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Research Article

Synthesis, Antimicrobial Properties, and Inhibition of Catalase Activity of 1,4-Naphtho- and Benzoquinone Derivatives Containing N-, S-, O-Substituted

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A series of new 1,4-naphtho- and benzoquinone derivatives possessing N-, S-, O-substituted groups which has not been reported yet has been synthesized from 2,3-dichloro-1,4-naphthoquinone **1** and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** involving a Michael addition. In the synthesized compounds, antimicrobial activity at low concentrations against *Escherichia coli* B-906, *Staphylococcus aureus* 209-P, and *Mycobacterium luteum* B-917 bacteria and *Candida tenuis* VKM Y-70 and *Aspergillus niger* F-1119 fungi in comparison with controls was identified. 2-Chloro-3-((2-(piperidin-1-yl)ethyl)amino)naphthalene-1,4-dione **3g** and 2,5-dichloro-3-ethoxy-6-((2,4,6-trifluorophenyl)amino)cyclohexa-2,5-diene-1,4-dione **17** were the most potent, with a minimum inhibitory concentration value of 15.6 μg/mL against test-culture *M. luteum and S. aureus,* respectively. Furthermore, in this work, a catalase activity of benzo- and naphthoquinone derivatives was examined for the first time. The catalase activity of benzo- and naphthoquinone derivatives was determined, showing that compound **3g** had significant inhibition activity for catalase enzyme.

1. Introduction

Natural and synthetic quinonoid compounds are well-known substances which possess a variety of biological properties such as anticancer, antibacterial, or antimalarial drugs as well as fungicides [1]. The heterocyclic derivatives of 1,4-naphthoquinones have been identified that have potent biological activities towards viral [2], molluscicidal [3], malarial [4], leishmanial [5], cancer [6], and bacterial and fungal diseases [7] due to their redox potentials [8]. Some of these pharmacological effects have been attributed to the formation of DNA-damaging anion-radical intermediates formed by bioreduction of the quinone nucleus. Quinones are known to inhibit electron transport involved in photosynthesis and mitochondrial respiration. Quinone-based fungicides are classified as "organic fungicides" and are known multisite inhibitors. This may be advantageous in the prevention of resistance development in fungal pathogens. Similarly, quinone-based natural herbicides were also described with multisite inhibitors.

As a part of a program directed towards the design and synthesis of N-, S-, O-substituted quinones as potential antibacterial, antifungal, and anticancer agents, we have reported the synthesis and antimicrobial as well as anticancer activities of N-, S-, O-substituted quinones [6, 9, 10]. This paper describes the synthesis, characterization, and discovering promising pharmacologically active compounds. In this work, a catalase activity of benzo- and naphthoquinone

derivatives was examined for the first time. The catalase enzyme plays an important role in removing toxic H_2O_2 from the cells. For this purpose, the activities of the cells of this enzyme decompose H_2O_2 generated as a result of the cell activities H_2O and O_2 before dispersion into the body tissues. The catalase enzyme also exhibits peroxidic activity on compounds (i.e., formaldehyde, phenols, formic acid, and alcohols). In this reaction, low molecular weight alcohols serve as an electron donor. In addition to having peroxidase activity, this enzyme can use one molecule of H_2O_2 as an electron donor and the other as an oxidant [11, 12].

Consequently, the synthesis of new active derivatives with potential applications in this area and prepared by simple chemical procedures should be of increasing interest. Here we described the synthesis, characterization, antimicrobial activity, and inhibition of catalase of 1,4-naphtho- and benzoquinone derivatives. Their structures of synthesized compounds were characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, MS, and UV-Vis spectroscopy.

2. Experimental

2.1. Material and Methods. Infrared (FT-IR) spectra were recorded for liquids as film and for solids as KBr discs on a Perkin Elmer Precisely Spectrum One FTIR spectrometry. Microanalyses were carried out with a Thermo Finnigan Flash EA 1112 Elemental analyser. Mass spectra were obtained on a Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer according to either APCI or ESI techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III 500 MHz, Chemical shifts δ (ppm) were reported relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ refer to the solvent signal center at δ = 7.26 and δ = 77.0 ppm, respectively. Moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes. Spectrophotometric catalase enzyme activity measurements of synthesized compounds were performed by using a Perkin Elmer Lambda 35 UV-Vis spectrophotometer using a pair of matched quartz cuvettes of 1 cm thickness.

The following chemicals were supplied from the corresponding sources: sodium carbonate, sodium sulfate, aniline, ethanethiol, 2,3-diaminopyridine, 4-fluorobenzylamine, 2-(piperidin-1-yl)ethan-1-amine, 2,4,6-trifluoroaniline, 4-fluorothiophenol, 2,3-difluoroaniline, and 1,3-dimethylbutylamine from Merck Chemicals (Darmstadt, Germany); acetone, absolute ethanol, and neocuproine (Nc) from Sigma-Aldrich Chemicals (Steinheim, Germany); 2,3-dichloro-1,4-naphthoquinone (Fluka).

2.2. Antibacterial and Antifungal Evaluations [13, 14]. Tested microorganisms included the following: bacteria *Escherichia coli B-906, Staphylococcus aureus 209-P,* and *Mycobacterium luteum B-917* and fungi *Candida tenuis VKM Y-70* and *Aspergillus niger F-1119*. The antimicrobial activity of compounds was evaluated by diffusion in peptone on a nutrient medium (meat-extract agar for bacteria and wort agar for fungi). The microbial loading was 10^9 cells (spores)/1 mL. The required incubation periods were 24 h at 35°C for bacteria and 48–72 h at 28–30°C for fungi. The results were recorded by measuring the zones surrounding the disk. The control disk contained vancomycin (for bacteria) or nystatin (for fungi) as a standard. Testing was performed in a flat-bottomed 96-well tissue culture plate. The tested compounds were dissolved in DMSO applying the necessary concentration. The exact volume of the solution of compounds is brought into a nutrient medium. The bacteria and fungi were inoculated in a nutrient medium (meat-extract agar for bacteria and wort agar for fungi). The duration of incubation was 24–72 h at 37°C for bacteria and 30°C for fungi. The results were estimated according to the degree of the growth inhibition.

2.3. Catalase Enzyme Inhibition Activity of Quinone Derivatives. Catalase activity was determined by the rate of H_2O_2 decomposition, measured spectrophotometrically at 450 nm using the method described by Bekdeser et al. [15]. The reaction mixtures contained 1.0 mM H_2O_2, 3.691 U mL^{-1} catalase solution, and 1.0 mM synthesized compound. This mixture (total volume 2.6 mL) was then incubated at 25°C. After 30 min incubation period, the optical CUPRAC sensor was taken out and immersed in a test tube consisted of 2.0 mL of the incubation reaction mixture + 6.2 mL of EtOH. After 30 min agitation, the colored membrane was taken out and its absorbance was recorded at 450 nm and activities were expressed in U mL^{-1}.

*2.4. General Procedure for the Synthesis of N-, N,N- N,O- N,S-, and S,S- Substituted Naphtho- and Benzoquinone Compounds **3a, 3c, 3d, 3f, 3g, 4e, 6b, 7a, 17-25**.* Sodium carbonate was dissolved in ethanol (60 mL), and equimolar amounts of 2,3-dichloro-1,4-naphthoquinone **1** and amines or thiols were added slowly. The mixture was heated between 20-45°C and it was stirred in a single reaction vessel between 2 and 11 h. Similarly, sodium carbonate was dissolved in ethanol (50 mL), and equimolar amounts of 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** and amines were added slowly. Without heating, the mixture was stirred in a single reaction vessel between 3-6 h. The color of the solution quickly changed (from yellow to red color), and the extent of the reaction was monitored by 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.

*2.5. **2-Phenylamino-3-chloro-naphthalene-1,4-dione (3a)** [16, 17].* Compound **3a** was synthesized from aniline **2a** (0.4 ml, 4.404 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (1 g, 4.404 mmol) according to the general method. Yield: 94.7%. Red crystal. M.p.: 215-216°C. R_f (1PET:1CHCl$_3$): 0.44. FT-IR (KBr): υ (cm^{-1}) = 3065, 2918 (C-H), 1673 (C=O), 1588, 1537 (C=C), 3238 (N-H).

2.6. ***2-Chloro-3-((2,5-difluorobenzyl)amino)naphthalene-1,4-dione (3c).*** Compound **3c** was synthesized from (2,5-difluorophenyl) methanamine **2c** (0.308 ml, 2.634 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.6 g, 2.634 mmol) according to the general method. Yield: 77.9%. Orange crystal. R_f [PET/$CHCl_3$(5:2)]: 0.52. M.p.: 123–125°C. FT-IR (KBr) (cm^{-1}): 3276 (N-H), 3019 (C-$H_{arom.}$), 2925, 2851 (C-$H_{aliph.}$), 1676 (C=O), 1576 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 5.00 (d, 2H, *J* 6.68 Hz, -NH-C$\boldsymbol{H_2}$), 6.21 (bs, 1H, N$\boldsymbol{H}$), 6.88-7.00 (m, 3H, C$\boldsymbol{H}_{arom}$), 7.55-7.66 (tt, 2H, *J* 7.54, 1.46 Hz, C$\boldsymbol{H}_{napht.}$), 7.96-8.08 (dd, 2H, *J* 7.72, 1.46 Hz, C$\boldsymbol{H}_{napht.}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 155.6, 157.8 (-F-$\boldsymbol{C}_{arom}$), 115.6, 116.7, 116.9 ($\boldsymbol{C}$H$_{arom}$), 129.8 ($\boldsymbol{C}_{arom}$), 143.7 (-NH-$\boldsymbol{C}_{napht.}$), 115.8 (-Cl-$\boldsymbol{C}_{napht.}$), 126.9,128.8, 130.9, 132.4 ($\boldsymbol{C}$H$_{napht.}$), 132.7, 135.0 ($\boldsymbol{C}_{napht.}$), 177.1, 180.2 ($\boldsymbol{C}$=O). MS [+ESI] = m/z 334.1 $[M+H]^+$, Anal. Calc. for $C_{17}H_{10}ClF_2NO_2$ (333.04): C 61.18, H 3.02, N 4.20. Found: C 61.41, H 3.34, N 4.14%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 210(2.2), 274(2.4), 336(1.4), 559(1.5).

