

## SYNTHESIS OF SOME SULFONAMIDE DERIVATIVES WITH POTENTIAL ANTIBACTERIAL ACTIVITY

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*Some new quinoxaline-6-sulfonamide and phthalazine-6-sulfonamide derivatives were synthesized. The majority of the prepared compounds showed antibacterial activity.*

**Keywords:** quinoxaline-6-sulfonamides, phthalazine-6-sulfonamides.

Sulfonamide derivatives represent a class of compounds having interesting pharmacological activities. Many representatives of this class of compounds were reported to have antibacterial activity [1-4]. Some of them are HIV protease inhibitors [5, 6], carbonic anhydrase inhibitors [7-12], antiepileptic agents [13, 14], and anticonvulsant agents [15-18], and are used as ETA, being a selective antagonist [19, 20]. Some of the quinoxaline derivatives show antibacterial activity [21-23], neuroprotective effect [24], anticonvulsive activity and antiischemic effect in both global and local ischemia models [25], and antianxiety activity [26, 27], and are applied as excitatory amino acid receptor antagonists [28, 29]. Moreover, several phthalazine derivatives were reported to exhibit antibacterial [30] and antifungal activity [31] and were described as antiarrhythmic agents [32], tranquilizers, and cardiotoxic agents [33].

These observations prompted the incorporation of a sulfonamide moiety into quinoxaline or phthalazine to make use of both functionalities in the potentiation of pharmacological activities. Herein, the new sulfonamide derivatives were evaluated for antibacterial activity.

The compounds set forth in this study are given in Table 1 and their preparation is outlined in Scheme 1.

The starting 1,4-dihydroquinoxaline-2,3-dione (**1**) was obtained from phenylenediamine and oxalic acid according to the previously reported method [34]. The new quinoxaline-6-sulfonylchloride (**2**) was prepared by the reaction of compound **1** with chlorosulfonic acid at 0-5°C. Compound **2** reacted with glycine, *p*-aminobenzoic acid, propylamine, or 1-aminopropan-2-ol to afford the corresponding N-substituted sulfonamides **3a-d**. Compounds **3e** and **3f** were also prepared via the reaction of compound **2** with morpholine and piperazine. On the other hand, 2,3-dihydrophthalazine-1,4-dione (**4**) was synthesized from phthalic acid and hydrazine hydrate using the method reported [35]. Compound **4** reacted with chlorosulfonic acid at 0-5°C to give the corresponding sulfonyl chloride **4**. N-Substituted sulfonamide derivatives **6a-f** were produced in the reaction of compound **5** with glycine, *p*-aminobenzoic acid, propylamine, morpholine, and piperazine.

The antibacterial activity of the compounds prepared was examined using the agar diffusion method [36]. Compounds **2a-d** were found to possess antibacterial activity against the bacteria tested. While compounds **2e**, **2f**, **6b** and **6c** demonstrated a significant activity against *S. aureus*, the other compounds showed a moderate activity against *S. aureus*. Other pharmacological studies are in progress.

