Synthesis of Novel Naphtho[2,1-b]-1,4,5-oxa- or thiadiazepines as Potential Antimicrobial and Anticancer Agents

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Two novel series of quinone derivatives have been synthesized. Thus, condensation of 2-ethoxycarbonylmethylthio-; 3-ethoxycarbonylmethylthio-2-methyl- and 3-ethoxycarbonylmethoxy-2-methyl derivatives of 1,4-naphthoquinone with substituted phenylhydrazines afforded the corresponding hydrazones, while cyclization of the same quinones with the same substituted hydrazines in glacial acetic acid gave the corresponding naphtho[2,1-b]-1,4,5-oxa- or thiadiazepine derivatives. The antimicrobial and anticancer activities of the synthesized compounds were studied.

Synthesen von neuen Naphtho[2,1-b]-1,4,5-oxa- oder thiadiazepin-Derivaten als antimikrobielle und kanzerostatische Wirkstoffe

Zwei Serien von Chinon-Derivaten wurden hergestellt: Die Reaktion von 2-Ethoxycarbonylmethylthio-, 3-Ethoxycarbonylmethylthio-2-methyl und 3-Ethoxycarbonylmethoxy-2-methyl-Derivaten von 1,4-Naphthochinonen mit substituierten Phenylhydrazinen gab die entspr. Hydrazone. Cyclizierung der gleichen Chinone mit den gleichen substituierten Phenylhydrazinen in Essigsäure lieferte die entspr. Naphtho[2,1-b]-1,4,5-oxa oder thiadiazepin-Derivate. Die antimikrobiellen bzw. cytostatischen Aktivitäten von repräsentativen Verbindungen wurden untersucht.

Considerable interest has been focused on quinone compounds which have possess a broad spectrum of biological activities. Among the most important effects are antibacterial[1,2], antifungal[3], antiviral[4], antiinflammatory[5], antihypertensive[6], and anticancer activities[7]. On the other hand, oxadiazepine and thiadiazepine derivatives possess antifungal[8], antihypertensive[9,10], and CNS stimulant[11] properties.

Therefore, it was designed in this investigation to synthesize compounds containing both quinone and oxa- or thiadiazepine moieties fused together in order to study their antimicrobial and anticancer activities.

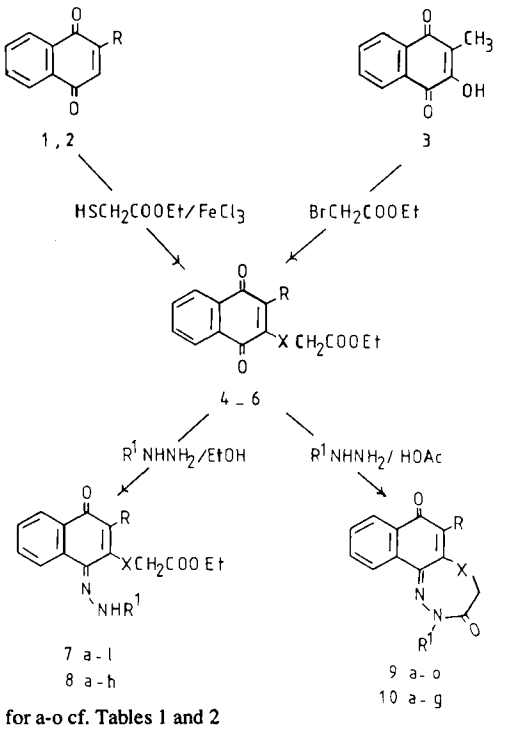
The target oxa- or thiadiazepine derivatives were prepared following the sequences outlined in the Scheme. The key intermediates, 2-ethoxycarbonylmethylthio-1,4-naphthoquinone (**4**) and 3-ethoxycarbonylmethylthio-2-methyl-1,4-naphthoquinone (**5**) have been prepared from 1,4-naphthoquinone (**1**) and 2-methyl-1,4-naphthoquinone (menadione) (**2**), respectively, as reported[12]. The new quinone intermediate, 3-ethoxycarbonylmethoxy-2-methyl-1,4-naphthoquinone (**6**) was prepared from 3-hydroxy-2-methyl-1,4-naphthoquinone (Phthiocol, **3**) and ethyl bromoacetate/K_2CO_3. Condensation of these quinone intermediates **4**, **5**, and **6** with substituted phenylhydrazines as hydrochlorides in EtOH afforded the corresponding hydrazones, namely, 2-ethoxycarbonylmethylthio-1,4-naphthoquinone-1-(substituted phenylhydrazones) **7a-f**, 3-ethoxycarbonylmethylthio-2-methyl-1,4-naphthoquinone-4-(substituted phenylhydrazones) **7g-l**, and 3-ethoxycarbonylmethoxy-2-methyl-1,4-naphthoquinone-4-(substituted phenylhydrazones) **8a-h**. On the other hand, when the quinone intermediates **4**, **5**, and **6** were cyclized by substituted phenylhydrazines in the presence of glacial acetic acid as a solvent, the oxa- and thia-diazepines were obtained, namely, 4-substituted-2,4-dihydronaphtho[2,1-b]-1,4,5-thiadiazepine-3,10-diones **9a-g**, 4-substituted-11-methyl-2,4-dihydronaphtho[2,1-b]-1,4,5-thiadiazepine-3,10-diones **9h-o**, and 4-substituted-11-methyl-2,4-dihydronaphtho[2,1-b]-1,4,5-oxadiazepine-3,10-diones **10a-g**.

