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

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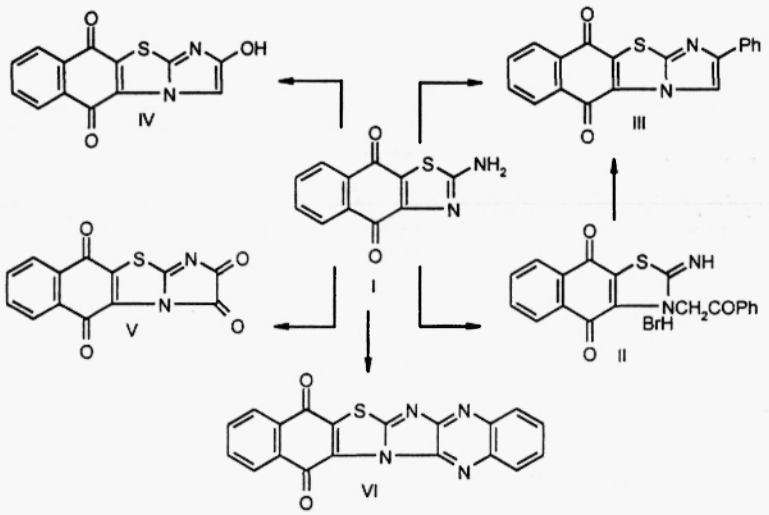
Abstract: Imidazonaphthothiazole derivatives III-VI were prepared by treatment of I with phencyl bromide, chloroacetic acid, diethyl oxalate and 2,3-dichloroquinoxaline respectively. The reaction of I with ethyl acrylate, ethyl acetoacetate and diethyl malonate gave the corresponding naphthothiazolopyrimidine derivatives VIII-XI.

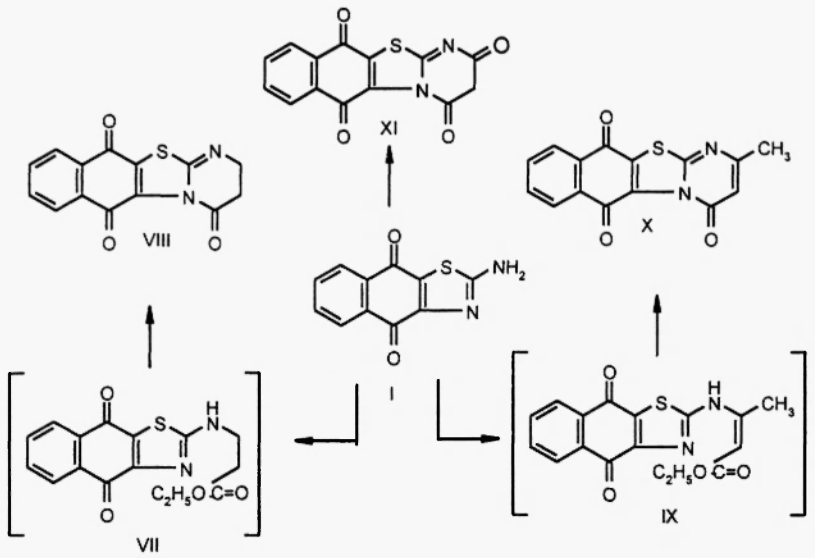
Imidazo[2,1-b]thiazole and its derivatives are useful heterocycles for pharmacological[1-5]. Therefore a number of methods has been developed for the preparation of these derivatives[1,3,6,7]. Quinones are also reported to have a wide variety of biological activities[8-10]. In extension of our work on the synthesis of nitrogen heterocyclic quinones[11,12], we report here the synthesis of fused imidazothiazolo and thiazolopyrimidino-quinone 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-4,5-dione I[13]. Treatment of I with phencyl bromide following the method of Saldabols et al[14], yielded the 2-imino-3-benzoylmethylnaphtho[2,3-d]thiazole-4,9-dione hydrobromide II 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 III [Scheme 1]. Compound III was also obtained directly by refluxing I with phencyl bromide in absolute ethanol. The reaction of I with chloroacetic acid afforded 2-hydroxyimidazo[2',1'-b]-naphtho[2,3-d]thiazole-5,10-dione IV. On the other hand, refluxing of I 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 V in good yield. Compound I when 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 VI [Scheme 1]. The structures of II-VI were confirmed based on its correct microanalytical results and spectral data [cf. Table 2].



