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INTERACTION OF 5-SUBSTITUTED 1,4-NAPHTHOQUINONES AND AMINO THIOTRIAZOLES: REACTION WAYS AND REGIOSELECTIVITY

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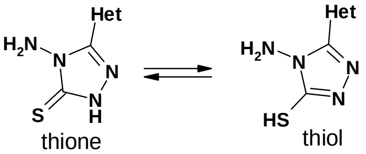
Abstract. Reactions of nucleophilic substitution between 5-R-2,3-dichloro-1,4-naphthoquinones and 4-amino-5-heteryl-4H-1,2,4-triazoles-3-thiols were carried out. It is shown that the interaction can take place in two alternative ways and the reaction direction is controlled by reaction conditions. Search of differences in atoms reactivity in investigated molecules by comparing the calculated Fukui atonic indices was conducted. The influence of electron donor and electron acceptor substituent in 2,3-dichloro-1,4-naphthoquinone 5th position on the nucleophilic substitution reaction regioselectivity was shown experimentally. Comparison of obtained ^{1}H NMR spectra with DFT calculated for both possible isomers of obtained products allowed to uniquely attribute synthesized compounds to relevant structures. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

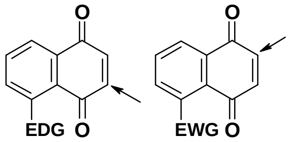
Keywords: 1,4-naphthoquinones, nucleophilic substitution, regioselectivity, Fukui indices.

1. Introduction

Thiotriazole is the core of various therapeutic agents that have shown an antimicrobial activity [1]. Condensation of such heterocycle with various pharmacophore fragments, including 1,4-quinoid, enables design of thiadiazine systems with potential anti-microbial, anti-inflammatory and anti-tumor activities [1-9]. Thiotriazole molecule is a bifunctional nucleophile and has two reactive centers. Due to the presence of thione-thiol tautomerism in the molecule *S*-nucleophilic center activation can be held by shifting a tautomeric equilibrium. So, in nonpolar solvents the thione form of bifunctional nucleophile prevails, and in polar solvents – thiol tautomeric form [8, 10].



The nature and arrangement of substituent in quinones have a strong steering effect in the reaction. So, it was established that in the studied reaction a big difference of its regioselectivity was observed in the case of the introduction of the substituent in the aromatic nucleus of the naphthoquinoid system [9].



The presence of electron donor substituent in the 5th position of 1,4-naphthoquinone directs the attack of nucleophilic center of corresponding nucleophile to the 3rd position of 1,4-naphthoquinone by creating a partial positive charge, and the presence of electron acceptor substituent – in the 2nd position of 1,4-naphthoquinone [11, 12].

2. Experimental

All the chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by precoated aluminum silica gel 60F 254 thin layer plates (TLC analysis) procured from Merck (Germany). Preparative thin layer chromatography was performed on glass plates Stratocrom SI 200 mm×200 mm×3 mm procured from Farmitalia Carlo Erba (Italy). Melting points (m.p.) were determined using an SRS-EZMelt automated melting point instrument without correction. Infrared (IR) spectra

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were recorded on a Specord-80M spectrophotometer in potassium bromide pellets. The nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra of the compounds were recorded in deuterated dimethyl sulfoxide (DMSO-d$_6$) with “Varian VXR” (300 MHz) NMR spectrometer and chemical shifts were expressed in δ parts per million (ppm). Shifts reported are relative to the signal of the solvent used in each case and coupling constants are reported in Hz (s: singlet, bs: broad singlet, d: doublet, t: triplet, dd: double doublet, m: multiplet). LC-MS spectra were recorded using a chromatography/mass spectrometric system that consists of high-performance liquid chromatograph “Agilent 1100 Series” equipped with diode-matrix and mass-selective detector “Aligent LC/MSD SL”.

2.1. General Procedure for the Synthesis of Heterocyclic Derivatives of 1,4-Quinones. Path A

5-amino-2-chloro-3-{[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazole-4-yl]amino} naphthalene-1,4-dione (6)

0.51 g (0.0026 mol) of 4-amino-5-(2-methylfuran)-4H-1,2,4-triazoles-3-thiols **5a** were added to 0.59 g (0.0026 mol) of 5-amino-2,3-dichloro-1,4-naphthoquinone **1** in 10 ml of toluene in the presence of triethylamine (Et$_3$N). The reaction mass was heated to 333–353 K and stirred for 4 h (the reaction was monitored by TLC analysis). The precipitate was filtered off and recrystallized in dimethylformamide (DMF)/ethanol (EtOH). Yield 64 %, mp = 446 K. IR (KBr), cm^{-1}: 3320 (NH$_2$), 3210, 3090 (NH), 1730, 1690 (C=O), 1455 (C=S), 710 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8.81 (s, 1H, NH); 8.43 (bs, 2H, NH$_2$); 7.70 (d, 1H, J=2.45 Hz, CH); 7.66 (dd, 1H, J_1=7.5 Hz, J_2=1.3 Hz, Ar-H); 7.52 (t, 1H, J=7.6, Hz, Ar-H); 7.38 (dd, 1H, J_1=7.8, J_2=1.3 Hz, Ar-H); 6.78 (d, 1H, J=2.4 Hz, CH); 2.32 (s, 3H, CH$_3$). ^{13}C NMR (DMSO) δ: 13.3 (CH$_3$), 104.7 (C), 106.6 (C), 115.6 (CH), 116.1 (CH), 119.7 (CH), 122.2 (C), 134.2 (C), 134.3 (C), 136.0 (CH), 138.9 (C), 139.2 (C), 142.6 (CH), 150.6 (C), 167.4 (C), 172.8 (CO), 175.1 (CO). LC-MS (*m*/*z*): calculated for $[C_{17}H_{12}ClN_5O_3S + H]^+$ 402.8269, observed 402.8. Calcd. for ($C_{17}H_{12}ClN_5O_3S$), %: C=50.81, H=3.01, Cl=8.82, N=17.43, S=7.98. Found, %: C=50.83, H=2.99, Cl=8.84, N=17.41, S=8.00.

