Synthesis and Characterization of New Naphtho- and Tetracyclic Diazaquinone Derivatives

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Summary: In this study, new 1,4-naphtho- and 5-nitro-1,4-naphtho derivatives containing *N*- and *N,N*-substituted groups which has not been reported yet, have been synthesized from 2,3-dichloronaphthalene-1,4-diones **(1,9)**. Compounds of 2-choloro-3-((2,4,6-triflorophenyl)amino)naphthalene-1,4-dione **(3)** and 2-chloro-3-((4-florophenyl)amino)naphtalene-1,4-dione **(7)** were obtained by reactions of 2,3-dichloronaphthalene-1,4-dione **1** with 4-fluoroaniline **(6)** and 2,4,6-trifloroaniline (**2**), respectively involving a Michael addition. We reported the cyclization reactions of compounds **1** to benzo[g]pirido[3,2-b]quinoxaline-6,11(5H,12H)-dione **(5)** synthesized. The *N*-substituted naphthoquinone **7** was reacted with sodium azide in dimethylformamide and 2-florobenzo[b]phenazin-6,11-dione **(8)** was obtained as the one cyclized compound. Regioisomers 3-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-2-chloro-5-nitronaphthalene-1,4-dione **11** and 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-chloro-5-nitronaphthalene-1,4-dione **12** were obtained from reaction of 2,3-dichloro-5-nitronaphthalene-1,4-dione **9** with 1-piperonylpiperazine **(10)**.

Keywords: Synthesis; Naphthalen-1,4-dione; Phenazin; Michael addition.

Introduction

Synthesis of new *N*-, *N,N*-substituted heterocyclic molecules is important recent years with the reason that are biologically active substances. Especially, compounds with quinone moiety in their structure, show a wide range of pharmacological activity such as antibacterial, antifungal, anticancer and antioxidant [1-5]. 2,3-Dichloronaphthalene-1,4-dione contains two ketone groups and two chlorine atoms as extremely important moieties, which are responsible for many biological activities and reactivity of nucleophiles because of their abilities to accept electrons [6].

The synthesis and biological evaluation as antifungal, antibacterial, antioxidant, and cytotoxic/anticancer agents of N-, S-, O-substituted-1,4-naphtho- and 2,5-bis(amino-substituted)-1,4-benzoquinone derivatives have been published, 2-(*N*-diphenylmethylpiperazin-1-yl)-3-chloro-1,4-naphthoquinone showed a high level of activity against *M. luteum*., and 2,2-[1-(2-aminoethyl)piperazin-1-yl]-3,3-dichloro-bis(1,4-naphthoquinone) showed excellent antioxidant capacity and cytotoxic activity [5].

We have earlier reported the synthesis of novel nitrogen, oxygen and sulfur containing 1,4-naphthoquinones [7-9]. Usually, 2-substituted and 2,3-disubstituted-1,4-naphthoquinones, or a mixture of both, can be obtained by classical substitution reactions depending on the nucleophilic character and the reaction conditions [7-9].

It is known that the reactions of quinones with amines such as primary/secondary aliphatic amines, cyclic amines and anilines substituted with electron donating groups are highly reactive and provide high yields, of aminoquinones. Treatment of 2,3-dichloronaphthalene-1,4-dione with amines gives mono amino derivatives. Both halogen atoms can be replaced by using nitrogen containing heterocycles such as piperazine, morpholine, etc [10]. When aryl amines with enhanced nucleophilicity react with 2,3-dichloronaphthalene-1,4-dione, only a chlorine atom can displace due to the electronic enrichment of the quinone system. The second substitution of the chlorine atom can be carried out with the quinone unit containing an electron withdrawing group (EWG) [11] or using a catalyst [12].

The 2,3-dichloro-5-nitronaphthalene-1,4-dione is reported to be more reactive towards amines affording regioisomeric mixtures of mono-substituted quinone derivatives [13]. We decided to investigate the role of the electron withdrawing group (NO_2) at the quinone ring in this substitution.