2.7. ***2-Chloro-3-((2,3-difluorophenyl)amino)naphthalene-1,4-dione (3d).*** Compound **3d** was synthesized from 2,3-difluoroaniline **2d** (0.287 g, 2.212 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.5 g, 2.212 mmol) according to the general method. Yield: 71.1%. Orange crystal. R_f [PET/$CHCl_3$(5:2)]: 0.51. M.p.: 106–109°C. FT-IR (KBr) (cm^{-1}): 3019 (C-$H_{arom.}$), 2925 (C-$H_{aliph.}$), 1650 (C=O), 1520 (C=C), 3340 (N-H). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 7.33 (bs, 1H, N$\boldsymbol{H}$), 6.81-6.03, 7.45-7.48 (m, 3H, C$\boldsymbol{H}_{arom}$), 7.63-7.75 (tt, 2H, *J* 7.54, 1.56 Hz, C$\boldsymbol{H}_{napht.}$), 8.04-8.14 (dd, 2H, *J* 7.71, 1.56 Hz, C$\boldsymbol{H}_{napht.}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 129.8 (-NH-$\boldsymbol{C}_{arom}$), 146.2, 149.7 (-F-$\boldsymbol{C}_{arom}$), 114.5, 121.4, 123.0 ($\boldsymbol{C}$H$_{arom}$), 135.1 (-NH-$\boldsymbol{C}_{napht.}$), 116.6 (-Cl-$\boldsymbol{C}_{napht.}$), 127.1, 127.2, 130.9, 141.5 ($\boldsymbol{C}$H$_{napht.}$), 133.2, 132.2 ($\boldsymbol{C}_{napht.}$), 177.5, 179.9 ($\boldsymbol{C}$=O). MS [-ESI] = 318.2 $[M-H]^-$, Anal. Calc. for $C_{16}H_8ClF_2NO_2$ (319.02): C 60.11, H 2.52, N 4.38. Found: C 60.12, H 2.50, N 4.40%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 223(3.9), 274(4.0), 348(3.2), 453(3.1).

2.8. ***2-Chloro-3-((4-methylpentan-2-yl)amino)naphthalene-1,4-dione (3f).*** Compound **3f** was synthesized from 4-methylpentan-2-amine **2f** (0.433 ml, 3.083 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.7 g, 3.083 mmol) according to the general method. Yield: 89.6%. Orange crystal. R_f [PET/$CHCl_3$ (2:1)]: 0.48. M.p.: 98–99°C. FT-IR (KBr) (cm^{-1}): 3015 (C-$H_{arom.}$), 2959, 2928 (C-$H_{aliph.}$), 1643 (C=O), 1600, 1573 (C=C), 3322 (N-H). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 0.85 (d, 3H, *J* 7.52 Hz, -C$\boldsymbol{H_3}$), 0.87 (d, 3H, *J* 6.62 Hz, -C$\boldsymbol{H_3}$), 1.20 (d, 3H, *J* 6.37 Hz, -C$\boldsymbol{H_3}$), 4.65-4.75, 1.56-1.66 (m, 2H, -C$\boldsymbol{H}$), 1.44-1.51, 1.26-1.34 (m, 2H, -C$\boldsymbol{H_2}$), 5.81 (bs, 1H, N$\boldsymbol{H}$), 7.52-7.66 (tt, 2H, *J* 7.54, 1.56 Hz, C$\boldsymbol{H}_{napht.}$), 7.94-8.06 (dd, 2H, *J* 7.71, 1.56 Hz, C$\boldsymbol{H}_{napht.}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 22.4, 22.6, 22.9 (-$\boldsymbol{C}$H$_3$), 25.2, 48.2 (-$\boldsymbol{C}$H-), 47.1 (-$\boldsymbol{C}$H$_2$-), 143.5 (-NH-$\boldsymbol{C}_{napht.}$), 126.9 (-Cl-$\boldsymbol{C}_{napht.}$), 128.8, 129.8, 130.9, 132.2 ($\boldsymbol{C}$H$_{napht.}$), 132.5, 135.0 ($\boldsymbol{C}_{napht.}$), 176.4, 182.1 ($\boldsymbol{C}$=O). MS [+ESI] = m/z 292.1 $[M+H]^+$, Anal. Calc. for $C_{16}H_{18}ClNO_2$ (291.78) C 65.86, H 6.22, N 4.80. Found: C 65.82, H 6.24, N 4.81%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 238(3.2), 277(3.4), 343(3.4), 469(2.6).

2.9. ***2-Chloro-3-((2-(piperidin-1-yl)ethyl)amino)naphthalene-1,4-dione (3g)*** *[18].* Compound **3g** was synthesized fro m 2-(piperidin-1-yl) ethan-1-amine **2 g** (0.317 ml, 2.202 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.5 g, 2.202 mmol) according to the general method. Yield: 80.9%. Red crystal. R_f [PET/$CHCl_3$ (3:1)]: 0.48. M.p.: 108–110°C. FT- IR (KBr) (cm^{-1}): 3016 (C-$H_{arom.}$), 2938, 2853 (C-$H_{aliph.}$), 1677 (C=O), 1603, 1573 (C=C), 3355 (N-H). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 1.36-1.58 (m, 6H, -C$\boldsymbol{H}_{2circle}$-), 2.34-2.42 (m, 4H, -N-C$\boldsymbol{H}_{2circle}$), 2.53 (t, 2H, *J* 5.96 Hz, -C$\boldsymbol{H_2}$-N-), 3.80 (t, 2H, *J* 5.88 Hz, -NH-C$\boldsymbol{H_2}$), 6.98 (bs, 1H, N$\boldsymbol{H}$), 7.48-7.63 (tt, 2H, *J* 7.55, 1.46 Hz, C$\boldsymbol{H}_{napht.}$), 7.86-8.02 (dd, 2H, *J* 7.25, 1.46 Hz, C$\boldsymbol{H}_{napht}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 24.4, 26.1 ($\boldsymbol{C}$H$_{2piper.}$), 41.2 (-NH-$\boldsymbol{C}$H$_2$), 56.8 (-N-$\boldsymbol{C}$H$_2$), 53.8 (-N-$\boldsymbol{C}$H$_{2piper.}$), 144.8 (-NH-$\boldsymbol{C}_{napht.}$), 110.9 (-Cl-$\boldsymbol{C}_{napht.}$), 126.5, 129.8, 132.2 ($\boldsymbol{C}$H$_{napht.}$), 132.7, 134.6 ($\boldsymbol{C}_{napht.}$), 176.2, 180.4 ($\boldsymbol{C}$=O). MS [+ESI] = m/z 319.2 $[M+H]^+$, Anal. Calc. for $C_{17}H_{19}ClN_2O_2$ (318.11): C 64.05, H 6.01, N 8.79. Found: C 63.97, H 6.26, N 8.69%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 211(2.8), 277(3.4), 339(2.3), 473(2.5).

