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Synthesis of Heterocyclic Quinones Containing Bridgehead Nitrogen Atom from 2-Aminonaphtho[2,3-*d*]thiazole-4,9-dione

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Imidazonaphthothiazole derivatives **3**~**6** were prepared by treatment of 2-aminonaphtho[2,3-*d*]-thiazole-4,9-dione(**1**) with phenacyl bromide, chloroacetic acid, diethyl oxalate and 2,3-dichloroquinoxaline respectively. The reaction of **1** with ethyl acrylate, ethyl acetoacetate and diethyl malonate gave the corresponding naphthothiazolopyrimidine derivatives **8**~**11**.

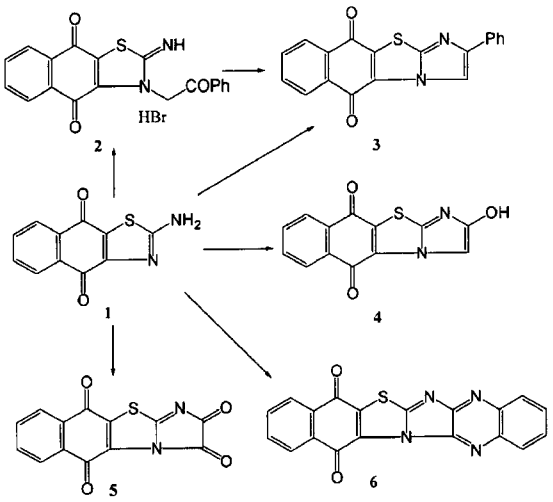
Key words: Naphthothiazole, Imidazonaphthothiazole, Naphthothiazolopyrimidine, Antifungal activity

INTRODUCTION

Imidazo[2,1-*b*]thiazole and its derivatives are useful heterocycles for pharmacological targets (Andreani *et al.*, 1982a; Andreani *et al.*,1982b; Andreani *et al.*,1987; Mase *et al.*,1986; Mohan *et al.*,1975). Therefore, a number of methods has been developed for the preparation of these derivatives (Balse *et al.*,1980; Mase *et al.*,1986; Mohan *et al.*,1975). Quinones are also reported to have a wide variety of biological activities (Bullcck *et al.*,1970; Dulley *et al.*,1970; Ling *et al.*,1973).

In extension of our work on the synthesis of nitrogen heterocyclic quinones (Fandy *et al.*,1997; Hassen *et al.*, 2000), we report here the synthesis of fused imidazothiazolo and thiazolopyrimidinoquinone ring system and evaluation of their biological activities have been undertaken. Thus, 2,3-dichloro-1,4-naphthoquinones reacted with thiourea to give 2-amino-naphtho[2,3-*d*]-thiazole-4,9-dione(**1**) (Hammam and Bayoumy, 1985). Treatment of **1** with phenacyl bromide following the method from the Saldabols group (Saldabols *et al.*, 1967) yielded the 2-imino-3-benzoylmethylnaphtho[2,3-*d*]-thiazole-4,9-dione hydrobromide(**2**) as a cyclic intermediate product, which on heating in absolute ethanol underwent cyclization giving 2-phenylimidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-5,10-dione (**3**) (Scheme 1). Compound **3** was also obtained directly by refluxing **1** with phenacyl bromide in absolute ethanol. The reaction of **1** with chloroacetic acid afforded 2-hydroxyimidazo[2′,1′-*b*]-naphtho[2,3-*d*]thiazole-5,10-dione (**4**). On the other hand, refluxing of **1** with diethyl oxalate (Scheme 1) in absolute ethanol gave 2,3-dihydroimidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-2,3,5,10-tetrone(**5**) in a good yield. Compound **1** which was refluxed with 2,3-dichloroquinoxaline in absolute ethanol gave quinoxalino [2,3:4′,5′]imidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-8,13-dione (**6**) (Scheme 1). The structures of compounds **2**~**6** were confirmed based on its correct micro analytical results and spectral data (Table II).

