

## Pyridazine and its related compounds. Part 35 [1]: Synthesis, characterization and antimicrobial activity of some novel pyridazine and triazolopyridazine containing sulfonamides

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### ABSTRACT

The present study describes the chemical synthesis and antimicrobial evaluation of some new pyridazine and triazolopyridazine derivatives. The structure assignments of the new compounds are based on chemical and spectroscopic evidences. The Study results showed that derivatives **6a**, **6b**, **6g** and **6i** have promising inhibitory activity against (*Micrococcus luteus*). Compound **6i** has also noticeable inhibition activity against (*Escherichia coli*) and compound **3g** show remarkable activity against (*Candida albicans*). Rest of compounds showed moderate to low activity against the examined microorganisms.

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### 1. Introduction

In recent years, there has been increasing interest in the chemistry of pyridazine family of heterocycles due to their diverse biological significance studied in large number of papers [1], this variety of biological activities includes anti-HIV [2], anti-tobacco mosaic virus Tobacco Mosaic Virus (TMV) [3], antidepressant [4], antiviral [5], anti-cancer [6], analgesic, anti-inflammatory [7], and selective CB2 agonists for the treatment of inflammatory pain [8].

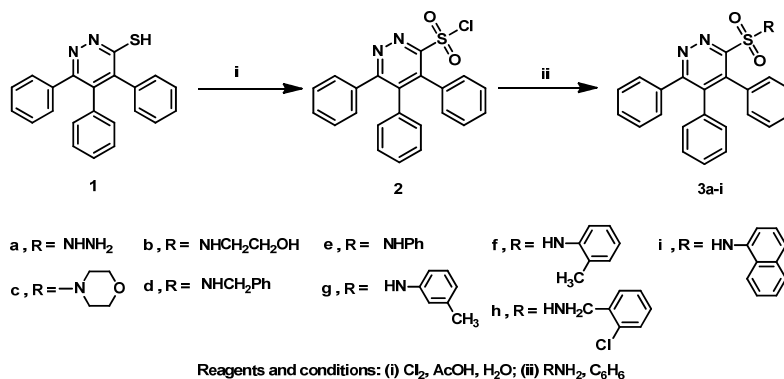
Moreover, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance, such as antitumor, anti-inflammatory, antimicrobial, anti-thrombotic and anticonvulsant activities [9], also a large number of triazole-containing ring systems exhibit antifungal and antiviral properties [10]. Sulfonamide group forms the bioactive moiety of many therapeutic agents such as diuretics, antidiabetics, antibiotics, and antibacterials [11-16]. So, our efforts were directed towards the synthesis of new heterocyclic compounds containing pyridazine moiety with anticipated biological activities. In this paper, the synthesis of

new pyridazine and triazolopyridazine derivatives carrying sulfonamide groups is reported. These compounds were characterized by various spectroscopic methods. Antimicrobial activities for some derivatives were assessed against representative Gram positive bacteria (*Micrococcus luteus*, *Staphylococcus aureus*), Gram negative bacteria (*Escherichia coli*) and fungi (*Candida albicans*).

### 2. Experimental

#### 2.1. Chemistry

All melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a Bruker Vector 22 Germany spectrometer (KBr). <sup>1</sup>H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer and <sup>13</sup>C NMR spectra on JMS-AX500 (125 MHz), using tetramethylsilane (TMS) as an internal reference. The electron impact mass spectra were obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60F<sub>254</sub> aluminum sheets (Merck) and spots were detected by



Scheme 1

UV lamp at 254-365 nm. The synthesis of 4,5,6-triphenylpyridazine-3(2*H*)-thione (**1**) [17], 6,7,8-triphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-thiol (**4**) [18] and their corresponding sulfonylchloride derivatives **2** and **5** were performed according to known procedure [19].

## 2.2. Antimicrobial activity

Antimicrobial activity study was performed using standard cultures of *Micrococcus luteus* (ATCC10240), *Staphylococcus aureus* (ATCC6538P), *Escherichia coli* (ATCC10536) and *Candida albicans* (ATCC2091). *Micrococcus luteus*, *Staphylococcus aureus* *Staphylococcus aureus* and *E. coli* cultures were incubated in Nutrient Broth (NB) (Difco), while *Candida albicans* was incubated in Sabouraud Dextrose Broth (SDB) (Difco), dimethylformamide was used as a solvent for tested compounds. A blank disc impregnated with dimethylformamide followed by drying off was used as a negative control. Sulfadoxine, sulfadimidine and nystatin at concentration of 0.4 mg/0.1 mL in dimethylformamide were used as positive control (Table 1).