IR- and ^{1}H-NMR-spectra of the prepared compounds are in agreement with the proposed structures (cf. Experimental part).

Biological evaluation

A. *Preliminary antimicrobial screening*

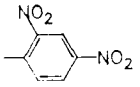
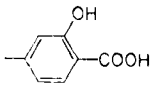
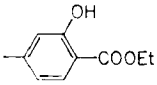
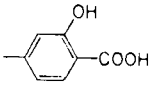
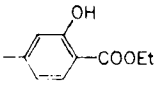
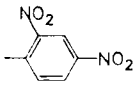
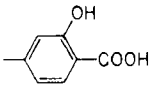
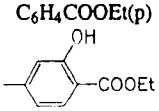
The antimicrobial activity of the prepared compounds was determined by the agar diffusion technique[13]. The test



for a-o cf. Tables 1 and 2

  0365-6233/90/0808-0471 $ 3.50 + .25/0

Table 1: *2-Ethoxycarbonylmethylthio-1,4-naphthoquinone-1-(substituted phenylhydrazones)* **7 a-f**; *3-Ethoxycarbonylmethylthio-2-methyl-1,4-naphthoquinone-4-(substituted phenylhydrazones)* **7 g-l** *and 3-Ethoxycarbonylmethoxy-2-methyl-1,4-naphthoquinone-4-(substituted phenylhydrazones)* **8 a-h**

