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SYNTHESIS OF SOME NEW QUINOLINE DERIVATIVES OF POTENTIAL ANTIMICROBIAL ACTIVITY

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ABSTRACT

A series of quinolinoxymethyl triazole (**5**), oxadiazole (**6,8**), isoxazolidin-3,5-diones (**10**), pyrazolidin-3,5-diones (**$11_{a,b}$**), and other related pyrimidin-2,4,6-triones (**12_a**) and pyrimidin-4,6-dione-2-thiones (**12_b**) were synthesized. Four of the synthesized compounds were tested for antimicrobial activity; two of them displayed high activity against a variety of bacterial strains.

INTRODUCTION

The chemistry of quinoline derivatives is of increasing interest since many of these compounds find useful applications as chemotherapeutic agents especially against malaria and other parasites, cancer, and microorganisms.[1-8] On the other hand, it has been reported that substituted triazole and oxadiazole derivatives possess bactericidal activity.[13,14]

Furthermore, several 5-pyrazolones and pyrazolidin-3,5-diones are reported to possess marked anti-inflammatory[9] and uricosuric[10] activities. In addition, certain isoxazole[11] and pyrimidine-2,4,6-trione[12] derivatives have been shown to interfere with nucleic acid biosynthesis. Based on these findings, synthesis of some new quinoline derivatives incorporated into triazole, oxadiazole, isoxazolidin-3,5-dione, pyrazolidin-3,5-dione, pyrimidin-2,4,6-trione and pyrimidin-4,6-dione-2-thione ring systems was carried out for the purpose of evaluation as antimicrobial agents.

RESULTS AND DISCUSSION:

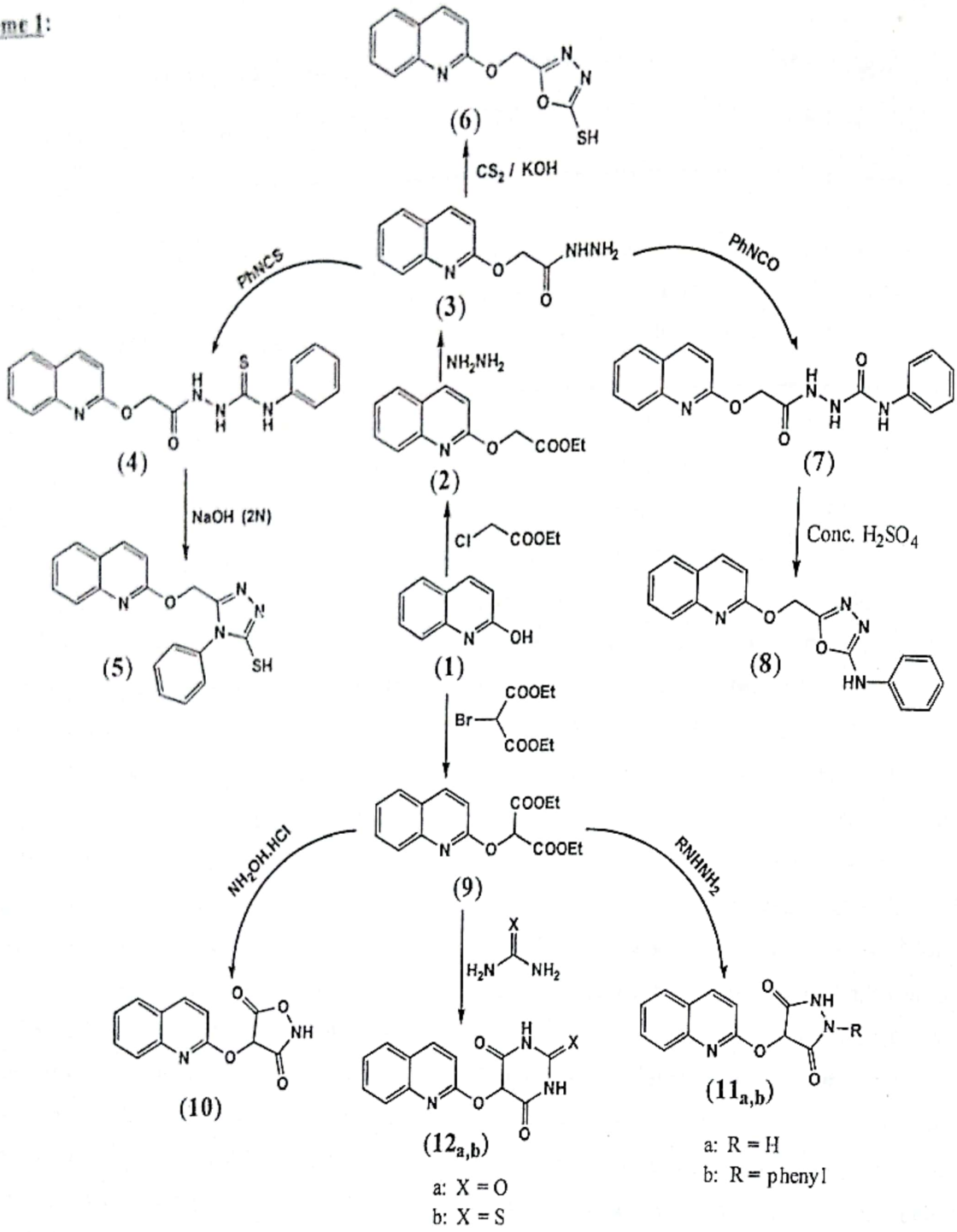
The two key intermediates used for synthesis of the target compounds namely, ethyl 2-(2-quinolinoxy)acetate (**2**) and 2-(2-quinolinoxy)malonic acid diethyl ester (**9**) were prepared by stirring a solution of 2-hydroxyquinoline in ethanolic KOH with ethyl chloroacetate and diethyl bromomalonate, respectively. The structure of these intermediates was elucidated by elemental and spectral analyses. The treatment of **2** with hydrazine hydrate (99%) led to the formation of the hydrazide (**3**), which was converted to the thiosemicarbazide derivative (**4**) by treatment with phenyl isothiocyanate. The target triazole (**5**) was obtained by refluxing **4** with 2N. NaOH. The oxadiazole derivative (**6**) was prepared according to the method described by **Young and Wood**[15] by heating the hydrazide (**3**) with CS_2 in presence of KOH. Also, the oxadiazole (**8**) was obtained through acid-catalyzed cyclization of compound (**7**) which was synthesized by treatment of the hydrazide (**3**) with phenyl isocyanate. Furthermore, condensation of the diester (**9**) with hydroxylamine hydrochloride[16] in the presence of pyridine gave the corresponding 4-(2-quinolinoxy)isoxazolidin-3,5-diones (**10**). On the other hand, condensation of **9** with excess hydrazine hydrate in the presence of KOH gave the corresponding 4-(2-quinolinoxy)pyrazolidin-3,5-diones (**11_b**). In addition, the treatment of **9** with urea and thiourea in ethanolic KOH afforded the corresponding 5-(2-quinolinoxy)pyrimidin-2,4,6-triones (**12_a**) and 5-(2-quinolinoxy)pyrimi-din-4,6-dione-2-thiones (**12_b**).

