Synthesis and Antimicrobial Evaluation of Novel Oxa(thia)diazolylquinolines and Oxa(thia)diazepino[7,6-*b*] quinolines

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Three novel series of quinoline derivatives have been prepared by cyclization of the intermediate 3[(substituted)thiocarbamoyl-hydrazonomethyl]-2-chloroquinolines and 3-aroylhydrazonomethyl-2-chloroquinolines: 3-(3-Acetyl-5-(substituted)-2,3-dihydro-1,3,4-oxa(thia)diazol-2-yl)-2-chloroquinolines (**4**; **5**), 3-(5-(substituted)-1,3,4-oxa(thia)diazol-2-yl)-2-chloroquinolines (**6**; **7**), and 2-(substituted)-1,3,4-oxa(thia)diazepino[7,6-*b*]quinolines (**8**; **9**). The antimicrobial activity of these compounds was studied.

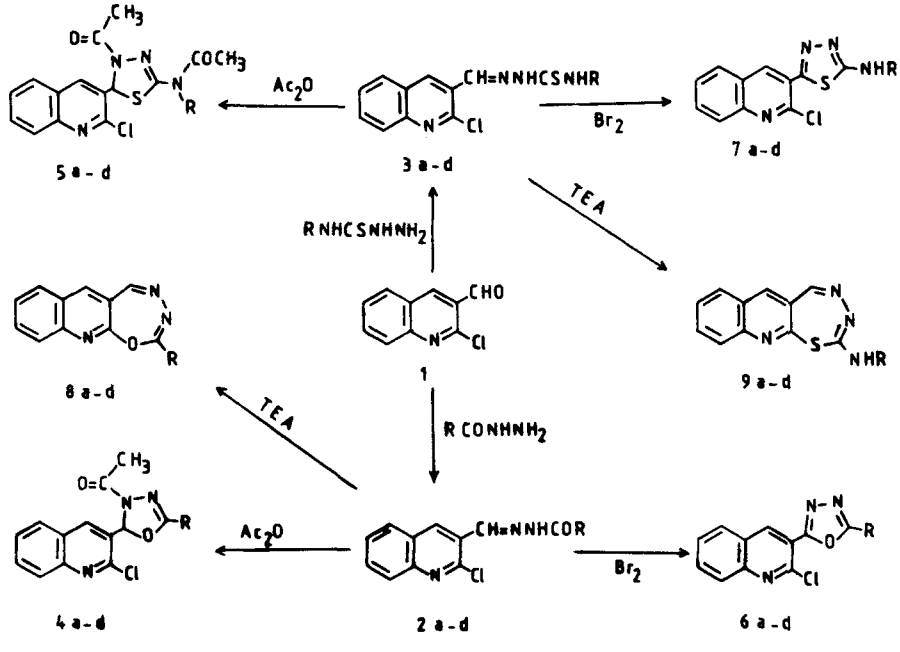
Synthese und Antimikrobielle Aktivität von Oxa(thia)diazolyl-chinolinen und Oxa(thia)diazepino[7,6-*b*]chinolinen

Drei neuen Serien von Chinolin-Derivaten wurden hergestellt durch Cyclisierung von 2-Chlor-3-(substituierten thiocarbamoylhydrazono-methyl)-chinolinen und 3-Aroylhydrazonomethyl-2-chlorchinolinen: 3-(3-Acetyl-5-(substituierte)-2,3-dihydro-1,3,4-oxa(thia)diazol-2-yl)-2-chlorchinoline (**4**; **5**), 3-(5-substituierte)-1,3,4-oxa(thia)diazol-2-yl)-2-chlorchinoline (**6**; **7**) und 2-(substituierte)-1,3,4-oxa(thia)diazepino[7,6-*b*]chinoline. Die antimikrobielle Aktivität der synthetisierten Verbindungen wurde studiert.

Thiadiazole and oxadiazole derivatives exhibit antitubercular[1-3], antifungal, and antimicrobial[4-8] activities. In addition, oxadiazepines and thiadiazepines possess antifungal and antimicrobial[9] activities. Moreover, quinoline derivatives possess a wide variety of pharmacological activities, *inter alia* antitubercular[10], and antibacterial[11] efficacy.