Scheme 1

Treatment of I with ethyl acrylate yielded 2-(ß-ethoxycarbonylethylimino)naphtho[2,3-d]thiazole-4,9-dione VII which was cyclized to 2,3,4-trihydronaphtho[2,3-d]thiazolo[3 ,2 -a]pyrimidine-4,6,11-trione VIII. Cyclization of I 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 X and 2,3,4-trihydronaphtho[2,3-d]thiazolo[3 ,2 -a]pyrimidine-2,4,6,11-tetrone XI respectively (Scheme 2). The structures of compounds VII-XI were elucidated from their spectral and analytical data [cf. Table 2].



Scheme 2

Biological Screening:

In this study, we have screened the effect of the newly synthesized compounds on the rate of growth of certain fungi by the technique of Skipp and Bailey method[15]. The concentration of the tested compounds was 200 ug/ml. The results were obtained from theses studies are shown in Table 1. It is to be noted first that most of listed compounds has marked activity against the tested fungi.

Table 1

Antifungal activity of synthesized products

Compound No.	Fungi		
	Aspergillus niger	Aspergillus flavus	Penicillium chrysogen
Control	108	176	140
I	96	90	124
II	83	89	128
III	73	79	110
IV	94	163	114
V	103	128	127
VI	128	120	156
VIII	78	105	120
X	130	167	129
XI	122	146	118

Table 2 Elemental analyses and Spectral data of Compounds I-XI

Comp. No.	Molecular Formula	Elemental Analyses % Calcd./ Found C	H	N	S	MS m/e	IR ν (cm^{-1})	^{1}H-NMR (δ ppm) (DMSO)
I	$C_{11}H_6N_2O_2S$ 230.22	57.39 57.22	2.63 2.70	12.17 12.06	13.92 13.86	230 (M^+, 12.60) 50 (100)	3380, 3300 (ν NH_2); 1680, 1650 (ν CO, qu); 1620 (ν C=N).	7.81-8.11 (m, 4H, Ar-H); 9.20 (s, 2H, NH_2).
II	$C_{19}H_{13}N_2O_3SBr$ 429.26	53.16 53.21	3.03 3.10	6.53 6.49	7.47 7.39	429 (M^+, 10.64) 178 (100)	3290 (ν NH); 1715 (ν CO, benzoyl; 1685, 1650 (ν CO, qu) 1610 (ν C=N).	4.97 (s, 2H, CH_2); 7.36-8.0 (m, 9H, Ar-H); 8.3 (s, 1H, NH).
III	$C_{19}H_{10}N_2O_2S$ 330.34	69.08 69.20	3.05 3.14	8.48 8.42	9.70 9.58	330 (M^+, 2.00) 76 (100)	1670, 1655 (ν CO, qu); 1615 (ν C=N).	7.52 (s,1H -CH= of imidazo); 7.72-7.90 (m, 9H, Ar-H).
IV	$C_{13}H_6N_2O_3S$ 270.23	57.78 57.72	2.24 2.31	10.37 10.40	11.86 11.71	270 (M^+, 7.33) 86 (100)	3300 (ν OH); 1670,1655 (ν CO, qu.); 1630 (ν C=N).	3.39 (s,1H, OH); 6.70 (s, 1H, -CH= of imidazo); 8.07-8.2 (m, 4H, Ar-H).
V	$C_{13}H_8N_2O_4S$ 284.21	54.94 55.04	1.42 1.38	9.86 9.79	11.28 11.37	284 (M^+, 1.40) 210 (100)	1710 (ν CO, amidic); 1665, 1650 (ν CO, qu); 1620 (ν C=N).	7.73 -7.79 (m, 4H, Ar-H).
VI	$C_{19}H_8N_4O_2S$ 356.34	64.04 64.20	2.26 2.35	15.72 15.58	9.00 8.88	356 (M^+, 4.72) 260 (100)	1670, 1655 (ν CO, qu.); 1630 (ν C=N).	7.74-7.98 (m, 4H, Ar-H); 8.16-8.33 (m, 4H, Ar-H).
VIII	$C_{14}H_8N_2O_3S$ 284.26	59.15 59.28	2.84 2.75	9.86 9.78	11.28 11.33	284 (M^+, 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).
X	$C_{15}H_8N_2O_3S$ 296.27	60.81 60.84	2.72 2.78	9.46 9.32	10.82 10.68	296 (M^+, 2.30) 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).
XI	$C_{14}H_6N_2O_4S$ 298.24	56.38 56.26	2.03 2.05	9.39 9.32	10.75 10.82	298 (M^+, 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).