The synthetic routes for the preparation of the new compounds are outlined in **Scheme 1**.

ANTIMICROBIAL ACTIVITY:

Four of the synthesized compounds namely, **5**, **6**, **11a**, and **11b**, were tested for antimicrobial activity. The test compounds were dissolved in dimethylformamide (DMF) at 5 mg/ml concentration. Ciprofloxacin, being a quinolone derivative, was chosen as a control and was used in a concentration of 0.25 µg / ml. The test was carried out by the cup-plate

Scheme 1:



method.[17] About 1.2×10^6 CFU/ml from each test organism was inoculated to the nutrient agar. Cups were done then filled with about 100 µl from each compound solution. The organisms used were *Bacillus subtilis* (Gram +ve rods); *Staphylococcus aureus* and *Sarcina lutea* (Gram +ve cocci); and *E. coli* (Gram –ve rods). The results of the test are shown in the **Table 1**. Compounds $\mathbf{11_a}$ and $\mathbf{11_b}$ showed high antimicrobial activity against the test organisms. Compound **6** was totally inactive while compound **5** displayed only weak activity against *Sarcina lutea* and no activity against other bacterial strains.

EXPERIMENTAL:

All melting points are uncorrected and were taken in open capillaries on a GallenKamp apparatus. Infrared spectra were determined in KBr on a Perkin Elmer Model-137 infracord. The ^{1}H-NMR spectra were obtained at 90 MHz using TMS as an internal standard. Analytical data were obtained from the microanalytical data center at Cairo University.