Treatment of **1** with ethyl acrylate yielded 2-(β-ethoxycarbonylethylimino)naphtho[2,3-*d*]-thiazole-4,9-dione(**7**) which was cyclized to 2,3,4-trihydronaphtho[2,3-*d*]thiazolo[3′,2′-*a*]-pyrimidine-4,6,11-trione(**8**). Cyclization of



Scheme 1. Structures of compounds **2**~**6**

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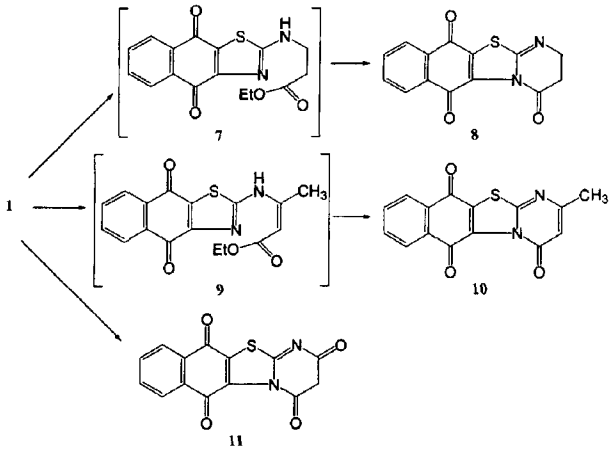
Table I. Antifungal activity of synthesized products

Compound No.	Fungi		
	Aspergillus niger	*Aspergillus flavus*	*Penicillium chrysoen*
Control	108	176	140
1	96	90	124
2	83	89	128
3	73	79	110
4	94	103	114
5	103	128	127
6	128	120	156
8	78	105	120
10	130	167	129
11	122	146	118

1 with ethyl acetoacetate and/or diethyl malonate in the presence of PPA gave 2-methyl-4-hydronaphtho[2,3-*d*] thiazolo[3',2'-*a*']pyrimidine-4,6,11-trione(**10**) and 2,3,4-trihydronaphtho[2,3-*d*]thiazolo[3',2'-*a*']pyrimidine-2,4,6,11-tetrone(**11**) respectively (Scheme 2). The structures of compounds **7~11** were elucidated from their spectral and analytical data (Table II).



Scheme 2. Structures of compounds **7~11**

MATERIALS AND METHODS

Bioassay

Test organisms; the fungi selected for this study Aspergillus niger, Aspergillus flavus and Penicillium chrysogenum. These organisms are plant pathogenic fungi and were isolated from infected tomato plants. A series of conical flasks (250 ml) containing 50 ml Czapek-Dox liquid medium were used for each fungus by the technique of Skipp and