As a continuation of our syntheses of antimicrobial agents[12-16], in the present investigation we describe oxa(thia)diazole increments joined to the quinoline nucleus and oxa(thia)diazepine groups fused with the quinoline ring.

The title compounds were prepared through the key intermediates aroylhydrazones **2a-d** and the thiosemicarbazones **3a-d**[17] (scheme). The intermediates **2a-d** were prepared by condensation of 2-chloroquinoline-3-carboxaldehyde (**1**)[18] with the proper aroylhydrazine. Heating the intermediates



Scheme

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2a-d or **3a-d** with acetic anhydride[12,19] yields the oxa or thiadiazoline derivatives **4a-d** or **5a-d**, respectively. Oxidative cyclization[20,21] of **2a-d** or **3a-d** with Br_2 in glacial acetic acid afforded the oxa or thiadiazole derivatives **6a-d** or **7a-d**, respectively.

Heating **2a-d** or **3a-d** with triethylamine (TEA) afforded the corresponding quinilino[7,6-*b*]oxa- or thiadiazepines **8a-d** or **9a-d**.

IR and ^{1}H-NMR spectra of the compounds agree with the proposed structures (Experimental Part).

Antimicrobial screening:

The synthesized compounds were evaluated for their antimicrobial activity by the agar diffusion technique[22]. A 0.1% solution in dimethylformamide (DMF) was used. The test organisms were *Staphylococcus aureus* NCTC 4163, *Escherichia coli* NCTC 5933, and *Candida albicans* 3501. Inhibition zones against *Escherichia coli* for **2a**: 18 mm; **2b**: 21 mm; **2c**: 16 mm; **4b**, **4d**, **6a**, **7d**, **8a**, **8d**: 14 mm, **9a** and **9b**: 17 mm. The remaining compounds showed no inhibition zones against *E. coli*. The reference compound was Streptomycin (inhibition zone: 34 mm). DMF showed no inhibition zone. The MIC (minimum inhibitory concentrations) for compounds **2a**, **2b**, **4b**, **8a**, and **8d** were 0.05, 0.0125, 0.025, 0.1 and 0.025 mg/ml, respectively. The MIC for Streptomycin was 0.006 mg/ml. None of the tested compounds was superior to streptomycin in the test against *E. coli*.

The compounds showed no inhibition against *Staphylococcus aureus* and *Candida albicans*.

Experimental Part

Melting points are uncorrected.- IR spectra (Nujol): Beckman 4210.- ^{1}H-NMR: EM-360 L in $CDCl_3$, TMS as internal standard, chemical shift in δ (ppm).- Analytical data: analytical unit, Faculty of Science, Cairo University.

3-Aroylhydrazonomethyl-2-chloroquinolines **2a-d**

A solution of 2-chloroquinoline-3-carboxaldehyde (**1**)[18] (1.92 g, 0.01 mole) in ethanol (20 ml) and the proper aroylhydrazine (0.01 mole) was heated under reflux for 3 h, cooled and poured into water. The separated product was filtered and recrystallized from ethanol, Table 1.- IR: 3330-3320 (NH); 1665-1650 (C=O); 1630, 1550, 1530 (C=N, NH, C=C).- ^{1}H-NMR of **2a**: 4.1 (s, 2H, CH_2), 7.3-8 (m, 9H aromat.), 8.6 (s, 1H, 4-H), 8.6 (s, 1H, CH=N), 9.9 (s, 1H, NH, D_2O exchangeable).

3-(3-Acetyl-5-substituted-2,3-dihydro-1,3,4-oxadiazol-2-yl)-2-chloroquinolines **4a-d** *and*
3-[3-Acetyl-5-(N-substituted acetamido)-2,3-dihydro-1,3,4-thiadiazol-2-yl]-2-chloroquinolines **5a-d**

A mixture of the appropriate **2a-d** or **3a-d** (0.001 mole) and acetic anhydride (5 ml) was heated under reflux for 1 h. The mixture was cooled and poured into water to decompose the excess of acetic anhydride. The separ-