By the same method there were obtained:

5-amino-2-chloro-3-{[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazole-4-yl] amino} – naphthalene-1,4-dione (8). Yield 59 %, mp = 423 K. IR (KBr), cm^{-1}: 3320 (NH$_2$), 3205, 3085 (NH), 1735, 1685 (C=O), 1460 (C=S), 705 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8.81 (s, 1H, NH); 8.43 (bs, 2H, NH$_2$); 7.69 (d, 1H, J_1=7.8 Hz, Ar-H); 7.63 (d, 1H, J=1.8 Hz, CH); 7.52-7.38 (m, 2H, Ar-H); 6.80 (d, 1H, J=1.8 Hz, CH); 2.21 (s, 3H, CH$_3$). ^{13}C NMR (DMSO) δ: 12.5 (CH$_3$), 104.7 (C), 106.1 (C), 110.5 (C), 112.2 (CH), 115.6 (CH), 119.7 (CH), 131.3 (C), 134.3 (C), 136.0 (CH), 139.2 (C), 140.5 (CH), 150.6 (C), 155.6 (C), 167.1(C), 172.8 (CO), 175.5 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{12}ClN_5O_3S + H]^+$ 402.82, observed 402.8. Calcd. for ($C_{17}H_{12}ClN_5O_3S$), %: C=50.81, H=3.01, Cl=8.82, N=17.43, S=7.98.Found, %: C=50.82, H=3.00, Cl=8.84, N=17.41, S=7.98.

2-chloro-5-methoxy-3-{[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino}naphthalene-1,4-dione (10). Yield 58 %, mp = 441 K. IR (KBr), cm^{-1}: 3205, 3090 (NH), 1700, 1675 (C=O), 1660, 1590 (NH), 1455 (OCH$_3$), 1415 (C=S), 710 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7.80-7.70 (m, 2H, Ar-H); 7.62 (d, 1H, J=1.8 Hz, CH);7.43 (d, 1H, J=7.8 Hz, Ar-H); 6.98 (s, 2H, NH$_2$); 6.80 (d, 1H, J=1.8 Hz, CH); 3.96 (s, 3H, OCH$_3$); 2.19 (s, 3H, CH$_3$). ^{13}C NMR (DMSO) δ: 13.3 (CH$_3$), 56.4 (OCH$_3$), 107.1 (C), 116.1 (CH), 117.7 (CH), 118.8 (C), 119.8 (CH), 122.2 (C), 130.6 (C), 134.2 (C), 135.1 (CH), 139.1 (C), 140.0 (C), 142.6 (CH), 159.2 (C), 167.4 (C), 173.0 (CO), 173.5 (CO). LC-MS(*m*/*z*): calculated for $[C_{18}H_{13}ClN_4O_4S + H]^+$ 417.83, observed 417.8. Calcd. for ($C_{18}H_{13}ClN_4O_4S$), %: C=51.86, H=3.14, Cl=8.51, N=13.44, S=7.69. Found, %: C=51.84, H=3.15, Cl=8.49, N=13.42, S=7.70.

2-chloro-5-methoxy-3-{[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino}naphthalene-1,4-dione (12). Yield 62 %, mp = 438 K. IR (KBr), cm^{-1}: 3205, 3090 (NH), 1705, 1680 (C=O), 1653, 1596 (NH), 1475 (OCH$_3$), 1410 (C=S), 720 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7.77-7.72 (m, 2H, Ar-H); 7.70 (d, 1H, J=2.4 Hz, CH);7.43 (d, 1H, J=7.8 Hz, Ar-H); 7.02 (s, 2H, NH$_2$); 6.78 (d, 1H, J=2.4 Hz, CH); 3.96 (s, 3H, OCH$_3$); 2.32 (s, 3H, CH$_3$). ^{13}C NMR (DMSO) δ: 12.5 (CH3), 56.4 (OCH$_3$), 106.6 (C), 110.5 (C), 112.2 (CH), 117.7 (CH), 118.8 (C), 119.8 (CH), 130.6 (C), 131.3 (C), 135.1 (CH), 140.5 (CH), 147.0 (C), 155.7 (C), 159.2 (C), 167.1 (C), 173.0 (CO), 173.7 (CO). LC-MS(*m*/*z*): calculated for $[C_{18}H_{13}ClN_4O_4S + H]^+$ 417.83, observed 417.8. Calcd. for ($C_{18}H_{13}ClN_4O_4S$), %: C=51.86, H=3.14, Cl=8.51, N=13.44, S=7.69. Found, %: C=51.84, H=3.15, Cl=8.49, N=13.42, S=7.70.

3-chloro-2-{[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazoles-4-yl] amino} -5-nitro-naphthalene-1,4-dione (22). Yield 67 %, mp = 445 K. IR (KBr), cm^{-1}: 3225, 3085 (NH), 1745, 1690 (C=O), 1654, 1591 (NH), 1531, 1348 (NO$_2$), 1445 (C=S), 720 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 9.46 (s, 1H, NH); 8.81 (s, 1H, NH); 8.17 (dd, 1H, J_1=7.5, J_2=1.4 Hz, Ar-H); 7.77 (dd, J_1=7.5, J_2=1.4 Hz, 1H, Ar-H); 7.70 (d, 1H, J=2.4 Hz, CH); 7.52 (t, 1H, J=7.5, Hz, Ar-H); 6.78 (d, 1H, J=2.4 Hz, CH); 2.32 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 13.3 (CH_3), 105.6 (C), 116.1 (CH), 122.2 (C), 122.6 (C), 129.4 (CH), 129.9 (CH), 132.8 (C), 133.4 (CH), 134.2 (C), 138.7 (C), 139.1 (C), 142.6 (CH), 148.5 (C), 167.2 (C), 171.3 (CO), 177.7 (CO). LC-MS(m/z): calculated for $[C_{17}H_{10}ClN_5O_5S + H]^+$ 432.80, observed 432.8. Calcd. for ($C_{17}H_{10}ClN_5O_5S$), %: C=47.29, H=2.33, Cl=8.21, N=16.22, S=7.43. Found, %: C=47.30, H=2.32, Cl=8.19, N=16.21, S=7.45.

3-chloro-2-{[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazoles-4-yl]amino}-5-nitro-naphthalene-1,4-dione (24). Yield 55 %, mp = 428 K. IR (KBr), cm^{-1}: 3210, 3090 (NH), 1710, 1670 (C=O), 1649, 1597 (NH), 1512, 1323 (NO_2), 1465 (C=S), 725 (C-Cl). ^1H NMR (300 MHz, DMSO-d6) δ, ppm: 9.76 (s, 1H, NH); 8.81 (s, 1H, NH); 8.17 (dd, 1H, J_1=7.5, J_2=1.4 Hz, Ar-H); 7.77 (dd, 1H, J_1=7.5, J_2=1.4 Hz, Ar-H); 7.62 (d, 1H, J=1.8 Hz, CH); 7.52 (t, 1H, J=7.5, Hz, Ar-H); 6.80 (d, 1H, J=1.8 Hz, CH); 2.19 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.5 (CH_3), 105.1 (C), 110.5 (C), 112.2 (CH), 122.6 (C), 129.4 (CH), 129.9 (CH), 131.3 (C),132.8 (C), 133.4 (CH), 140.5 (CH), 148.5 (C), 155.7 (C), 167.0 (C), 171.3 (CO), 178.0 (CO). LC-MS(m/z): calculated for $[C_{17}H_{10}ClN_5O_5S + H]^+$ 432.80, observed 432.8. Calcd. for ($C_{17}H_{10}ClN_5O_5S$), %: C=47.29, H=2.33, Cl=8.21, N=16.22, S=7.43. Found, %: C=47.32, H=2.34, Cl=8.21, N=16.23, S=7.44.

