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Chemical Reaction of 5-Substituted 1,4-Naphthoquinones with Crotonaldehyde-N,N-Dimethylhydrazone and Investigation of Derived Compounds Antimicrobial Activity.

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ABSTRACT

A Diels-Alder reaction between 5-substituted 1,4-naphthoquinones and crotonaldehyde-N,N-dimethylhydrazone was carried out. The optimization of [4+2]–cycloaddition reaction conditions was held. The dependence of the substituent nature in 1,4-naphthoquinone 5th position on the Diels-Alder reaction regioselectivity was established determined . A number of 5-R-1,4-naphthoquinone tricarbocyclic derivatives were synthesized. Investigation of antimicrobial activity of the synthesized compounds was conducted.
Keywords: 5-R-1,4-naphthoquinones, cycloaddition, heterodienes, regioselectivity.

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INTRODUCTION

Synthesis of heterocompounds is important in terms of getting new biologically active substances. Such substances can be obtained from basic heterocyclic substrates and then modified. However, heterocyclic systems also can be synthesized by reacting of carbocyclic compound with acyclic heterodiene by Diels-Alder reaction.

Polyheterocyclic derivatives containing quinoid systems are proven to be biologically active compounds with a wide spectrum of pharmacological activity [1,2]. In particular, arylmethylidenethioxothiazolidone derivatives exhibit hypoglycemic properties, diuretic effect and have affinity to many enzyme systems [3]. Thus, the combination of these fragments with a number of 1,4-quinones derivatives can lead to obtaining new compounds that have selective affinity to many biological targets [4]. Using crotonaldehyde-N,N-dimethylhydrazone as diene is interesting because it allows to build a tricyclic quinoid systems containing pyridine ring. Compounds with such structure are known as antiprotozoal and antimicrobial agents [5].

MATERIALS AND METHODS

Reagents and equipment

All the chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by precoated aluminium silica gel 60F 254 thin layer plates procured from Merck (Germany). Melting points (m.p.) were determined using an SRS-EZMelt automated melting point instrument without correction. The ^{1}H-NMR spectra of the compounds were recorded in DMSO-d_6 with "Varian VXR" (300 MHz) NMR spectrometer and chemical shifts were expressed in δ (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).

Characterization of synthesized compounds

1-(Dimethylamino)-9-methoxy-4-methyl-1,4,4a,10a-tetrahydrobenzo[g]quinoline-5,10-dione (7)

Yield 53%; m.p. 163-164^{0}C ; Anal. calc for ($C_{17}H_{20}N_2O_3$), %: C=67.98, H=6.71, N=9.33, O=15.98; found: C=67.95, H=6.69, N=9.35. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,65 (t, J=8,14, 7,80, 1H, CH); 7,54 (d, J=7,80, 1H, CH); 7,42 (dd, J=8,14, 1,44, 1H, CH); 6,19 (d, J=8,75, 1H, CH); 4,57 (t, J=8,75, 5,70, 1H, CH); 3,95 (s, 3H, OCH_3); 3,68-3,65 (m, 1H, CH); 3,40-3,32 (m, 1H, CH); 2,86-2,73 (m, 1H, CH); 2,59 (s, 6H, $N(CH_3)_2$); 1,12 (dd, J=7,38, 4,47, 1H, CH_3).

1-(Dimethylamino)-9-methoxy-4-methyl-1,4-dihydrobenzo[g]quinoline-5,10-dione (8)

Yield 15%; m.p. 184-185^{0}C ; Anal. calc for ($C_{17}H_{18}N_2O_3$), %: C=68.44, H=6.08, N=9.39, O=16.09; found: C=68.45, H=6.10, N=9.36. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,77 (t, J=8,14, 7,13, 1H, CH); 7,69 (dd, J=7,13, 1,36, 1H, CH); 7,45 (dd, J=8,14, 1,36, 1H, CH); 6,33 (dd, J=7,80, 2,00, 1H, CH); 4,95 (dd, J=7,80, 5,10, 1H, CH); 3,99 (s, 3H, OCH_3); 3,95-3,91 (m, 1H, CH); 3,00 (s, 6H, $N(CH_3)_2$); 1,18 (d, J=6,60, 1H, CH_3).

1-(Dimethylamino)-4-methyl-5,10-dioxo-1,4,4a,5,10,10a-hexahydrobenzo[g]quinolin-9-yl acetate (9)

Yield 54%; m.p. 155-157^{0}C ; Anal. calc for ($C_{18}H_{20}N_2O_4$), %: C=65.84, H=6.14, N=8.53, O=19.49. found: C=65.86, H=6.11, N=8.57. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,72 (t, J=7,90, 7,80, 1H, CH); 7,66 (d, J=7,80, 1H, CH); 7,55 (dd, J=7,90, 1,44, 1H, CH); 6,19 (d, J=8,75, 1H, CH); 4,57 (t, J=8,75, 5,70, 1H, CH); 4,01-3,92 (m, 1H, CH); 3,79 (d, J=6,54, 1H, CH); 3,56-3,46 (m, 1H, CH); 2,59 (s, 6H, $N(CH_3)_2$); 2,44 (s, 3H, $OCOCH_3$); 1,13 (d, J=7,38, 1H, CH_3).