## 2.3. Synthesis

### 2.3.1. Preparation of 4,5,6-triphenylpyridazine-3-sulfonyl chloride (**2**)

In a solution of 3-mercapto derivative **1** (2.9 mmol) in acetic acid (19 mL) and water (1 mL), chlorine gas was bubbled at 0 °C for 1 h. The reaction mixture was poured into water (250 mL) portion-wise with stirring; the precipitate was filtered, washed with water several times and dried to give 3-sulfonylchloride derivative **2** in 92% yield. The respective crude sulfonylchloride was used in the next step without further purification (Scheme 1).

### 2.3.2. Preparation of 4,5,6-triphenylpyridazine-3-sulfonamide derivatives (**3a-i**)

To a solution of sulfonylchloride derivative **2** (2.46 mmol) in benzene (20 mL), substituted amine was added (2.46 mmol), the reaction mixture was refluxed for 3 hours, the solvent was evaporated *in vacuo*, the solid product was collected and recrystallized from ethanol (Scheme 1).

**4,5,6-Triphenylpyridazine-3-sulfonohydrazide (3a)**: Prepared from hydrazine hydrate. Color: White crystals. Yield: 85%. M.p.: 295-298 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3390 (NH), 3230, 3150 ( $\text{NH}_2$ ), 1617 (C=N), 1350, 1160 ( $\text{SO}_2$ ).  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 8.10 (s, 1H, NH), 7.89-7.42 (m, 15H, Ar-H), 2.80 (s, 2H,  $\text{NH}_2$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 158.9 (C-6), 157.9 (C-3), 137.4 (C-4), 136.7 (C-5), 135.7 (C-5), 134

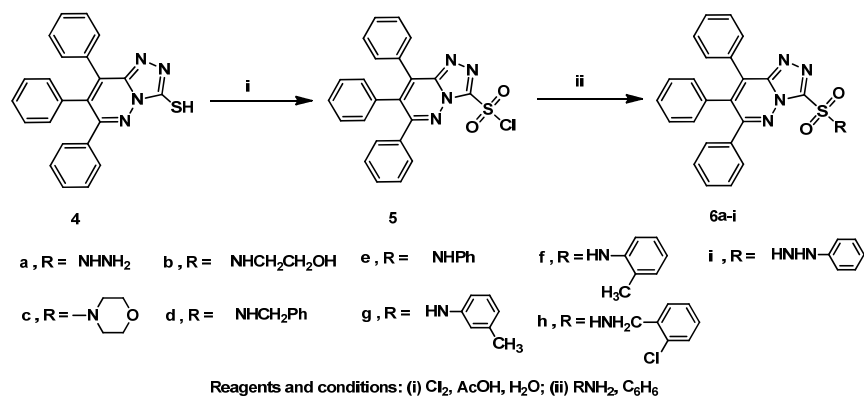
(C-4), 130.2-128.5 (3Ph). MS ( $m/z$  (%)): 402 ( $\text{M}^+$ , 7.87), 338 ( $\text{M}^+ - \text{SO}_2$ , 100,  $\text{F}_1$ ), 322 ( $\text{F}_1 - \text{NH}_2$ , 39.29,  $\text{F}_2$ ), 296 ( $\text{F}_2 - \text{CH}_2 = \text{NH}$ , 2.81), 236 ( $\text{F}_2 - \text{Ph}$ , 3.47). Anal. calcd. for  $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ : C, 65.65; H, 4.51; N, 13.92. Found: C, 65.50; H, 4.35; N, 13.76%.

**N-(2-Hydroxyethyl)-4, 5, 6-triphenylpyridazine-3-sulfonamide (3b)**: Prepared from ethanolamine. Color: White crystals. Yield: 75.4%. M.p.: 285-287 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3420 (OH), 3285 (NH), 2921 ( $\text{CH}_{\text{aliph}}$ ), 1639 (C=N), 1368, 1167 ( $\text{SO}_2$ ).  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 8.30 (s, 1H, NH), 7.89-7.42 (m, 15H, Ar-H), 2.90 (t, 2H,  $\text{CH}_2\text{NH}$ ), 3.50 (t, 2H,  $\text{CH}_2\text{OH}$ ), 3.75 (s, 1H, OH).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 157.9 (C-6), 156.9 (C-3), 136.4 (C-4), 135.7 (C-5), 134.7 (C-5), 133 (C-4), 129.2-127.5 (Ar-C), 61.1 (C-OH), 46.5 (C-NH). MS ( $m/z$  (%)): 431 ( $\text{M}^+$ , 8.02), 386 ( $\text{M}^+ - \text{CH}_2\text{CH}_2\text{OH}$ , 7.39,  $\text{F}_1$ ), 371 ( $\text{F}_1 - \text{NH}_2$ , 8.56,  $\text{F}_2$ ), 346 ( $\text{F}_2 - \text{N}_2$ , 9.18,  $\text{F}_3$ ), 271 ( $\text{F}_3 - \text{Ph}$ , 7.62,  $\text{F}_4$ ). Anal. calcd. for  $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ : C, 66.80; H, 4.91; N, 9.74. Found: C, 66.65; H, 4.76; N, 9.60%.

