Reaction of quinaldine with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone. Dependence of the outcome on the reaction conditions and a deeper insight into the mechanism

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ABSTRACT

Condensation of quinaldine with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone results in the formation of 5,7-di (*tert*-butyl)-2-(quinoline-2-yl)-1,3-tropolone, 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-1,3-tropolone, 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-*tert*-butyl-6-quinoline-2-yl-pyridine-2-yl)butanoic acid, 6-(2,2-dimethylprop-3-yl)-5-*tert*-butyl-4-nitro-2-(quinoline-2-yl)-pyridine-3-ol, 1,7-di (*tert*-butyl)-3-(quinoline-2-yl)-2-azabicyclo-[3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide. The formation of 1,3-tropolone and pyridine-2-yl butanoic acid derivatives proceeds through a ring expansion and 2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide via the contraction of the o-quinone ring. The structure of the heterocyclic compounds obtained was justified by X-ray diffraction analysis, NMR spectroscopy, IR- and HRMS-spectrometry, and the proposed mechanisms of their formation include the participation of an intermediate product of the expansion reaction of the *o*-quinone cycle - 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-cyclohepta-1,3,5-triene-1,3-diol, which was first isolated preparatively. The DFT/B3LYP/ 6–311++G** methods were used to determine the thermodynamic stability of tautomeric forms of intermediate products, as well as the relative stability of NH and OH tautomers of 5,7-di (*tert*-butyl)-2-(quinolin-2-yl)-1,3-tropolone and 5,7-di (*tert*-butyl)-4-nitro-2-(quinolin-2-yl)-1,3-tropolone.

1. Introduction

The molecular design of new heterocyclic compounds with high biological activity is an urgent task of synthetic organic chemistry. 1,2-Benzoquinones represent a prospective class of precursors that possess bioactivity [1,2] and can act as building blocks of molecules of biologically important compounds [3,4], particularly those formed in *o*-quinone ring expansion reactions providing the formation of hardly accessible 2-hetaryl-1,3-tropolones [5,6] possessing high antibacterial [7] and antitumor activities [8]. We have recently shown [8] that 2-quinolyl-1,3-tropolones with electron-withdrawing groups on the periphery of the tropolone ring (NO$_2$ or Cl) exhibit high activity (<5 μM) in relation to several cancer cell lines (human ovarian cancer - OVCAR-8, OVCAR-3; human lung cancer - H441, A549; human colon cancer - HCT 116; human pancreatic cancer - Panc-1). For this reason, 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone is an attractive scaffold to obtain highly biologically active 2-hetaryl-4-nitro-1,3-tropolones.

The reactivity of 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone in reactions with 2-methylenactive nitrogen heterocycles differs significantly and can result in the development of other reaction pathways competing with the *o*-quinone ring expansion. These processes are accompanied by the formation not only of the corresponding 2-hetaryl-4-nitro-1,3-tropolones as the main products, but also of other heterocycles [9,10], which can also act as ligand systems to obtain metal complex compounds with high biological activity [11–16].

The most significant results in terms of biological activity were shown by 2-quinolin-2-yl-1,3-tropolones [8]. Therefore, the study of the conditions for the expansion reaction of the *o*-quinone ring and the optimization of synthetic methods for obtaining 1,3-tropolones is one of the key tasks of this chemistry. The study of competing reactions with the *o*-quinone ring expansion and the mechanisms of formation of previously unknown side products can provide valuable information in the development of preparative methods for the synthesis 1,3-tropolones. In this work, we have shown that the reaction conditions between 2-methylquinoline and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone can strongly affect the formation and yield of final products and even completely inhibit the direction of the expansion reaction of the *o*-quinone cycle. In addition, the intermediate product of the *o*-quinone ring expansion, 5,7-di (*tert*-butyl)-4-nitro-2-(quinolin-2-yl)cyclohepta-1,3,5-triene-1,3-diol, beeing one of the most stable tautomers, was preparatively isolated for the first time. The thermodynamic stability of all tautomeric forms C^1-C^7 of the intermediate was determined by DFT/B3LYP/6–311++G** calculations.

Previously, we have found [17] that boiling of 2-methylquinaldine with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone in an *o*-xylene solution in the presence of catalytic amounts of *p*-toluenesulfonic acid results in the formation of 5,7-di (*tert*-butyl)-2-(quinoline-2-yl)-1,3-tropolone and 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-1,3-tropolone with low yields of 3% and 7%, respectively. The low yields of tropolone formation are due to the harsh reaction conditions, accompanied by tarring of the reaction mixture. The later proposed optimized method with moderate heating reagents in acetic acid (60–80 °C) allowed us to significantly increase the yields of the formation of 1,3-tropolones during condensation of 1,2-benzoquinones with substituted 2-methylquinoline [18].

In this study, the condensation reaction of quinaldine with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone was investigated under various conditions using acetic acid as the solvent. It was found that along with the formation 5,7-di (*tert*-butyl)-2-(quinoline-2-yl)-1,3-tropolone, 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-1,3-tropolone as main products a series of derivatives of other heterocyclic systems (3,3-dimethyl-2-(5-hydroxy-4-nitro-3-*tert*-butyl-6-quinoline-2-yl-pyridine-2-yl)butanoic acid, 6-(2,2-dimethylprop-3-yl)-5-*tert*-butyl-4-nitro-2-(quinoline-2-yl)-pyridine-3-ol and 1,7-di (*tert*-butyl)-3-(quinoline-2-yl)-2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide) – emerge, can be isolated and characterized. The structure of the synthesized heterocycles was investigated and confirmed by X-ray diffraction analysis. Mechanisms for the formation of new heterocycles are proposed taking into account 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-cyclohepta-1,3,5-triene-1,3-diol as an intermediate product of the *o*-quinone cycle expansion reaction.

Therefore, the reaction of quinaldine with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone can serve as a model of interactions that occur in a series of 2-methylnitrorgen heterocycles in acid-catalyzed reactions with nitroquinones.

2. Materials and methods

2.1. General

^{1}H and ^{13}C NMR spectra (CDCl$_3$) were recorded on a Bruker Avance 600 spectrometer. Chemical shifts are given with respect to the signal of SiMe4 (tetramethylsilane) as an internal standard. IR spectra were measured on a Varian 3100 FT-IR Excalibur Series spectrometer (in the range of 400–4500 cm^{-1}). HRMS were registered on a Bruker UHR-TOF MaxisTM Impact instrument. The IR and NMR spectra were recorded using equipment from the Shared Use Centre "Molecular spectroscopy" of the Southern Federal University. Chromatography was performed on columns packed with Al$_2$O$_3$ (Brockmann activity II—III) and silica gel 60 (0.063–0.2 mm) (Sigma Aldrich). The melting point was measured on a Fisher-Johns apparatus. All reactions were provided in glacial acetic acid (99.4%), CAS 64-19-7 (Alfa Aesar). All solvents and 2-methylquinoline (**1**) (97%), CAS 91-63-4 were purchased from Alfa Aesar and used as received. 4,6-Di (*tert*-butyl)-3-nitro-1,2-benzoquinone (**2**) was prepared according to the procedure [19].

2.2. Synthesis

2.2.1. Method A. Synthesis of 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-cyclohepta-1,3,5-triene-1,3-diol (3) and 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4)

A solution of 2-methylquinoline **1** (1.43 g, 10 mmol) and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone **2** (2.385 g, 9 mmol) in glacial

acetic acid (10 mL) was kept at room temperature for 2 days. The precipitate obtained was filtered and washed with acetic acid and then with water. The sediment was dried, collecting yellow compound **3** ($R_f \sim 0.09$, silica gel, eluent - dichloromethane). In this case, compound **4** ($R_f \sim 0.36$, silica gel, eluent - dichloromethane) is present in trace amounts and has not been isolated. However, compound (**4**) has been formed in higher yields under different conditions in subsequent experiments.