In this work, we report the cyclization reaction of 2,3-dichloronaphthalene-1,4-dione **1** to benzo[g]pirido[3,2-b]quinoxaline-6,11(5H,12H)-

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dione **5**, 2-florobenzo[b]phenazin-6,11-dione **8** synthesized and we also obtained 2-choloro-3-(2,4,6-triflorophenylamino)naphthalen-1,4-dione **3**, 3-(4-((benzo[d][1,3]dioxol-5-yl)methyl)piperazin-1-yl)-2-chloro-5-nitro-naphthalene-1,4-dione **11**, 2-(4-((benzo[d][1,3]dioxol-5-yl)methyl)piperazin-1-yl)-3-chloro-5-nitronaphthalene-1,4-dione **12** involving a Michael addition from 2,3-dichloro-5-nitronaphthalene-1,4-dione **9**.

Experimental

General

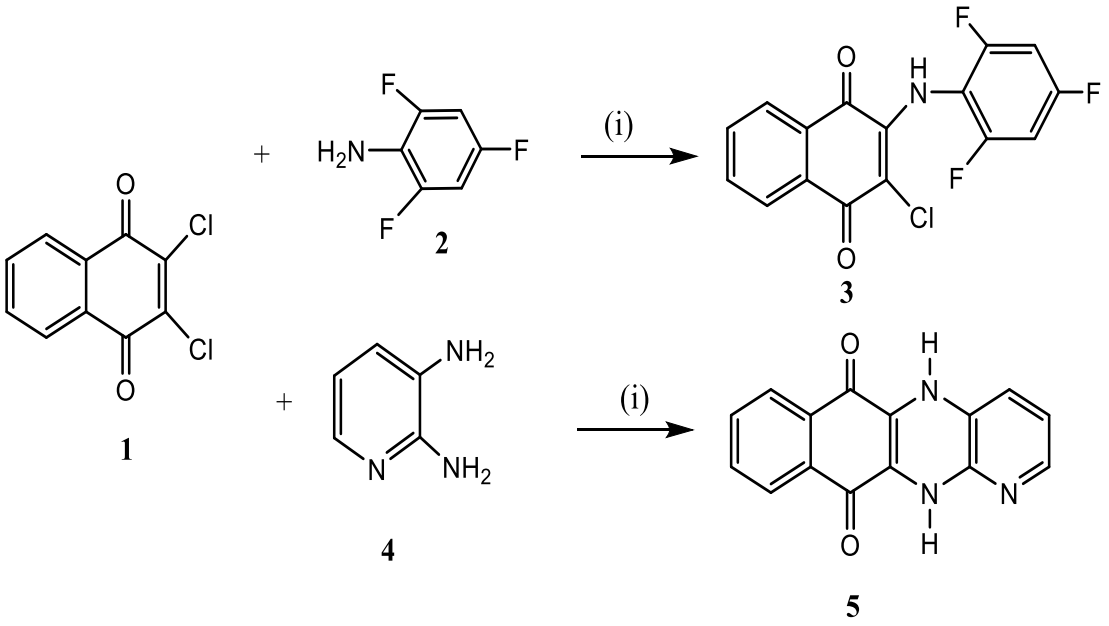
Elemantal analysis were performed on a Thermo Finnigan Flash EA 1112 Elemental analyser. Infrared (FT-IR) spectra were recorded in KBr pellets in Nujol mulls on a Perkin Elmer, Inc. Precisely Spectrum One FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on VarianUNITYINOVA operating at 500 MHz. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ refer to the solvent signal center at $\delta = 7.26$ and $\delta = 77.0$ ppm, respectively. Mass spectra were obtained on a Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer using an ESI probe. Products were isolated by column chromatography on Silica gel (Fluka Silica gel 60, particle size 63-200 µm). Melting points were measured on a Buchi B-540 melting point apparatus.

Analytical thin layer chromatography plate (TLC) was purchased from Merck KGaA (silica gel 60 F_{254}) based on Merck DC-plates (aluminum based). Visualization of TLC images were performed under 254 nm UV light. Moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes.

Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use, and all other chemicals (reagent grade) were used without further purification.

General procedure I for the synthesis of **3, 5** *and* **7**

Sodium carbonate was dissolved in ethanol (60 mL), and equimolar amounts of 2,3-dichloronaphthalene-1,4-dione **1** and amines **(2,4** and **6)** were added slowly. The reaction mixture was stirred until the reaction is complete at room temp. The colour of the reaction solution changed quickly from yellow to red colour. The reaction progress was monitored by thin layer chromatography (TLC). Chloroform (30 mL) was added to the reaction mixture. The organic layer was separated, washed with water (4 × 30 mL), and dried with Na_2SO_4. After the solvent was evaporated, the residue was purified by column chromatography on silica gel (Scheme-1,2).



