IRSTI 31.21.19
Section: Chemistry
Article

Synthesis of N-acylalkylpyrazoles and the influence of their structure on cytotoxicity properties

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Abstract: Pyrazole and its derivatives are π-electron-excess aromatic heterocyclic compounds, the ring structure of which contains two bonded nitrogen atoms. Pyrazoles are attracting increasing attention of scientists due to their extensive and diverse range of biologically active properties.

In this study a series of *N*-(acylalkyl)pyrazole derivatives were synthesized by reactions of aliphatic and aromatic α-bromideketones with pyrazole and its 3,5-dimethyl- and 3,5-diphenyl- derivatives via a two-stage *one-pot* reaction, in the presence of the K_2CO_3 base. Thus, new, previously undescribed N-pinacolopyrazoles with yields of 65–92% and N-phenacylpyrazoles with yields of 38–91% were obtained.

The structures of the products were characterized by NMR, IR, X-ray diffraction and GC-mass spectrometry. According to the X-ray diffraction results, *N*-(acylalkyl)pyrazoles are conjugated π-systems, in the formation of crystals of which carbonyl groups participate.

The cytotoxicity of the studied *N*-acylalkylpyrazoles towards *Artemia Salina* crustaceans has been determined, and the toxicity depends on the type of substituents. Thus, *N*-phenacylpyrazole has a cytotoxicity 6 times higher than the cytotoxicity of *N*-pinacolonpyrazole, and the cytotoxicity of *N*-phenacylpyrazoles varies depending on the substituents in the benzene ring, and decreases in the presence of acceptors. The results of the cytotoxicity study can be used to develop drugs with their further modification.

Keywords: pyrazole, *N*-acylalkylation, α-bromoketones, NMR, X-ray structural analysis, cytotoxicity, *Artemia Salina*.

Citation: Alzhapparova, N., Panshina, S., Ibrayev, M., Zhumina, A., Orazbay, A. (2025). Synthesis of N-acylalkylpyrazoles and the influence of their structure on cytotoxicity properties. Bulletin of the L.N. Gumilyov ENU. Chemistry. Geography. Ecology Series, 152(3), 42-56. https://doi.org/10.32523/2616-6771-2025-152-3-42-56

Academic Editor:
E.Ye. Kopishev

Received: 26.08.2025
Revised: 17.09.2025
Accepted: 18.09.2025
Published: 30.09.2025

1. Introduction

Pyrazoles are five-membered π-electron-rich aromatic heterocyclic compounds that have two linked nitrogen atoms (N–N bond) in the ring structure (Elguero, J., et al., 1995; Rague Schleyer, P., et al., 1996; Schmidt A., 2011; Stanovnik, B., et al., 2003), in addition, the molecules of pyrazole 1a are planar and strongly associated due to hydrogen bonds (Cour, T. et al., 1973; Sikora, M. et al., 2013) (Figure 1a).

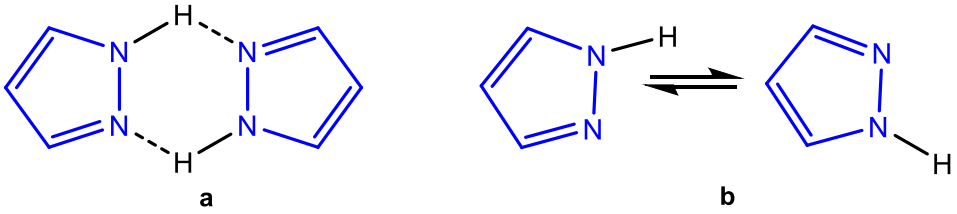


Figure 1. Hydrogen bonds in the molecule of pyrazole **1a** (a) and its prototropic tautomerism (b)

Pyrazole ring derivatives have wide applications in various fields of human activity such as technology, medicine and agriculture (Al-Aizari, F.A. et al., 2018). Pyrazoles are considered an important class of nitrogen-containing heterocyclic compounds due to their wide range of biological activities (Ansari, A. et al., 2017; Schmidt A., 2011). In medical sources, pyrazole derivatives are described as substances with antibacterial (Alan, R. K., 1997; Karrouchi, K. et al., 2018; Secrieru, A. et al., 2019), analgesic, antimicrobial, antiviral, antidepressant and anticancer properties (Karrouchi K. et al., 2018). In addition, pyrazole is the main component of many pharmaceutical and agrochemical substances (Unnava, R. et al., 2016). Thus, pyrazole systems as biomolecules are currently attracting more and more attention from scientists due to their interesting pharmacological properties (Calenda S., et al., 2024; Özdemir, Z., et al., 2015; Salerno, L., et al., 2012; Sharma, T., et al., 2020; Sharma, T., et al., 2021).

Pyrazoles are usually synthesized by classical cyclocondensation of hydrazine derivatives with a,b-unsaturated aldehydes and ketones (Karrouchi, K., et al., 2018; Katritzky, A. R. et al., 2001; Lei, J., et al., 2021).

The presence of a mobile hydrogen atom of the NH-group and the main center – a nitrogen atom of the pyridine type, in the pyrazole molecule is the reason for the manifestation of prototropic, or so-called azole tautomerism (Secrieru, A., et al., 2019). Prototropic tautomerism of pyrazole and its homologues is due to the migration of a proton from the NH-group (Alan, R.K., 1997) (Figure 1, b).

The acid-base properties of pyrazole are due to the presence of pyrrole and pyridine nitrogen atoms in its structure (Secrieru, A., et al., 2019). Due to the pyridine nitrogen atom, pyrazole exhibits basic properties (pK_b = 11.5), and due to the pyrrole nitrogen atom, it exhibits weak acidic properties (pK_a = 2.49) (Perrin, D. D., 1965). Moreover, the acidic proton of the NH-group is easily subject to N-alkylation and N-acylation and N-alkylacylacylation reactions (Castillo, J.M., et al., 2019).