Scheme 1

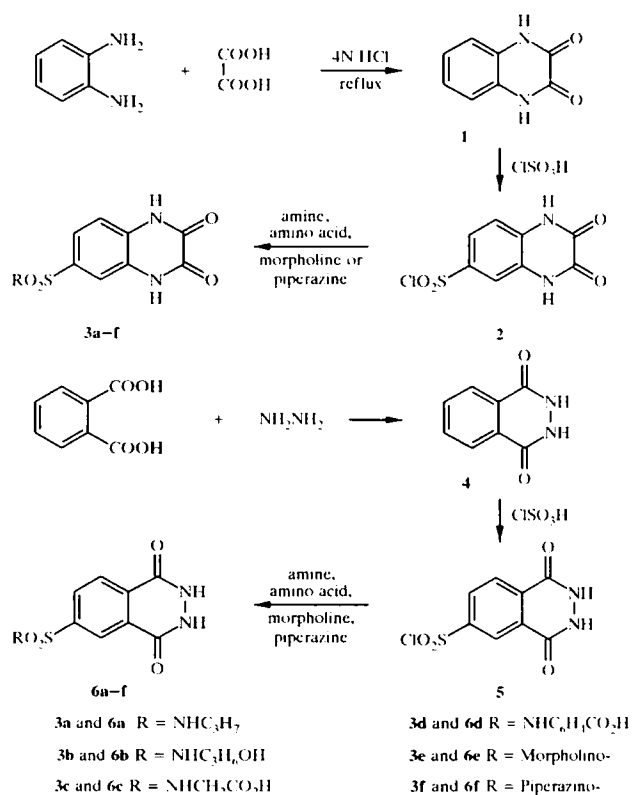


TABLE I. Melting Points, Yields and Analyses of the Compounds Prepared

| Compound  | Empirical formula   | Found, %      |             |              | mp, °C  | Yield, % |
|-----------|---|---------------|-------------|--------------|---------|----------|
|           |   | Calculated, % |             |              |         |          |
|           |   | C             | H           | N            |         |          |
| <b>3a</b> | C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S     | <u>46.64</u>  | <u>4.59</u> | <u>14.84</u> | 264-265 | 61       |
|           |   | 46.8          | 4.4         | 14.5         |         |          |
| <b>3b</b> | C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S     | <u>44.14</u>  | <u>4.3</u>  | <u>14.04</u> | 293-294 | 63       |
|           |   | 44.5          | 4.5         | 14.0         |         |          |
| <b>3c</b> | C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sub>6</sub> S      | <u>40.13</u>  | <u>3.01</u> | <u>14.04</u> | 210-211 | 64       |
|           |   | 40.0          | 3.3         | 14.4         |         |          |
| <b>3d</b> | C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>6</sub> S     | <u>49.86</u>  | <u>3.04</u> | <u>11.63</u> | 218-219 | 65       |
|           |   | 49.5          | 3.3         | 11.5         |         |          |
| <b>3e</b> | C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S     | <u>46.30</u>  | <u>4.18</u> | <u>13.50</u> | 175-176 | 64       |
|           |   | 46.6          | 4.4         | 13.2         |         |          |
| <b>3f</b> | C <sub>12</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> S     | <u>46.45</u>  | <u>4.51</u> | <u>18.06</u> | 249-250 | 66       |
|           |   | 46.2          | 4.3         | 18.1         |         |          |
| <b>6a</b> | C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S     | <u>46.64</u>  | <u>4.59</u> | <u>14.84</u> | 161-162 | 64       |
|           |   | 46.3          | 4.3         | 14.5         |         |          |
| <b>6b</b> | C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S     | <u>44.14</u>  | <u>4.34</u> | <u>14.04</u> | 235-236 | 67       |
|           |   | 44.3          | 4.4         | 14.3         |         |          |
| <b>6c</b> | C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sub>6</sub> S      | <u>40.13</u>  | <u>3.01</u> | <u>14.04</u> | 284-285 | 68       |
|           |   | 40.5          | 3.5         | 14.3         |         |          |
| <b>6d</b> | C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>6</sub> S     | <u>49.86</u>  | <u>3.04</u> | <u>11.63</u> | 270-271 | 67       |
|           |   | 49.7          | 3.2         | 11.4         |         |          |
| <b>6e</b> | C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S     | <u>46.30</u>  | <u>4.18</u> | <u>13.50</u> | 217-218 | 61       |
|           |   | 46.1          | 4.0         | 13.2         |         |          |
| <b>6f</b> | C <sub>12</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> S·HCl | <u>41.61</u>  | <u>4.33</u> | <u>16.18</u> | 283-284 | 63       |
|           |   | 41.2          | 4.1         | 16.4         |         |          |

