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Research Article

Synthesis and Reactions of 3-(2-Chloromethyl-carbonylamino) tetrachloroquinazolin-2,4-dione

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A series of tetrachloroquinazolin-2,4-dione derivatives were synthesized using appropriate synthetic route and characterized by IR, ^{1}H NMR, MS, and elemental analysis. The synthesized compounds were evaluated for their preliminary in vitro antibacterial activity towards *Salmonella typhi, Staphylococcus aureus*, and *Bacillus cereus*.

1. Introduction

Pyrimidine and quinazoline derivatives have occupied a unique position in medicinal chemistry; the pyrimidine ring is present in a large number of biological important compounds [1] such as alkaloids, drugs, and agrochemicals. Furthermore, pyrimidine and condensed pyrimidines have received much attention over the years because of their interesting biological and pharmacological properties as sedatives [2] and antibacterial [3–8], antimalarial [2], analgesic [2, 4, 7], anti-inflammatory [2, 3, 7], anticonvulsant [8], antipyretic [5], antiparasitic [5], antifungal [6, 9], antitoxic [10], antiviral [8, 10, 11], anticancer [12–15], and DNA-binding activities [14]. This encouraged us to develop new synthetic route for the synthesis of new quinazoline derivatives by introducing a heterocyclic moiety directly or through side chain in position 3 starting with 3-(2-chloromethylcarbonylamino)tetrachloroquinazolin-2,4-dione **2**. We anticipated that these novel heterocyclic compounds would possess certain pharmacological activities.

2. Results and Discussion

The reaction sequences employed for synthesis of the target compounds are shown in Scheme 1, and their physical properties are depicted in Table 1. The key intermediate in the present study, 3-(2-chloromethylcarbonylamino)tetrachloroquinazolin-2,4-dione **2**, was prepared by the reaction of 3-aminotetrachloroquinazolin-2,4-dione [16] **1** with chloroacetyl chloride. Reaction of the starting compound **2** with potassium isothiocyanate gave **3**. It was expected that the imino group could be hydrolyzed but ammonia odour was not detected during the reaction. The preparation of **4a**,**b** was achieved by the reaction of compound **2** with urea and/or thiourea under basic condition. Compound **5** was synthesized by heating compound **2** with piperidine in dioxane.

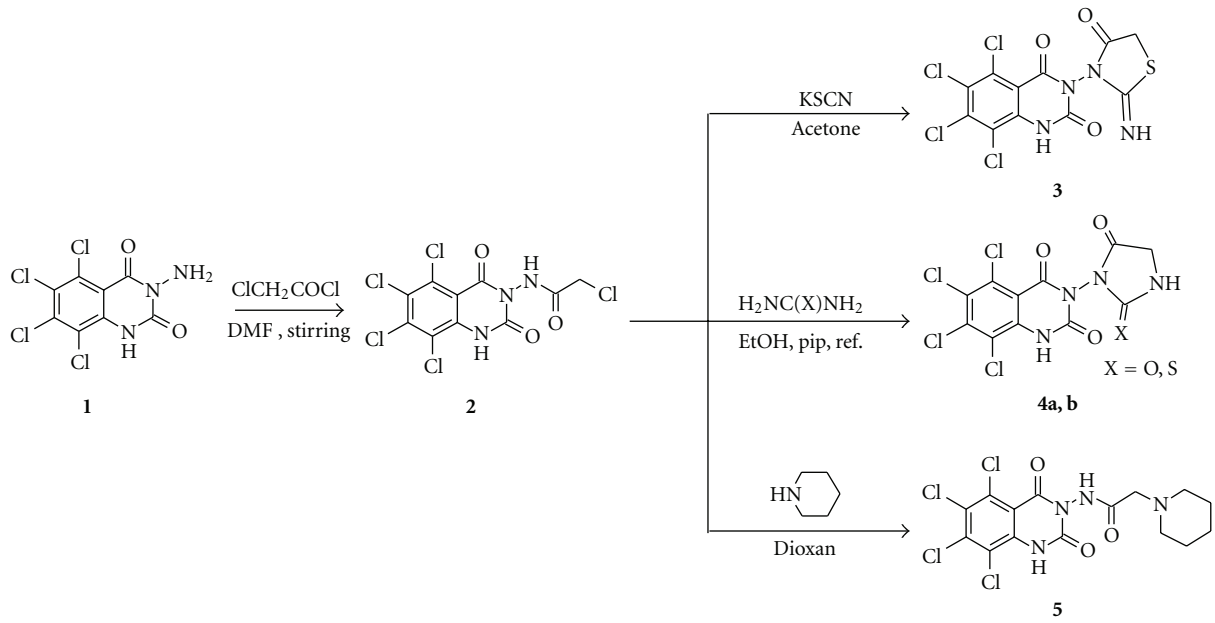
The reaction of compound **2** with potassium isothiocyanate may proceed according to the mechanism (Dimroth-type rearrangement) [17] shown in Scheme 2.