Reagent and conditions: (i) Na_2CO_3,ethanol, room temp. (**3, 5**); General procedure I

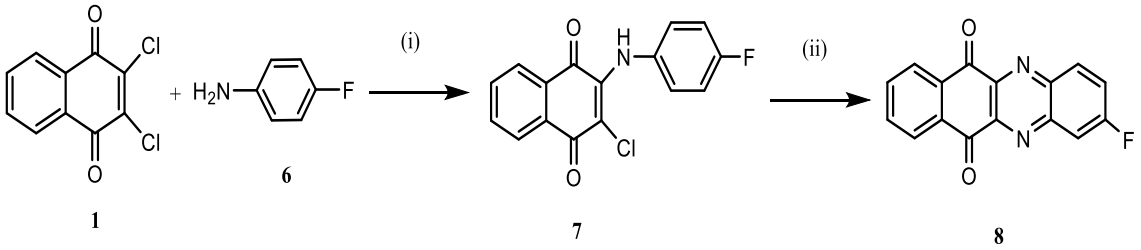
Scheme-1: The synthesis of naphthoquinone **3** and tetracyclic diazaquinone **5** derivatives.

General procedure II for the synthesis of **8**

2-Chloro-3-((4-florophenyl)amino)naphtalene-1,4-dione **7** [14] (1 mole) was dissolved in DMF (100 mL) and sodium azide (NaN_3) (2 mole) dissolved in 10 ml of water was slowly added. The reaction was heated to 40 ºC with stirring for 32 h. The color of the solution quickly changed (from yellow to red color), and the extent of the reaction was monitored by TLC. Chloroform (40 mL) was added to the reaction mixture. The organic layer was separated, washed with water (4×50 mL), and dried with Na_2SO_4. After the solvent was evaporated, the residue was purified by column chromatography on silica gel by using EtAC (Scheme-2,4).

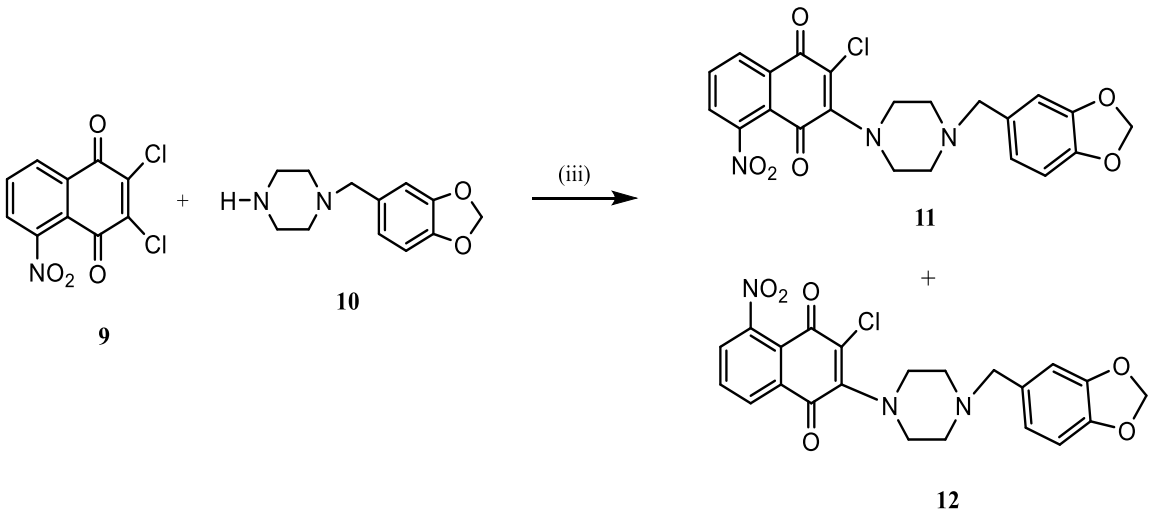
General procedure III for the synthesis of 11 and 12

2,3-Dichloro-5-nitronaphthalene-1,4-dione **9** and nucleophile **10** were stirred in ethanol (25 mL) for 3-4 h at room temperature. Chloroform (30 mL) was added to the reaction mixture. The organic layer was washed with water (4×30 mL), and dried with Na_2SO_4. After the solvent was evaporated, the residue was purified by column chromatography on silica gel (Scheme-3).