1-(Dimethylamino)-4-methyl-5,10-dioxo-1,4,5,10-tetrahydrobenzo[g]quinolin-9-yl acetate (10)

Yield 13%; m.p. 198-199^{0}C ; Anal. calc for ($C_{18}H_{18}N_2O_4$), %: C=66.25, H=5.56, N=8.58, O=19.61. found: C=66.28, H=5.52, N=8.55. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,80 (dd, J=7,13, 1,00, 1H, CH); 7,74 (t, J=7,90, 7,13, 1H,

CH); 7,58 (dd, J=7,90, 1,00, 1H, CH); 6,33 (dd, J=7,80, 2,00, 1H, CH); 4,95 (dd, J=7,80, 5,10, 1H, CH); 4,00-3,91 (m, 1H, CH); 3,00 (s, 6H, $N(CH_3)_2$); 2,44 (s, 3H, $OCOCH_3$); 1,18 (d, J=6,60, 1H, CH_3).

9-Methoxy-4-methyl-1,4-dihydrobenzo[g]quinoline-5,10-dione (11)

Yield 24%; m.p. 148-150^{0}C ; Anal. calc for ($C_{15}H_{13}NO_3$), %: C=70.58, H=5.13, N=5.49, O=18.80. found: C=70.45, H=5.07, N=5.47. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 9,62 (bs, 1H, NH); 7,77 (t, J=8,14, 7,13, 1H, CH); 7,71 (dd, J=7,13, 1,36, 1H, CH); 7,43 (dd, J=8,14, 1,36, 1H, CH); 6,22 (dd, J=7,80, 2,00, 1H, CH); 4,93 (dd, J=7,80, 5,10, 1H, CH); 3,96 (s, 3H, OCH_3); 3,76-3,67 (m, 1H, CH); 1,15 (d, J=6,60, 1H, CH_3).

4-Methyl-5,10-dioxo-1,4,5,10-tetrahydrobenzo[g]quinolin-9-yl acetate (12)

Yield 19%; m.p. 141-143^{0}C ; Anal. calc for ($C_{16}H_{13}NO_4$), %: C=67.84, H=4.63, N=4.94, O=22.59. found: C=67.82, H=4.60, N=4.89. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 10,03 (bs, 1H, NH); 7,80 (dd, J=7,13, 1,00, 1H, CH); 7,74 (t, J=7,90, 7,13, 1H, CH); 7,56 (dd, J=7,90, 1,00, 1H, CH); 6,19 (dd, J=7,80, 2,00, 1H, CH); 4,93 (dd, J=7,80, 5,10, 1H, CH); 3,76-3,67 (m, 1H, CH); 2,44 (s, 3H, $OCOCH_3$); 1,15 (d, J=6,60, 1H, CH_3).

9-Methoxy-4-methylbenzo[g]quinoline-5,10-dione (13)

Yield 62%; m.p. 131-133^{0}C ; Anal. calc for ($C_{15}H_{11}NO_3$), %: C=71.14, H=4.38, N=5.53, O=18.95. found: C=71.12, H=4.35, N=5.56. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,80 (d, J=4,90, 1H, CH); 7,85 (t, J=8,14, 7,76, 1H, CH); 7,70 (d, J=8,14, 1H, CH); 7,65 (d, J=7,74, 1H, CH); 7,59 (d, J=4,90, 1H, CH); 4,03 (s, 3H, OCH_3); 2,62 (s, 3H, CH_3).

6-Methoxy-4-methylbenzo[g]quinoline-5,10-dione (14)

Yield 12%; m.p. 145-147^{0}C ; Anal. calc for ($C_{15}H_{11}NO_3$), %: C=71.14, H=4.38, N=5.53, O=18.95. found: C=71.15, H=4.39, N=5.57. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,84 (d, J=4,90, 1H, CH); 7,87 (t, J=8,14, 7,76, 1H, CH); 7,71 (d, J=7,76, 1H, CH); 7,62 (d, J=8,14, 1H, CH); 7,52 (d, J=4,90, 1H, CH); 3,99 (s, 3H, OCH_3); 2,54 (s, 3H, CH_3).

4-Methyl-5,10-dioxo-5,10-dihydrobenzo[g]quinolin-9-yl acetate (15)

Yield 71%; m.p. 164-165 ^{0}C ; Anal. calc for ($C_{16}H_{11}NO_4$), %: C=68.32, H=3.94, N=4.98, O=22.75. found: C=68.29, H=3.92, N=4.95.
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,80 (d, J=4,90, 1H, CH); 8,16 (dd, J=7,76, 1,20, 1H, CH); 8,03 (t, J=7,90, 7,76, 1H, CH); 7,73 (dd, J=7,90, 1,20, 1H, CH); 7,59 (d, J=4,90, 1H, CH); 2,62 (s, 3H, CH_3); 2,44 (s, 3H, $OCOCH_3$).

4-Methyl-5,10-dioxo-5,10-dihydrobenzo[g]quinolin-6-yl acetate (16)

Yield 11%; m.p. 141-143^{0}C ; Anal. calc for ($C_{16}H_{11}NO_4$), %: C=68.32, H=3.94, N=4.98, O=22.75. found: C=68.34, H=3.93, N=4.96. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,83 (d, J=4,90, 1H, CH); 8,05 (t, J=7,90, 7,76, 1H, CH); 8,00 (dd, J=7,76, 1,20, 1H, CH); 7,71 (dd, J=7,90, 1,20, 1H, CH); 7,52 (d, J=4,90, 1H, CH); 2,55 (s, 3H, CH_3); 2,45 (s, 3H, $OCOCH_3$).

1-(Dimethylamino)-6-hydroxy-4-methyl-1,4,4a,10a-tetrahydrobenzo[g]quinoline-5,10-dione (17)

Yield 54%; m.p. 147-148^{0}C ; Anal. calc for ($C_{16}H_{18}N_2O_3$), %: C=67.12, H=6.34, N=9.78, O=16.76. found: C=67.16, H=6.29, N=9.75. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,73 (bs, 1H, OH); 7,83 (t, J=7,80, 7,71, 1H, CH); 7,43 (d, J=7,80, 1H, CH); 7,16 (dd, J=7,71, 1,44, 1H, CH); 6,31 (d, J=8,75, 1H, CH); 4,85 (t, J=8,75, 5,70, 1H, CH); 3,60 (dd, J=6,54, 1,58, 1H, CH); 3,56-3,49 (m, 1H, CH); 3,03-2,90 (m, 1H, CH); 2,62 (s, 6H, $N(CH_3)_2$); 1,15 (dd, J=7,38, 4,47, 3H, CH_3).