Compd. No.	X	R	R^1	Yield %	m.p.°C Cryst. Solv.	Molecular Formula	Analyses % Calcd/Found C	H	N	S
7a	S	H	$C_6H_4Br(p)$	70	77-78	$C_{20}H_{17}BrN_2O_3S$	53.9	3.84	6.3	7.2
					A	(445.3)	53.7	3.7	6.1	6.9
7b	S	H		75	227-8	$C_{20}H_{16}N_4O_7S$	52.6	3.53	12.3	7.0
					B	(456.4)	52.5	3.4	12.0	7.2
7c	S	H	$C_6H_4COOH(p)$	60	240-1	$C_{21}H_{18}N_2O_5S$	61.5	4.42	6.8	7.8
					B	(410.4)	61.7	4.3	6.8	7.5
7d	S	H		80	227-9	$C_{21}H_{18}N_2O_6S$	59.1	4.25	6.6	7.5
					B	(426.4)	59.1	4.3	6.1	7.3
7e	S	H	$C_6H_4COOEt(p)$	75	202-3	$C_{23}H_{22}N_2O_5S$	63.0	5.06	6.4	7.3
					B	(438.5)	62.8	4.7	6.7	7.5
7f	S	H		85	155-6	$C_{23}H_{22}N_2O_6S$	60.8	4.88	6.2	7.1
					B	(454.5)	60.6	4.9	5.8	7.3
7g	S	CH_3	$C_6H_4I(p)$	65	146-8	$C_{21}H_{19}IN_2O_3S$	49.8	3.78	5.5	6.3
					A	(506.3)	49.7	3.5	5.3	6.1
7h	S	CH_3	$C_6H_4Br(p)$	75	153-4	$C_{21}H_{19}BrN_2O_3S$	54.9	4.17	6.1	7.0
					A	(459.4)	55.0	4.2	6.0	6.7
7i	S	CH_3	$C_6H_4COOH(p)$	76	128-9	$C_{22}H_{20}N_2O_5S$	62.2	4.75	6.6	7.5
					B	(424.5)	61.9	5.0	6.9	7.3
7j	S	CH_3		68	135-7	$C_{22}H_{20}N_2O_6S$	60.0	4.58	6.4	7.3
					C	(440.5)	59.9	4.3	6.2	7.5
7k	S	CH_3	$C_6H_4COOEt(p)$	70	135-7	$C_{24}H_{24}N_2O_5S$	63.7	5.35	6.2	7.1
					B	(452.5)	63.4	5.2	6.1	6.8
7l	S	CH_3		75	120-1	$C_{24}H_{24}N_2O_6S$	61.5	5.16	6.0	6.8
					B	(468.5)	61.3	4.9	5.7	6.6
8a	O	CH_3	C_6H_5	80	164-6	$C_{21}H_{20}N_2O_4$	69.2	5.53	7.7	
					A	(364.4)	69.4	5.8	7.9	
8b	O	CH_3	$C_6H_4I(p)$	75	125-6	$C_{21}H_{19}IN_2O_4$	51.4	3.91	5.7	
					C	(490.3)	51.4	3.8	5.5	
8c	O	CH_3	$C_6H_4Br(p)$	73	155-6	$C_{21}H_{19}BrN_2O_4$	56.9	4.32	6.3	
					D	(443.3)	56.6	4.5	6.1	
8d	O	CH_3		75	172-3	$C_{21}H_{18}N_4O_8$	55.5	3.99	12.3	
					E	(454.4)	55.2	3.7	12.7	
8e	O	CH_3	$C_6H_4COOH(p)$	68	250-1	$C_{22}H_{20}N_2O_6$	64.7	4.94	6.9	
					B	(408.4)	64.6	4.8	7.1	
8f	O	CH_3		70	165-7	$C_{22}H_{20}N_2O_7$	62.3	4.75	6.6	
					E	(424.4)	62.3	5.0	6.8	
8g	O	CH_3	$C_6H_4COOEt(p)$	80	130-1	$C_{24}H_{24}N_2O_6$	66.0	5.54	6.4	
					E	(436.5)	65.8	5.4	6.1	
8h	O	CH_3		75	155-6	$C_{24}H_{24}N_2O_7$	63.7	5.35	6.2	
					E	(452.5)	64.0	5.5	5.8	

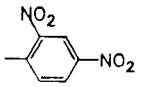
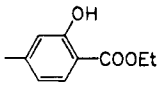
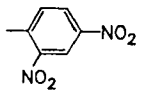
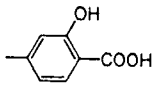
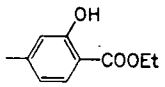
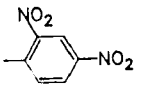
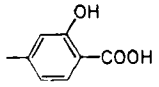
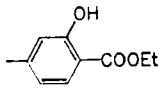
A = benzene/pet.ether (40-60)
B = alcohol
C = $CHCl_3$/pet.ether
D = benzene
E = alcohol/H_2O

organisms used were *Staphylococcus aureus* NCTC 4163. *Escherichia coli* NCTC 5933 and *Candida albicans* 3501.

The prepared compounds were dissolved in propylene glycol 2 mg/ml. A 0.1% solution of streptomycin was used as a reference. The resulting inhibition zones were measured. Propylene glycol showed no inhibition zones.