2.10. ***2-Ethoxy-3-((2-methyl-4-oxo-4H-chromen-7-yl)amino)naphthalene-1,4-dione (4e).*** Compound **4e** was synthesized from 7-amino-2-methyl-4H-chromen-4-one **2e** (0.385 g, 2.202 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.5 g, 2.202 mmol) according to the general method. Yield: 54.9%. Red crystal. R_f [PET/$CHCl_3$(5:2)]: 0.58. M.p.: 140–142°C. FT-IR (KBr) (cm^{-1}): 2971 (C-$H_{arom.}$), 2926, 2850 (C-$H_{aliph.}$), 1682 (C=O), 1599, 1520 (C=C), 3306 (N-H). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 0.83 (t, 3H, *J*= 7.52 Hz, C$\boldsymbol{H}_{3ethoxy}$), 1.17 (bs, 3H, C$\boldsymbol{H}_3$), 4.01-4.04 (q, 2H, *J* 7.06 Hz, O-C$\boldsymbol{H}_{2ethoxy}$), 5.65 (bs, 1H, C$\boldsymbol{H}_2$), 6.08 (bs, 1H, O-C$\boldsymbol{H}$), 6.28-6.29 (d, 1H, *J* 7.06 Hz, C$\boldsymbol{H}_{phenyl}$), 7.44-7.46 (d, 1H, *J* 7.06 Hz, C$\boldsymbol{H}_{phenyl}$), 7.54-7.66 (tt, 2H, *J* 7.53, 1.46 Hz, C$\boldsymbol{H}_{napht.}$), 5.96 (bs, 1H, N$\boldsymbol{H}$), 7.94-8.09 (dd, 2H, *J* 7.7, 1.46 Hz, C$\boldsymbol{H}_{napht.}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 11.0 (-$\boldsymbol{C}$H$_{3ethoxy}$), 14.1 (-$\boldsymbol{C}$H$_{3subst.}$), 68.2 (-O-$\boldsymbol{C}$H$_{2ethoxy}$), 109.9, 112.2, 119.4, 127.0 ($\boldsymbol{C}$H$_{subst.}$), 120.5 ($\boldsymbol{C}_{subst.}$), 167.3 (CH$_3$-$\boldsymbol{C}_{subst.}$), 162.0 ($\boldsymbol{C}$-O$_{subst.}$), 160.8 (NH-$\boldsymbol{C}_{subst.}$), 173.8 ($\boldsymbol{C}$=O$_{subst.}$), 134.9 (O-$\boldsymbol{C}_{napht.}$), 115.5 (-NH-$\boldsymbol{C}_{napht.}$), 128.0, 128.4, 130.8, 130.9 ($\boldsymbol{C}$H$_{napht.}$), 132.5 132.6 ($\boldsymbol{C}_{napht.}$), 176.9, 180.5 ($\boldsymbol{C}$=O). MS [-ESI] = m/z 372.9 $[M-2H]^-$, Anal. Calc. for $C_{22}H_{17}NO_5$ (375.11): C 70.39, H 4.56, N 3.73. Found: C 70.24, H 4.45, N 3.80%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 243(3.0), 276(3.1), 344(2.3), 468(2.1).

2.11. ***2,3-Bis((4-fluorophenyl)thio)naphthalene-1,4-dione (6b)*** *[19].* Compound **6b** was synthesized from 4-fluorobenzenethiol **5b** (0.375 ml, 3.523 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.4 g, 1.761 mmol) according to the general method. Yield: 79.1%. Orange crystal. R_f [PET/$CHCl_3$ (2:1)]: 0.55. M.p.: 175–177°C. FT-IR (KBr) (cm^{-1}): 3008 (C-$H_{arom.}$), 2923, 2853 (C-H), 1665 (C=O), 1586 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 7.41-7.46 ppm (m, 4H, C$\boldsymbol{H}_{arom}$), 7.01-7.06 (m, 4H, C$\boldsymbol{H}_{arom}$), 7.68-7.72 (m, 2H,

C$\boldsymbol{H}_{napht}$), 7.96-8.00 (m, 2H, C$\boldsymbol{H}_{napht}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 128.4 (-S-$\boldsymbol{C}_{arom}$), 161.6-163.6 (-F-$\boldsymbol{C}_{arom}$), 116.3-116.5, 133.7-133.9 ($\boldsymbol{C}H_{arom}$), 132.6 (-S-$\boldsymbol{C}_{napht}$), 127.2, 133.6 ($\boldsymbol{C}H_{napht}$), 148.9 ($\boldsymbol{C}_{napht}$), 178.7, 178.7 ($\boldsymbol{C}$=O). MS [+ESI] = m/z 411 $[M+H]^+$, Anal. Calc. for $C_{22}H_{12}F_2O_2S_2$ (410.02): C 64.38, H 2.95, S 15.62. Found: C 64.38, H 2.94, S 15.62%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 211(2.6), 253(2.5), 342(1.9), 458(1.7).

2.12. ***2-(Ethylthio)-3-(phenylamino)naphthalene-1,4-dione (7a)*** *[20].* Compound **7a** was synthesized from ethanethiol **5a** (0.110 ml, 1.762 mmol) and 2-chloro-3-(phenylamino) naphthalene-1,4-dione **3a** (0.5 g, 1.762 mmol) according to the general method. Yield: 91.5%. Red crystal. R_f [PET/$CHCl_3$ (5:2)]: 0.57 M.p.: 92–94°C. FT-IR (KBr) (cm^{-1}): 3008 (C-$H_{arom.}$), 2923, 2853 (C-H), 1665 (C=O), 1586 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 0.96 (t, 3H, *J* 7.38 Hz, C$\boldsymbol{H}_3$), 2.56 (q, 2H, *J* 7.39 Hz, S-C$\boldsymbol{H}_2$), 6.97 (d, 2H, *J* 7.74 Hz, C$\boldsymbol{H}_{arom}$), 7.08 (t, 1H, *J* 7.44 Hz, C$\boldsymbol{H}_{arom}$), 7.27 (t, 2H, *J* 7.56 Hz, C$\boldsymbol{H}_{arom}$), 7.58-7.68 (tt, 2H, *J* 7.53, 1.46 Hz, C$\boldsymbol{H}_{napht.}$), 7.76 (bs, 1H, N$\boldsymbol{H}$), 8.00-8.09 (dd, 2H, *J* 7.7, 1.46 Hz, C$\boldsymbol{H}_{napht}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 14.5 (-$\boldsymbol{C}H_3$), 28.0 (S$\boldsymbol{C}H_2$-), 122.5, 124.7, 126.6 ($\boldsymbol{C}H_{arom.}$), 124.5 (S-$\boldsymbol{C}_{napht.}$), 126.8 (-NH-$\boldsymbol{C}_{napht.}$), 129.4, 130.8, 132.8 ($\boldsymbol{C}H_{napht.}$), 134.6, 138.5 ($\boldsymbol{C}_{napht.}$), 145.0 (NH-$\boldsymbol{C}$), 180.5, 181.1 ($\boldsymbol{C}$=O). MS [-ESI] = m/z 308.01 $[M-H]^-$, Anal. Calc. for $C_{18}H_{15}NO_2S$ (309.08): C 69.88, H 4.69, N 4.53. Found: C 70.04, H 4.88, N 4.57%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 210(2.4), 283(2.6), 382(1.9), 511(1.7).

2.13. ***2-Chloro-3-(o-tolylamino)naphthalene-1,4-dione (9)*** *[16, 21].* Compound **9** was synthesized from o-toluidine **8** (0.235 g, 2.202 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.5 g, 2.202 mmol) according to the general method. Yield: 72.7%. Red crystal. R_f [PET/$CHCl_3$ (1:1)]: 0.41. M.p.: 162–163°C. FT-IR (KBr) (cm^{-1}): 3060, 2946 (C-H), 1672 (C=O), 1595, 1573 (C=C), 3244 (N-H).

2.14. General Procedure for the Synthesis of N,N-Substituted Naphthoquinone Compounds (1-Methylbenzo[b]phenazine-6,11-dione ***11*** *and 2-Methylbenzo[b]phenazine-6,11-dione* ***14*** *[22]).* Mono substituted naphthoquinone derivatives **9** [21] and **13** (1 mol) were dissolved in DMF (100 mL) and sodium azide (NaN_3) (2 mol) dissolved in 10 ml of water was slowly added. The reaction was heated to reflux with stirring. 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.

2.15. ***1-Methylbenzo[b]phenazine-6,11-dione (11)****.* Compound **11** was synthesized from sodium azide **10** (0.131 g, 2.015 mmol) and 2-chloro-3-(o-tolylamino) naphthalene-1,4-dione **9** [21] (0.3 g, 1.007 mmol) according to the general method. Yield: 75.7%. Dark blue crystal. R_f [PET/$CHCl_3$(1:1)]: 0.53. M.p.: 139–141°C. FT-IR (KBr)(cm^{-1}): 3019 (C-$H_{arom.}$), 2926, 2860 (C-H), 1624 (C=O), 1524 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 2.30 (bs, 3H, -CH_{3arom}), 7.13 (d, 1H, *J* 7.81 Hz, -C$\boldsymbol{H}_{arom}$-), 7.08 (t, 1H, *J* 7.83 Hz, -C$\boldsymbol{H}_{arom}$-), 6.37 (d, 1H, *J* 7.88 Hz, -C$\boldsymbol{H}_{arom}$-), 7.53-7.61 (m, 2H, C$\boldsymbol{H}_{napht.}$), 7.95-7.99 (m, 2H, C$\boldsymbol{H}_{napht.}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 18.1 ($\boldsymbol{C}H_{3arom}$) 114.1, 120.7, 128.0 (-$\boldsymbol{C}H_{arom}$), 132.6 (CH_3-$\boldsymbol{C}_{arom}$), 137.7, 139.0 (-N=$\boldsymbol{C}_{arom}$), 131.7, 133.7 (-N-$\boldsymbol{C}_{napht.}$), 121.8, 126.0, 126.2 ($\boldsymbol{C}H_{napht.}$), 130.6, 130.7 ($\boldsymbol{C}_{napht.}$), 180.7, 180.8 $\boldsymbol{C}$=O). MS [+ESI] = 276.1 $[M+2H]^+$. Anal. Calc. for $C_{17}H_{10}N_2O_2$ (274.07): C 74.44, H 3.68, N 10.21. Found: C 74.63, H 3.45, N 10.18%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 241(2.5), 298(2.6), 429(1.2), 544(1.6).

