature and the salt was separated by filtration. After evaporating the solvent under reduced pressure, an oily product appeared. On treating it with water, a solid was obtained. This crude product was recrystallized from ethanol to afford compound **IV**. Yield 27%, m.p.: 133–134°C. IR (KBr,  $\text{cm}^{-1}$ ): 3240 (NH), 1729 (C=O), 1651 (C=O).  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 4.13 (s, 2H,  $\text{CH}_2$ ), 4.88 (s, 2H,  $\text{CH}_2$ ), 6.61 (brs, 1H, ArH),

7.16 (s, 1H, ArH), 7.23-7.36 (m, 5H, ArH), 7.85 (s, 1H, ArH), 10.82 (s, 1H, NH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): 30.6 (S-CH<sub>2</sub>), 62.10 (CH<sub>2</sub>), arom C: [111.70 (CH), 112.87 (CH), 127.06 (2CH), 128.04 (2CH), 128.47 (CH), 145.60 (C), 146.01 (CH), 147.11 (C)], 151.7 (C=N), 167.20 (C=O), 171.45 (thiazol C=O). MS: m/z (%): 124.25 (100), 211.24 (62), 301.36 (28), 316.25 ([M + 1])<sup>+</sup>, 84). Analysis: calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>S: 57.13 C, 4.16 H, 13.33 N, 10.17 S%; found: 57.26 C, 4.16 H, 13.07 N, 9.72 S%.

#### 4-Benzyl-5-(furan-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (V)

A solution of compound **II** (10 mmol) in ethanol/water (1:1, v/v) was refluxed in the presence of 2M NaOH for 3 h then, the resulting solution was cooled to room temperature and acidified to pH 4 with 37% HCl. The precipitate formed was filtered off, washed with water and recrystallized from ethyl acetate : petroleum ether (1:3, v/v) to afford the desired compound **V**. Yield 92%, m.p.: 181-182°C. IR (KBr, cm<sup>-1</sup>): 3420 (NH), 1202 (C=S). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ, ppm): 5.47 (s, 2H, CH<sub>2</sub>), 6.61-6.64 (dd, 1H, ArH, *J* = 1.6, 1.6 Hz), 6.90 (d, 1H, ArH, *J* = 0.8 Hz), 7.14-7.32 (m, 5H, ArH), 7.88 (d, 1H, ArH, *J* = 1.0 Hz), 10.21 (s, 1H, NH), 14.21 (s, 1H, SH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): 47.53 (CH<sub>2</sub>), arom C: [112.75 (CH), 113.63 (CH), 127.16 (2CH), 128.26 (CH), 129.32 (2CH), 136.34 (2C), 140.29 (CH), 146.99 (C)], 140.39 (triazole C-5), 168.64 (triazole C-3). MS: m/z (%): 137.88 (48), 257.96 ([M]<sup>+</sup>, 23), 280.05 ([M + Na]<sup>+</sup>, 76), 296.07 ([M + K]<sup>+</sup>, 31), 358.09 (19), 383.30 (100). Analysis: calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>OS: 60.68 C, 4.31 H, 16.33 N, 12.46 S%; found: 60.30 C, 4.38 H, 16.00 N, 12.16 S%.

#### General method for the synthesis of compounds VI-X

The appropriate secondary amine (10 mmol) was added into a solution of compound **V** (10 mmol) in dry tetrahydrofuran and the mixture was stirred at room temperature in the presence of formaldehyde (40%, 1.5 mL) for 3 h. Then, the solvent was evaporated under reduced pressure and a solid appeared. The crude product was recrystallized from ethanol (for **VI**, **IX** and **X**), ethyl acetate (for **VIII**) or benzene: petroleum ether (1:1, v/v) (for **VII**) to yield the target compound.