2.2. General Procedure for the Synthesis of Heterocyclic Derivatives of 1,4-Quinones. Path B

5-amino-3-{[4-amino-5-(2-methylfuran-3-yl)-4H-1,2,4-triazole-3-yl]sulfanyl}-2-chloro-naphthalene-1,4-dione (7)

0.51 g (0.0026 mol) of 4-amino-5-(2-methylfuran)-4H-1,2,4-triazoles-3-thiols **5a** and an equivalent amount of K_2CO_3 were added to 0.59 g (0.0026 mol) of compound **1** in 10 ml of ethanol. The reaction mass was heated to 403–413 K and stirred for 4 h (the reaction was monitored by TLC analysis). The precipitate was filtered off and recrystallized in dimethylformamide (DMF)/ethanol (EtOH). Yield 57 %, mp = 446 K. IR (KBr), cm^{-1}: 3490, 3390, 3290 (NH_2), 1720, 1680 (C=O), 720 (C-Cl), 655 (C-S). ^1H NMR (300 MHz, DMSO-d6) δ, ppm: 8.81 (bs, 2H, NH_2); 7.69 (dd, 1H, J_1=7.5, J_2=1.3 Hz, Ar-H); 7.51 (t, J=7.5 Hz, 1H, Ar-H); 7.51 (d, 1H, J=2.4 Hz, CH); 7.26 (dd, 1H, J_1=7.8, J_2=1.3 Hz, Ar-H); 7.14 (d, 1H, J=2.4 Hz, CH); 7.05 (s, 2H, NH_2); 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 11.3 (CH_3), 105.0 (C), 116.0 (CH), 116.3 (CH), 120.2 (CH), 124.0 (C), 133.5 (C), 134.3 (C), 136.8 (CH), 140.3 (C), 142.7 (CH), 143.2 (C), 147.0 (C), 151.9 (C), 153.2 (C), 175.1 (CO), 180.0 (CO). LC-MS(m/z): calculated for $[C_{17}H_{12}ClN_5O_3S + H]^+$ 402.82, observed 402.8. Calcd. for ($C_{17}H_{12}ClN_5O_3S$), %: C=50.81, H=3.01, Cl=8.82, N=17.43, S=7.98. Found, %: C=50.83, H=2.99, Cl=8.83, N=17.42, S=8.00.

By the same method there were obtained:

5-amino-3-{[4-amino-5-(3-methylfuran-2-yl)-4H-1,2,4-triazole-3-yl]sulfanyl}-2-chloro-naphthalene-1,4-dione (9). Yield 65 %, mp = 475 K. IR (KBr), cm^{-1}: 3525, 3390, 3295 (NH_2), 1740, 1680 (C=O), 730 (C-Cl), 595 (C-S). ^1H NMR (300 MHz, DMSO-d6) δ, ppm: 8.81 (bs, 2H, NH_2); 7.69 (dd, 1H, J_1=7.5, J_2=1.3 Hz, Ar-H); 7.51 (t, J=7.5 Hz, 1H, Ar-H); 7.50 (d, 1H, J=2.4 Hz, CH); 7.26 (dd, 1H, J_1=7.8, J_2=1.3 Hz, Ar-H); 7.17 (d, 1H, J=2.4 Hz, CH); 7.09 (s, 2H, NH_2); 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.6 (CH3), 105.0 (C), 109.3 (C), 112.2 (CH), 116.0 (CH), 120.2 (CH), 129.0 (C), 133.5 (C), 134.3 (C), 136.8 (CH), 142.3 (CH), 147.7 (C), 150.9 (C), 152.2 (C), 153.2 (C), 175.1 (CO), 180.0 (CO). LC-MS(m/z): calculated for $[C_{17}H_{12}ClN_5O_3S + H]^+$ 402.82, observed 402.8. Calcd. for ($C_{17}H_{12}ClN_5O_3S$), %: C=50.81, H=3.01, Cl=8.82, N=17.43, S=7.98. Found, %: C=50.82, H=3.00, Cl=8.82, N=17.44, S=7.99.

3-{[4-amino-5-(3-methylfuran-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-2-chloro-5-methoxynaphthalene-1,4-dione (11). Yield 65 %, mp = 443 K. IR (KBr), cm^{-1}: 3495, 3305 (NH_2), 1700, 1675 (C=O), 1460 (OCH_3), 710 (C-Cl) , 580 (C-S). ^1H NMR (300 MHz, DMSO-d6) δ, ppm: 7.89 (d, 1H, J=7.8 Hz, Ar-H); 7.79 (d, 1H, J=1.5 Hz, CH); 7.74-7.45 (m, 2H, Ar-H); 6.69 (d, 1H, J=1.5 Hz, CH); 6.34 (s, 2H, NH_2); 3.98 (s, 3H, OCH_3); 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 11.3 (CH_3), 56.5 (OCH_3), 110.0 (C), 110.5 (C), 112.2 (CH), 116.3 (C), 118.4 (CH), 120.2 (CH), 124.0 (C), 131.8 (C), 134.7 (C), 135.3 (CH), 140.3 (C), 142.7 (CH), 147.0 (C), 152.0 (C), 161.8 (C), 175.3 (CO), 176.0 (CO). LC-MS(m/z): calculated for $[C_{18}H_{13}ClN_4O_4S + H]^+$ 417.83, observed 417.8. Calcd. for ($C_{18}H_{13}ClN_4O_4S$), %: C=51.86, H=3.14, Cl=8.51, N=13.44, S=7.69. Found, %: C=51.84, H=3.15, Cl=8.49, N=13.42, S=7.70.

3-{[4-amino-5-(2-methylfuran-3-yl)-4H-1,2,4-triazole-3-yl]sulfanyl}-2-chloro-5-methoxynaphthalene-1,4-dione (13). Yield 75 %, mp = 451 K. IR (KBr), cm^{-1}: 3480, 3305 (NH_2), 1700, 1675 (C=O), 1523, 1335 (NO_2), 710 (C-Cl), 678 (C-S). ^1H NMR (300 MHz, DMSO-d6) δ, ppm: 8.37-8.13 (m, 2H, Ar-H); 7.57 (t, 1H, J=7.5 Hz, Ar-H); 7.51 (d, 1H, J=2.1 Hz, CH); 7.17 (d, 1H, J=2.1 Hz, CH); 7.14 (s, 2H, NH_2); 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 11.3 (CH_3), 116.3 (CH), 123.9 (C), 124.2 (C), 128.6 (C), 130.2 (CH), 131.0 (C), 131.4 (CH), 133.5 (CH), 133.9 (C), 140.3 (C), 142.7 (CH), 147.0 (C), 150.0 (C), 151.7 (C), 173.6 (CO), 177.4 (CO). LC-MS(m/z): calculated for $[C_{17}H_{10}ClN_5O_5S + H]^+$ 417.83, observed 417.8. Calcd. for ($C_{17}H_{10}ClN_5O_5S$), %: C=47.29, H=2.33, Cl=8.21, N=16.22, S=7.43. Found, %: C=47.30, H=2.31, Cl=8.20, N=16.20, S=7.42.