**4-((4,5,6-Triphenylpyridazin-3-yl)sulfonyl)morpholine (3c)**: Prepared from morpholine. Color: White crystals. Yield: 80.3%. M.p.: 188-190 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3057 ( $\text{CH}_{\text{arom}}$ ), 2915 ( $\text{CH}_{\text{aliph}}$ ), 1624 (C=N), 1351, 1158 ( $\text{SO}_2$ ).  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 7.89-7.42 (m, 15H, Ar-H), 2.98 (t, 4H,  $\text{CH}_2\text{NCH}_2$ ), 3.85 (t, 4H,  $\text{CH}_2\text{OCH}_2$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 158.4 (C-6), 157.4 (C-3), 136.9 (C-4), 136.2 (C-5), 135.2 (C-5), 134.0 (C-4), 130.1-128.2 (Ar-C), 67.3 (C-O-C), 49.2 (C-N-C). MS ( $m/z$  (%)): 455 ( $\text{M}^+ - 2$ , 0.62), 393 ( $\text{M}^+ - \text{SO}_2$ , 4.54,  $\text{F}_1$ ), 308 ( $\text{F}_1 - \text{NC}_4\text{H}_8\text{O}$ , 88.63,  $\text{F}_2$ ), 280 ( $\text{F}_2 - \text{N}_2$ , 4.40). Anal. calcd. for  $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ : C, 68.25; H, 5.07; N, 9.18. Found: C, 68.10; H, 4.90; N, 9.01%.

**N-Benzyl-4, 5, 6-triphenylpyridazine-3-sulfonamide (3d)**: Prepared from benzyl amine. Color: White crystals. Yield: 76.9%. M.p.: 275-277 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3381 (NH), 2890 ( $\text{CH}_{\text{aliph}}$ ), 1636 (C=N), 1377, 1146 ( $\text{SO}_2$ ).  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 8.54 (s, 1H, NH), 7.31-7.10 (m, 15H, Ar-H), 7.08-7.05 (m, 5H, Ar-H), 4.10 (s, 2H,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 157.9 (C-6), 156.9 (C-3), 136.4 (C-4), 135.7 (C-5), 134.7 (C-5), 133.0 (C-4), 129.2-126.7 (Ar-C), 48.5 (C-NH). MS ( $m/z$  (%)): 478 ( $\text{M}^+ + 1$ , 17.29), 341 (100). Anal. calcd. for  $\text{C}_{29}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$ : C, 72.93; H, 4.85; N, 8.80. Found: C, 72.79; H, 4.70; N, 8.65%.

**N, 4, 5, 6-Tetraphenylpyridazine-3-sulfonamide (3e)**: Prepared from aniline. Color: White crystals. Yield: 92.6%. M.p.: 290-292 °C. FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3316 (NH), 3036 ( $\text{CH}_{\text{arom}}$ ), 1644 (C=N), 1354, 1222 ( $\text{SO}_2$ ).  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 8.10 (s, 1H, NH), 7.89-6.82 (m, 20H, Ar-H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ ,  $\delta$ , ppm): 158.9 (C-6), 157.9 (C-3), 137.4 (C-4), 136.7 (C-5), 135.7 (C-5), 134.0 (C-4), 129.2-119.4 (Ar-C). MS ( $m/z$  (%)): 464 ( $\text{M}^+$ , 30.6), 370 ( $\text{M}^+ - \text{NHPh}$ , 0.72,  $\text{F}_1$ ), 308 ( $\text{F}_1 - \text{SO}_2$ , 1.14,  $\text{F}_2$ ), 2804 ( $\text{F}_2 - \text{N}_2$ , 3.75,  $\text{F}_3$ ). Anal. calcd. for  $\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ : C, 72.55; H, 4.57; N, 9.06. Found: C, 72.40; H, 4.41; N, 8.83%.