Thus, in the scientific literature (Dhiman, Sh., et al., 2018; Marcos, A.P.M., et al., 2010; Solomons, T.W., et al., 1965) one can find a large number of examples and conditions for the synthesis of *N*-alkylated and *N*-alkylacylated pyrazoles 1 at the nitrogen atom of the NH-group (Alan, R.K., 1997), in addition, pyrazoles have the ability to be alkylated again to form salts (Solomons, T.W., et al., 1965). The formation of salts occurs due to interaction with the nitrogen atom of the pyridine type, which exhibits weak basic properties. Pyrazole salts are quite stable compounds and their stability is due to the delocalization of the positive charge in the pyrazolium cation (Figure 2), or the negative charge in the pyrazolide anion between all the atoms of the ring (Solomons, T.W., et al., 1965)

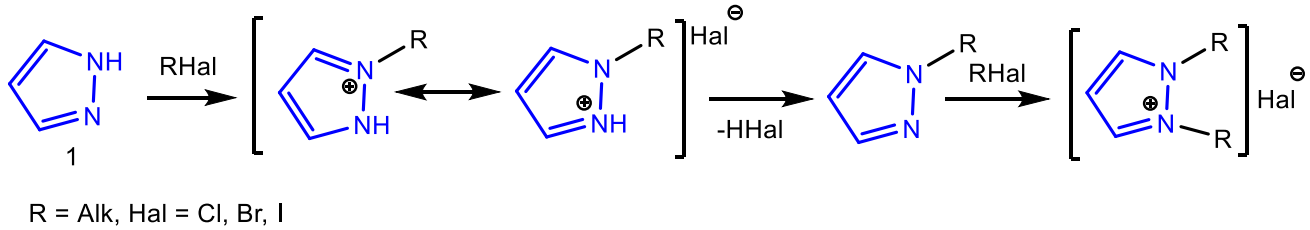


Figure 2. Formation of pyrazole salts by delocalization of the positive charge in the pyrazolium cation

Taking into account the above-described properties of pyrazole **1a**, in this work, we investigated a series of *N*-acylalkylation reactions of pyrazoles **1a-c** with *α*-bromoketones **2a**, **4a-g** via *one-pot* reaction in the presence of a base to release the intermediate salt and eliminate hydrogen bromide. The resulting series of products were characterized by IR and NMR spectroscopy, GC-mass spectrometry. The structural features of 1-tertbutyl-2-(1H-pyrazol-1-yl)ethan-1-one **3a** and 1-phenyl-2-(1H-pyrazol-1-yl)ethan-1-one **5a** were studied by X-ray diffraction, and the cytotoxicity properties of *N*-acylalkylpyrazoles **3a, 5a-c, e, g** on crustaceans *Artemia Salina* were considered.

2. Materials and methods

The starting materials for the syntheses were reagents purchased from Acros, Merck and Aldrich, which were used without further purification. All reactions and purity were monitored by thin-layer chromatography (TLC) on Silufol plates with detection by iodine vapor. Melting and boiling points were determined in open capillaries using a Buchi M560 device.

^{1}H NMR and ^{13}C NMR spectra were obtained using Agilent 400-MR (400 MHz for ^{1}H, 100 MHz for ^{13}C) spectrometer in $CDCl_3$ (chemical shift: δ = 7.26 for ^{1}H, δ = 77.76 for ^{13}C) and DMSO-d_6 (chemical shift: δ = 2.47 for ^{1}H, δ = 40.03 for ^{13}C). Hexamethyldisiloxane was used as an internal standard. Splitting is reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and coupling constants are given in Hz. High-resolution mass spectra were recorded on a GC-Mass analysis was performed on an Agilent 7890A gas chromatograph with an Agilent 5975C mass-selective detector on an Rtx DHA-100 column; carrier gas was helium. The samples were dissolved in 1 ml of acetone. Analysis time was 32 minutes. X-ray analysis was done on a single-crystal diffractometer STADIVARI Pilatius 100K with *λ* Cu-K*α* radiation using focusing mirrors. The IR spectra were obtained using a FSM 1201 FT-IR spectrophotometer in a KBr pellet, in the frequency range: 400 – 4000 cm^{-1}.

Methodology for studying cytotoxic properties

Artificial sea water, 1 liter in volume, was prepared from the following substances, according to the method (Kester, D.R. et al., 1967): NaCl (0.409 mol), Na_2SO_4 (0.028 mol), KCl (0.009 mol), $NaHCO_3$ (0.009), KBr (0.0008 mol), H_3BO_3 (0.0004 mol), NaF (0.00007 mol).

The cytotoxic activity of the extract was determined according to the method (Solis, P.N. et al., 1992; Suleimenov, E.M., 2009). For the analysis, 200 mg of Artemia salina eggs in 1 liter of artificial seawater were used. *Artemia Salina* cysts were kept under aeration conditions with constant illumination and a temperature of 25°C for 2–3 days until hatching. Then one side of the vessel was covered with aluminum foil, and 5 minutes later, the larvae that had gathered on the bright side were removed with a Pasteur pipette. Each sample was tested in three parallel experiments. 20–40 larvae (nauplii) were placed in 0.990 ml of seawater in a 2 ml cell of a laboratory plate. A 10 mg/ml stock solution of the studied substance **3a, 5a-c, e, g** was prepared in dimethyl sulfoxide, and 0.10 ml of this solution was added to the cell. For the negative control, only 0.10 ml of dimethyl sulfoxide was added. The relative deviation of the percentage of dead *Artemia* from the control values was calculated. Solutions with 10 μg/ml of the studied substances **3a**, **5a-c**, **e**, **g** were added and the number of dead larvae was counted. The results were read by counting under a dissecting microscope.

The cytotoxic activity was determined using the method (Meyer, B.N. et al., 1982). The number of dead individuals was calculated after 1, 4 and 24 hours, with the determination of the concentration of the studied toxicant **3a**, **5a-c**, **e**, **g,** which causes the death of 50% of crustaceans in 24 hours. The percentage of mortality (P) was calculated using the following formula:

$$P = \frac{(A - N - B)}{Z} * 100\%$$

where *A* is the number of dead larvae after 24 h; *N* is the number of dead larvae before the experiment; *B* is the average number of dead larvae in the control sample; *Z* is the total number of larvae. The results are shown in Table 1.

Based on the number of dead larvae, the cytotoxic activity of the studied compounds on Artemia salina larvae was determined, where the LC_{50} (μg/ml) (lethal concentration) at which 50% of the larvae die was determined.