Reagent and conditions: (i) Na_2CO_3,ethanol, room temp. (**7**); General procedure I. (ii) NaN_3, DMF, 40 ºC (**8**); General procedure II.

Scheme-2: The synthesis of phenazine compound **8**.



Reagent and conditions: (iii) Ethanol, room temp. (**11,12**); General procedure III.

Scheme-3: The synthesis of regioisomers **11** and **12**.

Spectral Characterization

2-Chloro-3-((2,4,6-trifluorophenyl)amino)naphthalene-1,4-dione **3**

According to general procedure I, compound **3** was synthesized from 2,4,6-trifloroaniline **2** (0.259 g, 1.761 mmol) and 2,3-dichloronaphthalene-1,4-dione **1** (0.4 g, 1.761 mmol). The reaction mixture was stirred for 4h at room temperature.

Yield 62.6 % (0.372 g), Orange crystal, m.p.: 139-141 °C. R_f (5PET:2$CHCl_3$): 0.49. FT-IR (KBr): υ (cm^{-1}) = 3316, 3019, 2926, 2854, 1606, 1522, 1215. ^{1}H NMR (499.74 MHz, $CDCl_3$): δ 8.04–8.14 (dd, J = 7.7, 1.5 Hz, 2H, ArH), 7.62–7.76 (dd, J = 7.7, 1.5 Hz, 2H, ArH), 6.93 (brs, 1H, NH), 6.67–6.71 (m, 2H, ArH).^{13}C NMR (125.66 MHz, $CDCl_3$): δ = 179.5, 177.4, 156.2, 154.4, 152.5, 135.6, 135.1, 134.7, 133.8, 133.2, 128.9, 127.7, 127.0, 114.1, 100.6, 100.2. MS (+ESI): m/z 338.1 $(M+H)^+$, $C_{16}H_7ClF_3NO_2$ (M, 337.01).

5,12-Dihydrobenzo[g]pyrido[2,3-b]quinoxaline-6,11-dione **5**

According to general procedure I, compound **5** was synthesized from 2,3-diaminopyridine **4** (0.144 g, 1.321 mmol) and 2,3-dichloronaphthalene-1,4-dione **1** (0.3 g, 1.321 mmol). The reaction mixture was stirred for 6h at room temperature.

Yield: 75.2 % (0.261 g), Orange solid, m.p.: 85-87 °C. R_f (2PET:1$CHCl_3$): 0.60. FT-IR (KBr): υ (cm^{-1})= 3341, 3018, 2926, 2855, 1678, 1645, 1602, 1574, 1294. ^{1}H NMR (499.74 MHz, $CDCl_3$): δ = 7.97–8.08 (dd, 2H, J = 7.7, 1.5 Hz, ArH), 7.63–7.65 (m, 1H, ArH), 7.54–7.59 (m, 2H, ArH), 7.45–7.49 (m, 2H, ArH), 1.19 (brs, 1H, NH), 1.52 (brs, 1H, NH), ^{13}C NMR (125.66 MHz, $CDCl_3$): δ = 181.1, 176.0, 143.3,142.9, 135.3, 134.9, 131.2, 128.2, 126.9, 126.0, 123.4, 120.8. MS (-ESI): *m/z* = 262.2 $(M-H)^-$, $C_{15}H_9N_3O_2$ (M, 263.25).

2-Chloro-3-((4-fluorophenyl)amino)naphthalene-1,4-dione **(7) [**14]:

Compound **7** was synthesized from 4-fluoroaniline **6** (0.21 ml, 2.202 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.5 g, 2.202 mmol) according to the general procedure I. The reaction mixture was stirred for 6h at room temperature. Yield: 88.7 %. Red crystal. m.p.: 233-234 °C. R_f (1PET:1$CHCl_3$): 0.43. FT-IR (KBr): υ (cm^{-1})= 3261, 3066, 2918, 1671,1634, 1591, 1561, 1214.

2-Florobenzo[b]phenazin-6,11-dione **8**

According to the general procedure II, compound **8** was synthesized from 2-Chloro-3-((4-florophenyl)amino)naphtalene-1,4-dione **7** (0.5 g, 1.657 mmol) and sodium azide (0.215 g, 3.314 mmol).