Scheme 2

**4,5,6-Triphenyl-N-(*o*-tolyl)pyridazine-3-sulfonamide (3f):** Prepared from *o*-tolidine. Color: White crystals. Yield: 81.1%. M.p.: 280-282 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 3350 (NH), 2915 (CH<sub>aliph</sub>), 1640 (C=N), 1304, 1137 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 9.10 (s, 1H, NH), 7.94-7.42 (m, 19H, Ar-H), 3.1 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 158.9 (C-6), 157.9 (C-3), 137.4 (C-4), 136.7 (C-5), 135.7 (C-5), 134.0 (C-4), 130.2-128.5 (Ar-H), 19.3 (CH<sub>3</sub>). MS (*m/z* (%)): 477 (M<sup>+</sup>, 37.82), 308 (M<sup>+</sup>-SO<sub>2</sub>NHC<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, 7.64, F<sub>1</sub>), 280 (F<sub>1</sub>-N<sub>2</sub>, 7.64, F<sub>2</sub>), 204 (F<sub>2</sub>-Ph, 16.77, F<sub>3</sub>), 106 (F<sub>3</sub>-C<sub>8</sub>H<sub>8</sub>, 100, F<sub>4</sub>). Anal. calcd. for C<sub>29</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>S: C, 72.93; H, 4.85; N, 8.80. Found: C, 72.88; H, 4.70; N, 8.65%.

**4,5,6-Triphenyl-N-(*m*-tolyl)pyridazine-3-sulfonamide (3g):** Prepared from *m*-tolidine. Color: White crystals. Yield: 76.9%. M.p.: 218-220 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 3279 (NH), 3107 (CH<sub>arom</sub>), 2918 (CH<sub>aliph</sub>), 1636 (C=N), 1365, 1163 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 9.10 (s, 1H, NH), 7.94-6.70 (m, 19H, Ar-H), 3.20 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 159.9 (C-6), 158.9 (C-3), 138.4 (C-4), 137.7 (C-5), 136.7 (C-5), 135.0 (C-4), 129.2-119.4 (Ar-C), 22.5 (CH<sub>3</sub>). MS (*m/z* (%)): 477 (M<sup>+</sup>, 1.96), 387 (M<sup>+</sup>-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, 0.4, F<sub>1</sub>), 323 (F<sub>1</sub>-SO<sub>2</sub>, 100, F<sub>2</sub>), 308 (F<sub>2</sub>-NH<sub>2</sub>, 0.92, F<sub>3</sub>), 280 (F<sub>3</sub>-N<sub>2</sub>, 3.82, F<sub>4</sub>), 204 (F<sub>4</sub>-Ph, 8.01, F<sub>5</sub>), 106 (F<sub>5</sub>-C<sub>8</sub>H<sub>8</sub>, 0.67, F<sub>6</sub>). Anal. calcd. for C<sub>29</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>S: C, 72.93; H, 4.85; N, 8.80. Found: C, 72.90; H, 4.72; N, 8.63%.

**N-(2-Chlorobenzyl)-4,5,6-triphenylpyridazine-3-sulfonamide (3h):** Prepared from 2-chlorobenzylamine. Color: White crystals. Yield: 79.3%. M.p.: 211-213 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 3390 (NH), 2885 (CH<sub>aliph</sub>), 1642 (C=N), 1376, 1105 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.54 (s, 1H, NH), 7.64-7.51 (m, 15H, Ar-H), 7.43-7.40 (m, 4H, Ar-H), 4.10 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 159.9 (C-6), 158.9 (C-3), 138.4 (C-4), 137.7 (C-5), 136.7 (C-5), 134.0 (C-4), 129.2-126.6 (4Ph), 43.2 (C-NH). MS (*m/z* (%)): 512 (M<sup>+</sup>, 11.56), 476 (M<sup>+</sup>-HCl, 100, F<sub>1</sub>), 387 (F<sub>1</sub>-CH<sub>2</sub>Ph, 15.34, F<sub>2</sub>), 370 (F<sub>2</sub>-NH<sub>2</sub>, 14.36, F<sub>3</sub>), 307 (F<sub>3</sub>-SO<sub>2</sub>, 20.42, F<sub>4</sub>), 323 (F<sub>2</sub>-SO<sub>2</sub>, 57.84, F<sub>5</sub>), 308 (F<sub>5</sub>-NH<sub>2</sub>, 0.92, F<sub>6</sub>). Anal. calcd. for C<sub>29</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>2</sub>S: C, 68.03; H, 4.33; N, 8.21. Found: C, 67.86; H, 4.15; N, 8.04%.