2.2.1.1. 5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-cyclohepta-1,3,5-triene-1,3-diol (3). Yield 2.02 g (56%), yellow crystals, mp 175–176 °C. IR (ν, cm^{-1}): 1745, 1634, 1549, 1464, 1384, 1315, 1223, 1210, 1167, 1140, 1125, 824, 757, 608.^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 1.10 (9H, s, Bu^t(7)), 1.13 (9H, s, Bu^t(5)), 2.80 (1H, d, H(7)$_{trop}$, $J = 6$ Hz) 5.88 (1H, d, H (6)$_{trop}$, $J = 6$ Hz), 7.37–7.42 (1H, m, H$_{Ar}$), 7.61–7,66 (4H, m, H$_{Ar}$), 7.78–7.81 (1H, m, H$_{Ar}$), 7.89–7.92 (1H, m, H$_{Ar}$), 15.23 (1H, s, OH(1)), 16.76 (1H, s, OH(3)). ^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm): 27.7 (3C), 30.8 (3C), 36.3 (1C), 58.0 (1C), 98.2 (1C), 118.1 (1C), 120.5 (1C), 122.9 (1C), 124.9 (1C), 126.9 (1C), 127.1 (1C), 128.3 (1C), 131.1 (1C), 135.6 (1C), 137.4 (1C), 138.3 (1C), 141.5 (1C), 153.8 (1C), 168.5 (1C), 194.9 (1C). HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{24}$H$_{28}$N$_2$O$_4$: 431,1947; found: 431.1948. Anal. Calcd (%) for C$_{24}$H$_{28}$N$_2$O$_4$: C, 70.57; H, 6.91; N, 6.86. Found (%): C, 70.49; H, 6.85; N, 6.77.

2.2.1.2. 5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4). Yield <1%, yellow crystals, mp 257–258 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **4** obtained by Method B.

2.2.2. Method B. Synthesis of 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-cyclohepta-1,3,5-triene-1,3-diol (3), 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4), 5,7-di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5) and 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6)

A solution of 2-methylquinoline **1** (1.43 g, 10 mmol) and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone **2** (2.385 g, 9 mmol) in glacial acetic acid (15 mL) was kept at room temperature for 3 weeks. The reaction mixture was diluted with distilled water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and then dried with anhydrous Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography with dichloromethane/ethyl acetate/petroleum ether 40–70 (50:5:45), collecting 4 fractions. The first fraction is compound **4** ($R_f \sim 0.72$), the second fraction is **5** ($R_f \sim 0.61$), the third fraction is **3** ($R_f \sim 0.26$), the fourth fraction contained compound **6** ($R_f \sim 0.06$) that was isolated by ethyl acetate in the same column. After removal of the solvent *in vacuo*, each residue was recrystallized from propane-2-ol.

2.2.2.1. 5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-cyclohepta-1,3,5-triene-1,3-diol (3). Yield 0.54 g (30%), orange crystals, mp 175–176 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **3** obtained by Method A.

2.2.2.2. 5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4). Yield 0.10 g (3%), yellow crystals, mp 257–258 °C. IR (ν, cm^{-1}): 1647, 1626, 1607, 1590, 1548, 1531, 1505, 1465, 1377, 1302, 1273, 1251, 1226, 1150, 965, 839, 812, 758, 612.^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 1.28 (9H, s, Bu^t(7)), 1.29 (9H, s, Bu^t(5)), 6.35 (1H, s, H(6)$_{trop}$), 7.48–7.51 (1H, m, H$_{Ar}$), 7.67–7,71 (2H, m, H$_{Ar}$), 7.74–7.75 (1H, m, H$_{Ar}$), 8.10–8.11 (1H, m, H$_{Ar}$), 8.16–8.17 (1H, m, H$_{Ar}$), 17.95 (1H, s, OH). ^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm): 29.1 (3C), 30.4 (3C), 37.2 (1C), 37.9 (1C), 114.3 (1C), 118.9 (1C), 119.5 (1C), 119.8 (1C), 124.8 (1C), 126.5 (1C), 127.7 (1C), 132.2 (1C), 136.3 (1C), 139.5 (1C), 142.3 (1C), 150.7 (1C), 152.5 (1C), 154.1 (1C), 175.0 (1C), 194.4 (1C). HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{24}$H$_{26}$N$_2$O$_4$: 429,1790; found: 429.1791. Anal. Calcd (%) for C$_{24}$H$_{26}$N$_2$O$_4$: C, 70.92; H, 6.45; N, 6.89. Found (%): C, 70.76; H, 6.28; N, 6.72.

2.2.2.3. 5,7-Di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5). Yield 1.24 g (38%), yellow crystals, mp 127–129 °C. IR (ν, cm^{-1}): 1690, 1644, 1625, 1510, 1463, 1422, 1394, 1297, 1240, 1155, 1126, 1070, 1033, 1019, 988, 968, 892, 868, 841, 759.^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 1.23 (9H, s, Bu^t(7)), 1.37 (9H, s, Bu^t(5)), 6.61 (1H, d, H(4)$_{trop}$, $J = 1.9$ Hz), 6.68 (1H, d, H (6)$_{trop}$, $J = 1.9$ Hz), 7.43–7.46 (1H, m, H$_{Ar}$), 7.65–7.70 (1H, m, H$_{Ar}$), 7.72 (1H, m, H$_{Ar}$), 7.77–7.78 (1H, m, H$_{Ar}$), 8.02–8.04 (1H, m, H$_{Ar}$), 8.10–8.11 (1H, m, H$_{Ar}$), 19.21 (1H, s, OH). ^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm): 29.9 (3C), 31.1 (3C), 36.9 (1C), 38.2 (1C), 114.5 (1C), 120.3 (1C), 122.5 (1C), 122.7 (1C), 125.4 (1C), 125.8 (1C), 126.0 (1C), 127.5 (1C), 130.9 (1C), 137.6 (1C), 139.7 (1C), 153.3 (1C), 155.2 (1C), 155.8 (1C), 176.5 (1C), 195.3 (1C). HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{24}$H$_{27}$NO$_2$: 362,2120; found: 362.2123. C$_{24}$H$_{27}$NO$_2$. Anal. Calcd (%) for C$_{24}$H$_{27}$NO$_2$: C, 79.74; H, 7.53; N, 3.87. Found (%): C, 79.62; H, 7.38; N, 3.64.

2.2.2.4. 3,3-Dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6). Yield 1.07 g (18%), orange crystals, mp 179–180 °C. IR (ν, cm^{-1}): 3071, 1731, 1698, 1596, 1538, 1503, 1462, 1431, 1407, 1396, 1373, 1319, 1303, 1248, 1210, 1179, 1164, 1137, 1103, 1037, 985, 957, 912, 828, 764, 753, 738, 647, 619.^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 1.07 (9H, s, Bu^t), 1.55 (9H, s, Bu^t), 4.41 (1H, s, CH), 7.68 (1H, t, H$_{Ar}$, $J = 9$ Hz), 7.84 (1H, t, H$_{Ar}$, $J = 9$ Hz), 7.94 (1H, d, H$_{Ar}$, $J = 9$ Hz), 8.05 (1H, d, H$_{Ar}$, $J = 9$ Hz), 8.27 (1H, d, H$_{Ar}$, $J = 9$ Hz), 8.50 (1H, d, H$_{Ar}$, $J = 9$ Hz), 12.12 (1H, s, COOH), 16.59 (1H, s OH). ^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm): 28.6 (3C), 30.8 (3C), 36.3 (1C), 37.0 (1C), 59.4 (1C), 116.1 (1C), 126.5 (1C), 127.4 (1C), 127.5 (1C), 127.9 (1C), 131.3 (1C), 133.1 (1C), 137.8 (1C), 139.1 (1C), 143.2 (1C), 148.1 (1C), 148.2 (1C), 149.2 (1C), 154.4 (1C), 169.7 (1C). HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{24}$H$_{27}$N$_3$O$_5$: 460.1848; found: 460.1847. Anal. Calcd (%) for C$_{24}$H$_{27}$N$_3$O$_5$: C, 65.89; H, 6.22; N, 9.60. Found (%): C, 65.73; H, 6.15; N, 9.49.

2.2.3. *Method C. Synthesis of 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4), 5,7-di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5) and 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6)*

A solution of 2-methylquinoline **1** (1.43 g, 10 mmol) and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone **2** (5.30 g, 20 mmol) in glacial acetic acid (15 mL) was heated at 60–70 °C for 11 h. After being cooled to room temperature, the reaction mixture was diluted with distilled water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and then dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography with dichloromethane, collecting 3 yellow fractions. The first fraction is compound **4** ($R_f \sim 0.36$), the second fraction is compound **5** ($R_f \sim 0.13$), the third fraction containing compound **6** ($R_f \sim 0.06$) was isolated by ethyl acetate in the same column. After removal of the solvent *in vacuo*, each residue was recrystallized from propane-2-ol.