2.16. ***2-Chloro-3-(m-tolylamino)naphthalene-1,4-dione (13)*** *[16, 23].* Compound **13** was synthesized from m-toluidine **12** (0.188 g, 1.761 mmol) and 2,3-dichloro-1,4-naphthoquinone **1** (0.4 g, 1.761 mmol) according to the general method. Yield: 75.3%. Red crystal. R_f [PET/$CHCl_3$ (1:1)]: 0.41. M.p.: 177–179°C. FT-IR (KBr) (cm^{-1}): 3045, 2915 (C-H), 1675 (C=O), 1593, 1560 (C=C), 3237 (N-H).

2.17. ***2-Methylbenzo[b]phenazine-6,11-dione (14)*** *[22].* Compound **14** was synthesized from sodium azide **10** (0.087 g, 1.344 mmol) and 2-chloro-3-(m-tolylamino) naphthalene-1,4-dione **13** (0.2 g, 0.672 mmol) according to the general method. Yield: 73.0%. Dark navy blue crystal. R_f [PET/$CHCl_3$)(2:1)]: 0.50. M.p.: 193–195°C. IR (KBr) (cm^{-1}): 3019 (C-$H_{arom.}$), 2926, 2850 (C-H), 1616 (C=O), 1577, 1522 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 2.35 (bs, 3H, -CH_{3arom}), 7.18-7.22 (t, 1H, *J* 7.81 Hz, -C$\boldsymbol{H}_{arom}$-), 6.78-6.82 (d, 1H, *J* 7.49 Hz, -C$\boldsymbol{H}_{arom}$-), 6.57-6.60 (d, 1H, *J* 7.52 Hz, -C$\boldsymbol{H}_{arom}$-), 7.63-7.69 (m, 2H, C$\boldsymbol{H}_{napht.}$), 8.04-8.08 (m, 2H, C$\boldsymbol{H}_{napht.}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 21.5 ($\boldsymbol{C}H_{3arom}$) 119.0, 120.3, 122.4 (-$\boldsymbol{C}H_{arom.}$), 132.8 (CH_3-$\boldsymbol{C}_{arom}$), 139.1, 139.7 (-N=$\boldsymbol{C}_{arom}$), 131.8, 133.7 (-N-$\boldsymbol{C}_{napht.}$), 115.5, 126.0, 126.2 ($\boldsymbol{C}H_{napht.}$), 128.9, 129.5 ($\boldsymbol{C}_{napht.}$), 180.7, 180.8 ($\boldsymbol{C}$=O). MS [+ESI] = m/z 276.0 $[M+2H]^+$, Anal. Calc. for $C_{17}H_{10}N_2O_2$ (274.07): C 74.44, H 3.68, N 10.21. Found: C 74.49, H 3.34, N 10.19%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 212(2.2), 241(2.1), 298(2.2), 539(1.2).

2.18. ***2,5-Dichloro-3-ethoxy-6-((2,4,6-trifluorophenyl)amino)cyclohexa-2,5-diene-1,4-dione (17)****.* Compound **17** was synthesized from 2,4,6-trifluoroaniline **16** (0.597 g, 2.440 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (1.0 g, 4.067 mmol) according to the general method. Yield: 28.3%. Red crystal. R_f [PET/$CHCl_3$(3:1)]: 0.51. M.p.: 131–132°C. FT-IR (KBr) (cm^{-1}): 3341 (N-H), 3018, 2956 (C-H_{arom}), 2923, 2851 (C-H), 1712, 1640 (C=O), 1588-1522 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 0.80 (t, 3H, *J* 7.08 Hz, -C$\boldsymbol{H}_{3ethoxy}$), 4.33 (q, 2H, *J* 7.05 Hz, -O-C$\boldsymbol{H}_{2ethoxy}$), 6.52 (bs, 1H, -N$\boldsymbol{H}$-), 6.63-6.67 (m, 6H, -C$\boldsymbol{H}_{arom}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 100.5, 100.5 (-$\boldsymbol{C}H_{arom}$), 150.3-152.1, 152.1-154.0 ($\boldsymbol{C}$-F-), 124.3 (NH- $\boldsymbol{C}_{arom}$), 14.2 (-C$\boldsymbol{H}_{3ethoxy}$), 68.1 (-C$\boldsymbol{H}_{2ethoxy}$), 146.9 (-NH-$\boldsymbol{C}_{benzo}$), 114.2, 118.9 ($\boldsymbol{C}$-Cl-), 158.0 ($\boldsymbol{C}$-O-), 164.5, 166.1 ($\boldsymbol{C}$=O). MS

[-ESI] = m/z 364.0 $[M]^-$, Anal. Calc. for $C_{14}H_8Cl_2F_3NO_3$ (364.98): C 45.93, H 2.20, N 3.83. Found: C 45.98, H 2.19, N 3.94%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 225(2.2), 301(2.7), 377(1.4), 462(1.2).

2.19. ***2,5-Dichloro-3,6-bis((2,4,6-trifluorophenyl)amino)cyclohexa-2,5-diene-1,4-dione (18).*** Compound **18** was synthesized from 2,4,6-trifluoroaniline **16** (0.597 g, 2.440 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (1.0 g, 4.067 mmol) according to the general method. Yield: 39.2%. Light yellow crystal. R_f [PET/$CHCl_3$(3:1)]: 0.55. M.p.: 154–156°C. FT-IR (KBr) (cm^{-1}): 3380 (N-H), 3019, 2961 (C-H_{arom}), 2927, 2858 (C-H), 1716 (C=O), 1519 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 4.26 (bs, 2H, -N***H***-), 7.93-7.98 (m, 4H, -C***H***$_{arom}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 101.2 (-***C***H$_{arom}$), 153.9-155.8, 155.8-157.3 (***C***-F-), 124.3 (NH- ***C***$_{arom}$), 141.0 (-NH-***C***$_{benzo}$), 111.3 (***C***-Cl-), 166.0 (***C***=O). MS [-ESI] = m/z 464.9 $[M-H]^-$, Anal. Calc. for $C_{18}H_6Cl_2F_6N_2O_2$ (465.97 g/mol): C 46.28, H 1.29, N 6.00. Found: C 46.40, H 1.25, N 6.09%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 247(3.1), 292(3.0), 377(2.7), 462(2.4).

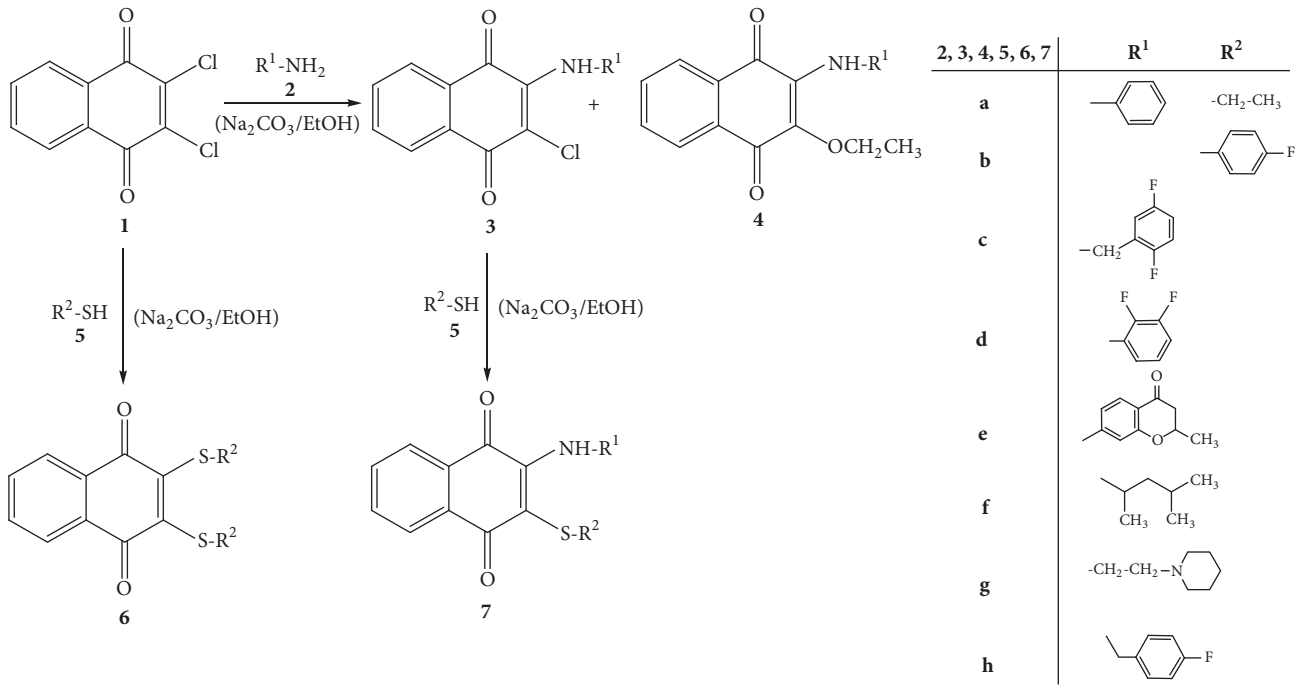
2.20. ***2-Chloro-3,6-diethoxy-5-((4-fluorobenzyl)amino)cyclohexa-2,5-diene-1,4-dione (19).*** Compound **19** was synthe-sized from (4-fluorophenyl) methanamine **2h** (0.275 ml, 2.440 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.6 g, 2.440 mmol) according to the general method. Yield: 21.1%. Dark red crystal. R_f [(PET/$CHCl_3$(5:2)]: 0.58. M.p.: 60–62°C. FT-IR (KBr) (cm^{-1}): 3345 (N-H), 3001 (C-H_{arom}), 2982, 2929 (C-H), 1682 (C=O), 1570 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 1.37 (t, 3H, *J* 7.06 Hz, -C***H***$_{3ethoxy}$), 1.36 (t, 3H, *J* 7.06 Hz, -C***H***$_{3ethoxy}$), 4.12-4.52 (m, 4H, -O-C***H***$_{2ethoxy}$), 1.71 (d, 2H, *J* 4.97 Hz, -NH-C***H***$_{2-}$), 5.66 (bs, 1H, -N***H***-), 6.13-6.35 (m, 4H, -C***H***$_{arom-}$).^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 171.5-173.3 (-C-F$_{arom}$), 140.5, 138.6, 110.8, 111.4 (-CH$_{arom}$), 144.3 (-C$_{arom}$), 29.5 (-N-***C***H$_2$-) 70.3, 71.5, 15.9, 20.7 (-***C***H$_{2ethoxy}$), (-***C***H$_{3ethoxy}$), 125.8 (-***C***$_{benzo}$-NH-) 102.0 (***C***-Cl-), 143.9, 154.4 (***C***-O-), 171.7, 172.8 (***C***=O). MS [-ESI] = m/z 352.3 $[M-H]^-$, Anal. Calc. for $C_{17}H_{17}ClFNO_4$ (353.08): C 57.72, H 4.84, N 3.96. Found: C 57.89, H 4.58, N 3.98%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 217(1.7), 241(1.8), 298(2.1), 430(0.3).