2-{[4-amino-5-(2-methylfuran-3-yl)-4H-1,2,4-triazole-3-yl]sulfanyl}-3-chloro-5-nitronaphthalene-1,4-dione (23). Yield 77 %, mp = 448–449 K. IR (KBr), cm^{-1}: 3480, 3300 (NH_2), 1730, 1690 (C=O), 1520, 1330 (NO_2), 71 (C-Cl), 590 (C-S). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8.45-8.18 (m, 2H, Ar-H); 7.72 (d, 1H, J=2.4 Hz, CH); 6.74 (d, 1H, J=2.4 Hz, CH); 7.57 (t, 1H, J=7.5 Hz, Ar-H); 6.74 (s, 2H, NH_2); 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 13.5 (CH_3), 109.13 (C), 112.4 (CH), 124.2 (C), 128.6 (C), 130.3 (CH), 131.4 (C), 131.5 (CH), 133.3 (CH), 133.5 (C), 142.3 (CH), 147.7 (C), 150.0 (C), 150.8 (C), 152.2 (C), 173.6 (CO), 177.4 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{10}ClN_5O_5S + H]^+$ 432.80, observed 432.8. Calcd. for ($C_{17}H_{10}ClN_5O_5S$), %: C=47.29, H=2.33, Cl=8.21, N=16.22, S=7.43. Found, %: C=47.31, H=2.32, Cl=8.21, N=16.20, S=7.44.

2-{[4-amino-5-(3-methyl furan-2-yl) -4H-1,2,4-triazole-3-yl]sulfanyl}-3-chloro-5-nitronaphthalene-1,4-dione (25). Yield 83 %, mp = 462 K. IR (KBr), cm^{-1}: 3475, 3290 (NH_2), 1725, 1685 (C=O), 1517, 1328 (NO_2), 715 (C-Cl), 592 (C-S). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8.39-8.15 (m, 2H, Ar-H); 7.79 (d, 1H, J=1.5 Hz, CH); 7.57 (t, 1H, J=7.5 Hz, Ar-H); 6.89 (d, 1H, J=1.5 Hz, CH); 6.74 (s, 2H, NH_2); 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.6 (CH_3), 109.3 (C), 112.2 (CH), 124.2 (C), 128.6 (C), 130.1 (CH), 131.1 (C), 131.5 (CH), 133.3 (CH), 133.8 (C), 142.3 (CH), 147.7 (C), 150.0 (C), 150.8 (C), 152.2 (C), 173.6 (CO), 177.4 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{10}ClN_5O_5S + H]^+$ 432.80, observed 432.8. Calcd. for ($C_{17}H_{10}ClN_5O_5S$), %: C=47.29, H=2.33, Cl=8.21, N=16.22, S=7.43. Found, %: C=47.31, H=2.32, Cl=8.21, N=16.20, S=7.44.

Obtained mixture of regioisomers (**14, 15; 16, 17; 18, 19; 20, 21**) was separated by a preparative thin layer chromatography on glass plates Stratocrom SI 200mm×200mm×3mm. Plates with a uniform layer of silica gel were dried in the oven at the temperature of 383 K, then cooled. The samples were dissolved in DMF and applied on a thin tube with a diameter of 1 mm, plate dried. The dried plate was placed in a chamber for chromatography; eluent methanol-toluene (2:1) was used. After separation of substances plates were dried. Then individual separated bands were removed by a scalpel. Obtained mixture was placed in a miniature silica gel column, which was eluted with methanol-chloroform (1:2) solvent. The resulting eluate was evaporated under vacuum; the residue was recrystallized in dimethylformamide (DMF)/ethanol (EtOH).

3-chloro-5-hydroxy-2-{[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazole-4-yl]amino} naphthalene-1,4-dione (14). Yield 48 %, mp = 468 K. IR (KBr), cm^{-1}: 3510 (OH), 3205, 3095 (NH), 1735, 1675 (C=O), 1655, 1592 (NH), 1455 (C=S), 980 (OH), 725 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10.50 (s, 1H, OH); 8.81 (s, 1H, NH); 8.43 (s, 1H, NH); 7.84 (t, 1H, J=7.1 Hz, Ar-H); 7.73 (dd, J_1=7.1, J_2=2.0 Hz, 1H, Ar-H); 7.69 (d, 1H, J=2.4 Hz, CH); 7.42 (dd, 1H, J_1=7.7, J_2=2.0 Hz, Ar-H); 6.78 (d, 1H, J=2.4 Hz, CH); 2.32 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 13.3 (CH_3), 108.9 (C), 111.9 (C), 116.1 (CH), 117.3 (CH), 122.2 (C), 122.9 (CH), 132.3 (C), 134.2 (C), 137.0 (CH), 139.1 (C), 142.6 (CH), 149.9 (C), 161.5 (C), 167.2 (C), 174.3 (CO), 176.9 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 432.80, observed 432.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96. Found, %: C=50.70, H=2.77, Cl=8.79, N=13.91, S=7.95.

2-chloro-5-hydroxy-3-{[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino} naphthalene-1,4-dione (15). Yield 10 %, mp = 451 K. IR (KBr), cm^{-1}: 3496 (OH), 3200, 3090 (NH), 1720, 1675 (C=O), 1643, 1590 (NH), 1460 (C=S), 976 (OH), 710 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7.77 (dd, 1H, J_1=7.1, J_2=2.0 Hz, Ar-H); 7.72 (t, 1H, J= 7.1 Hz, Ar-H); 7.67 (d, 1H, J=1.8 Hz, CH); 7.20 (dd, 1H, J_1=7.7, J_2=2,0 Hz, Ar-H); 6.80 (d, 1H, J=1.8 Hz, CH); 2.19 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 13.3 (CH3), 107.9 (C), 112.2 (C), 116.1 (CH), 117.5 (CH), 122.2 (C), 123.3 (CH), 130.0 (C), 134.2 (C), 136.8 (CH), 139.1 (C), 141.0 (C), 142.6 (CH), 158.5 (C), 167.4 (C), 173.1 (CO), 177.7 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.81, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96. Found, %: C=50.70, H=2.77, Cl=8.79, N=13.91, S=7.95.