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Table 1: The antimicrobial activity of the test compounds:

Comp.	Microorganisms** Inhibition zone diameter (mm)			
	Gram +ve			Gram –ve
	Sarcina lutea	*Staph. aureus*	*Bacillus subtilis*	*E. coli*
5	15	-	-	-
6	-	-	-	-
11_a	25	20	30	20
11_b	40	30	35	25
Control*	-	35	20	30

*Control is ciprofloxacin; a quinolone antibacterial (MIC ≈ 0.2 µg / ml).
** All bacterial strains were isolated and identified in Microbiology Department, Faculty of Pharmacy, University of Zagazig.

Ethyl (2-quinolinoxy)acetate (2):

To a solution of 2-hydroxyquinoline (1; 1.45 g, 0.01 mole) in ethanol (50 ml), a solution of potassium hydroxide (0.56 g, 0.01 mole) was added, followed by ethyl bromoacetate (0.015 mole). The reaction mixture was stirred for 3 hr. The resulting solid was collected, washed with water and recrystallized from ethanol; m.p 189°, yield 82%.

Analysis: $C_{13}H_{13}NO_3$ (231):

	C%	H%	N%
Calcd	67.53	5.62	6.06
Found	67.7	5.5	5.9

(2-Quinolinoxy)acetic acid hydrazide (3):

A mixture of ethyl (2-quinolinoxy)acetate (2; 2.31 g, 0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol (50 ml) was heated at reflux for 5 hr. The reaction mixture was cooled and diluted with ice water. The precipitated solid was filtered, washed with water, and recrystallized from ethanol; m.p 204°, yield 75%.

Analysis: $C_{11}H_{11}N_3O_2$ (217):

	C%	H%	N%
Calcd	60.83	5.06	19.35
Found	61.0	4.9	19.5

4-Phenyl-1-[(2-quinolinoxy)acetyl]thiosemicarbazide (4):

A mixture of the hydrazide (3; 2.17 g, 0.01 mole) and phenyl isothiocyanate (1.35 g, 0.01 mole) in dioxan (50 ml) was refluxed for 6 hr. The reaction mixture was evaporated under vacuum. The residue was recrystallized from ethanol; m.p 195°, yield 85%.

Analysis: $C_{18}H_{16}N_4O_2S$ (352):

	C%	H%	N%
Calcd	61.36	4.54	15.90
Found	61.5	4.6	16.0

4-Phenyl-3-(2-quinolinoxymethyl)-1,2,4-triazole-5-thiol (5):

A solution of the thiosemicarbazide (4; 3.52 g, 0.01 mole) in 2N sodium hydroxide (20 ml) was heated under reflux for 3 hr. The reaction mixture was cooled and acidified with dilute hydrochloric acid. The precipitated solid was filtered, washed with water, dried, and recrystallized from aqueous ethanol; m.p 181°, yield 87%.

Analysis: $C_{18}H_{14}N_4OS$ (334):

	C%	H%	N%
Calcd	64.67	4.19	16.76
Found	64.5	4.3	16.9

^{1}H-NMR of **5** (DMSO-D_6, δ ppm): δ 5.2 (s, 2H, OCH_2), 6.8-7.9 (complex m, 11H, aromatic protons), 10.2 (s, 1H, NH).

2-(2-Quinolinoxymethyl)-1,3,4-oxadiazole-5-thiol (6):

To a solution of 3 (2.17 g, 0.01 mole) in ethanol (100 ml), was added a solution of potassium hydroxide (0.84 g, 0.015 mole) followed by carbon disulphide (20 ml) and the mixture was heated under reflux for 8 hr. The reaction mixture was concentrated under reduced pressure and acidified with dilute hydrochloric acid. The resulting solid was collected, washed with water, and recrystallized from aqueous ethanol; m.p 129°, yield 65%.

Analysis: $C_{12}H_9N_3O_2S$ (259):

	C%	H%	N%
Calcd	55.59	3.47	16.21
Found	55.7	3.3	16.1

4-Phenyl-1-[(2-quinolinoxy)acetyl]semicarbazide(7):

A mixture of 3 (2.17 g, 0.01 mole) and phenyl isocyanate (1.19 g, 0.01 mole) in dioxan (50 ml) was refluxed for 6 hr. The reaction mixture was evaporated under vacuum. The residue was recrystallized form aqueous ethanol; m.p 206°, yield 80%.

Analysis: $C_{18}H_{16}N_4O_3$ (336):

	C%	H%	N%
Calcd	64.28	4.76	16.66
Found	64.1	4.9	16.7

2-(2-Quinolinoxymethyl)-5-phenylamino-1,3,4-oxadiazole (8):

A solution of 7 (3.36 g, 0.01 mole) in concentrated sulphuric acid (10 ml) was cooled and allowed to stand for 15 minutes. The reaction mixture was quenched with ice and treated with concentrated ammonium hydroxide solution till neutral to litmus. The resulting precipitate was filtered, washed with water, and recrystallized from ethanol; m.p 178°, yield 50%.