#### 4-Benzyl-5-(furan-2-yl)-2-[(4-methylpiperazin-1-yl)methyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione (VI)

Yield: 97%, m.p.: 139-140°C. IR (KBr, cm<sup>-1</sup>): 3097 (ArCH), 1283 (C=S). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ,

ppm): 2.11 (s, 3H, CH<sub>3</sub>), 2.28 (s, 4H, 2CH<sub>2</sub>), 2.71 (s, 4H, 2CH<sub>2</sub>), 5.15 (s, 2H, CH<sub>2</sub>), 5.54 (s, 2H, CH<sub>2</sub>), 6.64-6.65 (m, 1H, ArH), 6.97 (d, 1H, ArH, *J* = 4.0 Hz), 7.13-7.31 (m, 5H, ArH), 7.91 (s, 1H, ArH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): 48.36 (CH<sub>3</sub>), 50.77 (2CH<sub>2</sub>), 52.36 (2CH<sub>2</sub>), 57.22 (CH<sub>2</sub>), 72.03 (CH<sub>2</sub>), arom C: [105.00 (CH), 108.10 (CH), 115.05 (CH), 116.46 (CH), 118.20 (CH), 126.12 (C), 129.16 (CH), 130.51 (CH), 131.57 (CH), 138.28 (C)], 142.71 (triazole C-5), 168.66 (triazole C-3). MS: m/z (%): 112.78 (100), 370.05 ([M + 1]<sup>+</sup>, 23). Analysis: calcd. (%) for C<sub>19</sub>H<sub>23</sub>N<sub>5</sub>OS: 61.76 C, 6.27 H, 18.95 N, 8.68 S; found: 61.61 C, 6.45 H, 18.68 N, 8.94 S.

#### 4-Benzyl-5-(furan-2-yl)-2-(morpholin-4-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (VII)

Yield: 95%, m.p.: 148-149°C. IR (KBr, cm<sup>-1</sup>): 3060 (ArCH), 1280 (C=S). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ, ppm): 2.71 (s, 4H, 2CH<sub>2</sub>), 3.55 (s, 4H, 2CH<sub>2</sub>), 5.15 (s, 2H, CH<sub>2</sub>), 5.54 (s, 2H, CH<sub>2</sub>), 6.64 (brs, 1H, ArH), 6.98 (brs, 1H, ArH), 7.15-7.30 (m, 5H, ArH) 7.91 (brs, 1H, ArH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): 48.64 (2CH<sub>2</sub>), 50.98 (2CH<sub>2</sub>), 66.72 (CH<sub>2</sub>), 70.04 (CH<sub>2</sub>), arom C: [112.90 (CH), 114.33 (CH), 126.99 (2CH), 128.37 (CH), 129.42 (2CH), 146.00 (CH), 136.06 (C), 140.00 (C)], 142.04 (triazole C-5), 169.72 (triazole C-3). MS: m/z (%): 127.80 (100), 357.04 ([M + 1]<sup>+</sup>, 40), 383.12 (69). Analysis: calcd. for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S: 60.65 C, 5.66 H, 15.72 N, 9.00 S%; found: 60.28 C, 5.78 H, 16.00 N, 8.65 S%.

#### 4-Benzyl-5-(furan-2-yl)-2-[(4-phenylpiperazin-1-yl)methyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione (VIII)

Yield: 90%, m.p.: 157-158°C. IR (KBr, cm<sup>-1</sup>): 3058 (ArCH), 1318 (C=S). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ, ppm): 2.87 (s, 4H, 2CH<sub>2</sub>), 3.12 (s, 4H, 2CH<sub>2</sub>), 5.23 (s, 2H, CH<sub>2</sub>), 5.54 (s, 2H, CH<sub>2</sub>), 6.63-6.66 (m, 1H, ArH), 6.78 (t, 1H, ArH, *J* = 8.0 Hz), 6.89 (d, 2H, ArH, *J* = 8.2 Hz), 6.97 (d, 1H, ArH, *J* = 3.4 Hz), 7.13-7.30 (m, 7H, ArH) 7.91 (d, 1H, ArH, *J* = 1.6 Hz). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): 48.66 (2CH<sub>2</sub>), 49.01 (2CH<sub>2</sub>), 50.56 (CH<sub>2</sub>), 69.87 (CH<sub>2</sub>), arom C: [112.90 (CH), 114.30 (2CH), 116.36 (2CH), 119.72 (CH), 126.98 (2CH), 128.34 (CH), 129.41 (2CH), 129.60 (2CH), 136.07 (C), 139.90 (C), 142.72 (C)], 151.71 (triazole C-5), 169.66 (triazole C-3). MS: m/z (%): 119.79 (85), 162.82 (100), 174.83 (31), 383.12 (29), 432.16 ([M+1]<sup>+</sup>, 9). Analysis: calcd. for C<sub>24</sub>H<sub>25</sub>N<sub>5</sub>OS: 66.80 C, 5.84 H, 16.23 N, 7.43 S%; found: 66.82 C, 5.44 H, 16.00 N, 7.11 S%.