2.21. ***2-Chloro-5-ethoxy-3,6-bis((4-fluorobenzyl)amino)cyclohexa-2,5-diene-1,4-dione (20).*** Compound **20** was synthesized from (4-fluorophenyl) methanamine **2h** (0.275 ml, 2.440 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.6 g, 2.440 mmol) according to the general method. Yield: 37.3%. Orange crystal. R_f [PET/$CHCl_3$(5:2)]: 0.55. M.p.: 82–84°C. FT-IR (KBr) (cm^{-1}): 3300 (N-H), 3009, 2961 (C-H_{arom}), 2930, 2874 (C-H), 1682 (C=O), 1624, 1579 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 1.35 (t, 3H, *J* 7.05 Hz, -C***H***$_{3ethoxy}$), 4.40 (q, 2H, *J* 7.05 Hz, -O-C***H***$_{2ethoxy}$), 4.50 (d, 4H,, *J* 8.09 Hz, -NH-C***H***$_{2-}$), 5.81, 6.78 (bs, 2H, -N***H***-), 7.08-7.65 (m, 8H, -C***H***$_{arom-}$).^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 174.2-176.3 (-C-F$_{arom}$), 123.4, 125.9, 128.9, 131.0 (-CH$_{arom}$), 132.4 (-C$_{arom}$), 29.0, 30.3 (-N-***C***H$_2$-), 71.3, 15.9 (-***C***H$_{2ethoxy}$) ve (-***C***H$_{3ethoxy}$), 154.1, 153.1 (-***C***$_{benzo}$-NH-), 105.9 (***C***-Cl-), 129.6 (***C***-O-), 171.5, 175.3 (***C***=O). MS [+ESI] = m/z 433.3 $[M+H]^+$, Anal. Calc. for $C_{22}H_{19}ClF_2N_2O_3$ (432.11): C 61.05, H 4.42, N 6.47. Found: C 61.14, H 4.76, N 6.51%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 205(1.9), 240(1.7), 303(2.1), 430(0.5).

2.22. ***2-Chloro-5,6-diethoxy-3-((4-fluorobenzyl)amino)cyclohexa-2,5-diene-1,4-dione (21).*** Compound **21** was synthesized from (4-fluorophenyl) methanamine **2h** (0.275 ml, 2.440 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.6 g, 2.440 mmol) according to the general method. Yield: 18.2%. Dark red crystal. R_f [PET/$CHCl_3$(5:2)]: 0.51. M.p.: 104–106°C. FT-IR (KBr) (cm^{-1}): 3242 (N-H), 3003-2957 (C-H_{arom}), 2926, 2855 (CH), 1690 (C=O), 1579-1519 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 1.35 (t, 3H, *J* 7.05 Hz, -C***H***$_{3ethoxy}$), 1.37 (t, 3H, *J* 7.05 Hz, -C***H***$_{3ethoxy}$), 4.19-4.53 (q, 4H, *J* 7.05 Hz, -O-C***H***$_{2ethoxy}$), 1.68 (d, 2H, *J* 4.97 Hz, -NH-C***H***$_{2-}$), 5.49 (bs, 1H, -N***H***-), 6.15-6.30 (m, 4H, -C***H***$_{arom-}$). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 163.6-161.7 (-C-F$_{arom}$), 129.4, 129.6, 116.0, 116.2 (-CH$_{arom}$), 132.9 (-C$_{arom}$), 29.8 (-N-***C***H$_2$-), 68.2, 71.6, 11.0, 14.1 (-***C***H$_{2ethoxy}$) ve (-***C***H$_{3ethoxy}$), 143.5 (-***C***$_{benzo}$-NH-), 128.7 (***C***-Cl-), 135.9, 142.0 (***C***-O-), 169.9, 174.2 (***C***=O). MS [-ESI] = m/z 352.33 $[M-H]^-$, Anal. Calc. for $C_{17}H_{17}ClFNO_4$ (353.08): C 57.72, H 4.84, N 3.96. Found: C 57.92, H 4.68, N 3.98%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 206(2.0), 241(2.1), 298(2.4), 430(0.5).

2.23. ***2,5-Diethoxy-3,6-bis((4-fluorobenzyl)amino)cyclohexa-2,5-diene-1,4-dione (22).*** Compound **22** was synthesized from (4-fluorophenyl)methanamine **2h** (0.275 ml, 2.440 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.6 g, 2.440 mmol) according to the general method. Yield: 16,4%. Pale pink crystal. R_f [PET/$CHCl_3$ (5:2)]: 0.48. M.p.: 226–228°C. FT-IR (KBr) (cm^{-1}): 3244 (N-H), 3019 (C-H_{arom}), 2929, 2850 (CH), 1663 (C=O), 1586 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 0.84 (t, 6H, *J* 7.46 Hz, -C***H***$_{3ethoxy}$), 4.10-4.18 (m, 4H, -O-C***H***$_{2ethoxy}$), 4.88 (d, 2H, *J* 6.18 Hz, -NH-C***H***$_{2-}$), 6.00 (bs, 2H, -N***H***-), 6.98-7.64 (m, 8H, -C***H***$_{arom-}$).^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 161.2, 163.0 (-C-F$_{arom}$), 130.8, 131.0, 112.9,113.1 (-CH$_{arom}$), 140.2 (-C$_{arom}$), 32.0 (-N-***C***H$_2$-), 71.4, 15.9 (-***C***H$_{2ethoxy}$) ve (-***C***H$_{3ethoxy}$), 122.4 (-***C***$_{benzo}$-NH-), 132.7 (***C***-O-), 175.1 (***C***=O). MS [+ESI] = m/z 445.0 $[M+2H]^+$, Anal. Calc. For $C_{24}H_{24}F_2N_2O_4$ (443.17): C 65.15, H 5.47, N 6.33. Found: C 65.08, H 5.80, N 6.27%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 219(3.7), 245(3.8), 462(2.4), 557(2.6).

2.24. ***2,5-Dichloro-3-((2,5-difluorobenzyl)amino)-6-ethoxycyclohexa-2,5-diene-1,4-dione (23).*** Compound **23** was synthesized from (2,5-difluorophenyl)methanamine **2c** (0.290 g, 2.033 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.5 g, 2.033 mmol) according to the general method. Yield: 52.4%. Dark purple crystal. R_f [PET/$CHCl_3$(3:1)]: 0.47. M.p.: 73–74°C. FT-IR (KBr) (cm^{-1}): 3346 (N-H), 3020 (C-H_{arom}), 2927, 2856 (CH), 1667 (C=O), 1522 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 1.36 (t, 3H, *J* 7.05 Hz, -C***H***$_{3ethoxy}$), 4.62 (q, 2H, *J* 7.03 Hz, -O-C***H***$_{2ethoxy}$), 4.95 (d, 2H, *J* 6.72 Hz, -NH-C***H***$_2$), 6.27 (bs, 1H,



Scheme 1: The synthesis of N-, S-, O-substituted naphthoquinone derivatives (**3a, 3c-d**, **3f-g**, **4e**, **6b**, **7a**).