1-(Dimethylamino)-6-hydroxy-4-methyl-1,4-dihydrobenzo[g]quinoline-5,10-dione (18)

Yield 15%; m.p. 163-164^{0}C ; Anal. calc for ($C_{16}H_{16}N_2O_3$), %: C=67.59, H=5.67, N=9.85, O=16.88. found: C=67.63, H=5.71, N=9.81. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 9,22 (bs, 1H, OH); 7,62 (t, J=7,71, 7,13, 1H, CH); 7,37

(dd, J=7,13, 2,07, 1H, CH); 7,20 (dd, J=7,71, 2,07, 1H, CH); 6,49 (dd, J=7,80, 2,00, 1H, CH); 4,87 (dd, J=7,80, 5,10, 1H, CH); 3,98-3,89 (m, 1H, CH); 3,04 (s, 6H, $N(CH_3)_2$); 1,31 (d, J=6,60, 3H, CH_3).

1-(Dimethylamino)-4-methyl-6-nitro-1,4,4a,10a-tetrahydrobenzo[g]quinoline-5,10-dione (19)

Yield 52%; m.p. 205-207^{0}C ; Anal. calc for ($C_{16}H_{17}N_3O_4$), %: C=60.94, H=5.43, N=13.33, O=20.30. found: C=60.89, H=5.41, N=13.35. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,25 (d, J=7,73, 1H, CH); 8,08 (dd, J=7,50, 2,00, 1H, CH); 7,61 (t, J=7,73, 7,50, 1H, CH); 6,31 (d, J=8,75, 1H, CH); 4,49 (t, J=8,75, 5,70, 1H, CH); 3,77 (d, J=6,54, 1H, CH); 3,54-3,45 (m, 1H, CH); 2,94-2,81 (m, 1H, CH); 2,62 (s, 6H, $N(CH_3)_2$); 1,12 (dd, J=7,38, 4,47, 3H, CH_3).

1-(Dimethylamino)-4-methyl-6-nitro-1,4-dihydrobenzo[g]quinoline-5,10-dione (20)

Yield 17%; m.p. ≥250 ^{0}C ; Anal. calc for ($C_{16}H_{15}N_3O_4$), %: C=61.34, H=4.83, N=13.41, O=20.43. found: C=61.30, H=4.81, N=13.44. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,10 (d, J=7,52, 1H, CH); 8,06 (d, J=7,50, 1H, CH); 7,47 (t, J=7,52, 7,50, 1H, CH); 6,50 (dd, J=7,80, 2,00, 1H, CH); 4,78 (dd, J=7,80, 5,10, 1H, CH); 4,02-3,93 (m, 1H, CH); 3,04 (s, 6H, $N(CH_3)_2$); 1,28 (d, J=6,60, 3H, CH_3).

6-Amino-1-(dimethylamino)-4-methyl-1,4,4a,10a-tetrahydrobenzo[g]quinoline-5,10-dione (21)

Yield 25%; m.p. 195-197^{0}C ; Anal. calc for ($C_{16}H_{19}N_3O_2$), %: C=67.35, H=6.71, N=14.73, O=11.21. found: C=67.36, H=6.69, N=14.75. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,84 (s, 2H, NH_2); 7,56 (d, J=7,73, 1H, CH); 7,48 (t, J=7,87, 7,73, 1H, CH); 6,96 (dd, J=7,87, 1,60, 1H, CH); 6,31 (d, J=8,75, 1H, CH); 4,57 (t, J=8,75, 5,70, 1H, CH); 3,63 (d, J=6,54, 1H, CH); 3,22-3,12 (m, 1H, CH); 3,00-2,87 (m, 1H, CH); 2,62 (s, 6H, $N(CH_3)_2$); 1,09 (dd, J=7,38, 4,47, 3H, CH_3).

6-Amino-1-(dimethylamino)-4-methyl-1,4-dihydrobenzo[g]quinoline-5,10-dione (22)

Yield 14%; m.p. 203-204^{0}C ; Anal. calc for ($C_{16}H_{17}N_3O_2$), %: C=67.83, H=6.05, N=14.83, O=11.29. found: C=67.85, H=6.02, N=14.86. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,87 (bs, 2H, NH_2); 7,55 (dd, J=7,52, 1,37, 1H, CH); 7,51 (t, J=7,87, 7,52, 1H, CH); 7,22 (dd, J=7,87, 1,37, 1H, CH); 6,49 (dd, J=7,80, 2,00, 1H, CH); 4,92 (dd, J=7,80, 5,10, 1H, CH); 4,57 (t, J=8,75, 5,70, 1H, CH); 4,00-3,91 (m, 1H, CH); 3,04 (s, 6H, $N(CH_3)_2$); 1,26 (d, J=6,60, 3H, CH_3).

6-Hydroxy-4-methyl-1,4-dihydrobenzo[g]quinoline-5,10-dione (23)

Yield 12%; m.p. 187-188^{0}C ; Anal. calc for ($C_{14}H_{11}NO_3$), %: C=69.70, H=4.60, N=5.81, O=19.90. found: C=69.67, H=4.56, N=5.77. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 10,98 (bs, 1H, OH); 10,42 (s, 1H, NH); 7,71 (t, J=7,80, 7,71, 1H, CH); 7,65 (dd, J=7,13, 2,07, 1H, CH); 7,19 (dd, J=7,71, 2,07, 1H, CH); 6,27 (dd, J=7,80, 2,00, 1H, CH); 4,92 (dd, J=7,80, 5,10, 1H, CH); 3,78-3,69 (m, 1H, CH); 1,15 (dd, J=7,38, 4,47, 3H, CH_3).