Table 1: 3-Aroylhydrazonomethyl-2-chloroquinolines **2a-d**

Comp. No.	R	Yield %	M.P. °C	Molecular Formula	Analyses %-Calc./Found C	H	N	Cl
2a	$CH_2C_6H_5$	85	193-4	$C_{18}H_{14}ClN_3O$	66.8	4.35	13.0	10.9
				(323.8)	66.5	4.3	12.6	10.7
2b	$CH_2OC_6H_5$	80	158-9	$C_{18}H_{14}ClN_3O_2$	63.6	4.15	12.4	10.4
				(339.8)	63.4	3.9	12.0	10.6
2c	C_6H_5	80	210-1	$C_{17}H_{12}ClN_3O$	65.9	3.9	13.6	11.4
				(309.7)	66.0	4.1	13.2	11.2
2d	4-pyridyl	85	170-1	$C_{16}H_{11}ClN_4O$	61.8	3.56	18.0	11.4
				(310.7)	61.5	3.3	18.0	11.3

Table 2: 3-(3-Acetyl-5-substituted-2,3-dihydro-1,3,4-oxadiazol-2-yl)-2-chloroquinolines **4a-d**

Comp. No.	R	Yield %	M.P. °C	Molecular Formula	Analyses %-Calc./Found C	H	N	Cl
4a	$CH_2C_6H_5$	65	140-1	$C_{20}H_{16}ClN_3O_2$	65.7	4.41	11.5	9.7
				(365.8)	65.5	4.3	11.2	9.5
4b	$CH_2OC_6H_5$	70	115-6	$C_{20}H_{16}ClN_3O_3$	62.9	4.22	11.0	9.3
				(381.8)	62.7	4.1	10.8	9.1
4c	C_6H_5	65	200-1	$C_{19}H_{14}ClN_3O_2$	64.9	4.01	11.9	10.1
				(351.8)	64.9	4.1	12.1	10.0
4d	4-pyridyl	60	185-6	$C_{18}H_{13}ClN_4O_2$	61.3	3.71	15.9	10.0
				(352.8)	61.0	3.5	15.7	9.9

Table 3: 3-[3-Acetyl-5-(*N*-substituted acetamido-2,3-dihydro-1,3,4-thiadiazol-2-yl)-2-chloroquinolines **5a-d**

Comp. No.	R	Yield %	M.P. °C	Molecular Formula	Analyses %-Calc./Found C	H	N	S	Cl
5a	C_6H_{11} (cyclo)	50	162-4	$C_{21}H_{23}ClN_4O_2S$	58.5	5.37	13.0	7.5	8.2
				(431.0)	58.4	5.1	12.8	7.3	8.0
5b	$CH_2C_6H_5$	75	182-3	$C_{22}H_{19}ClN_4O_2S$	60.2	4.36	12.8	7.4	8.1
				(438.9)	59.9	4.3	13.0	7.3	7.9
5c	C_6H_5	70	159-60	$C_{21}H_{17}ClN_4O_2S$	59.4	4.03	13.2	7.5	8.3
				(424.9)	59.2	3.8	13.0	7.5	8.1
5d	$C_6H_4CH_3$ (p)	70	258-9	$C_{22}H_{19}ClN_4O_2S$	60.2	4.36	12.8	7.4	8.1
				(438.9)	60.1	4.1	12.5	7.1	7.8

Table 4: 3-(5-Substituted-1,3,4-oxadiazol-2-yl)-2-chloroquinolines **6a-d**

Comp. No.	R	Yield %	M.P. °C	Molecular Formula	Analyses%-Calc./Found C	H	N	Cl
6a	$CH_2C_6H_5$	85	99-100	$C_{18}H_{12}ClN_3O$	67.2	3.76	13.0	11.0
				(321.8)	67.0	3.6	13.0	10.8
6b	$CH_2OC_6H_5$	72	118-9	$C_{18}H_{12}ClN_3O_2$	64.0	3.58	12.5	10.5
				(337.8)	63.8	3.4	12.3	10.4
6c	C_6H_5	65	105-6	$C_{17}H_{10}ClN_3O$	66.4	3.28	13.6	11.5
				(307.8)	66.1	3.1	13.5	11.3
6d	4-pyridyl	55	110-2	$C_{16}H_9ClN_4O$	62.2	2.9	18.1	11.5
				(308.7)	62.1	2.8	18.0	11.1

Table 5: 3-(5-Substituted amino)-1,3,4-thiadiazol-2-yl)-2-chloroquinolines **7a-d**

ated solid was washed with water and recrystallized from ethanol (Tables 2 and 3).- IR: 1680-1660 (C=O); 1640-1630 (C=N).- ^{1}H-NMR of **5b**: 2.4, 2.5 (two s, each 3H, 2 CH_3CO), 5.4 (s, 2H, CH_2), 7.1 (s, 1H, thiadiazoline 2-H), 7.4-7.9 (m, 9H aromat.), 8.4 (s, 1H, 4-H).