3-chloro-5-hydroxy-2-{[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino} naphthalene-1,4-dione (16).Yield 52 %, mp = 425 K. IR (KBr), cm^{-1}: 3487 (OH), 3210, 3090 (NH), 1730, 1690 (C=O), 1652, 1595 (NH), 1450 (C=S), 987 (OH), 705 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10.50 (s, 1H, OH); 8.81 (s, 1H, NH); 8.43 (s, 1H, NH); 7.84 (t, 1H, J=7.1 Hz, Ar-H); 7.72 (dd, 1H, J_1=7.1, J_2=2.0 Hz, Ar-H); 7.62 (d, 1H, J=1.8 Hz, CH); 7.27 (dd, 1H, J_1=7.7, J_2=2.0 Hz, Ar-H); 6.81 (d, 1H, J=1.8 Hz, CH); 2.19 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.5 (CH_3), 109.8 (C), 110.5 (C), 111.9 (C), 112.2 (CH), 117.3 (C), 122.9 (CH), 131.3 (C), 132.3 (C), 137.0 (CH), 140.5 (CH), 147.2 (C), 155.7 (C), 161.5 (C), 167.0 (C), 174.5 (CO), 176.9 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.81, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96.Found, %: C=50.70, H=2.76, Cl=8.79, N=13.90, S=7.97.

2-chloro-5-hydroxy-3-{[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino} naphthalene-1,4-dione (17). Yield 12 %, mp = 451 K. IR (KBr), cm^{-1}: 3495 (OH), 3210, 3100 (NH), 1725, 1680 (C=O), 1660, 1593 (NH), 1465 (C=S), 995 (OH), 710 (C-

Cl). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7.82 (t, 1H, J=7.2 Hz, Ar-H); 7.75 (d, 1H, J=2.4 Hz, CH); 7.70 (dd, 1H, J_1=7.1, J_2=2.0 Hz, Ar-H); 7.19 (dd, 1H, J_1=7.7, J_2=2.0 Hz, Ar-H); 6.78 (d, 1H, J=2.4 Hz, CH); 2.32 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.5 (CH3), 107.4 (C), 110.5 (C), 112.0 (C), 112.2 (CH), 117.5 (CH), 123.3 (CH), 130.0 (C), 131.3 (C), 136.8 (CH), 140.5 (CH), 146.8 (C), 155.7 (C), 158.5 (C), 167.1 (C), 173.1 (CO), 178.0 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.81, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96.Found, %: C=50.70, H=2.76, Cl=8.79, N=13.90, S=7.97.

2-{[4-amino-5-(2-methylfuran-3-yl)-4H-1,2,4-triazole-3-yl]sulfanyl}-3-chloro-5-hydroxy-naphthalene-1,4-dione (18). Yield 55 %, mp = 457 K. IR (KBr), cm^{-1}: 3515, 3310 (NH_2), 3475 (OH), 1735, 1670 (C=O), 975 (OH), 715 (C-Cl) , 595 (C-S). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10.50 (bs, 1H, OH); 7.72 (t, 1H, J=7.5 Hz, Ar-H); 7.65 (dd, 1H, J_1=7.5, J_2=1.3 Hz, Ar-H); 7.50 (d, 1H, J=2.1 Hz, CH); 7.35 (dd, 1H, J_1=7.8, J_2=1.3 Hz, Ar-H); 7.17 (d, 1H, J=2.1 Hz, CH); 7.06 (s, 2H, NH_2); 2.34 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 11.3 (CH_3), 112.3 (C), 116.3 (CH), 118.9 (CH), 122.9 (CH), 124.0 (C), 131.5 (C), 132.5 (C), 135.5 (C), 137.1 (CH), 140.3 (C), 146.8 (C), 142.7 (CH), 147.0 (C), 151.7 (C), 162.6 (C), 178.9 (CO), 179.2 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.8116, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96. Found, %: C=50.69, H=2.77, Cl=8.81, N=13.92, S=7.95.

3-{[4-amino-5-(3-methylfuran-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-2-chloro-5-hydroxynaphthalene-1,4-dione (19). Yield 11 %, mp = 438 K. IR (KBr), cm^{-1}: 3512, 3205 (NH_2), 3480 (OH), 1730, 1675 (C=O), 980 (OH), 710 (C-Cl), 653 (C-S). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7.82 (dd, 1H, J_1=7.8, J_2=1.3 Hz, Ar-H); 7.79 (d, 1H, J=1.5 Hz, CH); 7.66 (t, 1H, J=7.5 Hz, Ar-H); 7.22 (dd, 1H, J_1=7.5, J_2=1.3 Hz, Ar-H); 7.05 (s, 2H, NH_2); 6.70 (d, 1H, J=1.5 Hz, CH); 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 11.3 (CH_3), 113.5 (C), 116.3 (CH), 118.0 (CH), 123.9 (CH), 124.3 (C), 131.1 (C), 132.5 (C), 135.5 (C), 137.6 (CH), 140.3 (C), 142.7 (CH), 147.0 (C), 151.9 (C), 161.8 (C), 175.4 (CO), 182.9 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.81, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96. Found, %: C=50.69, H=2.77, Cl=8.81, N=13.92, S=7.95.

2-{[4-amino-5-(3-methylfuran-2-yl)-4H-1,2,4-triazole-3-yl]sulfanyl}-3-chloro-5-hydroxynaphthalene-1,4-dione (20). Yield 61 %, mp = 471 K. IR (KBr), cm^{-1}: 3489, 3220 (NH_2), 3454 (OH), 1735, 1695 (C=O), 994 (OH), 705 (C-Cl), 671 (C-S). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10.50 (*s*, 1H, OH); 7.85 (t, 1H, J=7.5 Hz, Ar-H); 7.79 (d, 1H, J=1,5 Hz, CH); 7.57-7.20 (m, 2H, Ar-H); 7.11 (s, 2H, NH_2); 6.70 (d, H, J=1.5 Hz, 1CH); 2.23 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.6 (CH_3), 109.3 (C), 112.0 (CH), 112.3 (C), 118.9 (CH), 122.9 (C), 131.5 (C), 132.5 (C), 135.0 (C), 137.1 (CH), 142.3 (CH), 147.7 (C), 150.8 (C), 152.2 (C), 162.6 (C), 178.9 (CO), 179.2 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.81, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96. Found, %: C=50.68, H=2.74, Cl=8.80, N=13.92, S=7.96.