4-Methyl-6-nitro-1,4-dihydrobenzo[g]quinoline-5,10-dione (24)

Yield 19%; m.p. ≥250 ^{0}C ; Anal. calc for ($C_{14}H_{10}N_2O_4$), %: C=62.22, H=3.73, N=10.37, O=23.68. found: C=62.20, H=3.75, N=10.39. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 10,62 (s, 1H, NH); 8,32 (dd, J=7,50, 1,40, 1H, CH); 8,19 (dd, J=7,52, 1,40, 1H, CH); 7,24 (t, J=7,52, 7,50, 1H, CH); 6,16 (dd, J=7,80, 2,00, 1H, CH); 4,93 (dd, J=7,80, 5,10, 1H, CH); 3,89-3,80 (m, 1H, CH); 1,15 (d, J=6,60, 3H, CH_3).

6-Amino-4-methyl-1,4-dihydrobenzo[g]quinoline-5,10-dione (25)

Yield 11%; m.p. 200-203^{0}C ; Anal. calc for ($C_{14}H_{12}N_2O_2$), %: C=69.99, H=5.03, N=11.66, O=13.32. found: C=69.96, H=5.06, N=11.59. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 9,78 (s, 1H, NH); 7,87 (bs, 2H, NH_2); 7,51 (t, J=7,87, 7,52, 1H, CH); 7,44 (dd, J=7,52, 1,37, 1H, CH); 7,16 (dd, J=7,87, 1,37, 1H, CH); 5,75 (dd, J=7,80, 2,00, 1H, CH); 4,93 (dd, J=7,80, 5,10, 1H, CH); 3,83-3,74 (m, 1H, CH); 1,15 (d, J=6,60, 3H, CH_3).

9-Hydroxy-4-methylbenzo[g]quinoline-5,10-dione (26)

Yield 59 %; m.p. 137-140^{0}C ; Anal. calc for ($C_{14}H_9NO_3$), %: C=70.29, H=3.79, N=5.86, O=20.06. found: C=70.26, H=3.73, N=5.87. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 9,32 (bs, 1H, OH); 8,78 (d, J=4,90, 1H, CH); 7,78 (t, J=7,76, 7,71, 1H, CH); 7,60 (d, J=4,90, 1H, CH); 7,56 (d, J=7,76, 1H, CH); 7,45 (dd, J=7,71, 1,18, 1H, CH); 2,62 (s, 3H, CH_3).

6-Hydroxy-4-methylbenzo[g]quinoline-5,10-dione (27)

Yield 18%; m.p. 151-152 ^{0}C ; Anal. calc for ($C_{14}H_9NO_3$), %: C=70.29, H=3.79, N=5.86, O=20.06. found: C=70.26, H=3.75, N=5.85. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,42 (bs, 1H, NH); 8,83 (d, J=4,90, 1H, CH); 7,84 (t, J=7,76, 7,71, 1H, CH); 7,71 (dd, J=7,76, 1,18, 1H, CH); 7,58 (d, J=4,90, 1H, CH); 7,33 (dd, J=7,71, 1,18, 1H, CH); 2,68 (s, 3H, CH_3).

4-Methyl-9-nitrobenzo[g]quinoline-5,10-dione (28)

Yield 64%; m.p. 191-193^{0}C ; Anal. calc for ($C_{14}H_8N_2O_4$), %: C=62.69, H=3.01, N=10.44, O=23.86. found: C=62.65, H=3.05, N=10.46. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,86 (d, J=4,90, 1H, CH); 8,31 (dd, J=7,50, 2,00, 1H, CH); 8,10 (dd, J=7,50, 2,00, 1H, CH); 7,59 (d, J=4,90, 1H, CH); 7,43 (t, J=7,50, 7,50, 1H, CH); 2,62 (s, 3H, CH_3).

4-Methyl-6-nitrobenzo[g]quinoline-5,10-dione (29)

Yield 15%; m.p. ≥250^{0}C ; Anal. calc for ($C_{14}H_8N_2O_4$), %: C=62.69, H=3.01, N=10.44, O=23.86. found: C=62.64, H=3.04, N=10.47. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,83 (d, J=4,90, 1H, CH); 8,26 (dd, J=7,50, 2,00, 1H, CH); 8,11 (dd, J=7,50, 2,00, 1H, CH); 7,57 (d, J=4,90, 1H, CH); 7,51 (d, J=4,90, 1H, CH); 2,65 (s, 3H, CH_3).

9-Amino-4-methylbenzo[g]quinoline-5,10-dione (30)

Yield 67%; m.p. 174-175^{0}C ; Anal. calc for ($C_{14}H_{10}N_2O_2$), %: C=70.58, H=4.23, N=11.76, O=13.43. found: C=70.53, H=4.20, N=11.75. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,76 (d, J=4,90, 1H, CH); 7,72 (bs, 2H, NH_2); 7,66 (dd, J=7,87, 7,60, 1H, CH); 7,61 (dd, J=7,60, 1,60, 1H, CH); 7,59 (d, J=4,90, 1H, CH); 6,86-6,80 (m, 1H, CH); 2,62 (s, 3H, CH_3).