TABLE 2. Antibacterial Activity

| Compound        | Zone diameter (mm) |                |
|-----------------|--------------------|----------------|
|                 | <i>S. aureus</i>   | <i>E. coli</i> |
| 3a              | 13                 | 11             |
| 3b              | 15                 | 10             |
| 3c              | 12                 | 10             |
| 3d              | 14                 | 8              |
| 3e              | 10                 | -              |
| 3f              | 11                 | -              |
| 6a              | 8                  | ---            |
| 6b              | 10                 | ---            |
| 6c              | 10                 | ---            |
| 6d              | ---                | 7              |
| 6e              | 8                  | -              |
| 6f              | 7                  | -              |
| Control (solv.) | ---                | ---            |
| Sulfadiazine    | 14                 | 13             |

## EXPERIMENTAL

Infrared spectra were taken in KBr disks using the Testscan Shimadzu FTIR 8000 series, and  $^1\text{H}$  NMR spectra were obtained on a Varian EM 390L spectrophotometer. Microanalyses were performed on the Microanalytical Unit, Cairo University. Melting points were measured on the melting points apparatus SMP<sub>2</sub> and were uncorrected. Biological activity was tested at the Microbiology Department.

**1,4-Dihydroquinoxalinedione-2,3 (1) [34].** 4 N HCl (50 ml) was added to the mixture of phenylenediamine and oxalic acid (0.1 mol of each). The reaction mixture was heated to reflux for 12 h. The resulting precipitate was collected and washed with water to give compound **1**. HCl, yield 88%; mp > 300°C.

**2,3-Dioxo-1,4-dihydroquinoxaline-6-sulfonyl Chloride (2).** Cold chlorosulfonic acid (0.3 mol) was added to compound **1** (0.1 mol), with stirring for 30 min while maintaining the temperature at 0-5°C. The reaction mixture was stirred at room temperature for 1 h, then heated at 60°C until the evolution of HCl gas ceased (TLC control). The mixture was cooled to 0-5°C and poured into ice water gradually with vigorous stirring. The pale gray crystalline product was separated by filtration. Yield 78%; mp 164°C. IR spectrum (KBr): 3350-3150 (NH/OH taut.), 3080 (Ph), 1650 (C=O amide), 1360, 1165  $\text{cm}^{-1}$  ( $\text{SO}_2$ ).

**2,3-Dioxo-1,4-dihydroquinoxaline-6-(N-propyl)sulfonamide (3a).** A cold solution of compound **2** (0.01 mol) in DMF (10 ml) was added to a cold solution of propylamine (0.01 mol) in abs. alcohol (10 ml). The temperature of the reaction mixture was maintained at 0-5°C until complete addition. The reaction mixture was stirred at room temperature for 24 h (TLC control). The solvent was vacuum evaporated. The crude product was recrystallized from a methanol-ether mixture. The pale yellow crystalline product was collected by filtration and dried (Table 1). IR spectrum (KBr): 3250-3150 (br, NH/CO, taut.), 3080 (Ph), 2950, 2850 (alkyl), 1640 (amide), 1370, 1165 ( $\text{SO}_2$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ): 1.5 (3H, t,  $\text{CH}_3$ ); 3.1 (2H, sex,  $\text{CH}_2$ ); 4.1 (2H, t,  $\text{CH}_2$ ); 7.3-7.85 (m, arom.); 8.9 (1H, br, NH); 10.85-11.2 ppm (2H, s, NHCO, quinox.).

**2,3-Dioxo-1,4-dihydroquinoxaline-6-(N-carboxymethyl)sulfonamide (3e).** A cold solution of compound **2** (0.01 mol) in DMF (10 ml) was added to a cold solution of glycine (0.01 mol) in 1 N NaOH solution (10 ml). The temperature was maintained at 0-5°C until complete addition. The mixture was heated at 60°C for 4 h (TLC control). The solvent was evaporated to half volume and cooled, and the yellow crystalline product precipitated was filtered off and dried (Table 1). IR spectrum (KBr): 3250-2800 (br, NH, COOH), 3080 (Ph), 2926 ( $\text{CH}_2$ ), 1700 (C=O), 1635 (C=O, amide), 1370, 1165 ( $\text{SO}_2$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (DMSO- $d_6$ ): 3.1 (2H, s,  $\text{CH}_2$ ), 7.25-7.9 (3H, m, arom.), 8.9 (1H, br., NH), 10.9, 11.2 ppm (2H, s, NHCO, quinox.).

