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Synthesis and reactions of 3-aminotetrachloroquinazolin-2,4-dione

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ABSTRACT

N-phenylsulphonyloxytetrachlorophthalimide was obtained by treatment of *N*-hydroxy tetrachlorophthalimide with benzenesulphonyl chloride. Also, the titled compound **3** was obtained by reaction of compound **2** with hydrazine hydrate via Lossen rearrangement. Compound **3** used as starting material for the synthesis of new pyrimidine and quinazolinedione derivatives containing four chlorine atoms which have pharmacological activity.

1. Introduction

Owing to the importance of tetrachlorophthalimides as good α-glucosides inhibitors that decrease glucose level [1,2] in blood and their use as potentially valuable for various diseases, we aimed in the present study to synthesize another class of new tetrachloroheterocyclic compounds such as tetrachloro quinazolindione derivatives. It has been recently shown that pyrimidines and quinazolindiones are important compounds posses pharmacological activity including use as anticonvulsant, electroshock, pentylenetetrazole induced seizures in mice [3], sedative, hypotensive [4], antinflammatory, antigonisys [5,6], vasodilator [7-9], contractile smooth muscles and posses inhibitory activity toward the calcium independent phosphordiesteras enzyme [10]. This encouraged us to synthesize quinazolinedione derivatives containing four chlorine atoms in benzene ring starting with tetrachlorophthalic anhydride which may possess greater certain pharmacological activities.

2. Experimental

2.1. Instrumentation

Melting points were uncorrected 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 by 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 GC-MS sp.1000 Shimadzu. Elemental analyses were carried out at Microanalysis Unit at Cairo University; purity of the compounds was detected by TLC.

2.2. Synthesis

2.2.1. N-phenylsulphonyloxytetrachlorophthalimide (2)

Benzenesulphonyl chloride was added dropwisely with stirring in ice bath to a solution of *N*-hydroxytetrachloro phthalimide (6.3 g, 20 mmol) in pyridine (15 mL) [11]. The reaction mixture was vigorously stirred for 15 min., the solid formed was acidified with cold dilute hydrochloric acid (1:1), and the solid formed was filtered off and dried. The target product was crystallized from petroleum ether (80-100) and benzene (3:1) to give *N*-phenylsulphonyloxytetrachlorophthalimide (3 g, 6.8 mmol) **2** in yield 35 % as yellow crystals (Scheme 1). M.p.: 244 °C. FT-IR (KBr, cm^{-1}): 1808 and 1750 (C=O), 1360 and 1180 (SO_2-O-). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): 7.70- 8.11 (m, 5H, Ph-SO_2). MS (*m/z*, %): 439 (1.01%) correspond to the molecular formula ($C_{14}H_5Cl_4NO_5S$) in addition to the characteristic peaks for compounds containing four chlorine atoms [13] at (M+2), (M+4) and (M+6). Anal. calcd. for $C_{14}H_5Cl_4NO_5S$: C, 38.12; H, 1.14; N, 3.18. Found: C, 38.31; H, 1.16; N, 3.18%.

2.2.2. 3-aminotetrachloroquinazolin-2,4-dione (3)

A mixture of *N*-phenylsulphonyloxytetrachlorophthalimide, **2**, (4.41 g, 10 mmole) and hydrazine hydrate in dry benzene (40 mL) using Dean & starks' apparatus was refluxed for 2 hours [12]. After cooling; the solid formed was filtered off and crystallized from water to give 3-aminotetrachloroquinazolin-2,4-dione (2.4 g, 7.6 mmole) **3** in yield 76 % as white crystal (Scheme 2). M.p.: 274 °C. FT-IR (KBr, cm^{-1}): 3457 (NH), 3313 and 3206 (NH_2), 1726 and 1675 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 5.62 (s, 2H, NH_2) and also showed the disappearance of NH signal in DMSO-d_6 while FT-IR spectrum revealed the presence of a band for νNH at 3457 cm^{-1}.