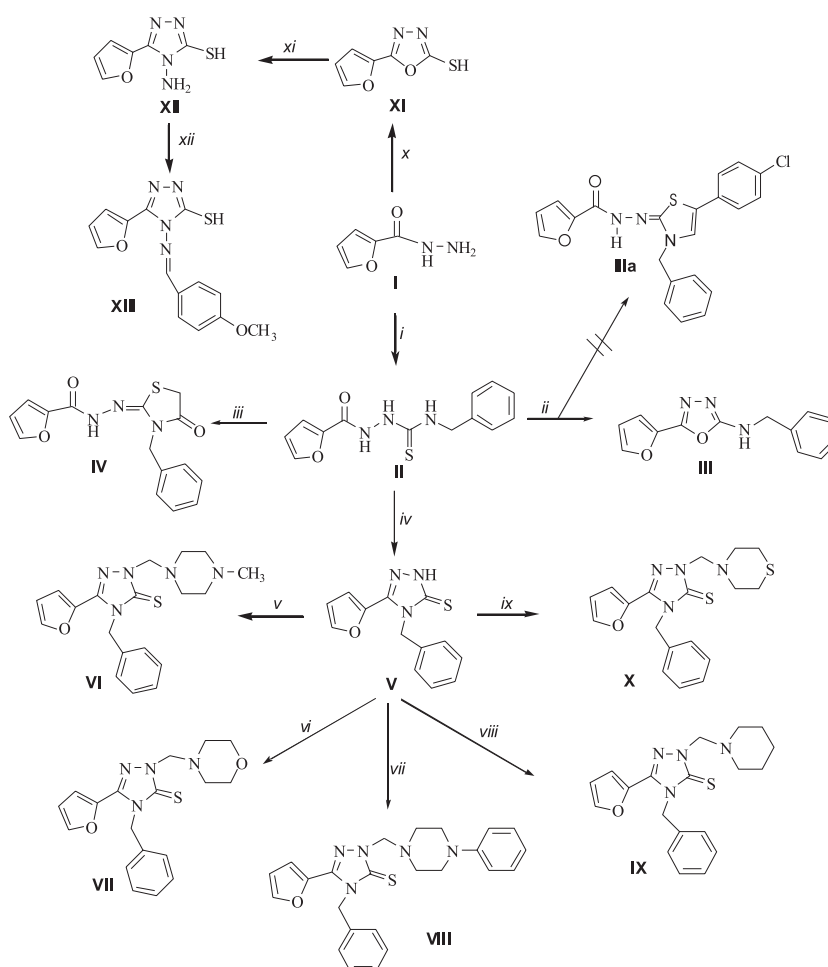
**4-Benzyl-5-(furan-2-yl)-2-(piperidin-1-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IX)**

Yield: 83%, m.p.: 108-109°C. IR (KBr,  $\text{cm}^{-1}$ ): 3104 (ArCH), 1317 (C=S).  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 1.31 (brs, 2H,  $\text{CH}_2$ ), 1.47 (brs, 4H,  $2\text{CH}_2$ ), 2.68 (s, 4H,  $2\text{CH}_2$ ), 5.12 (s, 2H,  $\text{CH}_2$ ), 5.54 (s, 2H,  $\text{CH}_2$ ), 6.65 (brs, 1H, ArH), 6.97 (d, 1H, ArH,  $J = 4.0$  Hz), 7.17 (brs, 2H, ArH), 7.23-7.30 (m, 3H, ArH), 7.91 (s, 1H, ArH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 24.09 ( $\text{CH}_2$ ), 26.17 ( $\text{CH}_2$ ), 48.57 ( $2\text{CH}_2$ ), 51.89 ( $2\text{CH}_2$ ), 71.01 ( $\text{CH}_2$ ) arom C: [112.84 ( $2\text{CH}$ ), 114.18 (CH), 127.03 ( $2\text{CH}$ ), 128.29 (CH), 129.37 ( $2\text{CH}$ ), 136.16 (C), 140.00 (C)], 142.55 (triazole C-5), 169.54 (triazole C-3). MS:  $m/z$  (%): 354.18 ( $[\text{M}]^+$ , 100), 355.15 ( $[\text{M} + 1]^+$ , 26). Analysis: calcd. for