3-{[4-amino-5-(2-methylfuran-3-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-2-chloro-5-hydroxynaphthalene-1,4-dione (21). Yield 15 %, mp = 447 K. IR (KBr), cm^{-1}: 3505, 3205 (NH_2), 3485 (OH), 1740, 1675 (C=O), 985 (OH), 710 (C-Cl), 658 (C-S). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7.83-7.77 (m, 1H, Ar-H); 7.50 (d, 1H, J=2.1 Hz, CH); 7.49-7.22 (m, 2H, Ar-H); 7.17 (d, 1H, J=2.1 Hz, CH); 6.92 (s, 2H, NH_2); 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 12.6 (CH_3), 109.3 (C), 112.2 (CH), 113.5 (C), 118.0 (CH), 124.3 (CH), 131.1 (C), 131.9 (C), 135.5 (C), 137.6 (CH), 142.3 (CH), 147.7 (C), 151.0 (C), 152.2 (C), 161.8 (C), 175.4 (CO), 182.9 (CO). LC-MS(*m*/*z*): calculated for $[C_{17}H_{11}ClN_4O_4S + H]^+$ 403.81, observed 403.8. Calcd. for ($C_{17}H_{11}ClN_4O_4S$), %: C=50.69, H=2.75, Cl=8.80, N=13.91, S=7.96. Found, %: C=50.69, H=2.77, Cl=8.81, N=13.92, S=7.95.

3. Results and Discussion

3.1. Calculated Fukui Atomic Indices

Based on the results of our previous studies, where optimization of the reaction conditions has been described and optimum regimes of interactions were determined, we conducted a series of synthesis of new heterocyclic derivatives of 1,4-naphthoquinone.

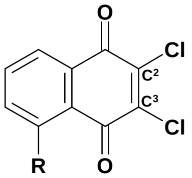
As naphthoquinones with the substituent in the 5th position, namely with an electron donor 5-amino-2,3-dichloro-1,4-naphthoquinone **1**, 5-hydroxy-2,3-dichloro-1,4-naphthoquinone **2**, 5-methoxy-2,3-dichloro-1,4-naphthoquinone **3** were used, and with an electron acceptor – 5-nitro-2,3-dichloro-1,4-naphthoquinone **4** was chosen.

To predict and explain the regioselectivity of nucleophilic substitution reaction, we calculated Fukui atomic indices [9, 13-15] of reacting atoms. Investigated compounds were calculated using Jaguar software [16] on B3LYP/6-31G(d,p) level in PBF solvent model (ethanol). Local Fukui indices are helpful in searching differences in the reactivity of some atoms in the ranks of the molecules and make possible to predict the regioselectivity of nucleophilic substitution reactions in our case. The calculated indices of quinones reacting atoms are shown in Table 1.

Table 1

Atomic Fukui indices of C^2 and C^3 atoms in 5-R-2,3-dichloro-1,4-naphthoquinones 1, 2, 3, 4

R	H		NH_2		NO_2		OH		OCH_3	
Atom number	C^3	C^2	C^3	C^2	C^3	C^2	C^3	C^2	C^3	C^2
f_NN HOMO	0.12	0.12	0.00	0.01	0.18	0.18	0.00	0.01	0.00	0.00
f_NN LUMO	0.12	0.12	0.13	0.10	0.10	0.11	0.11	0.11	0.12	0.10



Since C^2 and C^3 atoms in the quinone molecule show electrophilic properties, we are interested in comparing and analyzing the values of f_NN LUMO, which high positive values indicate more electrophilic properties of reacting atoms compared with other compounds. Based on the obtained data we can assume that more electrophilic centers of molecule 5-R-2,3-dichloro-1,4-naphthoquinone must react with nucleophilic atoms of 4-amino-5-heteryl-4H-1,2,4–triazole-3-thiols **5a, 5b** faster.

3.2. Synthesis of Heterocyclic Derivatives of 1,4-Quinones

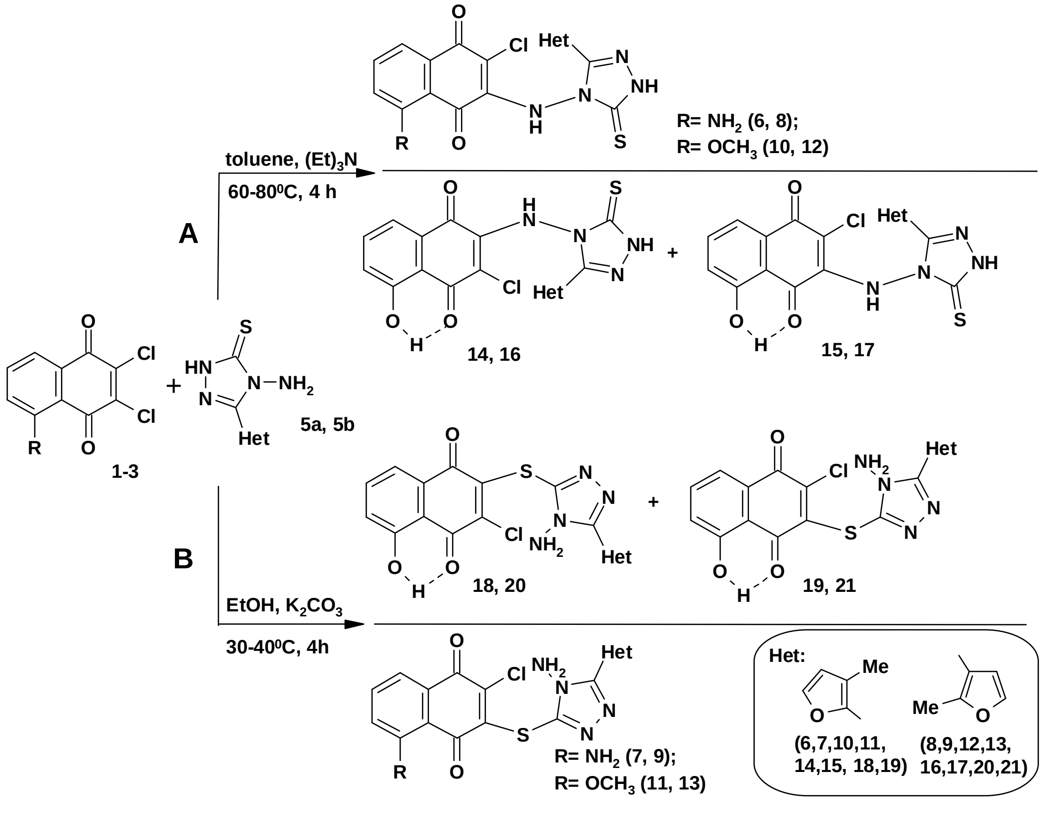
Interaction of 5-amino-2,3-dichloro-1,4-naphthoquinone **1**, 5-hydroxy-2,3-dichloro-1,4-naphthoquinone **2** and 5-methoxy-2,3-dichloro-1,4-naphthoquinone **3** with 4-amino-5-heteryl-4H-1,2,4-triazole-3-thiols **5a**, **5b** was held by two alternative paths **A** and **B** (Scheme 1). As a result of *N*-nucleophilic substitution of chlorine atom **6, 8, 10, 12, 14-17** derivatives were formed. The reaction was carried out in toluene in the presence of Et_3N. The reaction mass was heated and maintained at 353 K for 4 h. The precipitate was filtered and recrystallized (Path **A**). While carrying out the reaction in ethanol in the presence of an equivalent amount of K_2CO_3 we obtained products of *S*-nucleophilic substitution **7, 9, 11, 13, 18-21**. The reaction mass was heated and maintained at 313 K for 2 h and the precipitate was filtered and recrystallized (Path **B**).