Yield : 71.6 % (0.330 g), Dark blue crystal, m.p.: 155-157 ˚C. R_f (EtAC): 0.55. FT-IR (KBr): υ (cm^{-1}) = 3019, 2927, 2850, 1618, 1522, 1215. ^{1}H NMR (499.74 MHz, $CDCl_3$): δ = 8.39–8.43 (m, 1H, ArH), 8.20–8.13 (m, 2H, ArH), 7.81–7.84 (m, 1H, ArH), 7.74–7.76 (m, 2H, ArH), 7.63–7.66 (m, 1H, ArH). ^{13}C NMR (125.66 MHz, $CDCl_3$): δ = 180.2, 179.8, 165.0, 163.1, 149.0, 139.7, 139.5, 135.0, 134.9, 130.0, 129.8, 122.4, 118.1, 118.0, 113.7, 110.8. MS (-ESI): *m/z* = 276.8 $(M-H)^-$, $C_{16}H_7FN_2O_2$ (M, 278.05).

Regioisomers 3-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-2-chloro-5-nitronaphthalene-1,4-dione ***11*** *and 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-chloro-5-nitronaphthalene-1,4-dione* **12**

According to general procedure III, regioisomers **11** and **12** were synthesized from 1-piperonylpiperazine **10** (0.25 g, 1.130 mmol) and 2,3-dichloro-5-nitronaphthalene-1,4-dione **9** (0.30 g, 1.000 mmol) (0.4 g, 1.761 mmol). Purification via column chromatography on silica gel.

11 : Yield: 44%, pink solid, m.p.: 89-91 °C; R_f : 0.73 (3Hexane/2EtAc); FT-IR (in KBR pellet, cm^{-1}): 3079, 2905, 2811, 2772, 1676, 1644, 1590, 1537, 1492, 1439, 1235. ^{1}H NMR (499.74 MHz, $CDCl_3$): δ = 8.18–8.24 (dd, J = 9.27, 1.46 Hz, 1H, ArH), 7.77–7.82 (t, J = 7.81 Hz, 1H, ArH), 7.64–7.68 (dd, J = 9.27, 1.46 Hz, 1H, ArH), 6.74–6.94 (m, 3H, ArH), 5.96 (s, 2H, CH_2), 3.64 (brs, 4H, CH_2), 3.52 (brs, 4H, CH_2), 2.62 (s, 2H, CH_2), ^{13}C APT-NMR (125.66 MHz, $CDCl_3$): δ = 179.84, 173.97, 149.33, 147.86, 133.70, 132.32, 129.16, 127.63, 122.67, 109.73, 108.07, 101.08, 62.39, 53.26. MS (+ESI): *m/z* = 456.0 $(M)^+$, $C_{22}H_{18}N_3O_6Cl$ (M, 455.85).

12 : Yield: 20%, red solid, m.p.: 131-132 °C; R_f : 0.8 (3Hexane/2EtAc); FT-IR (in KBR pellet, cm^{-1}): 3094, 2912, 2809, 2772, 2659, 1679, 1640, 1590, 1555, 1494, 1438, 1240. ^{1}H NMR (499.74 MHz, $CDCl_3$): δ = 8.30–8.34 (dd, J = 9.27, 1.46 Hz, 1H, ArH), 7.76–7.84 (m,2H, ArH), 6.74–6.94 (m, 3H, ArH), 5.96 (s, 2H, CH_2), 3.64 (brs, 4H, CH_2), 3.52 (brs, 4H, CH_2), 2.62 (s, 2H, CH_2), ^{13}C APT-NMR (125.66 MHz, $CDCl_3$): δ = 179.07, 175.74,

150.40, 147.80, 134.17, 132.64, 130.49, 129.42, 127.07, 122.60, 109.56, 108.01, 101.12, 62.43, 60.39, 53.31, 51.15. MS (+ESI): *m/z* = 456.0 $(M)^+$, $C_{22}H_{18}N_3O_6Cl$ (M, 455.85).