**2,3-Dioxo-1,4-dihydroquinoxaline-6-[N-(p-carboxyphenyl)]sulfonamide (3d).** A cold solution of compound **2** (0.01 mol) in DMF (10 ml) was added to a cold solution of *p*-aminobenzoic acid (0.01 mol) in abs.

alcohol (10 ml). The temperature of the reaction mixture was maintained at 0-5°C until complete addition. The reaction mixture was heated at 60°C for 5 h (TLC control), then cooled to give a pale yellow crystalline product, which was filtered off and dried (Table 1). IR spectrum (KBr): 3330-2820 (br, NH, COOH), 3090 (Ph), 1700 (C=O), 1645 (C=O, amide), 1380, 1170 cm<sup>-1</sup> (SO<sub>2</sub>).

2,3-Dioxo-1,4-dihydroquinoxaline-6-[N-(2-hydroxypropyl)]sulfonamide (**3b**) was prepared similarly from 1-aminopropan-2-ol.

**2,3-Dioxo-1,4-dihydroquinoxaline-6-morpholinosulfonamide (3e).** A cold solution of compound **2** (0.01 mol) in DMF (10 ml) was added to a cold solution of morpholine (0.01 mol) in abs. alcohol (10 ml). The temperature was maintained at 0-5°C until complete addition. The reaction mixture was stirred at room temperature for 18 h (TLC control). The solvent was vacuum evaporated. The crude product was dissolved in methanol and one drop of 10% NaOH was added to give a buff colored crystalline product, which was filtered off and dried. (Table 1). IR spectrum (KBr): 3350-3180 (NH/CO, taut.), 3085 (Ph), 2990 (CH<sub>2</sub>CH<sub>2</sub>), 1635 (amide), 1380, 1170 (SO<sub>2</sub>) cm<sup>-1</sup>. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.53, 3.7 (8H, tt, CH<sub>2</sub>CH<sub>2</sub>, morphol.); 7.25-7.85 (3m, arom.); 9.4, 9.7 ppm (2H, s, NHCO, quinox.).

2,3-Dioxo-1,4-dihydroquinoxaline-6-piperazinosulfonamide (**3f**) was prepared in a similar way. The crude product was crystallized from methanol-ether mixture, filtered off, and dried.

**2,3-Dihydro-1,4-phthalazine (4)** was prepared by treating phthalic acid with hydrazine hydrate according to the method reported [35].

**1,4-Dioxo-2,3-dihydrophthalazine-6-sulfonyl Chloride (5).** Cold chlorosulfonic acid (0.3 mol) was added to compound **4** (0.1 mol) with stirring, the temperature of the reaction mixture being maintained at 0-5°C until complete addition. The mixture was heated at 60°C until the HCl gas evolution ceased. The solution was cooled and cold acetone was added with stirring. The product obtained was washed with cold dry benzene to give a crystalline product **5** in 72% yield; mp 145°C. IR spectrum (KBr): 3250-2900 (NH/OH taut.), 1640 (C=O amide), 1370, 1170 cm<sup>-1</sup> (SO<sub>2</sub>).

**1,4-Dioxo-2,3-dihydrophthalazine-6-(N-propyl)sulfonamide (6a).** A cold solution of compound **5** (0.01 mol) in DMF (10 ml) was added to a cold solution of propylamine (0.01 mol) in abs. alcohol (10 ml), maintaining the reaction medium at 0-5°C until complete addition. The reaction mixture was stirred at room temperature for 24 h. The solvent was vacuum evaporated. The crude product was crystallized from methanol-chloroform mixture (Table 1).