$\text{C}_{19}\text{H}_{22}\text{N}_4\text{OS}$ : 64.38 C, 6.26 H, 15.81 N, 9.05 S%; found: 64.30 C, 6.15 H, 15.60 N, 9.45 S%.

**4-Benzyl-5-(furan-2-yl)-2-(thiomorpholin-4-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (X)**

Yield: 85%, m.p.: 128-129°C. IR (KBr,  $\text{cm}^{-1}$ ): 3131 (ArCH), 1281 (C=S).  $^1\text{H}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 2.60 (s, 4H,  $2\text{CH}_2$ ), 3.00 (s, 4H,  $2\text{CH}_2$ ), 5.16 (s, 2H,  $\text{CH}_2$ ), 5.54 (s, 2H,  $\text{CH}_2$ ), 6.66 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.17 (brs, 2H, ArH), 7.27 (brs, 3H, ArH), 7.92 (s, 1H, ArH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ,  $\delta$ , ppm): 27.81 ( $\text{CH}_2$ ), 48.64 ( $2\text{CH}_2$ ), 53.02 ( $2\text{CH}_2$ ), 71.44 ( $\text{CH}_2$ ), arom C: [112.87 ( $2\text{CH}$ ), 114.28 (CH), 127.03 ( $2\text{CH}$ ), 128.32 (CH), 129.38 ( $2\text{CH}$ ), 136.11



Scheme 1. Synthetic pathway for the preparation of compounds II-XIII. *i*:  $\text{PhCH}_2\text{NCS}$ , *ii*:  $\text{ClC}_6\text{H}_4\text{COCH}_2\text{Cl}$ , *iii*:  $\text{BrCH}_2\text{CO}_2\text{Et}$ , *iv*:  $\text{NaOH}$ , *v*:  $\text{HCHO}$  and methyl piperazine, *vi*:  $\text{HCHO}$  and morpholine, *vii*:  $\text{HCHO}$  and 4-fluorophenyl piperazine, *viii*:  $\text{HCHO}$  and piperidine, *ix*:  $\text{HCHO}$  and thiomorpholine, *x*:  $\text{CS}_2$  and  $\text{KOH}$ , *xi*:  $\text{NH}_3(\text{aq})$ , *xii*:  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHO}$ .

(C), 139.96 (C)], 142.74 (triazole C-5), 169.52 (triazole C-3). MS: m/z (%): 258.15 (100), 373.34 ([M]<sup>+</sup>, 46), 383.41 (86), 413.45 ([M+2+K]<sup>+</sup>, 55). Analysis: calcd. for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>OS<sub>2</sub>: 58.04 C, 5.41 H, 15.04 N, 17.22 S%; found: 58.30 C, 5.15 H, 15.00 N, 17.16 S%.

#### 5-(Furan-2-yl)-1,3,4-oxadiazole-2-thiol (XI)

Furan-2-carbohydrazide (10 mmol) and CS<sub>2</sub> (10 mmol) were added to a solution of KOH (0.56 g, 10 mmol) in 50 mL H<sub>2</sub>O and 50 mL ethanol and the mixture was refluxed for 4 h. Then, the reaction content was acidified with conc. HCl. The precipitate was filtered off, washed with H<sub>2</sub>O and recrystallized from benzene to afford compound XI. Yield 89%, m.p.: 166-167°C. IR (KBr, cm<sup>-1</sup>): 3104 (ArCH), 2774 (SH). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ, ppm): 6.73-6.76 (dd, 1H, ArH, J = 1.6, 1.6 Hz), 7.31 (t, 1H, ArH, J = 3.4 Hz), 8.00 (d, 1H, ArH, J = 0.6 Hz). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): arom C: [113.34 (CH), 115.75 (CH), 138.16 (C), 147.87 (CH)], 154.21 (oxadiazole C-5), 177.36 (oxadiazole C-2). MS: m/z (%): 108.85 (44), 110.79 (100), 113.86 (38), 125.75 (58), 134.82 (33), 168.87 ([M]<sup>+</sup>, 23). Analysis: calcd. for C<sub>6</sub>H<sub>4</sub>N<sub>2</sub>O<sub>2</sub>S: 42.85 C, 2.40 H, 16.66 N, 19.07 S%; found: 43.66 C, 2.27 H, 16.65 N, 19.25 S%.