Preparation of 1-(pinacolone)pyrazoles 3a-c

Synthesis of 1-tertbutyl-2-(1H-pyrazol-1-yl)ethan-1-one **3a**

2 g (0.0294 mol) of pyrazole **1a** and 15 ml of acetone were placed in a 100 ml round-bottomed flask. Then, 4 g (0.0294 mol) of anhydrous potassium carbonate was added to the mixture. Then, 3.95 ml (5.3 g, 0.0294 mol) of 1-brompinecolone **2a** was added to the mixture while stirring. The reaction mass was stirred for 24 hours at room temperature. Then the reaction mixture was filtered of inorganic salts. The solvent was evaporated on a rotary evaporator. The precipitated yellowish crystals **3a** were dried in air. The yield of product **3a** is 4 g (84%). M.p. 56°C. ^{1}H NMR ($CDCl_3$) δ (ppm) 8.54 (d, J = 3.0, 1H, Pyr), 8.08 (d, J = 6.8, 1H, Pyr), 6.71 (t, J = 3.0, 1H, Pyr), 4.67 (s, 2H, CH_2), 1.28 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ (ppm) 205.92 (C=O), 139.34 (CH, Pyr), 129.81 (CH, Pyr), 107.48 (CH, Pyr), 56.53 (CH_2), 43.89 ($\underline{C}(CH_3)_3$), 26.34 ($C(\underline{CH_3})_3$). GC-MS Retention time 11.759 min, m/z (EI) = 166, 151, 138, 109, 85, 81, 57, 41, 29, 28. IR ν, cm^{-1} (KBr, neat): 2959 (CH_3), 1716 (C=O), 1597 (C=N).

The synthesis of 1-tertbutyl-2-(3,5-dimethyl-1H-pyrazol-1-yl)ethan-1-one **3b** and 1-tertbutyl-2-(3,5-diphenyl-1H-pyrazol-1-yl)ethan-1-one **3c** was carried out in strict accordance with the method for the preparation of **3a** using the appropriate reagents.

Yield of product **3b** is 3.7 g (65%), light yellow crystals. M.p. 82°C. ^{1}H NMR (DMSO-d_6) δ (ppm) 5.82 (s, 1H, Pyr), 5.15 (s, 2H, CH_2), 2.05 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.14 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6) δ (ppm) 209.55 (C=O), 146.27 (C, Pyr), 140.67 (C, Pyr), 105.42 (CH, Pyr), 53.97 (CH_2), 43.26 ($\underline{C}(CH_3)_3$), 26.27 ($C(CH_3)_3$), 13.60 (CH_3), 10.88 (CH_3). GC-MS Retention time 15.409 min, m/z (EI) = 194, 180, 166, 137, 109, 85, 57, 41, 29, 28. IR ν, cm^{-1} (KBr, neat): 2959 (CH_3), 1620 (C=O), 1593 (C=N).

Yield of product **3c** is 8.6 g (92%), light beige crystals. M.p. 110°C ^{1}H NMR (DMSO-d_6) δ (ppm) 7.81 (d, J = 7.1, 2H, Ph), 7.46 – 7.42 (m, 2H, Ph), 7.42 – 7.35 (m, 5H, Ph), 7.29 (t, J = 7.3, 1H, Ph), 6.87 (s, 1H, Pyr), 5.34 (s, 2H, CH_2), 1.02 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6) δ (ppm) 209.52 (C=O), 150.16 (C, Pyr), 145.95 (C, Pyr), 133.62, 130.58, 129.30, 129.28, 129.22, 128.88, 128.15, 125.62 (Ph), 104.03 (CH, Pyr), 55.54 (CH_2), 43.39 ($\underline{C}(CH_3)_3$), 26.16 ($C(CH_3)_3$). GC-MS Retention time 28.480 min, m/z (EI) = 220, 191 165, 117, 77, 51, 39. IR ν, cm^{-1} (KBr, neat): 3015 (CH), 2959 (CH_3), 1720 (C=O), 1620 (C=N).

Preparation of 1-(phenacyl)pyrazoles 5a-g

Synthesis of 1-phenyl-2-(1H-pyrazol-1-yl)ethan-1-one **5a.**

3.4 g (0.05 mol) of pyrazole **1a** and 15 ml of acetone were placed in a 250 ml round-bottomed flask. Then, 6.9 g (0.05 mol) of anhydrous potassium carbonate was added to the mixture. Then, 10 g, (0.05 mol) of phenacylbromide **4a** was added to the mixture while stirring. The reaction mass was stirred for 24 hours at room temperature. Then the reaction mixture was filtered of inorganic salts. The solvent was evaporated on a rotary evaporator. The precipitated yellowish crystals **5a** were dried in air. The yield of product **5a** is 8.4 g (91%). M.p. 95°C. ^{1}H NMR ($CDCl_3$) δ (ppm)

7.95 – 7.89 (m, 2H, Ph), 7.59 – 7.52 (m, 2H, Ph), 7.48 – 7.42 (m, 4H, Ph, Pyr), 6.31 (t, J = 4.4, 1H, Pyr), 5.54 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ (ppm) 192.62 (C=O), 139.98 (CH, Pyr), 134.66 (C, Ph), 134.12 (CH, Pyr), 131.03 (C, Ph), 129.03 (CH, Ph), 128.19 (CH, Ph), 106.59 (CH, Pyr), 57.75 (CH_2). GC-MS Retention time 17.590 min, m/z (EI) = 186, 158, 105, 77, 51, 41, 28. IR ν, cm^{-1} (KBr, neat): 3013 (CH), 2986 (CH_2), 1685 (C=O), 1601 (C=N)

The synthesis of 1-(4-bromophenyl)-2-(1H-pyrazol-1-yl)ethan-1-one **5b**, 1-(2-methoxyphenyl)-2-(1H-pyrazol-1-yl)ethan-1-one **5c** and 1-(4-trifluoromethoxyphenyl)-2-(1H-pyrazol-1-yl)ethan-1-one **5d** was carried out in strict accordance with the method for the preparation of 5a using the appropriate reagents.