During the analysis of chromatographic data of the reaction products by TLC it was established that the synthesis proceeds regiospecifically with the formation of high yields of compounds **6-13** (57–71 %). Guided by the analysis of reactivity it can be assumed that the isolated compounds **6-13** are products of *S*- and *N*- nucleophilic substitution by chlorine atom in C^3 position of naphthoquinoid system. So, in comparing values of LUMO f_NN of compound **1** it was established that (LUMO f_NN_C^3 0.13) > (LUMO f_NN_C^2 0.10), which indicates about more electrophilic properties of C^3 reactive atom. A similar pattern is evident for compound **3** (LUMO f_NN_C^3 0.12) > (LUMO f_NN_C^2 0.10). Analysis of the reaction of 5-hydroxy-2,3-dichloro-1,4-naphthoquinone **2** showed that the interaction takes place with the formation of two products towards path **A** and two products on the interaction way **B**. In comparing the LUMO f_NN values of compound **2** it was found that (LUMO f_NN_C^3 0.11) = (LUMO f_NN_C^2 0.11). It shows the equivalent electrophilic properties of C^2 and C^3 reactive atoms. Analyzing the reaction products **14-21** it was determined that the process takes place with the formation of two regioisomers that were identified in almost equal amounts with a dominant quantity of the product nucleophilic substituted by C^2 carbon atom. Thus, yields of products **14, 16, 18, 20** (F1) were in the range of 48–61 %, and products **15, 17, 19, 21** (F2) in the range of 10–15 %.

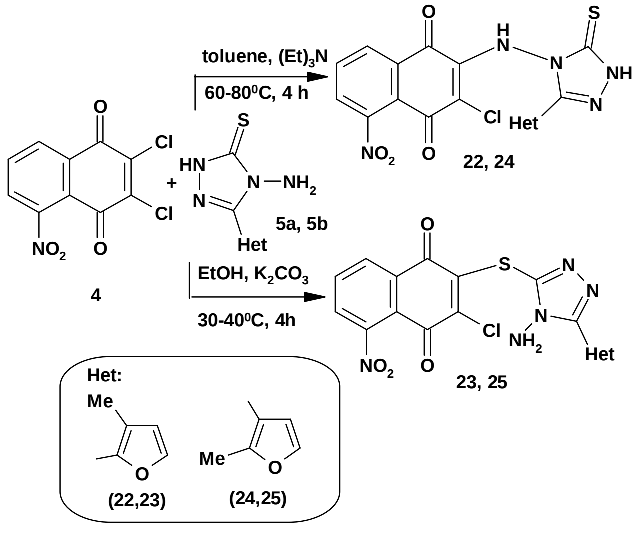
The reaction of 5-nitro-2,3-dichloro-1,4-naphthoquinone **4** with heterylaminothiotriazoles **5a, 5b** was subordinated by described above rules for the electron acceptor influence of substituents, as the result *N*- and *S*-substituted products of chlorine atom at C^2 carbon position were obtained (Scheme 2).

Analyzing the reaction products it was found that synthesis takes place exclusively regiospecifically to form products of nucleophilic substitution **22-25**. Comparing the 5-nitro-2,3-dichloro-1,4-naphthoquinone **4** LUMO f_NN it was found that (LUMO f_NN_C^2 0.11) > > (LUMO f_NN_C^3 0.10). This indicates more electrophilic properties of C^2 reactive atom. Based on this, we assume that the isolated products **22-25** are products of nucleophilic attack on the C^2 carbon atom of the quinoid system.

On IR spectra of compounds **6, 8, 10, 12, 14-17, 22, 24** are clearly prescribed signals that characterized by fluctuations of νNH-group in the range of 3250–3050 cm^{-1} and also characterized fluctuations of νCO groups at 1730–1670 cm^{-1}. Moreover, for compounds there are characteristic fluctuations – intense absorption bands that are prescribed at 1660–1590 cm^{-1} ("amide-II"), describing the mixed valence and deformation vibrations of NH and CN bonds. In the IR spectra of compounds **6, 8, 10, 12, 14-17, 22, 24** there are present bands of fluctuations, characteristic for thiocarbonyl groups (C=S), which are prescribed in the diapason of 1465–1410 cm^{-1}.



Scheme 1. Preparation of 1,4-naphthoquinone derivatives **6-21**



Scheme 2. Preparation of 1,4-naphthoquinone derivatives **22-25**

As for the IR spectra of compounds **7, 9, 11, 13, 18-21, 23, 25**, they are characterized by intense bands characteristic for asymmetric and symmetric stretching vibrations of NH_2-group at 3530–3275 cm^{-1}; fluctuation *ν*CO groups are prescribed at 1734–1631 cm^{-1}. In addition, compounds are characterized by low-intensity vibrations strips of *ν*C=C bond at 1643–1465 cm^{-1}. In the IR spectra of compounds **7, 9, 11, 13, 18-21, 23, 25** fluctuation bands are absent, characteristic for thiocarbonyl groups and fluctuation band characteristic for C-S group, which are written at 690–570 cm^{-1}, are attended. As for the IR spectra of compounds **22-25**, they are characterized by symmetric and asymmetric stretching vibrations of the group $\nu(NO_2)$ at 1532–1505 and 1354–1309 cm^{-1}.

For compounds **6-9** characteristic signals corresponding fluctuations of NH_2-group of naphthoquinoid fragment are observed. From the nature of the signal it can be seen the possibility of establishing a hydrogen bond, due to the presence in the IR spectrum bands bound and free stretching vibration ν(NH) at 3330–3290 cm^{-1}, respectively, and the disappearance of bands of deformation vibrations δ(NH) at 1530 cm^{-1}. The band of stretching vibrations ν(C=O) of the carbonyl group at 1690–1660 cm^{-1} shifts to the range of higher frequencies and is shown at 1740–1720 cm^{-1}.

In turn, for compounds **14-21** IR spectra are characterized by the existence of bands associated with stretching vibration of νOH at 3510–3430 cm^{-1} and unplaned deformation vibrations (OH...O)-fragment at 995–955 cm^{-1}. The band of stretching vibrations ν(C=O) of the carbonyl group shifts at high frequencies and is shown at 1740–1720 cm^{-1}.