**N-(Naphthalen-1-yl)-4, 5, 6-triphenylpyridazine-3-sulfonamide (3i):** Prepared from  $\alpha$ -naphthylamine. Color: White crystals. Yield: 86.09%. M.p.: 228-230 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 3350 (NH), 3034 (CH<sub>arom</sub>), 1628 (C=N), 1391, 1120 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 10.10 (s, 1H, NH), 8.20-7.41 (m, 22H, Ar-H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.9 (C-6), 156.9 (C-3), 142 (C-1), 136.4 (C-4), 135.7 (C-5), 134.7 (C-5), 133.0 (C-4), 129.2-127.5 (Ar-C), 127-109 (1-Naphthyl-C). MS (*m/z* (%)): 513 (M<sup>+</sup>, 26.59), 449 (M<sup>+</sup>-SO<sub>2</sub>, 16.12, F<sub>1</sub>), 323 (F<sub>1</sub>-C<sub>10</sub>H<sub>7</sub>, 27.74, F<sub>2</sub>), 307 (F<sub>2</sub>-NH<sub>2</sub>, 9.51, F<sub>3</sub>), 280 (F<sub>3</sub>-N<sub>2</sub>, 7.71, F<sub>4</sub>). Anal. calcd. for C<sub>32</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>S: C, 74.83; H, 4.51; N, 8.18. Found: C, 74.68; H, 4.36; N, 8.03%.

### 2.3.3. 6,7,8-Triphenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-3-sulfonyl chloride (5)

To a solution of 3-mercapto derivative **4** (2.6 mmol) in acetic acid (19 mL) and water (1 mL), chlorine gas was bubbled at 0 °C for 1 h. The reaction mixture was poured into water (250 mL) portion-wise with stirring; the precipitate was filtered, washed with water several times and dried to give 3-sulfonylchloride derivative **5** yield 90.5%. The respective crude sulfonylchloride was used in the next step without further purification. Color: White crystals. Yield: 90.5%. M.p.: 130-132 °C (Scheme 2).

### 2.3.4. 3-Substituted sulfamoyl-6,7,8-triphenyl [1,2,4]triazolo [4,3-*b*]pyridazine (6a-i)

To a solution of sulfonyl chloride derivative **5** (2.20 mmol) in benzene (20 mL), substituted amine was added (2.20 mmol), the reaction mixture was refluxed for 3 hours, the solvent was concentrated, the solid product was collected and recrystallized from ethanol (Scheme 2).

**6,7, 8-Triphenyl [1, 2, 4]triazolo[4, 3-*b*]pyridazine-3-sulfonamide (6a):** Prepared from hydrazine hydrate. Color: White crystals. Yield: 80.7%. M.p.: 260-262 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 3350 (NH), 1621 (C=N), 1322, 1171 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.20 (s, 1H, NH), 7.80-7.41 (m, 15H, Ar-H), 2.9 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 155.7 (C-8), 150.1 (C-5), 147.0 (C-3), 135.4 (C-6), 135.0 (C-6), 134.4 (C-7), 133.7 (C-7), 132.0 (C-8), 128.2-126.5 (Ar-C). MS (*m/z* (%)): 442 (M<sup>+</sup>, 3.17), 426 (M<sup>+</sup>-NH<sub>2</sub>, 1.67, F<sub>1</sub>), 411 (F<sub>1</sub>-NH<sub>2</sub>, 3.44, F<sub>2</sub>). Anal. calcd. for C<sub>23</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub>S: C, 62.43; H, 4.10; N, 18.99. Found: C, 62.28; H, 3.93; N, 18.82%.

**N-(2-Hydroxyethyl)-6, 7, 8-triphenyl [1, 2, 4]triazolo[4, 3-*b*]pyridazine-3-sulfonamide (6b):** Prepared from ethanolamine. Color: White crystals. Yield: 55.2%. M.p.: 148-150 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 3416 (OH), 3325 (NH), 2914 (CH<sub>aliph</sub>), 1640 (C=N), 1302, 1100 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.20 (s, 1H, NH), 7.80-7.41 (m, 15H, Ar-H), 4.10 (t, 2H, CH<sub>2</sub>OH), 3.80 (s, 1H, OH), 2.9 (t, 2H, CH<sub>2</sub>NH). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 155.7 (C-8), 150.1 (C-5), 147 (C-3), 135.4 (C-6), 135.0 (C-6), 134.4 (C-7), 133.7 (C-7), 132.0 (C-8), 128.2-126.5 (Ar-C), 59.1 (C-OH), 44.5 (C-NH). MS (*m/z* (%)): 472 (M<sup>+</sup>+1, 4.27), 347 (M<sup>+</sup>-SO<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>OH, 4.81, F<sub>1</sub>), 348 (F<sub>1</sub>-C<sub>4</sub>H<sub>8</sub>NO, 59.56, F<sub>2</sub>), 324 (F<sub>2</sub>-N<sub>2</sub>, 4.40, F<sub>3</sub>). Anal. calcd. for C<sub>25</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S: C, 63.68; H, 4.49; N, 14.85. Found: C, 63.50; H, 4.31; N, 14.70%.