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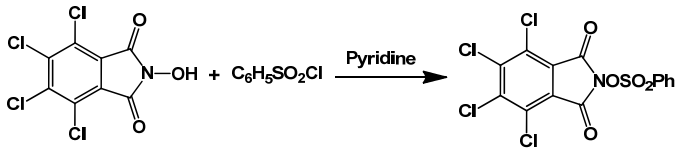
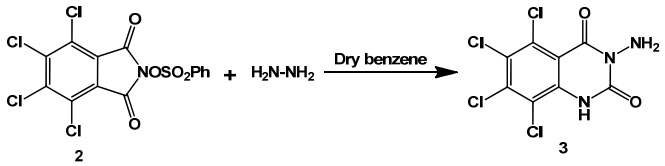


Scheme 1



Scheme 2

Anal. calcd. for $C_8H_3Cl_4N_3O_2$: C, 30.52; H, 0.96; N, 13.34. Found: C, 30.75; H, 0.97; N, 13.34 %.

2.2.3. 3-(N-acetylamino)tetrachloroquinazolin-2,4-dione (4)

To a solution of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.315 g, 1 mmole) in dry pyridine (10 mL), acetylchloride (1 mL) was added drop wisely at room temperature. The reaction mixture was stirred for 2 hours, and a cold diluted HCl (1:1) was added to the reaction mixture and the solid formed was filtered off and crystallized from benzene/ethanol to give 3-(*N*-acetylamino)tetrachloroquinazolin-2,4-dione (0.29 g, 0.81 mmole) **4** in yield 81 % as white crystal (Scheme 3). M.p.: 306 ^{o}C. FT-IR (KBr, cm^{-1}): 3200 (NH), 1780 and 1750 (C=O) (imide carbonyl). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 1.93 (s, 3H, CH_3), 10.6 (S, 1H, NH), 11.4 (S, 1H, NH). Anal. calcd. for $C_{10}H_5Cl_4N_3O_3$: C, 33.65; H, 1.41; N, 11.77. Found: C, 33.86; H, 1.42; N, 11.98%.

2.2.4. 3-(phenylsulphonylamino)tetrachloroquinazolin-2,4-dione (5)

3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) in dry pyridine (10 mL) was cooled in ice bath; benzenesulphonyl chloride was added drop wisely. The reaction mixture with stirred at room temperature for 4 hours. A cold diluted HCl (1:1) was added to the reaction mixture and the solid formed was filtered off and crystallized from benzene/ethanol to give 3-(phenylsulphonylamino)tetrachloro quinazolin-2,4,dione (0.27 g, 0.59 mmole) **5** in yield 59 % as yellow crystal (Scheme 3). M.p.: 300 ^{o}C. FT-IR (KBr, cm^{-1}): 3200 (NH), 1810, 1750 (C=O), 1360, 1180 (SO_2). ^{1}H NMR (200 MHz, DMSO-d_6): 7.30-7.90 (m, 5H, Ar-H), 9.75 (s, 1H, NH), 11.40 (s, 1H, NH). Anal. Calcd. for $C_{14}H_7Cl_4N_3O_4S$. C, 36.95; H, 1.55; N, 9.23. Found: C, 37.23; H, 1.56; N, 9.34 %.

2.2.5. 3-(2-thiophenecarbonylamino)tetrachloroquinazolin-2,4-dione (6)

A solution of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) in dry pyridine (10 mL) was cooled in ice bath; 2-thiophenecarbonyl chloride was added drop wisely with stirring for 4 hours. A cold diluted HCl (1:1) was added to the reaction mixture and the solid formed was filtered off and crystallized from benzene/ethanol to give 3-(2-thiophene-carbonylamino)tetrachloroquinazolin-2,4-dione (0.28 g, 0.729 mmole) **6** in yield 67 % as white crystal (Scheme 3). M.p.: 308 ^{o}C. FT-IR (KBr, cm^{-1}): 3200 (NH), 1740 and 1680 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 7.26-7.28 (dd, 1H, H_X), 7.96 (dd, 1H, H_M), 7.98-8.02 (dd, 1H, H_A), 11.34 (s, 1H, NH), 11.55 (s, 1H, NH). MS (*m/z*, %): 423 (0.59 %) (M^+) in addition to the characteristic peaks for compounds containing four chlorine atoms at *m/z* = 425 (0.66 %) (M+2), 427 (0.41 %) (M+4) and 429 (0.08 %) (M+6). Anal. calcd. for $C_{13}H_5Cl_4N_3O_3S$: C, 36.74; H, 1.18; N, 9.88. Found: C, 36.98; H,1.19; N 10.05 %.