6-Amino-4-methylbenzo[g]quinoline-5,10-dione (31)

Yield 11%; m.p. 197-198^{0}C ; Anal. calc for ($C_{14}H_{10}N_2O_2$), %: C=70.58, H=4.23, N=11.76, O=13.43. found: %: C=70.53, H=4.21, N=11.74. ^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,83 (d, J=4,90, 1H, CH); 7,81 (dd, J=7,60, 1,60, 1H, CH); 7,73 (t, J=7,87, 7,60, 1H, CH); 7,67 (bs, 2H, NH_2); 7,55 (d, J=4,90, 1H, CH); 6,81 (d, J=7,87, 1,60, 1H, CH); 2,57 (s, 3H, CH_3).

RESULTS AND DISCUSSION

Chemistry

General procedure for the synthesis of heterocyclic derivatives of 1,4-quinones

The aim of the work was to use regioselective Diels-Alder reaction to expand the base of potentially biologically active compounds [6]. 5-substituted 1,4-naphthoquinones - 5-hydroxy- (1), 5-methoxy- (2), 5-acetoxy- (3), 5-nitro- (4), 5-amino - (5) 1,4-naphthoquinone which have come to be known as active dienophiles in Diels-Alder reaction were chosen as carbocyclic substrate [7,8].

To predict reaction regioselectivity atomic Fukui indices [9,10] for dienophiles were calculated on B3LYP/6-31G(d,p) level of theory in PBF solvent model (ethanol) using Jaguar software [11]. Local Fukui indices are useful in finding the differences in reactivity of some atoms in the ranks of molecules, and can predict Diels-Alder reaction regioselectivity. Calculated indices for reacting atoms of dienophiles are shown in the

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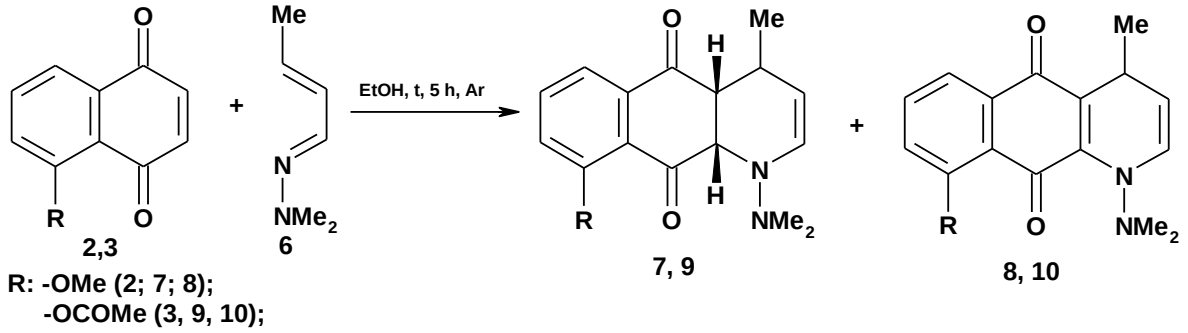
table 1. These positions in quinone are known as electrophiles, so we are interested in LUMO f_NN, which high positive values are showing the most electrophilic atoms and more electrophilic position should react with nucleophilic Nitrogen of diene.

Quinone substituent	5-OAc		5-NH_2		5-NO_2		5-OH		5-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	0,02	0,01	0,00	0,01	0,02	0,03	0,00	0,00	0,03	0,01
f_NN LUMO	0,11	0,11	0,12	0,10	0,10	0,11	0,11	0,11	0,12	0,11

Table 1. Fukui atomic indices on reacting atoms of dienophiles

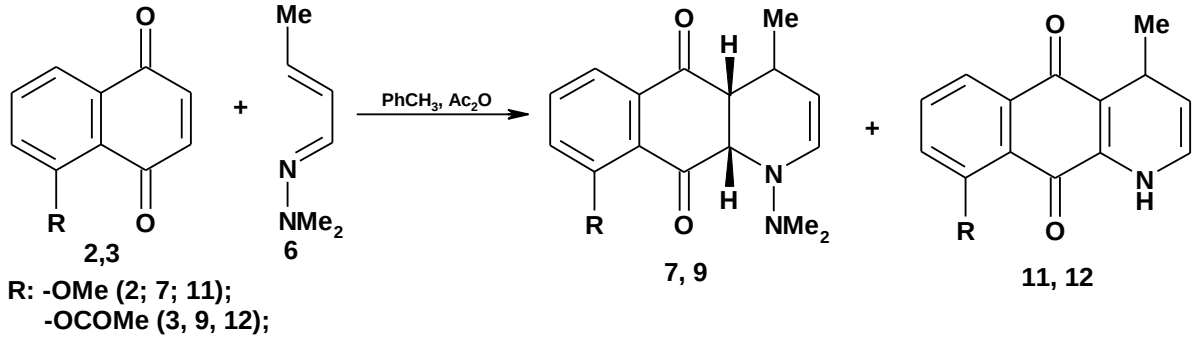
Reaction products analysis revealed that effect of the quinone 5-th position substituent is considerable factor in the reaction regioselectivity [12].

Interaction of crotonaldehyde-N,N-dimethylhydrazone **6** with 5-methoxy- (**2**) and 5-acetoxy- (**3**) 1,4-naphthoquinone was conducted in ethanol at 55-60^{0}C under argon atmosphere. The mixture of products that could be separated by column chromatography was formed as a result of reaction. In both cases of reaction regioisomers **7, 9** with yields of 53% and 54% are dominated. There have been isolated compounds **8, 10** (yield 15% and 13%), whose formation is explained by elimination of two hydrogen atoms of 4th and 10th positions, as evidenced by the absence of signals CH groups in NMR spectra of compounds **8** and **10.**



Scheme 1. Interaction of crotonaldehyde-N,N-dimethylhydrazone 6 with 5-methoxy- (2) and 5-acetoxy- (3) 1,4-naphthoquinone among ethanol.