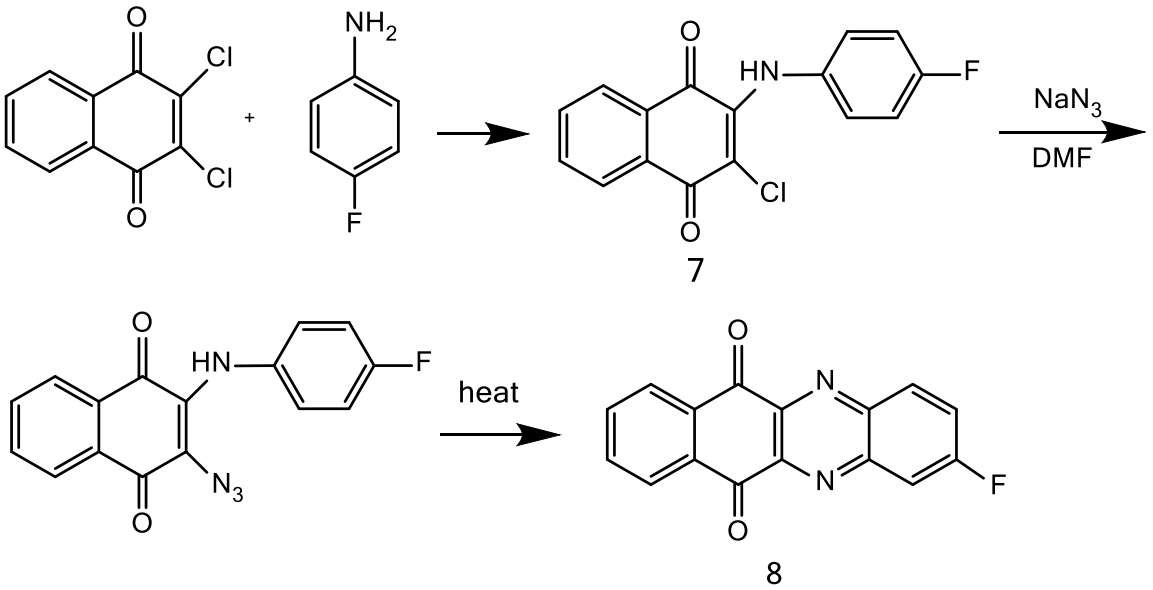
Results and Discussion

Chemistry

In this work, we synthesized *N*-substituted-1,4-naphthoquinones **3, 7** by the reaction of 2,3-dichloronaphthalene-1,4-dione **1** with 4-fluoro aniline **6** and 2,4,6-trifloroaniline **2** in the presence of a base at room temperature. Compound **8** is obtained by the cyclization of **7** with sodium azide (NaN_3) in DMF. Tetracyclic diaza compound **5** is synthesized by the reaction of 2,3-dichloronaphthalene-1,4-dione **1** and 2,3-diaminopyridine **4**. Regioisomers of **11** and **12** are synthesized from the reaction of 2,3-dichloro-5-nitronaphthalene-1,4-dione **9** and 1-piperonylpiperazine **10.** (Scheme-1to 4)

The cyclization reactions of 2-arylamino-3-chloro-l,4-naphthoquinones were first examined in 1963 and it is reported 2-arylamino-3-amino-l,4-napthoquinones and benzophenazine-quinones. Some of their reactions by the treatment of 2-arylamino-3-chloro-l,4-naphthoquinones with sodium azide (NaN_3) in dimethylformamide (DMF) at high temperature gave 2-(arylamino)-3-amino-1,4-naphthoquinones and heterocyclic quinones [15]. To obtaine the our target phenazin compound **8**, we first decided to perform reaction of 2,3-dichloro-1,4-naphthoquinone **1** with 4-fluorophenylamine **6** to give 2-Chloro-3-((4-florophenyl)amino)naphtalene-1,4-dione **7** according to the reported literature [14] and then, reacted 2-Chloro-3-((4-florophenyl)amino)naphtalene-1,4-dione **7** with NaN_3 at 40 ºC according to the standard procedures [15].

^{1}H- and ^{13}C NMR spectra were recorded in order to obtain characterization of the synthesized all new compounds (**3**, **5, 8, 11** and **12**). In the ^{1}H NMR spectrum of **3**, the signals for protons of the naphthaquinone ring in the range δ 7.62-7.76 ppm firstly split into doublets because of adjacent proton and then split into doublets of doublets. Similarly, the other doublets of doublets could be detected in the range δ 8.04-8.14 ppm. ^{1}H NMR signal of the hydrogen atoms of the adjacent to the nitrogen atom (-NH) in compounds **3** and **5** were shifted to a higher field and displayed singlet at 1.19 and 1.52 for **5** and 6.93 ppm as singlet broad for **3** respectively. Substituted aromatic ring hydrogens showed peaks around 6.67-8.03. ^{13}C NMR spectra of **3**, **5, 8, 11** and **12** showed two signals for the carbonyl (C=O) carbons at about 173.97-181.10 ppm, as expected. With the aid of the positive ion mode of electron spray ionization (ESI) mass spectrum of the compounds **3**, **5, 8, 11** and **12** the respective molecular ion peaks were observed at *m/z* 338.1 (100) $[M+H]^+$, 262.2 (100) $[M-H]^-$, 278.05 (100) $[M-H]^-$, 456.0 (100) $[M]^+$ and 456.0 (100) $[M]^+$, respectively.