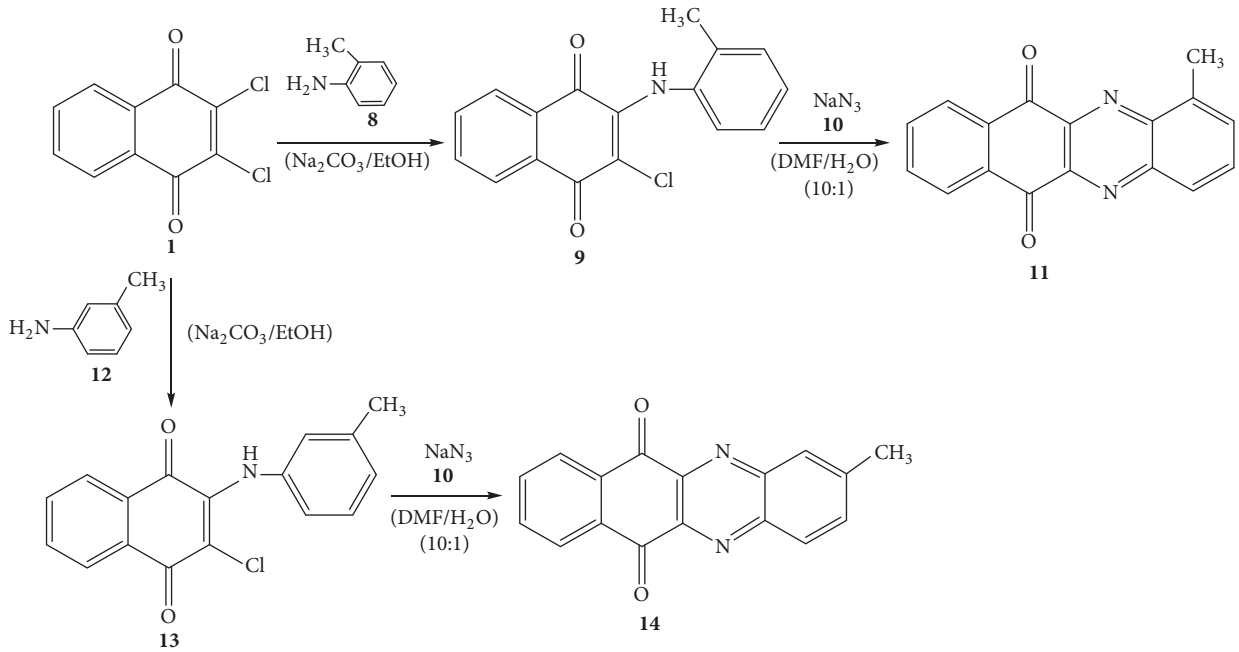
-N***H***-), 6.85-7.15 (m, 3H, -C***H***$_{circle}$).^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 116.4, 117.5, 120.3 (-***C***H$_{arom}$), 126.5 (-***C***$_{arom}$), 155.5-157.4, 157.8-159.7 (***C***-F-), 42.4 (-***C***H$_2$-NH-), 16.1 (-C***H***$_{3ethoxy}$), 68.0 (-C***H***$_{2ethoxy}$), 156.4 (-NH-***C***$_{benzo}$), 115.8, 119.4 (***C***-Cl-), 162.2 (***C***-O-), 175.9, 173.8 (***C***=O). MS [-ESI] = m/z 360.0 [M-H]$^-$, Anal. Calc. for $C_{15}H_{11}Cl_2F_2NO_3$ (361.01): C 49.75, H 3.06, N 3.87. Found: C 49.96, H 3.00, N 3.91. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 219(2.2), 241(2.4), 311(2.3), 492(1.2).

2.25. ***2,3,5-Trichloro-6-((2-(piperidin-1-yl)ethyl)amino)cyclohexa-2,5-diene-1,4-dione (24).*** Compound **24** was synthesized from 2-(piperidin-1-yl) ethan-1-amine **2 g** (0.208 g, 1.626 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.4 g, 1.626 mmol) according to the general method. Yield: 33.3%. Dark red crystal. R_f [PET/$CHCl_3$ (3:1)]: 0.51. M.p.: 60–62°C. FT-IR (KBr) (cm^{-1}): 3332 (N-H), 3019, 2932 (CH), 1639 (C=O), 1522 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 1.22-1.32, 2.44-2.76 (m, 10H, -N$_{circle}$-C***H***$_2$), 3.15 (t, 2H, *J* 5.67 Hz, -C***H***$_{2circle}$-N-), 4.17-4.20 (m, 2H, -NH-C***H***$_2$), 8.03 (bs, 1H, -NH). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 20.0, 23.8, 23.9, 54.1, 54.2 (-CH$_{2circle}$), 44.0, 56.1 (-N-***C***H$_2$-***C***H$_2$-N-), 148.4 (-***C***-NH-), 120.0, 140.1, 142.7 (***C***-Cl-), 162.3, 174.9 (***C***=O). MS [+ESI] = m/z 339.4 [M+2H]$^+$, Anal. Calc. for $C_{13}H_{15}Cl_3N_2O_2$ (337.63): C 46.25, H 4.48, N 8.30. Found: C 46.22, H 4.72, N 8.25%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 217(2.8), 293(1.9), 354(2.0), 587(1.9).

2.26. ***2-Chloro-5-ethoxy-3,6-bis((2-(piperidin-1-yl)ethyl)amino)cyclohexa-2,5-diene-1,4-dione (25).*** Compound **25** was synthesized from 2-(piperidin-1-yl)ethan-1-amine **2 g** (0.208 g, 1.626 mmol) and 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** (0.4 g, 1.626 mmol) according to the general method. Yield: 36.3%. Dark red crystal. R_f [PET/$CHCl_3$ (3:1)]: 0.54. M.p.: 241–243°C. FT-IR (KBr) (cm^{-1}): 3295 (N-H), 3019, 2923 (CH), 1678 (C=O), 1570 (C=C). ^{1}H NMR (499.74 MHz, $CDCl_3$) δ (ppm) = 0.81 (t, 3H, *J* 7.03 Hz,-C***H***$_{3ethoxy}$), 1.15-1.55, 2.10-2.24 (m, 20H, -C***H***$_{2circle}$-N-), 2.26-2.28, 2.38-2.41 (m, 4H, -N$_{circle}$-C***H***$_2$), 4.13-4.23 (m, 4H, -NH-C***H***$_2$), 4.50 (q, 2H, *J*= 5.35 Hz, O-C***H***$_{2ethoxy}$-), 5.67, 5.90 (bs, 2H, -NH). ^{13}C NMR (125.66 MHz, $CDCl_3$) δ (ppm) = 23.0, 23.7, 55.7 (-CH$_{2circle}$), 44.4, 58.6 (-N-***C***H$_2$-***C***H$_2$-N-), 14.8 (-C***H***$_{3ethoxy}$), 66.1 (-C***H***$_{2ethoxy}$) 136.3, 140.5 (-***C***-NH-), 100.2 (***C***-Cl-), 127.8 (***C***-O-), 169.2, 175.0 (***C***=O). MS [+ESI] = 441.4 [M+2H]$^+$, Anal. Calc. for $C_{22}H_{35}ClN_4O_3$ (439.0): C 60.19, H 8.04, N 12.76. Found: C 60.14, H 8.21, N 12.68%. UV-vis [$CHCl_3$, λ_{max} (nm)(log ε)]: 223(2.8), 292(3.0), 333(1.7), 483(1.5).

3. Results and Discussion

3.1. Chemistry. In this study that we have done, reactions of thiol and amine compounds with 2,3-dichloro-1,4-naphthoquinone and 2,3,5,6-tetrachloro-1,4-benzoquinone as a starting compounds were investigated. Firstly, the multicomponent reactions of 2,3-dichloro-1,4-naphthoquinone **1** with various thiol and amine nucleophiles were investigated. Similarly, 2,3,5,6-tetrachloro-1,4-benzoquinone **15** with various amine nucleophiles was investigated. As shown in Scheme 1, the reaction of **1** with different amines **2a**, **2c**, **2d**, **2e**, **2f**, **2 g** in ethanol in the presence of Na_2CO_3 gave known and unknown compounds **3a** [16, 17], **3c**, **3d**, **3f**, **3g** [18], **4e**. Compound **6b** [19] obtained the reaction of **1** with