2.2.6. 3-(2-chloromethylcarbonylamino)tetrachloro quinazolin-2,4-dione (7)

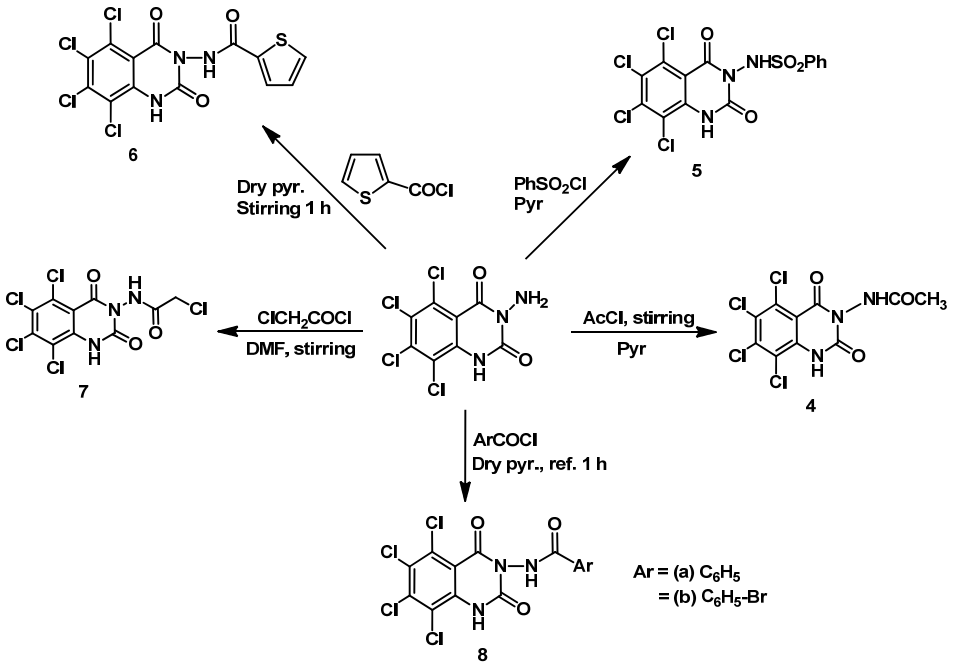
To a stirred solution of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) in DMF (10 mL), chloroacetylchloride (1 mL) was added drop wisely at room temperature. The reaction mixture was stirred for 2 hours, and then dilute with cold water. The solid formed was filtered off and crystallized from benzene/ethanol to give 3-(2-chloromethylcarbonyl-amino)tetrachloroquinazolin-2,4-dione (0.35 g, 0.89 mmole) **7** in yield 89 % as white crystal (Scheme 3). M.p.: 320 ^{o}C. FT-IR (KBr, cm^{-1}): 3211 (NH), 3021 (CH Aliph.), 1741 and 1700 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 4.04 (s, 2H, CH_2), 11.2 (s, 1H, NH), 11.58 (s, 1H, NH). Anal. calcd. for $C_{10}H_4Cl_5N_3O_3$: C, 30.69; H, 1.03; N, 10.73. Found: C, 30.81; H, 1.02; N 10.90%.