2.2.3.1. *5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4)*. Yield 0.4 g (10%), yellow crystals, mp 257–258 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **4** obtained by Method B.

2.2.3.2. *5,7-Di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5)*. Yield 1.0 g (28%), yellow crystals, mp 127–129 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **5** obtained by Method B.

2.2.3.3. *3,3-Dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6)*. Yield 1.3 g (30%), orange crystals, mp 179–180 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **6** obtained by Method B.

2.2.4. *Method D. Synthesis of 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4), 5,7-di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5), 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6) and 6-(2,2-dimethylprop-3-yl)-5-tert-butyl-4-nitro-2-(2-quinolyl)-pyridin-3-ol (7)*

A solution of 2-methylquinoline **1** (1.43 g, 10 mmol) and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone **2** (5.30 g, 20 mmol) in glacial acetic acid (15 mL) was heated at 60–70 °C in an oil bath for 5 days. The reaction mixture was diluted with distilled water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and then dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography with dichloromethane/ethyl acetate (19:1), collecting 3 fractions. The first fraction is compound **7** ($R_f \sim 0.88$), the second fraction is compounds **4** and **5** ($R_f \sim 0.60$). The third fraction is compound **6** that was isolated with ethyl acetate in the primary column. Compounds **4** and **5** containing in the second fraction were separated by alumina column with dichloromethane/petroleum ether (1:2) with R_f (**4**) ~ 0.55 and R_f (**5**) ~ 0.77, respectively. After removal of the solvent *in vacuo*, each residue was recrystallized from propane-2-ol.

2.2.4.1. *5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4)*. Yield 0.47 g (20%), yellow crystals, mp 257–258 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **4** obtained by Method B.

2.2.4.2. *5,7-Di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5)*. Yield 0.12 g (3%), yellow crystals, mp 127–129 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **5** obtained by Method B.

2.2.4.3. *3,3-Dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6)*. Yield 0.56 g (10%), orange crystals, mp 179–180 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **6** obtained by Method B.

2.2.4.4. *6-(2,2-Dimethylprop-3-yl)-5-tert-butyl-4-nitro-2-(2-quinolyl)-pyridin-3-ol (7)*. Yield 0.11 g (3%), orange crystals, mp 137–138 °C. IR (ν, cm^{-1}): 1600, 1578, 1544, 1506, 1464, 1405, 1377, 1330, 1289, 1218, 1193, 1134, 1098, 1029, 997, 957, 911, 866, 835, 748, 729. ^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 1.10 (9H, s, Bu^t), 1.54 (9H, s, Bu^t), 3.06 (2H, s, CH$_2$), 7.59 (1H, t, H$_{Ar}$, $J = 12$ Hz), 7.75 (1H, t, H$_{Ar}$, $J = 12$ Hz), 7.85 (1H, d, H$_{Ar}$, $J = 6$ Hz), 7.98 (1H, d, H$_{Ar}$, $J = 12$ Hz), 8.34 (1H, d, H$_{Ar}$, $J = 6$ Hz), 8.55 (1H, d, H$_{Ar}$, $J = 12$ Hz), 15.87 (1H, s, OH). ^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm): 30.97 (3C), 31.00 (3C), 33.09 (1C), 36.45 (1C), 48.54 (1C), 118.27 (1C), 127.21 (1C), 127.49 (1C), 127.74 (1C), 127.86 (1C), 130.86 (1C), 133.67 (1C), 135.87 (1C), 138.31 (1C), 144.06 (1C), 146.60 (1C), 147.68 (1C), 151.85 (1C), 157.34 (1C). HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{23}H_{27}N_3O_3$: 416.19520; found: 416.1952. Anal. Calcd (%) for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found (%): C, 70.13; H, 6.79; N, 10.56.

2.2.5. *Method E. Synthesis of 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4), 5,7-di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5), 6-(2,2-dimethylprop-3-yl)-5-tert-butyl-4-nitro-2-(2-quinolyl)-pyridin-3-ol (7) and 1,7-di (tert-butyl)-3-(2-quinolyl)-2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-N-oxide (8)*

A solution of 2-methylquinoline **1** (1.43 g, 10 mmol) and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone **2** (5.30 g, 20 mmol) in glacial acetic acid (15 mL) was refluxed at 117 °C for 8 h. After being cooled to room temperature, the reaction mixture was diluted with distilled water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and then dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography with dichloromethane/ethyl acetate (19:1), collecting 3 fractions. The first fraction is compounds **7** and **4** ($R_f \sim 0.80$), the second fraction is compound **5** ($R_f \sim 0.66$), the third fraction is compound **8** ($R_f \sim 0.43$). Compounds **7** and **4** containing in the first fraction were separated by a silica gel column with dichloromethane ($R_f \sim 0.65$ for **7** and $R_f \sim 0.36$ for **4**, respectively). After the

removal of the solvent *in vacuo*, each residue was recrystallized from propane-2-ol.

2.2.5.1. 5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4). Yield 0.60 g (16%), yellow crystals, mp 257–258 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **4** obtained by Method B.

2.2.5.2. 5,7-Di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5). Yield 0.30 g (8%), yellow crystals, mp 127–129 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **5** obtained by Method B.

2.2.5.3. 6-(2,2-Dimethylprop-3-yl)-5-tert-butyl-4-nitro-2-(2-quinolyl)-pyridin-3-ol (7). Yield 0.32 g (8%), yellow crystals, mp 137–138 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **7** obtained by Method D.

2.2.5.4. 1,7-Di (tert-butyl)-3-(2-quinolyl)-2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-N-oxide (8). Yield 1.66 g (42%), colorless crystals, mp 198–199 °C. IR (ν, cm^{-1}): 1732, 1715, 1700, 1595, 1530, 1504, 1459, 1431, 1398, 1375, 1315, 1304, 1267, 1188, 1166, 1030, 988, 822, 760. ^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm): 1.21 (18H, s, Bu^t), 3.78 (1H, s, CH), 7.56 (1H, t, H$_{Ar}$, $J = 12$ Hz), 7.58 (1H, s, H$_{bic}$), 7.71 (1H, t, H$_{Ar}$, $J = 12$ Hz), 7.79 (1H, d, H$_{Ar}$, $J = 12$ Hz), 8.06 (1H, d, H$_{Ar}$, $J = 6$ Hz), 8.19–8.21 (2H, m, H$_{apoM}$). ^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm): 25.41 (3C), 27.60 (3C), 32.31 (1C), 36.19 (1C), 60.34 (1C), 87.34 (1C), 120.67 (1C), 126.89 (1C), 127.42 (1C), 129.33 (1C), 129.84 (1C), 135.68 (1C), 137.07 (1C), 144.76 (1C), 147.60 (1C), 148.74 (1C), 157.71 (1C), 184.82 (1C), 191.76 (1C). HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{24}$H$_{26}$N$_2$O$_3$: 391.2022; found: 391.2028. Anal. Calcd (%) for C$_{24}$H$_{26}$N$_2$O$_3$: C, 73.82; H, 6.71; N, 7.17. Found (%): C, 73.70; H, 6.63; N, 7.09.

2.2.6. Counter-synthesis. Decarboxylation reaction of 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6) in acetic acid

A solution of acid **6** 0.3 g (0.7 mmol) in glacial acetic acid (10 mL) was refluxed at 117 °C. for 11 h. After being cooled to room temperature, the reaction mixture was diluted with distilled water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (3 × 150 mL) and then dried with anhydrous Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The residue was purified by alumina column chromatography with dichloromethane, collecting 2 fractions. The first fraction is compound **7** (R$_f$ ∼ 0.65), the second fraction is compound **6** (R$_f$ ∼ 0.05). After removal of the solvent *in vacuo*, the residue of **7** was recrystallized from propane-2-ol. Longer reflux leads to accumulation of the decarboxylation product **7**.

2.2.6.1. 6-(2,2-Dimethylprop-3-yl)-5-tert-butyl-4-nitro-2-(2-quinolyl)-pyridin-3-ol (7). Yield 0.04 g (15%), yellow crystals, mp 137–138 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **7** obtained by Method B.