3-(5-Substituted-1,3,4-oxadiazol-2-yl)-2-chloroquinolines **6a-d** *and 3-(5-Substituted amino-1,3,4-thiadiazol-2-yl)-2-chloroquinolines* **7a-d**

The mixture of the appropriate **2a-d** or **3a-d** (0.001 mole) in acetic acid (5 ml), anhydrous sodium acetate (1.64 g, 0.02 mole) and bromine (0.66 ml) was stirred for 30 min at room temp. then poured into water (100 ml). The formed precipitate was washed with water and recrystallized from ethanol (Table 4 and 5).- IR: 1640-1620 (C=N); in addition, compounds **7a-d** showed bands at 3300-3200 (NH).- ^{1}H-NMR of **7b**: 4.7 (d, 2H, J = 4 Hz, Ar-CH_2, singlet after NH/D_2O-exchange), 7.3-8.0 (m, 9H aromat.), 8.3 (s, 1H, 4-H), 8.6 (s, 1H, NH, D_2O exchange).

2-Substituted-1,3,4-oxadiazepino[7,6-b]quinolines **8a-d** *and 2-Substituted amino-1,3,4-thiadiazepino[7,6-b]quinolines* **9a-d**

A mixture of the appropriate **2a-d** or **3a-d** (0.001 mole) and triethylamine (3 ml) was heated under reflux for 6 h. The mixture was cooled and poured into water. The precipitate was washed with water and recrystallized from ethanol (Table 6 and 7).- IR for **8a-d**: 1630-1625; 1520-1510 (C=N, C=C).- IR for **9a-d**: 3480-3320 (NH); 1625-1620; 1580-1570;

Table 6: 2-Substituted-1,3,4-oxadiazepino[7,6-*b*]quinolines **8a-d**

Comp. No.	R	Yield %	M.P. °C	Molecular Formula	Analyses%-Calc./Found C	H	N
8a	$CH_2C_6H_5$	60	200-1	$C_{18}H_{13}N_3O$	75.2	4.56	14.6
				(287.3)	75.1	4.3	14.9
8b	$CH_2OC_6H_5$	60	198-9	$C_{18}H_{13}N_3O_2$	71.3	4.32	13.8
				(303.3)	71.0	4.2	13.5
8c	C_6H_5	43	215-6	$C_{17}H_{11}N_3O$	74.7	4.06	15.4
				(273.3)	74.6	4.0	15.0
8d	4-pyridyl	45	229-30	$C_{16}H_{10}N_4O$	70.1	3.67	20.4
				(274.3)	69.8	3.4	20.1

Table 7: 2-(Substituted amino)-1,3,4-thiadiazepino[7,6-*b*]quinolines **9a-d**

Comp. No.	R	Yield %	M.P. °C	Molecular Foumula	Analyses %-Calc./Found C	H	N	S
9a	C_6H_{11} (cyclo)	65	99-100	$C_{17}H_{18}N_4S$	65.8	5.84	18.0	10.3
				(310.4)	65.5	5.5	17.8	10.1
9b	$CH_2C_6H_5$	75	195-6	$C_{18}H_{14}N_4S$	67.9	4.43	17.6	10.1
				(318.4)	67.8	4.3	17.8	10.2
9c	C_6H_5	50	115-6	$C_{17}H_{12}N_4S$	67.1	3.96	18.4	10.5
				(304.4)	66.9	3.7	18.1	10.4
9d	$C_6H_4CH_3$ (p)	70	109-10	$C_{18}H_{14}N_4S$	67.9	4.43	17.6	10.1
				(318.4)	67.7	4.1	17.2	9.8

1515-1510 (C=N, NH, C=C).- ^{1}H-NMR of **9b**: 4.93 (d, 2H, J = 4 Hz, CH_2, singlet after D_2O exchange of NH), 7.3-8 (m, 9H aromat.), 8.3 (s, 1H, 6-H), 8.53 (s, 1H, 5-H), 9.7 (s, 1H, NH, D_2O exchange).

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