Analysis: $C_{18}H_{14}N_4O_2$ (318):

	C%	H%	N%
Calcd	67.92	4.40	17.6
Found	68.1	4.3	17.5

2-(2-Quinolinoxy)malonic acid diester (9):

To a solution of **1** (1.45 g, 0.01 mole) in ethanol (50 ml), was added a solution of potassium hydroxide (0.56 g, 0.01 mole) followed by diethyl bromomalonate (0.01 g). The reaction mixture was stirred for 3 hr. The formed precipitate was filtered, washed with water, dried, and recrystallized from aqueous ethanol; m.p 216° yield 82%.

Analysis: $C_{16}H_{17}NO_5$ (303):

	C%	H%	N%
Calcd	63.36	5.61	4.62
Found	63.1	5.7	4.5

^{1}H-NMR of 9 (DMSO-D_6, δ ppm): δ 1.2-1.4 (6H, t, 2-CH_3 of ester), 4.2-4.4 (4H, q, 2-CH_2 of ester), 5.1 (1H, s, OCH of malonate), 7.2-7.6 (6H, m, aromatic protons).

4-(2-Quinolinoxy)isoxazolidin-3,5-diones (10):

A mixture of 9 (3.03 g, 0.01 mole), hydroxylamine hydrochloride (0.01 mole) in pyridine (3 ml) was heated under reflux for 5 hr. The reaction mixture was cooled and neutralized with dilute hydrochloric acid. The formed precipitate was filtered, dried and recrystallized from aqueous methanol; m.p 181°, yield 78%.

Analysis: $C_{12}H_8N_2O_4$ (244):

	C%	H%	N%
Calcd	59.01	3.27	11.47
Found	59.2	3.0	11.4

4-(2-Quinolinoxy)pyrazolidin-3,5-diones (11_a) and 1-phenyl-4-(2-Quinolinoxy)pyrazolidin-3,5-diones (11_b):

A mixture of 9 (3.03 g, 0.01 mole), 99% hydrazine hydrate or phenyl hydrazine (0.01 mole) in ethanol (20 ml) was heated at reflux for 6 hr. The reaction mixture was cooled and neutralized with dilute hydrochloric acid. The precipitate was filtered, dried and recrystallized from aqueous ethanol.

Compound	yield	m.p	MF
11_a	75	219	$C_{12}H_9N_3O_3$ (243)
11_b	78	210	$C_{18}H_{13}N_3O_3$ (319)

Analysis:

		C%	H%	N%
11_a:	Calcd	59.25	3.7	17.28
	Found	58.9	3.8	17.1
		C%	H%	N%
11_b:	Calcd	67.71	4.07	13.16
	Found	67.5	4.2	13.2

5-(2-Quinolinoxy)pyrimidin-2,4,6-triones (12_a) and 5-(2-Quinolinoxy)pyrimidin-4,6-dione-2-thiones (12_b):

A mixture of 9 (3.03 g, 0.01 mole), urea or thiourea (0.02 mole), and potassium hydroxide (1.12 g

0.02 mole) in ethanol (50 ml) was heated under reflux with stirring for 5 hr. The reaction mixture was cooled and neutralized with dilute hydrochloric acid. The crude product was washed with water, dried and recrystallized from aqueous ethanol.

IR Spectra of 12_a: 3300 (NH), 1690 (C=O).

IR Spectra of 12_b: 3200 (NH), 1720 (C=O), 1200 (C=S).

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تشييد بعض مشتقات الكينولين الجديدة كمضادات للبكتريا

السيد لاشين ، صبحي العدل ، كامل عبدالرحيم ، منصور أبوكل
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لقد تم فى هذا البحث تحضير مركبات كينولين أوكسى ميثيل تريازول (٥)وأوكساديازول (٨ر٦) وأيزوكسازوليدين -٣ ر٥ - دايون (١٠) وبيرازوليدين -٣ر٥-دايون (١١ أ ، ب) ومشتقات بيريميدين -٢ر٤ر٦ - ترايون (١٢أ) وبيريميدين -٤ر٦-دايون ٦ - ثيون (١٢ ب) . أربعة من المركبات الجديدة قد تم دراسة تأثيرها كمضادات للبكتريا ووجد أن لبعض منها تأثير عال.