The results show that the compounds exhibit high activity against *Staphylococcus aureus* (inhibition zone = 15-22 mm). Only a few compounds **7d,h,j,k** and **9i,j** show low activity against *E. coli* (inhibition zones were 12,12,12,14,12,12 mm, respectively), while compounds **7d,k** and **9a** show low activity against *C. albicans* (inhibi-

Table 2: *4-Substituted-2,4-dihydronaphtho[2,1-b]-1,4,5-thiadiazepine-3,10-diones* **9 a-g**; *4-Substituted-11-methyl-2,4-dihydronaphtho[2,1-b]-1,4,5-thiadiazepine-3,10-diones* **9 h-o** *and 4-Substituted-11-methyl-2,4-dihydronaphtho[2,1-b]-1,4,5-oxadiazepine-3,10-diones* **10 a-g**.

Compd. No.	X	R	R^1	Yield %	m.p.°C Cryst. Solv.	Molecular Formula	Analyses % Calcd/Found C	H	N	S
9a	S	H	C_6H_5	60	85-87 A	$C_{18}H_{12}N_2O_2S$ (320.4)	67.5 67.2	3.78 3.6	8.7 8.5	10.0 9.8
9b	S	H	C_6H_4I(p)	65	95-7 B	$C_{18}H_{11}IN_2O_2S$ (446.3)	48.4 48.4	2.48 2.5	6.3 6.0	7.2 7.1
9c	S	H	C_6H_4Br(p)	65	165-7 C	$C_{18}H_{11}BrN_2O_2S$ (399.3)	54.1 53.9	2.78 2.6	7.0 6.8	8.0 8.0
9d	S	H		60	185-6 D	$C_{18}H_{10}N_4O_6S$ (410.4)	52.7 52.5	2.46 2.3	13.6 13.4	7.8 7.6
9e	S	H	C_6H_4COOH(p)	68	201-2 A	$C_{19}H_{12}N_2O_4S$ (364.4)	62.6 63.0	3.32 3.5	7.7 7.4	8.8 8.7
9f	S	H	C_6H_4COOEt(p)	58	125-6 E	$C_{21}H_{16}N_2O_4S$ (392.4)	64.3 64.1	4.11 3.9	7.1 6.9	8.2 7.9
9g	S	H		50	218-9 C	$C_{21}H_{16}N_2O_5S$ (408.4)	61.8 61.6	3.95 3.7	6.9 7.2	7.9 7.9
9h	S	CH_3	C_6H_5	45	139-40 E	$C_{19}H_{14}N_2O_2S$ (334.4)	68.2 67.9	4.22 4.3	8.4 8.1	9.6 9.7
9i	S	CH_3	C_6H_4I(p)	50	105-6 A	$C_{19}H_{13}IN_2O_2S$ (460.3)	49.6 49.2	2.85 2.6	6.1 6.4	7.0 7.0
9j	S	CH_3	C_6H_4Br(p)	60	111-2 E	$C_{19}H_{13}BrN_2O_2S$ (313.3)	55.2 54.9	3.17 2.9	6.8 6.5	7.8 8.0
9k	S	CH_3		65	187-8 D	$C_{19}H_{12}N_4O_6S$ (424.4)	53.8 53.5	2.85 2.6	13.2 13.0	7.6 7.2
9l	S	CH_3	C_6H_4COOH(p)	55	153-4 D	$C_{20}H_{14}N_2O_4S$ (378.4)	63.5 63.5	3.73 3.5	7.4 7.3	8.5 8.4
9m	S	CH_3		58	145-7 D	$C_{20}H_{14}N_2O_5S$ (394.4)	60.9 60.8	3.58 3.8	7.1 6.9	8.1 8.3
9n	S	CH_3	C_6H_4COOEt(p)	63	109-10 E	$C_{22}H_{18}N_2O_4S$ (406.5)	65.0 65.3	4.46 4.3	6.9 6.6	7.9 7.9
9o	S	CH_3		50	120-1 D	$C_{22}H_{18}N_2O_5S$ (422.5)	62.5 62.5	4.29 4.0	6.6 6.5	7.6 7.3
10a	O	CH_3	C_6H_5	67	129-3 D	$C_{19}H_{14}N_2O_3$ (318.3)	71.7 71.5	4.43 4.4	8.8 8.6	
10b	O	CH_3	C_6H_4Br(p)	58	205-7 E	$C_{19}H_{13}BrN_2O_3$ (397.2)	57.4 57.3	3.30 3.2	7.0 7.0	
10c	O	CH_3		60	161-2 D	$C_{19}H_{12}N_4O_7$ (408.3)	55.9 55.6	2.96 2.7	13.7 13.4	
10d	O	CH_3	C_6H_4COOH(p)	65	127-8 A	$C_{20}H_{14}N_2O_5$ (362.3)	66.3 66.1	3.89 3.7	7.7 8.0	
10e	O	CH_3		49	102-4 D	$C_{20}H_{14}N_2O_6$ (378.3)	63.5 63.6	3.73 4.0	7.4 7.2	
10f	O	CH_3	C_6H_4COOEt(p)	45	183-5 C	$C_{22}H_{18}N_2O_5$ (390.4)	67.7 67.4	4.65 4.4	7.2 7.0	
10g	O	CH_3		50	165-7 E	$C_{22}H_{18}N_2O_6$ (406.4)	65.0 65.5	4.46 4.1	6.9 7.2	