2.2.7. 3-(N-benzamido)tetrachloroquinazolin-2,4-dione (8a)

A solution of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) in dry pyridine (10 mL) was cooled in ice bath; benzoylchloride was added drop wisely with stirring for 4 hours. A cold diluted HCl (1:1)was added to the reaction mixture and the solid formed was filtered off and crystallized from benzene/ethanol to give 3-(*N*-benzamido)tetrachloro quinazolin-2,4-dione (0.32 g, 0.76 mmole) **8a** in yield 78 % as white crystal (Scheme 3). M.p.: 310 ^{o}C. FT-IR (KBr, cm^{-1}): 3200 (NH), 3000 (CH arom.), 1740 and 1660 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 7.30-8.00 (m, 5H, Ar-H), 11.30 (s, 1H, NH), 11.40 (s, 1H, NH). Anal. calcd. for $C_{15}H_7Cl_4N_3O_3$. C, 42.99; H, 1.68; N, 10.03. Found: C, 43.20; H, 1.66; N 10.07%.

2.2.8. 3-[(N-(4-bromobenzamido)tetrachloroquinazolin-2,4-dione (8b)

A mixture of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) and *p*-bromobenzoylchloride (0.21 g, 1 mmole) in dry pyridine (10 mL) was heated under reflux for 1/2 hour. After cooling, the reaction mixture was poured into cold diluted HCl (1:1). The solid formed was filtered off and crystallized from benzene/ethanol to give 3-[(*N*-(4-bromo benzamido)tetrachloroquinazolin-2,4-dione (0.28 g, 0.56 mmole) **8b** in yield 56 % as white crystal (Scheme 3). M.p.: 314 ^{o}C.



Scheme 3

FT-IR (KBr, cm^{-1}): 3200 (NH), 3000 (CH Arom.), 1740 and 1660 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 7.70-7.90 (two doublet 4H, A_2B_2 Arom.), 10.65 (s, 1H, NH), 11.47 (s, 1H, NH). Anal. calcd. for $C_{15}H_6BrCl_4N_3O_3$: C, 36.18; H, 1.21; N, 8.44. Found: C, 36.28; H, 1.22; N 8.68%.

2.2.9. 3-arylidineaminotetrachloroquinazolin-2,4-diones (9a-d)

3-Aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) was heated under reflux for 10-12 hours with the appropriate aromatic aldehydes namely benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and thiophenecarbaldehyde (1 mmole) in absolute ethanol (20 mL) and in prescence of pipridine as a catalyst. After cooling; the reaction mixture was filtered off and crystallized from appropriate solvent to give the arylidine derivatives, **9a-d**, respectively (Scheme 4).

3-(Benzylidene-amino)-5,6,7,8-tetrachloro-1H-quinazoline-2,4-dione (**9a**): Yield: 77 % as yellow crystal. M.p.: 360 ^{o}C. FT-IR (KBr, cm^{-1}): 3221 (NH), 1731,1685 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 7.54-7.95 (m, 5H, arom. H), 8.6 (s, 1H, CH=N), 11.45 (s, 1H, NH). Anal. calcd. for $C_{15}H_7Cl_4N_3O_2$: C, 44.71; H, 1.75; N, 10.42. Found: C, 44.94; H, 1.76; N 10.59%.

3-(Nitrobenzylidene-amino)-5,6,7,8-tetrachloro-1H-quinazoline-2,4-dione (**9b**): Yield: 64 % as brown silky. M.p.: 360 ^{o}C. FT-IR (KBr, cm^{-1}): 3389 (NH), 1726, 1623 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 8.24-8.42 (two d, 4H, A_2B_2 arom.), 8.93 (s, 1H, CH=N), 11.20 (s, 1H, NH). Anal. calcd. for $C_{15}H_7Cl_4N_3O_2$: C, 40.22; H, 1.35; N, 12.51. Found: C, 40.51; H, 1.36; N 12.65 %.

3-(Chlorobenzylidene-amino)-5,6,7,8-tetrachloro-1H-quinazoline-2,4-dione (**9c**): Yield: 60 % as yellow crystal. M.p.: 272 ^{o}C. ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 7.63-7.90 (two d, 4H, A_2B_2 arom.), 8.79 (s, 1H, CH=N), 11.4 (s, 1H, NH). Anal. calcd. for $C_{15}H_6Cl_5N_3O_2$: C, 41.19; H, 1.38; N, 9.60. Found: C, 41.29; H, 1.39; N 9.89%.