2.2.7. Counter-synthesis. Reaction of 5,7-di (tert-butyl)-4-nitro-2-(2-quinolyl)-cyclohepta-1,3,5-triene-1,3-diol (3) with sodium nitrite

A solution of **3** (0.10 g, 0.2 mmol) and sodium nitrite (0.10 g, 1.4 mmol) in glacial acetic acid (5 mL) was kept at room temperature for 2 days. The reaction mixture was diluted with distilled water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (3 × 100 mL) and then dried with anhydrous Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography with dichloromethane, collecting 4 fractions. The first fraction is compound **7** (R$_f$ ∼ 0.65), the second fraction is compounds **4** (R$_f$ ∼ 0.36), the third fraction is compound **5** (R$_f$ ∼ 0.13). The fourth fraction is compound **6** that was isolated with ethyl acetate in the same column. After removal of the solvent *in vacuo*, each residue was recrystallized from propane-2-ol.

2.2.7.1. 5,7-Di (tert-butyl)-4-nitro-2-(2-quinolyl)-1,3-tropolone (4). Yield 0.025 g (25%), yellow crystals, mp 257-258° °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **4** obtained by Method B.

2.2.7.2. 5,7-Di (tert-butyl)-2-(2-quinolyl)-1,3-tropolone (5). Yield 0.013 g (15%), yellow crystals, mp 127–129 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **5** obtained by Method B.

2.2.7.3. 3,3-Dimethyl-2-(5-hydroxy-4-nitro-3-tert-butyl-6-(2-quinolyl)-pyridin-2-yl)butanoic acid (6). Yield 0.03 g (30%), orange crystals, mp 179–180 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **6** obtained by Method B.

2.2.7.4. 6-(2,2-Dimethylprop-3-yl)-5-tert-butyl-4-nitro-2-(2-quinolyl)-pyridin-3-ol (7). Yield 0.0036 g (4%), orange crystals, mp 137–138 °C. The IR and ^{1}H NMR spectra coincide with the spectra of compound **7** obtained by Method B.

2.3. X-ray diffraction study

The X-ray diffraction data set was recorded on an Agilent SuperNova diffractometer using a microfocus X-ray radiation source with copper anode and Atlas S2 two-dimensional CCD detector. Reflections were recorded and unit cell parameters were determined and refined using the dedicated CrysAlisPro software suite [20]. The structure was solved with the ShelXT program [21] and refined with the ShelXL program [21], the graphics were rendered using the Olex2 software suite [22]. The complete X-ray structural data set for compounds **4**–**8** was deposited at the Cambridge Crystallographic Data Centre (deposit CCDC 2161836 (**4**), 2,161,835 (**5**), 2,161,821

(**6**), 2,161,824 (**7**), 2,161,837 (**8**)).

2.4. Computational methods

DFT quantum chemical studies were performed using B3LYP [23–25] with the standard 6–311++G (d,p) basis set. Geometry optimization was carried out using Bemy's analytical gradient optimization method. The stationary points of the MEPs were characterized by frequency calculations. The stationary points of the tautomers were characterized by frequencies calculations. Solvent effects were considered in the context of a polarizable continuum model (PCM). Acetic acid was chosen as the solvent. All calculations were carried out using the Gaussian 16 suite of programs [26].

3. Results and discussion

3.1. Synthesis

Although many substituted 2-methylquinolines react with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone under moderate conditions in acetic acid solutions to form the corresponding tropolones in good yields [17], the reaction of quinaldine **1** with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone **2** results in the formation of a complex mixture of products **3–8** (Scheme 1), the content of which significantly depends on the reaction conditions (Table 1).

Reaction of 2-methylquinaldine **1** with 3-nitro-1,2-benzoquinone **2** in acetic acid occurring at room temperature for 2 days (method A) gives rise to 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-cyclohepta-1,3,5-triene-1,3-diol **3** with a yield of 56%. Compound **3** should be considered in our opinion as an intermediate preceding the formation of 1,3-tropolones **4, 5** and heterocycle **6**.

Prolonged exposure of the reaction mixture for 3 weeks (method B) leads to the accumulation of tropolone **5** (38%), as well as the formation of previously unknown 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-*tert*-butyl-6-quinoline-2-yl-pyridine-2-yl)butanoic acid **6** (18%).

At 11 h of heating at 70 °C (method C), the further transformation of intermediate **3** results in the addition to tropolones **4** and **5** of acid **6** that was isolated from the reaction mixture with a yield of 30%.

Prolonged exposure of the reagents for 5 days at the same temperature (70 °C) (method D) results in the formation of acid **6** with a lower yield (10%) and nitrotropolone **4** (20%), as well as a small amount of the product of decarboxylation **6** - 6-(2,2-dimethylprop-3-yl)-5-*tert*-butyl-4-nitro-2-(quinoline-2-yl)-pyridine-3-ol **7**. By counter synthesis, it was found that prolonged boiling of product **6** in acetic acid leads to **7** with a yield of 15%. This observation explains the accumulation of product **7** in the reaction mixture during prolonged heating of **1** and **2** in acetic acid (methods D and E).

Boiling of reagents **1** and **2** for 10 h (method E) in glacial acetic acid results in the formation of 1,7-di (*tert*-butyl)-3-(quinolin-2-yl)-2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide **8** as the main product (42%).

The composition of the reaction mixtures and the yields of the products obtained under various reaction conditions are given in Table 1.

3.2. Spectroscopic characterization

The structure of products **3–8** was studied using ^{1}H, ^{13}C NMR, IR spectroscopy, high resolution mass spectrometry HRMS (ESI), and X-ray diffraction analysis for **4–8**.

In the ^{1}H NMR spectra, the proton signals of the OH groups of tropolones **4** and **5** appear in the weak field at 17.95 and 19.21 ppm, respectively. The ^{1}H NMR spectrum of the bicyclic product **8** is characterized by the presence of a bridged proton signal of the [3.3.0]
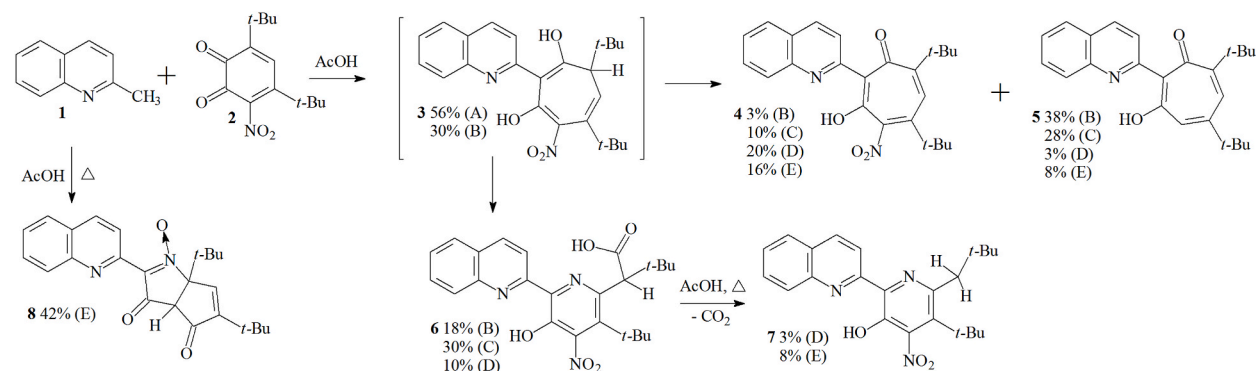
Method A - AcOH, rt, 2d; Method B - AcOH, rt, 21d ; Method C - AcOH,70 °C, 11h;
Method D - AcOH,70 °C, 5d; Method E - AcOH,118 °C.

Scheme 1. Interaction of quinaldine **1** with hydroquinone **2** under conditions of acid catalysis, resulting in the formation products **3–8**.

Table 1

The composition of the reaction mixtures and the yields of heterocyclic compounds **3–8** obtained by methods A-E.