A = $CHCl_3$-pet.ether (40-60°C)
B = benzene-pet.ether (40-60)
C = EtOH
D = aqueous acetic acid
E = EtOH/H_2O

tion zones were 12 mm each). The remaining compounds show no activity against *E. coli* and *C. albicans*.

In conclusion the cyclized compounds **9** and **10** are more active against *S. aureus* than the open chain hydrazones, and the thiadiazepines **9** (inhibition zones 19-22) are more active than the oxadiazepines **10** (inhibition zones 15-19 mm). However, none of the tested compounds showed superior activity than streptomycin.

B. Anticancer testing

Compounds **7c**, **7e**, **9e**, and **9f** were evaluated for anticancer activity in P-388 lymphocytic Leukemia and assays were performed in accordance with the specification of the Drug Evaluation Branch, National Cancer Institute, Bethesda, Meryland 20910, U.S.A. The products failed to show any significant activities and all T/C values were below 125.

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Experimental Part

Melting points: uncorrected, open glass capillaries.- IR spectra (Nujol): Beckman 4210 spectrophotometer.- ^{1}H-NMR: Varian EM-360L spectrometer, TMS as intern. standard, chemical shift as δ (ppm).- Analytical data: Microanalytical Unit, Faculty of Science, Cairo University, Egypt.

3-Ethoxycarbonylmethoxy-2-methyl-1,4-naphthoquinone (**6**)

A mixture of 3-hydroxy-2-methyl-1,4-naphthoquinone (Phthiocol, **3**), (1.88 g, 0.01 mole), ethyl bromoacetate (1.76 g, 0.01 mole) and anhydrous K_2CO_3 (1.5 g) in dry acetone (25 ml) was heated under reflux for 20 h (untill no more red colour is observed). The mixture was filtered while hot and then concentrated. After cooling, the separated product was filtered and crystallized from acetone as yellow needles, yield 85%, m.p. 74-75°C.- IR (KBr): 1750 (C=O, ester); 1675; 1645 (C=O, 1,4-quinone); 1280; 1240; 1090; 1040 cm^{-1} (C-O-C, asym. and sym.).- ^{1}H-NMR ($CDCl_3$/DMSO-d_6): 1.26 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$); 2.15 (s, 3H, CH_3); 4.15 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$); 5.1 (s, 2H, OCH_2); 7.6-8.2 (m, 4H, Ar-H).- $C_{15}H_{14}O_5$ (274.3) Calcd. C 65.7 H 5.14 Found C 65.5 H 4.9.