Yield of product **5b** is 11.9 g (90%), light beige crystals. M.p. 156°C. ^1H NMR ($CDCl_3$) δ (ppm) 7.84 (d, J = 8.6, 2H, Ph), 7.65 (d, J = 8.6, 2H, Ph), 7.59 (d, J = 1.9, 1H, Pyr), 7.50 (d, J = 2.3, 1H, Pyr), 6.37 (t, J = 2.2, 1H, Pyr), 5.56 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ (ppm) 193.45 (C=O), 139.40 (CH, Pyr), 134.08 (C, Ph), 132.41 (2CH, Ph), 131.95 (CH, Pyr), 130.47 (2CH, Ph), 128.43 (C, Ph), 106.01 (CH, Pyr), 58.01 (CH_2). GC-MS Retention time 21.176 min, m/z (EI) = 264, 236, 183, 155, 104, 76, 50, 41, 28. IR ν, cm^{-1} (KBr, neat): 3117 (CH), 2996 (CH_2), 1709 (C=O), 1589 (C=N), 991, 551 (C-Br)

Yield of product **5c** is 4.1 g (38%), light beige crystals. M.p. 70°C. ^1H NMR ($CDCl_3$) δ (ppm) 7.84 (dd, J = 7.8, 1.9, 1H, Ph), 7.52 (d, J = 1.9, 1H, Pyr), 7.49 (ddd, J = 8.6, 7.4, 1.9, 1H, Ph), 7.44 (d, J = 2.3, 1H, Pyr), 6.99 (td, J = 8.3, 3.3, 2H, Ph), 6.30 (t, J = 2.2, 1H, Pyr), 5.53 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ (ppm) 193.82 (C=O), 159.48 (C, Ph), 139.65 (CH, Pyr), 135.07 (CH, Ph), 131.28 (CH, Ph), 131.07 (CH, Pyr), 125.00 (C, Ph), 121.21 (C, Ph), 111.71 (CH, Ph), 106.15 (CH, Pyr), 62.11 (OCH_3), 55.71 (CH_2). GC-MS Retention time 20.714 min, m/z (EI) = 216, 188, 157, 135, 105, 92, 77, 64, 51, 41, 28. IR ν, cm^{-1} (KBr, neat): 3016 (CH), 2996 (CH_2), 1689 (C=O), 1597 (C=N), 1288, 1022 (C-O-C).

Yield of product **5d** is 9.9 g (73%), light beige crystals. M.p. 138°C. ^1H NMR ($CDCl_3$) δ (ppm) 7.93 (d, J = 8.8, 2H, Ph), 7.49 (d, J = 1.9, 1H, Pyr), 7.41 (d, J = 2.3, 1H, Pyr), 7.22 (d, J = 8.4, 2H, Ph), 6.27 (t, J = 2.1, 1H, Pyr), 5.49 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ (ppm) 191.22 (C=O), 153.27 (C, Ph), 140.10 (CH, Pyr), 132.76 (C, Ph), 130.86 (CH, Pyr), 130.32 (2CH, Ph), 120.61 (2CH, Ph), 106.70 (CH, Pyr), 57.66 (CH_2). GC-MS Retention time 17.040 min, m/z (EI) = 270, 242, 189, 161, 133, 95, 84, 70, 64, 51, 28. IR ν, cm^{-1} (KBr, neat): 3096 (CH), 2996 (CH_2), 1709 (C=O), 1612 (C=N), 1300, 1030 (C-O-C), 1200 (C-F).

Synthesis of 1-(4-nitrophenyl)-2-(1H-pyrazol-1-yl)ethan-1-one 5e

3.4 g (0.05 mol) of pyrazole **1a** and 15 ml of acetone were placed in a 250 ml round-bottomed flask. Then, 6.9 g (0.05 mol) of anhydrous potassium carbonate was added to the mixture. Then, 12,2 g, (0.05 mol) of 4-nitrophenacylbromide **4e** was added to the mixture while stirring. The reaction mass was stirred for 24 hours at room temperature. Then the precipitate was filtered, washed with acetone, and then washed with water to remove impurities of inorganic salts, and dried in air. A light beige powder of **5e** was obtained. The yield of product **5e** is 10.4 g (90%). M.p. 202°C. ^1H NMR (DMSO-d_6) δ (ppm) 8.37 (d, J = 8.5, 2H, Ph), 8.23 (d, J = 8.5, 2H, Ph), 7.74 (d, J = 2.3, 1H, Pyr), 7.48 (d, J = 1.8, 1H, Pyr), 6.32 (t, J = 2.2, 1H, Pyr), 5.90 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ (ppm) 195.77 (C=O), 150.71 (C, Ph), 140.22 (C, Ph), 139.45 (CH, Pyr), 129.65 (CH, Pyr), 128.65 (2CH, Ph), 124.35 (2CH, Ph), 106.17 (CH, Pyr), 58.46 (CH_2). IR ν, cm^{-1} (KBr, neat): 3097 (CH), 2995 (CH_2), 1709 (C=O), 1611 (C=N), 1523, 1350 (NO_2).

The synthesis of 1-(4-hydroxyphenyl)-2-(1H-pyrazol-1-yl)ethan-1-one **5f** and 1-(4-(methylsulfonyl)phenyl)-2-(1H-pyrazol-1-yl)ethan-1-one **5g** was carried out exactly according to the method for the preparation of **5e** using the appropriate reagents.

Yield of product **5f** is 8.5 g (84%), light beige powder. M.p. 255°C. ^1H NMR (DMSO-d_6) δ (ppm) 10.01 (s, 1H, OH), 8.08 (s, 1H, Pyr), 8.06 (s, 2H, Ph), 7.60 (s, 2H, Ph), 7.25 (s, 1H, Pyr), 6.34 (s, 1H, Pyr), 4.66 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ (ppm) 192.30 (C=O), 163.13 (C, Ph), 138.24 (CH, Pyr), 130.57 (2CH, Ph), 128.55 (CH, Pyr), 127.82 (C, Ph), 115.19 (2CH, Ph), 100.72

(CH, Pyr), 70.49 (CH_2). IR ν, cm^{-1} (KBr, neat): 3500 (OH), 2995 (CH_2), 1701 (C=O), 1593 (C=N), 1230 (C-O).

Yield of product **5g** is 10.3 g (78%), light beige powder. M.p. 178°C. ^{1}H NMR (DMSO-d_6) δ (ppm) 8.24 (d, J = 8.5, 2H, Ph), 8.11 (d, J = 8.5, 2H, Ph), 7.74 (d, J = 2.4, 1H, Pyr), 7.49 (d, J = 2.0, 1H, Pyr), 6.33 (t, J = 2.3, 1H, Pyr), 5.90 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6) δ (ppm) 193.82 (C=O), 145.29 (C, Ph), 139.50 (CH, Pyr), 138.79 (C, Ph), 131.96 (CH, Pyr), 129.42 (2CH, Ph), 127.87 (2CH, Ph), 106.11 (CH, Pyr), 58.37 (CH_2), 43.59 (CH_3). GC-MS Retention time 25.751 min, m/z (EI) = 249, 247, 223, 183, 155, 121, 103, 76, 70, 50, 28, 15.