Scheme-4: Proposed mechanism of the synthesis of phenazine compound **8.**

The mechanism by which tetracyclic diazaquinone **8** is formed from substance **7** can be explained as follows. Firstly, the nucleophilic substitution of the chlorine by azide (N_3) takes place, followed by the elimination of nitrogen gas (N_2). The regioselective intermolecular C-H bond insertion reaction of the nitrene with the benzene moiety yield to cyclic compound **8**. The proposed regioselective intramolecular C-H bond insertion reaction mechanism of compound **8** agree well with the literature [15-17].

The synthesis of some 3-amino-2-chloro-5-nitro-naphthalene-1,4-diones and 2-amino-3-chloro-5-nitro-naphthalene-1,4-diones has been reported in recent years [18]. Another study described the synthesis of 2-amino-3-chloro-5- and 8-nitro-1,4-naphthoquinones as regioisomeric mixtures in high purities. 2-Chloro-5-nitro-3-(propylamino) naphthalene-1,4-dione and 3-chloro-5-nitro-2-(propylamino)naphthalene-1,4-dione were synthesized as regioisomer. The H NMR spectra of these isomers were indicated that the peaks of the 3-chloro isomer of aromatic protons are shifted more down field than the aromatic protons of the 2-chloro isomer. Also, it has been found that, In the case of mixture regioisomer, the higher R_f component was shown to be the 5-nitro(2-amino-3-chloro-5-nitro-naphthalene-1,4-dione) isomer and the lower R_f component the 8-nitro(3-amino-2-chloro-5-nitro-naphthalene-1,4-dione) isomer by ^1H–^{13}C (HMBC) analysis [13].

Regioisomers **11** and **12** are obtained from the reaction of 2,3-dichloro-5-nitronaphthalene-1,4-dione **9** and 1-piperonylpiperazine **10**. Then two regioisomer are separated by column chromatography on Silica gel by using Hexane/EtAc solvent system. Isomers **11** and **12** have different colour, R_f value and melting points (red and pink colour, 0.73 and 0.8 (3Hexane/2EtAc),131-132 °C and 89-91 °C, respectively). In the ^1H NMR spectrum of regioisomers **11** and **12**, the signals for protons of the naphthoquinone ring are observed as different pattern [13, 19]. In the ^1H NMR spectrum of one isomer **11**, the signal for one proton of the naphthoquinone ring is shown in the range δ 7.64–7.68 ppm as doublets of doublets. The other proton detected at δ 7.77–7.82 ppm as triplet, last one is splitted into doublets of doublets at δ 8.18–8.24 ppm. But, ^1H NMR signal of the hydrogen atoms at naphthoquinone ring of second isomer **12** is detected as multiplets and doublets of doublets at δ 7.76–7.84, 6.74–6.94 and 8.30–8.34 ppm, respectively. The observed proton NMR results of the regioisomers and the structure-R_f relationship are consistent with the similar isomers described above. Also, the mass data of regioisomer **11** and **12** exhibited the molecular peak m/z 456.0 (100%) $[M]^+$, which is agreement with the molecular formula $C_{22}H_{18}N_3O_6Cl$ (455.85g/mol).

Conclusion

The aim of this study was to synthesize to new quinone derivatives by reaction of 2,3-dichloronaphthalene-1,4-dione and 2,3-dichloro-5-nitronaphthalene-1,4-dione compounds with some nucleophiles such as containing nitrogen atom in different condition. Their structures of newly synthesized compounds (**3**, **5, 8, 11** and **12**) were characterized by using nuclear magnetic resonance spectroscopy (^1H and ^{13}C NMR), mass spectrometry (MS), and Fourier transform infrared spectroscopy (FT-IR).

Naphthoquinones are most famous quinone derivatives with their excellent pharmacological properties as antifungal, antibacterial, and anti-tumour agents. Therefore we consider to evaluation the biological activity (antibacterial, antifungal, anticancer) properties of the newly synthesized quinone compounds. We also plan to investigate the antioxidant capacity of these compounds in the future.

Acknowledgments

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