Experimental

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 II:

A mixture of I (1.15 g, 0.005 mole) and phencyl bromide (o.99 g, 0.005 mole) in dry benzene (30 ml) was kept at room temperature for 48 hrs. The crystals, which separated, were collected by filtration and washed with a small amount of ethanol to yield brownish gray fine crystals II, 1.26 g (72 %), m.p. 232 °C.

2-Phenylimidazo[2 ,1 -b]naphtho[2,3-d]thiazole-5,10-dione III:

a- A suspension of I (0.23g, 0.001 mole) and phencyl bromide (0.199 g, 0.001 mole) in absolute ethanol (20 ml) was heated under reflux for about 8 hrs, cooled and neutralized with sodium bicarbonate solution. The solid thus obtained was recrystallized from ethanol to give III as violet crystals, yield 0.31 g (94 %), m.p. 284 °C.

b- 0.5 g of II in (15 ml) absolute ethanol was heated under reflux for 6 hrs, cooled and neutralized with sodium bicarbonate solution. The solid which separated was collected by filtration and recrystallized from ethanol to give III as violet crystals, yield 0.42 g (89 %), m.p. and m.m.p. 284 °C.

2-Hydroxyimidazo[2 ,1 -b]naphtho[2,3-d]thiazole-5,10-dione IV :

A mixture of I (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 hrs. Cooled to room temperature and the separated product filtered, washed with water and crystallized from ethanol giving pale brown fine crystals, yield 1.1 g (81 %), m.p. 175 °C.

2,3-Dihydroimidazo[2 ,1 -b]naphtho[2,3-d]thiazole-2,3,5,10-tetrone V:

A mixture of I (1.15 g, 0.005 mole) and diethyl oxalate (3ml) in absolute ethanol (30 ml) was heated under reflux for 8 hrs. The solvent as well as the excess ester, was distilled off under reduced pressure and the remaining solid product was crystallized from ethanol to give deep brown fine crystals, yield 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 VI :

A mixture of I (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 hrs. Cooled to room temperature, and the separated product filtered, washed with water and crystallized from ethanol as deep violet fine crystals, yield 1.28 g (72 %), m.p. 297 °C.

2,3,4-Trihydronaphtho[2,3-d]thiazolo[3 ,2 -a]pyrimidine-4,6,11-trione VIII:

To a stirred solution of I (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 hrs. The solvent was removed under reduced pressure and the remaining precipitate was crystallized from ethanol to give brown micro crystals, yield 0.95 g (68 %), m.p. 228 °C.

2-Methyl-4-hydronaphtho[2,3-d]thiazolo[3 ,2 -a]pyrimidine-4,6,11-trione X:

A mixture of freshly distilled ethyl acetoacetate (2 ml), PPA (2 ml) and I (1.15 g, 0.005 mole) was refluxed in absolute ethanol (25 ml) for 4 hrs, cooled and neutralized with $NaHCO_3$ solution. The solid obtained was filtered, washed with water and crystallized from ethanol to give gray crystals, yield 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 XI :
A mixture of I (1.15 g, 0.005 mole), diethyl malonate (2 ml) and PPA (2 ml) was refluxed in absolute ethanol (25 ml) for about 4 hrs, then cooled and neutralized with $NaHCO_3$ solution. The precipitate was separated washed with ethanol and crystallized from dioxane to give reddish brown crystals, yield 0.99 g (66 %), m.p. >300 °C.

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