3. Results

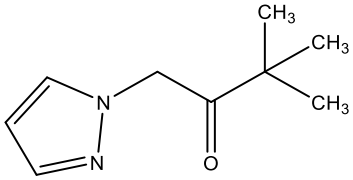
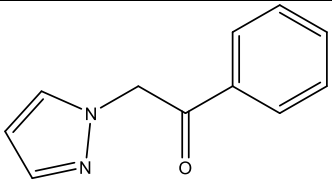
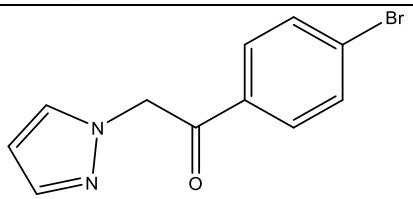
The results of this study are presented in a series of reactions to create new N-acylalkylated pyrazoles **3a-c, 5c**, **f**, **g**. Thus, the interaction of pyrazoles **1a-c** with α-bromoketones **2a**, **4a-g** was carried out via a one-pot reaction in the presence of a base to neutralize the released hydrogen bromide. Probable reaction mechanism of the N-acylalkylation reaction with α-bromoketones **2a**, **4a-g** are considered.

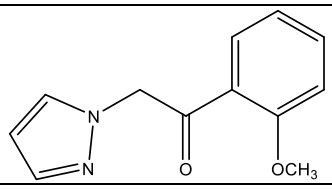
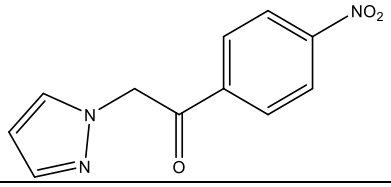
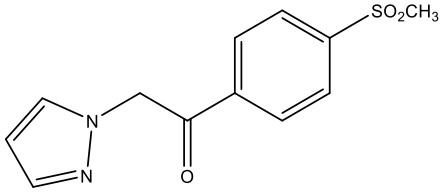
The structures of the obtained products are characterized by NMR, IR, and GC-mass spectrometry. The crystal structures of tert-butyl-1-(pyrazol-1-yl)butan-2-one **3a** and 1-phenyl-2-(pyrazol-1-yl)ethan-1-one **5a** were described by X-ray diffraction, according to which, N-(acylalkyl)pyrazoles **3a** and **5a** are conjugated π-systems, and carbonyl groups participate in the formation of their crystals.

The studied compounds **3a**, **5a-c, e, g** showed some manifestation of cytotoxicity towards the crustacean Artemia Salina (Table 1).

The results of the cytotoxicity study show the possibility of varying the cytotoxic properties of the substance by introducing a certain functional group. Thus, N-phenacylpyrazole **5a** showed the highest toxicity, and in the presence of an acceptor group in the benzene ring of the N-phenacyl substituent (**5e**), the toxicity of the studied compounds decreases.

Table 1. Results of cytotoxicity test of **3a**, **5a-c, e, g** on *Artemia Salina*

№	Formula	Concentration (mg/ml)	Mortality (after 24 hours), %	LC_{50} μg/ml)
3a		100	1.87	**644.00**
		500	2.41	
		1000	96	
5a		100	18.75	**108.89**
		500	92.59	
		1000	99	
5b		100	76.64	**153.00**
		500	82.86	
		1000	91.84	

5c		100	4.04	**264.00**
		500	94.32	
		1000	96.04	
5e		100	7.07	**3045.00**
		500	12.5	
		1000	13.00	
5g		100	7.23	**723.00**
		500	49.00	
		1000	50.00	

4. Discussion

Thus, *N*-acylalkylpyrazoles can be synthesized by two methods (Babaev et al., 2025), where the first involves *N*-acylalkylation of pyrazoles **1a-c** with *α*-bromoketones **2a, 4a-g** with the isolation of an intermediate salt, from which the *N*-acylalkylation products are released by treatment with a base; the second approach involves *one-pot* reaction in the presence of a base, bypassing the stage of obtaining salts. Taking into account the convenience of the latter method, we obtained a series of substances **3a-c, 5a-g** with the simultaneous use of a base – K_2CO_3.

In the scientific literature, one can find a large number of examples and conditions for carrying out *N*-alkylation reactions with *α*-haloketones in the presence of alkaline reagents (Dago et al., 2018; Solomons et al., 1965). The base K_2CO_3 was chosen as the base due to previous experience with its use (Babaev et al., 2025) and its easy availability; in addition, stronger bases may lead to unwanted side effects (Balasubrahmanya, K.S. et al., 2023).

To obtain a series of products **3a-c, 5a-g**, unsubstituted pyrazole **1a** and two of its derivatives **1b, c**, two types of *α*-haloketones, were used: aliphatic brompinacolone **2a** (Figure 3) and a series of aromatic phenacyl bromides **4a-g** (Figure 4).

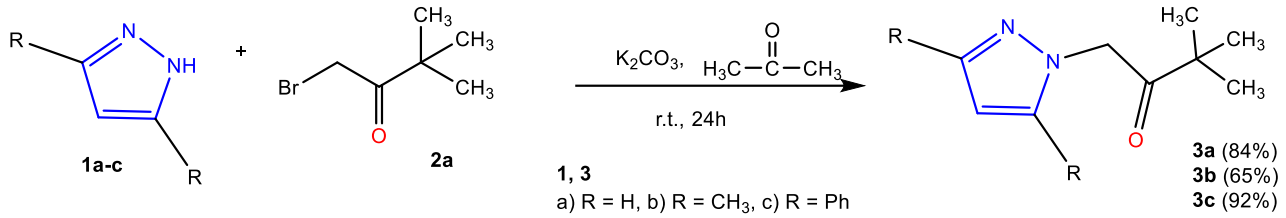


Figure 3. Scheme for the synthesis of pinacolonpyrazoles **3a-c**

Thus, under the conditions we have chosen, the reaction (Figure 3) occurs in the presence of a base – potassium carbonate, which, in parallel with the N-alkylation reaction one-pot, neutralizes the released hydrobromide with the formation of inorganic salts, as well as target products 3a-c. Substance 3a was obtained with a yield of 84% and is a low-melting light-yellow crystal. In reactions with substituted pyrazoles 1b, c, N-acylalkylation products 3b and 3c were obtained in yields of 65% and 92%, respectively. The higher yield of 3c is probably due to the lipophobicity of the phenyl substituents. With long-term standing of mother solutions 3b, an additional 10–20% of the product can be extracted. Compounds 3a-c were characterized by IR, NMR spectroscopy and

GC-MS. The structure of tert-butyl-1-(pyrazol-1-yl)butan-2-one 3a was described using X-ray diffraction analysis (Figure 7).