Formation of compounds **4a** and **4b** may proceed according to the mechanism shown in Scheme 3.

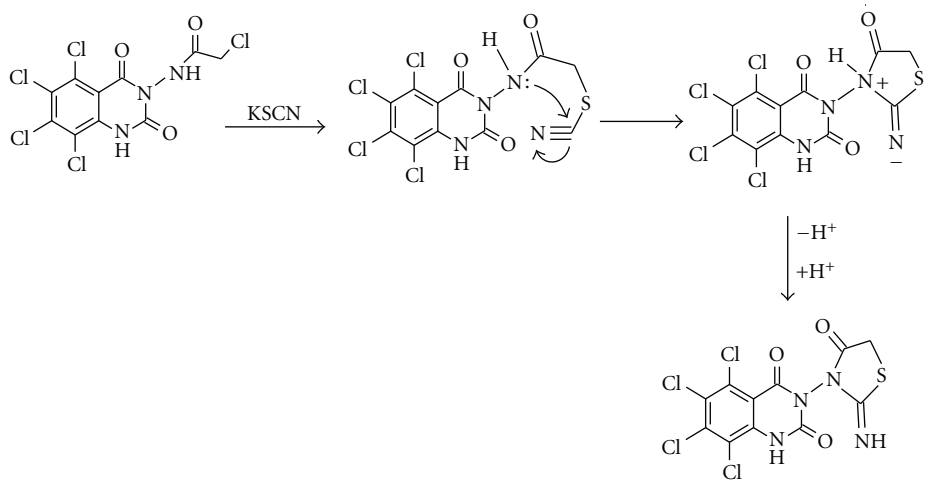
3. Biological Activity

Salmonella typhi, Staphylococcus aureus, and *Bacillus cereus* were obtained from the Faculty of Veterinary Medicine, Pathology Department. The three kinds of selected bacteria were grown on the appropriate media.

The two most active compounds tested are compounds **2** and **5**. The activity of these compounds against all microorganisms tested showed positive reactions as indicated by zone of inhibition (Table 2); this may be due to four and



Scheme 1



Scheme 2

five chlorine atoms [18], respectively. Compound **1** has approximately the same antibacterial activity against *Staph. areus* and *Bacillus cereus*. Compound **1** did not show any inhibition activity against *Salmonella typhi*. However, **1** showed a moderate antibacterial effect compared to other compounds, and this may be due to the tetrachloro pyrimidine [19–21].