Compd.	Method A AcOH, rt, 2 days	Method B AcOH, rt, 21 days	Method C AcOH, 60–70 °C, 11 h	Method D AcOH, 60–70 °C, 5 days	Method E AcOH, 118 °C, 10 h
fx1	**56%**[a]	30%	–	–	–
fx2	<1%	3%	10%	**20%**	16%
fx3	–	**38%**	28%	3%	8%
fx4	–	18%	**30%**	10%	–
fx5	–	–	<1%	3%	**8%**
fx6	–	–	–	–	**42%**

[a] The maximum yields of the reaction products are highlighted in bold.

bicycle in the region of 3.8 ppm. The signals of protons of the OH group, carboxyl group and a proton in an asymmetric carbon atom of acid **6** appear at 16.6, 12.1 and 4.4 ppm, respectively. The ^{1}H NMR spectrum of decarboxylated product **7** contains signals of geminal protons of the CH_2 group in the region of 3.1 ppm. IR spectra of **4** and **5** contain absorption bands of CO groups at 1646 cm^{-1} and 1645 cm^{-1}, respectively. Figure S1 shows the ^{1}H NMR spectrum of intermediate **3**. This spectrum contains the signals of protons of hydroxyl groups, and the signal of the proton of OH group, closing the six-membered chelate cycle, is located in the weakest field at 16.76 ppm. The signal of the proton in the 7-position of cycloheptatriene manifests itself in the region of 2.8 ppm in the form of a doublet with a spin-spin coupling constant $J = 6.0$ Hz, and the proton signal in the 6-position is also a doublet with $J = 6.0$ Hz. The mass spectra of the obtained compounds **3–8** confirm their molecular mass and are characterized by molecular peaks of the obtained ions $[M+H]^+$ or $[M+Na]^+$. The HRMS (ESI) mass spectrum of **3** confirms the presence of a sodium adduct ion (431.1948 $[M+Na]^+$). The above data suggest the structure of intermediate **3** as 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-cyclohepta-1,3,5-triene-1,3-diol.

3.3. Structural characterization

The molecular structures of 1,3-tropolones **4, 5** and heterocycles **6–8** are shown in Figs. 1–5 (bond lengths, bond angles and other crystal data are given in Tables S1–S20).

As follows from the X-ray data, tropolones **4, 5** capable of prototropy exist in aminoenone form in the crystalline state (Figs. 1 and 2). In both cases, the hydrogen atom is localized at the nitrogen atom N (1) at a distance of 0.958 (12) and 1.02 (2) Å, respectively. Both tropolones **5** and **6** are stabilized by intramolecular hydrogen bond involving a sterically less hindered oxygen atom of the carbonyl group with the following parameters: O (1)–C (11) = 1.2630 (13) Å (**5**), 1.2939 (16) Å (**6**); H (1)–O (11) = 1.682 Å (**5**), 1.536 Å (**6**). The angle N (1)–H (1)–O (11) in the cycle formed by the intramolecular hydrogen bond is equal to 143.49° and 150.70°, respectively, and a tropolone cycle in the crystal is in the "bath" conformation.

The quinoline and pyridine fragments of acid **6** are coplanar, apparently due to their effective conjugation, accompanied by additional stabilization with an intramolecular hydrogen bond formed by a quinoline nitrogen atom and a hydroxyl group with the following characteristics: O (1)–C (11) = 1.328 (2) Å, (N)1–(H) = 1.822 Å and the angle N (1)–H (1)–O (1) = 145.13°. The 1-carboxy-2,2-dimethylpropyl fragment is symmetrically disordered due to rotation along the C (14)–C (19) bond and in both cases is fixed by an intramolecular hydrogen bond between the carboxyl OH group and the pyridine nitrogen atom (Fig. 3).
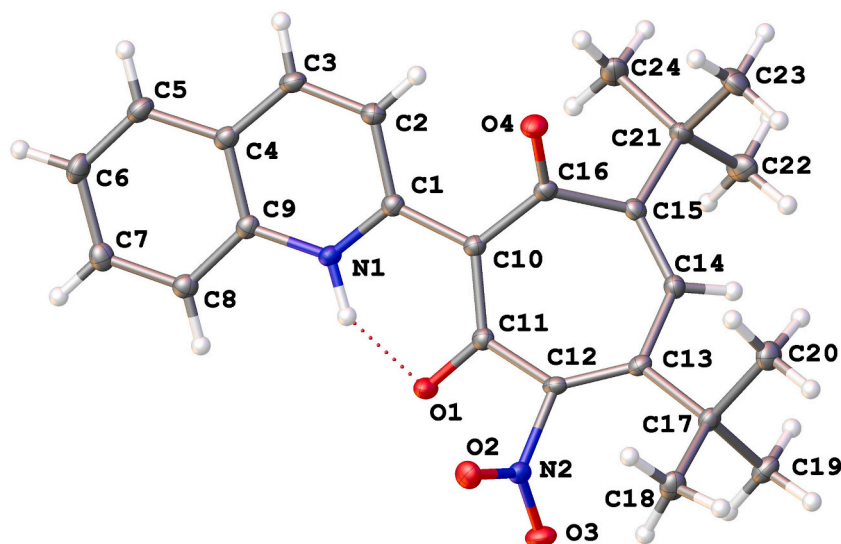
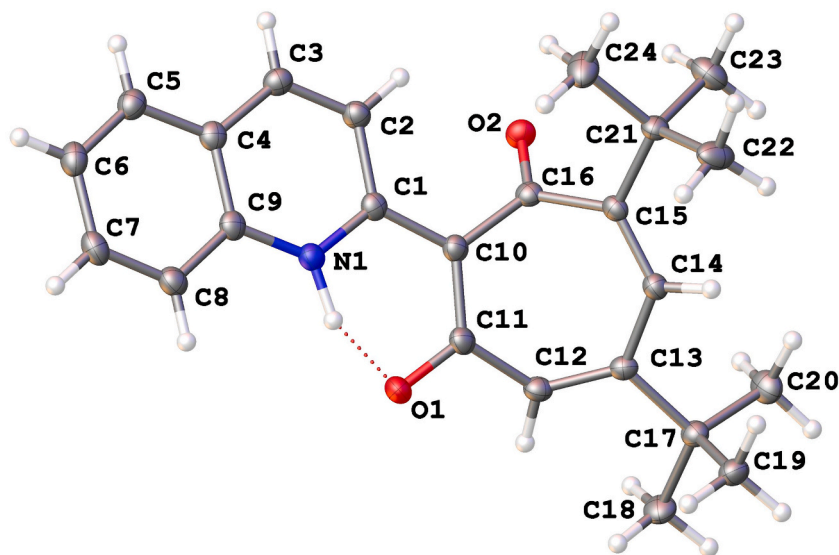**Fig. 1.** Molecular structure of 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-1,3-tropolone **4**.

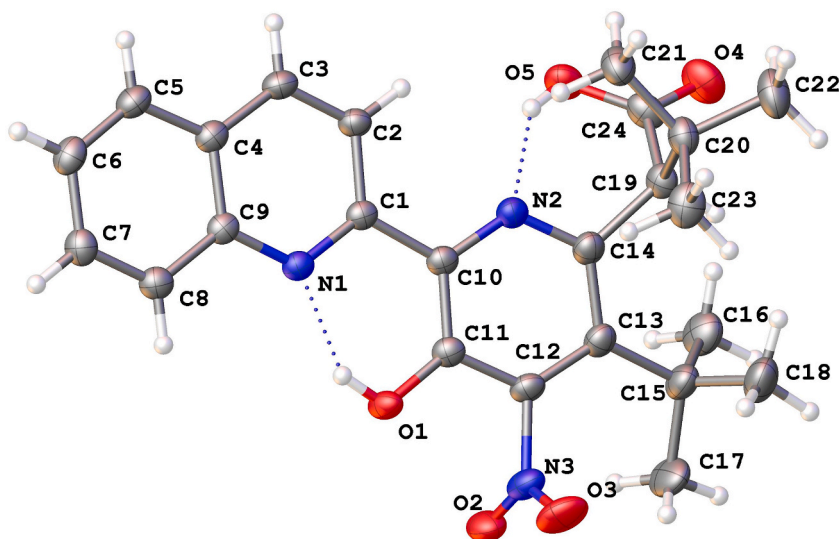**Fig. 2.** Molecular structure of 5,7-di (*tert*-butyl)-2-(quinolone-2-yl)-1,3-tropolone **5**.

