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SYNTHESIS OF SOME SULFONAMIDE DERIVATIVES WITH A POTENTIAL ANTIBACTERIAL ACTIVITY

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 an 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 quinoxaline derivatives showed an antibacterial activity [21–23], neuroprotective effect [24], anticonvulsive activity and antiischaemic effect in both global and local ischaemia models [25], antianxiety activity [26, 27], and are applied as excitatory amino acid receptor antagonists [28, 29]. Moreover, several phthalazine derivatives were reported to exhibit an antibacterial [30], antifungal activity [31], described as antiarrhythmic agents [32], tranquilizers and cardiotonic agents [33].

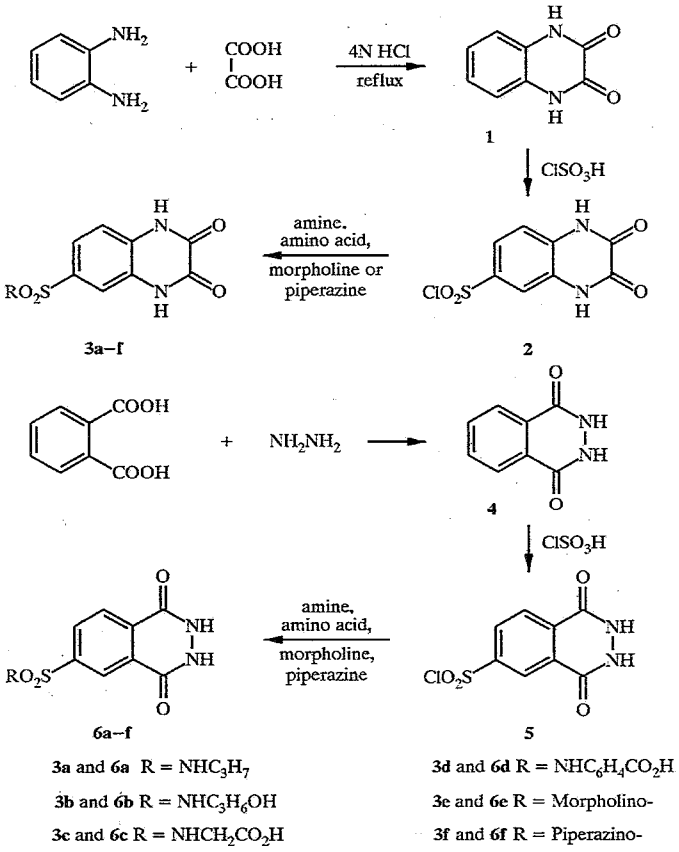
These observations prompted the incorporation of a sulfonamide moiety into quinoxaline or phthalazine to make use of both functionalities in potentiation of pharmacological activities. Herein, the new sulfonamide derivatives were evaluated for the antibacterial activity.

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. Compoud **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 an 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.



3a–f **1** **2** **4** **5** **6a–f**

3a and **6a** R = NHC_3H_7
3b and **6b** R = NHC_3H_6OH
3c and **6c** R = $NHCH_2CO_2H$
3d and **6d** R = $NHC_6H_4CO_2H$
3e and **6e** R = Morpholino-
3f and **6f** R = Piperazino-

Table 1

Melting points, yields and analyses of the compounds prepared

Compounds	mp °C	Molecular formula	Calculated, % / Found, %			Yield, %
			C	H	N	
1	2	3	4	5	6	7
3a	264–265	$C_{11}H_{13}N_3O_4S$	46.64 46.8	4.59 4.4	14.84 14.5	61
3b	293–294	$C_{11}H_{13}N_3O_5S$	44.14 44.5	4.3 4.5	14.04 14.0	63
3c	210–211	$C_{10}H_9N_3O_6S$	40.13 40.0	3.01 3.3	14.04 14.4	64
3d	218–219	$C_{15}H_{11}N_3O_6S$	49.86 49.5	3.04 3.3	11.63 11.5	65
3e	175–176	$C_{12}H_{13}N_3O_5S$	46.30 46.6	4.18 4.4	13.50 13.2	64
3f	249–250	$C_{12}H_{14}N_4O_4S$	46.45 46.2	4.51 4.3	18.06 18.1	66

1	2	3	4	5	6	7
6a	161–162	$C_{11}H_{13}N_3O_4S$	46.64 46.3	4.59 4.3	14.84 14.5	64
6b	235–236	$C_{11}H_{13}N_3O_5S$	44.14 44.3	4.34 4.4	14.04 14.3	67
6c	284–285	$C_{10}H_9N_3O_6S$	40.13 40.5	3.01 3.5	14.04 14.3	68
6d	270–271	$C_{15}H_{11}N_3O_6S$	49.86 49.7	3.04 3.2	11.63 11.4	67
6e	217–218	$C_{12}H_{13}N_3O_5S$	46.30 46.1	4.18 4.0	13.50 13.2	61
6f	283–284	$C_{12}H_{14}N_4O_4S$ · HCl	41.61 41.2	4.33 4.1	16.18 16.4	63