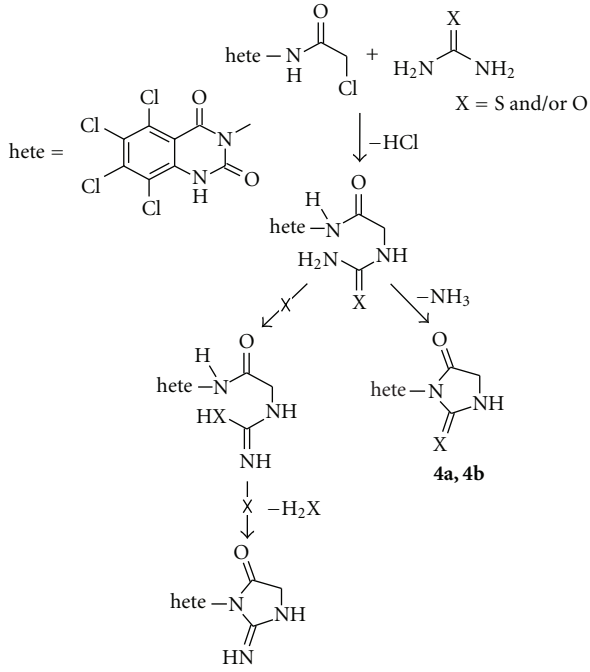
4. Experimental

4.1. Chemical Protocols. Melting points were uncorrected and determined on an electric melting point apparatus (Kofler). The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H-NMR spectra were recorded using 200 MHz varian EM 390 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. Elemental analyses were carried out at the Microanalysis Unit at Cairo University. The purity of the compounds was detected by TLC.

*4.1.1. Synthesis of 3-(2-Chloromethylcarbonylamino)tetrachloroquinazolin-2,4-dione (**2**).* To a stirred solution of 3-aminotetrachloroquinazolin-2,4-dione **1** (0.31 gm, 1 mmol) in DMF (10 mL), chloroacetyl chloride (1 mL) was added dropwise at room temperature. The reaction mixture was stirred for 2 h and then diluted with cold water. The solid formed was filtered off and crystallized by benzene/ethanol to give **2** as white crystalline material (0.35 gm, 89% yield), m.p. 320–322 C. FT.IR (KBr) (cm ^{1}): 3211 (NH), 3021 (CH aliph.), 1741 and 1700 (C=O's). ^{1}HNMR (200 MHz, DMSO-d_6) δ

Table 1: Physical properties and elemental analysis data.

Comp.	Molecular formula	Molecular weight	Elemental analysis (%)	
			Anal calcd.	Found
1	$C_8H_3Cl_4N_3O_2$	314.94	C-30.52; H-0.96; N-13.34; Cl-45.03	C-30.75; H-0.97; N-13.52; Cl-45.01
2	$C_{10}H_4Cl_5N_3O_3$	391.43	C-30.69; H-1.03; N-10.73; Cl-45.29	C-30.81; H-1.02; N-10.90; Cl-45.31
3	$C_{11}H_4Cl_4N_4O_3S$	414.06	C-31.91; H-0.97; N-13.53; Cl-34.25	C-32.15; H-0.98; N-13.72; Cl-34.27
4a	$C_{11}H_4Cl_4N_4O_4$	397.99	C-33.20; H-1.01; N-14.08; Cl-35.63	C-33.45; H-1.07; N-14.18; Cl-35.65
4b	$C_{11}H_4Cl_4N_4O_3S$	414.06	C-31.91; H-0.97; N-13.53; Cl-34.25	C-32.02; H-0.99; N-13.56; Cl-34.30
5	$C_{15}H_{14}Cl_4N_4O_3$	440.12	C-40.94; H-3.20; N-12.73; Cl-32.22	C-41.21; H-3.21; N-12.94; Cl-32.25



Scheme 3

Table 2: Antibacterial activity of some resulted compounds.

Compound no. (5×10^{-2} mg/mL)	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus cereus*
	Zone of inhibition (mm)		
1	−ve	8	15
2	7	9	18
5	7	10	16

(ppm): 4.04 (s, 2H, CH_2), 11.2 (s, 1H, NH), 11.58 (s, 1H, NH).