Fig. 3. Molecular structure of 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-*tert*-butyl-6-(quinoline-2-yl)-pyridine-2-yl)butanoic acid **6**. Disordered 1-carboxy-2,2-dimethylpropyl fragments are omitted for clarity.

Unlike acid **6**, the heterocyclic fragments of the product of its decarboxylation **7** are slightly twisted with a torsion angle C (11)–C (10)–C (1)–N (1) of 9.648° (Fig. 4). This molecule also contains an intramolecular hydrogen bond with the following parameters: O (1)–C (11) = 1.3401 (14) Å, (N)1–(H)1 = 1.733 Å and angle N (1)–H (1)–O (1) = 149.203°.

The bond lengths of the carbonyl groups in **8** have a pronounced double bond character and are of 1.2115 (13) Å for O (1)–C (11) and 1.2111 (11) Å for O (2)–C (13) (Fig. 5). The angle between the planes formed by five-member cycles of 2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide, corresponds to the sp³-hybrid character of carbon atoms at the junction C (12)–C (16) and is equal to 66.26°.

3.4. Computational studies

Compounds **4** and **5** can exist in two tautomeric (OH) and (NH) forms (Scheme 2).

To theoretically evaluate geometry of the tautomeric forms of tropolones **4** and **5** in the gas phase and solvent (acetic acid) and the relative stability of the NH and OH tautomers, DFT B3LYP/6–311++G** calculations were performed, the results of which are given in Table 2. The calculations reproduce experimentally determined geometry of tropolones quite good, as well as their main structural
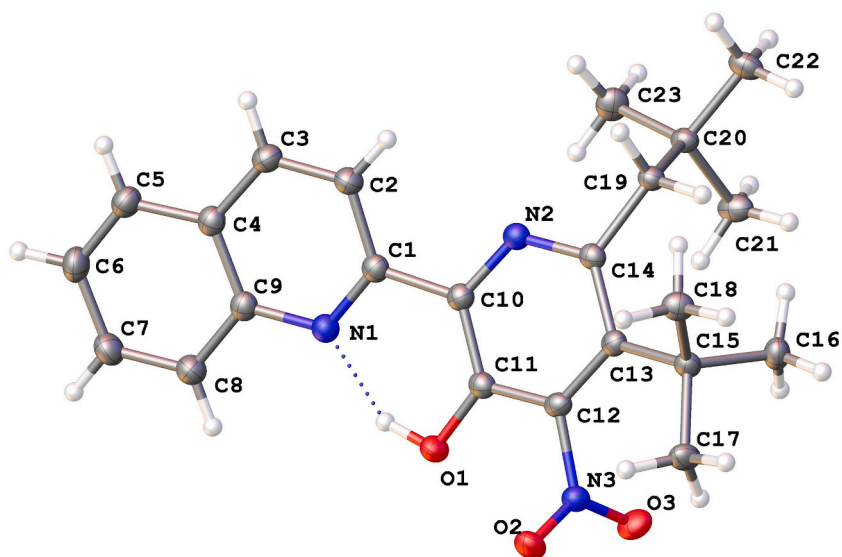
Fig. 4. Molecular structure of 6-(2,2-dimethylprop-3-yl)-5-*tert*-butyl-4-nitro-2-(quinoline-2-yl)-pyridine-3-ol **7**.
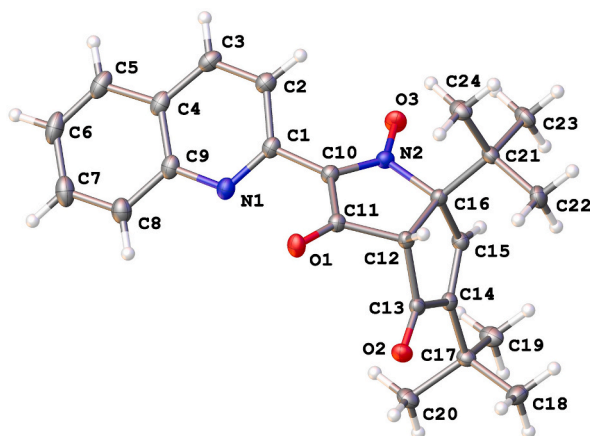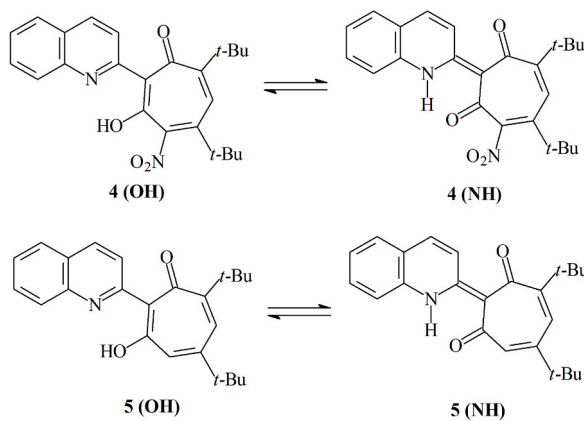

Fig. 5. Molecular structure of 1,7-di (*tert*-butyl)-3-(quinolin-2-yl)-2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide **8**.

Scheme 2. Intramolecular proton transfer in **4** and **5**.

Table 2

Total energies with zero-point energy correction (E_{tot} + ZPE, a.e.) and relative energies (ΔE, kcal mol^{-1}) of the NH and OH tautomers of **4** and **5**, calculated by the B3LYP/6–311++G** method in the gas phase (g) and acetic acid solution (s).

Structure	E_{tot} + ZPE (g)	ΔE_g	E_{tot} + ZPE (s)	ΔE_{sol}
4 (OH)	−1340.39931	0	−1340.41107	0
4 (NH)	−1340.40225	−1.85	−1340.41598	−3.08
5 (OH)	−1135.86197	0	−1135.87007	0
5 (NH)	−1135.86127	0.44	−1135.87106	−0.62

features, such as very short distances O···N and folding of the seven-membered rings. The largest difference between the experimental and calculated bond lengths does not exceed 0.02 Å.

According to theoretical evaluation, in the gas phase and in solution, the NH tautomeric form of **4** is the energy preferable to the OH form. In the case of tropolone **5**, the OH and NH tautomeric forms are energetically almost equivalent.

3.5. The proposed mechanism of o-quinone ring expansion and formation of compounds 4, 5 and 6

The proposed mechanism of formation of compounds **4, 5** and **6** is shown in Scheme 3.

The formation of 1,3-tropolones **4** and **5** proceeds through the reaction of *o*-quinone ring expansion. First, aldol condensation of 2-methylquinoline **1** with 1,2-benzoquinone **2** leads to the formation of intermediate adduct **A** – derivative of 6-(quinoline-2-ilmethylene)-6-hydroxy-2,4-cyclohexadiene-1-one, the structural analogue of which we have isolated and studied earlier [17]. The limiting stage of the reaction is a proton transfer from the methylene group of intermediate adduct **A** to the heterocyclic nitrogen atom with the formation of the methylenylidene intermediate **A′**. The calculated energy barrier for this stage for the reaction of 2-methyl-quinoline with 1,2-benzoquinone is 25.4 kcal mol^{-1} [17]. The intermediate **A′** is a bifurcation point from which the reaction can diverge into two channels, the first pathway of which corresponds to the reaction of *o*-quinone ring expansion, and the second to the contraction reaction. The *o*-quinone ring expansion is accompanied by a concert reaction of double proton transfer in the presence of acetic acid as shown for the transition state **A″** and undergoes cyclization with the formation of norcaradiene **B** ($\Delta E \sim 12.7$ kcal mol^{-1}) [17], which rearranges into cycloheptatriene **3 (C)** ($\Delta E \sim 0.9$ kcal mol^{-1}) [17]. In the reaction of the *o*-quinone ring contraction, proton transfer occurs only from the hydroxyl group, as shown for transition state **A′**, and is not accompanied by proton transfer from the heteroatom. This reaction pathway can be fully realized in the case of a highly basic heterocyclic nitrogen atom, as we have proved by the example of 2,3,3-trimethylindoline [9]. It should be mentioned that the reaction of *o*-quinone ring contraction competes with the expansion reaction only at high temperatures and, in this case, it is not realized at all at room temperature or moderate temperature (60–70 °C).