Corresponding approaches have been implemented in other examples of N-acylalkylation of pyrazole 1a with phenyl-substituted α-haloketones 4a-g (Figure 4).

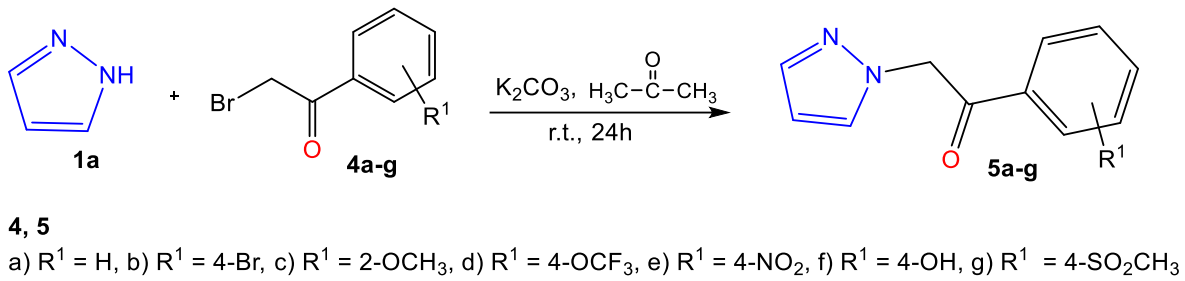


Figure 4. Scheme for the synthesis of phenacylpyrazoles **5a-g**

Referring to the author's reasoning (Baker, J., 1941), it can be assumed that the interaction of *α*-haloketones **2a, 4a-g** with pyrazoles **1a-c** involves the carbonyl group taking an active part in the process in the reactions of substitution of the bromine atom by the pyrazole anion. In particular, when bromine is exchanged for a pyrazole group, the primary interaction of the reagent with the carbon atom of the carbonyl group occurs. In the formed anion, an electron shift occurs, shown by the arrows (pinacol electron shift), which ends with the release of a bromine ion and the shift of a proton to the adjacent NH-group (Figure 5).

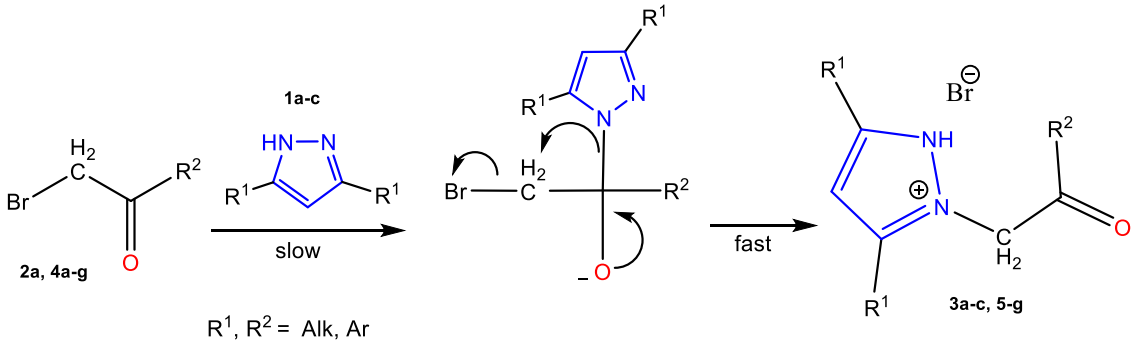


Figure 5. Probable routes of *N*-acylalkylation of pyrazoles

N-acylalkylation reactions (Figure 3, 4) are accompanied by the formation of resin-forming by-products 6, as well as by-product self-condensation reactions (Balasubrahmanya, K.S. et al., 2023) of *α*-bromoketones 2a, 4a-g (Figure 6), especially when the temperature of the reaction mixture increases, in this regard, it is not recommended to heat reaction mixtures, even partially, during the process of lyophilization of the solvent.

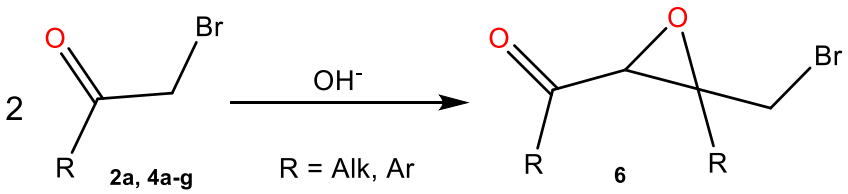


Figure 6. Scheme of side reactions of self-condensation of α-bromoketones **2a, 4a-g**

The use of the *one-pot* approach reduces the reaction time and the number of manipulations, which gives on average yields of compounds **5a-g** varying in the range of 38–91%. *N*-phenacyl-substituted pyrazoles. Pyrazole **5c** with a methoxy group in position 2 of the phenyl ring was isolated with the lowest yield (38%). Other substances were obtained in yields of (61–91%). Products **5a–g** were characterized by IR, NMR spectroscopy and GC-MS. The structure of 1-phenyl-2-(pyrazol-1-yl)ethan-1-one **5a** was described using X-ray structural analysis (Figure 7).