Analysis of IR spectra allowed to make a foregone conclusion that the direction of the reaction of *N*-nucleophilic products and, accordingly, *S*-nucleophilic substitution can be monitored by conditions of synthesis, and the main factor is the choice of the solvent.

3.3. NMR Characterization of Obtained Products

The difficult challenge was to attribute isolated products to corresponding structural formulas by their ^{1}H NMR spectra. For the purpose of attributing compounds to the relevant structures using their ^{1}H NMR spectra it was made their GIAO calculations for both possible forms of established products by GAUSSIAN 09 program package using B3LYP/6-311+G(2d,p)// 6-31G(d,p) level in PCM solvent model (DMSO).

The main differences between the calculated NMR spectra of forms $N_S\_C^2$ and $N_S\_C^3$ are changes in the shifts of H^6, H^7, H^8 proton signals of quinoid fragment aromatic nucleus, due to the influence of the substituent at C^2 or C^3 positions. The calculated and experimental spectral data of ^{1}H NMR for **14, 15, 18, 19** are shown in Table 2.

Position of the H^6 and H^8 protons signals in the relation to proton H^7 signal that is prescribed as triplet can be attributed to obtained spectra of isolated compounds F1 and F2 and to the calculated spectra of possible formed nucleophilic substitution at C^2 ($N_S\_C^2$) or C^3 ($N_S\_C^3$) carbon atom products.

Table 2

Calculated and experimental ^{1}H NMR spectral data of products 14, 15, 18, 19

Proton number	Chemical shift (DMSO), ppm			
	GIAO ^{1}H NMR		Obtained ^{1}H NMR	
	$N_S\_C^2$	$N_S\_C^3$	Form 1	Form 2
	N-derivatives			
6	7.62	7.63	7.42 (dd)	7.20 (dd)
7	7.89	8.10	7.84 (t)	7.72 (t)
8	7.83	8.12	7.73 (dd)	7.77 (dd)
	S-derivatives			
6	7.67	7.59	7.35 (dd)	7.22 (dd)
7	7.95	8.01	7.72 (t)	7.66 (t)
8	7.90	8.12	7.65 (dd)	7.82 (dd)

Table 3

Δδ Values, ppm, GIAO calculated/found for products 14, 15, 18, 19

Proton number	$\Delta\delta$, ppm, GIAO calculated/found from spectrum			
	$N_S\_C^2$	$N_S\_C^3$	$N_S\_C^2$	$N_S\_C^3$
	N-derivatives			
H_6–H_7	0.27	0.57	0.42	0.52
H_7–H_8	0.06	0.02	0.11	0.05
H_6–H_8	0.21	0.59	0.31	0.57
	S-derivatives			
H_6–H_7	0.28	0.42	0.37	0.44
H_7–H_8	0.05	0.11	0.07	0.16
H_6–H_8	0.23	0.53	0.30	0.50

Thus, the nature of the relative arrangement of proton signals of quinoid fragment aromatic nucleus for **14, 18** (F1) is responsible to calculated regioisomer $N_S\_C^2$ and is prescribed in spectrum in combination of signals t, H^7; dd, H^8; dd, H^6. In return for compounds **15, 19** (F2) location of signals on the spectrum dd, H^8; t, H^7; dd, H^6 corresponds to calculated regioisomer $N_S\_C^3$.

Comparison of the calculated values of the relative arrangement of the protons H_6, H^7, H_8 with experimental obtained data ($\Delta\delta$, ppm, GIAO calculated/found from the spectrum) allowed to confirm the unambiguous assignment to the appropriate structures of the obtained compounds in Table 3.

4. Conclusions

To predict and explain regioselectivity of investigated nucleophilic substitution reactions atomic Fukui indices of reacting atoms of investigated compounds were calculated using Jaguar software on B3LYP/6-31G(d,p) level in PBF solvent model (ethanol). It was established that the interaction of 5-amino-2,3-dichloro-1,4-naphthoquinone **1**, 5-hydroxy-2,3-dichloro-1,4-naphthoquinone **2** and 5-methoxy-2,3-dichloro-1,4-naphthoquinone **3** with 4-amino-5-heteryl-4H-1,2,4-triazoles-3-thiol **5a, 5b** was held by two alternative paths **A** and **B**. As a result of bimolecular nucleophilic substitution of chlorine atoms *N*-substituted products **6, 8, 10, 12, 14-17** were formed, unimolecular nucleophilic substitution *S*-substituted products **7, 9, 11, 123, 19-21** were also formed. GIAO DFT calculations of ^{1}H NMR spectra for obtained products both possible forms by GAUSSIAN 09 package using B3LYP/6-311+G(2d,p)//6-31G(d,p) level in PCM solvent model (DMSO) showed that the main differences between the calculated NMR spectra $N_S\_C^2$ and $N_S\_C^3$ forms are changing of proton H^6, H^7, H^8 signals shifts of quinoid fragment aromatic nucleus, due to the influence of the substituent at C^2 or C^3 positions. Comparison of obtained ^{1}H-NMR spectra with DFT calculated allow to unambiguously attribute obtained compounds to relevant structures. Experimentally, the influence of electron donor and electron acceptor substituent in the 5th position of 2,3-dichloro-1,4-naphthoquinone on regioselectivity of the nucleophilic substitution reaction was shown.

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ВЗАЄМОДІЯ 5-ЗАМІЩЕНИХ 1,4-НАФТОХІНОНІВ І АМІНОТІОТРИАЗОЛІВ: НАПРЯМИ РЕАКЦІЇ ТА РЕГІОСЕЛЕКТИВНІСТЬ

Анотація. *Проведено реакції нуклеофільного заміщення між 5-R-2,3-дихлоро-1,4-нафтохінонами і 4-аміно-5-гетерил-4Н-1,2,4-триазол-3-тіолами. Показано, що взаємодія може відбуватися за двома альтернативними напрямами, які регулюються за допомогою умов реакції. Проведено пошук відмінностей в реагуючих атомах досліджуваних молекул внаслідок порівняння розрахованих індексів Фукуї. Експериментально показано вплив електронодонорних та електроноакцепторних замісників у 5 положенні 2,3-дихлор-1,4-нафтохінону на регіоселективність перебігу реакції нуклеофільного заміщення. Порівняння отриманих спектрів* ^{1}*Н ЯМР з DFT розрахованими для обох можливих форм одержуваних продуктів дає можливість однозначно віднести синтезовані сполуки відповідним структурам. Синтезовані сполуки охарактеризовані за допомогою ІЧ,* ^{1}*Н ЯМР,* ^{13}*С ЯМР спектроскопії та елементного аналізу.*

Ключові слова: *1,4-нафтохінони, нуклеофільне заміщення, регіоселективність, індекси Фукуї.*