#### 4-Amino-5-(furan-2-yl)-4H-1,2,4-triazole-3-thiol (XII)

To the solution of compound XI (10 mmol) in butanol, hydrazine hydrate (25 mmol) was added

and the reaction mixture was refluxed for 4 h. On cooling it overnight in cold, a solid was obtained. The precipitate was filtered off and recrystallized from ethanol to afford compound XII. Yield 54%, m.p.: 187-188°C. IR (KBr, cm<sup>-1</sup>): 3328 (NH<sub>2</sub>), 2917 (SH). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ, ppm): 5.81 (s, 1H, NH<sub>2</sub>), 6.69-6.72 (dd, 1H, ArH, J = 1.6, 2.0 Hz), 7.37 (d, 1H, ArH, J = 3.4 Hz), 7.91 (d, 1H, ArH, J = 1.0 Hz), 13.93 (s, 1H, SH). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, δ, ppm): arom C: [111.75 (CH), 113.87 (CH), 139.65 (C), 145.06 (CH)], 142.71 (triazole C-5), 166.35 (triazole C-3). MS: m/z (%): 182.20 ([M]<sup>+</sup>, 100), 183.30 ([M+1]<sup>+</sup>, 18). Analysis: calcd. for C<sub>6</sub>H<sub>4</sub>N<sub>2</sub>OS: 39.55 C, 3.32 H, 30.75 N, 17.60 S%; found: 39.91 C, 3.14 H, 30.87 N, 17.65 S%.

#### 5-(Furan-2-yl)-4-[(4-methoxyphenyl)methylene]amino-4H-1,2,4-triazole-3-thiol (XIII)

To the solution of compound XII (10 mmol) in ethanol anisaldehyde (10 mmol) was added and the reaction mixture was heated under reflux for 3 h. On cooling it overnight in cold, a solid appeared. The precipitate was filtered off and recrystallized from ethyl acetate to give compound XIII. Yield 62%, m.p.: 210-211°C. IR (KBr, cm<sup>-1</sup>): 3099 (ArCH), 2974 (SH), 1568 (C=N). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ, ppm): 3.85 (s, 3H, O-CH<sub>3</sub>), 6.70 (s, 1H, ArH), 7.07 (d, 1H, ArH, J = 3.6 Hz), 7.12 (d, 2H, ArH, J = 8.6 Hz), 7.90 (d, 1H, ArH, J = 3.8 Hz), 7.94 (d, 2H, ArH, J = 4.0 Hz), 9.54 (s, 1H, N=CH). <sup>13</sup>C NMR

Table 1. Screening for antimicrobial activity of the compounds (mm).

Comp. no.	Microorganisms and inhibition zone (mm)									
	Ec	Ea	Yp	Pa	Sa	Ef	Bc	Ms	Ca	Sc
V	8	10	12	-	-	-	-	-	-	-
VI	-	-	10	10	13	-	10	15	8	8
VII	8	8	12	10	13	10	13	20	6	8
VIII	6	6	8	8	6	6	6	10	6	6
IX	6	6	10	10	13	6	10	15	8	8
X	-	-	-	-	10	6	6	20	-	-
XI	-	-	-	-	-	-	-	20	-	-
XII	-	-	-	-	12	-	-	15	9	20
XIII	-	-	-	-	-	-	-	-	7	20
Amp.	10	10	18	18	35	10	15			
Strep.								35		
Flu									25	> 25

Ec: *Escherichia coli* ATCC 25922, Ea: *Enterobacter aerogenes* ATCC 13048 Yp: *Yersinia pseudotuberculosis* ATCC 911, Pa: *Pseudomonas aeruginosa* ATCC 43288, Sa: *Staphylococcus aureus* ATCC 25923, Ef: *Enterococcus faecalis* ATCC 29212, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis* ATCC607, Ca: *Candida albicans* ATCC 60193, Sc: *Saccharomyces cerevisiae* RSKK 251, Amp.: ampicillin, Strep.: streptomycin, Flu.: fluconazole.