Table 2

Antibacterial activity

Compounds	Zone diameter (mm)	
	S. aureus	*E. coli*
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 Testscan Shimadzu FTIR 8000 Series, and NMR ^1H spectra were obtained on a Varian EM 390L Spectrophotometer. Microanalyses were perfomed on Microanalytical Unit, Cairo University. Melting points were measured on Melting Points Apparatus SMP_2 and were uncorrected. Biological activity was tested at the Microbiology Department.

1,4-Dihydroquinoxalinedione-2,3 (1) [34]. 4N 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). A cold chlorosulfonic acid (0.3 mol) was added to compound **1** (0.1 mol), upon stirring within a 30 min period 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 was ceased (TLC control).The mixture was cooled to 0–5 °C and poured into ice water gradually with vigorous stirring. A 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 (SO_2) cm^{-1}.

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 a 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. A 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 (SO_2) cm^{-1}. NMR ^1H (DMSO-d_6): 1,5 (3H, t, CH_3), 3.1 (2H, sex, CH_2), 4.1 (2H, t, CH_2), 7.3–7.85 (m, arom.), 8.9 (1H, br., NH), 10.85–11.2 (2H, s, NHCO, quinox.) ppm.

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 1N NaOH solution (10 ml). The temperature was maintained at 0–5 °C until complete addition. The mixture was heated at 60 ^{0}C for 4 h (TLC control). The solvent was evaporated to a half volume, cooled, the yellow crystalline product precipitated was filtered off and dried (Table 1). IR spectrum (KBr): 3250–2800 (br., NH, COOH), 3080 (Ph), 2926 (CH_2), 1700 (C=O), 1635 (C=O, amide), 1370, 1165 (SO_2) cm^{-1}. NMR ^1H (DMSO-d_6): 3.1 (2H, s, CH_2), 7.25–7.9 (3H, m, arom.), 8.9 (1H, br., NH), 10.9, 11.2 (2H, s, NHCO, quinox.) ppm.

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*-amino-benzoic 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 (SO_2) cm^{-1}.

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 coloured crystalline product, filtered off and dried. (Table 1). IR spectrum (KBr): 3350–3180 (NH/CO, taut.), 3085 (Ph), 2990 (CH_2CH_2), 1635 (amide), 1380, 1170 (SO_2) cm^{-1}. NMR ^1H (DMSO-d_6): 2.53, 3.7 (8H, t t, CH_2CH_2, morphol.), 7.25–7.85 (3m, arom.), 9.4, 9.7 (2H, s, NHCO, quinox.) ppm.

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). A cold chlorosulfonic acid (0.3 mol) was added to compound **4** (0.1 mol), with stirring, the temperature of the reaction mixture was maintained at 0–5 °C until complete addition. The mixture was heated at 60 °C until the HCl gas evolution was ceased. The solution was cooled and a cold acetone was added with stirring. The product obtained was washed with a cold dry benzene to give a crystalline product of **5** in 72% yield, mp 145 °C. IR spectrum (KBr): 3250–2900 (NH/OH taut.), 1640 (C=O amide), 1370, 1170 (SO_2) cm^{-1}.

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 the 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 (SO_2) cm^{-1}. NMR ^1H (DMSO-d_6): 1,6 (3H, d, CH_3), 3,8 (2H, d, CH_2), 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 (1H, br., NH) ppm.

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 1N 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 the methanol–chloroform mixture (Table 1). IR spectrum (KBr): 3350–2800 (br., NH, COOH), 3095 (Ph), 2930 (CH_2), 1705 (C=O), 1650 (amide), 1380, 1170 (SO_2) cm^{-1}.

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, a 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 (SO_2) cm^{-1}. NMR ^1H (DMSO-d_6): 7.0–7.8 (3H, m, arom.), 8.8 (1H, br., NH), 9.1., 9.4 (2H, s, NH-NH) ppm.

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 the 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_2CH_2 of piperazine), 1650 (amide), 1370, 1165 (SO_2) cm^{-1}. NMR ^1H (DMSO-d_6): 2.9, 3.5 (8H, t t, piperazino-), 5.1 (1H, br., NH), 7.2–7.8 (3H, m, arom.), 8.3, 8.65 (2H, s, NH-NH) ppm.

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 the Whatman filter paper containing 15 µl of the above solution were placed over the surface of nutrient agar containing standardized inculum 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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