*4.1.2. Synthesis 5,6,7,8-Tetrachloro-3-(2-imino-4-oxo-thiazolidin-3-yl)(1H,3H)-quinazolin-2,4-dione (**3**).* 3-(2-Chloromethylcarbonylamino)tetrachloroquinazolin-2,4-dione **2** (0.39 gm, 1 mmol) was heated under reflux with potassium isothiocyanate in acetone (25 mL) for 6 h. After cooling, the solid formed was filtered off and crystallized by ethanol to give **3** as white crystalline material (0.24 gm, 58% yield), m.p. 286–288 C. FT.IR (KBr) (cm^{-1}): 3200 (NH), 1740 and 1660 (C=O's). ^{1}HNMR (200 MHz, DMSO-d_6) δ (ppm): 4.37 (s, 2H, CH_2), 9.44 (s, 1H, C=NH), 10.9 (s, 1H, NH).

*4.1.3. General Procedure for the Synthesis of (**4a** and **4b**).* To a solution of 3-(2-chloromethylcarbonylamino)tetrachloroquinazolin-2,4-dione **2** (0.39 gm, 1 mmol) in absolute ethanol (20 mL), urea and/or thiourea (1 mmol) was added in presence of piperidine as a catalyst, and the reaction mixture was heated under reflux for 6 h. After cooling, the precipitate formed was filtered off and crystallized from benzene to give **4a**-**b**.

*5,6,7,8-Tetrachloro-3-(2,5-dioxo-imidazolidin-1-yl)-1H-quinazolin-2,4-dione **4a**.* Pale yellow crystals (0.27 gm, 67% yield), m.p. 306–308 C. FT.IR (KBr) (cm^{-1}): 3211 (NH), 3021 (CH aliph.), 1751 and 1695 (C=O's). ^{1}HNMR (200 MHz, DMSO-d_6) δ (ppm): 4.37 (s, 2H, CH_2), 11.1 (s, 1H, NH), 11.43 (s, 1H, NH).

*5,6,7,8-Tetrachloro-3-(5-oxo-2-thioxoimidazolidin-1-yl)-1H-quinazolin-2,4-dione **4b**.* White crystalline material (0.27 gm, 66% yield), m.p. 300–302 C. FT.IR (KBr) (cm^{-1}): 3308 (NH), 1746 and 1669 (C=O's), 1200 (C=S). ^{1}HNMR (200 MHz, DMSO-d_6) δ (ppm): 4.38 (s, 2H, CH_2), 11.11 (s, 1H, NH), 11.41 (s, 1H, NH). MS: m/z (%) 412 (M), 414 (M + 2), 416 (M + 4).

*4.1.4. Synthesis of 2-(Piperidine-1-yl)-N-(5,6,7,8-tetrachloro-2,4-dioxo-1,3-dihydro-2H,4H-quinazolin-3-yl)acetamide (**5**).* A mixture of 3-(2-chloromethylcarbonylamino)tetrachloroquinazolin-2,4-dione **3** (0.39 gm, 1 mmol) and piperidine (3 mmol) in dioxane (20 mL) was heated under reflux for 6 h. After cooling, the precipitate formed was filtered off and crystallized from benzene/ethanol to give **5** as white crystalline material (0.31 gm, 70% yield), m.p. 190–192 C. FT.IR (KBr) (cm^{-1}): 3405, 3196 (NH's), 2960 (CH_2 aliph.), 1751 and 1700 (C=O' s). ^{1}HNMR (200 MHz, DMSO-d_6) δ (ppm): 1.5–1.7 (m, 6H, $3CH_2$), 2.99 (t, 4H, 2CH2), 4.4 (s, 2H, CH_2–CO), 9.06 (s, 1H, C=NH), 11.2 (s, 1H, NH).