Intermediate **3 (C)** can exist in several tautomeric forms ($3C^1 \rightleftharpoons 3C^7$) due to proton migration in cycloheptatrienone, however, apparently the most thermodynamically stable is tautomer **3 (C^7)** that we have isolated. We consider the tautomeric form **3** as an intermediate in the formation of tropolones **4, 5** and acid **6**. Oxidation of intermediate **3 (C)** with an excess of 1,2-benzoquinone **2** can lead to the formation of 2-(quinoline-2-yl)-1,3-tropolone **4**, and the cleavage of the nitric acid molecule - to tropolone **5**.

The thermodynamic stability of **3 (C^1–C^7)** was studied using quantum chemical calculations, as shown in Fig. 6. The most thermodynamically stable tautomers are **3 (C^1)**, **3 (C^4)**, **3 (C^5)** and **3 (C^7)**. They are intermediates for the formation of tropolones **4, 5** and acid **6**. Tropolone **4** is formed by oxidation of intermediate **3 (C^2)**, the cleavage of the nitric acid molecule from **3 (C^4)** leads to tropolone **5**, and acid is formed from **3 (C^7)**. Tautomer **3 (C^5)** in this reaction probably does not participate in the formation of target compounds.

The formation of 3,3-dimethyl-2-(5-hydroxy-4-nitro-3-*tert*-butyl-6-quinoline-2-yl-pyridine-2-yl)butanoic acid **6** may be the result of cascade reactions **D→E→F**, which may include the stage of addition of a nitric acid molecule to intermediate **3 (C^7)**, the recyclization of the seven-membered cycle in **D** and the subsequent formation of the pyridine cycle in **F** from **E**, the dehydration of which leads to product **6**.

We performed a counter synthesis of acid **6** by treating compound **3** with sodium nitrite in acetic acid at room temperature to confirm that the isolated intermediate **3** is a synthon for the formation of this acid. As a result, acid **6** was obtained with a yield of 30%, which indirectly confirms the participation of nitrogen monoxide in the proposed mechanism of formation of **6**. Since sodium nitrite also has oxidizing properties, along with acid **6** nitrotropolone **4** (25%), tropolone **5** (15%) and the product of decarboxylation **7** in trace amounts (4%) were isolated in a counter synthesis.

3.6. The proposed mechanism of the reaction of the o-quinone ring contraction and the formation of compound 8

A competing process in the interaction of 2-methylquinoline **1** with hydroquinone **2** is the reaction of the *o*-quinone ring contraction, which results in the formation of a 2-azabicyclic product **8**. This reaction proceeds under more harsh conditions, which is confirmed by higher yields of **8** when boiling **1** and **2** in acetic acid (Table 1, method E). The detailed mechanism of the *o*-quinone ring contraction was studied using quantum chemical calculations on the example of the interaction of 2,3,3-trimethylindolines with quinone **2** [9]. The structural 2-*tert*-butylcyclopent-2-enone fragment in product **8** can be formed by contraction of the *o*-quinoline ring of nitroquinone **2**. A similar structural transformation of the *o*-quinone occurs after photodecarbonylation of 1,2-benzoquinones and is also the outcome of the interaction of 3,5-di (*tert*-butyl)-1,2-benzoquinone or 3,4,5,6-tetrachloro-1,2-benzoquinone with hydrogen
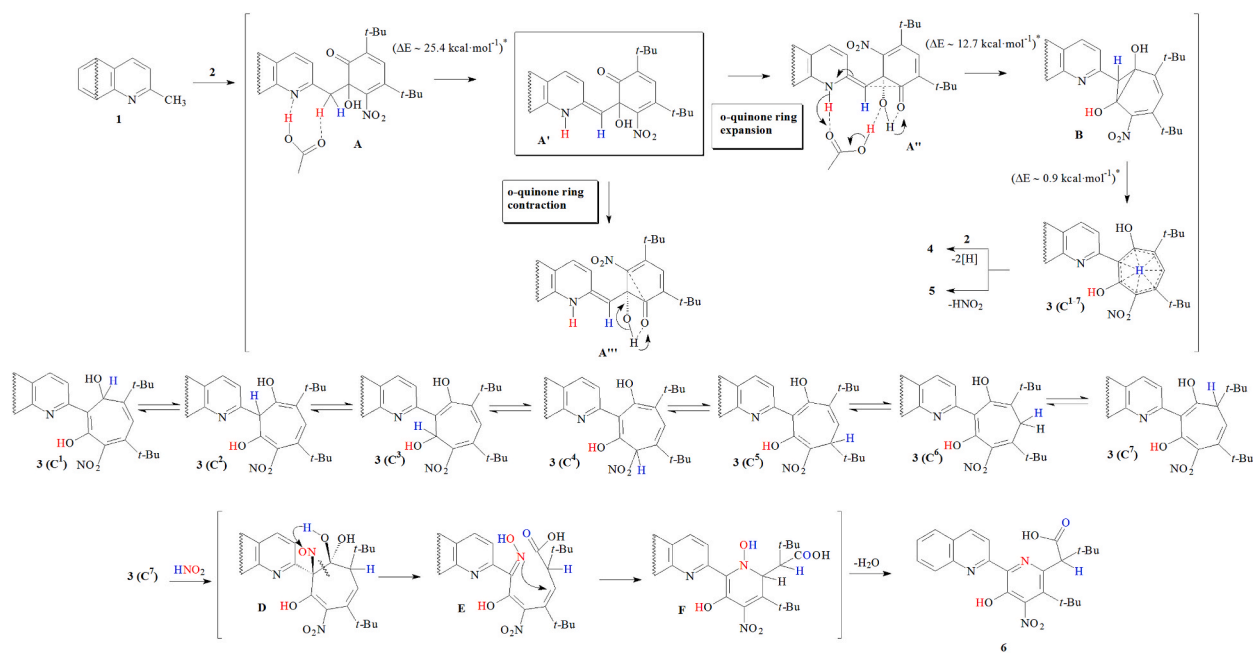
Scheme 3. The proposed mechanism of formation of tropolones **4**, **5** and acid **6**. * Calculated energy barrier of the main stage of the reaction of 2-methylquinoline with 1,2-benzoquinone [17]. ** Calculated energy barrier of the main stage of the reaction of 2,3,3-trimethylindoline with 1,2-benzoquinone [9].
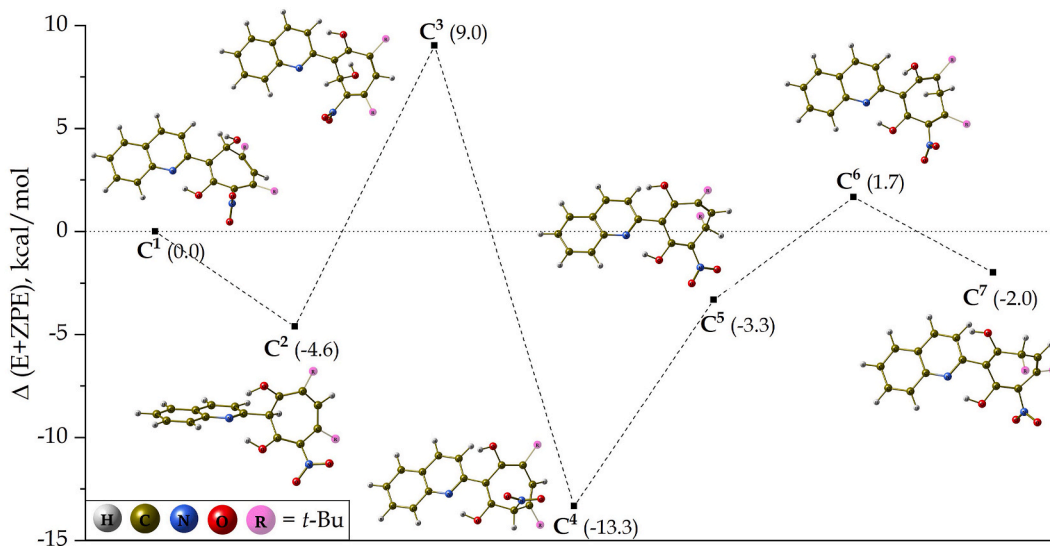

Fig. 6. Relative energies of $\mathbf{C^1}$–$\mathbf{C^7}$ isomers calculated using the DFT/B3LYP/6–311++G** (PCM, acetic acid) method. (Cartesian coordinates and energies of all stationary points are given in SM).

peroxide in the presence of catalytic amounts of iodine, leading to 2,4-di (*tert*-butyl)cyclopentadienone and 2,3,4,5-tetrachlorocyclopentadienone, respectively [27,28].