It was proposed to analyze the dependence of reaction conditions and regioisomers ratio. The interaction of compounds 5-methoxy- (**2**) and 5 acetoxy- (**3**) 1,4-naphthoquinones with crotonaldehyde-N,N-dimethylhydrazone **6** was performed in toluene medium with the addition of acetic anhydride. Analysis of the products mixture showed that in addition to the formation of two dihydrobenzoquinolindione derivatives **7, 9** with yields of 54% and 59%, a new structure was formed that was not registered in the previous reactions. Compounds **11** and **12** with yield 24% and 19% appropriately were formed as the result of splitting of the two hydrogen atoms in 4th and 10th positions, as well as eliminating of dimethylamine.



Scheme 2. Interaction of crotonaldehyde-N,N-dimethylhydrazone 6 with 5-methoxy- (2) and 5-acetoxy- (3) 1,4-naphthoquinone among toluene.

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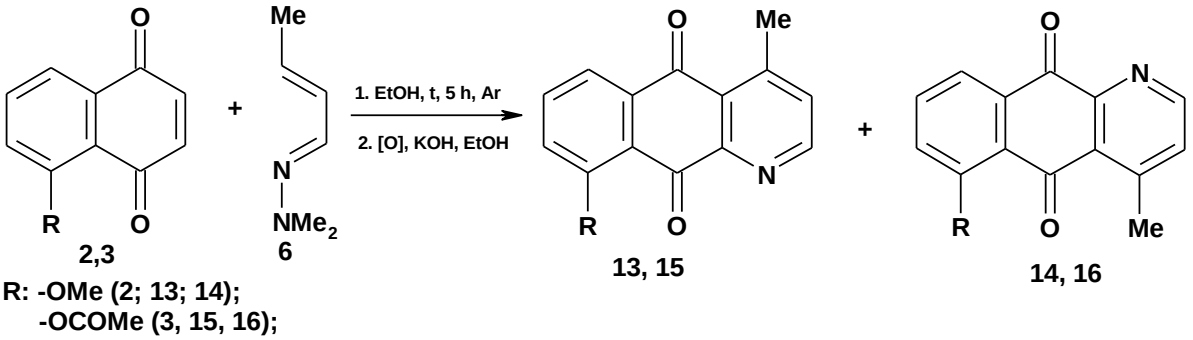
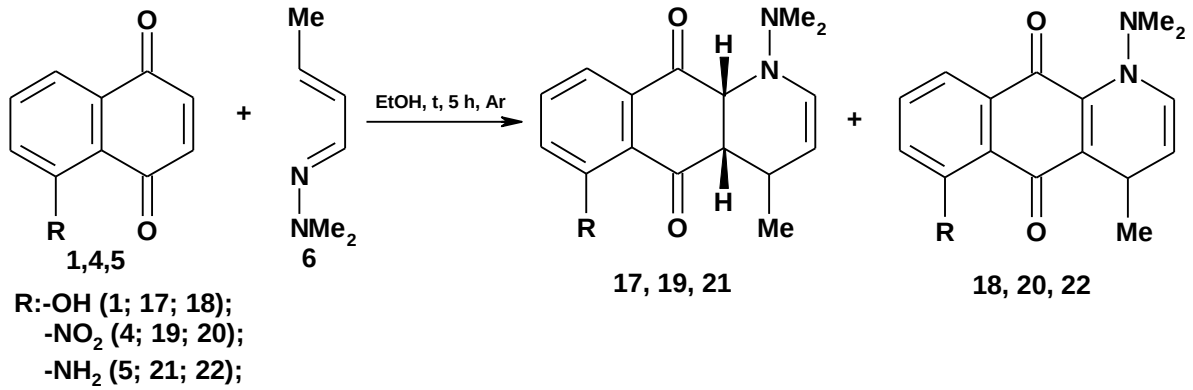
Oxidation of interaction products of **2, 3** and crotonaldehyde N, N-dimethylhydrazone **6** was performed in alkaline ethanol with air bubbling for 24 hours. Compounds **13, 15** with yields 62%, 71% and **14, 16** with yields 12%, 11% were obtained, which were identified as pyridine containing 1,4-quinones and the other products in minor amounts.



Scheme 3. Oxidation of interaction products of 2, 3 and crotonaldehyde N, N-dimethylhydrazone 6.

Interaction of 1,4-naphthoquinones **1, 4, 5** with crotonaldehyde N,N-dimethylhydrazone **6** in ethanol was carried out at 55-60^{0}C under argon atmosphere for 5 hours. A mixture of regioisomers were isolated, in particular compounds **17, 19, 21** with yields 54%, 52%, 25%, and the compounds **18, 20, 22** with the yield 15%, 17%, 14% respectively. In the case of nitro group structure of prevailing regioisomer is caused by substituent electron properties, like in methoxy and acetoxy group (electron-donor substituent directs the accession of diene nucleophylic center in 3-dposition and electron-acceptor in 2-d position). However, in the case of amino and hydroxy groups this pattern is disrupted that can be explained by the formation of intramolecular H-bond with transformation of quinoid system to semiaromatic and molecular charges redistribution.



Scheme 4. Interaction of 5-hydroxy (1), 5-nitro (4), 5-amino (5) 1,4-naphthoquinones with crotonaldehyde-N,N-dimethylhydrazone 6 among ethanol.