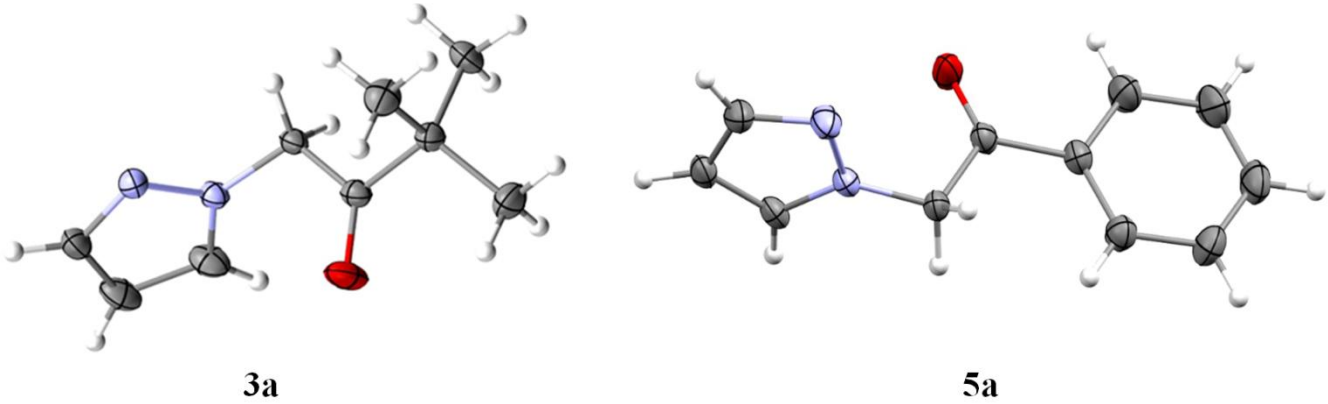


Figure 7. Crystal structures of 1-tertbutyl-2-(1H-pyrazol-1-yl)ethan-1-one **3a** and 1-phenyl-2-(pyrazol-1-yl)ethan-1-one **5a** according to X-ray diffraction data

During X-ray diffraction analysis it was determined that the crystal **3a**, formed by ordered molecules **3a**, has an orthorhombic crystal lattice with symmetry type C_2, with 2 vertical planes of symmetry located along the axis (space group $Pna2_1$). And crystal **5a** has a triclinic crystal lattice with symmetry type C_1 (space group $P1_{(2)}$) and molecules **5a** fit more tightly to each other due to additional π-stacking interactions of phenyl rings.

Thus, crystals of substances **3a** and **5a** are formed from a pair of molecules connected to each other by two hydrogen bonds, in the formation of which carbonyl groups participate. The formation of the crystal structure **3a** involves the C=O group of the tert-butyl fragment of one molecule and the hydrogen H–C of the tert-butyl fragment of the second molecule. The mechanism of hydrogen bond formation in **5a** is similar, but the donor of hydrogen interaction is the H–C hydrogen of the adjacent phenyl fragment. The pyrazole fragment in both molecules is planar and lies in the same plane as the carbonyl group.

In light of recent advances in anticancer drug development, pyrazole derivatives have been extensively studied due to their pronounced cytotoxic activity. It is important to note that the studies are not limited to cytotoxicity alone; many of these compounds also demonstrate other valuable biological properties. The paper (Zhang, Y., et al., 2023) details how pyrazole derivatives have already been tested for cytotoxicity. The authors highlight that many of these compounds have shown strong inhibitory activity against various cancer cell lines. However, there is no information in the available sources on the study of *N*-acylalkyl derivatives of pyrazole for the manifestation of toxic properties. In order to fill the gap in this information, we determined the cytotoxic properties of the studied compounds **3a, 5a-c, e, g** on *Artemia salina* crustaceans. The *Artemia salina* model is a useful initial screening tool and helps to quickly eliminate known toxic compounds (Solis, P.N. et al., 1992). However, it should be considered as a preliminary method. More complex and specific methods are needed for accurate assessment of cytotoxicity.

Standard research methods were used for the experiment. The cytotoxic activity of the extract was determined using the generally accepted method (Suleimenov, E.M., 2009). For the analysis, 200 mg of Artemia salina eggs in 1 liter of artificial seawater were used. The water was prepared

using the method specified in (Kester, D.R. et al., 1967). The cytotoxic activity was determined using the method (Meyer, B.N. et al., 1982) of survival of *Artemia salina* crustaceans in 3 parallel experiments with concentrations of 10, 5 and 1 mg/ml, at a temperature of 25°C, with a larval density of 20–40 specimens in each test tube. During the biotesting, *Artemia salina* larvae were 1 day old.

The obtained LC_{50} values (μg/ml) (Table 1) indicate that all the studied compounds **3a, 5a-c**, **e, g,** have cytotoxicity towards *Artemia salina* crustaceans, since the LC_{50} value (lethal concentration at which 50% of crustaceans die) is below 1000 μg/ml. However, it was determined that *N*-acylalkylpyrazole **5e** with the presence of a nitro-group in the *para*-position does not have cytotoxicity, since the LC_{50} value is 3045, which is higher than 1000 μg/ml.

When comparing the cytotoxicity of *N*-pinacolone pyrazole **3a** with *N*-phenacylpyrazole **5a**, it was shown that when the phenacyl substituent is replaced by a pinocolone substituent, the cytotoxicity drops almost 6 times (from LC_{50} 108.89 μg/ml to 644.00 μg/ml).

So, substances **5a-c** have medium toxicity, substances **3a**, **5g**, exhibit low toxicity, **5e** is not toxic. This can be compared to the toxicity of some fungicides and herbicides, as well as some plant extracts or fungal toxins (Libralato, G., et al., 2016). For example, the LC_{50} of some toxic fungal metabolites for *Artemia salina* can range from 9.78 to 40.84 μg/ml, which is also high (Favilla, M., et al., 2006). In the series of *N*-phenacylpyrazoles **5a-c, e, g**, the cytotoxicity decreases in the presence of an acceptor group in the benzene ring of the *N*-phenacyl substituent.

5. Conclusion

Thus, based on known *N*-acylalkylation methods, a series of *N*-acylalkylated pyrazoles 3a-c and 5a-g were synthesized, including new, previously undescribed *N*-pinacolone pyrazoles 3a-c and *N*-phenacylpyrazoles 5c, f, g. The course of the reaction is affected by temperature, since with an increase in temperature the reaction shifts toward the formation of by-products.

The structures of the obtained products were characterized by NMR, IR, X-ray diffraction and GC-mass spectrometry.

The studied compounds 3a, 5a-c, e, g, showed a certain manifestation of cytotoxicity in relation to crustaceans *Artemia Salina*. It is shown that in the presence of an acceptor group in the benzene ring of the N-phenacyl substituent (5e), the toxicity of the studied compounds decreases, relative to unsubstituted phenacylpyrazole 5a.