Table II. Elemental analyses and spectral data of compounds **1~11**

Comp. No.	Molecular Formula	Elemental Analyses % Calcd./ Found				MS m/e	IR ν (cm^{-1})	^{1}H-NMR (δ ppm) (DMSO-d_6)
		C	H	N	S			
1	$C_{11}H_6N_2O_2S$ 230.22	57.39 57.22	2.63 2.70	12.17 12.06	13.92 13.86	230($M^{+\cdot}$, 8.60) 104(100)	3380, 3300 (ν NH_2); 1680, 1650 (ν CO, qu.); 1620 (ν C=N).	7.38-8.00(m, 4H, Ar-H); 9.80 (s, 2H, NH_2).
2	$C_{19}H_{13}N_2O_3SBr$ 429.26	53.16 53.21	3.03 3.10	6.53 6.49	7.47 7.39	349($M^{+\cdot}$, 3.7) 350($M^{+\cdot}$+1, 2.9) 76(100)	3290 (ν NH); 1715 (ν CO, benzoyl; 1685, 1650 (ν CO, qu.); 1610 (ν C=N).	4.97 (s, 2H, CH_2); 7.36-8.00 (m, 9H, Ar-H); 8.3 (s, 1H, NH).
3	$C_{19}H_{10}N_2O_2S$ 330.34	69.08 69.20	3.05 3.14	8.48 8.42	9.70 9.58	330($M^{+\cdot}$, 59.10) 239(100)	1670, 1655 (ν CO, qu.); 1615 (ν C=N).	7.35 (s,1H, -CH=of imidazo); 7.74-8.33 (m, 9H, Ar-H).
4	$C_{13}H_6N_2O_3S$ 270.23	57.78 57.72	2.24 2.31	10.37 10.40	11.86 11.71	270($M^{+\cdot}$, 7.33) 86(100)	3300 (νOH); 1670,1655 (n CO, qu.); 1630 (ν C=N).	3.39 (s,1H, OH); 6.70 (s, 1H, -CH= of imidazo); 8.07-8.20 (m, 4H, Ar-H).
5	$C_{13}H_4N_2O_4S$ 284.21	54.94 55.04	1.42 1.38	9.86 9.79	11.28 11.37	284($M^{+\cdot}$, 21.10) 210(100)	1710 (ν CO, amidic); 1665, 1650 (ν CO, qu.); 1620 (ν C=N).	7.91-8.16 (m, 4H, Ar-H).
6	$C_{19}H_8N_4O_2S$ 356.34	64.04 64.20	2.26 2.35	15.72 15.58	9.00 8.88	356($M^{+\cdot}$, 4.72) 260(100)	1670, 1655 (νCO, qu.); 1630 (ν C=N).	7.74-7.98 (m, 4H, Ar-H); 8.16-8.33 (m, 4H, Ar-H).
8	$C_{14}H_8N_2O_3S$ 284.26	59.15 59.28	2.84 2.75	9.86 9.78	11.28 11.33	284($M^{+\cdot}$, 13.63) 78(100)	1710 (ν CO, amidic); 1670, 1660 (ν CO, qu.); 1625 (ν C=N).	3.18 (t, 2H, CH_2); 3.86 (t, 2H, CH_2); 7.68-7.80 (m, 4H, Ar-H).
10	$C_{15}H_8N_2O_3S$ 296.27	60.81 60.84	2.72 2.78	9.46 9.32	10.82 10.68	296($M^{+\cdot}$, 26.0) 103(100)	1705 (ν CO, amidic); 1665, 1650(ν CO, qu.); 1620 (ν C=N).	3.15 (s, 3H, CH_3); 6.94 (s, 1H, -CH= of pyrimidine); 7.80-7.96 (m, 4H, Ar-H).
11	$C_{14}H_6N_2O_4S$ 298.24	56.38 56.26	2.03 2.05	9.39 9.32	10.75 10.82	298($M^{+\cdot}$, 100)	1705 (ν CO, amidic); 1670, 1655 (ν CO, qu.); 1625 (ν C=N).	4.70 (s, 2H, CH_2); 7.58-7.75 (m, 4H, Ar-H).

Bailey method(Skipp and Bailey, 1976). Each of the flasks was supplemented with 200 μg/ml of each quinone derivatives. The flasks were inoculated with a 5-mm diameter agar disc cut from the margin of actively growing colonies. The flasks were incubated at 28°C for 7 days after which the produced mycelia felts were collected, washed several times with distilled water and oven-dried at 80°C to constant mass.

Preparation

Melting points were determined on an electric melting points apparatus (Gallenkamp) and were uncorrected. The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H-NMR spectra were recorded by 300 MHz Varian NMR spectrometer; chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GCMS sp. 1000 Shimadzu, at Cairo University. Elemental analysis was also carried out at Microanalysis Unit.

2-Imino-3-benzoylmethylnaphtho[2,3-*d*]thiazole-4,9-dione hydrobromide (2)

A mixture of **1** (1.15 g, 0.005 mole) and phenacyl bromide (0.99 g, 0.005 mole) in dry benzene (30 ml) was kept at room temperature for 48 h. The crystals, which separated, were collected by filtration and washed with a small amount of ethanol to yield brownish gray fine crystals **2**. (1.26 g, 72%, m.p. 232°C)

2-Phenylimidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-5,10-dione (3)