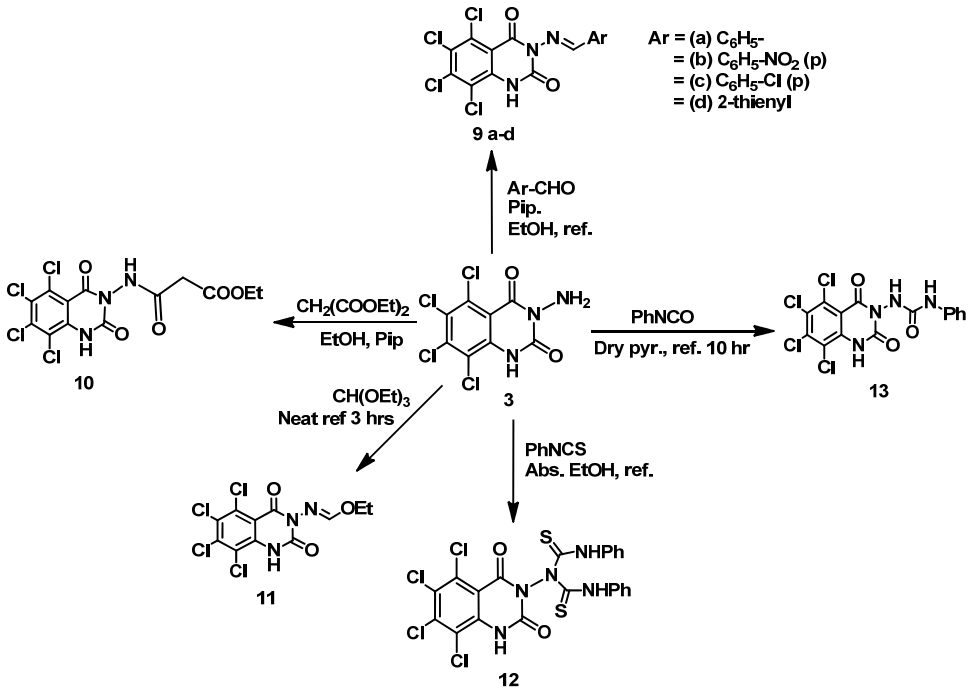
5,6,7,8-Tetrachloro-3-[(thiophen-2-ylmethylene)-amino]-1H-quinazoline-2,4-dione (**9d**): Yield: 74 % as yellow crystal. M.p.: 320 ^{o}C. FT-IR (KBr, cm^{-1}): 3493 (NH), 3108-3032 (CH aliph), 1751, 1695 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6): 7.30 (dd, 1H, H_X), 7.78 (dd, 1H, H_M), 7.96 (dd, 1H, H_A), 8.8 (s, 1H, CH=N), 11.22 (s, 1H, NH). Anal. calcd. for $C_{13}H_5Cl_4N_3O_2S$: C, 38.17; H, 1.23; N, 10.27. Found: C, 38.38; H, 1.24; N 10.51%.

2.2.10. N-(5,6,-7,8-tetrachloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-malonamic acid ethyl ester (10)

A mixture of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) and diethylmalonate was refluxed for 6 hours. After cooling; the reaction mixture was filtered off and crystallized from benzene/ethanol to give *N*-(5,6,7,8-tetrachloro-2,4-dioxo-1,4-di-hydro-2H-quinazolin-3-yl)malon-amic acid ethyl ester (0.34 g, 0.75 mmole) **10** in yield 78 % as white crystal (Scheme 4). M.p.: 310 ^{o}C. FT-IR (KBr, cm^{-1}): 3200 (NH), 1740 and 1660 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 1.18 (t, 3H, CH_3), 3.50 (s, 2H, CH_2-CO), 4.13 (q, 2H, CH_2-O), 10.90 (s, 1H, NH), 11.44 (s, 1H, NH). Anal. calcd. for $C_{13}H_9Cl_4N_3O_5$: C, 36.39; H, 2.11; N, 9.79. Found: C, 36.69; H, 2.12; N 9.98%.