2-Ethoxycarbonylmethylthio-1,4-naphthoquinone-1-(substituted phenylhydrazones) **7a-f**;
3-Ethoxycarbonylmethylthio-2-methyl-1,4-naphthoquinone-4-(substituted phenylhydrazones) **7g-l** *and*
3-Ethoxycarbonylmethoxy-2-methyl-1,4-naphthoquinone-4-(substituted phenylhydrazones) **8a-h**

General procedure

A solution of equimolar amounts (0.01 mole) of the appropriate quinone **4**, **5**, or **6** and the properly substituted phenylhydrazine hydrochloride in absol. EtOH (30 ml) was heated under reflux for 2 h. The mixture was concentrated and the separated product was filtered and recrystallized from the proper solvent (Table 1).- IR: 3300-3200 (NH); 1740-1730 (C=O, ester side chain); 1675-1655 (C=O, quinone); 1645-1625 (C=N), 1570-1540 (δ NH), two bands at 1260-1240 and two bands at 1075-1050 cm^{-1} (C-O-C, asym. and sym.). Compounds containing benzoic- or salicyclic acid moiety, or their esters show additional bands at 3500-3300 (broad OH) and 1710-1700 cm^{-1} (C=O).- ^{1}H-NMR of **7c** in $CDCl_3$/CF_3COOH: 1.3 (t, 3H, $CH_2\underline{CH_3}$); 4.1 (s, 2H, SCH_2); 4.29 (q, 2H, $\underline{CH_2}CH_3$), 7.5-8.5 (m, 10H, Ar-H and NH).- ^{1}H-NMR of **7f** in $CDCl_3$/DMSO-d_6 (δ ppm): 1.3 (t, 6H, 2 x $CH_2\underline{CH_3}$), 3.9 (s, 2H, SCH_2), 4.3 (q, 4H, 2 x $\underline{CH_2}CH_3$), 7.6-8.1 (m, 9H, Ar-H and NH) and 11.1 (br., s, 1H, OH, D_2O exchange).- ^{1}H-NMR of **8d** in $CDCl_3$/CF_3COOH: 1.4 (t, 3H, $CH_2\underline{CH_3}$), 2.2 (s, 3H, CH_3); 4.1 (s, broad, 1H, NH D_2O exchange); 4.5 (q, 2H, $\underline{CH_2}CH_3$), 5.2 (s, 2H, OCH_2) and 7.9-8.6 (m, 7H, Ar-H).

4-Substituted-2,4-dihydronaphtho[2,1-b]-1,4,5-thiadiazepine-3,10-diones **9a-g**;
4-Substituted-11-methyl-2,4-dihydronaphtho-[2,1-b]-1,4,5-thiadiazepine-3,10-diones **9h-o** *and*
4-substituted-11-methyl-2,4-dihydronaphtho[2,1-b]-1,4,5-oxadiazepine-3,10-diones **10a-g**

General procedure

A solution containing an equimolar amounts (0.01 mole) of compound **4**, **5**, or **6** and the properly substituted phenylhydrazine hydrochloride in glacial acetic acid (20 ml) was heated under reflux for 2 h. The mixture was concentrated, cooled and then diluted with water. The precipitated product was filtered, washed with water and recrystallized from the proper solvent (Table 2).- IR of **9a-o**: 1720-1700 (C=O of thiadiazepine ring); 1685-1665 (C=O at position 10); 1635-1620 (C=N).- IR of **10a-g** 1710-1700 (C=O, oxadiazepinone); 1680-1655 (C=O at C-10); 1640-1620 (C=N), two bands at 1270-1220 and two bands at 1070-1015 cm^{-1} (C-O-C, asym. and sym.).- ^{1}H-NMR of **9j** in $CDCl_3$/CF_3COOH: 2.4 (s, 3H, CH_3), 4.05 (s, 2H, SCH_2); 7.8-8.6 (m, 8H, Ar-H).- ^{1}H-NMR of **10c** $CDCl_3$/CF_3COOH: 2.3 (s, 3H, CH_3), 5.1 (s, 2H, OCH_2), and 7.3-8.6 (m, 7H, Ar-H).

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