(DMSO- $d_6$ ,  $\delta$ , ppm): 56.28 (OCH<sub>3</sub>), arom C: [112.81 (CH), 115.19 (CH), 115.51 (2CH), 124.87 (C), 131.60 (2CH), 132.51 (CH), 140.19 (C), 142.17 (C)], 162.49 (triazole C-5), 163.84 (triazole C-3), 167.40 (N=CH). MS:  $m/z$  (%): 300.34 ([M]<sup>+</sup>, 85), 323.38 ([M + Na]<sup>+</sup>, 78), 182.20 (45). Analysis: calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>S: 55.99 C, 4.03 H, 18.65 N, 10.68 S%; found: 56.25 C, 4.44 H, 18.47 N, 10.97 S%.

### Microbiology

All tested microorganisms were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* (*E. coli*) ATCC35218, *Enterobacter aerogenes* (*E. aerogenes*) ATCC13048, *Yersinia pseudotuberculosis* (*Y. pseudotuberculosis*) ATCC911, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC43288, *Staphylococcus aureus* (*S. aureus*) ATCC25923, *Enterococcus faecalis* (*E. faecalis*) ATCC29212, *Bacillus cereus* (*B. cereus*) 709 Roma, *Mycobacterium smegmatis* (*M. smegmatis*) ATCC607, *Candida albicans* (*C. albicans*) ATCC60193, *Candida tropicalis* (*C. tropicalis*) ATCC 13803, *Aspergillus niger* (*A. niger*) RSKK 4017 and *Saccharomyces cerevisiae* (*S. cerevisiae*) RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethyl sulfoxide to prepare extract stock solution of 5.000  $\mu\text{g/ml}$ .

### Agar-well diffusion method.

Screening test using agar-well diffusion method (37) as adapted earlier (38) was used for all newly synthesized compounds. Each microorganism was suspended in Mueller Hinton (MH) (Difco, Detroit, MI) broth and diluted approximately to 10<sup>6</sup> colony forming unit (cfu)/mL. They were "flood-inoculated" onto the surface of MH agar and Sabouraud Dextrose Agar (SDA) (Difco, Detroit, MI) and then dried. For *C. albicans* and *C. tropicalis*, SDA were used. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 mL of the extract substances was delivered into the wells. The plates were incubated for 18 h at 35°C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10  $\mu\text{g}$ ), streptomycin (10  $\mu\text{g}$ ) and fluconazole (5  $\mu\text{g}$ ) were standard drugs. Dimethyl sulfoxide and ethanol were used as solvent controls. The antimicrobial activity results are summarized in Table 1.

Microbiological results of the synthesized compounds screened are presented in Table 1. The compounds not included in Table 1 were found to be inactive against the tested microorganisms.

According to the obtained results, only the compounds having a triazole nucleus in their structures displayed varying degrees of activities with the inhibition zone between 8-20 mm. Among these, compound **V** and its Mannich base **VI** containing methyl piperazine moiety showed good activity against *E. coli*, *E. aerogenes* and *Y. pseudotuberculosis*. When compared to ampicillin, these compounds (**V** and **VI**) exhibited equal activity on *E. aerogenes* with the inhibition zone 10 mm.

Among the Mannich bases [**VI-X**] the substitution of methyl piperazine moiety by other heterocyclic rings such as morpholine (for **VII**), phenyl piperazine (for **VIII**) or piperidine (for **IX**) resulted in the additional activities towards the other tested microorganisms. The activity of **VII** against *E. faecalis* was equal to that of ampicillin. On the other hand, the introduction of thiomorpholine nucleus to the 1,2,4-triazole skeleton resulted in the activity against *S. aureus*, *E. faecalis*, *B. cereus* and *M. smegmatis*.

### Acknowledgment

The support provided by Karadeniz Technical University, BAP, Turkey (Ref. No. 2007.111.002.5) is gratefully acknowledged.

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*Received: 5. 01. 2012*