2.2.11. 3-(ethoxymethylidineamino)tetrachloroquinazolin-2,4-dione (11)

Triethylorthoformate is added to 3-aminotetrachloro quinazolin-2,4-dione **3** (0.31 g, 1 mmole). The mixture was refluxed for 6 hours, and then allowed to stand overnight. The precipitated product was collected and crystallized from benzene to give 3-(ethoxymethylidineamino)tetrachloro quinazolin-2,4-dione (0.27 g, 0.72 mmole) **11** in yield 72 % as yellow crystal (Scheme 4). M.p.: 182 ^{o}C. FT-IR (KBr, cm^{-1}): 3293 (NH), 1741 and 1660 (C=O). ^{1}H NMR (200 MHz, DMSO-d_6, ppm): 1.37 (two interfered triplets for the two isomeric CH_3 protons), 4.39 two quartets for CH_2 (Z), 4.55 for CH_2 (E) in integration ratio (2:3), respectively, 7.98 (s, 1H, CH (*Z*)), 8.20 (s, 1H, CH (*E*)), 11.22 (s, 1H, NH). Anal. calcd. for $C_{11}H_7Cl_4N_3O_3$: C, 35.61; H, 1.90; N, 11.33. Found: C, 35.85; H, 1.91; N 11.52%.



Scheme 4

2.2.12. N-phenylthiocarbamoyl-N-tetrachloroquinazolin-2,4-dione-N'-pheny-lthiourea (12)

Heating of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) with phenylisothiocyanate in absolute ethanol (20 mL) under reflux for 6 hours gave after cooling a solid product which was filtered off and crystallized from benzene to give *N*-phenylthiocarbamoyl-*N*-tetrachloroquinazolin-2,4-dione-*N'*-phenylthiourea (0.37 g, 0.62 mmole) **12** in yield 63 % as white crystal (Scheme 4). M.p.: 210 °C. FT-IR (KBr, cm^{-1}): 3231, 3185, 3129 (NH), 1731 and 1695 (C=O).^{1}H NMR (200 MHz, DMSO-d_6, ppm): 6.90-7.57 (m, 10 H, aromatic), 9.80 (s, 1H, HN-CS), 11.20 (s, 1H, quinazoline NH). Anal. calcd. for $C_{22}H_{13}Cl_4N_5O_2S_2$: C, 45.15; H, 2.24; N, 11.96. Found: C, 45.41; H, 2.25; N 12.15%.

2.2.13. N-phenyl-N'-[(1H,3H)-5,6,7,8-tetrachloroquinazolin-2,4-dion-3-yl]urea (13)

When a mixture of 3-aminotetrachloroquinazolin-2,4-dione **3** (0.31 g, 1 mmole) and phenyl thiocyanate in dry pyridine (10 mL) was refluxed for 10 hours. After cooling; the reaction mixture was poured into ice-water and the solid formed was filtered off and crystallized from benzene to give *N*-phenyl-*N'*-[(1*H*,3*H*)-5,6,7,8-tetrachloro-quinazolin-2,4-dion-3-yl]urea (0.25 g, 0.57 mmole) **13** in yield 57 % (Scheme 4). M.p.: 194 °C. FT-IR (KBr, cm^{-1}): 3200 (NH), 1740 and 1660 (C=O).^{1}H NMR (200 MHz, DMSO-d_6, ppm): 6.98-7.50 (m, 5 H, aromatic), 8.70 (s, 1H, NH), 10.90 (s, 1H, NH), 11.80 (s, 1H, NH). Anal. calcd. for $C_{15}H_8Cl_4N_4O_3$: C, 41.51; H, 1.85; N, 12.91. Found: C, 41.78; H, 1.86; N 13.18%.