**4-((6, 7, 8-Triphenyl-[1, 2, 4]triazolo[4, 3-*b*]pyridazin-3-yl)sulfonyl)morpholine (6c):** Prepared from morpholine. Color: White crystals. Yield: 84.1%. M.p.: 223-225 °C. FT-IR (KBr, v, cm<sup>-1</sup>): 2920 (CH<sub>aliph</sub>), 1622 (C=N), 1309, 1115 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 7.80-7.41 (m, 15H, Ar-H), 4.10 (t, 4H, CH<sub>2</sub>-O-CH<sub>2</sub>), 3.50 (t, 4H, CH<sub>2</sub>-N-CH<sub>2</sub>).

**Table 1.** Anti-microbial activity of synthesized compounds \*.

| Compound      | <i>Micrococcus luteus</i> | <i>Staphylococcus aureus</i> | <i>Escherichia coli</i> | <i>Candida albicans</i> |
|---------------|---------------------------|------------------------------|-------------------------|-------------------------|
| 3a            | +++                       | ++                           | +++                     | +++                     |
| 3b            | +++                       | ++                           | +++                     | +++                     |
| 3c            | +++                       | ++                           | +++                     | +++                     |
| 3d            | ++                        | +++                          | ++                      | +++                     |
| 3e            | +++                       | ++                           | ++                      | +++                     |
| 3f            | +++                       | ++                           | ++                      | +++                     |
| 3g            | +++                       | ++                           | ++                      | +++                     |
| 3h            | +++                       | ++                           | ++                      | +++                     |
| 3i            | +++                       | ++                           | ++                      | +++                     |
| 6a            | ++++                      | +++                          | +++                     | +++                     |
| 6b            | ++++                      | ++                           | ++                      | +++                     |
| 6c            | +                         | ++                           | +                       | +++                     |
| 6d            | ++                        | ++                           | +++                     | +++                     |
| 6e            | +++                       | +                            | ++                      | +++                     |
| 6f            | +                         | ++                           | +                       | ++                      |
| 6g            | ++++                      | +                            | +                       | ++++                    |
| 6h            | ++                        | +                            | +                       | +++                     |
| 6i            | ++++                      | ++                           | ++++                    | +++                     |
| DMF           | -                         | -                            | -                       | -                       |
| Sulfadoxine   | +++                       | +++                          | ++                      | +++                     |
| Sulfadimidine | +++                       | +++                          | ++                      | +++                     |
| Nystatin      | -                         | -                            | -                       | ++++                    |

\* Values are mean inhibition zone (mm) of two replicates, 25-35 mm = +++, 18-24 mm = ++, 11-16 mm = +, - = negative inhibition.

<sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 155.7 (C-8), 150.1 (C-5), 147.0 (C-3), 135.4 (C-6), 135.0 (C-6), 134.4 (C-7), 133.7 (C-7), 132.0 (C-8), 128.2-126.5 (Ar-C), 64.3 (C-O-C), 46.2 (C-N-C). MS (*m/z* (%)): 497 (M<sup>+</sup>, 0.75), 433 (M<sup>+</sup>-SO<sub>2</sub>, 2.72, F<sub>1</sub>), 348 (F<sub>1</sub>-C<sub>4</sub>H<sub>8</sub>NO, 59.56, F<sub>2</sub>), 324 (F<sub>2</sub>-N<sub>2</sub>, 4.40, F<sub>3</sub>). Anal. calcd. for C<sub>27</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S: C, 65.17; H, 4.66; N, 14.08. Found: C, 65.01; H, 4.50; N, 13.92%.

*N*-Benzyl-6, 7, 8-triphenyl-[1, 2, 4]triazolo[4, 3-*b*]pyridazine-3-sulfonamide (**6d**): Prepared from benzylamine. Color: White crystals. Yield: 69.5%. M.p.: 237-239 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3390 (NH), 2891 (CH<sub>aliph</sub>), 1624 (C=N), 1312, 1151 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.20 (s, 1H, NH), 7.80-7.41 (m, 15H, Ar-H), 7.35-7.25 (m, 5H, Ar-H), 3.50 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.7 (C-8), 152.1 (C-5), 149.0 (C-3), 137.4 (C-6), 137.0 (C-6), 136.4 (C-7), 135.7 (C-7), 134.0 (C-8), 130.2-127.7 (Ar-C), 47.2 (C-NH). MS (*m/z* (%)): 516 (M<sup>+</sup>-1, 3.32), 425 (M<sup>+</sup>-CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 3.23). Anal. calcd. for C<sub>30</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S: C, 69.61; H, 4.48; N, 13.53. Found: C, 69.44; H, 4.30; N, 13.37%.