Interaction of 5-hydroxy (**1**), 5-nitro (**4**), 5-amino (**5**) 1,4-naphthoquinones with crotonaldehyde-N,N-dimethylhydrazone **6** was performed in toluene medium in the presence of acetic anhydride. As a result, the main products of the reaction were compounds **17, 19, 21,** with the yields 58%, 61% and 29%. In smaller quantities compounds **23, 24, 25** formed by eliminating two hydrogen protons of the provisions of the 4th and 10th were allocated with yields of 12%, 19% and 11% respectively.

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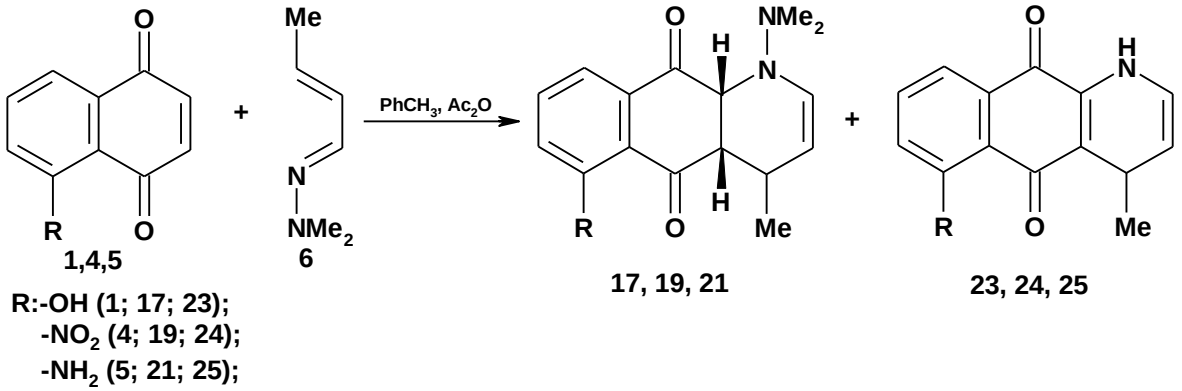
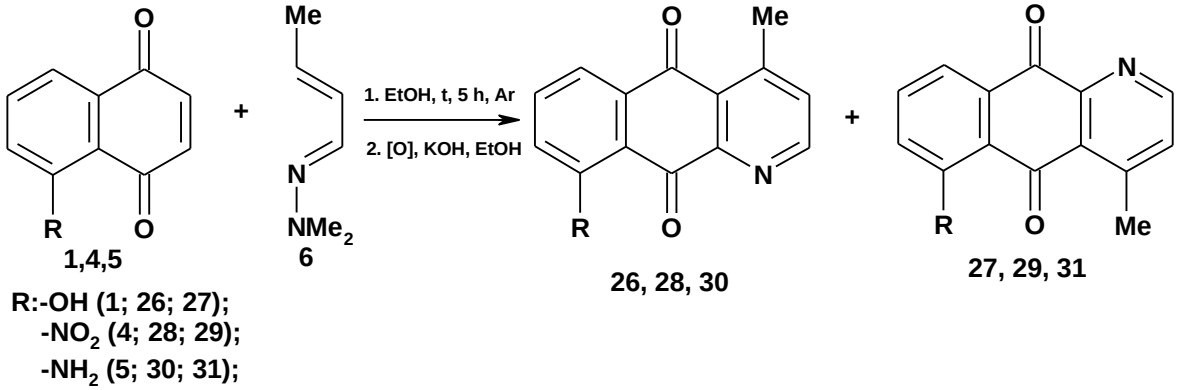


Scheme 5. Interaction of 5-hydroxy (1), 5-nitro (4), 5-amino (5) 1,4-naphthoquinones with crotonaldehyde-N,N-dimethylhydrazone 6 among toluene.

Oxidation of interaction products of compounds **1, 4, 5** with crotonaldehyde N,N-dimethylhydrazone **6** was performed in alkaline ethanol by passing air for 24 hours.



Scheme 6. Oxidation of interaction products of 1, 4, 5 and crotonaldehyde N, N-dimethylhydrazone 6.

Compounds **26, 28, 30** were obtained with yields 59%, 64%, 67% and **27, 29, 31** with yields 18%, 15%, 11 % respectively, which were identified as pyridine containing 1,4-quinones and the other products in minor amounts.

Pharmacology

Predicted biological activity.

For synthesized substances **7-31** computer biological screening with program PASS was carried out [4,13]. The main results of biological activity prediction (Pa> 0,7) defined for synthesized compounds are presented in the Table 2.

According to the *in silico* biological activity prediction by the program PASS for a series of synthesized substances it can be concluded that almost all compounds have potential antibacterial activity, and probably reveals inhibitory effect on several enzymes (Ubiquinol-cytochrome-c reductase, Gluconate 2-dehydrogenase (acceptor), Aspulvinone dimethylallyltransferase, Oxidoreductase, Testosterone 17beta-dehydrogenase (NADP+), NAD(P)+ - arginine ADP-ribosyltransferase, Histidine kinase, Membrane permeability) and binding with the substrates (CYP2C12, CYP2J, CYP2B, SYP1A1, UGT1A9).

Thus, the determined probability of antibacterial activity displaying provides an opportunity to study and carry out the modification of the synthesized compounds for biological effects enhance.

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№	Pa	Pi	ACTIVITY
7	0,777	0,015	Antibacterial
9	0,821	0,022	Antibacterial
10	0,775	0,015	Antibacterial
11	0,775	0,015	Antibacterial
13	0,759	0,017	Antibacterial
14	0,716	0,023	Antibacterial
16	0,738	0,020	Antibacterial
18	0,744	0,019	Antibacterial
20	0,716	0,023	Antibacterial
21	0,734	0,020	Antibacterial

Table 2. List of predicted Antibacterial activity by PASS

Determination of synthesized compounds antimicrobial activity

The synthesized compoundands were evaluated for their antibacterial and antifungal activity against *Escherichia coli B-906*, *Staphylococcus aureus 209-P*, *Mycobacterium luteum* B-*917*, *Candida tenuis VKM Y-70* and *Aspergillus niger VKM F-1119* strains by the diffusion method. Their activity was compared tothat of the known antibacterial agent vancomycin and the antifungal agent nystatin [14].