2.2.14. Antibacterial studies

Sallmonela typhi, *staphylococcus aureus*, *bacillus cereus* and *bacillus subtilis* were obtained from the Faculty of Veterinary Medicine, Pathology Department, Qena, Egypt. All the bacteria were grown on the desired media until the desired growth was obtained.

Disc diffusion test [14]: Whatman paper No. 1 filter paper was used to make sterile disc in order to screen for the antibacterial activity of *Sallmonela typhi, Staphylococcus aureus, Bacillus cereus* and *Bacillus subtilis.* This filter paper was punctured to the shape of commercial antibiotic disc and discs were autoclaved at 121 °C for 15 min. The suspension of bacteria culture was prepared according to the MacFarland standard 0.5 and was lawned onto the Mueiller Hinton agar plates to produce the bacteria field. A sterile of punctured filter papers was placed on the bacteria field by sterile forceps and the solubilized extract then was pipetted out onto the surface of filter paper on the bacteria field. Tetracycline and DMF was used as a positive and negative control. The concentration of the compounds tested was 50 mg/mL. Finally, the plate was incubated at 37 °C and the zone inhibition is observed after 24-48 h and measured as mm.

3. Results and discussion

3.1. Synthesis

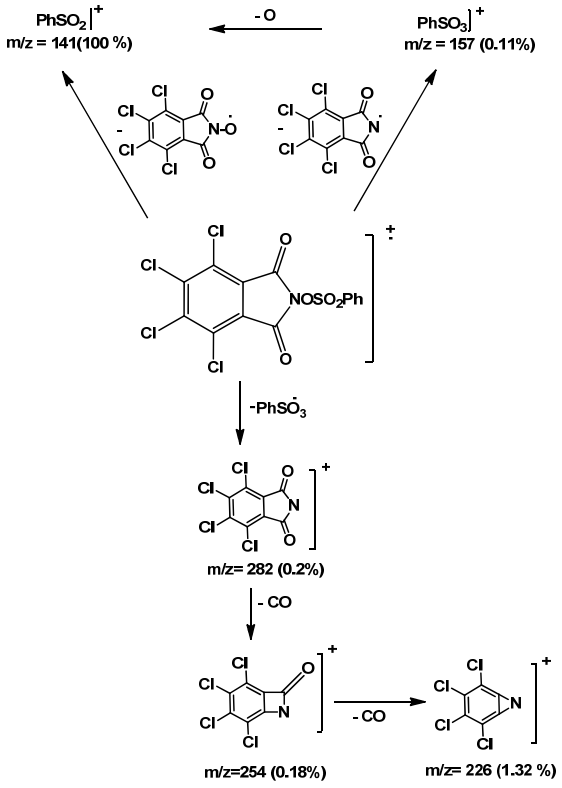
As a part of our program aimed to synthesize new pyrimidine derivatives as potential pharmaceuticals and/or agrochemicals, we report here the synthesis of new tetrachloroheterocyclic compounds such as tetrachloro quinazolindione derivatives. Treatment of *N*-hydroxytetra chlorophthalimide with benzenesulphonyl chloride gave compound **2**, which identified as *N*-phenylsulphonyloxytetra-chlorophthalimide (Scheme 1). The main fragmentation routes for compound **2** are shown in Scheme 5.

Treatment of *N*-phenylsulphonyloxytetrachlorophthalimide **2** with excess hydrazine hydrate in dry benzene afforded 3-aminotetrachloroquinazolin-2,4-dione, **3** (Scheme 3). The reaction of *N*-phenylsulphonyloxytetrachlorophthalimide, **2**, with hydrazine may proceed according to the following mechanism (Scheme 6).

The reaction of compound **3** with different acid chlorides was intensively investigated. Several 3-substituted

tetrachloroquinazolin-2,4-diones, **4**, **5**, **6**, **7**, **8a** and **8b** were prepared via treatment of 3-aminotetrachloroquinazolin-2,4-dione **3** with acid chlorides namely acetylchloride, benzene sulphonylchloride, 2-thiophenecarbonyl-chloride, chloroacetyl chloride, benzoylchloride and *p*-bromobenzoylchloride (Scheme 3).