The key stages of the proposed mechanism for the formation of product **8** are shown in Scheme 4.

We believe that the main stage of contraction of the quinoid fragment occurs from the isomeric methylenylidene form **A′**, and the recyclization of this fragment is accompanied by a proton transfer from the hydroxyl to the carbonyl group, as shown for **A‴** [9]. Quantum chemical calculations [9] showed that it is one of the energy-expending stages and in the case of the reaction of 2,3,3-methylindoline with quinone **2** occurs through a barrier of 37 kcal mol^{-1}. The following two [1,5]-sigmatropic shifts, first of the heteroacyl group in **G** and then of the nitro group in **H**, can occur with low barriers of 20 kcal mol^{-1} [9] and lead to product **I**. The further reaction pathway involves the formation of a bicyclic structure **K** by means of coordinated double-proton transfer in **J** from a heterocyclic
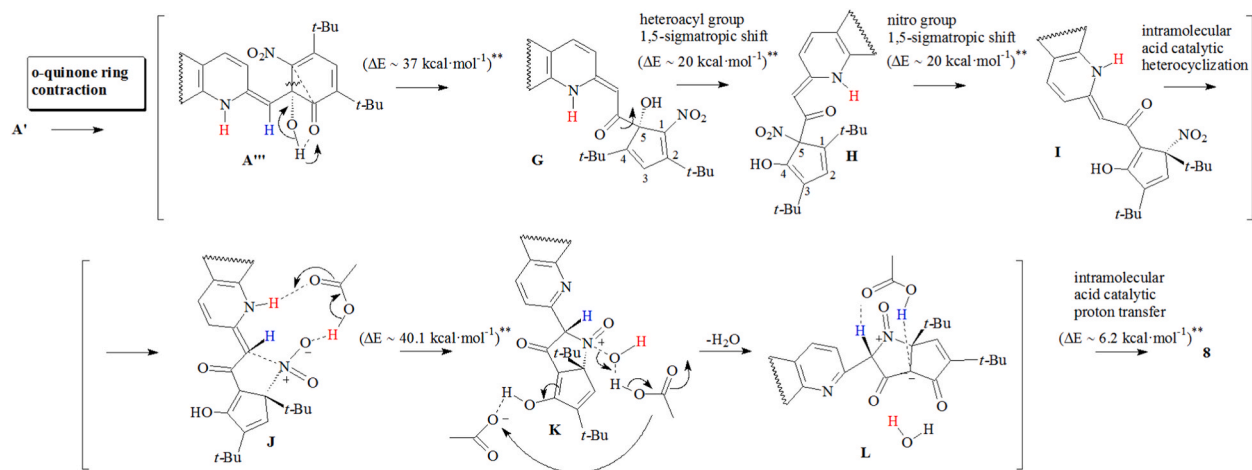
Scheme 4. The proposed mechanism for the formation of compound **8**. ** Calculated energy barrier of the main stage of the reaction of 2,3,3-tri-methylindoline with 1,2-benzoquinone [9].

nitrogen atom to an oxygen atom of a nitro group with an acetic acid molecule as the reaction catalyst. This is the most energy-consuming stage of the reaction **J→K**, which proceeds with a barrier of 40.1 kcal mol^{-1} [9]. The structure of the final reaction product **8** implies that the intermediate **K** must be dehydrated, followed by the transfer of a proton to the carbon atom of the bicyclic bridge fragment. The cleavage of a water molecule in intermediate **K** and the final low energy proton transfer (6.2 kcal mol^{-1}) [9] in intermediate **L** using acetic acid leads to a bicyclic product **8**.

It should be mentioned that the o-quinone ring contraction reaction proceeds at high temperatures and the formation of the bicyclic product **8** probably takes place under conditions of thermodynamic control. Consequently, the reaction products of the o-quinone ring expansion **3–6** are formed predominantly at room or moderate temperature as a result of kinetic control and overcoming a smaller energy barrier. At high temperatures, the o-quinone ring expansion can be completely inhibited due to the formation of a more thermodynamically favorable bicyclic product **8**. Thus, the expansion reaction of the o-quinone ring of 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone proceeds with maximum yields with prolonged heating of the reagents at room temperature or with moderate heating at 60 °C for a short time. In this case, 1,3-tropolone **5** without the nitro group is predominantly formed at room temperature. The results of the study can be used in investigation of interactions of methylene active heterocycles with 1,2-benzoquinones, to optimize methods of the o-quinone ring expansion and obtaining novel biologically active compounds.

4. Conclusions

In summary, this study have demonstrated that the condensation reaction of quinaldine with 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone can proceed with both expansion and contraction of the 1,2-benzoquinone o-quinone ring and result in the formation of heterocyclic compounds **3–8**. The formation of 1,3-tropolone derivatives **4,5** and pyridine-2-yl butanoic acid **6** proceeds through an expansion reaction, and the substituted 2-azabicyclo [3.3.0]octa-2,7-diene-4,6-dione-*N*-oxide **8** is formed through a contraction re-action of the o-quinone ring. It has been proposed that the formation of the reaction products of the expansion of the o-quinone ring of 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone is a result of kinetic control, and the formation of the product of the contraction of the o-quinone ring is realized due to thermodynamic control of reaction. The structure of the newly obtained heterocycles was studied using X-ray diffraction analysis, NMR spectroscopy, IR- and HRMS-spectrometry. Mechanisms of formation of tropolones **4,5** and acid **6** including the participation of an intermediate product of the o-quinone ring expansion - 5,7-di (*tert*-butyl)-4-nitro-2-(quinoline-2-yl)-cyclohepta-1,3,5-triene-1,3-diol **3** - were proposed. The proposed mechanisms of o-quinone ring expansion and contraction reactions suggest the formation of a methylenylidene intermediate **A′**, from which the reaction can diverge into two channels. The first pathway implies that the methylenylidene intermediate **A′**, due to a concerted reaction of double proton transfer from a heterocyclic nitrogen atom to a carbonyl oxygen atom involving an acetic acid molecule, undergoes cyclization with the o-quinone ring expansion and formation of norcaradiene **B**, rearrangement of which leads to intermediates **3(C^1-C^7)**. Quantum chemical calculations by the DFT PCM/B3LYP/6–311++G (d,p) method showed that tautomers **3 (C^1)**, **3 (C^4)**, **3 (C^5)** and **3 (C^7)** are the most thermodynamically stable, which in turn are key intermediates in the formation products of tropolones **4, 5** and acid **6**. According to theoretical evaluation of the relative stability of the NH and OH tautomers (**4** and **5**), the NH form of **4** is energy more preferable than the OH form. In the case of tropolone **5**, these tautomeric forms are practically energetically equivalent. The second way implies that the methylenylidene in-termediate **A'**, due to proton transfer only from the hydroxyl group to the carbonyl oxygen atom of the quinone fragment, undergoes recyclization with the o-quinone ring contraction and the formation of a derivative of cyclopent-2-enone **G**. Reactions between qui-naldine and 4,6-di (*tert*-butyl)-3-nitro-1,2-benzoquinone can be considered as model processes that occur in a group of 2-methylnitro-gen heterocycles in acid-catalyzed reactions with nitroquinones.

Author contribution statement

Tatyana A. Krasnikova, Inna O. Tupaeva, Evgeny A. Gusakov: Performed the experiments; Analyzed and interpreted the data.

Yurii A. Sayapin, Tran Dai Lam: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ilya V. Ozhogin: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Anton V. Lisovin, Mikhail V. Nikogosov: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Oleg P. Demidov: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Duong Nghia Bang, Nguyen Thi Thu Trang, Alexander D. Dubonosov: Analyzed and interpreted the data; Wrote the paper.

Vladimir I. Minkin: Conceived and designed the experiments.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

CCDC 2161836, 2161835, 2161821, 2161824 and 2,161,837 contain the supplementary crystallographic data for compounds **4**, **5**, **6**, **7** and **8**, correspondingly. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223–336–033; or by e-mail: deposit@ccdc.cam.ac.uk. Supplementary material associated with this article can be found at http://

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16943.

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