Method A: A suspension of **1** (0.23 g, 0.001 mole) and phenacyl bromide (0.199 g, 0.001 mole) in absolute ethanol (20 ml) was heated under reflux for about 8 h, cooled and neutralized with sodium bicarbonate solution. The solid thus obtained was recrystallized from ethanol to give **3** as violet crystals. (0.31 g, 94%, m.p. 284°C)

Method B: 0.5 g of **2** in (15 ml) absolute ethanol was heated under reflux for 6 h, cooled and neutralized with sodium bicarbonate solution. The solid, which separated, was collected by filtration and recrystallized from ethanol to give **3** as violet crystals. (0.42 g, 89%, m.p. 284°C)

2-Hydroxyimidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-5,10-dione (4)

A mixture of **1** (1.15 g, 0.005 mole), chloroacetic acid (0.47 g, 0.005 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) in dry methanol (30 ml) was refluxed for about 6 h. Cooled to room temperature and the separated product filtered, washed with water and crystallized from ethanol giving pale brown fine crystals. (1.1 g, 81%, m.p. 175°C)

2,3-Dihydroimidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-2,3,5,10-tetrone (5)

A mixture of **1** (1.15 g, 0.005 mole) and diethyl oxalate (3 ml) in absolute ethanol (30 ml) was heated under reflux for 8 h. The solvent as well as the excess ester, was distilled off under reduced pressure and the remaining solid pro-duct was crystallized from ethanol to give deep brown fine crystals. (1.14 g, 80%, m.p. >300 °C)

Quinoxalino[2,3:4′,5′]imidazo[2′,1′-*b*]naphtho[2,3-*d*]thiazole-8,13-dione (6)

A mixture of **1** (1.15 g, 0.005 mole), 2,3-dichloroquinoxaline (1 g, 0.005 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) in absolute ethanol (30 ml) was refluxed for 8 h. Cooled to room temperature, and the separated product filtered, washed with water and crystallized from ethanol as deep violet fine crystals. (1.28 g, 72%, m.p. 297°C)

2,3,4-Trihydronaphtho[2,3-*d*]thiazolo[3′,2′-*a*′]pyrimidine-4,6,11-trione (8)

To a stirred solution of **1** (1.15 g, 0.005 mole) in dry benzene (30 ml), ethyl acrylate (0.5 g, 0.005 mole) was added and the mixture was refluxed for about 8 h. The solvent was removed under reduced pressure and the remaining precipitate was crystallized from ethanol to give brown micro crystals. (0.95 g, 68%, m.p. 228°C)

2-Methyl-4-hydronaphtho[2,3-*d*]thiazolo[3′,2′-*a*′]pyrimidine-4,6,11-trione (10)

A mixture of freshly distilled ethyl acetoacetate (2 ml), PPA (2 ml) and **1** (1.15 g, 0.005 mole) was refluxed in absolute ethanol (25 ml) for 4 h, cooled and neutralized with $NaHCO_3$ solution. The solid obtained was filtered, washed with water and crystallized from ethanol to give gray crystals. (0.9 g, 61%, m.p. >300°C)

2,3,4-Trihydronaphtho[2,3-*d*]thiazolo[3′,2′-*a*′]pyrimidine-2,4,6,11-tetrone (11)

A mixture of **1** (1.15 g, 0.005 mole), diethyl malonate (2 ml) and PPA (2 ml) was refluxed in absolute ethanol (25 ml) for about 4 h, then cooled and neutralized with $NaHCO_3$ solution. The precipitate was separated washed with ethanol and crystallized from dioxane to give reddish brown crystals. (0.99 g, 66%, m.p. >300°C)

RESULTS AND DISCUSSION

The results in Table I compared with untreated nutrient media cultivated with the above species (control), showed that the naphthothiazole **1** has a biologically active effect where markedly decrease in the weight of the mycelia in all fungal. But in case of imidazonaphthothiazole **3**~**5**,

we found that increasing in their antifungal activity, which demonstrates the positive effect of the imidazole ring in increasing the antimicrobial properties. On the other side, a comparison of the antimicrobial effect of the naphthothiazolopyrimidine **8**~**11** caused a decrease in their antimicrobial activity.

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