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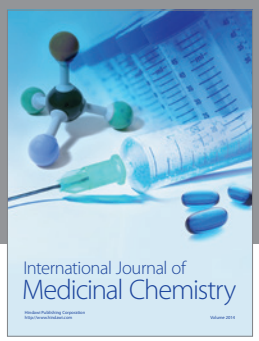

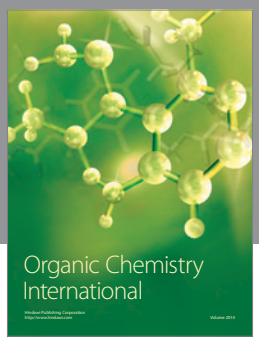

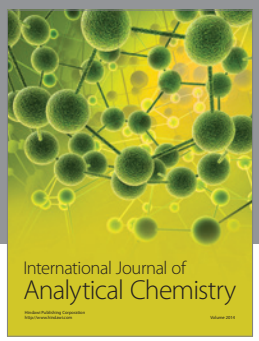

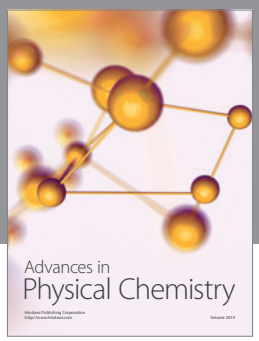

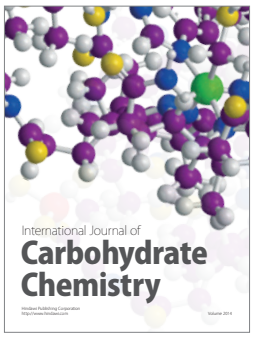

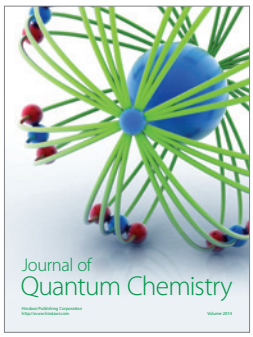

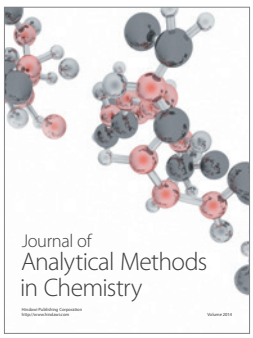

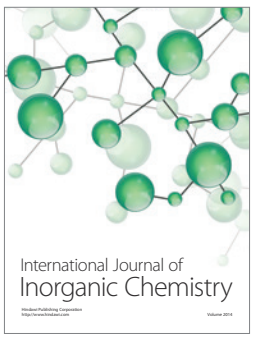

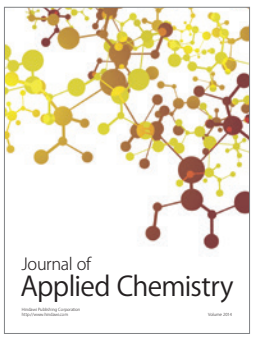

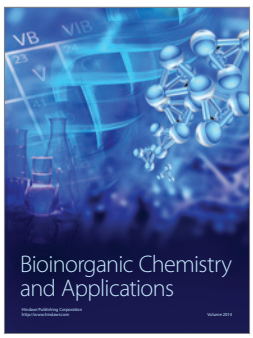

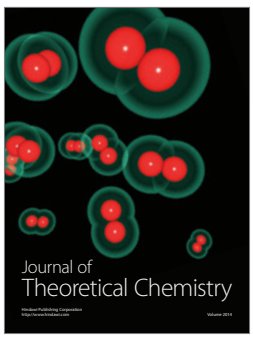

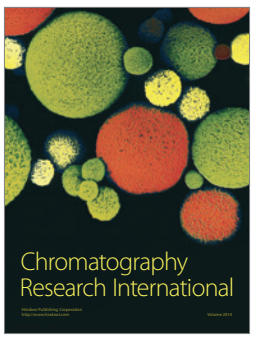

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