**1,4-Dioxo-2,3-dihydrophthalazine-6-[N-(2-hydroxypropyl)]sulfonamide (6b)** was prepared similarly from 1-aminopropan-2-ol. IR spectrum (KBr): 3350-3180 (NH/OH, taut.), 3080 (Ph), 2950, 2850 (alkyl), 1645 (amide), 1375, 1170 cm<sup>-1</sup> (SO<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.6 (3H, d, CH<sub>3</sub>); 3.8 (2H, d, CH<sub>2</sub>); 4.4 (1H, sex. CH); 5 (1H, s, OH); 7.3-7.9 (3H, m, arom.); 8.15, 8.35 (2H, s, NH-NH); 8.7 ppm (1H, br, NH).

**1,4-Dioxo-2,3-dihydrophthalazine-6-(N-carboxymethyl)sulfonamide (6c).** A cold solution of compound **5** (0.01 mol) in DMF (10 ml) was added to a cold solution of glycine (0.01 mol) in 1 N NaOH solution (10 ml), maintaining the temperature of the reaction mixture at 0-5 °C. The reaction mixture was stirred at 60°C for 5 h (TLC control), then the solvent was vacuum evaporated. The crude product was crystallized from methanol-chloroform mixture (Table 1). IR spectrum (KBr): 3350-2800 (br, NH, COOH), 3095 (Ph), 2930 (CH<sub>2</sub>), 1705 (C=O), 1650 (amide), 1380, 1170 cm<sup>-1</sup> (SO<sub>2</sub>).

**1,4-Dioxo-2,3-dihydrophthalazine-6-[N-*p*-carboxyphenyl]sulfonamide (6d).** A cold solution of *p*-aminobenzoic acid (0.01 mol) in abs. alcohol was added to a cold solution of compound **5** (0.01 mol) in DMF (10 ml). The reaction temperature was maintained at 0-5°C until complete addition. The reaction mixture was heated at 60°C for 7 h (TLC control). After cooling, the pale crystalline product was separated by filtration and recrystallized from ethanol (Table 1). IR spectrum (KBr): 3350-2820 (br, NH, COOH), 3090 (Ph), 1700 (C=O), 1645 (amide), 1370, 1160 cm<sup>-1</sup> (SO<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 7.0-7.8 (3H, m, arom.); 8.8 (1H, br, NH); 9.1, 9.4 ppm (2H, s, NH-NH).

**1,4-Dioxo-2,3-dihydrophthalazine-6-(morpholino)sulfonamide (6e).** A cold solution of compound **5** (0.01 mol) in DMF (10 ml) was added to a cold solution of morpholine (0.01 mol) in abs. alcohol (10 ml). The reaction temperature was maintained at 0-5°C until complete addition. The mixture was stirred at room

temperature for 18 h (TLC control). The solvent was vacuum evaporated and the crude product was crystallized from ethanol–chloroform mixture, the product being collected by filtration (Table 1).

**1,4-Dioxo-2,3-dihydrophthalazine-6-(piperazino)sulfonamide (6f)** was prepared in a similar way from piperazine. The crude product was dissolved in methanol, then HCl gas was passed through the solution to give a white crystalline product of compound **6f**·HCl. The crystalline product was collected by filtration (Table 1). IR spectrum (KBr): 3250-2850 (br., NH/OH), 3080 (Ph), 2990 (CH<sub>2</sub>CH<sub>2</sub> of piperazine), 1650 (amide), 1370, 1165 cm<sup>-1</sup> (SO<sub>2</sub>). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.9, 3.5 (8H, tt, piperazino-); 5.1 (1H, br, NH); 7.2-7.8 (3H, m, arom.); 8.3, 8.65 ppm (2H, s, NH–NH).

The compounds prepared were tested against bacteria (*S. aureus* and *E. coli*) by the agar diffusion method [36]. The compounds to be tested were dissolved in 10% KOH solution in a concentration of 20 mg/ml. Sterile discs of Whatman filter paper containing 15 µl of the above solution were placed over the surface of nutrient agar containing standardized inoculum from the microorganisms examined. The plates were incubated at 37°C for 24 h. The inhibition zones appearing after incubation were measured. A disc impregnated with 10% KOH solution was used as a control, and another disc was applied as a standard using sulfadiazine solution in 10% KOH solution. The results are presented in Table 2.

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