Results of estimate diameter of microorganism growth inhibition zones according to the parameters are listed in Table 3.

№ compound	Concentration,%	Diameter of the zones of microbial growth inhibition, mm	Test cultures
10	0,5	14,0	*S.aureus*
	0,5	17,5	*C.tenuis*
11	0,5	15,1	*S.aureus*
12	0,5	14,8	*S.aureus*
	0,5	13,1	*A.niger*
15	0,5	12,0	*C.tenuis*
16	0,5	15,0	*C.tenuis*
17	0,5	22,0	*S.aureus*
	0,5	20,0	*M.luteum*
18	0,5	14,7	*S.aureus*
	0,5	18,0	*C.tenuis*
19	0,5	15,1	*S.aureus*
20	0,5	14,4	*S.aureus*
	0,5	13,9	*A.niger*
25	0,5	21,0	*S.aureus*
26	0,5	14,8	*S.aureus*
	0,5	17,1	*C.tenuis*
28	0,5	25,0	*S.aureus*
	0,5	19,1	*M.luteum*
30	0,5	18,0	*S.aureus*
	0,5	16,0	*C.tenuis*
C*	0,5	18,0	*E. coli*
	0,5	23,6	*S.aureus*
	0,5	25,8	*M.luteum*
	0,5	28,0	*C.tenuis*
	0,5	31,1	*A.niger*

Notes:*Vancomycinwas used as a control in the tests of antibacterial acitvity of the synthesized compounds, and nystatin was used in the tests of antifungal activity.

Table 3. Results of microorganism growth inhibition zones.

Antimicrobial activity data analysis of heterocyclic quinoid derivatives series showed that studied microorganisms were predominantly insensitive to the synthesized derivatives The compounds **17, 25, 28** had good activity against strain *S. aureus* at a concentration of 0.5% and compounds **10, 11, 12, 15, 16, 21, 18, 19,**

20 were found to exhibit low antibacterial activity against *S. aureus.* The strain *M. luteum* was most sensitive to compounds **17, 28** a concentration of 0.5%. The compounds **10, 12, 15, 16, 18, 20 26, 30** had low antibacterial activity against *C.tenuis* and *A.niger.* Other compounds had no antibacterial activity against *E. coli, S.aureus* and *M.luteum* at 0.5% concentration evaluated by the diffusion method. The results obtained are presented in Table 3

CONCLUSION

Passing the reactions between 5-R-1,4-naphthoquinones and 2-butenal-N,N-dimethylhydrazone were investigated and reaction conditions were optimized to obtain nitrogen-containing cyclic quinone derivatives. Effect of the substituent nature in 1,4-naphthoquinone 5-th position on the reaction regioselectivity was shown. This results are in good agreement with calculations, except of 5-amino-1,4-naphthoquinone that is probably due to some inaccuracies in H-bond strength calculations. Under the other Diels-Alder reaction conditions the products were dihydrobenzoquinolindione derivatives. Their further oxidation resulted in obtaining 1,4-quinone derivatives with condensed pyridine ring. Investigation of antimicrobial activity of the synthesized compounds showed that cultures of *E. coli*, *Aspergillus niger* and *Candida tenuis* are practically not sensitive to 1,4-naphthoquinone heterocyclic derivatives **10-30**, but showed medium to high activity value to *S. aureus* and *M. luteum*. Thus, compounds **17, 25, 28** have found to possess high antibacterial activity with respect to these cultures.

REFERENCES

[1] Ryu C.K., Kim D.H., Arch. Pharm. Res. 15, 1992, 263-268.
[2] Castro S.L., Emery F.S., da Silva E.N. Júnior, Eur. J. Med. Chem. 69, 2013, 678-700.
[3] Lawrence H.R., Kazi A., Luo Y., Kendig R., Ge Y., Jain S., Daniel K., Santiago D., Guida W.C., Sebti S.M., Bioorg. Med. Chem. 18, 2010, 5576-5592.
[4] Verma R.P., Anticancer. Agents. Med. Chem. 6, 2006, 489-499.
[5] Sarciron M.-E., Nebois P., Pautet F., Petavy A.-F., Fillion H., Walchshofer N., Parasitol Res., 2002, 88: 969–971
[6] Polovkovych S. et al., Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013, Vol. 4, (4), 128-144.
[7] Bouaziz Z., Nebois P., Fillion H., Luche J.-L., Jenner G., Tetrahedron, 1995, Volume 51, Issue 14, Pages 4057–4064.
[8] Tandon V.K., Maurya H.K, Mishra N.N., Shukla P.K., Eur. J. Med.Chem. 44, 2009, 3130-3137.
[9] Contreras, R. R.; Fuentealba, P.; Galvan, M.; Perez, P., Chem. Phys. Lett., 1999, 304, 405.
[10] Chamorro, E.; Perez, P., J. Chem. Phys. 2005, 123, 114107.
[11] Bochevarov Art. et al., *Int. J. Quantum Chem.*, **2013**, *113(18)*, 2110-2142
[12] Polovkovych S. et al., J. Chem. Pharm. Res., 2015, 7(8):697-702.
[13] Polovkovych S., et al., Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013, Vol. 4, (4), 1471-1479.
[14] Labinskaya A. Microbiology of microbiological research technique/AS Labinskaya.- M .: Medicine, 1972. – 500. - 91–93 p.