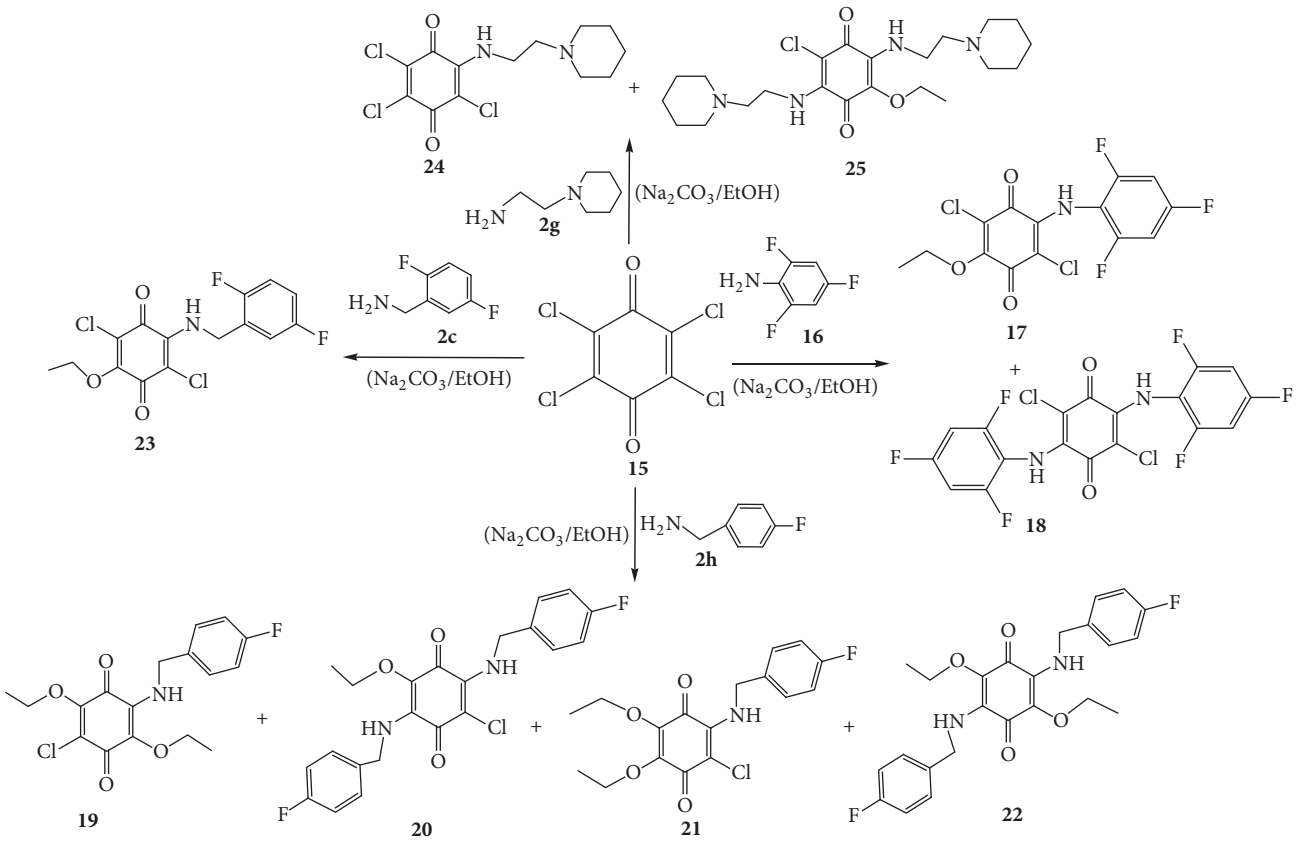
Scheme 2: The synthesis of phenazine compounds **11** and **14** via the condensation reaction of naphthoquinones **9** and **13**.

5b. The reaction of **3a** with **5a** gave compound **7a** [20]. When **1** reacted with an equimolar amount of various amines and thiols in ethanol in the presence of sodium carbonate solution at room temperature but under different conditions, the corresponding products (**3c**, **3d**, **3f**, **3g**, **4e**, **6b**, **7a**) were obtained in different yields. All synthesized compounds were confirmed by spectroscopic methods comprising ^{1}H NMR and ^{13}C NMR, FT-IR, elemental analysis, and MS.

In the second step of this study, different molar amount of N-substituted naphthoquinone compounds **9** [16, 21], **13** [16, 23] was reacted with sodium azide in DMF. The phenazine compounds **11** and **14** [22] were synthesized and compound **11** has not yet been described in the literature (Scheme 2).

In the last step of this study, 2,3,5,6-tetrachloro-1,4-benzoquinone **15** compound was reacted with compounds containing N-nucleophiles **(2b**, **2c**, **2 g**, **16)** that novel benzoquinones (**17-25**) not yet described in the literature were synthesized in Scheme 3. The synthesis, spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, UV, FT-IR), elemental analysis, and melting points of compounds were reported in studies. The ^{1}H NMR signal of the hydrogen atoms of the naphthoquinone unit of compounds **3c**, **3d**, **3f**, **3g**, **4e**, **7a** was observed at (CH) δ= 7.9-8.1 and 7.5-7.7 ppm like as doublet of doublets and triplet of triplets, respectively. Similarly, **6b**, **11**, **14** were observed at (CH) δ= 7.9-8.1 and 7.5-7.7 ppm like as multiplets, respectively. Substituted aromatic ring hydrogens showed peaks around 6.8-7.4 ppm. Aliphatic groups in compounds **3f**, **7a** were shifted to a higher field and displayed peaks at 0.8-1.2 ppm. The ^{13}C NMR spectra of compound **3d** gave two carbonyl signals at 177.5 and 179.9 ppm (C=O). Unlike other studies, the carbon atoms attached to the fluorine atoms in the **3c** compound give cleavage peaks 155.6, 157.8 ppm (F-C_{arom}) in aromatic unit. Compound **3d** gave one carbonyl signal at 116.6 ppm (-Cl-$C_{napht.}$) similarly giving a single peak at 126.9 ppm in the compound **3f**. The FT-IR spectra of compounds **3c**, **3d**, **3f**, **3g**, **4e**, **7a** showed bands around at 3300 cm^{-1} for the (–NH) stretching. Also, (C-H_{arom}) bond was observed ν = 3000 cm^{-1}. With the aid of the positive ion mode of electron spray ionization (ESI) mass spectrum of the compounds **3c**, **6b,** and **3f**, the respective molecular ion peaks were observed at *m/z* (%) 334 (100) [M+H]$^{+}$, 411 (100) [M+H]$^{+}$, 292 (100) [M+H]$^{+}$, respectively.

2-Chloro-3-(o-tolylamino)naphthalene-1,4-dione **9** and sodium azide **10** required for the synthesis of **11**, similarly, 2-chloro-3-(m-tolylamino)naphthalene-1,4-dione **13** and sodium azide (NaN_3) **10** required for the synthesis of compound **14** have been synthesized according to Scheme 2. The nucleophilic displacement reaction of compound **9** with sodium azide (NaN_3) in DMF-H_2O (10:1) afforded 1-methylbenzo[b]phenazine-6,11-dione **11** and this analog 2-methylbenzo[b]phenazine-6,11-dione **14** as the only isolated products as exhibited in Scheme 2. The proposed mechanism of condensation reaction of naphthoquinones agrees well with the related literatures [24, 25]. Both synthesized compounds were characterized by using the ^{1}H NMR, ^{13}C NMR, FT-IR spectral data, and elemental analysis. The first compound **11** was obtained by an interesting ring closure and is a phenazine derivative. The ^{13}C NMR spectra of compound **11** gave two carbonyl signals at 180.7 and 180.8 ppm (C=O). The FT-IR spectra of compounds **11** and **14** showed bands at 3019 cm^{-1} for the (C-H_{arom}) stretching and (–NH) bonds were not observed in the FT-IR. ^{1}H NMR peak of the hydrogen atoms of the naphthoquinone group gave on (CH_{arom}) δ= 7.53-7.61 ppm and 7.95-7.99 ppm as multiplets for compound **11.** Molecular ion peaks were observed at *m/z* (%) 276.1 (100)



Scheme 3: The synthesis of N,O-substituted benzoquinone derivatives.

$[M+2H]^+$. The UV-Vis spectroscopy values for compound **14** were also observed at 212(2.2), 241(2.1), 298(2.2), 539(1.2).

It is known that the reactions of 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4 dione **15** with amines proceed by Michael addition reaction. A series of 2-arylamino-1,4-benzoquinone derivatives **17-25** were synthesized via the nucleophilic substitution reaction of 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione **15** by appropriate aryl amines **2c**, **2 g**, **2h**, **16** in ethanol as shown in Scheme 3. The reactions were found to be exceptionally selective and lead to mainly 2- and/or 2,5-bis(amino substituted)-3,6-dichloro-1,4-benzoquinones of the corresponding amine. From these reactions we could not obtain 2,6-bis(amino substituted)-1,4-benzoquinone derivatives. The steric factors arising from the substituent effect predominates in these reactions. The result of selective formation of 2,5-isomer may be assumed to be due to attack of two amines to 1,4-benzoquinone. For such attack to give exclusive product of one isomer (2,5-) would require approach of two amines from the furthest possible distance. Thus, exclusively 2- and/or 2,5-isomer were formed due to electrostatic reasons for compounds **17-25**. The results agree well with the corresponding mechanism in the similar compounds [6, 26].

In ^{1}H NMR spectrum of compounds **17-23**, the hydrogen signals were observed at between $\delta = 6.1$-8.0 ppm as multiplet peak, assigned to the ($-CH_{arom}$). In the ^{13}C NMR, characteristic signals of two carbonyl carbons of benzoquinones were visible at around 175.9 and 173.8 ppm. For compound **23**, substitute ethoxy group carbons ($-CH_{2etoxy}$) and ($-CH_{3etoxy}$) at 68.0 and 16.1 ppm, respectively. Like the naphthoquinone derivatives, carbon atoms attached to the fluorine atoms in the **23** compound give cleavage peaks 155.5 and 157.8 ppm ($F-C_{arom}$). The FT-IR spectra of compounds **17-25** showed the absorption bands of the N–H group at around 3240-3380 cm^{-1}. The characteristic stretching band of carbonyl groups (C = O) was observed at between $\nu = 1650$-1700 cm^{-1}. In the MS of quinone derivatives, the molecular ion peaks of compounds **17**, **22,** and **23** were observed at 364 (100) $[M]^-$, 445 (100) $[M+2H]^+$, 360 (100) $[M-H]^-$.