*N*, 6, 7, 8-Tetraphenyl-[1, 2, 4]triazolo[4, 3-*b*]pyridazine-3-sulfonamide (**6e**): Prepared from aniline. Color: White crystals. Yield: 62.5%. M.p.: 261-263 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3360 (NH), 3054 (CH<sub>arom</sub>), 1640 (C=N), 1360, 1161 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.40 (s, 1H, NH), 7.31-7.10 (m, 15H, Ar-H), 7.08-7.05 (m, 5H, Ar-H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.7 (C-8), 152.1 (C-5), 149.0 (C-3), 137.5 (C-6), 137.0 (C-6), 136.4 (C-7), 135.7 (C-7), 134.0 (C-8), 130.2-127.7 (Ar-C), 129.5-119.4 (Ar-C). MS (*m/z* (%)): 503 (M<sup>+</sup>, 19.27), 439 (M<sup>+</sup>-SO<sub>2</sub>, 50.47, F<sub>1</sub>), 348 (F<sub>1</sub>-NHPh, 14.31, F<sub>2</sub>). Anal. calcd. for C<sub>29</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub>S: C, 69.17; H, 4.20; N, 13.91. Found: C, 69.00; H, 4.03; N, 13.76%.

6,7,8-Triphenyl-*N*-(*o*-tolyl)-[1,2,4]triazolo[4, 3-*b*]pyridazine-3-sulfonamide (**6f**): Prepared from *o*-toluidine. Color: White crystals. Yield: 67.2%. M.p.: 268-270 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3396 (NH), 2962 (CH<sub>aliph</sub>), 1635 (C=N), 1342, 1165 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.30 (s, 1H, NH), 7.32-7.22 (m, 15H, Ar-H), 6.90-6.80 (m, 4H, Ar-H), 2.28 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.7 (C-8), 152.1 (C-5), 149.0 (C-3), 137.5 (C-6), 137.0 (C-6), 136.4 (C-7), 135.7 (C-7), 134.0 (C-8), 129.5-123.7 (Ar-C), 18.3 (CH<sub>3</sub>). MS (*m/z* (%)): 517 (M<sup>+</sup>, 33.45), 453 (M<sup>+</sup>-SO<sub>2</sub>, 58.90, F<sub>1</sub>), 438 (F<sub>1</sub>-NH<sub>2</sub>, 5.48, F<sub>2</sub>), 348 (F<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, 1.20, F<sub>3</sub>), 324 (F<sub>3</sub>-N<sub>2</sub>, 1.60, F<sub>4</sub>). Anal. calcd. for C<sub>30</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S: C, 69.61; H, 4.48; N, 13.53. Found: C, 69.44; H, 4.30; N, 13.36%.

6,7,8-Triphenyl-*N*-(*m*-tolyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-3-sulfonamide (**6g**): Prepared from *m*-toluidine. Color: White crystals. Yield: 76.3%. M.p.: 210-212 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3270 (NH), 2916 (CH<sub>aliph</sub>), 1638 (C=N), 1381, 1161 (SO<sub>2</sub>). <sup>1</sup>H

NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.20 (s, 1H, NH), 7.32-7.22 (m, 15H, Ar-H), 6.90-6.80 (m, 4H, Ar-H), 2.38 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.7 (C-8), 152.1 (C-5), 149.0 (C-3), 137.5 (C-6), 137.0 (C-6), 136.4 (C-7), 135.7 (C-7), 134.0 (C-8), 129.5-117.4 (Ar-C), 12.3 (CH<sub>3</sub>). MS (*m/z* (%)): 517 (M<sup>+</sup>, 37.78), 453 (M<sup>+</sup>-SO<sub>2</sub>, 19.79, F<sub>1</sub>), 348 (F<sub>1</sub>-NHC<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, 19.93, F<sub>2</sub>). Anal. calcd. for C<sub>30</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S: C, 69.61; H, 4.48; N, 13.53. Found: C, 69.45; H, 4.31; N, 13.35%.

*N*-(2-Chlorobenzyl)-6, 7, 8-triphenyl-[1, 2, 4]triazolo[4, 3-*b*]pyridazine-3-sulfonamide (**6h**): Prepared from 2-chlorobenzyl amine. Color: White crystals. Yield: 75%. M.p.: 218-220 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3330 (NH), 2891 (CH<sub>aliph</sub>), 1588 (C=N), 1322, 1109 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.20 (s, 1H, NH), 7.80-7.41 (m, 15H, Ar-H), 7.30-7.10 (m, 4H, Ar-H), 3.60 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.7 (C-8), 152.1 (C-5), 149.0 (C-3), 137.5 (C-6), 137.0 (C-6), 136.4 (C-7), 135.7 (C-7), 134.0 (C-8), 130.2-127.4 (Ar-C), 43.1 (C-NH). MS (*m/z* (%)): 552 (M<sup>+</sup>, 38.06), 106 (100). Anal. calcd. for C<sub>30</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub>S: C, 65.27; H, 4.02; N, 12.69. Found: C, 65.10; H, 3.88; N, 12.51%.