The above method using *Artemia Salina* is a simple and inexpensive screening test for cytotoxic compounds. It has the advantages of requiring only small amounts of compounds and the employment of microplate technology facilltates the testing of large number of samples and dilutions. Although the assay did not detect those compounds which require metabollc activation in man, it maybe conveniently used where, as in the case of the quassinoids, the brine shrimp is a reliable detector of biological activity.

The results of the cytotoxicity study show the possibility of varying the cytotoxic properties of the substance by introducing a certain functional group into *N*-acylalkylpyrazole derivatives, and can be used as a trend for further molecular design or pharmacological optimization.

6. Supplementary Materials:

No supplementary material**.**

7. Author Contributions

Conceptualization - S.Yu.; methodology - N.A.; software - M.K., S.Yu.; validation - M.K.; formal analysis - A.D.; investigation - M.K.; resources - A.G.; data curation - X.X.; writing, original draft preparation - N.A.; writing, review and editing - S.Yu.; visualization - A.G.; supervision - M.K.; project administration - M.K.; funding acquisition - M.K. All authors have read and agreed to the published version of the manuscript.

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9. Funding: The work was carried out within the framework of grant funding from the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan, project IRN AP19677175 «Development of a new affordable class of fluorescent labels based on diazapentalenes»

10. Acknowledgments: We express our deep gratitude to Lomonosov Moscow State University for cooperation in research.

11. Conflicts of interest: No conflict of interest.

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N-Ацилалкилпиразолдардың синтезі және олардың құрылымының цитоуыттылық қасиеттеріне әсері

Назым Алжаппарова, Светлана Паньшина, Марат Ибраев, Асель Жумина, Ақнұр Оразбай

Аңдатпа. Пиразолдар және олардың туындылары сақина құрылымында екі байланысқан азот атомы бар π-электронды ароматты гетероциклді қосылыстар. Пиразол туындылары биологиялық белсенді қасиеттерінің кең және алуан түрлілігіне байланысты ғалымдардың назарын аударады. Пиразол және оның гомологтары молекулалардың қышқылдық-негіздік қасиеттеріне ықпал ететін NH-тобы протонының миграциясы нәтижесінде пайда болатын прототропты таутомериямен сипатталады.

Бұл зерттеуде пиразолдардың қасиеттерін ескере отырып, алифатты және ароматты α-бромидкетондардың пиразолмен және оның 3,5-диметил-және 3,5-дифенил-туындыларымен өзара әрекеттесу реакцияларының бірқатар *N*-(ацилалкил)пиразолдары бөлме температурасында аралық тұздар мен бромсутектің бөлінуі үшін K_2CO_3 негізінің қатысуымен ацетондағы екі сатылы «*One-pot*» реакциясы арқылы синтезделді. Зерттелетін қосылыстардың ішінде 65–92% шығымы бар жаңа, бұрын сипатталмаған пинаколонпиразолдар және 38–91% шығымы бар фенацилпиразолдар синтезделді. *N*-ацилалкилдену реакциясының ықтимал жолдары қарастырылады.
Алынған өнімдердің құрылымдары ЯМР, ИҚ, РҚТ және ГХ-Масс-спектрометриямен сипатталды. РҚТ нәтижелері бойынша *N*-(ацилалкил)пиразолдар кристалдарының түзілуіне карбонил топтары қатысатын жазық конъюгацияланған π-жүйелер болып табылады.
Artemia Salina шаян тәрізділеріне қатысты зерттелетін *N*-ацилалкилпиразолдардың цитоуыттылығының көрінісі анықталды және уыттылық орынбасарлардың түріне байланысты екені көрсетілген. Сонымен, фенацилпиразолдың цитоуыттылығы пинаколонпиразолдың цитоуыттылығынан 6 есе көп, ал фенацилпиразолдардың цитоуыттылығы бензол сақинасындағы орынбасарларға байланысты өзгереді және бензол ядросында акцепторлар болған кезде төмендейді. Цитоуыттылықты зерттеу нәтижелері оларды одан кейінгі модификация кезінде дәрілік заттарды жасау үшін қолданылуы мүмкін.

Түйін сөздер: пиразол, *N*-ацилалкилдену, α-бромкетондар, ЯМР, РҚТ, цитоуыттылық, *Artemia Salina.*

Синтез N-ацилалкилпиразолов и влияние их структуры на свойства цитотоксичностим

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Аннотация: Пиразолы и его производные – это π-электронизбыточные ароматические гетероциклические соединения, в структуре кольца которых имеются два связанных атома азота. Производные пиразола привлекают все больше внимания ученых, благодаря своему обширному и разнообразному ряду биологически активных свойств. Пиразолам и его гомологам свойственна прототропная таутомерия.
Учитывая свойства пиразолов, в данном исследовании синтезирован ряд производных *N*-(ацилалкил)пиразолов реакций взаимодействия алифатических и ароматических α-бромидкетонов с пиразолом и его 3,5-диметил- и 3,5-дифенилпроизводными через двухстадийную реакцию «*One-pot*» в ацетоне, при комнатной температуре, в присутствии основания K_2CO_3 для высвобождения промежуточной соли и отщепления бромоводорода. Среди исследуемых соединений получены новые, ранее не описанные пинаколонпиразолы с выходами 65–92% и фенацилпиразолы с выходами 38–91%**.** Рассмотрены вероятные пути реакции *N*-ацилалкилирования.
Структуры полученных продуктов охарактеризованы методами спектроскопии ЯМР, ИК, РСА и ГХ-Масс-спектрометрии. Согласно результатам РСА, *N*-(ацилалкил)пиразолы – плоские, сопряженные π-системы, в формировании кристаллов которых участвуют карбонильные группы.
Определено проявление цитотоксичности изучаемых *N*-ацилалкилпиразолов в отношении рачков *Artemia Salina*, причем показано, что токсичность зависит от типа заместителей. Так, фенацилпиразол имеет цитотоксичность, в 6 раз превышающую цитотоксичность пинаколонпиразола, а цитотоксичность фенацилпиразолов меняется в зависимости от заместителей в бензольном кольце, причем падает при наличии акцепторов в бензольном

ядре. Результаты исследования цитотоксичности могут быть использованы для разработки лекарственных средств при их дальнейшей модификации.

Ключевые слова: пиразол; *N*-ацилалкилирование; α-бромкетоны; ЯМР, РСА, цитотоксичность, *Artemia Salina*.