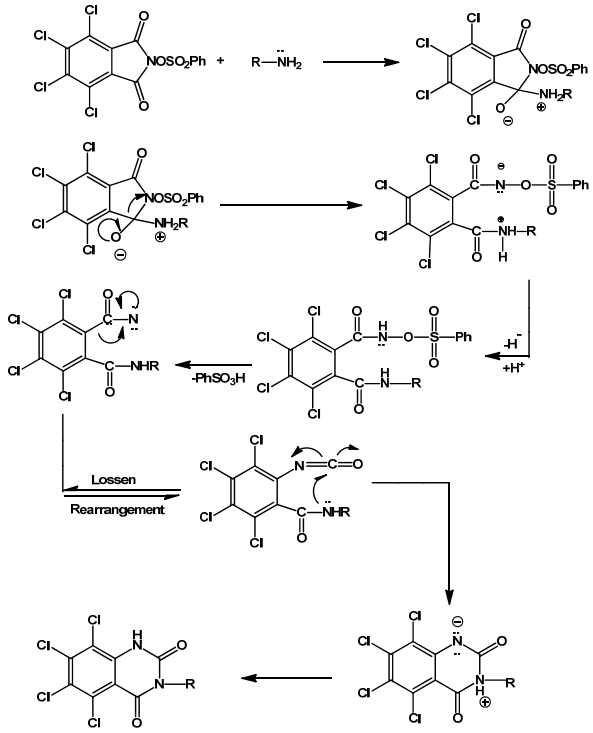
The reactions of compound **3** with different aldehydes, diethylmalonate, triethylorthoformate, phenyl isothiocyanate and phenyl thiocyanate were intensively investigated. Several 3-arylidineaminotetrachloroquinazolin-2,4-diones **9a-d** have been prepared via treatment of 3-aminotetrachloroquinazolin-2,4-dione, **3**, with different aldehydes, namely benzaldehyde, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and thiophene carbaldehyde (Scheme 4). Also, 3-aminotetrachloroquinazolin-2,4-dione, **3**, reacted with diethylmalonate, triethylorthoformate, phenyl isothiocyanate and phenyl thiocyanate to give *N*-(5,6,-7,8-tetrachloro-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-malonamic acid ethyl ester, **10**, 3-(ethoxymethylidine-amino)tetrachloroquinazolin-2,4-dione, **11**, *N*-phenylthio carbamoyl-*N*-tetrachloroquinazolin-2,4-dione-*N*'-phenyl-thiourea, **12**, and *N*-phenyl-*N*'-[(1H,3H)-5,6,7,8-tetrachloro quinazolin-2,4-dion-3-yl]urea, **13**, respectively (Scheme 4).



Scheme 5

3.2. Antibacterial Assays

The compound **3** exhibited anti-bacterialactivity against *Staph. areus* (8 mm), *Bacillus cereus* (15 mm) and *Bacillus subtilis* (9 mm). On the other hand this compound didn't show any inhibition activity against *Salmonella typhi*. This may be due to four chlorine [15] atoms and pyrimidine ring [16-18]. The activity of compound **7** against all microorganisms tested showed positive reactions as indicated by zone of inhibition **7**, **9**, **18**, **10** mm, respectively, this may be due to and five chlorine atoms, respectively. The compound **8a** showed the most activity against bacteria such as *Bacillus Subtilis* (29 mm) which is 2 mm more than the zone around tetracycline disc (27 mm); this may be due to presence of (HN-CO-Ph). The Compound **8b** has antimicrobial effect due to presence of bromine atom [19]. The Compound **9b** has antimicrobial effect due to presence of (NO_2) group. The compounds **9d** and **10** showed most activity against *Bacillus Subtilis* (18 mm and 19 mm, respectively). This may be due presence of (HN-CO) group in two compounds.



Scheme 6

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