*N*', 6, 7, 8-Tetraphenyl-[1, 2, 4]triazolo[4, 3-*b*]pyridazine-3-sulfonylhydrazide (**6i**): Prepared from phenyl hydrazine. Color: White crystals. Yield: 60.3%. M.p.: 188-190 °C. FT-IR (KBr, ν, cm<sup>-1</sup>): 3337, 3202 (2NH), 3033 (CH<sub>arom</sub>), 1640 (C=N), 1306, 1159 (SO<sub>2</sub>). <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 8.0 (s, 1H, NH), 7.80-7.41 (m, 15H, Ar-H), 7.37-6.90 (m, 5H, Ar-H), 4.20 (s, 1H, NHPh). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>, δ, ppm): 157.7 (C-8), 152.1 (C-5), 149.0 (C-3), 137.5 (C-6), 137.0 (C-6), 136.4 (C-7), 135.7 (C-7), 134.0 (C-8), 130.2-115.4 (Ar-C). MS (*m/z* (%)): 514 (M<sup>+</sup>-4, 9.59), 105 (100). Anal. calcd. for C<sub>29</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>S: C, 67.17; H, 4.28; N, 16.21. Found: C, 67.00; H, 4.11; N, 16.04%.

### 3. Results and discussion

#### 3.1. Synthesis

The sulfonamide derivatives as the target compounds depicted in (Scheme 1 and 2) were obtained by allowing the pyridazinethiol derivatives **1** [17] and triazolopyridazinethiol **4** [18] to oxidatively chlorinate with chlorine gas in presence of 90% acetic acid at 0 °C, the corresponding sulfonyl chlorides **2** and **5** were obtained [19].

Because of the instability of sulfonyl chlorides, the crude products of sulfonyl chloride derivatives **2** and **5** were converted directly to the more stable sulfonamides **3** and **6** by amidation. The sulfonyl chloride derivatives **2** and **5** were identified by their corresponding sulfonamides. The IR spectra



of compounds **3a-i** and **6a-i** are characterized by bands at 3300-3200  $\text{cm}^{-1}$  (NH), and characteristic absorption bands in the regions of 1134-1152 and 1358-1377  $\text{cm}^{-1}$  corresponding to symmetrical and asymmetrical vibrations of  $\text{SO}_2$  group. Moreover, for SAR study, we aimed to synthesize a new series of sulfonamides **3a-i** and **6a-i** to investigate the effect of attaching triazole ring (of the known pharmacological activity) to pyridazine nucleus upon the required activity as antimicrobial agents. The synthesized compounds were characterized by various spectroscopic methods such as IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and MS, elemental and spectral analyses of all prepared compounds described are consistent with the assigned structures.

### 3.2. Antimicrobial activity

Applying the agar plate diffusion technique [20], the newly synthesized sulfonamide derivatives were screened *in vitro* for antimicrobial activity against Gram positive bacteria (*Staphylococcus aureus* and *Micrococcus luteus*), Gram negative bacteria (*Escherichia coli*) and yeast (*Candida albicans*). In this method, a standard 5 mm diameter sterilized filter paper disc impregnated with the compounds (0.4 mg/0.1 mL of dimethylformamide) was placed on the agar plates which had previously been inoculated with the above organisms; The petri dishes were left at 4 °C for 2 h, then the injected plates with bacteria were incubated at 37±0.1 °C for 24 h, and those inoculated with fungi were incubated at 25±0.1 °C for 48 h. At the end of the period, diameter of inhibition zones were measured in mm, these studies were performed in two replicates. The screening results given in Table 1 indicated that all the compounds exhibited antimicrobial activity against all the test organisms.

### 4. Conclusion

In summary, we have developed a novel class of sulfonamide derivatives substituted with pyridazine and triazolopyridazine derivatives as potential antimicrobial agents and the following was concluded: compounds **6a, b** and **6g, i** with triazole ring fused with pyridazine nucleus showed a remarkable antimicrobial activity against *Micrococcus luteus* greater than that of the non-condensed pyridazine nucleus in case of compounds **3a, b** and **3g, i**. This in turn reveals that there's a significant relation between activity and nature of the pyridazine nucleus, Rest of the compounds showed moderate to low activity against the examined micro-organisms.

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