3.2. Antimicrobial Studies. The profound antifungal and antibacterial activity exhibited by quinone compounds has prompted us to synthesize new heteroatom substituted 1,4-naphtho- and benzoquinones. In our new endeavors, we have synthesized new 1,4-naphtho- and benzoquinones and evaluated their antibacterial and antifungal activity by diffusion [13] and serial dilution[14] methods with a view to search new perspective compounds having broad spectrum of biological activity. Antibacterial and antifungal activity of compounds **3c**, **3d**, **3f**, **3g**, **6b**, **11**, **17**, **21**, and **25** was elucidated against *Escherichia coli B-906*, *Staphylococcus aureus 209-P*, *Mycobacterium luteum B-917, Candida tenuis VKM Y-70,* and *Aspergillus niger F-1119* by diffusion method (Tables 1 and 2) and by serial dilution method as shown in Tables 3 and 4.

Table 1: Antibacterial activity of the compounds determined by diffusion method.

Compound	Concentration %	Diameter of inhibition of growth of microorganisms, mm		
		E. coli	*S. aureus*	*M. luteum*
3c	0.5	0	0	0
	0.1	0	0	0
3d	0.5	0	16	24
	0.1	0	12	12
3f	0.5	0	0	0
	0.1	0	0	0
3g	0.5	11	20	20
	0.1	0	14	16
6b	0.5	0	0	11
	0.1	0	0	8
11	0.5	0	0	0
	0.1	0	0	0
17	0.5	0	10	11
	0.1	0	6	9
21	0.5	0	0	0
	0.1	0	0	0
25	0.5	0	0	0
	0.1	0	0	0
Control∗	0.5	14	15	18

∗Vancomycin was used as a control in the tests of antibacterial activity of the synthesized compounds.

Table 2: Antifungal activity of the compounds determined by diffusion method.

Compound	Concentration %	Diameter of inhibition of growth of microorganisms, mm	
		C. tenuis	*A. niger*
3c	0.5	0	0
	0.1	0	0
3d	0.5	0	0
	0.1	0	0
3f	0.5	0	0
	0.1	0	0
3g	0.5	0	0
	0.1	0	0
6b	0.5	15	0
	0.1	13	0
11	0.5	0	0
	0.1	0	0
17	0.5	0	15
	0.1	0	10
21	0.5	7	12
	0.1	0	6
25	0.5	15	10
	0.1	0	0
Control∗	0.5	19	20

∗Nystatin was used in the tests of antifungal activity of the synthesized compounds.

Table 3: Antibacterial activity of the compound determined by serial dilution method.

Compound	Microorganism		
	E. coli	*S. aureus*	*M. luteum*
	MIC (μg/mL)		
3c	+	+	+
3d	+	62.5	31.2
3f	+	+	+
3g	250.0	31.2	15.6
6b	+	+	+
11	+	+	+
17	+	15.6	62.5
21	+	+	+
25	+	500.0	250.0
Control	31.2 ± 0.8	3.9 ± 0.2	7.8 ± 0.2

+: growth of microorganisms.

Table 4: Antifungal activity of the compounds determined by serial dilution method.

Compound	Microorganism	
	C. tenuis	*A. niger*
	MIC (μg/mL)	
3c	125.0	+
3d	+	+
3f	+	+
3g	500.0	500.0
6b	+	+
11	+	+
17	15.6	250.0
21	62.5	125.0
25	31.2	250.0
Control	7.8 ± 0.2	15.6 ± 0.8

+: growth of microorganisms.

Activities of quinone compounds were compared with those of the known antibacterial agent vancomycin and antifungal agent nystatin (control C).

The test-culture *E. coli* appeared not to be sensitive to any compounds except that **3g**. Compound **3g** has moderate activity against *E. coli* at a concentration of 0.5% and the diameter of the inhibition zone was 11 mm by diffusion method. Compounds **3d** and **3g** have strong activity against *S. aureus* (16 and 20 mm at 0.5% concentration) and have moderate activity at a concentration of 0.1% (the diameter of the inhibition zones were 12 and 14 mm). The *M. luteum* strain was sensitive to compounds **3g**, **6b,** and **17** at a concentration of 0.5% and the diameter of the inhibition zone was 20 and 11 mm, respectively (Table 1). Compound **3d** has good antibacterial activity against *M. luteum* at concentration of 0.5% and the diameter of the inhibition zone was 24 mm by diffusion method (for vancomycin was 18 mm). Compounds **3d** and **3g** were found to exhibit strong antibacterial activity against *S. aureus* and *M. luteum* (at concentration of 0.5%) on comparison with antibacterial drug vancomycin evaluated by diffusion method.

Antifungal activity against *C. tenuis* was observed for **6b**, **21**, and **25** at concentration of 0.5% (d = 15, 7 and 15 mm, respectively). Compound **17** showed antifungal activity against *A. niger* at 0.5% concentration (d = 15 mm) by the diffusion method (Table 2). Compounds **3c**, **3f**, and **11** have no antibacterial and antifungal activity against *E. coli, S. aureus, M. luteum, C. tenuis,* and *A. niger* at 0.5 and 0.1% evaluated concentrations by diffusion method (Tables 1 and 2).

The biological activity results of the synthesized compounds were classified as follows: the antimicrobial activities were considered as significant when the minimum inhibition concentration (MIC) was 100 μg/mL or less; moderate, when the MIC was 100.0–500.0 μg/mL; weak, when the MIC was 500.0–1.000 μg/mL; and inactive when the MIC was above 1.000 μg/mL. Evaluation of the antibacterial activity of the synthesized compounds showed that **3g** and **17** was the most potent with MIC=15.6 μg/mL for *M. luteum* and *S. aureus*, respectively (Table 3). Evaluation of antibacterial activity of synthesized compounds showed that **3d** and **3g** have MIC=31.2 μg/mL for *M. luteum* and *S. aureus*, respectively (Table 3).

Significant antifungal activity for **17** and **25** was observed against *C. tenuis* fungi at 15.6 and 31.2 μg/mL, respectively. Evaluation of antifungal activity of compounds **3c, 3g,** and **21** showed their activity in concentrations 62.5–500.0 μg/mL against test-culture *C. tenuis* (Table 4). Compounds **3g**, **17**, **21**, and **25** showed moderate antifungal activity with MIC value in the range of 125.0–500.0 μg/mL against *A. niger* in Table 4.

Table 5: Catalase enzyme activities of the compounds.

Compound	Catalase activities (U/mL)
3c	0.599
3d	0.705
3f	0.715
3g	0.722
4e	0.689
6b	0.606
7a	0.608
14	0.470
17	0.581
19	0.550
22	0.709
23	0.585

3.3. Catalase Enzyme Inhibition Activity of Quinone Derivatives. Catalase is a common heme containing enzyme found in nearly all living organisms that are exposed to O_2, where it functions to catalyze the decomposition of H_2O_2 to H_2O and O_2. Compounds **3c**, **3d**, **3f**, **3g**, **4e**, **6b**, **7a**, **14**, **17**, **19**, **22**, and **23** were tested *in vitro* for their catalase activities and the results are shown in Table 5 and Figure 1. As shown in Figure 1, compound **3g** caused significant elevation of catalase activity.

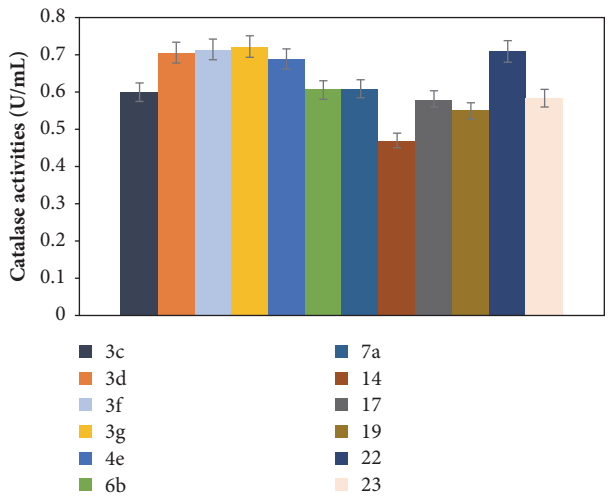


Figure 1: Catalase enzyme activities of the compounds, U mL^{-1}.

4. Conclusion

In this study we have done, the aim is to synthesize known and unknown quinone derivatives by reacting quinone compounds with some nucleophiles such as containing sulfur, nitrogen, and oxygen atoms in various conditions. In the synthesized compounds, antimicrobial activity at low concentrations against *E. coli*, *S. aureus,* and *M. luteum* bacteria and *C. tenuis* and *A. niger* fungi in comparison with controls was identified. Furthermore, a catalase activity of benzo- and naphthoquinone derivatives was examined for the first time in this work. Their structures of new synthesized compounds were determined by microanalysis, FT-IR, ^{1}H NMR, ^{13}C NMR, MS, and UV-Vis.

Compound **3d** has good antibacterial activity against test-culture *M. luteum* at concentration of 0.5% and the diameter of the inhibition zone was 24 mm by diffusion method (for vancomycin was 18 mm). Compounds **3d** and **3g** were found to exhibit high antibacterial activity against *S. aureus* and *M. luteum* (at concentration of 0.5%) on comparison with antibacterial drug vancomycin evaluated by diffusion method. Then, inhibitory activities of the benzo- and naphthoquinone derivatives against catalase enzyme were measured and especially **3g** exhibited better catalase enzyme inhibition activity than the other quinone derivatives.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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